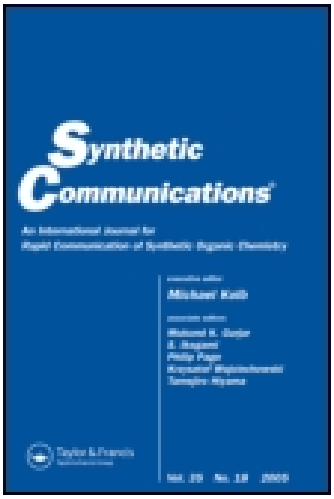

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EFFICIENT SYNTHESIS OF KEY INTERMEDIATE TOWARD LIPHAGAL SYNTHESIS

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Liphagal (A) is a very potent and selective inhibitor of PI3Kα (p110α) and is under development for an oncolytic drug. We herein report the new and concise synthesis of key intermediates (7, 8), which have been used for liphagal synthesis and will be useful for generating liphagal-based chemical entities for drug discovery purposes.

Keywords: Anticancer; isoform selective inhibitor; liphagal; natural product synthesis; PI3K

INTRODUCTION

Phosphatidylinositol-3-kinases (PI3Ks) are members of a family of lipid kinases that regulate cellular metabolism and growth by phosphorylation of the 3-position of phosphatidylinositol diphosphate (PIP_2) to phosphatidylinositol triphosphate (PIP_3). The PI3K signaling pathway is negatively regulated by phosphatase and tensin homolog (PTEN), which is most frequently mutated in human cancer. This leads to amplification of signaling and as such is a promising target for small-molecule inhibition, with potential therapeutic targets for anticancer drug development.[1–5] Based on the primary structure and mechanism of action, PI3Ks are divided into two major classes, class I and class II.[6,7] The class I PI3Ks are further divided into class IA enzymes: p110α, p110β, and p110δ, which are activated by tyrosine kinase receptors, whereas the only member of class IB enzyme, p110γ, is activated by G-protein-coupled receptor. The class II PI3Ks, C2α, C2β, and C2γ, are characterized by the presence of a C2 domain at the C terminus. The recent studies with isoform-specific small-molecule inhibitors helped to elucidate the distinct cellular function of different class I isoforms (p110α, p110β, p110δ, and p110γ). It has been reported that inhibition of p110α is essential for affecting growth suppression in malignant cell lines.[8] The other class I isoforms have their therapeutic potential in other disease areas, namely, inflammation, autoimmune disease (p110δ and p110γ), and thrombosis (p110β).[1,3,9–11] The isoform specific molecules capable of attenuating PI3 K signaling should have significant therapeutic potential for

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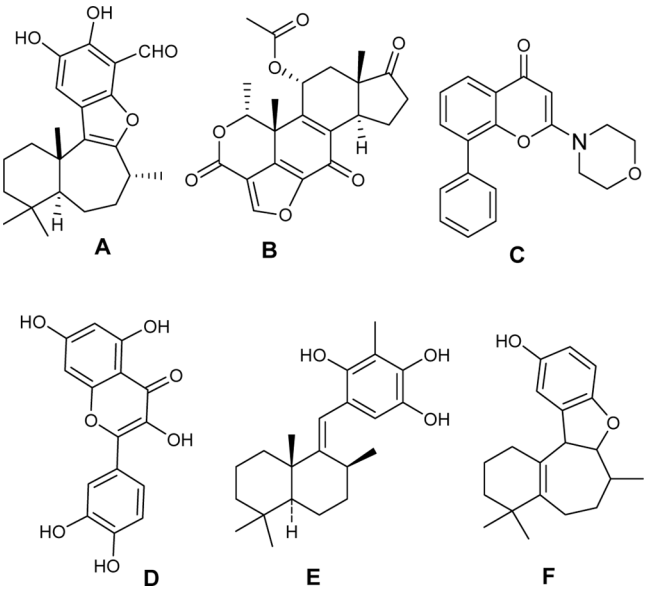


Figure 1. PI3 kinase inhibitors (**A–F**).

treatment of various diseases such as inflammation, autoimmune diseases, cardiovascular diseases, and cancer.[3,4] There are several PI3k inhibitors under active development (Fig. 1), namely wortmannin (**B**), LY294002 (**C**), a synthetic analog of the flavanoid quercetin (**D**), siphonodictyal B (**E**), and frondosin B (**F**), that have been described in patent literature.[12–14] All reported advance molecules (**B–F**) are pan-PI3 K inhibitors and have also been reported to inhibit other kinases (AKT, mTOR, etc.). Liphagal (**A**) is the only molecule that has been reported not only as a selective PI3 K inhibitor but also has shown selectivity among the various isoforms (P110α, p110β, p110γ, p110δ). It significantly inhibits p110α at low concentrations. It was reported to be 10-fold more active toward the α-isoform of PI3 K than the γ-isoform.[15]

Liphagal was isolated from the marine sponge *Aka coralliphaga,* and its synthesis[15,16] and structural elucidation have been reported.[15] The total synthesis of liphagal involves starting with 2,4,5-trimethoxy benzaldehyde to get the key intermediate (E)-7-bromo-2-(6,10-dimethylundeca-5,9-dien-2-yl)-5,6-dimethoxybenzofuran (**7**) in 12 steps, which on treatment with chlorosulfonic acid yielded cyclic compound (**8**). The cyclic intermediate (**8**) on formylation followed by deprotection with BI_3 in two steps resulted in liphagal (**A**). Thus, the total synthesis of liphagal was a 15-step transformation. Since liphagal is the only known isoform selective PI3 K inhibitor, Andersen's paper[15] is of prime scientific importance in the drug discovery program. Typically, for a medicinal chemistry program, a large number of new chemical entities (NCEs) are synthesized to generate a lead compound. For such a purpose, starting with a 15-step synthesis and then subsequently generating NCEs is unrealistic. The task in hand was to synthesize the key intermediate (**7**) in the fewest possible steps. We devised a synthetic scheme where intermediate **7** could be synthesized in six steps starting from readily available and cost-effective starting

material 2,4,5-trimethoxy benzaldehyde. For the purpose of synthesizing NCEs, intermediate **7** or **8** would be a suitable starting point where the bromo group can be used for the diversification. These modifications will subsequently lead to liphagal-based novel molecules as PI3 K inhibitors.

RESULTS AND DISCUSSION

We started with trimethoxy benzaldehyde, which on reaction with BBr_3 at room temperature yielded 2-hydroxy-4,5-dimethoxy benzaldehyde (**2**). Compound **2,** on treatment with bromine acetic acid, yielded 3-bromo-2-hydroxy-4,5-dimethoxy benzaldehyde (**3**); both compounds **2** and **3** have been synthesized as per literature procedure.[15] Compound **3**, on treatment with chloroacetone and potassium carbonate in dimethyl formamide (DMF), yielded 2-acetyl-7-bromo-5,6-dimethoxy benzofuran (**4**).

The challenge at this stage was to do a geranylation at the carbonyl carbon. At first, we started with geranyl bromide and converted it to geranylmagnesium bromide and reacted the same with the ketone compound **4**. Under many different reaction conditions, this Grignard yielded no significant amount of the desired products. Resorting to an alternative route, we thought of executing a SN_2 reaction on the methyl functionality of the acetyl group. Thus, we treated compound **4** with NaH and then subsequently reacted it with geranyl bromide for 15 min. This gave us a mixture of both mono- and digeranyl product (data not shown). On further optimization, we realized that attenuating the quantity of NaH can help to push the reaction toward monogeranylation to yield compound **5.** We also observed that geranyl chloride yielded more desired monogeranyl product (**5**) than geranyl bromide. Treatment of 7-bromo-2-gernoyl-5,6-dimethoxybenzofuran (**5**) with methyl magnesium bromide yielded tertiary hydroxyl compound **6** in decent yields. The hydroxyl group of compound **6** was further reduced by treatment with ZnI and $NaCNBH_3$ in dichloroethane at 80 °C to yield the key intermediate **7**. The intermediate **8** was synthesized from intermediate **7** by cyclization using chlorosulfonic acid at −78 °C as per published procedure.[15] The bromo- and dimethoxy functionality of intermediates **7** and **8** will serve as a tool for developing new compounds of therapeutic importance and will be published subsequently. Also, intermediate **8** can be converted to liphagal on treatment with BuLi, DMF, and BI_3 using the literature procedure.[15]

In conclusion, we report an efficient and facile method for the synthesis of key intermediates **7** and **8** of liphagal. The concise synthesis of these intermediates will make liphagal-based NCE synthesis more practical in a pharmaceutical setup. The intermediates are also designed in such a fashion so that there are points of diversification, a critical aspect for NCE generation toward drug discovery.

EXPERIMENTAL

Material and Method

2,4,5-Trimethoxy benzaldehyde**,** chloroacetone, geranyl chloride/bromide, sodium cyanoborohydride, and methylmagnesium bromide were purchased from Sigma-Aldrich, USA. All other solvents and reagents were analytical grade and were

used without any further purification. ^{1}H and ^{13}C NMR was recorded on Bruker 300 (BBO) and Bruker 500 (TXI). The mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on ESI-QTOF (Bruker Daltonics microTOFQ).

2-Hydroxy-4,5-dimethoxybenzaldehyde (2)

BBr_3 (1,0 M in CH2Cl2, 20 mmol) was added to a solution of 2,4,5-trimethoxybenzaldehyde (**1**) (4.2 g, 20 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The resulting dark mixture was stirred at rt for 16 h. Water (250 mL) was then added, and the mixture was stirred for 30 min. The aqueous phase was extracted with CH_2Cl_2 (3×200 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the residue on silica gel (CH_2Cl_2) afforded the phenol (3.2 g) in 88% yield. ^{1}H NMR (500 MHz, $DMSOd_6$): δ 10.76 (s, 1H), 10.03 (s, 1H), 7.14 (s, 1H), 6.56 (s, 1H), 3.83 (s, 3H), 3.73 (s, 3H) ppm. MS m/z $[M-H]^-$ m/z 181.

3-Bromo-2-hydroxy-4,5-dimethoxybenzaldehyde (3)

Bromine (0.8 mL, 15.3 mmol) was added at rt to a solution of the phenol (2.76 g, 15.2 mmol) and NaOAc (1.9 g, 23 mmol) in AcOH (100 mL). The resulting yellow solution was stirred for 2 h. The solvent was removed under vacuum, and the residue was poured into an aqueous solution of $NaHCO_3$. The aqueous phase was extracted with EtOAc. The combined EtOAc layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under pressure. Chromatography of the residue on silica gel (3:7 EtOAc/hexanes) afforded the bromophenol **3** in 54% yields. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.60 (s,1H), 9.78 (s,1H), 7.05 (s,1H), 4.02 (s,3H), 3.91 (s,3H) ppm. MS m/z $[M+Na]^+$ m/z 283.

1-(7-Bromo-5,6-dimethoxybenzofuran-2-yl)ethanone (4)

3-Bromo-2-hydroxy-4,5-dimethoxybenzaldehyde (5 g, 19.23 mmol) is added to a solution of potassium carbonate (3.2 g, 23 mmol) and DMF (50 ml). Chloroacetone (95%, 2.25 g, 23 mmol) is then added dropwise, while stirring, over a period of 30 min. The mixture was stirred and heated at 100 °C for 4 h, cooled to rt, and filtered. The filtrate was evaporated, and the residue was column chromatographed (2% $MeOH/CHCl_3$) to furnish the desired product in 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (s, 1H), 7.07 (s, 1H), 3.94 (s, 3H), 3.83 (s, 3H) 2.62 (s, 3H) ppm. MS m/z $[M+H]^+$ m/z 299.

1-(7-Bromo-5,6-dimethoxybenzofuran-2-yl)-5,9-dimethyldeca-4,8-dien-1-one (5)

(7-Bromo-5,6-dimethoxybenzofuran-2-yl)ethanone (**4**) (500 mg, 1.67 mmol) was added to dry DMF (15 mL) in a nitrogen atmosphere. The reaction flask was cooled to 0 °C, and sodium hydride (47 mg, 1.17 mmol) was added. After 15 min, geranyl bromide (254 mg, 1.17 mmol) was added, and the mixture was stirred at rt for 1 h. The solvent was removed under vacuum, and the residue was subjected to

column chromatography by using 2% MeOH/$CHCl_3$ as an eluent to afford compound **5** in 30% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (s, 1H), 7.09 (s, 1H), 5.24–5.19 (t, 1H), 5.09–5.07 (t, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.05–3.00 (t, 2H), 2.52–2.45 (q, 2H), 2.08–2.00 (m, 4H), 1.68 (s, 6H), 1.60 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.92, 153.88, 151.70, 148.45, 136.75, 131.45, 124.20, 122.78, 122.38, 112.47, 102.89, 100.76, 100.01, 61.24, 56.51, 39.67, 39.16, 29.71, 26.63, 25.69, 22.69, 17.69, 16.08. HRMS [M +H]$^+$ m/z 435.1165 ($C_{22}H_{28}BrO_4$, calcd. 435.1148).

2-(7-Bromo-5,6-dimethoxybenzofuran-2-yl)-6,10-dimethylundeca-5,9-dien-2-ol (6)

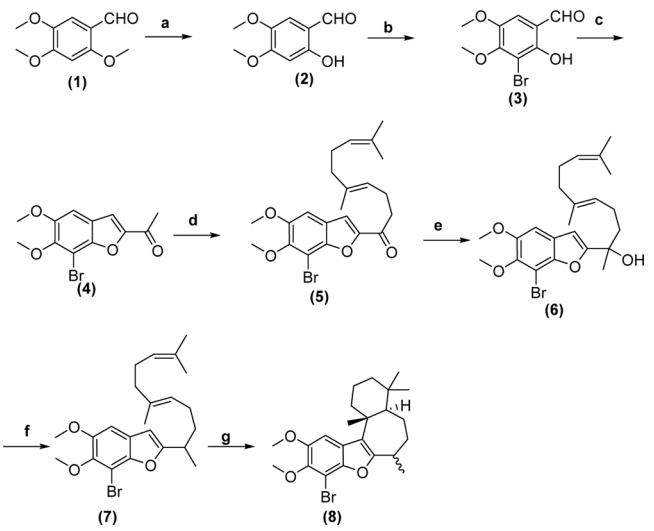
A solution of ketone 5 (2.0 g, 4.60 mmol) in anhydrous THF (50 mL) was cooled to 0 °C, and methylmagnesium bromide (3.0 M in Et_2O, 3.4 mL, 10.2 mmol) was added via syringe. The reaction mixture was stirred for 30 min at 0 °C and quenched with 1 N HCl. The solution was diluted with ethyl acetate (50 mL) and washed with H_2O, saturated $NaHCO_3$, and brine (30 mL each). The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. Column chromatography on silica (10% ethylacetate/hexane) gave 1.7 g (82%) of the desired product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (s,1H), 6.58 (s, 1H), 5.14–5.06 (m, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 1.94–2.03(m, 9H), 1.68 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H), 1.54 (s, 3H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.33, 150.25, 146.52, 144.25, 135.74, 131.06, 123.76, 123.47, 123.12, 101.82, 101.73, 99.60, 72.0, 60.74, 56.24, 40.81, 39.19, 26.70, 26.13, 25.26, 22.45, 17.25, 15.62. HRMS [M +H]$^+$ m/z 473.127 ($C_{23}H_{31}BrNaO_4$ calcd. 473.1298).

7-Bromo-2-(6,10-dimethylundecA-5,9-dien-2-yl)-5,6-dimethoxybenzo Furan (7)

Compound **6** (1.6 g, 3.54 mmol) was dissolved in anhydrous 1,2-dichloroethane (50 mL), and zinc iodide (1.7 g, 5.32 mmol) was added in a single portion, followed by sodium cyanoborohydride (1.6 g, 25 mmol). The resultant solution was heated to reflux with vigorous stirring for 2 h. The reaction was cooled to rt and poured into H_2O (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under pressure. Column chromatography on silica (5% ethylacetate/hexane) yielded 1.3 g (85%) of **7**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92 (s, 1H), 6.34 (s, 1H), 5.14–5.08 (m, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 2.98–2.94 (m, 1H), 2.06–1.81 (m, 8H), 1.71 (s, 3H), 1.67 (s, 3H), 1.57 (s, 3H), 1.32 (d, 3H, $J = 6$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.22, 150.42, 146.71, 144.09, 135.62, 131.36, 124.41, 124.34, 123.83, 101.97, 101.31, 61.17, 56.73, 39.71, 35.42, 33.09, 29.71, 26.66, 25.70, 25.49, 19.08, 17.70, 16.05. MS [M +H]+m/z 435.2 ($C_{23}H_{31}BrO_3$, calcd. 434.15).

Synthesis of Compound 8

Chlorosulfonic acid (0.27 mL, 2 mmol) was added to a solution of benzofuran **7** (218 mg, 0.5 mmol) in nitropropane (25 mL), at − 78 °C. The resulting mixture was



Scheme 1. Reagent and conditions: (a) DCM, BBr_3, rt; (b) Br_2, acetic acid; (c) chloroacetone, K_2CO_3, DMF; (d) geranyl chloride, NaH, DMF, 60 °C; (e) CH_3MgBr; (f) ZnI, $NaBH_3CN$, DCE, 80 °C; (g) nitropropane, $ClSO_3H$, −78 °C, 30 min.

allowed to stir at − 78 °C for 30 min. An aqueous solution of $NaHCO_3$ was then added, and the aqueous phase was extracted with EtOAc. The EtOAc layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the residue on silica gel (3:97 EtOAc/hexanes) afforded the tetracyclic compound **8** (93 mg) in 40% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.34–3.32 (m, 1H), 2.56–2.53 (m, 1H), 1.94–1.77 (m, 3H), 1.75–1.69 (m, 2H), 1.55–1.46 (m, 2H), 1.43 (s, 3H), 1.42–1.39 (m, 2H), 1.35–1.30 (m, 2H), 1.28 (s, 3H), 1.01 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.36, 138.87, 134.88, 133.07, 126.50, 106.32, 63.44, 59.48, 52.40, 47.01, 41.71, 38.72, 38.09, 36.83, 36.02, 34.16, 33.41, 25.08, 24.64, 22.47, 21.20, 20.84, 20.53. HRMS $[M+H]^+$ m/z 435.1468 ($C_{23}H_{32}BrO_3$, calcd. 435.1529).

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