12th International Conference on Recent Innovations in Science, Engineering and Management
Sri Venkateswara College of Engineering & Technology,Etcherla, Srikakulam (ICRISEM'18)
17th February 2018 www.conferenceworld.in ISBN: 978-93-87793-01-9

Design, synthesis and isoform selective PI3K inhibitory activity of modified B-ring Liphagal analogs

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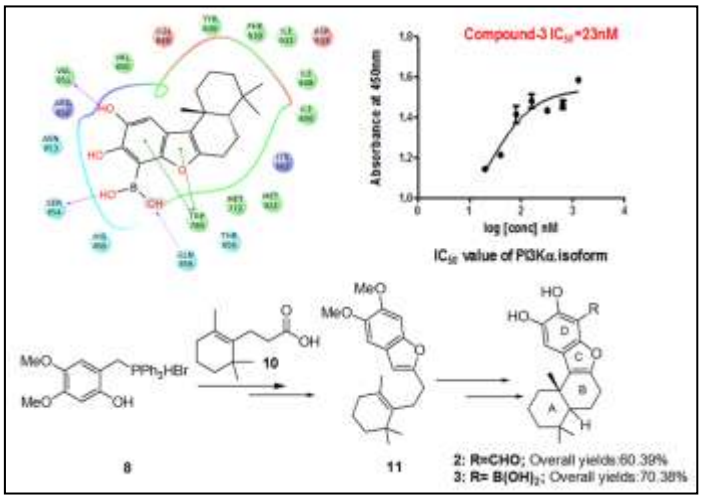
ABSTRACT

*Herein, we report the design, synthesis and isoform selective PI3K-α inhibitory activity (IC_{50} 23 nM) of liphagal analog **3** with contracted B ring having boronic acid functionality. The rational for design of **3** is based on remarkable selectivity of natural liphagal (IC_{50} 100 nM) and its analog **2** (IC_{50} 66 nM) reported for PI3K-α isoform. Moreover, here we present formation of novel tetracyclic liphagene meroterpenoid skeleton in two steps and the synthesis of **2** and **3** is achieved in four steps using linear approach with good and scalable yields.*



Keywords: Meroterpenoid, Liphagal, Boronic acid, PI3K inhibitor, Isoform selectivity

I.INTRODUCTION

The phosphatidylinositol 3-kinase (PI3K) signaling axis impacts on cancer and is an important drug target for developing tumor treatments, due to their involvement with various signaling pathways and cell functions such as cell growth, survival, motility, proliferation, apoptosis, intracellular trafficking, metabolism and many others. However, therapeutics targeting the PI3K pathway are being developed at a rapid pace, and preclinical as well as early clinical studies are beginning to suggest specific strategies to be effectively evolved and use them.[1] The

isoform specific molecules capable of attenuating PI3K signaling targeting specific p110 isoform possess significant therapeutic potential for treatment of various diseases such as inflammation, autoimmune diseases, cardiovascular diseases and cancer.[2]

Fig. 1: Liphagal and its analogs as selective PI3K inhibitors

In 2006, Andersen *et al.*, reported the isolation of a novel meroterpenoid molecule liphagal **1** from the marine sponge *Aka coralliphaga*, the first member of a new 'liphagane' type, bearing a tetracyclic carbon skeleton.[3] The PI3K-α isoform selectivity exhibited by liphagal **1** is highly significant as compared to other first generation PI3K inhibitors such as natural product wortmannin, the natural flavonoids quercetin and myrecetin, and the synthetic analog of quercetin LY 294002, which have been deployed extensively during last two decades to analyze PI3K signaling pathways.[4] Due to non-selectivity for PI3K isoforms and high toxicity, these molecules could not make the success towards the clinical development. But they opened the way to several other chemo-types for development as PI3K inhibitors and this has led to a race amongst the pharmaceutical companies. Until now, over 20 compounds targeting PI3K have been in clinical evaluation for cancer therapy.

Since beginning, discovery of PI3K-α specific inhibitors has been pursued for cancer therapy based on the understanding that only PI3K-α gene (PIK3CA) mutations and amplifications observed in human cancers, and inhibition of other isoforms might cause side effects. However, most PI3K inhibitors in clinical evaluation are pan-PI3K inhibitors (without obvious isoform selectivity).[5] Because of isoform selectivity and potency of liphagal **1**, it has gained attention of many pharmaceutical companies as starting point for the development of synthetic PI3K inhibitors that would represent potential drug candidate for cell biology tools.

From a structural viewpoint, natural liphagal **1** has number of chemical stability issues that limits its development into a drug candidate. Formation of orthoquinone by metabolic air/enzymatic oxidation of catechol moiety is one of the major issue that needs to be solved for this structure. Other limitation is the presence of aldehyde functionality, which is a reactive electrophile that could form imines and thiohemiacetals and offers non-selectively with off-target proteins, and this functionality is also susceptible for oxidation to the corresponding carboxylic acid.[6] Therefore, modified analog of liphagal with similar or more activity and

selectivity without structural stability issues is highly desirable for taking the molecule to further preclinical development.

To the best of our knowledge, till date there are very few reports available on the synthesis and analogs of liphagal and there is no concrete SAR established yet on this molecule.[6,7] Recent report on synthetic analog of liphagal **2**[6] (Fig. 1) with an IC_{50} of 66 nM and selectivity towards PI3K-*α*, suggests that this analog possess greater chemical structure stability and gives opportunity for developing this skeleton into lead preclinical candidate. As a part of our ongoing program on developing isoform selective PI3K inhibitors,[8] it occurred to us that it would be interesting to embark a program on the preparation of analogs based on structure **2**, leveraging the evidence of biological activity exhibited by **2**. In this direction, we initiated our efforts and at very first instance, we planed to replace aldehyde functionality with boronic acid expecting that it will help in solving the chemical stability issues associated with the structure. Further, the 14-formyl-15,16-dihydroxy substitution pattern in the aromatic ring of liphagal **1** is required to achieve nanomolar potency. It is also demonstrated that the absence of the C-14 formyl group appears to destabilize the liphagane heterocyclic ring system, making it more susceptible to air oxidation and skeletal rearrangements involving ring B contraction. This evidence suggests that the C-8 desmethyl analog with contracted B ring to six-membered, must be ultimately responsible for the activity, which supports our envision. Therefore, instead of formyl at the C-14, we designed a contracted B ring analog without formyl functionality having boronic acid at C-13 position, assuming that this analog **3** would offer more rigidity to the structure. Also, using a boronic acid instead of an aldehyde could circumvent the associated drawbacks. Moreover, boron has ability to biomimic carbon and forms the covalent adducts with the serine or histidine residues of the active site.[9] The boron-containing marketed drug by Millenium's Bortezomib/Velcade,[10] is the first compound reported as proteasome inhibitor used for multiple myeloma and mantle cell lymphoma. Thereafter, boron atom containing many molecules started appearing for various applications in preclinical and clinical studies.[11] Keeping in view the role of boron, the importance of boronic acid analog of liphagal **3** was visualized as potential PI3K inhibitor because of its additional benefits. On computational docking of this boronic acid analog **3** with PI3K showed excellent H-bonding interactions with key amino acids, which suggested that it is worth pursuing the synthesis of this molecule and explore its biological potential. Therefore, a very short and convenient route was designed for the chemical synthesis of **3** as well as we planed to synthesize **2** also, as it could be prepared easily with many common steps. The evidence from the *in silico* docking studies supported the importance of boron containing two hydroxyl groups, which showed H-bond interaction of both these –OH with key amino acid residue Val851 and Ser854, and 16-hydroxy from the phenolic –OH interacts with Gln859 of **3**, which is also previously reported as a key amino acid to be involved in inhibitory interactions in the p110α active site of PI3K-α.[12] This analog has also shown improved docking score of -8.08 over **1** and **2**. The biological potential of **3** as PI3K inhibitor was also studied, it has shown PI3K-*α* isoform selectivity and excellent inhibitory activity with an IC_{50} 23 nM.

II.RESULTS AND DISCUSSION

2.1MOLECULAR MODELING

From the protein ligand interaction figure (Fig. 2; C), it is observed that **3** is involved in H-bonds interaction with three amino acids *i.e.* Val851 (1.79Å); Ser854 (1.65Å); Gln859 (1.99Å) respectively. These three strong H-bonds are proposed to provide stability to the ligand within the kinase binding pocket. Also the possibility of π-π interaction between the benzofuran ring of **3** and Trp780 residue of the protein is shown, that may contribute in providing some extra stability to the complex. Hence it is predicted that the orientation of the benzofuran ring towards the hinge region of the kinase domain of the protein facilitates the above mentioned interactions and thereby makes the complex stable within the binding pocket. The comparative docking scores amongst these molecules are found to be better for analog **3** (Table 1). Moreover, as shown in the figure (Fig. 2:C), boron atom is oriented in such a fashion that it is proposed to facilitate a covalent interaction as discussed earlier with -OH and -NH of Ser854 at 2.866Å and 2.914Å respectively.

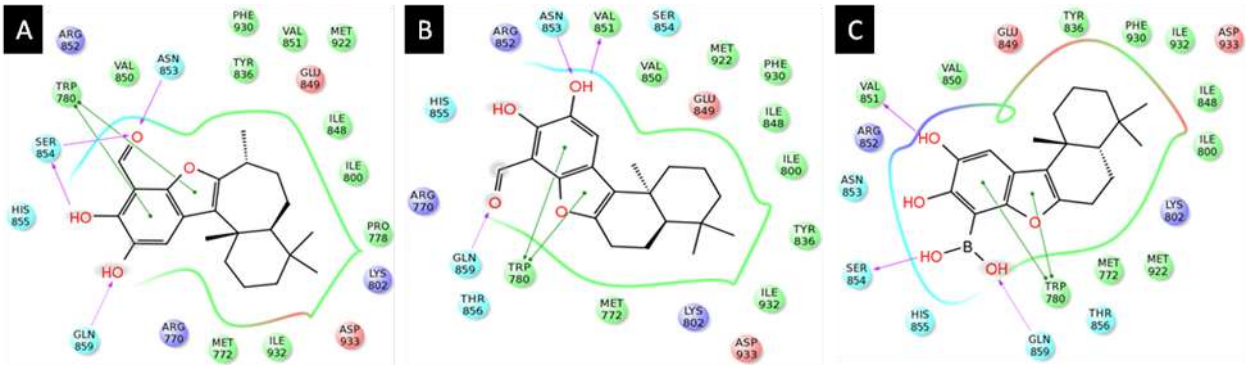


Fig. 2: Interactions between PI3K-α isoform and inhibitors 1, 2 and 3

Table 1: Docking score and H-bond interactions between inhibitors and key amino acid residues of PI3K-*α*

Compound	PI3K-*α* (Model: 3HHM)		
	Docking Score	Interactions	
		H-Bond	π-π Bond
1	-7.144	Asn853 (2.15Å); Ser854 (1.87Å); Ser854 (2.08Å); Gln859 (2.1Å)	Trp780
2	-7.554	Val851 (1.69Å); Asn853 (2.32Å); Gln859 (1.83Å)	Trp780
3	-8.08	Val851 (1.79Å); Ser854 (1.65Å); Gln859 (1.99Å)	Trp780

2.2CHEMISTRY:

The molecules **2** and **3** have been prepared by short and very convenient route as shown in the Scheme 3 and 4. The synthesis has been achieved by separate preparations of the starting materials viz. intermediate **8** and **10** for the synthesis of **2** and **3**.

Scheme 1: Synthesis of key intermediate 8; triphenyl phosphonyl hydrogen bromide salt of 2-(hydroxymethyl)-4,5-dimethoxyphenol

Reagents and conditions: a) BBr_3, DCM, rt b) Methoxymethylchloride, DIPEA, DCM c) $NaBH_4$, MeOH d) PPh_3HBr, ACN, reflux, 2h

Scheme 2: Synthesis of intermediate 10; 3-(2,6,6-trimethylcyclohex-1-enyl)propanoic acid

Scheme 3: Synthesis of contracted B ring containing liphagal analog 2

Reagents and conditions: a) DCC, DMAP, DCM, rt, 18h, b) ii) Et_3N, THF, reflux, 5h c) $ClSO_3H$, 2-Nitropropane, -78°C, 0.5h d) *n*-BuLi, THF, DMF, 0 ^{o}C, 1.5 h. e) $AlCl_3$, dimethylsulfide, DCM, rt, 1h.

Scheme 4: Synthesis of contracted B-ring boronic acid liphagal analog 3

Reagents and conditions: a) *n*-BuLi, 0 ^{o}C, triethylborate, 45 min b) $AlCl_3$, thiourea, DCM, rt, 2h.

The synthesis of liphagal analogs **2** and **3** both, was started with conversion of commercially available 2,4,5-trimethoxybenzaldehyde **4** into mono demethylated aldehyde **5** by treating with boron tribromide in dichloromethane at room temperature. The free phenolic hydroxyl obtained was protected with MOM group to get **6** and this protected aldehyde was reduced to alcohol **7** using $NaBH_4$ as a reducing agent. This primary alcohol is treated with PPh_3HBr to obtain its triphenyl phosphonium salt **8** (Scheme 1) in the MOM deprotected phenolic form. The acid **10** *i.e.* 3-(2,6,6-trimethylcyclohex-1-enyl)propanoic acid was prepared from its ketone **9** (Scheme 2), which was coupled with the phenol **8** by using dicyclohexylcarbodiimide and catalytic amount of 4-dimethylaminopyridine (DCC/DMAP) coupling strategy, the ester formed was subsequently cyclized without further purification. The crude was taken as such in THF and triethylamine was added and refluxed, this gives cyclized product 5,6-dimethoxy-2-(2-(2,6,6-trimethylcyclohex-1-enyl)ethyl)benzofuran **11**. The double bond of cyclohexene ring was utilized for intramolecular cyclization using chlorosulphonic acid as cyclizing agent at -78 ^{o}C with the benzofuran moiety to form six membered cyclized product **12**, which offers the liphagane skeleton to the structure. This cyclized intermediate was utilized by diversifying it into two ways for synthesis of **2** and **3**. Further, for preparation of **2**, formylation reaction on this liphagane skeleton *i.e.* intermediate **12** was carried out using *n*-BuLi and TMEDA at -10 ^{o}C on the C-13 position of aryl ring to give formylated product **13**. Finally, the demethylation was performed by $AlCl_3$/dimethylsulfide mixture to obtain the target molecule **2** (Scheme 3).

However, as discussed earlier, similar strategy was followed for the preparation of boronic acid analog **3** from intermediate **12**. The boronylation was carried out on intermediate **12** using *n*-BuLi at 0 ^{o}C and treating with triethylborate at same temperature to obtain **14**. The demethylation of **14** was carried out by $AlCl_3$ and thiourea mixture (6:4) in DCM to get the final product boronic acid liphagal analog **3** (Scheme 4).

PI3K enzyme inhibition assay: The PI3K assay was performed for compound 3 using PI3 Kinase inhibitor assay kit, where PI3 kinase reaction was set up in glutathione-coated strips/plate for inhibitor reaction.[13] The liphagal analog **3** inhibited PI3K enzyme activity for its α-isoform in dose dependent pattern with varying concentrations *i.e* 20, 40, 80, 160, 320 and 640 nM respectively and the IC_{50} values were determined using Graph Pad Prism5 software for the readings obtained on absorbance at 450 nm.

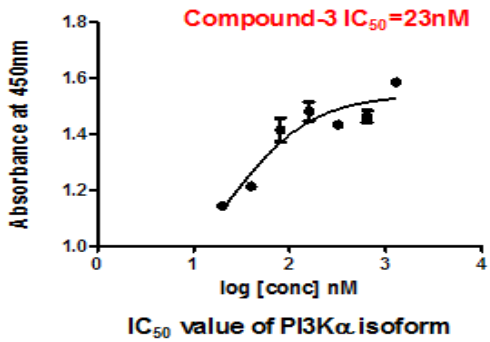


Fig. 3: Graph showing IC_{50} value of PI3K-α isofrm for compound-3

Table 2: Showing IC_{50} values of PI3K isoforms for compound-3

Compound	PI3K (IC_{50})			
3	α	β	γ	δ
	23 nM	5.7 µM	85.39 µM	303 µM

The observed IC_{50} value for this compound is 23 nM for PI3K-α isoform (Fig. 3). However, for all other isoforms *viz*. β, γ and δ, the assays were performed and the observed IC_{50} values for these isoforms are shown in table 2.

In conclusion, we have synthesized analogs of liphagal **2** and **3** in simple, convenient and efficient manner with excellent yields. The pharmacological studies pertaining to liphagal analog **3**, in particular it's PI3K-α isoform selectivity and inhibitory activity is found to be highly significant, hence this analog could be a promising candidate for exploitation of its in detailed biological potential and further preclinical development. The exploration of pre-clinical studies like PK-ADME and *in vivo* animal studies are presently undertaken and will be published in due course.

III.EXPERIMENTAL SECTION:

Procedure for the synthesis of 2-hydroxy-4,5-dimethoxybenzaldehyde (5) :

To a solution of 3,4,5-trimethoxybenzaldehyde (5g, 25.510 mmol) in CH_2Cl_2 (125 ml) at 0 ^oC, BBr_3 (6.39 g, 25.510 mmol) was added. The resulting dark mixture was stirred at rt for 9 h. Water (100 mL) was charged and the mixture was stirred for 10 min, the aqueous phase was extracted by CH_2Cl_2. Organic phase was dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography using plain dichloromethane as eluent, afforded the 2-hydroxy-4,5-dimethoxybenzaldehyde **5** (4.3g, 87%) isolated as yellow solid: ^1H NMR ($CDCl_3$, 400 MHz): δ 11.40 (br. s, 1H), 9.70 (s, 1H), 6.91 (s, 1H), 6.48 (s, 1H), 3.94 (s, 3H), 3.88 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): 194.03, 159.31, 157.28, 142.92, 113.26, 112.86, 100.09, 56.40, 56.32. HRMS *(m/z)*: calcd for C9H10O4: 182.0579; Found: $[M+H]^+$: 183.0653

Procedure for the synthesis of 4,5-dimethoxy-2-(methoxymethoxy)benzaldehyde (6):

A solution of **5** (1g, 5.49 mmol) in anhydrous CH_2Cl_2 under nitrogen was cooled to 0 ^oC, to it diisopropyl ethylamine (DIPEA) (1.77g, 13.736 mmol) and MOMCl (0.66g, 8.241 mmol) were added. The reaction mixture was stirred at room temperature for 1h. After completion of the reaction, water was added extracted with dichloromethane. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure, the resultant product **6** (2.15g, 98%) colorless liquid was used for further reaction without purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.34 (s, 1H), 7.30 (s, 1H), 6.77 (s, 1H), 5.26 (s, 2H), 3.95 (s, 3H), 3.88 (s, 3H), 3.54 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): 188.02, 156.39, 155.53, 144.44, 118.13, 108.25, 99.18, 95.45, 56.43, 56.19, 56.08. HRMS *(m/z)*: calcd for C11H14O5: 226.0841; Found: $[M+H]^+$: 227.0897

Procedure for the synthesis of (4,5-dimethoxy-2-(methoxymethoxy)phenyl methanol (7):

The solution of compound **6** (1g, 4.423 mmol) and sodium hydroxide (0.177g, 4.423 mmol) in MeOH was taken in round bottom flask, to it $NaBH_4$ (0.25g, 6.635 mmol) was added. The reaction mixture was stirred for half hour at room temperature. The reaction mixture was concentrated under reduced pressure to remove MeOH, added water and was extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure afforded colorless liquid **7** (0.99g, 98%), the resultant product was used for further reaction without purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.86 (s, 1H), 6.75 (s, 1H), 5.16 (s, 2H), 4.65- 4.62 (d, *J* = 5.29 Hz, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.52 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): 149.15, 149.05, 144.13, 122.10, 112.46, 101.26, 96.03, 60.69, 56.26, 56.12, 55.99. HRMS *(m/z)*: calcd for C11H16O5:228.0998; Found: $[M+Na]^+$: 251.0874

Procedure for the synthesis of triphenylphosphine salt of 2-(hydroxymethyl)-4,5-dimethoxyphenol (8) :

A solution of compound **7** (1g, 4.384 mmol) in acetonitrile was taken, to this PPh_3HBr (1.8g, 5.260 mmol) was added at room temperature and refluxed for about 2 h. After completion of the reaction solvent was removed under reduced pressure and washed with ether, gave compound **8** (1.69g, 90%) as a white amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.62 (br. s, 1H,), 7.75-7.71 (m, 3H), 7.60-7.52 (m, 12H), 7.03 (s, 1H), 6.44-6.43 (d, *J* = 12.8 Hz, 1H), 4.48-4.45 (d, *J* = 12 Hz, 2H), 3.69 (s, 3H), 3.48 (s, 3H) ppm.^{13}CNMR ($CDCl_3$, 125 MHz): 134.75, 134.72, 134.27, 130.00, 129.87, 113.94, 113.90, 101.98, 101.94, 56.27, 55.96, 25.31, 24.83. HRMS *(m/z)*: calcd for C27H26O3P: 429.1620 (-HBr); Found: $[M]^+$: 429.1615 (loss of HBr).

Procedure for the synthesis of intermediate 3-(2,6,6-trimethylcyclohex-1-enyl) propanoic acid (10):

17g (425.001 mmol) of NaOH was dissolved in water to make a 70 ml solution in a 250 ml conical flask with a magnetic stirrer. The alkali solution was then cooled in an ice bath and 17g (106.25 mmol) of bromine was added to the solution after stirring for 1h, 4.5g (23.19 mmol) of dihydro-*β*-ionone in 10 ml of dioxane was dropped into the solution, the stirring was continued at rt for 4 h. The excess of hypobromite was neutralized with 10% sodium bisulfite and solution was extracted with ether to remove remaining impurities. Acidification of the alkaline solution with conc. hydrochloric acid was done under usual workup, gave **10** (4.1g, 90.1%) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.44-2.39 (m, 2H), 2.37-2.31 (m, 2H), 1.93-1.89 (t, *J* = 8Hz, 2H), 1.61 (s, 3H), 1.58-1.54 (s, 2H), 1.44-1.41 (m, 2H), 1.00 (s, 6H). ^{13}CNMR ($CDCl_3$, 100MHz): 180.30,

135.45, 128.53, 39.71, 34.98, 34.77 (merged peak), 32.72, 28.38, 23.50, 19.65, 19.41. HRMS *(m/z)*: calcd for C12H20O2: 196.1463; Found: $[M+H]^+$ 197.1530.

Procedure for the synthesis of 5,6-dimethoxy-2-(2-(2,6,6-trimethylcyclohex-1-enyl)ethyl)benzofuran (11):

The intermediate **8** (2g, 4.651 mmol) was taken in dry DCM along with dihydro-*β*-ionicacid **10** (0.91g, 4.65mmol) in round bottom flask, in dry conditions and cooled to 0 ^oC. To it DCC (2.87g, 13.953 mmol) and DMAP (0.56g, 4.651 mmol) were added and stirred at room temperature for 18 h. DCM was evaporated under reduced pressure and the crude reaction mixture was dissolved in THF and to it was added triethylamine and refluxed for 3 h. THF was evaporated under reduced pressure and purified by column chromatography 5 % ethyl acetate: hexane afforded **11** (1.42g, 93%) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 6.93 (s, 1H), 6.85 (s, 1H), 6.20 (d, *J* = 0.6 Hz, 1H), 3.81 (d, 6H), 2.70-2.66 (m, 2H), 2.34-2.30 (m, 2H), 1.87-1.85 (t, *J* = 6.1 Hz, 2H), 1.58 (s, 3H), 1.54-1.44 (m, 2H), 1.51-1.49 (m, 2H), 0.96 (s, 6H). $^{13}CNMR$ ($CDCl_3$, 100 MHz): 158.81, 149.11, 146.98, 146.15, 136.20, 128.14, 102.70, 101.06, 95.28, 56.40, 56.22, 39.7, 39.76, 35.00, 32.74, 29.27, 28.53, 27.20, 19.82, 19.48 (merged peak). HRMS *(m/z)*: calcd for C21H28O3: 328.3028; Found: $[M+H]^+$: 329.2099.

Procedure for the synthesis of cyclized product 12:

The solution of compound **11** (1g, 3.049 mmol) was prepared in 2-nitro propane and cooled to -78 ^oC, to it chlorosulfonic acid (1.06 g, 9.146 mmol) was added under inert atmosphere. The reaction mixture was stirred for 30 min. The reaction mixture was quenched with $NaHCO_3$ and extracted by ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure and purified by column chromatography using 5 % ethyl acetate: hexane afforded **12** (0.9g, 90% yield) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.00 (s, 1H), 6.97 (s, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 2.79-2.74 (m, 1H), 2.72-2.65 (m, 1H), 2.42 (d, *J* = 13.0 Hz, 1H), 2.06-1.91 (m, 2H), 1.87-1.76 (m, 2H), 1.50-1.63 (m, 2H), 1.45-1.39 (m, 2H), 1.31 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H).$^{13}CNMR$ ($CDCl_3$, 125 MHz): 151.20, 149.20, 146.43, 145.40, 124.28, 118.82, 102.44, 95.51, 56.58, 56.18, 52.65, 41.80, 37.66, 35.95, 33.52, 33.15, 24.96, 21.82, 21.32 (merged peaks), 18.83; HRMS *(m/z)*: calcd for C21H28O3: 328.3028; Found: $[M+Na]^+$: 351.1931

Procedure for the synthesis of 13:

The solution of compound **12** (0.5g, 1.524 mmol) in dry THF was prepared, and was cooled to 0 ^oC under dry condition. To it *n*-BuLi (0.195g, 3.048 mmol) was added and the reaction mixture was kept stirring for 20 minutes, and DMF (1.114g, 15.243 mmol) was added and stirred for 1 h. Quenched with ammonium chloride solution and extracted by ethyl acetate. Concentrated the crude under reduced pressure and purified by column chromatography using 6% ethyl acetate: hexane afforded **13** (0.48g, 88%) as a pale yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 10.55 (s, 1H), 7.32 (s, 2H), 3.98 (s, 2H), 3.94 (s, 1H), 2.92-2.87 (m, 1H), 2.84-2.76 (m, 1H), 2.39 (d, *J* = 12.0 Hz, 1H), 2.04-2.00 (m, 2H), 1.83-1.78 (m, 2H), 1.74-1.67 (m, 4H), 1.43–1.37 (m, 2H), 1.30 (s, 3H), 0.98 (s, 3H), 0.95 (s, 3H).$^{13}CNMR$($CDCl_3$, 100 MHz): δ 188.72, 154.60, 149.45, 148.56, 123.70, 123.64, 115.45, 110.15, 62.88, 56.91, 52.65, 41.72, 37.73, 35.97, 33.51, 33.18 (merged peak), 25.17, 21.96, 21.33, 18.88, 18.78. HRMS *(m/z)*: calcd for $C_{22}H_{28}O_4$: 356.1988; Found: $[M+1]^+$: 357.2068, $[M+Na]^+$: 379.1888, $[M+K]^+$: 395.1631.

Procedure for the synthesis of 2:

$AlCl_3$ (0.374g, 2.809 mmol) was taken along with dimethylsulfide (2 ml) under dry atmosphere in a flask and cooled to -5 to -10 ^oC. To it compound **13** (0.1g, 0.280 mmol) was added and stirred for about 1 h. After completion of reaction, water was charged and extracted with ethyl acetate. Organic phase was dried (Na_2SO4) and concentrated under reduced pressure. Silica gel column chromatography 7% EtOAc/hexane, afforded **2** (0.075g, 82%) as a yellowish solid. ^1H NMR (500 MHz, $CDCl_3$) δ 11.21 (s, 1H), 10.45 (s, 1H), 7.37 (s, 1H), 5.39 (s, 1H), 2.81-2.71 (m, 2H), 2.36 (d, *J* = 12 Hz, 1H), 2.04-1.99 (m, 2H), 1.84-1.68 (m, 2H), 1.62 (m, 2H, merged signals), 1.43-1.37 (m, 2H), 1.28 (s, 3H), 0.98 (s, 3H), 0.94 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): 192.46, 152.07, 148.83, 145.10, 140.02, 124.43, 118.74, 113.40, 106.79, 52.59, 41.75, 37.55, 35.91, 33.53, 33.18, 29.68, 24.89, 21.92, 21.32, 18.81. HRMS *(m/z)*: calcd for $C_{20}H_{24}O_4$: 328.1675; Found: $[M+Na]^+$: 351.1560

Procedure for the synthesis of 14:

The solution of compound **12** (1g, 3.048 mmol) was prepared in dry THF, and cooled to 0 ^oC under dry condition. To it *n*-BuLi (0.195g, 3.048 mmol) was added and the reaction mixture was kept for 20 minutes stirring, to it triethyl borate (0.45g, 3.048 mmol) was added and continued stirring for another 1 h at rt. Quenched with ammonium chloride solution and extracted by ethyl acetate. Concentrated under reduced pressure and purified by column chromatography using 6 % ethyl acetate: hexane afforded **14** (1.043g, 92%) as a colorless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H), 6.83 (s, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 2.80-2.73 (m, 2H), 2.42 (d, *J* = 12.0 Hz, 1H), 2.03 (m, 2H, merged signals), 1.89-1.76 (m, 2H), 1.73-1.66 (m, 2H), 1.45-1.40 (m, 2H), 1.32 (s, 3H), 0.99 (s, 3H), 0.96 (s, 3H).^{13}C NMR ($CDCl_3$, 100 MHz) 153.08, 152.90, 151.04, 148.38, 124.30, 122.40, 107.10, 61.89, 56.70, 52.71, 41.81, 36.06, 33.55, 33.24 (merged peaks), 25.07, 21.86, 21.38, 18.92, 18.82. HRMS *(m/z)*: calcd for $C_{21}H_{29}BO_5$: 372.2108; Found:$[M]^+$: 372.2231.

Procedure for the synthesis of 3:

To (0.5g, 4.301 mmol) of dry aluminium chloride, 5 ml of dichloromethane was poured, then (0.245g, 3.225 mmol) of crystalline thiourea was added in small portions and stirred for 20 minutes. The reaction mixture becomes transparent oily solution. Then compound 14 (0.1g, 0.268 mmol) dissolved in dichloromethane was added to this over a period of 5 minutes and stirred for 2 h at rt. The excess of $AlCl_3$ was removed by quenching with ice and extracted by dichloromethane and then purified by column chromatography using 15% ethylacetate: hexane afforded **3** (0.077g, 85% yield) as a colorless liquid. ^1H NMR (500 MHz, $CDCl_3$): δ 7.10 (s, 1H), 6.74 (s, 1H), 6.48 (br.s, 1H), 3.94 (s, 2H), 2.80-2.71 (m, 2H), 2.39 (d, *J* = 10 Hz, 1H), 2.20-2.03 (m, 2H), 1.80-1.70 (m, 2H), 1.54-1.51 (m, 2H), 1.44-1.37 (m, 2H), 1.30 (s, 3H), 0.98 (s, 3H), 0.95 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): 153.39, 151.14, 147.95, 142.90, 124.26, 118.08, 114.06, 105.1, 52.65, 41.79, 37.71, 36.01, 33.55, 29.51, 25.00, 21.88, 21.37, 18.91, 18.84; HRMS *(m/z)*: calcd for $C_{19}H_{25}BO_5$: 344.1795; Found: $[M^+-1]$: 343.0000.

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