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Synthesis of functionalized hydroxy-thiophene motifs as amido- and sulfonamido-phenol bioisosteres

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ABSTRACT

Novel highly substituted hydroxy thiophene motifs were designed and synthesized as viable amido phenol and sulfonamido phenol bioisosteres. Hydroxy group-directed regioselective bromination and palladium-catalyzed amination of thienyl bromide via Buckwald protocol are the key elements of the synthetic approach. The hydroxy thiophene-containing compounds displayed good binding inhibitions.

Bioisostere replacement is a commonly used approach by medicinal chemists in rational drug design.[1] It is often employed to address potential undesirable side effects or adverse metabolism issues that could be associated with lead compounds. Sometimes, it is explored simply for the purpose of finding new physical and biological properties without significant changes to the core structure in an existing drug development program.

During our investigation of CXCR2 and CXCR1 chemokine receptor antagonists, we have discovered a novel class of phenolic cyclobutenedione compounds which exhibited potent inhibitory activities toward one or both of these receptors, as exemplified by structures **1** and **2** (Fig. 1), a key structural element is the amido phenol moiety.[2] Disclosed by GlaxoSmithKline scientists, a series of *N,N′*-diarylurea compounds, represented by structure **3** (Fig. 1), also displayed potent CXCR2 inhibitory activity.[3] In the latter class of antagonists, the sulfonamido phenol moiety is a prominent feature.

With the goal of discovering new chemical series that would enrich our existing scope of antagonists, we searched for potential bioisosteric replacements of the phenol group in structures **1**–**3**. Thiophene has frequently been utilized as a potential phenyl bioisostere due largely to their similarities in aromaticity and shape, while maintaining enough structural differences to impart different physical and biological properties. Accordingly, we envisioned that hydroxy thiophenes **4** and **5** could be viable replacements of the corresponding amido-**6** and sulfonamido phenols **7** (Fig. 2). The development of synthetic approaches leading to **4** and **5** is the focus of this report. Biological data of representative hydroxy-thiophene analogs will only be briefly discussed.

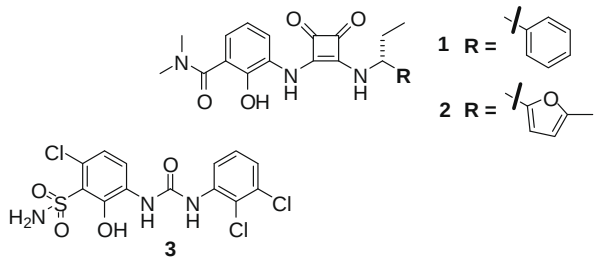

Figure 1. Examples of phenolic CXCR2/CXCR1 antagonists.

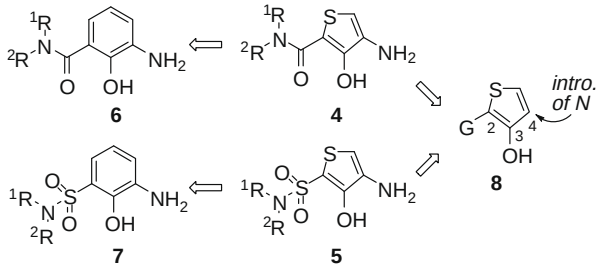

Figure 2. Hydroxy-thiophenes as potential phenol bioisosteres.

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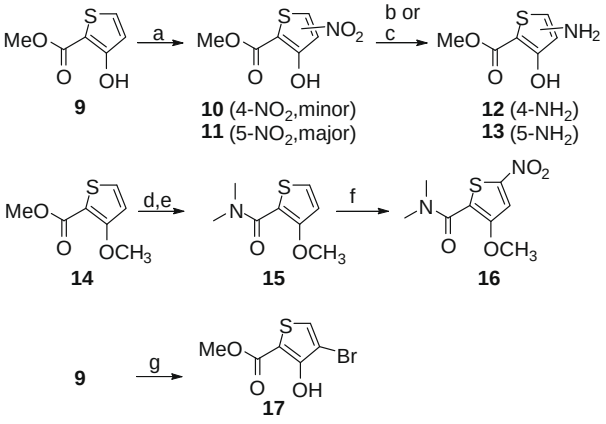
Synthetic analysis of hydroxy-amino-thiophenes **4** and **5** led us to a general precursor **8** (Fig. 2). 3-Hydroxy-4-amino-thiophenes were not reported previously in the literature to the best of our knowledge, and there was no synthetic precedent closely related to fully functionalized thiophenes **4** and **5**. Starting from **8**, with the requisite 3-hydroxy group preinstalled, it would be the most efficient approach to the targeted motifs. The key structural manipulation would then be the introduction of a 4-amino group.

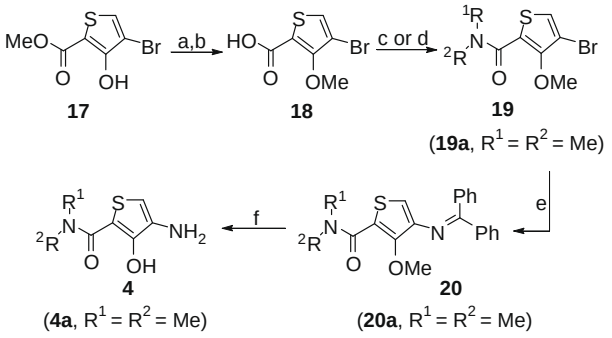
Nitration of the commercially available methyl-3-hydroxy-2-thiophene carboxylate **9**, using concentrated H_2SO_4 and fuming HNO_3 produced a mixture of isomers 4-nitro **10** and 5-nitro **11** in a 1:2 ratio and 70% yield, the desired 4-isomer being a minor product (Scheme 1).[4] When the 3-hydroxy group was masked as a methoxy group, nitration of **15** (prepared from **14** in two steps) afforded 5-nitro isomer **16** in 65% yield while its 4-nitro isomer was not detected. The free 3-hydroxy group apparently played an *ortho*-directing role to allow the formation of 4-nitro isomer **10**; however, the steric hinderance might have prevented regioselective formation of **10** over **11**. Reduction of the nitro group in **10** and **11** was problematic which afforded amino compounds **12** and **13** in low yields, either by using $SnCl_2{\cdot}2H_2O$-mediated reduction or $Pd(OH)_2$/C-catalyzed hydrogenation (Scheme 1). This approach lacked the robustness desired for extensive elaboration.

Bromination of a 2,3-disubstituted thiophene system, when the 3-hydroxy group was masked, was similar to nitration, which generated the 5-bromo isomer regioselectively.[5] However, when the 3-hydroxy group was free, the selectivity was different from nitration. As reported in the literature,[6] and from our own studies, bromination of **9** afforded predominantly 4-bromo isomer **17** (Scheme 1). The 3-hydroxy group plays a dominant *ortho*-directing role in the electrophilic bromination of the thiophene system, and as such 4-bromo isomer was formed near exclusively. To take advantage of this selective transformation, we sought to install the requisite amino group via a 4-bromo precursor, applying the palladium-catalyzed amination method.

Palladium-catalyzed amination of aryl halides has been extensively utilized for aryl systems, though not broadly applied to heteroaryls. For phenyl halides and triflates, Buckwald et al. have reported a convenient method to convert these substrates to the corresponding primary anilines through the use of benzophenone imine as an ammonia equivalent.[7] The Buckwald approach appears to be promising for our purpose. Compound **17** was first converted to the bromo precursor **19** in three high yielding steps: methylation, NaOH-mediated hydrolysis, and amide formation (Scheme 2).[8] Catalytic amination of **19**, under the conditions of benzophenone imine (1.5 equiv), $Pd(OAc)_2$ (3 mol %), *rac*-BINAP (4.5 mol %), and cesium carbonate (2.0 equiv) in refluxing toluene overnight, smoothly generated the imine adduct **20**. Greater than 50% yield was achieved for most of the substrates, and 80% in the case of *N*,*N*′-dimethyl amide **20a**.[9] Neither R^1 nor R^2 group can be a H in this amination reaction. Subsequently, demethylation of **20** using boron tribromide provided the hydroxy imine intermediate, which was further subjected to a facile imine cleavage to give 3-hydroxy-4-amino-thiophene **4** in good yield.[10] The imine cleavage can be effected either by acidic aqueous condition or the combination of NaOAc and hydroxylamine hydrochloride in methanol. This five-step sequence is efficient and flexible allowing easy derivatization at the 2-position of the thiophene (Scheme 2).



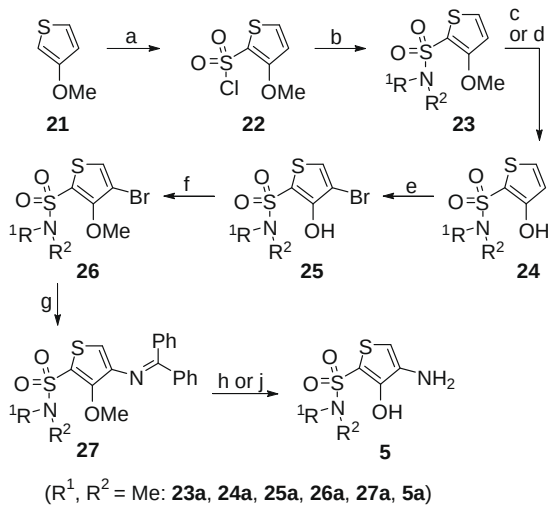
Scheme 1. Hydroxy group-directed nitration and bromination. Reagents and conditions: (a) H_2SO_4 (concd), HNO_3 (fuming), 0 °C, 2 h, 70%, **10**–**11**: ~1:2; (b) $SnCl_2{\cdot}2H_2O$, EtOAc, 85 °C, 1.5 h, <10%; (c) $Pd(OH)_2$ (20 wt % on C), H_2, EtOH, 75 °C, 12 h, 20%; (d) NaOH, THF, rt, overnight, 99%; (e) $(ClC{=}O)_2$, DMF (cat.), CH_2Cl_2, rt, 1 h; then Me_2NH in THF, 90%; (f) H_2SO_4 (concd), HNO_3 (fuming), −5 °C, 1 h, 65%; (g) Br_2, AcOH, rt, overnight, 60%.[6b]



Scheme 2. Reagents and conditions: (a) K_2CO_3, MeI, acetone, reflux, 6 h, 100%; (b) NaOH, THF, rt, overnight, 96%; (c) PyBroP, DIEA, R_1R_2NH, CH_2Cl_2, rt, >90%; (d) $(ClC{=}O)_2$, DMF (cat), CH_2Cl_2, rt, 45 min; K_2CO_3, rt, 5 min; then R^1R^2NH, >60%; (e) $Pd(OAc)_2$ (3 mol %) (±)BINAP (4.5 mol %), Cs_2CO_3 (2.0 equiv) $Ph_2C{=}NH$ (1.5 equiv), toluene (0.1 M), 110 °C, 16 h, 80% for **20a**, >50% avg; (f) BBr_3, CH_2Cl_2, −78 °C to −15 °C, 3 h; work-up; then NaOAc, NH_2OH–HCl, MeOH, rt, 1–18 h, 90% for **4a**, 50–90% avg.

Synthesis of the sulfonamido motif **5** required a little more synthetic maneuvering than the amido analog **4**, since 2-chlorosulfonyl-3-hydroxy thiophene, equivalent to **9**, was not readily available. Installation of the 2-chlorosulfonyl group was achieved by treatment of 3-methoxy thiophene **21** with chlorosulfonic acid, providing **22** regioselectively and in good yields (60–83%, Scheme 3).[11] 2-Sulfonyl chloride **22** was converted to the corresponding sulfonamide **23** in above 90% yield by reacting with various amines under mild conditions. Upon treatment of boron tribromide or sodium ethanethiolate, sulfonamide **23** was demethylated to the hydroxy compound **24**, which was in turn brominated to furnish 3-hydroxy-4-bromide **25** regioselectively.[12] This bromination occured via the hydroxy group's *ortho*-direction, similar to the conversion of **9**–**17**. Methylation of **25** thus afforded the requisite amination precursor **26**.[13] Conversion of **26** to sulfonamido **5** was straightforward: palladium-catalyzed amination using benzophenone imine provided the imine adduct **27** (50–85%),[14] subsequent demethylation and imine cleavage furnished **5** in good yields.[15] To ensure efficient and complete conversion of sulfonamido bromide **26**–**27**, increased amounts of $Pd(OAc)_2$ (10 mol %) and BINAP (14 mol %) were employed in this reaction. Additionally, when substrates containing sulfonamido group were sensitive toward boron tribromide condition, demethylation was carried out using sodium ethanethiolate in DMF at 95 °C. The synthesis depicted in Scheme 3 represents a practical approach toward the sulfonamido motif **5**, yields are generally high for each step and consistent in scaling up.

An alternative approach for the synthesis of **5** was also investigated. Decarboxylation of acid **18** in H_2SO_4 (concd) at 60 °C within a 4.5-h period provided 3-methoxy-4-bromo thiophene **28** in moderate to good yield (Scheme 4).[16] Regioselective sulfonylation of **28** by chlorosulfonic acid was possible leading to 2-sulfonyl chloride

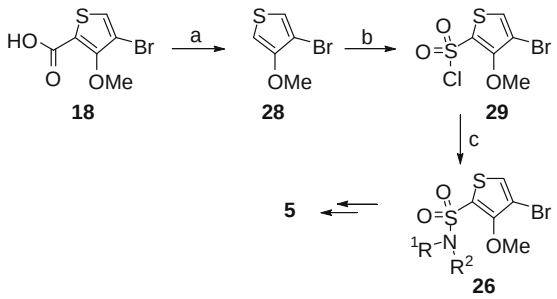


Scheme 3. Reagents and conditions: (a) $ClSO_3H$, CH_2Cl_2, −78 °C, 15 min, then rt, 2–3 h, 60%; (b) R^1R^2NH, NEt_3 or Pyr, CH_2Cl_2, rt, 94% for **23a**; (c) BBr_3, CH_2Cl_2, −78 °C to 10 °C, 4–12 h, >90% avg, 98% for **24a**; (d) NaH, EtSH, DMF, 90–95 °C, 4 h, >95%; (e) Br_2, K_2CO_3, CH_2Cl_2, rt, 5 h, 70–90%, 77% for **25a**; (f) K_2CO_3, CH_3I, acetone, reflux, 3.5 h, 60–95%, 60% for **26a**; (g) $Pd(OAc)_2$ (10 mol %), (±)BINAP (14 mol %), Cs_2CO_3 (2.0 equiv) $Ph_2C{=}NH$ (1.5 equiv), toluene (0.1 M), 110 °C, 16–42 h, 85% for **27a**, >50% avg; (h) BBr_3, CH_2Cl_2, −78 °C to 10 °C, 4 to 12 h, work-up, then NaOAc, NH_2OH–HCl, MeOH, rt, 1–2 h, 70% for **5a**, 50–85% avg; (j) NaH, EtSH, DMF, 90–95 °C, 4 h, work-up, then NaOAc, NH_2OH–HCl, MeOH, rt, 1–2 h, 65% avg.

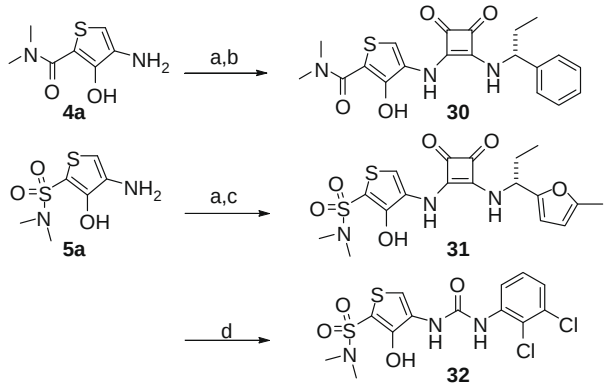
29;[17] however, the conversion was low yielding (38%) and inconsistent, plagued by unknown polar byproducts. This approach was not suitable for large-scale synthesis. It served as a quick access to the amination precursor **26**, which can be easily prepared from **29**. In addition, it was useful when R^1 and/or R^2 groups were sensitive to the reaction conditions described in Scheme 3.

Conversions of amido moiety **4** and sulfonamido moiety **5** to the desired targets are straightforward, as illustrated in Scheme 5 with **4a** and **5a**. By reacting with 3,4-diethoxycyclobutene-1,2-dione, followed by treatment of an appropriate amine, amido-hydroxy-thiophene-amine **4a** was transformed to cyclobutenedione-centered product **30**[18] while sulfonamido-hydroxy-thiophene-amine **5a** was transformed to **31**.[19] When **5a** was reacted with 2,3-dichloro-phenylisocyanate, urea **32** was formed.[20] The initial studies of these compounds in the receptor competition binding assays (vs IL-8) showed promise, good inhibitions were realized with **30** (K_i of CXCR2, CXCR1 = 4.5 nM, >500 nM), **31** (K_i of CXCR2, CXCR1 = 5 nM, 15 nM), and **32** (K_i of CXCR2, CXCR1 = 17 nM, 3100 nM).[21] These activities are comparable to the phenolic compounds **1** and **2**,[2b] and **3**.[3a]

In summary, highly functionalized hydroxy thiophenes **4** and **5** were designed and synthesized as potential bioisosteres of phenolic amides and phenolic sulfonamides. The hydroxy group-directed *ortho*-bromination and palladium-catalyzed amination of the resulted bromide are key transformations in the synthetic approaches (Schemes 3 and 4). These routes are efficient and versatile, allowing rapid functionalization of the amido and sulfonamido groups for structure–activity relationship (SAR) studies. Preliminary biological assessments have shown that the hydroxy thiophene-containing compounds have comparable receptor binding inhibitions to their phenolic analogs.



Scheme 4. Reagents and conditions: (a) H_2SO_4 (concd), 60–65 °C, 4.5 h, 83%; (b) $ClSO_3H$, CH_2Cl_2, rt, 1.5 h, 38%; (c) R^1R^2NH, NEt_3 or Pyr, CH_2Cl_2, rt, 50% avg.



Scheme 5. Reagents and conditions: (a) EtOH, 3,4-diethoxycyclobut-3-ene-1,2-dione, K_2CO_3, rt, 9 h, 50%; (b)EtOH, (*R*)-1-phenyl-1-propylamine, rt, 1.5 h, 63%; (c) EtOH, (*R*)-1-(5-methylfuran-2-yl)-1-propylamine,[3b] rt, 48 h, 34%; (d) 2,3-dichloro-phenylisocyanate, CH_2Cl_2, rt, overnight, 73%.

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4. (a) ^{1}H NMR (400 MHz, CDCl3): δ (ppm) for 10 (4-NO_2), 10.15 (s, 1H), 8.50 (s, 1H), 4.03 (s, 3H); δ (ppm) for 11 (5-NO_2), 9.57 (s, 1H), 7.52 (s, 1H), 4.03 (s, 3H).; (b) Barker, J. M.; Huddleston, P. R.; Wood, M. L.; Burkitt, S. A. *J. Chem. Res. (S)* **2001**, 401–402; (c) Marques, M. A.; Doss, R. M.; Urbach, A. R.; Dervan, P. B. *Helv. Chim. Acta* **2002**, *85*, 4485–4517.
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8. *N,N′-Dimethyl-3-methoxy-4-bromo-2-thiophene carboxamide* **19a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27 (s, 1H), 3.88 (s, 3H, OMe), 3.09 (s, 6H, NMe); *m/z* $(M+H)^+$: 264, 266.
9. *N,N′-Dimethyl-3-methoxy-4-benzophenoniminyl-2-thiophene carboxamide* **20a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.76 (dt, *J* = 1.8, 7.2, 2H), 7.48 (tt, *J* = 1.2, 7.2, 1H), 7.40 (br t, 2H), 7.35–7.32 (m, 3H), 7.21–7.18 (m, 2H), 6.28 (s, 1H), 3.74 (s, 3H, OMe), 3.01 (br s, 3H, NMe), 2.86 (br s, 3H, NMe); *m/z* $(M+H)^+$:365.
10. *N,N′-dimethyl-3-hydroxy-4-amino-2-thiophene carboxamide* **4a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 12.91 (s, 1H, OH), 6.26 (s, 1H), 3.67 (br s, 2H, NH_2), 3.24 (s, 6H, NMe); *m/z* $(M+H)^+$:187.
11. *2-Chlorosulfonyl-3-methoxy thiophene* **22**: A solution of 3-methoxy thiophene **21** (7.0 g, 61.31 mmol) in 50 mL of CH_2Cl_2 was added dropwise to a stirred

solution of chlorosulfonic acid (10.2 mL, 153.18 mmol) in 250 mL of CH_2Cl_2 at −78 °C. The mixture was stirred for 15 min at −78 °C, continued for 2 h at room temperature, then poured carefully into 600 mL of crushed ice. The aqueous mixture was separated, the aqueous layer was further extracted with CH_2Cl_2 (200 mL × 2), and the combined organic layers were washed with brine, dried over $MgSO_4$. The organic solution was filtered through a 1-inch silica gel pad, rinsing with CH_2Cl_2. The filtrate was concentrated in vacuo to a greenish solid, triturated with hexanes several times, then dried on vacuum to afford 7.87 g of **22** as a fluffy green solid (60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.69 (d, J = 5.2, 1H), 6.90 (d, J = 5.6, 1H), 4.09 (s, OMe).

12. *N,N′-Dimethyl-3-hydroxy-4-bromo-2-thiophene sulfonamide* **25a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.48 (s, 1H, OH), 7.48 (s, 1H), 2.80 (s, 6H, NMe).
13. *N,N′-dimethyl-3-methoxy-4-bromo-2-thiophene sulfonamide* **26a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.45 (s, 1H), 3.99 (s, 3H, OMe), 2.85 (s, 6H, NMe); m/z $(M+H)^+$: 300, 302.
14. *N,N′-Dimethyl-3-methoxy-4-benzophenoniminyl-2-thiophene sulfonamide* **27a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.79–7.77 (m, 2H), 7.50 (d, J = 7.2, 2H), 7.42 (tt, J = 1.6, 7.6, 2H), 7.37–7.35 (m, 2H), 7.20–7.17 (m, 2H), 6.38 (s, 1H), 3.94 (s, 3H, OMe), 2.66 (s, 6H, NMe); m/z $(M+H)^+$: 401.
15. *N,N′-Dimethyl-3-hydroxy-4-amino-2-thiophene sulfonamide* **5a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.31 (s, 1H, OH), 6.35 (s, 1H), 3.71 (br s, 2H, NH_2), 2.78 (s, 6H, NMe); m/z $(M+H)^+$: 223.
16. *3-Bromo-4-methoxy thiophene* **28**: A mixture of thiophene 2-carboxylic acid **18** (5.0 g, 21.09 mmol) and 50 mL of concentrated sulfuric acid was heated in a sealed tube at 58–65 °C for 4.5 h. The mixture was cooled, poured into 400 mL of crushed ice, and extracted with CH_2Cl_2 (150 mL × 3). The organic extracts were washed successively with H_2O (100 mL × 2), satd $NaHCO_3$ (100 mL × 2), and brine (100 mL). The organic solution was dried (Na_2SO_4) and concentrated in vacuo to a brown solution, purified by flash column chromatography (hexanes–CH_2Cl_2 = 4:1, v/v) to afford 3.37 g (83%) of **28** as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.20 (d, J = 3.6, 1H), 6.25 (d, J = 3.6, 1H), 3.88 (s, 3H, OMe).
17. *2-Chlorosulfonyl-3-methoxy-3-bromo thiophene* **29**: To a stirred solution of chlorosulfonic acid in 20 mL of CH_2Cl_2 at room temperature was added dropwise in 1.5 h, via an addition funnel, a solution of 3-bromo-4-methoxy thiophene **28** (1.02 g, 5.28 mmol) in 25 mL of CH_2Cl_2. Reaction was allowed to continue for 15 min after the completion of addition. The mixture was then filtered through a 1-inch silica gel pad, rinsing with excess volume of CH_2Cl_2. The filtrate was concentrated in vacuo to give 0.59 g of **29** (38%) as a greenish oil, which was used in the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.65 (s, 1H), 4.19 (s, 3H, OMe).
18. *Compound* **30**: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.54 (br s, 1H, OH), 7.76 (s, IH), 7.40–7.28 (m, 5H), 5.05 (br d, J = 7.9, 1H), 3.11 (s, 3H), 2.48 (s, 3H), 1.89–1.86 (m, 2H), 0.87 (t, J = 7.2, 3H); m/z $(M+H)^+$: 400.46.
19. *Compound* **31**: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.75 (br s, 1H, OH), 7.54 (s, 1H, 6.20 (d, J = 2.7, 1H), 6.02 (d, J = 2.0, 1H), 5.11 (br d, J = 7.6, 1H), 4.10 (br s, 1H), 2.58 (s, 3H), 2.46 (s, 3H), 2.25 (s, 3H), 1.95–1.88 (m, 1H), 1.84–1.77 (m, 1H), 0.90 (t, J = 7.4, 3H); m/z $(M+H)^+$: 440.09.
20. *Compound* **32**: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 9.31 (br s, 1H), 9.18 (br s, 1H), 8.07 (s, 1H), 7.40 (s, 1H), 7.31–7.25 (m, 2H), 2.65 (s, 3H), 2.50 (s, 3H); m/z $(M+H)^+$: 409, 411.
21. For assay conditions, see Refs. 2b and 2c.