รายงานวิจัยฉบับสมบูรณ์

โครงการวิจัย “การพัฒนาสารผลิตภัณฑ์ธรรมชาติในกลุ่มลาเมลลารินที่มีศักยภาพเป็นสารต้านมะเร็ง” ในชุดโครงการวิจัยแบบมุ่งเป้า สมุนไพร ยารักษาโรคและสารเสริมสุขภาพ

โดย ดร. มนทกานติ์ จิตต์แจ้ง

สถาบันบัณฑิตศึกษาจุฬาภรณ์ และ สถาบันวิจัยจุฬาภรณ์

สิงหาคม 2558

สัญญาเลขที่ DBG5480011

รายงานวิจัยฉบับสมบูรณ์

โครงการวิจัย “การพัฒนาสารผลิตภัณฑ์ธรรมชาติในกลุ่ม ลาเมลลารินที่มีศักยภาพเป็นสารต้านมะเร็ง” ในชุดโครงการวิจัยแบบมุ่งเป้า สมุนไพร ยารักษาโรคและสารเสริมสุขภาพ

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สนับสนุนโดยสำนักงานกองทุนสนับสนุนการวิจัย

(ความเห็นในรายงานนี้เป็นของผู้วิจัย

สกว. ไม่จำเป็นต้องเห็นด้วยเสมอไป)

สัญญาเลขที่ DBG5480011

โครงการ “การพัฒนาสารผลิตภัณฑ์ธรรมชาติในกลุ่มลาเมลลารินที่มีศักยภาพเป็นสารต้านมะเร็ง”

รายงานวิจัยฉบับสมบูรณ์

ระยะเวลาดำเนินการ: วันที่ 31 กรกฎาคม 2554 ถึงวันที่ 31 สิงหาคม 2558

ชื่อหัวหน้าโครงการวิจัยผู้รับทุน: ดร. มนทกานติ์ จิตต์แจ้ง

หน่วยงาน: สถาบันบัณฑิตศึกษาจุฬาภรณ์ และ สถาบันวิจัยจุฬาภรณ์

บทคัดย่อ

ถึงแม้ว่าสารผลิตภัณฑ์ธรรมชาติในกลุ่มลาเมลลารินจะมีฤทธิ์ทางชีวภาพที่หลากหลาย โดยเฉพาะฤทธิ์ในการฆ่าเซลล์มะเร็ง แต่ที่ผ่านมาปัญหาการละลายเป็นอุปสรรคที่สำคัญในการพัฒนาสารในกลุ่มนี้ คณะผู้วิจัยจึงได้พยายามที่จะปรับปรุงคุณสมบัติของสารในกลุ่มลาเมลลารินโดยการแทนที่หมู่ฟังก์ชันที่ไม่จำเป็นต่อการออกฤทธิ์ด้วยหมู่ที่ช่วยเพิ่มการละลายน้ำ ดังนั้น โครงการวิจัยนี้จึงเริ่มจากการออกแบบสารอนุพันธ์อย่างเป็นระบบ เพื่อใช้ในการศึกษาความสัมพันธ์ระหว่างสูตรโครงสร้างกับการออกฤทธิ์ฆ่าเซลล์มะเร็ง ซึ่งทำให้ทราบถึงความสำคัญของหมู่ฟังก์ชันเพิ่มเติมจากที่เคยพบก่อนหน้านี้ จนกระทั่งสามารถเลือกสารลาเมลลารินที่มีหมู่ฟังก์ชันที่สำคัญต่อการออกฤทธิ์เป็นไปตามที่ต้องการมากที่สุด จำนวน 2 ตัว สำหรับใช้เป็นต้นแบบในการปรับเปลี่ยนสูตรโครงสร้างต่อไป จากการทดสอบคุณสมบัติทางเคมีกายภาพพบว่า สารลาเมลลารินทั้ง 2 ตัว มีความชอบไขมันในระดับปานกลาง แต่มีค่าการละลายน้ำในระดับไมโครโมลาร์เท่านั้น และเมื่อเปลี่ยนหมู่แลคโตนในสูตรโครงสร้างเป็นหมู่แลคแตมแล้ว สารอนุพันธ์เอซาลาเมลลารินที่สังเคราะห์ได้มีความชอบไขมันลดลงอย่างมีนัยสำคัญ แต่ค่าการละลายน้ำยังไม่เปลี่ยนแปลงมากนัก อย่างไรก็ตาม สารเอซาลาเมลลารินมีฤทธิ์ในการฆ่าเซลล์มะเร็งได้ดี อีกทั้งยังสามารถยับยั้งเอนไซม์ไกลโคเจนซินเทสไคเนส-3β ได้อย่างมีประสิทธิภาพมากกว่าสารลาเมลลารินต้นแบบด้วย ซึ่งคณะผู้วิจัยจะใช้ผลการศึกษาเหล่านี้เป็นแนวทางสำหรับการพัฒนาสารอนุพันธ์ลาเมลลารินที่มีคุณสมบัติเหมาะสมกับการเป็นยาต้านมะเร็งต่อไป

Project Number DBG5480011

"Development of Lamellarin Natural Products as Potential Anticancer Agents"

Final Report

Project Period: 31 July 2011 – 31 August 2015

Principal Investigator: Dr. Montakarn Chittchang

Affiliations: Chulabhorn Graduate Institute and Chulabhorn Research Institute

Abstract

Although lamellarin natural products exhibit a broad spectrum of biological activities, especially cytotoxicity towards cancer cells, their preclinical development has been complicated by a lack of aqueous solubility, which is also indispensable for drug candidates. Therefore, we first attempted to streamline their structure with the aim to replace non-essential functional groups with some solubility-enhancing moieties. Using a library of lamellarins and their systematically designed analogs, we identified additional important structural elements towards the inner part of the molecule, including those on the orthogonal ring. According to the overall findings from our structure-activity relationship studies to date, lamellarin D contains most of the required substituents, and thus, it was used along with its structural isomer, lamellarin N, as our templates for further modifications. Initially, both compounds were subjected to comparative physicochemical profiling, which indicated that the aqueous solubility of these moderately lipophilic molecules was in the low micromolar range under physiologically relevant conditions. Interestingly, a simple lactone-to-lactam replacement significantly reduced the lipophilicity of both compounds even though their aqueous solubility was not much improved. Nevertheless, the resulting azalamellarin derivatives not only maintained appreciate cytotoxicity against cancer cells, but also exhibited more potent GSK-3β inhibitory activity than their parent compounds. These findings provide insights for further development of more drug-like lamellarin analogs into anticancer agents.

Keywords: lamellarins, structure-activity relationship, drug-likeness, lipophilicity, solubility, cytotoxicity, glycogen synthase kinase-3

Executive Summary

Lamellarins with broad spectrum biological activities represent an attractive class of natural products for scientists in various fields. Unfortunately, these molecules severely suffer from poor aqueous solubility, preventing their development into drug candidates. In order to construct lamellarin analogs with improved drug-likeness, our research group has been streamlining the structure of these compounds so that the less important substituents might be subsequently replaced with some solubility-enhancing moieties.

During the first two years, 59 analogs were carefully designed, synthesized, tested, and finally employed along with 25 parent lamellarins for our systematic SAR studies. The results unveiled additional structural requirements towards the inner part of these molecules, including the orthogonal ring preferably with a *p*-hydroxyl group, as well as an oxygen-containing substituent at C9 to both maintain the activity and avoid further increase in their lipophilicity. In addition, the benefits and drawbacks of catechol incorporation into lamellarin molecules were clearly demonstrated.

With most of the required substituents and their promising activities, lamellarin D and lamellarin N structural isomers were then selected as our lead compounds. Using the methods specifically optimized for lamellarins, comparative physicochemical profiling showed that these 2 molecules were moderately lipophilic with a log P value around 3.5, while their aqueous solubility fluctuated in the low micromolar range under physiologically relevant conditions even in the presence of dimethyl sulfoxide (DMSO) as a cosolvent.

Interestingly, a simple lactone-to-lactam replacement without changing any other substituents resulted in less lipophilic azalamellarin derivatives although their intrinsic solubility was not much improved. While appreciable cytotoxicity towards cancer cells could be maintained, azalamellarins exhibited promising inhibitory activity against the multifaceted GSK-3β enzyme, presumably *via* a different mode of inhibition from that of the parent lamellarins. In addition, possible interactions underlying the affinity of our inhibitor molecules for the GSK-3β target were probed by molecular modelling studies.

These results provide insights for further development of drug-like lamellarin analogs as potential anticancer agents. Our findings have been successfully disseminated through 2 full-length research articles in the Chemistry – An Asian Journal, as well as a series of poster and oral presentations at international venues.

ผลงานวิจัย

Lamellarins are a family of pyrrole alkaloids originally isolated from prosobranch mollusks in 1985 and later found in ascidians and sponges. These compounds exhibit potent cytotoxic effects against tumor cells from different origins, along with multidrug resistance reversal activity, HIV-1 integrase inhibition, and antioxidant properties. For a few decades, lamellarins have attracted attention from not only synthetic organic chemists, but also scientists from various fields as continuously documented in the literature. Wide-ranging research activities have been directed towards these marine alkaloids, encompassing their total synthesis, biological activities and molecular mechanisms, structure-activity relationships (SAR), as well as pharmaceutical development.

Apart from potent activities, optimum physicochemical properties are also indispensable for drug candidates. The preclinical development of lamellarins has been complicated by their extremely poor aqueous solubility on top of their limited selectivity for cancer cells over normal cells. Therefore, our research group has continuously explored the medicinal chemistry of these compounds with the ultimate goal to develop drug-like lamellarin analogs as potential anticancer agents. Over the first two years of this project, most efforts were directed towards the synthesis, cytotoxicity evaluations, as well as SAR studies of lamellarin analogs in order to streamline the structural requirements for their activity. In parallel, physicochemical profiling of these molecules was also performed in terms of lipophilicity and aqueous solubility, a balance of which is important for *in vivo* effectiveness. The results obtained were then used to design more drug-like lamellarin derivatives, which were synthesized and subsequently evaluated for both the biological activities and physicochemical properties as described below. Details of our investigations can be found in the attached publications.

<u>Streamlining of Lamellarin Structure</u>

Our previous SAR studies focusing on the cytotoxicity of lamellarins clearly indicate the importance of the C5=C6 olefin, a hydroxyl group at either C7 or C8, as well as the hydroxyl group at C20, all of which are located on periphery of the pentacyclic lamellarin skeleton (**Figure 1a**). In an attempt to both simplify their structure and improve their drug-likeness, a library of 59 analogs (**Figure 1b–d**) were designed and used to systematically explore the possibility of modifying the substituents towards the inner part, especially those on the orthogonal ring, of these molecules to affect both the cytotoxicity improvement and lipophilicity reduction.

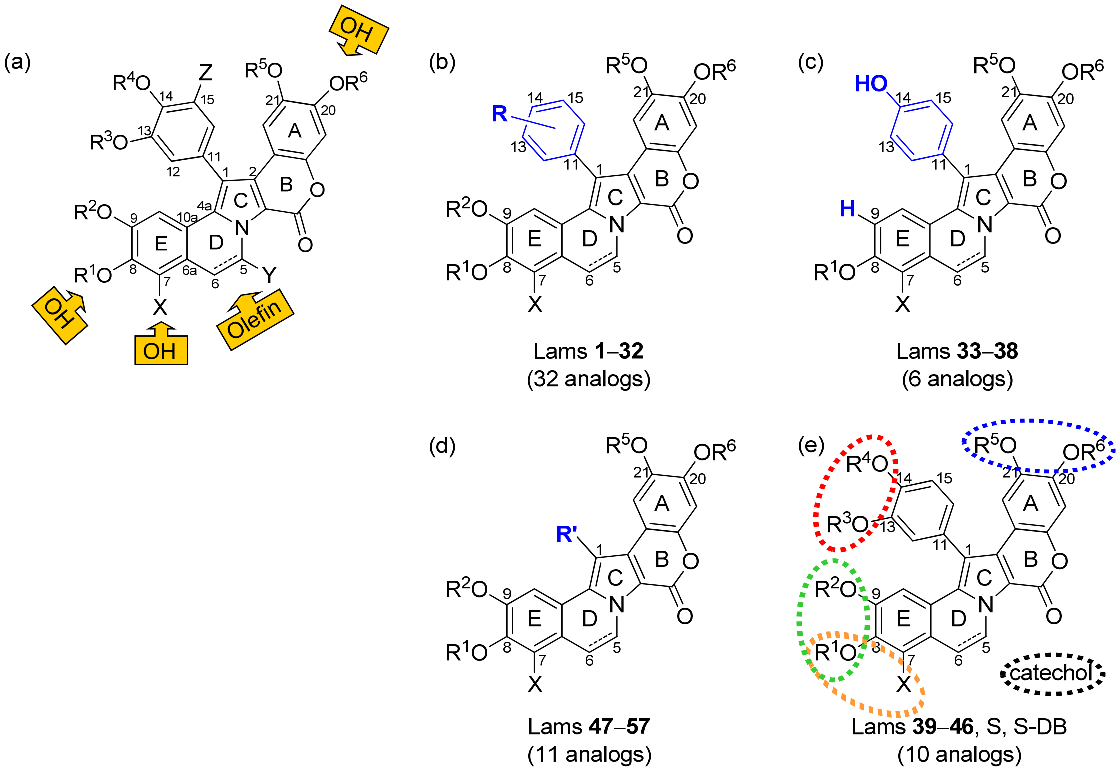
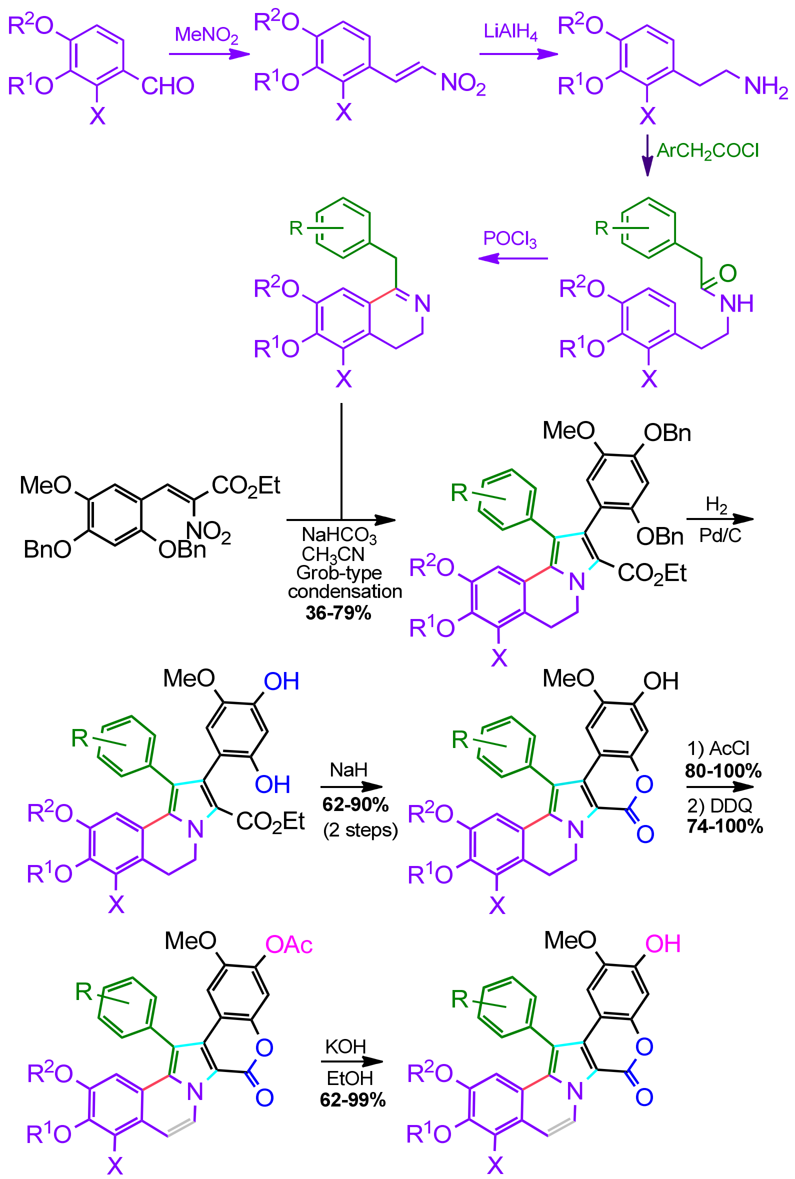


Figure 1. (a) Reported structural requirements around the lamellarin skeleton, (b) lamellarin analogs with a modified orthogonal ring, (c) C9-unsubstituted analogs, (d) C1-dearylated analogs, and (e) catechol-containing lamellarins.

Except for the C1-dearylated analogs and catechol-containing lamellarins, the designed compounds were synthesized using our previously established method for natural lamellarins with some modifications. As exemplified in **Scheme 1**, aryl ethylamines were synthesized using appropriately substituted benzaldehyde derivatives as building blocks and were subsequently coupled with arylacetic acids, *via* the intermediacy of acid chlorides, to provide the corresponding amides and benzyldihydroisoquinolines, respectively. Next, pyrrole formation was achieved *via* the Grob-type Michael addition-ring closure (Mi-RC) with the α-nitrocinnamate. The pyrrole ester intermediates then underwent global hydrogenolysis and NaH-mediated lactonization to furnish the lamellarin analogs with a saturated D-ring. Finally, sequential reactions of acetylation, DDQ-mediated oxidation, and deacetylation yielded the corresponding analogs with an unsaturated D-ring.



Scheme 1. Synthetic route for lamellarin analogs with a modified orthogonal ring.

All the synthesized lamellarin analogs along with the 25 parent compounds were then subjected to lipophilicity determination, as well as cytotoxicity assay against a panel of 11 cancer cell lines and the MRC-5 normal cells. Matched molecular pairs analysis was carefully conducted to systematically evaluate the contributions of each substituent from both the activity and lipophilicity standpoints. Our findings indicated that the orthogonal ring must be present and could not be replaced with other functional groups. More importantly, at least one oxygen-containing substituent, preferably as a hydroxyl group at the *para* position (**Figure 2a**), on this ring was required for both maintaining the cytotoxic activity and avoiding further increase in the lipophilicity of lamellarins. In addition, the presence of an oxygen-containing group at C9 was also beneficial for the cytotoxicity (**Figure 2b**). On the other hand, while the incorporation of a catechol moiety occasionally resulted in more active analogs (**Figure 2c**), it caused instability problems in many cases and prevented the synthesis of the potentially more potent version with the C5=C6 olefin. All the important structural elements around the lamellarin skeleton are summarized in **Figure 3**.

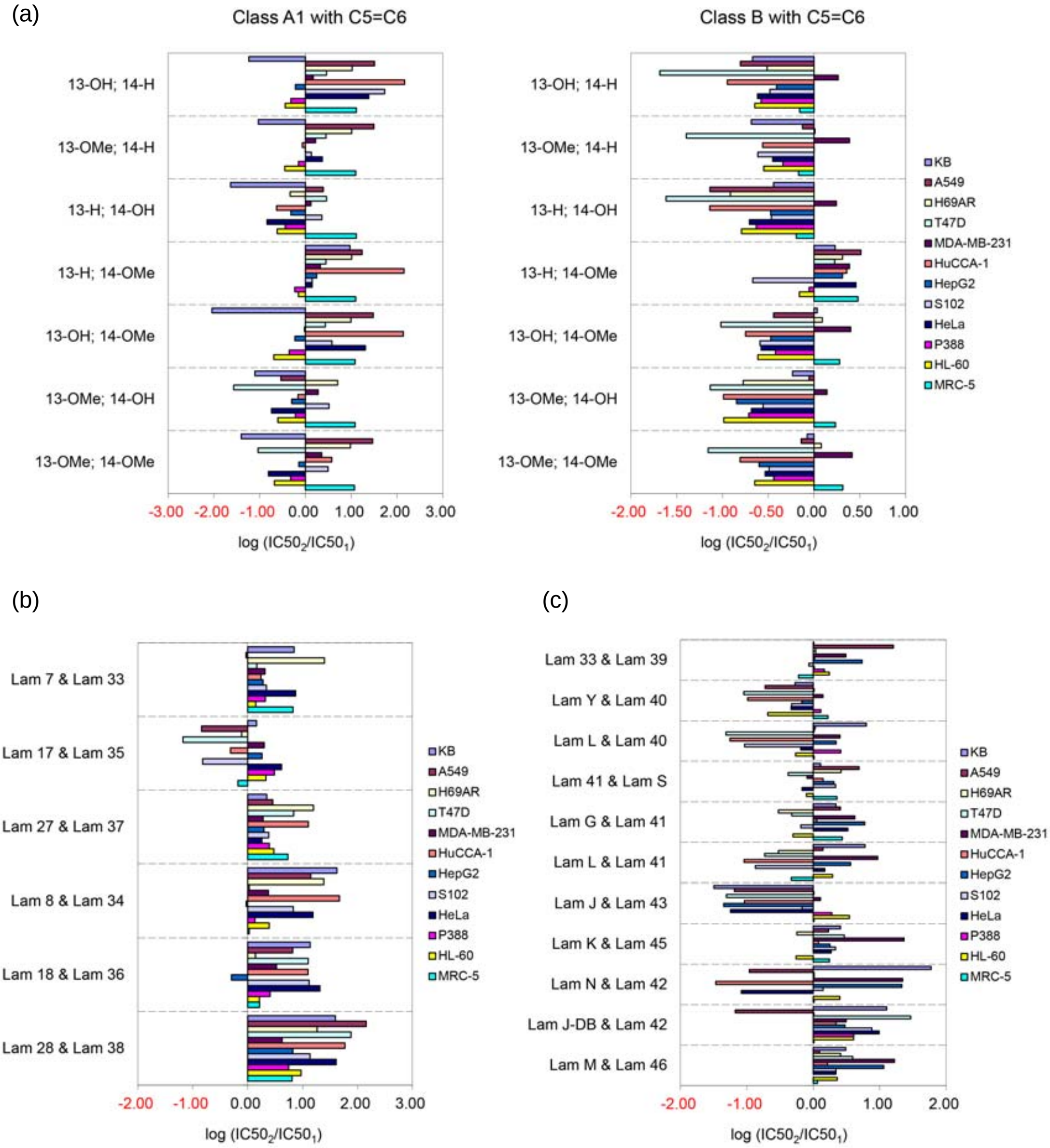


Figure 2. Effects of (a) the substituents on the orthogonal ring, (b) C9-substituent removal, and (c) catechol incorporation on the cytotoxicity against various cancer cell lines. On the x-axis, negative logarithmic ratios of the IC_{50} values indicate the increased cytotoxic effects, while positive ratios suggest the loss of activity upon the modification being considered.

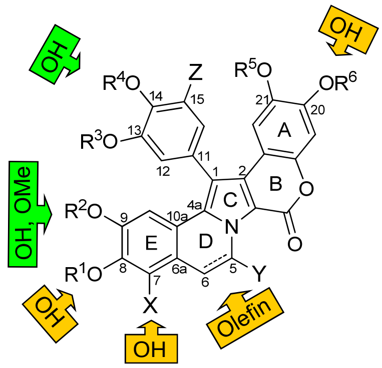


Figure 3. Important structural requirements around the lamellarin skeleton based on our SAR studies to date.

<u>Physicochemical Profiling of Lamellarins</u>

Based on the above-mentioned SAR findings, the naturally-occurring lamellarin D possesses most of the required substituents (**Figure 4**) and exhibits promising biological activities such that it has been the most extensively studied compound in the series, especially for the molecular mechanisms underlying its cytotoxic effects. Additionally, lamellarin N, its structural isomer with the only difference in the positions of the hydroxyl and methoxy groups on the orthogonal ring (**Figure 4**), also shows interesting cytotoxicity against certain cancer cell lines and appears significantly less toxic to normal MRC-5 cells.

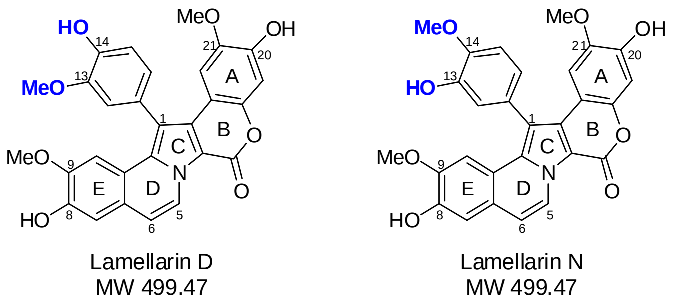


Figure 4. Structures of lamellarin D and lamellarin N structural isomers.

With the aim to use lamellarin D and lamellarin N as the templates for structure optimization, we then proceeded to conduct a comparative study on the physicochemical studies of these two structural isomers. Our main focus was to determine their aqueous solubility and lipophilicity since lamellarins are highly lipophilic, and thus, usually precipitate in biological media. While lipophilicity determination using reversed-phase HPLC has been previously established in our laboratory, solubility measurement had yet to be set up.

In pharmaceutical literature, there are two types of solubility data. Thermodynamic solubility has been defined as the concentration at the end of the dissolution process, in which a saturated solution is in equilibrium with excess solid. This parameter is useful for lead optimization and drug development. In contrast, kinetic solubility has been defined as the concentration remaining in solution after the pre-dissolved compound is added into an aqueous medium, which is similar to the routine practice during biological assays of poorly soluble compounds. Therefore, kinetic solubility data can be used to predict potential screening and bioavailability problems.

Traditional shake-flask method was used to determine both types of solubility data for lamellarin D and lamellarin N. The measurements started with adding an excess amount of compound (as either solid or stock solution in DMSO) into the medium, agitating or stirring the suspension for a defined period of time, separating the undissolved solid by filtration or centrifugation, and finally measuring the compound concentration in the filtrate or supernatant. In our study, various experimental parameters were investigated in terms of the amount of excess solid, DMSO concentration, shaking speed, incubation time, and separation technique. The optimized conditions were subsequently used for determining the thermodynamic and kinetic solubility of both lamellarin D and lamellarin N. The results shown in **Figure 5** clearly confirmed that both compounds were poorly soluble with the thermodynamic solubility of less than 1 μM. The presence of DMSO in kinetic solubility measurements helped accommodate these molecules at slightly higher concentrations.

In addition, the thermal stability of lamellarin D and lamellarin N at 4 different temperatures was also investigated. To avoid precipitation at a concentration significantly higher than their aqueous solubility, the 100 μM samples of each compound were first prepared in a mixture of MeOH/water (75:25 v/v) and then divided into 4 identical aliquots, each of which were stored for 8 weeks 4, 25, 37, and 60 °C, respectively. All samples were subjected to weekly HPLC analysis for the parent compounds and any degradation products. The percent remaining of lamellarins at any temperatures were determined by comparing their peak areas with that obtained for the refrigerated aliquot of the same sample. As shown in **Figure 6**, both compounds appeared sufficiently stable throughout the 8-week incubation period. The observed increase in the percent remaining over time possibly resulted from methanol evaporation upon storage. Therefore, the most challenging issue for the development of these compounds is to improve their aqueous solubility.

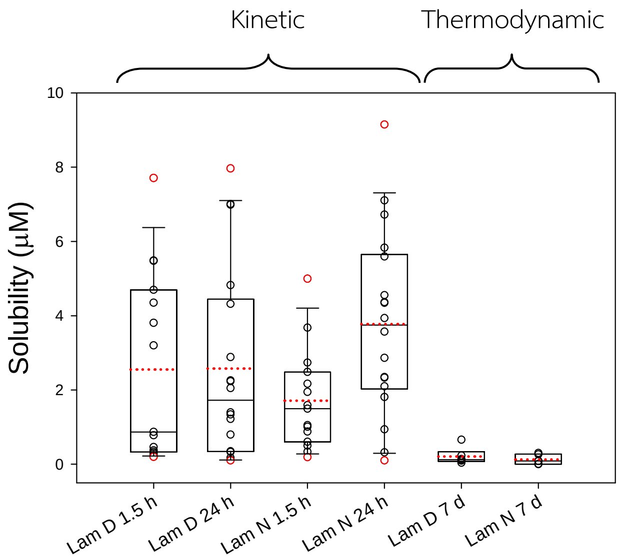


Figure 5. Kinetic and thermodynamic solubility of lamellarin D and lamellarin N.

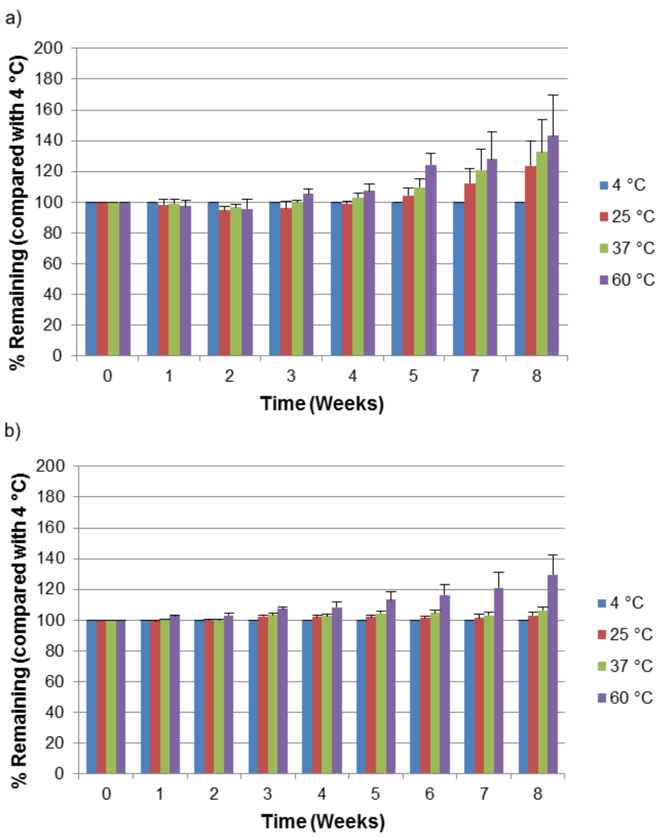
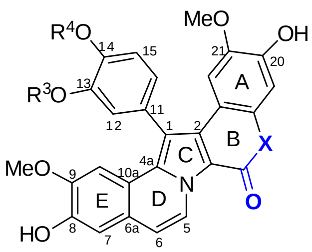


Figure 6. Percent remaining of (a) lamellarin D and (b) lamellarin N in MeOH/water (75:25 v/v) at different temperatures.

<u>Development of More Drug-like Lamellarin Derivatives</u>

Previously, Kamiyama *et al*. has reported that hydrophilic *O*-sulfated lamellarin analogs at 100 μM concentration were hardly incorporated into HeLa cells and exhibited no cytotoxicity upon 24 h incubation. In contrast, Pla *et al*. has demonstrated that poly(ethylene glycol) derivatives of lamellarin D exhibited more potent cytotoxicity against cancer cells than the parent compound, but their approach resulted in even larger molecules that might have different behaviors in biological systems. In this study, we focused on a more subtle approach of simple lactone-to-lactam replacement as previously reported by Thasana and coworkers for simultaneous enhancement of the stability and solubility of lamellarin D. The corresponding aza derivatives of lamellarin D and lamellarin N (**Figure 7**) were successfully synthesized and then subjected to further investigations as described below.



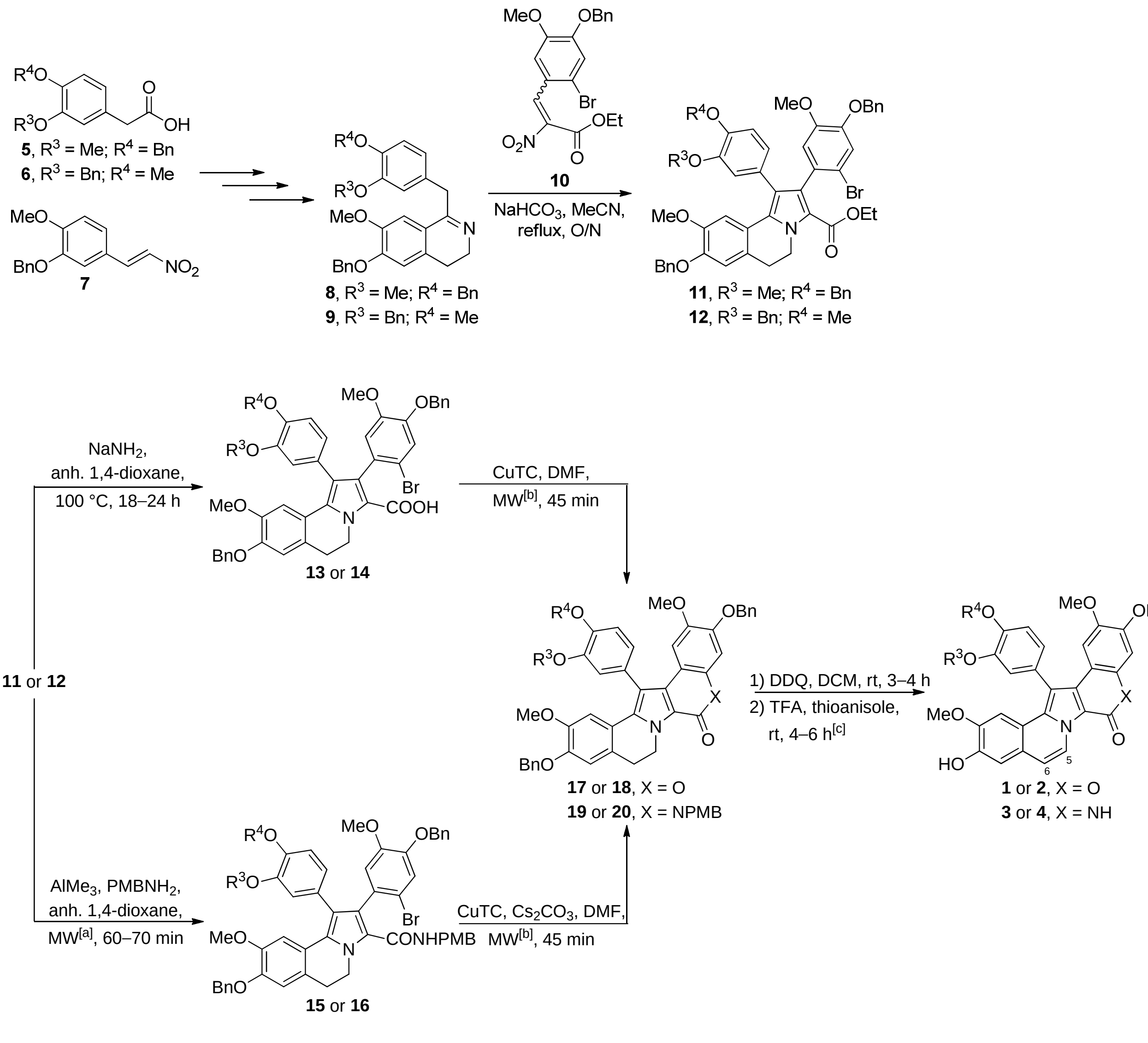
1–4

1, lamellarin D, X = O; R^3 = Me; R^4 = H
2, lamellarin N, X = O; R^3 = H; R^4 = Me
3, azalamellarin D, X = NH; R^3 = Me; R^4 = H
4, azalamellarin N, X = NH; R^3 = H; R^4 = Me

Figure 7. Structures of the compounds used in this study.

Due to the relatively long sequence (8 steps starting from the pyrrole esters) with some low yielding steps, the previously reported route gave azalamellarin D in only 11% overall yield. Hence, this study started with the design of an efficient simplified total synthetic scheme for azalamellarins. Through the use of *O*-benzyl and *N*-PMB protecting groups that remain intact until the final acid-mediated cleavage (**Scheme 2**), we could avoid not only the additional acetylation and deacetylation steps originally required for C5=C6 installation, but also the problematic removal of the previously attempted *N*-allyl and *N*-*n*Pr protecting groups.

More importantly, our new synthetic route allowed the same pyrrole ester intermediate (**11** or **12**) to undergo similar sets of reactions to furnish both the parent lamellarin and its azalamellarin derivative (*i.e.*, **1** and **3** or **2** and **4**) as summarized in **Scheme 2**. Over 4 steps from the corresponding pyrrole esters, lamellarin D (**1**), lamellarin N (**2**), azalamellarin D (**3**), and azalamellarin N (**4**) could be obtained in 53, 35, 71, and 66% yields, respectively.



Scheme 2. Divergent synthetic route of lamellarins and azalamellarins.

[a] 200 W, 150–170 °C, 200 psi; [b] 200 W, 150 °C, 100 psi. [c] For **19** and **20**, the mixture was subsequently heated at 60 °C for an additional 16 h. For compounds **13**, **15**, **17**, and **19**, R^3=Me; R^4=Bn. For compounds **14**, **16**, **18**, and **20**, R^3=Bn; R^4=Me. For compounds **1** and **3**, R^3=Me; R^4=H. For compounds **2** and **4**, R^3=H; R^4=Me.

All the synthesized compounds **1–4** were then subjected to comparative profiling in terms of lipophilicity, aqueous solubility, cytotoxicity, and GSK-3β inhibitory activity. The results in **Tables 1 and 2** revealed that the introduced lactone-to-lactam replacement rendered these molecules less lipophilic while maintaining their cancer cytotoxicity. Interestingly, such subtle modification not only enhanced their GSK-3β inhibitory activity, but also led to a distinct mode of inhibition as indicated by different dependencies on the ATP concentrations. The possible interactions underlying the affinity of azalamellarins were also explored by molecular docking studies.

Table 1. Physicochemical parameters of lamellarins and azalamellarins.

Parameter	**1**	**2**	**3**	**4**
Exp. log P[a]	3.55 ± 0.02	3.49 ± 0.01	2.65 ± 0.01	2.63 ± 0.01
Thermodynamic (3 d)[b]	ND	ND	ND	ND
Thermodynamic (7 d)[b]	0.21 ± 0.23	0.12 ± 0.13	0.11 ± 0.07	0.05 ± 0.04
Kinetic (1.5 h)[b]	2.55 ± 2.53	1.71 ± 1.34	5.91 ± 1.57	5.58 ± 1.80
Kinetic (24 h)[b]	2.57 ± 2.58	3.78 ± 2.46	5.43 ± 2.16	3.07 ± 0.77

[a]HPLC method. [b]Solubility in μM determined using the shake-flask method at pH 7.4 and 37 °C. Exp. = experimental, ND = not detectable.

Table 2. Cytotoxicity against cancer cells and GSK-3β inhibitory activity of lamellarins and azalamellarins.

	IC_{50} (μM)						
Target	**1**	**2**	**3**	**4**	Doxo-rubicin	Eto-poside	SB 415286
A549[a]	1.51	I	0.82	0.38	0.59	ND	ND
HepG2[a]	0.30	0.40	0.23	0.09	0.26	ND	ND
HuCCA-1[a]	0.29	0.18	0.13	0.12	0.69	ND	ND
MOLT-3[b]	0.006	0.01	0.04	0.01	ND	0.05	ND
MRC-5[a]	56.94	I	0.30	8.29	3.09	ND	ND
GSK-3β[c] (10 μM ATP)	0.32	0.036	0.018	0.008	ND	ND	0.24
GSK-3β[c] (100 μM ATP)	0.52	0.053	0.022	0.009	ND	ND	0.78

[a]MTT assay. [b]XTT assay. [c]ADP-Glo™ assay. I = inactive (IC_{50} >100 μM), ND = not determined.

Output ที่ได้จากโครงการ

1. ผลงานวิจัยที่ตีพิมพ์ในวารสารวิชาการระดับนานาชาติ

1.1 Tangdenpaisal K, Worayuthakarn R, Karnkla S, Ploypradith P, Intachote P, Sengsai S, Saimanee B, Ruchirawat S, **Chittchang M**. Designing New Analogs for Streamlining the Structure of Cytotoxic Lamellarin Natural Products. Chem. Asian J. **2015**; *10*: 925-937. (Special Issue: 10 Years Asian Core Program (ACP): Cutting-Edge Organic Chemistry in Asia; ISI Journal Citation Reports® Impact Factor = 4.587 in 2014)

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กิตติกรรมประกาศ

ผู้วิจัยขอขอบคุณสำนักงานกองทุนสนับสนุนการวิจัย (สกว.) ที่ได้สนับสนุนเงินทุนสำหรับโครงการวิจัยนี้ นอกจากนี้ผู้วิจัยขอขอบคุณสถาบันวิจัยจุฬาภรณ์ที่ให้ความสนับสนุนอุปกรณ์ที่ใช้ในการวิจัยทั้งหมดด้วย

ผู้วิจัยขอขอบคุณบุคลากรของสถาบันวิจัยจุฬาภรณ์ สถาบันบัณฑิตศึกษาจุฬาภรณ์ และหน่วยงานอื่นๆ ที่มีส่วนช่วยให้โครงการวิจัยเชิงบูรณาการนี้สำเร็จลงได้ด้วยดี ดังรายนามต่อไปนี้

- ดร. พูนศักดิ์ พลอยประดิษฐ์ และผู้ช่วยวิจัยในห้องปฏิบัติการเภสัชเคมี สถาบันวิจัยจุฬาภรณ์ สำหรับความร่วมมือในการสังเคราะห์สารในกลุ่มลาเมลลาริน

- นางสาวผกามาส อินทโชติ นางสาวขจีลักษณ์ เฉียบแหลม นางสาวสุชาดา เสียงใส และนางสาวบุษกร สายมณี นักวิจัยในหน่วยทดสอบทางชีวภาพ (Bioassay Unit) สถาบันวิจัยจุฬาภรณ์ สำหรับความร่วมมือในการทดสอบความเป็นพิษต่อเซลล์มะเร็งของสารในกลุ่มลาเมลลาริน

- นายอติรุจ เทพวงศ์ นักศึกษาปริญญาโท สาขาวิชาเคมีชีวภาพ สถาบันบัณฑิตศึกษาจุฬาภรณ์ และผู้ช่วยวิจัยในห้องปฏิบัติการเภสัชเคมี สถาบันวิจัยจุฬาภรณ์ สำหรับการสังเคราะห์และทดสอบฤทธิ์ของสารอนุพันธ์เอซาลาเมลลาริน

- ดร. เกรียงศักดิ์ เลิศประภามงคล และ ดร. ลักขณา งิ้วสระ นักวิจัยในห้องปฏิบัติการชีวเคมี สถาบันวิจัยจุฬาภรณ์ สำหรับคำแนะนำในการพัฒนาวิธีทดสอบฤทธิ์ในการยับยั้งเอนไซม์ glycogen synthase kinase-3β

- ผศ.ดร. พิทักษ์ เชื้อวงศ์ จากภาควิชาเคมี คณะวิทยาศาสตร์ มหาวิทยาลัยเกษตรศาสตร์ สำหรับความร่วมมือในการประยุกต์ใช้เคมีเชิงคำนวณ ในการศึกษาอันตรกิริยาระหว่างสารลาเมลลารินและสารเอซาลาเมลลารินกับเอนไซม์ glycogen synthase kinase-3β

APPENDIX

ภาคผนวก

1. ผลงานวิจัยที่ตีพิมพ์ในวารสารวิชาการระดับนานาชาติ

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ผลงานวิจัยที่ตีพิมพ์
ในวารสารวิชาการ
ระดับนานาชาติ

DOI: 10.1002/asia.201403361

CHEMISTRY
AN ASIAN JOURNAL
Full Paper

Lamellarins

Designing New Analogs for Streamlining the Structure of Cytotoxic Lamellarin Natural Products

Kassrin Tangdenpaisal,[a] Rattana Worayuthakarn,[a] Supatra Karnkla,[a] Poonsakdi Ploypradith,[a, b] Pakamas Intachote,[c] Suchada Sengsai,[d] Busakorn Saimanee,[d] Somsak Ruchirawat,[a, b] and Montakarn Chittchang*[a, b]

Abstract: Despite the therapeutic potential of marine-derived lamellarin natural products, their preclinical development has been hampered by their lipophilic nature, causing very poor aqueous solubility. In order to develop more drug-like analogs, their structure was streamlined in this study from both the cytotoxic activity and lipophilicity standpoints. First, a modified total synthetic route was successfully devised to construct a library of 59 systematically designed lamellarin analogs, which were then subjected to cytotoxicity and log P determinations. Along with the 25 first-generation lamellarins previously synthesized in our laboratory, the structure–activity and structure–lipophilicity relationships were extensively evaluated. Our results clearly indicated the additional structural requirements around the lamellarin skeleton which, when combined with those reported previously, can provide invaluable guidance for further modifications to increase the aqueous solubility of these compounds.

Introduction

Lamellarins are marine alkaloids possessing a unique pentacyclic skeleton and an orthogonal ring (Figure 1 a). Considerable interest has been directed towards these polyaromatic natural products primarily due to their broad-spectrum biological activities with multiple underlying intracellular targets.[1] Unfortunately, their promising therapeutic potential, especially for multidrug-resistant tumors, has yet to be realized due to their lack of selectivity towards normal cells. Additionally, the preclinical development of these compounds has also been complicated by their extremely poor solubility in most solvents, except dimethyl sulfoxide (DMSO) and tetrahydrofuran (THF), which are not physiologically acceptable.

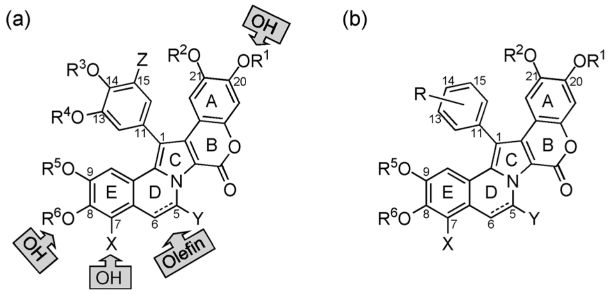

Figure 1. General structures of (a) first-generation lamellarins and (b) second-generation lamellarin analogs. (OR^1–OR^6 = OH or OMe; X, Y, Z, R = H or OH or OMe). Arrow boxes indicate the important substituents based on our previous SAR studies.

Our previous physicochemical profiling of 36 lamellarins using principal components analysis (PCA) revealed that these compounds dwell towards the edge of drug-like chemical space when compared with both natural product and small molecular drug data sets.[2] Nevertheless, their molecular properties are not as particularly extreme as those of some other natural product classes, thereby still allowing lamellarins to be used as a starting point for lead optimization campaign. Among the previously calculated molecular descriptors, their relatively high molecular weight of around 500 and high lipophilicity were identified as the two least drug-like properties that should be improved while optimizing the structures of lamellarins.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201403361.

The highly lipophilic nature of lamellarins has also been experimentally verified by our laboratory in terms of their chromatographic log P values, ranging from 2.59 to 5.19 with an average of 3.66 ± 0.71.[2] As a result, lamellarins are poorly soluble and commonly precipitate in biological media. A number of aqueous solubility-enhancing moieties, including amino acid residues,[3] poly(ethylene glycol),[4] and a nuclear localization signal peptide,[5] have been conjugated with various hydroxy groups of lamellarin molecules by a number of research groups. However, this approach resulted in even larger molecules and might have significantly altered their behavior in biological systems.

With the ultimate goal to develop lamellarin analogs possessing improved drug-likeness, our research group has been focusing on a more subtle approach through the modifications of less important substituent(s). Previous structure–activity relationship (SAR) studies have revealed the significance of the full pentacyclic lamellarin skeleton with an intact lactone ring.[6] In addition, we have confirmed that the presence of the C5 = C6 olefin and a hydroxy group at either C7 or C8, as well as another hydroxy group at C20, are all beneficial for their cytotoxicity against cancer cells (Figure 1 a).[7] Based on both the reported and our molecular modeling studies, the C5 = C6 olefin not only confers the planarity required for the lamellarin pharmacophore but also helps with the alignment of substituents, especially those on the E-ring, for better interactions with their molecular targets.

As shown in Figure 1 a, all the important substituents are located towards the periphery of the pentacyclic core. The C8- and C20-hydroxy groups have been shown to interact via hydrogen bonding with a number of amino acids in the biological targets, especially topoisomerase I enzyme.[8] In contrast, the contributions of the inner part, including the orthogonal ring and its substituents, to the cytotoxicity of lamellarins remain unclear. While some research groups have previously performed the deletion of this ring,[9] others speculated that it might be important. Recently, a number of derivatives of lamellarin D, the most studied compound in the series, were synthesized by introducing aminomethyl groups at different positions.[10] While the authors tried to maintain the reportedly important hydroxy groups at C8, C14, and C20, most of the derivatives were less active than the parent lamellarin D. Additionally, the improvement in aqueous solubility was not investigated.

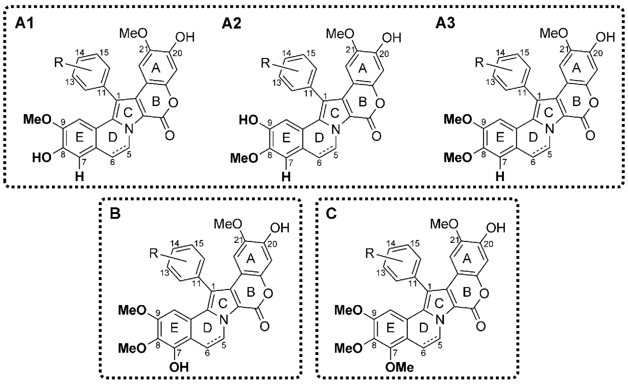
The aim of this study was to further streamline the structure of lamellarins with the focus on the substituents on the orthogonal ring and those for which the previous results are still unclear. Simplified analogs (as exemplified in Figure 1 b) were designed, synthesized, and tested for their cytotoxicity towards cancer cells, in parallel with the lipophilicity determinations. Systematic structure–cytotoxicity and structure–lipophilicity relationship studies were performed using matched molecular pairs analysis. The results were then used to design additional analogs through the classical design-make-test-analyze (DMTA) cycles to identify the structural requirements for these molecules.

Results and Discussion

Molecular Design of Lamellarin Analogs

As previously reported, our research group has successfully synthesized 22 naturally occurring and 3 unnatural lamellarins using our established strategy.[11] Except for lamellarin G, all the other 24 compounds share identical A–D rings and are mainly diversified by the substituents on the E- and orthogonal rings. In this study, we classified these so-called first-generation lamellarins into 5 subgroups, based on the substituents on the E-ring (Table 1). On the other hand, three substitution patterns

Table 1. Subgroups of lamellarins based on the substituents on the E-ring, along with the substitution patterns of the first-generation lamellarins and their second-generation analogs with a modified orthogonal ring.



Subgroup	Group 1 (C5-C6)	Group 2 (C5 = C6)	C7	C8	C9	C13	C14
A1	Lam χ	Lam D	H	OH	OMe	OMe	OH
	Lam L	Lam N	H	OH	OMe	OH	OMe
	Lam J	Lam J-DB	H	OH	OMe	OMe	OMe
	Lam **1**	Lam **2**	H	OH	OMe	H	H
	Lam **3**	Lam **4**	H	OH	OMe	OH	H
	Lam **5**	Lam **6**	H	OH	OMe	OMe	H
	Lam **7**	Lam **8**	H	OH	OMe	H	OH
	Lam **9**	Lam **10**	H	OH	OMe	H	OMe
	Lam **11**	Lam **12**	H	OH	OMe	H	F
	Lam **13**	Lam **14**	H	OH	OMe	F	F
A2	Lam Y	Lam Y-DB	H	OMe	OH	OH	OMe
	Lam **15**	Lam **16**	H	OMe	OH	H	H
	Lam **17**	Lam **18**	H	OMe	OH	H	OH
A3	Lam U	Lam α	H	OMe	OMe	OH	OMe
	Lam η-SB	Lam η	H	OMe	OMe	OMe	OMe
	Lam **19**	Lam **20**	H	OMe	OMe	H	H
B	Lam K	Lam M	OH	OMe	OMe	OMe	OH
	Lam E	Lam X	OH	OMe	OMe	OH	OMe
	Lam F	Lam ε	OH	OMe	OMe	OMe	OMe
	Lam **21**	Lam **22**	OH	OMe	OMe	H	H
	Lam **23**	Lam **24**	OH	OMe	OMe	OH	H
	Lam **25**	Lam **26**	OH	OMe	OMe	OMe	H
	Lam **27**	Lam **28**	OH	OMe	OMe	H	OH
	Lam **29**	Lam **30**	OH	OMe	OMe	H	OMe
C	Lam C	Lam B	OMe	OMe	OMe	OMe	OH
	Lam T	Lam W	OMe	OMe	OMe	OH	OMe
	Lam I	Lam ζ	OMe	OMe	OMe	OMe	OMe
	Lam **31**	Lam **32**	OMe	OMe	OMe	H	H

Lam = lamellarin, SB = single bond, DB = double bond.

are usually found on the orthogonal ring of most lamellarins, including (i) 13-OMe; 14-OH, (ii) 13-OH; 14-OMe, and (iii) 13-OMe; 14-OMe. In order to evaluate the functional significance of the orthogonal ring, two analogs were initially designed for each subgroup to contain only a simple phenyl group attached to C1 of the pentacyclic core (Table 1). Subsequently, additional analogs with a monosubstituted orthogonal ring were constructed for subgroups A1 and B as they contain the required hydroxy group at either C7 or C8 (Table 1).

To determine the contribution of the substituents at C9, a number of C9-unsubstituted analogs were also designed using the simplified analogs with an orthogonal *p*-hydroxyphenyl ring as their templates, as shown in Figure 2.

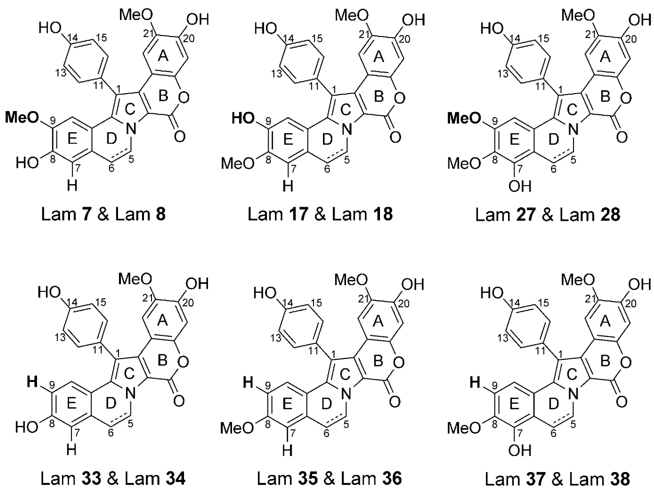


Figure 2. C9-unsubstituted analogs (bottom row) in comparison with their templates with an orthogonal *p*-hydroxyphenyl ring (top row). For each pair of compounds, the former contains a single bond between C5-C6, while the latter contains a C5=C6 olefin.

For the third-generation compounds, more synthetically challenging modifications were made. Firstly, a catechol moiety was introduced into various positions around the lamellarin skeleton, as well as on the orthogonal ring (Figure 3). Afterwards, the orthogonal ring was also replaced by different functional groups, as shown in Figure 4. It was anticipated that, without the orthogonal aromatic ring, these eleven analogs bearing other groups at C1 would possess a lower molecular weight, and their total volumes would also be reduced.

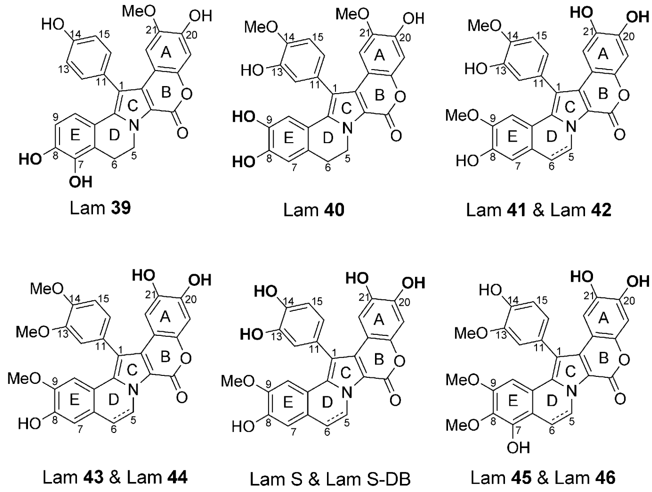


Figure 3. Catechol-containing lamellarins, including the naturally occurring lamellarin S and its double bond counterpart. For the compounds that are shown in pairs, the former contains a single bond between C5-C6, while the latter contains a C5=C6 olefin.

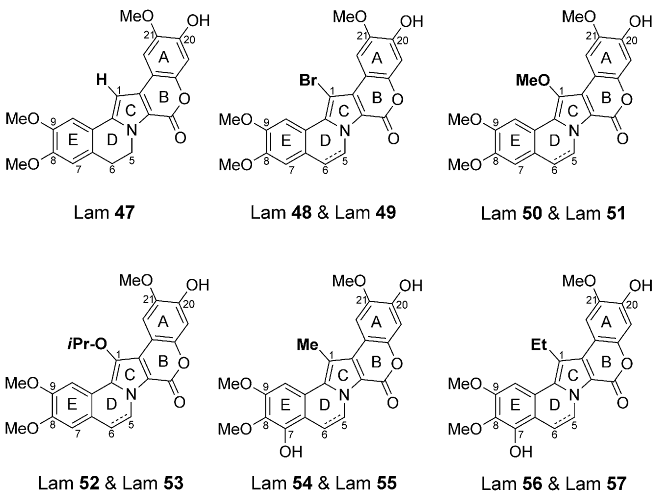
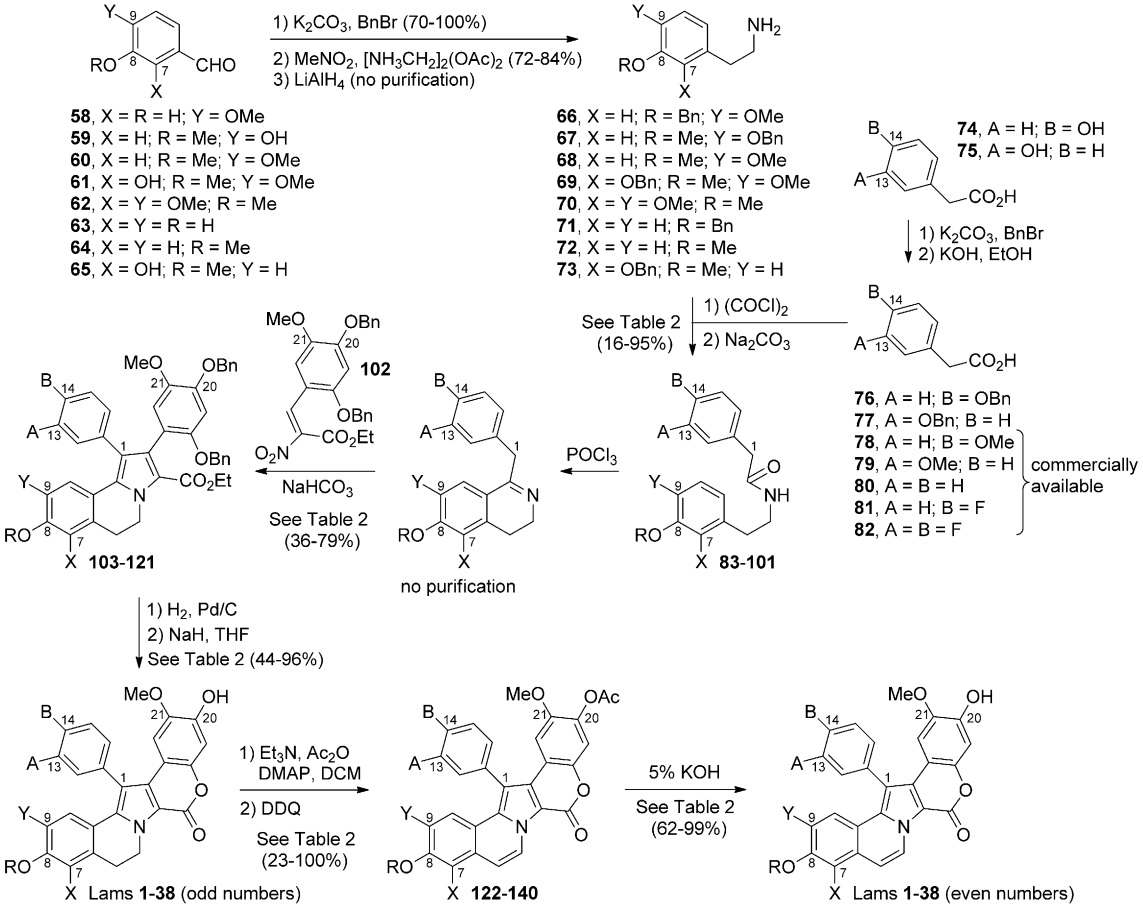


Figure 4. C1-dearylated analogs of lamellarins. For the compounds that are shown in pairs, the former contains a single bond between C5-C6, while the latter contains a C5=C6 olefin.

Chemistry

In general, except for the third-generation analogs (Lams **39**–**57**), the designed analogs, Lams **1**–**38**, were synthesized using our previously developed synthetic strategy.[11] As shown in Scheme 1, the appropriately substituted benzaldehyde derivatives **58**–**65** served as the building blocks for aryl ethylamines **66**–**73**, which could be directly coupled with arylacetic acids **76**–**82**, via the intermediacy of the corresponding acid chlorides, to form the amides **83**–**101** (Table 2). Subsequent Bischler–Napieralski cyclodehydration using $POCl_3$ furnished the benzyldihydroisoquinolines, which were used directly without purification in the Grob-type Michael addition–ring closure (MiRC) with α-nitrocinnamate **102** to furnish the pyrrole esters **103**–**121** in 36–79% yields. Global hydrogenolysis and NaH-mediated lactonization then afforded the lamellarins **1**–**38** (odd numbers) with a saturated D-ring in 44–96% yield. The free hydroxy groups were then protected as their acetates before the DDQ-mediated C5-C6 oxidation to furnish the corresponding lamellarin acetates **122**–**140** in 23–100% yield. Finally, KOH-mediated global deacetylation then provided the desired lamellarins **1**–**38** (even numbers) with an unsaturated D-ring in 62–99% yield.

For the third-generation lamellarin analogs **39**–**46** with one or two catechol moieties around the lamellarin core, the synthetic route was similar to that for Lams **1**–**38**, albeit with



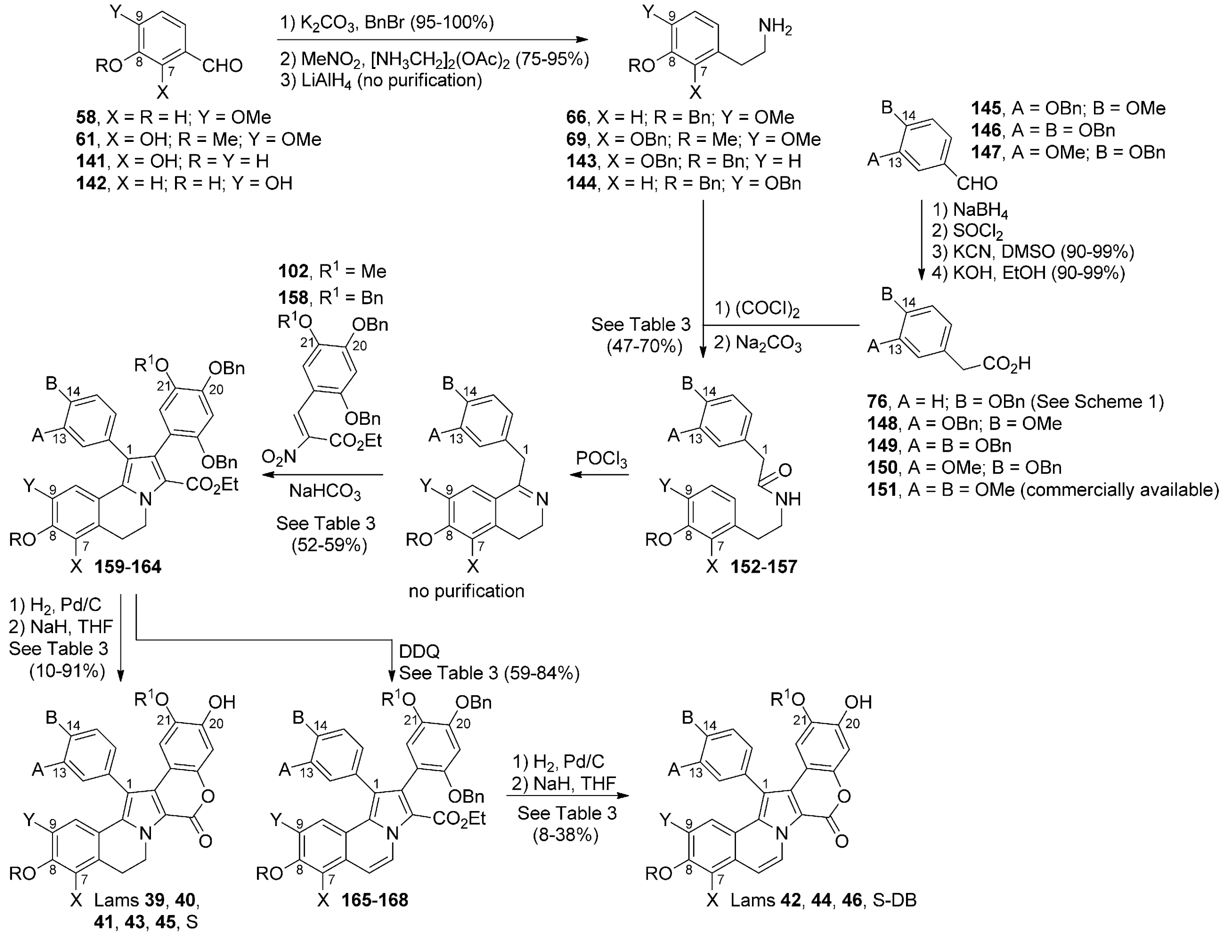
Scheme 1. Synthetic route for the second-generation lamellarins **1**–**38**.

Table 2. Synthesis of Lams **1**–**38**.

Entry	Amide	Mi-RC	H/L	A/DDQ	D
1	**83** (31)	**103** (52)	**1** (88)	**122** (100)	**2** (87)
2	**84** (61)	**104** (48)	**3** (76)	**123** (97)	**4** (62)
3	**85** (60)	**105** (36)	**5** (79)	**124** (80)	**6** (95)
4	**86** (76)	**106** (60)	**7** (90)	**125** (86)	**8** (96)
5	**87** (40)	**107** (62)	**9** (65)	**126** (93)	**10** (99)
6	**88** (67)	**108** (70)	**11** (76)	**127** (78)	**12** (69)
7	**89** (78)	**109** (66)	**13** (85)	**128** (67)	**14** (90)
8	**90** (16)	**110** (52)	**15** (72)	**129** (78)	**16** (71)
9	**91** (42)	**111** (51)	**17** (96)	**130** (23)	**18** (75)
10	**92** (95)	**112** (79)	**19** (88)	**131** (100)	**20** (87)
11	**93** (42)	**113** (51)	**21** (63)	**132** (86)	**22** (83)
12	**94** (66)	**114** (43)	**23** (81)	**133** (94)	**24** (85)
13	**95** (65)	**115** (60)	**25** (44)	**134** (96)	**26** (93)
14	**96** (77)	**116** (67)	**27** (67)	**135** (93)	**28** (91)
15	**97** (67)	**117** (43)	**29** (71)	**136** (88)	**30** (82)
16	**98** (66)	**118** (67)	**31** (76)	**137** (100)	**32** (92)
17	**99** (54)	**119** (63)	**33** (85)	**138** (77)	**34** (89)
18	**100** (75)	**120** (76)	**35** (88)	**139** (70)	**36** (88)
19	**101** (75)	**121** (53)	**37** (71)	**140** (50)	**38** (69)

Numbers in parentheses refer to isolated yields. Mi-RC = Michael addition–ring closure, H/L = hydrogenolysis/lactonization, A/DDQ = acetylation/DDQ oxidation, D = deacetylation.

some modifications. In general, all the catechol moieties on the A-, E-, and orthogonal rings were introduced as the corresponding benzyloxy ethers. For Lams **39** and **40**, the appropriate dihydroxybenzaldehydes **141** and **142** were employed as the starting materials to prepare the corresponding *O*-dibenzyloxyphenyl ethylamines **143** and **144** via the intermediacy of β-nitrostyrene derivatives (Scheme 2). Then, the arylacetic acid **76** was employed for Lam **39**, while homoveratric acid **151** was used for Lams **43**–**44**. Conversely, the arylacetic acids of all the other compounds in this series were synthesized from the corresponding benzaldehydes **145**–**147**. In contrast to our previously reported route, we decided to utilize a more efficient and reproducible process consisting of (i) $NaBH_4$ reduction, (ii) cyanation of the resulting benzyl alcohol via the intermediacy of the corresponding non-isolated benzyl chloride, and (iii) base-mediated hydrolysis of the cyanide to carboxylic acid. The aryl acetic acids **148**–**150** were reliably synthesized in 90–99% yields. All the amides **152**–**157** were subsequently prepared by coupling the appropriate arylethylamines **66**, **69**, **143**, and **144** with the arylacetic acids **76** and **148**–**151**. Synthesis of both Lam **39** and Lam **40**, without a catechol moiety on the A-ring, went smoothly via the Grob-type Mi-RC/hydrogenolysis/NaH-mediated lactonization using α-nitrocinnamate **102**. However, attempts to effect global acetylation, especially the diacetylation of catechol on the E-ring, failed. Therefore, their corresponding lamellarins with an unsaturated D-ring were not pursued.



Scheme 2. Synthetic route for the third-generation lamellarins **39**–**46**, lamellarin S, and lamellarin S-DB.

For Lams **41**–**46**, Lam S, as well as Lam S-DB, all of which contain a catechol moiety on the A-ring, the 2,4,5-tribenzyloxyphenyl α-nitrocinnamate **158** was prepared from 3,4-dibenzyloxybenzaldehyde in up to 72% yield over 5 steps using our previously reported route.[11] As summarized in Scheme 2 and Table 3, the synthesis of these lamellarin analogs proceeded in a similar fashion until the Grob-type Mi-RC reaction, which yielded the corresponding pyrrole esters **161**–**164** in moderate yields (52–59%). However, based on the results of Lams **39** and **40**, we anticipated that some modifications were needed to prepare the analogs containing a C5=C6 olefin without using those with a saturated C5-C6 bond as the precursors. Thus, Lams **41**, **43**, **45**, and Lam S with a saturated D-ring were synthesized employing our developed strategy. However, Lams **42**, **44**, **46**, and Lam S-DB with a C5=C6 olefin were prepared directly from the pyrrole esters **161**–**164** via DDQ-mediated oxidation, followed by hydrogenolysis and NaH-mediated lactonization. It should be noted that the combination of hydrogenolysis and NaH-mediated lactonization of both C5-C6 and C5=C6 series proceeded in low yields (8–42%), presumably due to the unavoidable formation of *p*-quinones under the reaction conditions.

For C1-dearylated lamellarin analogs **47**–**57** (Scheme 3 and Table 4), a synthetic strategy similar to that utilized for Lams **1**–

Table 3. Synthesis of Lams **39**–**46**, Lam S, and Lam S-DB.

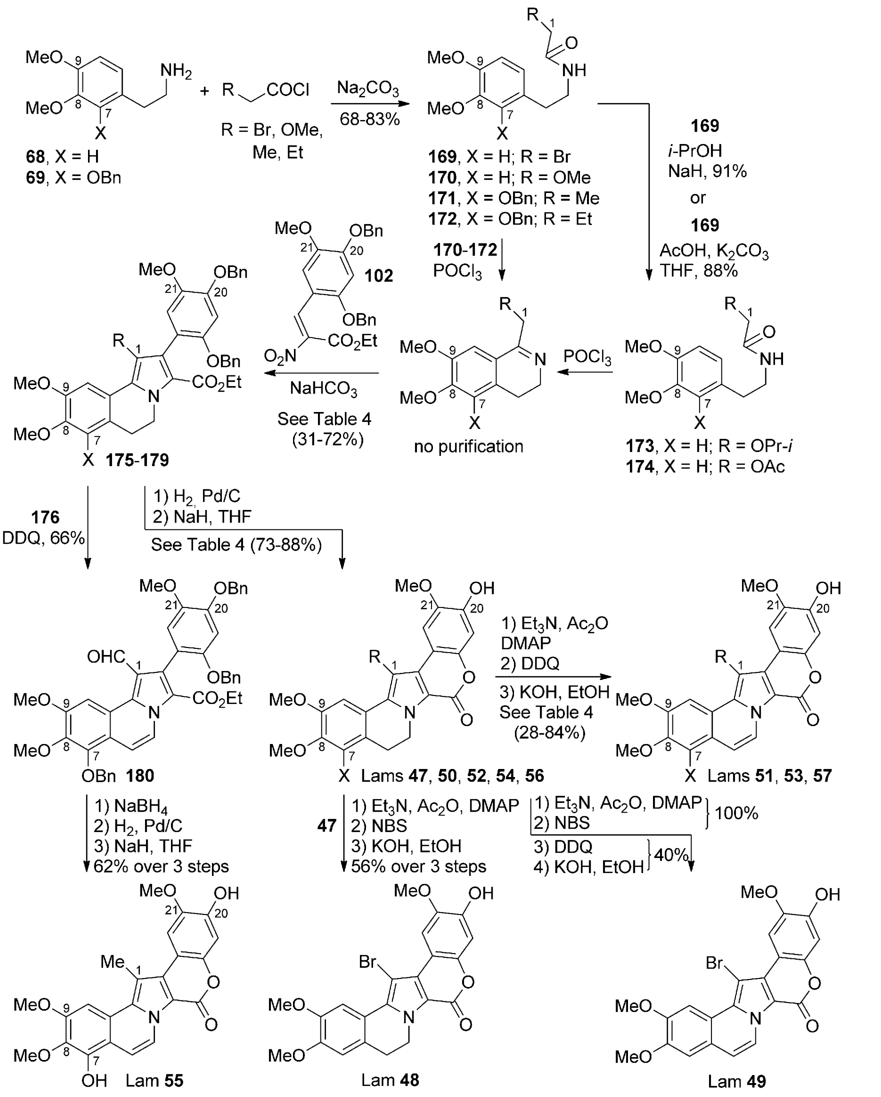
Entry	Amide	Mi-RC	H/L	DDQ	H/L
1	**152** (47)	**159** (58)	**39** (91)	NA	NA
2	**153** (47)	**160** (55)	**40** (86)	NA	NA
3	**154** (70)	**161** (59)	**41** (14)	**165** (59)	**42** (38)
4	**155** (58)	**162** (57)	**43** (10)	**166** (84)	**44** (8)
5	**156** (49)	**163** (52)	S (42)	**167** (71)	S-DB (8)
6	**157** (61)	**164** (59)	**45** (18)	**168** (80)	**46** (22)

Numbers in parentheses refer to isolated yields. Mi-RC = Michael addition–ring closure, H/L = hydrogenolysis/lactonization, DDQ = DDQ oxidation, NA = not available as described in the text.

Table 4. Synthesis of Lams **47**–**57**.

Entry	Amide	Mi-RC	H/L	A/DDQ/D
1	**170** (83)	**175** (31)	**50** (85)	**51** (84)
2	**171** (68)	**176** (72)	**54** (73)	NA (See Scheme 3 for **55**)
3	**172** (72)	**177** (64)	**56** (80)	**57** (28)
4	**173** (91)	**178** (49)	**52** (81)	**53** (71)
5	**174** (88)	**179** (57)	**47** (88)	NA

Numbers in parentheses refer to isolated yields. Mi-RC = Michael addition–ring closure, H/L = hydrogenolysis/lactonization, A/DDQ/D = acetylation/DDQ oxidation/deacetylation, NA = not available as described in the text.



Scheme 3. Synthetic route for the third-generation lamellarins **47**–**57**.

38 was contemplated. The appropriate amines **68** and **69** were employed to condense with the acid chlorides to yield the amides **169**–**174**. The synthesis of Lams **50**–**53** thus commenced with the formation of the appropriate amides **170** and **173**, as shown in Scheme 3. The amide **170** was formed in 80–83% yield by reacting homoveratrylamine **68** with 2-methoxyacetyl chloride generated from the corresponding acid. On the other hand, the amide **173** was formed in 91% yield from isopropoxylation of α-bromoamide **169** which, in turn, was produced in 70% yield by the reaction between homoveratrylamine **68** and bromoacetyl chloride. Subsequent Bischler–Napieralski and Grob-type Mi-RC reactions then gave the pyrrole esters **175** and **178** in 31% and 49% yields, respectively. Hydrogenolysis and NaH-mediated lactonization proceeded smoothly to furnish Lam **50** and Lam **52** in 81–85% yield. The three-step reaction sequence of acetylation, DDQ-mediated oxidation, and deacetylation then gave Lam **51** in 84% and Lam **53** in 71% overall yields.

Similarly, for Lams **54**–**57**, the appropriate amides **171** and **172** were prepared from the reaction between the amine **69** and propionyl chloride or butyryl chloride in 68% and 72% yield, respectively. The three-step reaction sequence of Grob-type Mi-RC, hydrogenolysis, and NaH-mediated lactonization then gave Lams **54** and **56** in 53% and 51% yield. Acetylation, DDQ oxidation, and basic deacetylation of Lam **56** proceeded smoothly to furnish Lam **57** in 28% yield. On the other hand, DDQ oxidation of the pyrrole ester **176** gave the C1-formyl pyrrole ester **180**. Subsequent borohydride reduction then converted the aldehyde to the primary alcohol. Hydrogenolysis not only removed the *O*-benzyl protecting group but also reduced the alcohol to the methyl group. Finally, NaH-mediated lactonization then yielded the desired Lam **55**.

However, for Lam **47**, the Grob-type Mi-RC reaction of 1-methyldihydroisoquinoline gave the desired pyrrole ester **179** in a low yield of 18%. After some experimentation, it was found that the Grob-type Mi-RC reaction of the imine, which was generated from the amide **174**, gave the desired pyrrole ester **179** in 52–57% yield. The amide **174**, in turn, was produced in 88% yield from the reaction of the α-bromoamide **169** with acetic acid under basic conditions. Hydrogenolysis and NaH-mediated lactonization of the pyrrole ester **179** proceeded to furnish Lam **47** in 88% yield. However, following acetylation of Lam **47**, which proceeded quantitatively, DDQ oxidation to give the C5=C6 analog of Lam **47** failed as the acetate decomposed under this oxidative condition. Bromination of Lam **47** acetate using NBS provided the corresponding Lam **48** acetate quantitatively. Subsequent basic deacetylation then gave Lam **48** in moderate 56% yield. On the other hand, DDQ oxidation followed by basic deacetylation of Lam **48** acetate gave Lam **49** in 40% overall yield.

Cytotoxicity and Lipophilicity Determinations

All the synthesized compounds were evaluated for their cytotoxicity against 11 cancerous and 1 normal cell lines, as well as characterized for their lipophilicity. The results are outlined in

Table 5. As mentioned earlier, lamellarins exert their cytotoxic activity through a number of intracellular targets. Thus, our research group has focused on the overall cytotoxicity, rather than the effects on any particular targets, in response to the exposure to various lamellarin analogs. MTT and XTT assays were used for adherent and suspended cells, respectively.

In our previous report,[7] the crystal violet staining technique was employed to determine the survival of adherent cells after having been exposed to our first-generation lamellarins. It is generally assumed that non-viable cells are washed away during the staining process and thus are not stained by the dye. In contrast, the viable cells should remain adherent to the culture surface and get stained by crystal violet upon its binding to DNA.[12] For MTT and XTT assays, cell viability is measured based on the activity of the mitochondrial dehydrogenase enzyme in metabolically active cells.[13] Considering the different underlying principles of these two techniques, a preliminary comparative study was conducted using selected lamellarins and revealed that the cytotoxic IC_{50} values obtained from the MTT assay were usually higher than those from crystal violet staining (data not shown), possibly due to the cell loss during the washing step in the latter. Therefore, the first-generation lamellarins previously synthesized in our laboratory were retested along with their analogs so that their cytotoxicity could be compared directly within this study.

While the goal of most lead optimization programs is usually to potentiate the desired biological activities, the significance of drug-likeness has been increasingly recognized. A large number of drug candidates with a potent pharmacological action actually turn out to be physiologically ineffective due to insufficient bioavailability. Among the physicochemical prop-

Table 5. Molecular properties and cytotoxic IC_{50} values (μM) of lamellarins and analogs against cancer and normal cell lines.

Test Cpd.	MW	Exp. Log P	KB	A549	H69AR	T47D	MDA-MB-231	HuCCA-1	HepG2	S102	HeLa	P388	HL-60	MRC-5
Lam χ	501.48	2.78	6.5	8.9	19.9	6.8	2.0	7.1	1.5	8.0	7.0	1.6	1.8	I
Lam D	499.47	3.45	0.9	1.0	51.1	1.0	1.3	0.5	0.4	6.5	0.8	0.1	0.04	I
Lam L	501.48	2.74	0.8	7.0	I	I	1.4	I	1.5	69.8	6.7	0.5	1.9	I
Lam N	499.47	3.37	0.1	I	I	I	0.7	I	0.5	7.5	90.1	0.1	0.04	I
Lam J	515.51	3.07	I	I	I	I	4.0	I	I	17.5	I	0.8	0.9	I
Lam J-DB	513.49	3.69	0.4	I	I	3.4	1.6	2.7	0.6	6.2	0.7	0.1	0.04	I
Lam **1**	455.46	3.85	4.3	9.5	50.5	32.9	0.5	3.3	8.2	7.7	5.4	0.8	3.2	15.4
Lam **2**	453.44	4.44	11.0	3.3	10.1	36.8	0.7	0.7	0.9	2.0	4.4	0.2	0.2	8.3
Lam **3**	471.46	3.04	3.4	I	I	I	1.8	I	10.6	I	80.6	1.1	2.0	I
Lam **4**	469.44	3.66	0.6	I	I	I	1.0	I	0.5	I	I	0.1	0.1	I
Lam **5**	485.48	3.76	0.9	9.3	8.0	2.9	1.9	6.0	6.2	2.4	4.5	0.9	3.4	21.1
Lam **6**	483.47	4.36	1.0	I	I	I	1.1	0.6	0.9	2.7	10.3	0.1	0.1	I
Lam **7**	471.46	3.01	0.8	6.6	3.4	4.2	1.5	3.8	1.9	5.6	0.8	0.6	1.6	17.0
Lam **8**	469.44	3.67	0.3	8.1	4.7	I	0.9	0.2	0.4	4.5	0.6	0.1	0.04	I
Lam **9**	485.48	3.81	2.7	6.6	5.1	4.7	1.5	4.3	4.1	2.0	4.1	0.6	2.1	9.8
Lam **10**	483.47	4.41	I	56.9	I	I	1.4	I	1.6	2.8	6.2	0.1	0.1	I
Lam **11**	473.45	3.86	8.3	5.2	17.3	14.8	10.9	3.7	9.8	7.2	8.8	2.1	1.0	37.3
Lam **12**	471.43	4.43	6.5	0.1	0.9	0.1	8.1	0.1	1.3	6.2	6.3	2.1	0.03	3.5
Lam **13**	491.44	4.01	8.8	73.7	77.1	7.0	52.7	11.0	11.1	12.7	8.1	ND	0.8	40.4
Lam **14**	489.42	4.57	55.4	9.5	41.1	I	14.0	2.9	0.8	10.9	I	ND	0.01	93.7
Lam Y	501.48	2.59	9.7	39.9	I	53.8	2.5	53.8	4.8	13.6	9.3	1.0	5.0	61.8
Lam Y-DB	499.47	3.21	5.5	45.0	65.1	39.0	1.6	40.0	4.1	13.0	7.7	0.9	3.4	54.1
Lam **15**	455.46	3.52	4.2	18.7	50.5	55.5	0.8	46.1	10.6	9.2	8.3	1.6	3.8	16.5
Lam **16**	453.44	4.12	8.8	21.0	75.0	70.6	0.5	64.0	9.7	6.6	10.6	1.2	2.9	19.3
Lam **17**	471.46	2.90	10.6	I	I	I	6.6	I	7.0	I	8.0	1.3	4.2	I
Lam **18**	469.44	3.59	6.2	8.5	79.9	8.7	3.4	6.6	6.5	8.4	3.9	1.5	4.1	67.1
Lam U	515.51	3.31	7.2	I	I	I	3.4	I	4.1	I	7.8	1.7	4.5	I
Lam α	513.49	3.98	8.3	I	I	I	10.7	I	1.0	I	I	1.7	10.5	I
Lam η-SB	529.54	3.65	5.5	9.0	I	7.1	1.8	9.0	4.0	11.3	5.5	ND	ND	12.3
Lam η	527.52	4.33	5.9	I	I	I	3.0	I	0.6	15.2	I	ND	ND	I
Lam **19**	469.49	4.51	61.8	14.5	63.9	54.1	0.8	36.2	13.0	38.3	76.7	3.6	18.6	11.2
Lam **20**	467.47	5.18	49.2	15.7	44.9	I	5.3	67.0	I	I	98.4	3.2	I	36.4
Lam K	531.51	3.15	3.6	7.3	54.6	7.9	1.0	9.4	3.2	8.2	4.0	3.3	3.8	24.5
Lam M	529.49	3.79	2.7	9.0	8.0	4.2	0.8	2.5	0.7	6.3	2.7	0.1	0.1	44.4
Lam E	531.51	3.14	5.2	33.9	52.7	8.9	1.9	32.9	6.6	12.2	6.5	2.6	4.5	47.0
Lam X	529.49	3.75	5.1	3.7	58.5	5.6	1.5	4.4	1.6	5.9	3.5	0.3	0.2	49.1
Lam F	545.54	3.49	4.7	8.5	65.1	6.4	1.7	27.5	4.0	5.5	5.2	3.1	3.6	48.6
Lam ε	543.52	4.10	4.0	7.4	57.0	4.0	1.6	3.9	1.2	7.4	3.9	0.2	0.1	53.4
Lam **21**	485.48	4.41	6.2	6.9	70.0	7.0	6.0	6.2	7.6	8.9	6.6	2.0	4.3	9.8
Lam **22**	483.47	5.01	4.7	10.2	47.6	57.9	0.6	24.8	4.8	22.8	13.2	0.7	0.6	25.9
Lam **23**	501.48	3.52	4.0	35.9	19.9	7.4	2.0	7.4	12.5	8.0	5.8	2.2	3.0	23.9
Lam **24**	499.47	4.14	1.0	1.6	14.6	1.2	1.1	2.8	1.9	7.5	3.2	0.2	0.1	18.0
Lam **25**	515.51	4.29	5.0	25.2	13.6	I	2.4	37.8	13.1	10.2	7.4	2.4	3.9	16.5
Lam **26**	513.49	4.90	1.0	7.6	48.7	2.3	1.5	6.8	4.8	5.6	4.7	0.3	0.2	17.5
Lam **27**	501.48	3.39	3.6	13.0	5.6	9.6	2.0	5.2	5.5	6.3	5.2	1.7	2.8	16.5
Lam **28**	499.47	4.00	1.7	0.7	5.8	1.4	1.1	1.8	1.6	7.8	2.6	0.2	0.1	16.5
Lam **29**	515.51	4.31	6.6	50.4	7.2	40.7	2.7	31.0	11.2	4.7	6.4	2.3	6.6	11.6
Lam **30**	513.49	4.93	8.0	33.1	I	I	1.5	56.5	9.7	4.9	38.0	0.6	0.4	77.9
Lam C	545.54	4.02	4.1	31.2	64.2	31.2	6.4	50.4	7.1	33.6	5.8	4.2	5.7	66.0
Lam B	543.52	4.93	5.9	40.5	65.3	37.7	8.5	57.0	6.8	32.5	7.6	6.1	6.2	59.8
Lam T	545.54	3.99	7.0	44.0	55.9	48.6	6.9	55.9	7.3	21.1	8.2	4.8	6.4	54.1
Lam W	543.52	4.83	8.3	47.8	I	42.3	8.7	58.0	9.2	23.9	6.7	5.6	6.7	54.3
Lam I	559.56	4.33	7.1	I	I	8.9	6.0	I	5.8	13.0	6.6	3.8	6.9	I
Lam ζ	557.55	5.19	6.4	I	69.1	81.6	9.0	I	9.9	I	33.2	7.2	12.3	I
Lam **31**	499.51	5.21	16.0	23.0	86.1	70.1	7.0	58.1	16.4	75.1	66.1	3.4	8.9	41.0
Lam **32**	497.50	6.03	66.3	56.9	I	84.4	42.2	80.4	31.5	75.7	78.4	6.0	11.6	60.3
Lam **33**	441.43	2.85	5.8	6.1	85.0	6.2	3.2	6.7	3.6	12.3	6.3	1.3	2.2	I
Lam **34**	439.42	3.55	10.8	I	I	I	2.2	8.0	0.4	30.7	9.9	0.1	0.1	I
Lam **35**	455.46	4.12	15.4	15.4	82.3	7.0	13.2	51.6	12.8	16.1	32.9	4.1	9.0	70.3
Lam **36**	453.44	4.82	84.9	56.2	I	I	11.4	82.7	3.3	I	81.6	3.9	6.7	I
Lam **37**	471.46	3.18	8.0	37.1	88.0	65.8	3.8	65.8	10.8	15.2	9.4	4.1	8.4	89.1
Lam **38**	469.44	3.80	67.1	I	I	I	4.5	I	10.7	I	I	0.9	0.9	I
Lam **39**	457.43	2.59	5.9	98.4	91.8	6.8	9.8	7.0	19.7	10.6	6.6	2.0	3.8	67.8

Table 5. (Continued)

Test Cpd.	MW	Exp. Log P	KB	A549	H69AR	T47D	MDA-MB-231	HuCCA-1	HepG2	S102	HeLa	P388	HL-60	MRC-5
Lam **40**	487.46	2.10	5.1	7.5	I	4.8	3.4	5.5	3.2	6.4	4.3	1.3	1.0	I
Lam **41**	487.46	2.59	4.9	9.7	29.7	18.5	12.7	9.0	5.3	9.4	9.9	2.1	3.7	46.5
Lam **42**	485.44	3.25	6.0	10.9	I	I	14.4	3.4	11.2	10.6	7.4	2.1	0.1	I
Lam **43**	501.48	2.79	3.1	6.3	I	4.8	5.2	8.9	4.3	11.8	5.5	1.5	3.1	I
Lam **44**	499.47	ND	5.6	6.5	I	I	4.9	6.0	1.9	47.0	6.7	0.3	0.2	I
Lam S	473.43	2.11	6.3	47.5	78.2	7.7	10.2	12.7	10.9	20.4	6.8	1.8	2.9	I
Lam S-DB	471.42	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lam **45**	517.48	2.92	9.2	12.5	30.9	23.2	23.8	11.3	5.6	17.7	7.3	1.9	2.1	43.0
Lam **46**	515.47	3.65	8.4	11.2	20.7	16.7	13.9	4.2	7.8	13.9	6.0	1.9	0.1	51.4
Lam **47**	393.39	3.26	I	I	I	I	I	I	I	I	I	2.5	I	I
Lam **48**	472.29	4.49	I	I	I	I	I	I	I	I	I	2.1	I	I
Lam **49**	470.27	5.28	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lam **50**	423.42	3.61	I	I	I	I	83.4	27.8	I	I	I	2.4	I	I
Lam **51**	421.4	4.26	I	I	I	I	I	I	I	I	I	2.4	I	I
Lam **52**	451.47	4.14	I	I	I	I	I	I	I	I	I	2.2	17.2	I
Lam **53**	449.45	4.78	24.1	21.5	44.1	40.8	49.7	20.1	31.9	52.3	25.4	2.2	8.8	I
Lam **54**	423.42	3.56	9.7	18.7	46.1	I	40.1	6.6	20.5	I	9.4	2.4	I	I
Lam **55**	421.4	4.17	64.1	0.8	I	I	I	0.1	2.8	I	10.3	2.4	0.2	I
Lam **56**	437.44	3.96	I	I	I	I	I	I	I	I	I	2.3	I	I
Lam **57**	435.43	4.49	9.5	59.7	38.6	25.1	53.6	6.9	4.6	I	10.7	2.3	0.1	I
Doxorubicin	579.99	ND	0.5	0.6	18.0	0.6	1.1	0.8	0.5	2.1	0.5	1.3	ND	2.6
Etoposide	588.58	ND	ND	ND	ND	ND	ND	ND	27.4	ND	ND	0.7	1.2	ND

Cpd. = compound, Exp. log P = experimental log P value, I = inactive ($IC_{50} > 100$ μM), MW = molecular weight, NA = not available due to insolubility in DMSO or stability issues, ND = not determined. Cell lines used (in alphabetical order): A549 = human non-small-cell lung carcinoma, H69AR = human multi-drug-resistant small-cell lung carcinoma, HeLa = human cervical adenocarcinoma, HepG2 = human hepato-cellular carcinoma, HL-60 = human promyelocytic leukemia, HuCCA-1 = human cholangiocarcinoma, KB = human oral epidermoid carcinoma, MDA-MB-231 = human hormone-independent breast cancer 231, MRC-5 = human fetal/embryonic lung fibroblast, P388 = mouse lymphoid neoplasm, S102 = human hepatocellular carcinoma, T47D = human hormone-dependent breast cancer.

erties that contribute to drug-likeness, molecular weight and lipophilicity were taken into consideration for lamellarins in the process of their structure optimization. When considering their poor aqueous solubility and extremely weak basicity of the pyrrole nitrogen existing as a part of a planar polyaromatic system, ionization of these molecules was expected to be insignificant. Thus, their log P, rather than log D, values were experimentally determined using the HPLC method, which is not only internationally accepted but has also been previously established in our laboratory for rapid physicochemical profiling of these compounds.[2] The obtained IC_{50} and log P values were then correlated with the structures using matched molecular pairs analysis for evaluating the contributions of various substituents to both the cytotoxic activity and lipophilicity of lamellarins, as described below.

Structure–Activity and Structure–Lipophilicity Relationships

In an attempt to improve the physicochemical properties of lamellarins by structure modifications, the possibility of replacing the substituent(s) on the orthogonal ring with an ionizable group was explored by first determining their functional importance. When compared with the first-generation lamellarins in the same subgroup, the analogs with an unsubstituted orthogonal ring (Lams **1**–**2, 15**–**16, 19**–**20, 21**–**22**, and **31**–**32**) possessed significantly decreased cytotoxicity in many cases (Table 5). In addition, an average of 1 log unit increase was observed with their chromatographic log P values (Tables 5 and 6). Such lipophilic nature, when combined with the extensive stacking interactions among these planar molecules, would additionally lower their aqueous solubility and cause even more profound precipitation of these analogs in cell culture media. Therefore, the presence of at least one oxygen-containing group might be required at least to alleviate the solubility issues.

As a result, our investigations were continued with subgroups A1 and B containing the required hydroxy group at either C7 or C8. For each subgroup, 8 additional analogs with a monosubstituted orthogonal ring were synthesized, that is,

Table 6. Differences in the log P values of lamellarin analogs with a structurally modified vs. unsubstituted orthogonal ring.

Entry	Modification	Δlog P (compared with 13-H; 14-H)									
		A1		A2		A3		B		C	
		C5-C6	C5=C6	C5-C6	C5=C6	C5-C6	C5=C6	C5-C6	C5=C6	C5-C6	C5=C6
1	Reference log P	3.85	4.44	3.52	4.12	4.51	5.18	4.41	5.01	5.21	6.03
2	13-OH; 14-H	−0.81	−0.78	NA	NA	NA	NA	−0.89	−0.87	NA	NA
3	13-OMe; 14-H	−0.09	−0.08	NA	NA	NA	NA	−0.12	−0.11	NA	NA
4	13-H; 14-OH	−0.84	−0.77	NA	NA	NA	NA	−1.02	−1.01	NA	NA
5	13-H; 14-OMe	−0.04	−0.03	NA	NA	NA	NA	−0.10	−0.08	NA	NA
6	13-OH; 14-OMe	−1.11	−1.07	−0.93	−0.91	−1.20	−1.20	−1.27	−1.26	−1.22	−1.20
7	13-OMe; 14-OH	−1.07	−0.99	NA	NA	NA	NA	−1.26	−1.22	−1.19	−1.10
8	13-OMe; 14-OMe	−0.78	−0.75	NA	NA	−0.86	−0.85	−0.92	−0.91	−0.88	−0.84

NA = not available.

Lams **3**–**10** for subgroup A1 and Lams **23**–**30** for subgroup B (Table 1). Using the analogs with an unsubstituted orthogonal ring (Lams **1**–**2** or Lams **21**–**22**) as the reference compounds for each subgroup, the Δlog P values were determined for various modifications of the orthogonal ring (Table 6). For any subgroups, the effects of a particular transformation on the log P values were generally comparable regardless of the type of the C5-C6 bond. In addition, the log P values of the analogs in subgroups A3, B, and C, which were more lipophilic possibly due to the two methoxy groups on the E-ring, appeared slightly more sensitive to the modifications on the orthogonal ring.

When analyzing the results shown in Table 6 in more detail, the presence of a hydroxy group at either C13 or C14 expectedly caused a significant decrease in the log P values by 0.8–1 log unit (entries 2 and 4), while adding another methoxy group further reduced the lipophilicity by 0.2–0.4 log unit (entries 6 and 7). In contrast, single methoxylation of the orthogonal ring minimally affected the lipophilic nature of these compounds (entries 3 and 5), whereas the introduction of an additional hydroxy or methoxy moiety further decreased the log P values by 0.75–1 log unit (entries 6–8). More importantly, double methoxylation of the orthogonal ring (entry 8) yielded comparable Δlog P values to those obtained by single hydroxylation (entries 2 and 4). All these findings suggested that the presence of one hydroxy group on the orthogonal ring should be sufficient for reducing the lipophilicity of lamellarins.

From the cytotoxicity standpoint, the log (IC_{50} ratio) was determined for each analog in comparison with the reference molecule containing an unsubstituted orthogonal ring. The results are exemplified for the compounds with the required C5=C6 olefin in Figure 5, where negative values of the log (IC_{50} ratio) indicate the increased cytotoxic effects on that particular cancer cell line, while the positive values show the loss of activity. Despite the variations generally observed with cell-based assays, the results appeared to suggest beneficial effects of the hydroxy group at C14 on their cytotoxic activity, which also corroborate with a previous report specifically for lamellarin D.[3] Interestingly, fluorine-containing analogs (Lams **11**–**14**), especially Lam **13** and Lam **14** with a difluorinated orthogonal ring, were not only more lipophilic (as evident by the higher log P values) but also possessed significantly less potent activity towards many cancer cell lines (Table 5). These results suggested the important role of an oxygen-containing moiety, especially a hydroxy group, possibly to serve as both a H-bond donor and an acceptor when interacting with either water or biological targets. Based on all these findings, the orthogonal ring of lamellarins was simplified to contain only a *p*-hydroxy group, leaving the other positions available for subsequent modifications to improve their aqueous solubility.

Next, the contribution of the substituents at C9 in the lamellarin skeleton was evaluated. Since methylation of the C9-hydroxy group has been previously reported to induce subtle changes in their cytotoxicity,[7] the possibility of removing this substituent to further streamline their structure was examined in this study. Using the simplified analogs with an orthogonal *p*-hydroxyphenyl ring as the templates, six additional analogs with unsubstituted C9 (Figure 2) were constructed, and the effects of removing the C9-substituent on the cytotoxicity are shown in Figure 6. The results clearly indicated that, without this substituent, the cytotoxic activity of Lams **33**–**38** was significantly lost (Table 5). In terms of the lipophilicity, total removal of the C9-hydroxy group (as in Lams **35**–**36**) caused a dramatic increase in the log P values by 1.2 log unit as expected, whereas the absence of C9-methoxy group (as in Lams **33**–**34** and **37**–**38**) actually resulted in a slight reduction in the lipophilicity by 0.1–0.2 log unit (Table 5). Such a decrease was rather unexpected, considering that these molecules usually became more lipophilic upon the removal of a methoxy group at either C7 on the pentacyclic core[2] or C13 and C14 on the orthogonal ring (Table 6). The reasons for such observations remain to be investigated.

Our investigations were then continued with other possible modifications around the molecules. Although our previous results indicated the beneficial effects of having a hydroxy group at either C7 or C8 on the E-ring (Figure 1 a), no lamellarin has ever been isolated or synthesized with two consecutive hydroxy groups at both positions. In fact, a number of catechol-containing lamellarins, including lamellarin H,[14] lamellarin S,[15] la-

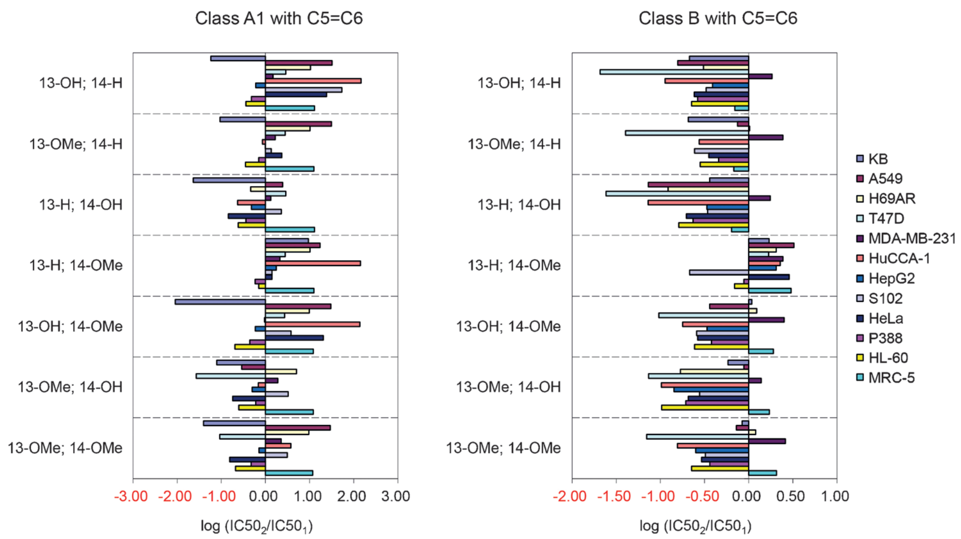


Figure 5. Contributions of the substituents on the orthogonal ring of the compounds in subgroups A1 and B with a C5=C6 double bond to their cytotoxic activity against various cancer cell lines (indicated by different colors as shown in the legend) when compared with the corresponding analog with an unsubstituted orthogonal ring (C13-H; C14-H). On the *x*-axis, negative log (IC_{50} ratio) values indicate the increased cytotoxic effects on that particular cancer cell line, while the positive values suggest the loss of activity upon the structural modification being considered.

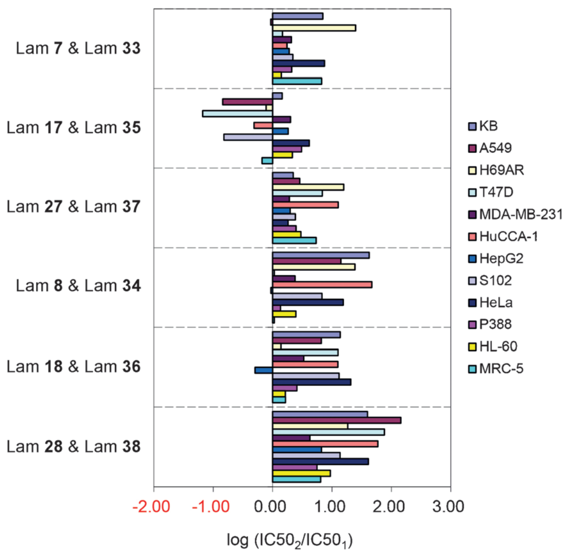


Figure 6. Effects of C9-substituent removal on the cytotoxic activity of lamellarins. Interpretation of the log (IC_{50} ratio) values is described in Figure 5.

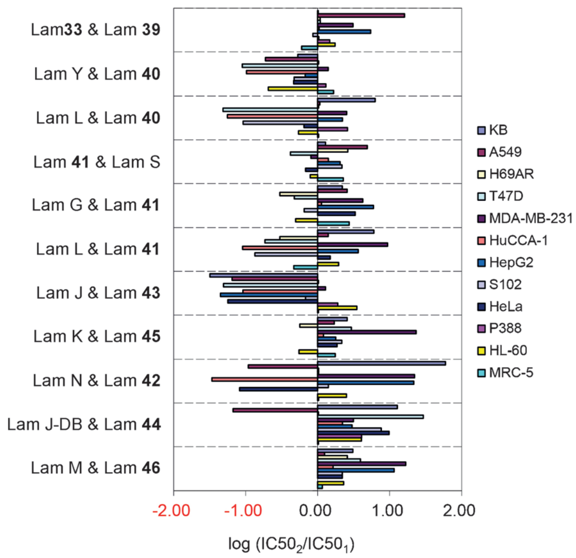


Figure 7. Effects of catechol incorporation on the cytotoxic activity of lamellarins. Interpretation of the log (IC_{50} ratio) values is described in Figure 5.

mellarin Z,[16] and lamellarin β,[17] have been isolated from natural sources. However, their total synthesis is more challenging than that of the other lamellarins, and only a few reports mainly for lamellarin H are available in the literature.[18]

In order to determine whether the presence of a catechol moiety would further enhance the activity of lamellarins, a number of analogs were synthesized in this study to contain 1–2 catechol moieties at various positions (Figure 3). As expected, such modification helped decrease the lipophilicity of the molecule (Table 5), but the effects were not as significant as when the adjacent group is not a hydroxy moiety. For the cytotoxicity, while enhancement was observed in some cases as indicated by negative log IC_{50} ratios (Figure 7), a significant loss of activity was experienced in many others. More importantly, such modification also caused instability issues, preventing the synthesis of the C5=C6 olefin-containing counterpart of the analogs in many cases.

The last structural modification that was explored involved the contributions of the orthogonal ring, which has been reported to orient perpendicularly to the pentacyclic core with unknown function. To examine whether this ring is essential for the cytotoxicity of lamellarins, it was replaced by other functional groups in **Lams 47**–**57**, as shown in Figure 4. Unfortunately, most of these compounds not only became more lipophilic but also were generally inactive (Table 5), indicating that the orthogonal ring is essential for the cytotoxicity of lamellarins.

Conclusions

Our efficient and versatile total synthetic strategy for lamellarins was successfully utilized to construct a library of 59 systematically designed analogs. To the best of our knowledge, this is the first report on the synthesis of catechol-containing lamellarins, including the naturally occurring lamellarin S and its unnatural counterpart with a C5=C6 olefin. These compounds are more synthetically challenging and had been inaccessible by the previously developed strategies for lamellarins.

In addition to 25 parent lamellarins, the availability of these analogs allowed us to carefully evaluate both the structure–cytotoxicity and structure–lipophilicity relationships. In summary, additional structural elements that are important for the cytotoxicity of lamellarins were identified (Figure 8). While the orthogonal ring appeared to be important, it could be simplified as a *p*-hydroxyphenyl ring. On the other hand, the substituent at C9 was also proved to be essential, but it could be either a hydroxy or methoxy group according to our previous report. In addition, the presence of catechol was not always beneficial for cytotoxicity and actually increased the risk of stability issues. From the drug-likeness point of view, we successfully reduced the molecular weight of these compounds (Table 7). Unfortunately, the analogs were either equally or even more lipophilic when compared with the first-generation lamellarins. Therefore, alternative approaches are currently under investi-

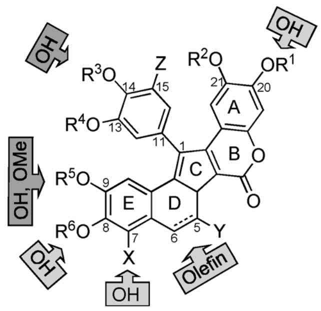


Figure 8. Important structure requirements (as indicated by arrow boxes) around the lamellarin skeleton based on the results from our studies.

Table 7. Average molecular weights and chromatographic log P values of lamellarins and analogs.

Lamellarins	*n*	MW	Exp. log P
First-generation	25	525.0 ± 19.7	3.66 ± 0.71
Second-generation	38	478.9 ± 20.5	4.08 ± 0.71
Third-generation	21	461.7 ± 34.4	3.58 ± 0.91

Abbreviations (alphabetical order): Exp. log P = experimental log P value, MW = molecular weight, *n* = number of compounds.

gations in our laboratory to develop more drug-like lamellarin analogs.

Experimental Section

General Information

Unless otherwise noted, reactions were run in oven-dried round-bottomed flasks. Tetrahydrofuran (THF) was either distilled from sodium benzophenone ketyl or purified by the solvent purification system (Innovative Technology, Amesbury, MA, USA), while dichloromethane (DCM) was also purified by the solvent purification system prior to use. All the other compounds were used as received from the suppliers. The crude reaction mixtures were concentrated under reduced pressure by removing organic solvents on a rotary evaporator. Column chromatography was performed using silica gel 60 (particle size 0.06–0.2 mm; 70–230 mesh ASTM). Analytical thin-layer chromatography (TLC) was performed with silica gel 60 F_{254} aluminum sheets. Chemical shifts for ^{1}H nuclear magnetic resonance (NMR) spectra were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), and doublet of doublet (dd). Resonances for infrared (IR) spectra were reported in wavenumbers (cm^{-1}). Low resolution mass spectrometry (LRMS) was performed using either electron ionization (EI) or time-of-flight (TOF), while high resolution mass spectrometry (HRMS) was carried out using time-of-flight (TOF). Melting points were uncorrected. All the compound characterization data are available in the Supporting Information.

General Procedure for the Synthesis of Amides

To a stirred solution of arylacetic acid (1.2 equiv) in CH_2Cl_2 (2.5 mL mmol^{-1}) was added oxalyl chloride (1.5 equiv) and catalytic amount of DMF (2–3 drops) at 0 °C. The reaction was allowed to warm up to room temperature, at which it was stirred until all starting material acid was consumed (typically 2–3 h). The reaction was concentrated under reduced pressure to give the crude arylacetyl chloride, which was used without further purification.

To a stirred solution of arylacetyl chloride in CH_2Cl_2 (3.5 mL mmol^{-1}) was added crude arylethylamine (1.0 equiv), Na_2CO_3 (1.3 equiv), and water (2.5 mL mmol^{-1}) at room temperature. The reaction was stirred for 4 h. At that time, the two phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 times) before the combined organic layers were then washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give the crude product, which was further purified by column chromatography (30–50 % EtOAc/hexanes) to furnish the desired product.

General Procedure for the Grob-type Mi-RC Synthesis of Pyrrole Esters

To a stirred solution of benzyldihydroisoquinoline derivatives (1.5 equiv) in anhydrous acetonitrile (10 mL mmol^{-1} of benzyldihydroisoquinoline) at room temperature was added sodium bicarbonate (1.5 equiv) and α-nitrocinnamate (1.0 equiv). The mixture was heated to reflux for 18 h. At that time, the reaction was cooled to room temperature, and sodium bicarbonate was filtered off. Successive washings (3 times) with EtOAc, followed by concentration under reduced pressure of the combined organic materials, furnished crude product, which was further purified by column chromatography on silica (30 % EtOAc/hexanes) to provide the desired product.

General Procedure for the Hydrogenolysis/lactonization for the Synthesis of Lamellarins with a Saturated D-ring

A high pressure Paar apparatus was charged with the pyrrole ester (1.0 equiv), EtOAc (15 mL mmol^{-1} of pyrrole ester), and palladium on activated charcoal (Pd/C; ca. 0.1 equiv) at room temperature. The reaction was flushed with hydrogen and kept under hydrogen atmosphere (75–200 psi). Progress of the reaction was monitored by TLC until all starting material was consumed (4–20 h). Palladium was filtered off using Celite. After concentration under reduced pressure and removal of trace solvent under vacuum, the crude material was dissolved in anhydrous THF (100 mL mmol^{-1}) at room temperature. The reaction mixture was cooled to 0 °C before NaH (55–60 % dispersion in paraffin; 1.5 equiv per each hydroxy group) was added. The reaction was stirred at 0 °C for 0.5 h and then slowly warmed to room temperature, at which the reaction was stirred for 4 h. At that time, a saturated solution of NH_4Cl and EtOAc was added. The two layers were separated, and the aqueous phase was extracted with EtOAc (3 times). The aqueous phase was allowed to stir with EtOAc for 6 h to ensure that all lamellarins partitioned into the organic layer. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude product, which was triturated with MeOH to furnish the desired lamellarin as solid.

General Procedure for Acetylation

To a mixture of lamellarin with a saturated D-ring (1.0 equiv) in CH_2Cl_2 (30 mL mmol^{-1}) at room temperature was added Et_3N (1.0 equiv per hydroxy group), DMAP (0.3 equiv per hydroxy group), and acetic anhydride/acetyl chloride (1.5 equiv per hydroxy group). The reaction was monitored by TLC until all starting material was consumed (4 h). At that time, water was added, and the two layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 times), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude product, which was purified by recrystallization (MeOH) to furnish lamellarin acetate.

General Procedure for DDQ Oxidation

To a solution of lamellarin acetate (1.0 equiv) in CH_2Cl_2 or $(ClCH_2)_2$ (20 mL mmol^{-1}) at room temperature was added DDQ (2.5 equiv). The resulting mixture was stirred at room temperature or heated to reflux in $(ClCH_2)_2$ for 18 h. At that time, water was added, and the two layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 times), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude product, which was purified by column chromatography on silica (1% MeOH/CH_2Cl_2) to furnish lamellarin acetate with an unsaturated D-ring.

General Procedure for the KOH/EtOH Deacetylation

To the lamellarin acetate (1.0 equiv) was added 5% KOH in EtOH (10 mL mmol^{-1}) at room temperature. The mixture was stirred at room temperature until a clear solution was obtained (5 min). At that time, the reaction was immediately acidified with 2 N HCl. The material was extracted with EtOAc (3 times), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide crude product, which was purified by recrystallization (MeOH/CH_2Cl_2) to furnish the desired lamellarin.

Cytotoxicity Assays

The cell lines used in this study were either purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA) or received as gifts from other sources (Supporting Information Table S1). Dulbecco's Modified Eagle Medium (DMEM), as well as Ham's F12 and RPMI 1640 media, were supplied in powder form by HyClone Laboratories (Logan, UT, USA), while fetal bovine serum (FBS) and 0.25% trypsin-EDTA were obtained from J R Scientific, Inc. (Woodland, CA, USA) and Gibco (Grand Island, NY, USA), respectively. In addition, bovine insulin, DMSO, doxorubicin, etoposide, glucose, L-glutamine, MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide), penicillin-streptomycin, phenazine methosulfate (PMS), and sodium pyruvate were supplied by Sigma–Aldrich (St. Louis, MO, USA), whereas XTT (2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2*H*-tetrazolium-5-carboxanilide) was from Fluka Chemie (St. Louis, MO, USA). All materials were used as received.

Among the 11 cancerous and 1 normal cell lines used for cytotoxicity screening of lamellarins and analogs, 10 cell lines were adherent to the culture wells, whereas only HL-60 and P388 grew in suspension. Each cell line was maintained in an appropriate culture medium supplemented with essential nutrients (Supporting Information Table S1) and maintained using standard procedures at 37 °C with 95% humidity and 5% CO_2. All the test compounds and positive controls, including doxorubicin and etoposide, were prepared as 10 mg mL^{-1} stock solutions in DMSO and freshly diluted with the corresponding cell culture medium for each cell line on the day of analysis.

Prior to the assay, the cells were inoculated as a suspension in the corresponding cell culture medium (100 μL for adherent cells and 75 μL for suspended cells) into 96-well microtiter plates (Costar No. 3599, Corning Incorporated, Corning, NY, USA) at a density of 5000–20 000 cells per well, depending on their growth rates. Adherent and suspended cells were then allowed to grow at 37 °C with 95% humidity and 5% CO_2 for 24 h and 30 min, respectively. The cytotoxicity assay was initiated by adding an equal volume of cell culture medium containing either each test compound, positive control, or DMSO, at predetermined concentrations. Following 48 h of exposure to various treatments, cell viability was determined using MTT assay for adherent cells or XTT assay for suspended cells, as described below.

For adherent cells, 100 μL of the MTT reagent (0.5 mg mL^{-1} in serum-free cell culture medium) was added to each well, and the microtiter plates were further incubated for 2.5–4 h at 37 °C with 95% humidity and 5% CO_2. The medium was subsequently replaced with 100 μL of DMSO to dissolve the purple formazan before the absorbance at 550 nm was measured using a SpectraMax Plus 384 microplate reader (Molecular Devices, Sunnyvale, CA, USA) with a reference wavelength of 650 nm.

For suspended cells, 75 μL of the XTT reagent (prepared from 5 mL of 1 mg mL^{-1} XTT sodium in water and 100 μL of 0.383 mg mL^{-1} PMS in water) was added to each well, and the cells were further incubated for 4 h at 37 °C with 95% humidity and 5% CO_2. Afterwards, the absorbance of orange formazan at 492 nm was measured with a reference wavelength of 690 nm using a SpectraMax Plus 384 microplate reader.

For each well, the background absorbance (averaged from the wells containing the same volume of complete culture medium) was subtracted from either A_{550} or A_{492} to get the absolute absorbance. The average value from the duplicate wells, which had been treated with each concentration of the test compounds, was then compared with that of the untreated wells to yield the percentage of surviving cells. The IC_{50} value was finally calculated from the dose-response curve as the concentration that inhibits the cell growth by 50% in comparison with the negative control following 48 h of exposure to each test compound. The results shown in Table 5 are expressed as the mean IC_{50} value from at least two independent experiments, excluding those with a variation greater than 10%. The standard deviations are omitted for visual clarity.

Lipophilicity Determinations

Formamide and 7 reference compounds, including benzyl alcohol, benzonitrile, methyl benzoate, benzophenone, naphthalene, benzyl benzoate, and diphenyl ether, were obtained from commercial sources with at least 98% purity and used as received without further purification. Methanol (HPLC grade) and deionized water with a resistivity of 18.2 MΩ·cm (freshly obtained from a Barnstead MicroPure water purification system, Thermo Scientific, Waltham, MA, USA) were employed in the preparation of all samples and mobile phase for HPLC analyses.

All lamellarins and analogs were predissolved in either THF or DMSO and further diluted to achieve the concentration of 0.1 mg mL^{-1} in MeOH and water (75:25). Similarly, all the 7 reference compounds were also prepared as a reference mixture in MeOH and water (75:25). The lamellarin samples were then subject to chromatographic log P determinations previously established for these compounds.[2]

As suggested by the OECD guidelines,[19] all HPLC analyses were performed using Isocratic elution with methanol:water (75:25) for 15–75 min. On a daily basis, an Agilent 1200 series LC system installed with a ZORBAX Eclipse Plus C18 column (Agilent Technologies, Santa Clara, CA, USA) was calibrated using the reference mixture. The retention time (t_R) of each reference compound was determined and subsequently converted to the retention factor (k) using the equation $k=(t_R-t_0)/t_0$, where t_0 is the column dead time determined using the unretained formamide. Next, the resulting log k values of 7 reference compounds were regressed against their corresponding literature log P data to generate a calibration curve. Afterwards, the same chromatographic conditions were then applied to each test compound to determine the retention factor, which was finally used to calculate the log P value from the calibration curve constructed on the same day. The results reported in Table 5 are the mean values from at least triplicate determinations with a standard deviation of less than ±0.1 log unit according to the OECD guidelines.

Structure–Activity and Structure–Lipophilicity Relationships

Whenever possible, matched molecular pairs analysis was carried out to systematically determine both the structure–cytotoxicity and structure–lipophilicity relationships of lamellarins and analogs.

Briefly, the experimental IC_{50} or log P data for any two compounds with identical structures, except at the position being considered, were used to determine the log (IC_{50} ratio) or Δlog P values. Based on our approach, negative values of the log (IC_{50} ratio) indicate the increased cytotoxicity, while the positive values represent the loss of activity. In contrast, the interpretation of Δlog P values was more straightforward as the positive values suggest higher lipophilicity, whereas negative values show reduced lipophilic nature.

Acknowledgements

Financial support from the Thailand Research Fund (TRF; DBG5180015 and DBG5480011 to M.C., BRG5580010 to P.P.) and the internal grants from Chulabhorn Research Institute are gratefully acknowledged. Special thanks are due to Dr. Wong Phakhodee, Mr. Paratchata Batsomboon, and Ms. Supannee Sualek for their helps with some synthetic work during their presence at the Chulabhorn Research Institute. We also thank Mr. Atiruj Theppawong (Laboratory of Medicinal Chemistry, Chulabhorn Research Institute) for his assistance with the compound characterization data compilation.

Keywords: cytotoxicity · lamellarins · lipophilicity · pyrrole alkaloids · structure–activity relationships

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Received: December 1, 2014
Published online on February 20, 2015

CHEMISTRY
AN ASIAN JOURNAL

Supporting Information

Designing New Analogs for Streamlining the Structure of Cytotoxic Lamellarin Natural Products

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Table S1. Cell culture media used for each cell line.

Cell Line	Full Name (Source)	Culture Medium
A549	Human non-small-cell lung carcinoma (ATCC® CCL-185™)	Ham's F-12 medium supplemented with 10% fetal bovine serum (FBS), 2 mM L-glutamine, and 100 U/mL penicillin-streptomycin
H69AR	Human multi-drug-resistant small-cell lung carcinoma (ATCC® CRL-11351™)	RPMI 1640 supplemented with 20% FBS, 4.5 g/L glucose, 1 mM sodium pyruvate and 100 U/mL penicillin-streptomycin
HeLa	Human cervical adenocarcinoma (ATCC® CRM-CCL-2™)	DMEM supplemented with 10% FBS, 2 mM L-glutamine, and 100 U/mL penicillin-streptomycin
HepG2	Human hepatocellular carcinoma (ATCC® HB-8065™)	DMEM supplemented with 10% FBS and 100 U/mL penicillin-streptomycin
HL-60	Human promyelocytic leukemia (ATCC® CCL-240™)	RPMI 1640 supplemented with 10% FBS and 100 U/mL penicillin-streptomycin
HuCCA-1	Human cholangiocarcinoma (Laboratory of Immunology, Chulabhorn Research Institute, Bangkok, Thailand)	Ham's F-12 medium supplemented with 10% FBS, 2 mL L-glutamine, and 100 U/mL penicillin-streptomycin
KB	Human oral epidermoid carcinoma (University of Illinois at Chicago, Chicago, IL, USA)	DMEM supplemented with 10% FBS, 2 mM L-glutamine, and 100 U/mL penicillin-streptomycin
MDA-MB-231	Human hormone-independent breast cancer 231 (University of Texas M. D. Anderson Cancer Center, Houston, TX, USA)	DMEM supplemented with 10% FBS and 100 U/mL penicillin-streptomycin
MRC-5	Human fetal/embryonic lung fibroblast (ATCC® CCL-171™)	DMEM supplemented with 10% FBS and 100 U/mL penicillin-streptomycin
P388	Mouse lymphoid neoplasm (University of Illinois at Chicago, Chicago, IL, USA)	RPMI 1640 supplemented with 10% FBS and 100 U/mL penicillin-streptomycin
S102	Human hepatocellular carcinoma (Biochemistry Laboratory, Phramongkutklao Hospital, Bangkok, Thailand)	RPMI 1640 supplemented with 10% FBS and 100 U/mL penicillin-streptomycin
T47D	Human hormone-dependent breast cancer (ATCC® HTB-133)	RPMI 1640 supplemented with 10% FBS, 2 mM L-glutamine, 4.5 g/L glucose, 0.2 U/mL bovine insulin, and 100 U/mL penicillin-streptomycin

Compound Characterization Data

103: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.45–7.07 (m, 20H), 6.74 (s, 1H), 6.56 (s, 1H), 6.55 (s, 1H), 6.42 (s, 1H), 5.15 (s, 2H), 5.01 (s, 2H), 4.75 (s, 2H), 4.60 (br s, 2H), 4.00 (q, *J*=7.1 Hz, 2H), 3.60 (s, 3H), 3.28 (s, 3H), 2.99 (t, *J*=6.6 Hz, 2H), 0.83 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.0, 150.6, 147.8, 147.1, 146.9, 143.4, 137.8, 137.1, 137.0, 135.8, 131.0, 130.8, 128.5, 128.4, 128.2, 128.1, 127.9, 127.7, 127.4, 127.3, 127.2, 126.9, 126.5, 125.6, 122.1, 121.5, 119.3, 118.5, 116.1, 113.1, 109.1, 103.2, 71.8, 71.1, 71.0, 59.6, 56.3, 55.1, 42.8, 29.0, 13.7; IR (UATR): 2935, 1687 (C=O), 1382, 1240 cm^{-1}; HRMS (APCI-TOF): *m/z calcd* for $C_{50}H_{45}NO_8+H^+$: 772.3269 [M+H$^+$]; found: 772.3277.

Lam 1: m.p. > 290.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.68 (br s, 1H), 9.45 (br s, 1H), 7.65–7.58 (m, 2H), 7.57–7.48 (m, 3H), 6.78 (s, 1H), 6.74 (s, 1H), 6.47 (s, 1H), 6.44 (s, 1H), 4.60 (t, *J*=6.7 Hz, 2H), 3.25 (s, 3H), 3.15 (s, 3H), 3.01 (t, *J*=6.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.3, 147.1, 146.8, 146.0, 145.6, 144.5, 135.7, 135.3, 131.1, 129.4, 128.1, 127.3, 127.2, 117.8, 115.4, 114.0, 112.5, 109.0, 108.6, 104.6, 103.7, 54.9, 54.5, 42.0, 27.5; IR (UATR): 3410, 1680 (C=O), 1410, 1249 cm^{-1}; MS: *m/z* 455 (100) [M^+]; HRMS (APCI-TOF): *m/z calcd* for $C_{27}H_{21}NO_6+H^+$: 456.1441 [M+H$^+$]; found: 456.1451.

Lam 1-OAc: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.60–7.46 (m, 5H), 7.08 (s, 1H), 6.95 (s, 1H), 6.69 (s, 1H), 6.63 (s, 1H), 4.82 (t, *J*=6.7 Hz, 2H), 3.33 (s, 3H), 3.23 (s, 3H), 3.13 (t, *J*=6.7 Hz, 2H), 2.30 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.0, 168.7, 155.1, 149.6, 147.4, 144.9, 139.2, 138.8, 135.3, 134.9, 131.2, 129.4, 128.3, 127.0, 126.0, 125.8, 122.5, 116.7, 116.2, 114.9, 111.8, 109.8, 105.5, 55.3, 55.0, 42.4, 28.1, 20.59, 20.56; MS: *m/z* 539(3) [M^+], 497 (8), 455 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{31}H_{25}NO_8+H^+$: 540.1653 [M+H$^+$]; found: 540.1639.

122: ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.21 (d, *J*=7.4 Hz, 1H), 7.68–7.61 (m, 4H), 7.61–7.54 (m, 1H), 7.37 (s, 1H), 7.13 (s, 2H), 7.03 (d, *J*=7.4 Hz, 1H), 6.70 (s, 1H), 3.35 (s, 3H), 3.33 (s, 3H), 2.33 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.8, 168.7, 155.0, 150.7, 147.5, 145.5, 144.8, 140.7, 139.6, 135.6, 133.4, 131.7, 129.6, 128.7, 128.1, 123.84, 123.77, 123.2, 120.6, 115.8, 113.1, 112.6, 112.1, 106.4, 106.2, 55.3, 55.1, 20.6; IR (UATR): cm^{-1}; MS: *m/z* 537 (6) [M^+], 453 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{31}H_{23}NO_8+H^+$: 538.1496 [M+H$^+$]; found: 538.1495.

Lam 2: m.p. > 290.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.92 (br s, 2H), 8.98 (d, *J*=7.5 Hz, 1H), 7.72–7.56 (m, 5H), 7.19 (d, *J*=7.5 Hz, 1H), 7.18, (s, 1H), 6.92 (s, 1H), 6.85 (s, 1H), 6.49 (s, 1H), 3.26 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.3, 148.6, 148.4, 147.8, 146.3, 144.6, 135.4, 133.6, 131.6, 129.6, 128.7, 128.5, 124.7, 122.0, 117.3, 112.5, 111.6, 110.4, 108.1, 106.7, 105.3, 105.1, 103.8, 54.8, 54.4; IR (UATR): 3450, 1678, 1423, 1192, 1041 cm^{-1}; MS: *m/z* 453 (100) [M^+]; HRMS (APCI-TOF): *m/z calcd* for $C_{27}H_{19}NO_6+H^+$: 454.1285 [M+H$^+$]; found: 454.1296.

84: m.p. 95.7–97.6°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.50–7.14 (m, 10H), 6.93–6.50 (m, 7H), 5.40 (br t, *J*=6.3 Hz, 1H), 5.08 (s, 2H), 5.01 (s, 2H), 3.80 (s, 3H), 3.46 (s, 2H), 3.36 (q, *J*=6.3 Hz, 2H), 2.60 (t, *J*=6.3 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=170.6, 159.1, 148.2, 148.1, 137.0, 136.6, 136.2, 130.9, 130.0, 128.54, 128.46, 128.0, 127.8, 127.4, 127.3, 121.9, 121.2, 115.8, 114.4, 113.7, 111.8, 70.9, 69.8, 55.9, 43.8, 40.6, 34.8; IR (UATR): 3296, 3063, 3033, 2932, 1645, 1583, 1513 cm^{-1}; MS: *m/z* 482 (9) [M^++H], 481 (32) [M^+], 331 (20), 240 (87), 150 (65), 91 (100), 77 (3), 65 (11); HRMS (APCI-TOF): *m/z calcd* for $C_{31}H_{31}NO_4+H^+$: 482.2326 [M+H$^+$]; found: 482.2325.

104: ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.48–7.16 (m, 18H), 7.16–7.06 (m, 3H), 6.86–6.76 (m, 3H), 6.74 (s, 1H), 6.63 (s, 1H), 6.58 (s, 1H), 6.44 (s, 1H), 5.14 (s, 2H), 5.01 (s, 2H), 4.80 (s, 2H), 4.75 (s, 2H), 4.60 (br s, 2H), 4.00 (q, *J*=7.0 Hz, 2H), 3.62 (s, 3H), 3.29 (s, 3H), 2.99 (t, *J*=6.6 Hz, 2H), 0.83 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=162.0, 158.6, 150.7, 147.9, 147.2, 143.4, 137.9, 137.2, 137.0, 130.8, 129.0, 128.5, 128.44, 128.41, 128.2, 127.84, 127.81, 127.7, 127.34, 127.26, 126.8, 125.6, 123.8, 121.9, 121.5, 119.3, 118.7, 117.0, 116.3, 113.7, 113.3, 109.3, 103.3, 71.7, 71.3, 71.1, 69.9, 59.6, 56.5, 55.2, 42.8, 29.0, 13.7; IR (UATR): 1684, 1606, 1531, cm^{-1}; MS: *m/z* 878 (1) [M^++H], 877 (11) [M^+], 787 (39), 696 (100), 650 (31), 623 (28), 606 (46), 532 (40); HRMS (APCI-TOF): *m/z calcd* for $C_{57}H_{51}NO_8+H^+$: 878.3687 [M+H$^+$]; found: 878.3691.

Lam 3: m.p. > 290°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.68 (s, 1H), 9.66 (s, 1H), 9.45 (s, 1H), 7.42 (t, *J*=7.8 Hz, 1H), 6.96–6.89 (m, 2H), 6.88–6.85 (m, 1H), 6.79 (s, 1H), 6.74 (s, 1H), 6.63 (s, 2H), 4.71–4.62 (m, 1H), 4.57–4.47 (m, 1H), 3.34 (s, 3H), 3.24 (s, 3H), 3.04–2.97 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=158.3, 154.3, 147.1, 146.8, 146.0, 145.6, 144.5, 136.3, 135.6, 130.5, 127.22, 127.18, 121.4, 117.8, 117.5, 115.3, 115.0, 114.0, 112.5, 109.2, 108.6, 104.9, 103.6, 54.9, 54.6, 42.0, 27.5; IR (UATR): 3451, 3214, 1662, 1589, 1487, 1417 cm^{-1}; MS: *m/z* 472 (27) [M^++H], 471 (100) [M^+]; HRMS (APCI-TOF): *m/z calcd* for $C_{27}H_{21}NO_7$+H$^+$: 472.1391 [*M*+H$^+$]; found: 472.1398.

Lam 3-OAc: m.p. 288.5–289.7°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.59 (t, *J*=7.8 Hz, 1H), 7.40 (d, *J*=7.8 Hz, 1H), 7.30–7.18 (m, 2H), 7.09 (s, 1H), 6.95 (s, 1H), 6.68 (s, 1H), 6.64 (s, 1H), 4.98–4.66 (m, 2H), 3.41 (s, 3H), 3.32 (s, 3H), 3.11 (t, *J*=6.9 Hz, 2H), 2.31 (s, 3H), 2.30 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=169.1, 168.9, 168.7, 155.1, 151.8, 149.9, 147.7, 145.0, 139.5, 139.0, 136.9, 135.0, 130.4, 128.6, 127.0, 126.0, 125.5, 124.5, 122.6, 121.9, 116.0, 115.4, 115.0, 111.9, 109.8, 105.5, 55.5, 55.2, 42.4, 28.1, 20.9, 20.6; IR (UATR): 1764, 1713 cm^{-1}; MS: *m/z* 598 (5) [M^++H], 597 (14) [M^+], 555 (22), 513 (58), 471 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{33}H_{27}NO_{10}$+H$^+$: 598.1708 [*M*+H$^+$]; found: 598.1692.

123: m.p. 239.3–240.0°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=9.23 (d, *J*=7.3 Hz, 1H), 7.68 (t, *J*=8.1 Hz, 1H), 7.52 (dd, *J*=8.1, 1.4 Hz, 1H), 7.42–7.27 (m, 3H), 7.13 (s, 2H), 7.06 (d, *J*=7.3 Hz, 1H), 6.71 (s, 1H), 3.43 (s, 6H), 2.34 (s, 3H), 2.32 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=169.1, 168.7, 168.6, 155.0, 151.9, 151.0, 147.8, 145.5, 140.9, 139.8, 137.3, 133.5, 130.5, 129.1, 128.2, 125.0, 123.9, 123.6, 123.1, 122.4, 120.7, 115.6, 112.8, 112.2, 111.8, 109.2, 106.4, 106.2, 55.5, 55.3, 20.9, 20.6; IR (UATR): 1762, 1714 cm^{-1}; MS: *m/z* 596 (10) [M^++H], 595 (37) [M^+], 553 (44), 511 (100), 469 (13), 436 (8), 408 (15); HRMS (APCI-TOF): *m/z calcd* for $C_{33}H_{25}NO_{10}$+H$^+$: 596.1551 [*M*+H$^+$]; found: 596.1553.

Lam 4: m.p. > 290°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.96 (s, 1H), 9.84 (s, 1H), 9.76 (s, 1H), 8.99 (d, *J*=7.4 Hz, 1H), 7.53–7.46 (m, 1H), 7.20 (d, *J*=7.4 Hz, 1H), 7.18 (s, 1H), 7.11 (s, 1H), 7.04 (d, *J*=7.5 Hz, 1H), 7.00 (d, *J*=7.0 Hz, 1H), 6.99 (s, 1H), 6.85 (s, 1H), 6.70 (s, 1H), 3.35 (s, 3H), 3.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.4, 154.3, 148.6, 148.3, 147.8, 146.3, 144.6, 136.4, 133.6, 130.7, 128.5, 124.7, 122.0, 121.8, 117.9, 117.3, 115.4, 112.5, 111.5, 110.5, 108.1, 106.6, 105.5, 105.2, 103.8, 54.9, 54.4; IR (UATR): 3452, 1682, 1604 cm^{-1}; MS: *m/z* 470 (32) [M^++H], 469 (100) [M^+], 454 (4), 436 (15), 408 (22); HRMS (APCI-TOF): *m/z calcd* for $C_{27}H_{19}NO_7^+$ H$^+$: 470.1234 [*M*+H$^+$]; found: 470.1231.

85: m.p. 101.7–102.7°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.48–7.17 (m, 5H), 7.15 (d, *J*=8.0 Hz, 1H), 6.86–6.67 (m, 4H), 6.64 (d, *J*=2.2 Hz, 1H), 6.55 (dd, *J*=8.0, 2.2 Hz, 1H), 5.39 (br s, 1H), 5.08 (s, 2H), 3.86 (s, 3H), 3.76 (s, 3H), 3.47 (s, 2H), 3.40 (q, *J*=6.4 Hz, 2H), 2.62 (t, *J*=6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.6, 160.0, 148.4, 148.2, 137.1, 136.3, 131.1, 129.9, 128.5, 127.8, 127.3, 121.6, 121.4, 114.9, 114.8, 112.8, 112.1, 71.1, 56.1, 55.1, 43.9, 40.6, 34.9; IR (UATR): 3298, 3059, 2935, 2836, 1646, 1603, 1585 cm^{-1}; MS: *m/z* 406 (10) [M^++H], 405 (47) [M^+], 255 (14), 240 (87), 225 (13), 166 (17), 150 (81), 121 (17), 91 (100), 77 (6), 65 (11); HRMS (APCI-TOF): *m/z calcd* for $C_{25}H_{27}NO_4$+H$^+$: 406.2013 [*M*+H$^+$]; found: 406.2019.

105: ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.52–7.00 (m, 15H), 6.80–6.53 (m, 6H), 6.57 (s, 1H), 6.42 (s, 1H), 5.14 (s, 2H), 5.02 (s, 2H), 4.75 (s, 2H), 4.60 (br s, 2H), 3.99 (q, *J*=7.2 Hz, 2H), 3.63 (s, 3H), 3.56 (s, 3H), 3.33 (s, 3H), 2.99 (t, *J*=6.2 Hz, 2H), 0.82 (t, *J*=7.2 Hz, 3H);^{13}C NMR (50 MHz, $CDCl_3$): δ=162.0, 159.4, 150.7, 147.9, 147.2, 147.1, 143.6, 137.9, 137.1, 137.0, 130.8, 128.9, 128.5, 128.4, 128.2, 127.8, 127.7, 127.3, 126.8, 125.6, 123.5, 121.9, 121.6, 119.3, 118.7, 116.3, 115.8, 113.4, 112.7, 109.3, 103.3, 71.7, 71.3, 71.1, 59.5, 56.5, 55.2, 55.1, 42.8, 29.0, 13.7; IR (UATR): 1684, 1603, 1531 cm^{-1}; MS: *m/z* 802 (5) [M^++H], 801 (10) [M^+], 710 (68), 620 (17), 546 (17), 528 (20), 91 (100), 77 (5), 65 (9); HRMS (APCI-TOF): *m/z calcd* for $C_{51}H_{47}NO_8$+H$^+$: 802.3374 [*M*+H$^+$]; found: 802.3368.

Lam 5: m.p. 261.5–262.7°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.68 (s, 1H), 9.46 (s, 1H), 7.53 (t, *J*=7.8 Hz, 1H), 7.12–7.06 (m, 3H), 6.78 (s, 1H), 6.74 (s, 1H), 6.57 (s, 1H), 6.52 (s, 1H), 4.66–4.52 (m, 2H), 3.77 (s, 3H), 3.35 (s, 3H), 3.20 (s, 3H), 3.00 (t, *J*=6.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=160.2, 154.2, 147.1, 146.9, 146.0, 145.7, 144.5, 136.6, 135.7, 130.6, 127.3, 127.2, 123.2, 117.8, 116.0, 115.4, 114.0, 113.8, 112.5, 109.1, 108.5, 104.8, 103.6, 55.4, 54.9, 54.5, 42.0, 27.5; IR (UATR): 3397, 2943, 2837, 1705, 1592cm^{-1}; MS: *m/z* 486 (31) [M^++H], 485 (100) [M^+]; HRMS (APCI-TOF): *m/z calcd* for $C_{28}H_{23}NO_7$+H$^+$: 486.1547 [*M*+H$^+$]; found: 486.1540.

Lam 5-OAc: m.p. 272.3–273.4°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.49 (td, *J*=7.4, 1.5 Hz, 1H), 7.20–7.00 (m, 4H), 6.95 (s, 1H), 6.79 (s, 1H), 6.71 (s, 1H), 4.99–4.66 (m, 2H), 3.81 (s, 3H), 3.38 (s, 3H), 3.29 (s, 3H), 3.12 (t, *J*=7.0 Hz, 2H), 2.31 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=168.9, 168.7, 160.6, 155.1, 149.7, 147.5, 145.0, 139.4, 138.9, 136.7, 134.9, 130.5, 127.0, 126.1, 125.8, 123.3, 122.5, 116.6, 116.1, 115.8, 114.9, 114.5, 111.9, 109.9, 105.7, 55.5, 55.4, 55.1, 42.4, 28.1, 20.6; IR (UATR): 1769, 1714, 1588 cm^{-1}; MS: *m/z* 570 (7) [M^++H], 569 (36) [M^+], 527 (49), 485 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{32}H_{27}NO_9$+H$^+$: 570.1759 [*M*+H$^+$]; found: 570.1755.

124: m.p. 264.3–265.2°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=9.23 (d, *J*=7.4 Hz, 1H), 7.57 (t, *J*=7.7 Hz, 1H), 7.39 (s, 1H), 7.28–7.08 (m, 5H), 7.05 (d, *J*=7.4 Hz, 1H), 6.80 (s, 1H), 3.84 (s, 3H), 3.40 (s, 3H), 3.39 (s, 3H), 2.35 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=168.8, 168.6, 160.8, 155.1, 150.9, 147.6, 145.6, 140.8, 139.7, 136.9, 133.4, 130.7, 128.1, 123.9, 123.7, 123.2, 120.6, 116.1, 115.8, 114.9, 113.0, 112.7, 112.1, 109.1, 106.6, 106.4, 55.5, 55.4, 55.2, 20.6; IR (UATR): 1766, 1708, 1622, 1589, 1503 cm^{-1}; MS: *m/z* 568 (13) [M^++H], 567 (56) [M^+], 525 (39), 483 (100), 450 (11), 422 (14); HRMS (APCI-TOF): *m/z calcd* for $C_{32}H_{25}NO_9$+H$^+$: 568.1602 [*M*+H$^+$]; found: 568.1601.

Lam 6: m.p. > 290°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.91 (br s, 2H), 8.99 (dd, *J*=7.4, 1.1 Hz, 1H), 7.61 (t, *J*=7.8 Hz, 1H), 7.23–7.16 (m, 5H), 7.02 (s, 1H), 6.86 (s, 1H), 6.60 (s, 1H), 3.80 (s, 3H), 3.32 (s, 3H), 3.31 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=160.3, 154.3, 148.6, 148.4, 147.9, 146.3, 144.6, 136.7, 133.7, 130.7, 128.6, 124.7, 123.5, 122.0, 117.3, 116.3, 114.5, 112.5, 111.5, 110.3, 108.1, 106.6, 105.4, 105.2, 103.8, 55.5, 54.9, 54.4; IR (UATR): 3390 (br s), 1694, 1596, 1507, 1480 cm^{-1}; MS: *m/z* 484 (31) [M^++H], 483 (100) [M^+], 450 (12), 422 (21); HRMS (APCI-TOF): *m/z calcd* for $C_{28}H_{21}NO_7$+H$^+$: 484.1391 [*M*+H$^+$]; found: 484.1391.

86: m.p. 128.4–128.9°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.50–7.20 (m, 10H), 7.05 (d, *J*=8.8 Hz, 2H), 6.90 (d, *J*=8.8 Hz, 2H), 6.75 (d, *J*=8.3 Hz, 1H), 6.65 (d, *J*=1.7 Hz, 1H), 6.56 (dd, *J*=8.3, 1.7 Hz, 1H), 5.32 (br m, 1H), 5.09 (s, 2H), 5.04 (s, 2H), 3.85 (s, 3H), 3.44 (s, 2H), 3.38 (q, *J*=6.6 Hz, 2H), 2.62 (t, *J*=6.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=171.2, 158.1, 148.5, 148.3, 137.1, 136.9, 131.1, 130.5, 128.6, 128.5, 128.0, 127.8, 127.41, 127.35, 127.0, 121.4, 115.3, 114.8, 112.1, 71.1, 70.0, 56.1, 42.9, 40.6, 34.9; IR (UATR): 1647, 1511, 1264, 1235, 1138, 1016, 731, 698 cm^{-1}; MS: *m/z* 481 (24) [M^+], 395 (5), 320 (12), 290 (100), 240 (22), 150 (3), 91 (73); HRMS (APCI-TOF): *m/z calcd* for $C_{31}H_{31}NO_4$+H$^+$: 482.2326 [*M*+H$^+$]; found: 482.2324.

106: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.45–7.20 (m, 18H), 7.11–7.04 (m, 4H), 6.84 (d, *J*=8.8 Hz, 2H), 6.73 (s, 1H), 6.61 (s, 1H), 6.56 (s, 1H), 6.43 (s, 1H), 5.13 (s, 2H), 5.03 (s, 2H), 5.02 (s, 2H), 4.75 (s, 2H), 4.59 (br s, 2H), 3.99 (q, *J*=7.1 Hz, 2H), 3.63 (s, 3H), 3.27 (s, 3H), 2.98 (t, *J*=6.5 Hz, 2H), 0.83 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.0, 157.3, 150.6, 147.8, 147.0, 146.9, 143.5, 137.8, 137.1, 137.0, 132.0, 130.8, 128.5, 128.4, 128.33, 128.29, 128.2, 127.9, 127.8, 127.7, 127.35, 127.30, 127.27, 127.2, 126.9, 125.6, 121.6, 119.1, 118.7, 116.1, 114.6, 113.2, 109.0, 103.2, 71.8, 71.2, 71.0, 69.8, 59.5, 56.4, 55.1, 42.7, 29.0, 13.7; IR (UATR): 1683, 1610, 1531, 1496 cm^{-1}; HRMS (APCI-TOF): *m/z calcd* for $C_{57}H_{51}NO_8$+H$^+$: 878.3687 [*M*+H$^+$]; found: 878.3684.

Lam 7: m.p. > 290°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.71 (s, 1H), 9.67 (s, 1H), 9.44 (s, 1H), 7.27 (d, *J*=8.5 Hz, 2H), 6.99 (d, *J*=8.5 Hz, 2H), 6.77 (s, 1H), 6.73 (s, 1H), 6.61 (s, 1H), 6.57 (s, 1H), 4.57 (t, *J*=6.6 Hz, 2H), 3.34 (s, 3H), 3.25 (s, 3H), 2.98 (t, *J*=6.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=157.3, 154.3, 147.0, 146.8, 146.0, 145.7, 144.5, 136.0, 132.1, 127.7, 127.2, 125.1, 118.1, 116.1, 115.4, 114.1, 112.4, 109.2, 108.8, 105.0, 103.6, 55.1, 54.7, 42.0, 27.6; IR (UATR): 3314 (br s), 1701, 1661, 1591, 1547, 1514, 1480, 1408, 1280, 1252, 1147, 1038, 1013 cm^{-1}; HRMS (APCI-TOF): *m/z calcd* for $C_{27}H_{21}NO_7$+H$^+$: 472.1391 [*M*+H$^+$]; found: 472.1403.

Lam 7-OAc: m.p. > 290°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.55 (d, *J*=8.4 Hz, 2H), 7.26 (d, *J*=8.4 Hz, 2H), 7.08 (s, 1H), 6.95 (s, 1H), 6.70 (s, 1H), 6.64 (s, 1H), 4.82 (t, *J*=6.6 Hz, 2H), 3.40 (s, 3H), 3.31 (s, 3H), 3.11 (t, *J*=6.6 Hz, 2H), 2.34 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=169.2, 168.9, 168.7, 155.1, 150.9, 149.8, 147.7, 145.0, 139.5, 139.0, 135.1, 133.0, 132.2, 127.1, 126.0, 125.6, 123.0, 122.6, 116.0, 115.6, 115.1, 112.0, 109.8, 105.5, 55.6, 55.3, 42.4, 28.1, 21.0, 20.6; IR (UATR): 1765, 1716, 1547 cm^{-1}; MS: *m/z* 597 (14) [M^+], 555 (34), 514 (96), 441 (16), 406 (76), 220 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{33}H_{27}NO_{10}$+H$^+$: 598.1708 [*M*+H$^+$]; found: 598.1704.

125: ^{1}H NMR (200 MHz, $CDCl_3$): δ=9.22 (d, *J*=7.8 Hz, 1H), 7.66 (dd, *J*=6.6, 2.2 Hz, 2H), 7.39 (s, 1H), 7.35 (dd, *J*=6.6, 2.2 Hz, 2H), 7.15 (s, 2H), 7.05 (d, *J*=7.8 Hz, 1H), 6.74 (s, 1H), 3.43 (s, 6H), 2.38 (s, 3H), 2.35 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=169.2, 168.7, 168.6, 155.0, 151.2, 151.0, 147.7, 145.5, 140.9, 139.8, 133.6, 133.3, 132.8, 128.3, 123.8, 123.7, 123.24, 123.16, 120.7, 115.7, 112.8, 112.2, 112.0, 109.2, 106.3, 106.1, 55.6, 55.5, 21.0, 20.6; IR (UATR): 1764, 1713, 1622, 1542, 1481 cm^{-1}; MS: *m/z* 595 (31) [M^+], 553 (42), 512 (100), 470 (12); HRMS (APCI-TOF): *m/z calcd* for $C_{33}H_{25}NO_{10}$+H$^+$: 596.1551 [*M*+H$^+$]; found: 596.1537.

Lam 8: m.p. > 290°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.92 (s, 1H), 9.81 (s, 1H), 9.77 (s, 1H), 8.96 (d, *J*=6.8 Hz, 1H), 7.37 (d, *J*=8.5 Hz, 2H), 7.17 (d, *J*=6.8 Hz, 1H), 7.16 (s, 1H), 7.09 (s, 1H), 7.06 (d, *J*=8.5 Hz, 2H), 6.84 (s, 1H), 6.65 (s, 1H), 3.36 (s, 3H), 3.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=157.6, 154.3, 148.4, 148.2, 147.7, 146.3, 144.5, 134.0, 132.6, 128.9, 125.0, 124.6, 122.0, 117.5, 116.3, 112.3, 111.5, 110.5, 108.3, 106.4, 105.5, 105.2, 103.7, 55.0, 54.5; IR (UATR): 3389, 1698, 1659, 1593 cm^{-1}; MS: *m/z* 470 (29) [M^++H], 469 (100)

[M^+], 454 (4), 436 (18), 408 (20); HRMS (APCI-TOF): *m/z calcd* for $C_{27}H_{19}NO_7+H^+$: 470.1234 [$M+H^+$]; found: 470.1241.

87: m.p. 113.0–115.0°C;^{1}H NMR (200 MHz, $CDCl_3$): δ=7.50–7.20 (m, 5H), 7.05 (d, J=8.0 Hz, 2H), 6.90–6.70 (m, 3H), 6.64 (d, J=1.9 Hz, 1H), 6.56 (dd, J=8.4, 1.9 Hz, 1H), 5.36 (br s, 1H), 5.08 (s, 2H), 3.84 (s, 3H), 3.77 (s, 3H), 3.43 (s, 2H), 3.37 (q, J=6.6 Hz, 2H), 2.61 (t, J=6.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=171.3, 158.7, 148.2, 148.1, 137.0, 130.9, 130.4, 128.5, 127.8, 127.3, 126.6, 121.2, 114.5, 114.3, 111.8, 70.9, 56.0, 55.2, 42.8, 40.5, 34.8; IR (UATR): 3300, 3053, 2934, 2836, 1645, 1611, 1510 cm^{-1}; MS: *m/z* 406 (10) [M^++H], 405 (41) [M^+], 255 (14), 241 (16), 240 (100), 166 (41), 150 (56), 121 (37), 91 (84); HRMS (APCI-TOF): *m/z calcd* for $C_{25}H_{27}NO_4+H^+$: 406.2013 [$M+H^+$]; found: 406.2020.

107: ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.48–7.18 (m, 13H), 7.08 (d, J=8.4 Hz, 4H), 6.77 (d, J=8.4 Hz, 2H), 6.74 (s, 1H), 6.63 (s, 1H), 6.56 (s, 1H), 6.43 (s, 1H), 5.14 (s, 2H), 5.02 (s, 2H), 4.76 (s, 2H), 4.60 (br s, 2H), 3.99 (q, J=7.2 Hz, 2H), 3.76 (s, 3H), 3.64 (s, 3H), 3.34 (s, 3H), 2.99 (t, J=6.6 Hz, 2H), 0.82 (t, J=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=162.0, 158.3, 150.7, 147.9, 147.1, 147.0, 143.6, 137.9, 137.2, 137.1, 132.0, 130.9, 128.5, 128.4, 128.2, 128.1, 127.9, 127.7, 127.3, 127.2, 126.9, 125.7, 121.8, 119.2, 118.9, 116.4, 113.6, 113.4, 109.2, 103.4, 71.8, 71.3, 71.1, 59.5, 56.5, 55.2, 42.8, 29.0, 13.7; IR (UATR): 1684, 1611, 1531 cm^{-1}; MS: *m/z* 802 (6) [M^++H], 801 (15) [M^+], 710 (100), 664 (5), 620 (55), 574 (22), 546 (35), 528 (19), 482 (17), 456 (24), 91 (51); HRMS (APCI-TOF): *m/z calcd* for $C_{51}H_{47}NO_8+H^+$: 802.3374 [$M+H^+$]; found: 802.3351.

Lam 9: m.p. dec. 261.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.68 (s, 1H), 9.45 (s, 1H), 7.40 (d, J=8.6 Hz, 2H), 7.17 (d, J=8.6 Hz, 2H), 6.78 (s, 1H), 6.73 (s, 1H), 6.54 (s, 1H), 6.51 (s, 1H), 4.58 (t, J=6.7 Hz, 2H), 3.82 (s, 3H), 3.32 (s, 3H), 3.22 (s, 3H), 2.99 (t, J=6.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=159.2, 154.3, 147.1, 146.8, 146.0, 145.7, 144.5, 136.0, 132.3, 127.6, 127.3, 126.9, 118.0, 115.4, 114.9, 113.6, 112.4, 109.1, 108.7, 104.8, 103.7, 55.5, 55.0, 54.6, 42.0, 27.5; IR (UATR): 3442, 3293, 1670, 1610 cm^{-1}; MS: *m/z* 486 (34) [M^++H], 485 (100) [M^+], 470 (8), 452 (9), 424 (7); HRMS (APCI-TOF): *m/z calcd* for $C_{28}H_{23}NO_7+H^+$: 486.1547 [$M+H^+$]; found: 486.1537.

Lam 9-OAc: m.p. dec. 270.0°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.45 (d, J=8.0 Hz, 2H), 7.11 (d, J=8.0 Hz, 2H), 7.09 (s, 1H), 6.95 (s, 1H), 6.75 (s, 1H), 6.72 (s, 1H), 4.82 (t, J=6.6 Hz, 2H), 3.87 (s, 3H), 3.40 (s, 3H), 3.31 (s, 3H), 3.11 (t, J=6.6 Hz, 2H), 2.31 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=168.9, 168.7, 159.8, 155.2, 149.7, 147.5, 145.0, 139.4, 138.8, 135.2, 132.4, 127.3, 127.2, 126.2, 126.0, 122.5, 116.3, 114.9, 111.9, 109.9, 105.7, 55.6, 55.5, 55.2, 42.4, 28.2, 20.6; IR (UATR): 1763, 1713, 1616, 1547 cm^{-1}; MS: *m/z* 570 (9) [M^++H], 569 (37) [M^+], 527 (50), 485 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{32}H_{27}NO_9+H^+$: 570.1759 [$M+H^+$]; found: 570.1760.

126: m.p. > 290.0°C;^{1}H NMR (400 MHz, $CDCl_3$): δ=9.22 (d, J=7.4 Hz, 1H), 7.54 (d, J=8.7 Hz, 2H), 7.38 (s, 1H), 7.22 (s, 1H), 7.18 (d, J=8.7 Hz, 2H), 7.14 (s, 1H), 7.04 (d, J=7.4 Hz, 1H), 6.79 (s, 1H), 3.91 (s, 3H), 3.42 (s, 3H), 3.41 (s, 3H), 2.34 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.8, 168.6, 159.9, 155.1, 150.7, 147.5, 145.5, 140.7, 139.6, 133.7, 132.8, 128.4, 127.3, 123.9, 123.2, 120.6, 116.0, 115.0, 112.8, 112.6, 112.1, 109.0, 106.5, 106.3, 55.6, 55.4, 55.2, 20.6; IR (UATR): 1761, 1706, 1541, 1481 cm^{-1}; MS: *m/z* 568 (15) [M^++H], 567 (58) [M^+], 525 (52), 483 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{32}H_{25}NO_9+H^+$: 568.1602 [$M+H^+$]; found: 568.1611.

Lam 10: m.p. dec. 284.5°C;^{1}H NMR (400 MHz, DMSO-d_6): δ=9.95 (s, 1H), 9.84 (s, 1H), 8.96 (d, J=7.4 Hz, 1H), 7.49 (d, J=8.6 Hz, 2H), 7.22 (d, J=8.6 Hz, 2H), 7.172 (s, 1H), 7.170 (d, J=7.4 Hz, 1H), 6.85 (s, 1H), 6.57 (s, 1H), 3.85 (s, 3H), 3.33 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=159.5, 154.3, 148.5, 148.3, 147.8, 146.3, 144.6, 134.0, 132.7, 128.9, 126.9, 124.7, 122.0, 117.4, 115.0, 112.4, 111.6, 110.1, 108.2, 106.9, 105.4, 104.0, 55.5, 55.0, 54.5; IR (UATR): 3452, 1673, 1612, 1555 cm^{-1}; MS: *m/z* 484 (30) [M^++H], 483 (100) [M^+], 468 (4), 450 (15), 422 (17); HRMS (APCI-TOF): *m/z calcd* for $C_{28}H_{21}NO_7+H^+$: 484.1391 [$M+H^+$]; found: 484.1401.

88: m.p. 124.8–125.8°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.44–7.28 (m, 5H), 7.12–6.92 (m, 4H), 6.74 (d, J=8.0 Hz, 1H), 6.65 (s, 1H), 6.55 (d, J=8.0 Hz, 1H), 5.47 (br m, 1H), 5.08 (s, 2H), 3.84 (s, 3H), 3.41 (s, 2H), 3.60–3.20 (m, 2H), 2.62 (t, J=6.8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=170.4, 161.8 (d, $J_{C–F}$=244.0 Hz), 148.3, 148.0, 136.9, 130.7 (d, $J_{C–F}$=6.4 Hz), 128.4, 127.7, 127.2, 121.2, 115.5 (d, $J_{C–F}$=21.3 Hz), 114.5, 111.8, 70.9, 55.9, 42.7, 40.5, 34.7; IR (UATR): 3302, 2934, 1646, 1508 cm^{-1}; MS: *m/z* 394 (8) [M^++H], 393 (29) [M^+], 241 (15), 240 (83), 225 (12), 166 (11), 109 (11), 91 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{24}H_{24}FNO_3+H^+$: 394.1818 [$M+H^+$]; found 394.1818.

108: ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.50–7.04 (m, 17H), 6.91 (t, J=8.6 Hz, 2H), 6.75 (s, 1H), 6.54 (s, 1H), 6.53 (s, 1H), 6.43 (s, 1H), 5.15 (s, 2H), 5.03 (s, 2H), 4.75 (s, 2H), 4.60 (br s, 2H), 3.99 (q, J=7.2 Hz, 2H), 3.64 (s, 3H), 3.35 (s, 3H), 2.99 (t, J=6.6 Hz, 2H), 0.83 (t, J=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=161.7, 161.4 (d, $J_{C–F}$=242.0 Hz), 150.3, 147.7, 147.08, 146.95, 143.4, 137.6, 136.9, 136.8, 132.3 (d, $J_{C–F}$=6.4 Hz), 131.6, 130.7, 128.4, 128.3, 128.0, 127.7, 127.6, 127.2, 127.15, 127.06, 126.7, 125.6, 121.2, 120.8, 119.1, 118.2, 116.1, 114.8 (d, $J_{C–F}$=21.3 Hz), 113.2, 108.8, 103.0, 71.5, 71.1, 70.8, 59.4, 56.3, 55.0, 42.6, 28.9, 13.6; IR (UATR): 1686, 1607, 1497 cm^{-1}; MS: *m/z* 789 (64) [M^+], 699 (79), 698 (100), 608 (41), 91 (33); HRMS (APCI-TOF): *m/z calcd* for $C_{50}H_{44}FNO_7+H^+$: 790.3175 [$M+H^+$]; found 790.3159.

Lam 11: m.p. dec. 262.4°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ=9.66 (s, 1H), 9.46 (s, 1H), 7.61–7.50 (m, 2H), 7.44 (t, J=8.6 Hz, 2H), 6.78 (s, 1H), 6.76 (s, 1H), 6.44 (s, 1H), 6.42 (s, 1H), 4.58 (t, J=6.0 Hz, 2H), 3.37 (s, 3H), 3.24 (s, 3H), 3.00 (t, J=6.0 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=162.0 (d, $J_{C–F}$=244.1 Hz), 154.2, 147.2, 146.9, 146.0, 145.6, 144.5, 135.8, 133.3 (d, $J_{C–F}$=8.0 Hz), 131.5 (d, $J_{C–F}$=3.2 Hz), 127.3, 117.7, 116.2 (d, $J_{C–F}$=21.2 Hz), 115.4, 112.64, 112.56, 109.0, 108.5, 104.5, 103.7, 54.9, 54.6, 41.9, 27.5; IR (UATR): 3429, 1677 cm^{-1}; MS: *m/z* 474 (30) [M^++H], 473 (100) [M^+], 472 (21) [M^+-H], 424 (15), 423 (56), 409 (8), 408 (27); HRMS (APCI-TOF): *m/z calcd* for $C_{27}H_{20}FNO_6+H^+$: 474.1347 [$M+H^+$]; found 474.1347.

Lam 11-OAc: m.p. 247.4–249.0°C; ^{1}H NMR (200 MHz, $CDCl_3+CD_3OD$): δ=7.59–7.52 (m, 2H), 7.38–7.28 (m, 2H), 7.11 (s, 1H), 6.99 (s, 1H), 6.65 (s, 1H), 6.63 (s, 1H), 4.81 (t, J=6.6 Hz, 2H), 3.41 (s, 3H), 3.32 (s, 3H), 3.14 (t, J=6.6 Hz, 2H), 2.32 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3+CD_3OD$): δ=169.1, 168.9, 162.5 (d, $J_{C–F}$=246.5 Hz), 155.2, 149.5, 147.4, 144.6, 139.0 (d, $J_{C–F}$=25.5 Hz), 132.9 (d, $J_{C–F}$=6.4 Hz), 130.9 (d, $J_{C–F}$=4.3 Hz), 127.1, 126.2, 125.3, 122.4, 116.2 (d, $J_{C–F}$=21.3 Hz), 115.8, 115.2, 111.7, 109.5, 105.1, 55.2, 54.9, 42.2, 27.8, 20.2; IR (UATR): 2927, 1777, 1767, 1715, 1547 cm^{-1}; MS: *m/z* 558 (15) [M^++H], 557 (46) [M^+], 516 (14), 515 (46), 474 (29), 473 (100), 472 (15); HRMS (APCI-TOF): *m/z calcd* for $C_{31}H_{24}FNO_8+H^+$: 558.1564 [$M+H^+$]; found 558.1556.

127: m.p. > 290.0°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.39 (s, 1H), 7.42–7.34 (m, 2H), 7.13 (s, 1H), 7.09 (s, 1H), 7.03 (d, J=7.4 Hz, 1H), 6.67 (s, 1H), 3.42 (s, 6H), 2.35 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=168.7, 168.6, 162.9 (d, $J_{C–F}$=246.5 Hz), 154.9, 150.8, 147.6, 145.5, 140.8, 139.8, 133.6 (d, $J_{C–F}$=6.4 Hz), 131.6 (d, $J_{C–F}$=4.4 Hz), 128.3, 124.0, 123.6, 123.2, 120.8, 116.6 (d, $J_{C–F}$=21.2 Hz), 115.6, 112.8, 112.3, 111.7, 109.1, 106.2, 106.0, 55.4, 55.2, 20.6; IR (UATR): 2927, 2353, 2133, 1767, 1710, 1541 cm^{-1}; MS: *m/z* 556 (12) [M^++H], 555 (33) [M^+], 514 (11), 513 (35), 472 (30), 471 (100), 438 (11), 410 (11), 49 (13), 43 (61); HRMS (APCI-TOF): *m/z calcd* for $C_{31}H_{22}FNO_8+H^+$: 556.1407 [$M+H^+$]; found 556.1414.

Lam 12: m.p. > 290.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.99 (s, 1H), 9.88 (s, 1H), 9.00 (d, J=7.5 Hz, 1H), 7.70–7.67 (m, 2H), 7.56–7.52 (m, 2H), 7.21 (d, J=7.5 Hz, 1H), 7.19 (s, 1H), 6.91 (s, 1H), 6.87 (s, 1H), 6.49 (s, 1H), 3.35 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=162.3 (d, $J_{C–F}$=244.7 Hz), 154.2, 148.6, 148.4, 147.9, 146.3, 144.6, 133.9 (d, $J_{C–F}$=5.5 Hz), 132.0, 128.8, 124.8, 122.0, 117.2, 116.5 (d, $J_{C–F}$=21.2 Hz), 112.6, 111.6, 109.2, 108.0, 106.7, 105.1, 104.9, 103.8, 54.9, 54.4; IR (UATR): 3442, 1677, 1425 cm^{-1}; MS: *m/z* 472 (28) [M^++H], 471 (00) [M^+], 456 (7), 438 (17), 410 (14), 359 (8), 326 (12), 298 (10); HRMS (APCI-TOF): *m/z calcd* for $C_{27}H_{18}FNO_6+H^+$: 472.1196 [$M+H^+$]; found 472.1195.

89: m.p. 99.7–100.2°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.45–7.24 (m, 5H), 7.12–6.89 (m, 2H), 6.87–6.79 (m, 1H), 6.76 (d, J=8.1 Hz, 1H), 6.67 (d, J=1.6 Hz), 6.57 (dd, J=8.1, 1.6 Hz, 1H), 5.53 (br s, 1H), 5.08 (s, 2H), 3.84 (s, 3H), 3.38 (q, J=6.7 Hz, 2H), 3.36 (s, 2H), 2.63 (t, J=6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=169.9, 150.1 (dd, $J_{C–F}$=248.7, 12.7 Hz), 149.4 (dd, $J_{C–F}$=247.9, 12.6 Hz), 148.5, 148.1, 137.0, 131.7 (dd, $J_{C–F}$=5.7, 4.1 Hz), 130.8, 128.4, 127.8, 127.3, 125.2 (dd, $J_{C–F}$=6.2, 3.7 Hz), 121.3, 118.1 (d, $J_{C–F}$=17.9 Hz), 117.4 (d, $J_{C–F}$=17.2 Hz), 114.7, 111.8, 71.0, 55.9, 42.5, 40.5, 34.6; HRMS (APCI-TOF): *m/z calcd* for $C_{24}H_{23}F_2NO_3+H^+$: 412.1719 [$M+H^+$]; found 412.1726.

109: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.46–7.41 (m, 2H), 7.41–7.28 (m, 8H), 7.28–7.18 (m, 3H), 7.11–7.05 (m, 2H), 7.04–6.91 (m, 2H), 6.90–6.84 (m, 1H), 6.76 (s, 1H), 6.55 (s, 1H), 6.54 (s, 1H), 6.46 (s, 1H), 5.14 (s, 2H), 5.04 (br s, 2H), 4.76 (br s, 2H), 4.69–4.49 (m, 2H), 4.04–3.93 (m, 2H), 3.67 (s, 3H), 3.39 (s, 3H), 2.99 (t, J=6.4 Hz, 2H), 0.83 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.8, 150.5, 149.6 (dd, $J_{C–F}$=221.8, 12.4 Hz), 149.1 (dd, $J_{C–F}$=244.7, 14.4 Hz), 147.9, 147.4, 147.3, 143.6, 137.6, 137.0, 136.93, 132.93, 132.86, 130.8, 128.6, 128.4, 128.2, 127.9, 127.8, 127.5, 127.3, 127.2, 170.0 (dd, $J_{C–F}$=5.8, 3.4 Hz), 126.8, 126.0, 121.0, 119.9, 119.6 (d, $J_{C–F}$=16.6 Hz), 119.3, 117.9, 116.7, 116.0, 113.3, 109.0, 103.0, 71.6, 71.2, 71.0, 59.6, 56.5, 55.3, 42.7, 29.0, 13.7; IR (UATR): 2936, 1686, 1247, 1128 cm^{-1}; MS: *m/z* 807 (32) [M^+], 716 (100), 552 (44); HRMS (APCI-TOF): *m/z calcd* for $C_{50}H_{43}F_2NO_7+H^+$: 808.3080 [$M+H^+$]; found 808.3084.

Lam 13: m.p. > 290.0°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ=9.70 (br s, 1H), 9.49 (br s, 1H), 7.77–7.62 (m, 2H), 7.46–7.38 (m, 1H), 6.81 (s, 1H), 6.78 (s, 1H), 6.44 (s, 2H), 4.72–4.49 (m, 2H), 3.39 (s, 1H), 3.30 (s, 3H), 3.01 (t, J=6.6 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=154.1, 149.8 (dd, $J_{C–F}$=248.2, 12.5 Hz), 149.3 (dd, $J_{C–F}$=247.5, 12.2 Hz), 147.6, 147.3, 147.0, 146.0, 145.6, 144.5, 135.9, 132.8 (dd, $J_{C–F}$=6.5, 4.1 Hz), 128.5 (dd, $J_{C–F}$=5.9, 3.0 Hz), 127.5 127.3, 120.3 (d, $J_{C–F}$=16.3 Hz), 118.5 (d, $J_{C–F}$=16.9 Hz), 117.5, 115.5, 112.6, 111.6, 108.9, 108.2, 104.4, 103.7, 55.0, 54.6, 27.5; IR (UATR): 3537, 3201, 2985, 1685, 1484, 1291 cm^{-1}; MS: *m/z* 491 (100) [M^+], 477 (11); HRMS (APCI-TOF): *m/z calcd* for $C_{27}H_{19}F_2NO_6$+H$^+$: 492.1253 [M+H$^+$]; found 492.1264.

Lam 13-OAc: ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD): δ=7.49–7.33 (m, 4H), 7.00 (s, 1H), 6.33 (s, 2H), 4.89–4.71 (m, 2H), 3.46 (s, 3H), 3.37 (s, 3H), 3.27 (t, J=6.7 Hz, 2H), 2.323 (s, 3H), 2.315 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD): δ=169.1, 169.0, 155.1, 150.8 (dd, $J_{C–F}$=235.5, 15.0 Hz), 150.1 (dd, $J_{C–F}$=240.0, 15.2 Hz), 149.7, 147.6, 144.8, 139.6, 139.0, 135.3, 132.2, 127.7, 126.9, 126.4, 125.1, 122.7, 120.3 (d, $J_{C–F}$=16.4 Hz), 118.2 (d, $J_{C–F}$=17.0 Hz), 115.6, 114.9, 114.1, 112.0, 109.5, 105.1, 55.3, 55.0, 42.3, 27.9, 20.30, 20.27; IR (UATR): 2967, 1762, 1714, 1193, 1149 cm^{-1}; MS: *m/z* 575 (19) [M^+], 533 (32), 491 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{31}H_{23}F_2NO_8$+H$^+$: 576.1465 [M+H$^+$]; found 576.1443.

128: m.p. 269.0–270.7°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.18 (d, J=7.4 Hz, 1H), 7.58–7.41 (m, 3H), 7.39 (s, 1H), 7.11 (s, 1H), 7.06 (s, 1H), 7.01 (d, J=7.4 Hz, 1H), 6.66 (s, 1H), 3.471 (s, 3H), 3.468 (s, 3H), 2.45 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.7, 168.6, 154.8, 151.0, 150.7 (dd, $J_{C–F}$=252.3, 26.5 Hz), 150.6 (dd, $J_{C–F}$=252.6, 26.3 Hz), 147.7, 145.6, 141.1, 140.0, 133.4, 132.7 (dd, $J_{C–F}$=6.0, 4.4 Hz), 128.4 (dd, $J_{C–F}$=5.7, 3.5 Hz), 128.1, 124.1, 123.3, 123.1, 120.99, 120.98 (d, $J_{C–F}$=16.2 Hz), 118.5 (d, $J_{C–F}$=17.0 Hz), 115.3, 112.9, 112.4, 110.4, 109.2, 105.9, 105.8, 55.5, 55.2, 20.58, 20.55; IR (UATR): 2935, 1765, 1708, 1199 cm^{-1}; MS (eV): *m/z* 573 (14) [M^+], 489 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{31}H_{21}F_2NO_8$+H$^+$: 574.1308 [M+H$^+$]; found 574.1310.

Lam 14: m.p. > 290.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=10.02 (s, 1H), 9.90 (s, 1H), 9.00 (d, J=7.4 Hz, 1H), 7.86–7.73 (m, 2H), 7.57–7.51 (m, 1H), 7.23 (d, J=7.4 Hz, 1H), 7.21 (s, 1H), 6.88 (s, 1H), 6.87 (s, 1H), 6.48 (s, 1H), 3.40 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.2, 150.0 (dd, $J_{C–F}$=247.3, 12.9 Hz), 149.6 (dd, $J_{C–F}$=246.9, 12.2 Hz), 148.8, 148.5, 148.0, 146.3, 144.6, 133.8, 132.9, 129.1, 128.8, 124.9, 122.0, 120.9 (d, $J_{C–F}$=16.3 Hz), 118.7 (d, $J_{C–F}$=16.8 Hz), 117.0, 112.7, 111.7, 108.1, 107.8, 106.8, 105.0, 104.8, 103.9, 55.0, 54.5; IR (UATR): 3455, 1680, 1426, 1280, 1165 cm^{-1}; MS: *m/z* 489 (100) [M^+]; HRMS (APCI-TOF): *m/z calcd* for $C_{27}H_{17}F_2NO_6$+H$^+$: 490.1097 [M+H$^+$]; found 490.1106.

90: m.p. 96.8–98.8°C ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.47–7.10 (m, 10H), 6.72 (d, J=8.1 Hz, 1H), 6.62 (s, 1H), 6.45 (d, J=8.1 Hz, 1H), 5.42 (br s, 1H), 5.11 (s, 2H), 3.82 (s, 3H), 3.50 (s, 2H), 3.42 (q, J=6.6 Hz, 2H), 2.65 (t, J=6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=170.8, 149.7, 146.7, 137.2, 134.8, 131.8, 129.3, 128.9, 128.5, 127.7, 127.19, 127.16, 120.5, 114.3, 112.3, 71.1, 55.9, 43.6, 40.6, 35.0; IR (UATR): 3295, 3063, 3031, 2935, 1646, 1513 cm^{-1}; MS: *m/z* 375 (5) [M^+], 240 (100), 137 (21), 91 (86); HRMS (APCI-TOF): *m/z calcd* for $C_{24}H_{25}NO_3$+H$^+$: 376.1907 [M+H$^+$]; found: 376.1907.

110: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.35–7.28 (m, 6H), 7.28–7.18 (m, 8H), 7.15–7.10 (m, 2H), 7.10–7.05 (m, 4H), 6.74 (s, 1H), 6.63 (s, 1H), 6.52 (s, 1H), 6.41 (s, 1H), 5.00 (s, 2H), 4.72 (s, 2H), 4.60 (br s, 2H), 4.53 (s, 2H), 3.99 (q, J=7.1 Hz, 2H), 3.88 (s, 3H), 3.60 (s, 3H), 3.04 (t, J=6.5 Hz, 2H), 0.83 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.0, 150.5, 148.4, 146.9, 146.3, 143.4, 137.8, 137.1, 136.8, 135.8, 131.0, 130.7, 128.4, 128.3, 128.2, 128.1, 127.7, 127.6, 127.34, 127.30, 127.2, 126.9, 126.4, 126.2, 71.8, 71.1, 70.0, 59.6, 56.4, 56.0, 42.7, 29.1, 13.7; IR (UATR): 2935, 1686, 1454, 1206 cm^{-1}; MS: *m/z* 771 (51) [M^+], 680 (100), 516 (89); HRMS (APCI-TOF): *m/z calcd* for $C_{50}H_{45}NO_7$+H$^+$: 772.3269 [M+H$^+$]; found: 772.3260.

Lam 15: m.p. 286.0–287.5°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.67 (s, 1H), 8.76 (s, 1H), 7.63–7.51 (m, 3H), 7.48–7.43 (m, 2H), 6.94 (s, 1H), 6.77 (s, 1H), 6.45 (s, 1H), 6.29 (s, 1H), 4.62 (t, J=6.6 Hz, 2H), 3.78 (s, 3H), 3.24 (s, 3H), 3.05 (t, J=6.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.3, 148.1, 146.8, 145.6, 144.7, 144.5, 135.3, 135.0, 130.9, 129.5, 128.3, 127.7, 127.5, 119.5, 114.5, 112.73, 112.67, 111.9, 108.6, 104.6, 103.6, 55.7, 54.9, 42.1, 27.9; IR (UATR): 3334, 1675, 1584, 1103 cm^{-1}; MS: *m/z* 455 (100) [M^+]; HRMS (APCI-TOF): *m/z calcd* for $C_{27}H_{21}NO_6$+H$^+$: 456.1442 [M+H$^+$]; found: 456.1447.

Lam 15-OAc: m.p. 241.6–243.6°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.58–7.52 (m, 2H), 7.52–7.46 (m, 3H), 7.07 (s, 1H), 6.87 (s, 1H), 6.65 (s, 1H), 6.60 (s, 1H), 4.83 (t, J=6.7 Hz, 2H), 3.84 (s, 3H), 3.33 (s, 3H), 3.18 (t, J=6.7 Hz, 2H), 2.30 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.8, 155.2, 151.0, 147.4, 144.9, 138.7, 138.3, 134.9, 134.7, 133.0, 131.0, 129.4, 128.3, 127.1, 120.3, 120.2, 116.24, 116.16, 114.6, 112.1, 111.8, 105.6, 55.9, 55.4, 42.1, 29.3, 20.6, 20.5; IR (UATR): 2940, 1765, 1709, 1412, 1197 cm^{-1}; MS: *m/z* 539 (25)

[M^+], 497 (90), 455 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{31}H_{25}NO_8$+H$^+$: 540.1653 [M+H$^+$]; found: 540.1652.

129: m.p. 226.0–226.9°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.28 (d, J=7.4 Hz, 1H), 7.66–7.54 (m, 5H), 7.21 (s, 1H), 7.16 (s, 1H), 7.13 (s, 1H), 7.07 (d, J=7.4 Hz, 1H), 6.61 (s, 1H), 3.92 (s, 3H), 3.34 (s, 3H), 2.31 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.7, 155.0, 151.6, 147.5, 145.5, 140.0, 139.6, 135.0, 133.6, 131.3, 129.8, 129.3, 128.64, 128.58, 124.7, 118.7, 118.3, 115.8, 112.64, 112.59, 112.0, 108.7, 108.6, 106.2, 56.0, 55.3, 20.6, 20.5; IR (UATR): 2940, 1767, 1710, 1476, 1276 cm^{-1}; MS: *m/z* 537 (23) [M^+], 495 (41), 453 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{31}H_{23}NO_8$+H$^+$: 538.1496 [M+H$^+$]; found: 538.1499.

Lam 16: m.p. > 290.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.82 (br s, 1H), 9.52 (br s, 1H), 9.01 (d, J=7.4 Hz, 1H), 7.70–7.59 (m, 3H), 7.57–7.52 (m, 2H), 7.36 (s, 1H), 7.25 (d, J=7.4 Hz, 1H), 6.94 (s, 1H), 6.83 (s, 1H), 6.30 (s, 1H), 3.88 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.3, 149.6, 147.7, 147.2, 146.2, 144.5, 135.2, 133.2, 131.2, 129.7, 128.8, 128.6, 123.7, 121.4, 118.7, 113.1, 111.0, 108.9, 108.4, 108.1, 106.7, 105.2, 103.8, 55.7, 54.9; IR (UATR): 3457, 1693, 1403, 1143 cm^{-1}; MS: *m/z* 453 (100) [M^+]; HRMS (APCI-TOF): *m/z calcd* for $C_{27}H_{19}NO_6$+H$^+$: 454.1285 [M+H$^+$]; found: 454.1287.

91: m.p. 112.4–113.4°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.45–7.27 (m, 10H), 7.05 (d, J=8.6 Hz, 2H), 6.89 (d, J=8.6 Hz, 2H), 6.73 (d, J=8.1 Hz, 1H), 6.63 (d, J=1.8 Hz, 1H), 6.47 (dd, J=8.1, 1.8 Hz, 1H), 5.38 (br s, 1H), 5.10 (s, 1H), 5.04 (s, 1H), 3.82 (s, 3H), 3.45 (s, 2H), 3.42 (q, J=6.6 Hz, 2H), 2.65 (t, J=6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.3, 158.0, 149.8, 146.8, 137.2, 136.8, 131.8, 130.5, 128.6, 128.5, 128.0, 127.8, 127.4, 127.2, 127.0, 120.6, 115.3, 114.3, 112.4, 71.1, 70.0, 55.9, 42.9, 40.6, 35.0; HRMS (M): *m/z calcd* for $C_{31}H_{31}NO_4$+H$^+$: 482.2326 [M+H$^+$]; found: 482.2331.

111: ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.39–7.11 (m, 16H), 7.09–6.93 (m, 6H), 6.82 (d, J=8.1 Hz, 2H), 6.70 (s, 1H), 6.63 (s, 1H), 6.51 (s, 1H), 6.39 (s, 1H), 4.98 (s, 2H), 4.70 (s, 2H), 4.53 (br s, 4H), 3.95 (q, J=7.0 Hz, 2H), 3.84 (s, 3H), 3.59 (s, 3H), 2.99 (br t, J=6.2 Hz), 0.79 (t, J=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=162.0, 157.6, 150.7, 148.5, 147.1, 146.5, 143.6, 137.9, 137.2, 137.0, 136.9, 132.0, 130.8, 128.5, 128.4, 128.3, 128.2, 127.9, 127.7, 127.6, 127.4, 127.3, 127.1, 126.9, 126.2, 121.6, 121.2, 119.2, 118.9, 116.5, 114.6, 111.4, 110.9, 103.5, 71.8, 71.3, 70.2, 70.0, 59.5, 56.5, 56.1, 42.7, 29.2, 13.7; HRMS (ESI-TOF): *m/z calcd* for $C_{57}H_{51}NO_8$+H$^+$: 878.3687 [M+H$^+$]; found: 878.3692.

Lam 17: m.p. > 290.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.76 (br s, 1H), 9.71 (br s, 1H), 8.81 (br s, 1H), 7.21 (d, J=8.4 Hz, 2H), 6.99 (d, J=8.4 Hz, 2H), 6.92 (s, 1H), 6.77 (s, 1H), 6.57 (s, 1H), 6.44 (s, 1H), 4.59 (br t, J=6.5 Hz, 2H), 3.78 (s, 3H), 3.34 (s, 3H), 3.04 (br t, J=6.5 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=157.4, 154.4, 148.1, 146.8, 145.7, 144.8, 144.5, 135.6, 132.0, 127.9, 125.4, 125.0, 119.8, 116.3, 114.7, 112.8, 112.6, 112.0, 108.9, 105.0, 103.7, 55.7, 55.1, 42.1, 28.0; IR (UATR): 3385, 2933, 1664 (C=O), 1418, 1404, 1264, 1194 cm^{-1}; HRMS (APCI-TOF): *m/z calcd* for $C_{27}H_{21}NO_7$+H$^+$: 472.1391 [M+H$^+$]; found: 472.1396.

Lam 17-OAc: m.p. 270.6–272.6°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.49 (d, J=8.5 Hz, 2H), 7.25 (d, J=8.5 Hz, 2H), 7.08 (s, 1H), 6.87 (s, 1H), 6.65 (s, 1H), 6.64 (s, 1H), 4.83 (t, J=6.6 Hz, 2H), 3.84 (s, 3H), 3.41 (s, 3H), 3.17 (t, J=6.6 Hz, 2H), 2.35 (s, 3H), 2.30 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=169.1, 168.9, 168.7, 155.1, 151.1, 150.8, 147.6, 144.9, 138.8, 138.4, 135.0, 133.0, 132.4, 132.1, 127.3, 123.0, 120.2, 120.1, 116.1, 115.1, 114.7, 112.2, 111.9, 105.4, 56.0, 55.7, 42.1, 29.3, 21.1, 20.6, 20.5; HRMS (ESI-TOF): *m/z calcd* for $C_{33}H_{27}NO_{10}$+H$^+$: 598.1708 [M+H$^+$]; found: 598.1694.

130: m.p. 285.9–287.5°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.22 (d, J=7.4 Hz, 1H), 7.55 (d, J=8.5 Hz, 2H), 7.32 (d, J=8.5 Hz, 2H), 7.18 (s, 1H), 7.13 (s, 1H), 7.11 (s, 1H), 7.02 (d, J=7.4 Hz, 1H), 6.64 (s, 1H), 3.90 (s, 3H), 3.42 (s, 3H), 2.38 (s, 3H), 2.31 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=169.1, 168.7, 168.6, 154.9, 151.7, 151.1, 147.6, 145.4, 140.0, 139.6, 133.7, 132.5, 132.4, 129.3, 128.6, 124.5, 123.3, 118.4, 118.2, 115.6, 112.6, 112.0, 111.4, 108.73, 108.67, 106.0, 55.9, 55.7, 21.0, 20.54, 20.49; HRMS (ESI-TOF): *m/z calcd* for $C_{33}H_{25}NO_{10}$+H$^+$: 596.1551 [M+H$^+$]; found: 596.1528.

Lam 18: ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.79 (s, 1H), 9.77 (s, 1H), 9.55 (s, 1H), 9.00 (d, J=7.4 Hz, 1H), 7.35 (s, 1H), 7.31 (d, J=8.4 Hz, 2H), 7.23 (d, J=7.4 Hz, 1H), 7.09 (s, 1H), 7.04, (d, J=8.4 Hz, 2H), 6.83 (s, 1H), 6.47 (s, 1H), 3.89 (s, 3H), 3.35 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=157.6, 154.3, 149.5, 147.6, 147.1, 146.2, 144.5, 133.5, 132.1, 129.1, 124.9, 123.6, 121.3, 118.9, 116.5, 112.9, 111.2, 109.0, 108.3, 106.5, 105.5, 103.7, 55.6, 55.0; HRMS (ESI-TOF): *m/z calcd* for $C_{27}H_{19}NO_7$+H$^+$: 470.1234 [M+H$^+$]; found: 470.1234.

112: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.34–7.14 (m, 13H), 7.15–7.08 (m, 2H), 6.72 (s, 1H), 6.56 (s, 1H), 6.54 (s, 1H), 6.42 (s, 1H), 5.01 (s, 2H), 4.75 (s, 2H), 4.63 (br s, 2H), 4.00 (q, *J*=7.1 Hz, 2H), 3.87 (s, 3H), 3.61 (s, 3H), 3.27 (s, 3H), 3.05 (t, *J*=6.6 Hz, 2H), 0.84 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.0, 150.6, 147.8, 147.1, 146.9, 143.4, 137.9, 137.1, 135.8, 131.0, 130.8, 128.4, 128.2, 128.1, 127.7, 127.35, 127.29, 126.9, 126.4, 125.7, 122.0, 119.2, 118.5, 116.1, 110.6, 108.7, 103.2, 71.8, 71.1, 59.6, 56.3, 55.8, 55.0, 42.8, 29.1, 13.7; IR (UATR): 2936, 1684, 1609 cm^{-1}; MS: *m/z* 695 (17) [M^+], 604 (72), 513 (26), 440 (100), 91 (20); HRMS (APCI-TOF): *m/z calcd* for $C_{44}H_{41}NO_7+H^+$: 696.2956 [*M*+H$^+$]; found: 696.2936.

Lam 19: m.p. 281.9–282.9°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.69 (s, 1H), 7.64–7.58 (m, 2H), 7.56–7.52 (m, 1H), 7.52–7.48 (m, 2H), 6.97 (s, 1H), 6.78 (s, 1H), 6.48 (s, 1H), 6.44 (s, 1H), 4.63 (t, *J*=6.6 Hz, 2H), 3.75 (s, 3H), 3.26 (s, 3H), 3.12 (s, 3H), 3.09 (t, *J*=6.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.3, 148.9, 146.94, 146.88, 145.6, 144.5, 135.3, 135.2, 131.0, 129.4, 128.2, 127.3, 127.0, 119.1, 114.4, 112.7, 111.8, 108.5, 108.4, 104.6, 103.7, 55.6, 54.9, 54.3, 42.0, 27.7; IR (UATR): 3326 (br), 1672 cm^{-1}; MS: *m/z* 470 (30) [M^++H], 469 (100) [M^+], 454 (14), 394 (12); HRMS (APCI-TOF): *m/z calcd* for $C_{28}H_{23}NO_6+H^+$: 470.1598 [*M*+H$^+$]; found: 470.1610.

Lam 19-OAc: m.p. 255.3–256.4°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.60–7.52 (m, 4H), 7.51–7.46 (m, 1H), 7.08 (s, 1H), 6.76 (s, 1H), 6.66 (s, 1H), 6.58 (s, 1H), 4.82 (t, *J*=6.8 Hz, 2H), 3.87 (s, 3H), 3.34 (s, 3H), 3.28 (s, 3H), 3.13 (t, *J*=6.8 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.8, 155.2, 149.0, 147.43, 147.4, 144.9, 138.7, 135.8, 135.6, 131.3, 129.3, 128.2, 127.1, 126.5, 119.8, 116.3, 115.6, 144.4, 111.8, 110.9, 108.6, 105.5, 55.9, 55.3, 55.0, 42.4, 28.6, 20.6; IR (UATR): 2936, 1770, 1709 cm^{-1}; MS: *m/z* 512 (8) [M^++H], 511 (25) [M^+], 469 (100), 455 (9), 394 (8); HRMS (APCI-TOF): *m/z calcd* for $C_{30}H_{25}NO_7+H^+$: 512.1704 [*M*+H$^+$]; found: 512.1690.

131: m.p. 281.2–282.8°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.21 (d, J=7.5 Hz, 1H), 7.67–7.61 (m, 4H), 7.60–7.53 (m, 1H), 7.13 (s, 1H), 7.06 (s, 1H), 7.04 (d, *J*=7.5 Hz, 1H), 7.03 (s, 1H), 6.70 (s, 1H), 3.97 (s, 3H), 3.39 (s, 3H), 3.35 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.7, 155.0, 150.1, 149.2, 147.4, 145.5, 139.5, 135.9, 134.1, 131.8, 129.5, 128.5, 128.2, 124.7, 123.1, 119.0, 116.0, 112.8, 112.0, 111.7, 108.3, 107.4, 106.2, 105.2, 55.9, 55.3, 55.1, 20.6; IR (UATR): 2937, 2836, 1770, 1708, 1615, 1512, 1480, 1429, 1414 cm^{-1}; MS: *m/z* 510 (9) [M^++H], 509 (31) [M^+], 467 (100), 434 (9), 420 (12), 406 (11); HRMS (APCI-TOF): *m/z calcd* for $C_{30}H_{23}NO_7+H^+$: 510.1547 [*M*+H$^+$]; found: 510.1547.

Lam 20: m.p. dec. 280.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.89 (s, 1H), 9.01 (d, *J*=7.4 Hz, 1H), 7.69–7.56 (m, 5H), 7.35 (s, 1H), 7.25 (d, *J*=7.4 Hz, 1H), 6.90 (s, 1H), 6.86 (s, 1H), 6.47 (s, 1H), 3.84 (s, 3H), 3.26 (s, 3H), 3.22 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.3, 150.0, 149.0, 147.9, 146.3, 144.6, 135.3, 133.4, 131.5, 129.6, 128.64, 128.57, 124.4, 122.2, 118.1, 112.7, 110.7, 108.2, 108.0, 106.8, 105.2, 104.5, 103.8, 55.6, 54.8, 54.3; IR (UATR): 1673, 1511, 1453, 1429, 1269, 1166, 1086, 1048 cm^{-1}; MS: *m/z* 468 (29) [M^++H], 467 (100) [M^+], 452 (3), 434 (12), 420 (14), 406 (14); HRMS (APCI-TOF): *m/z calcd* for $C_{28}H_{21}NO_6+H^+$: 468.1442 [*M*+H$^+$]; found: 468.1450.

93: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.50–7.23 (m, 8H), 7.15–7.10 (m, 2H), 6.69 (d, *J*=8.5 Hz, 1H), 6.58 (d, *J*=8.5 Hz, 1H), 5.72 (br s, 1H), 5.00 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.41 (s, 2H), 3.31 (q, *J*=6.4 Hz, 2H), 2.61 (t, *J*=6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.9, 152.5, 150.5, 142.3, 137.5, 135.0, 129.4, 128.8, 128.5, 128.3, 128.1, 127.1, 124.5, 107.6, 75.3, 60.8, 56.0, 43.8, 40.6, 29.5; IR (UATR): 3278, 2936, 1646, 1494, 1097 cm^{-1}; MS: *m/z* 405 (18) [M^+], 270 (100), 91 (48); HRMS (APCI-TOF): *m/z calcd* for $C_{25}H_{27}NO_4+H^+$: 406.2013 [*M*+H$^+$]; found 406.2015.

113: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.45–7.13 (m, 18H), 7.11–7.07 (m, 2H), 6.53 (s, 1H), 6.42 (s, 1H), 6.38 (s, 1H), 5.08 (s, 2H), 5.00 (s, 2H), 4.78 (s, 2H), 4.41 (br s, 2H), 3.99 (q, *J*=7.1 Hz, 2H), 3.88 (s, 3H), 3.60 (s, 3H), 3.26 (s, 3H), 2.92 (br s, 2H), 0.83 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=188.0, 161.9, 151.5, 150.6, 148.9, 146.9, 143.4, 141.2, 137.8, 137.3, 137.1, 135.8, 130.9, 130.3, 128.6, 128.5, 128.4, 128.2, 128.1, 127.7, 127.4, 127.3, 126.9, 126.5, 124.0, 122.7, 119.8, 119.5, 118.4, 116.1, 105.3, 103.2, 75.4, 71.8, 71.1, 61.0, 59.6, 56.4, 55.0, 42.5, 22.6, 13.7; IR (UATR): 2935, 1687, 1413, 1263 cm^{-1}; MS: *m/z* 801 (41) [M^+], 710 (100), 546 (84), 454 (56), 426 (59), 91 (61); HRMS (APCI-TOF): *m/z calcd* for $C_{51}H_{47}NO_8+H^+$: 802.3374 [*M*+H$^+$]; found 802.3377.

Lam 21: m.p. 287.0–288.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.66 (br s, 1H), 9.24 (br s, 1H), 7.63–7.57 (m, 2H), 7.56–7.46 (m, 3H), 6.78 (s, 1H), 6.40 (s, 1H), 6.14 (s, 1H), 4.60 (t, *J*=6.8 Hz, 2H), 3.64 (s, 3H), 3.24 (s, 3H), 3.14 (s, 3H), 3.01 (t, *J*=6.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.3, 150.8, 147.4, 146.9, 145.6, 144.5, 136.4, 135.3, 135.1, 131.0, 129.4, 128.1, 127.2, 122.2, 115.1, 114.4, 112.8, 108.5, 104.6, 103.7, 100.8, 60.3, 54.8, 54.5, 41.7, 21.2; IR (UATR): 3490, 3282, 2937, 1676, 1425, 1164 cm^{-1}; MS: *m/z* 485 (100) [M^+], 470 (63); HRMS (APCI-TOF): *m/z calcd* for $C_{28}H_{23}NO_7+H^+$: 486.1547 [*M*+H$^+$]; found 486.1545.

Lam 21-OAc: m.p. 266.0–268.0°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.61–7.47 (m, 5H), 7.08 (s, 1H), 6.62 (s, 1H), 6.59 (s, 1H), 4.78 (t, *J*=4.7 Hz, 2H), 3.80 (s, 3H), 3.33 (s, 3H), 3.26 (s, 3H), 2.98 (t, *J*=6.7 Hz, 2H), 2.40 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.8, 168.7, 115.1, 151.6, 147.4, 144.9, 141.6, 141.0, 138.8, 135.4, 134.8, 131.2, 129.4, 128.3, 127.1, 122.8, 119.3, 116.5, 116.2, 114.8, 111.8, 107.6, 105.5, 60.7, 55.3, 55.0, 41.8, 22.2, 20.6, 20.5; IR (UATR): 2928, 1762, 1713, 1420, 1194 cm^{-1}; MS: *m/z* 569 (27) [M^+], 527 (100), 485 (82), 470 (62); HRMS (APCI-TOF): *m/z calcd* for $C_{32}H_{27}NO_9+H^+$: 570.1759 [*M*+H$^+$]; found 570.1746.

132: m.p. 281.0–282.5°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.21 (d, *J*=7.6 Hz, 1H), 7.69–7.55 (m, 5H), 7.13 (s, 1H), 7.06 (d, *J*=7.6 Hz, 1H), 7.02 (s, 1H), 6.69 (s, 1H), 3.88 (s, 3H), 3.37 (s, 3H), 3.35 (s, 3H), 2.49 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.8, 168.6, 155.0, 152.9, 147.5, 145.5, 141.7, 139.6, 139.0, 135.6, 133.1, 131.7, 129.6, 128.7, 128.3, 123.4, 121.1, 118.2, 115.8, 112.9, 112.1, 108.9, 106.4, 106.2, 104.2, 60.8, 55.3, 50.0, 20.6; IR (UATR): 2925, 1769, 1712, 1419, 1192 cm^{-1}; MS: *m/z* 567 (19) [M^+], 525 (32), 483 (100), 436 (18); HRMS (APCI-TOF): *m/z calcd* for $C_{32}H_{25}NO_9+H^+$: 568.1602 [*M*+H$^+$]; found 568.1593.

Lam 22: m.p. 275.0–276.5°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ=9.91 (s, 1H), 9.83 (s, 1H), 9.01 (d, *J*=7.5 Hz, 1H), 7.75–7.59 (m, 5H), 7.47 (d, *J*=7.5 Hz, 1H), 6.87 (s, 1H), 6.59 (s, 1H), 6.50 (s, 1H), 3.72 (s, 3H), 3.28 (s, 3H), 3.27 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=154.3, 152.8, 147.8, 146.2, 145.7, 144.6, 135.8, 135.3, 132.9, 131.4, 129.5, 128.5, 120.9, 120.6, 114.8, 111.7, 108.0, 107.6, 107.1, 105.2, 103.8, 97.1, 60.5, 54.8, 54.5; IR (UATR): 3221, 2923, 1679, 1422, 1239 cm^{-1}; MS: *m/z* 483 (100) [M^+], 436 (32); HRMS (APCI-TOF): *m/z calcd* for $C_{28}H_{21}NO_7+H^+$: 484.1391 [*M*+H$^+$]; found 484.1392.

94: ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.47–7.14 (m, 11H), 6.92–6.52 (m, 5H), 5.71 (br s, 1H), 5.01 (s, 4H), 3.85 (s, 3H), 3.81 (s, 3H), 3.40 (s, 2H), 3.31 (q, *J*=6.6 Hz, 2H), 2.59 (t, *J*=6.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=170.6, 159.0, 152.5, 150.4, 137.4, 136.7, 136.4, 129.8, 128.5, 128.4, 128.2, 128.1, 127.9, 127.4, 125.0, 124.4, 121.9, 115.8, 113.4, 107.4, 75.2, 69.8, 60.8, 55.9, 43.8, 40.6, 29.4; IR (UATR): 3300, 2936, 1648, 1600, 1494, 1258, 1100 cm^{-1}; MS: *m/z* 511 (17) [M^+], 270 (40), 180 (96), 91 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{32}H_{33}NO_5+H^+$: 512.2431 [*M*+H$^+$]; found: 512.2434.

114: ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.49–7.02 (m, 21H), 6.86–6.73 (m, 3H), 6.55 (s, 1H), 6.45 (s, 1H), 6.43 (s, 1H), 5.08 (s, 2H), 5.01 (s, 2H), 4.82 (s, 2H), 4.75 (s, 2H), 4.39 (br s, 2H), 3.95 (q *J*=7.4 Hz, 2H), 3.89 (s, 1H), 3.61 (s, 3H), 3.27 (s, 3H), 2.91 (br s, 2H), 0.82 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=161.9, 158.6, 151.6, 150.7, 148.9, 147.2, 143.6, 141.3, 137.9, 137.4, 137.3, 137.2, 137.0, 130.4, 129.0, 128.6, 128.5, 128.4, 128.2, 128.1, 127.8, 127.7, 127.32, 127.28, 126.8, 123.9, 123.8, 122.5, 119.8, 119.6, 118.6, 117.1, 116.3, 113.6, 109.4, 105.4, 103.2, 100.4, 75.4, 71.8, 71.3, 69.9, 60.9, 59.6, 56.5, 55.1, 42.5, 22.6, 13.7; IR (UATR): 2935, 1687, 1413, 1250 cm^{-1}; MS: *m/z* 907 (4) [M^+], 91 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{58}H_{53}NO_9+H^+$: 908.3793 [*M*+H$^+$]; found: 908.3783.

Lam 23: m.p. dec. 250°C;^{1}H NMR (300 MHz, DMSO-d_6): δ=9.65 (s, 2H), 9.21 (s, 1H), 7.42 (t, *J*=7.4 Hz, 1H), 6.98–6.89 (m, 2H), 6.87 (s, 1H), 6.80 (s, 1H), 6.60 (s, 1H), 6.33 (s, 1H), 4.75–4.62 (m, 1H), 4.59–4.47 (m, 1H), 4.59–4.47 (m, 1H), 3.66 (s, 3H), 3.35 (s, 3H), 3.26 (s, 3H), 3.10–2.93 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=158.3, 154.3, 150.8, 147.3, 146.9, 145.6, 144.5, 136.5, 136.3, 134.9, 130.5, 127.1, 122.2, 121.3, 117.4, 115.2, 115.0, 114.4, 112.8, 108.5, 104.9, 103.6, 100.9, 60.3, 54.9, 54.6, 41.7, 21.2; IR (UATR): 3497, 1713, 1667, 1450 cm^{-1}; MS: *m/z* 501 (100) [M^+], 486 (43); HRMS (APCI-TOF): *m/z calcd* for $C_{28}H_{23}NO_8+H^+$: 502.1496 [*M*+H$^+$]; found: 502.1501.

Lam 23-OAc: m.p. 230.0–232.7°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.66–7.54 (m, 1H), 7.46–7.37 (m, 1H), 7.31–7.18 (m, 2H), 7.08 (s, 1H), 6.63 (s, 1H), 6.57 (s, 1H), 4.93–4.62 (m, 2H), 3.81 (s, 3H), 3.41 (s, 3H), 3.35 (s, 3H), 2.98 (t, *J*=6.6 Hz, 2H), 2.40 (s, 3H), 2.31 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=169.1, 168.7, 168.6, 155.0, 151.8, 151.7, 147.6, 144.9, 141.6, 141.2, 139.0, 137.0, 134.9, 130.3, 128.6, 127.0, 124.5, 122.5, 121.9, 115.9, 115.2, 114.8, 111.9, 107.6, 105.5, 60.7, 55.4, 55.2, 22.2, 20.9, 20.5, 20.4; IR (UATR): 2942, 1767, 1716, 1420, 1195 cm^{-1}; MS: *m/z* 627 (48) [M^+], 585 (100), 543 (50); HRMS (APCI-TOF): *m/z calcd* for $C_{34}H_{29}NO_{11}+H^+$: 628.1813 [*M*+H$^+$]; found: 628.1804.

133: m.p. 225.0–226.1°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=9.21 (d, *J*=8.0 Hz, 1H), 7.75–7.63 (m, 1H), 7.56–7.46 (m, 1H), 7.40–7.24 (m, 2H), 7.13 (s, 1H), 7.07 (d, *J*=8.0 Hz, 1H), 7.01 (s, 1H), 6.69 (s, 1H), 3.88 (s, 3H), 3.46 (s, 3H), 3.43 (s, 3H), 2.49 (s, 3H), 2.32 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=169.2, 168.8, 168.7, 154.9, 153.1, 147.6, 145.4, 141.8, 139.7, 138.9, 137.2, 133.1, 130.5, 129.0, 128.3, 125.0, 123.3, 122.3, 120.9, 118.2, 115.5, 112.1, 111.6, 108.9, 106.6, 106.0, 104.0, 60.8, 55.4, 55.2, 20.9, 20.5; IR (UATR): 2943, 1767, 1713, 1424, 1190 cm^{-1}; MS: *m/z* 625 (54) [M^+], 583 (58), 541 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{34}H_{27}NO_{11}+H^+$: 626.1657 [M+H$^+$]; found: 626.1652.

Lam 24: m.p. dec. 240.0°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ=9.92 (br s, 1H), 9.87 (br s, 1H), 9.77 (s, 1H), 9.01 (d, *J*=7.5 Hz, 1H), 7.51 (t, *J*=7.4 Hz, 1H), 7.47 (d, *J*=7.5 Hz, 1H), 7.06 (d, J=7.4 Hz, 1H), 7.01 (br d, *J*=7.4 Hz, 1H), 7.00 (s, 1H), 6.88 (s, 1H), 6.77 (s, 1H), 6.70 (s, 1H), 3.73 (s, 3H), 3.37 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=158.4, 154.3, 152.8, 147.8, 146.2, 145.6, 144.6, 136.3, 135.8, 132.9, 130.6, 128.4, 121.7, 121.0, 120.6, 117.8, 115.4, 114.8, 111.8, 108.0, 107.5, 107.0, 105.5, 103.8, 97.2, 60.5, 54.9, 54.6; IR (UATR): 3367, 1668, 1587, 1430, 1276 cm^{-1}; MS: *m/z* 499 (100) [M^+]; HRMS (APCI-TOF): *m/z calcd* for $C_{28}H_{21}NO_8+H^+$: 500.1340 [M+H$^+$]; found: 500.1343.

95: ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.45–7.10 (m, 6H), 6.90–6.49 (m, 5H), 5.66 (br s, 1H), 5.01 (s, 2H), 3.87 (s, 6H), 3.77 (s, 3H), 3.41 (s, 2H), 3.31 (q, *J*=6.3 Hz, 2H), 2.60 (t, *J*=6.3 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=170.7, 159.9, 152.6, 150.6, 142.4, 137.6, 136.5, 129.8, 128.5, 128.3, 128.1, 125.1, 124.5, 121.7, 115.0, 112.7, 107.7, 75.3, 60.8, 56.0, 55.2, 43.9, 40.5, 29.6; IR (UATR): 3301, 2937, 1646 (C=O), 1600, 1492, 1257, 1098 cm^{-1}; MS: *m/z* 435 (24) [M^+], 270 (48), 180 (100), 91 (66); HRMS (APCI-TOF): *m/z calcd* for $C_{26}H_{29}NO_5+H^+$: 436.2118 [M+H$^+$]; found: 436.2127.

115: ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.47–7.03 (m, 20H), 6.85–6.65 (m, 4H), 6.56 (s, 1H), 6.48 (s, 1H), 6.43 (s, 1H), 5.08 (s, 2H), 5.01 (s, 2H), 4.75 (s, 2H), 4.41 (br s, 2H), 3.99 (q, *J*=7.1 Hz, 2H), 3.89 (s, 3H), 3.62 (s, 3H), 3.57 (s, 3H), 3.31 (s, 3H), 2.92 (br s, 2H), 0.83 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=161.9, 159.4, 151.5, 150.6, 148.8, 147.0, 143.5, 141.3, 137.8, 137.3, 137.1, 130.3, 128.9, 128.6, 128.5, 128.46, 128.41, 128.2, 128.1, 127.7, 127.3, 127.2, 126.8, 123.9, 123.5, 122.5, 119.8, 119.5, 118.6, 116.2, 115.9, 112.7, 105.4, 103.2, 75.4, 71.7, 71.2, 60.9, 59.6, 56.5, 55.1, 55.0, 42.5, 22.6, 13.7; HRMS (ESI-TOF): *m/z calcd* for $C_{52}H_{49}NO_9+H^+$: 832.3480 [M+H$^+$]; found: 832.3470.

Lam 25: m.p. 241.5–242.4°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.72 (br s, 1H), 9.26 (br s, 1H), 7.53 (t, *J*=7.9 Hz, 1H), 7.13–7.04 (m, 3H), 6.79 (s, 1H), 6.48 (s, 1H), 6.25 (s, 1H), 4.60 (dt, *J*=131.1, 6.9 Hz, 2H), 3.76 (s, 3H), 3.64 (s, 3H), 3.29 (s, 3H), 3.20 (s, 3H), 3.10 (t, *J*=6.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=160.2, 154.3, 150.9, 147.3, 146.9, 145.7, 144.6, 136.6, 136.5, 135.1, 130.6, 127.3, 123.1, 122.4, 116.0, 115.1, 114.2, 114.0, 112.8, 108.5, 104.8, 103.7, 100.8, 60.3, 55.5, 54.9, 54.6, 41.8, 21.3; IR (UATR): 3442, 3384, 1709 (C=O), 1593, 1146, 1036 cm^{-1}; MS: *m/z* 515 (100) [M^+], 500 (46), 468 (16); HRMS (APCI-TOF): *m/z calcd* for $C_{29}H_{25}NO_8+H^+$: 516.1653 [M+H$^+$]; found: 516.1660.

Lam 25-OAc: m.p. 223.6–225.7°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.57–7.44 (m, 1H), 7.15 (d, *J*=7.4 Hz, 1H), 7.15–6.99 (m, 3H), 6.69 (s, 1H), 6.68 (s, 1H), 4.97–4.59 (m, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.38 (s, 3H), 3.32 (s, 3H), 2.99 (t, *J*=6.9 Hz, 2H), 2.41 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=168.72, 168.67, 160.6, 155.1, 151.7, 147.5, 145.0, 141.6, 141.2, 138.9, 136.7, 134.7, 130.5, 127.0, 123.4, 122.8, 119.3, 116.4, 116.1, 115.8, 114.8, 114.5, 111.8, 107.7, 105.7, 60.8, 55.5, 55.4, 55.1, 41.9, 22.3, 20.5, 20.4; IR (UATR): 2942, 1740, 1716, 1420, 1196 cm^{-1}; MS: *m/z* 599 (48) [M^+], 557 (100), 515 (56); HRMS (APCI-TOF): *m/z calcd* for $C_{33}H_{29}NO_{10}+H^+$: 600.1864 [M+H$^+$]; found: 600.1853.

134: m.p. 233.0–234.0°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=9.22 (d, *J*=7.4 Hz, 1H), 7.58 (t, *J*=7.2 Hz, 1H), 7.24 (d, *J*=7.4 Hz, 1H), 7.19–7.00 (m, 5H), 6.08 (s, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.43 (s, 3H), 3.40 (s, 3H), 2.50 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=168.7, 168.6, 160.8, 155.0, 153.0, 147.6, 145.6, 141.8, 139.8, 139.0, 137.0, 133.1, 132.8, 130.7, 128.3, 123.7, 123.5, 121.1, 118.3, 116.1, 115.8, 114.9, 112.9, 112.1, 106.5, 106.4, 104.3, 60.8, 55.5, 55.4, 55.1, 20.5; HRMS (ESI-TOF): *m/z calcd* for $C_{33}H_{27}NO_8+H^+$:598.1708 [M+H$^+$]; found: 598.1728.

Lam 26: m.p. 246.3–247.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.94 (br s, 1H), 9.91 (br s, 1H), 9.00–8.95 (m, 1H), 7.63–7.55 (m, 1H), 7.45 (dd, *J*=7.5, 2.1 Hz, 1H), 7.20–7.15 (m, 3H), 6.86 (s, 1H), 6.65 (s, 1H), 6.57 (s, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.31 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=159.9, 154.0, 152.5, 147.5, 145.9, 145.4, 144.3, 136.3, 135.5, 132.6, 130.3, 128.1, 123.1, 120.6, 120.3, 115.9, 114.6, 114.4, 111.3, 107.6, 107.2, 106.7, 105.0, 103.4, 96.8, 60.2, 55.1, 54.5, 54.2; IR (UATR): 3346, 1703 (C=O), 1433, 1144, 1040 cm^{-1}; MS: *m/z* 513 (100) [M^+], 466 (20); HRMS (APCI-TOF): *m/z calcd* for $C_{29}H_{23}NO_8+H^+$: 514.1496 [M+H$^+$]; found: 514.1502.

96: ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.51–7.28 (m, 10H), 7.04 (d, *J*=8.0 Hz, 2H), 6.88 (d, *J*=8.0 Hz, 2H), 6.71 (d, *J*=8.4 Hz, 1H), 6.58 (d, *J*=8.4 Hz, 1H), 5.67 (br s, 1H), 5.04 (s, 2H), 5.01 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.37 (s, 2H), 3.32 (q, *J*=6.5 Hz, 2H), 2.61 (t, *J*=6.5 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=171.2, 157.9, 152.6, 150.6, 142.4, 137.6, 136.9, 130.5, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.4, 127.3, 125.2, 124.5, 115.2, 107.7, 75.3, 70.1, 60.8, 56.0, 43.0, 40.5, 29.6; IR (UATR): 3302, 2935, 1646 (C=O), 1509 (C=O), 1238, 1098 cm^{-1}; MS: *m/z* 512 (13) [M^+], 270 (70), 180 (100), 91 (61); HRMS (APCI-TOF): *m/z calcd* for $C_{32}H_{33}NO_5+H^+$: 512.2431 [M+H$^+$]; found: 512.2438.

116: ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.54–7.18 (m, 18H), 7.16–7.00 (m, 4H), 6.84 (d, *J*=8.8 Hz, 2H), 6.53 (s, 1H), 6.434 (s, 1H), 6.427 (s, 1H), 5.07 (s, 2H), 5.04 (s, 2H), 5.02 (s, 2H), 4.75 (s, 2H), 4.40 (br s, 2H), 3.98 (q, *J*=7.3 Hz, 2H), 3.88 (s, 3H), 3.62 (s, 3H), 3.25 (s, 3H), 2.91 (br s, 2H), 0.82 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=161.9, 157.4, 151.5, 150.7, 148.9, 147.1, 143.6, 141.2, 137.9, 137.4, 137.2, 137.1, 132.0, 130.4, 128.59, 128.55, 128.5, 128.4, 128.2, 127.9, 127.7, 127.32, 127.26, 126.9, 124.1, 122.3, 119.8, 119.5, 118.8, 116.3, 114.6, 105.2, 103.4, 75.4, 71.8, 71.3, 69.8, 60.9, 59.8, 56.5, 55.1, 42.5, 22.7, 13.7; IR (UATR): 2936, 1686 (C=O), 1416, 1216 cm^{-1}; MS: *m/z* 817 (11) [M^+–C_7H_6], 726 (19), 91 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{58}H_{53}NO_9+H^+$: 908.3793 [M+H$^+$]; found: 908.3798.

Lam 27: m.p. 279.0–280.6°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.70 (br s, 2H), 9.23 (br s, 1H), 7.26 (d, *J*=8.5 Hz, 2H), 6.99 (d, *J*=8.5 Hz, 2H), 6.78 (s, 1H), 6.54 (s, 1H), 6.28 (s, 1H), 4.58 (t, *J*=6.8 Hz, 2H), 3.64 (s, 3H), 3.33 (s, 3H), 3.25 (s, 3H), 2.99 (t, *J*=6.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=157.4, 154.4, 150.8, 147.4, 146.9, 145.6, 144.5, 136.4, 135.4, 132.1, 127.6, 125.0, 122.5, 116.2, 115.3, 114.4, 112.7, 108.7, 104.9, 103.7, 100.9, 60.3, 55.0, 54.6, 41.7, 21.3; IR (UATR): 3329, 2939, 1662 (C=O), 1425, 1038 cm^{-1}; MS: *m/z* 501 (100) [M^+], 486 (48); HRMS (APCI-TOF): *m/z calcd* for $C_{28}H_{23}NO_8+H^+$: 502.1496 [M+H$^+$]; found: 502.1506.

Lam 27-OAc: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.56 (d, *J*=8.5 Hz, 2H), 7.28 (d, *J*=8.5 Hz, 2H), 7.09 (s, 1H), 6.64 (s, 1H), 6.59 (s, 1H), 4.78 (t, *J*=6.7 Hz, 2H), 3.81 (s, 3H), 3.40 (s, 3H), 3.35 (s, 3H), 2.98 (t, *J*=6.7 Hz, 2H), 2.40 (s, 3H), 2.35 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.2, 168.8, 168.7, 155.1, 151.7, 150.9, 147.6, 144.9, 141.6, 138.9, 135.0, 132.9, 132.3, 127.2, 123.0, 122.6, 119.2, 116.0, 115.4, 114.8, 111.9, 107.5, 105.4, 60.7, 55.5, 55.3, 41.9, 22.2, 21.0, 20.6, 20.5; HRMS (APCI-TOF): *m/z calcd* for $C_{34}H_{29}NO_{11}+H^+$: 628.1813 [M+H$^+$]; found: 628.1809.

135: m.p. 274.4–275.5°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=9.20 (d, *J*=8.0 Hz, 1H), 7.65 (d, *J*=8.0 Hz, 2H), 7.35 (d, *J*=8.0 Hz, 2H), 7.15 (s, 1H), 7.08 (d, *J*=8.0 Hz, 1H), 7.03 (s, 1H), 6.73 (s, 1H), 3.88 (s, 3H), 3.45 (s, 3H), 3.42 (s, 3H), 2.50 (s, 3H), 2.38 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=169.3, 168.7, 168.6, 155.0, 153.2, 151.2, 147.7, 145.5, 139.8, 139.1, 133.3, 132.8, 128.5, 123.5, 123.3, 121.0, 118.3, 115.7, 112.2, 111.8, 109.1, 106.6, 106.1, 104.1, 60.8, 55.6, 55.5, 21.0, 20.5; IR (UATR): 2942, 1769 (C=O), 1713 (C=O), 1479, 1192 cm^{-1}; MS: *m/z* 625 (60) [M^+], 583 (62), 541 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{34}H_{27}NO_{11}+H^+$: 626.1657 [M+H$^+$]; found: 626.1660.

Lam 28: m.p. 283.4–285.4°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.88 (br s, 2H), 9.80 (br s, 1H), 8.95 (d, *J*=7.5 Hz, 1H), 7.41 (d, *J*=7.5 Hz, 1H), 7.35 (d, *J*=8.4 Hz, 2H), 7.04 (d, *J*=8.4 Hz, 2H), 6.84 (s, 1H), 6.71 (s, 1H), 6.62 (s, 1H), 3.71 (s, 3H), 3.352 (s, 3H), 3.350 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=157.7, 154.4, 152.8, 147.8, 146.3, 145.7, 144.6, 135.9, 133.4, 132.5, 128.9, 125.0, 121.0, 120.9, 116.3, 114.8, 111.9, 108.3, 107.5, 107.0, 105.4, 103.8, 97.2, 60.6, 55.0, 54.7; IR (UATR): 3335, 2942, 1704, 1668 (C=O), 1479, 1202 cm^{-1}; HRMS (APCI-TOF): *m/z calcd* for $C_{28}H_{21}NO_8+H^+$: 500.1340 [M+H$^+$]; found: 500.1346.

97: ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.49–7.25 (m, 5H), 7.04 (d, *J*=8.8 Hz, 2H), 6.81 (d, *J*=8.8 Hz, 2H), 6.71 (d, *J*=8.8 Hz, 1H), 6.58 (d, *J*=8.8 Hz, 1H), 5.66 (br s, 1H), 5.01 (s, 2H), 3.87 (s, 6H), 3.79 (s, 3H), 3.38 (s, 2H), 3.32 (q, *J*=6.6 Hz, 2H), 2.61 (t, *J*=6.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=171.3, 158.6, 152.5, 150.5, 142.2, 137.4, 130.4, 128.4, 128.3, 128.1, 126.9, 125.0, 124.5, 114.1, 107.5, 75.2, 60.8, 55.9, 55.2, 42.8, 40.5, 29.5; IR (UATR): 3300, 2936, 1646, 1511, 1247 cm^{-1}; MS: *m/z* 435 (32) [M^+], 270 (49), 180 (100), 91 (49); HRMS (APCI-TOF): *m/z calcd* for $C_{26}H_{29}NO_5+H^+$: 436.2118 [M+H$^+$]; found 436.2125.

117: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.43–7.26 (m, 9H), 7.24–7.20 (m, 4H), 7.11–7.03 (m, 4H), 6.78 (d, *J*=8.8 Hz, 2H), 6.65 (s, 1H), 6.45 (s, 1H), 6.42 (s, 1H), 5.08 (s, 2H), 5.01 (br s, 2H), 4.75 (s, 2H), 4.40 (br s, 2H), 3.98 (q, *J*=7.1 Hz, 2H), 3.89 (s, 3H), 3.77 (s, 3H), 3.63 (s, 3H), 3.32 (s, 3H), 2.91 (br s, 2H), 0.82 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.9, 158.3, 151.5, 150.5, 148.8, 146.9, 143.4, 141.2, 137.8, 137.3, 137.1, 131.9, 130.4, 128.6, 128.5, 128.4, 128.23, 128.20, 128.0, 127.7, 127.4, 127.3, 126.9, 124.1, 122.3, 119.8, 119.4, 118.6, 116.0, 113.6, 105.2, 103.1, 75.4, 71.8, 71.1, 61.0, 59.6, 56.4, 55.2, 55.1, 42.5, 22.6, 13.7; IR (UATR):

2935, 1686 (C=O), 1416, 1206 cm^{-1}; MS: *m/z* 831 (45) [M^+], 740 (87), 650 (36), 512 (46), 91 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{52}H_{49}NO_9$+H^+: 832.3480 [M+H^+]; found: 832.3472.

Lam 29: m.p. 262.9–264.6°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.69 (br s, 1H), 9.25 (br s, 1H), 7.39 (d, *J*=8.7 Hz, 2H), 7.16 (d, *J*=8.7 Hz, 2H), 6.78 (s, 1H), 6.48 (s, 1H), 6.21 (s, 1H), 4.59 (t, *J*=6.8 Hz, 2H), 3.82 (s, 3H), 3.64 (s, 3H), 3.31 (s, 3H), 3.21 (s, 1H), 2.99 (t, *J*=6.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=159.3, 154.3, 150.8, 147.4, 146.9, 145.6, 144.5, 136.5, 135.3, 132.2, 127.5, 126.9, 122.4, 114.9, 114.4, 112.8, 108.6, 104.8, 103.7, 100.8, 60.3, 55.5, 55.0, 54.6, 41.7, 21.3; IR (UATR): 3389, 1712, 1676 (C=O), 1429, 1244 cm^{-1}; MS: *m/z* 515 (100) [M^+], 500 (46), 468 (14); HRMS (APCI-TOF): *m/z calcd* for $C_{29}H_{25}NO_8$+H^+: 516.1653 [M+H^+]; found: 516.1668.

Lam 29-OAc: ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.44 (d, *J*=8.8 Hz, 2H), 7.10 (d, *J*=8.8 Hz, 2H), 7.07 (s, 1H), 6.70 (s, 1H), 6.64 (s, 1H), 4.76 (t, *J*=6.6 Hz, 2H), 3.87 (s, 3H), 3.80 (s, 3H), 3.39 (s, 3H), 3.33 (s, 3H), 2.96 (t, *J*=6.6 Hz, 2H), 2.39 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=168.72, 168.67, 159.7, 155.1, 151.6, 147.5, 145.0, 141.6, 141.1, 138.9, 135.0, 132.4, 127.3, 127.2, 122.9, 119.4, 116.3, 116.2, 114.8, 111.8, 107.7, 105.7, 60.7, 55.6, 55.5, 55.2, 41.8, 22.3, 20.5, 20.4; IR (UATR): 2938, 1767 (C=O), 1715 (C=O), 1421, 1196 cm^{-1}; MS: *m/z* 599 (52) [M^+], 557 (100), 515 (42), 368 (39), 151 (40); HRMS (APCI-TOF): *m/z calcd* for $C_{33}H_{29}NO_{10}$+H^+: 600.1864 [M+H^+]; found: 600.1862.

136: m.p. 268.0–269.0°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=9.22 (d, *J*=7.6 Hz, 1H), 7.53 (d, *J*=8.8 Hz, 2H), 7.19 (d, *J*=8.8 Hz, 2H), 7.14 (s, 1H), 7.11 (s, 1H), 7.06 (d, *J*=7.6 Hz, 1H), 6.78 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.44 (s, 3H), 3.41 (s, 3H), 2.50 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=168.7, 168.6, 160.0, 155.0, 152.9, 147.6, 145.6, 141.8, 139.7, 139.0, 133.5, 132.8, 128.6, 127.4, 123.5, 121.2, 118.3, 115.9, 115.0, 112.6, 112.1, 108.9, 106.4, 104.2, 60.8, 55.6, 55.5, 55.2, 20.5; IR (UATR): 2943, 1770 (C=O), 1696 (C=O), 1479, 1196 cm^{-1}; MS: *m/z* 597 (45) [M^+], 555 (55), 513 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{33}H_{27}NO_{10}$+H^+: 598.1708 [M+H^+]; found: 598.1715.

Lam 30: m.p. 261.5–262.1°C;^{1}H NMR (400 MHz, DMSO-d_6): δ=9.94 (br s, 1H), 9.88 (br s, 1H), 8.97 (d, *J*=7.5 Hz, 1H), 7.49 (d, *J*=8.6 Hz, 2H), 7.43 (d, *J*=7.5 Hz, 1H), 7.22 (d, *J*=8.6 Hz, 2H), 6.85 (s, 1H), 6.65 (s, 1H), 6.56 (s, 1H), 3.84 (s, 3H), 3.37 (s, 3H), 3.32 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=159.5, 154.4, 152.9, 147.9, 146.3, 145.7, 144.6, 135.8, 133.3, 132.7, 128.8, 126.9, 121.0, 120.8, 115.0, 114.8, 111.5, 108.2, 107.6, 107.0, 105.4, 103.8, 97.1, 60.6, 55.5, 55.0, 54.7; IR (UATR): 3380, 2938, 1689 (C=O), 1479, 1241 cm^{-1}; MS: *m/z* 513 (100) [M^+], 466 (18); HRMS (APCI-TOF): *m/z calcd* for $C_{29}H_{23}NO_8$+H^+: 514.1496 [M+H^+]; found: 514.1508.

118: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.36–7.08 (m, 15H), 6.54 (s, 1H), 6.43 (s, 1H), 6.36 (s, 1H), 5.01 (s, 2H), 4.75 (s, 2H), 4.60 (br s, 2H), 4.01 (q, *J*=7.1 Hz, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 3.60 (s, 3H), 3.24 (s, 3H), 3.09 (br s, 2H), 0.84 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.0, 151.5, 150.6, 150.3, 146.9, 143.4, 141.0, 137.8, 137.1, 135.8, 130.9, 130.4, 128.4, 128.2, 128.1, 128.0, 127.7, 127.4, 127.3, 126.9, 126.5, 124.0, 122.7, 119.5, 119.2, 118.4, 116.1, 105.1, 103.2, 71.8, 71.1, 61.0, 60.9, 59.7, 56.4, 55.0, 42.6, 22.2, 13.7; IR (UATR): 2936, 2836, 1688, 1603, 1531 cm^{-1}; MS: *m/z* 726 (21) [M^++H], 725 (49) [M^+], 634 (100), 543 (23), 470 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{45}H_{43}NO_8$+H^+: 726.3061 [M+H^+]; found: 726.3069.

Lam 31: m.p. 264.2–264.7°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.71 (s, 1H), 7.65–7.59 (m, 2H), 7.57–7.53 (m, 1H), 7.53–7.48 (m, 2H), 6.79 (s, 1H), 6.41 (s, 1H), 6.39 (s, 1H), 4.61 (t, *J*=6.7 Hz, 2H), 3.78 (s, 3H), 3.71 (s, 3H), 3.25 (s, 3H), 3.16 (s, 3H), 3.06 (t, *J*=6.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.3, 151.4, 150.4, 147.0, 145.6, 144.6, 142.0, 135.1, 134.6, 131.0, 129.5, 128.3, 127.3, 122.3, 120.2, 115.3, 113.0, 108.4, 105.0, 104.6, 103.7, 60.9, 60.5, 54.9, 54.7, 41.7, 21.5; IR (UATR): 3338 (br), 2936, 2835, 1675, 1601 cm^{-1}; MS: *m/z* 500 (26) [M^++H], 499 (100) [M^+], 484 (48), 466 (8), 456 (8), 424 (11); HRMS (APCI-TOF): *m/z calcd* for $C_{29}H_{25}NO_7$+H^+: 500.1704 [M+H^+]; found: 500.1712.

Lam 31-OAc: m.p. 237.2–239.1°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.60–7.52 (m, 4H), 7.51–7.46 (m, 1H), 7.08 (s, 1H), 6.63 (s, 1H), 6.44 (s, 1H), 4.79 (t, *J*=6.8 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.33 (s, 3H), 3.26 (s, 3H), 3.15 (t, *J*=6.8 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.7, 155.2, 151.8, 150.6, 147.4, 144.9, 142.3, 138.7, 135.6, 135.3, 131.2, 129.4, 128.2, 127.0, 122.8, 120.0, 116.3, 116.2, 114.6, 111.8, 105.5, 105.2, 61.0, 60.9, 55.3, 55.0, 42.2, 21.8, 20.6; IR (UATR): 2936, 2833, 1769, 1713, 1601, 1542, 1508 cm^{-1}; MS: *m/z* 542 (9) [M^++H], 541 (33) [M^+], 500 (31), 499 (100), 484 (43); HRMS (APCI-TOF): *m/z calcd* for $C_{31}H_{27}NO_8$+H^+: 542.1809 [M+H^+]; found: 542.1817.

137: m.p. 253.4–255.2°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.23 (d, *J*=7.6 Hz, 1H), 7.68–7.62 (m, 4H), 7.60–7.54 (m, 1H), 7.43 (d, *J*=7.6 Hz, 1H), 7.14 (s, 1H), 6.87 (s, 1H), 6.70 (s, 1H), 4.03 (s, 3H), 3.93 (s, 3H), 3.36 (s,

3H), 3.35 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.7, 155.1, 153.3, 148.4, 147.5, 145.5, 142.2, 139.5, 135.9, 133.6, 131.7, 129.5, 128.6, 128.1, 122.7, 121.3, 119.3, 115.9, 112.7, 112.1, 108.7, 107.5, 106.2, 101.6, 61.7, 61.1, 55.3, 55.0, 20.6; IR (UATR): 2938, 2837, 1766, 1709, 1603, 1537, 1473, 1426, 1414 cm^{-1}; MS: *m/z* 540 (11) [M^++H], 539 (34) [M^+], 497 (100), 482 (23), 464 (6), 454 (7), 439 (11); HRMS (APCI-TOF): *m/z calcd* for $C_{31}H_{25}NO_8$+H^+: 540.1653 [M+H^+]; found: 540.1650.

Lam 32: m.p. 265.0–266.0°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.21 (d, *J*=7.6 Hz, 1H), 7.68–7.62 (m, 4H), 7.59–7.54 (m, 1H), 7.39 (d, *J*=7.6 Hz, 1H), 6.99 (s, 1H), 6.87 (s, 1H), 6.54 (s, 1H), 5.84 (s, 1H), 4.03 (s, 3H), 3.93 (s, 3H), 3.43 (s, 3H), 3.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=155.5, 153.2, 148.4, 146.9, 146.2, 143.3, 142.2, 136.2, 133.5, 131.8, 131.7, 129.5, 129.1, 128.4, 122.8, 121.2, 119.3, 111.9, 109.7, 106.9, 104.5, 103.5, 101.6, 61.6, 61.1, 55.3, 55.0; IR (UATR): 3386 (br), 2938, 2835, 1703, 1600, 1537, 1506, 1474, 1426 cm^{-1}; MS: *m/z* 498 (30) [M^++H], 497 (100) [M^+], 482 (25), 454 (10), 439 (15); HRMS (APCI-TOF): *m/z calcd* for $C_{29}H_{23}NO_7$+H^+: 498.1547 [M+H^+]; found: 498.1552.

99: m.p. 118.0–120.6°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.48–7.26 (m, 10H), 7.20–7.00 (m, 3H), 6.93–6.76 (m, 3H), 6.75–6.70 (m, 1H), 6.63 (d, *J*=7.6 Hz, 1H), 5.40 (br s, 1H), 5.01 (s, 4H), 3.46 (s, 2H), 3.44 (q, *J*=6.6 Hz, 2H), 2.70 (t, *J*=6.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=171.2, 159.0, 158.1, 140.3, 137.0, 136.9, 130.5, 129.6, 128.6, 128.0, 127.9, 127.4, 127.0, 121.3, 115.4, 112.7, 70.1, 69.9, 43.0, 40.5, 35.5; HRMS (ESI-TOF): *m/z calcd* for $C_{30}H_{30}NO_3$+H^+: 452.2220 [M+H^+]; found 452.2221.

119: ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.51–7.16 (m, 18H), 7.13–6.95 (m, 5H), 6.88–6.78 (m, 3H), 6.59 (dd, *J*=8.6, 2.4 Hz, 1H), 6.53 (s, 1H), 6.43 (s, 1H), 5.02 (s, 6H), 4.74 (s, 2H), 4.62 (br s, 2H), 3.99 (q, *J*=7.1 Hz, 2H), 3.62 (s, 3H), 3.07 (br t, *J*=6.1 Hz, 2H), 0.83 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=162.0, 157.8, 157.5, 150.7, 147.1, 143.7, 137.9, 137.3, 137.1, 136.9, 135.1, 131.7, 130.8, 128.6, 128.5, 128.4, 128.3, 128.2, 127.94, 127.88, 127.7, 127.5, 127.4, 127.3, 126.9, 126.7, 121.9, 121.7, 119.1, 119.0, 116.5, 114.6, 114.2, 112.8, 103.6, 71.8, 71.4, 70.0, 59.5, 56.5, 42.5, 30.0, 13.7; HRMS (ESI-TOF): *m/z calcd* for $C_{56}H_{49}NO_7$+H^+: 848.3582 [M+H^+]; found 848.3570.

Lam 33: m.p. > 290.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.78 (br s, 1H), 9.69 (br s, 1H), 9.63 (br s, 1H), 7.22 (d, *J*=8.4 Hz, 2H), 6.95 (d, *J*=8.4 Hz, 2H), 6.90 (d, *J*=8.6 Hz, 1H), 6.76 (s, 1H), 6.72 (d, *J*=2.4 Hz, 1H), 6.46 (s, 1H), 6.44 (dd, *J*=8.6, 2.4 Hz, 1H), 4.59 (br t, *J*=6.5 Hz, 2H,), 3.33 (s, 3H), 3.05 (br t, *J*=6.5 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=158.1, 157.6, 154.7, 147.1, 146.0, 144.8, 136.4, 136.2, 132.3, 128.2, 126.4, 125.5, 118.9, 166.6, 155.5, 144.5, 144.1, 122.6, 109.2, 105.3, 104.0, 55.4, 42.1, 29.0; IR (UATR): 3356, 2924, 1665, 1603, 1440, 1200 cm^{-1}; HRMS (APCI-TOF): *m/z calcd* for $C_{26}H_{19}NO_6$+H^+: 442.1285 [M+H^+]; found 442.1302.

Lam 33-OAc: m.p. 247.7–249.7°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.51 (d, *J*=8.6 Hz, 2H), 7.27 (d, *J*=8.6 Hz, 2H), 7.09 (d, *J*=8.6 Hz, 1H), 7.07 (s, 1H), 7.04 (d, *J*=2.3 Hz, 1H), 6.76 (dd, *J*=8.6, 2.3 Hz, 1H), 6.57 (s, 1H), 4.83 (t, *J*=6.6 Hz, 2H), 3.41 (s, 3H), 3.18 (t, *J*=6.6 Hz, 2H), 2.35 (s, 3H), 2.30 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=169.2, 169.1, 168.7. 155.1, 150.8, 150.3, 147.6, 144.8, 138.8, 135.3, 134.8, 132.5, 132.0, 127.3, 126.7, 125.1, 122.9, 121.5, 120.3, 116.0, 115.8, 114.9, 111.8, 105.4, 55.7, 42.0, 29.2, 21.1, 21.0, 20.5; HRMS (ESI-TOF): *m/z calcd* for $C_{32}H_{25}NO_9$+H^+: 568.1602 [M+H^+]; found 568.1622.

138: ^{1}H NMR (200 MHz, $CDCl_3$+CD_3OD): δ=9.29 (d, *J*=7.4 Hz, 1H), 7.67 (d, *J*=9.0 Hz, 1H), 7.61 (d, *J*=8.6 Hz, 2H), 7.47 (d, *J*=2.3 Hz, 1H), 7.37 (d, *J*=8.6 Hz, 2H), 7.15 (s, 1H), 7.11 (d, *J*=7.4 Hz, 1H), 7.57 (dd, *J*=9.0, 2.3 Hz, 1H), 6.63 (s, 1H), 3.43 (s, 3H), 2.40 (s, 3H), 2.35 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$+CD_3OD): δ=169.3, 169.2, 168.7, 155.1, 151.2, 150.2, 147.8, 145.3, 139.8, 133.7, 132.7, 132.3, 130.9, 128.9, 125.8, 125.0, 123.3, 122.6, 121.9, 119.1, 115.5, 113.0, 112.5, 112.1, 109.2, 106.1, 55.7, 20.9, 20.4.

Lam 34: m.p. > 290.0°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ=10.16 (br s, 1H), 9.81 (br s, 2H), 9.04 (d, *J*=7.5 Hz, 1H), 7.53 (d, *J*=8.8 Hz, 1H), 7.33 (d, *J*=8.4 Hz, 2H), 7.20 (d, *J*=7.5 Hz, 1H), 7.15 (d, *J*=2.4 Hz, 1H), 7.05 (d, *J*=8.4 Hz, 2H), 6.87 (dd, *J*=8.4, 2.4 Hz, 1H), 6.85 (s, 1H), 6.52 (s, 1H), 3.37 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=157.7, 157.6, 154.3, 147.8, 146.3, 144.5, 134.2, 132.1, 131.4, 129.5, 125.5, 125.0, 123.9, 117.5, 116.5, 112.6, 111.1, 108.2, 106.7, 105.5, 103.7, 55.0; HRMS (ESI-TOF): *m/z calcd* for $C_{26}H_{17}NO_6$+H^+: 440.1129 [M+H^+]; found 440.1128.

100: m.p. 92.5–93.1°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.48–7.28 (m, 5H), 7.14 (t, *J*=7.5 Hz, 1H), 7.07 (d, *J*=8.3 Hz, 2H), 6.91 (d, *J*=8.3 Hz, 2H), 6.73 (d, *J*=7.5 Hz, 1H), 6.63 (s, 1H), 6.61 (d, *J*=7.5 Hz, 1H), 5.38 (br s, 1H), 5.05 (s, 2H), 3.76 (s, 2H), 3.46 (s, 2H), 3.45 (q, *J*=6.6 Hz, 2H), 2.70 (t, *J*=6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.3, 159.8, 158.0, 140.2, 136.9, 130.5, 129.5, 128.6, 128.0, 127.4, 127.0, 121.0, 115.3, 114.4, 111.8, 70.0, 55.1, 42.9, 40.5, 35.5; HRMS (ESI-TOF): *m/z calcd* for $C_{24}H_{25}NO_3$+H$^+$: 376.1907 [M+H$^+$]; found: 376.1917.

120: ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.44–7.21 (m, 15H), 7.11–6.96 (m, 5H), 6.84–6.77 (m, 3H), 6.56–6.50 (m, 2H), 6.43 (s, 1H), 5.03 (s, 4H), 4.74 (s, 2H), 4.63 (br s, 2H), 3.99 (q, J=7.0 Hz, 2H), 3.78 (s, 3H), 3.62 (s, 3H), 3.09 (t, J=6.3 Hz, 2H), 0.83 (t, J=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=162.1, 158.5, 157.5, 150.7, 147.1, 143.7, 137.9, 137.3, 137.2, 135.1, 131.7, 130.9, 128.5, 128.4, 128.3, 128.2, 127.9, 127.7, 127.6, 127.4, 126.9, 126.7, 121.6, 119.1, 116.5, 114.6, 113.2, 112.0, 103.6, 71.8, 71.4, 70.0, 59.5, 56.5, 55.2, 42.5, 30.1, 13.7; IR (UATR): 3031, 2935, 1682, 1610, 1530, 1512 cm^{-1}; MS: *m/z*772 (37) [M^++H], 771 (41) [M^+], 681 (46), 680 (38), 591 (27), 590 (26), 238 (42), 223 (26), 195 (15), 180 (10), 152 (8), 91 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{50}H_{45}NO_7$+H$^+$: 772.3269 [M+H$^+$]; found: 772.3274.

Lam 35: m.p. dec. 275.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.70 (s, 1H), 9.64 (s, 1H), 7.23 (d, J=8.5 Hz, 2H), 6.99 (d, J=8.8 Hz, 1H), 6.95 (d, J=8.5 Hz, 2H), 6.93 (d, J=2.5 Hz, 1H), 6.76 (s, 1H), 6.66 (dd, J=8.8, 2.6 Hz, 1H), 6.48 (s, 1H), 4.61 (t, J=6.5 Hz, 3H), 3.71 (s, 3H), 3.33 (s, 3H), 3.11 (t, J=6.5 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=159.2, 157.3, 154.3, 146.8, 145.6, 144.4, 136.0, 135.4, 131.9, 127.8, 126.4, 125.0, 120.0, 116.3, 114.5, 113.8, 112.5, 112.4, 108.7, 104.9, 103.6, 55.2, 55.0, 41.7, 28.6; IR (UATR): 3377, 2926, 1669, 1610 cm^{-1}; MS: *m/z* 455 (7) [M^+], 413 (13), 412 (71), 370 (23), 329 (22), 328 (100), 313 (30), 285 (13), 164 (16); HRMS (APCI-TOF): *m/z calcd* for $C_{27}H_{21}NO_6$+H$^+$: 456.1442 [M+H$^+$]; found: 456.1447.

Lam 35-OAc: m.p. 247.9–249.5°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.53–7.49 (m, 2H), 7.29–7.24 (m, 2H), 7.08 (s, 1H), 7.01 (d, J=8.4 Hz, 1H), 6.82 (d, J=2.6 Hz, 1H), 6.58 (s, 1H), 6.60–6.55 (m, 1H), 4.82 (t, J=6.5 Hz, 2H), 3.79 (s, 3H), 3.41 (s, 3H), 3.16 (t, J=6.5 Hz, 2H), 2.36 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=169.1, 168.7, 159.7, 150.8, 147.6, 145.0, 138.9, 135.8, 135.7, 133.0, 132.2, 127.1, 122.8, 120.3, 116.2, 114.7, 114.5, 113.9, 112.5, 111.9, 105.5, 55.7, 55.3, 42.2, 29.6, 21.1, 20.5; IR (UATR): 3000, 2938, 2839, 1760, 1709, 1611 cm^{-1}; MS: *m/z* 540 (13) [M^++H], 539 (52) [M^+], 516 (18), 514 (13), 498 (31), 497 (100), 455 (34), 447 (34), 445 (33); HRMS (APCI-TOF): *m/z calcd* for $C_{31}H_{25}NO_8$+H$^+$: 540.1653 [M+H$^+$]; found: 540.1651.

139: m.p. 258.8–259.6°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=9.28 (d, J=7.8 Hz, 1H), 7.61–7.53 (m, 2H), 7.37–7.33 (m, 2H), 7.14 (s, 1H), 7.11 (d, J=2.4 Hz, 1H), 7.08 (d, J=7.2 Hz, 1H), 6.92 (dd, J=9.0, 2.6 Hz, 1H), 6.62 (s, 1H), 3.89 (s, 3H), 3.42 (s, 3H), 2.39 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=169.1, 168.6, 159.6, 155.1, 151.2, 147.8, 145.5, 139.8, 134.5, 133.2, 132.5, 131.7, 128.9, 125.9, 124.9, 123.2, 118.9, 117.2, 115.8, 113.2, 112.1, 111.3, 108.8, 108.7, 106.2, 55.8, 55.4, 21.1, 20.6; IR (UATR): 3520, 3067, 1757, 1702, 1614, 1544 cm^{-1}; MS: *m/z* 538 (17) [M^++H], 537 (44) [M^+], 496 (33), 495 (100), 454 (15), 453 (61), 421 (6), 420 (14), 392 (18); HRMS (APCI-TOF): *m/z calcd* for $C_{31}H_{23}NO_8$+H$^+$: 538.1496 [M+H$^+$]; found: 538.1491.

Lam 36: m.p. dec. 250.0°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ=9.84 (s, 1H), 9.81 (s, 1H), 9.09 (d, J=7.5 Hz, 1H), 7.59 (d, J=9.3 Hz, 1H), 7.38 (d, J=2.4 Hz, 1H), 7.34 (d, J=8.4 Hz, 2H), 7.28 (d, J=2.8 Hz, 1H), 7.09–7.01 (m, 3H), 6.85 (s, 1H), 6.53 (s, 1H), 3.84 (s, 3H), 3.37 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=159.1, 157.6, 154.3, 147.8, 146.3, 144.5, 133.8, 132.1, 129.4, 125.2, 124.8, 124.1, 118.2, 117.1, 116.6, 112.8, 111.3, 108.9, 108.1, 106.8, 105.5, 103.7, 55.4, 55.0; HRMS (APCI-TOF): *m/z calcd* for $C_{27}H_{19}NO_6$+H$^+$: 454.1285 [M+H$^+$]; found: 454.1288.

101: m.p. 70.4–72.0°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.46–7.25 (m, 10H), 7.03 (d, J=8.7 Hz, 2H), 6.94 (t, J=7.9 Hz, 1H), 6.86 (d, J=8.7 Hz, 2H), 6.81 (dd, J=7.9, 1.5 Hz, 1H), 6.62 (dd, J=7.9, 1.5 Hz, 1H), 5.64 (br s, 1H), 5.02 (s, 2H), 4.95 (s, 2H), 3.87 (s, 3H), 3.35 (q, J=6.4 Hz, 2H), 3.34 (s, 2H), 2.67 (t, J=6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.2, 157.9, 152.7, 145.8, 137.7, 136.9, 133.0, 130.4, 128.5, 128.4, 128.2, 128.0, 127.9, 127.4, 127.2, 124.1, 122.3, 115.1, 110.9, 74.7, 70.0, 55.7, 42.8, 40.3, 29.8; HRMS (ESI-TOF): *m/z calcd* for $C_{31}H_{32}NO_4$+H$^+$: 482.2326 [M+H$^+$]; found: 482.2322.

121: ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.52–7.19 (m, 18H), 7.13–7.07 (m, 2H), 7.04 (d, J=8.8 Hz, 2H), 6.84 (d, J=8.8 Hz, 2H), 6.81 (d, J=8.8 Hz, 1H), 6.59 (d, J=8.8 Hz, 1H), 6.53 (s, 1H), 6.43 (s, 1H), 5.05 (s, 2H), 5.04 (s, 4H), 4.75 (s, 2H), 4.39 (br s, 2H), 3.99 (q, J=7.1 Hz, 2H), 3.86 (s, 3H), 3.63 (s, 3H), 2.98 (br s, 2H), 0.83 (t, J=7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=161.9, 157.5, 151.6, 150.7, 147.0, 144.1, 143.6, 137.9, 137.5, 137.2, 137.1, 131.7, 130.7, 128.6, 128.5, 128.4, 128.2, 127.9, 127.7, 127.5, 127.3, 126.9, 122.2, 121.8, 121.6, 119.04, 118.96, 116.5, 114.4, 110.3, 103.5, 74.9, 71.8, 71.3, 69.9, 59.5, 56.5, 55.7, 42.2, 23.3, 13.7; HRMS (ESI-TOF): *m/z calcd* for $C_{57}H_{51}NO_8$+H$^+$: 878.3687 [M+H$^+$]; found: 878.3712.

Lam 37: m.p. > 290.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.66 (br s, 1H), 9.62 (br s, 1H), 8.94 (br s, 1H), 7.21 (d, J=8.4 Hz, 2H), 6.95 (d, J=8.4 Hz, 2H), 6.76 (s, 1H), 6.70 (d, J=8.7 Hz, 1H), 6.58 (d, J=8.7 Hz, 1H),

6.46 (s, 1H), 4.58 (br t, J=6.6 Hz, 2H), 3.74 (s, 3H), 3.32 (s, 3H), 3.06 (br t, J=6.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=157.2, 154.3, 147.7, 146.7, 145.6, 144.4, 142.8, 135.7, 131.9, 127.8, 125.2, 120.9, 120.5, 116.7, 116.2, 114.7, 112.3, 109.7, 108.8, 104.9, 103.6, 55.7, 55.0, 41.4, 21.7; IR (UATR): 3227, 1670, 1430, 1279, 1149 cm^{-1}; HRMS (ESI-TOF): *m/z calcd* for $C_{27}H_{21}NO_7$+H$^+$: 472.1391 [M+H$^+$]; found: 472.1383.

Lam 37-OAc: m.p. 288.7–289.8°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.52 (d, J=8.6 Hz, 2H), 7.28 (d, J=8.6 Hz, 2H), 7.09 (s, 1H), 6.98 (d, J=8.8 Hz, 1H), 6.67 (d, J=8.8 Hz, 1H), 6.59 (s, 1H), 4.80 (t, J=6.7 Hz, 2H), 3.80 (s, 3H), 3.42 (s, 3H), 3.07 (t, J=6.7 Hz, 2H), 2.40 (s, 3H), 2.37 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=169.2, 168.7, 168.5, 155.1, 151.3, 150.8, 147.6, 144.9, 138.8, 137.1, 135.1, 132.8, 132.1, 127.8, 127.4, 124.2, 122.8, 120.7, 116.1, 115.1, 114.5, 111.8, 110.4, 105.4, 55.9, 55.7, 41.5, 22.8, 21.1, 20.6, 20.4; HRMS (ESI-TOF): *m/z calcd* for $C_{33}H_{27}NO_{10}$+H$^+$: 598.1708 [M+H$^+$]; found: 598.1696.

140: m.p. > 290.0°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.29 (d, J=7.8 Hz, 1H), 7.59 (d, J=8.6 Hz, 2H), 7.53 (d, J=9.2 Hz, 1H), 7.36 (d, J=8.6 Hz, 2H), 7.15 (s, 1H), 7.13 (d, J=7.8 Hz, 1H), 7.03 (d, J=9.2 Hz, 1H), 6.62 (s, 1H), 3.88 (s, 3H), 3.42 (s, 3H), 2.48 (s, 3H), 2.39 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=169.2, 168.64, 168.55, 155.0, 151.2, 150.4, 147.8, 145.5, 139.8, 134.1, 133.7, 133.0, 132.4, 129.1, 125.5, 124.6, 123.3, 119.1, 115.6, 113.2, 112.2, 112.0, 109.1, 106.2, 106.1, 56.3, 55.7, 21.1, 20.6, 20.5; HRMS (ESI-TOF): *m/z calcd* for $C_{33}H_{25}NO_{10}$+H$^+$: 596.1551 [M+H$^+$]; found: 596.1572.

Lam 38: m.p. > 290.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.86 (br s, 2H), 9.60 (br s, 1H), 9.10 (d, J=7.6 Hz, 1H), 7.48 (d, J=7.6 Hz, 1H), 7.33 (d, J=8.4 Hz, 2H), 7.20–7.13 (m, 2H), 7.05 (d, J=8.4 Hz, 2H), 6.86 (s, 1H), 6.53 (s, 1H), 3.84 (s, 3H), 3.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=157.5, 154.2, 147.6, 146.1, 145.7, 144.4, 140.6, 133.7, 131.9, 129.2, 124.9, 122.4, 119.3, 118.7, 116.4, 115.1, 113.4, 111.7, 108.1, 107.1, 106.8, 105.3, 103.6, 56.1, 54.8; HRMS (ESI-TOF): *m/z calcd* for $C_{27}H_{19}NO_7$+H$^+$:470.1234 [M+H$^+$]; found: 470.1249.

152: ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.52–7.22 (m, 15H), 7.08–6.80 (m, 6H), 6.65 (dd, J=6.8, 2.4 Hz, 1H), 5.65 (br t, J=6.3 Hz, 1H), 5.12 (s, 2H), 4.99 (s, 2H), 4.98 (s, 2H), 3.36 (q, J=6.3 Hz, 2H), 3.35 (s, 2H), 2.70 (t, J=6.3 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=171.2, 157.9, 151.9, 146.4, 137.6, 137.0, 136.9, 133.3, 130.5, 128.6, 128.4, 128.0, 127.95, 127.5, 127.4, 127.3, 124.2, 122.8, 115.2, 112.7, 74.9, 70.9, 70.1, 42.9, 40.4, 29.9; IR (UATR): 3300, 3060, 3033, 1648, 1509 cm^{-1}; MS: *m/z* 557 (4) [M^+], 466 (14), 91 (100).

159: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.46–7.17 (m, 23H), 7.11–6.99 (m, 4H), 6.82 (d, J=8.9 Hz, 2H), 6.79 (d, J=8.9 Hz, 1H), 6.62 (d, J=8.9 Hz, 1H), 6.53 (s, 1H), 6.43 (s, 1H), 5.06 (s, 4H), 5.00 (s, 4H), 4.73 (s, 2H), 4.42 (br s, 2H), 3.98 (q, J=7.1 Hz, 2H), 3.60 (s, 3H), 3.00 (br s, 2H), 0.82 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=161.9, 157.4, 150.7, 150.6, 146.9, 144.4, 143.5, 137.8, 137.3, 137.1, 137.0, 136.8, 131.6, 130.5, 128.7, 128.5, 128.34, 128.32, 128.3, 128.2, 128.1, 127.89, 127.85, 127.6, 127.5, 127.33, 127.25, 126.8, 122.6, 121.8, 121.5, 119.0, 118.7, 116.2, 114.5, 112.0, 103.2, 74.9, 71.7, 71.1, 70.7, 69.8, 59.5, 56.5, 42.1, 23.2, 13.7; IR (UATR): 1682, 1608, 1532 cm^{-1}; HRMS (APCI-TOF): *m/z calcd* for $C_{63}H_{55}NO_8$+H$^+$: 954.4000 [M+H$^+$]; found: 954.3975.

Lam 39: m.p. > 290.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.66 (s, 1H), 9.64 (s, 1H), 9.59 (s, 1H), 8.66 (s, 1H), 7.20 (d, J=8.5 Hz, 2H), 6.94 (d, J=8.5 Hz, 2H), 6.75 (s, 1H), 6.46 (s, 2H), 6.43 (s, 1H), 4.57 (t, J=6.7 Hz, 2H), 3.32 (s, 3H), 3.04 (t, J=6.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=157.2, 154.3, 147.7, 145.8, 145.6, 144.3, 142.0, 136.1, 131.9, 127.8, 125.3, 121.5, 119.1, 117.0, 116.1, 114.3, 113.1, 112.0, 108.8, 104.9, 103.5, 55.0, 41.4, 21.8; IR (UATR): 3413, 1662 cm^{-1}; HRMS (APCI-TOF): *m/z calcd* for $C_{26}H_{19}NO_7$+H$^+$: 458.1234 [M+H$^+$]; found: 458.1229.

153: m.p. 139.0–141.0°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.55–7.20 (m, 15H), 6.85–6.60 (m, 5H), 6.47 (dd, J=8.0, 1.8 Hz, 1H), 5.32 (br t, J=6.6 Hz, 1H), 5.09 (s, 6H), 3.83 (s, 3H), 3.39 (s, 2H), 3.33 (q, J=6.6 Hz, 2H), 2.55 (t, J=6.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=171.1, 148.9, 148.2, 147.5, 137.5, 137.1, 136.7, 131.8, 128.5, 128.4, 127.8, 127.7, 127.68, 127.3, 127.2, 127.0, 122.1, 121.5, 115.4, 115.0, 112.0, 71.2, 70.7, 55.9, 43.2, 40.5, 34.8; IR (UATR): 3296, 1645, 1509 cm^{-1}; MS: *m/z* 587 (4) [M^+], 316 (27), 225 (27), 181 (34), 91 (100).

160: ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.55–7.00 (m, 25H), 6.85–6.65 (m, 5H), 6.55 (s, 1H), 6.43 (s, 1H), 5.16 (s, 2H), 5.01 (s, 2H), 4.75 (s, 2H), 4.70 (s, 2H), 4.59 (br s, 3H), 3.98 (q, J=7.0 Hz, 2H), 3.85 (s, 3H), 3.63 (s, 3H), 2.99 (br t, J=6.4 Hz, 2H), 0.82 (t, J=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=161.9, 150.6, 148.4, 148.1, 147.7, 147.3, 147.2, 143.7, 137.9, 137.3, 137.2, 137.1, 130.7, 128.5, 128.4, 128.3, 128.25, 128.20, 127.8, 127.7, 127.6, 127.5, 127.3, 127.25, 127.21, 126.9, 126.8, 126.2, 123.7, 121.8, 119.2, 118.9, 116.8, 116.4, 114.4, 111.7, 103.3, 71.7, 71.4, 71.3, 70.9, 70.4, 59.5, 56.5, 56.0, 42.7, 29.0, 13.7; IR (UATR): 1683, 1607 cm^{-1}; HRMS (APCI-TOF): *m/z calcd* for $C_{64}H_{57}NO_9$+H$^+$: 984.4106 [M+H$^+$]; found: 984.4120.

Lam 40: m.p. > 290.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.61 (s, 1H), 9.36 (s, 1H), 9.24 (s, 1H), 8.74 (s, 1H), 7.09 (d, *J*=7.7 Hz, 1H), 6.80 (dd, *J*=7.7, 1.9 Hz, 1H), 6.79 (s, 1H), 6.74 (s, 1H), 6.67 (s, 1H), 6.61 (s, 1H), 6.44 (s, 1H), 4.60–4.48 (m, 2H), 3.82 (s, 3H), 3.32 (s, 3H), 2.94 (t, *J*=6.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.3, 147.6, 147.3, 146.6, 146.2, 145.6, 144.4, 143.7, 135.7, 127.7, 127.2, 125.7, 121.5, 118.3, 117.7, 115.2, 114.0, 113.2, 112.2, 108.7, 104.9, 103.5, 55.7, 54.9, 42.0, 27.7; IR (UATR): 3750, 3360, 1664, 1428, 1287 cm^{-1}; MS: *m/z* 487 (100) [M^+], 454 (18), 426 (16); HRMS (APCI-TOF): *m/z calcd* for $C_{27}H_{21}NO_8$+H$^+$: 488.1340 [*M*+H$^+$]; found: 488.1332.

161: ^{1}H NMR (200 MHz, CDCl$_3$): δ=7.47–7.05 (m, 25H), 6.73 (s, 4H), 6.69 (s, 1H), 6.63 (s, 1H), 6.45 (s, 1H), 5.15 (s, 2H), 5.00 (s, 2H), 4.90 (s, 2H), 4.75 (s, 4H), 4.59 (br t, 2H), 3.93 (q, *J*=6.2 Hz, 2H), 3.82 (s, 3H), 3.30 (s, 3H), 2.98 (t, *J*=6.2 Hz, 2H), 0.77 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (50 MHz, CDCl$_3$): δ=161.9, 151.3, 148.1, 148.0, 147.7, 147.6, 147.0, 142.6, 137.7, 137.5, 137.1, 136.9, 136.8, 130.8, 128.5, 128.3, 128.2, 128.1, 127.8, 127.6, 127.5, 127.4, 127.3, 127.2, 127.1, 126.6, 125.5, 123.6, 121.7, 121.4, 119.8, 119.1, 119.0, 116.3, 113.0, 111.4, 109.0, 103.2, 72.2, 71.4, 70.9, 70.7, 59.4, 55.9, 55.1, 42.7, 28.9, 13.6; IR (UATR): 2934, 1684, 1251, 1172 cm^{-1}; HRMS (APCI-TOF): *m/z calcd* for $C_{64}H_{57}NO_9$+H$^+$: 984.4106 [*M*+H$^+$]; found 984.4073.

Lam 41: m.p. dec. 240.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.56 (s, 1H), 9.37 (s, 1H), 9.24 (s, 1H), 8.91 (s, 1H), 7.12 (d, *J*=8.1 Hz, 1H), 6.83–6.79 (m, 2H), 6.73 (s, 1H), 6.70 (s, 1H), 6.64 (s, 1H), 6.45 (s, 1H), 4.66–4.47 (m, 2H), 3.84 (s, 3H), 3.24 (s, 3H), 2.96 (t, *J*=6.3 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.4, 147.6, 147.4, 146.9, 145.94, 145.89, 144.7, 142.0, 135.9, 127.4, 127.2, 121.5, 118.1, 117.7, 115.2, 114.1, 113.3, 112.3, 109.12, 109.06, 108.6, 103.0, 55.8, 54.6, 41.9, 27.5; IR (UATR): 3525, 3466, 3400, 1677, 1596 cm^{-1}; MS: *m/z* 487 (49) [M^+], 453 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{27}H_{21}NO_8$+H$^+$: 488.1340 [*M*+H$^+$]; found 488.1332.

Lam 42: m.p. dec. 270.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.90 (s, 1H), 9.74 (s, 1H), 9.35 (s, 1H), 9.03 (s, 1H), 9.00 (d, *J*=7.4 Hz, 1H), 7.20 (d, *J*=8.1 Hz, 1H), 7.17 (d, *J*=7.4 Hz, 1H), 7.15 (s, 1H), 6.94 (d, *J*=2.0 Hz, 1H), 6.91 (d, *J*=5.5 Hz, 2H), 6.81 (s, 1H), 6.74 (s, 1H), 3.88 (s, 3H), 3.35 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.5, 148.4, 148.1, 147.9, 147.6, 147.0, 145.3, 142.2, 134.1, 128.5, 127.3, 124.6, 122.0, 121.9, 118.0, 117.4, 113.5, 112.3, 111.5, 110.7, 109.2, 108.6, 106.4, 105.2, 103.5, 55.8, 54.5; IR (UATR): 3405, 1677, 1552, 1488, 1427 cm^{-1}; HRMS (ESI-TOF): *m/z calcd* for $C_{27}H_{19}NO_8$+H$^+$: 486.1183 [*M*+H$^+$]; found 486.1197.

162: ^{1}H NMR (200 MHz, CDCl$_3$): δ=7.48–7.06 (m, 20H), 6.76–6.64 (m, 6H), 6.45 (s, 1H), 5.15 (s, 2H), 5.02 (s, 2H), 4.90 (s, 2H), 4.78 (s, 2H), 4.61 (br s, 2H), 3.94 (q, *J*=7.0 Hz, 2H), 3.83 (s, 3H), 3.51 (s, 3H), 3.36 (s, 3H), 3.00 (t, *J*=6.6 Hz, 2H), 0.78 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (50 MHz, CDCl$_3$): δ=161.8, 151.4, 148.5, 148.3, 147.9, 147.6, 147.2, 142.8, 137.8, 137.8, 137.5, 137.2, 137.0, 130.7, 128.5, 128.4, 128.3, 128.2, 128.1, 127.7, 127.6, 127.5, 127.3, 127.2, 127.1, 126.6, 125.7, 123.1, 121.8, 121.6, 120.1, 119.4, 119.1, 114.2, 113.5, 111.0, 109.3, 103.5, 72.4, 71.5, 71.4, 71.0, 59.3, 55.8, 55.6, 55.2, 42.7, 28.9, 13.6; IR(UATR): 2935, 1685, 1497 cm^{-1}; MS: *m/z* 908 (2) [M^+], 817 (7), 816 (9), 815 (6), 727 (7), 726 (10), 725 (9), 635 (7), 105 (7), 92 (46), 91 (100), 65 (16), 50 (9); HRMS (APCI-TOF): *m/z calcd* for $C_{58}H_{53}NO_9$+H$^+$: 908.3793 [*M*+H$^+$]; found 908.3781.

Lam 43: m.p. > 290.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=7.15 (d, *J*=8.1 Hz, 1H), 7.00 (d, *J*=1.8 Hz, 1H), 6.94 (dd, *J*=8.1, 1.8 Hz, 1H), 6.71 (s, 1H), 6.70 (s, 1H), 6.57 (s, 1H), 6.43 (s, 1H), 4.67–4.58 (m, 1H), 4.56–4.47 (m, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 3.21 (s, 3H), 2.97 (t, *J*=6.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.5, 149.6, 148.7, 147.1, 145.9, 144.8, 142.5, 136.0, 127.6, 127.3, 127.2, 123.0, 118.0, 115.3, 114.2, 114.0, 112.7, 112.2, 109.1, 108.5, 108.0, 103.2, 55.74, 55.66, 54.6, 42.0, 27.6; IR(UATR): 3375, 2933, 1690 cm^{-1}; HRMS (APCI-TOF): *m/z calcd* for $C_{28}H_{23}NO_8$+H$^+$: 500.1351 [*M*-H$^+$]; found 500.1342.

Lam 44: ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.91 (s, 1H), 9.72 (s, 1H), 9.08 (s, 1H), 9.04 (d, *J*=7.4 Hz, 1H), 7.26 (d, *J*=8.1 Hz, 1H), 7.19 (d, *J*=7.4 Hz, 1H), 7.17 (s, 1H), 7.14 (d, *J*=1.8 Hz, 1H), 7.09 (dd, *J*=8.1, 1.8 Hz, 1H), 6.87 (s, 1H), 6.83 (s, 1H), 6.73 (s, 1H), 3.89 (s, 3H), 3.76 (s, 3H), 3.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.5, 149.8, 148.9, 148.4, 148.2, 147.0, 145.3, 142.3, 134.2, 128.7, 127.2, 124.7, 123.5, 122.0, 117.5, 114.5, 112.9, 112.3, 111.5, 110.7, 109.1, 108.6, 106.5, 105.2, 103.5, 55.7, 54.5; IR(UATR): 3408, 3126, 1679 cm^{-1}; MS: *m/z* 500 (36) [M^++H], 499 (100) [M^+]; HRMS (APCI-TOF): *m/z calcd* for $C_{28}H_{21}NO_8$+H$^+$: 500.1340 [*M*+H$^+$]; found 500.1334.

163: ^{1}H NMR (200 MHz, CDCl$_3$): δ=7.45–7.07 (m, 30H), 6.79–6.65 (m, 5H), 6.61 (s, 1H), 6.46 (s, 1H), 5.13 (s, 2H), 5.10 (s, 2H), 4.99 (s, 2H), 4.89 (s, 2H), 4.77 (s, 2H), 4.74 (s, 2H), 4.58 (br s, 2H), 3.93 (q, *J*=7.0 Hz, 2H), 3.19 (s, 3H), 2.97 (t, *J*=6.2 Hz, 2H), 0.78 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (50 MHz, CDCl$_3$): δ=161.6, 151.1, 148.3, 148.0, 147.4, 146.9, 146.8, 142.4, 137.5, 137.3, 137.1, 136.9, 136.8, 136.7, 130.5, 128.7, 128.3, 128.2, 128.1, 128.0, 127.5, 127.4, 127.2, 127.0, 126.9, 126.8, 126.4, 125.3, 123.5, 121.4, 121.1, 119.6, 118.8, 117.0, 114.2, 112.8, 108.7, 102.9, 72.0, 71.1, 70.7, 70.6, 59.2, 54.8, 42.5, 28.6, 13.7, 13.5.

Lam S: m.p. > 290.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.55 (br s, 1H), 9.30 (br s, 1H), 9.14 (br s, 2H), 8.92 (br s, 1H), 6.94 (d, *J*=7.9 Hz, 1H), 6.75 (d, *J*=2.0 Hz, 1H), 6.74 (s, 1H), 6.71 (s, 1H), 6.69 (dd, *J*=7.9, 2.0 Hz, 1H), 6.68 (s, 1H), 6.51 (s, 1H), 4.70–4.61 (m, 1H), 4.54–4.44 (m, 1H), 3.28 (s, 3H), 3.02–2.91 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.4, 146.9, 146.1, 145.94, 145.88, 145.3, 144.7, 142.0, 136.0, 127.3, 127.1, 125.5, 121.6, 118.2, 117.7, 116.6, 115.2, 114.5, 112.2, 109.3, 109.2, 108.7, 103.3, 54.6, 41.9, 27.6; IR (UATR): 3367, 2927, 1671, 1593 cm^{-1}; MS: *m/z* 430 (12) [M^+-CO$_2$], 178 (69), 167 (69), 149 (100); HRMS (APCI-TOF): *m/z calcd* for $C_{26}H_{19}NO_8$-H$^+$: 472.1038 [*M*-H$^+$]; found: 472.1041.

Lam S-DB: ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.01 (d, *J*=7.6 Hz, 1H), 7.16 (d, *J*=6.8 Hz, 1H), 7.15 (s, 1H), 7.03 (d, *J*=7.6 Hz, 1H), 6.99 (s, 1H), 6.87 (s, 1H), 6.84–6.75 (m, 3H), 3.39 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.6, 148.4, 148.3, 146.4, 145.7, 145.4, 142.4, 134.2, 128.8, 125.5, 124.7, 122.0, 121.6, 118.1, 117.5, 116.9, 114.3, 112.2, 111.5, 111.1, 109.2, 108.4, 106.3, 105.4, 103.4, 54.5; HRMS (APCI-TOF): *m/z calcd* for $C_{26}H_{17}NO_8$+H$^+$: 472.1027 [*M*+H$^+$]; found:472.1035.

164: ^{1}H NMR (200 MHz, CDCl$_3$): δ=7.46–7.06 (m, 25H), 6.75–6.63 (m, 4H), 6.51 (s, 2H), 6.45 (s, 2H), 5.12 (s, 2H), 5.07 (s, 2H), 5.02 (s, 2H), 4.88 (s, 2H), 4.76 (s, 2H), 4.40 (br s, 2H), 3.99–3.92 (m, 2H), 3.88 (s, 3H), 3.52 (s, 3H), 3.21 (s, 3H), 2.91 (br s, 2H), 0.78 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (50 MHz, CDCl$_3$): δ=161.8, 151.5, 151.4, 149.2, 148.8, 148.3, 146.6, 142.8, 141.3, 137.8, 137.6, 137.4, 137.29, 137.26, 130.3, 128.9, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.72, 127.68, 127.6, 127.4, 127.3, 127.0, 126.7, 124.0, 123.1, 120.5, 120.1, 119.8, 119.4, 119.3, 114.7, 113.8, 105.3, 103.5, 75.3, 72.5, 71.6, 71.4, 70.8, 60.9, 59.5, 55.8, 55.2, 42.5, 22.6, 13.7; IR (UATR): 3032, 2935, 1687, 1603 cm^{-1}.

Lam 45: m.p. dec. 265.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.54 (s, 1H), 9.23 (s, 1H), 9.16 (s, 1H), 8.95 (s, 1H), 6.96 (d, *J*=8.0 Hz, 1H), 6.95 (d, *J*=1.8 Hz, 1H), 6.79 (dd, *J*=8.0, 1.8 Hz, 1H), 6.74 (s, 1H), 6.60 (s, 1H), 6.16 (s, 1H), 4.68–4.48 (m, 2H), 3.72 (s, 3H), 3.63 (s, 3H), 3.24 (s, 3H), 3.01–2.94 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.5, 150.7, 148.5, 147.2, 146.5, 146.0, 144.7, 142.1, 136.3, 135.4, 127.3, 125.5, 123.1, 122.5, 116.4, 115.7, 114.5, 114.3, 112.6, 109.6, 108.6, 103.3, 100.9, 60.3, 55.9, 54.6, 41.7, 21.3; IR (UATR): 3473, 3153, 1661, 1595 cm^{-1}; MS: *m/z* 518 (33) [M^++H], 517 (100) [M^+], 502 (36), 470 (15); HRMS (APCI-TOF): *m/z calcd* for $C_{28}H_{23}NO_9$+H$^+$: 518.1446 [*M*+H$^+$]; found 518.1454.

Lam 46: m.p. > 290.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=10.23 (br s, 1H), 9.87 (br s, 2H), 9.37 (br s, 1H), 9.04 (d, *J*=7.5 Hz, 1H), 7.44 (d, *J*=7.5 Hz, 1H), 7.08 (s, 1H), 7.07 (d, *J*=7.9 Hz, 1H), 6.93 (dd, *J*=7.9, 1.7 Hz, 1H), 6.84 (s, 1H), 6.72 (s, 1H), 6.58 (s, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.36 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.6, 152.7, 148.7, 147.1, 146.8, 145.6, 145.3, 142.4, 135.7, 133.5, 128.7, 125.4, 123.6, 121.0, 120.9, 116.6, 114.8, 112.4, 109.3, 108.6, 107.4, 106.9, 103.5, 97.3, 60.6, 55.9, 54.7; IR (UATR): 3515, 3241, 2926, 1671 cm^{-1}; MS: *m/z* 515 (100) [M^+], 500 (11), 468 (24); HRMS (APCI-TOF): *m/z calcd* for $C_{28}H_{21}NO_9$+H$^+$: 516.1289 [*M*+H$^+$]; found 516.1280.

179: ^{1}H NMR (400 MHz, CDCl$_3$): δ=7.42–7.16 (m, 10H), 7.03 (s, 1H), 6.86 (s, 1H), 6.75 (s, 1H), 6.58 (s, 1H), 6.42 (s, 1H), 5.13 (s, 2H), 4.83 (s, 2H), 4.61 (t, *J*=6.8 Hz, 2H), 4.03 (q, *J*=7.1 Hz, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 3.04 (t, *J*=6.8 Hz, 2H), 0.92 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=161.9, 149.9, 148.5, 148.1, 147.2, 143.8, 137.5, 137.1, 134.5, 129.4, 128.4, 128.1, 127.7, 127.4, 127.2, 127.1, 124.5, 120.9, 120.2, 119.4, 115.3, 110.9, 106.7, 106.1, 103.8, 72.2, 71.3, 59.5, 56.5, 55.9, 42.6, 28.5, 13.7; IR (UATR): 2936, 1682, 1501, 1414 cm^{-1}; MS: *m/z* 620 (7) [M^++H], 619 (19) [M^+], 529 (15), 528 (48), 365 (9), 364 (33), 92 (7), 91 (100), 65 (10); HRMS (APCI-TOF): *m/z calcd* for $C_{38}H_{37}NO_7$+H$^+$: 620.2643 [*M*+H$^+$]; found 620.2633.

Lam 47: m.p. dec. 270.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.66 (s, 1H), 7.40 (s, 1H), 7.35 (s, 1H), 7.26 (s, 1H), 6.98 (s, 1H), 6.81 (s, 1H), 4.55 (t, *J*=6.8 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.08 (t, *J*=6.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.2, 149.5, 148.1, 147.2, 145.5, 145.3, 139.8, 130.9, 125.5, 119.2, 113.7, 111.8, 108.6, 107.9, 105.7, 103.9, 96.3, 56.0, 55.7, 55.6, 41.8, 27.3; HRMS (APCI-TOF): *m/z calcd* for $C_{22}H_{19}NO_6$+H$^+$: 394.1285 [*M*+H$^+$]; found 394.1299.

Lam 47-OAc: m.p. 219.4–219.8°C; ^{1}H NMR (400 MHz, CDCl$_3$): δ=7.27 (s, 1H), 7.18 (s, 1H), 7.10 (s, 1H), 6.82 (s, 1H), 6.79 (s, 1H), 4.72 (t, *J*=6.8 Hz, 2H), 3.99 (s, 3H), 3.94 (s, 6H), 3.11 (t, *J*=6.8 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=168.8, 155.0, 149.9, 148.4, 148.2, 145.0, 140.1, 139.3, 130.2, 125.7, 119.7, 116.0, 115.5, 112.1, 111.2, 107.4, 105.1, 95.9, 56.3, 56.1, 56.0, 42.3, 28.2, 20.6; HRMS (APCI-TOF): *m/z calcd* for $C_{24}H_{21}NO_7$+H$^+$: 436.1391 [*M*+H$^+$]; found 436.1381.

Lam 48: m.p. 221.0–221.2°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.89 (s, 1H), 8.11 (s, 1H), 8.02 (s, 1H), 7.06 (s, 1H), 6.83 (s, 1H), 4.61 (t, J=6.6 Hz, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.04 (t, J=6.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=153.4, 149.5, 147.6, 147.1, 145.6, 144.6, 134.6, 127.8, 126.2, 118.1, 113.2, 111.9, 108.8, 107.7, 104.4, 103.7, 85.5, 55.9, 55.7, 55.6, 42.1, 27.8; HRMS (ESI-TOF): *m/z calcd* for $C_{22}H_{18}N^{79}BrO_6+H^+$: 472.0390 [$M$+H$^+$]; found: 472.0370 and calcd for $C_{22}H_{18}N^{81}BrO_6+H^+$: 474.0373 [$M$+H$^+$]; found: 474.0367.

Lam 48-OAc: m.p. 221.4–221.7°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.38 (s, 1H), 8.15 (s, 1H), 7.14 (s, 1H), 6.82 (s, 1H), 4.78 (t, J=6.6 Hz, 2H), 3.99 (s, 3H), 3.95 (s, 6H), 3.07 (t, J=6.6 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.6, 154.2, 149.6, 147.6, 144.8, 139.3, 135.3, 127.4, 126.0, 118.8, 115.4, 114.7, 111.9, 111.0, 108.8, 105.1, 56.2, 56.1, 55.9, 42.6, 28.7, 20.6; HRMS (ESI-TOF): *m/z calcd* for $C_{24}H_{20}N^{79}BrO_7+H^+$: 514.0496 [$M$+H$^+$]; found: 514.0505 and calcd for $C_{24}H_{20}N^{81}BrO_7+H^+$: 516.0479 [$M$+H$^+$]; found: 516.0476.

Lam 49: m.p. dec. 260.0°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ=10.0 (s, 1H), 9.07 (d, J=7.2 Hz, 1H), 8.74 (s, 1H), 8.21 (s, 1H), 7.35 (s, 1H), 7.28 (d, J=7.2 Hz, 1H), 6.86 (s, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H); HRMS (APCI-TOF): *m/z calcd* for $C_{22}H_{16}N^{79}BrO_6+H^+$: 470.0234 [$M$+H$^+$]; found: 470.0227 and calcd for $C_{22}H_{16}N^{81}BrO_6+H^+$: 472.02165[$M$+H$^+$]; found: 472.0213.

Lam 49-OAc: m.p. 273.0–273.6°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.20 (d, J=7.5 Hz, 1H), 8.77 (s, 1H), 8.36 (s, 1H), 7.13 (s, 1H), 6.99 (s, 1H), 6.98 (d, J=7.5 Hz, 1H), 4.08 (s, 3H), 4.00 (s, 3H), 3.95 (s, 3H), 2.38 (s, 3H); HRMS (APCI-TOF): *m/z calcd* for $C_{24}H_{18}N^{79}BrO_7+H^+$: 512.0339 [$M$+H$^+$]; found: 512.0357 and calcd for $C_{24}H_{18}N^{81}BrO_7+H^+$: 514.0319 [$M$+H$^+$]; found: 514.0334.

170: ^{1}H NMR (200 MHz, $CDCl_3$): δ=6.84–6.72 (m, 3H), 3.86 (s, 6H), 3.85 (s, 2H), 3.53 (q, J=7.0 Hz, 2H), 3.35 (s, 3H), 2.78 (t, J=7.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=169.3, 148.8, 147.5, 131.1, 120.4, 111.8, 111.3, 71.8, 59.0, 55.8, 55.7, 39.9, 35.1; IR (UATR): 3360, 3295, 1650, 1513 cm^{-1}; HRMS (APCI-TOF): *m/z calcd* for $C_{13}H_{19}NO_4+H^+$: 254.1387 [M+H$^+$]; found: 254.1375.

175: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.69 (s, 1H), 7.42–7.16 (m, 10H), 6.89 (s, 1H), 6.75 (s, 1H), 6.60 (s, 1H), 5.12 (s, 2H), 4.88 (s, 2H), 4.60 (t, J=6.6 Hz, 2H), 3.97 (q, J=7.1 Hz, 2H), 3.908 (s, 3H), 3.906 (s, 3H), 3.85 (s, 3H), 3.54 (s, 3H), 3.03 (t, J=6.6 Hz, 2H), 0.84 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.7, 150.3, 148.0, 147.8, 147.4, 143.9, 142.2, 137.6, 137.1, 128.4, 128.1, 127.7, 127.3, 127.2, 127.0, 124.3, 123.5, 120.8, 120.5, 117.1, 116.0, 115.6, 110.7, 107.4, 103.5, 71.9, 71.2, 61.0, 59.3, 56.5, 55.8, 42.5, 28.8, 13.6; IR (UATR): 2935, 1684, 1501, 1484 cm^{-1}; MS: *m/z* 650 (43) [M^++H], 649 (100) [M^+], 634 (13), 618 (12), 559 (25), 558 (69), 485 (10), 467 (13), 439 (16), 424 (18), 395 (13), 394 (43), 364 (11), 91 (10); HRMS (APCI-TOF): *m/z calcd* for $C_{39}H_{39}NO_8+H^+$: 650.2748 [M+H$^+$]; found: 650.2742.

Lam 50: m.p. 214.5–215.6°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.76 (br s, 1H), 7.62 (s, 1H), 7.45 (s, 1H), 7.01 (s, 1H), 6.83 (s, 1H), 4.54 (t, J=6.7 Hz, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.06 (t, J=6.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.0, 149.1, 148.0, 147.2, 145.3, 145.2, 136.5, 128.9, 125.8, 120.7, 118.3, 111.9, 109.5, 107.4, 105.1, 103.6, 61.5, 55.9, 55.6, 55.5, 41.9, 27.5; HRMS (ESI-TOF): *m/z calcd* for $C_{23}H_{21}NO_7+H^+$: 424.1391 [M+H$^+$]; found: 424.1397.

Lam 50-OAc: m.p. 269.8–271.3°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.70 (s, 1H), 7.65 (s, 1H), 7.09 (s, 1H), 6.79 (s, 1H), 4.68 (t, J=6.7 Hz, 2H), 3.98 (s, 3H), 3.95 (s, 3H), 3.94 (s, 3H), 3.93 (s, 3H), 3.08 (t, J=6.7 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.9, 154.8, 149.1, 148.2, 148.1, 144.3, 138.8, 137.4, 129.3, 125.5, 120.3, 118.8, 115.0, 111.6, 110.9, 110.8, 107.5, 105.5, 61.4, 56.0, 55.8, 55.7, 42.0, 28.1, 20.3; IR (UATR): 2935, 1770, 1698 cm^{-1}; HRMS (ESI-TOF): *m/z calcd* for $C_{25}H_{23}NO_8+H^+$: 466.1496 [M+H$^+$]; found: 466.1505.

Lam 51-OAc: m.p. > 290.0°C; ^{1}H NMR (300 MHz, $CDCl_3+CD_3OD$): δ=8.92 (d, J=7.4 1H), 7.99 (s, 1H), 7.69 (s, 1H), 7.07 (s, 1H), 7.00 (s, 1H), 6.91 (d, J=7.4 Hz, 1H), 4.01 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3+CD_3OD$): δ=168.9, 154.8, 150.3, 150.0, 148.3, 144.9, 139.8, 134.3, 128.2, 123.9, 122.5, 120.7, 118.0, 114.7, 112.8, 112.0, 109.5, 107.4, 106.4, 104.4, 61.6, 56.2, 55.8, 20.4; IR (UATR): 2933, 1759, 1701 cm^{-1}; HRMS (ESI-TOF): *m/z calcd* for $C_{25}H_{23}NO_8+H^+$: 464.1340 [M+H$^+$]; found: 464.1343.

Lam 51: m.p. dec. 265.6°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.98 (s, 1H), 8.90 (d, J=7.4 Hz, 1H), 8.02 (s, 1H), 7.59 (s, 1H), 7.42 (s, 1H), 7.22 (d, J=7.4 Hz, 1H), 6.91 (s, 1H), 4.00 (s, 3H), 3.98 (s, 3H), 3.93 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.0, 150.1, 149.9, 148.1, 145.8, 145.4, 133.5, 127.4, 123.5, 121.8, 121.4, 117.3, 112.5, 108.2, 106.8, 105.9, 104.0, 103.7, 103.1, 55.9, 55.6, 55.5; HRMS (ESI-TOF): *m/z calcd* for $C_{23}H_{19}NO_7+H^+$: 422.1234 [M+H$^+$]; found: 422.1231.

173: ^{1}H NMR (200 MHz, $CDCl_3$): δ=6.80 (s, 1H), 6.76 (dd, J=5.6, 1.8 Hz, 2H), 3.90 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.65–3.48 (m, 3H), 2.79 (t, J=7.1 Hz, 2H), 1.13 (d, J=6.1 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=170.0, 148.8, 147.5, 131.1, 120.5, 111.8, 111.3, 72.7, 67.5, 55.8, 55.7, 39.8, 35.1, 21.8; IR (UATR): 3411, 2971, 2933, 1668, 1513 cm^{-1}; MS: *m/z* 281 (11) [M^+], 165 (13), 164 (100), 151 (20), 149 (11); HRMS (APCI-TOF): *m/z calcd* for $C_{15}H_{23}NO_4+H^+$: 282.1700 [M+H$^+$]; found: 282.1689.

178: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.84 (s, 1H), 7.43–7.20 (m, 10H), 6.93 (s, 1H), 6.74 (s, 1H), 6.57 (s, 1H), 5.12 (s, 2H), 4.88 (s, 2H), 4.59 (br s, 2H), 3.98 (q, J=7.1 Hz, 2H), 3.93 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 3.03 (br s, 2H), 1.05 (d, J=6.1 Hz, 6H), 0.85 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.9, 150.3, 147.6, 147.2, 143.8, 139.4, 137.7, 137.0, 128.4, 128.1, 127.7, 127.3, 127.2, 126.8, 124.5, 124.3, 121.2, 120.8, 117.4, 116.3, 115.6, 110.7, 107.9, 103.1, 75.1, 71.4, 71.3, 59.4, 56.6, 55.8, 42.5, 28.8, 22.4, 13.7; IR (UATR): 2934, 1684, 1555 cm^{-1}; MS: *m/z* 678 (39) [M^++H], 677 (78) [M^+], 635 (36), 634 (86), 588 (22), 545 (31), 544 (100), 470 (14), 452 (22), 425 (17), 380 (18), 364 (15), 190 (10), 91 (7); HRMS (APCI-TOF): *m/z calcd* for $C_{41}H_{43}NO_8+H^+$: 678.3061 [M+H$^+$]; found: 678.3048.

Lam 52: m.p. dec. 250.0°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ=9.71 (s, 1H), 7.64 (s, 1H), 7.48 (s, 1H), 7.00 (s, 1H), 6.82 (s, 1H), 4.54 (t, J=6.3 Hz, 2H), 4.28 (sept, J=6.0 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.06 (t, J=6.3 Hz, 2H), 1.32 (d, J=6.0 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=154.0, 148.9, 147.5, 146.9, 145.11, 144.96, 133.1, 129.7, 125.9, 121.5, 118.8, 111.7, 109.7, 108.0, 107.6, 105.2, 103.5, 76.1, 55.7, 55.6, 55.5, 41.9, 27.6, 22.0; HRMS (ESI-TOF): *m/z calcd* for $C_{25}H_{25}NO_7+H^+$: 452.1704 [M+H$^+$]; found: 452.1709.

Lam 52-OAc: m.p. 226.0–226.5°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.74 (s, 1H), 7.71 (s, 1H), 7.11 (s, 1H), 6.80 (s, 1H), 4.70 (t, J=6.5 Hz, 2H), 4.50 (sept, J=6.2 Hz, 1H), 3.98 (s, 3H), 3.94 (s, 6H), 3.09 (t, J=6.5 Hz, 2H), 2.35 (s, 3H), 1.37 (d, J=6.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.8, 154.9, 149.1, 148.1, 147.9, 144.6, 138.9, 134.5, 130.1, 125.7, 121.3, 119.6, 115.5, 111.8, 111.3, 111.0, 108.4, 106.2, 76.5, 56.2, 56.03, 55.97, 42.3, 28.6, 22.4, 20.6; HRMS (ESI-TOF): *m/z calcd* for $C_{27}H_{27}NO_8+H^+$: 494.1809 [M+H$^+$]; found: 494.1824.

Lam 53-OAc: m.p. 245.8–247.2°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.09 (d, J=7.2 Hz, 1H), 8.19 (s, 1H), 7.76 (s, 1H), 7.16 (s, 1H), 7.06 (s, 1H), 6.96 (d, J=7.2 Hz, 1H), 4.55 (sept, J=6.0 Hz, 1H), 4.11 (s, 3H), 4.01 (s, 3H), 3.98 (s, 3H), 2.37 (s, 3H), 1.43 (d, J=6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.8, 154.7, 150.1, 149.5, 148.0, 145.2, 139.7, 131.3, 128.9, 124.1, 122.8, 121.5, 118.5, 115.1, 112.7, 112.1, 107.4, 107.0, 105.4, 104.8, 76.7, 56.2, 56.03, 55.97, 22.4, 20.6; HRMS (ESI-TOF): *m/z calcd* for $C_{27}H_{25}NO_8+H^+$: 492.1653 [M+H$^+$]; found: 492.1651.

Lam 53: m.p. dec. 260.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.91 (s, 1H), 8.84 (d, J=7.3 Hz, 1H), 8.00 (s, 1H), 7.49 (s, 1H), 7.30 (s, 1H), 7.10 (d, J=7.3 Hz, 1H), 6.85 (s, 1H), 4.46–4.41 (m, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.88 (s, 3H), 1.34 (d, J=5.6 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=153.9, 149.9, 149.2, 147.8, 145.7, 145.0, 129.9, 128.2, 123.5, 122.0, 121.7, 117.5, 112.3, 107.9, 107.1, 106.1, 104.8, 103.6, 103.3, 76.3, 55.7, 55.5, 55.4, 21.9; HRMS (ESI-TOF): *m/z calcd* for $C_{25}H_{23}NO_7+H^+$: 450.1547 [M+H$^+$]; found: 450.1555.

171: m.p. 86.0–88.0°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.49–7.34 (m, 5H), 6.84 (d, J=8.5 Hz, 1H), 6.65 (d, J=8.5 Hz, 1H), 5.95 (br s, 1H), 5.08 (s, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.37 (q, J=6.4 Hz, 2H), 2.70 (t, J=6.4 Hz, 2H), 2.04 (q, J=7.7 Hz, 2H), 1.02 (t, J=7.7 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=173.6, 152.3, 150.3, 142.1, 137.3, 128.3, 128.0, 127.9, 125.2, 124.3, 107.6, 75.1, 60.6, 55.8, 40.5, 29.4, 9.6; IR (UATR): 3301, 2937, 1646, 1544, 1495 cm^{-1}; MS: *m/z* 344 (13) [M^++H], 343 (37) [M^+], 271 (18), 270 (100), 255 (16), 252 (23), 239 (23), 238 (27), 196 (16), 180 (16), 179 (30), 167 (33), 91 (80); HRMS (APCI-TOF): *m/z calcd* for $C_{20}H_{25}NO_4+H^+$: 344.1862 [M+H$^+$]; found: 344.1864.

176: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.26–6.94 (m, 16H), 6.60 (s, 1H), 6.48 (s, 1H), 4.94 (s, 2H), 4.93 (s, 2H), 4.66 (d, J=2.8 Hz, 2H), 4.33–4.20 (m, 2H), 3.90–3.75 (m, 2H), 3.77 (s, 3H), 3.70 (s, 3H), 3.64 (s, 3H), 2.71 (q, J=6.3 Hz, 2H), 2.03 (s, 3H), 0.67 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.4, 151.8, 150.2, 148.8, 147.1, 143.6, 140.9, 137.4, 137.0, 136.8, 130.4, 129.2, 128.2, 128.09, 128.08, 127.8, 127.4, 127.0, 126.9, 126.7, 124.9, 119.8, 118.8, 118.1, 115.9, 104.5, 103.4, 75.0, 71.7, 70.9, 60.6, 58.9, 56.2, 55.7, 41.7, 22.7, 13.4, 11.8; IR (UATR): 2935, 1684, 1525 cm^{-1}; MS: *m/z* 741 (13) [M^++2H], 740 (49) [M^++H], 739 (100) [M^+], 650 (16), 649 (48), 648 (57), 559 (10), 558 (15), 531 (13), 484 (9), 369 (9), 368 (21), 342 (15), 311 (9), 236 (8), 181 (6), 91 (42); HRMS (APCI-TOF): *m/z calcd* for $C_{46}H_{45}NO_8+H^+$: 740.3223 [M+H$^+$]; found: 740.3209.

Lam 54: m.p. 247.7–248.4°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=7.45 (s, 1H), 6.91 (s, 1H), 6.83 (s, 1H), 4.50 (t, *J*=6.5 Hz, 2H), 3.884 (s, 3H), 3.880 (s, 3H), 3.74 (s, 3H), 2.91 (t, *J*=6.5 Hz, 2H), 2.71 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.2, 151.4, 147.4, 146.6, 145.4, 144.9, 136.6, 135.9, 127.5, 123.0, 115.0, 112.7, 109.6, 109.1, 105.7, 103.8, 101.5, 60.3, 56.0, 55.8, 41.3, 21.7, 12.5; IR (UATR): 3420, 3313, 2924, 1668 cm^{-1}; MS: *m/z* 425(5) [M^++2H], 424 (25) [M^++H], 423 (100) [M^+], 422 (4) [M^+-H], 409 (11); HRMS (APCI-TOF): *m/z calcd* for $C_{23}H_{21}NO_7$+H$^+$: 424.1396 [*M*+H$^+$]; found: 424.1396.

180: ^{1}H NMR (200 MHz, $CDCl_3$): δ=9.75 (S, 1H), 9.61 (s, 1H), 9.31 (d, *J*=7.6 Hz, 1H), 7.58–7.00 (m, 16H), 6.79 (s, 1H), 6.61 (s, 1H), 5.24 (s, 2H), 5.16 (d, *J*=2.4 Hz, 2H), 4.85 (s, 2H), 4.19 (s, 3H), 4.06 (S, 3H), 4.03 (t, *J*=6.7 Hz, 2H), 3.83 (s, 3H), 0.81 (t, *J*=6.7 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=186.6, 161.4, 153.5, 150.2, 148.4, 146.1, 143.7, 143.5, 139.2, 137.0, 136.8, 134.8, 128.5, 128.4, 128.2, 127.8, 127.5, 127.1, 126.8, 122.3, 121.8, 120.6, 116.4, 115.9, 115.6, 115.4, 109.9, 105.8, 102.6, 76.0, 71.4, 71.3, 61.1, 60.0, 56.7, 56.5, 13.6; IR (UATR): 2938, 1692, 1661 cm^{-1}; MS: *m/z* 753 (100) [M^++2H], 751 (5) [*M*]; HRMS (APCI-TOF): *m/z calcd* for $C_{46}H_{41}NO_9$+H$^+$: 752.2859 [*M*+H$^+$]; found: 752.2862.

Lam 55: m.p. dec. 260.0°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.90 (s, 2H), 8.97 (d, *J*=7.5 Hz, 1H), 7.65 (s, 1H), 7.52 (s, 1H), 7.38 (d, *J*=7.5 Hz, 1H), 6.89 (s, 1H), 4.01 (s, 3H), 3.93 (s, 3H), 3.81 (s, 3H), 3.00 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.0, 152.9, 147.4, 145.9, 145.4, 144.7, 135.4, 133.3, 128.1, 121.4, 120.6, 114.4, 108.8, 106.8, 106.7, 106.1, 106.0, 103.8, 97.2, 60.5, 55.8, 55.4, 13.1; IR (UATR): 3481, 2947, 1700 cm^{-1}; MS: *m/z* 422 (28) [M^++H], 421 (100) [M^+], 406 (25), 378 (8), 360 (12); HRMS (APCI-TOF): *m/z calcd* for $C_{23}H_{19}NO_7$+H$^+$: 422.1240[*M*+H$^+$]; found: 424.1241.

172: ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.67–7.44 (m, 5H), 7.02 (d, *J*=8.4 Hz, 1H), 6.83 (d, *J*=8.4 Hz, 1H), 6.30 (br s, 1H), 5.25 (s, 2H), 4.07 (s, 3H), 4.03 (s, 3H), 3.55 (q, *J*=6.1 Hz, 2H), 2.89 (t, *J*=6.6 Hz, 2H), 2.17 (t, *J*=7.5 Hz, 2H), 1.80–1.61 (m, 2H), 1.02 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=172.8, 152.3, 150.3, 142.1, 137.3, 128.3, 128.0, 127.9, 125.2, 124.3, 107.6, 75.1, 60.6, 55.8, 40.5, 38.4, 29.4, 18.9, 13.6; IR (UATR): 3300, 2962, 2933, 1645, 1544, 1495 cm^{-1}; MS: *m/z* 358 (4) [M^++H], 357 (5) [M^+], 270 (17), 196 (5), 179 (8), 167 (10), 92 (9), 91 (100), 65 (18), 43 (9), 41 (19); HRMS (APCI-TOF): *m/z calcd* for $C_{21}H_{27}NO_4$+H$^+$: 358.2018 [*M*+H$^+$]; found: 358.2020.

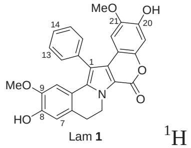
177: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.41–7.10 (m, 16H), 6.74 (s, 1H), 6.59 (s, 1H), 5.10 (s, 4H), 4.82 (s, 2H), 4.50–4.33 (m, 2H), 3.95 (s, 3H), 3.90 (s, 3H), 3.83 (s, 3H), 2.87 (t, *J*=6.4 Hz, 2H), 2.68–2.53 (m, 2H), 1.14 (t, *J*=7.3 Hz, 3H), 0.78 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.6, 152.1, 150.4, 149.0, 147.2, 143.7, 141.1, 137.7, 137.2, 137.1, 130.3, 129.0, 128.5, 128.4, 128.1, 127.7, 127.3, 127.2, 126.8, 124.9, 122.9, 120.3, 119.1, 118.6, 115.8, 104.4, 103.4, 75.2, 71.7, 71.1, 60.9, 59.2, 56.5, 55.9, 41.9, 22.8, 18.8, 14.9, 13.6; IR (UATR): 2960, 2934, 1684, 1603, 1524, 1490, 1463 cm^{-1}; HRMS (APCI-TOF): *m/z calcd* for $C_{47}H_{47}NO_8$+H$^+$: 754.3380 [*M*+H$^+$]; found: 754.3376.

Lam 56: m.p. dec. 281.7°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.76 (s, 1H), 9.30 (s, 1H), 7.38 (s, 1H), 6.85 (s, 2H), 4.53 (t, *J*=6.4 Hz, 2H), 3.88 (s, 6H), 3.75 (s, 3H), 3.13 (q, *J*=7.3 Hz, 2H), 2.91 (t, *J*=6.4 Hz, 2H), 1.48 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.2, 151.5, 147.5, 146.7, 145.4, 145.1, 136.6, 135.5, 126.8, 122.8, 115.8, 115.1, 112.9, 109.1, 105.4, 103.9, 100.6, 60.4, 55.9, 55.6, 41.3, 21.6, 18.8, 14.4; IR (UATR): 3439, 2959, 1703, 1599, 1540 cm^{-1}; MS: *m/z* 438 (29) [M^++H], 437 (100) [M^+], 423 (20), 422 (77); HRMS (APCI-TOF): *m/z calcd* for $C_{24}H_{23}NO_7$+H$^+$: 438.1553 [*M*+H$^+$]; found: 438.1557.

Lam 56-OAc: m.p. 260.0–261.4°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.51 (s, 1H), 7.24 (s, 1H), 7.13 (s, 1H), 4.69 (t, *J*=6.4 Hz, 2H), 3.97 (s, 3H), 3.94 (s, 3H), 3.91 (s, 3H), 3.18 (q, *J*=7.5 Hz, 2H), 2.87 (t, *J*=6.4 Hz, 2H), 2.42 (s, 3H), 2.36 (s, 3H), 1.57 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=168.7, 154.9, 152.1, 147.9, 144.8, 141.8, 141.2, 138.6, 135.1, 126.5, 123.4, 120.5, 116.7, 114.8, 112.2, 107.6, 105.6, 60.9, 56.2, 56.1, 41.4, 22.7, 20.7, 20.5, 19.4, 14.4; IR (UATR): 2961, 1770, 1751, 1703 cm^{-1}; MS: *m/z* 522 (15) [M^++H], 521 (48) [M^+], 480 (27), 479 (100), 438 (12), 437 (49), 423 (11), 422 (38), 43 (9); HRMS (APCI-TOF): *m/z calcd* for $C_{28}H_{27}NO_9$+H$^+$: 522.1764 [*M*+H$^+$]; found: 522.1781.

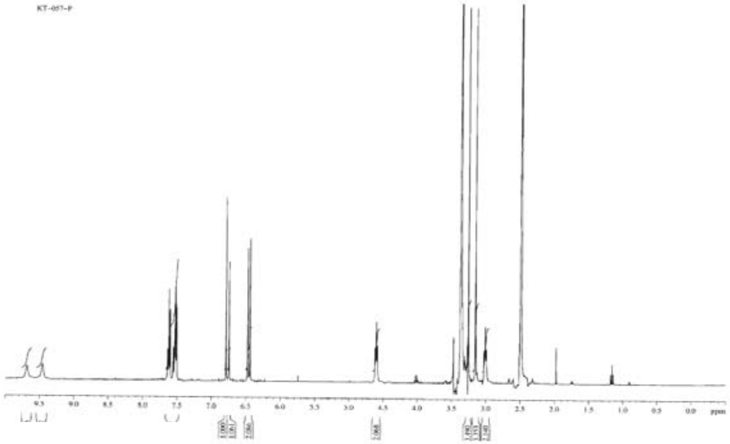
Lam 57-OAc: m.p. 252.7–254.0°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=9.07 (d, *J*=7.5 Hz, 1H), 7.70 (s, 1H), 7.54 (s, 1H), 7.10 (s, 1H), 6.88 (d, *J*=7.5 Hz, 1H), 4.04 (s, 3H), 3.98 (s, 3H), 3.93 (s, 3H), 3.29 (q, *J*=7.5 Hz, 2H), 2.49 (s, 3H), 2.36 (s, 3H), 1.52 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=168.6, 154.5, 153.2, 147.9, 145.2, 141.5, 139.5, 139.0, 132.8, 127.4, 123.3, 121.3, 118.3, 116.1, 114.1, 112.3, 108.7, 106.1, 105.9, 103.6, 60.9, 56.2, 55.9, 20.6, 20.5, 20.1, 13.6; IR (UATR): 2928, 1769, 1696, 1615, 1531 cm^{-1}; MS: *m/z* 521 (7) [M^++2H], 520 (30) [M^++H], 519 (100) [M^+], 478 (20), 477 (70), 436 (24), 435 (94), 421 (20), 420 (78), 43 (69); HRMS (APCI-TOF): *m/z calcd* for $C_{28}H_{25}NO_9$+H$^+$: 520.1607 [*M*+H$^+$]; found: 520.1618.

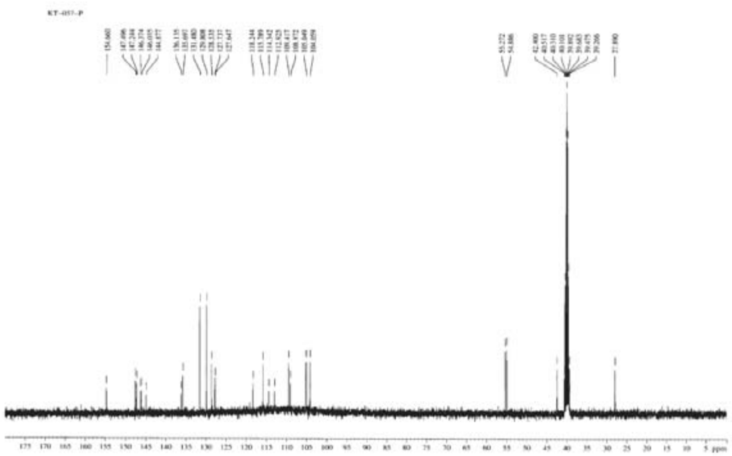
Lam 57: m.p. dec. 283.4°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.94 (s, 2H), 9.02 (d, *J*=7.4 Hz, 1H), 7.56 (s, 1H), 7.45 (s, 1H), 7.41 (d, *J*=7.4 Hz, 1H), 6.92 (s, 1H), 4.01 (s, 3H), 3.93 (s, 3H), 3.82 (s, 3H), 3.51–3.43 (m, 2H), 1.43 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=154.2, 153.3, 147.8, 146.1, 145.8, 145.2, 135.7, 133.0, 128.0, 121.1, 120.9, 114.8, 112.9, 108.5, 107.1, 107.0, 105.9, 104.1, 96.7, 60.6, 55.9, 55.5, 19.5, 13.8; IR (UATR): 3435, 2963, 1698 cm^{-1}; MS: *m/z* 436 (25) [M^++H], 435 (83) [M^+], 421 (26), 420 (100), 406 (7), 405 (18), 390 (7), 362 (8), 359 (9); HRMS (APCI-TOF): *m/z calcd* for $C_{24}H_{21}NO_7$+H$^+$: 436.1396 [*M*+H$^+$]; found: 436.1393.

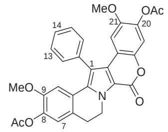


Lam **1**

^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

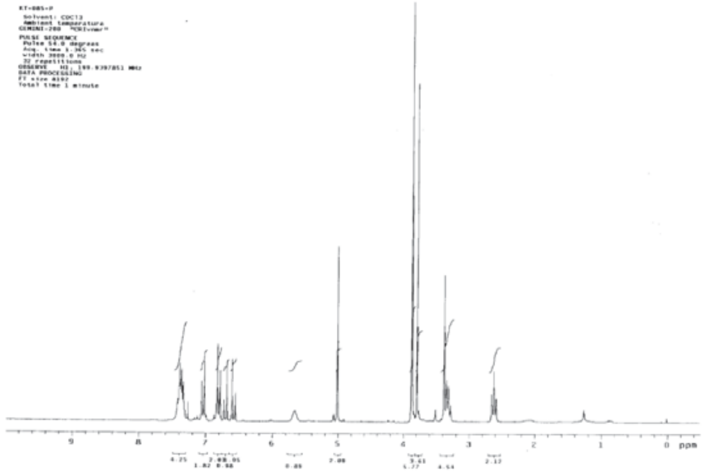


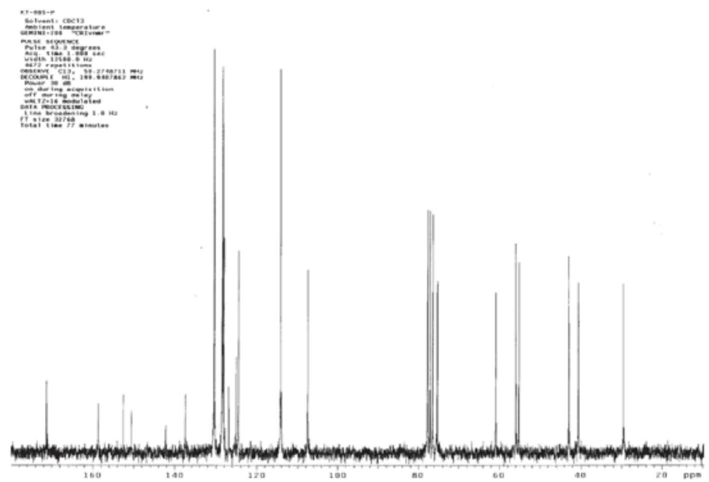


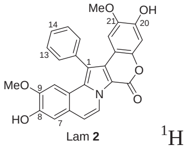


Lam **1-OAc**

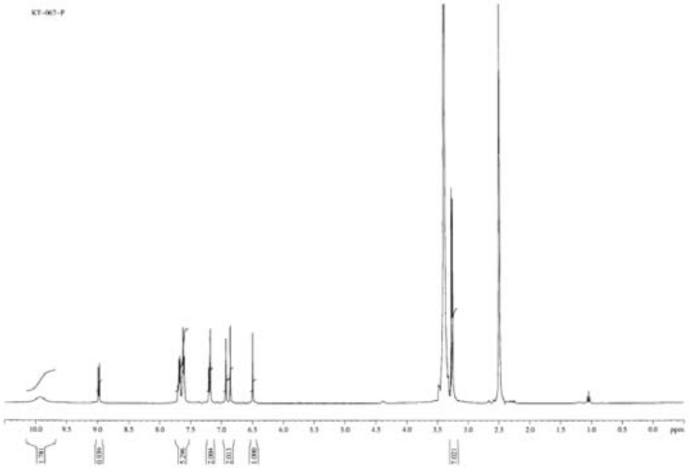
^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

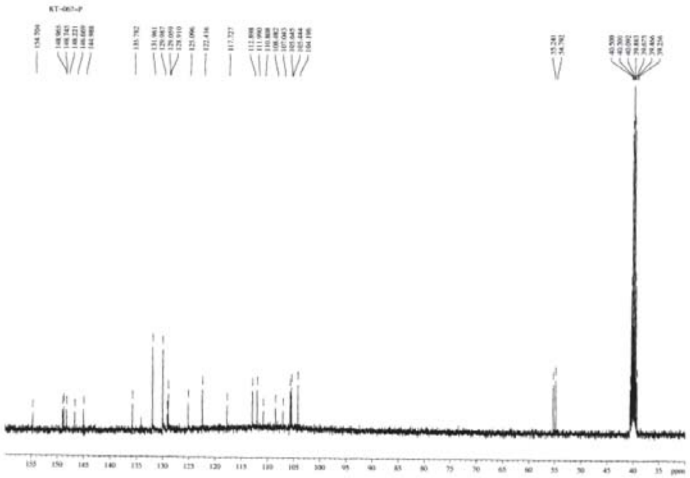


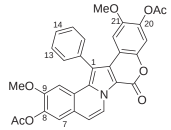




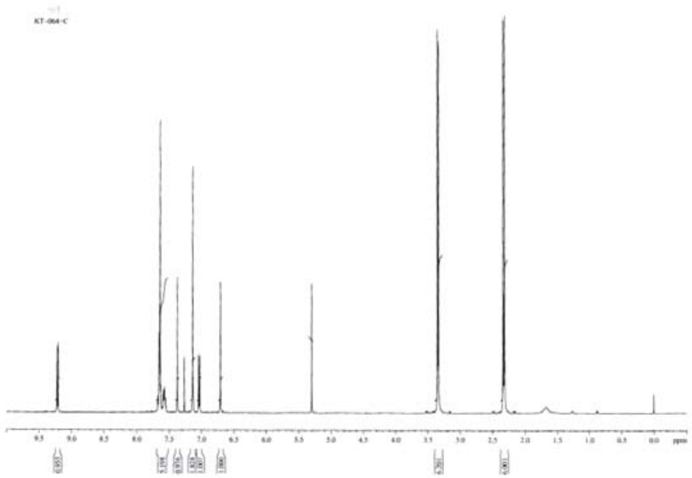
Lam **2** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

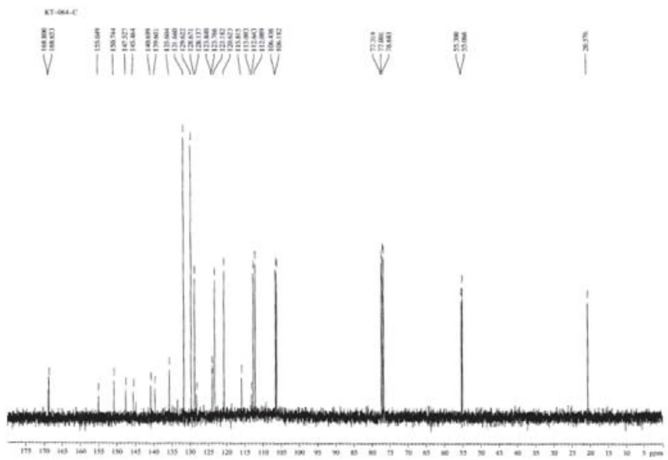


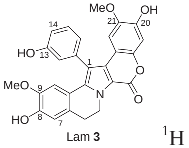




Lam **2-OAc** ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

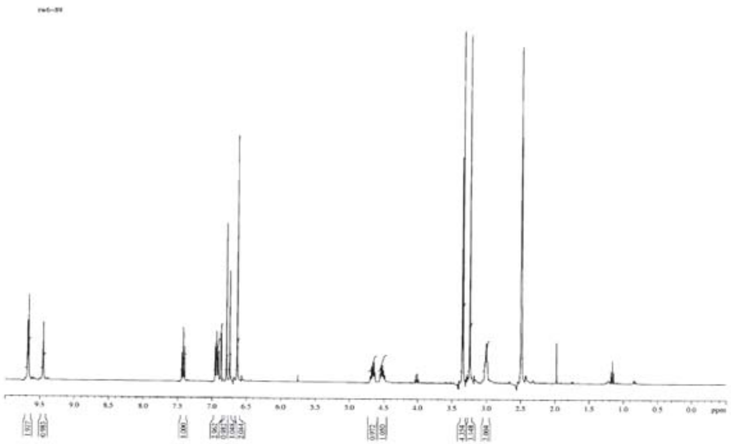


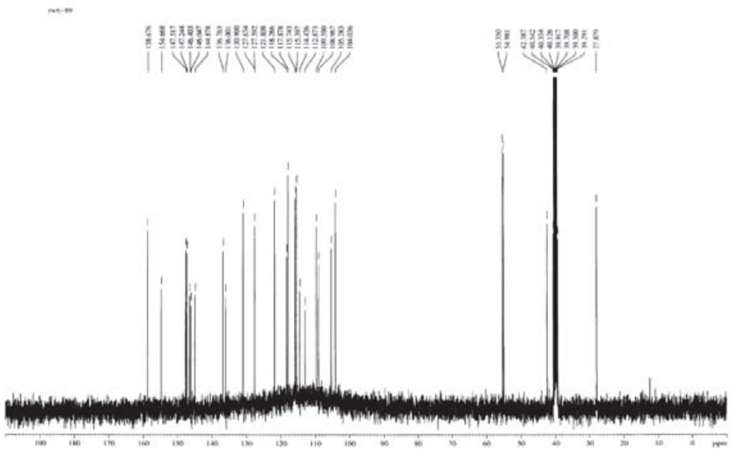


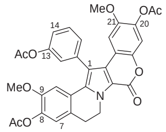


Lam **3**

^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

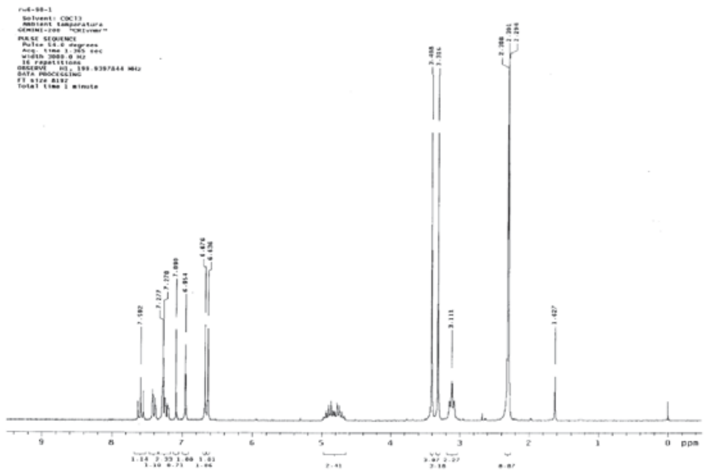


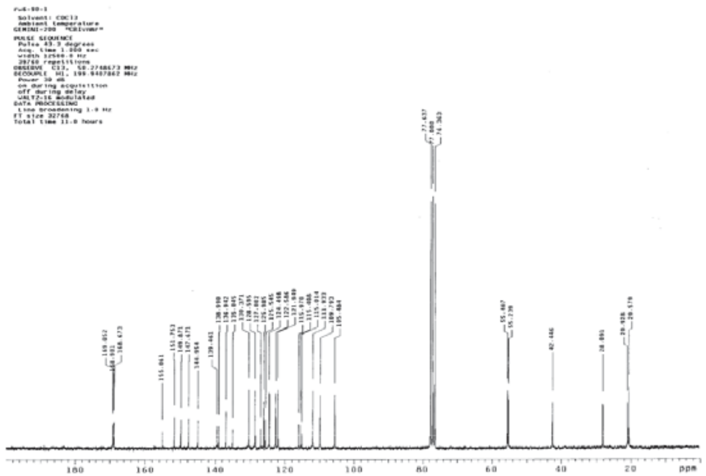


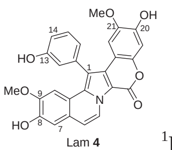


Lam **3-OAc**

^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

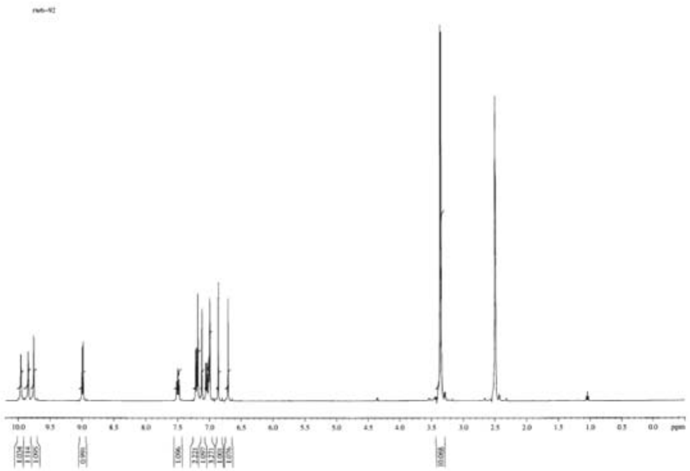


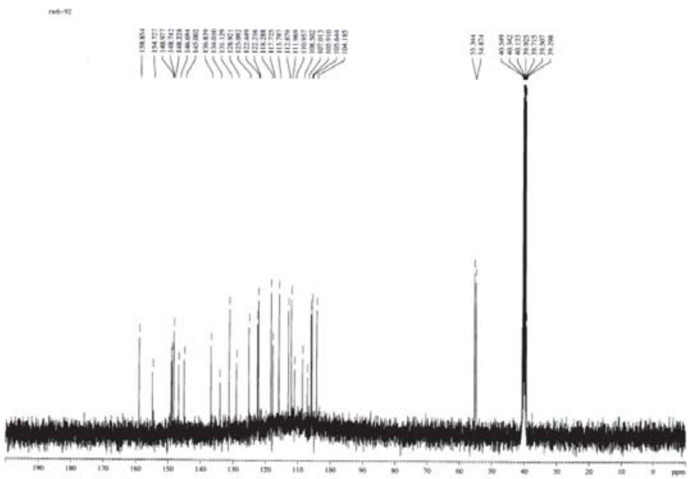


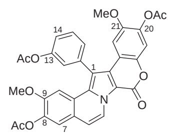


Lam **4**

^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

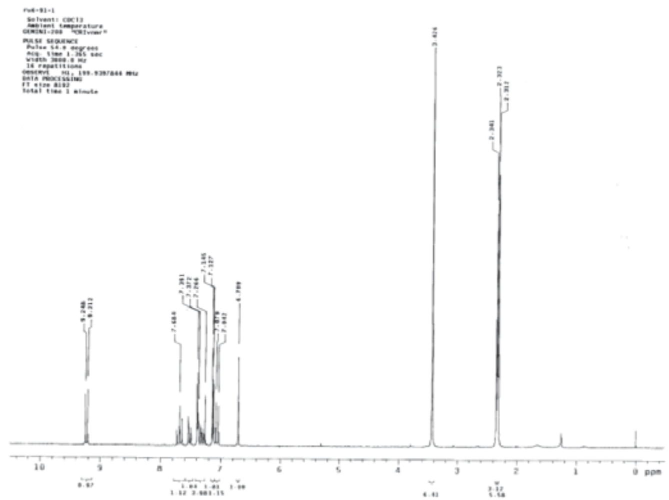


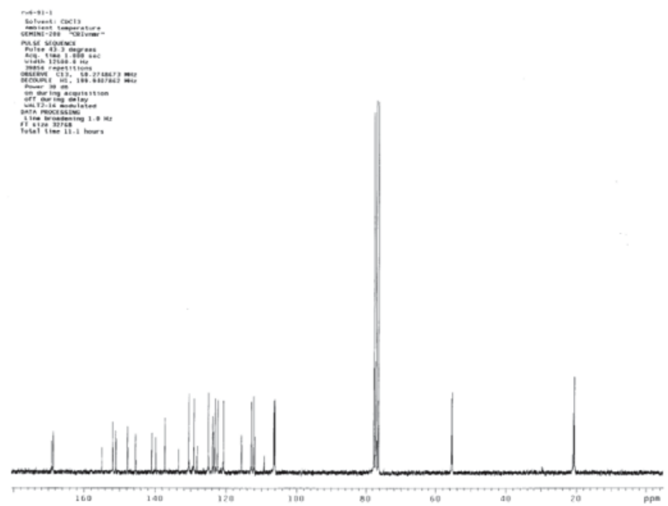


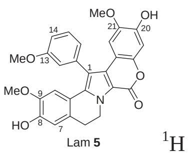


Lam **4-OAc**

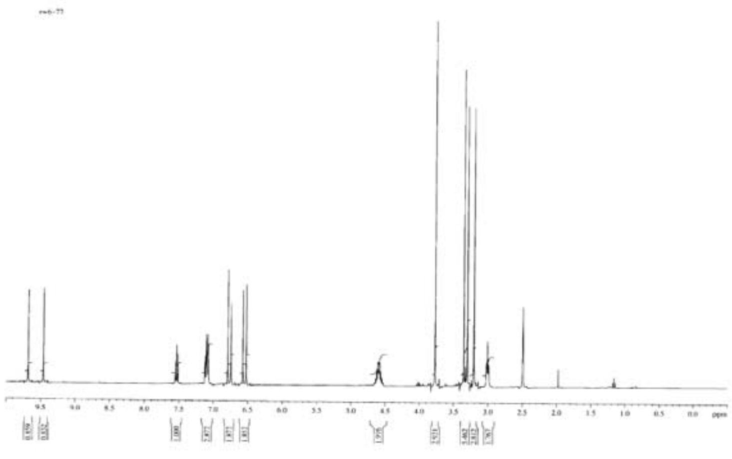
^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

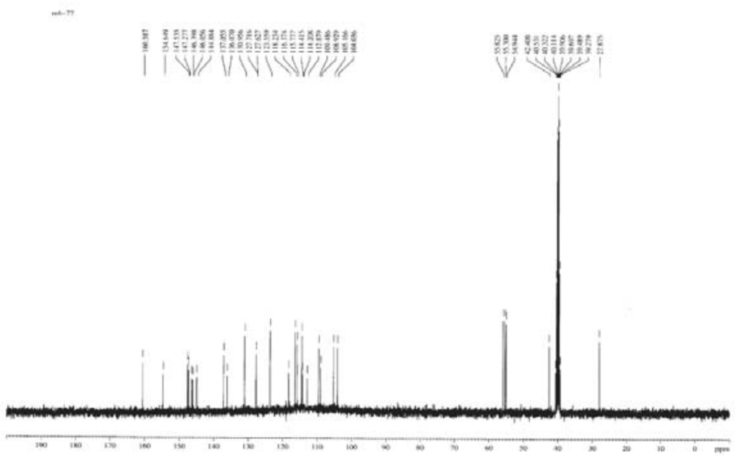


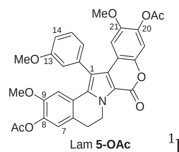




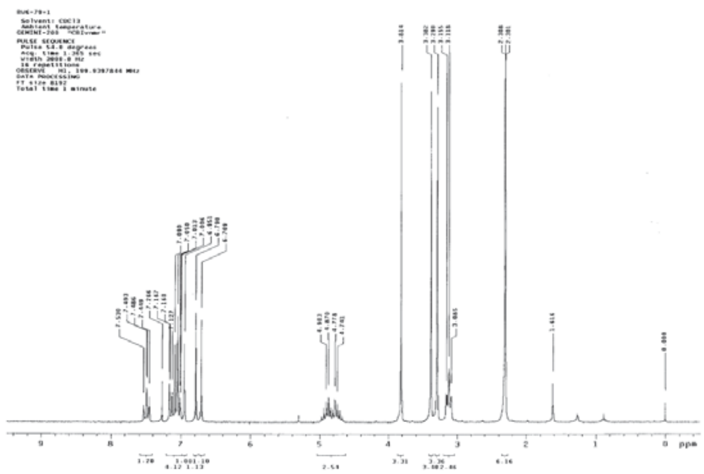
Lam **5** ^1H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

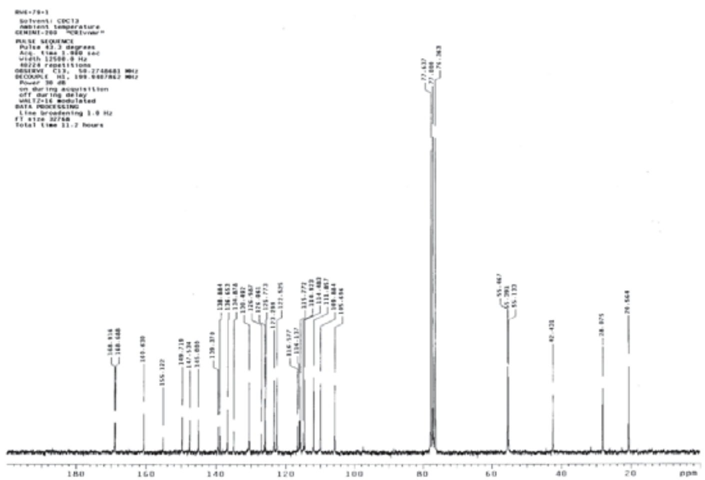


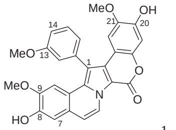




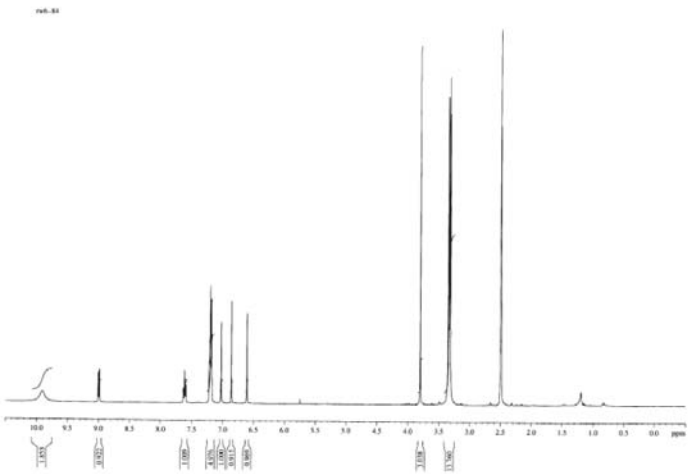
Lam **5-OAc** ^1H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

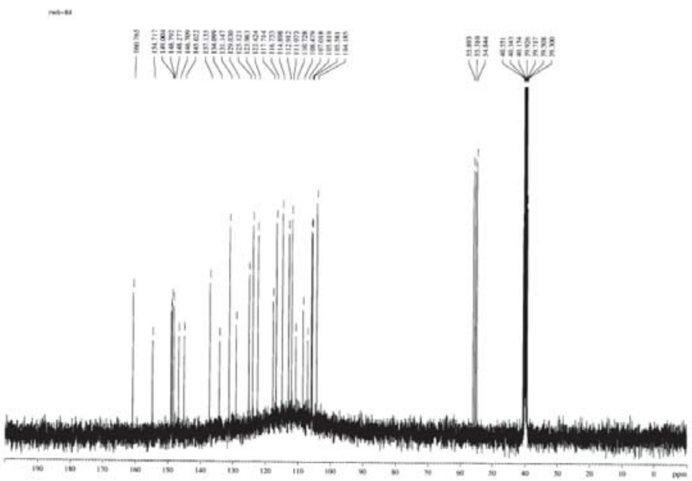


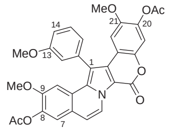




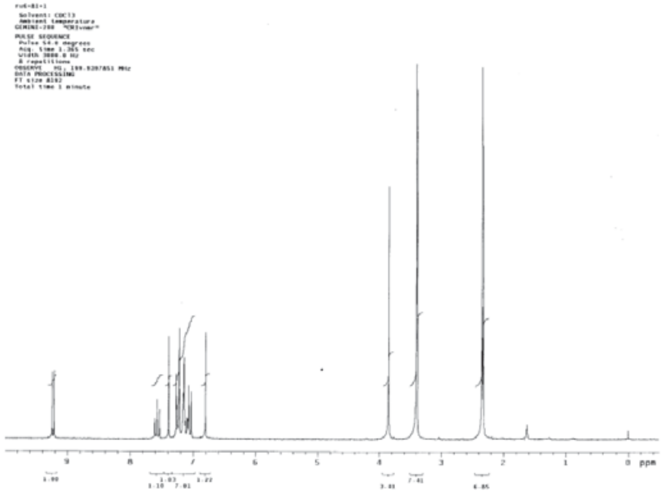
Lam **6** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

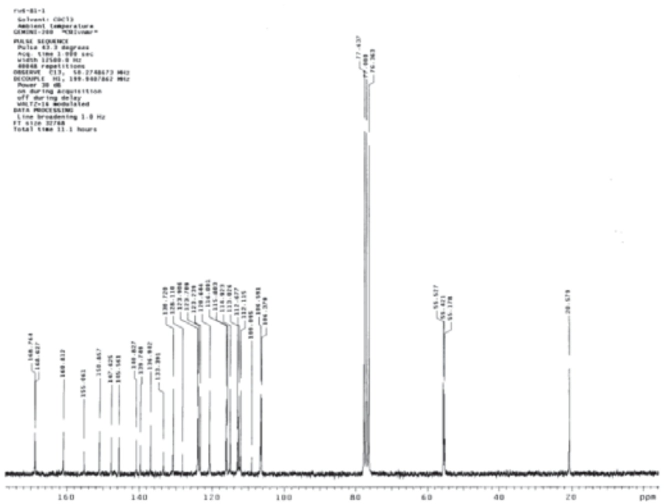


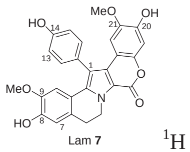




Lam **6-OAc** ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

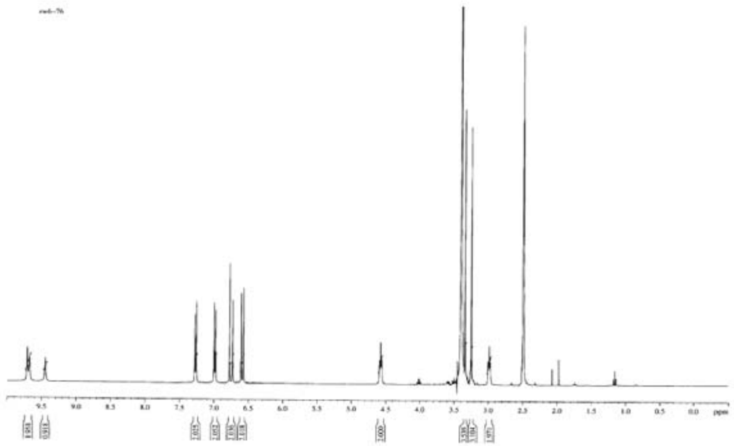


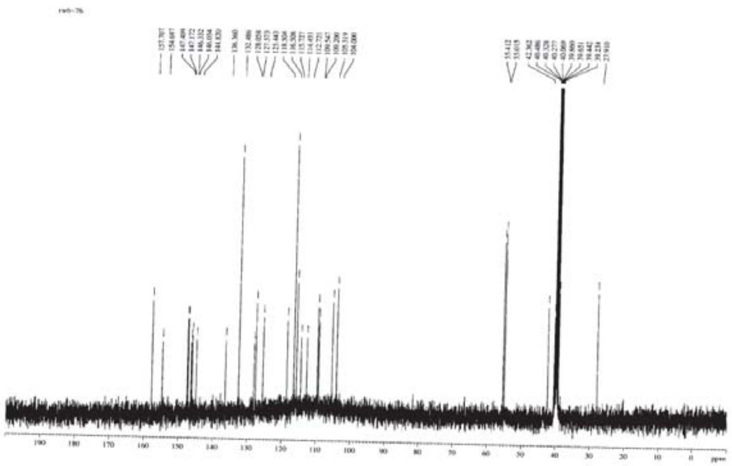


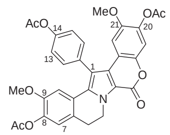


Lam **7**

^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

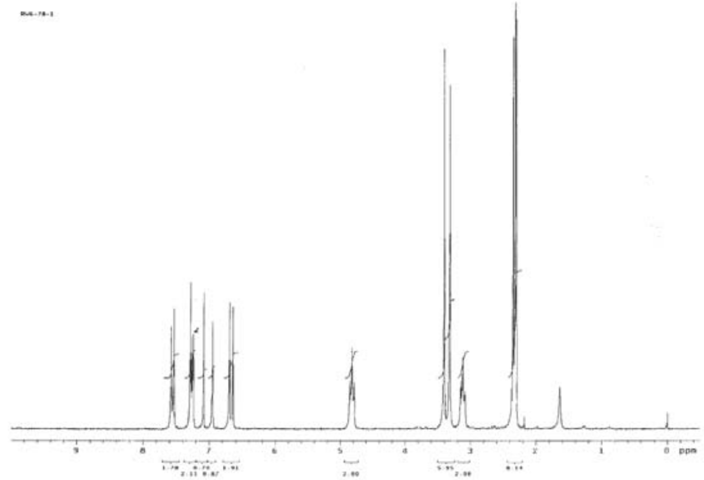


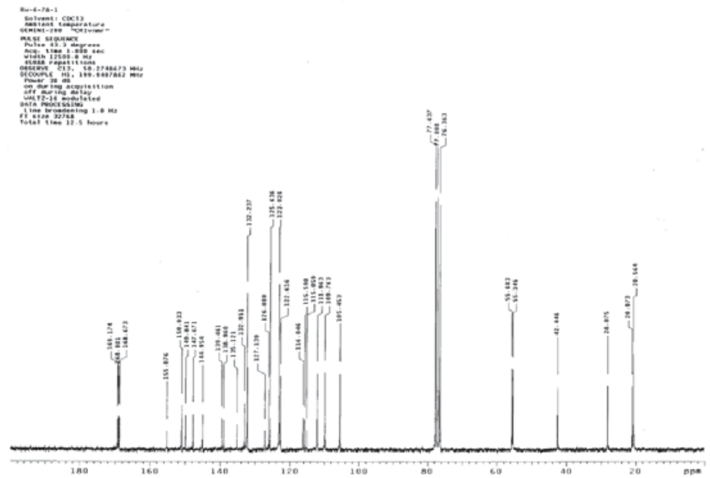


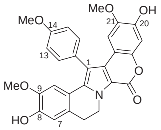


Lam **7-OAc**

^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

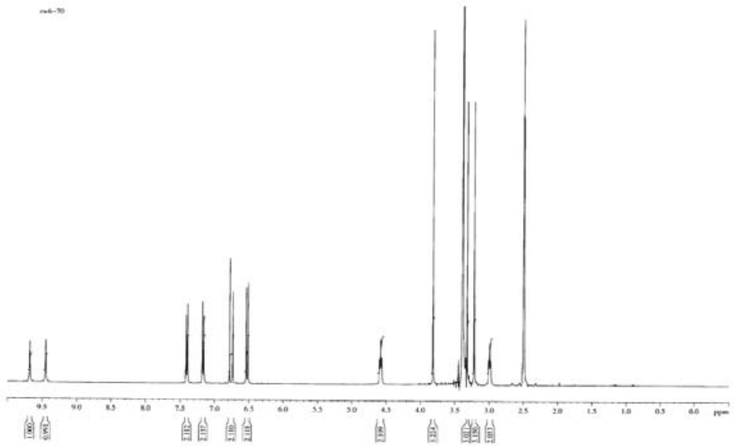


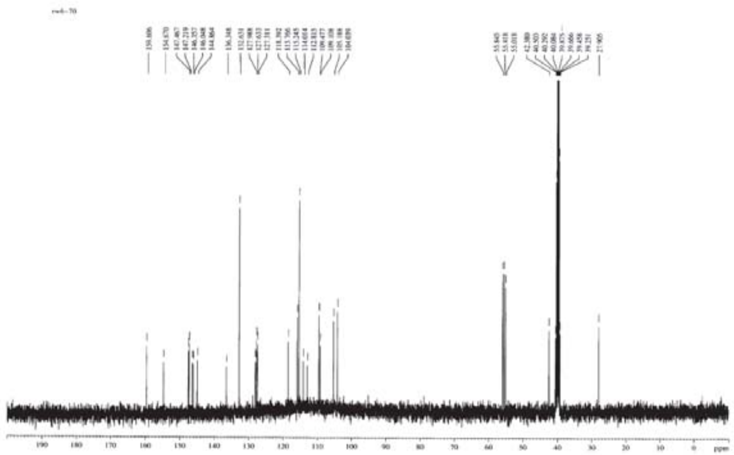


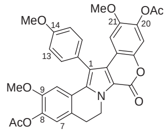


Lam **9**

^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

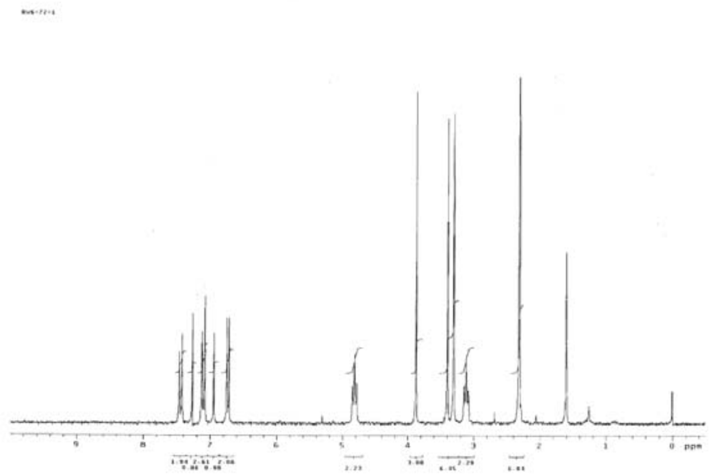


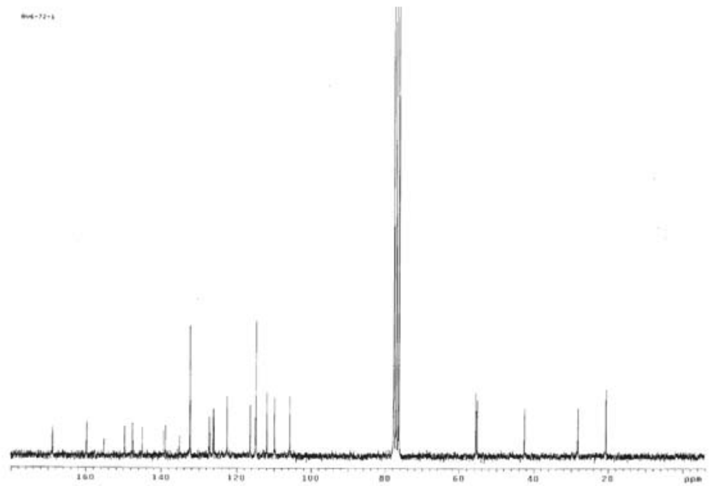


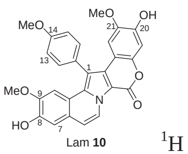


Lam **9-OAc**

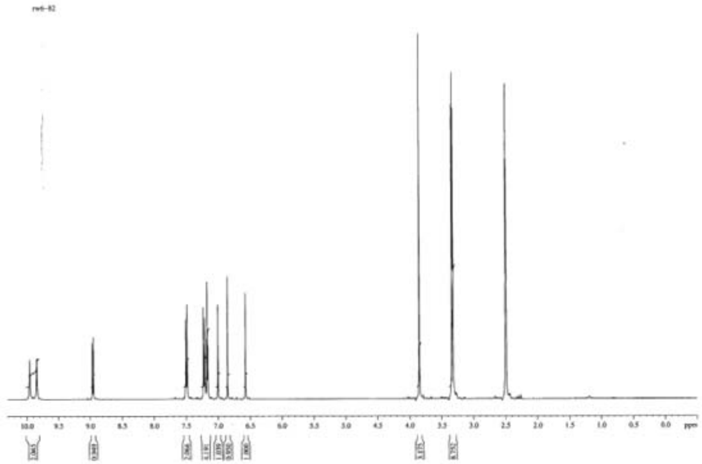
^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

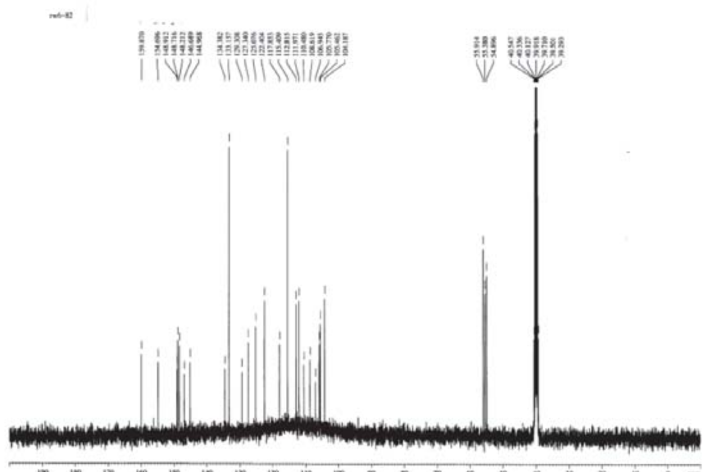


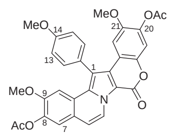




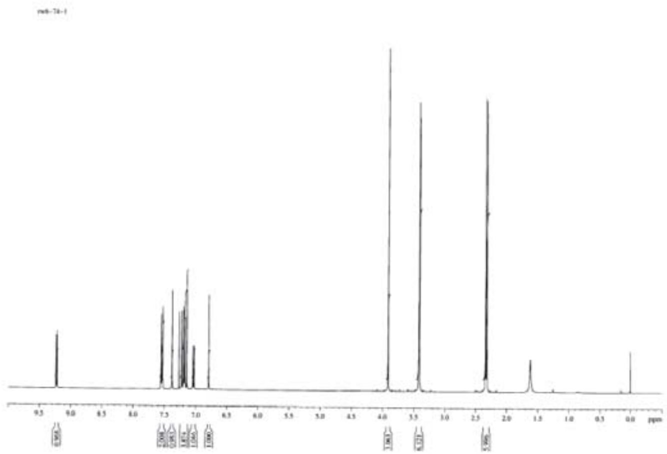
Lam **10** [1]H NMR (400 MHz, DMSO-d_6) and [13]C NMR (100 MHz, DMSO-d_6)

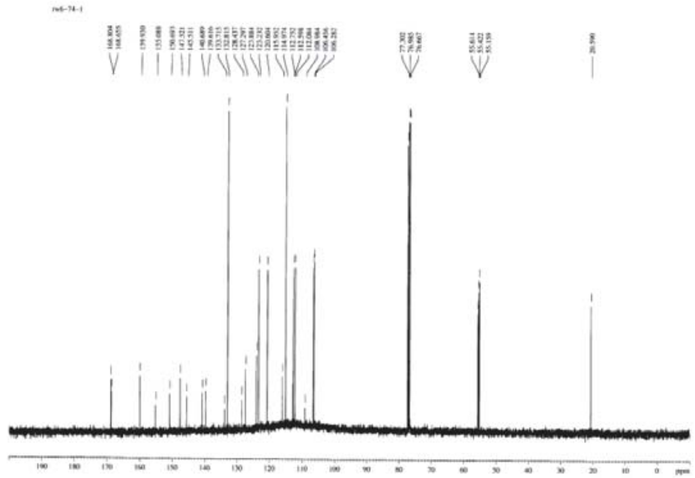


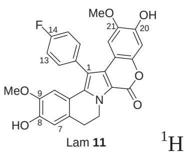




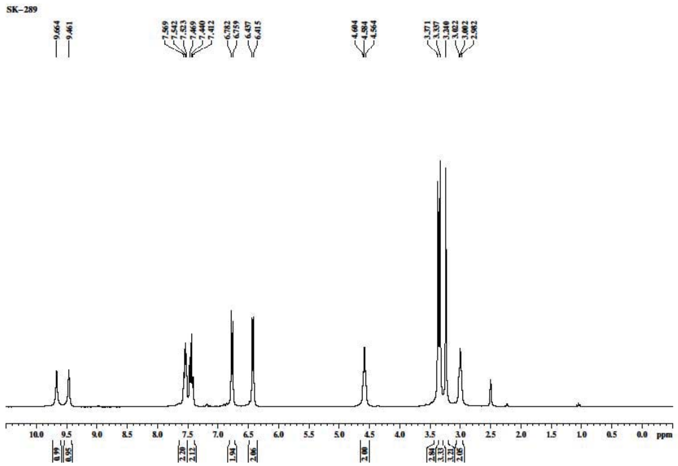
Lam **10-OAc** [1]H NMR (400 MHz, $CDCl_3$) and [13]C NMR (100 MHz, $CDCl_3$)

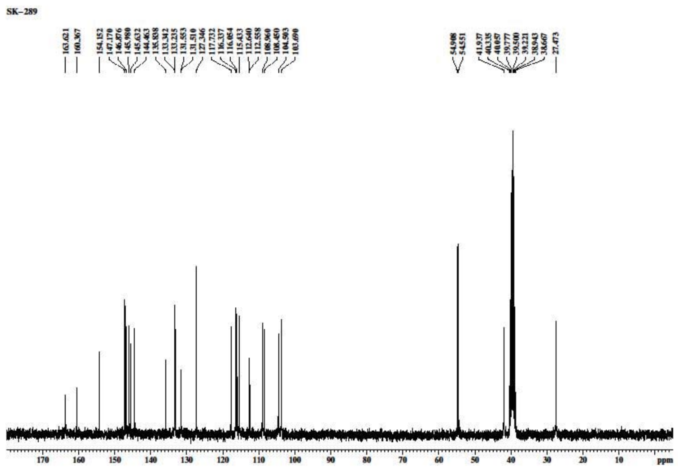


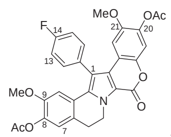




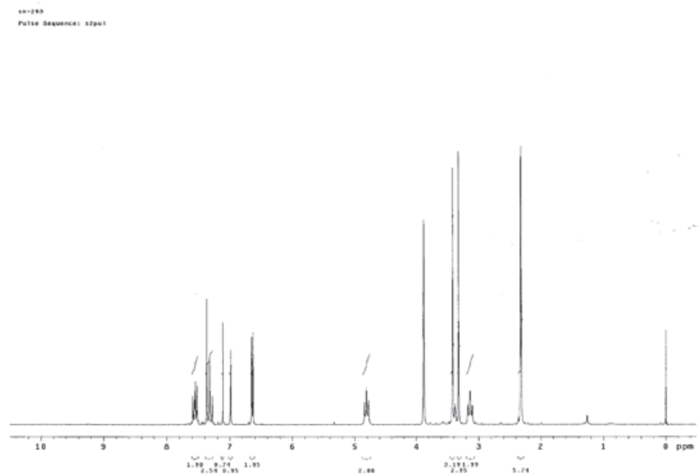
Lam **11** ^{1}H NMR (300 MHz, DMSO-d_6) and ^{13}C NMR (75 MHz, DMSO-d_6)

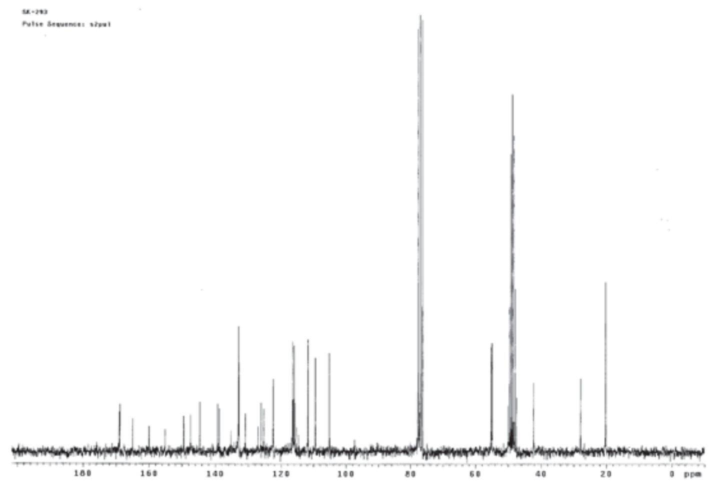


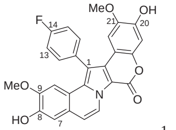




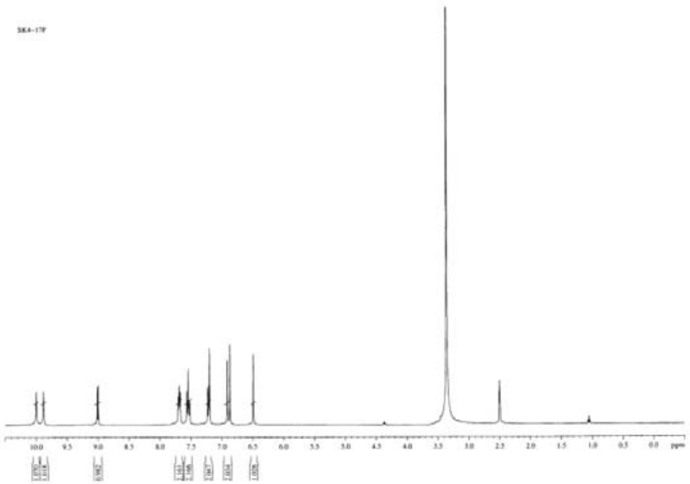
Lam **11-OAc** ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$)

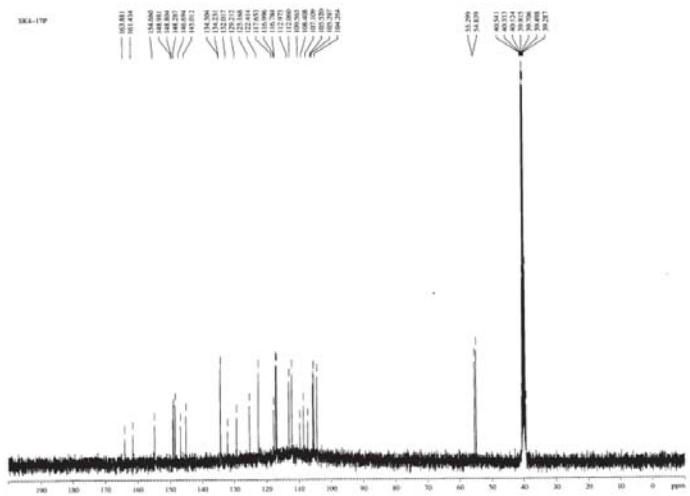


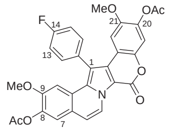




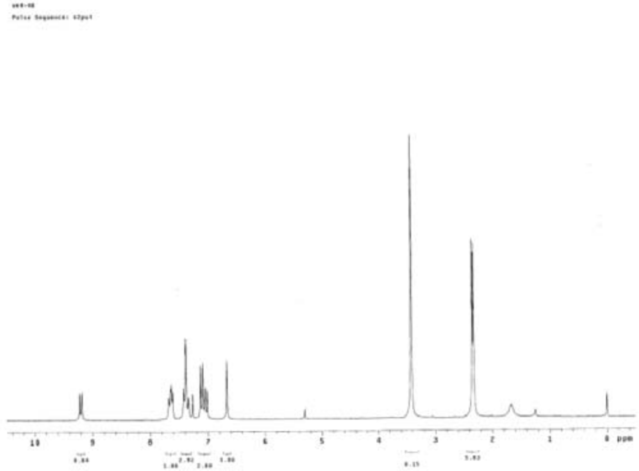
Lam **12** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

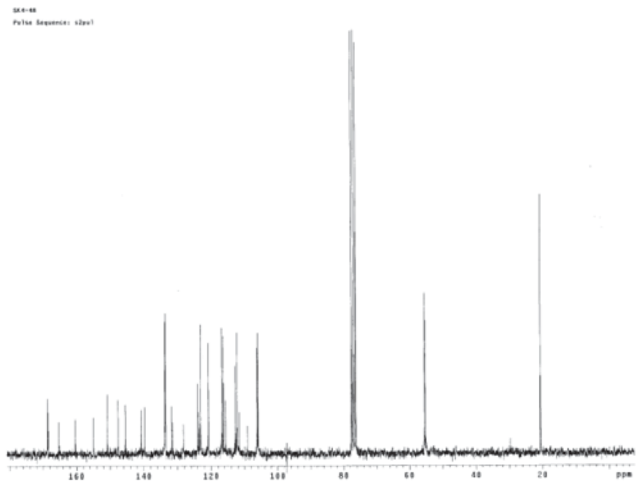


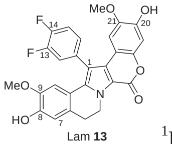




Lam **12-OAc** ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

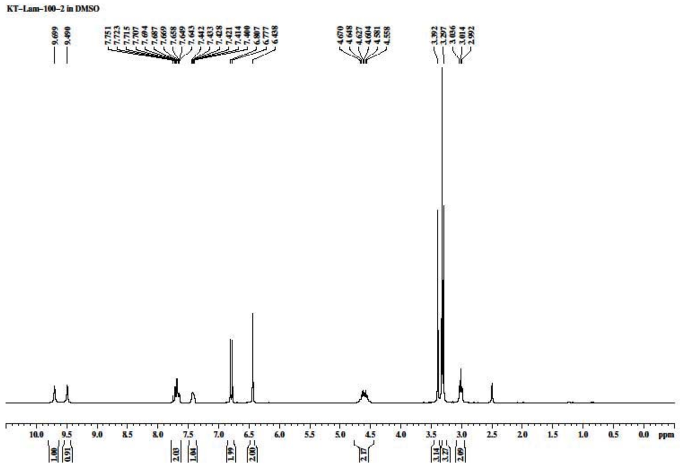


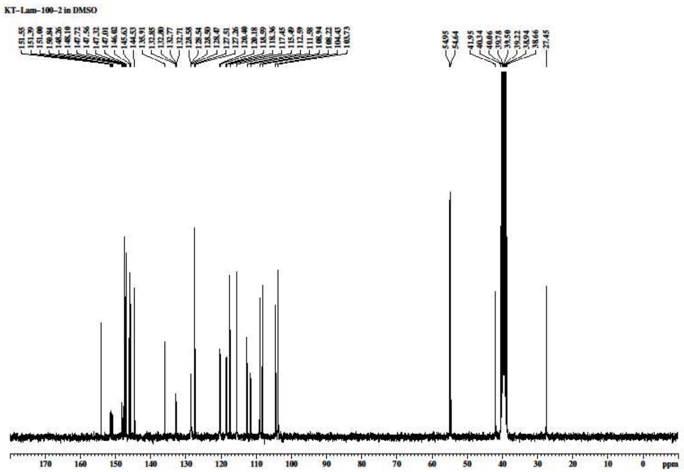


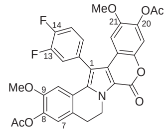


Lam **13**

^{1}H NMR (300 MHz, DMSO-d_6) and ^{13}C NMR (75 MHz, DMSO-d_6)

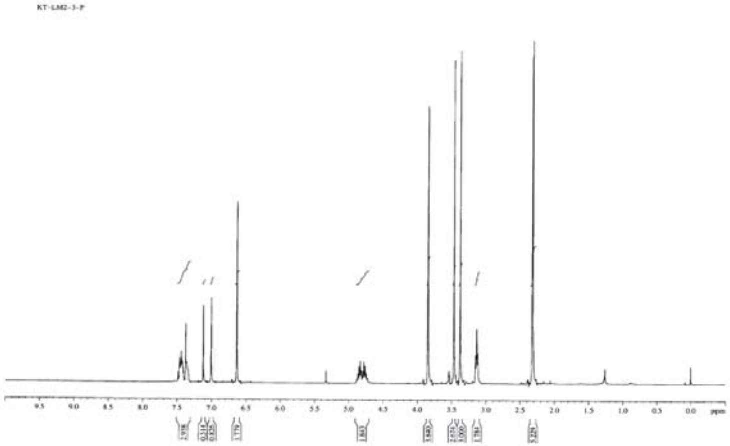


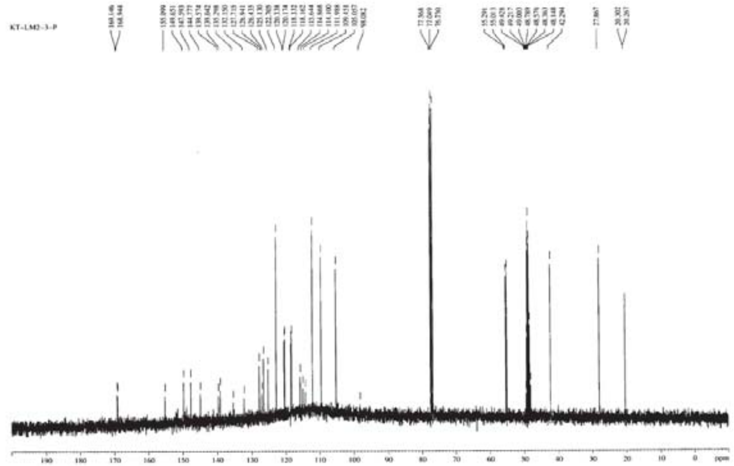


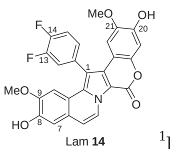


Lam **13-OAc**

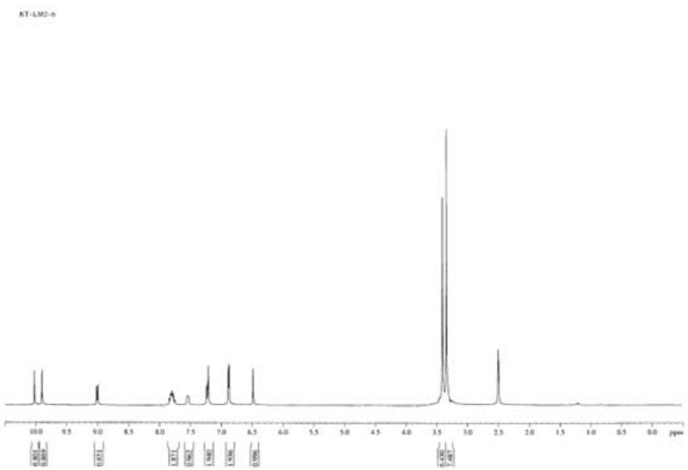
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

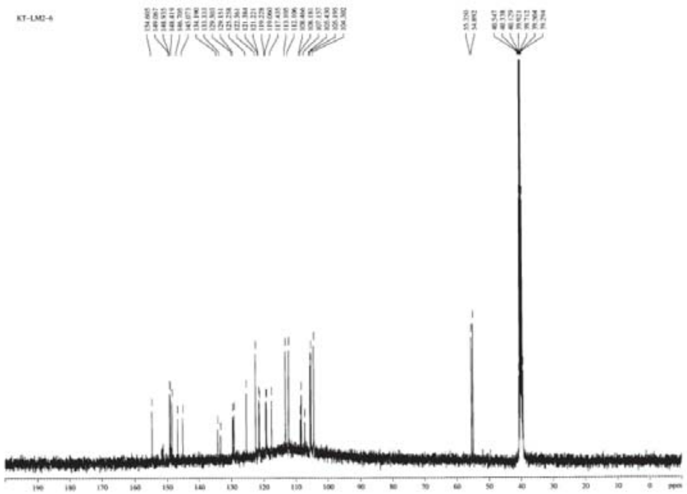


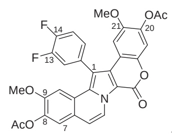




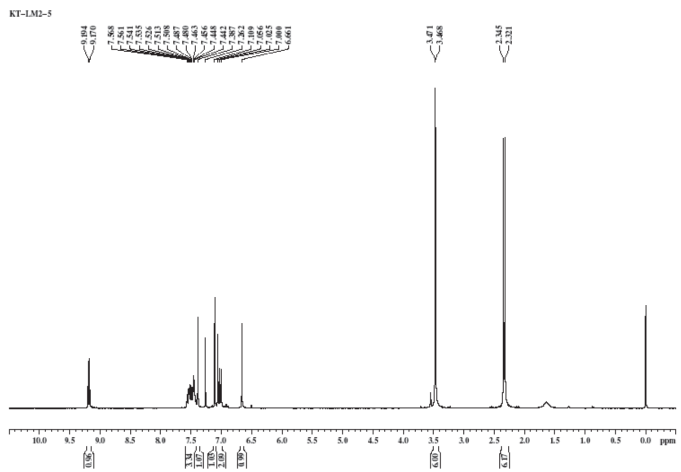
Lam **14** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

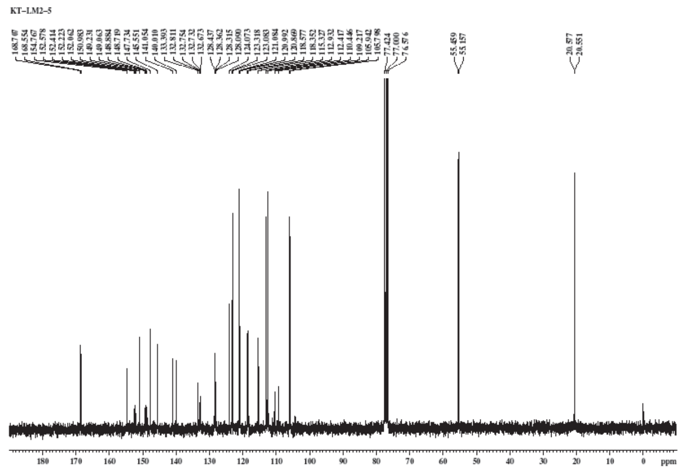


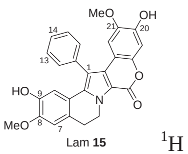




Lam **14-OAc** ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$)

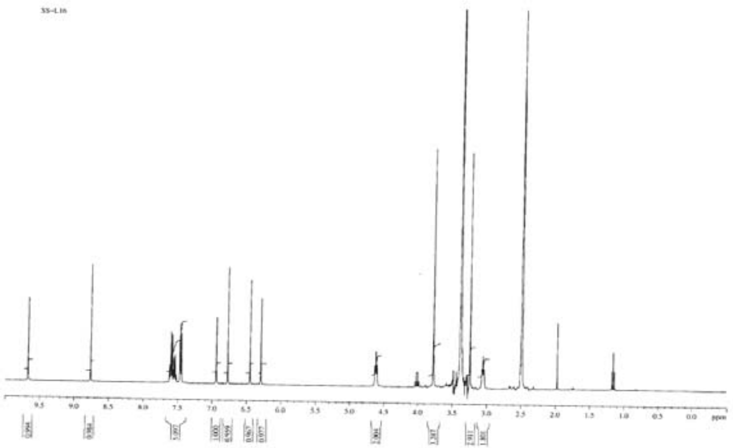


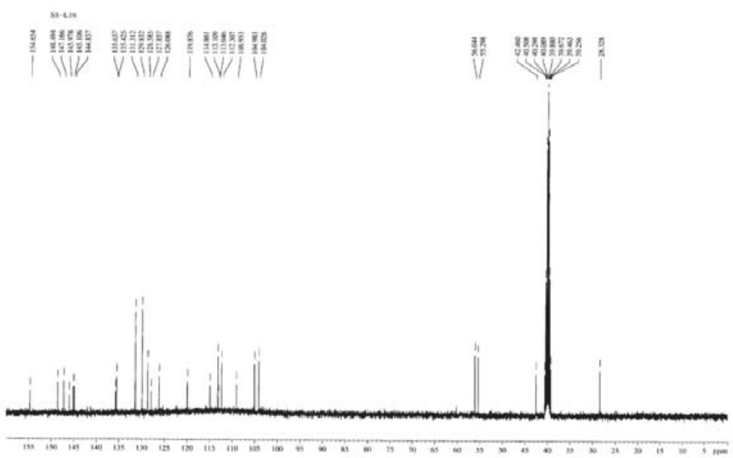


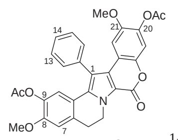


Lam **15**

^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

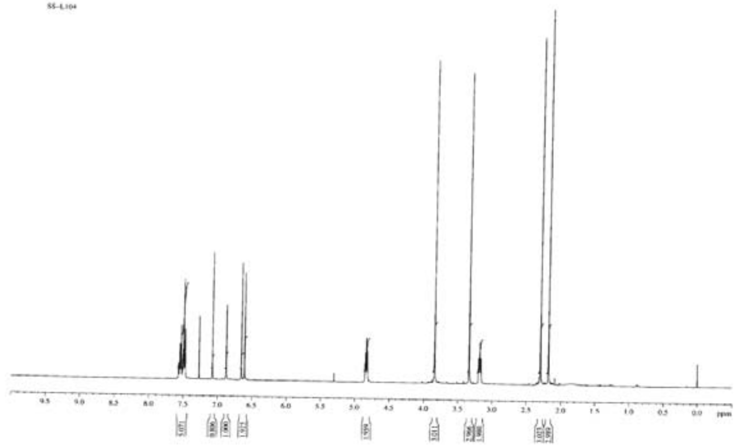


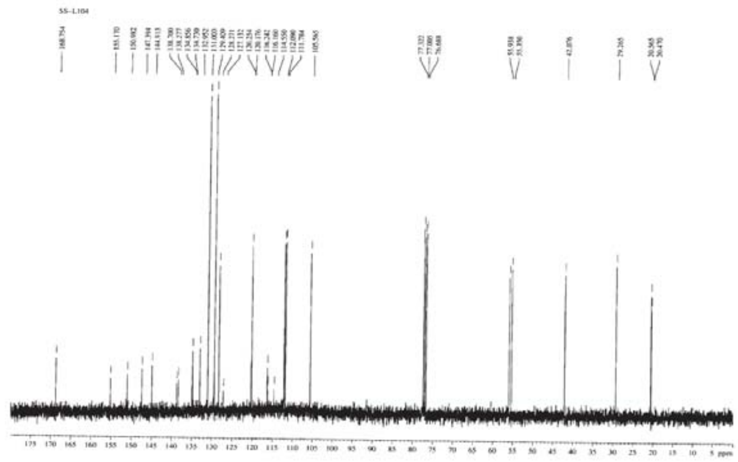


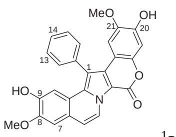


Lam **15-OAc**

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

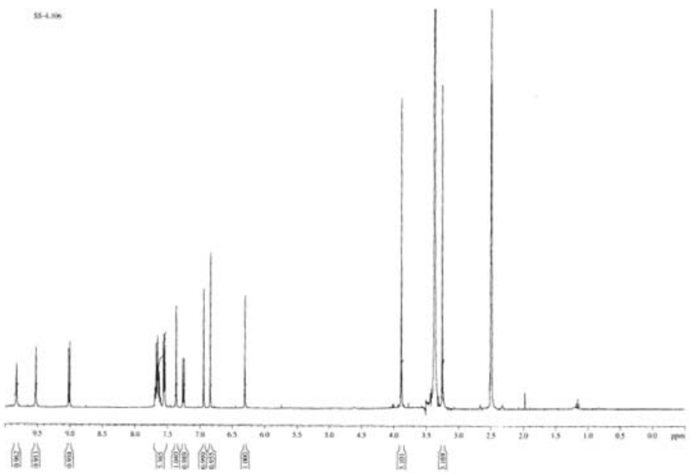


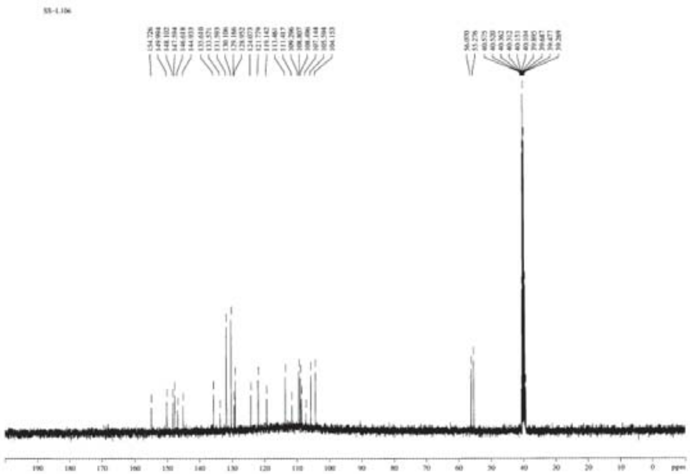


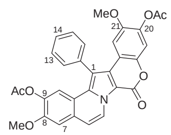


Lam **16**

^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

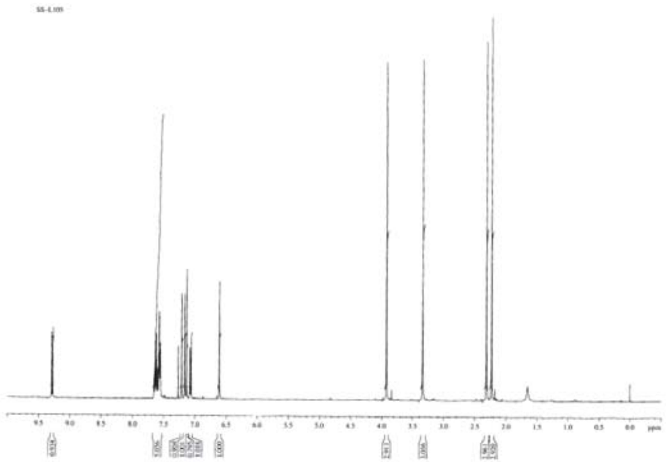


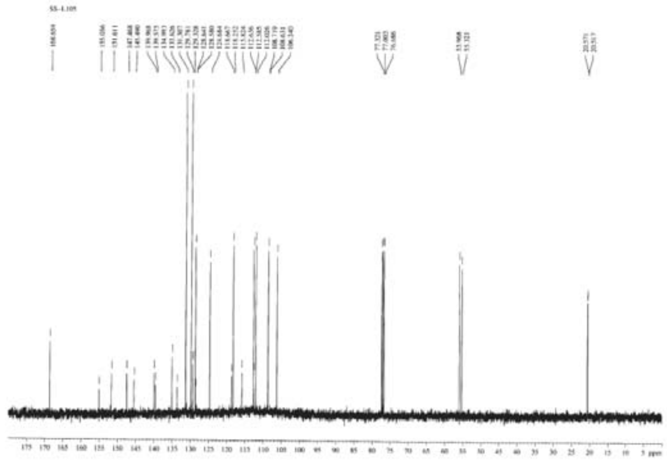


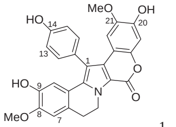


Lam **16-OAc**

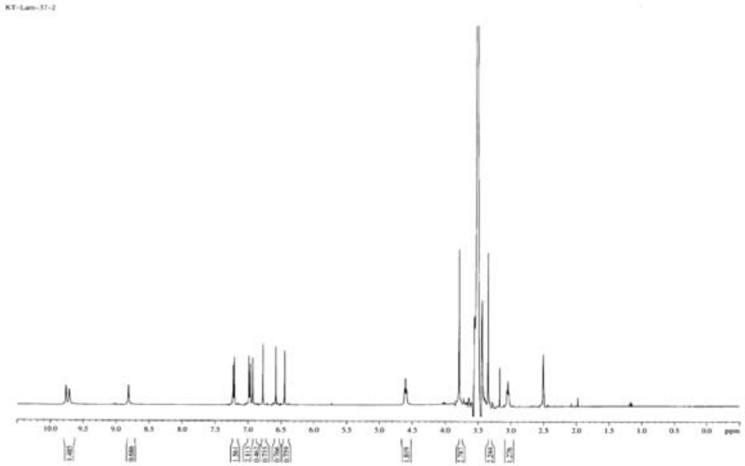
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

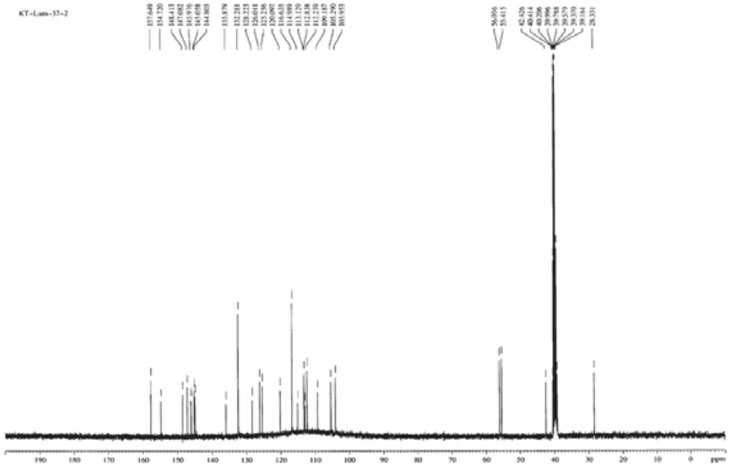


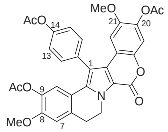




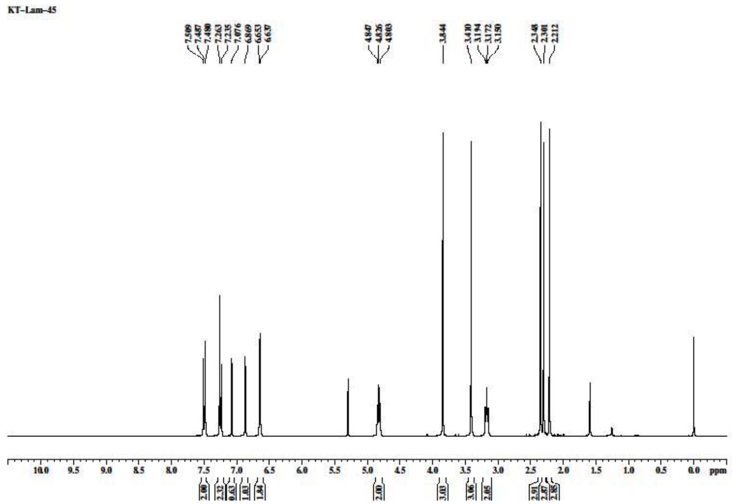
Lam **17** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

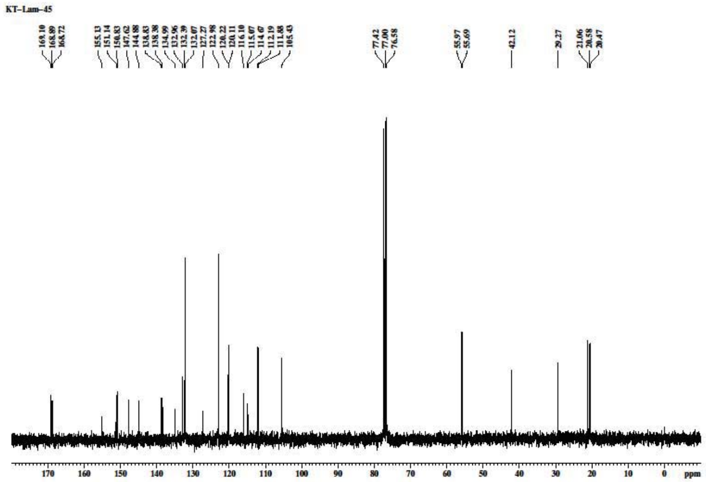


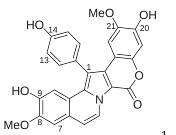




Lam **17-OAc** ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$)

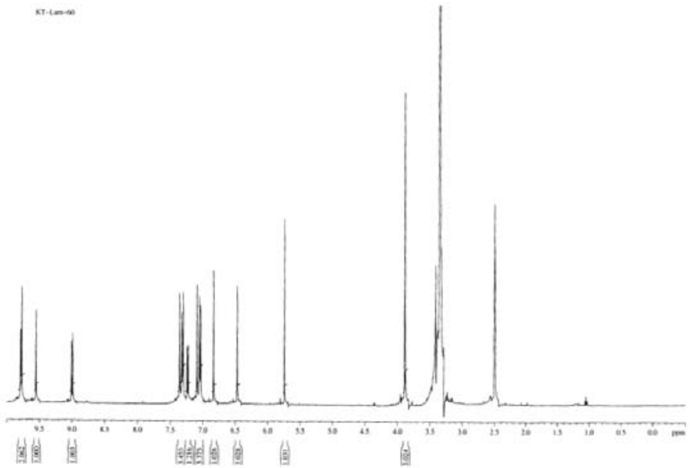


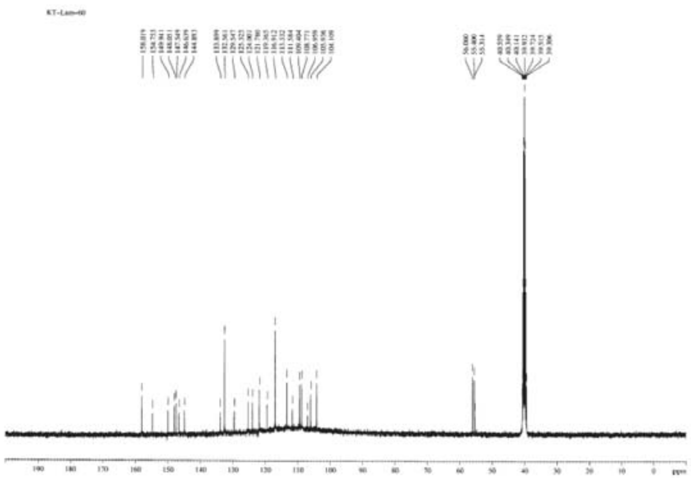


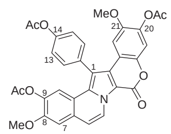


Lam **18**

^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

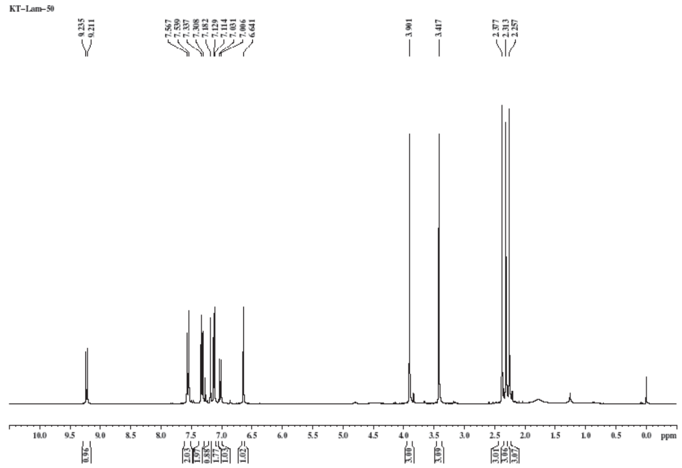


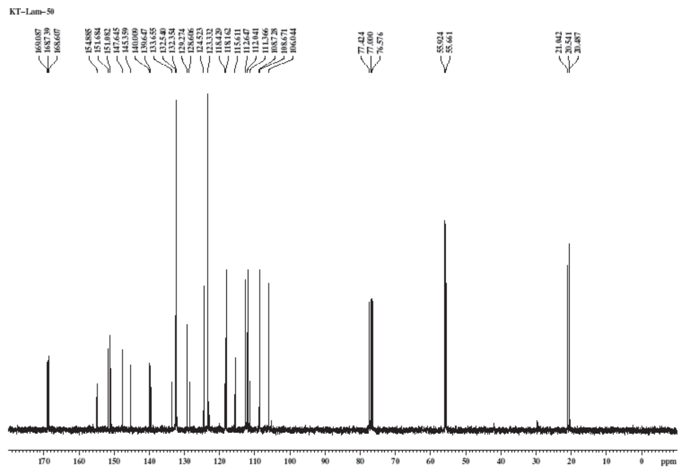


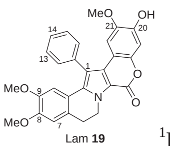


Lam **18-OAc**

^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$)

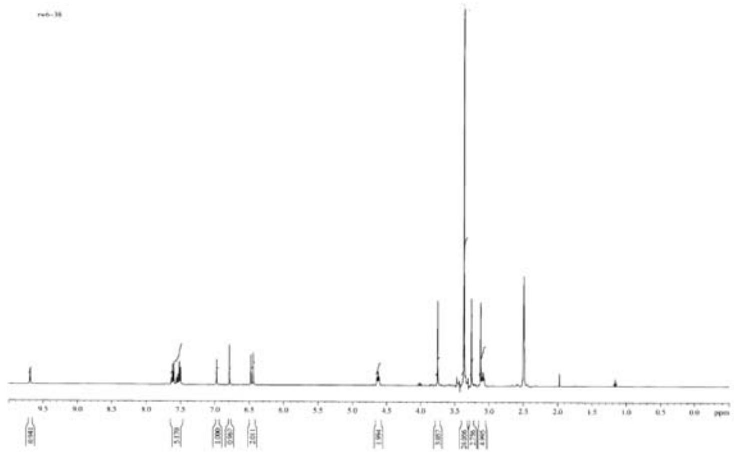


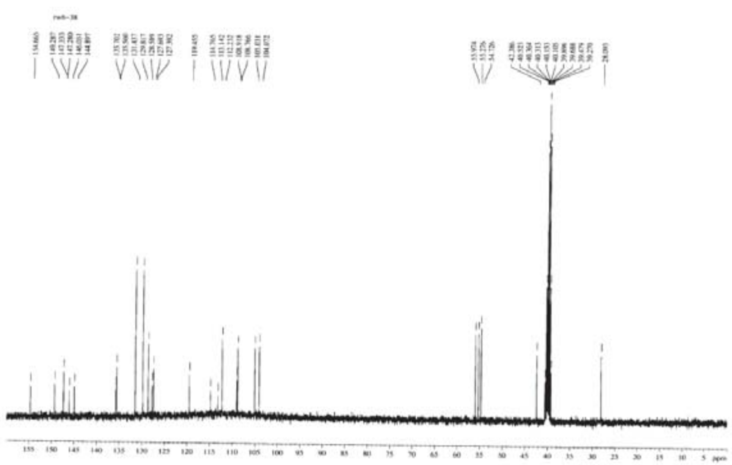


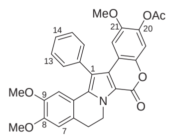


Lam **19**

^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

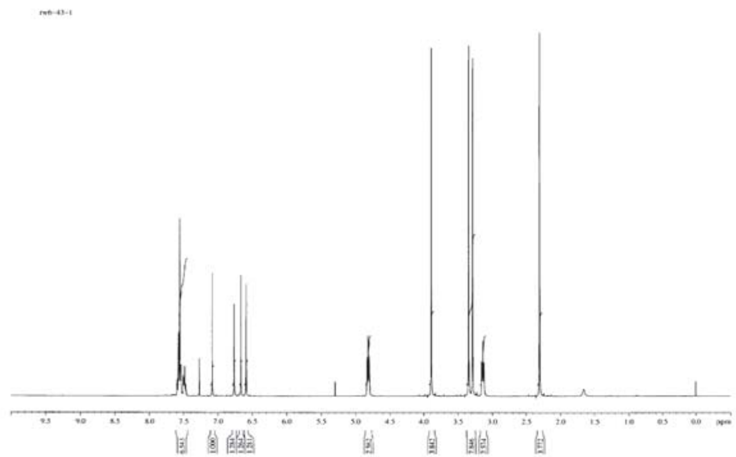


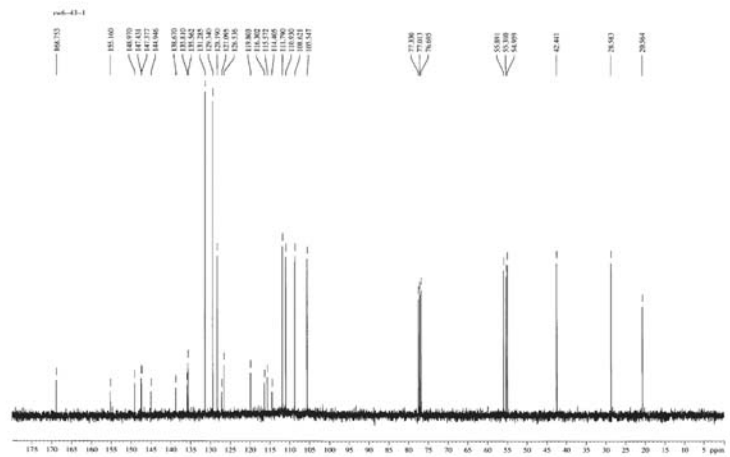


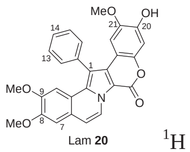


Lam **19-OAc**

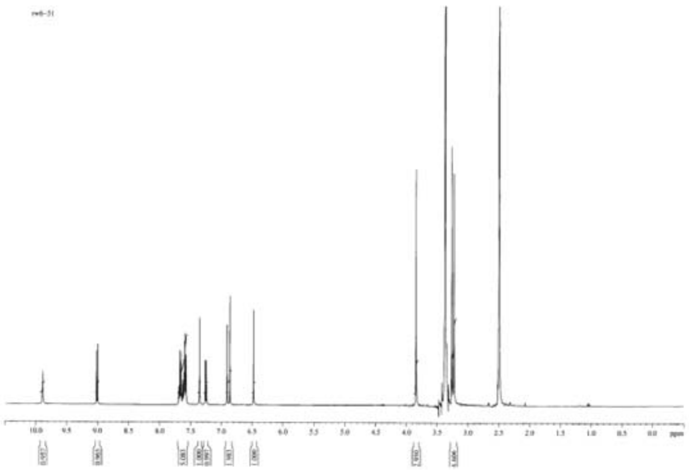
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

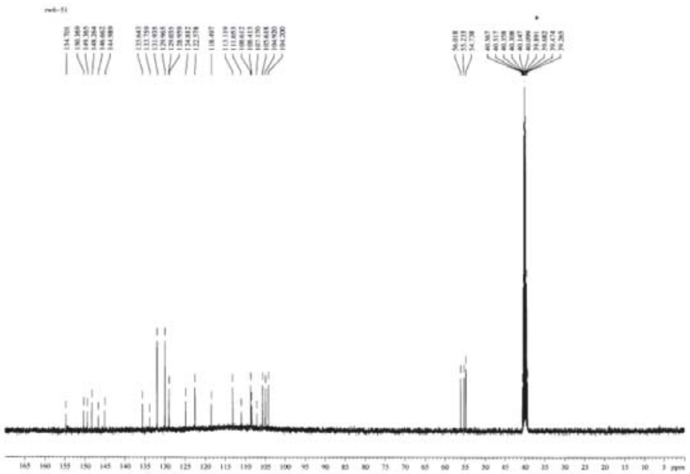


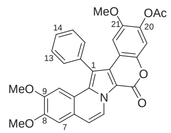




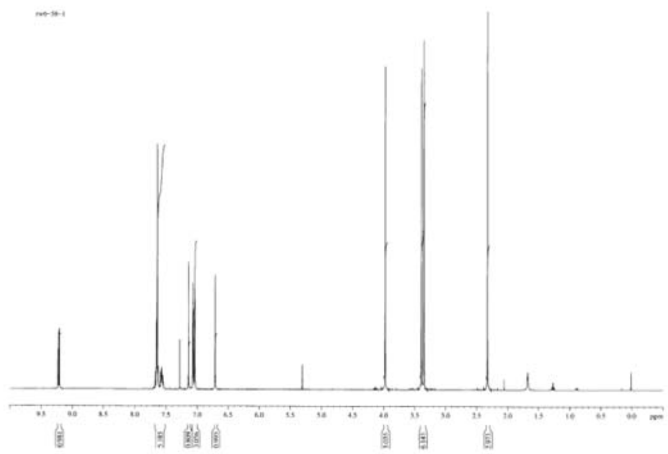
Lam **20** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

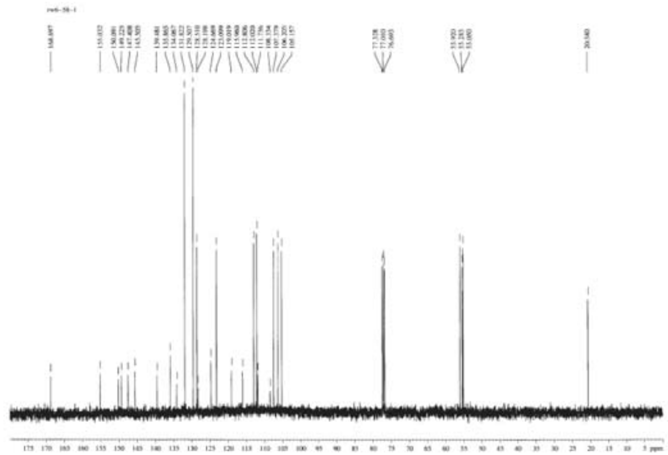


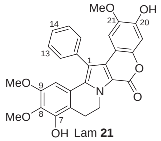




Lam **20-OAc** ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

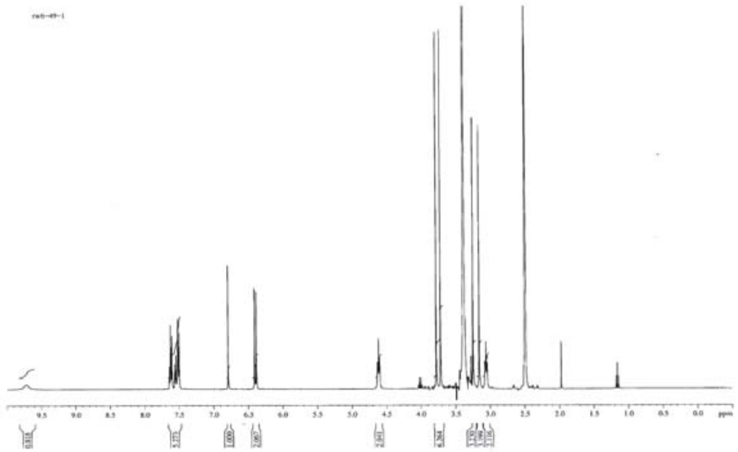


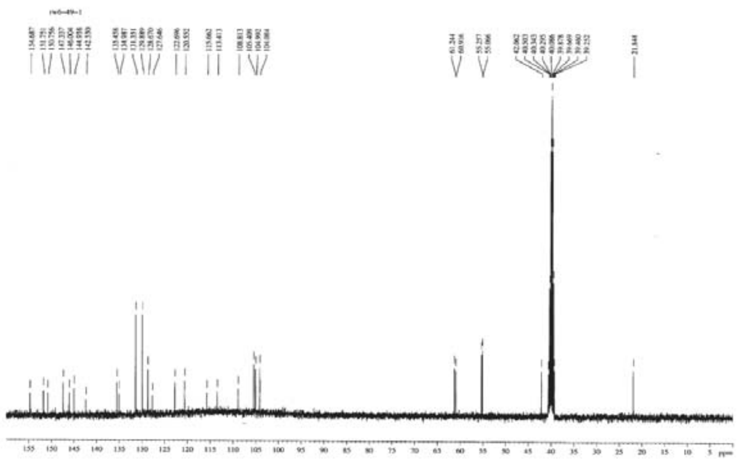


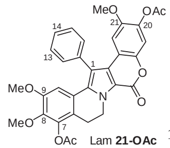


Lam **21**

^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

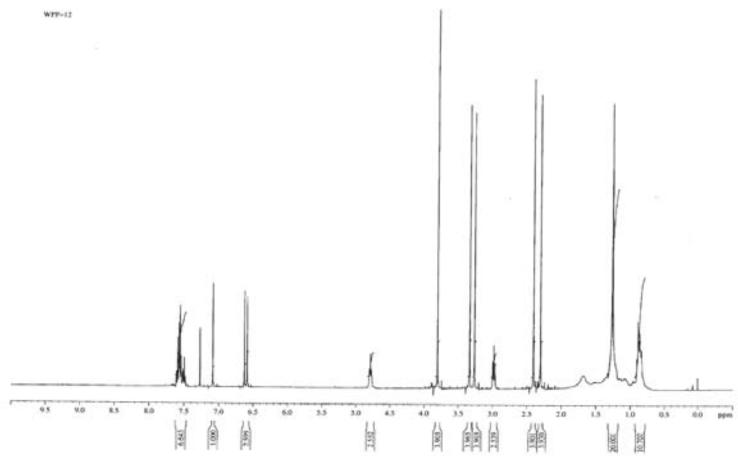


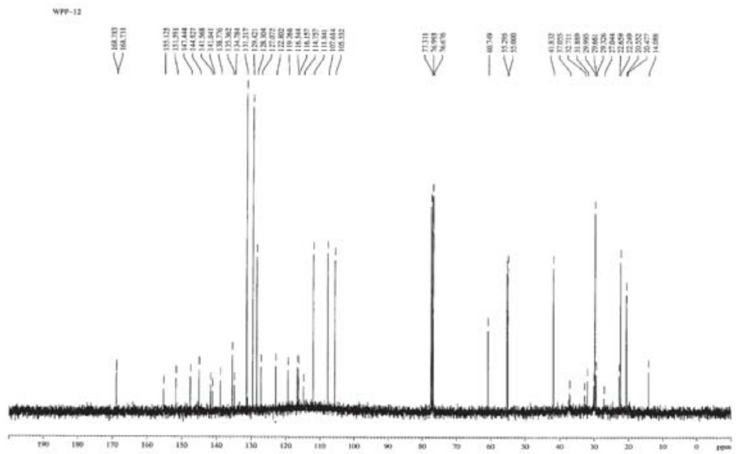


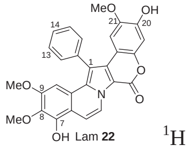


Lam **21-OAc**

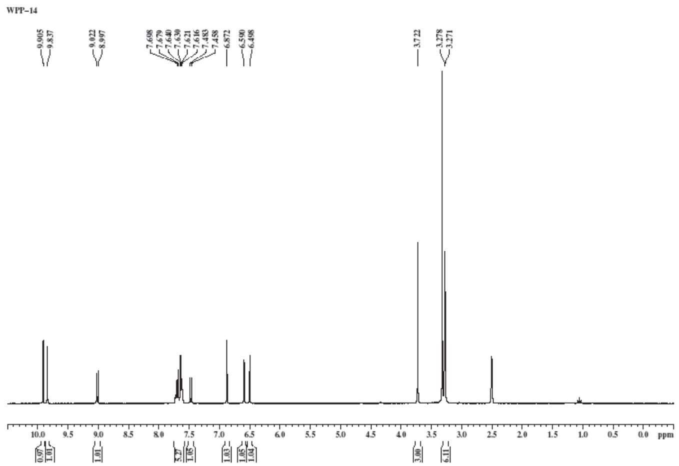
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

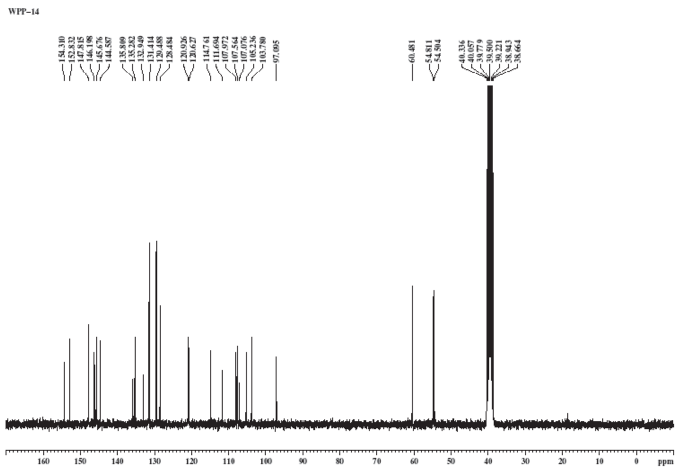


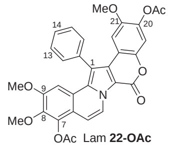




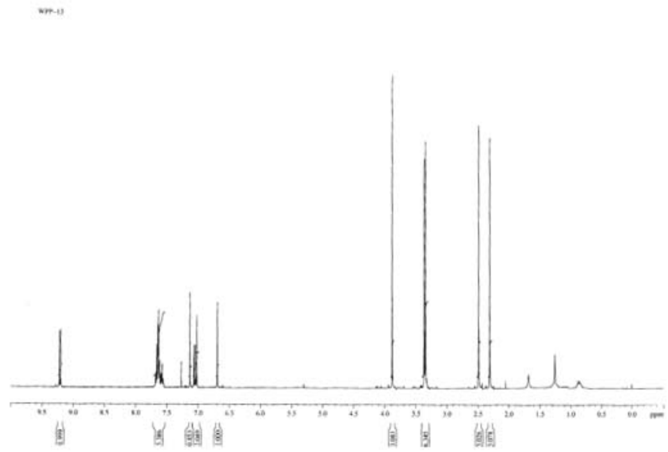
Lam **22** ^{1}H NMR (300 MHz, DMSO-d_6) and ^{13}C NMR (75 MHz, DMSO-d_6)

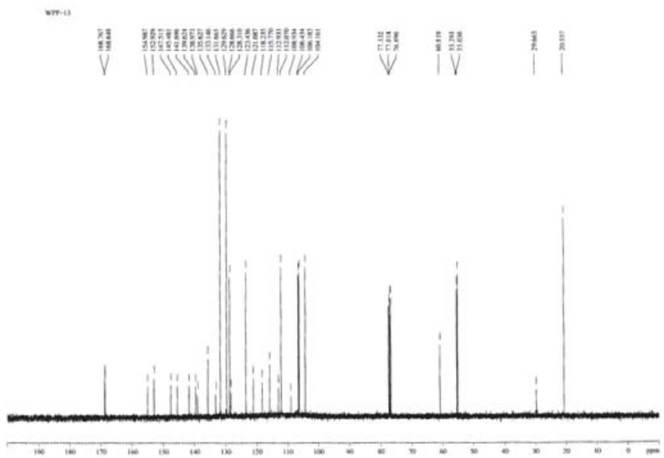


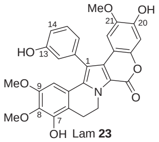




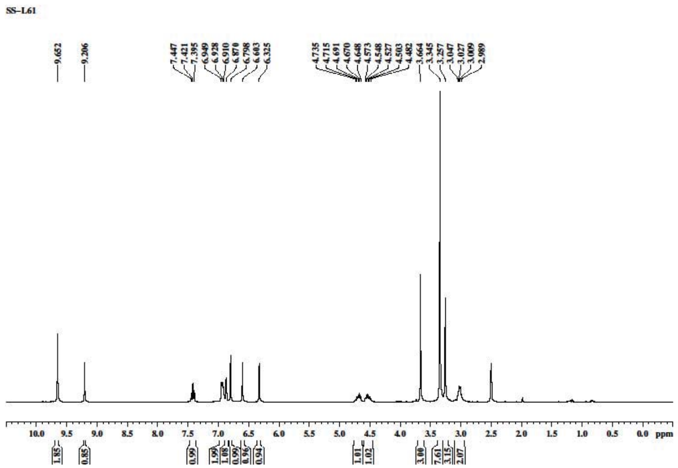
Lam **22-OAc** ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

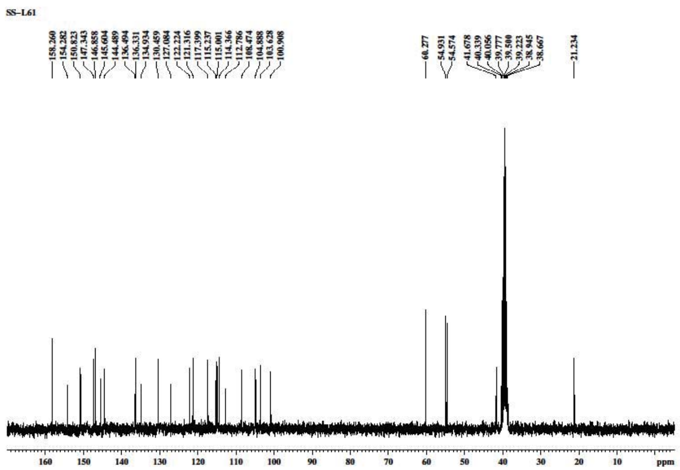


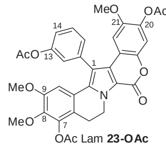




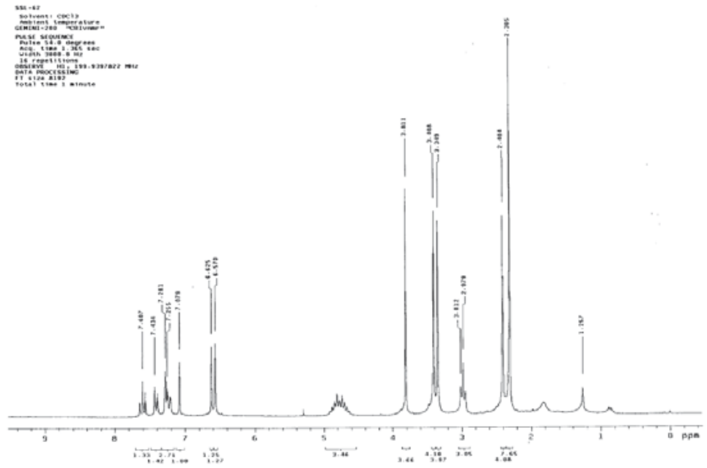
Lam **23** ^{1}H NMR (300 MHz, DMSO-d_6) and ^{13}C NMR (75 MHz, DMSO-d_6)

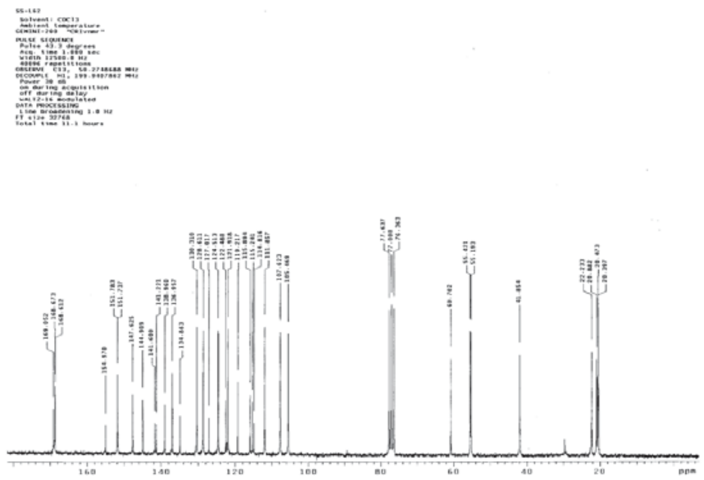


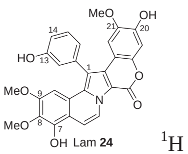




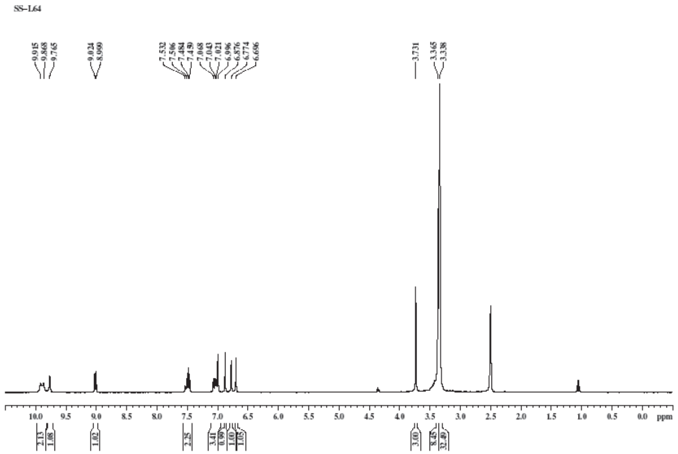
Lam **23-OAc** ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

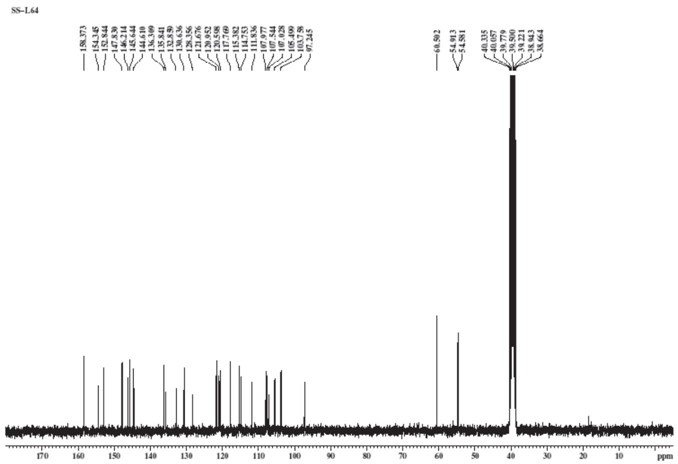


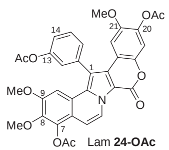




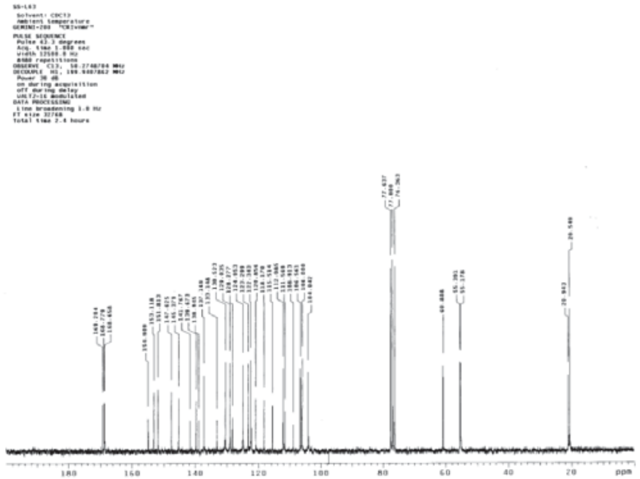
Lam **24** [1]H NMR (300 MHz, DMSO-d_6) and [13]C NMR (75 MHz, DMSO-d_6)

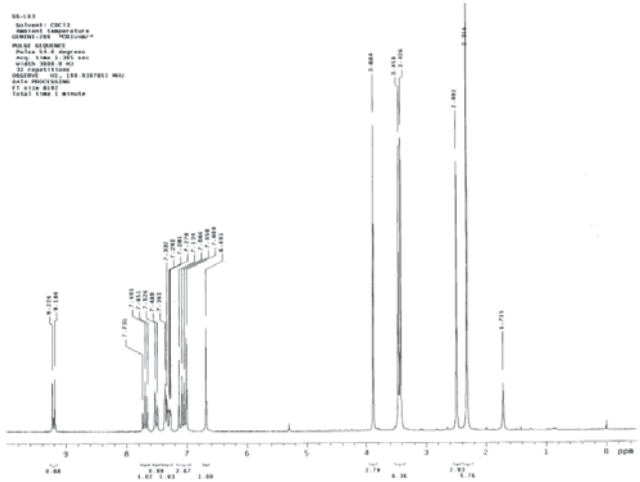


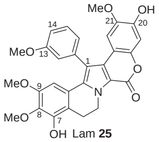




Lam **24-OAc** [1]H NMR (200 MHz, $CDCl_3$) and [13]C NMR (50 MHz, $CDCl_3$)

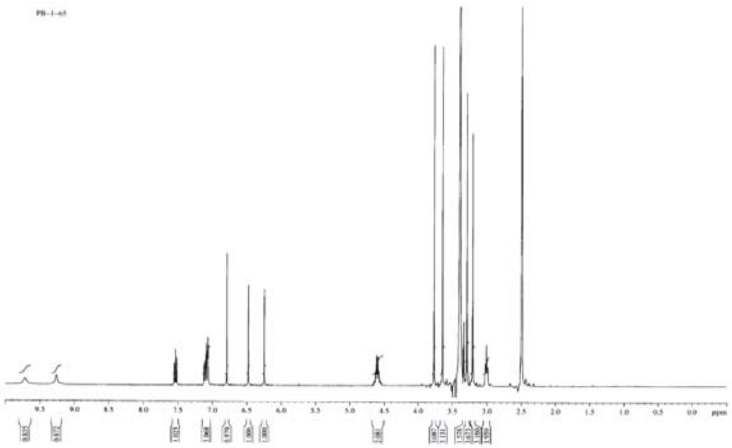


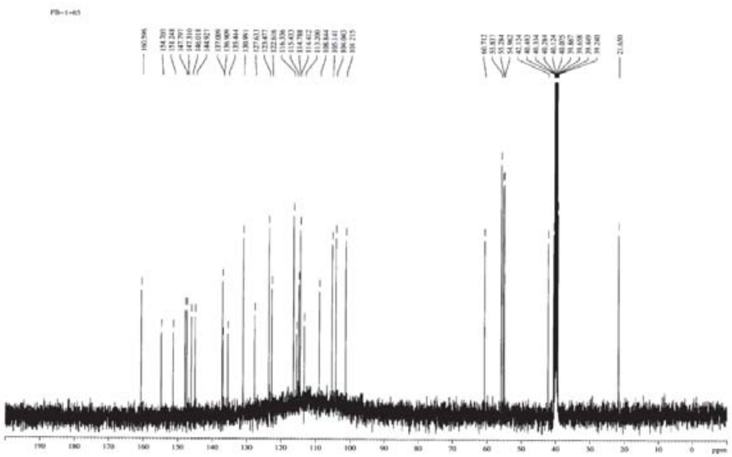


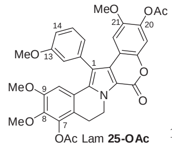


Lam **25**

^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

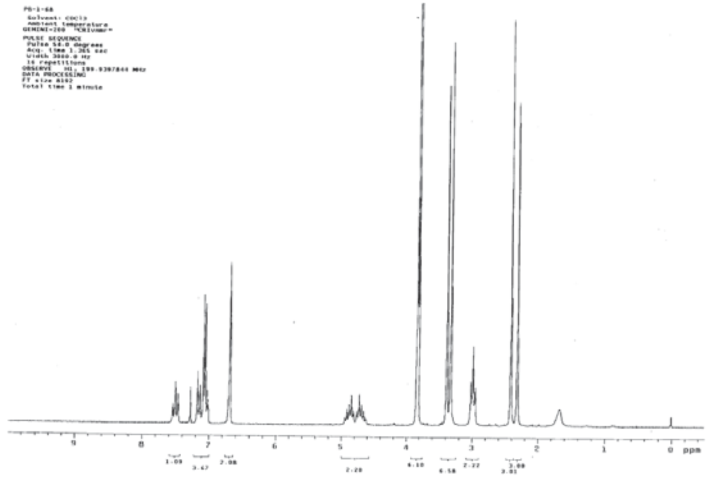


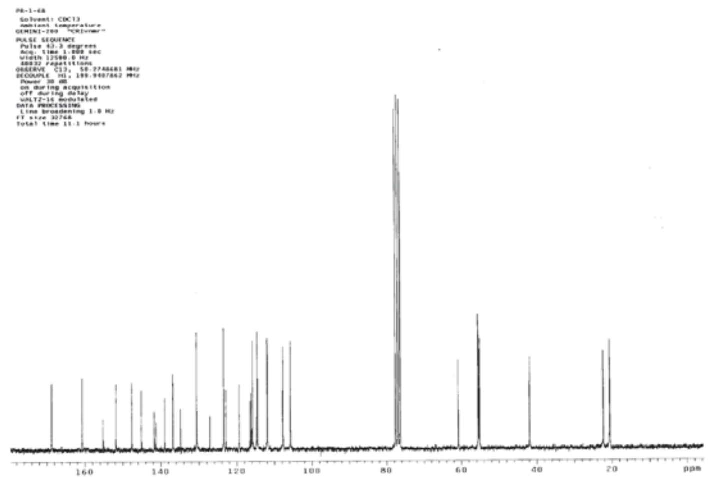


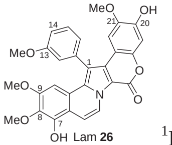


Lam **25-OAc**

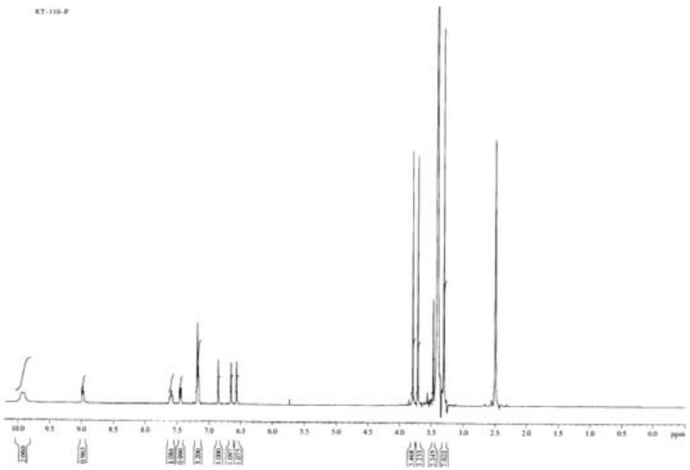
^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

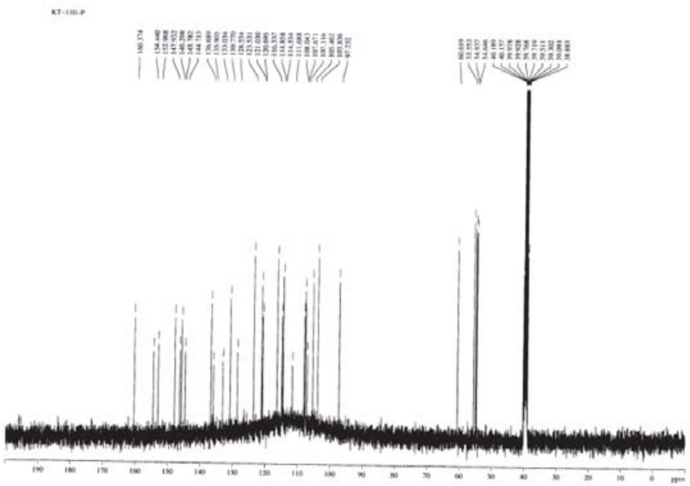


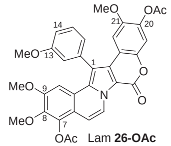




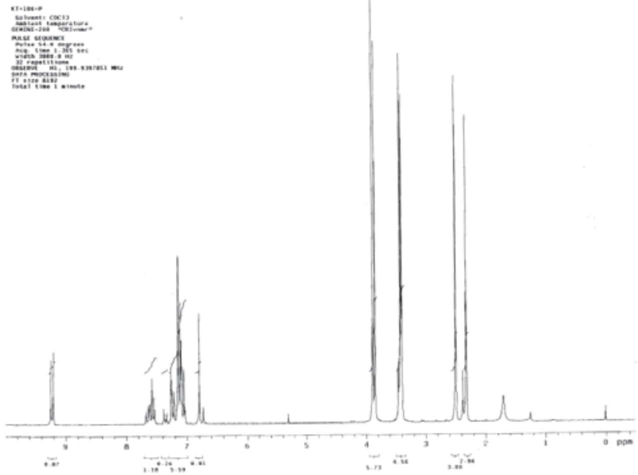
Lam **26** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

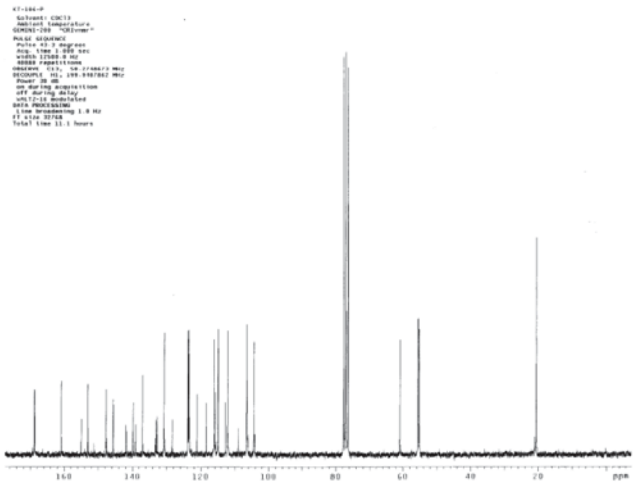


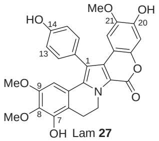




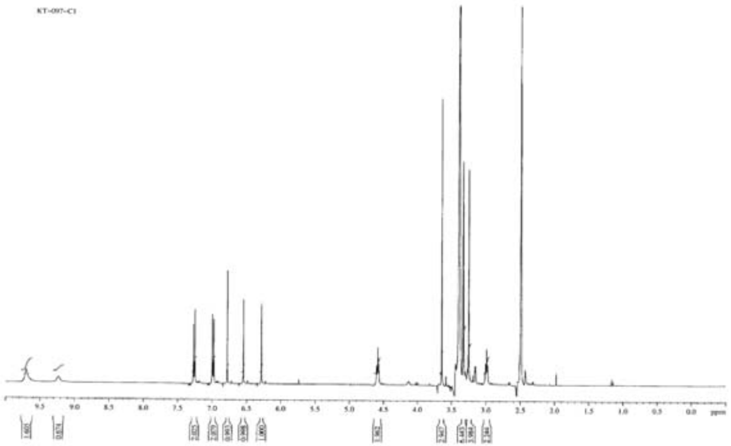
Lam **26-OAc** ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

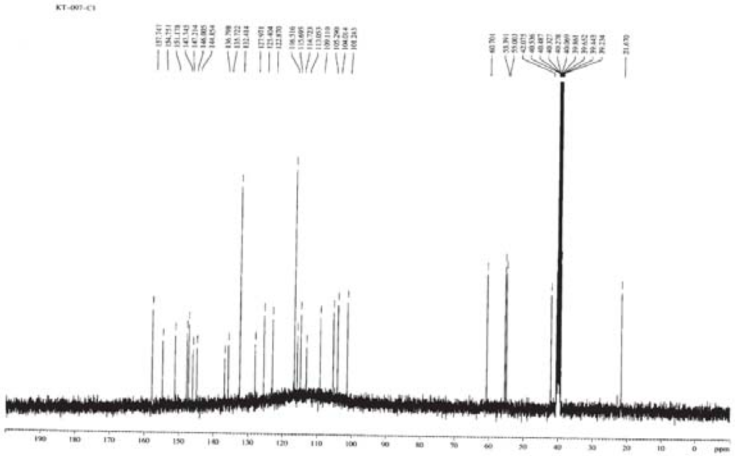


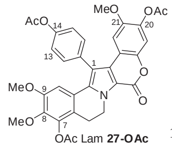




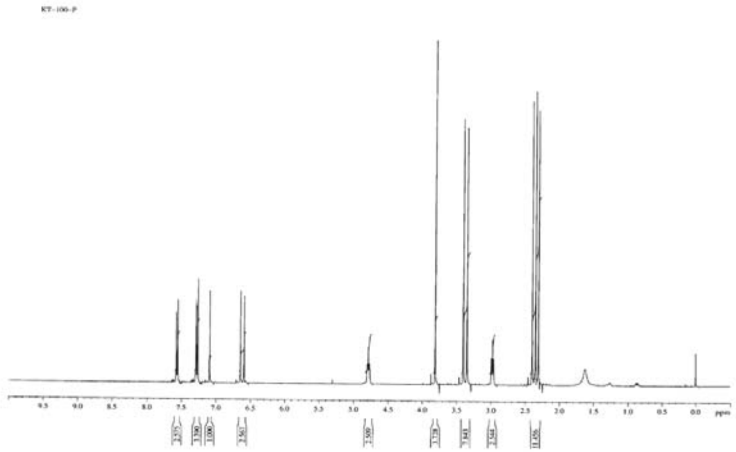
Lam **27** ^{1}H NMR (400 MHz, DMSO-d_6 and ^{13}C NMR (100 MHz, DMSO-d_6)

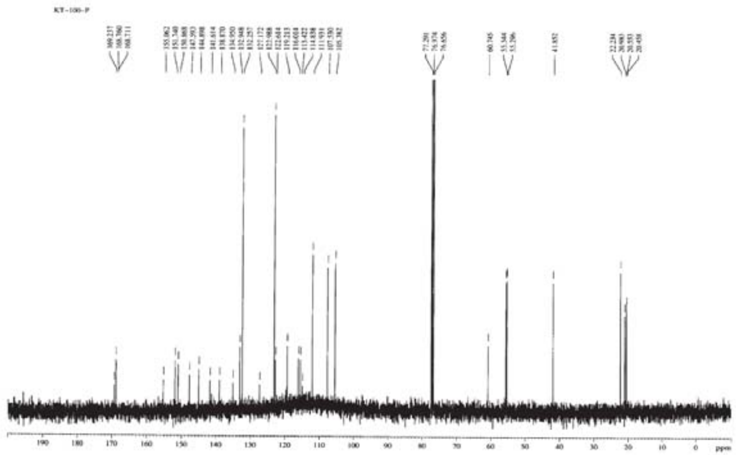


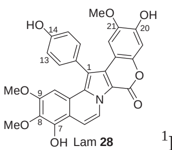




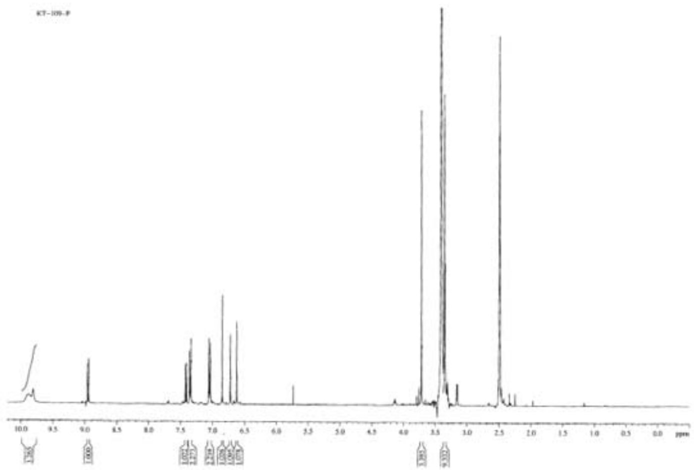
Lam **27-OAc** ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

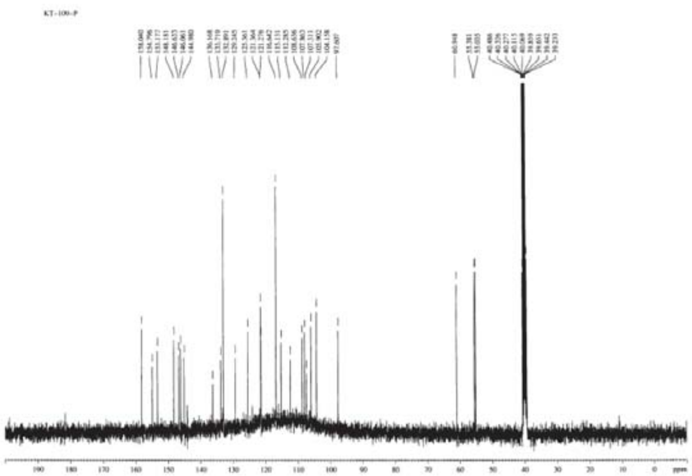


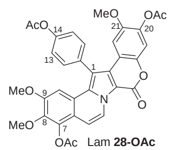




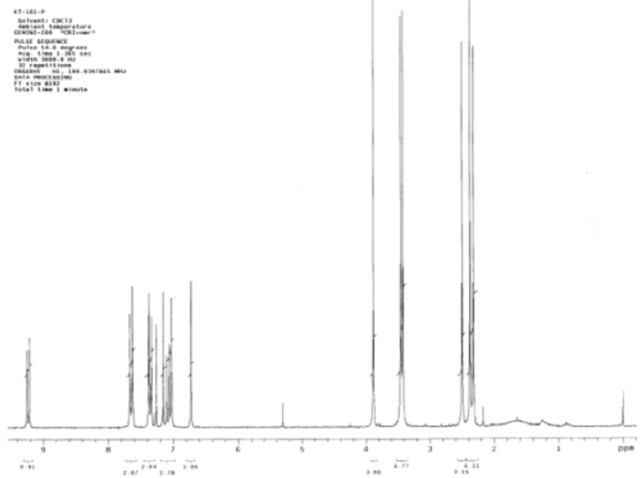
Lam **28** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

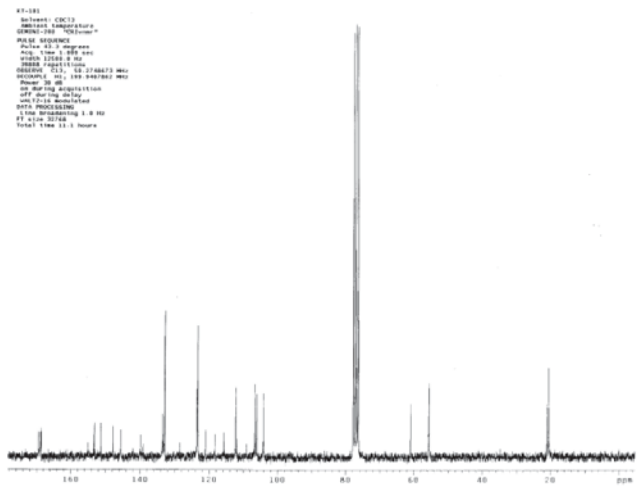


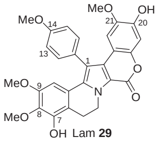




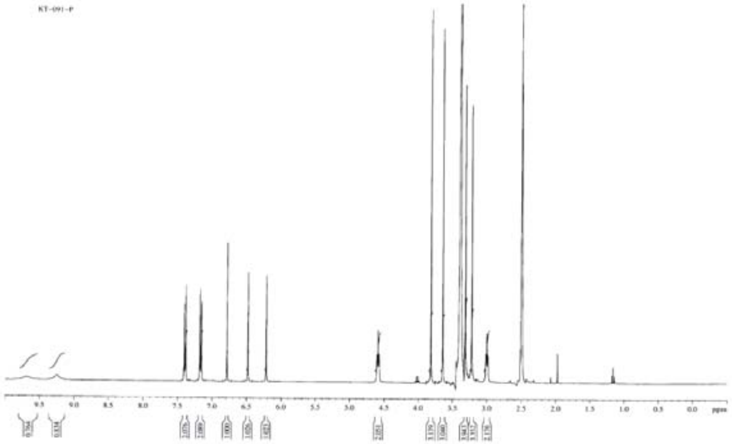
Lam **28-OAc** ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

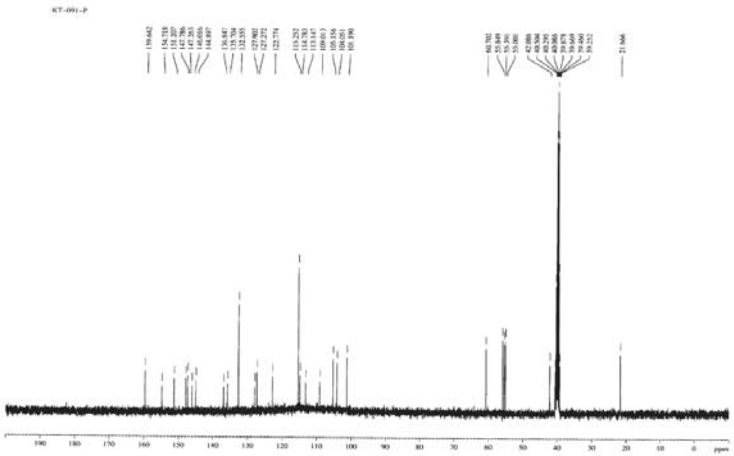


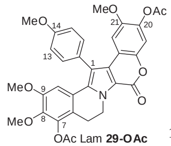




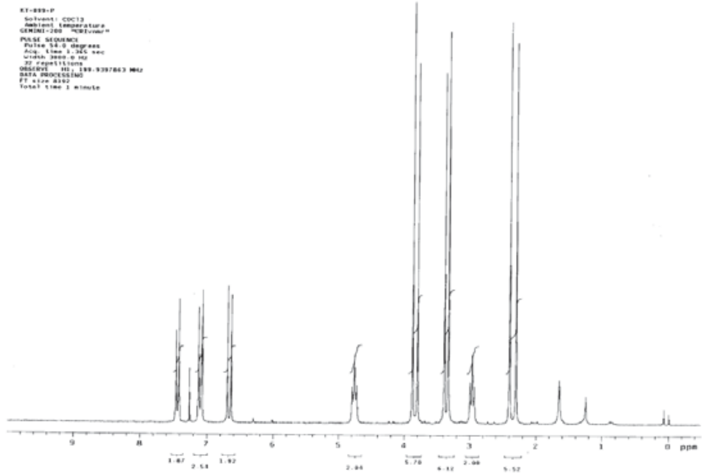
Lam **29** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

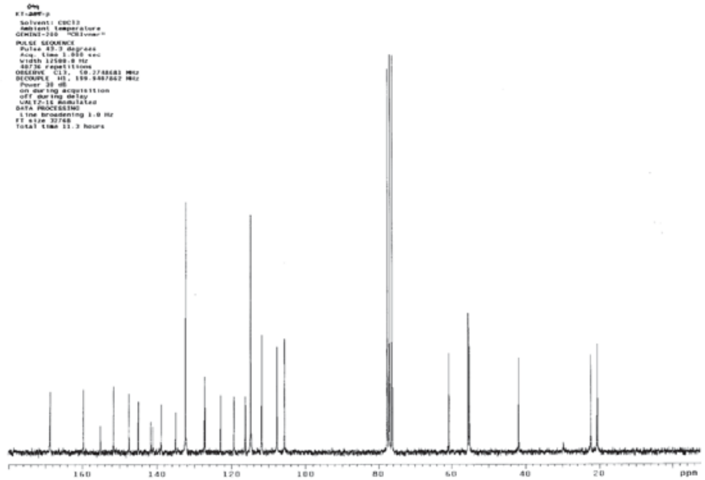


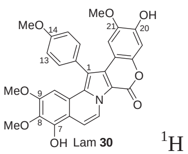




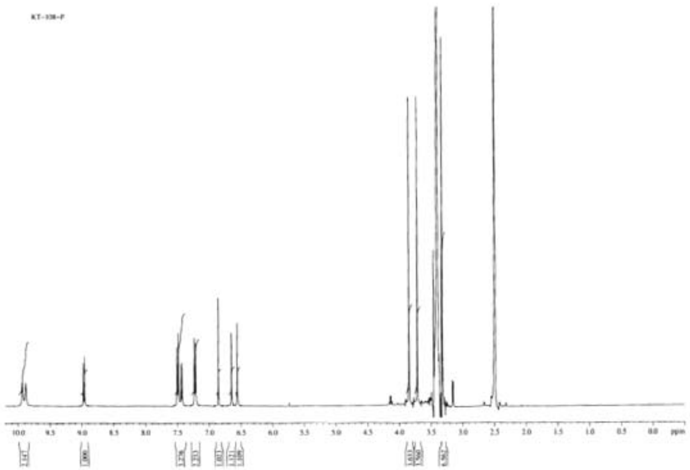
Lam **29-OAc** ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

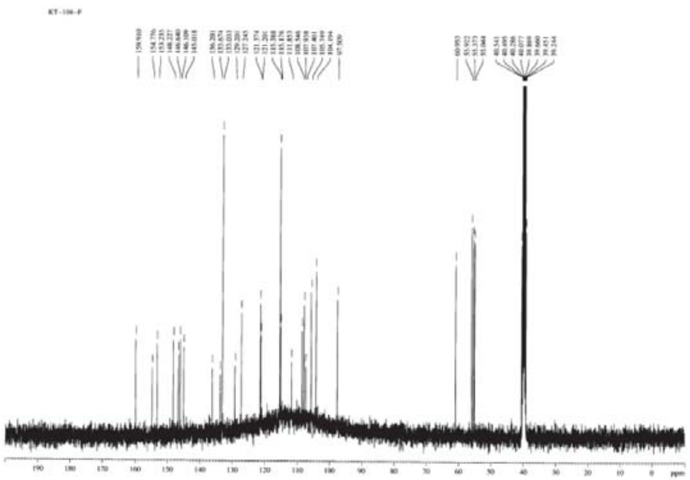


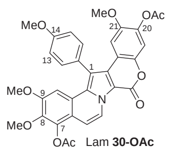




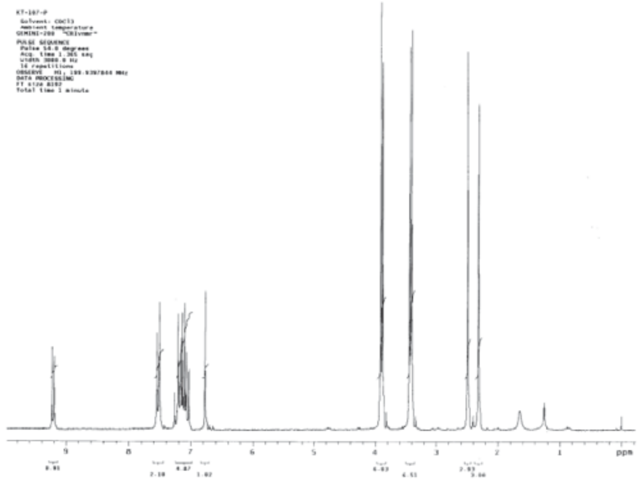
Lam **30** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

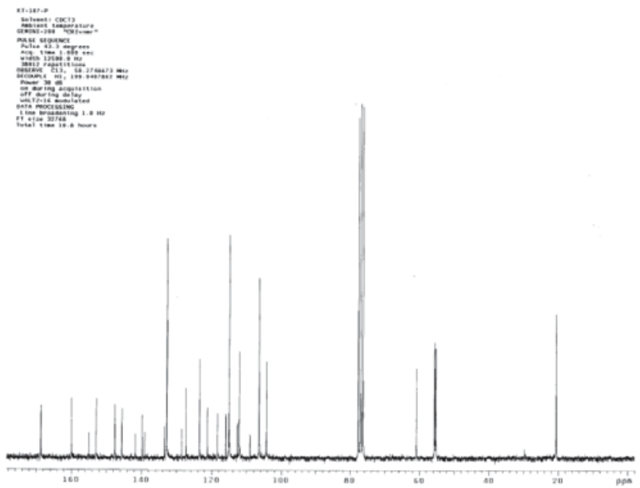


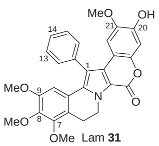




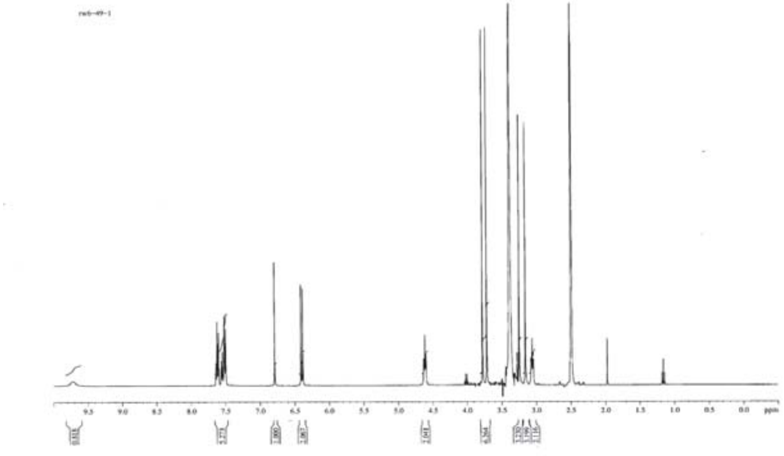
Lam **30-OAc** ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

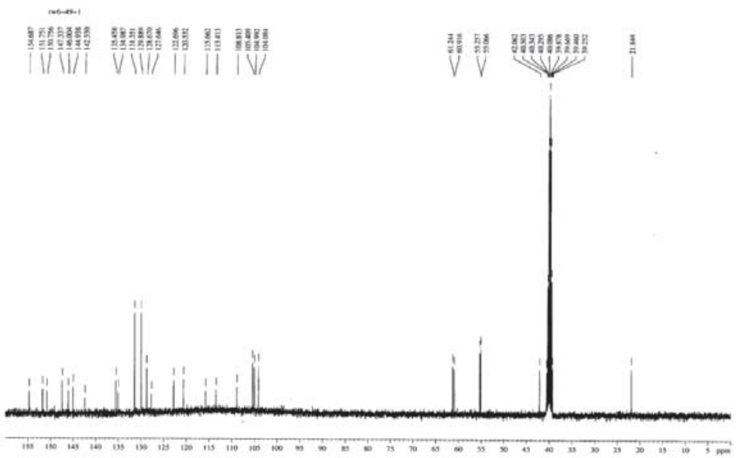


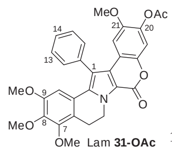




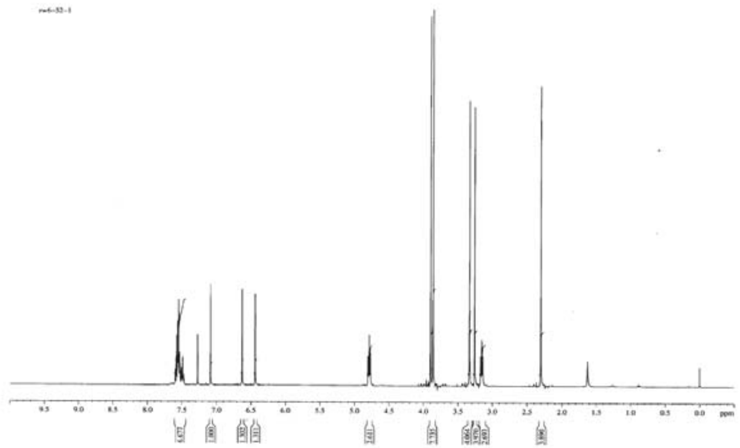
Lam **31** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

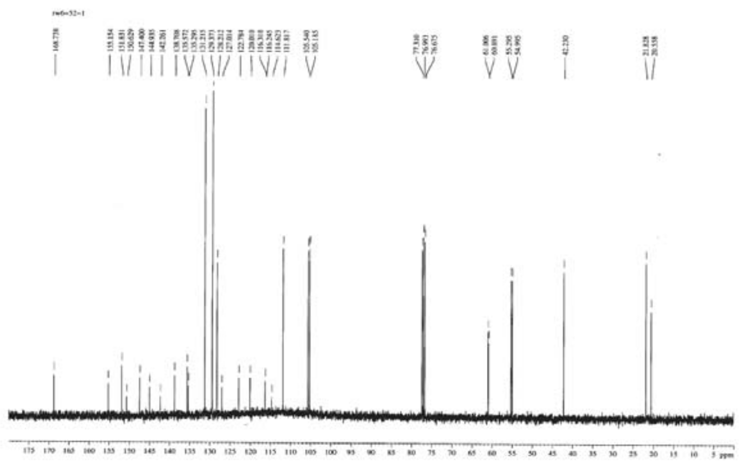


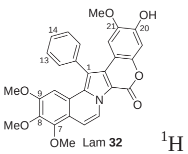




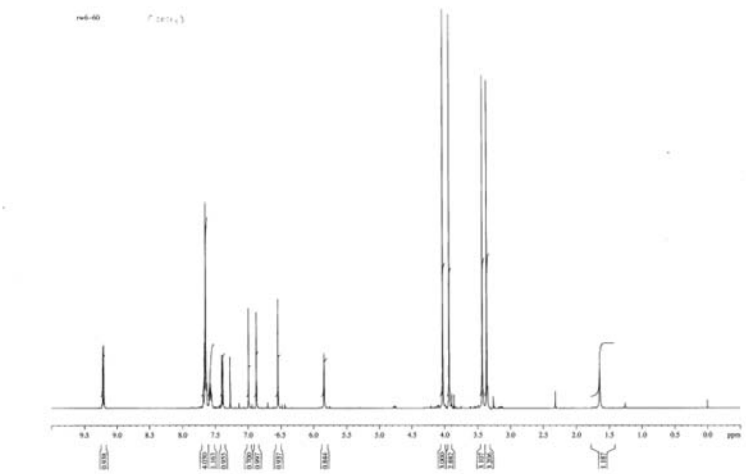
Lam **31-OAc** ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

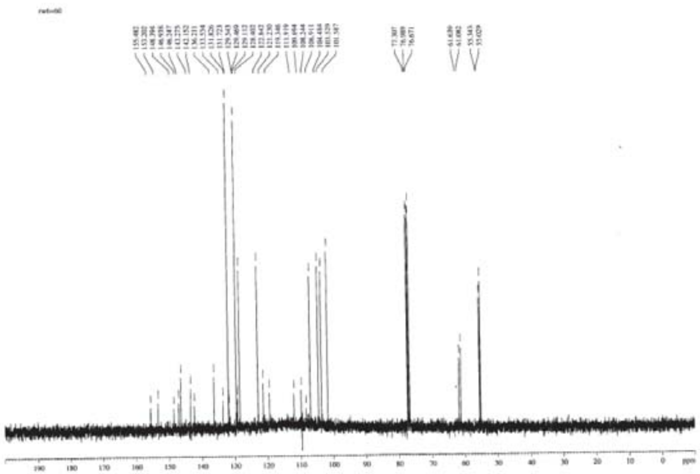


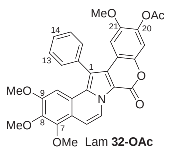




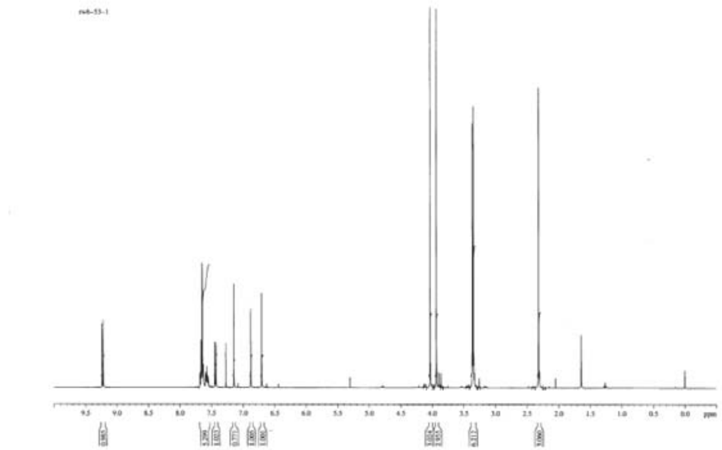
Lam **32** ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

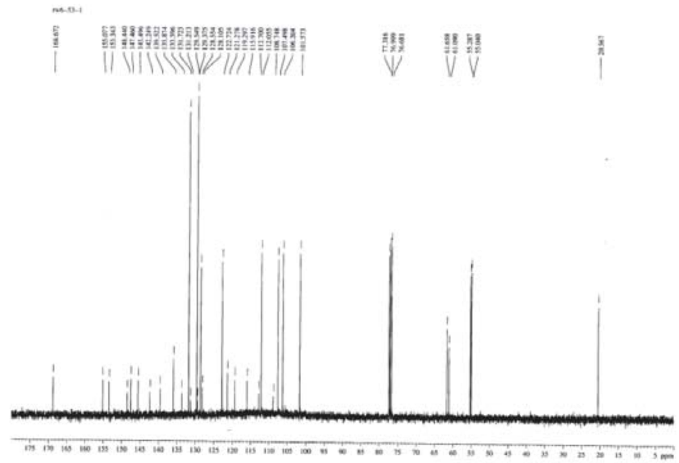


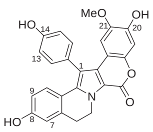




Lam **32-OAc** ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

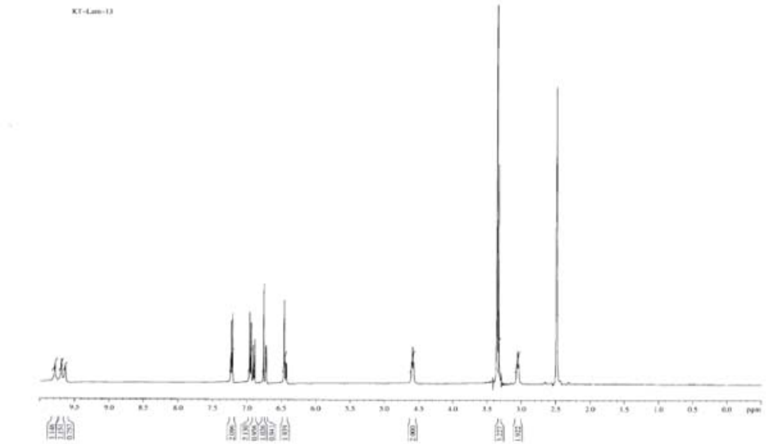


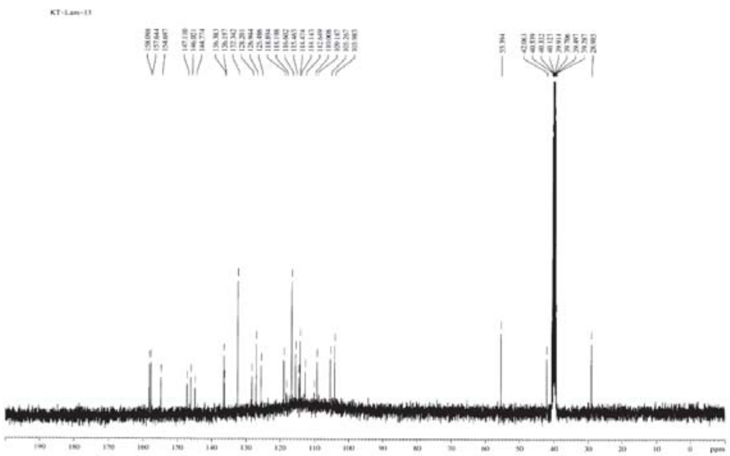


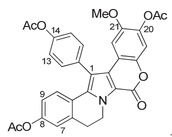


Lam **33**

^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

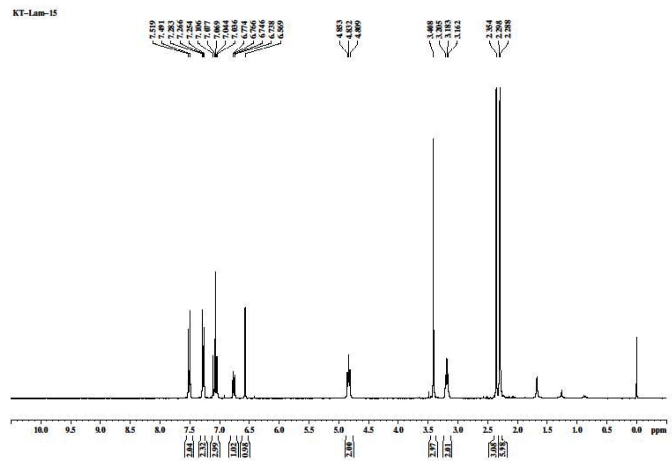


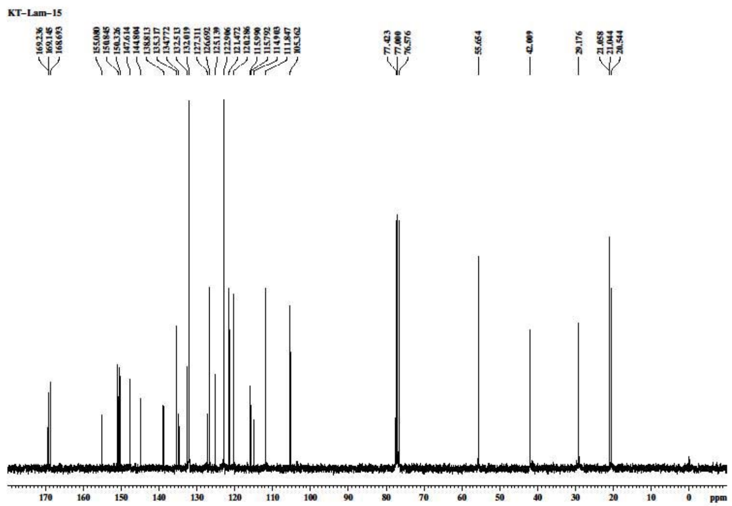


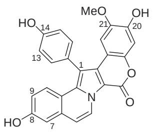


Lam **33-OAc**

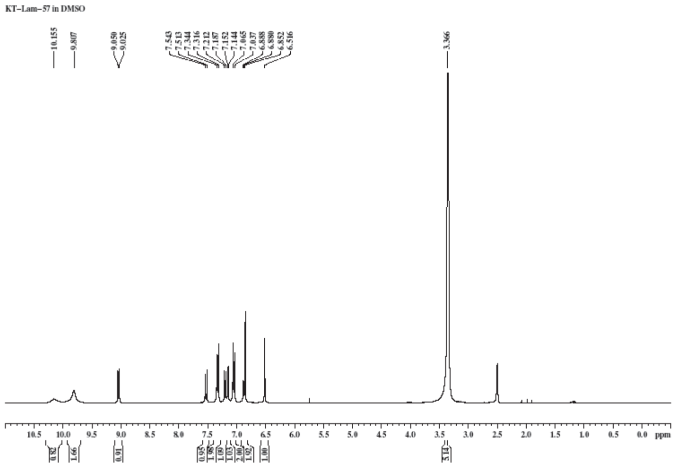
^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$)

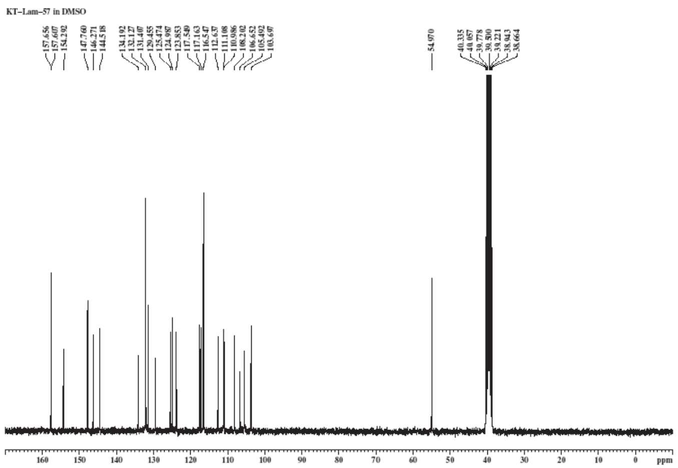


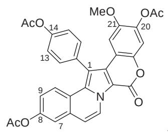




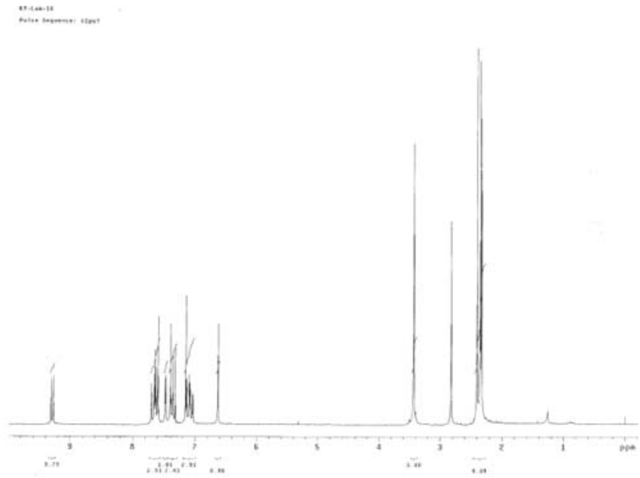
Lam **34** ^{1}H NMR (300 MHz, DMSO-d_6) and ^{13}C NMR (75 MHz, DMSO-d_6)

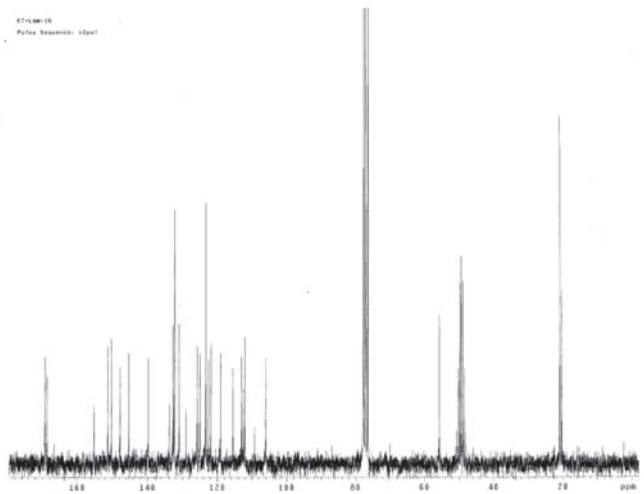


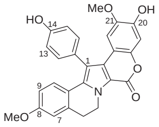




Lam **34-OAc** ^{1}H NMR (200 MHz, $CDCl_3$+CD_3OD) and ^{13}C NMR (50 MHz, $CDCl_3$+CD_3OD)

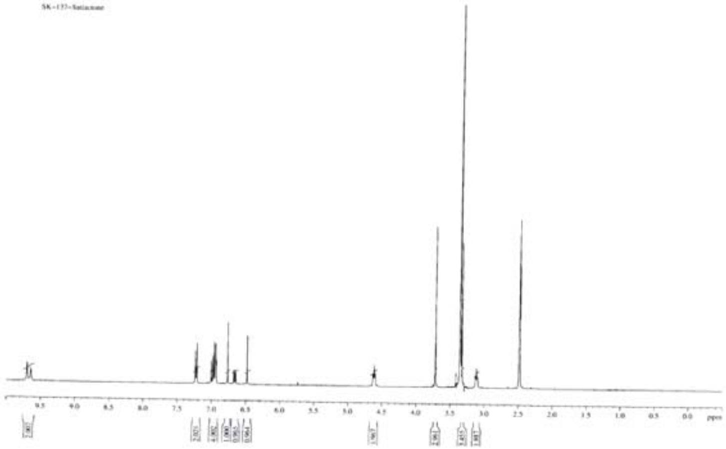


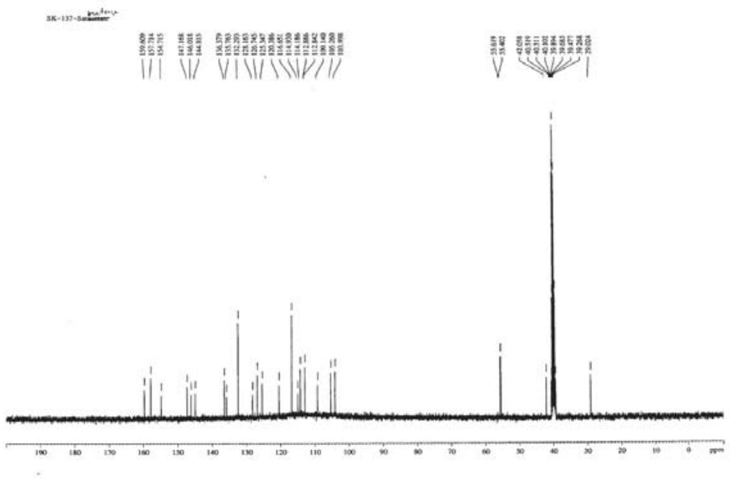


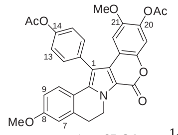


Lam **35**

^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

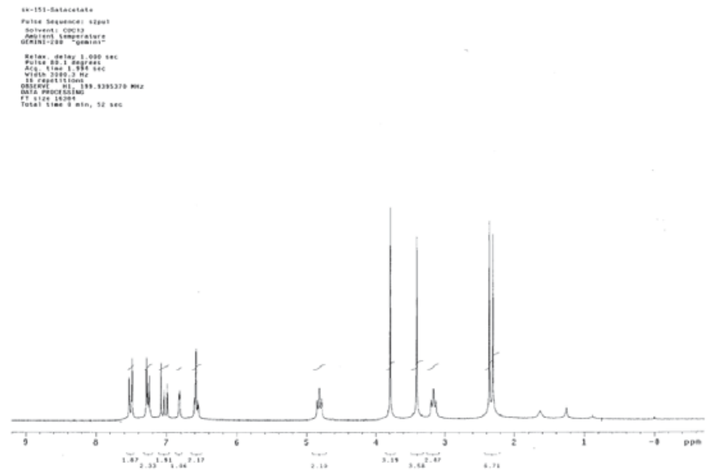


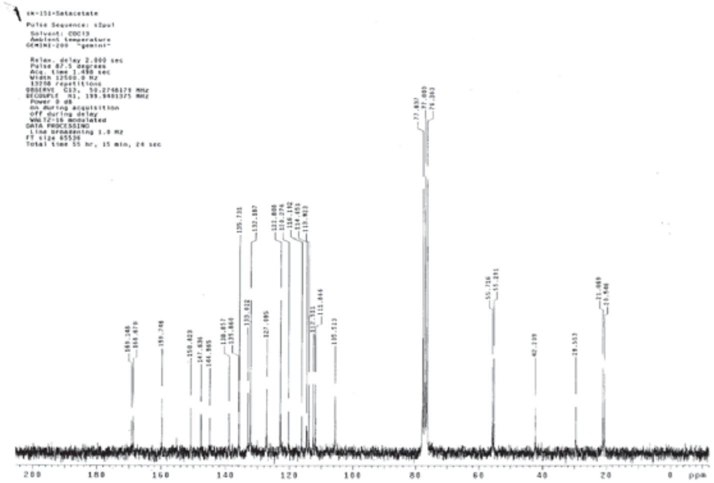


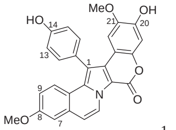


Lam **35-OAc**

^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

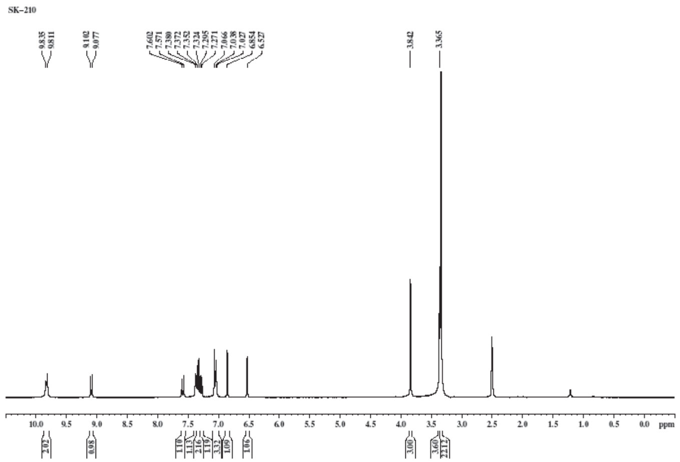


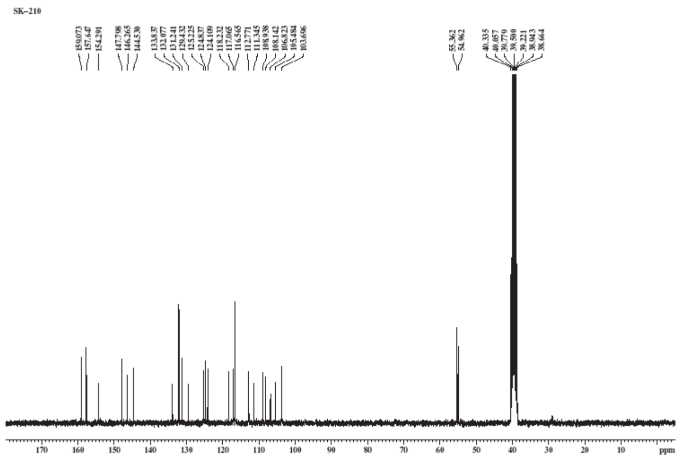


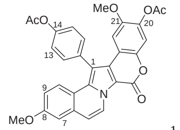


Lam **36**

^{1}H NMR (300 MHz, DMSO-d_6) and ^{13}C NMR (75 MHz, DMSO-d_6)

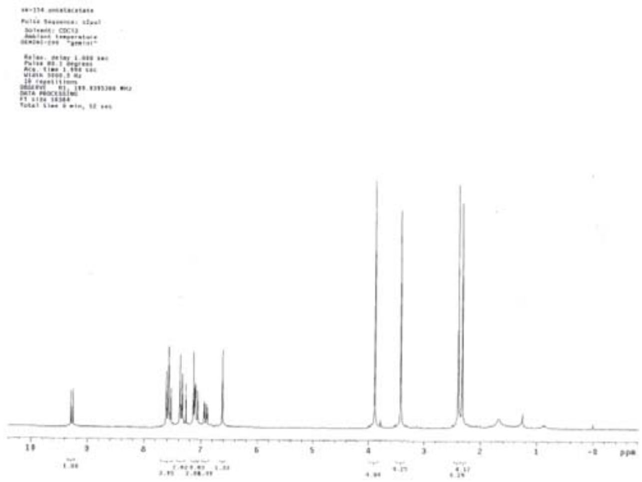


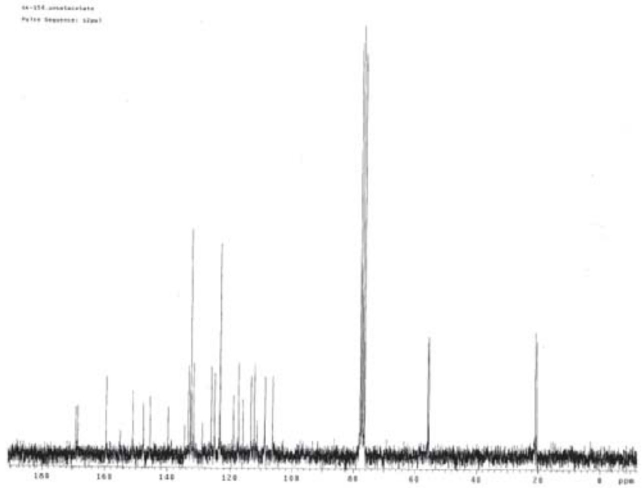


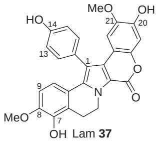


Lam **36-OAc**

^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

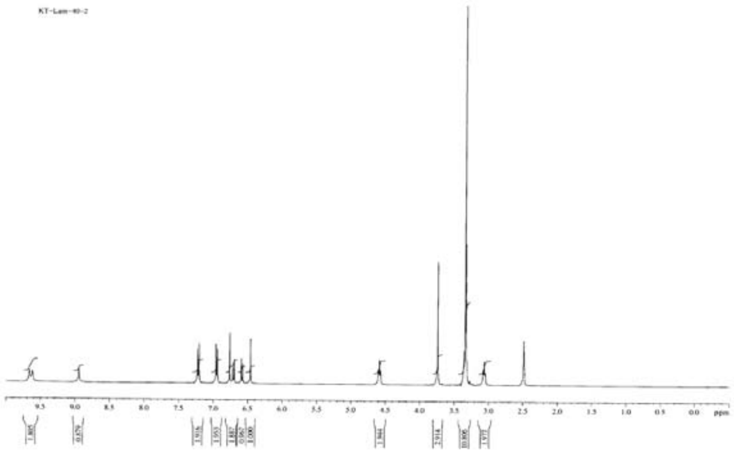


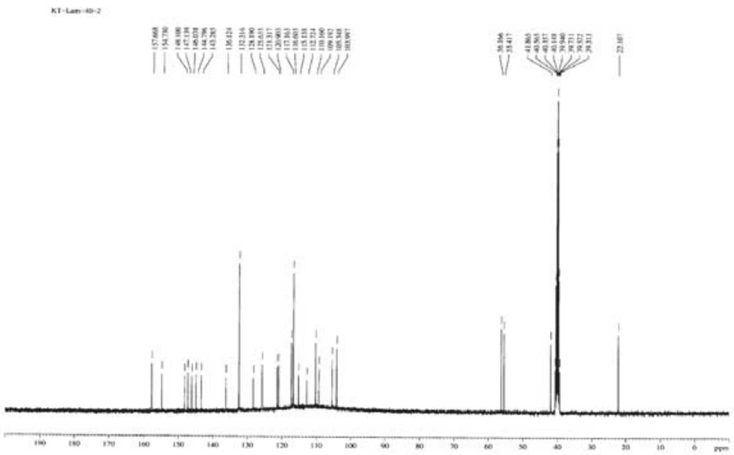


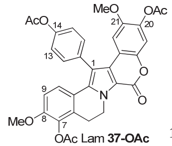


Lam **37**

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

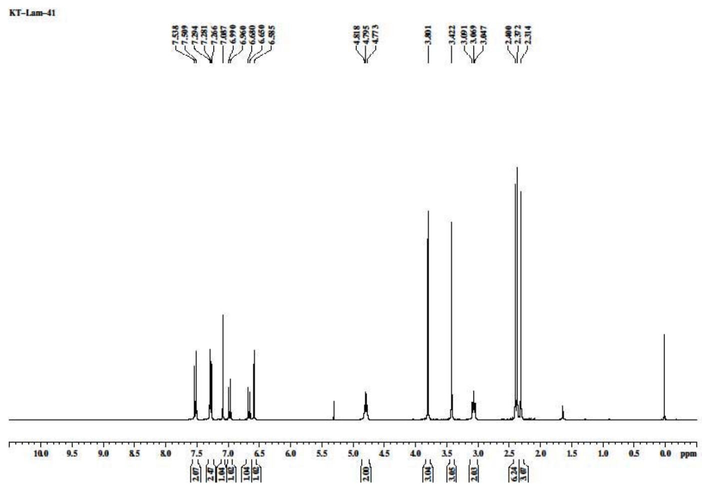


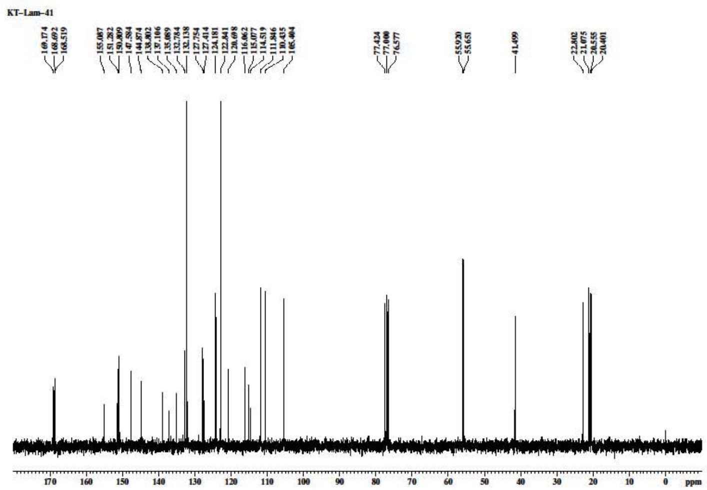


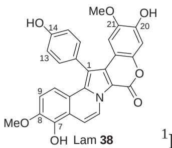


Lam **37-OAc**

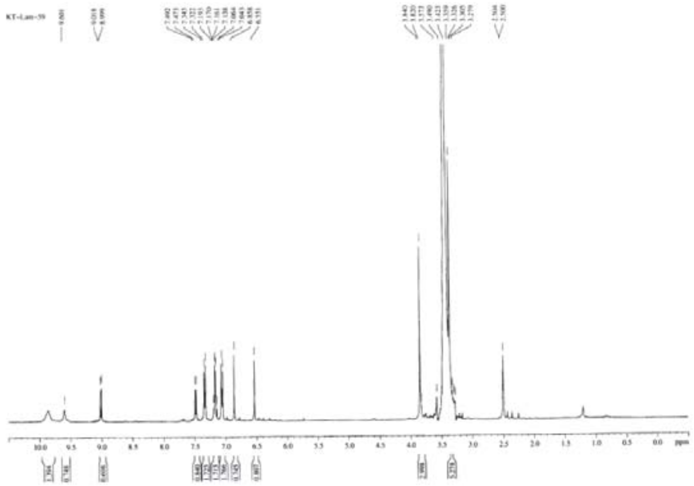
^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$)

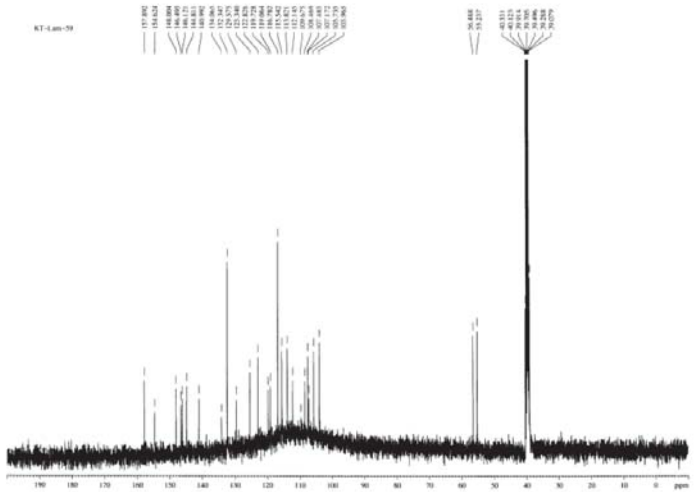


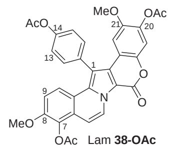




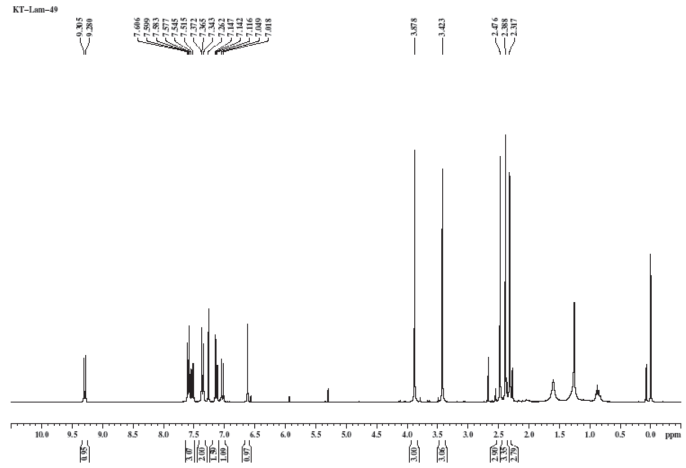
Lam **38** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

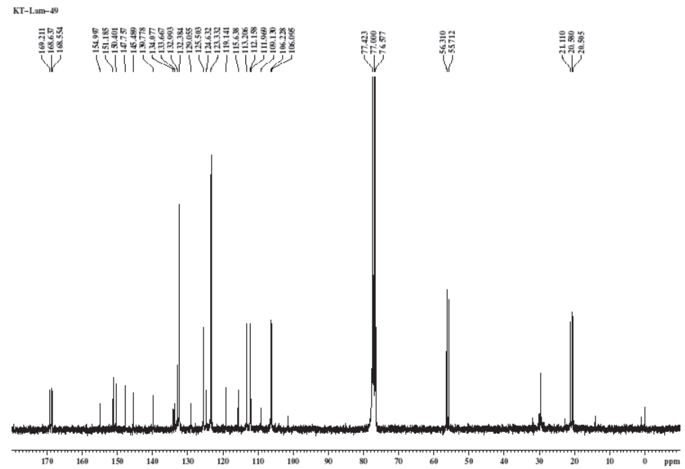


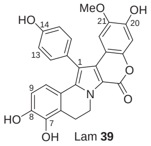




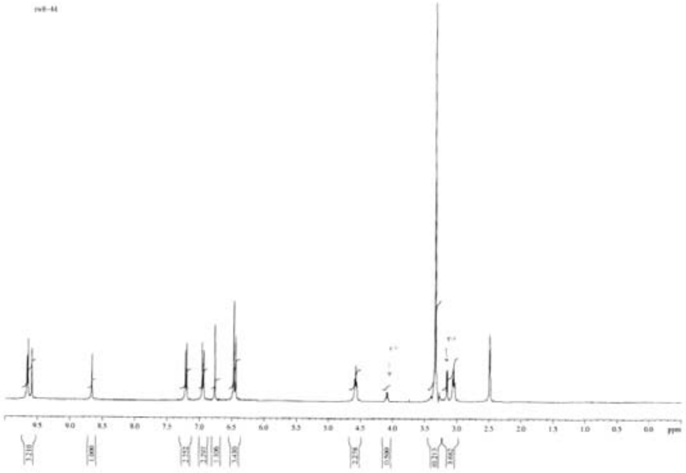
Lam **38-OAc** ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$)

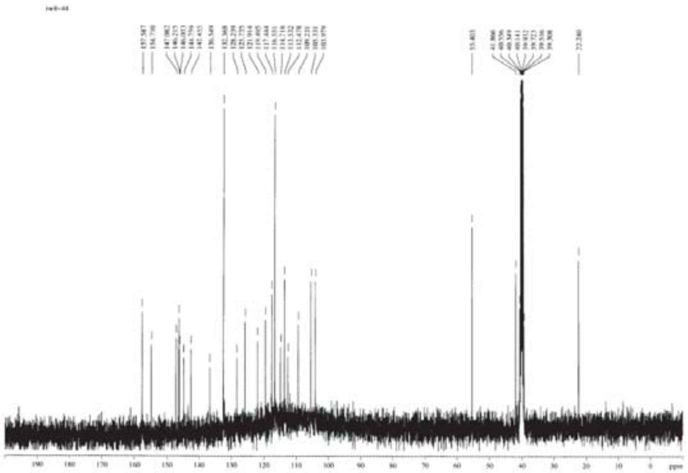


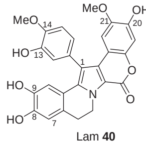




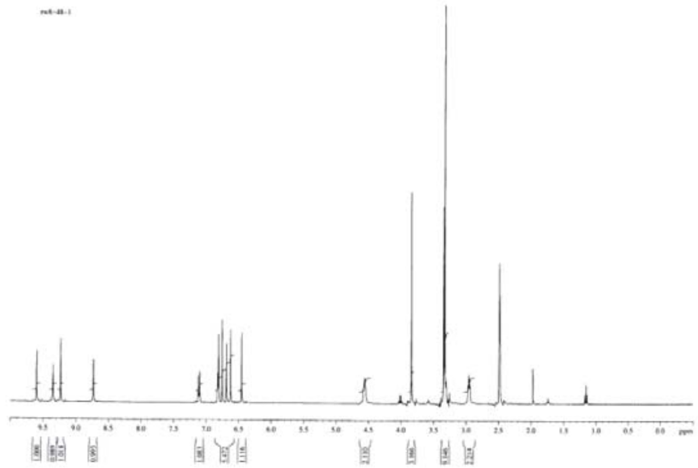
Lam **39** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

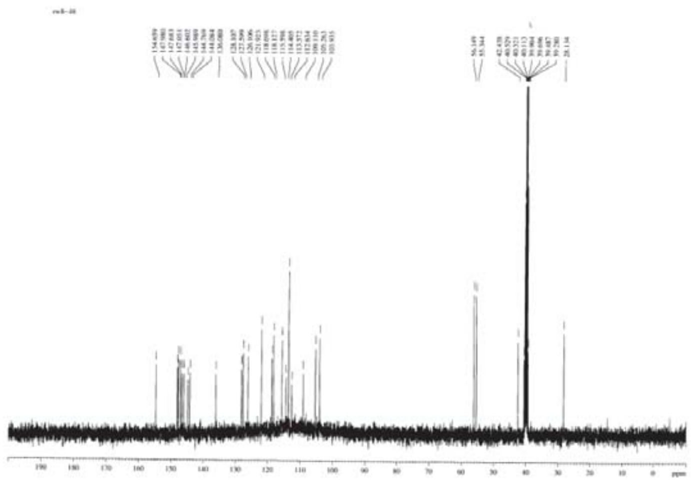


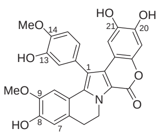




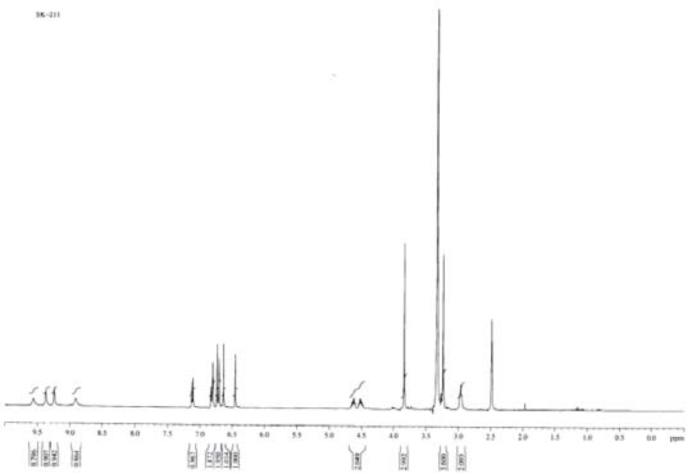
Lam **40** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

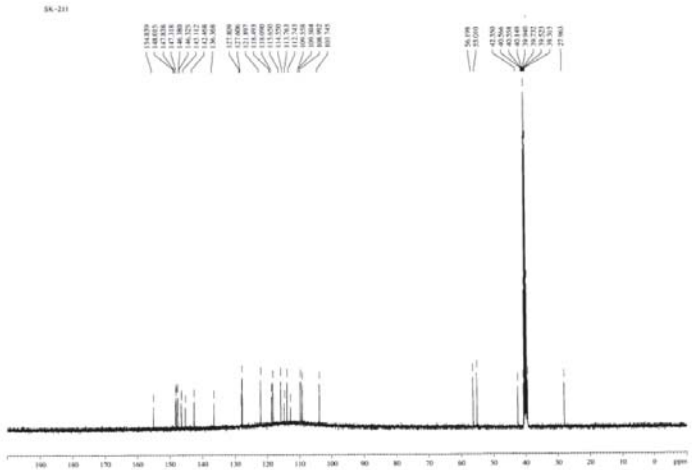


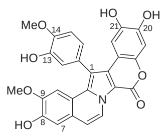




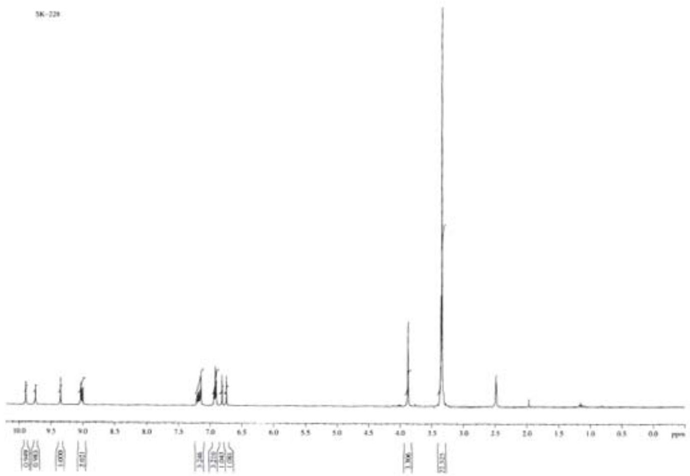
Lam **41** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

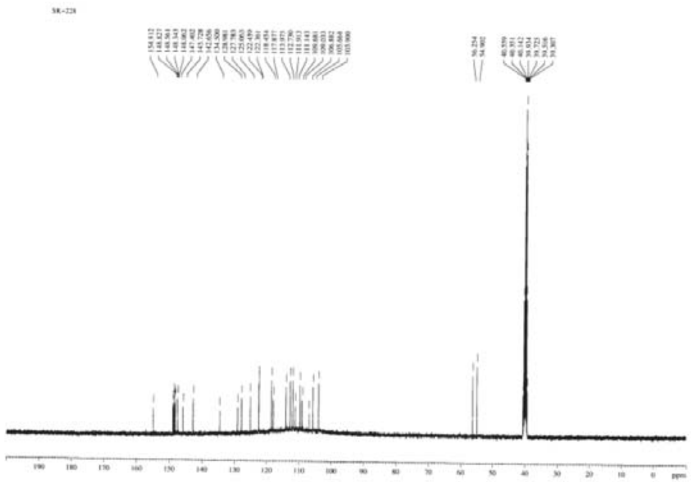


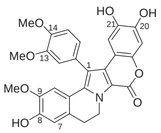




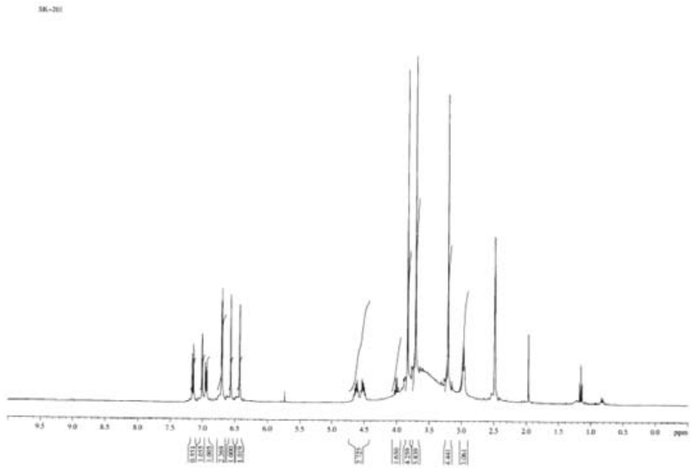
Lam **42** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

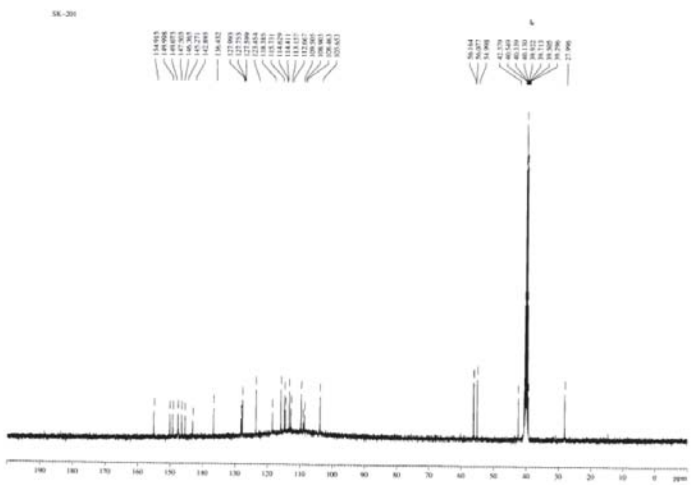


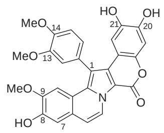




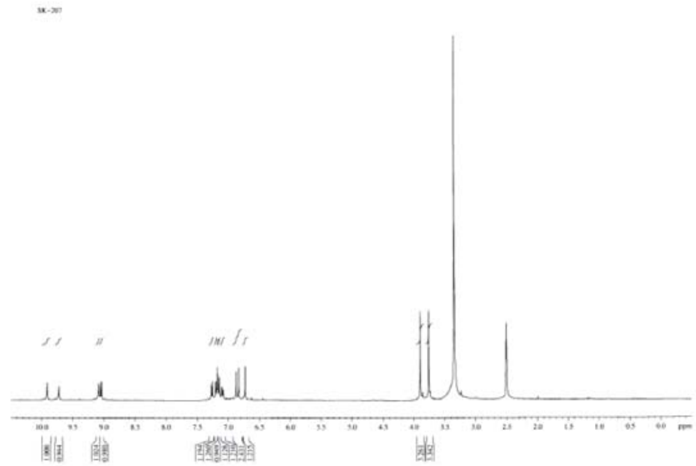
Lam **43** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

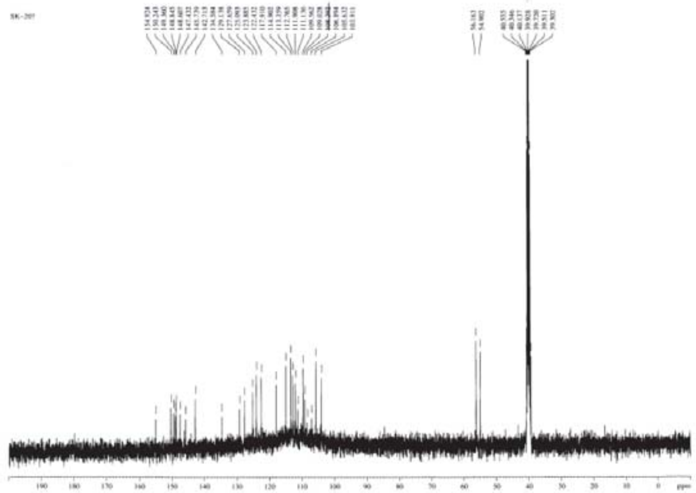


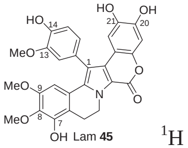




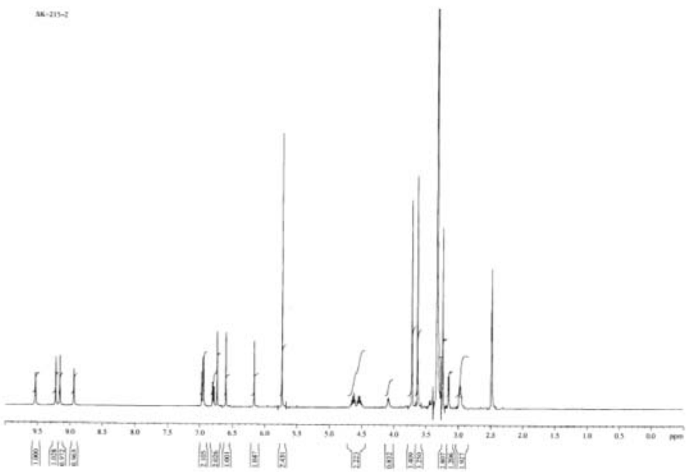
Lam **44** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

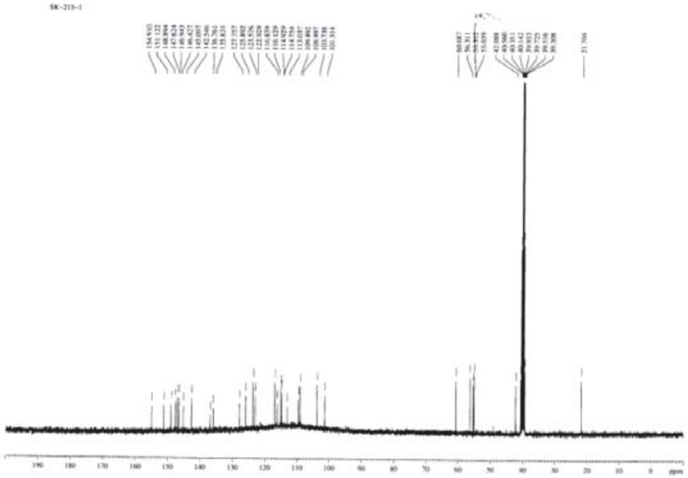


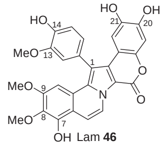




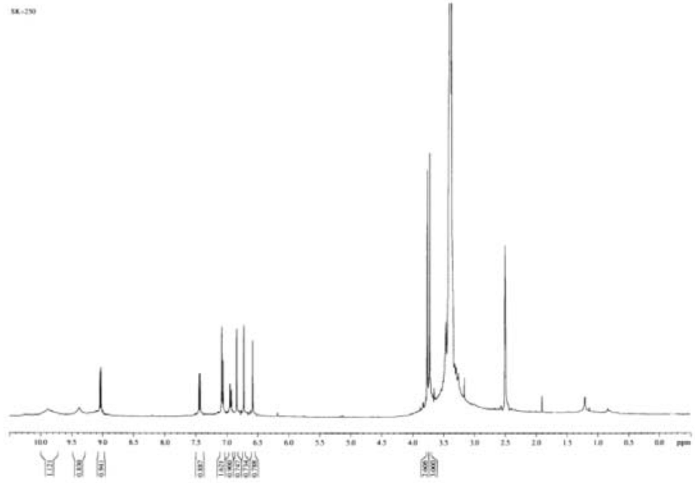
Lam **45** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

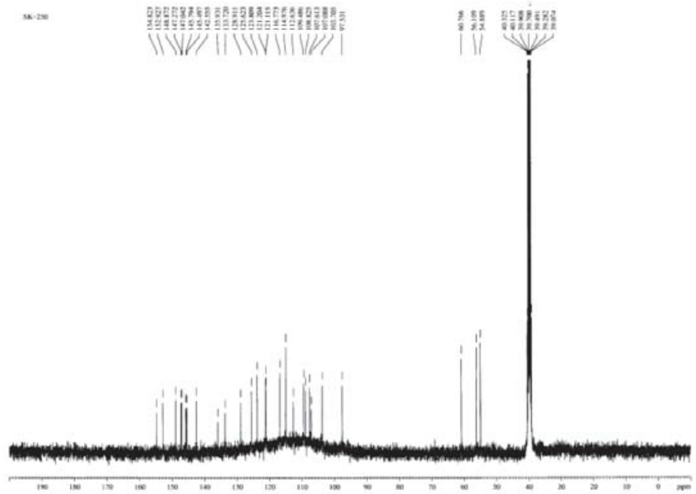


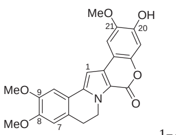




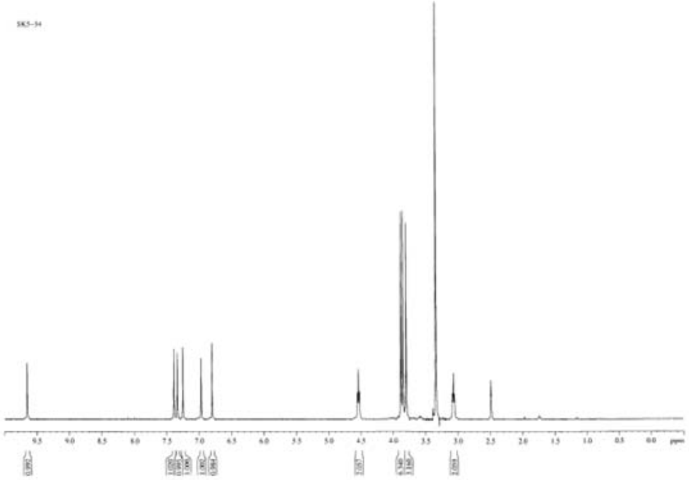
Lam **46** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

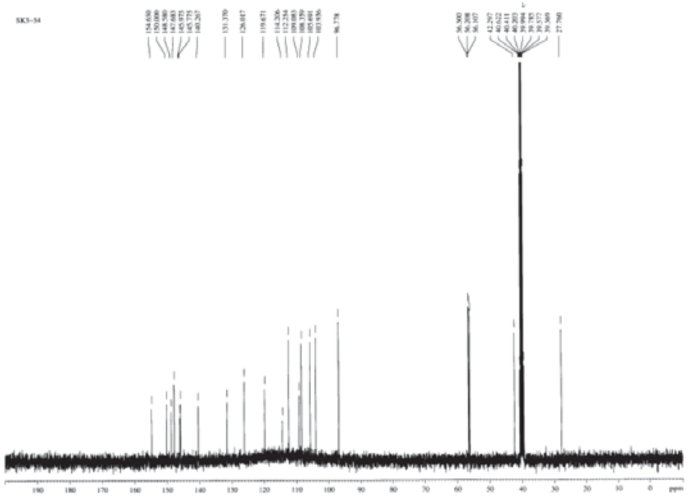


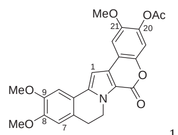




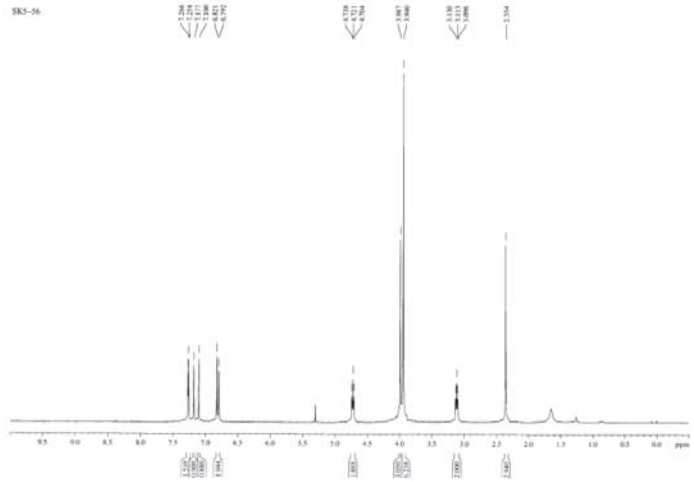
Lam **47** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

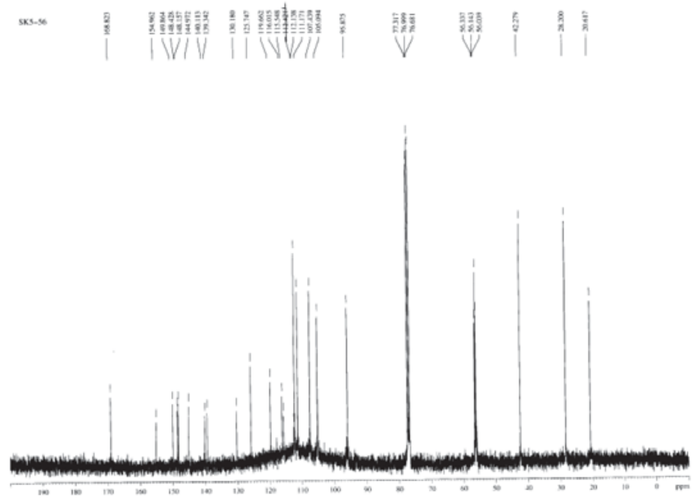


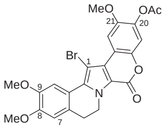




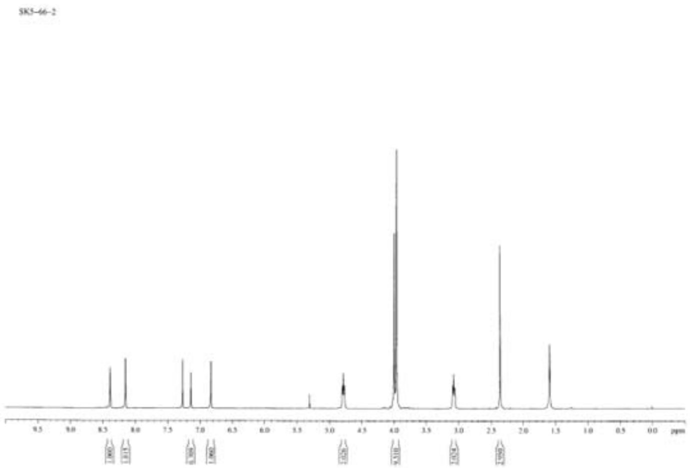
Lam **47-OAc** ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

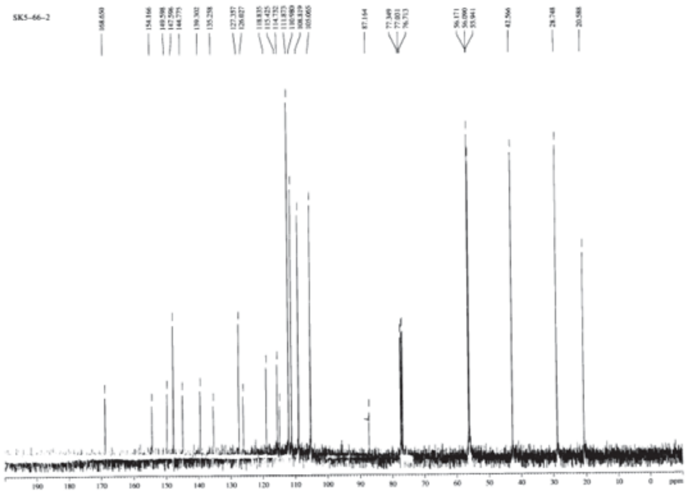


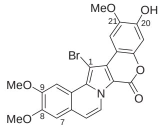




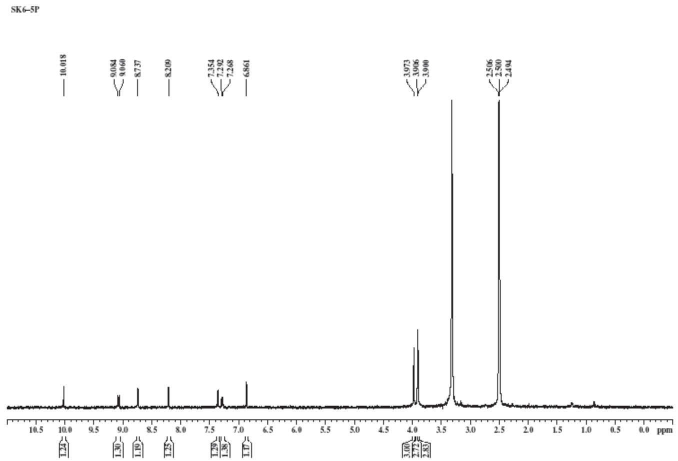
Lam **48-OAc** ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

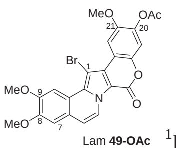




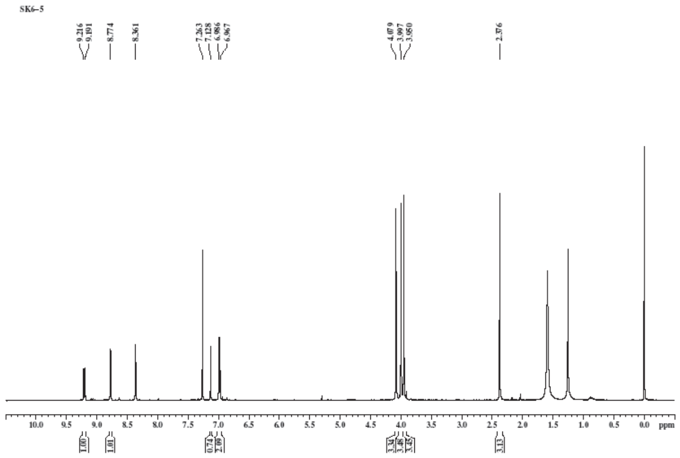


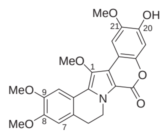
Lam **49** ^{1}H NMR (300 MHz, $CDCl_3$)



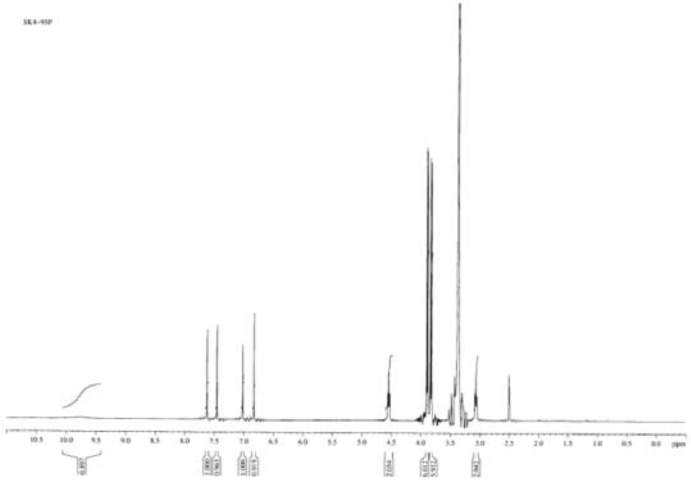


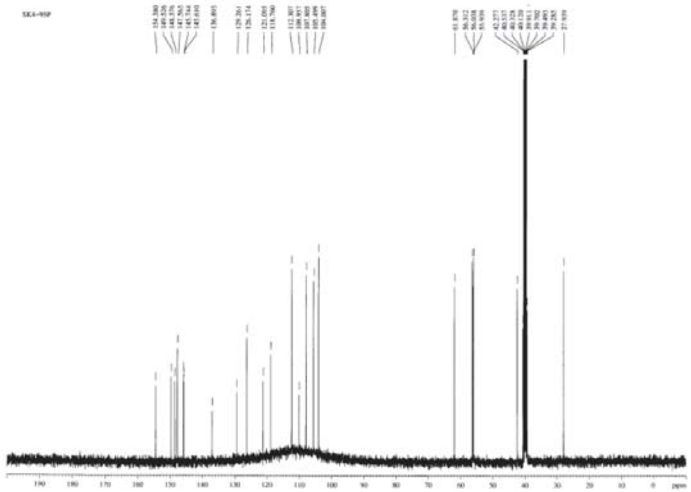
Lam **49-OAc** ^{1}H NMR (300 MHz, $CDCl_3$)

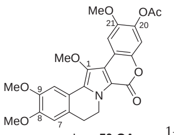




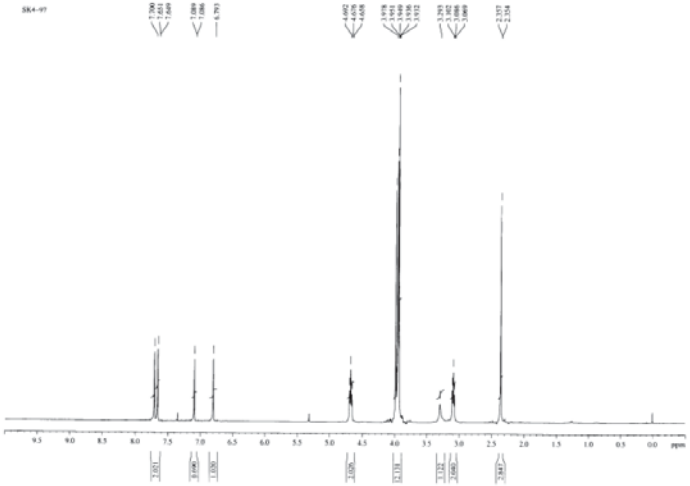
Lam **50** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

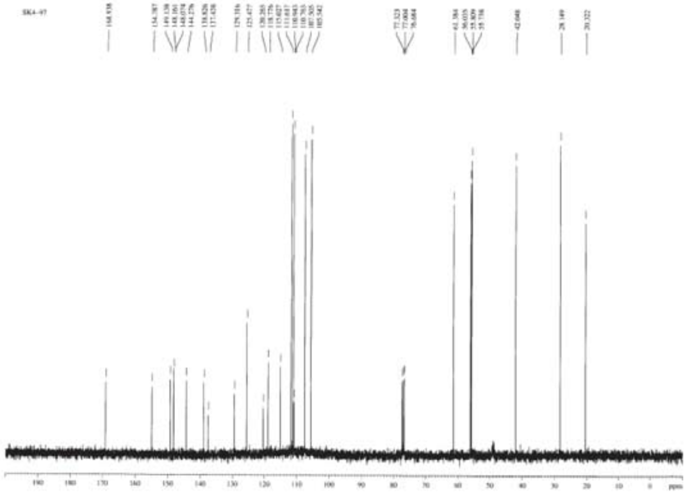


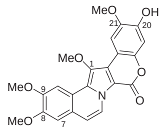




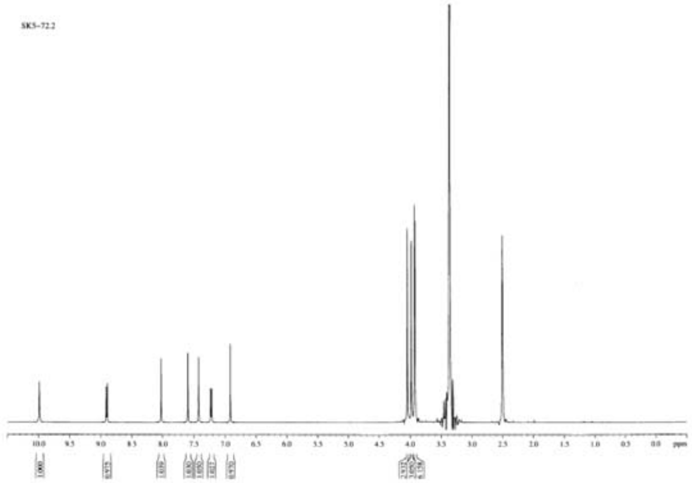
Lam **50-OAc** ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

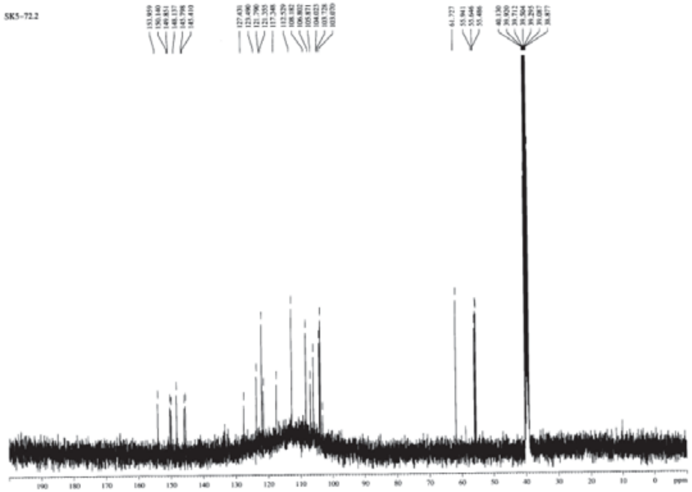


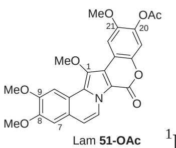




Lam **51** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

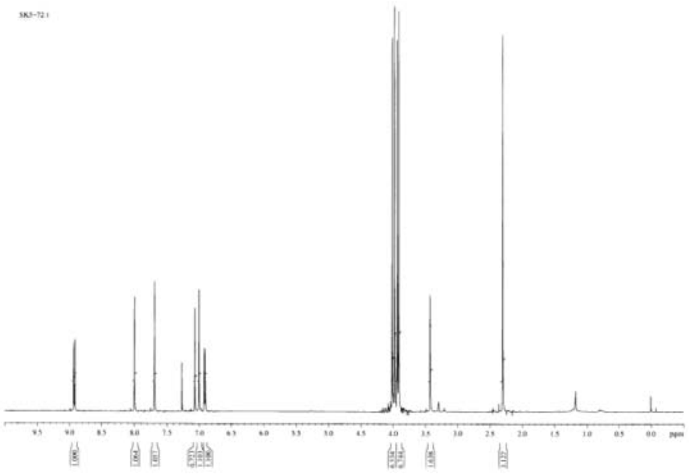


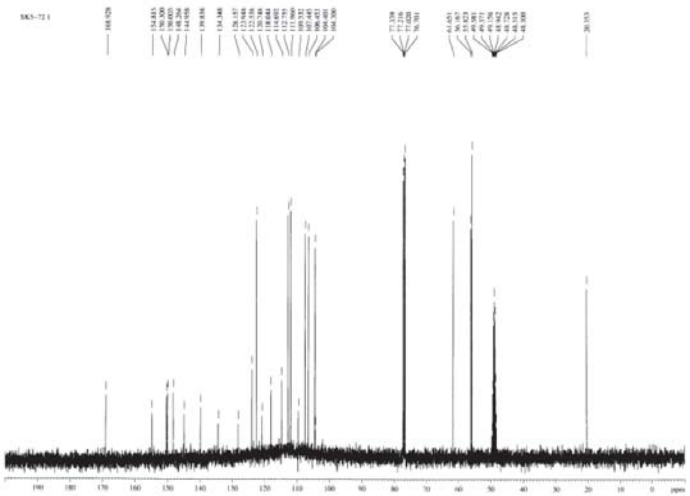


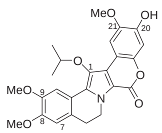


Lam **51-OAc**

^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD) and ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD)

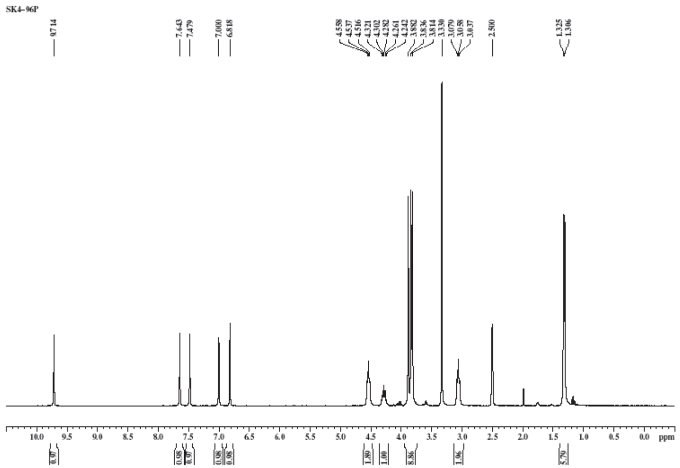


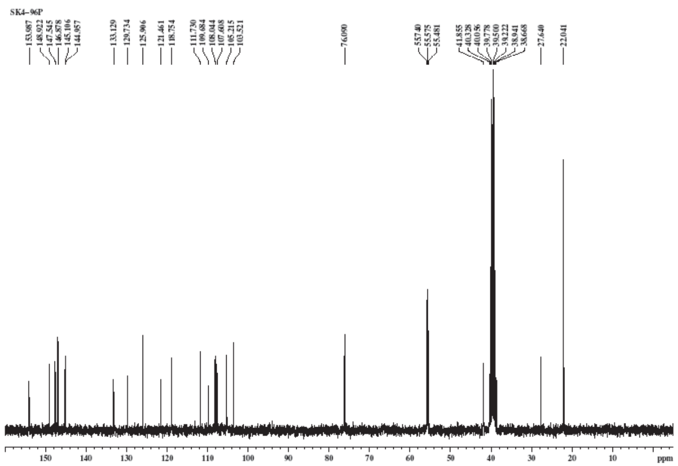


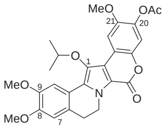


Lam **52**

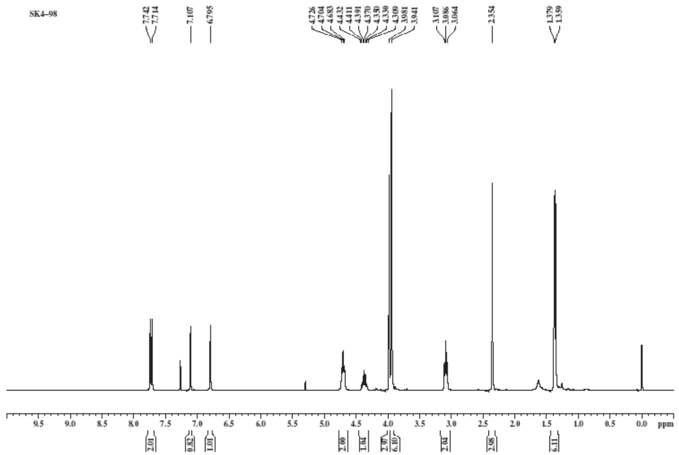
^{1}H NMR (300 MHz, DMSO-d_6) and ^{13}C NMR (75 MHz, DMSO-d_6)

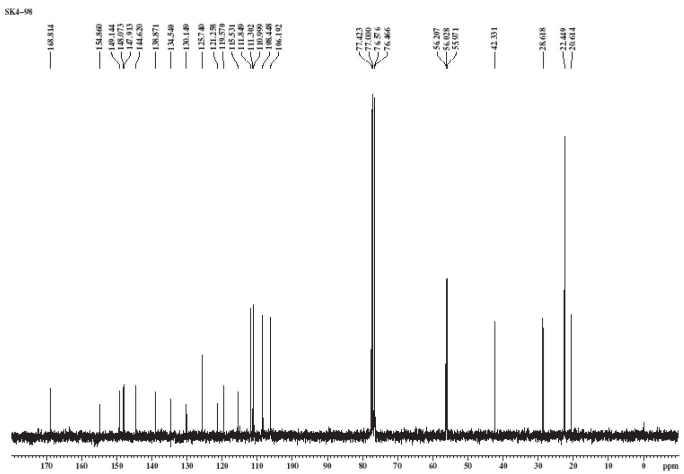


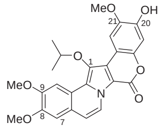




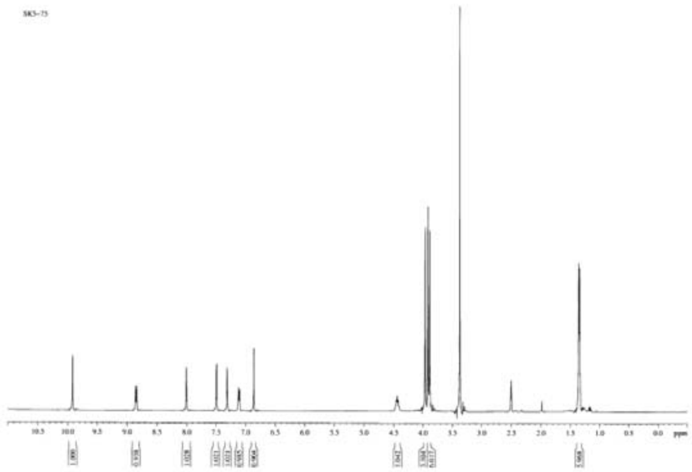
Lam **52-OAc** ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$)

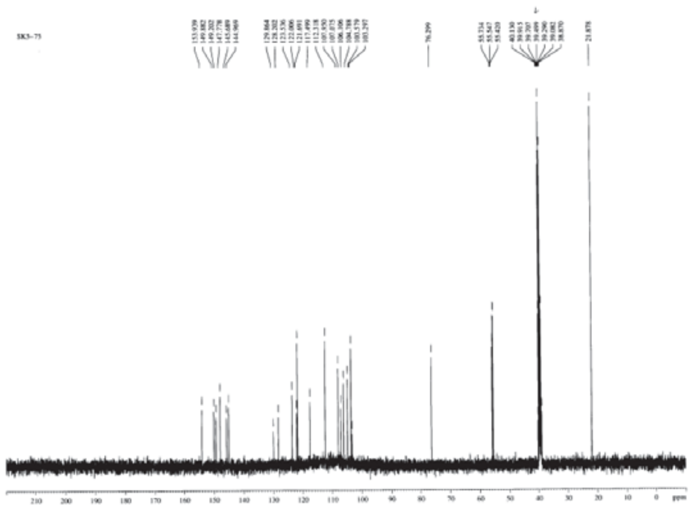


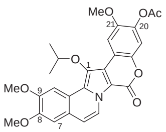




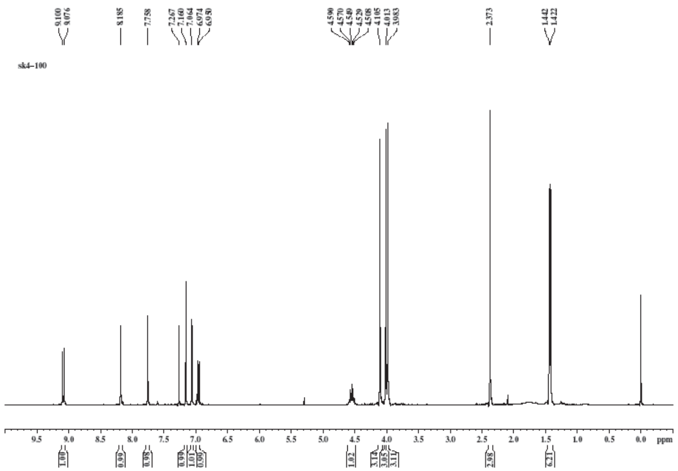
Lam **53** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

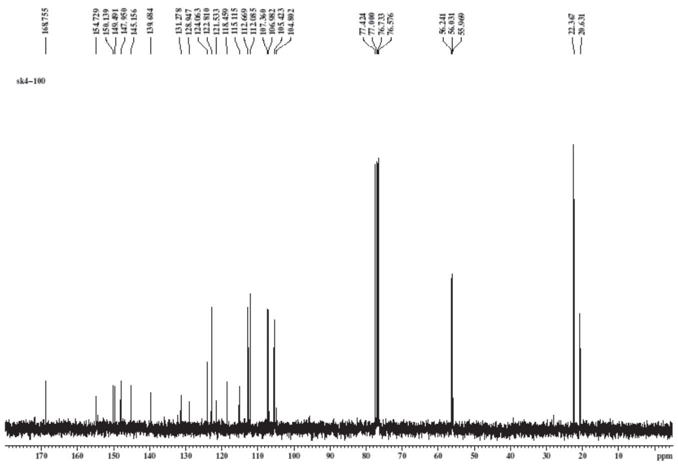


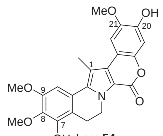




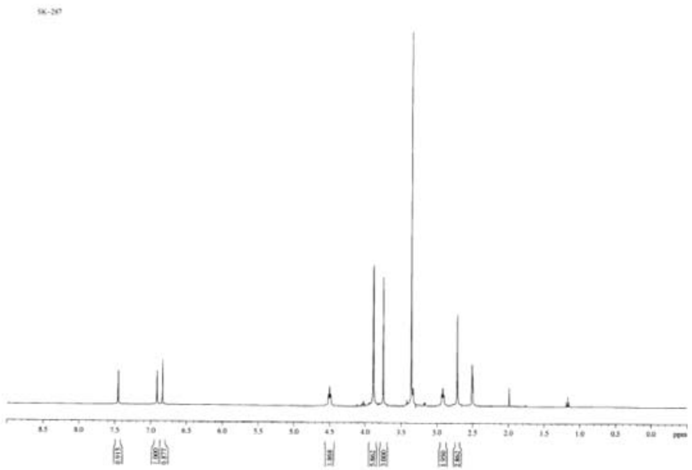
Lam **53-OAc** ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$)

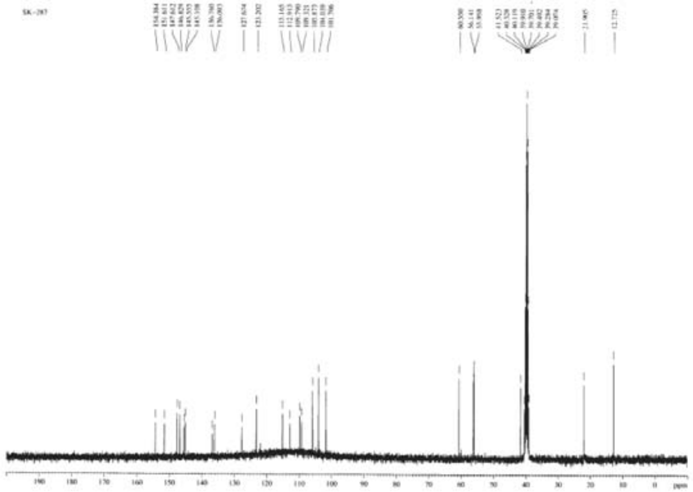


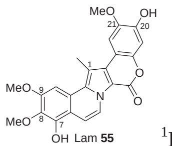




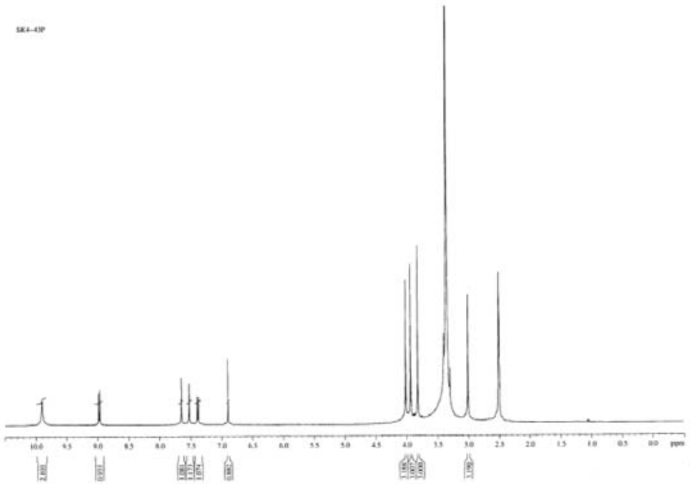
Lam **54** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

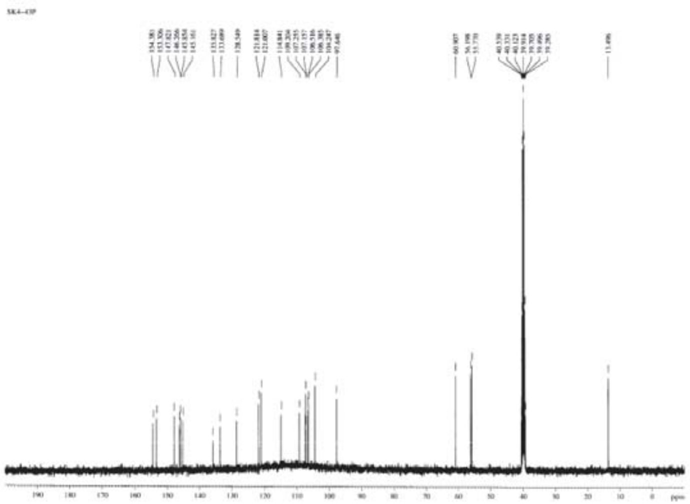


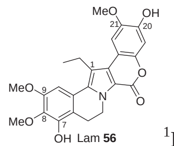




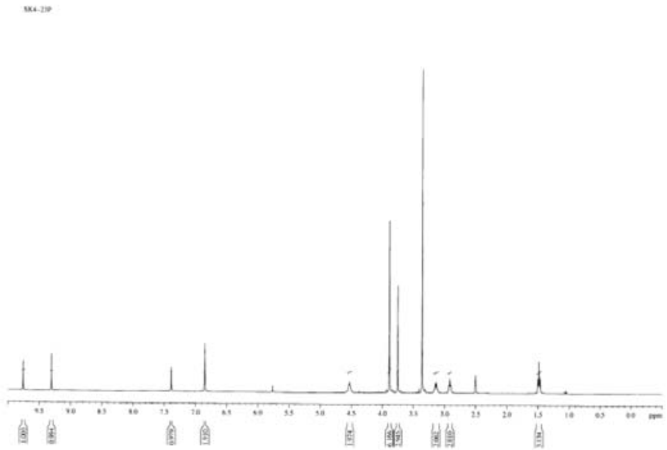
Lam **55** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

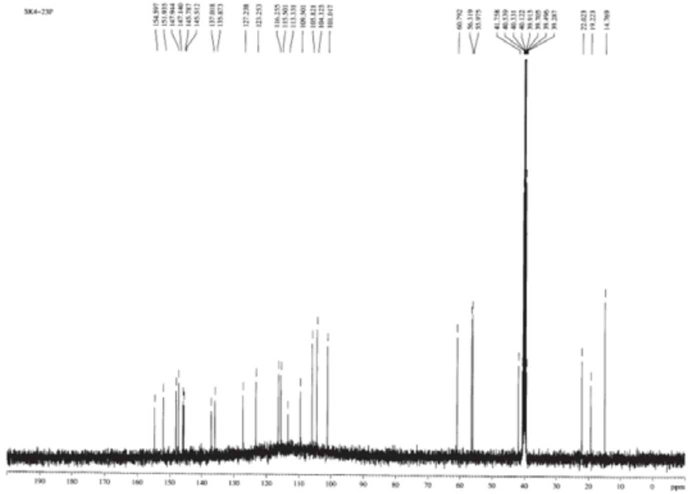


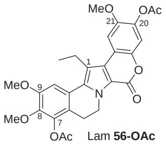




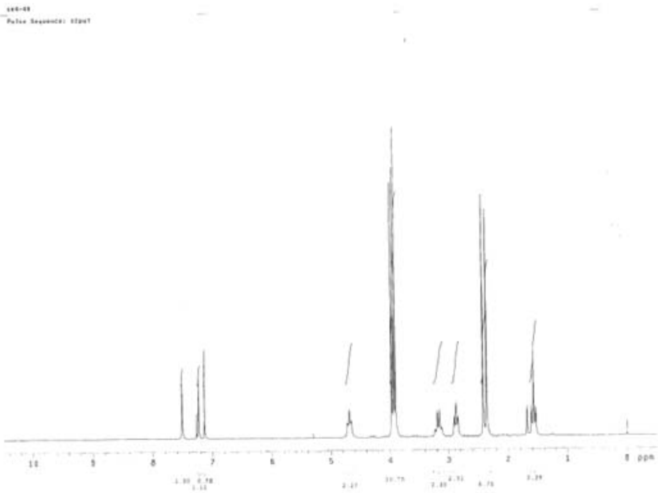
Lam **56** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

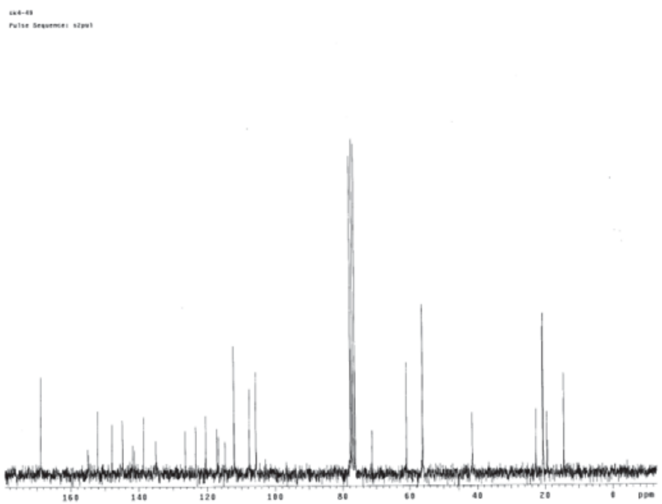


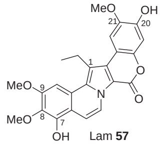




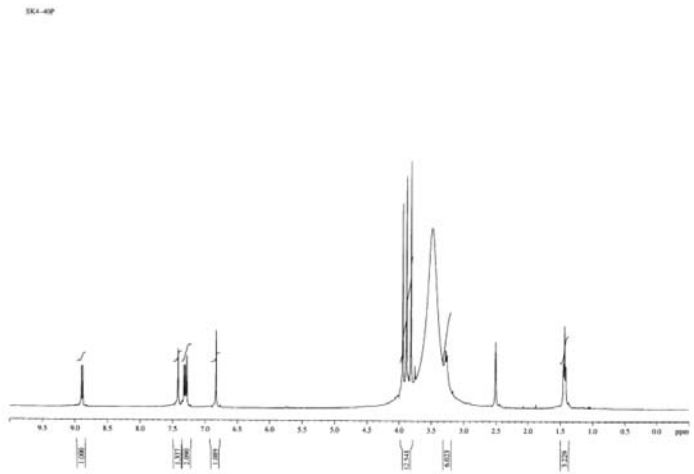
Lam **56-OAc** ^1H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

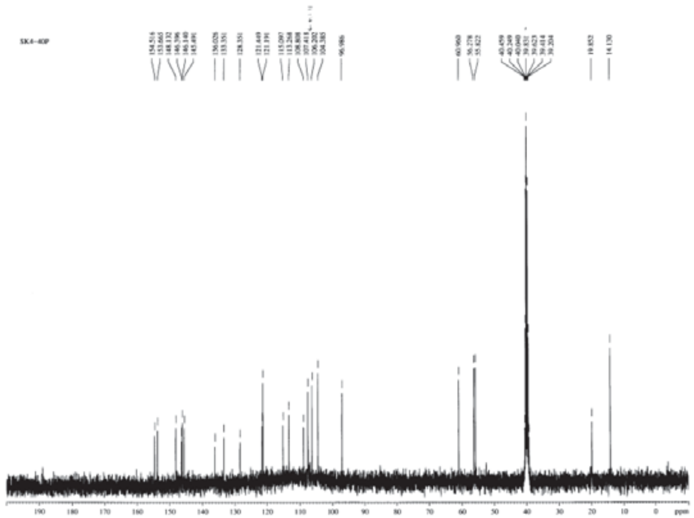


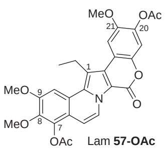




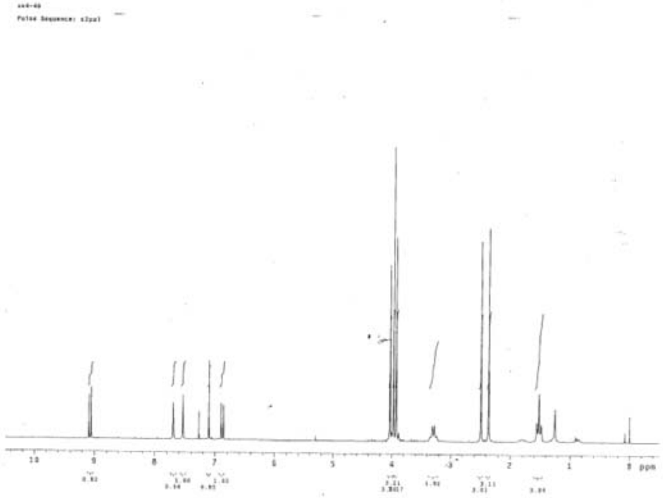
Lam **57** ^1H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

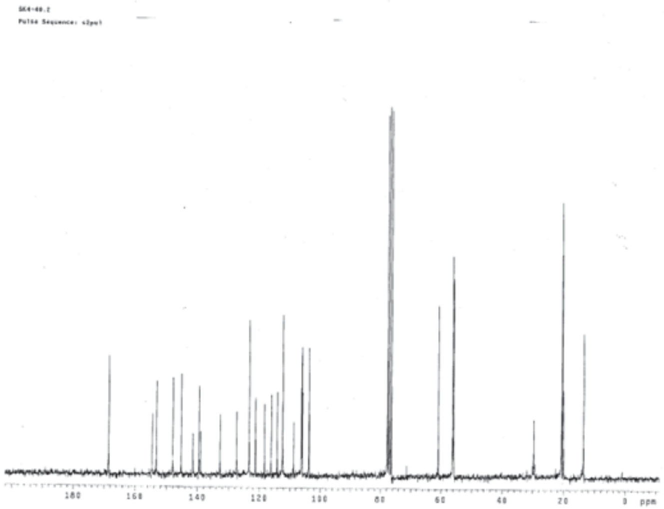


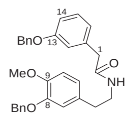




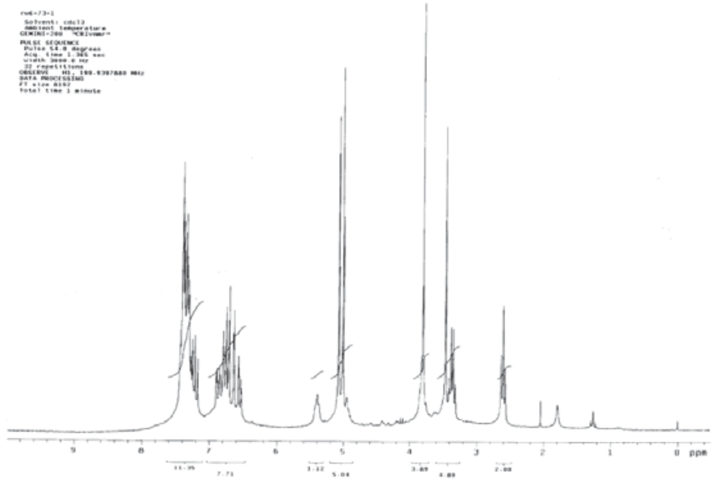
Lam **57-OAc** ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

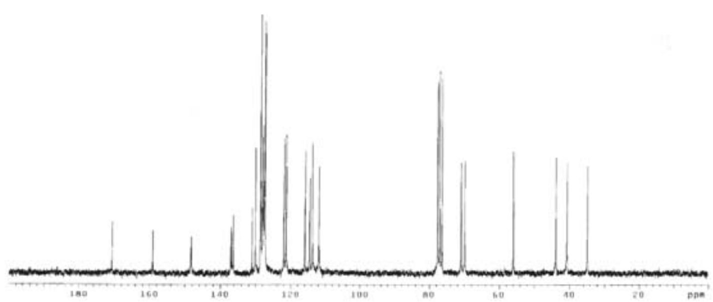


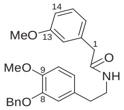




84 ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

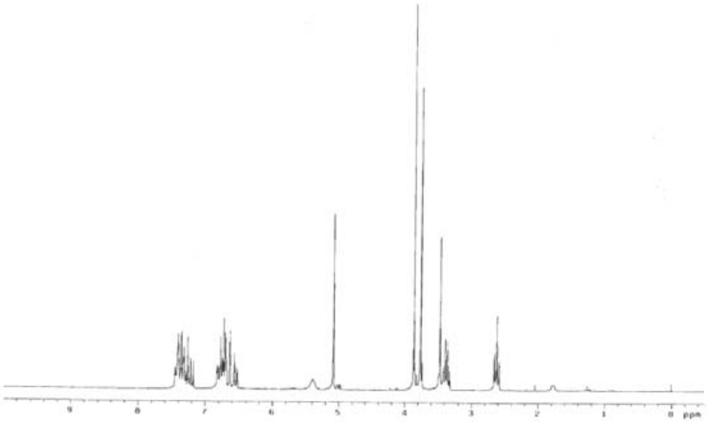


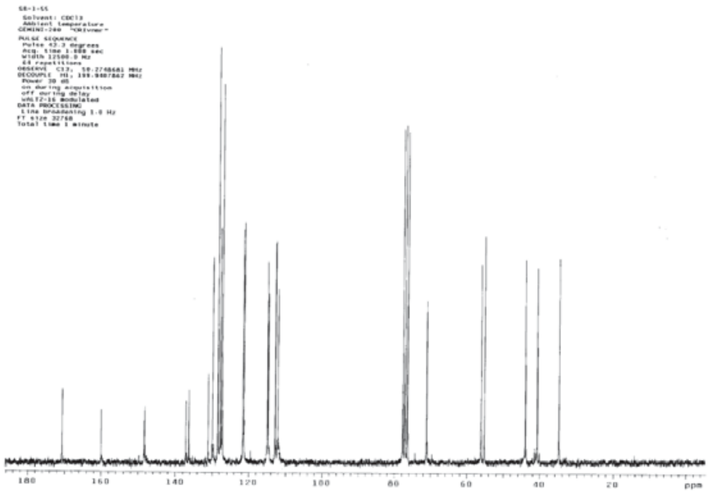


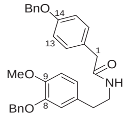


85

^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

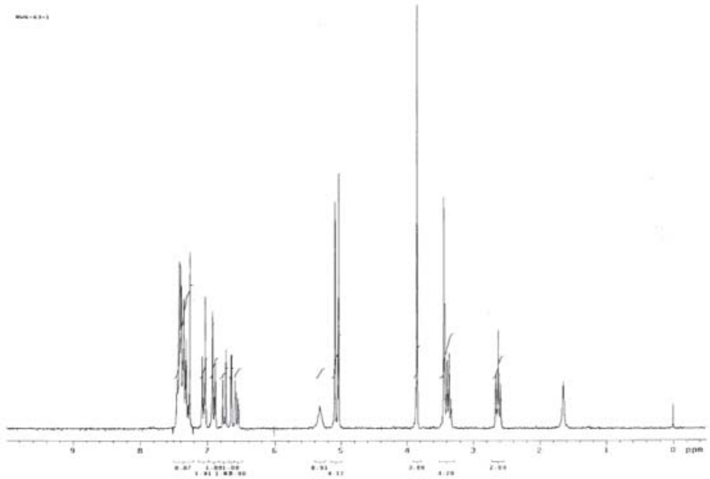


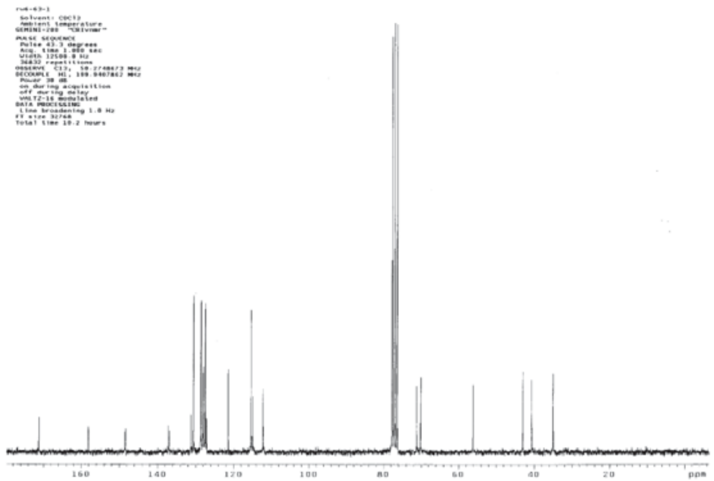


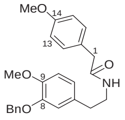


86

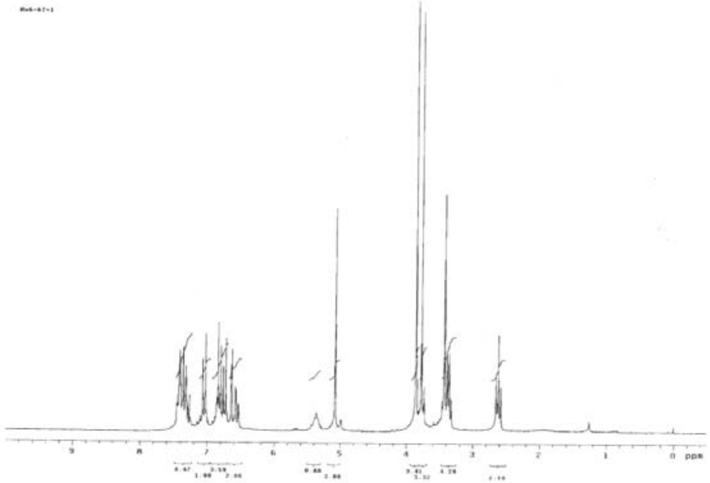
^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

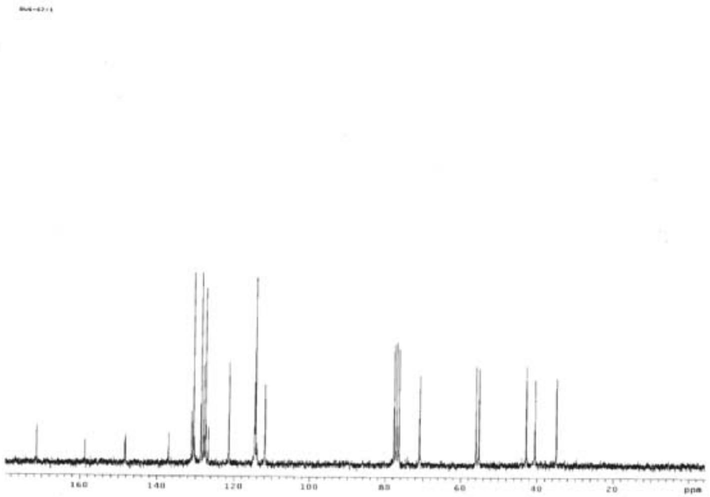


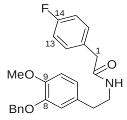




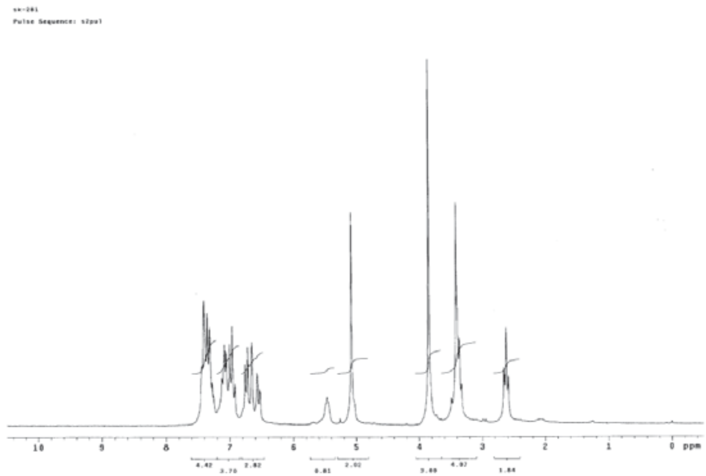
87 ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

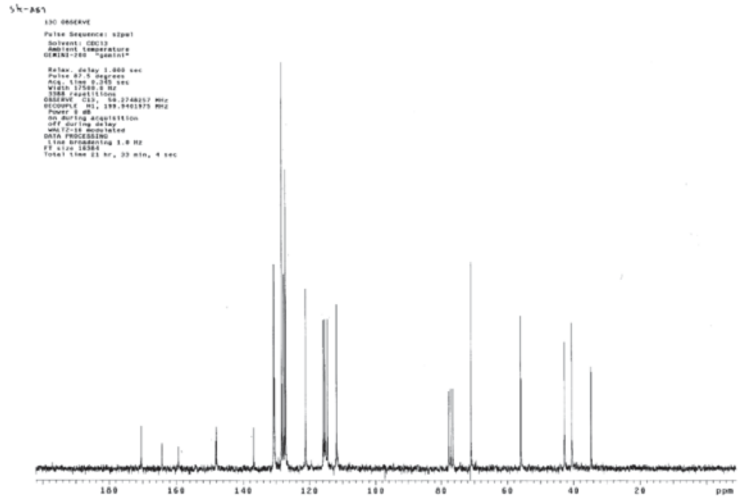


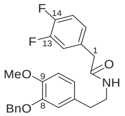




88 ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

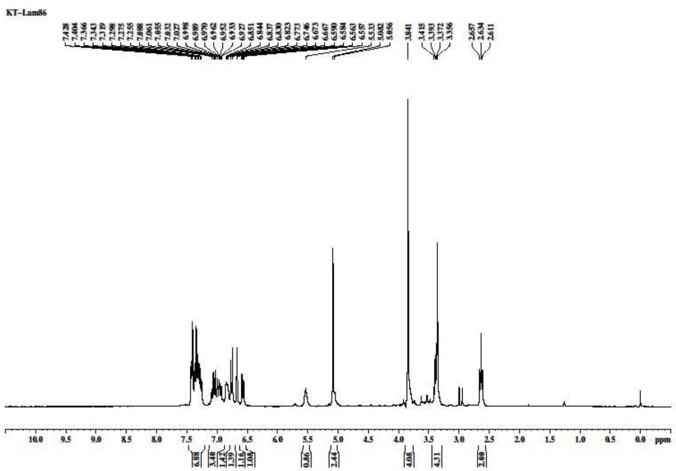


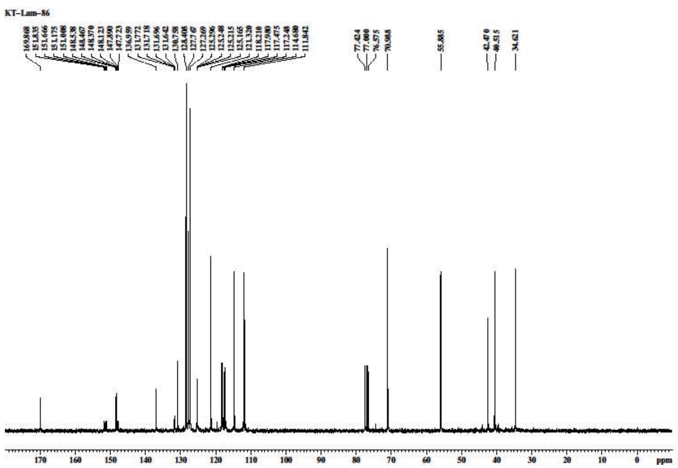


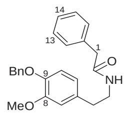


89

^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$)

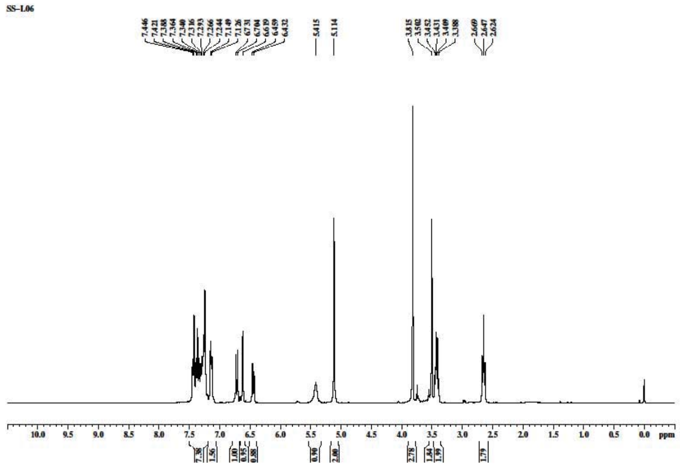


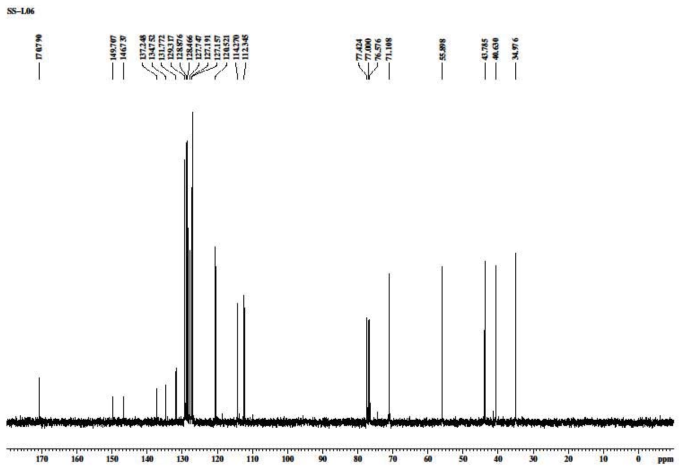


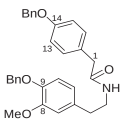


90

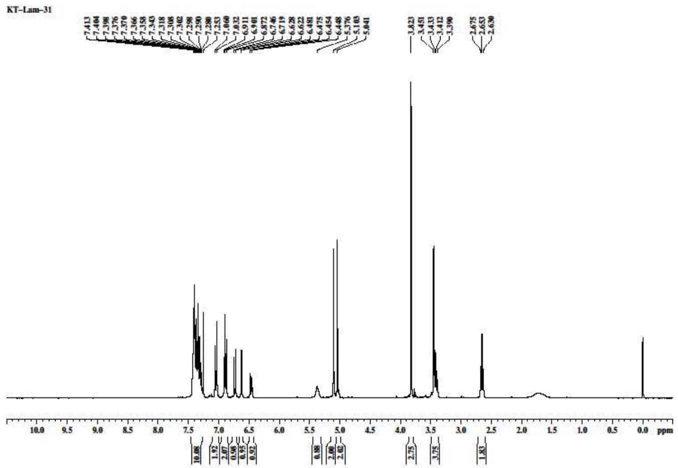
^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$)

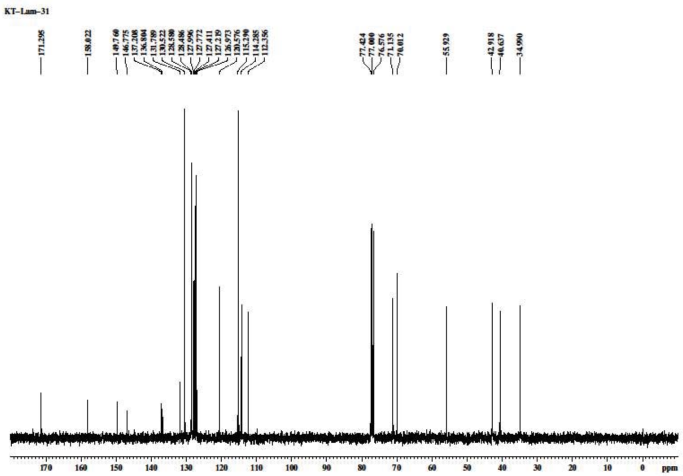


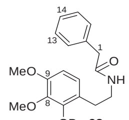




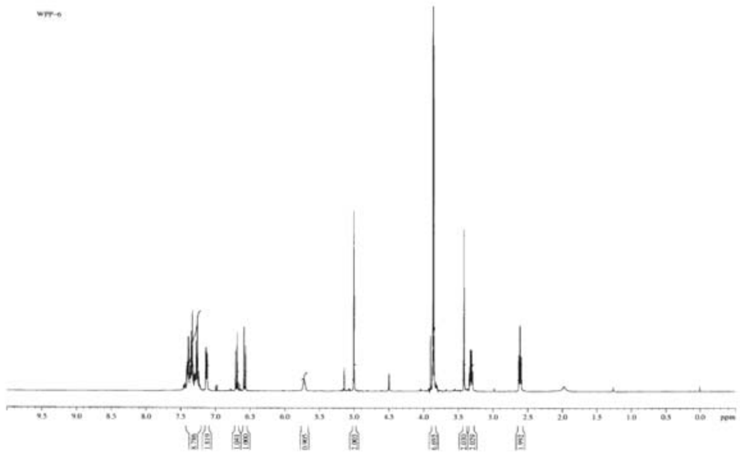
91 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$)

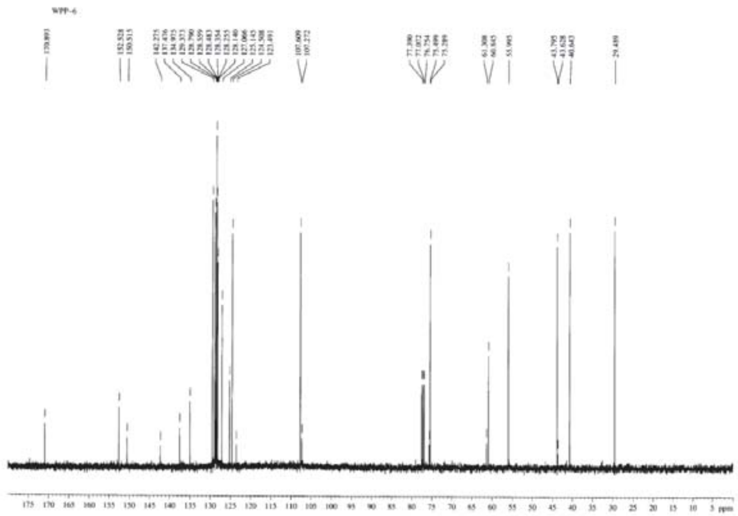


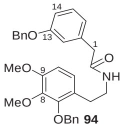




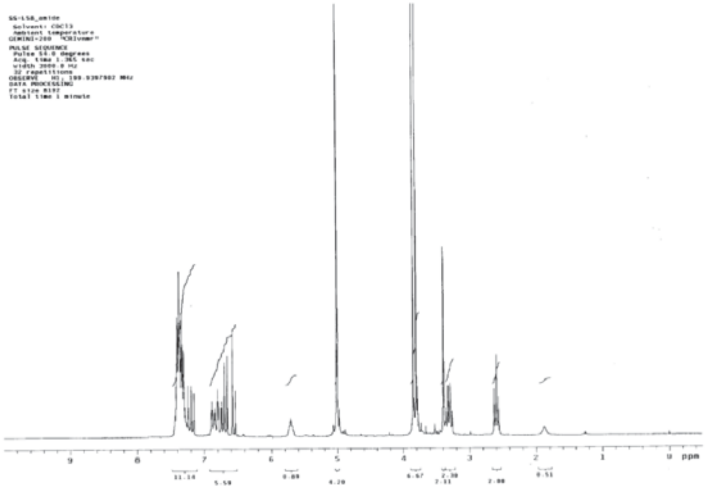
93 ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

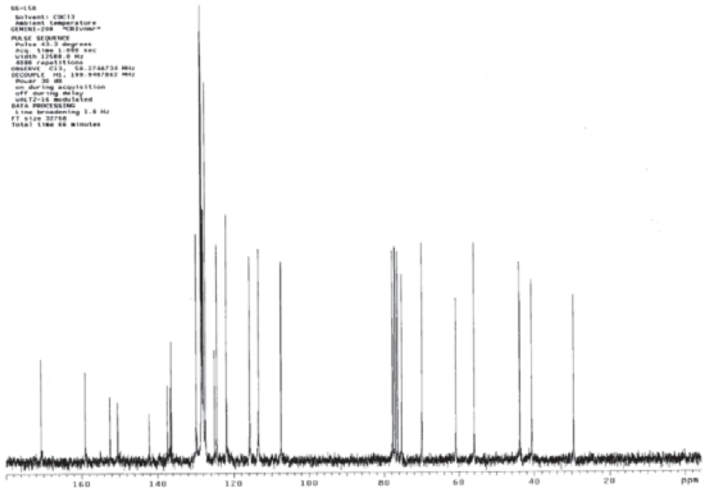


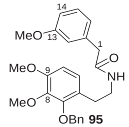




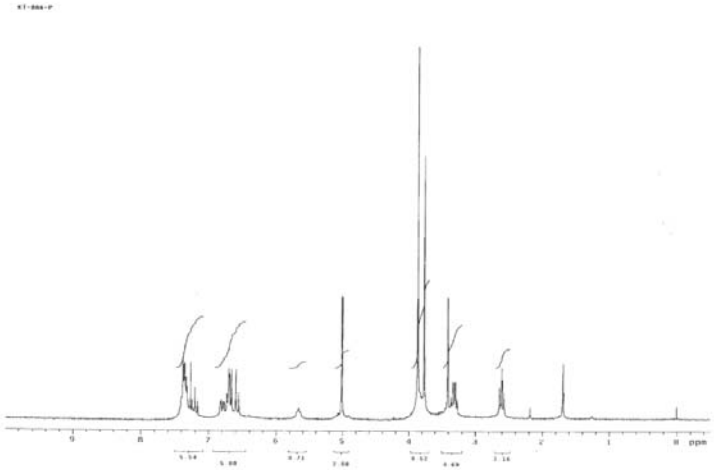
94 ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

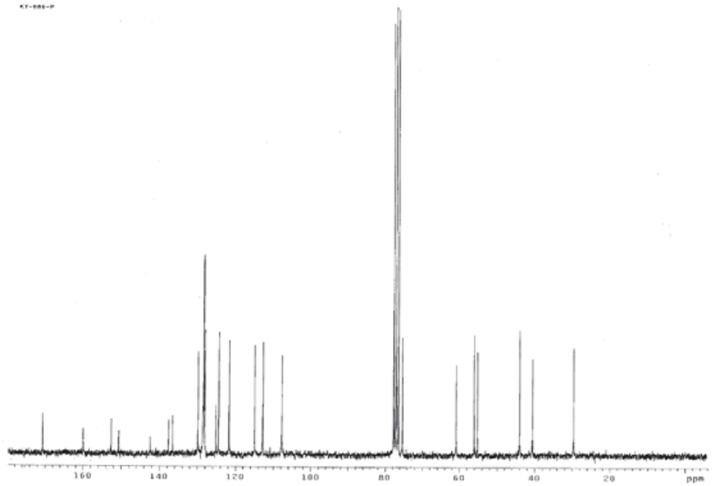


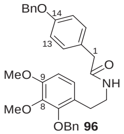




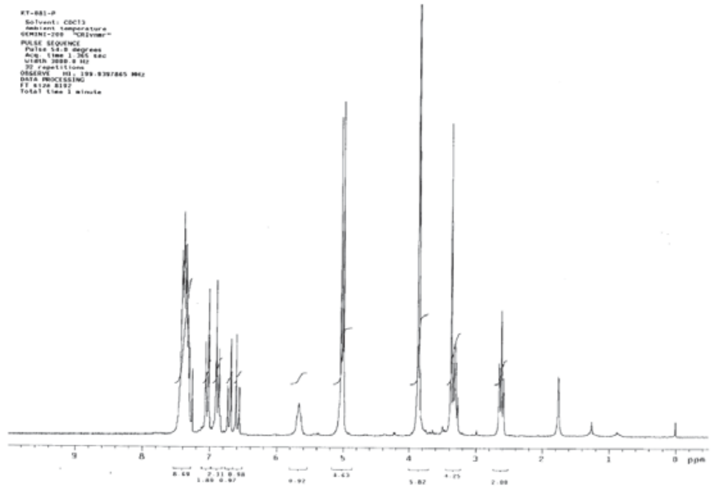
95 ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

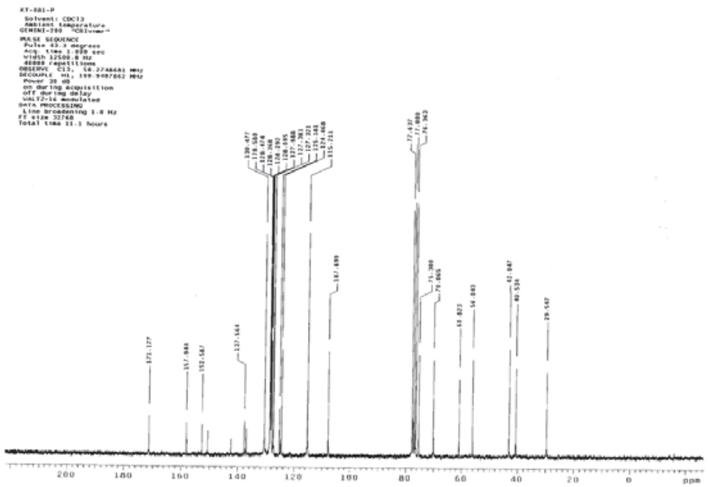


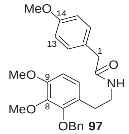




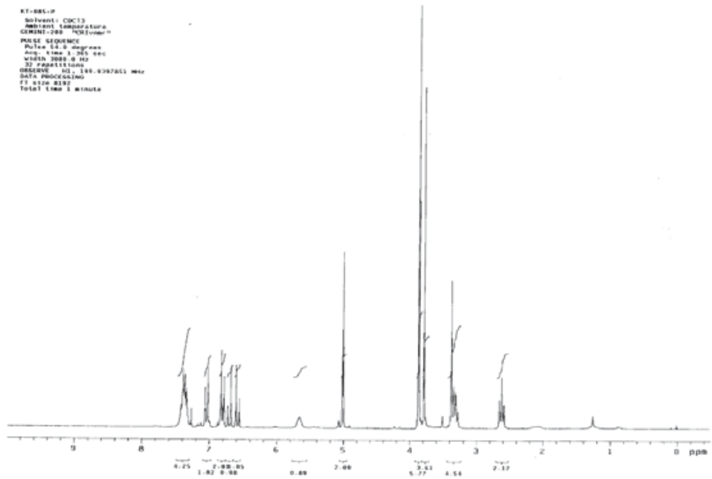
96 ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

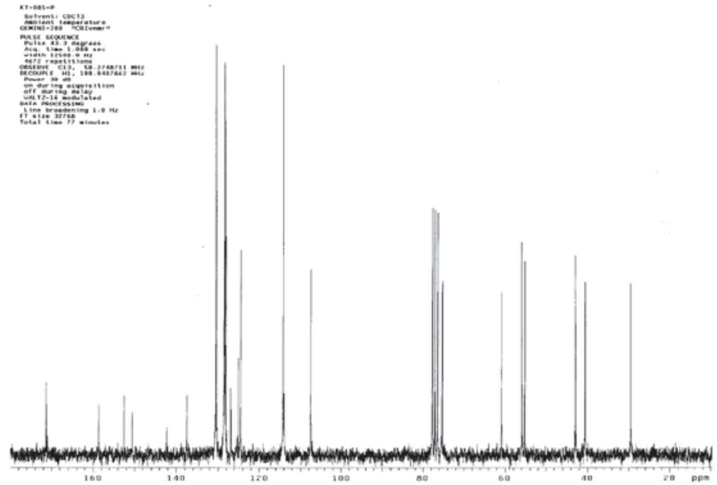


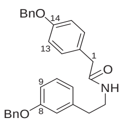




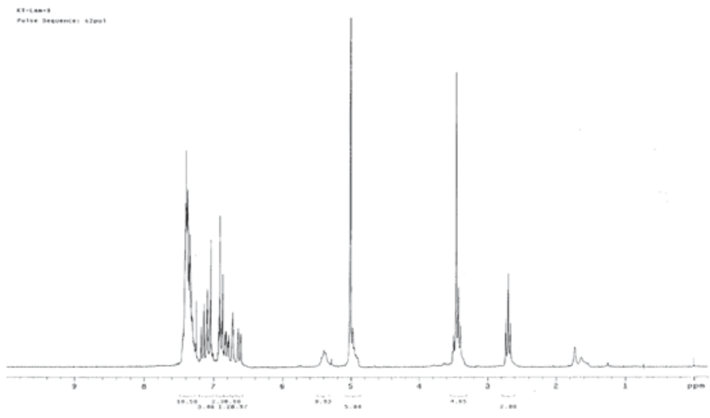
97 ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

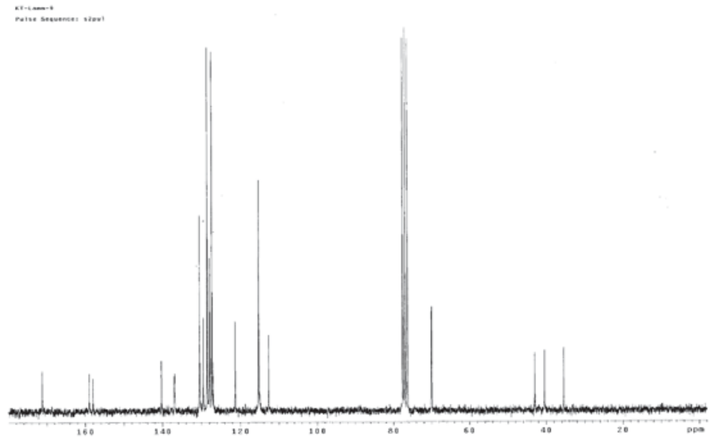


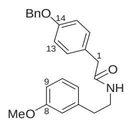




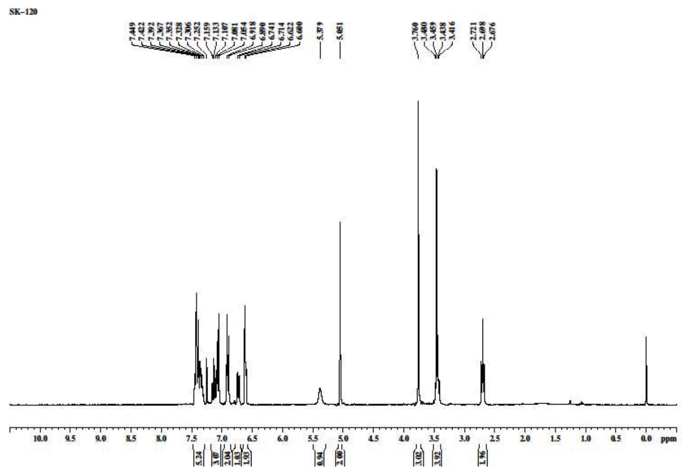
99 ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

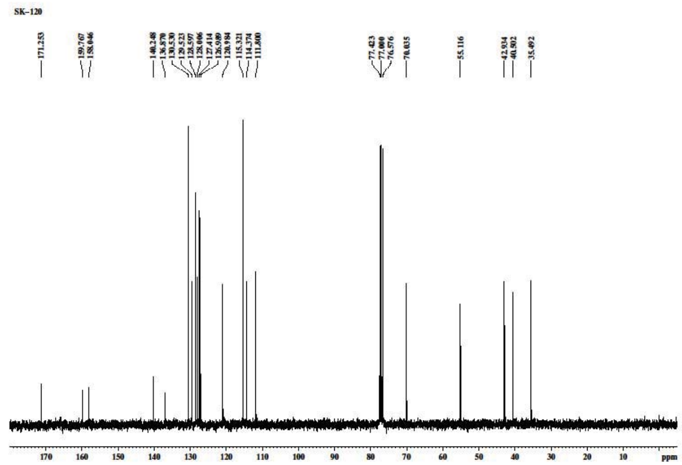


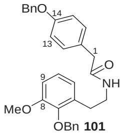




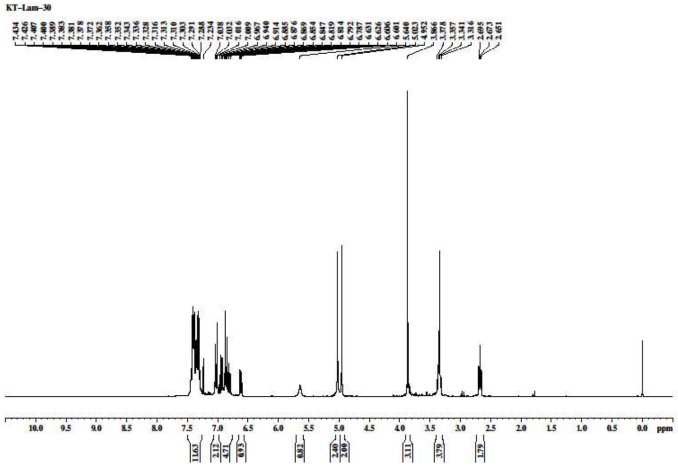
100 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$)

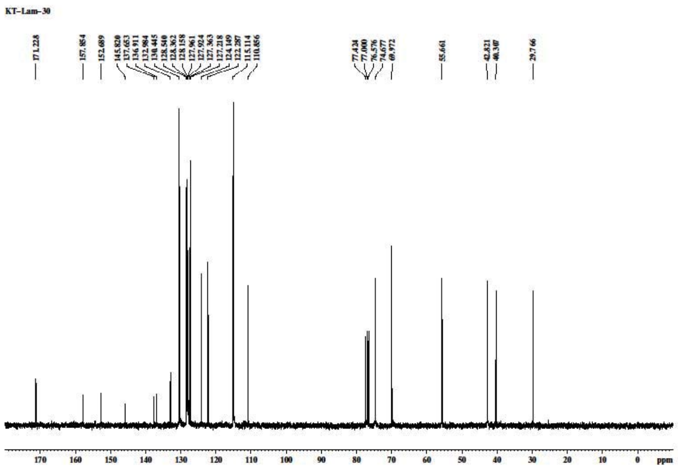


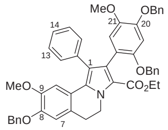




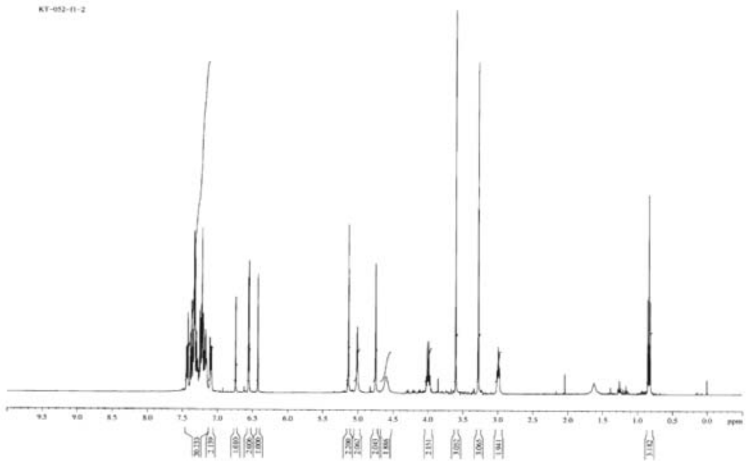
101 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$)

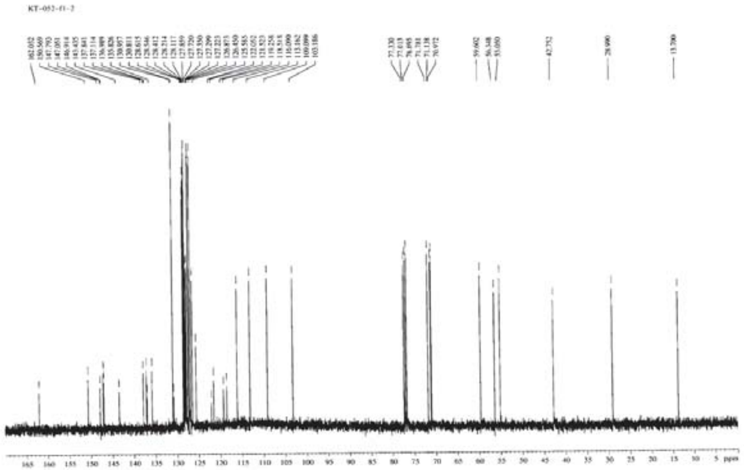


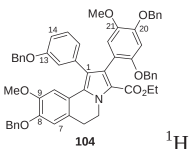




103 ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

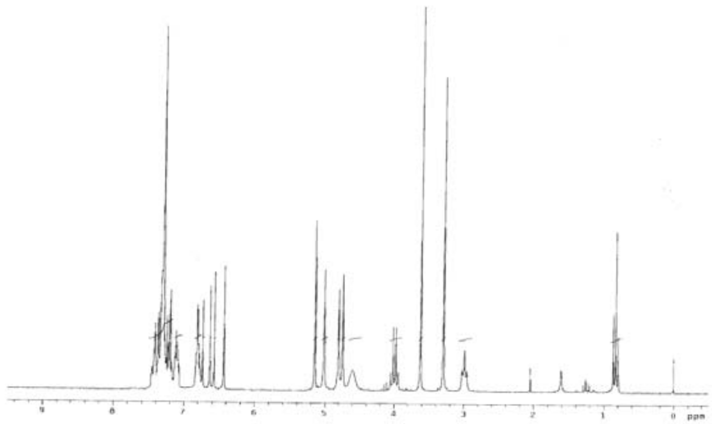


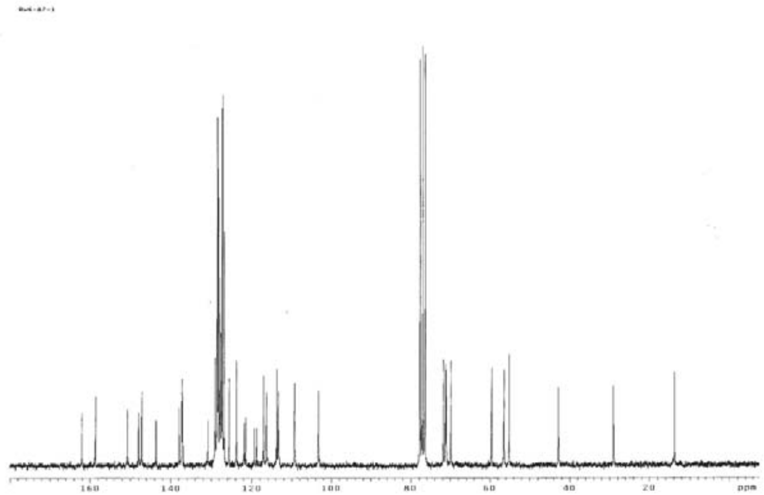


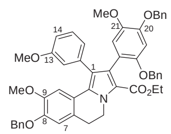


104

^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

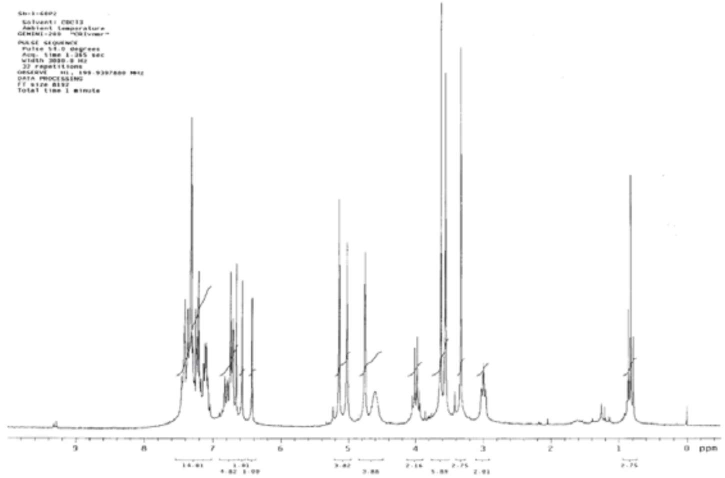


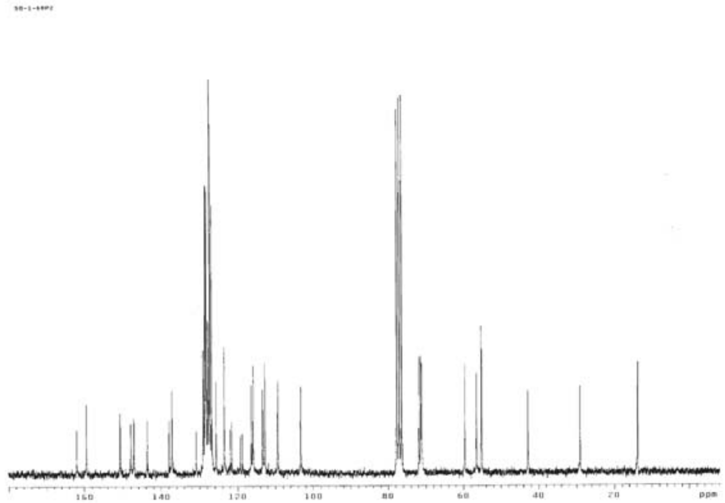


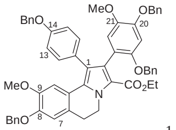


105

^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

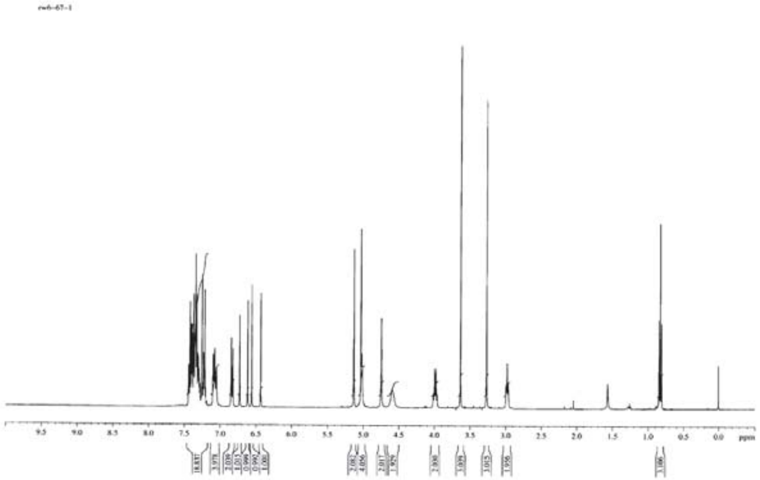


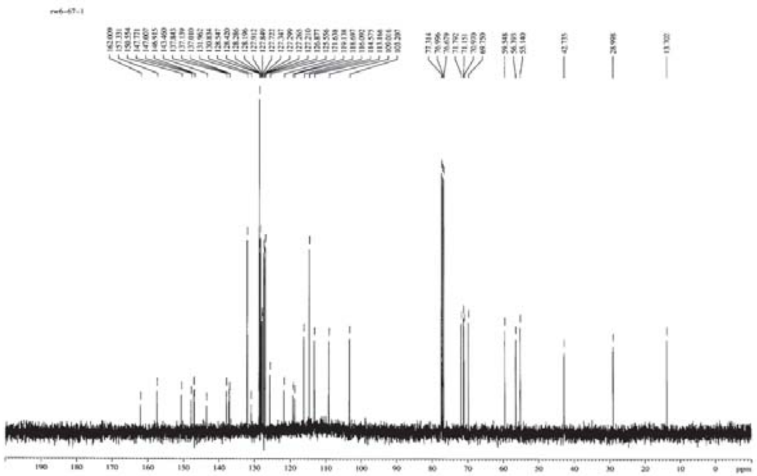


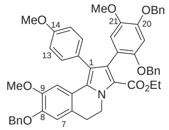


106

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

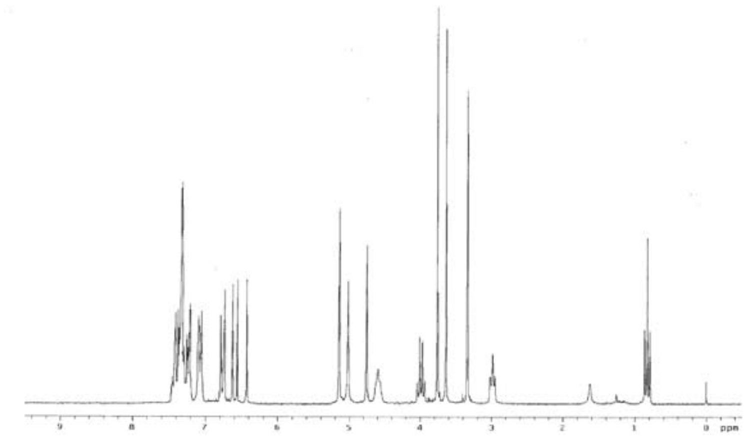


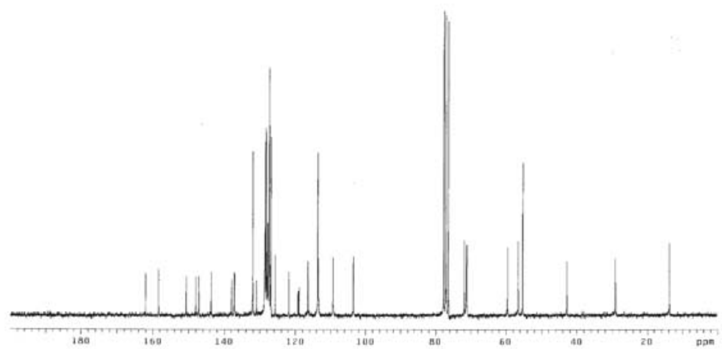


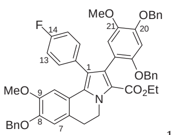


107

^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

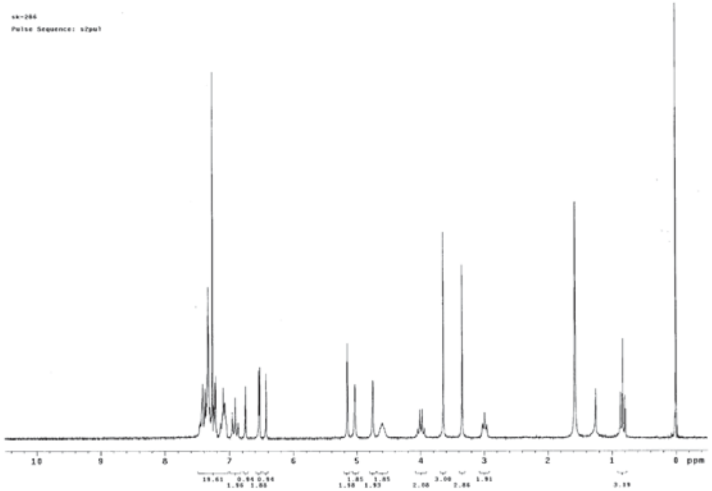


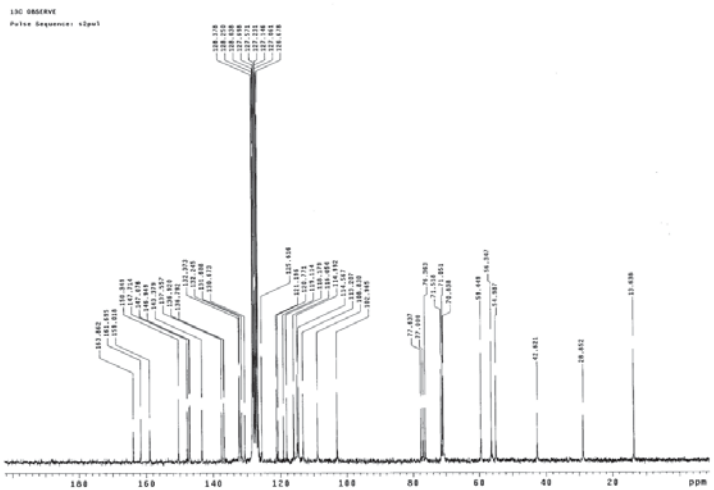


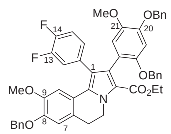


108

^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

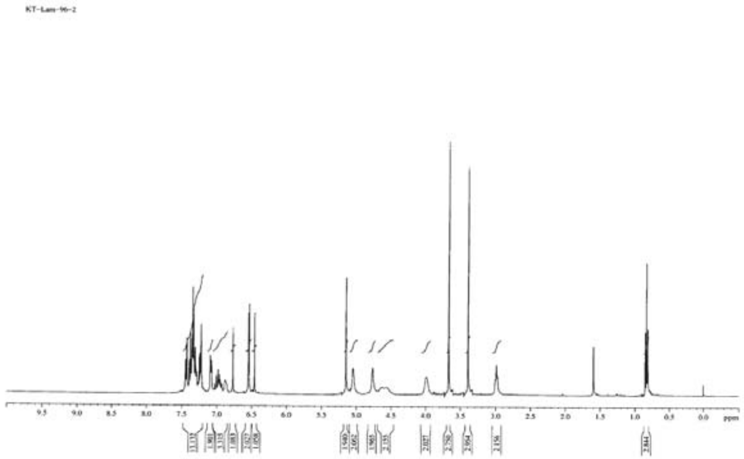


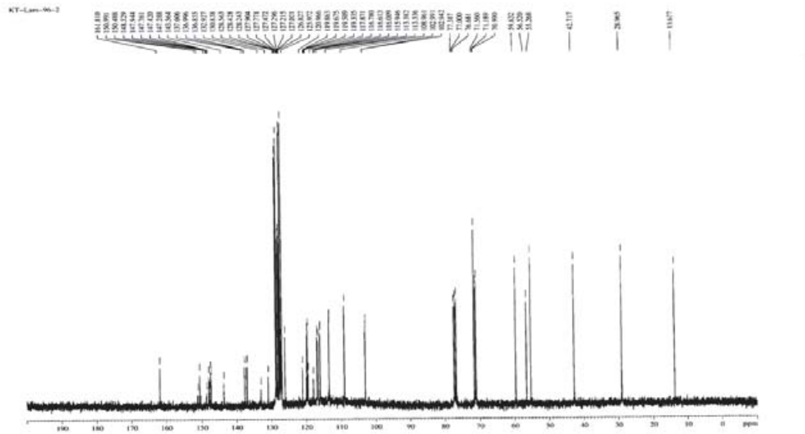


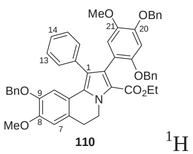


109

^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

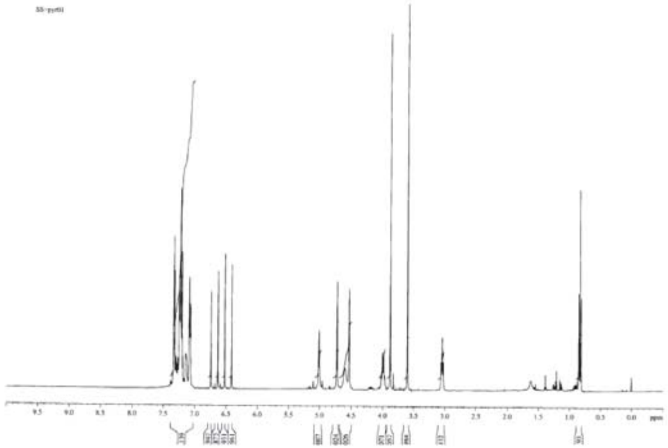


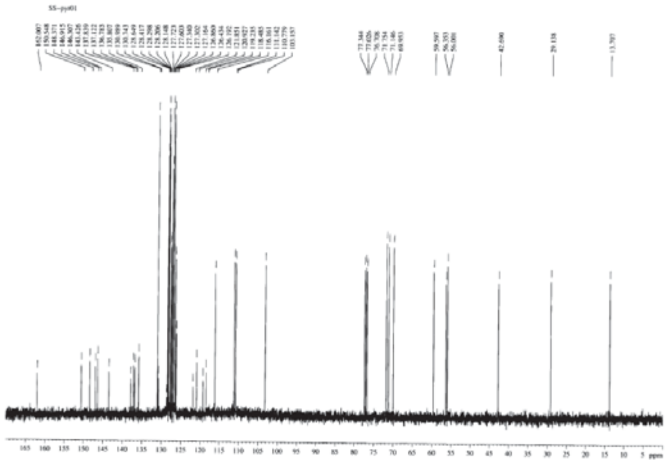


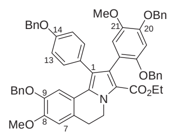


110

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

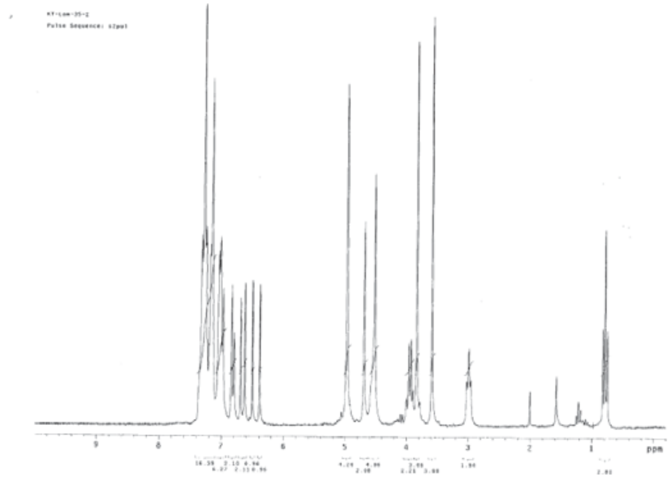


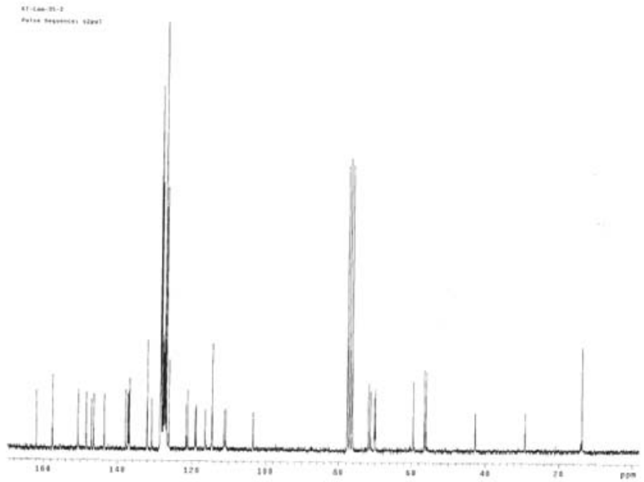


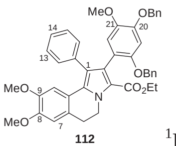


111

^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

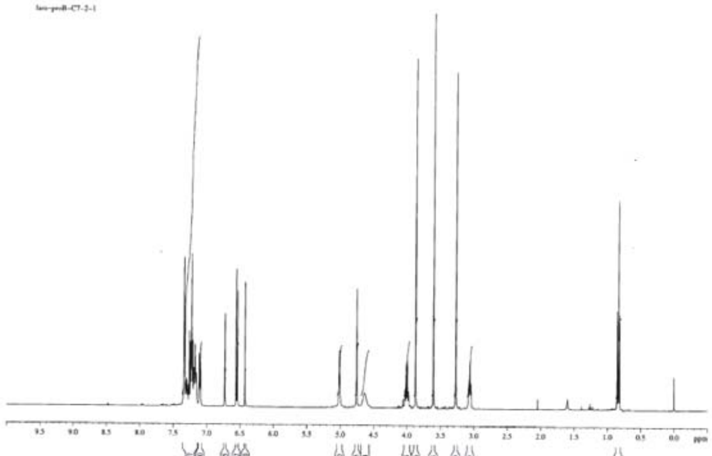


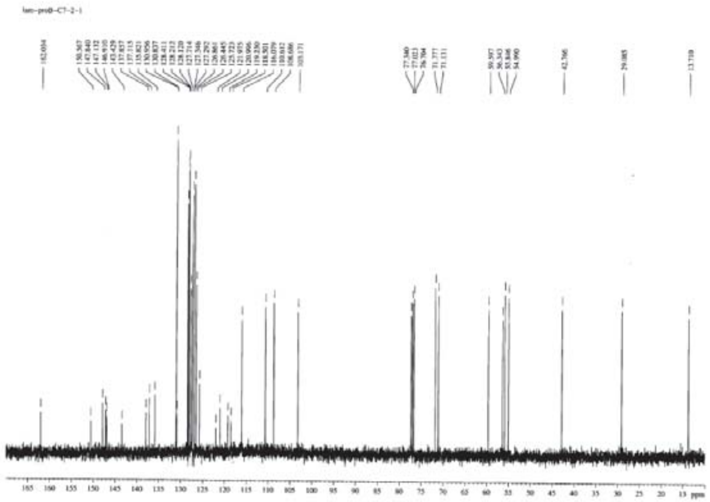


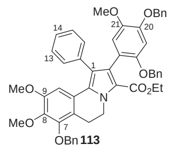


112

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

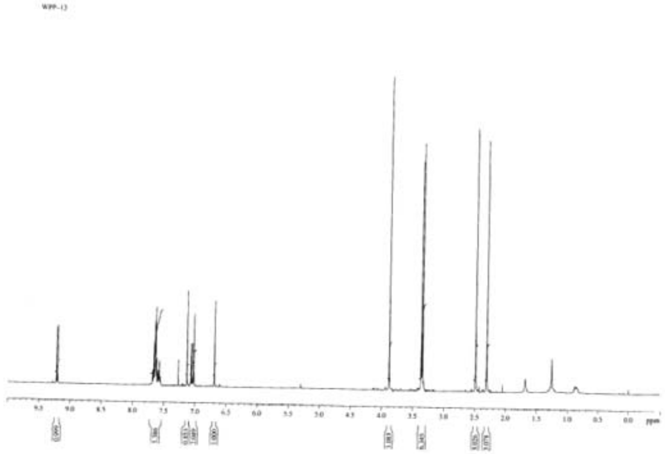


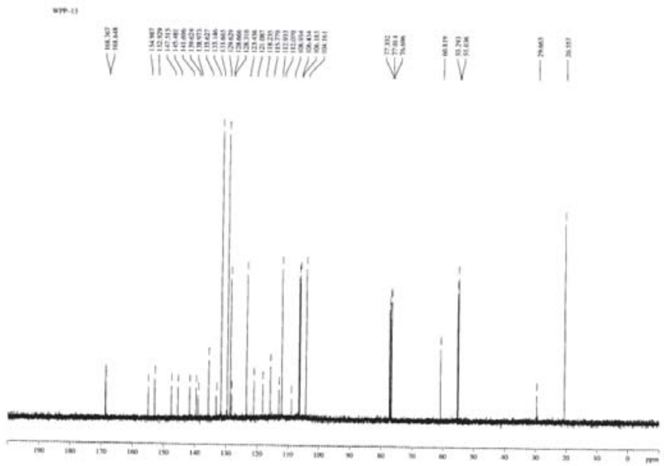


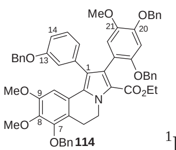


113

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

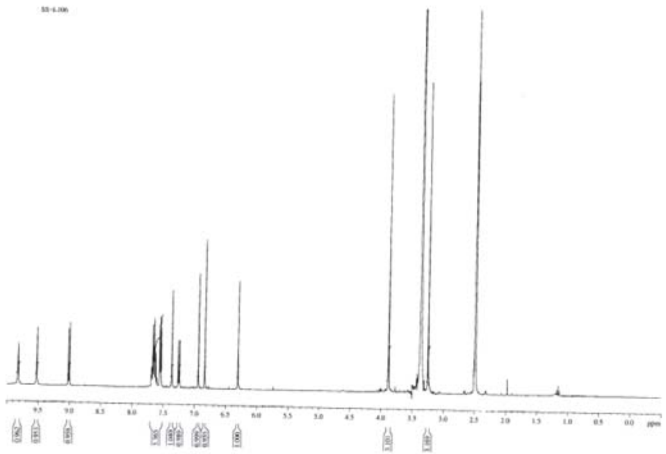


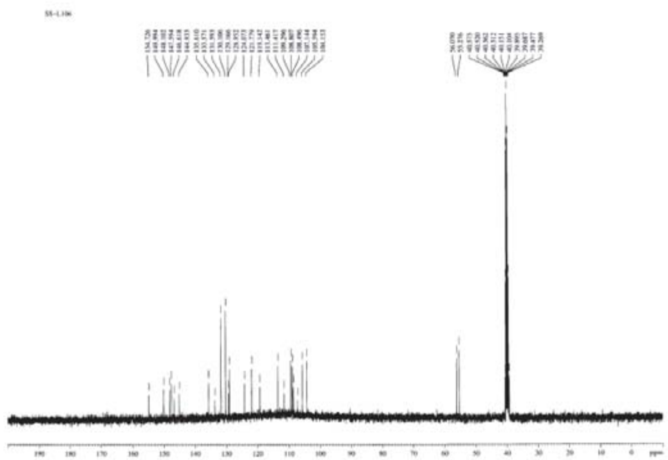


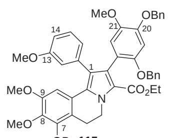


114

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

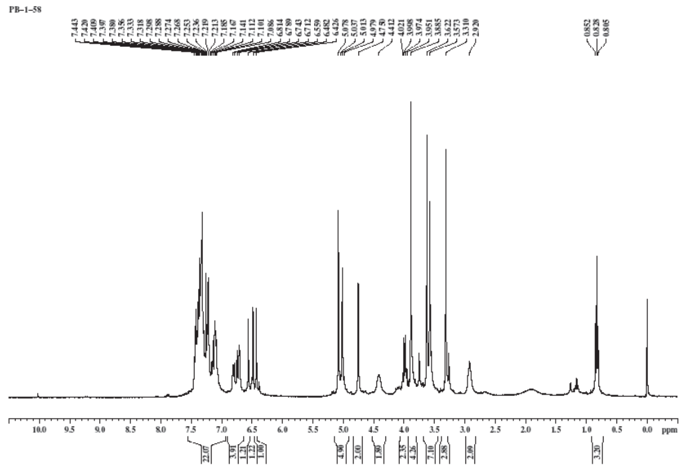


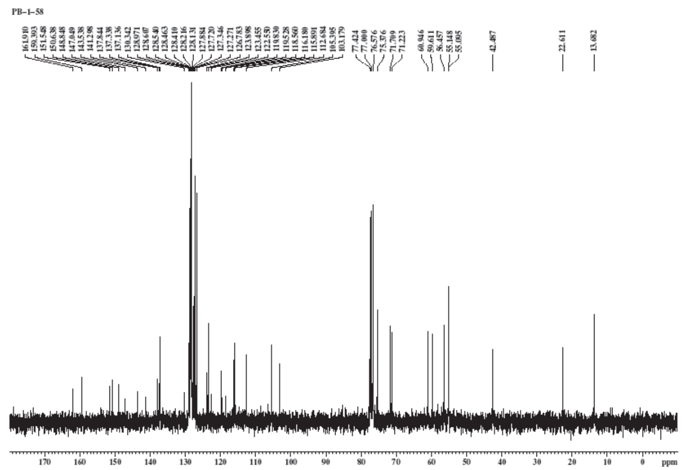


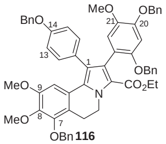


115

^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$)

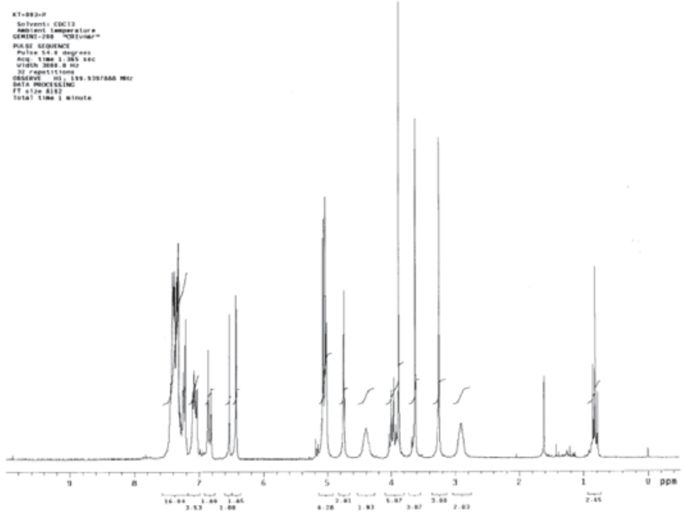


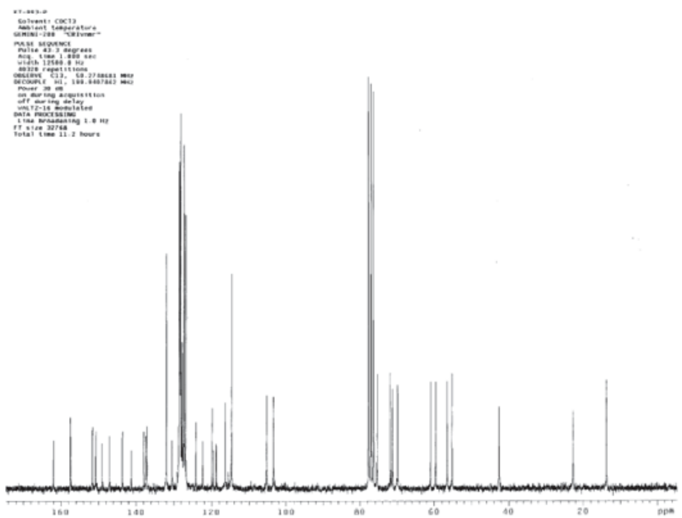


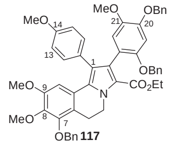


116

[1]H NMR (200 MHz, $CDCl_3$) and [13]C NMR (50 MHz, $CDCl_3$)

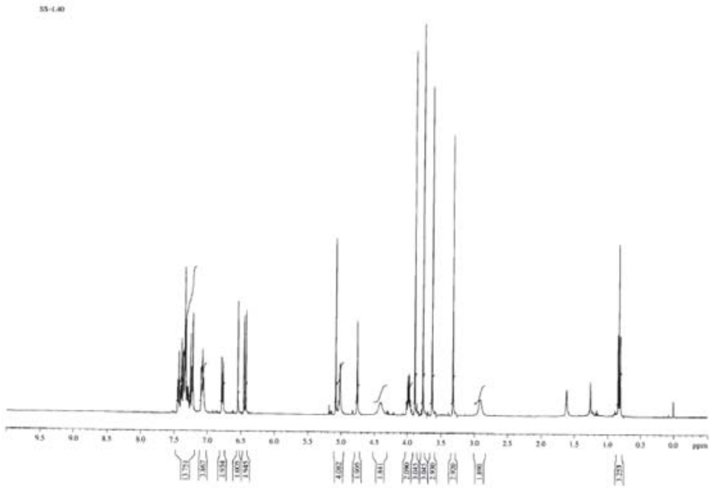


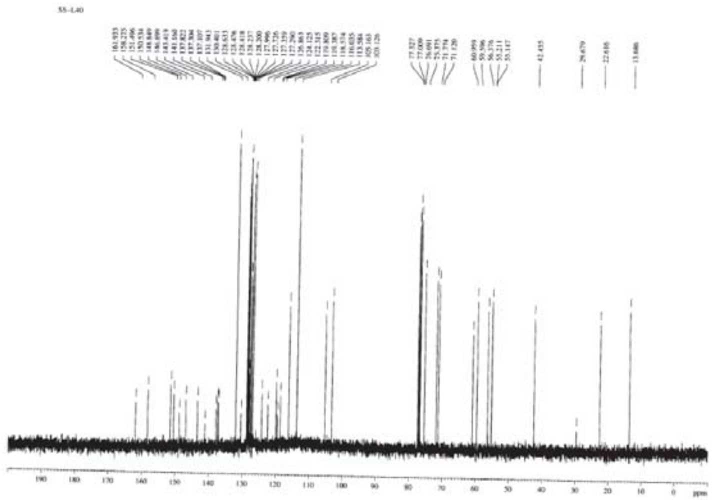


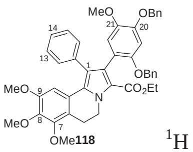


117

[1]H NMR (400 MHz, $CDCl_3$) and [13]C NMR (100 MHz, $CDCl_3$)

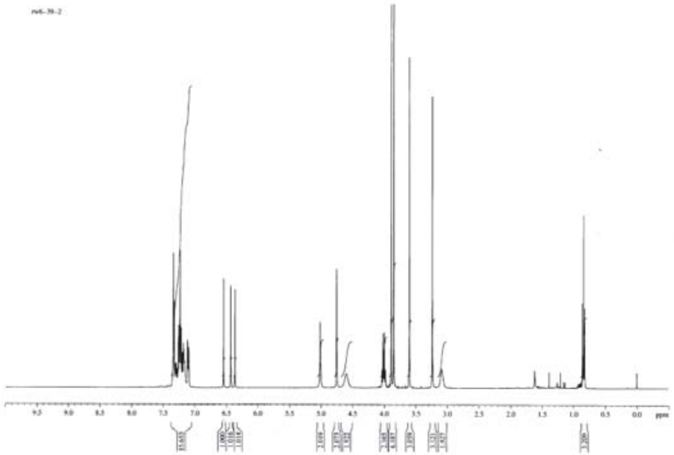


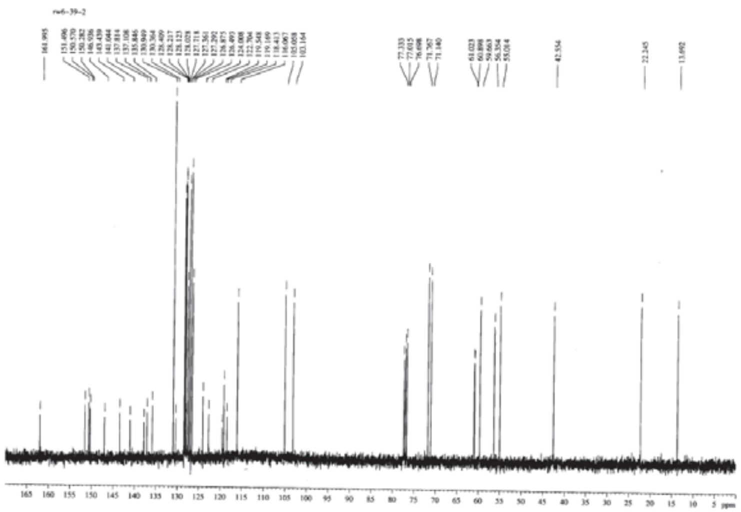


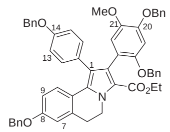


118

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

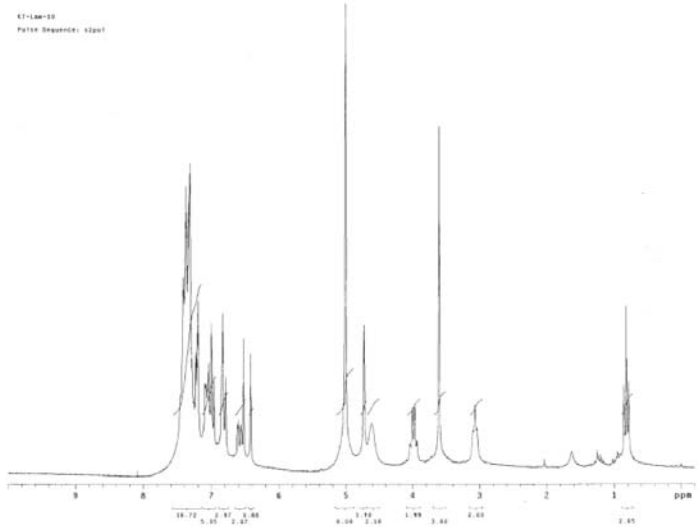


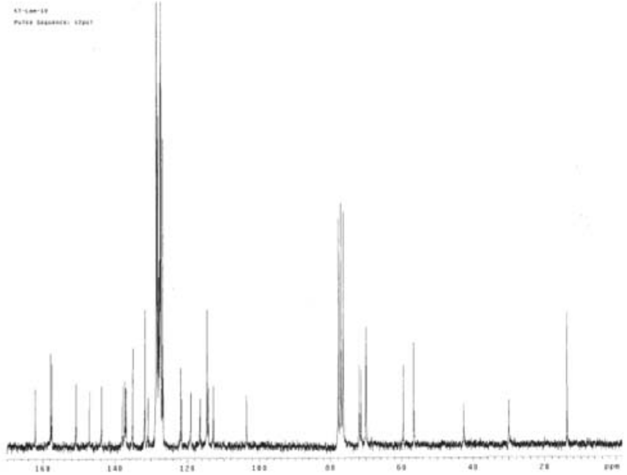


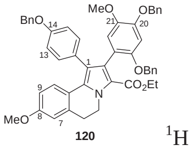


119

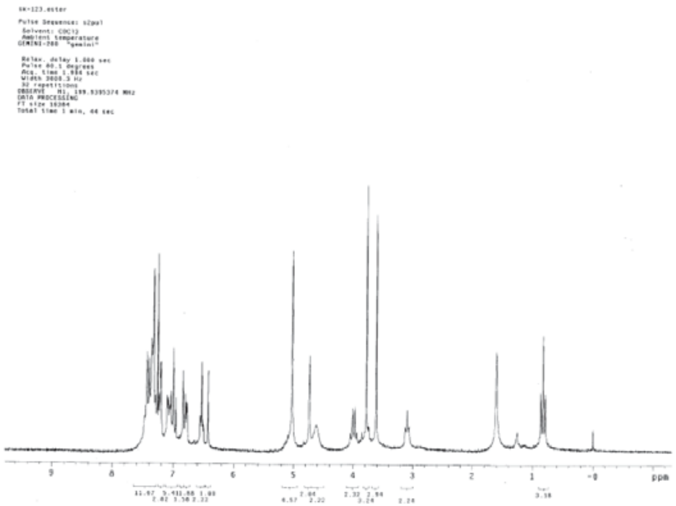
^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

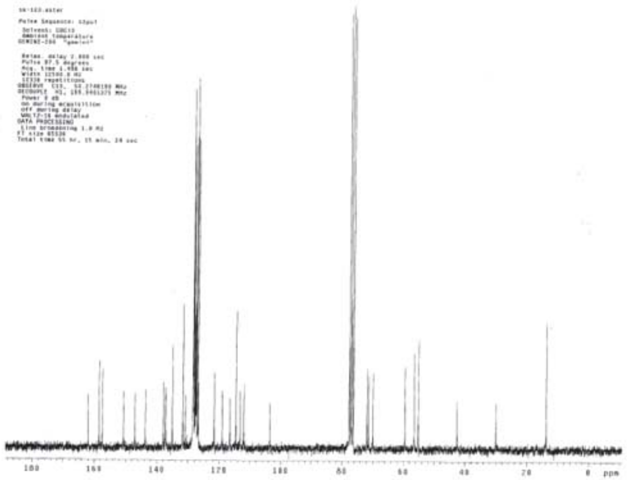


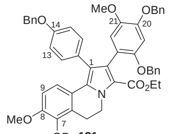




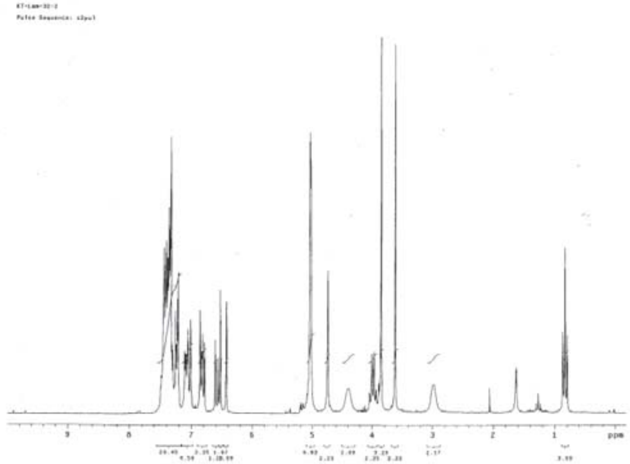
120 ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

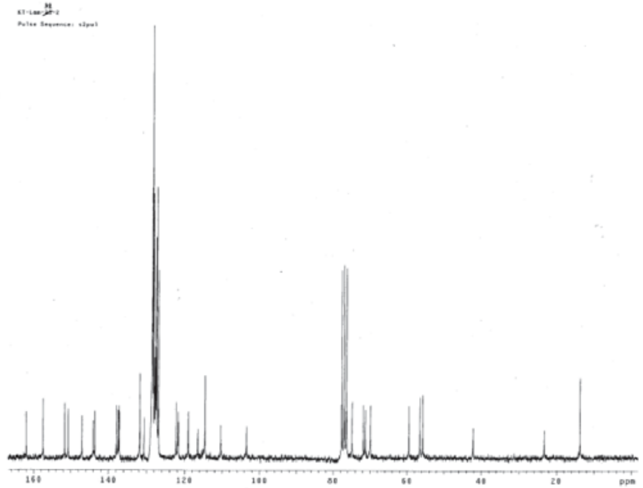


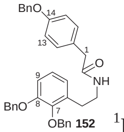




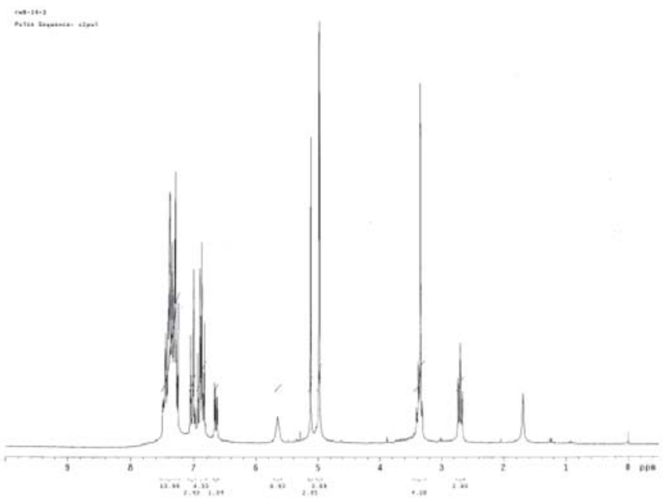
121 ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

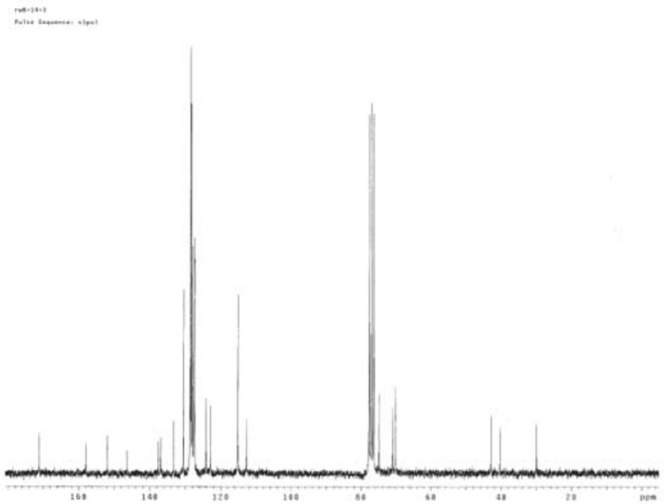


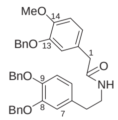




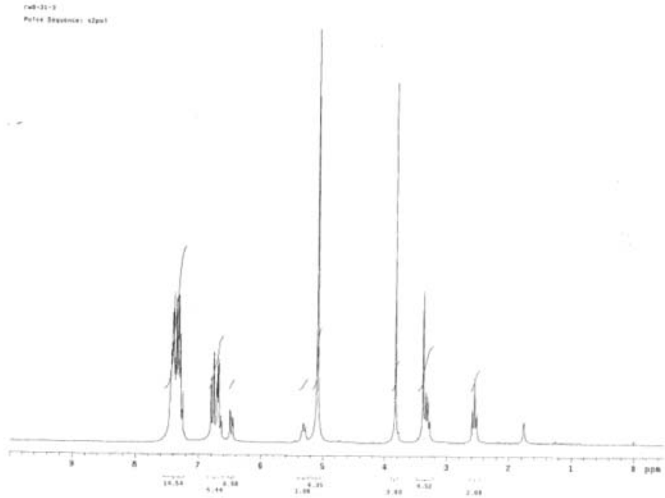
152 ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

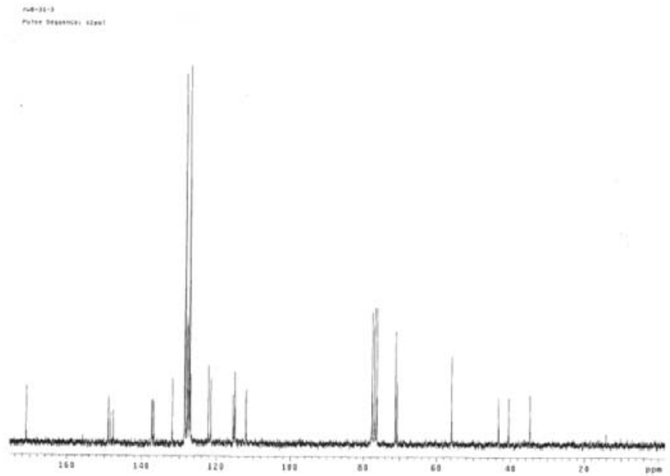


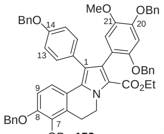




153 ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

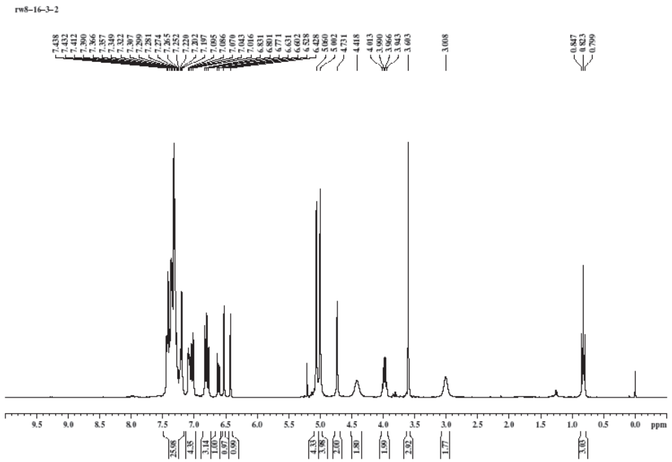


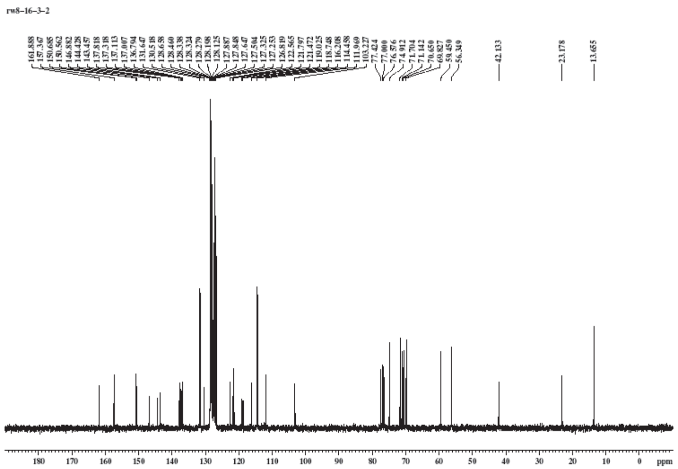


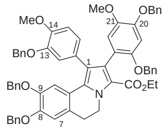


159

^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$)

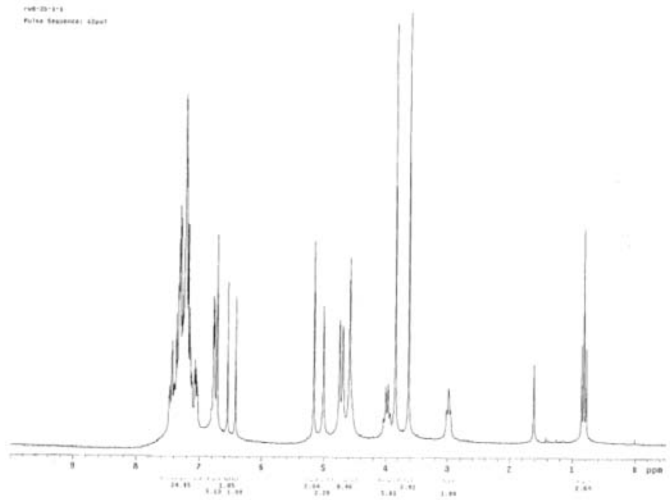


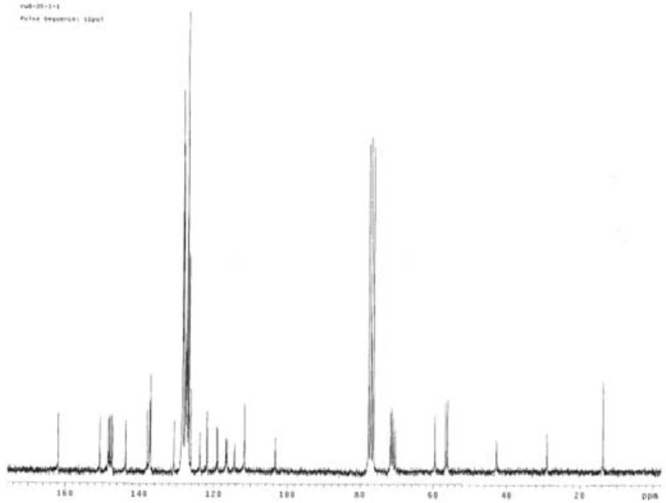


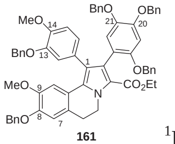


160

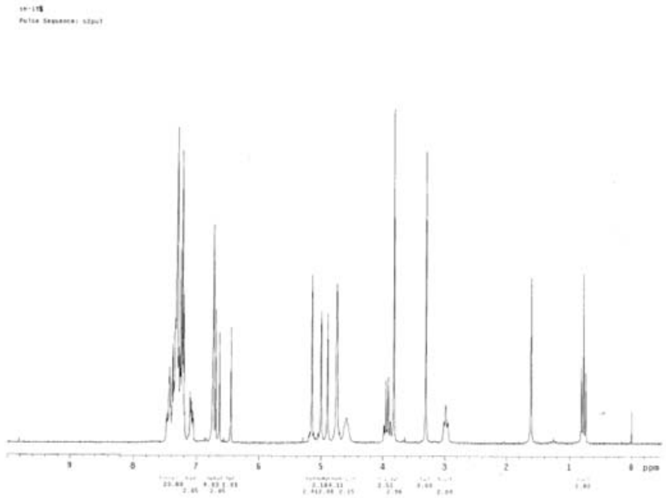
^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

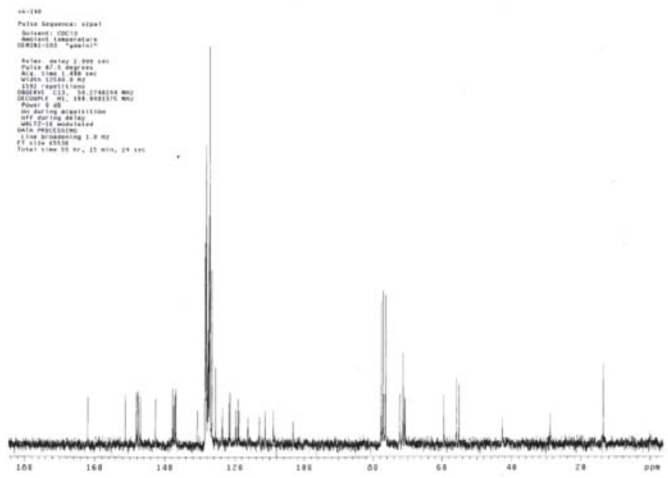


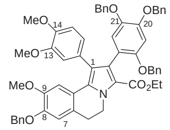




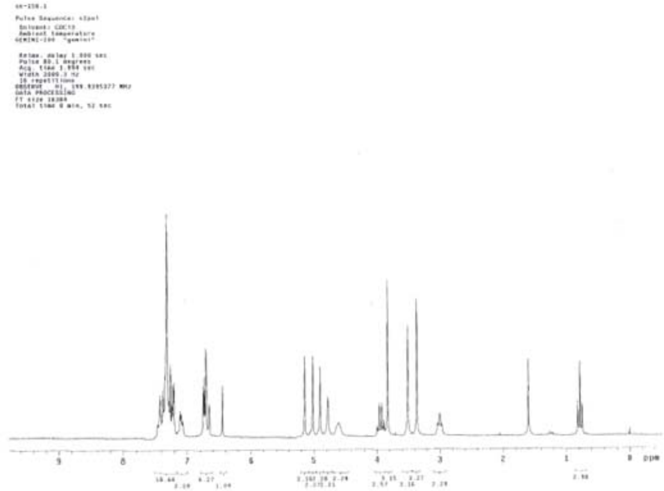
161 ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

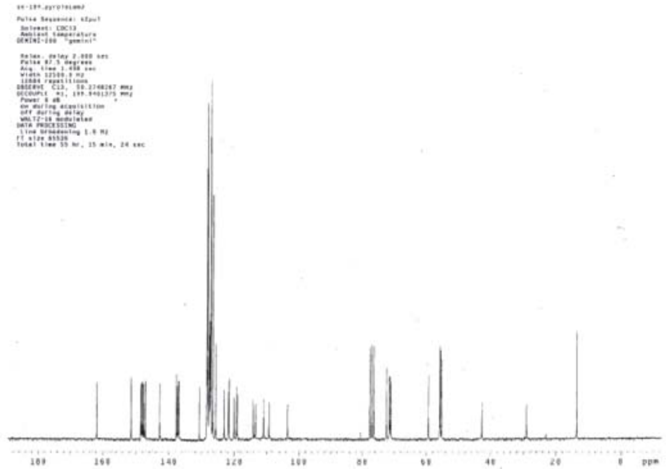


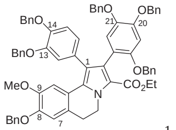




162 ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

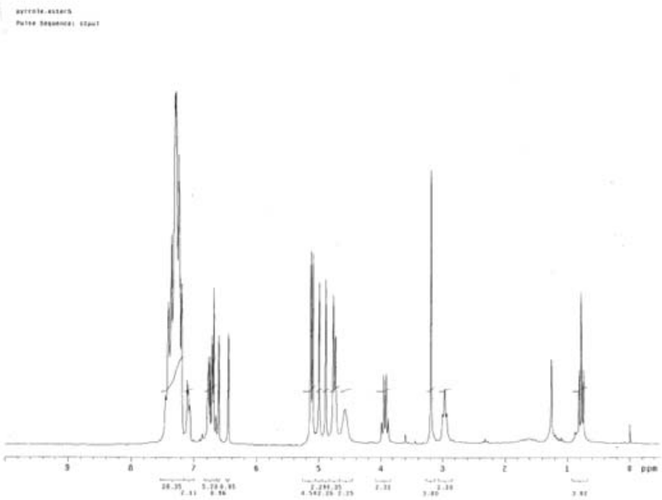


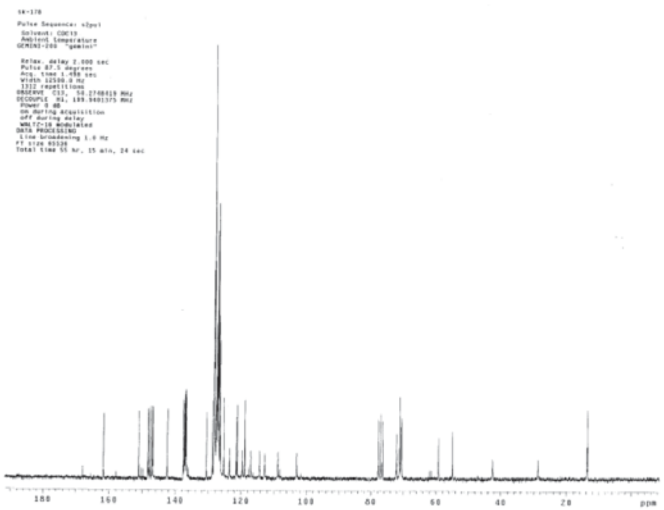


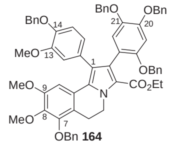


163

^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

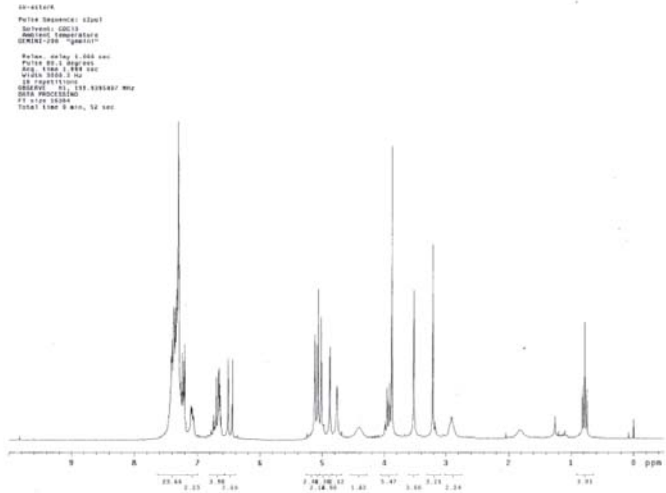


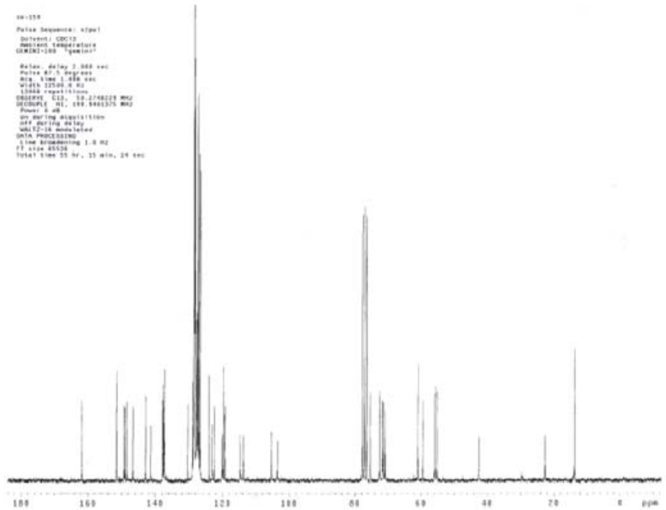


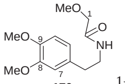


164

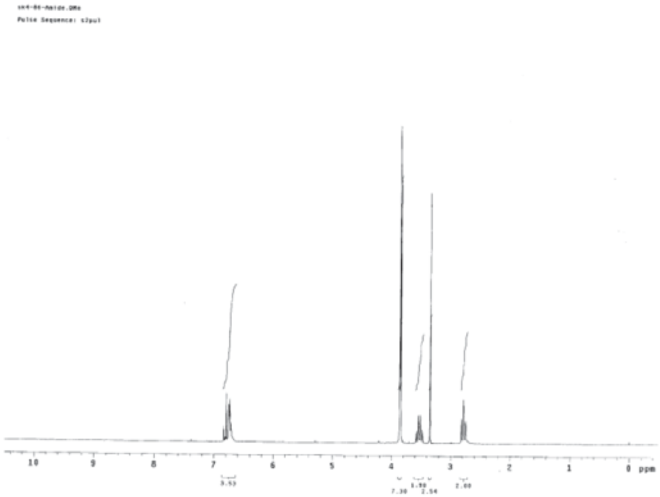
^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

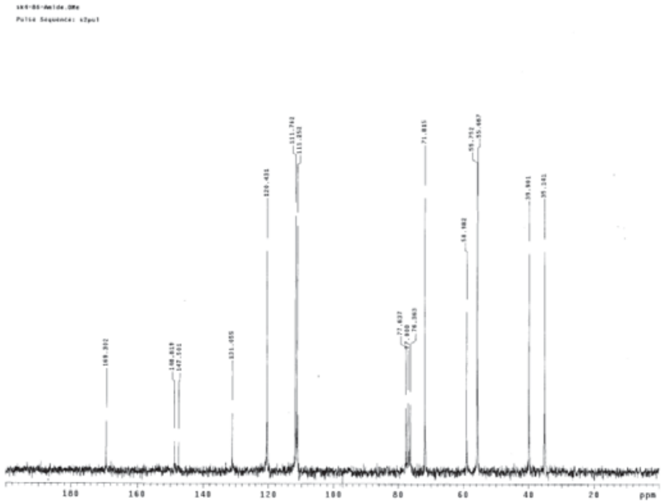


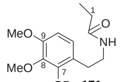




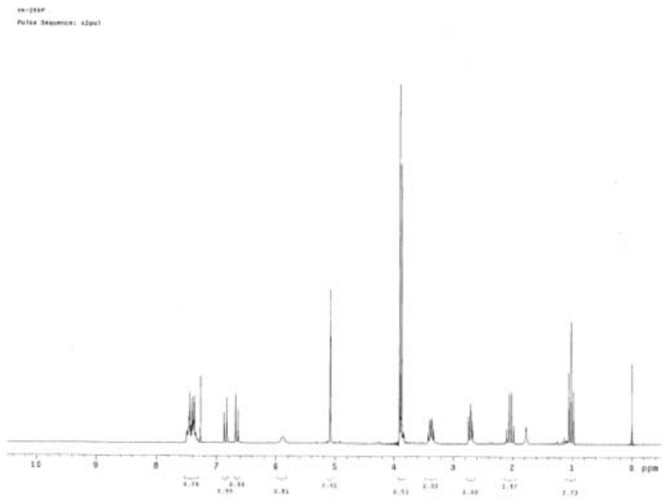
170 ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

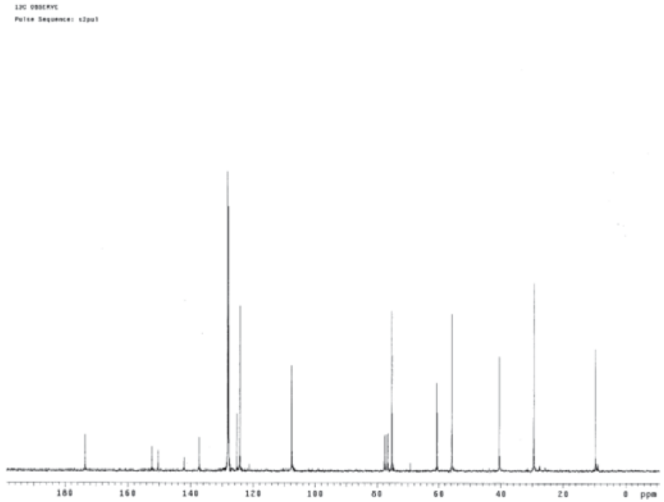


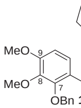




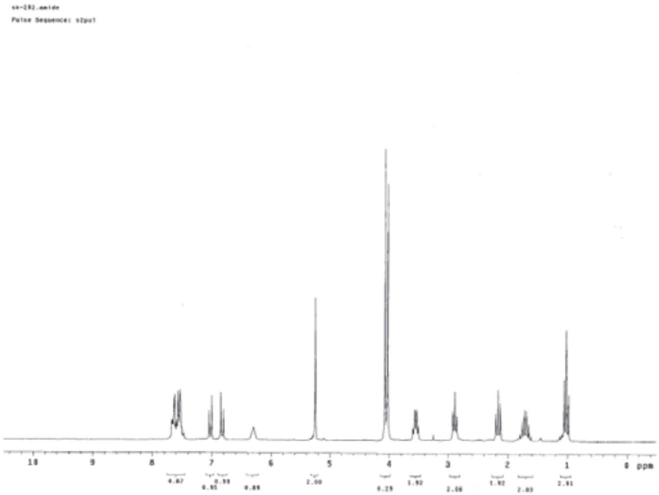
171 ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

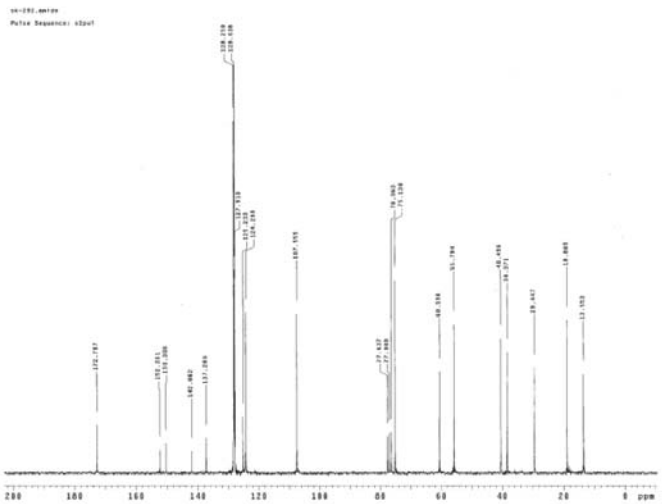


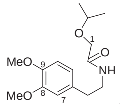




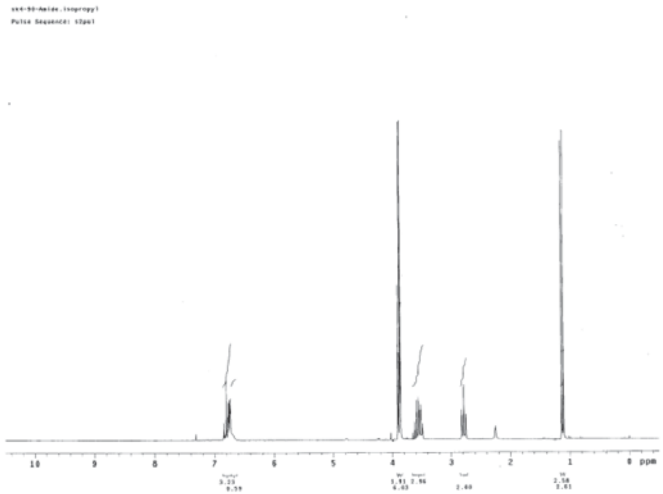
172 ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

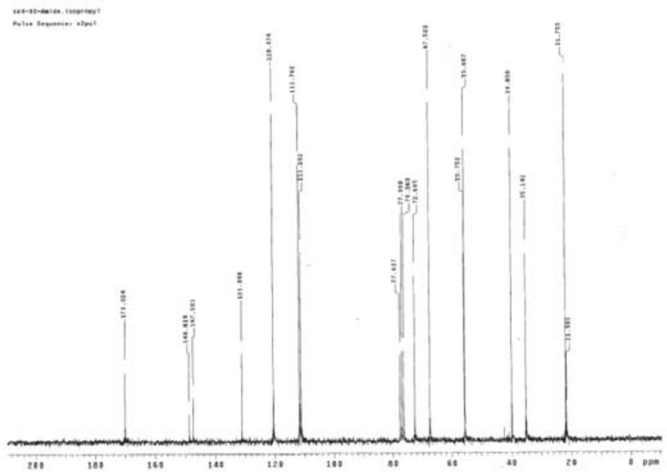


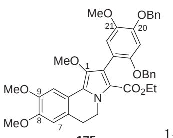




173 ^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

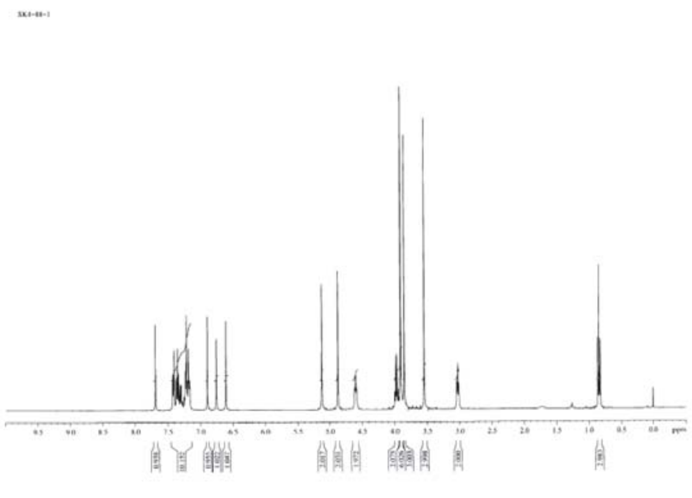


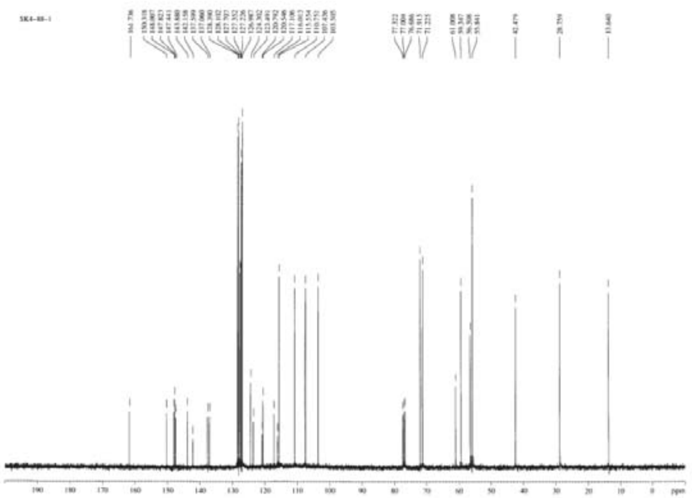


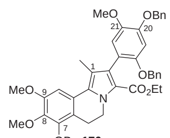


175

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

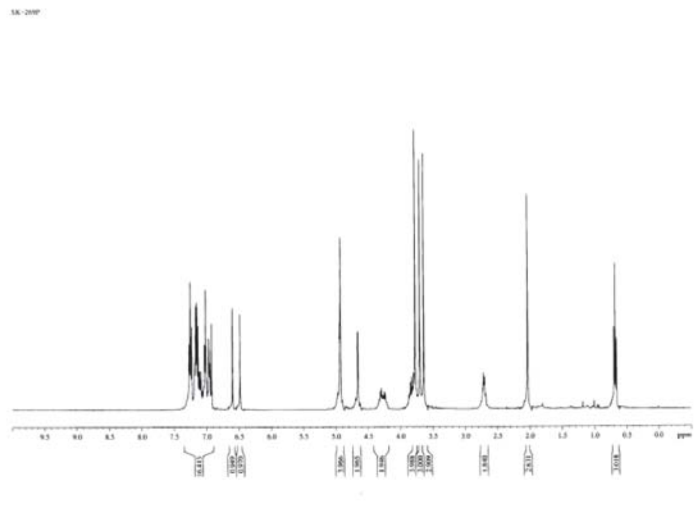


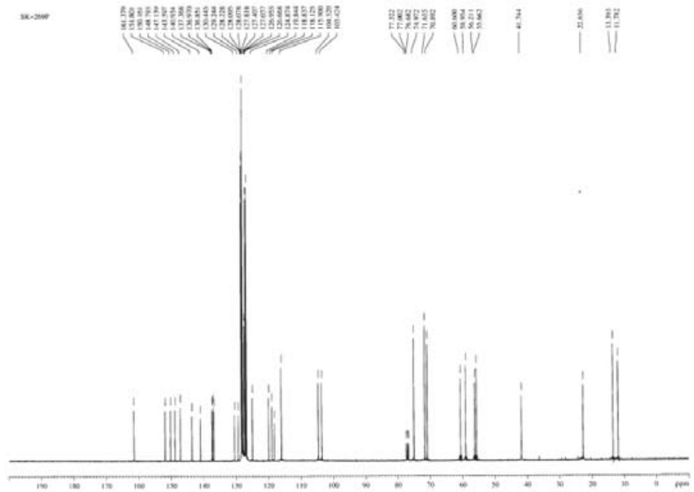


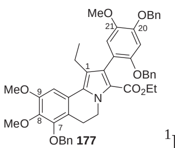


176

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

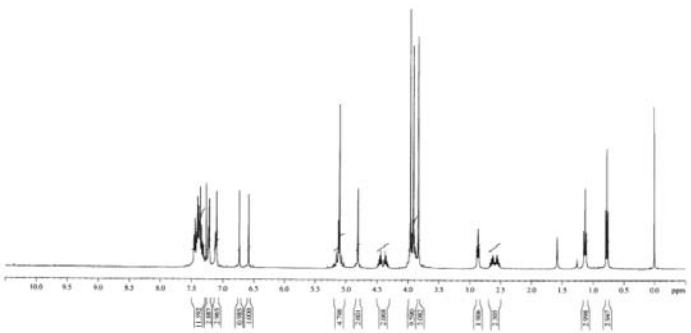


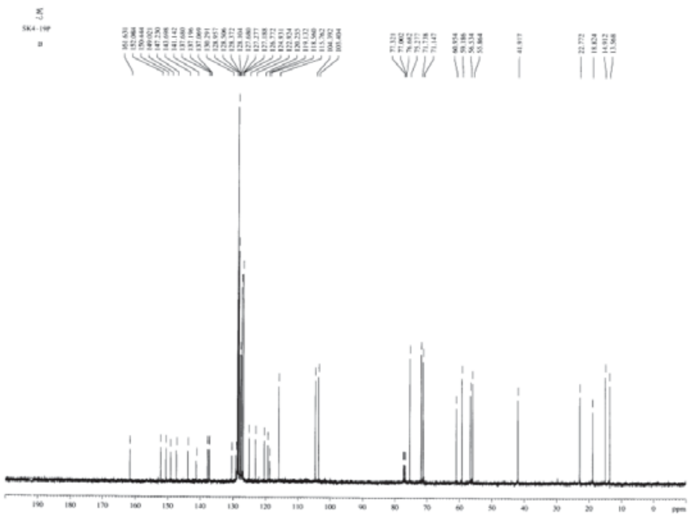


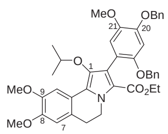


177

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

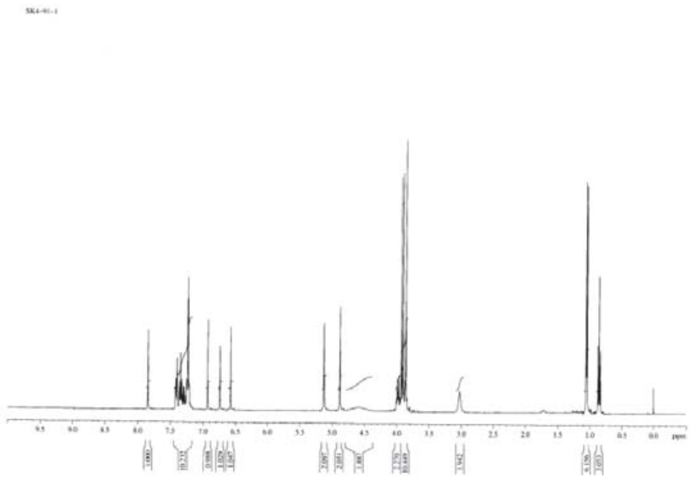


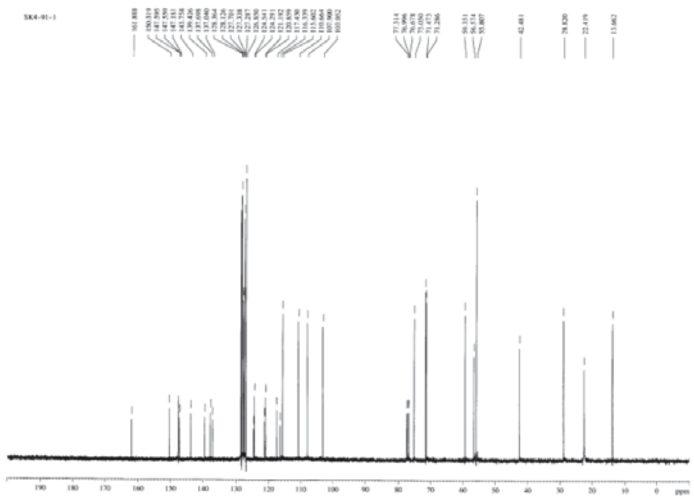


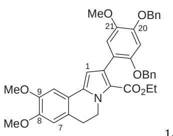


178

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

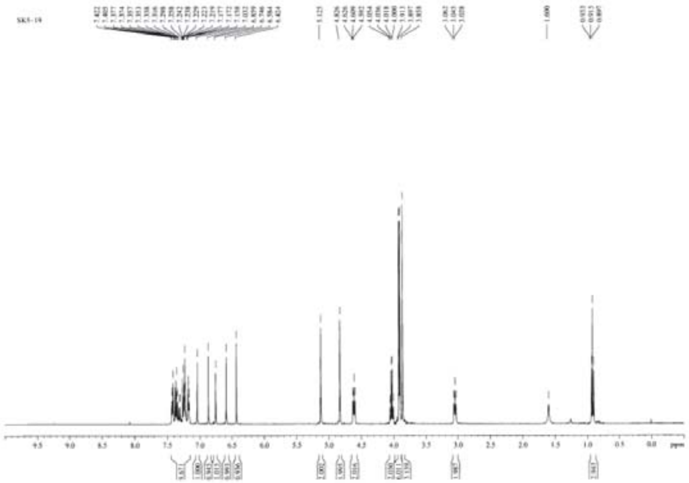


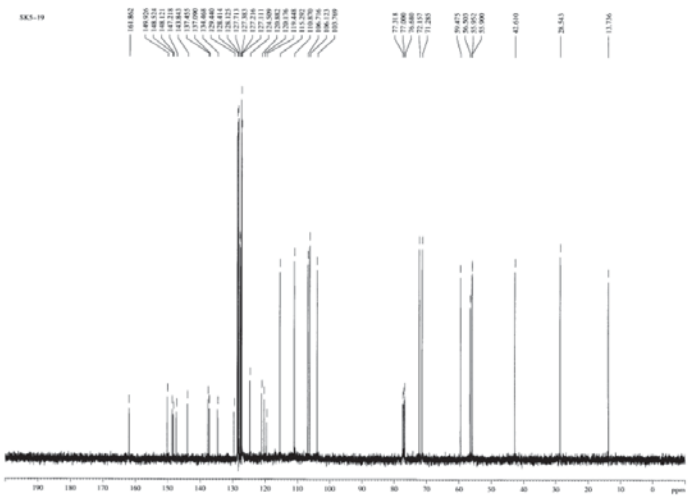


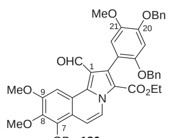


179

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)

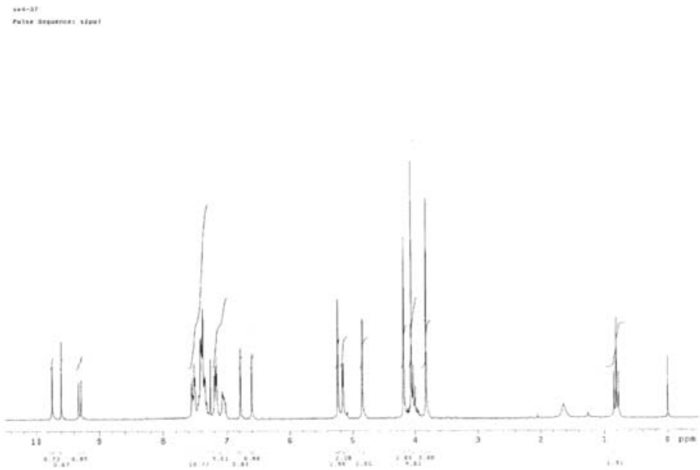


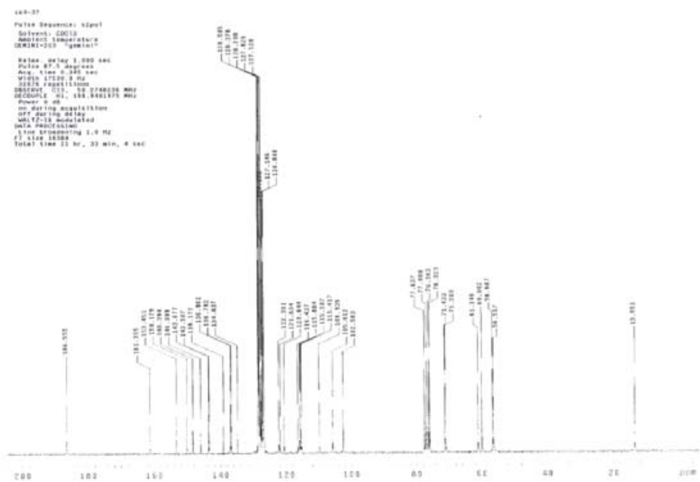


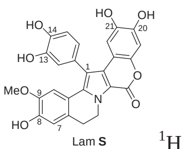


180

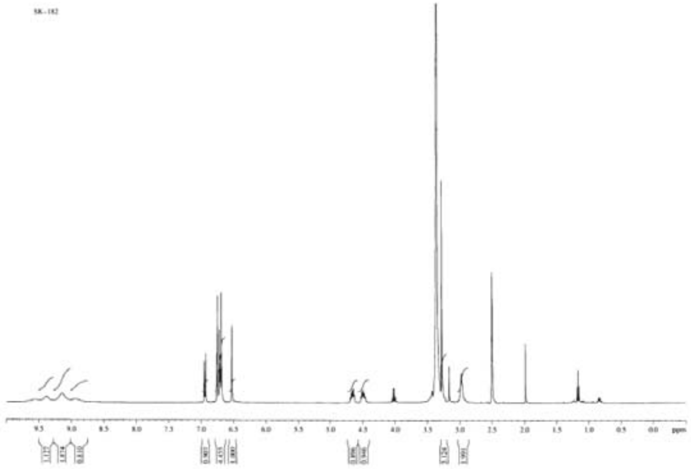
^{1}H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)

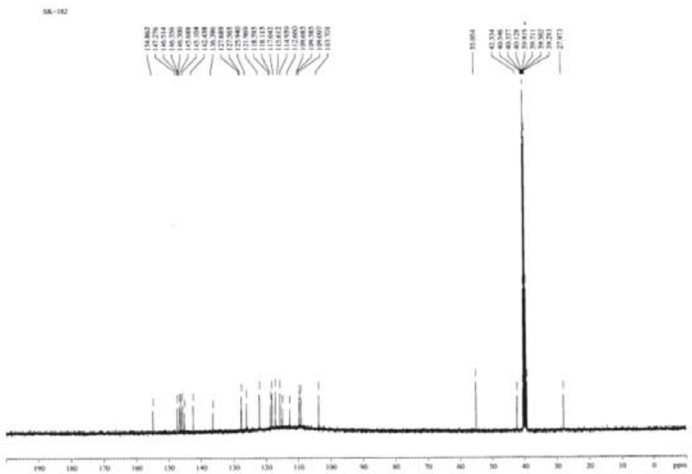


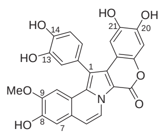




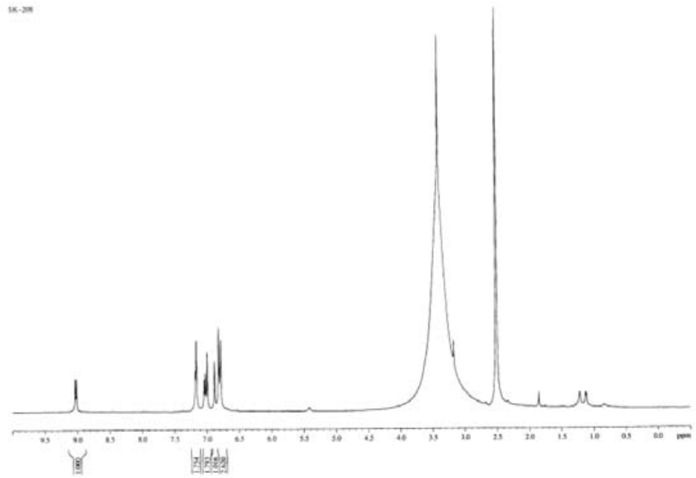
Lam **S** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)

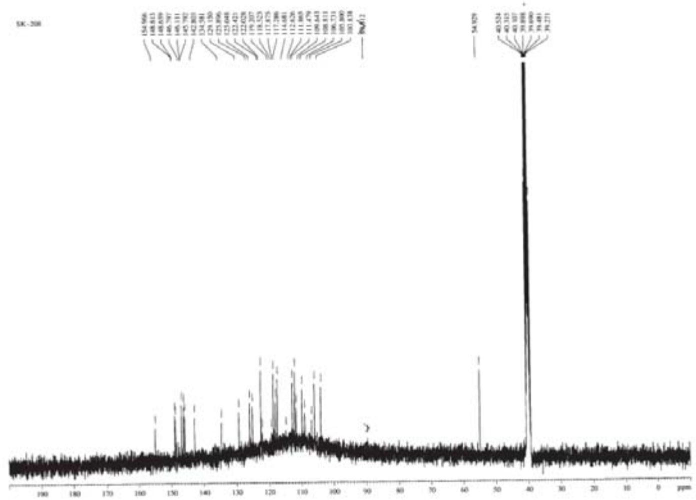






Lam **S-DB** ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6)





Natural Products

Facile and Divergent Synthesis of Lamellarins and Lactam-Containing Derivatives with Improved Drug Likeness and Biological Activities

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Abstract: With the goal to improve the aqueous solubility of lamellarins, the lactone ring in their skeleton was replaced with a lactam moiety in azalamellarins. However, the reported synthetic route produced such derivatives in very low yields. Hence, this study focused on developing an efficient simplified total synthetic scheme that could furnish both azalamellarins and the parent lamellarins from the same pyrrole ester intermediates. Subsequent comparative profiling revealed that the introduced lactone-to-lactam replacement rendered these molecules less lipophilic, whereas their cancer cytotoxicity remained equipotent to that of the parent compounds. Interestingly, their inhibitory activity was significantly enhanced towards the multifaceted GSK-3β enzyme. Our results clearly demonstrate the therapeutic potential of this promising class of marine-derived natural products and justify their further development, especially into anticancer agents.

Introduction

Lamellarins are polyaromatic alkaloids originally isolated from marine invertebrates, including mollusks, ascidians, and sponges.[1] Since 1985, approximately 50 lamellarins and derivatives have been discovered,[2] most of which contain the same pentacyclic skeleton and only differ in the number and position of the oxygen-containing substituents around the core structure, as shown in Figure 1 a. Interestingly, potent cytotoxic effects of these compounds have been demonstrated against a wide variety of tumor cells from different origins.[2,3] In addition, these compounds also exhibit multidrug resistance reversal activity, HIV integrase inhibition, and antioxidant properties.[2,3a]

Among all the members, lamellarin D (**2**) appears to possess the most promising therapeutic potential as an anticancer agent with multiple biological targets. This compound was originally reported to induce potent and dose-dependent stimulation of DNA cleavage by trapping the complex between topoisomerase I (Topo I) and DNA.[4] Lamellarin D at micromolar levels has also been demonstrated to induce caspase-dependent apoptosis through mitochondria-mediated signaling pathways.[5] Additionally, the inhibitory activities of lamellarins and their derivatives towards several protein kinases, including glycogen synthase kinase-3α/β (GSK-3α/β), have been documented.[6] Furthermore, induction of cellular senescence through both the inhibition of Topo I and the generation of reactive oxygen species has been proposed as another mechanism for the cytotoxicity of lamellarin D.[7]

Recently, the structural isomer of lamellarin D, namely, lamellarin N (**3**), has also attracted attention owing to its interesting cytotoxicity against certain cancer cell lines.[3b,6] More importantly, superior potency against GSK-3α/β was reported for lamellarin N with a half-maximal inhibitory concentration (IC_{50}) of 5 nM, compared with 300 nM for lamellarin D.[6] Overall, we selected lamellarin D and lamellarin N as lead compounds for further development into anticancer agents. Although not the most lipophilic compounds in the series, these two lamellarins still suffer from poor aqueous solubility and, thus, usually precipitate in biological media. Therefore, we aimed to develop lamellarin derivatives that possess improved aqueous solubility while maintaining their biological activities.

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Supporting Information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201500611.

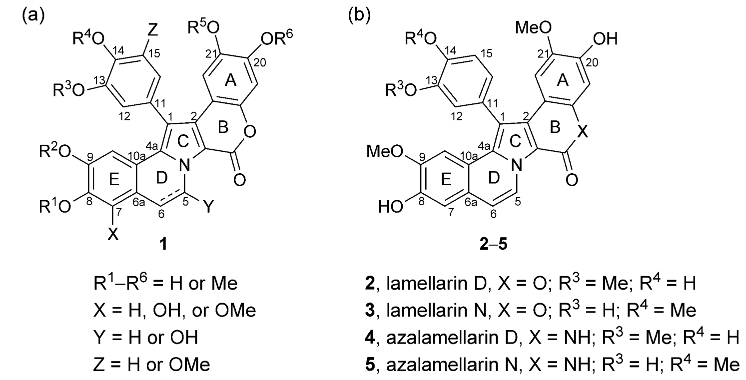


Figure 1. a) General structure of lamellarins and b) structures of the compounds used in this study.

As a means to simultaneously enhance the stability and solubility of lamellarins, a simple lactone-to-lactam replacement was performed by Thasana and co-workers to generate some aza derivatives of these compounds.[8] The synthesis of azalamellarins was accomplished in eight steps (starting from pyrrole esters). Owing to some low-yielding steps and the long sequence of their approach, the overall yield of azalamellarin D (**4**) was only 11 %. For the other azalamellarins, only the final products with either an *N*-allyl or *N*-propyl group were reported.

Herein, we report a new synthetic route that involves pyrrole esters as common intermediates for the preparation of both lamellarins and azalamellarins. The effects of structure modification on lipophilicity, aqueous solubility, cytotoxicity, as well as GSK-3β inhibitory activity were evaluated. Molecular modeling was also used to probe the interactions of lamellarins and azalamellarins with the GSK-3β target.

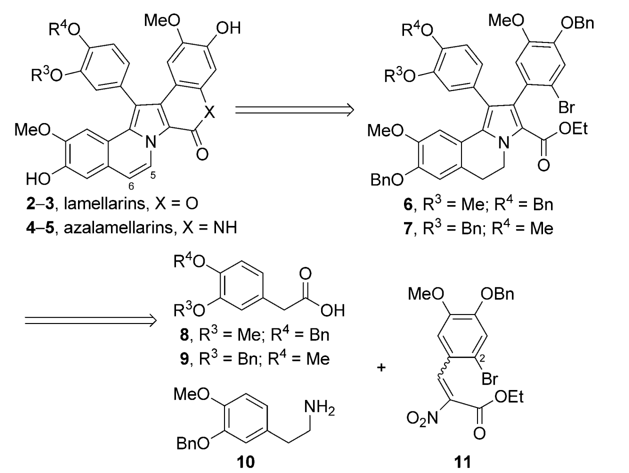
Results and Discussion

Chemistry

The synthetic approaches for lamellarins and azalamellarins previously reported by our laboratory[9] and Thasana's group,[8] respectively, share a common feature of pyrrole formation through efficient Michael addition/ring closure (Mi-RC) Grob-type condensation between benzyldihydroisoquinoline and α-nitrocinnamate derivatives. Nevertheless, the two routes are synthetically distinguishable from the very beginning by the different α-nitrocinnamate derivatives required for subsequent reactions. Whereas the 2-hydroxy group is involved in NaH-mediated lactonization to furnish lamellarins, the presence of a bromine atom at this particular position (see compound **11** in Scheme 1) is necessary for intramolecular C–N bond formation to generate the lactam moiety in azalamellarins.

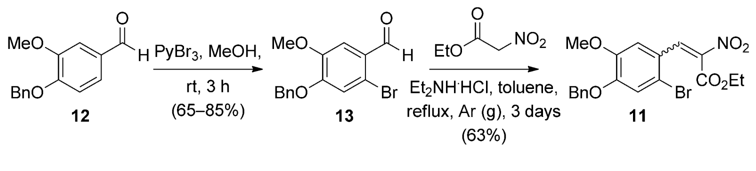
To develop an efficient and divergent method, the retrosynthetic analysis suggested the possibility of using three different benzaldehyde derivatives as simple building blocks to generate the pyrrole esters (i.e., **6** or **7**) as key common intermediates for both lamellarins and azalamellarins, as shown in Scheme 1. The synthetic route could then branch out with a few more steps to give the desired products. Starting from the pyrrole esters, sequential reactions comprising lactonization, C5–C6 oxidation, and global deprotection could furnish lamellarins, whereas azalamellarin synthesis would require an additional step to install a nitrogen atom prior to lactam ring closure, followed by oxidation and global deprotection.

Following our established methodology,[9] benzyldihydroisoquinoline derivatives were successfully synthesized from arylacetic acids **8** and **9** and aryl ethylamine **10**, both of which were generated by using appropriately substituted benzaldehyde derivatives as the building blocks (see the Experimental Section for details). For 2-bromo-α-nitrocinnamate (**11**), on the other hand, the conditions previously used to prepare 2-bromo-*O*-benzylvanillin (**13**) gave relatively low yield (25–45 %) and, thus, were optimized in this study.



Scheme 1. Retrosynthesis for lamellarins and azalamellarins. For compounds **2** and **4**, R^3 = Me; R^4 = H. For compounds **3** and **5**, R^3 = H; R^4 = Me.

After some experimentation, it was found that bromination of **12** by using either soluble or polymer-bound pyridinium tribromide ($PyBr_3$) in MeOH gave the desired product in 65–85 % yield (Scheme 2). In contrast, the use of Br_2 or *N*-bromosuccinimide (NBS) under other conditions gave lower yield. Subsequently, **13** could be converted into **11** in 63 % yield (based on recovered starting aldehyde **13**).



Scheme 2. Synthesis of α-nitrocinnamate **11**.

Synthetic development of azalamellarins

Upon obtaining sufficient amounts of the required starting materials (see the Experimental Section for details), pyrrole ester **6** was synthesized by using our reported method.[9] Then, the subsequent steps en route to azalamellarin D were carefully investigated, starting with tandem lactamization both to incorporate a nitrogen atom into the pyrrole ester and then to form a lactam moiety in situ. After several attempts, however, it appeared that the two-step reaction of pyrrole amide formation and lactam ring closure would be required for the azalamella rin synthesis.

As summarized in Scheme 3, we then optimized the amidation step by using different nitrogen sources, with or without microwave (MW) irradiation to assist the conversion of pyrrole ester **6** into the corresponding pyrrole amide. Desired product **17** or **18** was successfully obtained with either a benzyl or *p*-methoxybenzyl (PMB) protecting group, respectively. Afterwards, copper(I)-mediated lactam ring closure was performed under the optimized conditions, followed by the oxidation by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to yield N,O-protected azalamellarin D with an unsaturated D ring. In the final step, acidolytic reaction was anticipated to simultaneously remove all O- and N-protecting groups in the presence of thioanisole as a benzyl cation scavenger to produce azalamellarin D. By avoiding repetitive protection and deprotection steps, as required for **20**,[8] our current synthetic scheme is expectedly shorter than that previously reported.

Details of our investigations focusing on the lactamization and global deprotection steps are described below. Subsequently, the optimized conditions were used to synthesize the azalamellarin N (**5**) structural isomer (Figure 1 b). As proof of concept, our newly developed route was also applied to synthesize both lamellarin D and lamellarin N more efficiently.

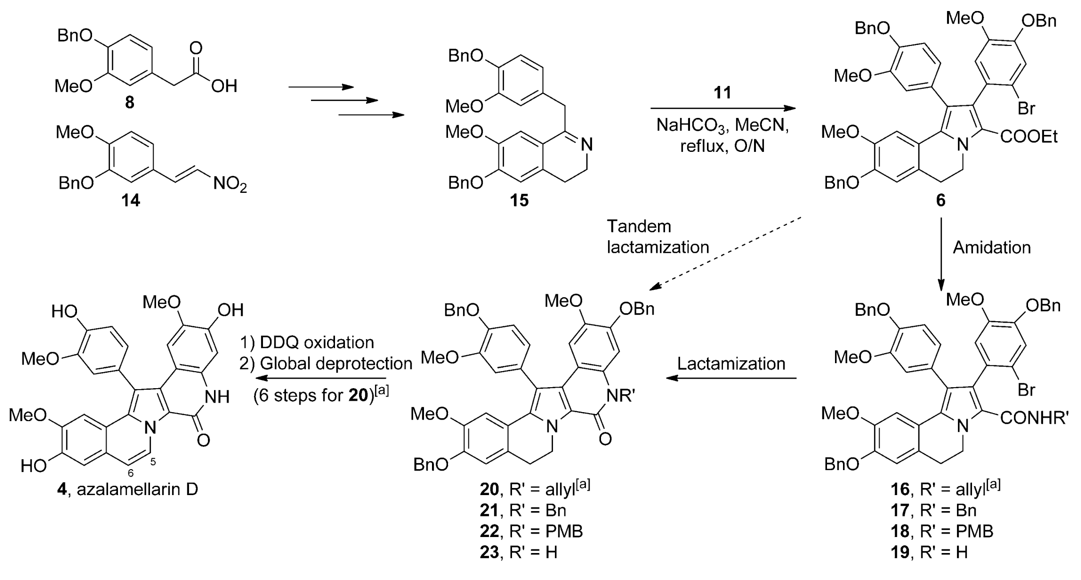
Tandem lactamization

Pd^{II}- and Cu^{I}-mediated intramolecular C–N bond formation to effect lactam ring closure in some biaryl systems is well established.[10] Therefore, a number of literature-based conditions were applied in this study to incorporate a lactam moiety into the lamellarin core structure, preferably in one step by tandem lactamization. In the presence of various nitrogen nucleophiles under different sets of reaction conditions (Scheme 4), only the starting material was recovered in most cases. Surprisingly, if sodium amide was used, pyrrole carboxylic acid **24** (Figure 2) was obtained.

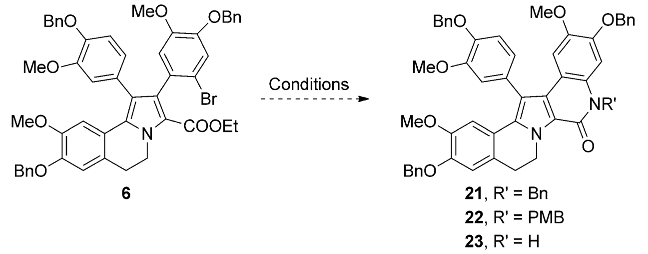
Direct amidation

Given that our attempts at tandem lactamization were unsuccessful, a two-step approach was employed by first converting pyrrole ester **6** into corresponding pyrrole amide **19** without an N-protecting group, if possible, to avoid the complications generally experienced during its removal. Thus, model studies were initially undertaken for direct amidation of methyl benzoate (see the Supporting Information for details). As shown in Scheme 5, the unique combination of either sodium amide or trimethylsilyl (TMS) azide as the nitrogen nucleophile and trimethylaluminum as the Lewis acid[11] unexpectedly gave product **26** in good yield (80–89 %). In contrast, the reactions performed with the use of other nitrogen sources (NaN_3, NH_4Cl, or $NH_2OH{\cdot}HCl$) under different conditions (tetrahydrofuran (THF), 1,4-dioxane, or toluene as solvent at 60–200 °C with 100–300 W of MW power for 30–45 min) either did not proceed or gave lower yields of the corresponding products.

These amidation conditions were next applied to our compounds. Pyrrole ester **6** was thus treated with TMS azide, sodium amide, or saturated ammonia under varying MW-assisted conditions. Unfortunately, all conditions failed to give desired product **19**, and either the starting material or a mixture



Scheme 3. Synthetic route of azalamellarin D. [a] See Thasana et al.[8] for details.



Scheme 4. Attempted tandem lactamization with or without N-protecting groups. Conditions: $AcNH_2$, $BocNH_2$, $BnNH_2$, $CbzNH_2$, $PMBNH_2$, or $NaNH_2$ as nitrogen source; $PdCl_2$, $Pd(OAc)_2$, or CuI as catalyst; Cs_2CO_3 or K_3PO_4 as base; Xantphos or 1,10-phenanthroline as ligand; 1,4-dioxane or toluene as solvent; performed at 90–100 °C for 8–24 h.

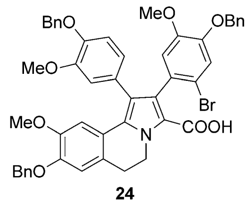
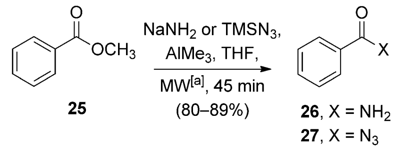


Figure 2. Unexpected product **24** from attempted tandem lactamization and pyrrole amide formation in the presence of sodium amide.

of unidentifiable products was obtained. Using conventional heating and/or a prolonged reaction time gave similar results. Interestingly, the use of sodium amide in refluxing 1,4-dioxane provided pyrrole carboxylic acid **24** in excellent yield of 99% through an unknown mechanism (see below). Notably, the same pyrrole carboxylic acid was also obtained from the attempted tandem lactamization of **6**.

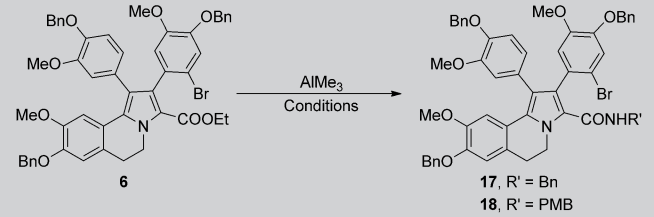


Scheme 5. Model studies for direct amidation by using MW irradiation. [a] 150 W, 150 °C, 200 psi for $NaNH_2$; 300 W, 200 °C, 200 psi for $TMSN_3$. Compound **27** was further reduced by using $NaBH_4$ to give **26** in 80% yield over two steps.

Amidation using N-protected nitrogen sources

In a report by the Thasana's group,[8] a number of N-protected amines were successfully used for the amidation of pyrrole esters. However, only the *N*-allyl group could be effectively removed to generate the final azalamellarin D product by a two-step process involving the use of $ClRh(PPh_3)_3$ as the catalyst, followed by OsO_4 with $NaIO_4$ as reagents. Therefore, we tried to develop a new approach focusing on the use of benzyl-type protecting groups for all the hydroxy moieties and the lactam nitrogen atom so that they could be later removed simultaneously in the final deprotection step. In addition to different nitrogen sources, the reaction conditions were also optimized in terms of solvent, temperature, and reaction time. The desired pyrrole amide was obtained only if either benzylamine or PMB amine was employed (Table 1). The use of *N-tert*-butoxycarbonyl (Boc) amine or benzyl carbamate ($CbzNH_2$) under similar

Table 1. Pyrrole amide formation with N-protecting groups and MW irradiation.[a]



Entry	Nitrogen source	Solvent	MW[b] [W]	*T* [°C]	*t* [h]	Product, yield [%]
1	$BnNH_2$	THF	300	200	0.75	**17**, 86–96
2	$PMBNH_2$	THF	300	200	0.75	**6**, 84
3	$PMBNH_2$	anh. 1,4-dioxane	150	100	1.7	**18**, 65
4	$PMBNH_2$	anh. 1,4-dioxane	150	100	2.5	**18**, 80
5	$PMBNH_2$	anh. 1,4-dioxane	200	150	1	**18**, 99

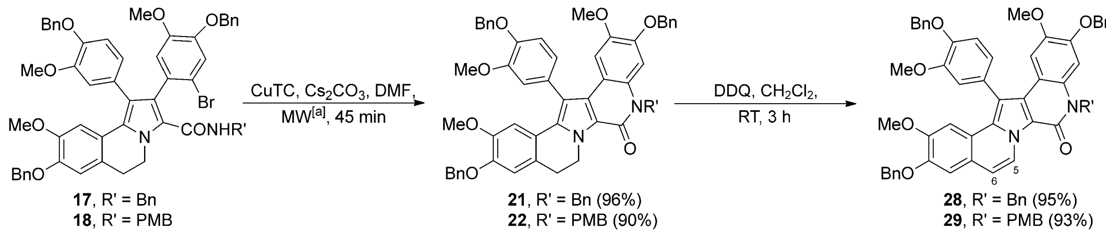
[a] anh. = anhydrous, Bn = benzyl, MW = microwave, PMB = *p*-methoxybenzyl, THF = tetrahydrofuran. [b] 200 psi.

conditions gave only recovered starting material **6** in 70–90% yield.

For benzylamine, the best yield (up to 96%) of **17** was obtained if THF was used as the solvent (Table 1, entry 1). However, under similar conditions but with the use of PMB amine instead, the reaction did not proceed to give **18** (Table 1, entry 2). After some optimization, the best conditions were found to furnish **18** in 99% yield (Table 1, entry 5). It is noteworthy that under MW-assisted conditions, the temperature for the reactions performed with the use of PMB amine must be kept under 200 °C to avoid undesired side reactions, whereas starting material **6** remained virtually unreacted.

Lactam ring closure and oxidation

From pyrrole amide **17** or **18**, intramolecular C–N bond formation was then performed by using copper(I) thiophene-2-carboxylate (CuTC) under MW-assisted conditions to generate the lactam ring, as previously reported,[8] except that Cs_2CO_3 was also added and the reaction time was extended to 45 min to drive the reaction to completion (Scheme 6). The resulting N,O-protected dihydroazalamellarin D (**21** or **22**) then underwent DDQ oxidation smoothly to install the C5=C6 olefin. In the previous synthetic routes for lamellarin D and azalamella rin D, this olefin installation was performed at a much later stage and required the acetate as the O-protecting group, which made it necessary to perform the reactions in refluxing 1,2-dichloroethane (DCE). For our current methodology, conducting the DDQ-mediated oxidation reaction of **21** or **22** with benzyl as the O-protecting group allowed such reactions to occur under much milder conditions (CH_2Cl_2, RT, 3 h). This further negated the possibility of premature deprotection of the *O*- and/or *N*-benzyl, as well as *N*-PMB groups by DDQ at higher temperatures.



Scheme 6. Lactam ring closure and oxidation en route to azalamellarin D. [a] 200 W, 150 °C, 100 psi.

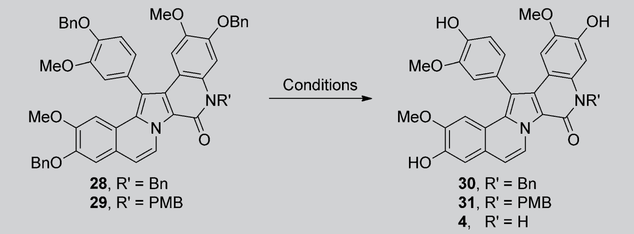
Global deprotection

The final step in the synthesis of azalamellarins was removal of all the protecting groups. A major advantage of our current approach is that all the O- and N-protecting groups remained intact throughout the synthetic route, which thus avoided the additional acetylation and deacetylation steps right before and after DDQ oxidation, respectively, as required in the previously reported route.[8] More importantly, these benzyl-type protecting groups for both oxygen and nitrogen atoms were expected to be removed altogether in a single step.

Initially, the Pd/C-catalyzed hydrogenolysis was found to remove only the *O*-benzyl groups, whereas the *N*-benzyl moiety was left intact. Moreover, under such reaction conditions, the C5=C6 olefin was also partially reduced. As an alternative method, trifluoroacetic acid (TFA)-mediated acidolysis was reported for cleavage of the *N*-benzyl group in some biaryl ring systems.[10c] The use of thioanisole as a benzyl cation scavenger was also described to effectively reduce the amount of undesired C-benzylated side products.[12] Therefore, these approaches were explored in this study.

As shown in Table 2, the use of TFA alone failed to remove the *N*-benzyl group and partially cleaved off the *N*-PMB group (Table 2, entries 1–2 and 5). In addition, some C-benzylated side products were also found as a result of benzyl cation attack on the electron-rich polyphenolic core structure of the lamellarin skeleton. In the presence of thioanisole, the *N*-benzyl group still remained unaffected under various conditions (Table 2, entries 3 and 4), whereas the *N*-PMB group was successfully removed to furnish azalamellarin D in 79–85% yield (Table 2, entries 6 and 7).[13] As described in the Experimental Section, all the optimized conditions were then employed to synthesize azalamellarin N, of which only the N-protected forms were obtained as the final products in the previous study.[8]

Table 2. Global deprotection conditions.



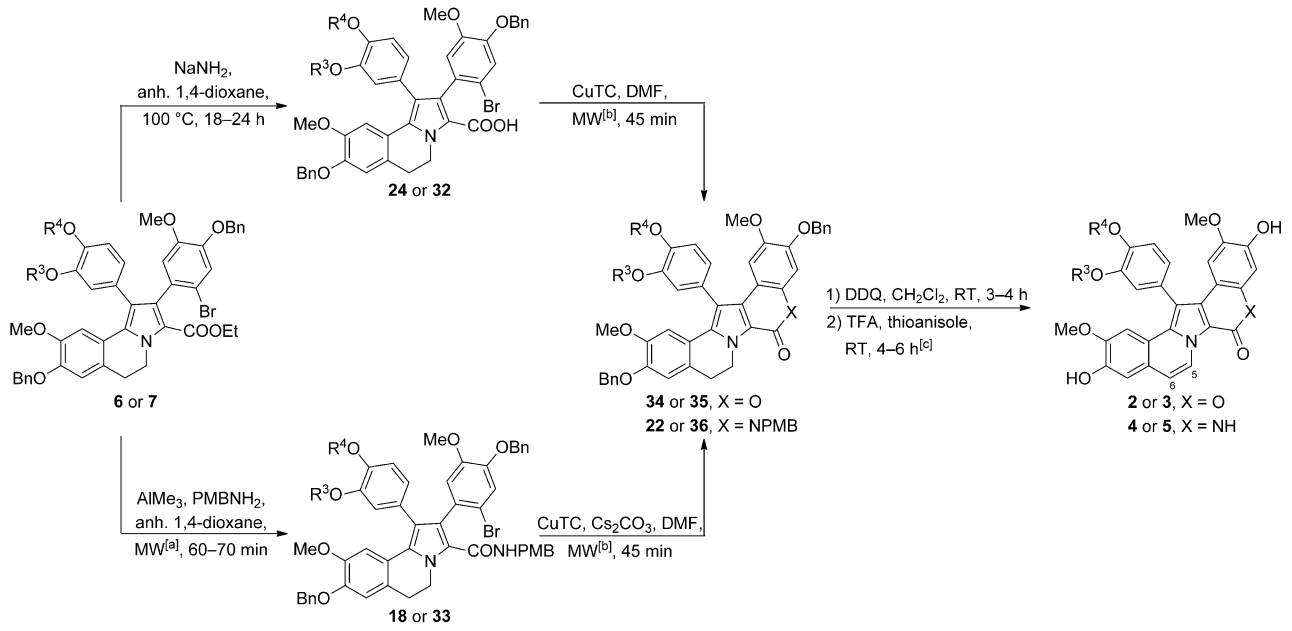
Entry	R′	Solvent	*T* [°C]	*t* [h]	Product, yield [%]
1	Bn	TFA	RT	22–24	30[a]
2	Bn	TFA	60	4	30[a]
3[b]	Bn	TFA + thioanisole	RT	16–20	30, trace[c]
4	Bn	TFA + thioanisole	60	24	30, 77
5	PMB	TFA	RT	4–6	4 and 31[a]
6	PMB	TFA + thioanisole	60	24	4, 85
7	PMB	TFA + thioanisole	RT, 4–6 h, then 60 °C, 16 h		4, 79

[a] A mixture of C-benzylated products was also obtained together with **30** or **31**. [b] Upon performing this reaction under MW irradiation (150 W, 100 °C, 100 psi) for 1 h, only a trace amount of **30** was obtained. [c] Determined by ^{1}H NMR spectroscopy. Bn = benzyl, MW = microwave, PMB = *p*-methoxybenzyl, RT = room temperature, TFA = trifluoroacetic acid.

Application to the synthesis of lamellarins

After successful improvement of the synthesis of azalamella rins, the possibility of diversifying our methodology to synthesize lamellarins was explored. As mentioned previously, treatment of pyrrole ester **6** with sodium amide in refluxing 1,4-dioxane resulted in its unexpected conversion into pyrrole carboxylic acid **24** (Figure 2) in quantitative yield.[14] Upon subjecting this intermediate to the Cu^{I}-mediated, MW-assisted conditions (Scheme 7), intramolecular C–O bond formation furnished O-benzylated dihydrolamellarin D (**34**) in 66% yield over two steps. Subsequent DDQ oxidation and acid-mediated *O*-benzyl cleavage successfully gave lamellarin D in 81% yield (over two steps). The developed approach was also applied to synthesize lamellarin N from pyrrole ester **7** via the intermediacy of pyrrole carboxylic acid **32**,[14] as shown in Scheme 7 and described in the Experimental Section.

In summary, starting from the same pyrrole ester intermediates, similar sets of reactions could be effectively employed to prepare lamellarins and azalamellarins. Functional group interconversion of pyrrole esters (**6** or **7**) to the corresponding amides (**18** or **33**) or to acids (**24** or **32**), followed by Cu^{I}-mediated, MW-assisted intramolecular C–O or C–N bond formation, DDQ-mediated C5–C6 oxidation, and acid-mediated global deprotection of all benzyl-type protecting groups furnished lamellarin D (53%), lamellarin N (35%), azalamellarin D (71%), and azalamellarin N (66%) over four steps. Notably, given that TFA was employed for the final deprotection, the potential risk of lactone ring opening under basic conditions otherwise required for the deacetylation step could be avoided. Therefore, our established methodology for lamellarin synthesis was significantly simplified.



Scheme 7. Our optimized conditions for the synthesis of lamellarins **2** and **3** and azalamellarins **4** and **5**. [a] 200 W, 150–170 °C, 200 psi; [b] 200 W, 150 °C, 100 psi. [c] For **22** or **36**, the mixture was subsequently heated at 60 °C for an additional 16 h. For compounds **6**, **18**, **22**, **24**, and **34**, R^3 = Me; R^4 = Bn. For compounds **7**, **32**, **33**, **35**, and **36**, R^3 = Bn; R^4 = Me. For compounds **2** and **4**, R^3 = Me; R^4 = H. For compounds **3** and **5**, R^3 = H; R^4 = Me.

Physicochemical studies

Because of their diverse biological activities, lamellarins have been subjected to extensive investigations focusing on both anticancer and anti-HIV effects. Since the 1990s, multiple patents have been in effect for their uses in multidrug-resistant tumors,[15] which further justifies their therapeutic potential. Nevertheless, an additional requisite of equal importance is drug likeness, the lack of which has caused a large percentage of designed compounds to fail along the development process.

With regard to drug action, sufficient lipophilicity is required for both membrane permeation and drug-target interactions, whereas solubility of bioactive compounds in aqueous-based media allows the dissolved molecules to exert pharmacological activities under physiological conditions. A balance of these two inversely correlated properties is essential for successful development into drug products. In the pharmaceutical arena, two types of solubility measurements have been established for different purposes. Generally, "thermodynamic solubility" resulting from the dissolution of solid materials can be used as an indicator to identify the need for bioavailability-promoting strategies. For in vitro bioactivity screening processes, potential precipitation issues can be predicted by measuring the "kinetic solubility" upon adding an aliquot of DMSO stock solutions into the desired medium.

Relative to most commercially available oral drugs, lamellarin molecules have high molecular weights and are extremely lipophilic;[16] thus, they severely suffer from precipitation in biological media. As one of the commonly used solubilizing techniques, lamellarin D has been conjugated with a number of aqueous solubility-enhancing moieties[17] to give rise to even bulkier molecules. Interestingly, in a recent study by Thasana et al. focusing on a subtle lactone-to-lactam replacement, the resulting azalamellarin D molecules were observed to form a smaller amount of precipitate in cell culture media, while still exhibiting appreciable cytotoxicity towards selected cancer cell lines.[8] However, their obtained azalamellarin materials were insufficient for in-depth physicochemical characterizations, which were conducted in this study to quantitatively evaluate their lipophilicity along with both kinetic and thermodynamic solubility. All the parameters obtained for azalamellarin D (**4**) and azalamellarin N (**5**) were then compared with those of their parent lamellarin D (**2**) and lamellarin N (**3**), as shown in Table 3.

Table 3. Physicochemical parameters of lamellarins **2** and **3** and azalamellarins **4** and **5**.

Parameter	**2**	**3**	**4**	**5**
Exp. log *P*[a]	3.55 ± 0.02	3.49 ± 0.01	2.65 ± 0.01	2.63 ± 0.01
Thermodynamic (3 days)[b]	ND	ND	ND	ND
Thermodynamic (7 days)[b]	0.21 ± 0.23	0.12 ± 0.13	0.11 ± 0.07	0.05 ± 0.04
Kinetic (1.5 h)	2.55 ± 2.53	1.71 ± 1.34	5.91 ± 1.57	5.58 ± 1.80
Kinetic (24 h)	2.57 ± 2.58	3.78 ± 2.46	5.43 ± 2.16	3.07 ± 0.77

[a] HPLC method. [b] Solubility in μM determined by using the shake-flask method at pH 7.4 and 37 °C. Exp. = experimental, ND = not detectable.

Lipophilicity determinations

In general, for compounds without ionizable functional groups, log *P* is commonly used to indicate their preferences for a lipophilic environment to aqueous media, that is log *P* is the logarithmic ratio between the concentration of an unionized solute in octanol and its concentration in water at equilibrium. Using the HPLC-based method previously established in our laboratory,[16] the log *P* values of lamellarin D and lamellarin N were determined to be approximately 3.5 (Table 3). Such a highly lipophilic nature of lamellarins has been attributed to the extensive stacking interactions among these perfectly planar molecules[16] that predominate over the H-bonding interactions between their phenolic hydroxy groups and water. Interestingly, simple replacement of the lactone oxygen atom in lamellarins **2** and **3** by a nitrogen atom in azalamellarins **4** and **5** led to a dramatic decrease in the log *P* values by almost 1 log unit (Table 3). On the basis of our preliminary molecular-modeling studies, such structural modification did not affect their molecular planarity (data not shown). However, the carbonyl group of an amide offers stronger H-bond acceptor capacity than an ester,[18] whereas the free N–H group can also act as an additional H-bond donor, which would lead to enhanced interactions between the azalamellarins and water molecules. This might explain why both azalamellarins appeared less lipophilic than their respective parent compounds. For each pair of structural isomers, that is, **2** vs. **3** and **4** vs. **5**, the switched OH and OMe groups at C13 and C14 on the orthogonal ring did not affect the lipophilicity of these molecules as expected.

Aqueous solubility measurements

In this study, both types of solubility data were determined for the synthesized lamellarins and azalamellarins by using the traditional shake-flask method that was specifically optimized for these compounds in our laboratory (unpublished results). Under physiological conditions, that is, pH 7.4 and 37 °C, both lamellarin D and lamellarin N exhibited extremely low thermodynamic solubility in the range of 100 to 200 nM, even after 7 days of incubation (Table 3). Rather unexpectedly, this parameter was not much improved in the presence of the lactam moiety, which effectively rendered azalamellarins **4** and **5** less lipophilic. However, upon considering the dissolution process of any solid material, the interactions among the solute molecules must be overcome prior to the solvation step. The amount of energy required to disrupt the crystal lattice can be realized by the melting points, which were equally high for both lamellarins and azalamellarins, and this makes it considerably difficult for these compounds to go into the solution form.

As a result of poor aqueous solubility commonly observed with most organic compounds, the use of cosolvents, mostly DMSO, is normally required to enable compound screening in preclinical studies. Unfortunately, upon dilution into aqueous media, precipitation can still occur and lead to erroneous results. Therefore, a second type of solubility measurements was established to mimic this situation by adding DMSO stock solutions of the test compounds into an aqueous medium, followed by determination of the concentration remaining in solution after a short incubation period.

As shown in Table 3, the kinetic solubility of both lamellarins **2** and **3** and azalamellarins **4** and **5** was dramatically higher than their thermodynamic solubility, possibly as a result of the fact that the predissolved molecules could readily interact with the surrounding water molecules without the need for a dissolution process. Another driving force could be the enhanced solvent power of the aqueous medium in the presence of 5% DMSO from the original stock solutions. Between the two classes of compounds, our results also demonstrated that the azalamellarin molecules were more effectively accommodated in the aqueous environment. Notably, the kinetic solubility of azalamellarins and their respective lamellarins might not appear significantly different, especially if taking into account the expectedly large variations associated with spontaneous precipitation of poorly soluble compounds. However, a much smaller amount of precipitate was visually observed with azalamellarins even at the 12.5 μM concentration used in the cytotoxicity assay. As previously discussed for the lipophilicity determinations, the lactam moiety can act as both an H-bond donor and an H-bond acceptor, which may possibly lead to interactions with water that are better than those of lactone-containing lamellarins.

Biological evaluations

After demonstrating that the drug likeness of lamellarin natural products was partly improved by lactone-to-lactam replacement, we then proceeded to further evaluate the effects of this structure modification on their biological activities. Whereas the precipitation issue could be successfully alleviated, it was also necessary to confirm that the reduced lipophilicity did not impair their membrane permeability such that the overall cytotoxicity against selected cancer cells would be severely abolished. In addition, their GSK-3β inhibitory activity was also evaluated, as both parent compounds, lamellarin D and lamellarin N, have been previously reported to potently inhibit this enzyme in vitro.[6]

Cytotoxic activity

Through various mechanisms as described in the Introduction, both lamellarin D and lamellarin N exhibit potent cytotoxic activity against a number of cancer cell lines according to previous reports.[2,3] Without focusing on any particular underlying mechanisms, the overall cytotoxic effects of the parent lamellarins and their structurally related analogues with altered molecular properties were evaluated by using three adherent cancer cell lines (i.e., A549, HepG2, and HuCCA-1) and one suspended cancer cell line (i.e., MOLT-3) for primary screening.[19]

As shown in Table 4, the IC_{50} values of azalamellarin D against three adherent cell lines were roughly comparable to those of lamellarin D within experimental errors, whereas the suspended MOLT-3 appeared more sensitive to the parent lamellarin D. Nonetheless, the activity of azalamellarin D was still comparable to that of the positive control, etoposide, against these leukemic cells. For lamellarin N and azalamellarin N, on the other hand, the analogue was apparently more active than the parent compound towards A549 and HepG2 cells, whereas equipotent effects of both compounds were observed with

Table 4. Cytotoxicity against cancer cells and GSK-3β inhibitory activity of lamellarins **2** and **3** and azalamellarins **4** and **5**.

Target	IC_{50}[a] [μм]						
	2	**3**	**4**	**5**	Doxorubicin	Etoposide	SB 415286
A549[b]	1.51	I	0.82	0.38	0.59	ND	ND
HepG2[b]	0.30	0.40	0.23	0.09	0.26	ND	ND
HuCCA-1[b]	0.29	0.18	0.13	0.12	0.69	ND	ND
MOLT-3[c]	0.006	0.01	0.04	0.01	ND	0.05	ND
MRC-5[b]	56.94	I	0.30	8.29	3.09	ND	ND
GSK-3β[d] (10 μм ATP)	0.32	0.036	0.018	0.008	ND	ND	0.24
GSK-3β[d] (100 μм ATP)	0.52	0.053	0.022	0.009	ND	ND	0.78

[a] Standard deviations are omitted for visual clarity. [b] MTT assay. [c] XTT assay. [d] ADP-Glo assay. A549 = human nonsmall cell lung carcinoma, HepG2 = human hepatocellular carcinoma, HuCCA-1 = human cholangiocarcinoma, MOLT-3 = human acute T-lymphoblastic leukemia, MRC-5 = human fetal/embryonic lung fibroblast, I = inactive ($IC_{50} > 100$ μм), ND = not determined.

HuCCA-1 and MOLT-3 cells. Our results for the D series compounds were mostly in agreement with those reported by the Thasana's group[8] and further confirmed by using the previously unobtained azalamellarin N that the cytotoxicity of lamellarins was not adversely affected by lactone-to-lactam replacement. Interestingly, although both analogues were significantly more toxic than the parent lamellarins against the MRC-5 cells originally derived from normal lung tissue,[20] azalamellarin N exhibited better selectivity in killing cancer over normal cells than azalamellarin D.

GSK-3β inhibitory activity

Among several protein kinases that are reportedly sensitive to lamellarins and derivatives,[6] GSK-3 was selected as the molecular target in this study owing to its implications in the pathology of several diseases, not only diabetes, but also Alzheimer's and other neurodegenerative diseases, bipolar affective disorder, as well as cancer.[21] Within the lamellarin family, lamellarin N has been demonstrated as the most potent inhibitor (IC_{50} = 5 nм) against GSK-3α/β from porcine brain in the presence of 15 μм adenosine triphosphate (ATP).[6] Although this enzyme could also be inhibited by lamellarin D, a higher IC_{50} value of 300 nм was observed. Recently, two HPLC-resolved atropisomers of 16-methyllamellarin N were developed to investigate the role of axial chirality towards their kinase selectivity.[22] However, both compounds were not only undistinguished by GSK-3β but were also substantially less active than lamellarin N.

Generally, kinase activity can be measured in terms of either product formation [i.e., phosphorylated peptide or adenosine diphosphate (ADP)] or substrate disappearance (i.e., peptide substrate or ATP). From both safety and sensitivity standpoints, the commercially available, luminescence-based ADP-Glo assay was used in this study to quantify ATP-to-ADP conversion by recombinant GSK-3β, either with or without the test compounds. As shown in Table 4, in the presence of 10 μм ATP, the IC_{50} value of lamellarin D coincided with that previously reported,[6] in spite of some differences in the experimental design. Our results also confirmed that the activity of lamellarin N is superior to that of lamellarin D, although there is a significant difference between the IC_{50} values obtained in the two studies. Interestingly, replacement of the lactone moiety with a lactam functionality further potentiated the GSK-3β inhibitory activity of these compounds.

Upon increasing the ATP concentration to 100 μм, only a 1.5-fold increase in the IC_{50} values was observed with lamellarins, whereas those of both analogues remained virtually unaffected. In contrast, the inhibitory activity of SB 415286, an ATP-competitive inhibitor of GSK-3, was significantly diminished with increasing ATP concentrations. However, caution should be exercised upon interpreting the results for lamella rins. As illustrated with some representative dose–response curves in Figure 3, over 90 % inhibition was always achieved with SB 415286 and azalamellarins at their maximum concentrations used in our experiments. In contrast, 20–40 % GSK-3β activity still remained if exposed to lamellarins at micromolar levels, which may potentially result in lower apparent IC_{50} values and overestimated potency of these compounds.

The incomplete GSK-3β inhibition by lamellarins at micromolar concentrations, possibly as a result of their limited aqueous solubility (Table 3), precluded our IC_{50} determinations at higher ATP levels. Nevertheless, we attempted to expose the GSK-3β enzyme to five different equimolar concentrations of various inhibitors in the presence of 1 mм ATP, which not only approaches its physiological concentrations[23] but is also suggested as the maximum limit to be used in the ADP-Glo assay. The results in Table 5 indicate that at any equimolar concentration of the inhibitors the enzyme was inhibited much more effectively by both azalamellarins than either their parent compounds or the positive control. On the basis of these results, it is unlikely that azalamellarins would inhibit GSK-3β enzyme by

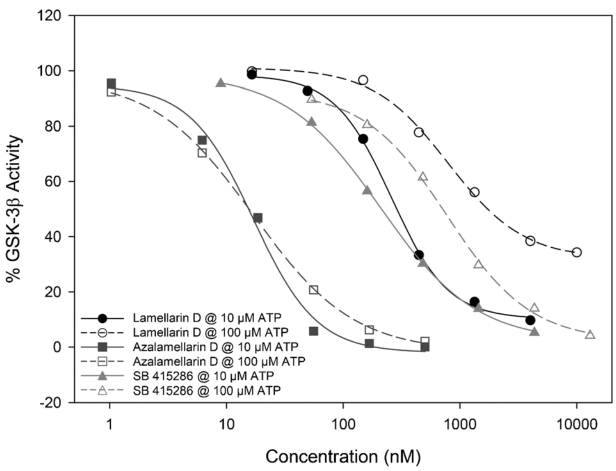


Figure 3. Representative dose–response curves of lamellarin D (**2**), azalamellarin D (**4**), and SB 415286 in the presence of 10 or 100 μм ATP.

competing with ATP molecules, as commonly observed with kinase inhibitors.

To preliminarily determine their mode of inhibition, an additional IC_{50} value of the less-active lamellarin D and SB 415286 was determined in the presence of 25 μM ATP, whereas that of lamellarin N and both azalamellarins was evaluated at 1 mM ATP. As depicted in Figure 4, an ATP-dependent shift in the potency[24] of lamellarins, especially lamellarin D, suggested the competition with ATP as a possible mode of GSK-3β inhibition, similar to that of SB 415286. Distinctively, the IC_{50} values of both azalamellarins remained at a maximum of 20 nM regardless of the ATP concentration up to 1 mM, which is indicative of ATP-noncompetitive inhibition. Such findings are of high importance for the development of kinase inhibitors into drug candidates, as ATP-competitive inhibitors usually suffer from limited selectivity among various kinases possessing conserved ATP-binding pockets, as well as the loss of potency if exposed to ATP at physiological levels.[24]

Molecular-modeling studies

Following the GSK-3β assay, molecular-docking studies were undertaken. Possible interactions underlying the affinity of our inhibitor molecules for the GSK-3β enzyme were explored to rationalize the different inhibitory activities exerted by each

Table 5. GSK-3β inhibition in the presence of 1 mM ATP.

Concentration [nM]	Inhibition[a] [%]				
	2	3	4	5	SB 415286
1	ND	ND	5.4	13.1	ND
10	ND	4.8	28.0	41.6	ND
100	ND	15.3	73.2	88.1	ND
1000	−3.0	49.6	96.5	96.1	11.4
10000	29.4	56.9	ND	ND	68.4

[a] Average values from duplicate wells with <10% standard deviations. ND = not determined.

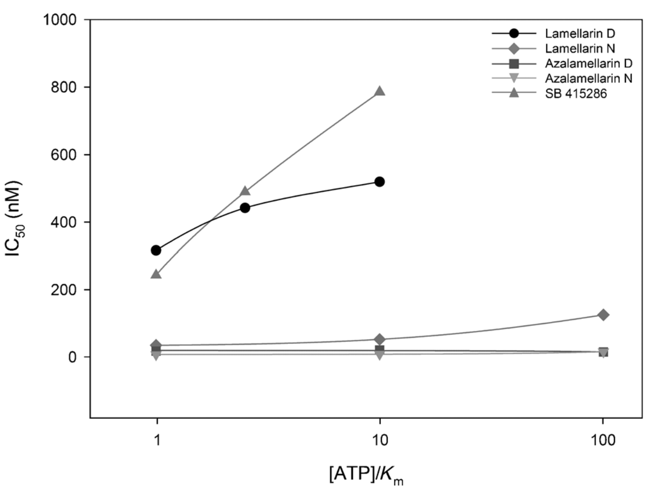


Figure 4. Dependence of the IC_{50} values on the ATP concentrations. A literature-based Michaelis–Menten constant (K_m) value of 10 μM for ATP and GSK-3β enzyme[25] was used for data analysis.

pair of structural isomers (i.e., **2** vs. **3** or **4** vs. **5**), as well as those observed between each lamellarin and its respective lactam-containing derivative (i.e., **2** vs. **4** or **3** vs. **5**). Notably, atropisomerism of lamellarins is generally expected to exist owing to the theoretically restricted C1−C11 rotation. However, our synthetic methods are nonstereoselective and are likely to generate a racemic mixture of these compounds, similarly to those isolated from natural sources (except for lamellarin S[1f]). Previously, our attempts to determine the optical activity of selected lamellarins, including lamellarin D, yielded fluctuating values of their specific rotation ($[\alpha]_D$) within the range of $\pm 10°$ ($c = 0.50$, THF), compared with $+66.5°$ ($c = 0.84$, MeOH) reported for optically active lamellarin S.[1f] Nevertheless, both a*R* and a*S* forms of compounds **2**–**5** were virtually constructed and optimized prior to use in our docking studies to confirm whether the GSK-3β enzyme is selective towards a particular atropisomer.

Whereas the actual binding site of lamellarins and derivatives on the GSK-3β enzyme is still unknown, the ATP-binding pockets are commonly used for molecular-docking studies of kinase inhibitors owing to the availability of the co-crystallized enzyme–inhibitor complexes in the Protein Data Bank (PDB). On the basis of a recent study by Yoshida et al.,[22] the GSK-3β/staurosporine co-crystal structure (PDB ID: 1Q3D[26]) was first used to simulate the interactions formed between the active site residues and our inhibitor molecules. To verify the employed docking method, the original ligand (staurosporine) was first removed and then redocked back onto GSK-3β. The best-docked conformation was found to be very similar to the original complex, which confirmed the suitability of the method utilized herein for GSK-3β. Subsequently, the a*R* and a*S* forms of compounds **2**–**5** were individually docked onto the ATP-binding pocket of GSK-3β, from which the original ligand had been removed. The best-docked conformation of each lamellarin was identified by assessing the binding energy between the ligand and the active site. However, the binding energy values obtained by using 1Q3D (data not shown) did not correlate with either the observed interactions or the experimentally determined inhibitory activities of our compounds, which might also interact with some other residues that are not involved in the current model.

Hence, another co-crystal structure between GSK-3β and 3-aryl-4-(arylhydrazono)-1*H*-pyrazol-5-ones (PDB ID: 3L1S[27]) was then selected, and the docking experiments were performed by the same protocols utilized earlier for 1Q3D. The docking results are illustrated in Figure 5 by using the a*S* form of each compound (see Figure S1 in the Supporting Information for the docking results of the a*R* form). We focused on hydrogen bonds, which usually play an important role in enzyme–ligand interactions. The comparable calculated binding energies and similar interactions observed for both atropisomeric forms of each lamellarin indicated that these isomers were not distinguished by the relatively large ATP-binding pocket of GSK-3β, as previously reported for the two HPLC-resolved atropisomers of 16-methyllamellarin N.[22]

As expected, the lactone carbonyl group as well as the hydroxy groups at both C8 and C20 of lamellarin D are all within the H-bond distances from Val135, Glu97, and Pro136, respectively (Figure 5 a,c). Additionally, the oxygen atoms of the hydroxy group at C8 and the methoxy group at C9 serve as H-bond acceptors that interact with Lys85. Unexpectedly, the C14 hydroxy moiety, which is also considered beneficial for the cytotoxicity of this compound,[17a] does not appear to interact with any residues in the ATP-binding pocket. Instead, if this phenolic hydroxy group was switched to C13 of lamellarin N, an additional hydrogen bond with Asn64 was observed (Figure 5 e,g). These observations, in conjunction with the C9 methoxy oxygen atom serving as a potential H-bond acceptor for the side-chain amino group of Lys85, might explain the significantly different inhibitory activities of these two isomeric lamellarins (Table 4). In addition, replacing the lactone of lamellarin D with a lactam in azalamellarin D resulted in simultaneous H-bond formation between the amide N–H group and both the carbonyl and N–H moieties of Val135 (Figure 5 a–d). Additive stabilizing effects were observed with azalamellarin N possessing both the C13 hydroxy group and the lactam moiety (Figure 5 f,h). Although the binding energy differences among **2**, **3**, **4**, and **5** are not drastic, our docking results are in line with the inhibitory activities towards the GSK-3β enzyme. On the basis of these results combined with those from the above-mentioned GSK-3β assays, it is possible that multiple H-bonding interactions between azalamellarins and their binding site could lead to strong binding to the enzyme, which might hamper its catalytic activity without affecting its binding to ATP owing to their structural nonsimilarities.

Conclusions

Herein, we reported significant advancements in the synthesis of marine-derived lamellarin natural products and their lactam-containing derivatives called azalamellarins. In this study, a general divergent method featuring the use of only a common 2-bromo-α-nitrocinnamate to prepare a late common pyrrole ester intermediate en route to both classes of compounds was successfully devised. Subsequently, either the novel $NaNH_2$-mediated or the $AlMe_3$-mediated conversion of the pyrrole ester was accomplished to furnish the corresponding pyrrole carboxylic acid or pyrrole amide, respectively. The desired lactonization or lactamization was effectively performed through a single and similar reaction type of the CuTC-mediated, microwave-assisted intramolecular C–O or C–N bond formation. Our designed approach also allowed the *O*-benzyl protecting groups to remain throughout the DDQ-mediated oxidation, which thereby avoided the additional acetylation and deacetylation steps that put lamellarin molecules at risk of lactone ring opening. Simple TFA-mediated acidolysis in the presence of thioanisole effectively removed all *O*- and *N*-benzyl-type protecting groups in one step, which furnished the desired lamellarins and azalamellarins in good overall yields over four steps starting from the pyrrole esters.

From detailed comparative physicochemical and biological profiling, our results clearly highlight the promising benefits of replacing the lactone oxygen atom in the lamellarin skeleton with a nitrogen atom. With lower lipophilicity, azalamellarin molecules could better interact with water molecules, which thereby alleviated their precipitation issues in aqueous media. Interestingly, both azalamellarin D and azalamellarin N could still effectively kill cancer cells, albeit with significant toxicity against normal cells. More importantly, such subtle structural modification led to substantially enhanced inhibitory activity towards the multifunctional GSK-3β enzyme with a distinct mode of inhibition from that of the parent lamellarins. Currently, additional analogues are being developed in our laboratory to further improve the aqueous solubility and cancer selectivity of these compounds.

Experimental Section

Synthesis: General

Acetonitrile and toluene were purified by a solvent purification system, whereas tetrahydrofuran (THF) was either distilled from sodium benzophenone ketyl or purified by the solvent purification system. All the other chemicals were used as received from suppliers. Unless stated otherwise, reactions were performed in oven-dried, round-bottomed flasks and were monitored by analytical thin-layer chromatography (TLC) on silica gel 60 F_{254} aluminum sheets. Crude reaction mixtures were concentrated under reduced pressure. Column chromatography and preparative TLC (P-TLC) were performed by using silica gel 60 (particle size 0.06–0.2 mm; 70–230 mesh ASTM).

The final lamellarin and azalamellarin products were purified by crystallization from appropriate solvent systems and, if necessary, were further subjected to semipreparative HPLC purification through a SymmetryPrep C18 column (7 μm, 19 mm i.d. ×300 mm). Stepwise elution (10 mL min^{-1}) started with MeOH/water (70:30 v/v) for 20 min, followed by a linear gradient over 5 min to 100% MeOH, which was then maintained for 10 min before the column was equilibrated for the next injection. The compound purity was then determined to be >95% on the basis of analytical HPLC through a ZORBAX Eclipse Plus C18 column (5 μm, 4.6 mm i.d. ×250 mm) by using two mobile phase systems at 1 mL min^{-1} and UV detection at $\lambda = 276$ nm, as described in the Supporting Information (Table S2). The purified lamellarins and azalamellarins were stored refrigerated at 4 °C until use.

Depending on the compound solubility, proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra of the synthesized materials were recorded with a 300 MHz spectrometer (300 MHz for ^{1}H; 75 MHz for ^{13}C) by using either $CDCl_3$ or [D$_6$]DMSO as solvent. The chemical shifts are reported in parts per million (ppm, δ) downfield from tetramethylsilane ($SiMe_4$), whereas the splitting patterns of the ^{1}H NMR spectra are listed as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), and doublet of doublet (dd), along with the coupling constants (Hz) and integration. Melting points (m.p.) are uncorrected, and infrared (IR) resonances are reported in wavenumber (cm^{-1}). Mass spectrometry (MS) was performed by using electron impact (EI) mode, whereas high-resolution mass spectrometry (HRMS) was conducted by using the time of flight (TOF) method with atmospheric-pressure chemical ionization (APCI) or electrospray ionization (ESI). Compound characterization data are as described below.

4-(Benzyloxy)-3-methoxybenzaldehyde (**12**): A mixture of vanillin (16.0 g, 105 mmol), ethanol (150 mL), potassium carbonate (22.8 g,

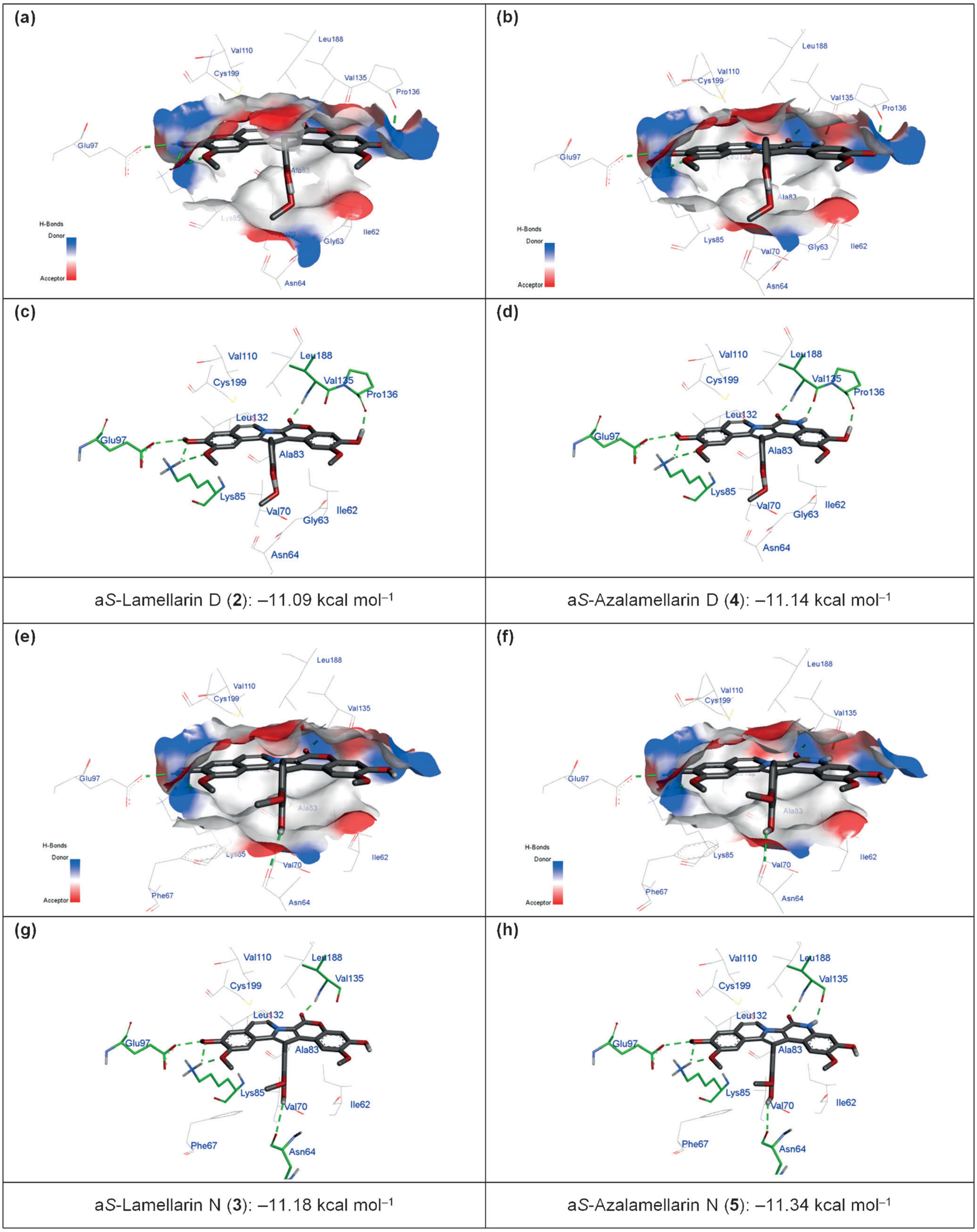


Figure 5. Lamellarins and azalamellarins in the best-docked conformations within the ATP-binding pocket of GSK-3β (PDB ID: 3L1S). Numbers indicate the calculated binding energies.

164 mmol), and benzyl bromide (13.7 mL, 116 mmol) was stirred at reflux for 6 h. Then, the mixture was concentrated, and the residue was diluted with water and extracted with EtOAc (3×30 mL). The combined organic extract was washed with water (3×30 mL) and brine (30 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was subsequently purified by recrystallization in 25–45% EtOAc/hexane to give white crystals of **12** (24.2 g, 95%). Physical and spectroscopic data are in agreement with those previously reported.[28]

3-(Benzyloxy)-4-methoxybenzaldehyde (**37**): A mixture of isovanillin (16.7 g, 110 mmol), ethanol (150 mL), potassium carbonate (22.8 g, 164 mmol), and benzyl bromide (14.4 mL, 121 mmol) was stirred at reflux. After 3 h, ethanol was evaporated, and this was followed by the addition of water and extraction with EtOAc (3×30 mL). Then, the combined organic layer was washed with water (3×30 mL) and brine (30 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. Next, the crude product was purified by recrystallization in 25–45% EtOAc/hexane to give pale yellow crystals of **37** (24.0 g, 91%). Physical and spectroscopic data are in agreement with those previously reported.[29]

4-(Benzyloxy)-2-bromo-5-methoxybenzaldehyde (**13**): Pyridinium tribromide (4.12 g, 12.9 mmol) was added to a stirred solution of **12** (2.00 g, 8.34 mmol) in MeOH (80 mL) at room temperature. After 3 h, MeOH was evaporated, and the mixture was diluted with water before extraction with EtOAc (3×30 mL). The combined organic layer was washed with water (3×30 mL) and brine (30 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The crude material was purified by recrystallization in 10–15% EtOAc/hexane to give pale orange crystals of **13** (2.30 g, 85%). Physical and spectroscopic data are in agreement with those previously reported.[30]

Ethyl 3-[4-(benzyloxy)-2-bromo-5-methoxyphenyl]-2-nitroacrylate (**11**): Diethylamine hydrochloride (4.11 g, 37.4 mmol) and ethyl nitroacetate (3.42 mL, 31.1 mmol) were added to a solution of **13** (8.00 g, 24.9 mmol) in toluene (300 mL). The reaction vessel was equipped with a Dean–Stark apparatus, and the mixture was stirred at reflux under an argon atmosphere for 3 days. Subsequently, toluene was removed under reduced pressure, and this was followed by the addition of water and extraction with EtOAc (2×100 mL). The combined organic layer was washed with water (3×100 mL) and brine (30 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography (20–30% EtOAc/hexane) to give a 1.5:1 mixture of **11**/**13** as a brown sticky product (3.76 g) along with the starting material (3.87 g). The spectroscopic data are in agreement with those previously reported.[8]

Synthesis: azalamellarin D (4) and lamellarin D (2)

[4-(Benzyloxy)-3-methoxyphenyl]methanol (**38**): Sodium borohydride (1.14 g, 30.2 mmol) was added to a solution of **12** (2.93 g, 12.1 mmol) in ethanol (120 mL) and THF (60 mL). The mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure; this was followed by the addition of water and extraction with EtOAc (3×30 mL). Then, the combined organic layer was washed with water (3×30 mL) and brine (30 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by recrystallization in 40–60% EtOAc/hexane to give white crystals of **38** (2.68 g, 91%). Physical and spectroscopic data are in agreement with those previously reported.[31]

1-(Benzyloxy)-4-(chloromethyl)-2-methoxybenzene (**39**): Thionyl chloride (1.96 mL, 16.4 mmol) was slowly added to a solution of **38** (2.68 g, 11.0 mmol) in CH_2Cl_2 (22 mL) at 0 °C. Then, the mixture was warmed up to room temperature. After 30 min, the reaction was quenched with water, and this was followed by the extraction with CH_2Cl_2 (3×20 mL) and washing with water (3×20 mL). The combined organic layer was then washed with 10% w/v sodium hydroxide (6×20 mL) until basic pH, as indicated by litmus paper, followed by washing with brine (30 mL) and drying with anhydrous sodium sulfate. The crude product was concentrated under reduced pressure, dried in vacuo, and used directly in the next step without further purification.

2-[4-(Benzyloxy)-3-methoxyphenyl]acetonitrile (**40**): Crude **39** was dissolved in a biphasic mixture of CH_2Cl_2/water (1:1, 40 mL), and this was followed by the addition of potassium cyanide (1.07 g, 16.4 mmol) and tetra-*n*-butylammonium bromide (3.53 g, 11.0 mmol). The mixture was stirred at room temperature overnight. Then, the crude product was extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was washed with water (3×50 mL) and brine (60 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. Finally, the crude product was purified by column chromatography (10–20% EtOAc/hexane) to give pale yellow crystals of **40** (2.14 g, 76%). M.p. 67.2–68.5 °C (lit.[32] 68.0–69.0 °C); ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$): $\delta=$ 3.70 (s, 2H), 3.92 (s, 3H), 5.17 (s, 2H), 6.79–6.89 (m, 3H), 7.28–7.46 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$): $\delta=$23.2, 56.1, 71.1, 111.5, 114.4, 120.2, 122.7, 127.2, 127.9, 128.6, 136.8, 147.9, 150.2 ppm; IR (UATR): $\tilde{\nu}=$2927, 2249, 1512, 1224 cm^{-1}; MS (EI): *m/z* (%): 253 (10) [M^+], 91 (100), 65 (12).

2-[4-(Benzyloxy)-3-methoxyphenyl]acetic acid (**8**): Potassium hydroxide (10.1 g, 181 mmol) was added to a mixture of **40** (5.72 g, 22.6 mmol) in ethanol (44 mL) and water (22 mL), and the mixture was stirred at reflux overnight. Afterwards, the mixture was cooled to room temperature, concentrated under reduced pressure, acidified with 6 N HCl (pH ~ 2–3), and extracted with EtOAc (3×60 mL). The combined organic layer was washed with water (3×60 mL) and brine (70 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. Finally, the crude product was purified by recrystallization in 50–80% EtOAc/hexane to yield **8** as a white solid (5.97 g, 97%). Physical and spectroscopic data are in agreement with those previously reported.[33]

2-[4-(Benzyloxy)-3-methoxyphenyl]acetyl chloride (**41**): Oxalyl chloride (2.80 mL, 32.9 mmol) and *N,N*-dimethylformamide (DMF) (2 drops) were sequentially added to a solution of acid **8** (5.97 g, 22.0 mmol) in CH_2Cl_2 (44 mL). The reaction vessel was equipped with a drying tube, and the mixture was stirred at room temperature. After 2 h, the crude product was evaporated to remove all organic solvents. The product was immediately used in the next step of the amide synthesis without further purification. Owing to its unstable nature, complete spectroscopic characterization was not performed.

(*E*)-2-(Benzyloxy)-1-methoxy-4-(2-nitrovinyl)benzene (**14**): Ammonium acetate (28.9 g, 395 mmol) and nitromethane (31.9 mL, 592 mmol) were sequentially added to a solution of **37** in glacial acetic acid (38 mL) at room temperature. Then, this mixture was stirred at reflux for 30 min. Afterwards, the mixture was cooled to room temperature, during which time crystallization of the crude product spontaneously occurred. The yellow crystals were filtered and washed with an excess amount of petroleum ether or hexane, followed by an excess amount of water to wash away impurities. After redissolving in heated absolute ethanol, the product was allowed to recrystallize at room temperature. Finally, the product was filtered and then dried in vacuo to obtain bright yellow crystals of **14** (25.0 g, 89%). Physical and spectroscopic data are in agreement with those previously reported.[34]

2-[3-(Benzyloxy)-4-methoxyphenyl]ethanamine (**10**): A solution of **14** (2.66 g, 70.1 mmol) in anhydrous THF (45 mL) was added to a stirred slurry of lithium aluminum hydride (5.00 g, 17.5 mmol) in anhydrous THF (45 mL) at 0 °C under an argon atmosphere. The mixture was then brought to room temperature and stirred overnight. Next, the reaction was quenched by adding a cold mixture of EtOAc/water (1:1) until the generation of gas ceased. The resulting mixture was filtered to remove all gray solid particles. The crude product was then concentrated under reduced pressure. Finally, amine **10** was immediately used for the synthesis of amide without further purification.

2-[4-(Benzyloxy)-3-methoxyphenyl]-*N*-[3-(benzyloxy)-4-methoxyphenethyl]acetamide (**42**): Acid chloride **41** (21.9 mmol) dissolved in CH_2Cl_2 (50 mL) was added to a solution of crude **10** (17.5 mmol) in CH_2Cl_2 (40 mL), and this was followed by the addition of a 10% w/v aqueous solution (46 mL) of sodium carbonate (4.64 g, 43.8 mmol). After 3 h at room temperature, the reaction was quenched with water and extracted with CH_2Cl_2 (3×30 mL). The combined organic layer was washed with water (3×30 mL) and brine (30 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. Finally, the crude product was purified by column chromatography (50–100% EtOAc/hexane) to provide pale yellow crystals of **42** (4.58 g, 52% over two steps from **14**). M.p. 108.7–112.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$): $\delta = 2.63$ (br t, $J = 6.6$ Hz, 2H), 3.39 (q, $J = 6.0$ Hz, 2H), 3.44 (s, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 5.11 (s, 2H), 5.14 (s, 2H), 5.35 (br s, 1H), 6.54 (d, $J = 8.1$ Hz, 1H), 6.62 (d, $J = 7.8$ Hz, 1H), 6.68 (s, 2H), 6.75 (d, $J = 8.4$ Hz, 1H), 6.82 (d, $J = 8.1$ Hz, 1H), 7.28–7.46 ppm (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$): $\delta = 34.9$, 40.7, 43.4, 55.9, 56.0, 71.1, 112.0, 113.0, 114.3, 114.7, 121.4, 121.5, 127.2, 127.4, 127.9, 128.51, 128.54, 137.09, 137.12, 147.4, 148.2, 148.6, 149.9, 171.2 ppm; IR (UATR): $\tilde{\nu} = 3300$, 2933, 1509, 1258 cm^{-1}; MS (EI): *m/z* (%): 511 (4) [M^+], 240 (20), 137 (22), 91 (100), 69 (42); HRMS (APCI-TOF): *m/z*: calcd for $C_{32}H_{33}NO_5 + Na^+$: 534.2251 [$M+Na^+$]; found: 534.2238.

6-(Benzyloxy)-1-[4-(benzyloxy)-3-methoxybenzyl]-7-methoxy-3,4-dihydroisoquinoline (**15**): Amide **42** (2.28 g, 4.47 mmol) was dissolved in anhydrous acetonitrile (20 mL) in a two-necked, round-bottomed flask, to which phosphorus oxychloride (1.23 mL, 13.4 mmol) was added. The mixture was heated at reflux under an argon atmosphere for 2 h. After that, the mixture was cooled to room temperature before acetonitrile was removed. The crude mixture was then basified with a 10% w/v aqueous solution (21 mL) of sodium carbonate (2.13 g, 20.1 mmol), which was followed by the extraction with EtOAc (3×40 mL). The combined organic layer was washed with water (3×40 mL) and brine (40 mL), dried with anhydrous sodium sulfate, concentrated under reduced pressure, and then dried in vacuo to yield key intermediate dihydroisoquinoline **15**, which was used in the next step without further purification.

Pyrrole ester **6**: Sodium bicarbonate (0.375 g, 4.47 mmol) and α-nitrocinnamate **11** (2.20 g, 3.44 mmol) were added to crude **15** dissolved in anhydrous acetonitrile (50 mL) at room temperature. The mixture was then stirred at reflux overnight before the solvent was removed. Next, the reaction was quenched with water, and the mixture was extracted with EtOAc (3×40 mL). The combined organic layer was washed with water (3×40 mL) and brine (30 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. Finally, the crude product was purified by column chromatography (30–50% EtOAc/hexane) to give pyrrole ester **6** (1.60 g, 51% over two steps from amide **42**). M.p. 76.4–77.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$): $\delta = 0.85$ (t, $J = 6.9$ Hz, 3H), 2.90–3.10 (m, 2H), 3.23 (s, 3H), 3.63 (s, 3H), 3.65 (s, 3H), 3.94–4.10 (m, 2H), 4.31–4.36 (m, 1H), 4.87–4.92 (m, 1H), 5.11 (s, 2H), 5.13 (s, 4H), 6.54 (s, 1H), 6.71–6.74 (m, 5H), 7.03 (s, 1H), 7.28–7.44 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$): $\delta = 13.6$, 28.9, 42.7, 55.2, 55.8, 56.0, 59.7, 70.7, 71.0, 71.1, 108.9, 113.2, 113.5, 114.3, 115.0, 115.6, 117.0, 118.6, 121.3, 121.4, 122.8, 125.5, 127.0, 127.2, 127.4, 127.8, 127.9, 128.0, 128.3, 128.5, 128.6, 128.7, 130.4, 130.8, 131.6, 136.5, 136.9, 137.2, 146.5, 147.1, 147.2, 147.8, 148.1, 149.2, 161.5 ppm; IR (UATR): $\tilde{\nu} = 2935$, 1686, 1495, 1454, 1422, 1402, 1383, 1322, 1248, 1210, 1176, 1134, 1022 cm^{-1}; MS (EI): *m/z* (%): 881 (44) [$M+2H^+$], 879 (50) [M^+], 618 (12), 368 (20), 91 (87); HRMS (ESI-TOF): *m/z*: calcd for $C_{51}H_{47}{}^{81}BrNO_8$: 882.2472 [$M+H^+$]; found: 882.2469; $C_{51}H_{47}{}^{79}BrNO_8$: 880.2479 [$M+H^+$]; found: 880.2452. These spectroscopic data are similar to those previously reported.[8]

Pyrrole amide **17**: Trimethylaluminum (1.0 M in toluene, 0.11 mL, 0.11 mmol) was added to a mixture of pyrrole ester **6** (0.0401 g, 0.0456 mmol) and benzylamine (0.024 mL, 0.23 mmol) in THF (1 mL). Then, microwave irradiation (300 W, 200 °C, 45 min) was used to convert the pyrrole ester into the corresponding pyrrole amide. Afterwards, the mixture was cooled to room temperature before the reaction was quenched with 2 N HCl and then extracted with EtOAc (2×20 mL). The combined organic layer was washed with water (3×20 mL) and brine (30 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. Finally, the crude product was purified by using P-TLC (30% EtOAc/hexane) to give pyrrole amide **17** (0.0381 g, 89%). M.p. 63.4–65.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$): $\delta = 2.90$–3.08 (m, 2H), 3.23 (s, 3H), 3.59 (s, 3H), 3.64 (s, 3H), 4.26 (dd, $J = 6.0$, 5.0 Hz, 1H), 4.37–4.41 (m, 1H), 4.44 (dd, $J = 6.1$, 5.0 Hz, 1H), 4.90–4.96 (m, 1H), 5.00 (s, 2H), 5.11 (s, 2H), 5.12 (s, 2H), 5.82 (t, $J = 5.4$ Hz, 1H), 6.60 (s, 1H), 6.68 (s, 1H), 6.73 (s, 4H), 6.93–6.97 (m, 3H), 7.18–7.43 ppm (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$): $\delta = 29.0$, 29.7, 43.0, 43.5, 55.2, 55.8, 56.0, 70.7, 71.0, 71.1, 108.8, 113.4, 113.6, 114.2, 115.4, 115.8, 117.2, 120.8, 121.5, 121.7, 122.8, 125.6, 126.7, 127.1, 127.2, 127.3, 127.4, 127.5, 127.8, 127.9, 128.0, 128.2, 128.4, 128.5, 128.56, 128.62, 128.7, 129.3, 136.2, 137.0, 137.2, 137.9, 146.6, 147.0, 147.9, 148.4, 148.9, 149.2, 161.6 ppm; IR (UATR): $\tilde{\nu} = 3416$, 2926, 1643, 1512, 1494, 1454, 1384, 1330, 1248, 1211, 1177, 1141, 1024 cm^{-1}; MS (EI): *m/z* (%): 941 (1) [M^+], 149 (12), 148 (13), 104 (100), 76 (65), 73 (13), 57 (12); HRMS (ESI-TOF): *m/z*: calcd for $C_{56}H_{50}{}^{81}BrN_2O_7$: 943.2790 [$M+H^+$]; found: 943.2653; $C_{56}H_{50}{}^{79}BrN_2O_7$: 941.2795 [$M+H^+$]; found: 941.2801.

Pyrrole amide **18**: Trimethylaluminum (1.0 M in toluene, 0.11 mL, 0.11 mmol) was added to a mixture of pyrrole ester **6** (0.0401 g, 0.0456 mmol) and *p*-methoxybenzylamine (0.032 mL, 0.23 mmol) in anhydrous 1,4-dioxane (1 mL). Then, microwave irradiation (200 W, 165 °C, 65 min) was used to convert the pyrrole ester into the corresponding pyrrole amide. Subsequent steps were performed as described for compound **17** to furnish compound **18** (0.0434 g, 98%). M.p. 74.9–76.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$): $\delta = 2.88$–3.09 (m, 2H), 3.23 (s, 3H), 3.59 (s, 3H), 3.64 (s, 3H), 3.70 (s, 3H), 4.20 (dd, $J = 9.4$, 4.9 Hz, 1H), 4.35 (dd, $J = 8.5$, 5.8 Hz, 1H), 4.42 (m, 1H), 4.89–4.91 (m, 1H), 4.93 (s, 2H), 5.10 (s, 2H), 5.12 (s, 2H), 5.73 (br t, $J = 6.0$ Hz, 1H), 6.58 (s, 1H), 6.68–6.76 (m, 7H), 6.88–6.91 (m, 3H), 7.25–7.44 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$; $SiMe_4$): $\delta =$ 29.0, 31.7, 43.0, 55.19, 55.24, 55.8, 56.0, 70.8, 71.1, 108.8, 113.5, 113.7, 113.8, 114.3, 115.5, 115.8, 117.3, 120.8, 121.6, 121.8, 122.9, 124.3, 125.6, 126.7, 127.1, 127.3, 127.4, 127.8, 127.9, 128.2, 128.5, 128.55, 128.64, 128.9, 129.3, 130.0, 136.2, 137.1, 137.2, 146.6, 147.0, 147.9, 148.4, 149.0, 149.2, 158.8, 161.5 ppm; IR (UATR): $\tilde{\nu} = 3418$, 2932, 2835, 1685, 1645, 1602, 1511, 1494, 1463, 1384, 1330, 1247, 1211, 1175, 1137, 1026 cm^{-1}; MS (EI): *m/z* (%): 972 (1) [M+2H$^+$], 281 (24), 208 (18), 207 (82), 135 (33), 129 (47), 99 (33), 97 (53), 85 (59), 83 (53), 73 (100); HRMS (ESI-TOF): *m/z*: calcd for $C_{57}H_{52}{}^{81}BrN_2O_3$: 973.2896 [$M$+H$^+$]; found: 973.2915; $C_{57}H_{52}{}^{79}BrN_2O_3$: 971.2902 [$M$+H$^+$]; found: 971.2888.

N,O-Arylmethylenated dihydroazalamellarin D (**21** and **22**): Pyrrole amide **17** (0.0250 g, 0.0266 mmol) was dissolved in DMF (2 mL). Copper(I) thiophene-2-carboxylate (CuTC; 0.0122 g, 0.0638 mmol) and cesium carbonate (0.0087 g, 0.027 mmol) were added. The mixture was heated under microwave irradiation (200 W, 150 °C, 45 min). Afterwards, the reaction was quenched with a saturated ammonium chloride solution (3 mL), and the mixture was extracted with EtOAc (3×15 mL). The combined organic layer was then washed with water (3×15 mL) and brine (20 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by using P-TLC (30% EtOAc/hexane) to give compound **21** (0.0227 g, 96%). M.p. 64.7–66.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$): $\delta = 3.04$ (br t, $J = 6.3$ Hz, 2H), 3.28 (s, 3H), 3.31 (s, 3H), 3.87 (s, 3H), 4.89 (s, 2H), 4.84–4.91 (m, 1H), 5.00–5.08 (m, 1H), 5.15 (s, 2H), 5.27 (s, 2H), 5.46 (br s, 2H), 6.72–6.75 (m, 3H), 6.88 (s, 1H), 7.06–7.21 (m, 5H), 7.26–7.48 ppm (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$): $\delta = 29.0$, 42.4, 45.7, 55.15, 55.18, 56.2, 70.8, 70.9, 71.1, 102.6, 105.8, 108.9, 112.5, 113.3, 114.2, 114.6, 114.7, 121.2, 123.6, 125.6, 126.3, 126.5, 126.96, 127.02, 127.1, 127.2, 127.89, 127.93, 128.04, 128.5, 128.6, 128.7, 128.75, 128.83, 130.5, 133.8, 136.6, 136.8, 137.0, 137.2, 144.9, 146.8, 147.4, 147.5, 147.9, 150.4, 155.9 ppm; IR (UATR): $\tilde{\nu} = 3027$, 2931, 1637, 1515, 1486, 1454, 1418, 1262, 1213, 1177 cm^{-1}; MS (EI): *m/z* (%): 861 (2) [M+H$^+$], 860 (3) [M^+], 129 (34), 104 (100), 91 (21); HRMS (ESI-TOF): *m/z*: calcd for $C_{56}H_{49}N_2O_7$: 861.3534 [M+H$^+$]; found: 861.3571.

Similarly, compound **22** (0.0207 g, 90%) was also synthesized from pyrrole amide **18** (0.0250 g, 0.0257 mmol). M.p. 114.9–116.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$): $\delta = 3.03$ (br t, $J = 6.3$ Hz, 2H), 3.28 (s, 3H), 3.32 (s, 3H), 3.76 (s, 3H), 3.87 (s, 3H), 4.89–4.95 (m, 1H), 4.99 (s, 2H), 4.99–5.06 (m, 1H), 5.14 (s, 2H), 5.27 (s, 2H), 5.38 (br s, 2H), 6.71 (s, 1H), 6.75–6.80 (m, 4H), 6.88 (s, 1H), 7.05–7.10 (m, 5H), 7.27–7.48 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$): $\delta = 29.0$, 42.4, 45.2, 55.18, 55.22, 55.3, 56.2, 70.2, 71.0, 102.7, 105.9, 109.0, 112.5, 113.5, 114.2, 114.75, 114.81, 118.9, 121.3, 123.6, 125.6, 126.5, 127.0, 127.1, 127.2, 127.6, 127.87, 127.94, 128.0, 128.5, 128.6, 128.7, 129.2, 129.9, 130.6, 133.8, 136.7, 136.9, 137.0, 144.9, 146.9, 147.5, 147.6, 148.0, 150.5, 156.0, 158.6 ppm; IR (UATR): $\tilde{\nu} = 3032$, 2931, 1636, 1512, 1486, 1455, 1441, 1418, 1252, 1213, 1176 cm^{-1}; MS (EI): *m/z* (%): 890 (3) [M^+], 551 (26), 129 (70), 111 (51), 104 (80), 98 (86), 97 (85), 91 (80), 73 (100); HRMS (ESI-TOF): *m/z*: calcd for $C_{57}H_{51}N_2O_7$: 891.3645 [M+H$^+$]; found: 891.3673.

N,O-Arylmethylenated azalamellarin D (**28** and **29**): Compound **21** (0.0230 g, 0.0267 mmol) was first dissolved in CH_2Cl_2 (2 mL). Then, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 0.0151 g, 0.0667 mmol) was added, and the mixture was stirred at room temperature for 3 h. Subsequently, water (2 mL) was added to quench the reaction, followed by the extraction with CH_2Cl_2 (3×10 mL). The combined organic layer was washed with water (3×20 mL) and brine (30 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. Finally, the crude product was purified by P-TLC (40% EtOAc/hexane) or column chromatography (35–60% EtOAc/hexane) to produce compound **28** (0.0220 g, 95%). M.p. 116.5–118.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$): $\delta = 3.34$ (s, 3H), 3.36 (s, 3H), 3.89 (s, 3H), 4.97 (s, 2H), 5.24 (s, 2H), 5.31 (s, 2H), 5.54 (br s, 2H), 6.79 (s, 1H), 6.88 (d, $J = 7.5$ Hz, 1H), 7.00 (s, 1H), 7.08 (s, 1H), 7.14–7.22 (m, 5H), 7.26–7.51 (m, 19H), 9.62 ppm (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$): $\delta = 45.6$, 55.1, 55.2, 56.2, 70.7, 70.9, 71.1, 102.5, 105.7, 106.5, 109.6, 110.2, 110.9, 111.9, 114.7, 115.1, 119.5, 123.8, 124.1, 126.4, 127.0, 127.1, 127.2, 128.0, 128.05, 128.11, 128.6, 128.67, 128.72, 128.8, 130.1, 131.4, 132.5, 136.5, 137.0, 137.2, 144.9, 147.6, 148.5, 149.2, 150.6, 156.0 ppm; IR (UATR): $\tilde{\nu} = 3336$, 3027, 2925, 1706, 1626, 1512, 1493, 1454, 1430, 1259, 1217, 1182, 1027 cm^{-1}; MS (EI): *m/z* (%): 859 (1) [M+H$^+$], 149 (24), 104 (100), 91 (16), 76 (60); HRMS (ESI-TOF): *m/z*: calcd for $C_{56}H_{47}N_2O_7$: 859.3383 [M+H$^+$]; found: 859.3347.

Using a similar procedure, compound **22** (0.0490 g, 0.0549 mmol) was employed to furnish corresponding product **29** (0.0454 g, 93%). M.p. 224.8–226.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$): $\delta =$ 3.34 (s, 3H), 3.36 (s, 3H), 3.76 (s, 3H), 3.89 (s, 3H), 5.02 (s, 2H), 5.24 (s, 2H), 5.30 (s, 2H), 5.47 (br s, 2H), 6.77–6.83 (m, 4H) 6.87 (d, $J =$ 7.5 Hz, 1H), 7.01 (s, 1H), 7.07–7.16 (m, 7H), 7.29–7.51 (m, 14H), 9.61 ppm (d, $J = 7.4$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$): $\delta =$ 45.1, 55.1, 55.22, 55.25, 56.2, 70.8, 70.9, 71.1, 102.5, 105.8, 106.6, 109.7, 110.2, 110.9, 112.0, 114.2, 114.8, 115.2, 119.6, 123.8, 124.2, 127.02, 127.05, 127.19, 127.25, 127.6, 127.9, 128.0, 128.1, 128.6, 128.66, 128.72, 129.2, 130.1, 131.4, 132.5, 136.6, 137.0, 145.0, 147.7, 148.6, 149.3, 150.7, 156.0, 158.6 ppm; IR (UATR): $\tilde{\nu} = 3749$, 2933, 2308, 1611, 1513, 1455, 1431, 1260, 1220, 1182 cm^{-1}; MS (EI): *m/z* (%): 889 (1) [M+H$^+$], 207 (36), 129 (55), 104 (100), 76 (58), 73 (86); HRMS (ESI-TOF): *m/z*: calcd for $C_{57}H_{49}N_2O_8$: 889.3483 [M+H$^+$]; found: 889.3486.

N-Benzylated azalamellarin D (**30**): Compound **28** (0.015 g, 0.0175 mmol) was treated with trifluoroacetic acid (TFA, 0.4 mL) in the presence of thioanisole (0.04 mL) at 60 °C. After 24 h, the mixture was cooled to room temperature and extracted with EtOAc (3×10 mL). The combined organic layer was washed with water (3×10 mL) and brine (20 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by crystallization (MeOH/Et_2O/hexane) to give product **30** (0.008 g, 77%). M.p. 278.6–281.1 °C (MeOH/Et_2O/hexane); ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 3.27$ (s, 3H), 3.32 (s, 3H), 3.71 (s, 3H), 5.52 (br s, 2H), 6.78 (s, 1H), 6.92–7.28 (m, 12H), 9.23 (br s, 1H), 9.41 (d, $J = 7.5$ Hz, 2H), 9.68 ppm (br s, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 44.9$, 55.0, 55.2, 56.5, 103.6, 106.0, 107.1, 110.1, 110.4, 111.1, 111.97, 112.00, 115.8, 117.0, 118.3, 123.1, 124.5, 124.6, 126.9, 127.3, 127.4, 129.1, 132.0, 132.5, 138.1, 143.7, 147.1, 147.4, 148.0, 148.5, 149.3, 155.6 ppm; IR (UATR): $\tilde{\nu} = 3429$, 2926, 1617, 1548, 1490, 1456, 1432, 1257, 1207, 1177 cm^{-1}; MS (EI): *m/z* (%): 589 (28) [M+H$^+$], 588 (61) [M^+], 207 (25), 149 (33), 104 (100), 97 (44), 84 (51); HRMS (ESI-TOF): *m/z*: calcd for $C_{35}H_{29}N_2O_7$: 589.1969 [M+H$^+$]; found: 589.1969.

Azalamellarin D (**4**): Using a procedure similar to that described for N-benzylated azalamellarin D (**30**), compound **29** (0.250 g, 0.281 mmol) underwent TFA/thioanisole-mediated acidolysis, which was performed at room temperature for 4–6 h to remove the *O*-benzyl groups. Then, the mixture was heated to 60 °C for 16 h, and subsequent steps were performed as described for compound **30** to give azalamellarin D (0.120 g, 86%). M.p. > 295 °C (MeOH/Et_2O/hexane, dec.); ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 3.34 (s, 3H), 3.37 (s, 3H), 3.76 (s, 3H), 6.80 (s, 1H), 6.89 (s, 1H), 7.00–7.03 (m, 2H), 7.08–7.13 (m, 4H), 9.27 (s, 1H), 9.38 (d, *J* = 7.5 Hz, 1H), 9.49 (s, 1H), 9.72 (s, 1H), 11.27 ppm (s, 1H); ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 55.0, 55.3, 56.4, 102.7, 106.0, 106.4, 109.0, 110.5, 110.8, 112.0, 112.5, 115.8, 116.9, 118.3, 123.1, 124.4, 127.3, 128.4, 131.8, 143.8, 147.0, 147.5, 147.8, 148.4, 149.1, 155.9 ppm; IR (UATR): $\tilde{\nu}$ = 3296, 2924, 1644, 1625, 1455, 1428, 1274, 1211 cm^{-1}; HRMS (ESI-TOF): *m/z*: calcd for $C_{28}H_{23}N_2O_7$: 499.1505 [M+H^+]; found: 499.1480. These spectroscopic data are similar to those previously reported.[8]

Benzylated dihydrolamellarin D (**34**): Pyrrole ester **6** (0.0305 g, 0.0346 mmol) underwent reaction with sodium amide (0.0067 g, 0.17 mmol) in anhydrous 1,4-dioxane (5 mL). The mixture was stirred at 100 °C for 18 h, and the reaction was then quenched with water. The mixture was extracted with EtOAc (2×30 mL). The combined organic extract was then washed with water (2×20 mL) and brine (20 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. Crude product **24** was dried in vacuo. ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$): δ = 2.91–3.03 (m, 2H), 3.22 (s, 3H), 3.64 (s, 3H), 3.65 (s, 3H), 4.42 (br s, 1H), 4.83–4.87 (m, 1H), 5.07 (s, 2H), 5.13 (s, 4H), 6.60 (s, 1H), 6.70–6.74 (m, 5H), 7.28–7.44 ppm (m, 16H); HRMS (ESI-TOF): *m/z*: calcd for $C_{49}H_{43}{}^{81}BrNO_8$: 854.2158 [$M$+$H^+$]; found: 854.2132; $C_{49}H_{43}{}^{79}BrNO_8$: 852.2167 [$M$+$H^+$]; found: 852.2159.

Subsequently, the lactone ring closure of crude product **24** was performed by using CuTC (0.0158 g, 0.0830 mmol) in DMF under microwave irradiation (200 W, 150 °C, 45 min). Afterwards, a saturated ammonium chloride solution (3 mL) was added to stop the reaction, and the mixture was then extracted with EtOAc (3×20 mL). The combined organic layer was washed with water (2×20 mL) and brine (40 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. Finally, the crude product was purified by P-TLC (30% EtOAc/hexane) to yield product **34** (0.0180 g, 66% over two steps). M.p. 181.0–182.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$): δ = 3.03 (br t, *J* = 6.6 Hz, 2H), 3.28 (s, 3H), 3.37 (s, 3H), 3.39 (s, 3H), 4.62–4.71 (m, 1H), 4.76–4.85 (m, 1H), 5.15 (s, 4H), 5.27 (s, 2H), 6.63 (s, 1H), 6.70 (s, 1H), 6.75 (s, 1H), 6.88 (s, 1H), 7.00–7.10 (m, 3H), 7.29–7.48 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$): δ = 28.6, 42.4, 55.2, 55.6, 56.3, 70.87, 70.93, 71.0, 102.7, 104.8, 109.1, 110.7, 113.3, 113.8, 114.4, 114.5, 114.9, 120.5, 123.4, 126.4, 127.0, 127.2, 127.3, 128.0, 128.1, 128.4, 128.68, 128.72, 135.9, 136.3, 136.7, 136.9, 145.8, 146.0, 147.6, 147.7, 148.0, 148.1, 150.4, 155.6 ppm; IR (UATR): $\tilde{\nu}$ = 2924, 2853, 1701, 1606, 1542, 1511, 1484, 1463, 1417, 1269, 1238, 1211, 1166, 1039, 1012 cm^{-1}; MS (EI): *m/z* (%): 771 (1) [M^+], 149 (18), 148 (18), 104 (100), 99 (16), 76 (63); HRMS (ESI-TOF): *m/z*: calcd for $C_{49}H_{42}NO_8$: 772.2910 [M+H^+]; found: 772.2899.

Benzylated lamellarin D (**43**): Compound **34** (0.0120 g, 0.0156 mmol) was oxidized by DDQ (0.0088 g, 0.039 mmol) by using a procedure similar to that described for compound **28** to furnish product **43** (0.0117 g, 99%) as a solid. M.p. 213.6–215.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$): δ = 3.36 (s, 3H), 3.39 (s, 3H), 3.90 (s, 3H), 5.19 (s, 2H), 5.25 (s, 2H), 5.31 (s, 2H), 6.72 (s, 1H), 6.95–6.96 (m, 2H), 7.10–7.14 (m, 4H), 7.30–7.50 (m, 16H), 9.19 ppm (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$): δ = 55.2, 55.6, 56.3, 70.8, 70.90, 70.94, 102.7, 105.4, 105.6, 107.9, 109.5, 110.3, 111.0, 112.4, 114.6, 114.9, 119.3, 123.2, 123.9, 124.6, 125.0, 127.0, 127.2, 127.9, 128.1, 128.7, 129.3, 134.3, 136.2, 136.3, 136.9, 146.0, 146.4, 147.9, 148.5, 149.2, 149.7, 150.6, 155.5 ppm; IR (UATR): $\tilde{\nu}$ = 2928, 1697, 1510, 1486, 1453, 1419, 1263, 1215, 1166, 1034, 1010 cm^{-1}; MS (EI): *m/z* (%): 770 (1) [M+H^+], 281 (12), 207 (41), 129 (42), 104 (100), 84 (69), 73 (81), 60 (57); HRMS (ESI-TOF): *m/z*: calcd for $C_{49}H_{40}NO_8$: 770.2748 [M+H^+]; found: 770.2730.

Lamellarin D (**2**): Using a procedure similar to that described for azalamellarin D (**4**), compound **43** (0.0105 g, 0.0136 mmol) underwent TFA/thioanisole-mediated O-debenzylation at room temperature for 4–6 h to furnish lamellarin D (0.0056 g, 82%). M.p. > 290 °C (MeOH/Et_2O, dec.); ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 3.386 (s, 3H), 3.390 (s, 3H), 3.78 (s, 3H), 6.72 (s, 1H), 6.87 (s, 1H), 7.02–7.08 (m, 1H), 7.11–7.21 (m, 5H), 9.00 (d, *J* = 7.5 Hz, 1H), 9.32 (s, 1H), 9.81 (s, 1H), 9.91 ppm (s, 1H); ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 54.5, 55.0, 56.0, 103.7, 105.3, 105.8, 106.4, 108.3, 110.8, 111.5, 112.3, 115.0, 116.4, 117.5, 122.0, 123.8, 124.6, 125.4, 128.9, 134.0, 144.6, 146.3, 146.8, 147.8, 148.3, 148.5, 148.7, 154.3 ppm. Physical and spectroscopic data are in agreement with those previously reported.[34]

Synthesis: azalamellarin N (5) and lamellarin N (3)

2-[3-(Benzyloxy)-4-methoxyphenyl]acetic acid (**9**): Using a procedure similar to that described for arylacetic acid **8**, benzaldehyde **37** (2.50 g, 10.3 mmol) was used to prepare arylacetic acid **9** (2.32 g, 83% over four steps). The physical and spectroscopic data are in agreement with those previously reported.[35]

2-[3-(Benzyloxy)-4-methoxyphenyl]acetyl chloride (**44**): Oxalyl chloride (1.09 mL, 12.7 mmol) and DMF (2 drops) were sequentially added to a solution of acid **9** (2.32 g, 8.45 mmol) in CH_2Cl_2 (20 mL). Subsequent steps were then performed as described for compound **41**, and the product was immediately used in the next step of amide synthesis without further purification. Owing to its unstable nature, complete spectroscopic characterization was not performed.

N-[3-(Benzyloxy)-4-methoxyphenethyl]-2-[3-(benzyloxy)-4-methoxyphenyl]acetamide (**45**): A solution of acid chloride **44** (8.45 mmol) in CH_2Cl_2 (30 mL) was added to a solution of amine **10** (6.76 mmol) in CH_2Cl_2 (20 mL); this was followed by the addition of a 10% w/v aqueous solution (18 mL) of sodium carbonate (1.79 g, 16.9 mmol). Subsequent steps were then performed as described for compound **42** to provide the desired amide (3.01 g, 87%). M.p. 113.1–114.8 °C (lit.[36] 113.5–115.0 °C); ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$): δ = 2.58 (t, *J* = 6.9 Hz, 2H), 3.35 (q, *J* = 6.6 Hz, 2H), 3.41 (s, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 5.11 (s, 4H), 5.31 (br s, 1H), 6.55 (d, *J* = 8.1 Hz, 1H), 6.62–6.84 (m, 5H), 7.28–7.46 ppm (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$): δ = 34.8, 40.5, 43.3, 59.9, 70.8, 70.9, 111.8, 112.0, 114.5, 115.0, 121.2, 122.1, 127.0, 127.3, 127.8, 127.9, 128.48, 128.50, 130.9, 136.8, 137.0, 148.1, 148.2, 148.3, 148.9, 171.1 ppm. HRMS (ESI-TOF): *m/z*: calcd for $C_{32}H_{34}NO_5$: 512.2431 [M+H^+]; found: 512.2431.

6-(Benzyloxy)-1-[3-(benzyloxy)-4-methoxybenzyl]-7-methoxy-3,4-dihydroisoquinoline (**46**): Amide **45** (3.01, 5.89 mmol) was dissolved in anhydrous acetonitrile (30 mL) in a two-necked, round-bottomed flask, to which phosphorus oxychloride (1.61 mL, 17.6 mmol) was added. Subsequent steps were then performed as described for dihydroisoquinoline **15** to yield key intermediate dihydroisoquinoline **46**, which was used in the next step without further purification.

Pyrrole ester **7**: Sodium bicarbonate (0.500 g, 5.89 mmol) and α-nitrocinnamate **11** (1.98 g, 4.53 mmol) were added to crude **46** dissolved in anhydrous acetonitrile (50 mL) at room temperature. Subsequent steps were then performed as described for compound **6** to give pyrrole ester **7** (2.90 g, 64% over two steps from amide **45**). M.p. 69.8–70.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$): $\delta=0.86$ (t, $J=6.9$ Hz, 3H), 2.89–3.10 (m, 2H), 3.32 (s, 3H), 3.62 (s, 3H), 3.82 (s, 3H), 3.94–4.09 (m, 2H), 4.34–4.42 (m, 1H), 4.84–4.86 (m, 1H), 4.90 (s, 2H), 5.08 (s, 2H), 5.14 (s, 2H), 6.55 (s, 1H), 6.65 (s, 1H), 6.73 (s, 1H), 6.78–6.81 (m, 3H), 7.03 (s, 1H), 7.25–7.44 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$): $\delta=13.7$, 28.9, 42.8, 55.2, 56.01, 56.03, 59.7, 70.9, 71.0, 71.2, 109.0, 111.6, 113.3, 115.1, 115.6, 116.4, 117.1, 118.6, 121.36, 121.39, 123.6, 125.6, 127.2, 127.3, 127.4, 127.8, 127.9, 128.0, 128.4, 128.56, 128.59, 130.4, 131.0, 131.6, 136.5, 136.98, 137.01, 147.2, 147.3, 147.9, 148.1, 148.4, 161.6 ppm; IR (UATR): $\tilde{\nu}=2925$, 1687, 1455, 1402, 1382, 1248, 1176, 1024 cm^{-1}; MS (EI): m/z (%): 880 (1) [M+H$^+$], 368 (51), 236 (52), 149 (41), 121 (86), 97 (91), 83 (83), 71 (86), 57 (100); HRMS (ESI-TOF): m/z: calcd for $C_{51}H_{47}{}^{81}BrNO_8$: 882.2472 [$M$+H$^+$]; found: 882.2441; $C_{51}H_{47}{}^{79}BrNO_8$: 880.2479 [$M$+H$^+$]; found: 880.2445. These spectroscopic data are similar to those previously reported.[8]

Pyrrole amide **33**: Trimethylaluminum (1.0 M in toluene, 0.19 mL, 0.19 mmol) was added to a mixture of pyrrole ester **7** (0.0705 g, 0.0800 mmol) and p-methoxybenzylamine (0.052 mL, 0.40 mmol) in anhydrous 1,4-dioxane (1 mL). Subsequently, microwave irradiation (200 W, 165 °C, 65 min) was used to convert the pyrrole ester into the corresponding pyrrole amide. Subsequent steps were then performed as described for compound **17** to give pyrrole amide **33** (0.077 g, 99%). M.p. 88.5–89.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$): $\delta=2.91$–3.04 (m, 2H), 3.31 (s, 3H), 3.58 (s, 3H), 3.70 (s, 3H), 3.81 (s, 3H), 4.16–4.22 (m, 1H), 4.32–4.44 (m, 2H), 4.85–4.95 (m, 1H), 4.89 (s, 2H), 4.95 (s, 2H), 5.13 (s, 2H), 5.71 (br t, $J=5.4$ Hz, 1H), 6.57 (s, 1H), 6.62 (s, 1H), 6.72–6.80 (m, 6H), 6.87 (s, 1H), 6.90 (s, 2H), 7.25–7.45 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$): $\delta=29.0$, 31.7, 42.9, 55.1, 55.2, 55.92, 55.94, 70.8, 70.99, 71.03, 108.8, 111.5, 113.3, 113.7, 115.3, 115.7, 116.2, 117.1, 120.7, 121.5, 121.7, 123.5, 124.2, 125.5, 126.6, 127.2, 127.4, 127.7, 127.8, 127.9, 128.1, 128.4, 128.5, 128.6, 128.8, 129.3, 129.9, 136.1, 136.9, 137.0, 146.9, 147.8, 148.29, 148.34, 148.8, 158.7, 161.4 ppm; IR (UATR): $\tilde{\nu}=3417$, 2931, 1643, 1510, 1494, 1246, 1210, 1174, 1024 cm^{-1}; MS (EI): m/z (%): 971 (1) [M+H$^+$], 970 (2) [M^+], 163 (21), 121 (100), 91 (92); HRMS (ESI-TOF): m/z: calcd for $C_{57}H_{52}{}^{81}BrN_2O_3$: 973.2896 [$M$+H$^+$]; found: 973.2818; $C_{57}H_{52}{}^{79}BrN_2O_3$: 971.2902 [$M$+H$^+$]; found: 971.2859.

N,O-Arylmethylenated dihydroazalamellarin N (**36**): Pyrrole amide **33** (0.170 g, 0.175 mmol) was dissolved in DMF (2 mL). CuTC (0.067 g, 0.350 mmol) and cesium carbonate (0.119 g, 0.350 mmol) were then added. Subsequent steps were then performed as described for compound **21** to give product **36** (0.137 g, 80%). M.p. 134.6–136.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$): $\delta=3.02$ (br t, $J=6.5$ Hz, 2H), 3.31 (s, 3H), 3.37 (s, 3H), 3.75 (s, 3H), 3.93 (s, 3H), 4.90–5.04 (m, 4H), 5.12 (s, 2H), 5.14 (s, 2H), 5.16 (s, 2H), 5.40 (br s, 2H), 6.66 (s, 1H), 6.75–6.80 (m, 4H), 6.89 (s, 1H), 7.06–7.41 ppm (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$): $\delta=29.0$, 42.5, 45.2, 55.1, 55.3, 56.5, 70.0, 71.1, 102.7, 105.9, 109.0, 112.6, 112.8, 113.4, 114.16, 114.20, 116.9, 118.8, 121.2, 124.3, 125.7, 126.5, 127.1, 127.2, 127.4, 127.6, 127.9, 128.0, 128.5, 128.57, 128.64, 129.3, 129.4, 130.6, 133.9, 136.5, 136.7, 137.0, 145.0, 146.9, 147.6, 148.0, 149.0, 149.3, 156.0, 158.6 ppm; IR (UATR): $\tilde{\nu}=2931$, 1635, 1512, 1485, 1454, 1418, 1250, 1212, 1176 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{57}H_{51}N_2O_7$: 891.3640 [M+H$^+$]; found: 891.3621.

N,O-Arylmethylenated azalamellarin N (**47**): Compound **36** (0.100 g, 0.112 mmol) was dissolved in CH_2Cl_2 (6 mL). Then, DDQ (0.051 g, 0.224 mmol) was added, and the mixture was stirred at room temperature for 4 h. Subsequent steps were then performed as described for compound **28** to yield product **47** (0.099 g, 100%). M.p. > 290 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$): $\delta=3.41$ (s, 3H), 3.42 (s, 3H), 3.79 (s, 3H), 4.00 (s, 3H), 5.05 (s, 2H), 5.16 (s, 2H), 5.27 (s, 2H), 5.50 (br s, 2H), 6.81–6.86 (m, 3H), 6.89 (d, $J=7.5$ Hz, 1H), 7.00 (s, 1H), 7.10–7.18 (m, 4H), 7.21–7.43 (m, 16H), 7.42–7.49 (m, 2H), 9.64 ppm (d, $J=7.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$): $\delta=45.1$, 55.1, 55.2, 55.3, 56.5, 70.8, 71.0, 71.1, 102.5, 105.7, 106.6, 109.7, 110.1, 110.9, 112.0, 112.9, 114.2, 117.3, 119.6, 123.8, 124.1, 124.8, 127.0, 127.17, 127.24, 127.5, 127.7, 127.9, 128.0, 128.1, 128.5, 128.6, 128.7, 129.3, 129.6, 131.4, 132.5, 136.3, 136.56, 136.62, 144.9, 147.8, 148.6, 149.1, 149.2, 149.6, 156.0, 158.6 ppm; IR (UATR): $\tilde{\nu}=2927$, 1727, 1638, 1627, 1452, 1431, 1247, 1220, 1179, 1019 cm^{-1}; MS (EI): m/z (%): 889 (1) [M+H$^+$], 888 (2) [M^+], 368 (23), 208 (71), 195 (100), 129 (42), 97 (43), 73 (70); HRMS (ESI-TOF): m/z: calcd for $C_{57}H_{49}N_2O_8$: 889.3483 [M+H$^+$]; found: 889.3504.

Azalamellarin N (**5**): Using a procedure similar to that described for azalamellarin D (**4**), TFA/thioanisole-mediated acidolysis of compound **47** (0.090 g, 0.101 mmol) gave azalamellarin N (0.041 g, 83%). M.p. > 290 °C (MeOH/Et_2O/hexane, dec.); ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta=3.36$ (s, 3H), 3.39 (s, 3H), 3.87 (s, 3H), 6.84 (s, 1H), 6.89 (s, 1H), 6.99–7.03 (m, 3H), 7.14 (d, $J=4.8$ Hz, 2H), 7.24 (d, $J=8.7$ Hz, 1H), 9.37 (d, $J=7.5$ Hz, 2H), 9.53 (br s, 1H), 9.76 (br s, 1H), 11.29 ppm (s, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta=55.0$, 55.3, 56.6, 102.8, 105.9, 106.3, 108.9, 110.2, 110.9, 112.1, 112.5, 114.2, 118.2, 119.0, 122.7, 123.1, 124.4, 128.1, 129.3, 131.6, 131.8, 143.8, 147.5, 147.9, 148.2, 148.5, 155.9 ppm; IR (UATR): $\tilde{\nu}=3124$, 2924, 1643, 1625, 1491, 1427, 1273, 1212 cm^{-1}; MS (EI): m/z (%): 498 (24) [M^+], 207 (36), 129 (46), 97 (63), 84 (100), 69 (72), 57 (90); HRMS (ESI-TOF): m/z: calcd for $C_{28}H_{23}N_2O_7$: 499.1505 [M+H$^+$]; found: 499.1480.

Benzylated dihydrolamellarin N (**35**): Pyrrole ester **7** (0.0380 g, 0.0431 mmol) underwent reaction with sodium amide (0.017 g, 0.431 mmol) in anhydrous 1,4-dioxane (10 mL) at 100 °C for 24 h. Subsequent steps were then performed as described for compound **34** to afford compound **32** as an intermediate. ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$): $\delta=2.91$–3.02 (m, 2H), 3.31 (s, 3H), 3.64 (s, 3H), 3.82 (s, 3H), 4.44 (br s, 1H), 4.79–4.89 (m, 1H), 4.84 (s, 2H), 5.03 (s, 2H), 5.14 (s, 2H), 6.61 (s, 1H), 6.64 (s, 1H), 6.77–6.79 (m, 4H), 7.05 (s, 1H), 7.26–7.44 ppm (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$): $\delta=28.9$, 43.0, 55.2, 56.0, 70.9, 71.0, 71.2, 109.2, 111.5, 113.1, 115.1, 115.4, 116.3, 117.0, 121.1, 122.0, 123.6, 125.9, 127.29, 127.32, 127.5, 127.6, 127.8, 128.0, 128.1, 128.4, 128.6, 129.6, 132.3, 133.2, 136.5, 136.9, 147.5, 147.7, 147.9, 148.2, 148.4, 164.9, 165.5 ppm; HRMS (ESI-TOF): m/z: calcd for $C_{49}H_{42}{}^{81}BrNO_8+Na^+$: 876.1977 [$M$+Na$^+$][P1] ; found: 876.1992; $C_{49}H_{42}{}^{79}BrNO_8+Na^+$: 874.1986 [$M$+Na$^+$]; found: 874.1994.

Subsequently, the lactone ring closure of **32** was performed by using a procedure similar to that described for **34** to yield product **35** (0.017 g, 51% over two steps). M.p. 87.9–90.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$): $\delta=3.01$ (br t, $J=6.6$ Hz, 2H), 3.34 (s, 3H), 3.48 (s, 3H), 3.98 (s, 3H), 4.71 (br t, 2H), 5.00 (s, 2H), 5.13 (s, 2H), 5.25 (s, 2H), 6.65 (d, $J=5.1$ Hz, 2H), 6.74 (d, $J=9.3$ Hz, 2H), 7.11 (s, 2H), 7.20–7.45 ppm (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$): $\delta=$

28.5, 42.2, 55.2, 55.5, 56.4, 70.6, 70.8, 102.3, 104.8, 109.0, 110.6, 112.6, 113.2, 113.6, 114.7, 116.6, 120.4, 124.0, 126.4, 127.1, 127.2, 127.4, 127.9, 127.96, 128.02, 128.5, 128.59, 128.65, 135.8, 136.3, 136.6, 136.7, 145.7, 145.9, 147.5, 148.0, 148.1, 148.8, 149.5, 155.5 ppm; IR (UATR): $\tilde{\nu}=2925$, 1698, 1509, 1454, 1259, 1214, 1168 cm^{-1}; MS (EI): m/z (%): 772 (1) $[M+H^+]$, 149 (37), 148 (22), 104 (100), 98 (70), 73 (94); HRMS (ESI-TOF): m/z: calcd for $C_{49}H_{42}NO_8$: 772.2905 $[M+H^+]$; found: 772.2896.

Benzylated lamellarin N (**48**): Compound **35** (0.076 g, 0.099 mmol) was oxidized by DDQ (0.045 g, 0.198 mmol) by using a procedure similar to that described for compound **28** to furnish product **48** as a solid (0.074 g, 97%). M.p. 203.4–206.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$, $SiMe_4$): $\delta=3.42$ (s, 3H), 3.46 (s, 3H), 4.01 (s, 3H), 5.13 (s, 2H), 5.20 (s, 2H), 5.24 (s, 2H), 6.69 (s, 1H), 6.89 (s, 1H), 6.96 (d, $J=$ 7.5 Hz, 1H), 7.09 (d, $J=9.0$ Hz, 2H), 7.19–7.48 (m, 18H), 9.16 ppm (d, $J=7.2$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$): $\delta=55.2$, 55.5, 56.5, 70.7, 70.9, 71.0, 102.6, 105.4, 105.5, 109.5, 110.2, 111.0, 112.3, 112.7, 117.1, 119.3, 123.1, 124.5, 124.6, 127.18, 127.22, 127.5, 128.07, 128.12, 128.2, 128.5, 128.67, 128.70, 129.3, 134.3, 136.28, 136.32, 146.0, 146.4, 148.5, 149.0, 149.2, 149.6, 149.8, 155.4 ppm; IR (UATR): $\tilde{\nu}=2924$, 1698, 1430, 1421, 1264, 1223, 1167 cm^{-1}; MS (EI): m/z (%): 770 (1) $[M+H^+]$, 207 (95), 111 (39), 105 (45), 104 (56), 98 (99), 91 (100), 83 (79), 69 (77); HRMS (ESI-TOF): m/z: calcd for $C_{49}H_{40}NO_8$: 770.2748 $[M+H^+]$; found: 770.2730.

Lamellarin N (**3**): Using a procedure similar to that described for azalamellarin D (**4**), TFA/thioanisole-mediated O-debenzylation of compound **48** (0.0656 g, 0.0853 mmol) at room temperature for 4–6 h gave lamellarin N (0.030 g, 70%). M.p. 312.4–314.6 °C (MeOH/Et_2O); ^{1}H NMR (300 MHz, $[D_6]$DMSO): $\delta=3.39$ (s, 3H), 3.40 (s, 3H), 3.87 (s, 3H), 6.76 (s, 1H), 6.87 (s, 1H), 7.01–7.04 (m, 2H), 7.18–7.26 (m, 4H), 9.01 (d, $J=7.2$ Hz, 1H), 9.38 (br s, 1H), 9.83 (br s, 1H), 9.94 ppm (br s, 1H); ^{13}C NMR (75 MHz, $[D_6]$DMSO): $\delta=55.0$, 55.5, 56.1, 104.2, 105.8, 106.2, 107.0, 108.7, 111.0, 112.0, 112.9, 114.2, 117.9, 118.7, 122.5, 112.6, 125.1, 127.9, 129.2, 134.3, 145.0, 146.8, 148.2, 148.3, 148.4, 148.8, 149.0, 154.8 ppm; HRMS (ESI-TOF): m/z: calcd for $C_{28}H_{22}NO_8$: 500.1340 $[M+H^+]$; found: 500.1349. Physical and spectroscopic data are similar to those previously reported.[1j,37]

Physicochemical characterizations: general

All chemicals were obtained from commercial sources with at least 98% purity. Unless otherwise mentioned, the test compounds were prepared as 10 mM stock solutions in DMSO and were further diluted as described for each experiment. The HPLC analyses mentioned below were performed by using isocratic elution with MeOH/water (75:25 v/v) for 15 min through a ZORBAX Eclipse Plus C18 column (5 μm, 4.6 mm i.d. ×250 mm). UV detection was performed at $\lambda=210$, 254, and 276 nm for formamide, reference compounds, and lamellarins, respectively.

Lipophilicity determinations

Experimental log *P* values of the lamellarins and azalamellarins were determined by using reverse-phase HPLC, as previously established in our laboratory.[16] Seven chemicals with known log *P* values, including benzyl alcohol, benzonitrile, methyl benzoate, benzophenone, naphthalene, benzyl benzoate, and diphenyl ether, were selected off the list of recommended reference substances[38] and were prepared as a reference mixture in MeOH/water (75:25 v/v) for daily system calibration. By using a standard equation, the retention time (t_R) of each reference compound was first corrected and then compared with the column dead time (t_0, determined from the retention time of unretained formamide) to give the retention factor (k), the logarithm of which was then plotted against the known log *P* value to construct a calibration curve. Subsequently, the 10 mM stock solutions of lamellarins and azalamellarins were freshly diluted with 3 volumes of MeOH and 1 volume of deionized water. Their retention factors were then determined as described for the reference compounds. Finally, their log *P* values were assessed from the calibration curve constructed on the same day.

Solubility measurements

Freshly prepared HEPES buffer (20 mM, pH 7.4) served as the medium for determining the aqueous solubility of lamellarins and azalamellarins by using the traditional shake-flask method coupled with HPLC analysis, as previously optimized for these compounds (unpublished results). Briefly, each sample for thermodynamic solubility measurements was prepared by adding the solid material (1 mg) into buffer (40 mL) in a 100 mL Erlenmeyer flask, which was then loaded into a shaking incubator operated at 37 °C and 250 rpm for up to 7 days. In contrast, kinetic solubility samples were prepared by adding 10 mM stock solutions (100 μL) of our test compounds into vials containing HEPES buffer (1900 μL) and were then incubated under the above-mentioned conditions for up to 24 h. All measurements were performed at least in triplicate.

At predetermined time points during the specified incubation period, an aliquot (500 μL) was taken from each sample without buffer replacement and was transferred into a microcentrifuge tube for centrifugation at 25 °C and 18000 rpm for 5 min. Subsequently, clear supernatant (198 μL) was carefully withdrawn from each sample into an HPLC insert containing DMSO (2 μL) to prevent precipitation. Lastly, HPLC analysis was then conducted on both the samples and the serially diluted standard solutions to determine the concentrations of the test compounds that either dissolved or remained in HEPES buffer, which represented their thermodynamic or kinetic solubility, respectively.

Biological evaluations: general

Each test compound or positive control was dissolved in DMSO at 20 mM for cytotoxicity assay and 10 mM for GSK-3β inhibition assay. The stock solutions for cytotoxicity assay were filter-sterilized before use, whereas the remaining solutions were aliquoted and stored at −20 °C for replicate experiments within the same week. The sources of cell lines and the culture media used for their propagation are described in the Supporting Information (Table S3). All reagents for cell culture, as well as those for 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2*H*-tetrazolium-5-carboxanilide (XTT) assays, were obtained from commercial sources and were used as received. The ADP-Glo Kinase Assay Kits, including the GSK-3β Kinase Enzyme Systems, were supplied by Promega Corporation (Madison, WI, USA).

Cytotoxicity assays

Throughout the assay, all cell lines were maintained by using standard procedures at 37 °C with 95% humidity and 5% CO_2. For adherent cells (i.e., A549, HuCCA-1, HepG2, and MRC-5), the MTT assay was performed to determine the number of cells that survived the cytotoxicity of each test compound, as previously reported.[3c] Briefly, 5000–10000 cells suspended in the corresponding media (100 μL) were first inoculated into each well of 96-well microtiter plates and were then incubated for 24 h. Afterwards, the attached cells were treated with an equal volume (100 μL per well) of the cell culture medium containing either each test compound or the positive control (doxorubicin) at various concentrations, except for the negative control cells, which were treated with 0.25% v/v DMSO. After 48 h of exposure, the cell viability was determined by adding the MTT reagent [0.5 $mg\,mL^{-1}$ in fetal bovine serum (FBS)-free medium, 100 μL per well] into each well, followed by 2.5–4 h of incubation. Then, the medium was replaced with an equal volume of DMSO to dissolve the insoluble purple formazan. Finally, the absorbance at $\lambda=550$ nm was measured with a reference wavelength of $\lambda=650$ nm by using a microplate reader.

On the other hand, the suspended MOLT-3 cell line was subjected to the XTT assay as follows. MOLT-3 cells in RPMI 1640 medium (50 μL) were seeded at a density of 20000 cells per well and allowed to acclimatize for 30 min. Subsequently, the cells were treated with an equal volume (50 μL per well) of the cell culture medium containing serial dilutions of each test compound or the positive control (etoposide), whereas the negative control cells were exposed to 0.05% v/v DMSO. Following an additional 44 h incubation, the XTT reagent (50 μL, prepared by mixing 5 mL of 1 $mg\,mL^{-1}$ XTT sodium in sterile water with 100 μL of 0.383 $mg\,mL^{-1}$ phenazine methosulfate in water) was added to each well, and the cells were then incubated for 4 h. As the orange formazan formed is water soluble, the final solubilization step could be avoided, which thus allowed the absorbance at $\lambda=$ 492 nm to be readily measured with a reference wavelength of $\lambda=$ 690 nm.

Data analysis was then performed by determining the percentage of surviving cells after 48 h exposure to each concentration of the test compounds or the positive controls. The background-subtracted absorbances of treated wells were averaged and then compared with those of the negative control wells. The dose–response curve was then constructed and regressed by using the SigmaPlot software (Systat Software, Inc., San Jose, CA, USA) to obtain the IC_{50} value. The results shown in Table 4 are the mean values determined from at least three independent experiments for each compound.

GSK-3β inhibition assays

According to the ADP-Glo Kinase Assay Protocol, the assay was performed at room temperature in 1X buffer containing 40 mM Tris (pH 7.50), 20 mM $MgCl_2$, and 0.1 $mg\,mL^{-1}$ bovine serum albumin (BSA). The optimized assay conditions were as follows. The GSK-3β enzyme (20 ng in 10 μL buffer) was first exposed for 10 min to each test compound or the positive control (i.e., SB 415286), all of which had been prepared at predetermined concentrations in buffer (5 μL). Likewise, the enzyme exposed to the DMSO-containing buffer (1% v/v, 5 μL) served as the negative control. Subsequently, the ATP/substrate mixture (10 μL) was added into each well to initiate the kinase-mediated phosphorylation of a primed peptide substrate derived from glycogen synthase [i.e., YRRAAVPPSPSLSRHSSPHQ(pS)EDEEE, in which pS represents phosphorylated serine]. Following 60 min incubation, the ADP-Glo Reagent (25 μL per well) was added to the mixture and was allowed to react for an additional 40 min to simultaneously terminate the kinase reaction and to remove all the remaining ATP. Finally, addition of the Kinase Detection Reagent (50 μL per well) mediated the conversion of the ADP product from the kinase reaction back to ATP, which was then used in the luciferase/luciferin reaction. After 30 min, the luminescence generated was then measured by using a SpectraMax L luminescence microplate reader (Molecular Devices, Sunnyvale, CA, USA) and was compared with that obtained in the absence of inhibitor. The percent inhibition averaged from duplicate wells was then plotted against the concentration of the test compound to determine the IC_{50} value by using nonlinear regression analysis. At least three independent experiments were conducted to get the mean IC_{50} value of each test compound, as shown in Table 4.

Molecular-docking studies

Three-dimensional structures of lamellarin D (**2**), lamellarin N (**3**), azalamellarin D (**4**), and azalamellarin N (**5**) were constructed and optimized by using the AM1 method implemented in the Gaussian 03 package.[39] The crystal structures of human GSK-3β were obtained from the Protein Data Bank (PDB ID: 1Q3D[26] and 3L1S[27]). Docking analysis was performed by using the AutoDock 4.0 program.[40] All ligands (i.e., compounds **2**–**5**) and the protein were prepared by using AutoDockTools 1.5.6.[41] Briefly, the Gastiger charges on all ligands were calculated, and all nonpolar hydrogen atoms were merged. For GSK-3β, hydrogen atoms were added to the structure, and the Gastiger charges were computed. All water molecules were removed from the crystal structure of GSK-3β. The nonpolar hydrogen atoms were merged, and the grid box was assigned to sufficiently include the ATP-binding site of the GSK-3β with spacing of 0.375 Å, whereas the number of points was set to be 60 in the *x*, *y*, and *z* axes. The search parameter used was Genetic Algorithm (GA) with 100 runs, and the population size was set to 150. The best-docked conformation for each compound was visualized and analyzed by using the Discovery Studio Visualizer (Accelrys, San Diego, CA, USA).

Acknowledgements

This work was financially supported by the Thailand Research Fund (TRF; DBG5480011 to M.C., BRG5580010 to P.P.) and the Scientist Development Project Commemorating His Majesty the King's 84th Birthday Anniversary (to A.T.). Insightful information on the previous synthetic route of azalamellarins from Dr. Nopporn Thasana (Laboratory of Medicinal Chemistry, Chulabhorn Research Institute) is gratefully acknowledged. The authors are thankful to Dr. Vilailak Prachyawarakorn (Laboratory of Natural Products, Chulabhorn Research Institute) for her kind suggestions for semipreparative HPLC purification. Special thanks go to Mr. Nitirat Chimnoi (Laboratory of Natural Products, Chulabhorn Research Institute) and Dr. Amornmart Jaratrungtawee and Dr. Jaran Jainhuknan (Bruker Biospin AG, Bangkok, Thailand) for LC–MS analysis. The authors are also grateful for generous advice from Dr. Kriengsak Lirdprapamongkol and Dr. Lukana Ngiwsara (Laboratory of Biochemistry, Chulabhorn Research Institute) during GSK-3β assay optimization. In addition, technical guidance on cell culture protocols and cytotoxicity assays from Ms. Pakamas Intachote (Laboratory of Immunology, Chulabhorn Research Institute), together with Ms. Suchada Sengsai and Ms. Busakorn Saimanee (Integrated Research Unit, Chulabhorn Research Institute) is greatly appreciated. Finally, the authors would like to thank Ms. Wandee Sirapat and Ms. Suchonnama Puttakan (Office of Academic Affairs, Chulabhorn Research Institute) for their kind assistance with the graphic design.

Keywords: cytotoxicity · drug likeness · inhibitors · lamellarins · total synthesis

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[13] Despite the use of thioanisole as a benzyl cation scavenger, some C-monobenzylated side products ($\approx$5–15%) as evidenced by the peak at m/z = 589.1962–589.1995 [M+H$^+$] from LC–MS analysis was found to contaminate the obtained crystallized azalamellarin products. Therefore, it was still necessary to use semipreparative HPLC for their final purification.

[14] In contrast to the previously reported labile nature towards decarboxylation of the 2-pyrrole carboxylic acids,[9] the structures of which are similar to those of **24** or **32** except for the proton in place of the bromine atom, these two intermediates could be isolated, chromatographically purified, and spectroscopically characterized. Structural assignments of **24** and **32** were based on their spectroscopic data (Supporting Information). Whereas the exact mechanism of their formation under the reaction conditions is not fully understood, the presence of the bromine atom appeared to direct **24** and **32** to preferentially undergo Cu^{I}-mediated, MW-assisted intramolecular C–O bond formation rather than decarboxylation. For detailed discussion, see the Supporting Information.

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[19] Following 48 h of exposure, the number of cancer cells that survived the toxicity of our test compounds was determined indirectly from reduction of the tetrazolium-based MTT and XTT reagents by the mitochondrial dehydrogenase enzyme in the adherent and suspended cells, respectively, that remained metabolically active. On the basis of nonlinear regression analysis of the dose–response curves, the half-maximal inhibitory concentration (IC_{50}) of each test compound was then calculated as the concentration that inhibited cell growth by 50% of the maximum response relative to untreated cells.

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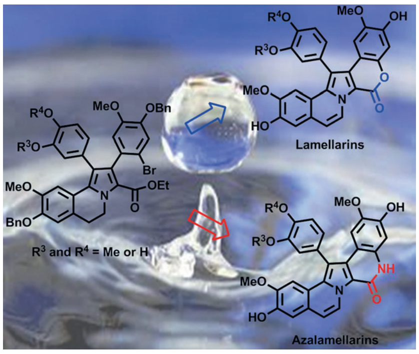
Manuscript received: June 12, 2015
Accepted Article published: July 16, 2015
Final Article published: ■■ ■■, 0000

FULL PAPER

Am-aza-ing results! A general divergent method is established to provide efficient access to lamellarin natural products and their lactam-containing counterparts through the same pyrrole ester intermediates. Comparative physicochemical and biological profiling along with molecular-modeling studies collectively highlight the benefits of a simple lactone-to-lactam replacement in the lamellarin skeleton.



Natural Products

*Atiruj Theppawong, Poonsakdi Ploypradith, Pitak Chuawong, Somsak Ruchirawat, Montakarn Chittchang**

■■ – ■■

Facile and Divergent Synthesis of Lamellarins and Lactam-Containing Derivatives with Improved Drug Likeness and Biological Activities

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CHEMISTRY
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Supporting Information

Facile and Divergent Synthesis of Lamellarins and Lactam-Containing Derivatives with Improved Drug Likeness and Biological Activities

Atiruj Theppawong,[a, b] Poonsakdi Ploypradith,[a, b] Pitak Chuawong,[c]
Somsak Ruchirawat,[a, b] and Montakarn Chittchang*[a, b]

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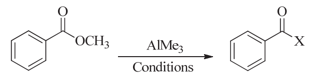
Table of Contents

Model Studies of $AlMe_3$-mediated Direct Amidation of Methyl Benzoate

General Procedure

Model studies for direct amidation were performed using methyl benzoate and several nitrogen sources (Table S1). The starting material was first dissolved in THF, 1,4-dioxane, or toluene as solvent. Different nitrogen sources (5 eq.) were then added into the reaction mixture, followed by addition of 1.0 M trimethylaluminum (5 eq.). Subsequently, the mixture was irradiated with microwave. After cooling down to room temperature, the reaction was quenched using 2 N HCl, and then, extracted with EtOAc (2x15 mL). The combined organic layers were washed with water (2x20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The produce **26** was isolated as white solid from both the conditions using sodium amide (entry 1) and trimethylsilyl azide (entry 2) as shown in Table S1.

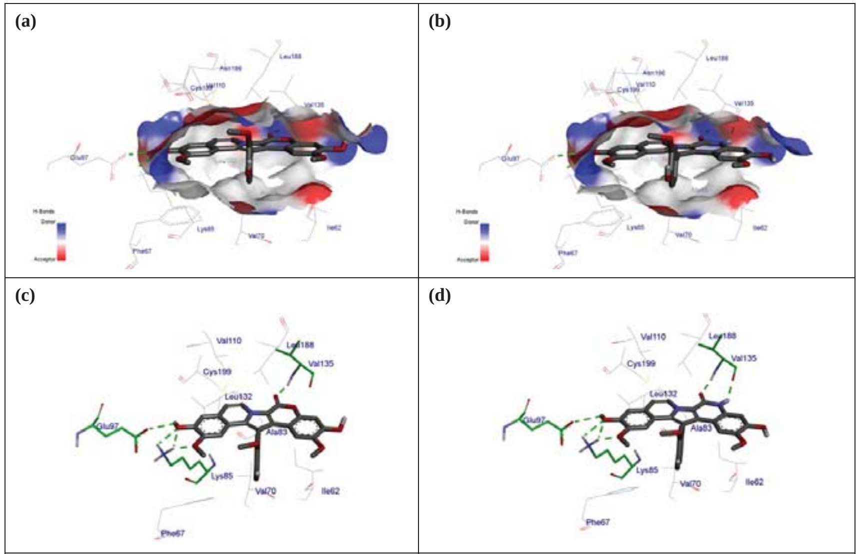
Table S1. Model studies for direct amidation using microwave irradiation.



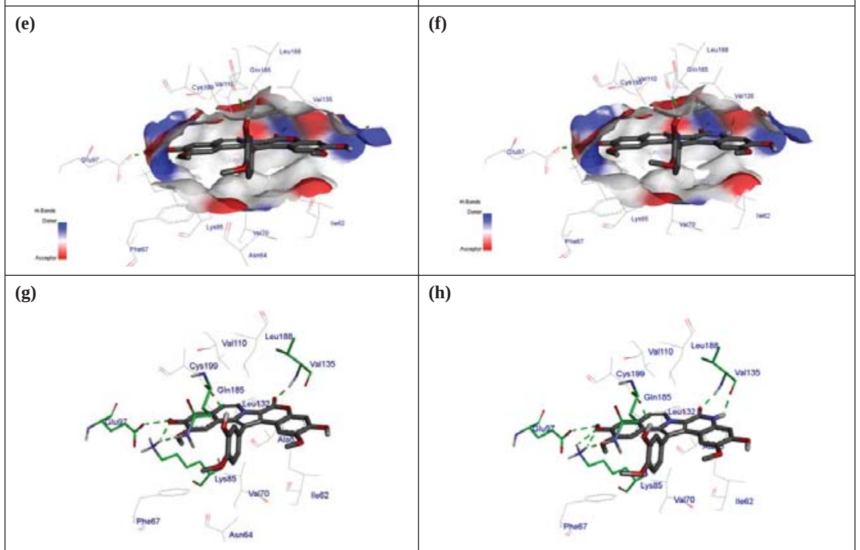
25 **26**, X = NH_2 **27**, X = N_3

Entry	Nitrogen Source	Solvent	MW[a] (W)	Temp (°C)	Time (h)	Results
1	$NaNH_2$	THF	150	150	0.75	**26** (89%)
2	$TMSN_3$	THF	300	200	0.75	**27**[b]
3	NaN_3	THF	150	150	0.75	**27** (30%)
4	NaN_3	1,4-dioxane	150	150	0.75	**25**
5	NH_4Cl	THF	150	150	0.75	**25**
6	NH_4Cl	toluene	100	60	5×0.2	**25**
7	$NH_2OH{\cdot}HCl$	THF	150	150	0.5	**25**

[a] 200 psi. [b] **27** was further reduced using $NaBH_4$ to give **26** in 80% yield over 2 steps. MW = microwave, THF = tetrahydrofuran, TMS = trimethylsilyl.



a*R*-Lamellarin D (**2**): –11.03 kcal mol^{-1} | a*R*-Azalamellarin D (**4**): –10.87 kcal mol^{-1}



a*R*-Lamellarin N (**3**): –11.30 kcal mol^{-1} | a*R*-Azalamellarin N (**5**): –11.49 kcal mol^{-1}

Figure S1. The a*R* form of lamellarins and azalamellarins in the best docked conformations within the ATP-binding pocket of GSK-3β (PDB ID: 3L1S). Numbers indicate the calculated binding energies.

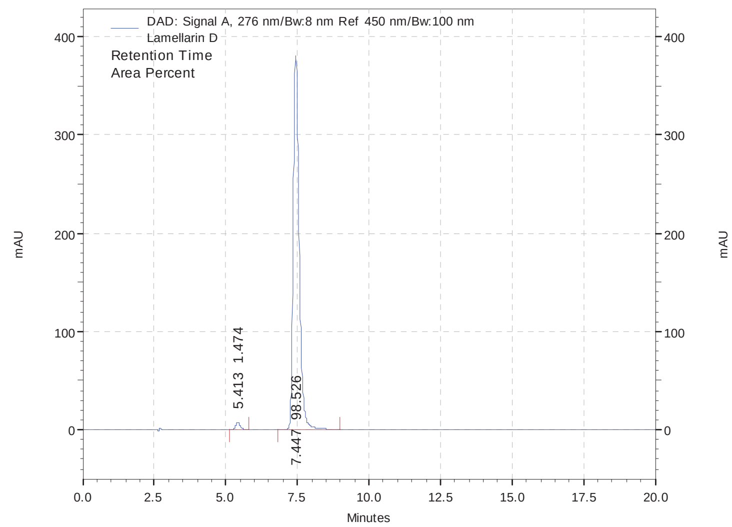
Table S2. Purity of the synthesized compounds determined by HPLC analysis[a]

Compound	Solvent System 1[b]		Solvent System 2[c]	
	t_R (min)	% Purity	t_R (min)	% Purity
Lamellarin D (**2**)	7.447	98.5	18.067	98.5
Lamellarin N (**3**)	7.140	100.0	19.327	99.8
Azalamellarin D (**4**)	4.827	100.0	6.467	100.0
Azalamellarin N (**5**)	4.773	100.0	6.907	100.0

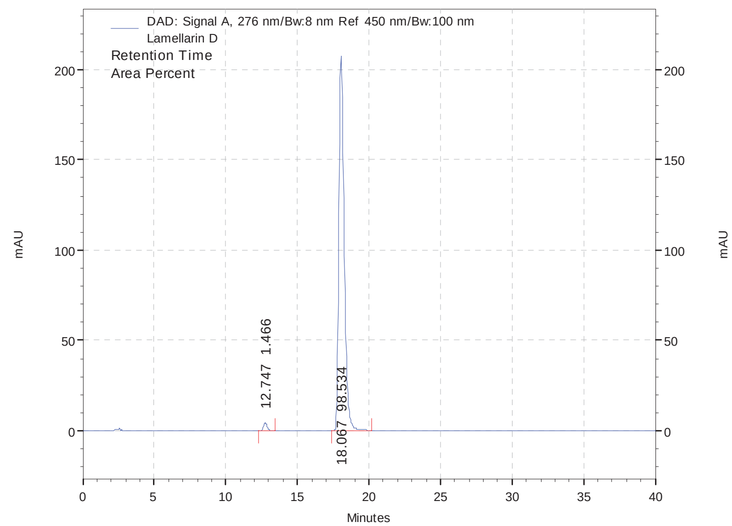
[a] Analysis was performed using a C18 column and two solvent systems at a flow rate of 1 mL min^{-1}. [b] MeOH/0.1% v/v formic acid in H_2O (75:25, v/v). [c] MeCN/0.1% v/v formic acid in H_2O (40:60, v/v).

Lamellarin D (2)

MeOH/0.1% v/v formic acid in H_2O (75:25, v/v)

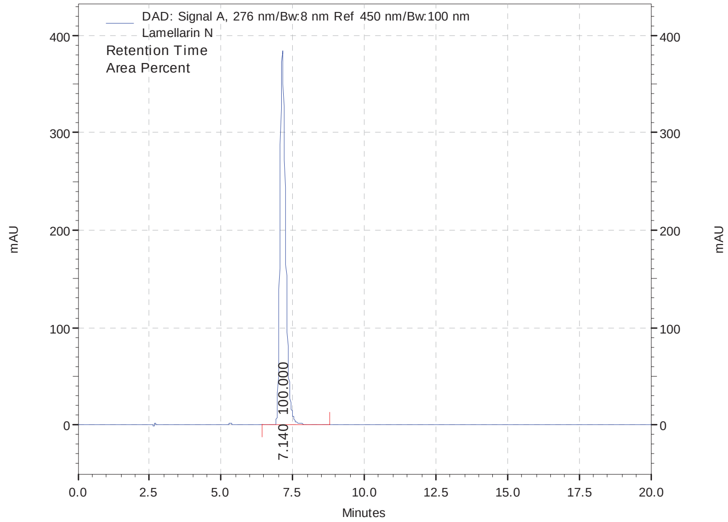


MeCN/0.1% v/v formic acid in H_2O (40:60, v/v)

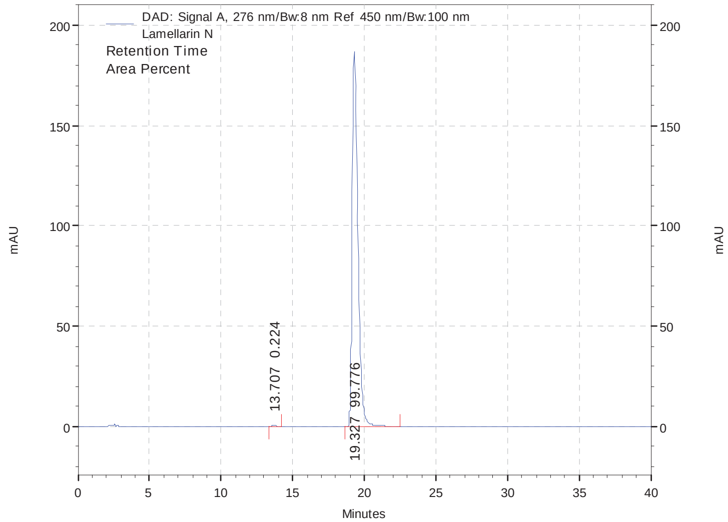


Lamellarin N (3)

MeOH/0.1% v/v formic acid in H_2O (75:25, v/v)

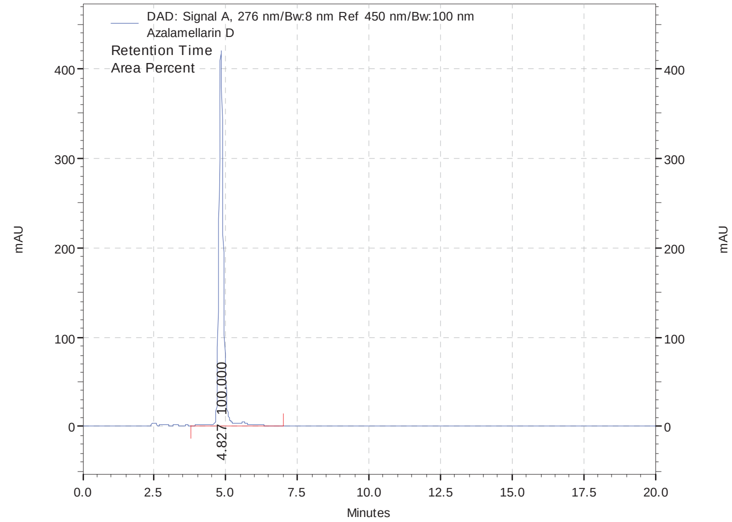


MeCN/0.1% v/v formic acid in H_2O (40:60, v/v)

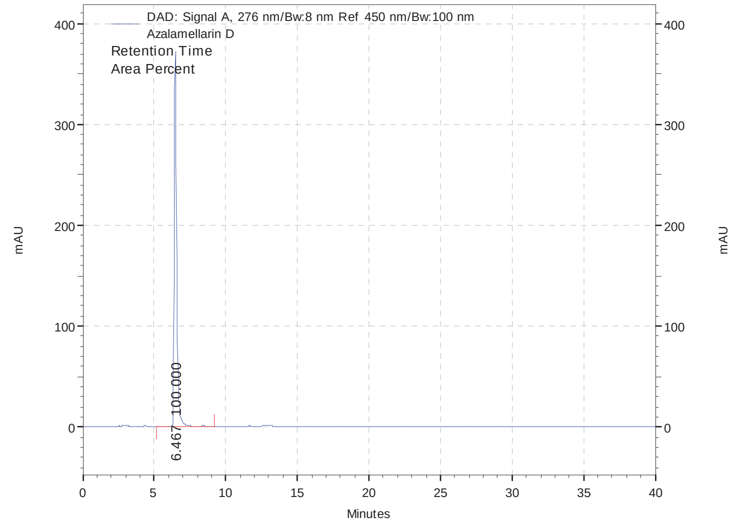


Azalamellarin D (4)

MeOH/0.1% v/v formic acid in H_2O (75:25, v/v)



MeCN/0.1% v/v formic acid in H_2O (40:60, v/v)



Azalamellarin N (5)

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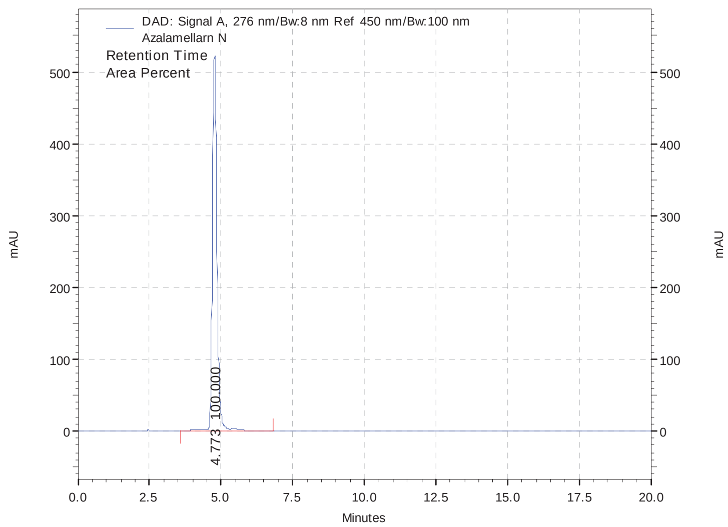


MeCN/0.1% v/v formic acid in H_2O (40:60, v/v)

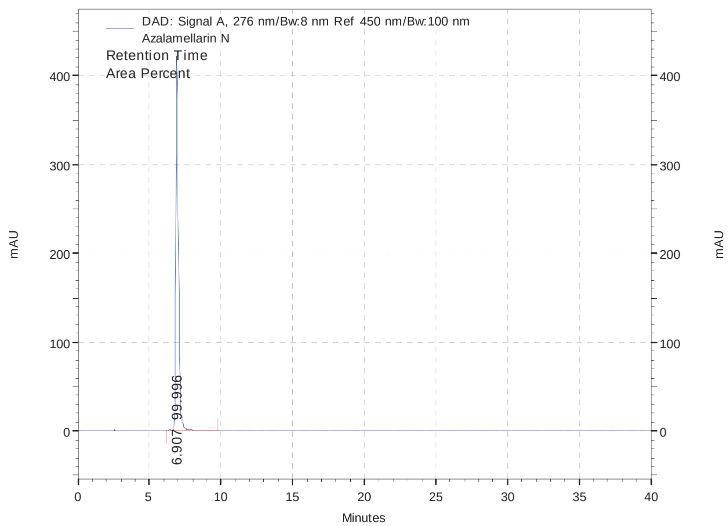
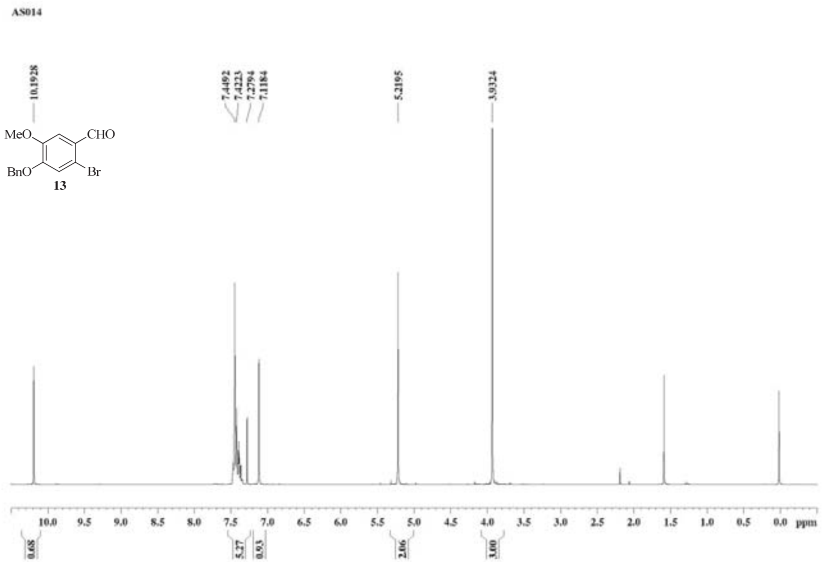


Table S3. Source and culture medium used for propagation of each cell line

Cell Line	Source	Culture Medium
A549	Human non-small cell lung carcinoma (ATCC® CCL-185™)	Ham's F-12 medium supplemented with 10% FBS, 2 mM L-glutamine, and 100 U mL^{-1} penicillin-streptomycin
HepG2	Human hepatocellular carcinoma (ATCC® HB-8065™)	DMEM supplemented with 10% FBS and 100 U mL^{-1} penicillin-streptomycin
HuCCA-1	Human cholangiocarcinoma (Laboratory of Immunology, Chulabhorn Research Institute, Bangkok, Thailand)	Ham's F-12 medium supplemented with 10% FBS, 2 mL L-glutamine, and 100 U mL^{-1} penicillin-streptomycin
MOLT-3	Human acute T-lymphoblastic leukemia (ATCC® CRL-1552™)	RPMI 1640 medium supplemented with 10% FBS, 4.5 g L^{-1} glucose, 1 mM sodium pyruvate, 2 mM L-glutamine, and 100 U mL^{-1} penicillin-streptomycin
MRC-5	Human fetal/embryonic lung fibroblast (ATCC® CCL-171™)	DMEM supplemented with 10% FBS and 100 U mL^{-1} penicillin-streptomycin

ATCC = American Type Culture Collection, DMEM = Dulbecco's Modified Eagle Medium, FBS = fetal bovine serum, RPMI = Roswell Park Memorial Institute.

^{1}H NMR (300 MHz, $CDCl_3$)



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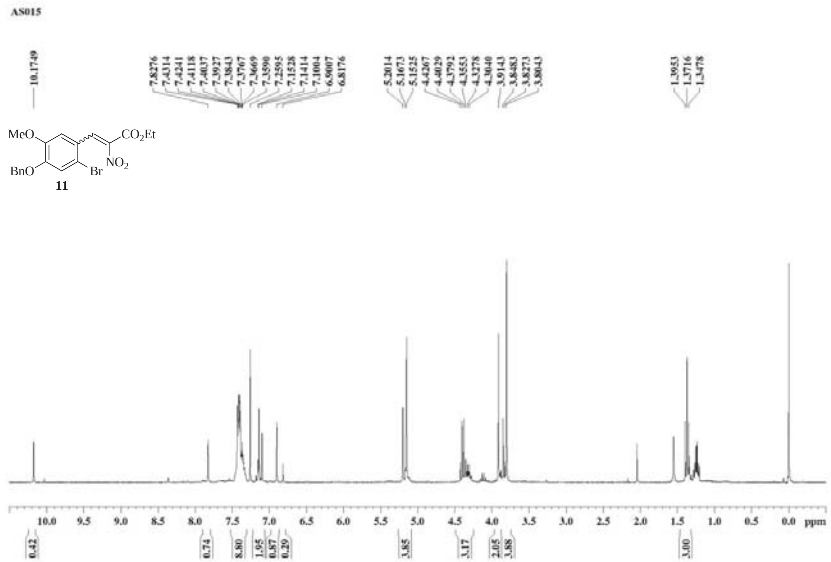

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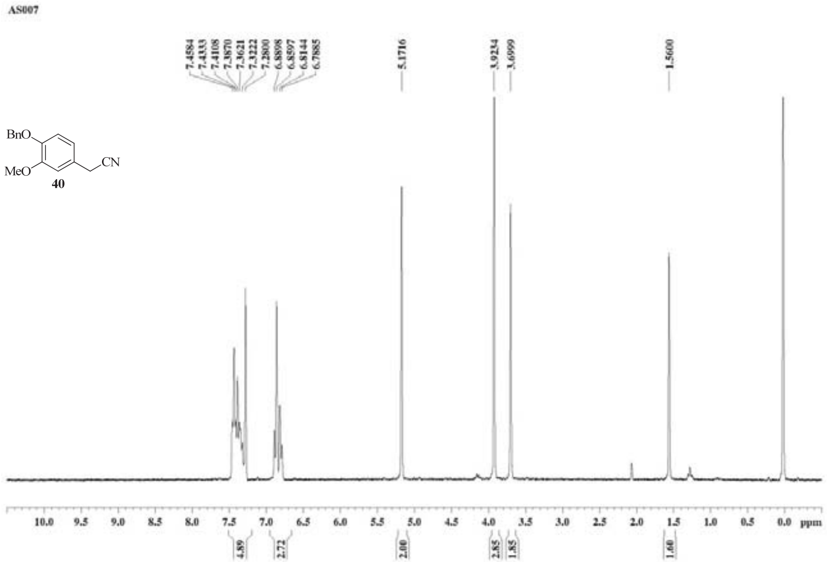

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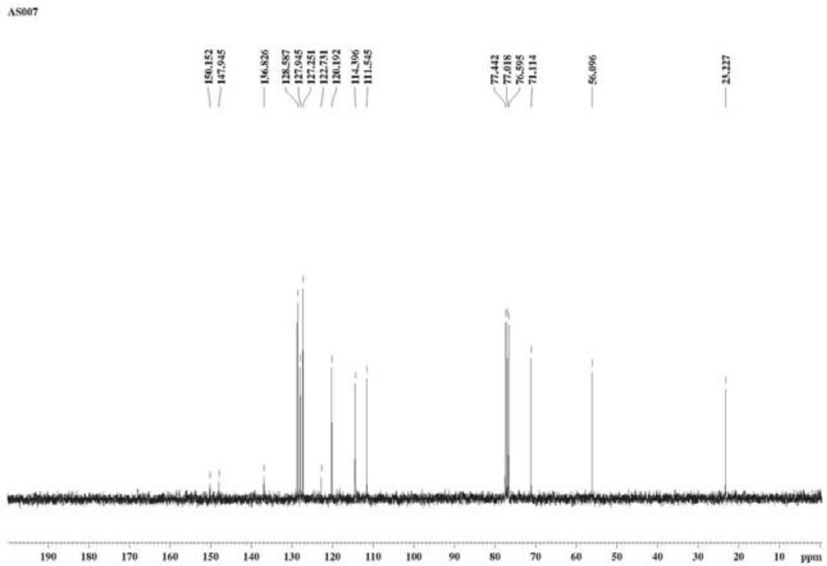

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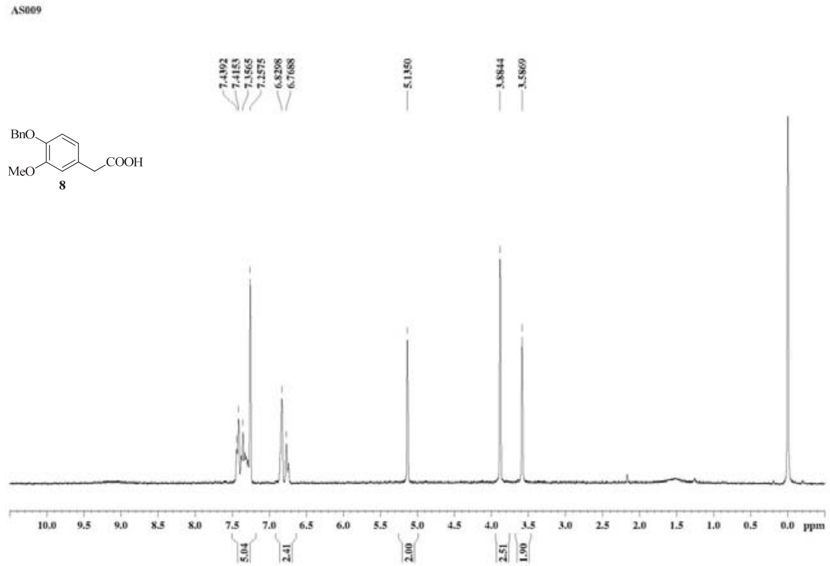

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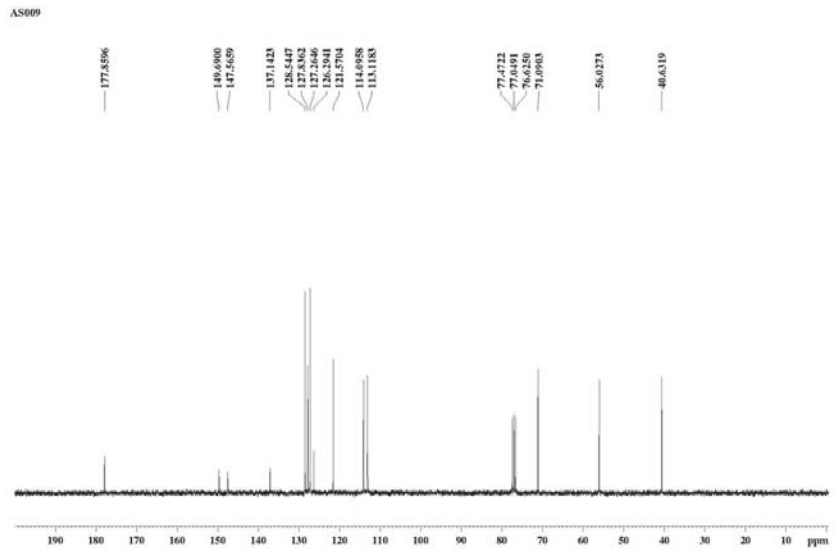

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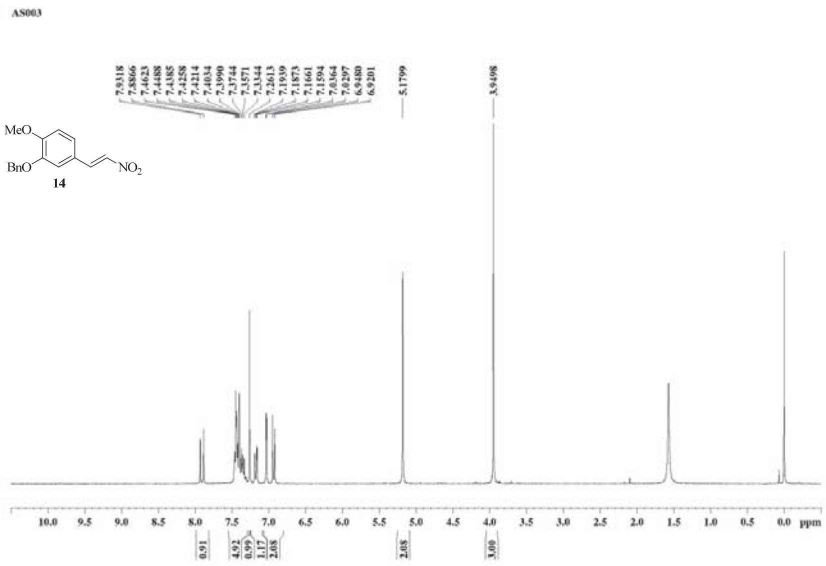

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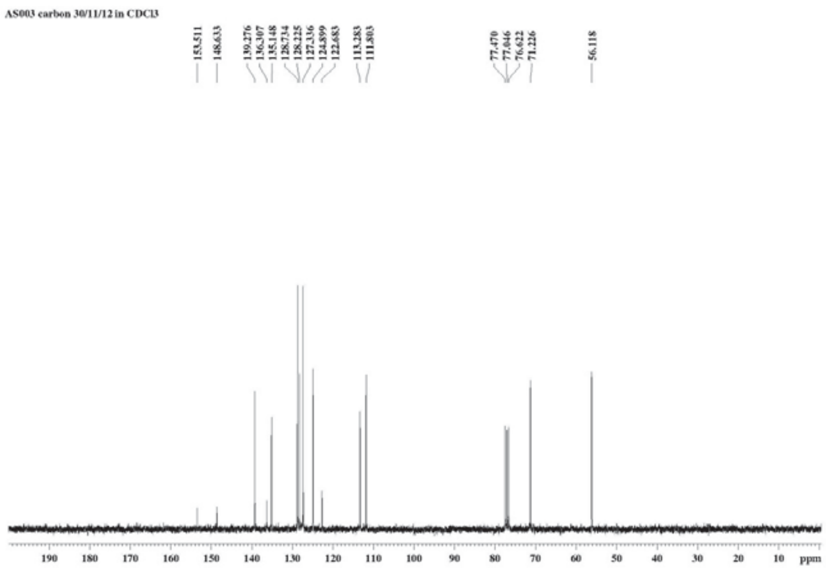

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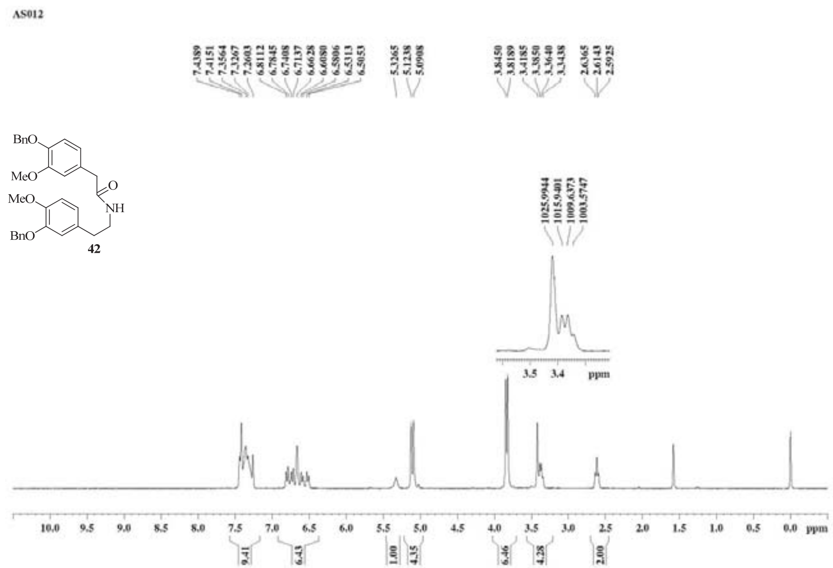

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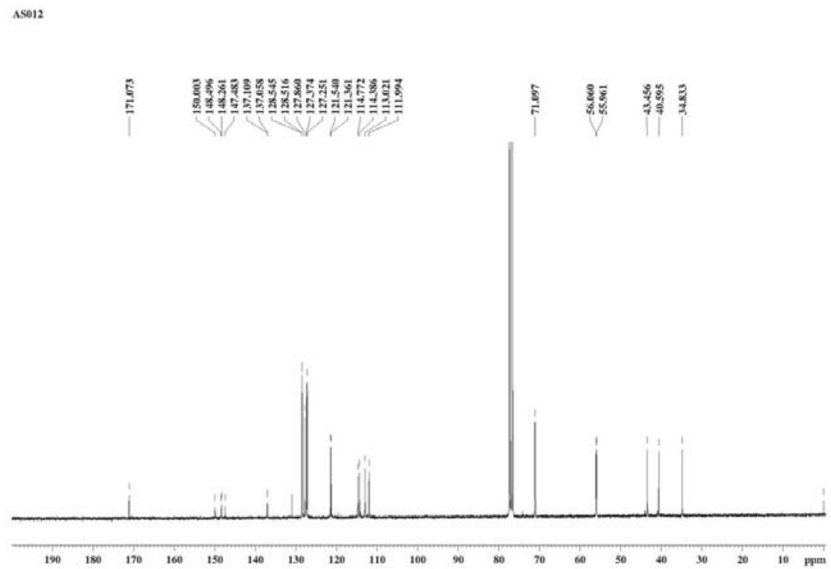

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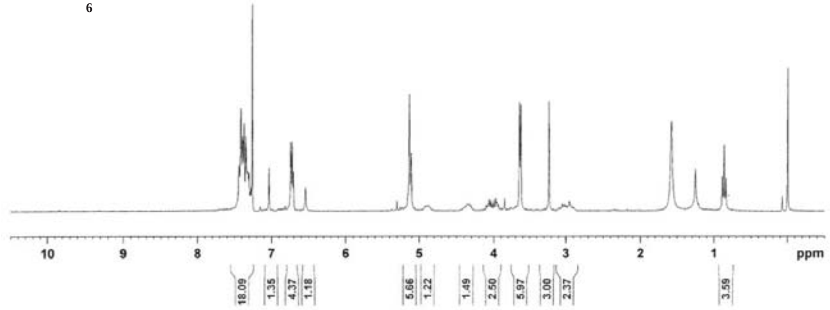

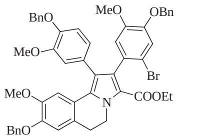

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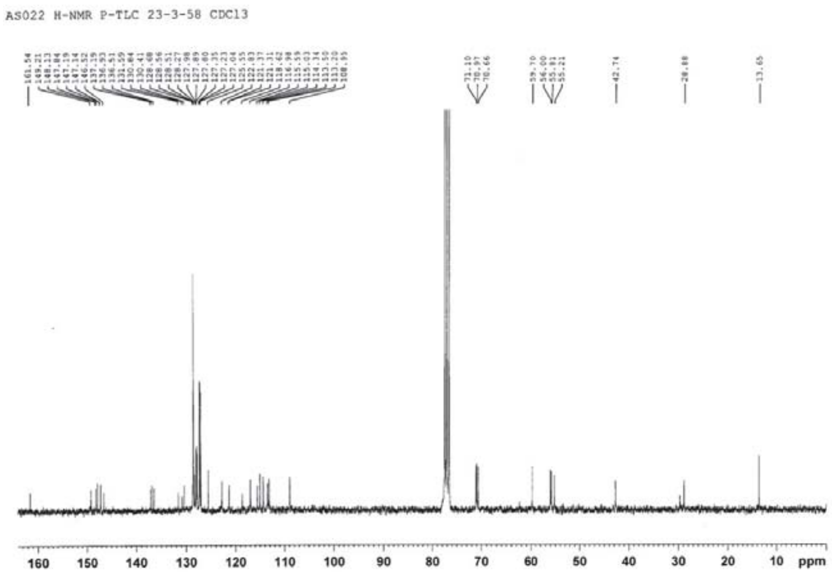

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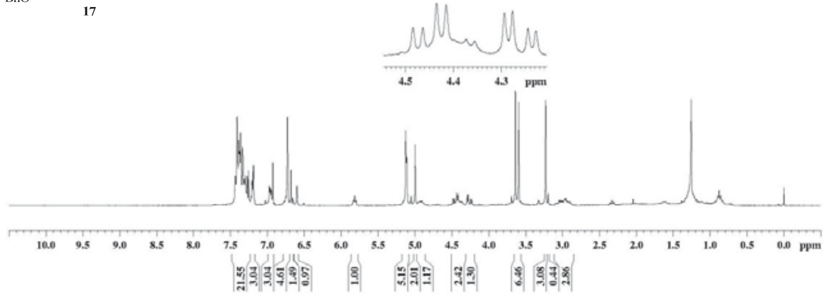

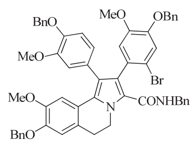

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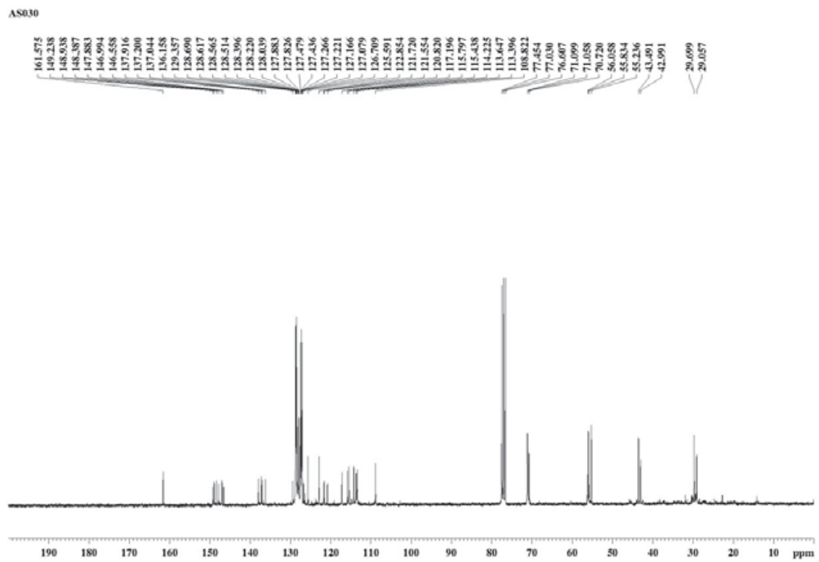

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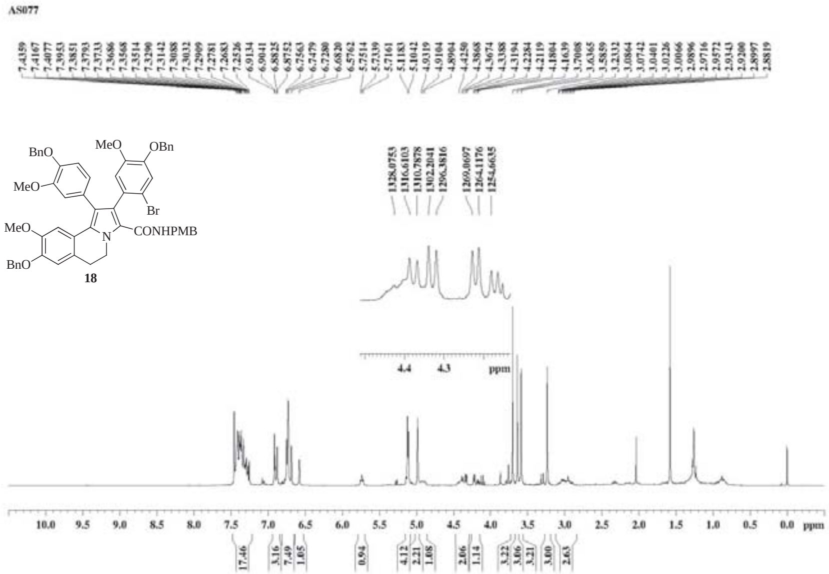

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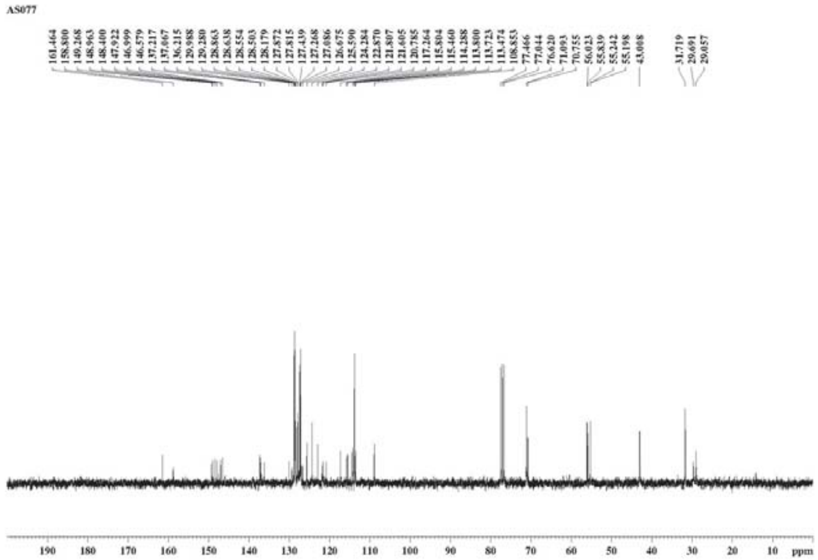

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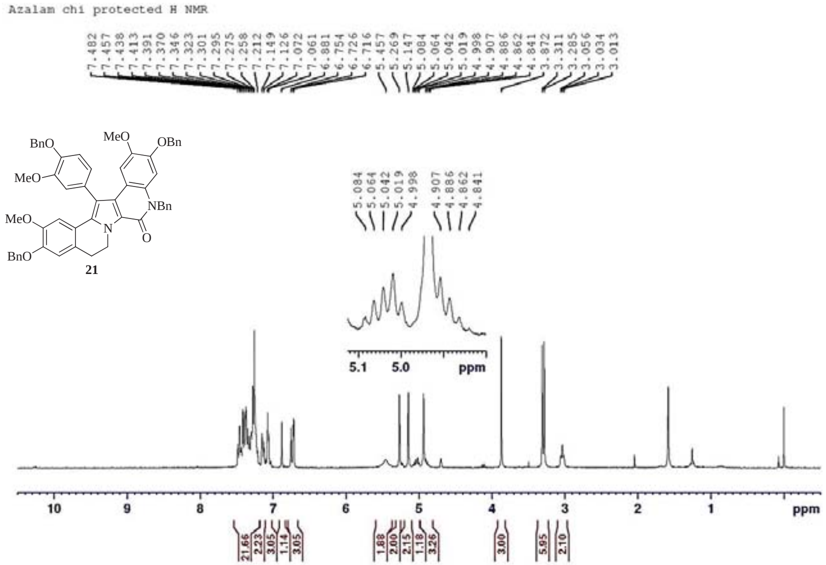

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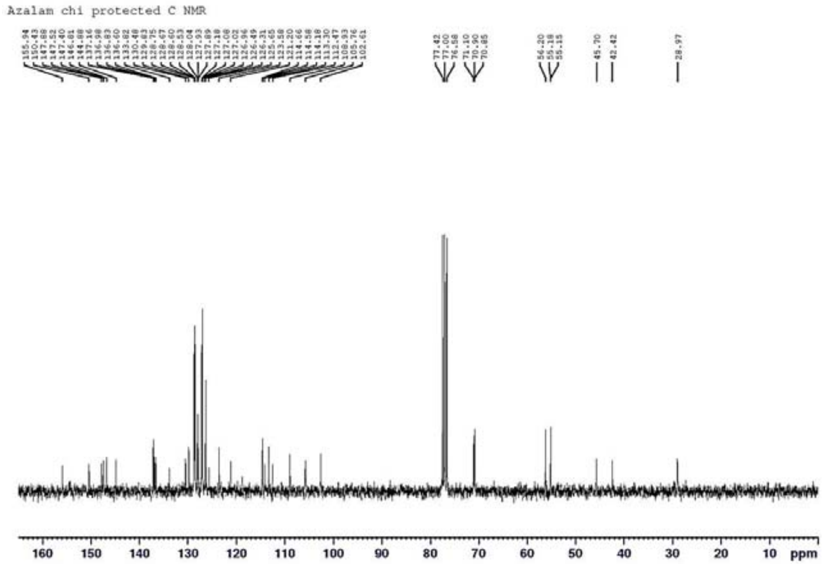

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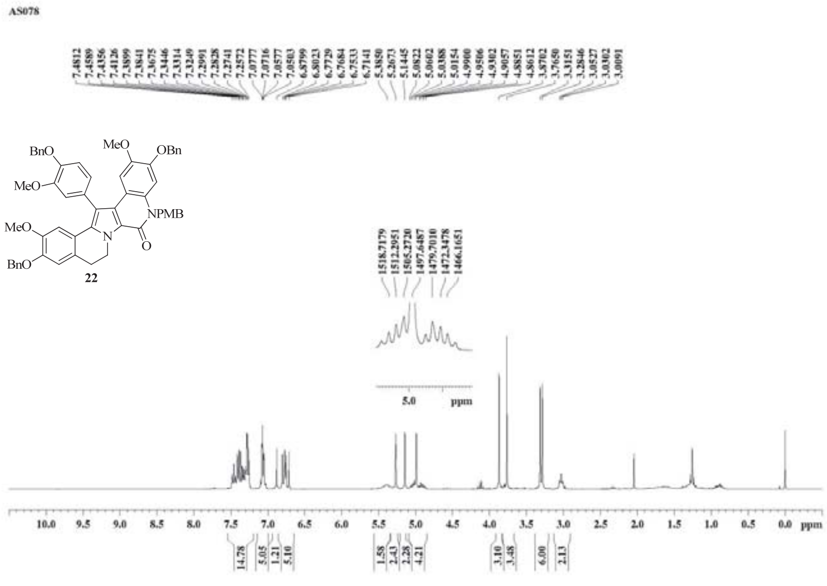

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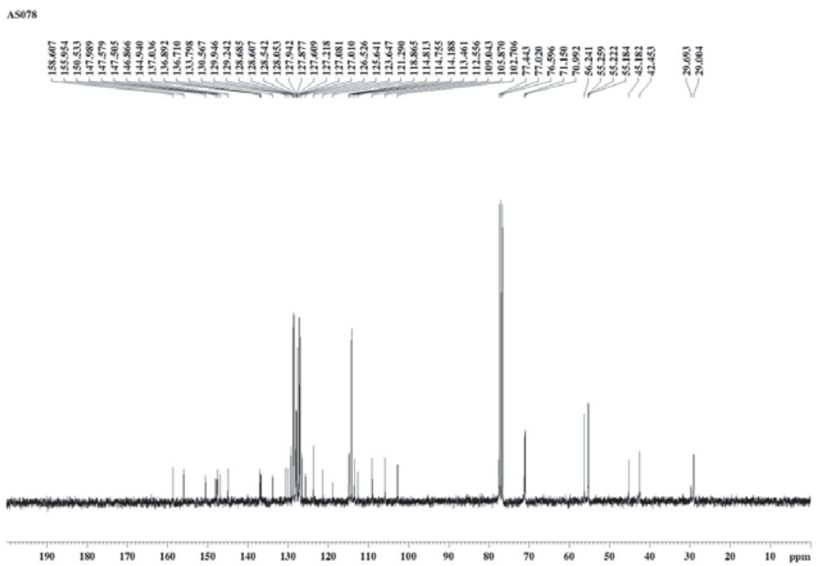

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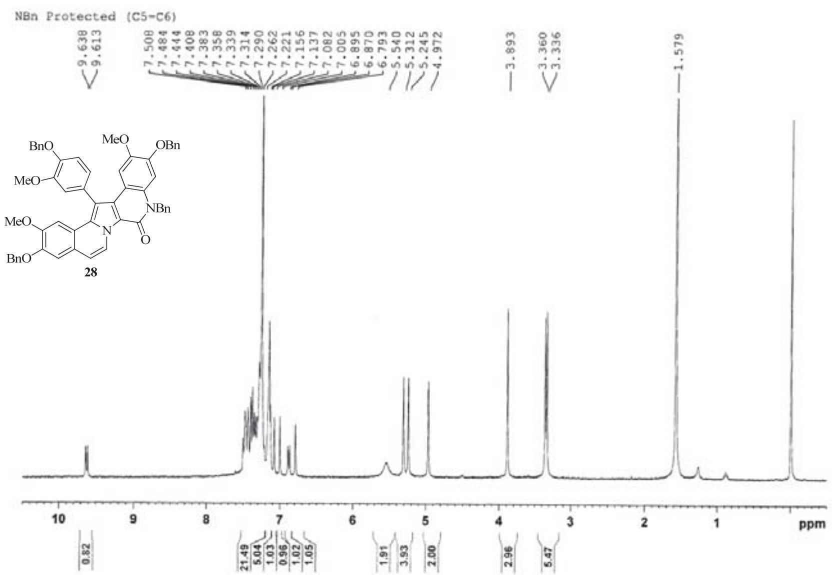

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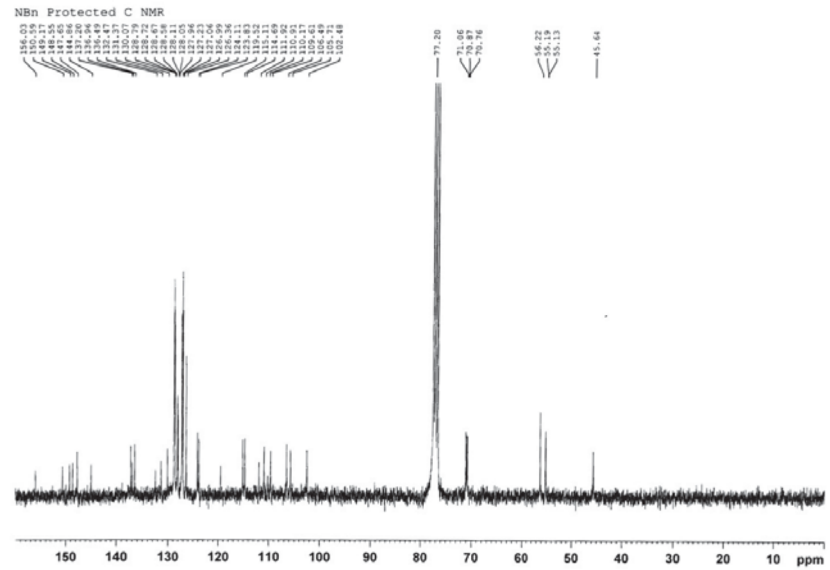

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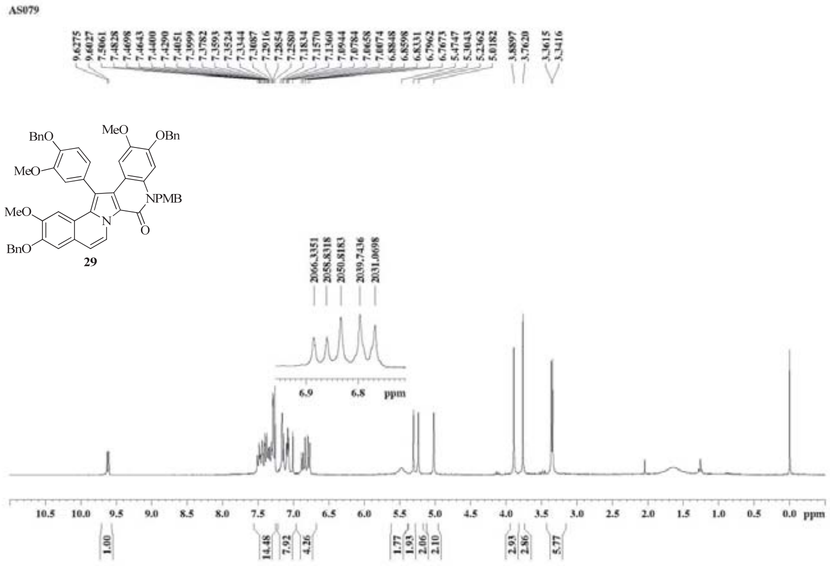

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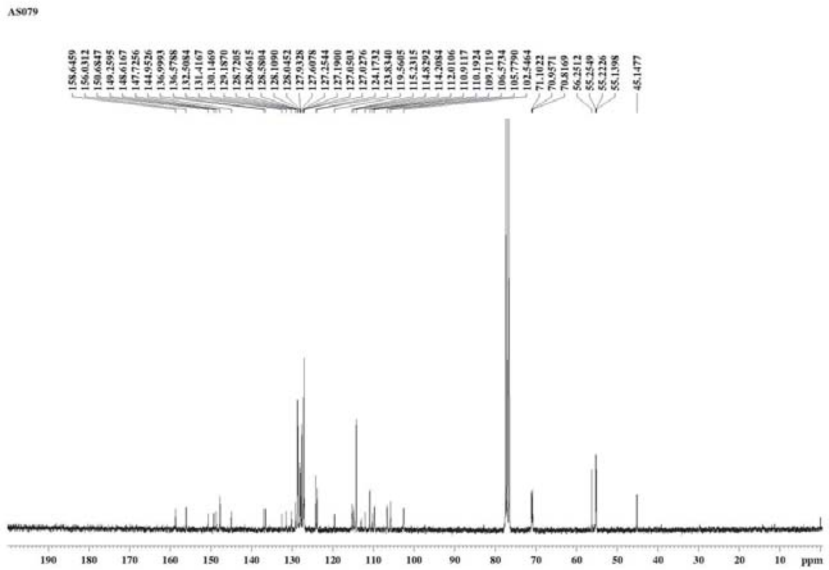

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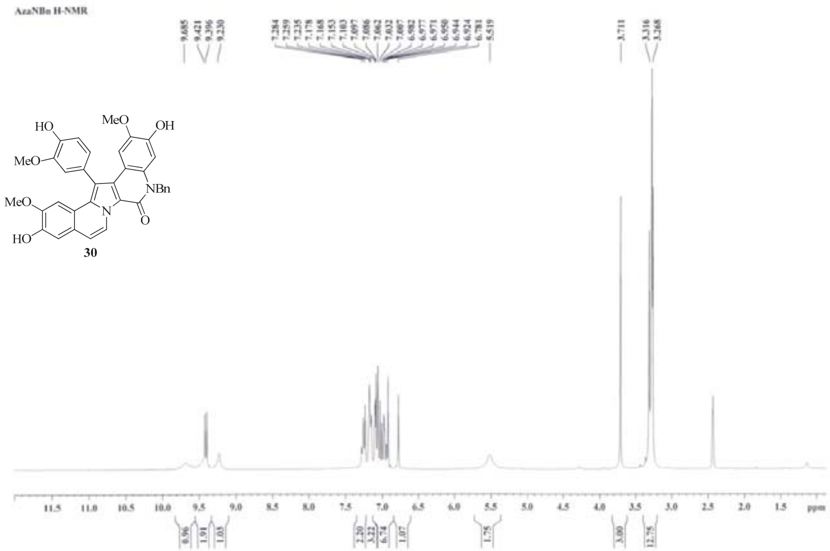

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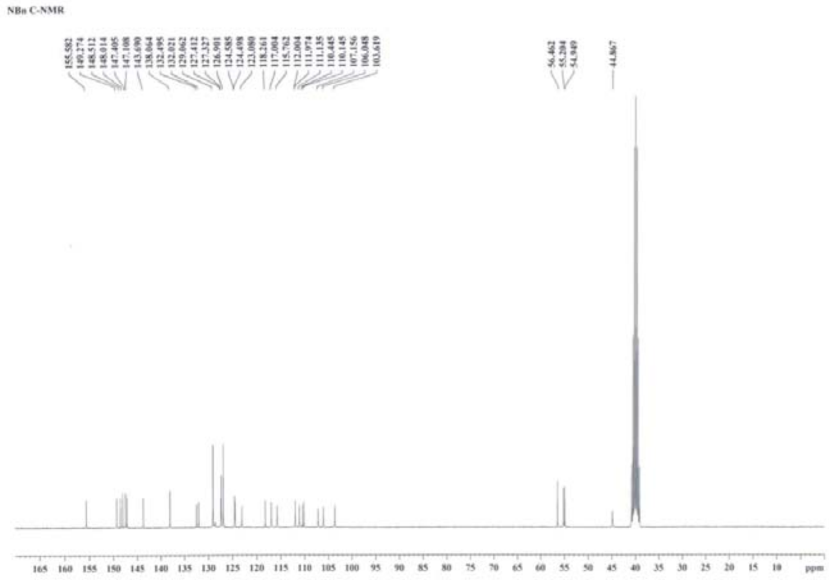

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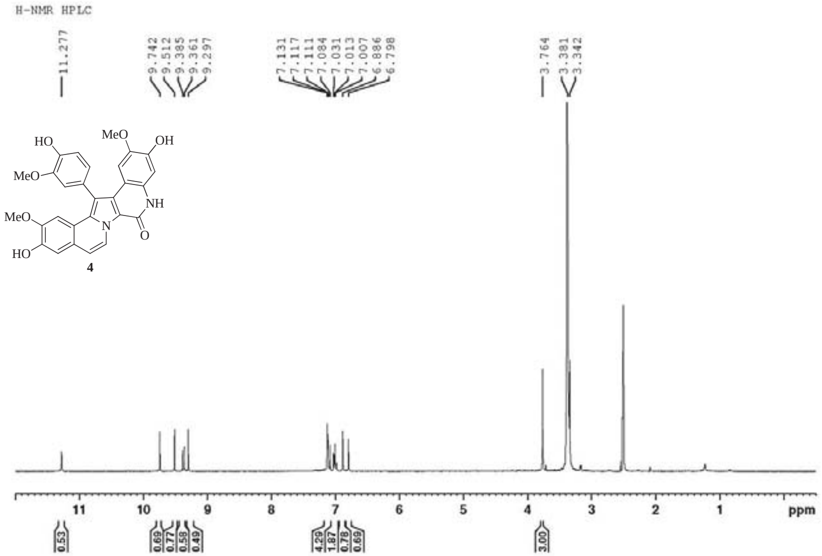

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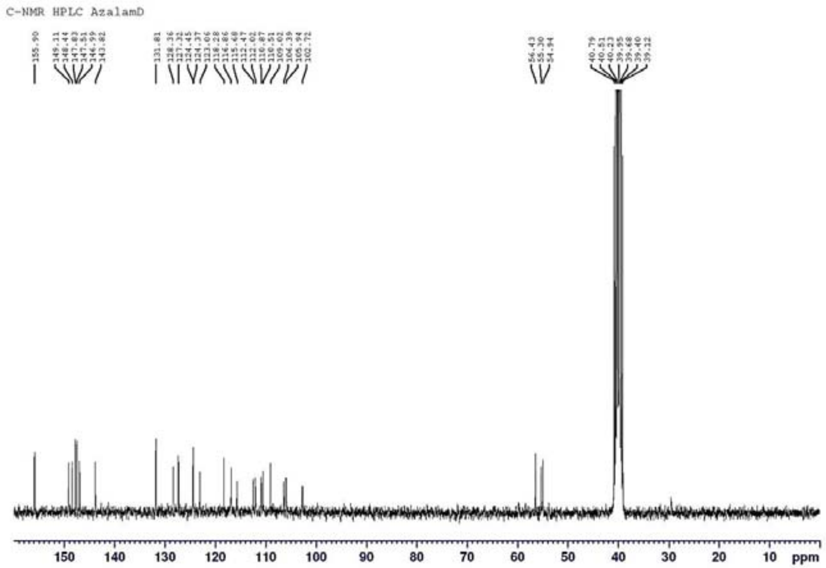

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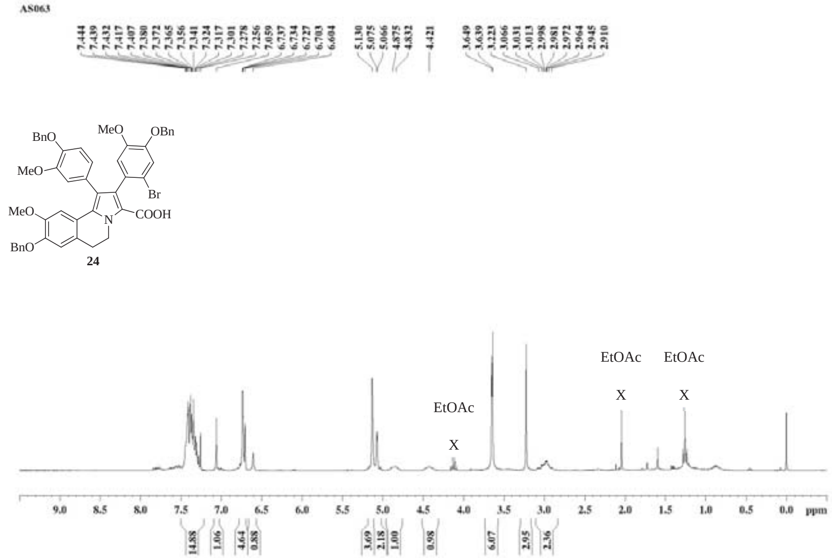
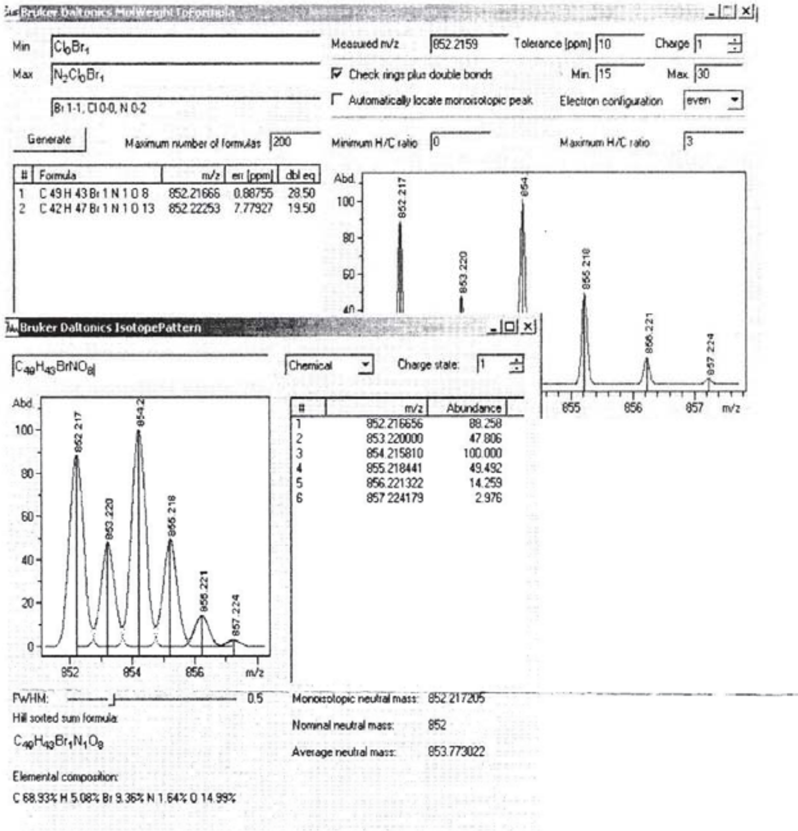


ESI-TOF [M+H$^+$] for Compound 24



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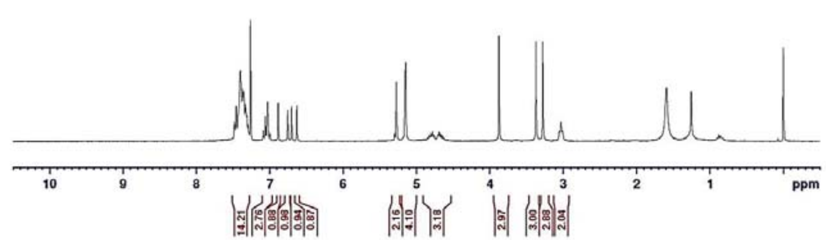

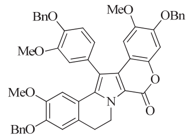

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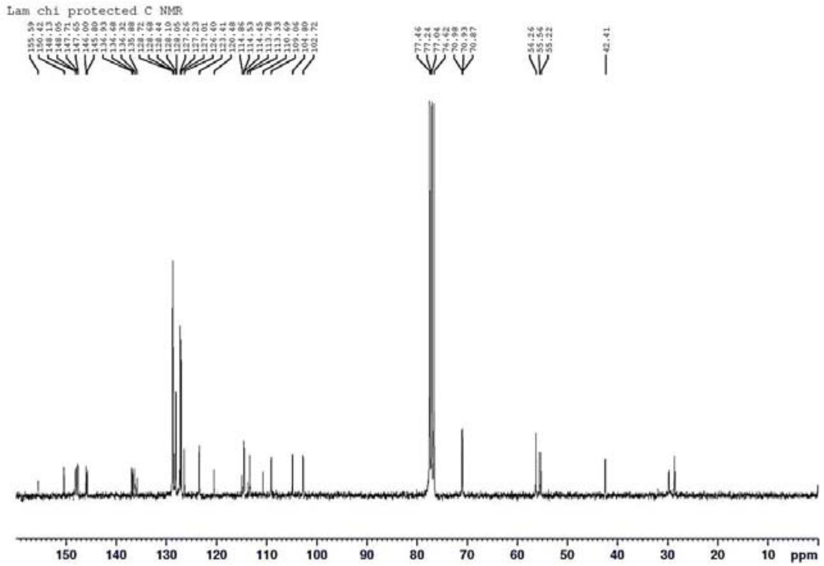
^{13}C NMR (75 MHz, CDCl$_3$)



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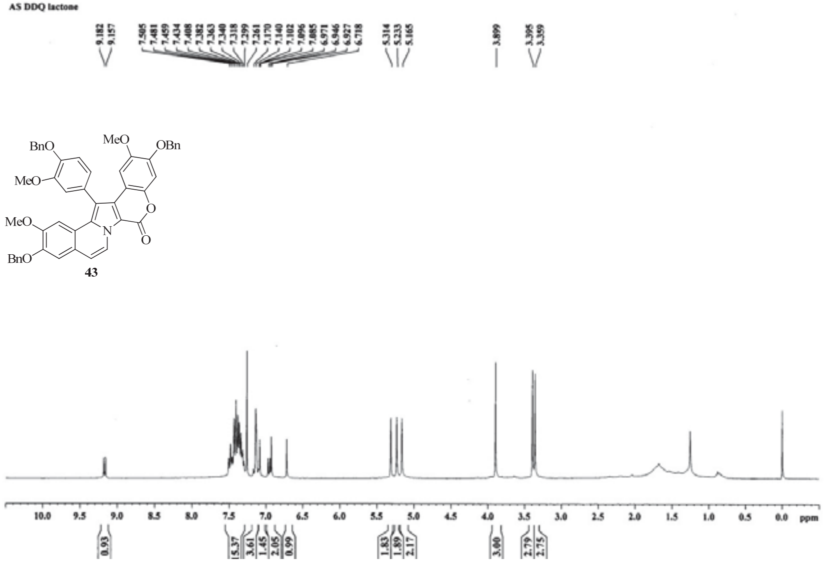

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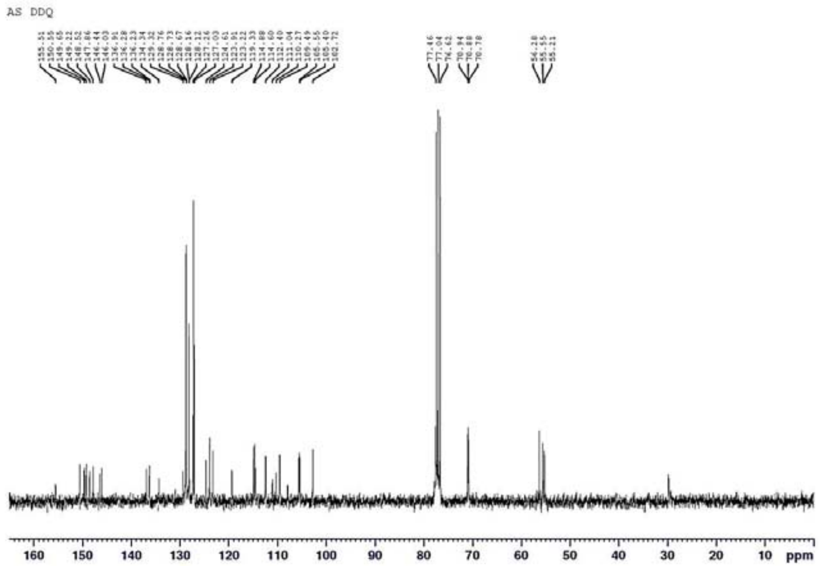

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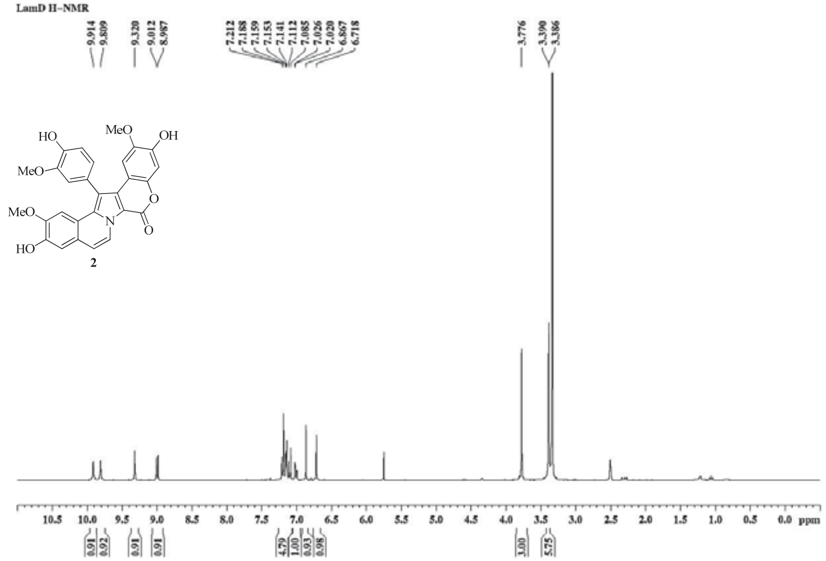

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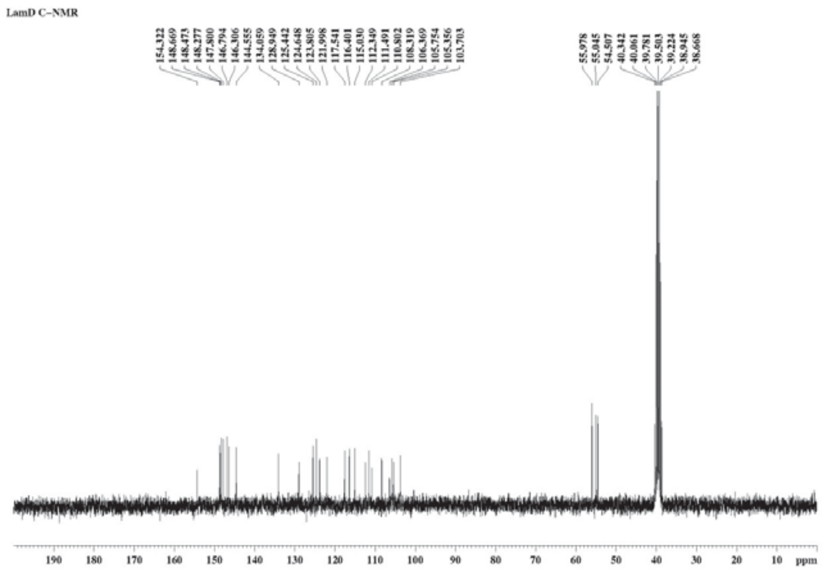

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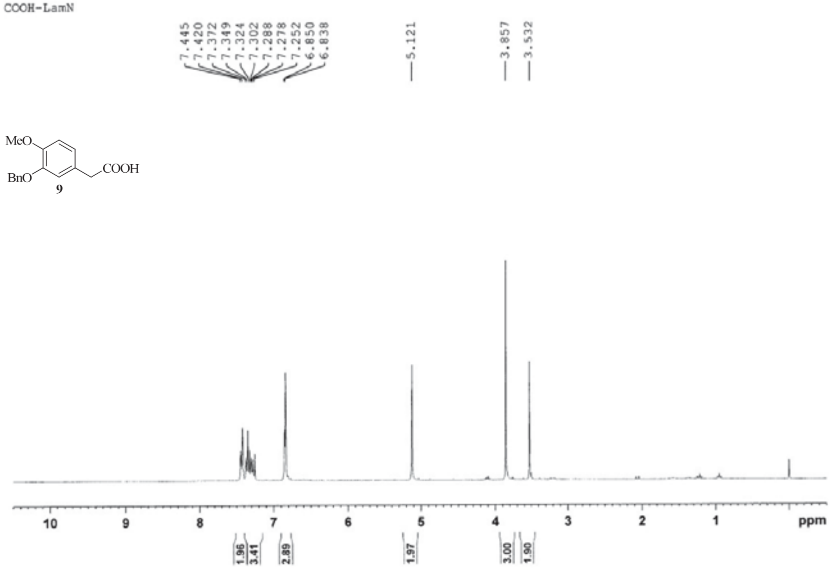

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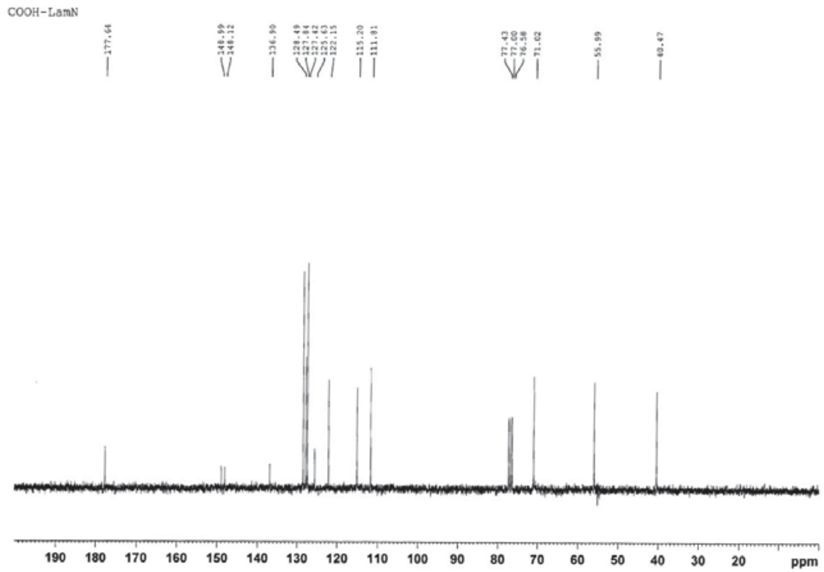

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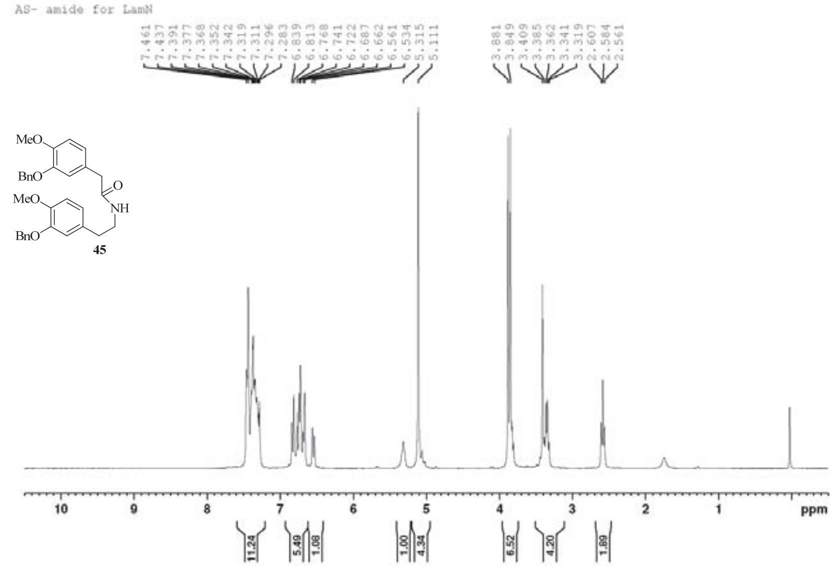

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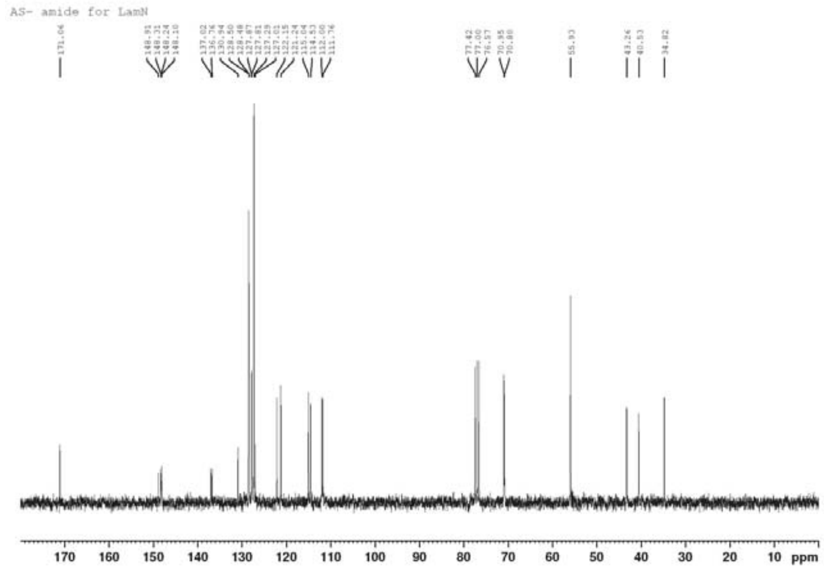

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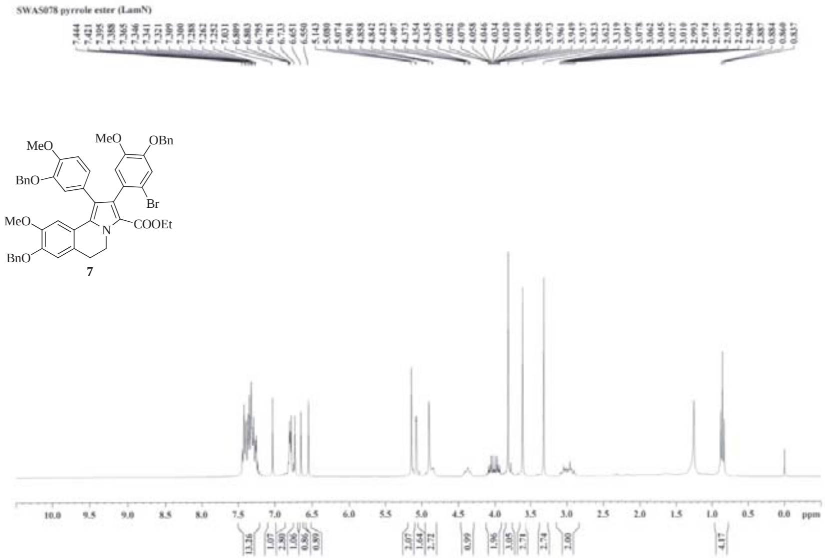

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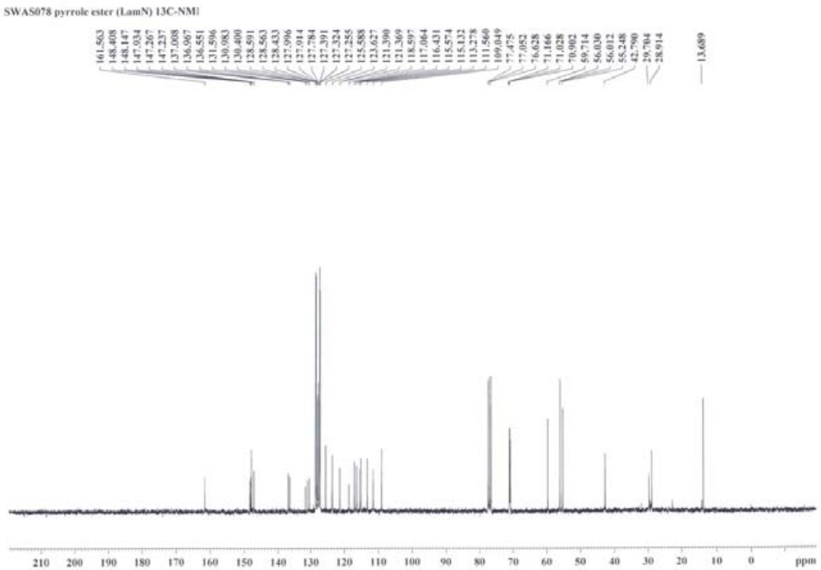

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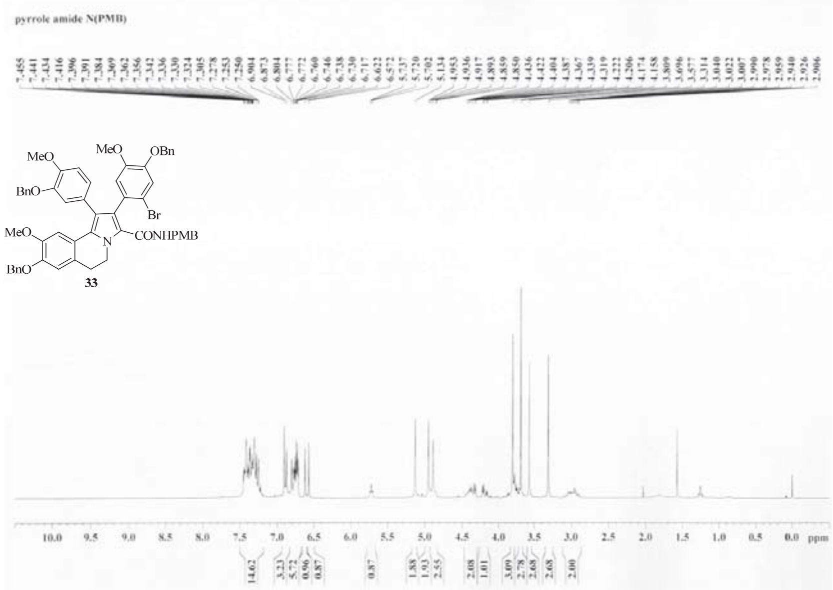
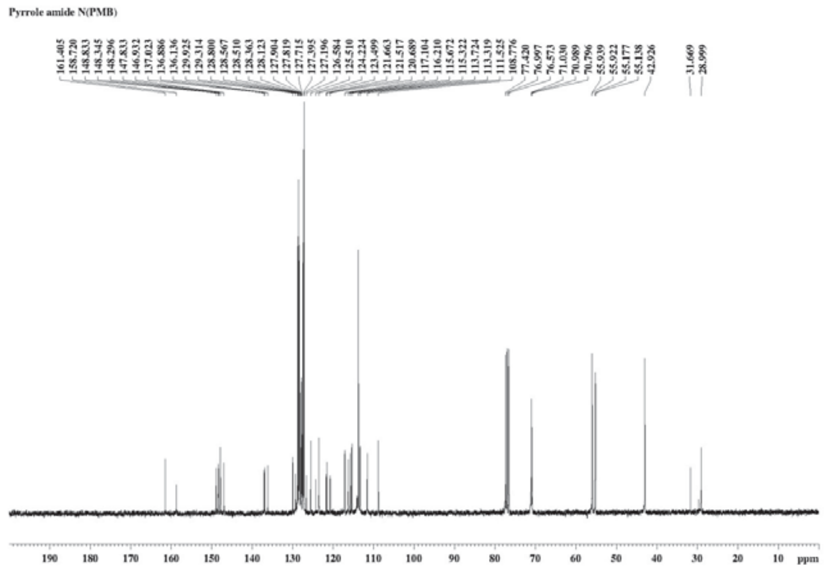


33

^{13}C NMR (75 MHz, $CDCl_3$)



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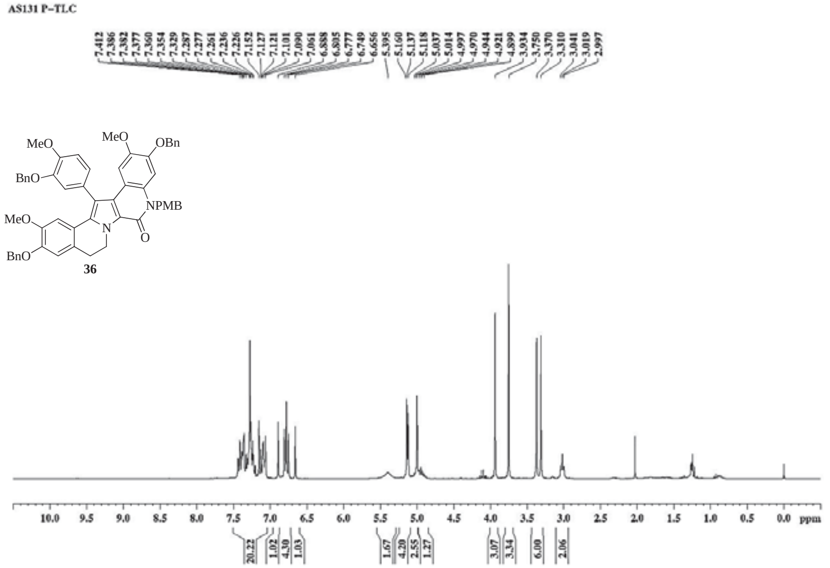

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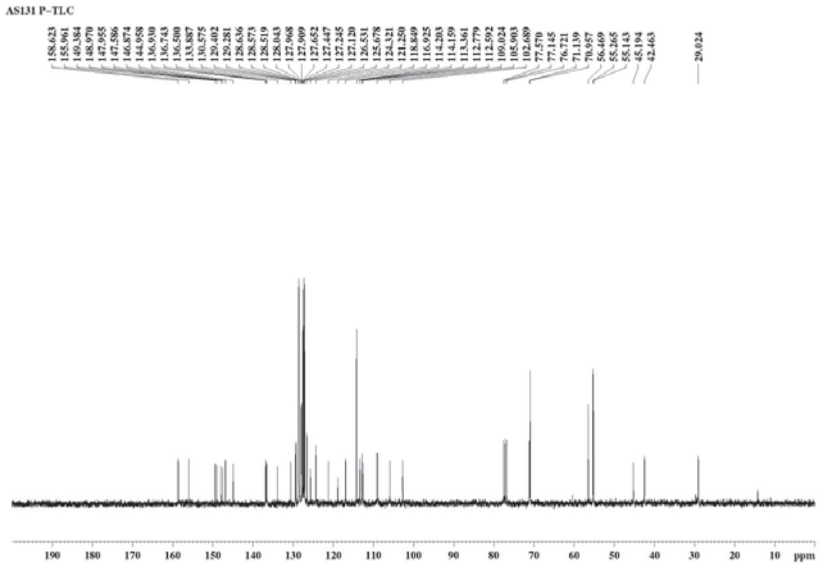

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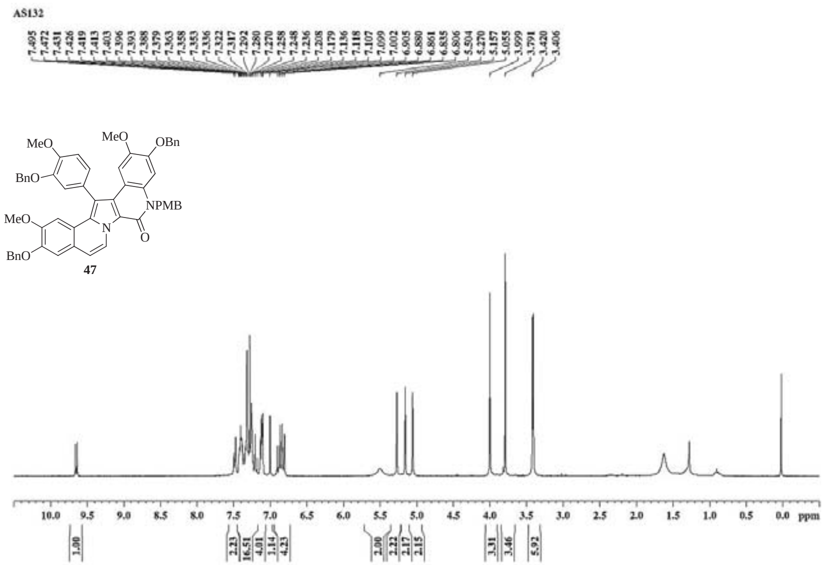
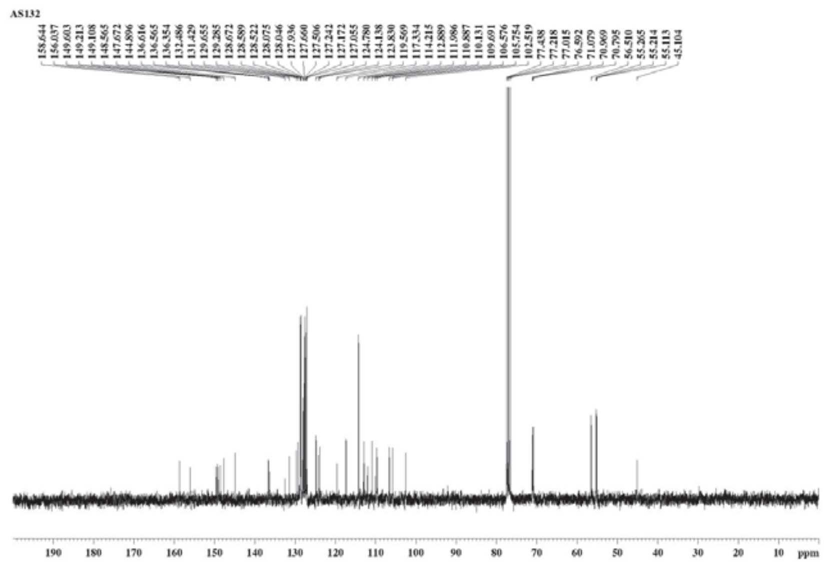
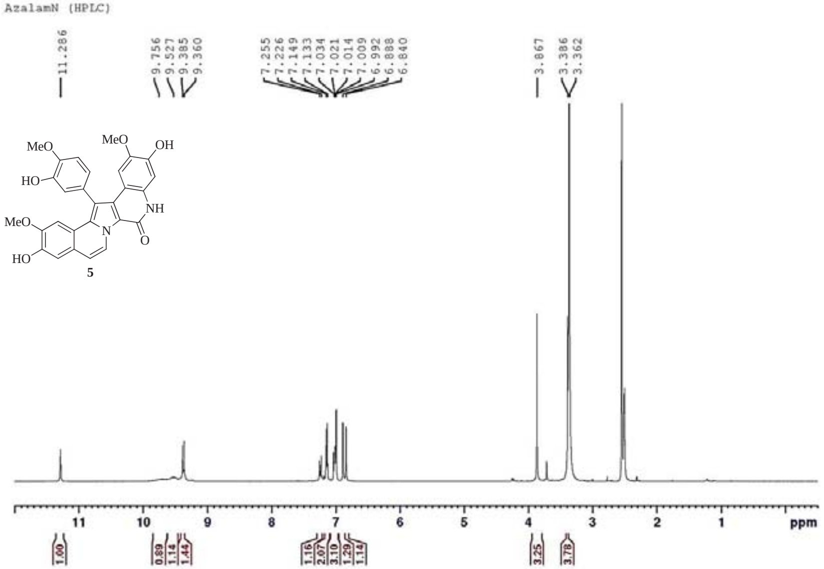


[13]C NMR (75 MHz, $CDCl_3$)



^{1}H NMR (300 MHz, DMSO-d_6)



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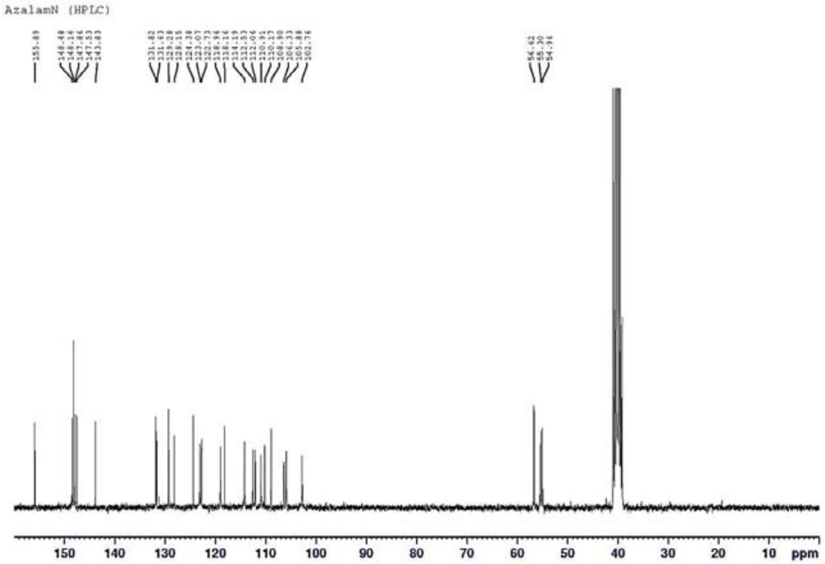

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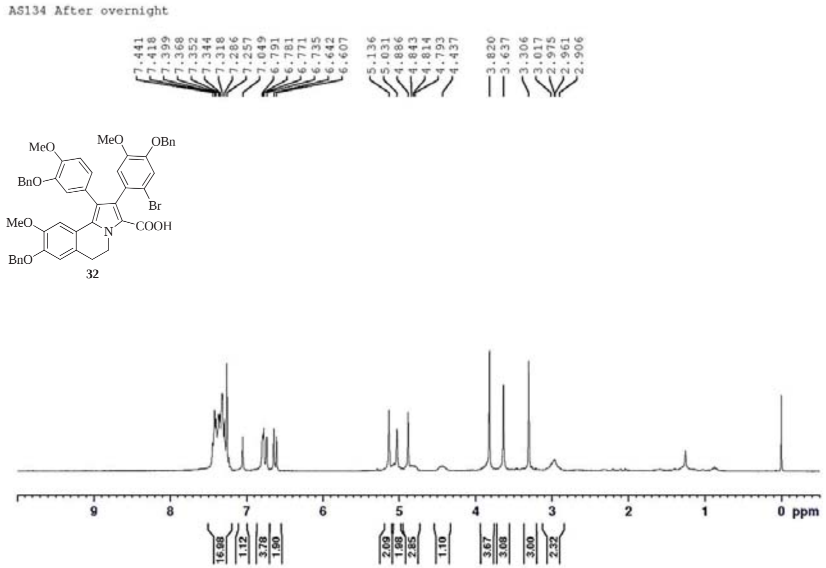
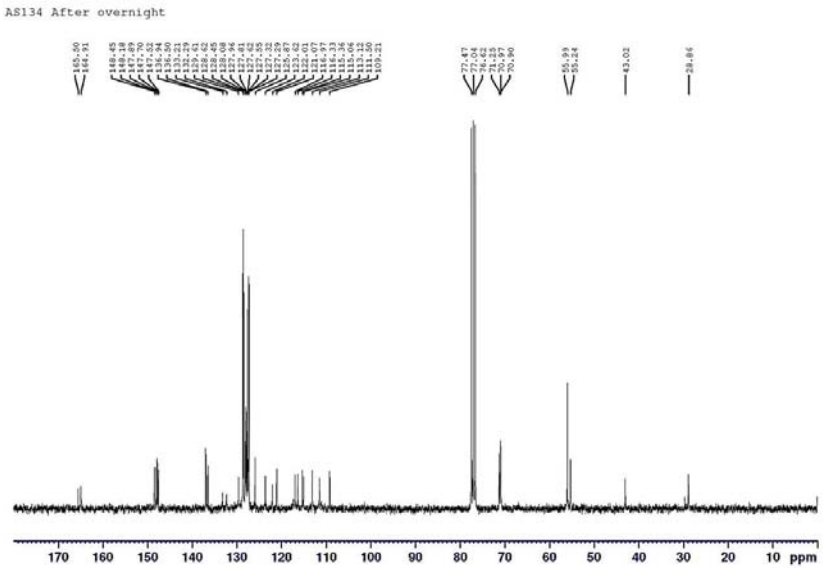
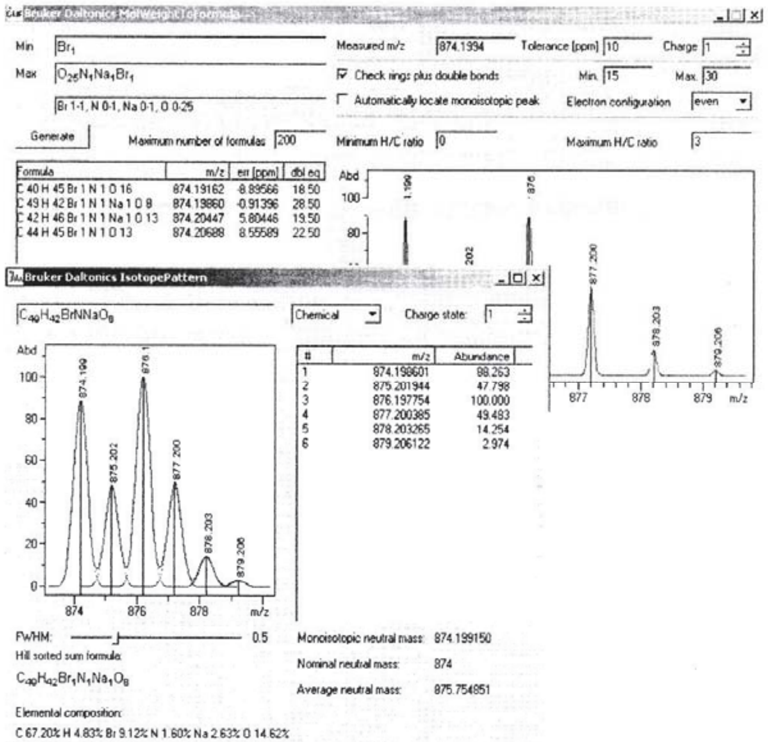


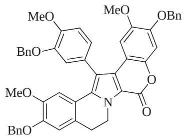
^{13}C NMR (75 MHz, $CDCl_3$)



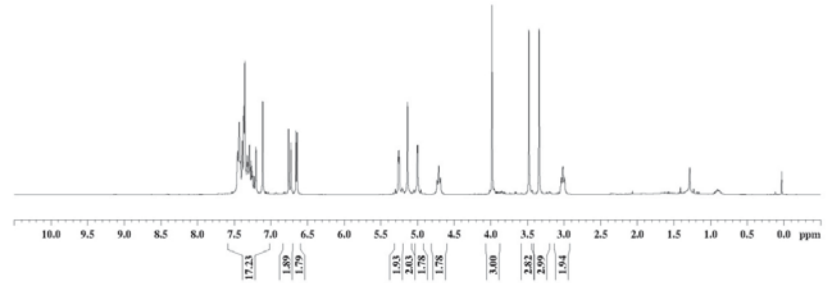
ESI-TOF [*M*+Na[+]] for Compound 32



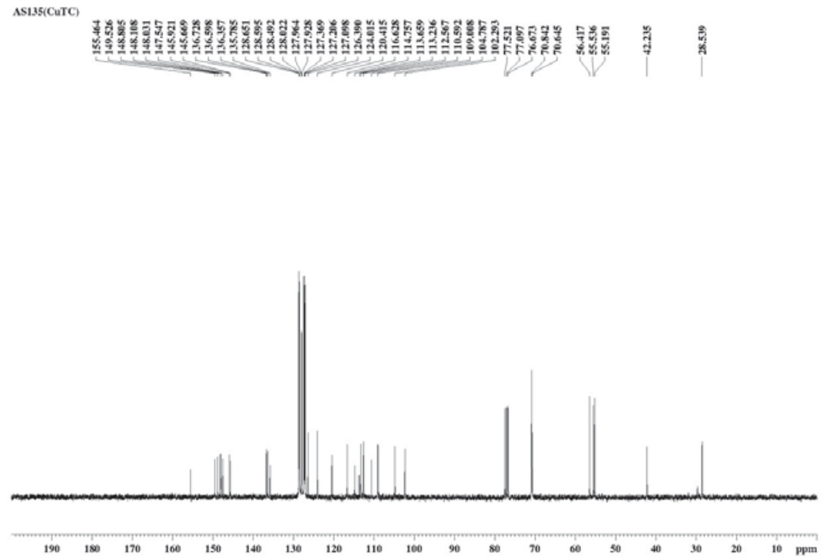
[1]H NMR (300 MHz, $CDCl_3$)



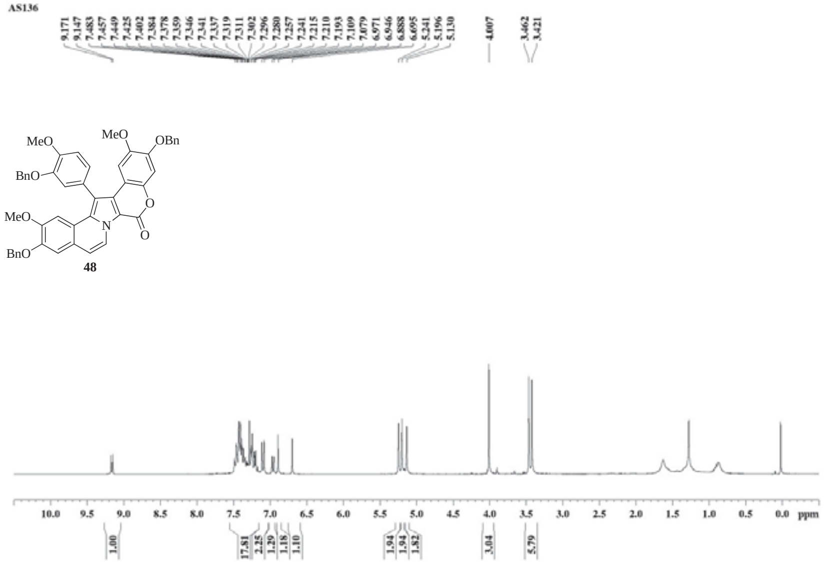
35



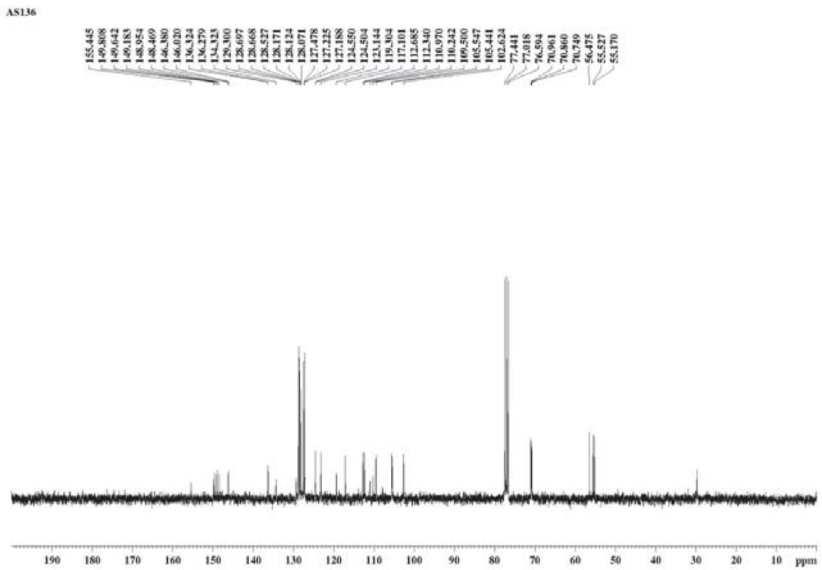
[13]C NMR (75 MHz, $CDCl_3$)



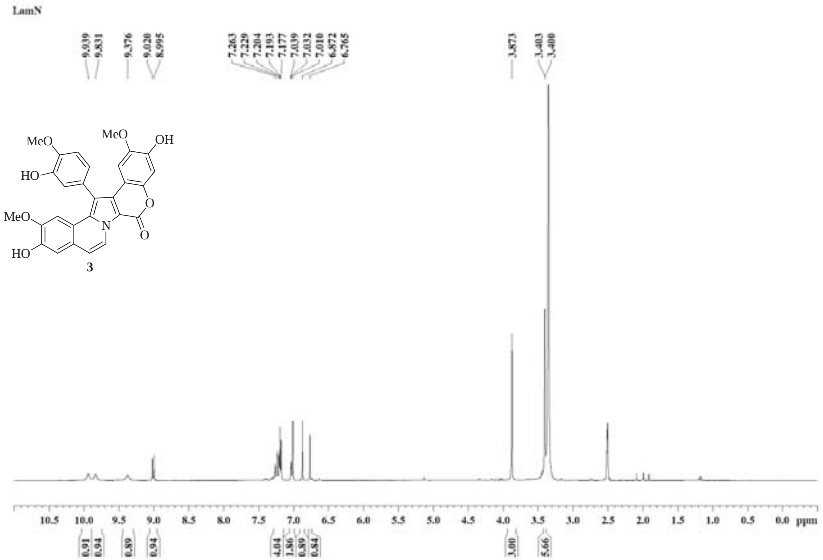
^{1}H NMR (300 MHz, $CDCl_3$)



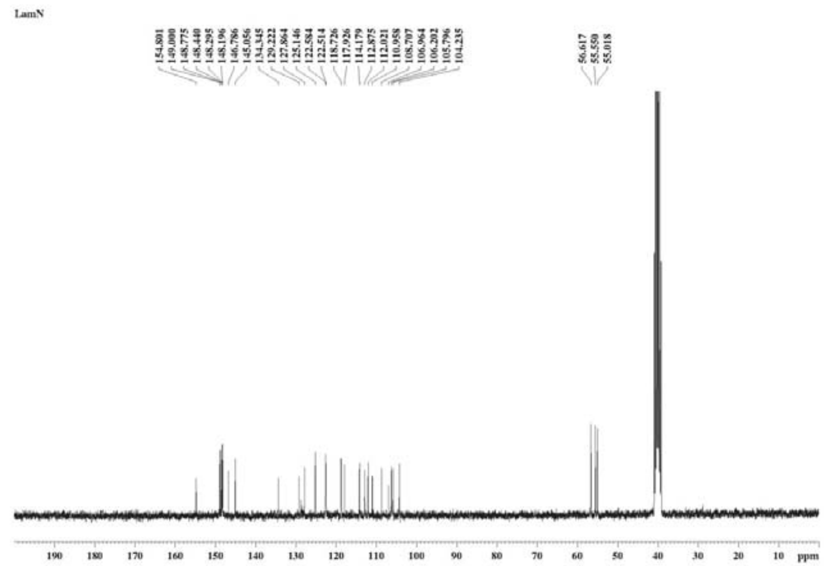
^{13}C NMR (75 MHz, $CDCl_3$)



^{1}H NMR (300 MHz, DMSO-d_6)



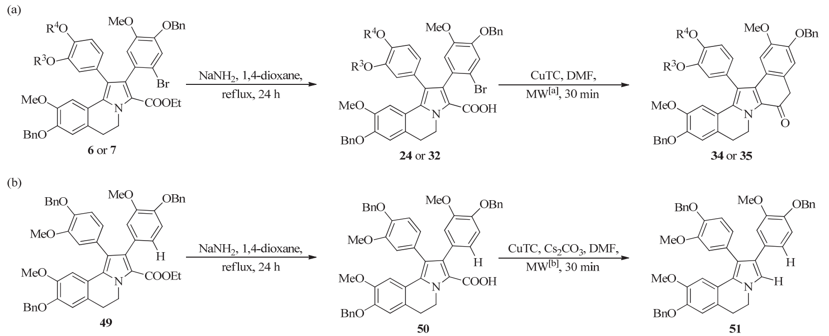
^{13}C NMR (75 MHz, DMSO-d_6)



CuTC-mediated Lactonization *vs*. Decarboxylation

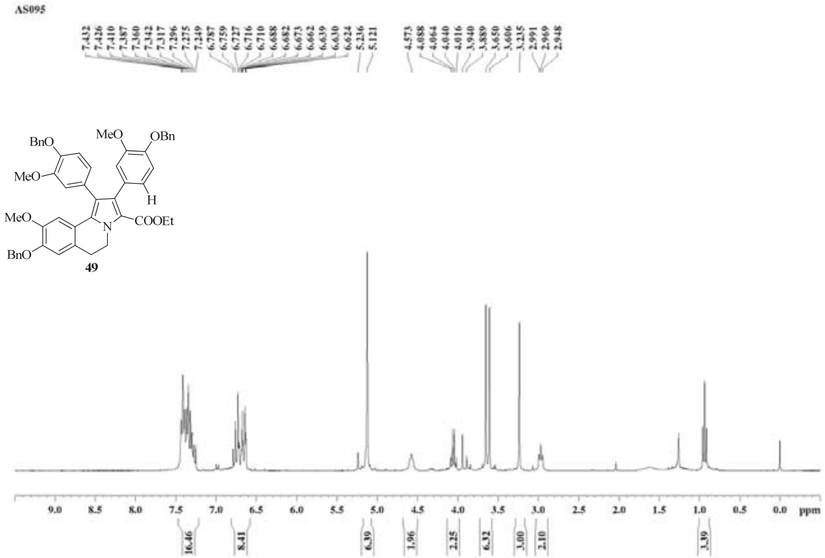
Spectroscopic data, especially ^{1}H and mass spectra, of both **24** and **32** led to the assignment of their structures. Upon comparing some characteristic chemical shifts of the aromatic methoxy protons (on C9 and C13 or C14), as well as those of the methylene protons alpha to the pyrrole nitrogen (on C5) between the uncyclized pyrrole esters (*e.g.*, **6** or **7**) and cyclized pyrrole lactones (*e.g.*, **34** or **35**), it can be confirmed that the intermediates **24** and **32** remained uncyclized. The mass spectra also clearly showed the presence of bromine atom in both **24** and **32**, eliminating any possible involvement of benzyne as intermediate which otherwise could, in principle, lead to the formation of the lactone **34** or **35** directly without the intermediacy of **24** or **32**. Thus, the structures of both **24** and **32** were postulated to be the corresponding carboxylic acids.

To the best of our knowledge, there have been no literature precedents on the conversion of an ethyl ester to the corresponding acid using $NaNH_2$ in refluxing 1,4-dioxane, and thus, the exact mechanism was not known. Nevertheless, in order to address the observed difference in the relative stability of these 2-pyrrole carboxylic acids, we decided to explore the conversion of pyrrole esters **6** and **49** to the corresponding acids **24** and **50** (Scheme S1), respectively, in the presence of either $NaNH_2$ or 5% NaOH in 1,4-dioxane. Under both reaction conditions, the pyrrole ester **6** gave the same intermediate which could be cyclized to form the lactone **34** *via* CuTC-mediated lactonization in good yields over 2 steps (66% using $NaNH_2$ and 46% using NaOH in 1,4-dioxane). Similarly, when **49** was reacted with $NaNH_2$ (Scheme S1), presumably the corresponding carboxylic acid **50** was obtained as evident by its IR and mass spectra (see below). Due to the anticipated labile nature of this intermediate, **50** was immediately subjected to the subsequent CuTC-mediated reaction to affect the lactonization. However, only the decarboxylated by-product **51**, as characterized by its ^{1}H, IR, and mass spectra (see below), was obtained in low 20% yield over 2 steps. Thus, without the bromine atom, the pyrrole carboxylic acid **50** underwent CuTC-mediated decarboxylation instead of the desired lactonization. These observations suggested that, it is the presence or absence of the bromine atom on the substrate, rather than the reaction condition, which governs and contributes primarily to not only the stability of the resulting acid, but also the course of the subsequent CuTC-mediated reactions (lactonization *vs*. decarboxylation).

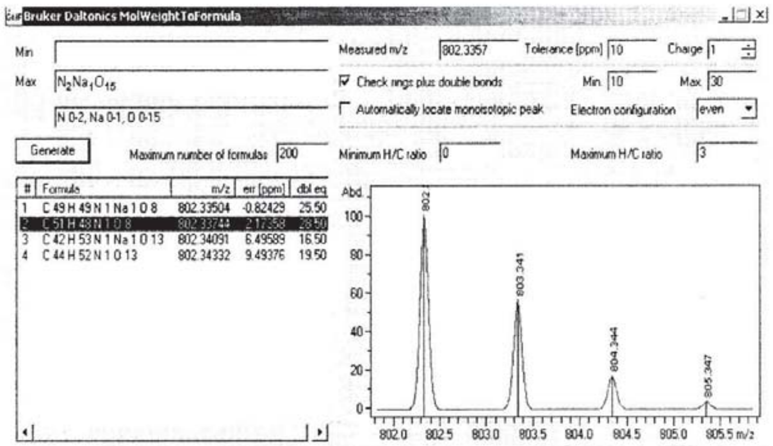


Scheme S1. CuTC-mediated lactonization *vs*. decarboxylation of pyrrole carboxylic acids **24**, **32**, and **50** to their corresponding products. [a] 200 W, 150 °C, 100 psi. [b] 200 W, 120 °C, 100 psi. For compounds **6**, **24**, and **34**, R^3 = Me; R^4 = Bn. For compounds **7**, **32**, and **35**, R^3 = Bn; R^4 = Me.

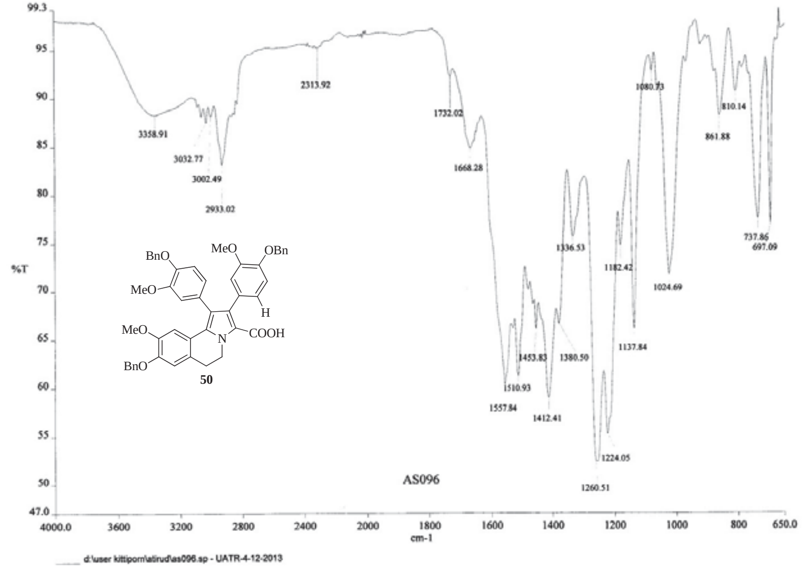
^{1}H NMR (300 MHz, $CDCl_3$)



ESI-TOF [M+H$^+$]



IR (UATR)



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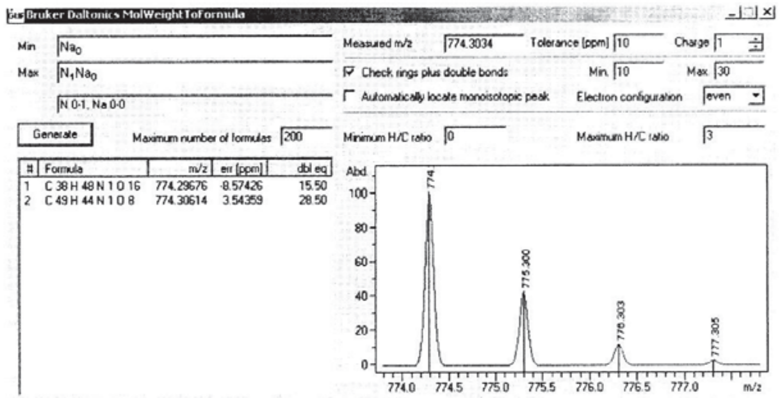
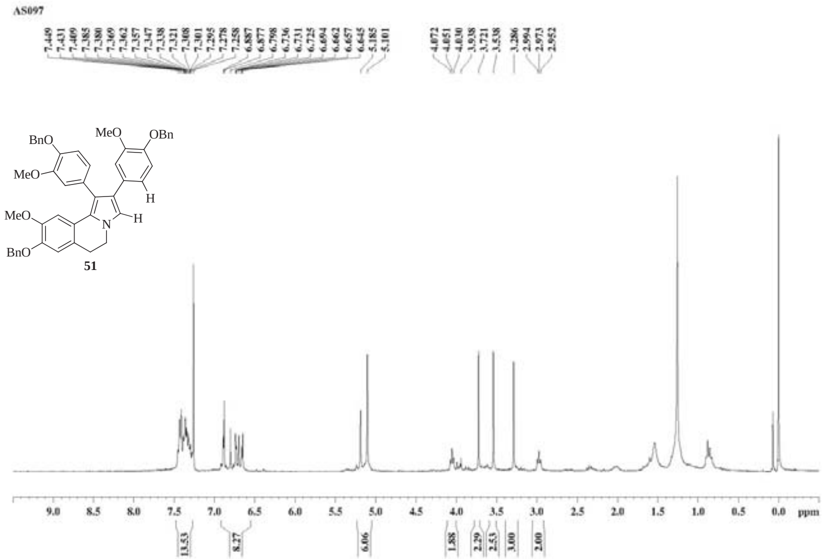
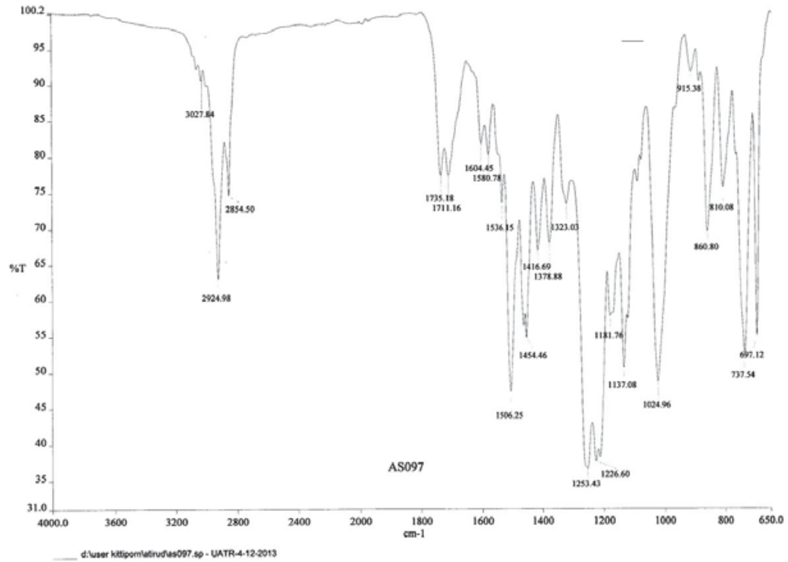


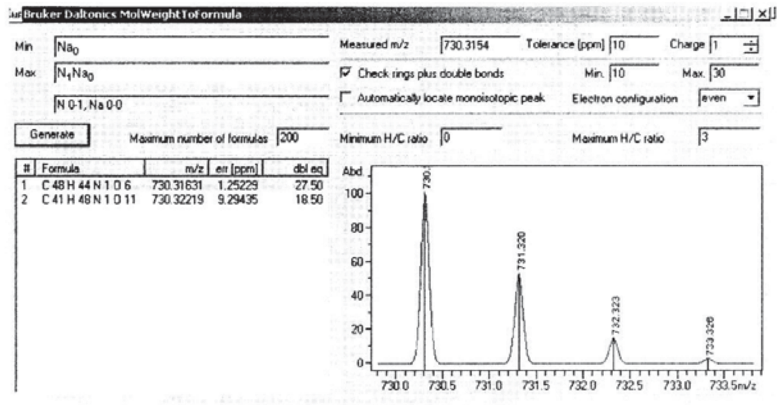
[1]H NMR (300 MHz, $CDCl_3$)



IR (UATR)



ESI-TOF [*M*+H[+]]



การนำเสนอ
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THE 6TH INTERNATIONAL CONFERENCE ON CUTTING-EDGE ORGANIC CHEMISTRY IN ASIA AND THE 2ND NEW PHASE INTERNATIONAL CONFERENCE ON CUTTING-EDGE ORGANIC CHEMISTRY IN ASIA

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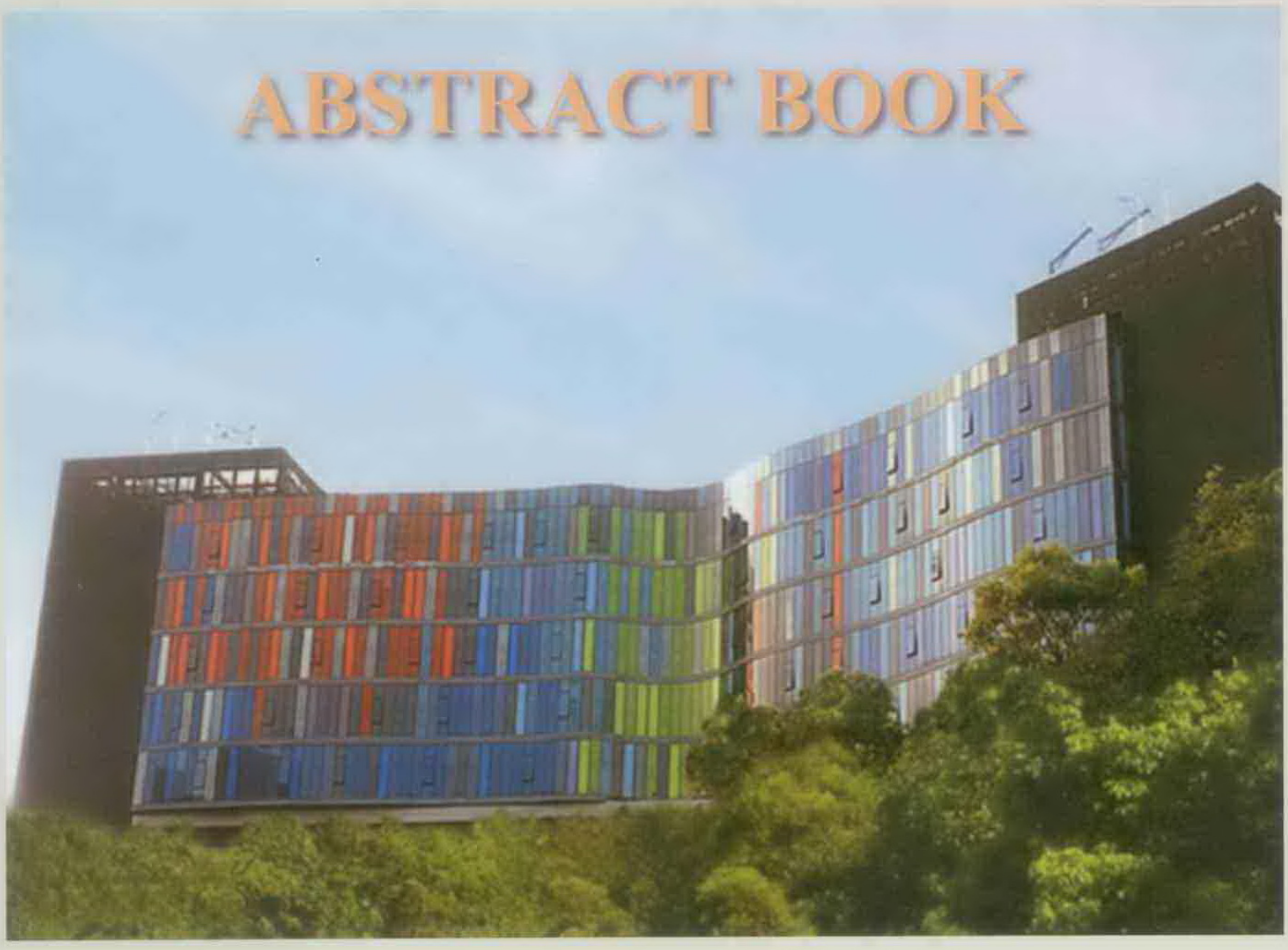

PA-4

Design and Synthesis of Structurally-modified Lamellarin Analogs

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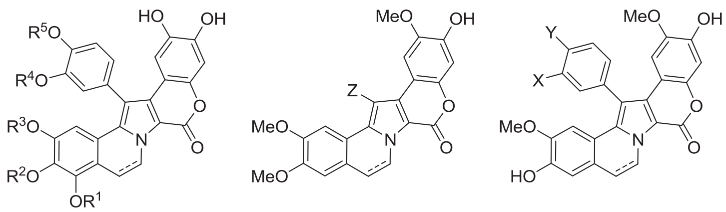
Marine organisms are valuable sources of various biologically active agents of great pharmaceutical potential, among which lamellarins constitute an interesting family with a pyrrolo-(dihydro)isoquinoline lactone core. The most promising therapeutic potential of these compounds reported to date involves multidrug-resistant cancer treatments.[1] Following the synthetic development[2a] to generate a large number of naturally-occurring lamellarins, our research group also systematically evaluated the structure-activity relationship (SAR)[2b] and drug-likeness[2c] of these compounds. Based on the obtained results, it is desirable to design analogs with increased aqueous solubility and decreased molecular volume since these two parameters are important for drug development, but have not been optimized for the lamellarins. To this end, we have contemplated the synthesis of some catechol-containing lamellarin analogs and simplified C1-dearylated analogs. For the latter, the orthogonal aryl group at C1 was replaced by other groups, such as OMe, O*i*-Pr, Br, Me, and Et. Additionally, we have designed a few analogs to probe the role and importance of the hydrogen bond donors/acceptors at C13 and/or C14 by replacing the hydroxy groups at these positions with fluorine. The syntheses of these analogs were similar to those reported previously for the lamellarins with some slight modifications.



R^1-R^5 = Me or H Z = OMe, O*i*-Pr, Br, Me, and Et X = H, Y = F or X = Y = F

Representative structures of the newly designed lamellarin analogs

References

1. Bailly, C. *Curr. Med. Chem. Anticancer Agents* **2004**, *4*, 363-78.
2. (a) Ploypradith, P.; Petchmanee, T.; Sahakitpichan, P.; Litvinas, N. D.; Ruchirawat, S. *J. Org. Chem.* **2006**, *71*, 9440-8; (b) Chittchang, M.; Batsomboon, P.; Ruchirawat, S.; Ploypradith, P. *ChemMedChem* **2009**, *4*, 457-65; (c) Chittchang, M.; Gleeson, M. P.; Ploypradith, P.; Ruchirawat, S. *Eur. J. Med. Chem.* **2010**, *45*, 2165-72.

Montakarn Chittchang (มนทกานติ์ จิตต์แจ้ง). Chulalongkorn University, Thailand Thailand (B.Sc., 1996), University of Missouri-Kansas City, USA (Ph.D., 2004). Pharmacist, Thai Food and Drug Administration (1996-1999). Research Scientist, Chulabhorn Research Institute (2005-present), Lecturer, Chulabhorn Graduate Institute (2007-present). Fields of research: Medicinal Chemistry, Pharmaceutics, Biopharmaceutics, Drug Delivery.

Design and Synthesis of Structurally-modified Lamellarin Analogs

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[b] Chemical Biology Program, Chulabhorn Graduate Institute, and the Center of Excellence on Environmental Health, Toxicology and Management of Chemicals (ETM), Vibhavadee-Rangsit Highway, Bangkok 10210, Thailand
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Introduction

As a promising group of candidates for further development as anticancer agents, lamellarins (**Figure 1**), a group of natural products from marine sources, exhibit potent cytotoxic activities against a panel of different cancer cell lines, as well as good selectivity for these cancer cells over the normal ones.[1] However, most lamellarins, from our systematic evaluation for their drug-likeness,[2] still suffer from their relatively low aqueous solubility and large molecular volume. Thus, it is desirable to design new analogs with appropriate structural modifications to address these issues, as well as to probe the nature of the requisite substituents at different positions around the periphery of the pyrroloisoquinoline lactone core of lamellarins.

A highly convergent synthetic approach for the preparation of lamellarin analogs has been developed in our research group,[3] featuring a Grob-type Michael addition/ring closure (Mi-RC) reaction cascade to form the pyrrole core as the key step. The C5-C6 olefin moiety could be established via a three-step sequence—acetylation, DDQ oxidation, and deacetylation.

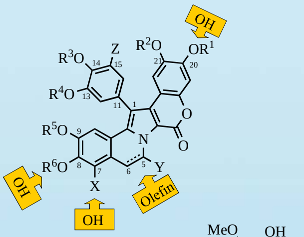
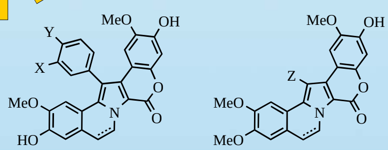
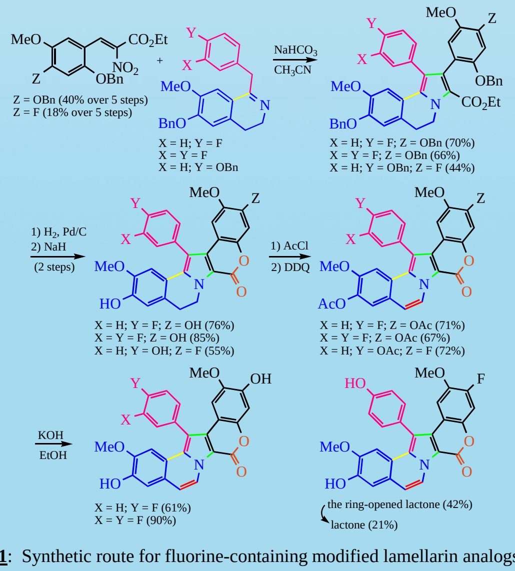


Figure 1: Important structural elements in the lamellarin skeleton (OR^1-OR^6 = OH or OMe; X, Y, Z = H or OH or OMe)



X = H, Y = F or X = Y = F   Z = OMe, Oi-Pr, Br, Me, and Et

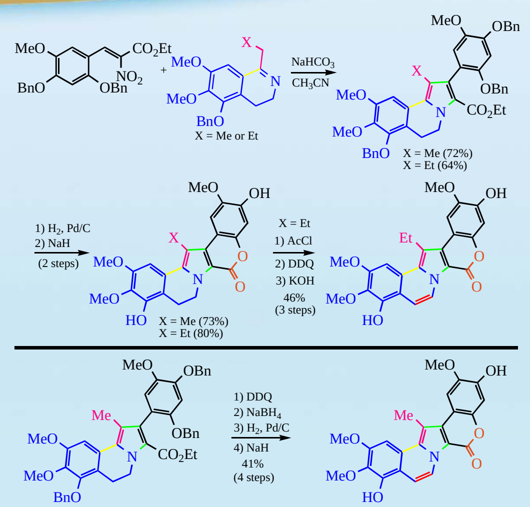
Synthetic Route



Scheme 1: Synthetic route for fluorine-containing modified lamellarin analogs

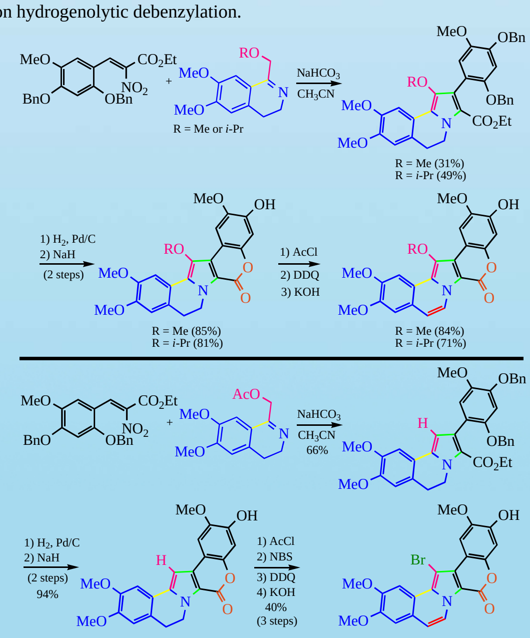
In order to probe the importance of hydrogen bonding at C13, C14, or C20, three fluorine-containing lamellarin analogs were synthesized (**Scheme 1**). The requisite imines were prepared according to the established protocols. It should be noted that the Henry reaction for the synthesis of the fluorine-containing nitrocinnamate proceeded in only moderate yield (33%) as a result of sluggish dehydration under reaction conditions. Additionally, the deacetylation step (5% KOH/EtOH) for the C20-fluoro analog initially resulted in only the ring-opened lactone product in 42% yield. The lactone could be reclosed albeit in low yield (21%).

Five C1-dearylated analogs were also designed and synthesized to reduce the molecular volume as the entire aromatic ring was replaced by a small alkyl group (methyl and ethyl) or a heteroatom-containing group (bromine, methoxy, and isopropoxy). Both the methyl and ethyl groups were introduced via propionyl chloride and butanoyl chloride, respectively, during the amide formation prior to the Bishler-Napieralski reactions to yield the corresponding imines (**Scheme 2**). Synthesis of C1-bromo, -methoxy, and-isopropoxy analogs followed the synthesis shown in **Scheme 3**.



Scheme 2: Synthetic route for C1-dearylated methyl/ethyl lamellarin analogs

The synthesis of C1-methyl analog required slight modifications by performing DDQ oxidation to introduce C5-C6 olefin first. However, under such conditions, the methyl group was oxidized to the corresponding pyrrole aldehyde, which was then reduced by $NaBH_4$. The primary alcohol was concomitantly reduced to the methyl group upon hydrogenolytic debenzylation.



Scheme 3: Synthetic route for C1-methoxy, -isopropoxy, and -bromo lamellarin analogs

In general, the syntheses followed the method developed in our group, starting from appropriate imines with CH_2OR (R = Me, Et, or Ac). It should be noted that the acetate was cleaved during the Grob-type condensation to yield the C1-H analog.

Conclusion

Eight lamellarin analogs were prepared with (1) modifications on the substituents of the C1-aryl group (C13 and/or C14) to probe the nature of the requisite groups (hydrogen bonding ability), as well as (2) methyl, ethyl, methoxy, isopropoxy or bromo group replacing the aryl group for further modifications to increase aqueous solubility.

Acknowledgement

Financial support from the Thailand Research Fund (TRF; DBG5480011 to M.C.; BRG5180013 to P.P.) and the National Research Council of Thailand (NRCT) is gratefully acknowledged.

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3. Ploypradith, P.; Petchmanee, T.; Sahakitpichan, P.; Litvinas, N. D.; Ruchirawat, S. *J. Org. Chem.* **2006**, *71*, 9440-9448.

THE 6th PURE AND APPLIED CHEMISTRY INTERNATIONAL CONFERENCE 2012

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STUDY AND SYNTHESIS OF LAMELLARIN NATURAL PRODUCTS

Kamil Prajapati[1, 2], Kassrin Tangdenpaisal[3], Montakarn Chittchang[1, 2, 3] and Poonsakdi Ploypradith[1, 2, 3]*

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[2] Center of Excellence on Environmental Health and Toxicology, Commission on Higher Education (CHE), Ministry of Education, Thailand.
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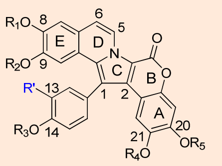
ABSTRACT

Lamellarins form a large group of pyrrole-derived poly-aromatic alkaloids with promising biological activities. Among them, lamellarin D has attracted considerable interests due to its potent cytotoxic activity against multidrug resistant cancer cells by inhibition of DNA topoisomerase I and induction of pro-apoptotic signals in mitochondria. However, it suffers from poor aqueous solubility, an important physicochemical property for drug development. With the aim to improve solubility, an analog of lamellarin D was designed and synthesized with a carboxylic acid functionality at C13. The key step involved the formation of the pyrrole core of lamellarins by Grob-type condensation between benzyldihydroisoquinoline and α-nitrocinnamate derivatives. Subsequently, the carboxylic acid group is anticipated to be incorporated via lithium-halogen exchange followed by the reaction of such lithiated species with carbon dioxide.

Keywords: Lamellarins, aqueous solubility, carboxylic acid functionality, physicochemical property

INTRODUCTION

Lamellarins are a group of marine natural products first isolated in 1985 by Faulkner and coworkers from mollusks in the genus *Lamellaria* sp. Since then, more than 70 different lamellarins have been isolated from various marine organisms [1]. Lamellarin D (Figure 1), K and M are among the most cytotoxic molecules with IC_{50} values ranging from sub-nanomolar range (0.08 nM) to micromolar range (3.2 μM) in a wide range of tumor cell lines, particularly human breast, lung, liver, oral, and cervical cancer cells, as well as leukemia cells [2].

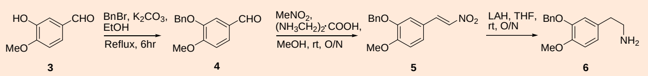


1 R_1, R_3 R_5 = H; R_2 = Me; R' = OMe
2 R_1, R_3, R_5 = H; R_2, R_4 = Me; R' = COOH

Figure 1. Structure of Lamellarin D **1** and its analog **2**

On the basis of SAR studies of lamellarin D, the hydroxy group at C14 and the two methoxy groups at C13 and C21 appear to play less important role for cytotoxic activity compared with the hydroxyl groups at C8 and C20, which are the main structural requirements for potent cytotoxicity towards cancer cell lines [2]. Introduction of a polar and ionizable group, such as an amine or carboxylic acid, at these positions may enhance the aqueous solubility [3]. With this regard, we are aiming to synthesize lamellarin D with a carboxylic acid functionality at C13 position that would have minor changes in the molecular weight.

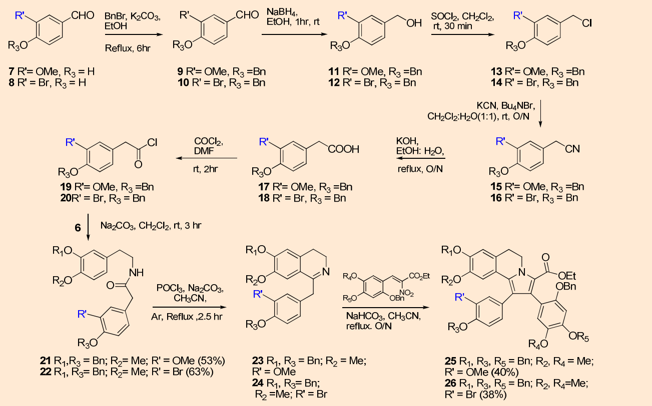
METHODOLOGY AND RESULTS



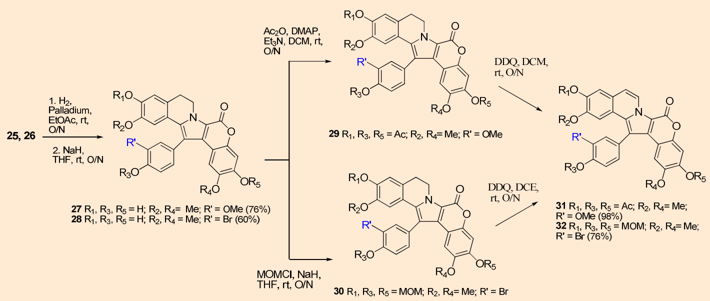
Scheme 1. Synthesis of aryl ethylamine

Synthesis of the pyrrole core for lamellarin analog **25** and **26** (Scheme 2) followed the convergent method developed by Ploypradith et al. [4]. The lamellarin framework was formed from three appropriately substituted integral parts which include aryl ethylamine **6**, aryl acetic acid **17** and **18**, and α-nitrocinnamate. The hydroxyl groups of each of these compounds were protected as their benzyl ethers. The first two parts were combined to form amides **21** and **22,** respectively, which were subsequently converted to imines **23** and **24,** respectively. Imines thus formed underwent Michael addition/ring closure (Mi-RC) Grob-type condensation with α-nitrocinnamate under basic conditions to give the corresponding pyrrole cores **25** and **26**, respectively. The yield of this reaction was highly temperature-dependent, especially with the bromine as the substituent at C13 position. This was probably due to the steric effect exerted by the bulky bromine group in contrast to the more flexible methoxy group present in lamellarin D.

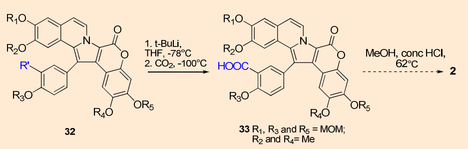
The hydroxyl groups of lamellarin χ (**27**) were protected as their acetates using acetic anhydride while the methoxy methyl (MOM) ether was used instead to protect the hydroxyl groups of compound **28**. Protected lamellarins were then oxidized at positions C5 and C6 by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) under refluxing conditions to give lamellarins with the unsaturated D-rings, as shown in Scheme 3. The acetyl groups of compound **31** were hydrolyzed under basic conditions to furnish lamellarin D (**1**) as the final product. For compound **32**, the optimal conditions required for the lithium-halogen exchange are being investigated (Scheme 4).



Scheme 2. Key steps involved in the synthesis of lamellarin analogs



Scheme 3. Synthesis of unsaturated lamellarin analogs



Scheme 4. Lithium halogen exchange strategy for the synthesis of **2**

CONCLUSION

In summary, Mi-RC Grob-type condensation followed by hydrogenolysis and base mediated lactonization was efficiently used to synthesize lamellarin D scaffold **32** with bromine at C13 position and hydroxyl group protected by MOM. The sole purpose of having bromine at position C13 was to provide a handle to generate an anion via lithium-halogen exchange at −78°C followed by the reaction of the resulting aryl anion with carbon dioxide at −40° C. However, the optimized conditions to convert the bromine into the carboxylic acid are currently under investigation in our group.

ACKNOWLEDGEMENTS

Financial supports from Thailand International Development Cooperation Agency (TICA; post-graduate scholarship to K.P.) and Thailand Research Fund (TRF; DBG5480011 to M.C.; BRG5180013 to P.P.) are gratefully acknowledged.

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SYNTHETIC STUDIES OF LAMELLARIN NATURAL PRODUCTS

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[2] Center of Excellence on Environmental Health and Toxicology, Commission on Higher Education (CHE), Ministry of Education, Thailand.
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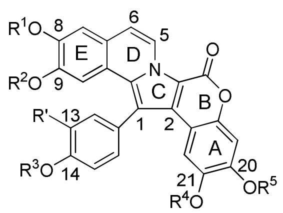
Abstract: Lamellarins form a large group of pyrrole-derived poly-aromatic alkaloids with promising biological activities. Among these compounds, lamellarin D has attracted considerable interests due to its potent cytotoxic activity against multidrug resistant cancer cells by inhibition of DNA topoisomerase I and induction of pro-apoptotic signals in mitochondria. However, it suffers from poor aqueous solubility, an important physicochemical property for drug development. With the aim to improve solubility, synthesis of an analog of lamellarin D with carboxylic acid functionality at C13 was attempted. The key step involved the formation of the pyrrole core of lamellarins by Grob-type condensation between benzyldihydroisoquinoline and α-nitrocinnamate derivatives. Subsequently, the carboxylic acid group is anticipated to be incorporated via lithium-halogen exchange followed by the reaction of such lithiated species with carbon dioxide.

1. Introduction



1 R^1, R^3, R^5 = H; R^2, R^4 = Me; R' = OMe
2 R^1, R^3, R^5 = H; R^2, R^4 = Me; R' = COOH

Figure 1. Structure of Lamellarin D **1** and its analog **2**

Lamellarins belong to a group of marine natural products first isolated in 1985 by Faulkner and coworkers from mollusks in the genus *Lamellaria* sp. Since then, more than 70 different lamellarins and related pyrrole derived alkaloids have been isolated from various marine organisms, mainly mollusks, ascidians, and sponges [1]. Lamellarins are classified as 3,4-diarylpyrroloisoquinoline lactones that can be further classified into two major groups from a structural perspective. The majority of lamellarins possess a pentacyclic skeleton with polyoxygenated aromatics on their periphery as shown in the Figure 1. Pentacyclic lamellarins may be saturated or unsaturated between positions C5 and C6. A small group of lamellarins have an open structure where the central pyrrole ring remains unfused [2]. Several synthetic strategies have been developed for lamellarins and related pyrrole-derived alkaloids since the pioneering synthetic work of Steglich and coworkers in 1997 [3]. These strategies mainly follow two main approaches—the formation of pyrrole core or the transformation of a pre-existing pyrrole derivative through metal-mediated cross-coupling reactions [4].

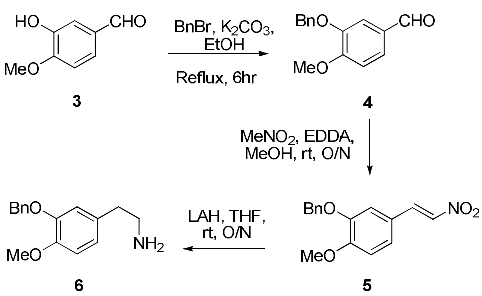
Lamellarins and their derivatives have attracted considerable attention due to their interesting bioactivities ranging from cytotoxicity, reversal of multidrug resistance in some cancer cell lines, HIV-1 integrase inhibition, and immunomodulation. Structure-activity relationship (SAR) studies of lamellarins for their cytotoxicity towards cancer cell lines have exclusively focused on lamellarin D and its derivatives even though lamellarin K and M are also among the most cytotoxic molecules in the series. These three molecules have IC_{50} values ranging from sub-nanomolar range (0.08 nM) to micromolar range (3.2 μM) in a wide range of tumor cell lines, particularly human breast, lung, liver, oral, and cervical cancer cells, as well as leukemia cells [5]. Lamellarin D has been illustrated as an effective stabilizer of human topoisomerase I–DNA covalent complexes ultimately stimulating DNA cleavage by DNA topoisomerase I [6]. More recently, lamellarin D has been demonstrated to induce apoptosis by disrupting transmembrane potential of mitochondria [7]. Furthermore, malate–aspartate shuttle [8] and several protein kinases relevant to cancer [9] are being identified as new molecular targets of lamellarin D. Despite the unique biological activities, lamellarin D still suffers from low aqueous solubility, an important physicochemical parameter required for further development of its drug candidacy.

On the basis of SAR studies of lamellarin D, the hydroxyl group at C14 and the two methoxy groups at C13 and C21 appear to play less important role for cytotoxic activity compared with the hydroxyl groups at C8 and C20, which are the main structural requirements for potent cytotoxicity towards cancer cell line [5]. Thus, introduction of a polar and ionizable group, such as an amine or carboxylic acid, at these positions may enhance the aqueous solubility.

Compounds with an ionizable functional group will be charged in appropriate pH buffers, and thus, may have increased solubility. Structural modification is one of the ways to improve drug solubility. While doing so, molecular weight of the compound should not be increased as it decreases the solubility [10]. With this regard, we are aiming to synthesize lamellarin D with carboxylic acid functionality at C13 position that would have minor changes in the molecular weight.

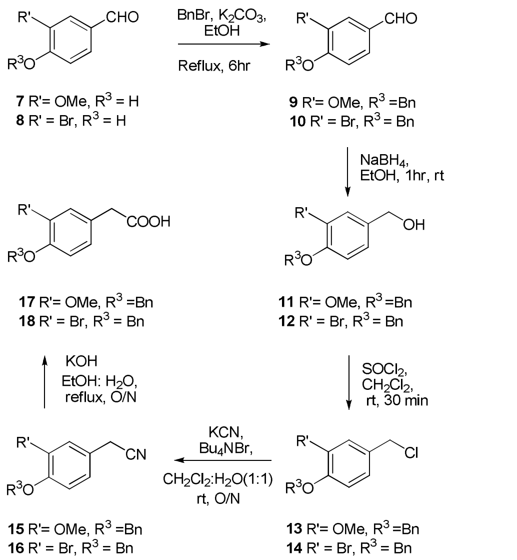
2. Materials and Methods

Synthesis of the pyrrole core for lamellarin analog **25** and **26** followed the convergent method developed by Ploypradith *et. al.* [2]. The key intermediates aryl ethylamine isovanillin **6** and aryl acetic acid **17** and **18** were synthesized as shown in Scheme 1 and 2 respectively. The corresponding amides **21** and **22** were prepared from the aryl ethylamine and aryl acetic acid derivatives, respectively. Subsequent Bishler-Napieralski reactions of these amides then provided the corresponding imines **23** and **24**. The condensation reaction between the benzyldihydroisoquinolines with α-nitrocinnamate under basic conditions is the key step to provide the lamellarin pyrrole framework **25** and **26**, as depicted in Scheme 3. All the benzyl ethers were effectively cleaved by Pd-catalyzed hydrogenolysis and the intermediates 2-pyrrole ester phenols were then subsequently lactonized by sodium hydride to give **27** and **28**, respectively.



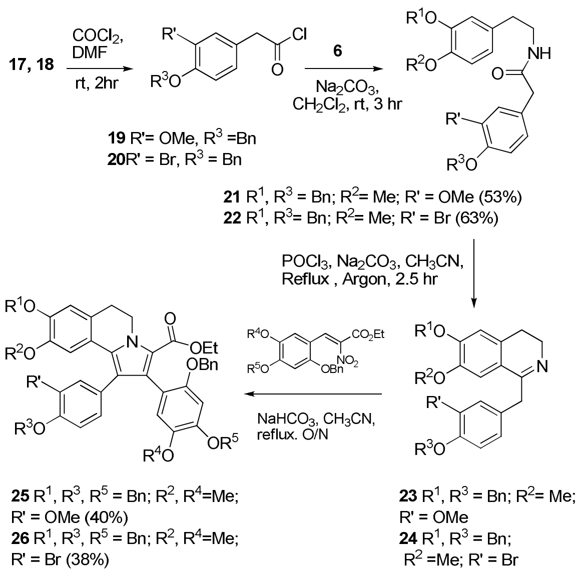
Scheme 1. Synthesis of aryl ethylamine

The hydroxyl groups of lamellarin **27** were protected as their acetates using acetic anhydride in the presence of DMAP and triethylamine at room temperature, while the methoxy methyl (MOM) ether was used instead to protect the hydroxyl groups of compound **28**. Protected lamellarins were then oxidized at positions C5 and C6 by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) under reflux conditions to give lamellarins with the unsaturated D-rings, as shown in Scheme 4.



Scheme 2. Synthesis of aryl acetic acid

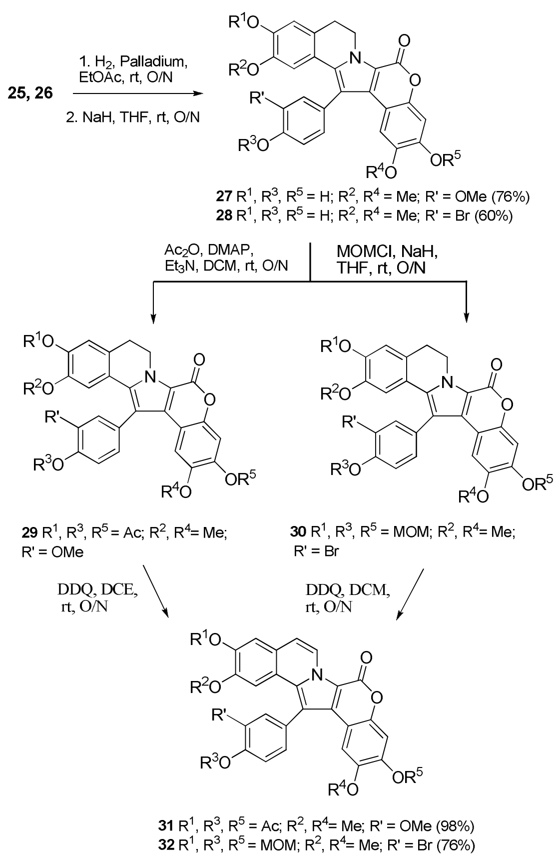
The acetyl groups of compound **31** were hydrolyzed under basic conditions to furnish lamellarin D **1** as the final product. For compound **32**, the optimal conditions required for the lithium-halogen exchange are being investigated (Scheme 5).



Scheme 3. Key steps involved in the synthesis of lamellarin analogs

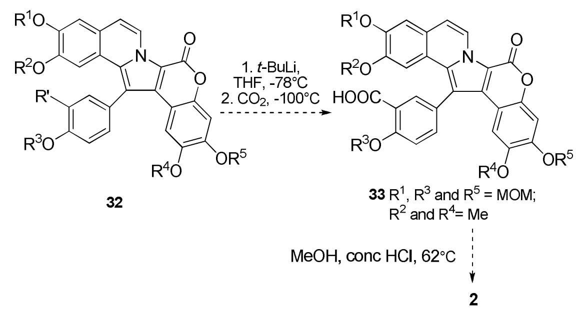
3. Results and Discussions

Construction of the pyrrole core through a number of convergent synthetic routes is one of the major strategies to synthesize the lamellarin skeleton. The lamellarin framework was formed from three appropriately substituted integral parts. These include aryl ethylamine, aryl acetic acid, and α-nitro-cinnamate. The hydroxyl groups of each of these compounds were protected as their benzyl ethers. The first two parts were combined to form amides **21** and **22** in good yields of 53% and 63%, respectively, which were subsequently converted to imines **23** and **24,** respectively. Imines thus formed underwent Michael addition/ring closure (Mi-RC) Grob-type condensation with α-nitrocinnamate under basic conditions to yield the corresponding pyrrole cores **25** and **26** in moderate yields of 40% and 38%, respectively. The yield of this reaction was highly temperature-dependent, especially with the bromine as the substituent at C13 position. This was probably due to the steric effect exerted by the bulky bromine group in contrast to the more flexible methoxy group present in lamellarin D.



Scheme 4. Synthesis of unsaturated lamellarin analogs

Lamellarins containing saturated D-rings **27** and **28** were synthesized by hydrogenolysis/base mediated lactonization in good yields of 76% and 60%, respectively. The hydroxyl groups of lactones were protected by acetyl groups for compound **27** while MOM ether was used for compound **28**. The different choices of protecting groups were due to the fact that compound **28** had to undergo lithium-bromine exchange by some strong alkyllithium base. Under these conditions, the MOM ether is more stable than the acetyl group, which can undergo deprotonation reaction. The protected lamellarins were oxidized by DDQ at C5-C6 position to give compounds **31** and **32**. The acetate groups for compound **31** were removed by 5% KOH in EtOH, which was immediately acidified with 2N HCl to yield lamellarin D.



Scheme 5. Lithium halogen exchange strategy for the synthesis of **2**

4. Conclusions

In summary, Mi-RC Grob-type condensation followed by hydrogenolysis and base mediated lactonization was efficiently used to synthesize lamellarin D scaffold **32** with bromine at C13 position and hydroxyl group protected by MOM. The sole purpose of having bromine at position C13 on orthogonal aryl group attached to the pentacyclic core was to provide a handle to generate an anion via lithium-halogen exchange at −78°C followed by the reaction of the resulting aryl anion with carbon dioxide at −40° C. However, the optimized conditions to convert the bromine into the carboxylic acid are currently under investigation in our group.

Acknowledgements

Financial supports from Thailand International Development Co-operation Agency (TICA; post-graduate scholarship to K.P.) and Thailand Research Fund (TRF; DBG5480011 to M.C.; BRG5180013 to P.P.) are gratefully acknowledged.

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PROGRAM AND ABSTRACTS

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PG-17

EFFICIENT SYNTHETIC METHODS FOR THE 2-ARYLCHROMAN SKELETON VIA [4+2]-CYCLOADDITION REACTIONS OF *ORTHO*-QUINONE METHIDES

Pakornwit Sarnpitak[1], Patchaya Sukjarean[1], Somsak Ruchirawat[1,2], Poonsakdi Ploypradith[1,2]

[1]Laboratory of Medicinal Chemistry, Chulabhorn Research Institute, 54 Kamphaeng Phet 6 Road, Laksi, Bangkok 10210, Thailand, [2]Chemical Biology Program, Chulabhorn Graduate Institute, 54 Kamphaeng Phet 6 Road, Laksi, Bangkok 10210, Thailand

ortho-Quinone methides (*o*-QMs) are reactive intermediates implicated in the biosynthesis of some lignins and lignans as well as the anticancer action of some cytotoxic agents. However, they have been rather underutilized as intermediates in organic synthesis due to their high reactivity. Our group has previously studied the acid-mediated cleavage of MOM aryl ethers and, thus, has designed a novel acid-mediated generation of *o*-QM. In addition, the subsequent [4+2]-cycloaddition reactions, where the *o*-QM serves as the heterodiene and styrene derivatives as the dienophile, were also mediated under the same reaction conditions. Most recently, we have also developed Pt(IV)-catalyzed generation and [4+2]-cycloaddition reactions of the *o*-QMs. The use of $PtCl_4$ offered several advantages over the use of other acids such as broader scope of the *o*-QM precursor as well as the olefins, better yields, and comparable stereoselectivity. Both intermolecular and intramolecular generation and the subsequent hetero-Diels-Alder reactions have been successfully performed to furnish the corresponding 2-arylchroman systems in good to excellent yields and moderate to excellent diastereoselectivity.

PG-18

STUDIES TOWARDS THE DEVELOPMENT OF LAMELLARIN NATURAL PRODUCTS AS POTENTIAL ANTICANCER AGENTS

Montakarn Chittchang[1,2], Poonsakdi Ploypradith[1,2], Somsak Ruchirawat[1,2]

[1]Laboratory of Medicinal Chemistry, Chulabhorn Research Institute, Bangkok, Thailand, [2]Chemical Biology Program, Chulabhorn Graduate Institute, and the Center of Excellence on Environmental Health, Toxicology and Management of Chemicals, Bangkok, Thailand

Bioactive compounds from marine natural sources have received vast interests from many research groups worldwide due to their structural diversity and promising therapeutic potential. Unfortunately, the major obstacles complicating the development of these compounds into drug candidates involve their low natural abundance, complex structures, poor physicochemical properties, and complex molecular mechanisms. Nevertheless, a number of marine-derived natural products have already been developed and approved for clinical uses. Our research group has continuing interests in a group of cytotoxic marine natural products called lamellarins containing a pyrrolo(dihydro)isoquinoline lactone core. Although these compounds have promising therapeutic potential for multidrug-resistant cancer treatments, they still suffer from poorly selective toxicity for normal cells and very limited aqueous solubility preventing further development into drug candidates. Our interests encompass not only the synthetic development, but also structure modifications, structure-activity relationship (SAR) evaluations, and drug-likeness assessments. The goal of this project is to obtain lamellarin analog(s) with improved efficacy and specificity towards cancer cell lines, as well as optimal drug-like properties for further development. Thus far, we have successfully developed a general synthetic route suitable for lamellarin analogs. In addition, the SAR studies also revealed structural elements required for strong cytotoxicity against a panel of cancer cells, which are important for streamlining and reducing structural complexity of the future lamellarin analogs. Currently, our focus has been shifted towards incorporating functional groups which enhance aqueous solubility, such as carboxylic acid or amine.

Studies towards the Development of Lamellarin Natural Products as Potential Anticancer Agents

Montakarn Chittchang,[a,b,c] Poonsakdi Ploypradith,[a,b,c] Somsak Ruchirawat[a,b,c]

[a] Laboratory of Medicinal Chemistry, Chulabhorn Research Institute (CRI), Kamphaeng Phet 6 Road, Lak Si, Bangkok 10210, Thailand
[b] Chemical Biology Program, Chulabhorn Graduate Institute (CGI), Kamphaeng Phet 6 Road, Lak Si, Bangkok 10210, Thailand
[c] Center of Excellence on Environmental Health and Toxicology (EHT), Commission on Higher Education, Ministry of Education, Rama VI Road, Ratchathewi, Bangkok 10400, Thailand

Introduction

Our research group has continuing interests in a group of cytotoxic marine alkaloids called lamellarins (Figure 1). Despite their promising therapeutic potential for multidrug-resistant cancer treatments, lamellarins not only suffer from lacking the essential selectivity between malignant and normal cells, but also exhibit very limited aqueous solubility preventing further development into drug candidates.

Upon the successful development of an efficient strategy to synthesize these compounds,[1] our interests have been extended to encompass biological and structure-activity relationship (SAR) evaluations,[2] and drug-likeness assessment[3] to provide a basis for subsequent structure modifications. The goal of this project is to obtain lamellarin analog(s) with improved efficacy and specificity towards cancer cell lines, as well as optimal drug-like properties for further development.

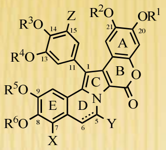
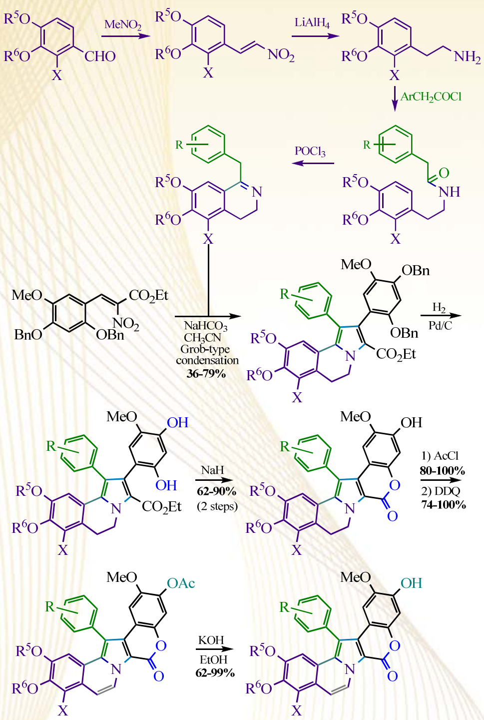


Figure 1: Structures of lamellarins (excluding lamellarins O-R)

R[1]-R[6] = H or Me
X, Y, Z = H or OH or OMe

Synthetic Route

A series of natural and unnatural lamellarins have been successfully synthesized in our laboratory.[1] Our synthetic route (Scheme 1) required appropriately substituted benzaldehyde derivatives as the building blocks. Aryl acetic acid derivatives were the requisite precursor for the condensation with aryl ethylamine derivatives to provide the corresponding amides. The Grob-type Michael addition-ring closure (Mi-RC) reaction cascade formed the pyrrole core. Hydrogenolysis and lactonization proceeded to furnish the lamellarins with a saturated D-ring, which then underwent DDQ oxidation to give the corresponding compounds with an unsaturated D-ring.



Scheme 1: Synthetic route for lamellarins and their analogs

Cytotoxicity Evaluations

Table 1: Cytotoxicity of some lamellarins against selected cancer and normal cell lines[2]

Compound	IC$_{50}$ (μM) [a]								
	A549	H69AR	T47D	MDA-MB-231	HuCCA-1	HepG2	HeLa	HL-60	MRC-5 [b]
Lamellarin D	0.06	0.42	0.00008	0.40	0.08	0.02	0.06	0.04	9.21
Lamellarin M	0.04	0.34	0.009	0.11	0.06	0.02	0.25	0.06	13.41
Lamellarin N	0.04	0.06	0.0006	0.60	0.008	0.02	0.04	0.04	> 100
Lamellarin X	0.26	0.28	0.006	0.08	0.04	0.21	0.09	0.15	10.10
Lamellarin ε	0.28	2.30	0.006	0.26	0.07	0.11	0.28	0.14	25.76
Etoposide	1.07	45.87	0.08	0.17	6.80	0.17	0.42	2.29	> 85

[a] n = 3, and the standard deviations are omitted for clarity; [b] Human fetal/embryonic lung fibroblasts (normal cells)

SAR Studies

The IC$_{50}$ values obtained were then used for comprehensive SAR studies to reveal the structural elements required for their overall anticancer activity.[2] Our results clearly indicated four important structural elements around the pentacyclic lamellarin core (Figure 2). On the other hand, the contributions of the orthogonal ring still remain unclear and have been under investigation in our laboratory.

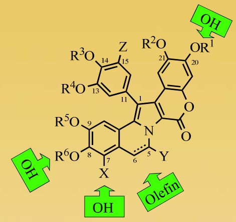


Figure 2: Important structural elements in the lamellarin skeleton

Assessment of Drug-likeness

A range of commonly used molecular descriptors were first computed. These molecular properties govern the key bulk property characteristics of molecules, and thus, are known to be important in defining drug-like property space. The results indicated that lamellarins do not have particularly extreme molecular properties so these compounds still represent a good starting point for further optimization towards a more optimal area of physicochemical parameter space. However, their relatively large molecular weights and, more importantly, highly lipophilic nature could be optimized to generate more drug-like lamellarin analogs.

Table 2: Selected molecular properties of lamellarins and other product classes[3]

Property	Lamellarins	Oral Drugs	Natural Product Drugs	Drugs in Development	Natural Products in Development
Molecular weight	521.68 ± 27.02	333.10 ± 121.09	568.20 ± 318.98	502.53 ± 485.41	711.87 ± 454.03
OE-xlogP	3.40 ± 0.91	2.48 ± 2.20	1.39 ± 3.51	2.40 ± 3.78	3.50 ± 3.07
Polar surface area	124.67 ± 12.56	70.55 ± 45.22	176.07 ± 128.62	131.49 ± 209.37	178.88 ± 152.85
Net charge	0.00 ± 0.00	0.26 ± 0.85	–0.30 ± 1.05	0.17 ± 1.26	0.34 ± 1.04
Negative charges	0.00 ± 0.00	0.21 ± 0.41	0.48 ± 0.51	0.28 ± 0.45	0.22 ± 0.42
Positive charges	0.00 ± 0.00	0.48 ± 0.50	0.28 ± 0.46	0.46 ± 0.50	0.53 ± 0.51
H-bond acceptors	1.06 ± 0.24	2.77 ± 2.23	8.17 ± 5.00	4.90 ± 7.49	7.22 ± 5.96
H-bond donors	2.67 ± 1.14	1.90 ± 1.68	4.57 ± 5.19	3.87 ± 8.51	5.09 ± 6.15
Chiral centers	0.06 ± 0.24	1.61 ± 2.73	7.39 ± 5.30	2.85 ± 5.65	7.44 ± 6.55
Rotatable bonds	4.88 ± 1.41	5.48 ± 3.82	9.96 ± 7.28	11.03 ± 20.35	10.88 ± 12.18
Rings	2.00 ± 0.00	1.84 ± 0.94	2.11 ± 1.14	2.44 ± 1.32	2.47 ± 1.29
No. of compounds	33	1791	46	2125	32

Structure Modifications

Using the synthetic strategy we have developed for lamellarins, a number of "simplified" analogs with deletion of the substituent(s) on the orthogonal ring were prepared (Figure 3). It appeared that total deletion of both C13 and C14 substituents, resulting in an unsubstituted orthogonal ring (R = H), led to dramatically increased lipophilicity of the compounds (causing poor solubility in cell culture media) and, in many cases, significant loss of cytotoxicity.

Additional analogs were then synthesized with at least one oxygen-containing substituent present on the orthogonal ring. Our results indicated that the presence of a hydroxyl group, preferably on C14, was beneficial for the cytotoxicity. These findings are critical for further development of lamellarins, in which substituents on C13 could be altered to address some physicochemical issues, such as low aqueous solubility.

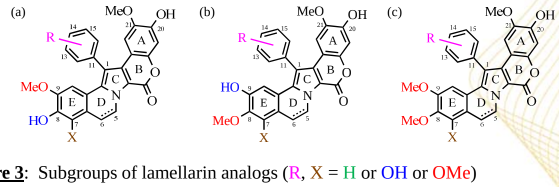


Figure 3: Subgroups of lamellarin analogs (R, X = H or OH or OMe)

Acknowledgement

Financial support from the Thailand Research Fund (TRF; DBG5180015 and DBG5480011 to M.C.; BRG5180013 to P.P.) is gratefully acknowledged.

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3. Chittchang, M.; Gleeson, M.P.; Ploypradith, P.; Ruchirawat, S. *Eur. J. Med. Chem.* **2010**, *45*, 2165-2172.

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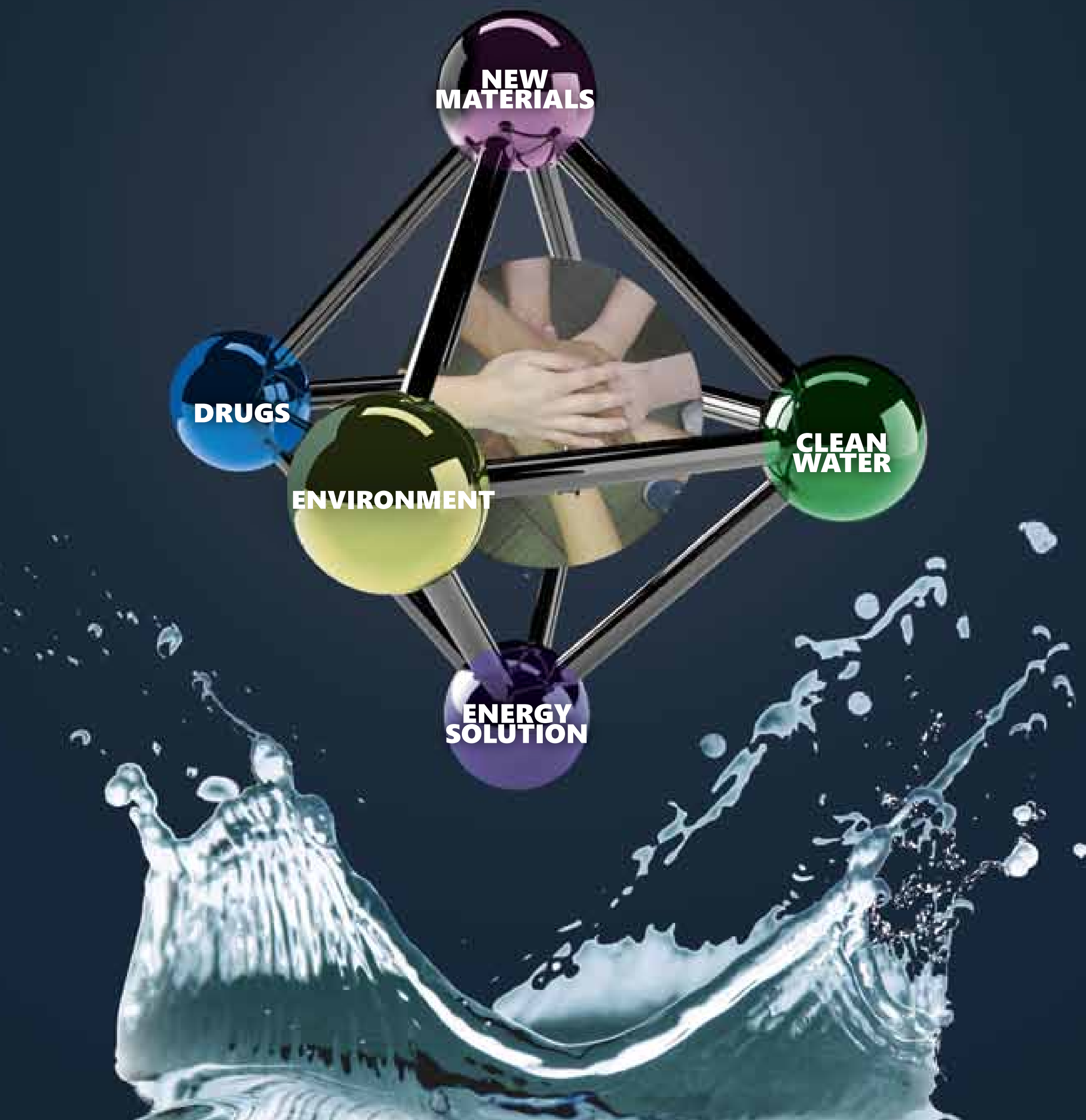

PB44

Synthetic Study of the Lamellarin Analogs Containing An Aqueous Solubility-enhancing Group

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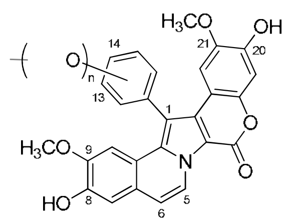
Traditional practice in drug discovery research usually results in rather lipophilic compounds with very poor aqueous solubility, causing significant challenges in further development. In spite of their promising therapeutic potential as anticancer agents,[1,2] lamellarin natural products are highly lipophilic in nature.[3] This undesirable property could be improved by installing a polar or ionizable functional group at a position with the least effects on the biological activities. While the phenolic hydroxyl groups around the pentacyclic core have been proved beneficial for the cytotoxicity of lamellarins, the substituents on the orthogonal ring are much less crucial,[1,2] and thus, may be replaced with an ionizable group to enhance the aqueous solubility of these compounds. In order to investigate this possibility, the two most potent compounds in this class, lamellarin D and lamellarin N, were subjected to detailed comparative physicochemical characterization, focusing on aqueous solubility, lipophilicity, and solution stability. Subsequently, the synthesis of their analogs with a carboxyl-containing substituent at C13 or C14 were attempted either via carboxylation/Pd-catalyzed carbonylation of a lithiated intermediate (n = 0) or via carboxy-methylation of the preexisting hydroxyl group with chloroacetic acid (n = 1).



Carboxyl-containing Lamellarin Analogs
(n = 0-1)

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3. Chittchang, M.; Gleeson, M. P.; Ploypradith, P.; Ruchirawat, S. *Eur. J. Med. Chem.* **2010**, *45*, 2165-2172.

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Synthetic Study of the Lamellarin Analogs Containing an Aqueous Solubility-enhancing Group

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Introduction

Traditional drug discovery research often generates rather lipophilic compounds with poor aqueous solubility. In spite of their promising therapeutic potential as anticancer agents,[1,2] lamellarin natural products are highly lipophilic in nature,[3] causing significant challenges in further development. While the phenolic hydroxyl groups around the pentacyclic core have been proved beneficial for the cytotoxicity of lamellarins (Figure 1a), the substituents on the orthogonal ring are much less crucial,[1,2] and thus, may be replaced with an ionizable group to enhance the aqueous solubility of these compounds.

The analogs of two most potent compounds in this class, lamellarin D (Lam D) and lamellarin N (Lam N), were designed to comprise a carboxyl-containing substituent at either C13 or C14 (Figure 1b). Their synthesis was then attempted either via carboxylation/Pd-catalyzed carbonylation of a lithiated intermediate (n = 0) or via carboxymethylation of the preexisting hydroxyl group with chloroacetic acid (n = 1).

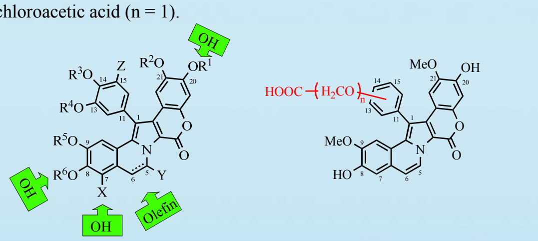
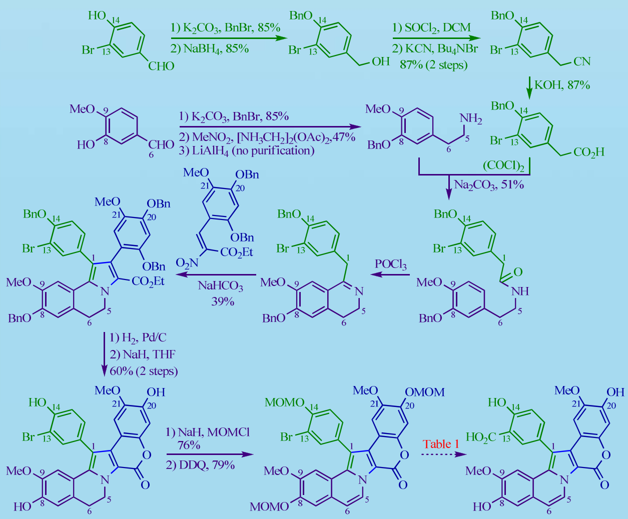


Figure 1: a) Important structural elements in the lamellarin skeleton (OR^1-OR^6 = OH or OMe; X, Y, Z = H or OH or OMe)
b) Designed analogs of lamellarin D and lamellarin N

Results and Discussion

First, we focused on the 13-carboxyl Lam D whereby the methoxy group at C13 would be replaced by a carboxylic acid group (Scheme 1). The synthesis followed our developed synthetic route for lamellarins[4] featuring the Michael addition/ring closure (Mi-RC) Grob-type condensation to form the pyrrole core. It was anticipated that the incorporation of carboxylic acid could be made at a late stage via lithium-bromine exchange, followed by the reaction of such lithiated species with carbon dioxide (Table 1).



Scheme 1: Synthetic study of 13-carboxyl Lam D via lithium-bromine exchange

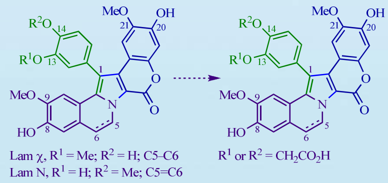
Table 1: Attempted final step of the synthesis of 13-carboxyl Lam D

#	Conditions (Li-Br exchange; addition of CO_2; acidic work-up)	Yield (%)	
		SM	DP
1[a]	*t*-BuLi (2.1 eq.), THF, -78°C, 0.25 h; -100°C, CO_2, 1 h; 5N HCl, rt, 1 h	100	0
2[b]	*t*-BuLi (2.1 eq.), THF, -78°C, 1 h; -78°C, CO_2, 1 h; 5N HCl, rt, 48 h	0	0
3[c]	*t*-BuLi (2.1 eq.), Et_2O, -40°C, 3 h; -100°C, CO_2, 1 h; 5N HCl, rt, 36 h	100	0
4	*t*-BuLi (2.1 eq.), THF, -40°C, 1.5 h; -100°C, CO_2, 1.5 h; 5N HCl, rt, 48 h	0	trace
5	*t*-BuLi (2.1 eq.), THF, -40°C, 3 h; -100°C, CO_2, 3 h; 5N HCl, rt, 48 h	0	0.2
6	*t*-BuLi (2.1 eq.), THF, -40°C, 3 h; -100°C, CO_2, 1 h; 5N HCl, rt, 36 h	0	25
7	*n*-BuLi (5.0 eq.), THF, -40°C, 0.25 h; -100°C, CO_2, 1 h; 5N HCl, rt, 1 h	100	0

[a] Ten equivalents of *t*-BuLi gave the same result.
[b] Only the deprotection of the MOM groups occurred, and the corresponding product was obtained in 99% yield.
[c] Similar result was obtained when a mixture of Et_2O and 1,4-dioxane was used.

Carboxymethylation of lamellarin χ (Lam χ) and Lam N was investigated (Table 2). However, under different conditions, our attempts to carboxymethylate at least one of the three hydroxyl groups of the lamellarin skeleton were not successful.

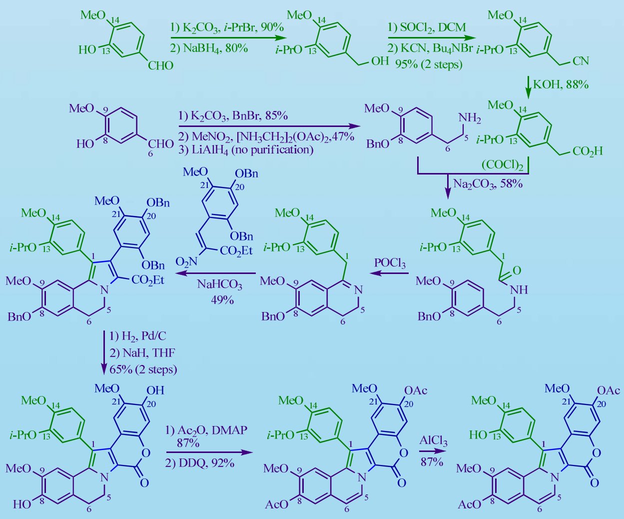
Table 2: Carboxymethylation of Lam χ and Lam N



#	Lam	Conditions	Yield (%)	
			SM	DP
1	χ	NaH (4.0 eq.), THF, HO_2CCH_2Cl (1.2 eq.), rt, 48 h	100	0
2	χ	NaH (6.0 eq.), THF, HO_2CCH_2Cl (3.0 eq.), 60°C, 48 h	100	0
3[a]	χ	NaH (6.0 eq.), DMSO, HO_2CCH_2Cl (3.0 eq.), NaI (3.0 eq.), 100°C, 48 h	--	--
4	N	DIPEA (8.5 eq.), DMF, HO_2CCH_2Cl (4.5 eq.), DMAP (8.5 eq.), rt, 24 h	100	0
5[a]	N	Et_3N (8.5 eq.), DMSO, HO_2CCH_2Cl (4.5 eq.), DMAP (8.5 eq.), NaI (cat.), 60°C, 48 h	--	--

[a] Complex mixture.

It was anticipated that the proton transfers among the three hydroxyl groups may render the carboxymethylation difficult. Thus, an analog of Lam N with one possible site for carboxymethylation was prepared (Scheme 2).



Scheme 2: Synthesis of a Lam N analog for carboxymethylation

However, all the attempts to carboxymethylate this analog were unsuccessful, giving either complete recovery of starting material (K_2CO_3 in acetone) or Lam N (NaH in THF at rt).

Conclusion

Appropriate precursors for direct carboxylation or carboxymethylation of Lam D or Lam N, respectively, were successfully prepared. However, all the attempts thus far to effect the final steps of carboxylation or carboxymethylation failed to give the desired analogs with such aqueous solubility-enhancing groups.

Acknowledgement

Financial support from the Thailand Research Fund (TRF; DBG5480011 to M.C.; BRG5180013 to P.P.) and the National Research Council of Thailand (NRCT) is gratefully acknowledged.

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Synthetic Study of the Lamellarin Analogs Containing an Aqueous Solubility-enhancing Group

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Abstracts

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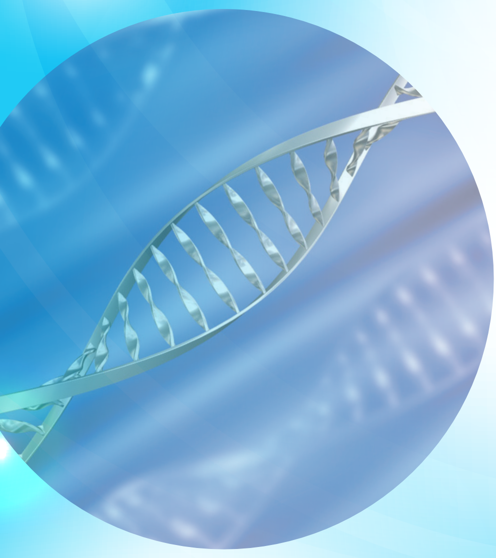

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Abstract: Bovine mastitis has led to worldwide economical loss, particularly with regards to livestock and dairy industries. *Staphylococcus aureus* (*S. aureus*) is recognized as a leading pathogen responsible for bovine mastitis. Although numbers of antibiotics are available for bovine mastitis treatments, the clearance of the infection and control of the pathogen transmission of *S. aureus*-mediated bovine mastitis is currently not highly effective. Herein, we hypothesized that the transcription factor sigma factor B (σ^B) would be a novel therapeutic target for *S. aureus*-mediated bovine mastitis. Sigma factor B involves in the regulation of general stress response and is required for the survival of pathogen under stress conditions. Hence, σ^B inhibitors would interfere with the pathogen stress defense mechanism. We designed and synthesized small molecules based on previously discovered *Listeria monocytogenes* σ^B inhibitor. Disk diffusion assay was performed to evaluate the susceptibility of *S. aureus* strain RF122, which is known to cause bovine mastitis, to the small library of compounds synthesized. Several potent sulfonamides were discovered as effective growth inhibitors. (full paper available on CD)

C3_C0055: MODIFIED TOTAL SYNTHESIS OF AZALAMELLARINS

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Abstract: Lamellarins are marine pyrrole alkaloids that display a wide range of bioactivities, including cytotoxicity against cancer cells, multidrug-resistance (MDR) reversal, and HIV integrase inhibition. Their core structure is a lactone-containing pentacyclic system with different substitution patterns. Despite their promising therapeutic potential and unique structures, their limited aqueous solubility hinders further development into anti-cancer drug candidates. In addition, these compounds also suffer from lactone ring opening under basic conditions. Consequently, the lactone ring in lamellarin D, one of the most potent compounds in the series, has been previously replaced with a more chemically robust lactam moiety, resulting in azalamellarin D and derivatives (Figure 1). However, the previously reported synthesis of azalamellarins required multiple steps, some of which were needed to remove different *N*- and *O*-protecting groups. Therefore, a shorter and more efficient synthetic route has been developed for azalamellarin D utilizing benzyl as the sole *N*- and *O*-protecting groups. Unlike in our previous reports, C5-C6 oxidation could occur without changing the *O*-protecting groups from benzyl to acetate. During the final global deprotection, all *N*- and *O*-benzyl groups were removed altogether using trifluoroacetic acid. This strategy, with a few modifications, will be applied to synthesize additional derivatives with further improved aqueous solubility. (abstract only)

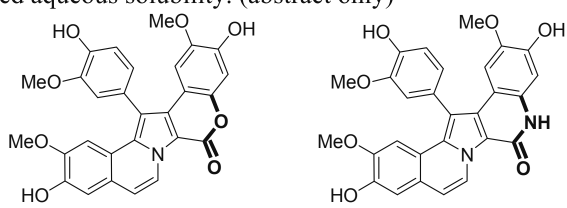

Figure 1. Structures of lamellarin D and azalamellarin D

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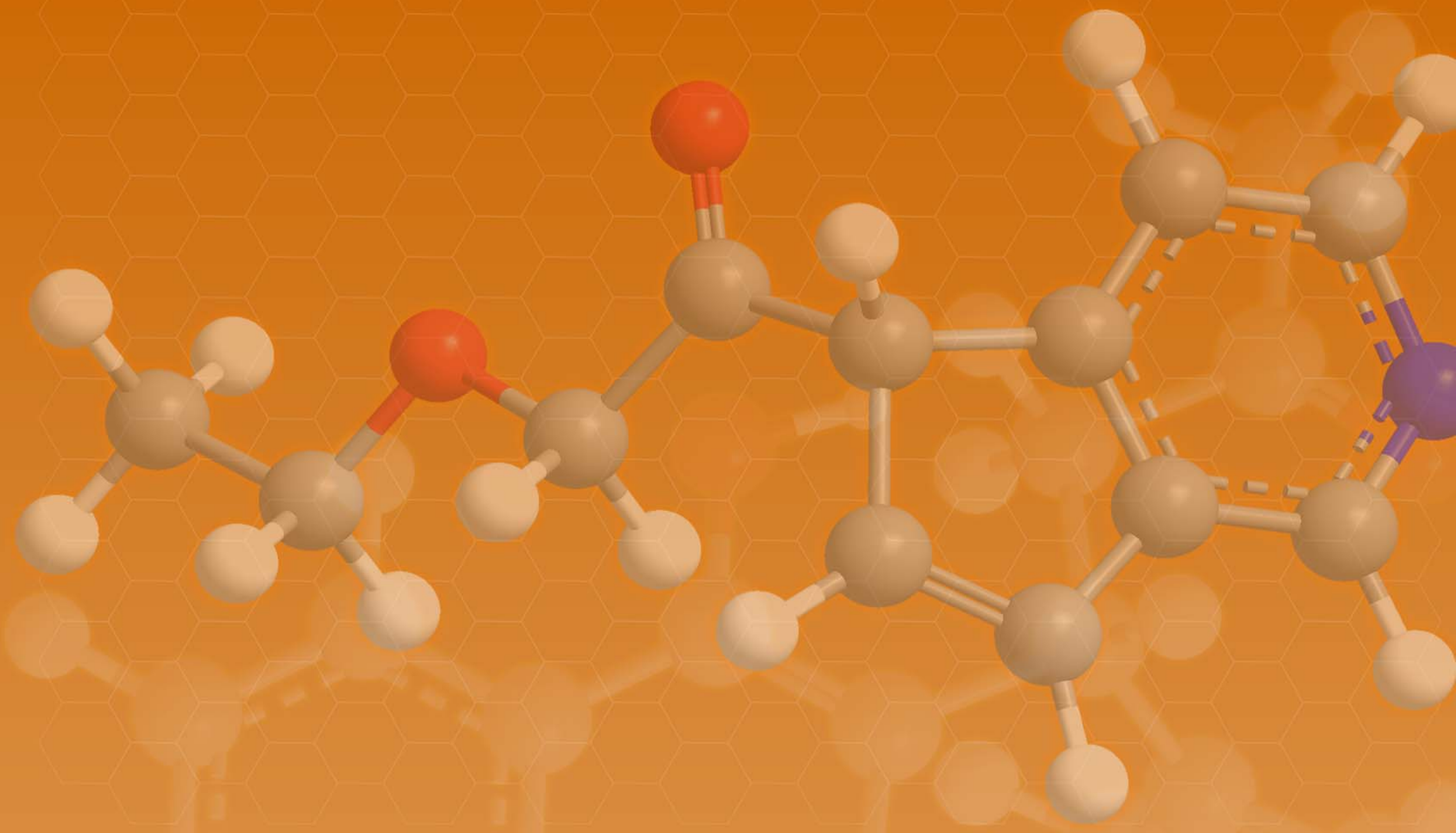

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Synthetic Studies of Azalamellarins *via* Direct Amidation of Pyrrole Esters with or without *N*-Protecting Group

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Azalamellarins are synthetic analogues of cytotoxic lamellarin marine alkaloids through simple replacement of the lactone ring with a lactam moiety. Previously, the synthesis of these compounds has been achieved using *allyl* as an *N*-protecting group, which required rather lengthy steps to remove. Starting from the pyrrole esters, the azalamellarins were obtained in 9 steps with 11% overall yield. A shorter and more efficient route should therefore be beneficial. The key step of our approach involved a construction of pyrrole amides from direct amidation of the corresponding pyrrole esters. In addition to conventional conditions, microwave-assisted synthesis was explored using different conditions and a variety of reagents as the amine source, including the benzyl-type amines and organic azides. After the pyrrole amides were obtained, the lactam moiety of the azalamellarin products was synthesized under Cu(I)-mediated, microwave-assisted conditions for C–N_{amide} bond formation. Using our new strategy, starting from the pyrrole esters, the *N*-protecting azalamellarin products were successfully prepared in 4 steps with 54% yield.

Keywords Pyrrole amide; C–N bond formation; Azallamellarin

Synthetic Studies of Azalamellarins *via* Direct Amidation of Pyrrole Esters with or without *N*-Protecting Group

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[2]Laboratory of Medicinal Chemistry, Chulabhorn Research Institute, Kamphaeng Phet 6 Road, Bangkok 10210, Thailand

Introduction

Lamellarins are a group of marine alkaloids isolated from marine invertebrates, such as mollusks, ascidians, and sponges. Lamellarins with a pyrroloisoquinoline lactone core structure displayed promising and interesting biological activities [1-2]. The importance of different substituents on the common structure has been reported [3], as shown in Figure 1a. In our previous studies, a series of lamellarins have been synthesized using a convergent method [4]. Although some of the lamellarin derivatives showed potent biological activities, there were some issues concerning poor aqueous solubility and stability under basic conditions. To address these issues, azalamellarin derivatives (Figure 1b) have been previously synthesized using allyl and benzyl as *N*- and *O*-protecting groups, respectively [5]. In this study, modifications of the synthetic strategy, especially for the use of benzyl as a single protecting group for both oxygen and nitrogen, have been contemplated to shorten the synthetic route of the azalamellarins, as shown in Schemes 1 and 2.

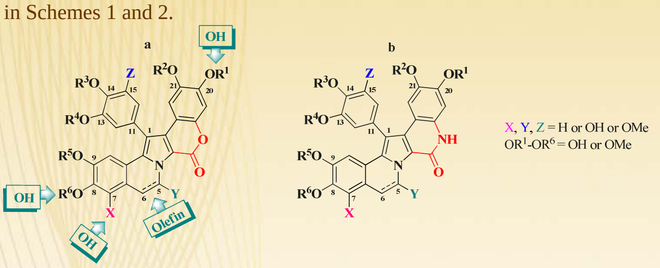
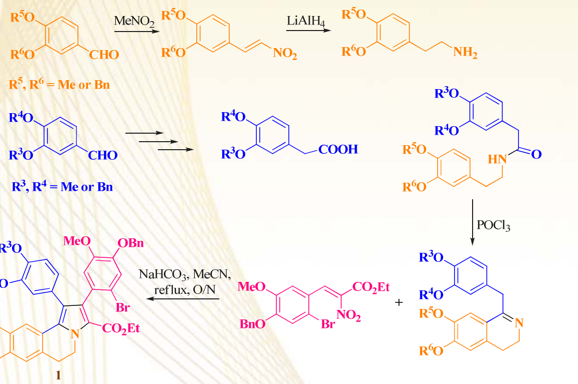
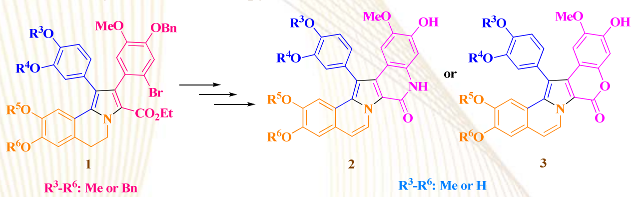


Figure 1: (**a**) Important structural elements in the lamellarin skeleton and (**b**) structure of azalamellarin derivatives



Scheme 1: Synthetic route of pyrrole esters



Scheme 2: Synthetic methodology of azalamellarin derivatives

Results and Discussion

Various amines with or without protecting groups were used to investigate the optimal conditions to incorporate the amide functionality into the lamellarin framework, as shown in Table 1.

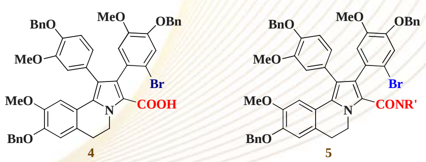


Figure 2: Pyrrole-2-carboxylic acid **4** and pyrrole-2-carboxamide derivative **5**

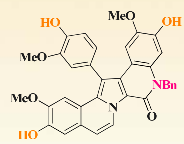
Results and Discussion (cont'd)

Table 1: Amidation/lactamization with or without *N*-protecting group

Entry	*Amine*	*Condition*	*Result*
1	Acetamide	$PdCl_2$, Cs_2CO_3, 1,4-dioxane, 100˚C, 24 h	**1** (60%)
2	N-Boc amine	$PdCl_2$, Cs_2CO_3, 1,4-dioxane, 100˚C, 24 h	**1** (50%)
		Me_3Al, THF, 200˚C, MW[a], 45 min	**1** (80%)
3	Benzyl carbamate	CuI, K_3PO_4, 1,10-phenanthroline, toluene, 90˚C, 24 h	**1** (99%)
		Me_3Al, THF, 200˚C, MW[a], 45 min	**1** (90%)
4	Benzylamine	$PdCl_2$, Cs_2CO_3, 1,4-dioxane, 100˚C, 24 h	**1** (40%)
		Me_3Al, THF, 200˚C, MW[a], 45 min	**5** (62-74%)
5	Sodium amide	$PdCl_2$, w/ or w/o Cs_2CO_3, 1,4-dioxane, 100˚C, 8-24 h	**4**[c]
		1,4-dioxane, reflux, O/N	**4** (99%)
6	Ammonia	EtOH, 60-150˚C, MW[b], 30 min	**1** (80-100%)

[a] 300 W, 250 psi, [b] 200 W, 250 psi
[c] Isolated yields were not determined.

Subsequent lactamization of **5** under Cu(I)-mediated, microwave-assisted conditions gave the lactam, which then underwent DDQ-mediated oxidation in 90% yield. Cleavage of the *O*- and *N*-protected benzyl groups under acidic conditions was performed. Unfortunately, only the *O*-benzyl groups were successfully cleaved to give the *N*-benzylated azalamellarin D **6** (Figure 3) as the product.



6

Figure 3: *N*-benzylated azalamellarin D **6**

Conclusions

We have successfully devised a more efficient synthetic route for azalamellarin D using benzyl as a sole protecting group for both phenolic and amide functionalities. Benzylamine was used as an amine source to incorporate nitrogen into the current core structure of the lamellarin framework. Thus far, the synthetic route for *N*-benzyl azalamellarin D was shortened to be only 4 steps starting from the pyrrole ester, with 54% overall yield. Final deprotection of the *N*-benzyl functionality is currently under investigations.

Acknowledgements

Financial supports from the Scientist Development Project Commemorating His Majesty the King's 84th Birthday Anniversary (to A.T.) and the Thailand Research Fund (TRF; DBG5480011 to M.C.) are gratefully acknowledged.

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SYNTHETIC STUDIES OF AZALAMELLARINS *VIA* DIRECT AMIDATION OF PYRROLE ESTERS WITH OR WITHOUT *N*-PROTECTING GROUP

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Abstract: Azalamellarins are derivatives of lamellarin marine alkaloids in which the lactone moiety is replaced with a lactam. In a previous study, these compounds were synthesized by using allyl as an *N*-protecting group. This synthetic route required a total of 9 steps with 11% overall yield starting from the pyrrole esters. Consequently, a shorter and more efficient route should be useful. Our approach involved the construction of pyrrole amides *via* direct/indirect amidation of the corresponding pyrrole esters as the key step. Microwave-assisted synthesis was carried out under different conditions and using a variety of reagents as the nitrogen source, including the benzyl-type amines and organic azides. The lactam formation was subsequently performed under Cu(I)-mediated, microwave-assisted conditions for C–N_{amide} bond formation. Using our new strategy, the *N*-benzylazalamellarin D was successfully prepared in 4 steps with 58% overall yield (starting from the pyrrole ester).

1. Introduction

Lamellarins are a group of marine alkaloids that have been isolated from marine invertebrates such as mollusks, ascidians, and sponges[1]. Until now, approximately forty lamellarins have been discovered, and a number of these compounds showed potent biological activities, including anti-tumor activity, HIV-1 integrase inhibition, and topoisomerase I inhibition[2-6]. These marine natural products contain a pentacyclic pyrrole alkaloid core with an orthogonal ring. There are different patterns of substituents around the pentacyclic core structure of lamellarins.

Structure-activity relationships (SARs) of lamellarins have been studied, showing the importance of various substituents on the common core structure[6-11]. The presence of C5–C6 olefin not only increases the aromatic character of the lamellarin core structure, but also enhances the cytotoxicity of these compounds. Either a hydroxyl or methoxy group can be placed at C9, C13, and C14. In contrast, C7, C8, and C20 should only be attached to a hydroxyl group to maintain the activity. Among the lamellarin members, lamellarin D complies with most of the requirements and possesses appreciable cytotoxicity. However, there are some issues regarding low aqueous solubility and poor stability under basic conditions. Therefore, a number of derivatives of lamellarins have been synthesized in order to address these issues and to streamline the structural requirement.

Reported synthetic routes of lamellarins can be categorized into two main strategies, which are pyrrole formation and transformation of preexisting pyrrole derivatives[12-15]. The first total synthesis of lamellarin D was reported, starting from condensation reaction between benzoate and benzylisoquinoline derivative. Quaternization of the reaction product with ethyl bromoacetate gave the desired ammonium salt, which was the key intermediate for the pyrrole ring closure and subsequent lactonization[16]. In an attempt to increase the solubility and stability of lamellarin D, its derivative called azalamellarin D has been previously synthesized with a lactam moiety replacing the lactone[17]. As nitrogen-containing heterocycles are the most important class of biologically active agents, a number of synthetic methods have been developed for these compounds *via* either inter- or intra-molecular approaches[18].

In this study, we attempted to shorten the synthetic route of azalamellarin D by using a new and effective synthetic methodology. Both the previously reported and our current routes shared the common pyrrole ester **3** (Scheme 1), but differed in the number of steps (9 for the previous route and 4 for ours). The established methodology could be used to synthesize a number of derivatives to further improve solubility, stability, and cytotoxic activity of azalamellarins.

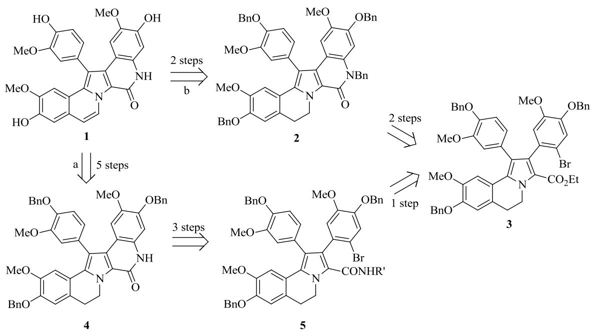
2. Materials and Methods

An efficient route to shorten the synthesis of azalamellarins using several *N*-protecting groups other than an allyl group was performed in this study. In addition, direct amidation using unprotected amines in the form of azides was also attempted to incorporate an amine into the core structure. The azide group could be transformed to give the lactam nitrogen *via* hydrogenolysis or reduction.

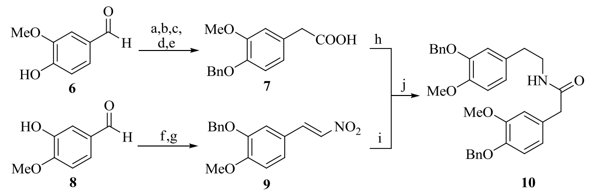
Our approach started with pyrrole formation using the convergent method previously established in our laboratory[15]. Scheme 2 demonstrates the synthetic route of the amide **10**. The corresponding imine was subsequently prepared using Bischler-Napieralski reaction. Then, condensation between the derivatives of benzyldihydroisoquinoline and α-nitrocinnamate **11**[17] was performed under basic conditions to furnish the desired pyrrole ester **3**.

Unlike in the synthesis of lamellarins, the nitrogen required for subsequent lactamization was first incorporated by converting the pyrrole esters to pyrrole amide intermediates using several types of amines either with or without microwave irradiation.

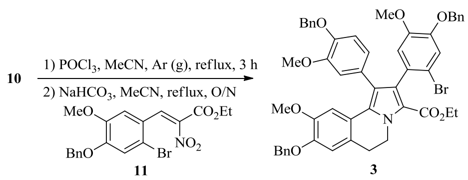
Afterwards, oxidation of the C5–C6 bond into an olefin was performed using dicyanodichlorobenzo-quinone (DDQ). Finally, removal of all the benzyl groups used to protect the hydroxyl moieties was performed to afford the desired azalamellarin D.



Scheme 1. Retrosynthesis of azalamellarin D (a) previously reported route; (b) our current route



Scheme 2. Synthesis of the amide intermediate **10** (a) BnBr, K_2CO_3, EtOH, reflux, 6 h, 84%; (b) $NaBH_4$, THF:EtOH (1:2), rt, 1 h, 91%; (c) $SOCl_2$, CH_2Cl_2, rt, 30 min; (d) KCN, Bu_4NBr, CH_2Cl_2:H_2O (1:1), rt, O/N, 70%; (e) KOH, EtOH:H_2O (2:1), reflux, O/N, 89%; (f) BnBr, K_2CO_3, EtOH, reflux, 3 h, 91%; (g) $MeNO_2$, NH_4OAc, AcOH, reflux, 40 min, 90%; (h) $(COCl)_2$, DMF (2 drops), CH_2Cl_2, 0˚C to rt, 2 h; (i) LAH, THF, 0˚C to rt, O/N; (j) Na_2CO_3, CH_2Cl_2, rt, 3 h, 51% (2 steps based on the acid **7**)



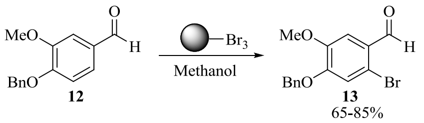
Scheme 3. Synthesis of the pyrrole ester **3**

3. Results and Discussion

3.1 Improvement of some steps in the previously developed synthesis of the lamellarin core

3.1.1 Bromination reaction

Previous synthesis of the requisite α-nitro-cinnamate **11** involved the use of molecular bromine in chloroform as a solvent to furnish the corresponding 2-bromo-*O*-benzylvanillin **13** in 25-35% yield, along with 11-43% yield of vanillin **6** from the undesired debenzylation of the starting material by HBr generated during bromination. After some experimentation, it was found that the best yield (65-85%) of **13** was obtained as the sole product using either polymer-bound or soluble pyridinium tribromide as the brominating agent in methanol (Scheme 4)[19].



Scheme 4. Bromination reaction

3.1.2 Pyrrole formation

The Michael addition/ring-closure (Mi-RC) reaction was performed between imine and α-nitro-cinnamate **11** for pyrrole formation (Scheme 3). In this study, the five-membered pyrrole **3** was synthesized in 51% yield for this step, compared with 33% yield in the previous report under the same method[17]. An issue of concern in order to get the best yield was the amount of limiting agent (α-nitrocinnamate), which should be sufficient for the reaction. Since **11** was synthesized from **13** but obtained as an inseparable mixture with **13** despite exhaustive purification techniques[14], the exact ratio of **11** and **13** was determined by ^{1}H NMR spectroscopy, and the amount of **11** required for pyrrole formation was calculated based on the NMR integral ratio. Following the completed Mi-RC reaction, **13** was separated from the desired pyrrole ester **3** *via* column chromatography.

3.2 Amidation and lactamization reactions

In the process of lactamization, the required nitrogen was incorporated into the core structure, either with or without a protecting group on this nitrogen.

3.2.1. With *N*-protecting group

Lactam ring closure was performed either with or without microwave irradiation. Under non-microwave conditions, either palladium (II) or copper (I) was used in a one-step lactam ring closure reaction (Table 1). The usage of palladium (II) and copper (I) has been previously demonstrated to form lactam moieties in biaryl system core structures[20-21]. Therefore, we employed similar conditions to incorporate a lactam ring into the lamellarin core structure to provide compound **14**. However, all non-microwave conditions in the current study yielded only the recovered starting material (Table 1).

Afterwards, microwave irradiation was used to assist the conversion of pyrrole ester **3** to the corresponding pyrrole amide **5**, in which the desired product was successfully obtained only when benzylamine was employed as the nitrogen source (Table 2). Then, the lactam ring closure was performed using Cu(I)-mediated, microwave-assisted reaction, followed by DDQ oxidation to give (*O*,*N*)-benzylated azalamellarin D **16** (Figure 1) in 95% yield.

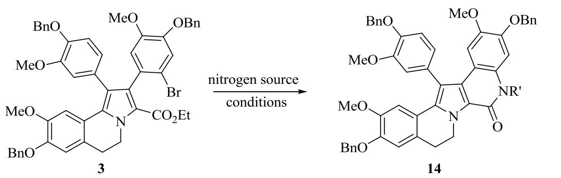


Table 1. Lactam ring closure with various *N*-protecting groups

Entry	*Nitrogen Source*	*Conditions*	*Result*
1	Acetamide	$PdCl_2$, Cs_2CO_3, Xantphos, 1,4-dioxane, 100°C, 24 h	**3** (60%)
2	*N*-Boc amine		**3** (50%)
3	Benzylamine		**3** (61%)
4		$Pd(OAc)_2$, Cs_2CO_3, Xantphos, 1,4-dioxane, 100°C, 24 h	**3** (40%)
5	*N*-Cbz amine	CuI, K_3PO_4, 1,10-phenanthroline, toluene, 90°C, 24 h	**3** (99%)

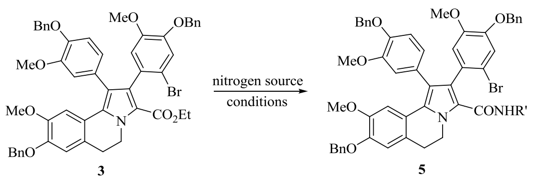
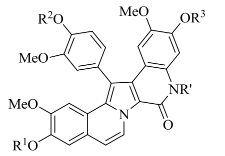


Table 2. Microwave-assisted pyrrole amide formation

Entry	*Nitrogen Source*	*Conditions*	*Result*
1	Benzylamine	Me_3Al, THF, 200°C, MW, 300 W, 250 psi, 45 min	**5** (62-94%)
2	*N*-Boc amine		**3** (80%)
3	*N*-Cbz amine		**3** (90%)

In this study, benzyl was used as the sole protecting group, with the expectation that all protecting groups could be simultaneously removed in one final step. Benzyl cleavage reactions have been reported using either hydrogenolysis or acidic cleavage[22]. While *O*-benzyl protecting groups could be easily removed by hydrogenolysis, this approach was not preferred in our route due to its incompatibility with C5–C6 olefin. Therefore, the acidic cleavage was selected to remove all benzyl protecting groups of the (*O*,*N*)-benzylated azalamellarin D **15**, which shortened the number of synthetic steps for azalamellarin D. Unfortunately, the benzyl group on the lactam nitrogen could not be removed, even when the reaction was allowed to stir overnight at 100°C. Therefore, the final product obtained from global deprotection of **15** was *N*-benzylated azalamellarin D **16** in 56-66 % yield.



15 R^1, R^2, R^3 = Bn; R' = Bn
16 R^1, R^2, R^3 = H; R' = Bn

Figure 1. Structures of benzylazalamellarin D **15**, **16**

3.2.2. Without *N*-protecting group

Due to the difficulties of removing the *N*-protecting group, we attempted to use TMS azide, sodium amide, and ammonia as the nitrogen sources to shorten the synthesis of azalamellarin D *via* **17** as an intermediate under both non-microwave and microwave-assisted conditions (Table 3). In the presence of sodium amide, the pyrrole ester was hydrolyzed to the carboxylic acid **18** (Figure 2), which then underwent lactone ring closure to furnish **19** under Cu(I)-mediated, microwave-assisted conditions, instead of the expected lactamization. When direct amidation without protecting group was performed using either ammonia in EtOH or TMS azide, the expected product was not observed.

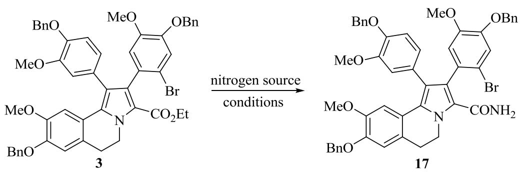


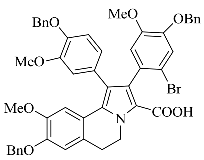
Table 3. Lactam ring closure without *N*-protecting group

Entry	*Nitrogen Source*	*Conditions*	*Result*
1	Sodium amide	$Pd(OAc)_2$, Cs_2CO_3, Xantphos, 1,4-dioxane, 100°C, 8 h	**18** [a]
2		$Pd(OAc)_2$, Cs_2CO_3, Xantphos, 1,4-dioxane, 100°C, 24 h	**18** [a]
3		$Pd(OAc)_2$, Xantphos, 1,4-dioxane, 100°C, 24 h	**18** [a]
4	TMS azide	Me_3Al, THF, 200°C, MW, 300 W, 250 psi, 45 min	Unknown side products

Table 3. (continued)

Entry	*Nitrogen Source*	*Conditions*	*Result*
5	TMS azide	Me_3Al, THF, rt (4 h) to 100°C, under Ar (g), O/N	Unknown side products
6		Me_3Al, THF, 100°C, MW, 150 W, 200 psi, 30-90 min	Unknown side products
7	NH_3	EtOH, 60-150°C, MW, 100-200 W, 200 psi, 30-70 min	**3** (80-100%)
8	Sodium amide	Me_3Al, THF, 150°C, MW, 200 W, 250 psi, 30 min	**18** [a]
9		1,4-dioxane, reflux, O/N	**18** (99%)

[a]Isolated yields were not determined. Compound **18** was used directly in the Cu(I)-mediated, microwave-assisted reaction to furnish **19** in 30-86% yields over two steps.



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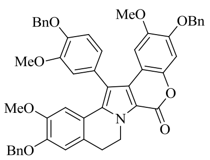

19

Figure 2. Pyrrole-2-carboxylic acid **18** and *O*-benzyl-lamellarin χ **19**

Using ammonia as reagent, the starting material was recovered in 80-100% yield. When sodium azide was used, no pyrrole azide was observed. Only unidentifiable by-products could be obtained.

4. Conclusions

We have successfully devised a more efficient synthetic route for azalamellarin D using benzyl as a sole protecting group for both phenolic and amide functionalities. Benzylamine was used as an amine source to incorporate nitrogen into the current core structure of the azalamellarin framework. Thus far, starting from the pyrrole ester **3**, *N*-benzylaza-lamellarin D **16** was synthesized with 58% overall yield over 4 steps of amidation (94%), lactamization (99%), DDQ oxidation (95%), and *O*-debenzylation (66%). Final deprotection of the *N*-benzyl functionality is currently under investigations.

Acknowledgements

Financial supports from the Scientist Development Project Commemorating His Majesty the King's 84th Birthday Anniversary (to A.T.) and Thailand Research Fund (TRF; DBG5480011 to M.C.) are gratefully acknowledged.

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การได้รับเชิญ
เป็นวิทยากร

Asian Core Program
NATIONAL TSING HUA UNIVERSITY
DEPARTMENT OF CHEMISTRY
HSINCHU, TAIWAN 300, REPUBLIC OF CHINA

Dr. Montakarn Chittchang
Laboratory of Medicinal Chemistry
Chulabhorn Research Institute
Kamphaeng Phet 6 Road, Laksi
Bangkok 10210, Thailand

September 26, 2012

Dear Dr. Montakarn Chittchang,

Congratulations on receiving 2011 Asian Core Program Lectureship Award!

As part of the Asian Core Program, we are conducting the activity on inviting Lectureship Awardees to visit Taiwan. I sincerely invite you to visit Taiwan during Nov 11 to Nov 17 and give a few lectures. We will cover the necessary costs during your stay in Taiwan.

We are looking forward to seeing you in Taiwan.

With our best regards,

Biing Jiun Uang

Dr. Biing Jiun Uang,
Coordinator (Taiwan) for Asian Core Program on
Cutting-Edge Organic Chemistry in Asia

國 立 清 華 大 學 化 學 系
NATIONAL TSING HUA UNIVERSITY
DEPARTMENT OF CHEMISTRY

Itinerary for the visit of Prof. Montakarn Chittchang

<table>
<tr><th>Date</th><th>Event</th><th>Host / Contact person</th></tr>
<tr><td>11/11
(Sun)</td><td>Arrival：THAI AIRWAYS TG634 BANGKOK 07:25 TAIPEI 11:55
Please kindly find the poster of your name in the Tao-Yuan airport lobby and identify yourself to the driver.

Hotel: Howard International House Taipei 台北福華文教會館
Confirmation #:RL39375；NT$1,800/per night
Address: 30, ShinSheng S. Rd. Sec. 3, Taipei, Taiwan 10660,R.O.C.
Tel: +886-2-7712-2323#2107</td><td>Driver:
上大車行+886-2-8287-7527 ext.10

Ms. Chao-Lin Yeh
Tel:+886-3-571-5131 ext.33340
Mobile:+886-939-507-035</td></tr>
<tr><td>11/12
(Mon)</td><td>National Taiwan Normal University (NTNU,台灣師範大學)
http://www.chem.ntnu.edu.tw/en/about/pages.php?ID=about1

10:00 Prof. Wu picks you up at the front door of the hotel and arrive at NTNU around 10:20
Lecture time: 15:30 -17:00
Speech Title: Studies towards More Drug-like Lamellarin Analogs</td><td>Prof. Hsyueh-Liang Wu (吳學亮)
Tel: +886-2-7734-6142
Mobile: +886-936-283-589
e-mail: hlw@ntnu.edu.tw

(台師大協助來回接送)</td></tr>
<tr><td>11/13
(Tues)</td><td>★Check out from Howard International House Taipei

10:30 Meet with Prof. Uang's students in the lobby at Howard International House Taipei and go for a short tour in Taipei

Hotel: Howard HsinChu 新竹福華大飯店(新竹市中正路 178 號)
Confirmation #: RP3615；NT$2,500/per night
Address: No.178, Zhongzheng Rd., North Dist., Hsinchu City 300, Taiwan (R.O.C.) Tel:+886-3-528-2220</td><td></td></tr>
<tr><td>11/14
(Wed)</td><td>National Tsing Hua University (NTHU,國立清華大學)
http://chem-en.web.nthu.edu.tw/bin/home.php

10:45 Driver picks you up at the front door of the hotel and arrive at NTHU around 11:00

Lecture time: 14:00 -15:30
Speech Title: Studies towards More Drug-like Lamellarin Analogs</td><td>Prof. Biing Jiun Uang (汪炳鈞)
Tel:+886-3-571-5131 ext.33410
Mobile: +886-926125268
e-mail: bjuang@mx.nthu.edu.tw
(去程/ 回程：八達車行)*

Ms. Chao-Lin Yeh
Tel: +886-3-571-5131 ext.33340
Mobile:+886-939-507-035</td></tr>
<tr><td>11/15
(Thurs)</td><td>Genomics Research Center, Academia Sinica (GRC, AS 中央研究院基因體中心) http://www.genomics.sinica.edu.tw/en

08:30 Driver picks you up at the front door of the hotel and arrive at GRC, AS around 10:00
Lecture time: 10:30 -12:00
Speech Title: Studies towards More Drug-like Lamellarin Analogs</td><td>Prof. Shang-Cheng Hung (洪上程)
Tel:+886-2-27871279
e-mail: schung@gate.sinica.edu.tw

(去程：八達車行/ 回程：上大車行)*</td></tr>
<tr><td>11/16
(Fri)</td><td>National Health Research Institutes (NHRI, 國家衛生研究院)
http://english.nhri.org.tw/NHRI_WEB/nhriw001Action.do?status=Show_Data&uid=20110614278757140000

10:30 Dr. Tseng of NHRI picks you up at the front door of the hotel and arrive at NHRI before 11:00
14:30-16:00 Lecture: Studies towards More Drug-like Lamellarin Analogs
Back to Hotel and take a rest
18:00 Prof. Uang's students will pick you up at hotel lobby for dinner</td><td>Prof. Kak-Shan Shia (夏克山)
E-mail：ksshia@nhri.org.tw

Contact: Ms. Ashley Chen (陳琦雯)
TEL: 886-37-246-166 ext. 35701</td></tr>
<tr><td>11/17
(Sat)</td><td>★Check out from Howard HsinChu Hotel
10:00 Prof. Uang's students pick you up at the front door of the hotel and go for a short tour then go to the airport.
Departure：THAIAIRWAYS TG635 TAIPEI 20:10 BANGKOK23:05</td><td>Driver:
八達車行+886-2-8287-7527 ext.10</td></tr>
</table>

Emergency contact person: Ms. Chao-Lin Yeh Cell: +886-939-507-035 / *上大車行+886-2-8287-7527 ext.10 / 八達車行+886-3-531-5492

Studies towards More Drug-like Lamellarin Analogs

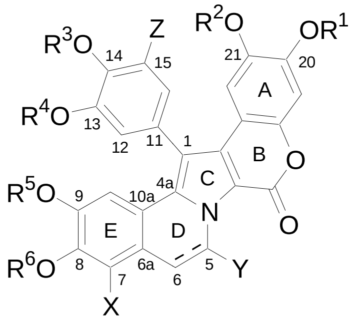
Montakarn Chittchang, Ph.D.

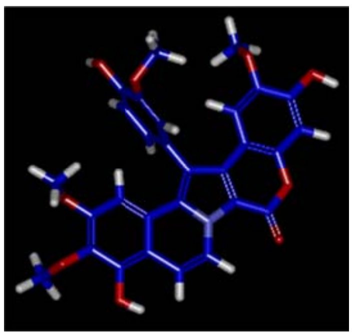
Laboratory of Medicinal Chemistry, Chulabhorn Research Institute

& Chemical Biology Program, Chulabhorn Graduate Institute

Kamphaeng Phet 6 Road, Laksi, Bangkok 10210, Thailand

Lamellarins constitute an interesting family of marine natural products with a pyrrolo(dihydro)isoquinoline lactone core. These compounds have shown promising therapeutic potential, especially for multidrug-resistant cancer treatments. Our interests in this group of compounds were originally focused on developing efficient methodologies for the total synthesis of both naturally-occurring and unnatural lamellarins. The scope was subsequently expanded to encompass extensive investigations of their cytotoxic activities against a panel of cancer cell lines, followed by systematic evaluations of their structure-activity relationships (SAR). More recently, drug-likeness of these compounds was also explored. The ultimate goal of our multidisciplinary research is to obtain lamellarin analog(s) with improved efficacy and specificity toward cancer cells, as well as optimal drug-like properties for further development.





Asian CORE Program Lectureship Tour in Taiwan
(November 11th – 17th, 2012)

Montakarn Chittchang, Ph.D.

Chulabhorn Research Institute & Chulabhorn Graduate Institute, Bangkok, Thailand

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Lecture Title: Studies towards More Drug-like Lamellarin Analogs

Host: Prof. Biing-Jiun Uang (National Tsing Hua University)

Institutions Visited: National Taiwan Normal University (NTNU), National Tsing Hua University (NTHU), Academia Sinica Genomics Research Center, and National Health Research Institutes (NHRI)

<u>Nov 11 (Sun)</u>: - Arrival at Taoyuan International Airport (TPE), Taipei

<u>Nov 12 (Mon)</u>:
- Visit to National Taiwan Normal University (**Host**: Prof. Hsyueh-Liang Wu)
- Discussion with Prof. Hsyueh-Liang Wu
- Lunch with Prof. Hsyueh-Liang Wu, Prof. Kwunmin Chen, Prof. Tun-Cheng Chien, Prof. Ying-Chieh Sun, Prof. Ming-Kang Tsai, and Dr. Po-Huang Liang (Academia Sinica Institute of Biological Chemistry)
- Discussion with Mr. Balraj Gopula (Prof. Hsyueh-Liang Wu's Ph.D. student)
- Lecture, followed by discussion with Prof. Kwunmin Chen
- Dinner with Prof. Hsyueh-Liang Wu and Prof. Way-Zen Lee

<u>Nov 13 (Tue)</u>:
- Short tour in Taipei with Mr. Wei-Ming Huang and Ms. Ying-Ying Shen (Prof. Biing-Jiun Uang's students)
- Visit to Chiang Kai-Shek Memorial Hall, followed by lunch at Din Tai Fung Restaurant
- Visit to National Palace Museum and Taipei 101 Observatory, followed by dinner at 1010 Restaurant
- Travel to Hsinchu by HSR high-speed train



<u>Nov 14 (Wed)</u>:
- Visit to National Tsing Hua University (**Host**: Prof. Biing-Jiun Uang)
- Discussion with Prof. Chun-Cheng Lin, followed by lunch with Prof. Biing-Jiun Uang and Prof. Chun-Cheng Lin
- Lecture, followed by discussion with Prof. Biing-Jiun Uang and Prof. Minoru Isobe
- Dinner with Prof. Biing-Jiun Uang, Prof. Minoru Isobe, Prof. Chun-Chen Liao, and Prof. Chun-Cheng Lin


<u>Nov 15 (Thu)</u>:
- Visit to Academia Sinica Genomics Research Center (**Host**: Prof. Shang-Cheng Hung)
- Lecture, followed by lunch with Prof. Shang-Cheng Hung, Dr. Rachel Cheng, Dr. Ying-Ta Wu, Dr. Shi-Shan Mao, and Dr. Cheng-Chung Wang (Academia Sinica Institute of Chemistry)
- Visit to the Museum of the Institute of History & Philology, Academia Sinica, guided by Ms. Chia-Wei Wang
- Visit to the High-Throughput Screening Center
- Discussion and a lab tour with Prof. Shang-Cheng Hung
- Dinner with Prof. Shang-Cheng Hung, Dr. Cheng-Chung Wang, and students



<u>Nov 16 (Fri)</u>:

- Visit to National Health Research Institutes (**Host**: Prof. Kak-Shan Shia)
- Visit to the facilities of the Institute of Biotechnology and Pharmaceutical Research, followed by a brief discussion with Dr. Lun Kelvin Tsou
- Lunch with Dr. Chiung-Tong Chen, Dr. Lun Kelvin Tsou, Dr. Shiow-Ju Lee, Dr. Shau-Hua Ueng, Dr. Jyh-Haur Chern, Dr. Weir-Torn Jiaang, and Dr. Tseng (post-doctoral fellow)
- Lecture, followed by a brief discussion with Prof. Kak-Shan Shia and Dr. Lun Kelvin Tsou
- Dinner with Mr. Wei-Ming Huang (Prof. Biing-Jiun Uang's student) and his wife, Ms. Yu Ching Huang

<u>Nov 17 (Sat)</u>:

- Short tour in Taoyuan with Mr. Yu-Ming Hung (Prof. Biing-Jiun Uang's Ph.D. student) and his girlfriend, Ms. Tzu-Tong Chen
- Visit to Shimen Reservoir and Daxi Mausoleum, followed by lunch at a nearby restaurant
- Visit to Cihu Mausoleum and Li Mei-shu Memorial Gallery
- Departure from the Taoyuan International Airport (TPE), Taipei



Acknowledgements:

This lectureship tour was truly beneficial for me, both scientifically and culturally. I would like to express my gratitude to all the host professors for their warm hospitality and kind arrangement during my visit to their institutions. I also would like to thank the National Science Council (NSC) in Taiwan and the National Research Council of Thailand (NRCT) for their generous financial support for my trip.

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Simposium Nasional Kimia Bahan Alam XXII

(SimNasKBA-2014)

"Pengembangan Kimia Bahan Alam untuk Mendukung Kemajuan Industri di Indonesia"

Bandung, 21-22 Oktober 2014

Bandung, 10 June 2014

Dr. Montakarn Chittchang
Chulabhorn Research Institute and Chulabhorn Graduate Institute, Bangkok (Thailand),

Dear,
Dr. Montakarn Chittchang,

Indonesian Society of Natural Products Chemistry in cooperation with Department of Educational Chemistry, Universitas Pendidikan Indonesia, Bandung, will organize the 22nd National Symposium of Natural Products Chemistry that will be conducted on 21-22 October 2014. Details of the symposium information are available in the leaflet that we attached.

On behalf of the organizing committee, I am pleased to invite you to attend the symposium as one of the invited speakers. During the symposium, we will also arrange congress of Indonesian Society of Natural Products Chemistry. Your attendance will be a great honor for us.

We can support your accommodation for four days and local transportation during your stay in Indonesia.

We will be waiting forward for your attendance confirmation. Please send the title and abstract of your lecturer by e-mail to simnaskba2014@gmail.com as soon as possible.

Sincerely yours,

Dr. Iqbal Musthapa
Chairperson of the organizing committee

Sekretariat:
Himpunan Kimia Bahan Alam Indonesia, Program Studi Kimia, Institut Teknologi Bandung,
Jalan Ganeca 10 Bandung, 40132. Telp.: 022-2534173; Fax.: 022-2504154;
E-mail: simnaskba2014@gmail.com

Jurusan Pendidikan Kimia FPMIPA Universitas Pendidikan Indonesia, Jalan Dr. Setiabudhi 229 Bandung 40154

SIMPOSIUM NASIONAL KIMIA BAHAN ALAM INDONESIA (SimNas KBA XXII)

UNIVERSITAS PENDIDIKAN INDONESIA, BANDUNG – 21,22 OKTOBER 2014

(TENTATIVE SCHEDULE)

DAY 1 : October 21, 2014

SESSION I

TIME	SPEAKER
08.00 – 09.30	**OPENING**
09.45 – 10.15	**Tomohisa Kuzuyama, Ph.D.** *Biotechnology Research Center, The University of Tokyo, Japan*
10.15 – 10.45	**Prof. Dr. Euis H. Hakim** *Institut Teknologi Bandung, Indonesia*
10.45 – 11.15	**Dr. Jalifah Latif** *Universiti Kebangsaan Malaysia, Malaysia*
11.15 – 11.45	**Prof. Dr. Asep Kadarohman** *Universitas Pendidikan Indonesia, Indonesia*
11.45 – 12.00	**DISCUSSION**

SESSION II

TIME	SPEAKER
13.00 – 13.30	**Prof. Minoru Isobe, Ph.D.** *National Tsing Hua University, Taiwan*
13.30 – 14.00	**Prof. Dr. Adel Zamri** *Universitas Riau, Indonesia*
14.00 – 14.30	**Prof. Dr. Khozirah Shaari** *Institute of Bioscience, Universiti Putra Malaysia, Malaysia*
14.30 – 15.00	**Dr. Tati Herlina** *Universitas Padjajaran, Indonesia*
15.00 – 15.15	**DISCUSSION**
15.30 – 17.15	**PARALLEL SESSIONS**

DAY 2 : October 22, 2014

SESSION I

TIME	SPEAKER
08.00 – 08.30	**Montakarn Chittchang, Ph.D.** *Chulabhorn Research Institute, Thailand*
08.30 – 09.00	**Prof. Dr. Yaya Rukayadi** *Universiti Putra Malaysia, Malaysia*
09.00 – 09.30	**Dr. Norizan Ahmat** *Universiti Teknologi MARA, Malaysia*
09.30 – 10.00	**Dr. Lia D. Juliawaty** *Institut Teknologi Bandung, Indonesia*
10.00 – 10.15	**DISCUSSION**
10.30 – 12.15	**PARALLEL SESSIONS**

SESSION II

TIME	SPEAKER
13.00 – 13.30	**Prof. Dr. Rohaya Ahmad** *Universiti Teknologi MARA, Malaysia*
13.30 – 14.00	**Prof. Dr. Sahidin** *Universitas Haluoleo, Indonesia*
14.00 – 14.30	**Dr. Mulyadi Tanjung** *Universitas Airlangga, Indonesia*
14.30 – 15.00	**Prof. Dr. Dayar Arbain** *Universitas Andalas, Indonesia*
15.00 – 15.15	**DISCUSSION**
15.30	**CLOSING**

SERTIFIKAT

diberikan kepada

Montakarn Chittchang, Ph.D.

yang telah berpartisipasi pada

Simposium Nasional Kimia Bahan Alam XXII

"Pengembangan Kimia Bahan Alam untuk Mendukung Kemajuan Industri di Indonesia"

sebagai

Invited Speaker

Auditorium FPMIPA Universitas Pendidikan Indonesia
Bandung, 21 - 22 Oktober 2014

diselenggarakan oleh

Himpunan Kimia Bahan Alam Indonesia

bekerjasama dengan

Jurusan Pendidikan Kimia - Universitas Pendidikan Indonesia

Ketua Himpunan Kimia Bahan Alam Indonesia,

HIMPUNAN KIMIA BAHAN ALAM INDONESIA

Prof. Dr. Unang Supratman

Ketua Panitia SimNasKBA - 2014

SimNasKBA-2014
Bandung, 21 - 22 Oktober 2014

Dr. Iqbal Musthapa, M.Si.