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Discovery and Synthesis of Hydronaphthoquinones as Novel Proteasome Inhibitors

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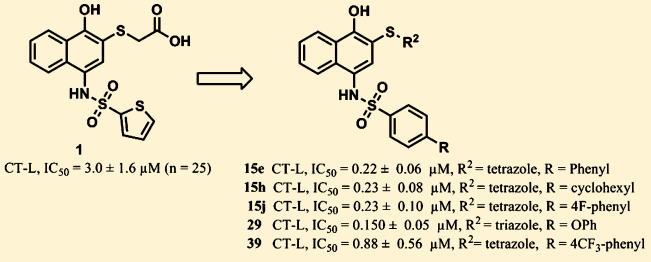
Supporting Information

ABSTRACT: Screening efforts led to the identification of PI-8182 (**1**), an inhibitor of the chymotrypsin-like (CT-L) activity of the proteasome. Compound **1** contains a hydronaphthoquinone pharmacophore with a thioglycolic acid side chain at position 2 and thiophene sulfonamide at position 4. An efficient synthetic route to the hydronaphthoquinone sulfonamide scaffold was developed, and compound **1** was synthesized in-house to confirm the structure and activity (IC_{50} = 3.0 ± 1.6 μM [n = 25]). Novel hydronaphthoquinone derivatives of **1** were designed, synthesized, and evaluated as proteasome inhibitors. The structure−activity relationship (SAR) guided synthesis of more than 170 derivatives revealed that the thioglycolic acid side chain is required and the carboxylic acid group of this side chain is critical to the CT-L inhibitory activity of compound **1**. Furthermore, replacement of the carboxylic acid with carboxylic acid isosteres such as tetrazole or triazole greatly improves potency. Compounds with a thio-tetrazole or thio-triazole side chain in position 2, where the thiophene was replaced by hydrophobic aryl moieties, were the most active compounds with up to 20-fold greater CT-L inhibition than compound **1** (compounds **15e**, **15f**, **15h**, **15j**, IC_{50} values around 200 nM, and compound **29**, IC_{50} = 150 nM). The synthetic iterations described here not only led to improving potency in vitro but also resulted in the identification of compounds that are more active such as **39** (IC_{50} = 0.44 to 1.01 μM) than **1** (IC_{50} = 3.54 to 7.22 μM) at inhibiting the proteasome CT-L activity in intact breast cancer cells. Treatment with **39** also resulted in the accumulation of ubiquitinated cellular proteins and inhibition of tumor cell proliferation of breast cancer cells. The hit **1** and its analogue **39** inhibited proteasome CT-L activity irreversibly.



INTRODUCTION

Regulated protein degradation is an essential aspect of cell signaling.[1] In 2004, Ciechanover,[2] Hershko,[3] and Rose[4] were awarded the Nobel Prize for chemistry in elucidating the importance of proteolytic degradation inside cells and the role of ubiquitin in proteolytic pathways. Proteasomes are highly conserved compartmentalized protease complexes belonging to the family of N-terminal nucleophilic hydrolases.[5] The proteasome degrades ubiquitinated proteins into small peptides,[6] and the ubiquitin proteasome system (UPS) is responsible for the degradation of cellular proteins (e.g., potentially toxic, oxidized, misfolded proteins, and cell cycle regulatory proteins). In cancer cells, the UPS is essential to the mechanisms underlying tumorigenesis, metastasis, angiogenesis, and apoptosis.[7−9] Therefore, targeting the regulation of protein production and degradation that mediates proliferation and other hallmarks characteristics of malignancy has been a major focus of cancer research. Since the approval of Bortezomib (Velcade) for multiple myeloma in 2003 by the FDA (Figure 1), the proteasome has been validated as an important target for cancer therapy.[10] In addition, several studies have shown that proteasome inhibition is also important for inflammatory and autoimmune diseases.[11,12] Most natural and synthetic proteasome inhibitors reported to date including Bortezomib contain a reactive moiety in the pharmacophore that forms an irreversible and/or slowly reversible covalent bond with the nucleophilic N-terminal Thr in the β5 subunit of the proteasome.[13,14] Proteasome inhibitors reported to date fall into five classes:[15] peptide boronates, peptide aldehydes, peptide vinyl sulfones, peptide epoxyketones, and β-lactones. Peptide aldehydes and vinyl sulfones also inhibit other proteases (cathepsin A, tripeptidyl peptidase II) in addition to the proteasome.[16] The β-lactone salinosporamide A[17,18] and tetrapeptide epoxyketone Carfilzomib[19] (Figure 1) represent two classes of irreversible and/or slowly reversible proteasome inhibitors that are in clinical trials.[20] The proteolytic activity of the chymotrypsin-like (CT-L) active site (β5 subunit) of the

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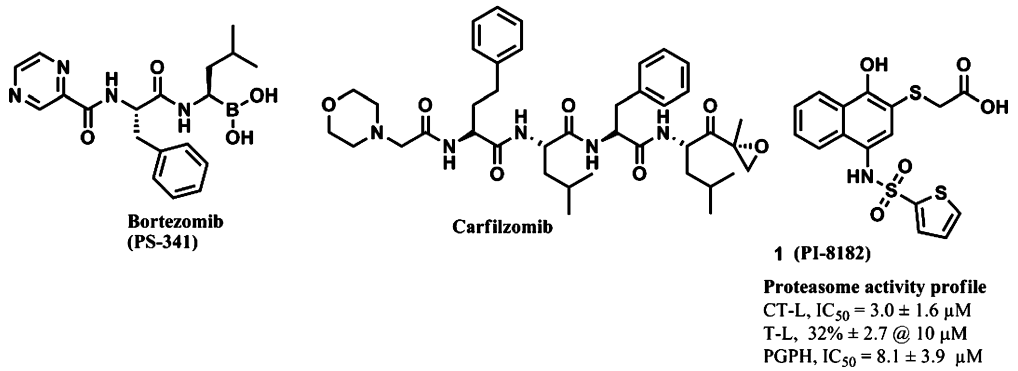

Figure 1. Structures of representative proteasome inhibitors: Bortezomib (clinically approved), Carfilzomib (in clinical trials), and the proteasome activity profile of the "hit" **1**.

proteasome cleaves peptides that contain amino acid residues with large hydrophobic side chains.[13] The trypsin-like (T-L, β2 subunit) and postglutamylpeptidase hydrolysis (PGPH, β1 subunit) proteolytic sites of the proteasome cleave peptides after acidic and basic amino acid residues, respectively.[13] Therefore, the selectivity of proteasome inhibition using peptide based compounds would be hard to achieve just by simply manipulating the peptide backbone. Examples of nonpeptidic, small drug-like synthetic molecules which act as proteasome inhibitors are rare, and these molecules would have potential advantages over the existing inhibitors for therapeutic interventions. Recently, we disclosed identification of PI-083 (NSC-45382), a small synthetic molecule with a naphthoquinone pharmacophore as a reversible proteasome inhibitor that selectively targets cancer cells over nontransformed cells in vitro as well as in vivo.[21,22] In the course of our search for new classes of inhibitors of the 20S proteasome, compound **1** (Figure 1) was recently identified and characterized as a "hit" for proteasome inhibition with CT-L inhibitory activity from our in-house ChemDiv library. The synthesis of compound **1** is not reported in the literature. Herein we describe an efficient synthetic route to **1** and detailed in vitro structure–activity relationship (SAR) studies of **1** via focused library synthesis as a part of our ongoing efforts in the development of proteasome inhibitors.

CHEMISTRY

Compound **1** was recently identified in our program as a "hit" from our in-house ChemDiv 20000 compound library that showed CT-L proteasome inhibitory activity with an IC_{50} value of 3.0 ± 1.6 (n = 25, >95% pure by HPLC). This result prompted us to further investigate **1** as a proteasome inhibitor and establish structure and activity relationship studies (SAR) via synthetic modifications around the hydronaphthoquinone pharmacophore. The hydronaphthoquinone pharmacophore in compound **1** exhibits desirable structural diversity that was exploited for focused library synthesis and medicinal chemistry. Synthetic modifications were primarily focused on the side chain at the 2-position of the hydronaphthoquinone pharmacophore (Figure 2), and the sulfonamide moiety of **1** to understand the structural moieties responsible for proteasome inhibition. Proposed synthetic modifications to probe binding interactions in the β5 subunit of the proteasome are described in Figure 2.

A synthetic route to compound **1** is not reported to the best of our knowledge. Initially, halogenated hydronaphthoquinones **4a–c** were synthesized starting from commercially available 4-

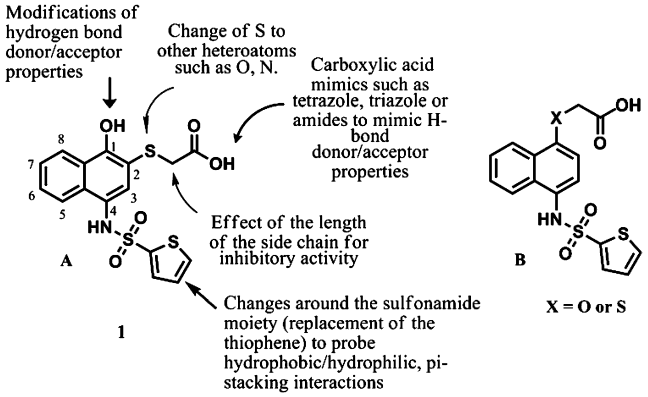

Figure 2. A. Proposed synthetic modifications around compound **1** (hit); B. side chain at 1-position to probe interactions.

aminonaphthol hydrochloride salt (**2**) and thiophene-2-sulfonyl chloride in good yields (Scheme 1). The intermediate **3** was easily obtained with high yields (Scheme 1, *condition a*, this reaction is reported with $NaHCO_3$ as a base with moderate yields[23]) and reacted with hydrogen peroxide and 4 M HCl in dioxane solution, similar to a literature reported protocol[24] to obtain the compound **4a**. Compounds **4b** and **4c** were also synthesized in a similar manner in the presence of bromine and iodine respectively with triethylamine in DMF (Scheme 1) according to a reported method[25] (see ^{1}H NMR and HRMS of **4a**, **4b**, and **4c** in the Experimental Section). Our strategy was to oxidize the hydronaphthoquinone **4a** to obtain the oxidized 2-chloronaphthoquinone (structure shown for oxidized **4a** in Scheme 1) that would facilitate the synthesis of the final compound **1**. Our attempts to oxidize compound **4a** (using H_2O_2, $Pb(OAc)_4$) were not successful. Furthermore, attempts to directly introduce the thioether carboxylic ester side chain in compound **1** via the intermediate **5** (Scheme 1), similar to a reported protocol with hydrazides[26] and thiols,[27] were not successful. Syntheses of derivatives of intermediate **5** are reported from derivatives of compound **3** using lead (IV) tetraacetate[22] in acetic acid, hydrogen peroxide,[23] or MnO_2[28] in methanol. In spite of repeated attempts, we were unable to obtain the required oxidized intermediate **5** from the hydroxynaphthalene sulfonamide intermediate **3** using these reported protocols. Our reactions produced unidentified impurities by ^{1}H NMR and TLC. Hence, this route to obtain compound **1** was abandoned.

To combine the hydronaphthoquinone ring and the thioether side chain in structure **1** as required, we then

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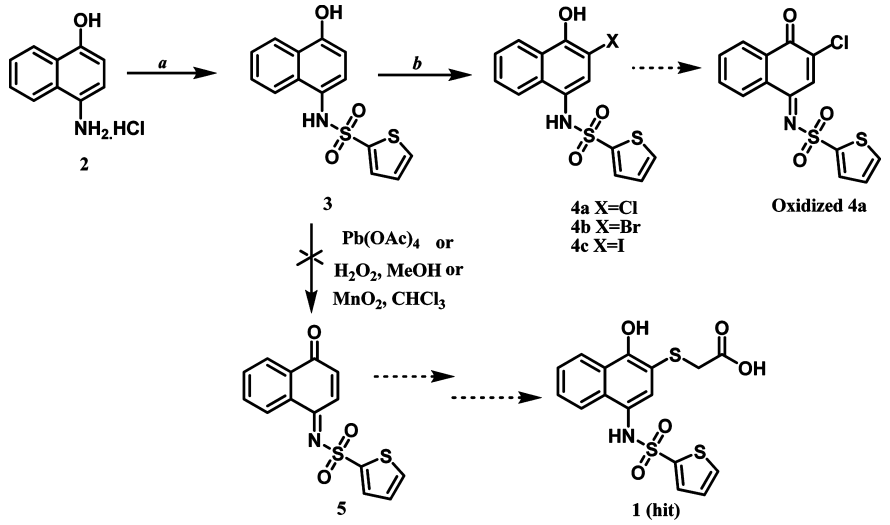
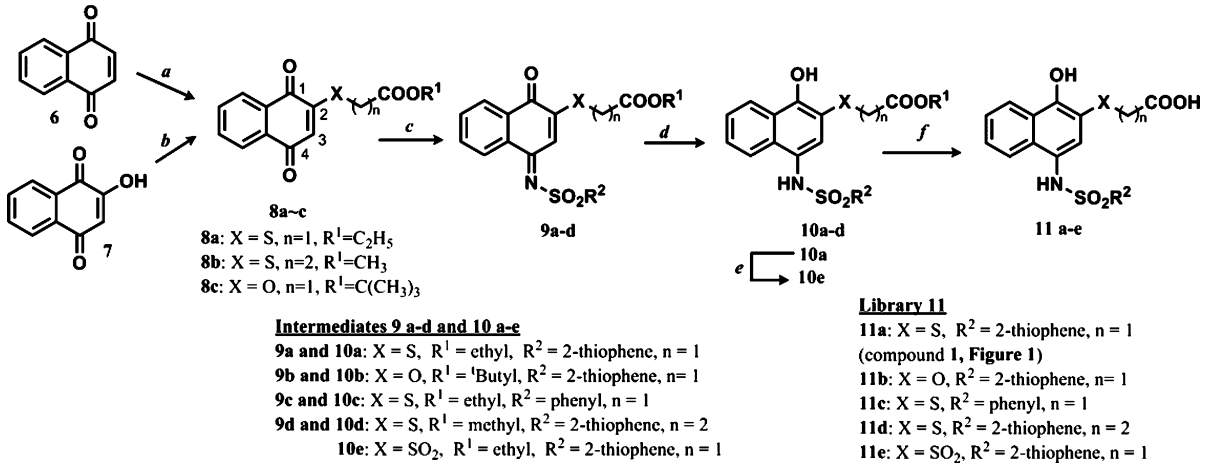
Scheme 1. Synthesis of Hydronaphthoquinone Sulfonamide Scaffold[a]



[a]Reagents and conditions: (a) thiophene-2-sulfonyl chloride, Et_3N, dichloromethane, rt, 14 h, 90%; (b) for **4a**, (i) H_2O_2 (35%), CH_3OH, rt, 2 h, (ii) 4 M HCl/dioxane, rt, 2 h, 22%; for **4b**, Br_2, Et_3N, DMF, 0 °C to rt, 12−14 h, 36%, and for **4c**, I_2, Et_3N, DMF, 0 °C to rt, 12 h, 100%.

Scheme 2. Synthetic Route to Compound 1 (Hit) and Derivatives of the Hit[a]



[a]Reagents and conditions: (a) $HS(CH_2)_nCOOR^1$ (R^1 = ethyl, n = 1 for **8a**, 89% and R^1 = methyl, n = 2 for **8b**, 94%), ethanol (2.5 mL/mmol), rt 0.5 h; (b) $BrCH_2COO^tBu$, Ag_2O, $CHCl_3$, cat. KI, reflux under Ar, 36 h, 33%; (c) $R^2SO_2NH_2$, $TiCl_4$·2THF, Et_3N, DCM, microwave, 60 °C, 5−20 min, 26−62%; (d) $Na_2S_2O_4$, THF, 1 h, rt or EtOAc, H_2O, rt 10 min, 59−93%; (e) oxone, H_2O, acetone, rt, 12−14 h, 100%; (f) conc HCl/dioxane (1:1, 16 mL/mol), rt 3−36 h or microwave, 100 °C, 10 min, 54−97%.

validated the synthetic protocols shown in Schemes 2 and 3. Commercially available 1,4-naphthoquinone (**6**) (Scheme 2), 2-hydroxy-1,4-naphthoquinone (**7**) (Scheme 2), or 2-chloro-1,4-naphthoquinone (**12**) (Scheme 3) were used as starting materials. First, naphthoquinone intermediates **8a** and **8b** were obtained in good yield using ethyl 2-mercaptoacetate (one carbon side chain) or methyl 3-mercaptopropionate (2-carbon side chain), respectively, with 2 equiv of 1,4-naphthoquinone (**6**) using EtOH as the solvent. (Scheme 2, *condition a*). The intermediate **8c** was obtained via alkylation of 2-hydroxy-1,4-naphthoquinone (**7**) with *tert*-butyl bromoacetate using silver(I) oxide as a base using a reported protocol (Scheme 2, *condition b*).[29] The sulfonamide building blocks that were not commercially available were synthesized according to a reported protocol.[30] The sulfonamide building blocks either commercially available or in-house synthesized were then regioselectively coupled to naphthoquinone intermediates **8a**−**c** according to a procedure that has been widely used in the formation of sulfonimide building blocks[31] using titanium(IV) chloride and triethylamine with conventional heating. We modified the conditions of this reaction (i.e., synthesis of intermediate **9** in Scheme 2, *condition c*) using microwave assisted heating (60 °C, 5−20 min, 26−62% yield) to accommodate parallel synthesis. This reaction was a key reaction in building the sulfonimide naphthoquinone scaffold **9** in our synthetic route to final compounds and microwave assisted heating was convenient for library synthesis. Coupling intermediates **8** with various sulfonamides proceeded regioselectively at the 4-carbonyl of the naphthoquinone ring. We observed the change of the chemical shift of hydrogen at 3-position of **8a** from 6.7 to 7.9 ppm in **9a** (see NMR spectra in Supporting Information). However, the coupling reactions of 3-methyl substituted naphthoquinone (i.e., **8** with a methyl group at 3-position, Scheme 2) with arylsulfonamides were not

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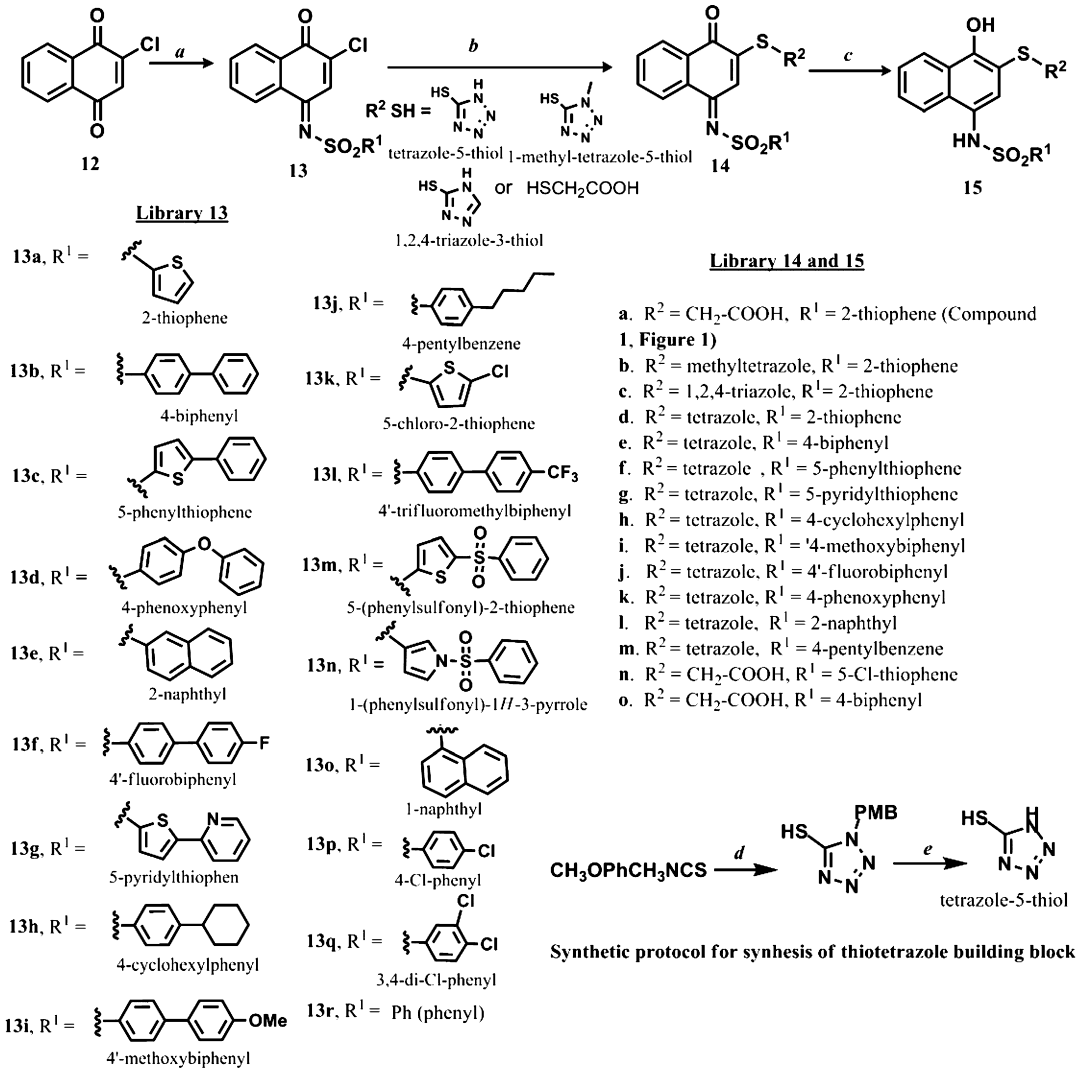
Scheme 3. Optimized Synthetic Route to Hit and Final Compounds[a]



[a]Reagents and conditions: (a) $R^1SO_2NH_2$, $TiCl_4$·2THF, or 1 M $TiCL_4$ in DCM, Et_3N, THF, microwave, 60 °C, 15−30 min, 30−86%; (b) EtOH:DCM (1:1) for tetrazole-5-thiol, rt, 2 h, THF for 1-methyl-tetrazole-5-thiol or 3-mercapto-1,2,4-triazole, rt, 2 h, THF, 1 equiv pyridine for thioglycolic acid, rt, 10−30 min; (c) $Na_2S_2O_4$, EtOAc, and H_2O (mixing in a separating funnel), 54−100%; (d) NaN_3, water, reflux 2 h, 67%; (e) TFA/anisole (5:1, 2 mL/mmol), microwave 100 °C, 2 h, 93%.

successful using this protocol, possibly due to the steric hindrance of the adjacent methyl group.

In the coupling reactions with intermediate **8**, formation of several impurities were observed by TLC, and one of the major byproduct formed was shown to be the reduced structure hydronaphthoquinone (i.e., compound **10**). We were able to isolate this impurity using SiO_2 chromatography and confirmed it to be, by NMR and LCMS, the hydronaphthoquinone derivative **10**. The key intermediates **9** were reduced in situ using sodium hydrosulfite[32] to hydronaphthoquinone carboxylic esters **10** (Scheme 2, *condition d*). Hydrolysis of **10** in a 1:1 mixture of concentrated HCl and dioxane gave the final hydronaphthoquinone acid library **11** in moderate yield (Scheme 2, *condition f*). Compound **1** (Figure 1) was synthesized via this route to confirm the structure and CT-L proteasome inhibitory activity. The sulfone moiety in compound **11e** was formed by oxidation of compound **10a** with oxone,[33] followed by acid hydrolysis (Scheme 2, *conditions e and f*). The byproduct formation in the sulfonamide coupling reaction (i.e., step **c** in Scheme 2) made the isolation of intermediates **9** laborious and inconvenient for library synthesis. Therefore, further optimization of the synthetic route was carried out with commercially available 2-chloro-1,4-naphthoquinone (**12**) as shown in the Scheme 3.

The hydronaphthoquinone focused library **15** (Scheme 3) was synthesized via coupling various sulfonamides to commercially available 2-chloro-1,4-naphthoquinone (**12**) using the same synthetic protocol validated for naphthoquinone intermediate **9** (Scheme 2, *condition c*). The yield of this reaction was significantly improved from 56% to 83% by replacing DCM with THF (Scheme 3, *condition a*). The key intermediates **13** (Scheme 3) were then easily purified by either recrystallization or triturating from appropriate solvents (see Experimental Section), which was more convenient for library synthesis. Substitution of the 2-chlorine intermediates **13** with various nucleophiles was carried out in the presence of pyridine when thioglycolic acid was used and without a base when tetrazole-5-thiol (Scheme 3, *condition b*), 1-methyl-tetrazole-5-thiol or 3-mercapto-1,2,4-triazole (commercially available building blocks) was used to generate the library **14** with the

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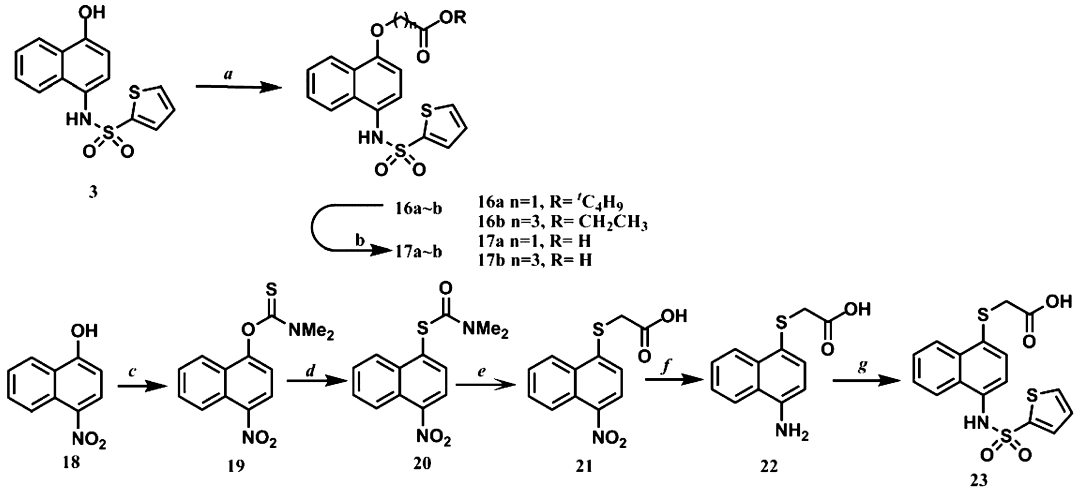
Scheme 4. Synthesis of the Thioglycolic Acid Side Chain at 1-Position[a]



[a]Reagents and conditions: (a) 15 equiv $Br(CH_2)_nCOOR$, 2 equiv DBU, DMF, microwave, 90 °C, 50−60 min, 51%; (b) conc HCl/dioxane (1:1, 20 mL/mmol), rt, 1−12 h, 50−80%; (c) Me_2NCSCl, K_2CO_3, NMP, 50 °C, 2 h, 90%; (d) NMP, microwave, 180 °C, 20 min, 72%; (e) (i) 4 equiv KOH, CH_3OH, inert conditions, rt, 12 h, (ii) $BrCH_2COOC(CH_3)_3$, rt, 12 h, 86%; (f) H-Cube, H_2 (40 bar, 25 °C), Pd/C (10%), CH_3OH, flow rate 1 mL/min, 100%; (g) (i) pyridine, THF/H_2O (4:1), 0 °C, (ii) thiophene-2-sulfonyl chloride, 0 °C → rt, 4 h, 58%.

appropriate thioether moieties.[34] Synthesis of the tetrazole-5-thiol building block (Scheme 3, *condition d*) was carried out from *para*-methoxybenzylisothiocyanate and sodium azide. Deprotection of the *para*-methylbenzyltetrazole intermediate was achieved with trifluoroacetic acid to synthesize the final tetrazole-5-thiol building block (*Caution!!! This reaction can be explosive, isolation and drying large quantities of the thiotetrazole building block should be avoided. Once prepared, the thio-tetrazole building block should be stored in a solvent until further use*). The final step in the Scheme 3 involved in situ reduction of the library **14** with thioether side chains (XR^2 = thioglycolic acid, thiolactic acid, thiotetrazoles, thiotriazoles, thiomethyltetrazoles, thioaromatic groups, thioalkyl and thioamide side chains [not reported here]) with high yields to afford the required final library **15** with >95% purity by NMR and LCMS. The purity of the most potent biologically active thioether analogues was >95% as determined by HPLC (see Experimental Section). Few of the intermediates of the library **14** leading to library **15** were characterized and confirmed by NMR, LCMS, and formula guided mass spectroscopy. The library members **15** with thioether side chains appeared more stable at room temperature compared to the compound bearing ether moiety (i.e., **11b**). The synthesis of the final library **15** with thioether side chains via **14** using the key naphthoquinone intermediate **13** proved to be more convenient (3 steps), and we used this optimized synthetic route to generate >170 compounds (varying the sulfonamide moiety and the side chain) including the original hit **1**.

Moving the carboxylic acid side chain from the 2-position to 1-position of the naphthalene ring in compound **1** (Figure 1) is outlined in the Scheme 4. Our aim was to synthesize a small number of derivatives of the hit with *O*-substituted and *S*-substituted carboxylic acid side chains at 1-position of the naphthoquinone ring to probe interactions in the CT-L subunit of the proteasome. First, compounds **16a** and **16b** were obtained by directly alkylating the compound **3** (synthesis of **3** is shown in Scheme 1) with 2-bromoacetate or 4-bromobutyrate using DBU (Scheme 4, *condition a*). Compound **3** was less reactive, and 15 equiv of 2-bromoacetate or 4-bromobutyrate were required to push the reactions. Acidic hydrolysis of the intermediate esters **16a** and **16b** gave **17a** and **17b**, respectively, in good yields. The synthesis of the intermediates **16a** and **16b** and the final compounds **17a** (one carbon side chain) and **17b** (3-carbon side chain) were confirmed by NMR, LCMS, and formula guided mass spectroscopy.

Reaction of commercially available 4-nitronaphthol with *N*,*N*-dimethylthiocarbamoyl chloride (Me_2NCSCl) produced thiocarbamate **19** in good yield. A Newman−Kwart rearrangement was employed to build the thioether scaffold (intermediate **20** in Scheme 4, *condition d*) in the 1-position of the naphthalene ring. Hydrolysis of *N*,*N*-dimethylthioamide **20** in KOH solution (1 M, 4 equiv) under inert conditions, followed by alkylation with *tert*-butyl 2-bromoacetate, directly gave the acid intermediate **21**. Hydrogenation of the 4-nitro group using an H-cube reactor (Scheme 4, *condition f*) gave intermediate **22** in quantitative yield. The intermediate **22** was used in the final step that involved sulfonamide formation with thiophene-2-sulfonyl chloride and pyridine in an aqueous solution to afford the desired compound thioether carboxylic acid **23** in good yield. Formation of compound **23** was confirmed by NMR, LCMS, and formula guided mass spectroscopy and the purity of **23** was shown to be >95% as determined by HPLC.

RESULTS AND DISCUSSION

The in-house synthesis (via both Schemes 2 and 3) of compound **1** confirmed the structure and CT-L proteasome inhibitory activity (IC_{50} = 3.0 ± 1.6 μM [n = 25]), which in turn allowed us to develop novel compounds with improved activity and selectivity. In an effort to determine the important moieties of the pharmacophore that are critical to its CT-L inhibitory activity and to improve its in vitro and whole cell activities, we have synthesized over 170 derivatives and performed SAR studies using a fluorogenic assay as previously described.[21,22] In the initial screen, the % of CT-L inhibitory activity was determined, and on the basis of these results a dose−response (IC_{50} values) was obtained for compounds that

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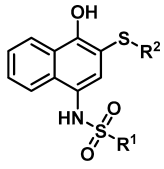
Table 1. SAR around the Side Chain S-R^2, Sulfonamide Moiety R^1 of Compound 1



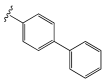
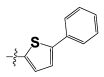
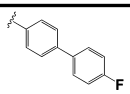
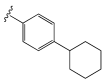
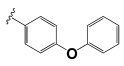
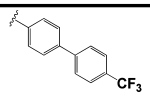
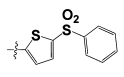
Compound ID	S-R^2	R^1	IC_{50}[a] (μM) Proteasome Activity (*In Vitro*) CT-L	T-L
1 (15a and 11a)	S-CH_2COOH		3.0 ± 1.6	ND
15b			4.2 ± 2.1	ND
15c			4.2 ± 2.7	ND
24			4.05 ± 2.64	ND
25			0.28± 0.8	4.22 ± 0.30
26			0.73 ± 0.03	2.35 ± 0.05
27			0.18 ± 0.08	2.37 ± 0.05
28			0.3 ± 0.07	7 ± 0.8
29			0.150 ± 0.05	4.2 ± 1.8
30			2.47 ± 0.52	7.2 ± 0.9
31			1.97 ± 0.08	ND

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Table 1. continued

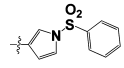
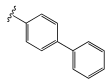
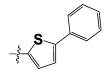
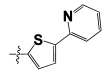
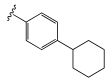
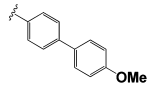
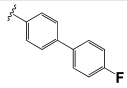
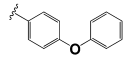
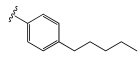
Compound ID	S-R^2	R^1	IC_{50}[a] (μM) Proteasome Activity (*In Vitro*) CT-L	T-L
32			1.61 ± 0.06	ND
33			0.30± 0.01	2.0 ± 0.2
34			0.65 ± 0.09	ND
15d			0.51 ± 0.12	0.20 ± 0.10
15e			0.22 ± 0.06	4.80 ± 0.54
15f			0.23 ± 0.02	0.55 ± 0.32
15g			0.480 ± 0.09	1.55 ± 0.45
15h			0.23 ± 0.08	1.85 ± 0.67
15i			0.40 ± 0.12	2.80 ± 0.12
15j			0.23 ± 0.1	2.0 ± 0.60
15k			0.22 ± 0.01	1.3 ± 0.4
15l			0.40 ± 0.14	1.35 ± 0.56
15m			0.47 ± 0.18	1.45 ± 0.14

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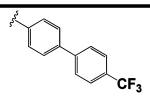
Table 1. continued

Compound ID	S-R^2	R^1	IC_{50}[a] (μM) Proteasome Activity (*In Vitro*) CT-L	T-L
35			0.570 ± 0.06	0.75 ± 0.13
36			0.54 ± 0.08	0.57 ± 0.31
37			0.6 ± 0.1	1.38 ± 0.60
38			0.63 ± 0.1	1.10 ± 0.16
39			0.88 ± 0.56	1.14 ± 0.16

[a]Each IC_{50} is at least the mean of 3 determinations. ND: IC_{50} not determined, these compounds showed less than 70% T-L inhibition at 10 μM.

displayed >70% inhibition at 10 μM. The compounds that displayed potent CT-L inhibitory activity were also tested for in vitro trypsin-like (T-L) inhibitory activity (Table 1).[21,22]

In the hit-to-lead optimization chemistry, we first investigated in detail the importance of the thioglycolic acid side chain while maintaining the thiophene sulfonamide moiety in structure **1** (Figure 2A). Removal of the side chain from **1** as in the 2-unsubstituted counterpart **3** (Scheme 1, IC_{50} > 30 μM) was not tolerated, indicating that the thioglycolic acid side chain is required for CT-L inhibitory activity. Hydronaphthoquinone analogues bearing halogens Cl, Br, and I at the 2-position **4a**, **4b**, and **4c**, respectively (Scheme 1), resulted in loss of CT-L inhibitory activity (IC_{50} > 30 μM), further confirming the importance of the thioglycolic acid side chain. Furthermore, direct replacement of "sulfur" by "oxygen" (ether side chain, **11b** in Scheme 2) or "sulfone" (**11e** in Scheme 2) was also detrimental to CT-L inhibitory activity (IC_{50} > 100 μM), indicating that the thio-ether moiety in compound **1** is important. The replacement of the thioglycolic acid with groups, such as *S*-ethyl, *O*-ethyl, *S*-ethanol, thio-*N*,*N*-dimethylpropionamide ($S(CH_2)_2CO\text{-}N\text{-}Me_2$), and thio-*N*-methylpropionamide ($S(CH_2)_2CO\text{-}NH\text{-}CH_3$), showed weaker CT-L proteasome activity (IC_{50} > 5 μM, compounds not reported here), suggesting that the carboxylic acid moiety was essential for proteasome activity. The compound **10a** (Scheme 2) with ethyl ester was shown to be less potent (IC_{50} > 10 μM) than the corresponding acid, further confirming the importance of the H-bond donor/acceptor features of the carboxylic group for CT-L activity. The length of the side chain is also important, as demonstrated by the 2-fold decreased potency in the extended thioether carboxylic acid side chain as in **11d** (Scheme 2, IC_{50} = 5.7 μM). The position of the thioglycolic acid side chain is critical, as demonstrated by the loss of CT-L inhibitory activity (IC_{50} >100 uM) in compound **23** (Scheme 4), where the thioglycolic acid side chain was moved from the 2 to the 1-position. Our attempts to substitute the thioglycolic acid chain of **1** with amines (not reported here) were not successful due to oxidized impurities formed in the final products. Finally, the naphthoquinone analogues of library **14** (Scheme 3) showed 2−3-fold weaker activity compared to the corresponding active analogues of hydronaphthoquinone library **15**, indicating that the H-bond donor properties of the hydronaphthoquinone may be important for binding interactions with the β5 subunit of the protein. The SAR studies described above demonstrate that the thioglycolic acid side chain is required for the CT-L inhibitory activity of compound **1** and that the carboxylic acid moiety in this side chain is critical. Subsequently, our chemistry efforts for side chain modifications were focused on substituting the carboxylic acid moiety with carboxylic acid isosteres such as tetrazoles or triazoles with a thioether moiety. By incorporating the tetrazole or triazole moieties, we were aiming to improve the potency, solubility, and cell permeability of this class of compounds. Replacement of the carboxylic acid moiety with tetrazole is well-known and has increasingly been used with success in drug discovery.[35] Comparison of carboxylic acid and tetrazole groups at physiological pH reveals that tetrazole group is almost 10 times more lipophilic while having similar acidity, pK_a = 4.9, to that observed for carboxylic acids (pK_a = 4.2−4.4).[36]

The replacement of the thioglycoloic acid side chain in structure **1** (Figure 1) with thio-tetrazole (compound **15d** in Scheme 3) showed improved CT-L inhibitory activity (IC_{50} =

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0.51 ± 0.12 μM, Table 1). Furthermore, replacement of the thioglycoloic acid side chain with thio-methyltetrazole (**15b**, Scheme 3), thio-triazole (**15c**, Scheme 3), and thiobenzoic acid (**24**, Table 1) resulted in retention of the CT-L proteasome activity (IC_{50} = 4.2, 4.2, and 4, respectively, Table 1). We were encouraged by these results, and our next generation of compounds (Scheme 3) were synthesized with thio-tetrazole, -triazole, or -methyl tetrazole to mimic the H-bond donor/acceptor features of the carboxylic acid moiety in our original hit. The compound **24** (Table 1) with thiobenzoic acid side chain was not further pursued for library synthesis due to poor solubility. In the next generation of analogues, we varied the sulfonamide moiety while keeping the thio-tetrazole, -triazole, or -methyltetrazole moieties as side chains at the 2-position of the hydronaphthoquinone pharmacophore. Compounds with thio-tetrazole and thio-triazole side chains containing biaryl sulfonamide moieties (Table 1) displayed the best CT-L activities. For example, compounds **15e**, **15f**, **15h**, **15j**, **15k**, **27**, and **29** (Table 1) displayed up to 20-fold (IC_{50} values around 150−250 nM) improved CT-L inhibitory activity. These results indicate that aromatic hydrophobic sulfonamide groups are tolerated in the binding region. Interestingly, compounds bearing 5-methyl-thio-tetrazole side chain with biaryl sulfonamide moieties (analogues of **15b** in Table 1, not reported here) failed to improve the CT-L activity indicating that the tetrazole anion is contributing to potency (tetrazole is deprotonated at pH 7 similar to a carboxylic acid group). Overall, compounds with methyl-thiotetrazole side chain did not improve the CT-L proteasome activity.

The stability of some of the potent hydronaphthoquinone analogues (**15f** and **25**, Table 1) with thioether side chain (thioglycolic acid, thio-tetrazole, thio-triazole) including the "hit" were examined by ^{1}H NMR in deuterated DMSO up to 3 weeks at room temperature. The HPLC and LCMS were also determined under the assay conditions (in tris buffer at room temperature). Our data concluded the hydronaphthoquinone class of compounds showed >95% purity by LCMS, HPLC, and ^{1}H NMR and were stable at room temperature for up to two weeks. Approximately 3−5% impurities (oxidized material) were shown after 2 weeks. Further analysis of stability of the compounds **1**, **15k**, and **39** was carried out using the two biological media we used for our in vivo studies (Dulbecco's Modified Eagle Medium [DMEM] and Roswell Park Memorial Institute-1640 [RPMI1640]) without serum. Stock solutions of compounds **1**, **15k**, and **39** (1 mM solutions) were prepared using DMSO, and 10 μL aliquot of the each of the stock solution was diluted to 1 mL using the biological medium. The final concentration of each of the samples was 10 μM with 1% DMSO. These samples were left in an incubator at 37 °C and analyzed by HPLC to determine the amount of respective compound present in each sample vial at 1, 3, 5, and 7 day time intervals. The HPLC results, peak area against time were plotted as shown in the Figure 3, which shows the peak area of each of the compounds in either DMEM or RPMI, did not significantly change or deviate with the time. From these data we concluded compounds **1**, **15k**, and **39** were stable up to 7 days at 37 °C in the biological media we used.

One of the important aims in this study was to obtain a compound highly selective for CT-L activity. Therefore, we next determined if those compounds that are potent proteasome inhibitors are selective for CT-L over the T-L activity of the proteasome. Table 1 shows that most compounds were more selective for CT-L over T-L activity

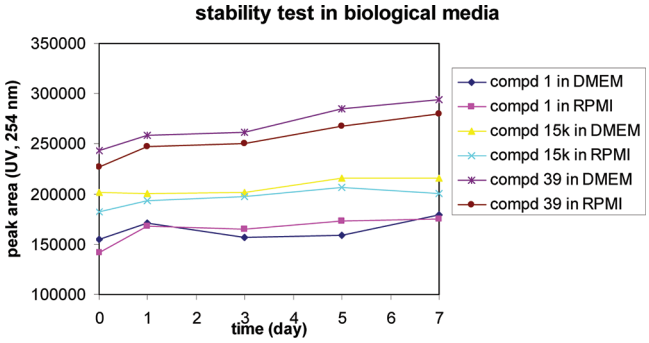

Figure 3. Stability assessment of compounds **1**, **15k**, and **39** in biological medium (DMEM and RPMI-1640) up to 7 days.

of the proteasome. The most potent and selective CT-L activity (28-fold, in vitro) was displayed by compound **29** (Table 1). Interestingly, compounds **35** and **36** were equipotent against CT-L and T-L activities while compound **15d** was more selective for T-L over CT-L.

Our initial goal was to identify compounds that were more potent in the primary in vitro assay as well as the cell culture assay. Our in vitro study showed several tetrazole containing analogues to be more potent than the initial hit (Table 1). We, therefore, determined whether some of these compounds were cell permeable and could inhibit the CT-L activity of the proteasome in intact cells. Treatment of the human breast cancer cell lines MDA-MB-468 and MDA-MB-231 with various doses of **1** for 48 h resulted in inhibition of the CT-L activity in these cells with an IC_{50} value of 7.22 and 3.54 μM, respectively. Out of several compounds tested for intact cell CT-L inhibitory activity in MDA-MB-468 and MDA-MB-231 cells, we identified **39** that potently inhibited CT-L activity with IC_{50} values of 1.01 and 0.44 μM, respectively. To determine if the most potent compound **39** could inhibit CT-L activity at earlier time points, and if this results in the accumulation of ubiquitinated cellular proteins, we treated MDA-MB-468 cells with various concentrations of **39** for 11 h and processed the cells for CT-L assays and Western blotting as described in Experimental Section. After 11 h of treatment, **39** inhibited CT-L activity in MDA-MB-468 cells with an IC_{50} value of 15.6 μM (Figure 4A). Figure 4B shows that treatment of MDA-MB-468 cells with **39** resulted in a concentration-dependent increase in ubiquitination. Finally, to determine the effects of **39** on MDA-MB-468 tumor cell proliferation, we treated the cells as described above and analyzed cell proliferation by MTT assay after 11 h. Figure 4C shows that **39** inhibited tumor cell proliferation with an IC_{50} value of 17.0 μM.

To investigate whether compound **1**- and **39**-mediated proteasome inhibition is reversible or irreversible; we performed a dialysis experiment with compounds **1**, **39**, and Bortezomib, a covalent slowly reversible proteasome inhibitor that was used as an internal control. Figure 5 shows that in the absence of dialysis, **1**, **39**, and Bortezomib were able to inhibit the CT-L activity of the 20S proteasome by 68%, 73%, and 87%, respectively. During dialysis, the CT-L activity did not show any recovery in the compounds **1** and **39** treated samples. By contrast, in the Bortezomib treated samples, CT-L activity recovery started within 4 h. These results suggest that both compounds **1** and **39** behave differently than Bortezomib. It is likely that both **1** and **39** behave as irreversible CT-L proteasome inhibitors.

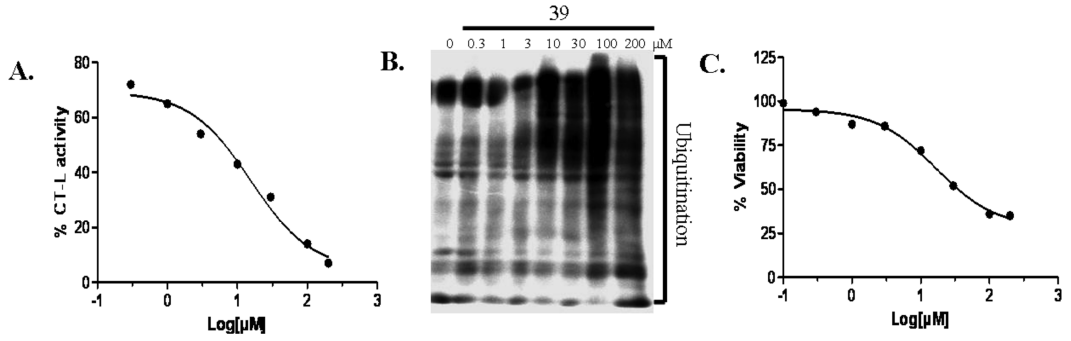

Figure 4. Effects of compound **39** on proteasomal CT-L activity, ubiquitination, and tumor cell viability in human breast cancer MDA-MB-468 cells. Exponentially growing human breast cancer cells were treated with different concentrations of compound **39** for 11 h, followed by measurement of CT-L activity in whole cell extracts (A), determination of ubiquitination by Western blot analysis (B), and cell viability as measured by MTT assay (C).

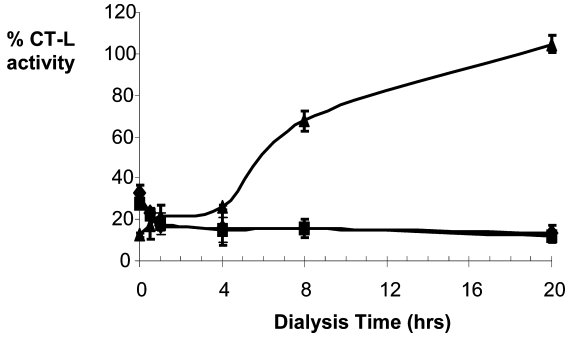

Figure 5. Recovery of CT-L activity upon dialysis of the 20S proteasome−compound complexes after preincubation with Bortezomib (▲), compound **39** (■), and compound **1** (●).

■ CONCLUSIONS

In this report, we describe the design and synthesis of novel class of compounds as proteasome inhibitors. The hit **1** was identified from screening of an in-house ChemDiv 20000 compound library. The synthetic route to 1-hydroxy-4-thiophenesulfonamido naphthalene-2-thioacetic acid (**1**) class of compounds was established, and analogues of **1** were shown to be potent inhibitors of CT-L activity of protesome both in vitro and in vivo. The SAR-guided lead optimization showed that incorporation of the tetrazole moiety, a carboxylic acid isostere and triazole at the 2-position of the hydronaphthoquinone moieties was crucial to achieving improved potency. The most potent compounds **25**, **27**, **29**, **15e**, **15f**, **15h**, **15j**, and **15k** (Table 1) with IC_{50} values 150−300 nM were obtained with hydrophobic sulfonamide moieties. Compounds **1** and **39** (that showed improved whole cell activity) were further tested to understand the binding mode with the proteasome. It was concluded that compounds that contain 1-hydroxy-4-thiophenesulfonamidonaphthalene scaffold with 2-thoacetic acid or thio-tetrazole moieties as side chains are irreversible proteasome inhibitors. Furthermore, compound **39** was much more potent than **1** at inhibiting CT-L activity in intact human breast cancer cells. Compound **39** also induced the accumulation of ubiquitinated cellular proteins and inhibited breast tumor cell proliferation.

■ EXPERIMENTAL SECTION

All reagents were purchased from commercial suppliers and used without further purification. Melting points were determined using a Barnstead international melting point apparatus and remain uncorrected. ^{1}H NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer with CD_2Cl_2, $CDCl_3$, CD_3CN, or DMSO-d_6 as the solvent. ^{13}C NMR spectra are recorded at 100 MHz. All coupling constants are measured in hertz (Hz), and the chemical shifts (δ_H and δ_C) are quoted in parts per million (ppm) relative to TMS (δ 0), which was used as the internal standard. The definition apparent is used as app to describe ^{1}H NMR signals. Liquid chromatography mass spectroscopy (LCMS) and high resolution mass spectroscopy (HRMS) were carried out on an Agilent 6210 LC/MS (ESI-TOF). For LCMS and HRMS, the compounds were eluted between 2 and 5 min using Rapid Resolution Cartridge (2.1 mm × 30 mm, particle size 3.5 μm) from Agilent Technologies. LCMS was used to detect ions of mass 100−1000 Da, and single peak was observed in the chromatogram after purification. HPLC was carried out using Jasco UV-2075 plus UV−vis detector (column: ultra C18, 5 μm, 150 mm × 4.6 mm). H-Cube (ThalesNano) continuous-flow hydrogenation reactor was used for hydrogenation reactions. Microwave reactions were performed in CEM Discover 908005 model and Biotage initiator 8 machines. Thin layer chromatography was performed using silica gel 60 F254 plates (Fisher), with observation under UV when necessary. Anhydrous solvents were used as purchased: dichloromethane (DCM) (anhydrous, 99.8% contains 50−150 ppm hydrocarbon as stabilizer from Aldrich), dimethyl formamide (DMF) (anhydrous, 99.9% from Aldrich), tetrahydrofuran (THF) (anhydrous, 99.9%, inhibitor free, Aldrich), acetonitrile (anhydrous, 99.8%, Aldrich), toluene (anhydrous, 99.8%, Aldrich), methanol (MeOH) (anhydrous, 99.8%, Aldrich), and ethanol (EtOH) (absolute, 99.5%, Aldrich). *N*-Methyl-2-pyrolidinone was purchased from Acros (99%) and used as a solvent. All biologically characterized compounds were >95% pure as determined by HPLC and LCMS except **4b**, **10a**, **10c**, **11b**, **11c**, **15b**, **15c**, **15e**, **15i**, **24**, and **37** that showed purity between 89 and 94% by HPLC. All biologically characterized compounds were analyzed by ^{1}H NMR, ^{13}C NMR, and HRMS (formula guided mass spectroscopy). Most of the intermediates of the library **14** were not isolated because the reaction produced a mixture of naphthoquinone sulfonimides (**14**) and hydronathoquinone sulfonamides (**15**). This mixture was treated with $Na_2S_2O_4$ to get the final library **15** with high purity. However, the **14a**, **14b**, and **14c** were isolated and reported here.

Analysis of Stability of Compounds 1, 15, and 39 Using HPLC. Using fresh powder, 1 mM stock solutions were made (in DMSO) for each compound **1**, **15k**, and **39**. Then a 10 μL aliquot from each stock solution was taken and diluted to 1 mL with biological media (DMEM and RMPI). We prepared five replicates per sample per media, and the final concentration of each solution was 10 μM with 1% DMSO. These sample solutions were incubated at 37 °C for 1, 3, 5, and 7 days, respectively. The vials containing the sample solution were taken out from the incubator at day-1, day-3, day-5, and day-7 and cooled to 0 °C in an ice bath. The sample solutions were analyzed immediately with HPLC. Peak areas were plotted against time (day). HPLC conditions: Agilent Eclipse XDB-C18, 5 μm, 4.6 mm × 150 mm, 35% CH_3CN, 65% H_2O (with 0.1% TFA), 1 mL/min,

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30 min for compound **1**; 50% CH_3CN, 50% H_2O (with 0.1% TFA), 1 mL/min, 30 min for compounds **15k** and **39**.

Cell Culture and Cell Lysate Preparation and Determination of Proteolytic Activity in Cell Lysates. Human MDA-MB-468 breast cancer cells were cultured in DMEM medium containing 10% fetal calf serum (FCS) and 100 units/mL of penicillin and 100 μg/mL of streptomycin. Cells were maintained at 37 °C in a humidified incubator in an atmosphere of 5% CO_2. Cells were treated with different concentrations of compounds **1**, **39**, or vehicle control (DMSO) for 48 or 11 h. Cells were then harvested, washed with PBS twice, and homogenized in lysis buffer (50 mM Tris-HCl, pH = 8.0, 5 mM EDTA, 150 mM NaCl, 0.5% NP-40) for 30 min at 4 °C. Cell lysates were centrifuged at 12000*g* for 15 min, and the supernatants were collected as cell lysates. To determine the proteasome CT-L activity in whole cell extracts from cultured cells, we used the same method[21,22] described for in vitro CT-L activity assay, except instead of using 20S rabbit proteasome, we used 5 μg of cell lysates.

Western Blot Analysis. Cell lysates (30 μg) were separated by SDS-PAGE and transferred to a nitrocellulose membrane, probed with ubiquitin antibody (Santa Cruz Biotechnnology Inc. (Santa Cruz, CA), and signals were visualized by enhanced chemoluminescence (ECL, Amersham, Piscataway, NJ) according to the manufacturer's protocol.

MTT (3-(4,5-Dimethythiazol-2-yl)-2,5-diphenyltetrazolium bromide) Metabolism Assay. Cells were plated in 96-well plates in 100 μL medium and allowed to attach overnight. Cells were then incubated for 11 h with varying concentrations of compound **39** and appropriate control. Media was aspirated and replaced with 100 μL of complete media containing 1 mg/mL MTT and incubated for 3 h at 37 °C in 5% CO_2 humidified incubator. Media was then aspirated, and DMSO was added. Cells were incubated for 10 min at room temperature while shaking, and the absorbance was determined at 540 nm using a μQuant spectrophotometric plate reader (Bio-TEK, Winooski, VT).

Dialysis Using Purified Rabbit 20S Proteasome. To measure the effect of dialysis on CT-L activity, compounds **1**, **39**, Bortezomib (10 μM), or vehicle (0.1% DMSO) were added to rabbit 20S proteasome at a final concentration of 1.5 nM in proteasome assay buffer (50 mM Tris-HCl, pH = 7.6) and incubated at room temperature for 30 min. After 30 min of incubation, proteasome−compound mixtures were added to 3500 MWCO Thermo Scientific Slide-A-Lyzer MINI Dialysis Unit (Rockford, IL) and dialyzed against proteasome assay buffer. Immediately (t = 0) and 0.5 h, 1 h, 4 h, 8 h, and 18 h of dialysis at 4 °C, samples were removed from the dialysis unit and the CT-L 20S proteasome activity was determined as described previously.[21,22] Proteasome activity was normalized against proteasome activity of DMSO control.

*N-(4-Hydroxynaphthalen-1-yl)thiophene-2-sulfonamide (**3**).* The 4-aminonaphthol hydrochloride salt (**2**) (1.957 g, 0.01 mol) was suspended in DCM (80 mL) and added triethylamine (3.0 mL, 22 mmol) at 0 °C (the suspension became a dark brown solution). Thiophene-2-sulfonyl chloride (1.827 g, 0.01 mol) was added, and the reaction mixture was stirred at rt overnight (14 h). The reaction mixture was diluted with DCM (200 mL) washed with aqueous HCl (1 N, 30 mL × 3), water (30 mL × 3), and brine (30 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated to obtain a dark-brown solid. The crude solid was suspended in methanol/water (1:1, ∼50 mL), filtered, and washed with methanol/H_2O (1:1, ∼15 mL × 2) to obtain pure compound **3** (2.7 g, 90%) as a brown solid; R_f = 0.23 (TLC, EtOAc/hexane [1:2]); mp 146−148 °C. HPLC 96% (R_t = 3.51 min, 60% CH_3CN in 0.1% TFA water, 20 min). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.83−1.78 (m, 2H), 7.70 (dd, J = 5.8, 1.2 Hz, 1H), 7.60 (dd, J = 3.6, 1.2 Hz, 1H), 7.49−7.42 (m, 2H), 7.07 (d, J = 8.0 Hz, 1H), 7.06 (dd, J = 5.2, 4.0 Hz 1H), 6.66 (d, J = 8.4 Hz, 1H), 4.30 (br s, 2H, disappeared on D_2O shake). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.83, 138.30, 135.52, 135.19, 134.61, 128.06, 127.69, 126.93, 125.81, 124.11, 122.19, 121.18, 119.63, 108.26. LC-MS (ESI+) 306.03 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{14}H_{12}NO_3S_2$ $(M + H)^+$ 306.0253, found 306.0266.

*N-(3-Chloro-4-hydroxynaphthalen-1-yl)thiophene-2-sulfonamide (**4a**).* The compound **3** (987 mg, 3.2 mmol) was suspended in MeOH (10 mL), hydrogen peroxide added (35% in water, 3 mL), and stirred at rt for 2 h. Additional hydrogen peroxide (3 mL) was added, followed by HCl (4 M in dioxane, 1 mL) and continued stirring at rt for another 2 h. The organic phase was evaporated, and the residue was dissolved in ethyl acetate (100 mL) and washed with water (20 mL × 3) and brine (20 mL × 2). The organic phase was dried (Mg_2SO_4), filtered, and concentrated to obtain a crude solid. The crude solid was purified using SiO_2 chromatography (hexane/EtOAc gradient elution) to obtain pure compound **4a** (244 mg, 22.2%) as a brown solid. R_f = 0.46 (TLC, EtOAc/hexane [1:2]); mp 113−115 °C. HPLC 98% (R_t = 6.79 min, 60% CH_3CN in 0.1% TFA water, 20 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.64 (dd, J = 4.8, 1.1 Hz, 1H), 7.60 (dd, J = 4.0, 1.2 Hz, 1H), 7.44−7.35 (m, 2H), 7.19 (s, 1H), 7.02 (dd, J = 5.2, 4.0, Hz, 1H), 4.46 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.07, 137.40, 135.81, 134.98, 134.78, 127.84, 126.96, 126.92, 126.82, 123.74, 122.44, 121.08, 120.54, 111.99. LC-MS (ESI+) 339.98 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{14}H_{11}ClO_3S_2$ $(M + H)^+$ 339.9863, found 339.9856.

*N-(3-Bromo-4-hydroxynaphthalen-1-yl)thiophene-2-sulfonamide (**4b**).* The compound **3** (306 mg, 1 mmol) was dissolved in DMF (1 mL) at 0 °C, and Br_2 (320 mg in 1 mL of DCM solution, 2 mmol) was added and stirred at rt for 1 h. Triethylamine (0.558 mL, 4 mmol) was added at 0 °C and continued stirring at rt overnight (12−14 h). The reaction mixture was diluted with ethyl acetate (50 mL), washed with water (10 mL) and brine (10 mL), dried (Na_2SO4), and concentrated to obtain a brown crude solid. The crude product was purified using SiO_2 chromatography (hexane/EtOAc gradient elution) to obtain **4b** (140 mg, 36.4%) as an orange−red solid. R_f = 0.38 (TLC, EtOAc/hexane [1:2]); mp 128−130 °C. HPLC 88% (R_t = 7.33 min, 60% CH_3CN in 0.1% TFA water 20 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.66 (appdd, J = 4.8, 1.2 Hz, 1H), 7.61 (appdd, J = 4.0, 1.2 Hz, 1H), 7.47−7.39 (m, 2H), 7.32 (s, 1H), 7.04 (dd, J = 4.8, 3.6 Hz, 1H), 4.75 (br s, 2H). LC-MS (ESI+) 383.93 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{14}H_{11}BrO_3S_2$ $(M + H)^+$ 383.9358, found 383.9348.

*N-(3-Iodo-4-hydroxynaphthalen-1-yl)thiophene-2-sulfonamide (**4c**).* This compound was prepared using the procedure described for compound **4b**, except using I_2 (152 mg, 0.6 mmol). The pure product **4c** (129.4 mg, 100%) was obtained as a brown solid. R_f = 0.45 (TLC, EtOAc/hexane [1:2]); mp 134−136 °C. HPLC 97% (R_t = 8.19 min, 60% CH_3CN in 0.1% TFA water 20 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.81 (m, 1H), 7.75−7.72 (m, 1H), 7.68 (dd, J = 4.8, 1.2 Hz, 1H), 7.62 (dd, J = 4.0, 1.2 Hz, 1H), 7.46−7.41 (m, 3H), 7.06 (dd, J = 5.0, 3.8 Hz, 1H), 4.7 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.59, 137.62, 135.83, 134.95, 134.82, 128.37, 127.89, 127.83, 127.28, 126.82, 122.64, 122.62, 121.56, 75.24. LC-MS (ESI+) 431.92 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{14}H_{11}IO_3S_2$ $(M + H)^+$ 431.9220, found 431.9216.

*Ethyl 2-(1,4-Dioxo-1,4-dihydronaphthalen-2-ylthio)acetate (**8a**).* The 1,4-naphthoquinone (791 mg, 5 mmol) was added portionwise to EtOH (10 mL) containing ethyl mercaptoacetate (0.27 mL, 25 mmol) at room temperature. The reaction mixture was stirred at room temperature for 30 min. The yellow solid obtained was filtered, washed with ethanol, and dried under vacuum to obtain naphthoquinone intermediate **8a** (491 mg, 88.9%) as a yellow solid. R_f = 0.60 (TLC, EtOAc/hexane = 1:2); mp 150−152 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11−8.07 (m, J = 7.4 Hz, 2H), 7.78−7.69 (m, 2H), 6.70 (s, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.66 (s, 2H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.15, 181.73, 167.68, 153.42, 134.69, 133.67, 132.27, 131.88, 128.12, 127.08, 126.84, 62.60, 33.14, 14.33. LC-MS (ESI+) 299.01 $(M + Na)^+$. HRMS (ESI+) m/z calculated for $C_{14}H_{13}O_4S$ $(M + H)^+$ 277.0529, found 277.0529.

*Methyl 3-(1,4-Dioxo-1,4-dihydronaphthalen-2-ylthio)-propanoate (**8b**).* This compound was prepared using the procedure described for compound **8a** except using methyl 3-mercaptopropionate (1.582 g, 0.01 mol). The pure product **8b** (1.298 g, 93.9%) was obtained as a yellow solid. R_f = 0.40 (TLC, EtOAc/hexane [1:2]); mp 108−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (t, J = 7.6 Hz, 2H), 7.76 (td, J = 7.6, 1.6 Hz, 1H), 7.71 (td, J = 7.6, 1.2 Hz, 1H), 6.64 (s,

1H), 3.74 (s, 3H), 3.13 (t, J = 7.4 Hz, 2H), 2.78 (t, J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.16, 181.66, 171.43, 154.29, 134.63, 133.59, 132.31, 132.02, 127.36, 127.10, 126.81, 52.42, 32.29, 25.46. LC-MS (ESI+) 299.04 $(M + Na)^+$, 277.05 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{14}H_{13}O_4S$ $(M + H)^+$ 277.0529, found 277.0539.

*tert-Butyl 2-(1,4-Dioxo-1,4-dihydronaphthalen-2-yloxy)acetate (**8c**).* A mixture of 2-hydroxynaphthalene-1,4-dione **6** (174.2 mg, 1.0 mmol), *tert*-butyl 2-bromoacetate (0.2 mL, 1.33 mmol), silver oxide (308 mg, 1.33 mmol), and potassium iodide (16.6 mg, 0.1 mmol) in chloroform (5 mL) was refluxed under argon atmosphere for 12 h. Additional *tert*-butyl 2-bromoacetate (1.5 mL, 10 mmol) was added, and the reaction was continued under reflux for further 24 h. The reaction mixture was filtered through a pad of Celite, washed with DCM (3 × 10 mL), and the filtrate was concentrated to obtain a gray−yellow solid. The crude product was purified using SiO_2 chromatography (5 g silica gel, EtOAc/hexane gradient elution) to give pure compound **8c** (93.2 mg, 32%) as a light-yellow solid. R_f = 0.50 (TLC, EtOAc/hexane [1:2]); mp 120−122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (m, 1H), 8.08 (m, 1H), 7.77−7.71 (m, 2H), 6.04 (s, 1H), 4,61 (s, 2H), 1.41 (s, 9H). LC-MS (ESI+) 233.03 (M + H-^{t}Bu)$^+$, 289.10 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{16}H_{17}O_5$ $(M + H)^+$ 289.1071, found 289.1090.

*Ethyl 2-(1-Oxo-4-(thiophen-2-ylsulfonylimino)-1,4-dihydronaphthalen-2-ylthio)acetate (**9a**).* To a mixture of **8a** (63 mg, 0.228 mmol) and thiophene-2-sulfonamide (37 mg, 0.228 mmol) in DCM (2.5 mL) at 0 °C was added $TiCl_4$·2THF complex (76 mg, 0.228 mmol) followed by triethylamine (70 μL, 0.5 mmol). The mixture was heated at 60 °C using the microwave reactor for 20 min. The reaction mixture was diluted with DCM (60 mL) and washed with water (∼15 mL) and brine (∼15 mL). The organic phase was separated, dried (Na_2SO_4), and concentrated to obtain a brown crude semisolid. The crude mixture was purified using SiO_2 chromatography (EtOAc/hexane gradient elution) to obtain the required pure compound **9a** (58 mg, 60%) as an orange oil which solidified on standing at room temperature. R_f = 0.30 (TLC, EtOAc/hexane [1:2]); mp 110−112 °C. HPLC 95% (R_t = 4.63 min, 70% CH_3CN in 0.1% TFA water, 20 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, J = 6.0, 3.2 Hz, 1H), 8.15 (dd, J = 5.6, 3.2 Hz, 1H), 7.96 (s, 1H), 7.83 (dd, J = 4.0, 1.6 Hz, 1H), 7.71−7.68 (m, 3H), 7.15 (dd, J = 5.0, 4.0 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 3.80 (s, 2H), 1.35 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.80, 167.34, 160.01, 153.40, 142.08, 134.42, 133.61, 133.59, 133.27, 133.00, 131.81, 127.56, 127.23, 120.91, 62.95, 33.56, 14.29. LC-MS (ESI+) 422.03 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{18}H_{16}NO_5S_3$ $(M + H)^+$ 422.0185, found 422.0192.

*tert-Butyl-2-(1-oxo-4-(thiophen-2-ylsulfonylimino)-1,4-dihydronaphthalen-2-yloxy)acetate (**9b**).* Triethylamine (0.12 mL, 0.88 mmol) was added to a mixture of *tert*-butyl 2-(1,4-dioxo-1,4-dihydronaphthalen-2-yloxy)acetate **8c** (115 mg, 0.4 mmol) and thiophene-2-sulfonamide (78 mg, 0.48 mmol) in anhydrous DCM (4 mL). $TiCl_4$·2THF (134 mg, 0.4 mmol) was added to the reaction mixture and heated at 60 °C using the microwave reactor for 20 min. The crude mixture was poured into EtOAC (20 mL), filtered using a Celite pad, and the filtrate was concentrated and purified (SiO_2 chromatography, EtOAc/hexane gradient elution) to give pure compound **9b** (0.068 g, 39%) as a yellow solid; mp 153−155 °C. HPLC 94% (R_t = 4.86 min, 70% CH_3CN in 0.1% TFA water 20 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−8.06 (m, 1H), 8.02−8.00 (m, 1H), 7.64 (appdd, J = 3.7, 1.2 Hz, 1H), 7.55−7.53 (m, 3H), 7.10 (s, 1H), 6.98 (t, J = 4.0 Hz, 1H), 4.58 (s, 2H), 1.39 (s, 9H). LC-MS (ESI+) 334.02 $(M + H)^+$.

*Ethyl 2-(1-Oxo-4-(phenylsulfonylimino)-1,4-dihydronaphthalen-2-ylthio)acetate (**9c**).* This compound was prepared using the procedure described for compound **9a** except using phenylsulfonamide (157 mg, 1 mmol) to give pure product **9c** (132 mg, 31.7%) as a yellow solid. R_f = 0.50 (TLC, EtOAc/hexane [1:2]); mp 93−95 °C. HPLC 95% (R_t = 5.11 min, 70% CH_3CN in 0.1% TFA water 20 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (appdd, J = 7.2, 2.4 Hz, 2H), 8.07 (appd, J = 7.2 Hz, 2H), 7.99 (s, 1H), 7.65−7.62 (m, 3H), 7.58 (appt, J = 8.0 Hz, 2H), 4.32 (q, J = 7.2 Hz, 2H), 3.81 (s, 2H), 1.34 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.89, 167.41, 160.31, 152.98, 141.25, 134.32, 133.74, 133.45, 133.37, 131.78, 129.26, 127.49, 127.46, 127.09, 121.29, 62.94, 33.56, 14.30. LC-MS (ESI+) 416.06 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{20}H_{18}NO_5S_2$ $(M + H)^+$ 416.0621, found 416.0621.

*Methyl 3-(1-Oxo-4-(thiophen-2-ylsulfonylimino)-1,4-dihydronaphthalen-2-ylthio) propanoate (**9d**).* This compound was prepared according to the procedure described for compound **9a** except using **8b** (276 mg, 1 mmol). The title compound **9d** (110 mg, 26.1%) was obtained as an orange color solid. R_f = 0.50 (TLC, EtOAc/hexane [1:2]); mp 140−142 °C. HPLC 99% (R_t = 4.47 min, 70% CH_3CN in 0.1% TFA water 20 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24−8.22 (m, 1H), 8.15−8.13 (m, 1H), 7.91 (s, 1H), 7.83−7.82 (m, 1H), 7.71−7.68 (m, 3H), 7.16−7.14 (m, 1H), 3.75 (s, 3H), 3.26 (t, J = 6.9 Hz, 2H), 2.85 (t, J = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.79, 171.35, 160.09, 154.37, 142.10, 134.39, 133.63, 133.53, 133.23, 132.95, 131.99, 127.59, 127.57, 127.23, 120.19, 52.46, 32.07, 25.88. LC-MS (ESI+) 422.03 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{18}H_{16}NO_5S_3$ $(M + H)^+$ 422.0185, found 422.0181.

*Ethyl 2-(1-Hydroxy-4-(thiophene-2-sulfonamido)naphthalen-2-ylthio)acetate (**10a**).* The (*E*)-ethyl 2-(1-oxo-4-(thiophen-2-ylsulfonylimino)-1,4-dihydronaphthalen-2-ylthio)acetate (**9a**) (52 mg, 0.123 mmol) was dissolved in THF (2 mL), and $Na_2S_2O_4$ (107 mg, 0.62 mmol in 2 mL of water) was added. The biphasic mixture obtained was stirred at rt for 1 h until it turned pale yellow. The mixture was diluted with ethyl acetate (∼30 mL) and washed with water (∼10 mL) and brine (∼10 mL). The organic phase was dried (Na_2SO_4) and filtered, and the filtrate was concentrated. The crude product obtained was purified (SiO_2 chromatography, EtOAc/hexane gradient elution) to obtain pure **10a** (0.025 g, 58.7%) as an off-white solid. R_f = 0.25 (TLC, EtOAc/hexane [1:2]); mp 116−118 °C. HPLC 93% (R_t = 4.72 min, 60% CH_3CN in 0.1% TFA water 20 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.29 (dd, J = 6.3, 3.2 Hz, 1H), 7.80 (dd, J = 6.3, 3.1 Hz, 1H), 7.52 (d, J = 4.0 Hz, 1H), 7.48 (dd, J = 6.4, 3.2 Hz, 2H), 7.38 (d, J = 2.4 Hz, 1H), 7.34 (s, 1H), 6.95 (t, J = 4.8 Hz, 1H), 6.7 (br s, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.48 (s, 2H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.46, 155.83, 139.71, 133.32, 132.69, 131.87, 128.70, 127.59, 126.46, 124.78, 124.05, 123.41, 122.18, 110.19, 62.75, 39.73, 14.24. LC-MS (ESI+) 441.05 $(M + NH_4)^+$. HRMS (ESI+) m/z calculated for $C_{18}H_{18}NO_5S_3$ $(M + H)^+$ 424.0342, found 424.0335.

*tert-Butyl-2-(1-hydroxy-4-(thiophene-2-sulfonamido)-naphthalen-2-yloxy)acetate (**10b**).* The *tert*-butyl-2-(1-oxo-4-(thiophen-2-ylsulfonylimino)-1,4-dihydronaphthalen-2-yloxy)acetate **9b** (70 mg, 0.16 mmol) was dissolved in THF (3 mL) and stirred at rt for 5 min. The $Na_2S_2O_4$ (139 mg, 0.8 mmol) and water (1 mL) was added to the mixture and stirred vigorously until $Na_2S_2O_4$ was completely dissolved. The reaction mixture was further stirred at rt for 10 min. The color changed from orange to light yellow. EtOAc (40 mL) was added into the mixture and washed with water (40 mL) followed by brine. The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated. The required product **10b** was obtained by crystallization with EtOAc/hexane as a light-yellow solid (50 mg, 71%); mp = 155−157 °C. HPLC 96% (R_t = 3.39 min, 70% CH_3CN in 0.1% TFA water 20 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (br s, 1H, disappeared on D_2O shake), 8.24 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.46 (dd, J = 4.8, 1.3 Hz, 1H), 7.44−7.40 (m, 1H), 7.35−7.29 (m, 2H), 7.23 (s, 1H), 6.90 (dd, J = 5.2, 4.0 Hz, 1H), 6.68 (s, 1H, disappeared on D_2O shake), 4.53 (s, 2H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.34, 143.83, 140.29, 139.79, 133.09, 132.62, 127.98, 127.54, 126.44, 125.97, 125.64, 123.13, 122.78, 121.04, 119.32, 84.20, 71.12, 28.29. LC-MS (ESI−) 434.07 $(M - H)^-$. HRMS (ESI−) m/z calculated for $C_{20}H_{20}NO_6S_2$ $(M - H)^-$ 434.0738, found 434.0755.

*Ethyl 2-(1-Hydroxy-4-(phenylsulfonamido)naphthalen-2-ylthio)-acetate (**10c**).* This compound was prepared using the procedure described for **10a** except using the starting material **9c** (83 mg, 0.2 mmol). The title compound **10c** was obtained as a pale-yellow solid (68 mg, 81.5%). R_f = 0.22 (TLC, EtOAc/hexane [1:2]); mp 118−120 °C. HPLC 92% (R_t = 5.04 min, 60% CH_3CN in 0.1% TFA water 20

min). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.51 (s, 1H), 8.27−8.24 (m, 1H), 7.87−7.85 (m, 1H), 7.69 (d, J = 7.4 Hz, 2H), 7.56 (t, J = 7.2 Hz, 1H), 7.51−7.47 (m, 2H), 7.43 (t, J = 7.9 Hz, 2H), 7.17 (s, 1H), 6.59 (br s, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.43 (s, 2H), 1.21 (t, J = 7.2 Hz, 3H). LC-MS (ESI+) 440.07 $(M + Na)^+$. HRMS (ESI+) m/z calculated for $C_{20}H_{19}NNaO_5S_2$ $(M + Na)^+$ 440.0597, found 440.0596.

*Methyl 3-(1-Hydroxy-4-(thiophene-2-sulfonamido)naphthalen-2-ylthio)propanoate (**10d**).* This compound was prepared using the procedure described for **10a** except using starting material **9d** (30 mg, 0.071 mmol). The title compound **10d** was obtained without any purification as a pale-yellow solid (28 mg, 93%). R_f = 0.20 (TLC, EtOAc/hexane [1:2]); mp 117−119 °C. HPLC 97% (R_t = 4.09 min, 60% CH_3CN in 0.1% TFA water 20 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (dd, J = 6.4, 3.2 Hz, 1H), 7.87 (dd, J = 6.4, 3.2 Hz, 1H), 7.60 (br s, 1H), 7.52−7.48 (m, 3H), 7.41 (dd, J = 3.6 1.2 Hz, 1H), 7.32 (s, 1H), 6.95 (dd, J = 4.8, 3.6 Hz, 1H), 6.91 (br s, 1H), 3.70 (s, 3H), 2.93 (t, J = 7.1 Hz, 2H), 2.51 (t, J = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.41, 154.89, 139.74, 133.29, 132.77, 132.48, 131.35, 128.54, 127.60, 126.54, 124.24, 123.76, 123.51, 122.35, 109.96, 52.31, 34.09, 31.79. LC-MS (ESI+) 446.01 $(M + Na)^+$. HRMS (ESI+) m/z calculated for $C_{18}H_{17}NNaO_5S_3$ $(M + Na)^+$ 446.0161, found 446.0157.

*Ethyl 2-(1-Hydroxy-4-(thiophene-2-sulfonamido)naphthalen-2-ylsulfonyl)acetate (**10e**).* Ethyl 2-(1-hydroxy-4-(thiophene-2-sulfonamido)naphthalen-2-ylthio)acetate (**10a**) (42.4 mg, 0.1 mmol) was dissolved in acetone (2 mL), to which was added oxone (307.4 mg in 2 mL of aqueous solution). The resulting mixture was stirred at rt overnight (12−14 h). The organic solvent was evaporated, and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with water and brine and dried over Na_2SO_4. The organic phase was filtered, and the filtrate was concentrated to obtain **10e** (47 mg, 100%) as a pale-yellow solid; mp 154−156 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ 10.02 (s, 1H), 8.43 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.62 (td, J = 8.0, 0.8 Hz, 1H), 7.58 (appdd, J = 5.0, 1.2 Hz, 1H), 7.43 (appdd, J = 4.0, 1.6 Hz, 1H), 7.29 (s, 1H), 7.00 (dd, J = 4.8, 3.6 Hz, 1H), 6.58 (s, 1H), 4.16 (q, J = 7.2 Hz, 2H), 4.12 (s, 2H), 1.15 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 162.16, 155.75, 139.23, 134.91, 133.62, 133.21, 131.25, 127.86, 127.66, 125.75, 124.53, 124.26, 122.85, 122.26, 112.67, 63.05, 61.22, 13.77. LC-MS (ESI−) 454.01 $(M - H)^-$. HRMS (ESI−) m/z calculated for $C_{18}H_{17}NO_7S_3$ $(M - H)^-$ 454.0094, found 454.0112.

*2-(1-Hydroxy-4-(thiophene-2-sulfonamido)naphthalen-2-ylthio)-acetic Acid **11a** (Compound **1**).* The ethyl 2-(1-hydroxy-4-(thiophene-2-sulfonamido)naphthalen-2-ylthio)acetate (**10a**) (8 mg, 0.019 mmol) was dissolved in dioxane, (0.5 mL) and HCl (0.5 mL, 4 N) added. The reaction mixture was heated at 100 °C using the microwave reactor for 10 min and diluted with ethyl acetate (20 mL) and washed with water and brine. The organic phase was dried (Na_2SO_4) and filtered, and the filtrate was concentrated to afford the title compound as a pale-yellow solid (6 mg, 80%). R_f = 0.25 (TLC, CH_3OH/DCM [1:10]); mp 175−177 °C. HPLC 97% (R_t = 15.6 min, 35% CH_3CN in 0.1% TFA water, 30 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (s, 1H, disappeared on D_2O shake), 9.87 (br s, 1H, disappeared on D_2O shake), 8.13 (d, J = 8.0 Hz, 1H), 7.85−7.83 (m, 1H, 2H), 7.48−7.39 (m, 2H), 7.33 (dd, J = 4.0, 1.6 Hz, 1H), 7.06−7.03 (m, 2H), 3.52 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.11, 152.44, 140.21, 133.13, 132.38, 131.31, 129.38, 127.61, 126.78, 125.82, 125.05, 123.95, 123.21, 122.41, 112.95, 36.83. LC-MS (ESI−) 393.99 $(M - H)^-$. HRMS (ESI−) m/z calculated for $C_{16}H_{12}NO_5S_3$ $(M - H)^-$ 393.9883, found 393.9885.

*2-(1-Hydroxy-4-(thiophene-2-sulfonamido)naphthalen-2-yloxy)-acetic Acid (**11b**).* The *tert*-butyl-2-(1-hydroxy-4-(thiophene-2-sulfonamido)naphthalen-2-yloxy)acetate (**10b**) (0.025 g, 0.057 mmol) was dissolved in dioxane and concentrated hydrochloric acid (dioxane/ HCl, 1:1, 4 mL) and stirred at rt for 3 h (the solution changed from clear to white cloudy). The solvent was evaporated, and the solid obtained was washed with DCM and hexane separately to get pure product as a gray solid (0.021 g, 97%); mp = 155−157 °C. HPLC 90% (R_t = 6.48 min, 40% CH_3CN in 0.1% TFA water 20 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (s, 1H, disappeared on D_2O shake), 9.68 (br s, 1H, disappeared on D_2O shake), 8.04 (d, J = 8.8 Hz, 1H), 7.82 (d, J = 4.0 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.38 (t, J = 7.2 Hz, 1H), 7.33 (appd, J = 2.4 Hz, 1H), 7.27 (t, J = 7.2 Hz, 1H), 7.03 (appt, J = 4.0 Hz, 1H), 6.89 (s, 1H), 4.55 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.66, 141.36, 140.97, 140.60, 133.76, 132.95, 128.26, 127.96, 125.98, 125.94, 125.26, 123.74, 123.56, 122.26, 117.23, 68.16. LC-MS (ESI−) 378.01 $(M - H)^-$. HRMS (ESI−) m/z calculated for $C_{16}H_{12}NO_6S_2$ $(M - H)^-$ 378.0112, found 378.0117.

*2-(1-Hydroxy-4-(phenylsulfonamido)naphthalen-2-ylthio)acetic Acid (**11c**).* This compound was prepared using the procedure described for **11a** except using **10c** (40 mg, 0.096 mmol) at rt overnight (12−14 h). The title compound was obtained as an off-white solid (20 mg, 53.6%); mp 100−102 °C. HPLC 94% (R_t = 9.3 min, 40% CH_3CN in 0.1% TFA water, 40 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.75 (br s, 1H), 9.91 (s, 1H), 9.80 (br s, 1H), 8.10 (d, J = 8.1 Hz, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.60 (d, J = 7.7 Hz, 2H), 7.56 (d, J = 7.3 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 7.39−7.36 (m, 2H), 6.96 (s, 1H), 3.47 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.74, 152.82, 140.39, 133.31, 131.82, 129.79, 129.72, 127.51, 127.33, 126.45, 125.71, 124.82, 124.02, 123.02, 113.60, 37.40. LC-MS (ESI−) 388.03 $(M - H)^-$. HRMS (ESI−) m/z calculated for $C_{18}H_{14}NO_5S_2$ $(M - H)^-$ 388.0319, found 388.0330.

*3-(1-Hydroxy-4-(thiophene-2-sulfonamido)naphthalen-2-ylthio)-propanoic Acid (**11d**).* This compound was prepared using the procedure described for **11a** except using **10d** (43 mg, 0.1 mmol) at rt overnight (12−14 h). The title compound was obtained as a white solid (38 mg, 90.4%); mp 185 °C (dec.). HPLC 96% (R_t = 8.8 min, 40% CH_3CN in 0.1% TFA water, 40 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35 (s, 1H), 10.07 (s, 1H), 9.70 (br s, 1H), 8.13 (d, J = 7.6 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.85 (td, J = 4.8, 0.5 Hz, 1H), 7.49−7.42 (m, 2H), 7.34 (td, J = 4.0, 1.6 Hz, 1H), 7.07−7.05 (m, 1H), 6.96 (s, 1H), 2.84 (t, J = 7.6 Hz, 2H), 2.37 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.40, 153.02, 140.76, 133.87, 133.07, 131.86, 129.69, 128.30, 127.31, 126.49, 125.77, 124.67, 124.06, 123.05, 113.58, 34.61, 29.92. LC-MS (ESI−) 408.00 $(M - H)^-$. HRMS (ESI−) m/z calculated for $C_{17}H_{14}NO_5S_3$ $(M - H)^-$ 408.0040, found 408.0054.

*2-(1-Hydroxy-4-(thiophene-2-sulfonamido)naphthalen-2-ylsulfonyl)acetic Acid (**11e**).* Ethyl 2-(1-hydroxy-4-(thiophene-2-sulfonamido)naphthalen-2-ylsulfonyl)-acetate (**10e**) (20 mg, 0.044 mmol) was dissolved in dioxane (2 mL) and conc HCl (2 mL) added. The mixture was stirred at rt for 36 h. The solvent was removed using the rotary evaporator, and the solid obtained was washed with dichloromethane affording title compound **11e** (18.3 mg, 97.3%) as an off-white solid, mp 210−212 °C. HPLC 97% (R_t = 7.45 min, 35% CH_3CN in 0.1% TFA water, 20 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.62 (br s, 1H), 10.24 (s, 1H), 8.37 (d, J = 7.6 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.86 (dd, J = 5.2, 0.8 Hz, 1H), 7.64−7.58 (m, 2H), 7.35 (s, 1H), 7.33 (dd, J = 4.0, 0.8 Hz, 1H), 7.05 (dd, J = 4.9, 3.9 Hz, 1H), 4.52 (s, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 164.35, 154.42, 139.92, 135.05, 132.84, 132.62, 129.98, 127.39, 126.83, 125.81, 124.99, 123.52, 123.48, 122.58, 115.59, 59.78. LC-MS (ESI−) 426.00 $(M - H)^-$. HRMS (ESI−) m/z calculated for $C_{16}H_{13}NO_7S_3$ $(M - H)^-$ 425.9781, found 425.9788.

*N-(3-Chloro-4-oxonaphthalen-1(4H)-ylidene)thiophene-2-sulfonamide (**13a**).* The 2-chloro-1,4-naphthoquinone **12** (385 mg, 2 mmol) was added to thiophene-2-sulfonamide (326 mg, 2 mmol) in DCM (15 mL) at 0 °C, followed by $TiCl_4$ (2 mL, 1 M solution in DCM) and TEA (0.613 mL, 4.4 mmol). The mixture was heated at 60 °C using the microwave reactor for 15 min, and the black mixture obtained was poured into ethyl acetate (100 mL). The insoluble particles were removed by filtering through a pad of Celite. The filtrate was concentrated, and the residue obtained was suspended in DCM (100 mL). The brown insoluble particles were removed by filtration, and the filtrate was again concentrated to dryness. The residue was suspended in ethyl acetate/hexane (1:1−20 mL), and the yellow solid obtained was filtered. The solid was washed with ethyl acetate/hexane (1:1, 5 mL × 2) and dried under vacuum to afford the title compound as a yellow solid (378 mg, 55.9%). When $TiCl_4$·2THF (668 mg, 2

mol), TEA (0.615 mL, 4.4 mmol), and THF (15 mL) were used instead of $TiCl_4$ in DCM, the reaction afforded the title compound with better yields also as a yellow solid (522 mg 77.3%). R_f = 0.53 (TLC, EtOAc/hexane [1:2]); mp 167−169 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.24−8.20 (m, 2H), 7.86 (dd, J = 3.6, 1.2 Hz, 1H), 7.78−7.70 (m, 3H), 7.18 (dd, J = 4.8, 3.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.11, 160.88, 145.59, 141.08, 134.45, 134.28, 134.04, 133.81, 132.98, 131.61, 129.60, 128.16, 127.73, 127.24. LC-MS (ESI+) 355.00 $(M + NH_4)^+$. HRMS (ESI+) m/z calculated for $C_{14}H_9ClNO_3S_2$ $(M + H)^+$ 337.9707, found 337.9708.

*N-(3-Chloro-4-oxonaphthalen-1(4H)-ylidene)biphenyl-4-sulfonamide (**13b**).* This compound was prepared using the procedure described for **13a** except using 4-biphenylsulfonamide (233 mg, 1 mmol). The title compound **13b** was obtained as a yellow solid (154 mg, 37.8%). When $TiCl_4$·2THF (668 mg, 2 mmol), TEA (0.615 mL, 4.4 mmol), and THF (15 mL) were used in the reaction, the title compound **13b** was obtained also as a yellow solid with improved yield (586.7 mg, 71.9%). R_f = 0.60 (TLC, EtOAc/hexane [1:2]); mp 190−192 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.24 (appt, J = 8.8 Hz, 2H), 8.14 (d, J = 8.6 Hz, 2H), 7.81 (d, J = 8.6 Hz, 2H), 7.74 (td, J = 7.2, 1.6 Hz, 1H), 7.69 (td, J = 8.0, 2.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 2H), 7.51 (t, J = 6.8 Hz, 2H), 7.46−7.43 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.21, 161.14, 146.82, 145.33, 139.40, 138.95, 134.37, 134.14, 133.12, 131.59, 129.91, 129.35, 128.93, 128.26, 128.11, 128.04, 127.64, 127.14. LC-MS (ESI+) 425.06 $(M + NH_4)^+$. HRMS (ESI+) m/z calculated for $C_{22}H_{15}ClNO_3S$ $(M + H)^+$ 408.0456, found 408.0460.

*N-(3-Chloro-4-oxonaphthalen-1(4H)-ylidene)-5-phenylthiophene-2-sulfonamide (**13c**).* This compound was prepared using the procedure described for **13a** except using 5-phenylthiophene-2-sulfonamide (477 mg, 2 mmol), $TiCl_4$ (2 mL, 1 M solution in DCM), TEA (0.615 mL, 4.4 mol), and THF (15 mL) as the solvent. The title compound was obtained as an orange solid (520 mg, 63.0%); mp 112.4 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.27−8.25 (m, 1H), 8.22−8.19 (m, 1H), 7.81 (d, J = 4.0 Hz, 1H), 7.77−7.70 (m, 2H), 7.65 (dd, J = 8.4, 1.6 Hz, 2H), 7.47−7.41 (m, 3H), 7.32 (d, J = 3.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.14, 160.72, 153.69, 145.55, 138.88, 134.73, 134.45, 134.25, 133.03, 132.73, 131.62, 129.73, 129.54, 129.52, 128.15, 127.28, 126.65, 123.29. LC-MS (ESI+) 414.00 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{20}H_{13}ClNO_3S_2$ $(M + H)^+$ 414.0020, found 414.0018.

*N-(3-Chloro-4-oxonaphthalen-1(4H)-ylidene)-4-phenoxybenzenesulfonamide (**13d**).* This compound was prepared using the procedure described for **13a** except using 4-phenoxyphenylesulfonamide (434 mg, 2 mmol), $TiCl_4$ (2 mL, 1 M solution in DCM), TEA (0.615 mL, 4.4 mmol), and THF (15 mL) as the solvent. The title compound was obtained as a yellow solid, (526 mg, 67.2%) mp 124.8 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.19 (appdd, J = 7.6, 1.6 Hz, 1H), 8.16 (appdd, J = 7.6, 1.6 Hz, 1H), 8.00 (d, J = 9.2 Hz, 2H), 7.73 (td, J = 7.6, 1.6 Hz, 1H), 7.67 (td, J = 7.6, 1.6 Hz, 1H), 7.44−7.40 (m, 2H), 7.26−7.22 (m, 1H), 7.15−7.08 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.22, 162.67, 160.78, 155.11, 145.21, 134.33, 134.08, 133.81, 133.15, 131.58, 130.48, 130.09, 129.78, 128.08, 127.07, 125.42, 120.69, 117.76. LC-MS (ESI+) 424.03 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{22}H_{15}ClNO_4S$ $(M + H)^+$ 424.0405, found 424.0403.

*N-(3-Chloro-4-oxonaphthalen-1(4H)-ylidene)naphthalene-2-sulfonamide (**13e**).* This compound was prepared using the procedure described for **13a** except using naphthalene-2-sulfonamide (415 mg, 2 mmol), $TiCl_4$·2THF (668 mg, 2 mmol), TEA (0.615 mL, 4.4 mmol), and THF (15 mL) as the solvent. The title compound was obtained as a yellow solid (0. 595 g, 77.9%). R_f = 0.55 (TLC, EtOAc/hexane [1:2]); mp 200−202 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.64 (s, 1H), 8.20 (appd, 7.6 Hz, 1H), 8.14 (appd, J = 8.0 Hz, 1H), 8.05−8.03 (m, 3H), 7.96 (d, 8.4 Hz, 1H), 7.72 (appq, J = 7.4 Hz, 2H), 7.66 (appt, J = 7.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.05, 160.98, 145.15, 137.09, 135.34, 134.38, 134.14, 132.92, 132.11, 131.42, 129.77, 129.64, 129.57, 129.00, 128.15, 127.95, 127.04, 122.61. LC-MS (ESI+) 382.03 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{20}H_{13}ClNO_3S$ $(M + H)^+$ 382.0299, found 382.0301.

*N-(3-Chloro-4-oxonaphthalen-1(4H)-ylidene)-4′-fluorobiphenyl-4-sulfonamide (**13f**).* This compound was prepared using the procedure described for **13a** except using 4′-fluorobiphenyl-4-sulfonamide (251 mg, 1 mmol), $TiCl_4$ (1 mL,1 M solution in DCM), TEA (308 mL, 2.2 mmol), and THF (10 mL) as the solvent. The title compound was obtained as a yellow solid (348 mg, 81.6%); mp 172.1−172.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.20 (dd, J = 7.6, 1.2 Hz, 1H), 8.17 (dd, J = 8.0, 1.2 Hz, 1H), 8.13 (d, J = 8.4 Hz, 2H), 7.77−7.75 (m, 2H), 7.72−7.66 (m, 2H), 7.60 (dd, J = 8.8, 5.2 Hz, 2H), 7.19 (t, J = 8.8 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.53 (m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.17, 163.46, (d, J = 245 Hz), 161.20, 145.74, 145.38, 139.04, 135.53 (d, J = 3.5 Hz), 134.36, 134.16, 133.09, 131.59, 129.35 (d, J = 8 Hz), 129.31, 128.33, 128.12, 127.87, 127.10, 116.36 (d, J = 21.5 Hz). LC-MS (ESI +) 426 $(M + H)^+$, 443.05 $(M + NH_4)^+$. HRMS (ESI+) m/z calculated for $C_{22}H_{14}ClFNO_3S$ $(M + H)^+$ 426.0362, found 426.0356.

*N-(3-Chloro-4-oxonaphthalen-1(4H)-ylidene)-5-(pyridin-2-yl)-thiophene-2-sulfonamide (**13g**).* This compound was prepared using the procedure described for **13a** except using 5-(pyridin-2-yl)-thiophene-2-sulfonamide (481 mg, 2 mmol), $TiCl_4$ (2 mL, 1 M solution in DCM), TEA (0.615 mL, 4.4 mmol), and THF (15 mL) as the solvent. The title compound was obtained as an orange solid (511 mg, 61.5%); mp 155.3 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 5.2 Hz, 1H), 8.60 (s, 1H), 8.28−8.26 (m, 1H), 8.21−8.18 (m, 1H), 7.87 (td, J = 7.8, 1.5 Hz, 1H), 7.84 (d, J = 4.0 Hz, 1H), 7.79 (s, 1H), 7.77 (s, 1H), 7.75−7.71 (m, 2H), 7.37 (dd, J = 6.7, 5.1 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.99, 162.05, 153.71, 150.64, 150.45, 145.71, 138.40, 135.74, 135.18, 135.13, 132.96, 132.22, 128.59, 128.00, 127.09, 125.94, 125.01, 120.42, 104.99. LC-MS (ESI+) 414.99 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{19}H_{12}ClN_2O_3S_2$ $(M + H)^+$ 414.9972, found 414.9969.

*N-(3-Chloro-4-oxonaphthalen-1(4H)-ylidene)-4-cyclohexylbenzenesulfonamide (**13h**).* This compound was prepared using the procedure described for **13a** except using 4-cyclohexylphenylsulfonamide (290 mg, 1.2 mmol), $TiCl_4$ (1.2 mL, 1 M solution in DCM), TEA (0.372 mL, 2.7 mmol), and THF (10 mL) as the solvent. The title compound was obtained as a yellow solid (213 mg, 42.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.19−8.15 (m, 2H), 7.97 (d, J = 8.4 Hz, 2H), 7.72 (td, J = 7.5, 1.5 Hz, 1H), 7.67 (td, J = 7.6, 1.6 Hz, 1H), 7.42 (d, J = 8.4 Hz, 2H), 2.64−2.58 (m, 1H), 1.91−1.85 (m, 4H), 1.79−1.75 (m, 1H), 1.50−1.34 (m, 4H), 1.31−1.23 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.24, 160.85, 154.67, 145.12, 137.66, 134.32, 134.03, 133.18, 131.56, 129.85, 128.03, 127.90, 127.83, 127.12, 44.93, 34.32, 26.87, 26.17. LC-MS (ESI+) 414.09 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{22}H_{21}ClNO_3S$ $(M + H)^+$ 414.0925, found 414.0924.

*N-(3-Chloro-4-oxonaphthalen-1(4H)-ylidene)-4′-methoxybiphenyl-4-sulfonamide (**13i**).* This compound was prepared using the procedure described for **13a** except using 4′-methoxybiphenyl-4-sulfonamide (527 mg, 2 mmol), $TiCl_4$ (2 mL, 1 M solution in DCM), TEA (0.615 mL, 4.4 mmol), and THF (15 mL) as solvent. The title compound was obtained as a yellow solid (650 mg, 74.2%); mp 168.1 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.19 (apptd, J = 8.8, 1.6 Hz, 2H), 8.10 (d, J = 8.6 Hz, 2H), 7.76 (d, J = 8.6 Hz, 2H, partially overlapped with the adjacent multiplet), 7.76−7.71 (m, 1H, partially overlapped with the adjacent doublet), 7.68 (td, J = 7.6, 1.6 Hz, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.21, 160.99, 160.48, 146.39, 145.26, 138.18, 134.34, 134.08, 133.15, 131.70, 131.58, 129.87, 128.77, 128.27, 128.07, 127.38, 127.12, 114.79, 55.65. LC-MS (ESI+) 438.04 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{23}H_{17}ClNO_4S$ $(M + H)^+$ 438.0561, found 438.0562.

*N-(3-Chloro-4-oxonaphthalen-1(4H)-ylidene)-4-pentylbenzenesulfonamide (**13j**).* This compound was prepared using the procedure described for **13a** except using 4-pentylphenylsulfonamide (455 mg, 2 mmoL), $TiCl_4$ (2 mL, 1 M solution in DCM), TEA (0.615 mL, 4.4 mmol), and THF (15 mL) as solvent, and the product was purified using SiO_2 chromatography (hexane/EtOAc gradient elution) to afford the title compound as a yellow solid (452 mg, 56.2%); mp 111.7−112.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.20

(dd, J = 7.6, 1.2 Hz, 1H), 8.16 (dd, J = 7.2, 1.6 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.73 (td, J = 7.5, 1.5 Hz, 1H), 7.68 (td, J = 7.6, 1.6 Hz, 1H), 7.40 (d, J = 8.4 Hz, 2H), 2.72 (t, J = 7.7 Hz, 2H), 1.66 (q, J = 7.5 Hz, 2H), 1.42−1.30 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.24, 160.86, 149.79, 145.15, 137.64, 134.30, 134.02, 133.19, 131.57, 129.86, 129.39, 128.04, 127.77, 127.10, 36.19, 31.62, 30.99, 22.70, 14.22. LC-MS (ESI+) 402 $(M + H)^+$, 419.11 $(M + NH_4)^+$. HRMS (ESI+) m/z calculated for $C_{21}H_{21}ClNO_3S$ $(M + H)^+$ 402.0925, found 402.0926.

*5-Chloro-N-(3-chloro-4-oxonaphthalen-1(4H)-ylidene)-thiophene-2-sulfonamide (**13k**).* This compound was prepared using the procedure described for **13a** except using 5-chlorothiophene-2-sulfonamide (395 mg, 2 mmol), $TiCl_4$ (2 mL, 1 M solution in DCM), TEA (0.615 mL, 4.4 mol), and DCM (15 mL) as solvent. The title compound was obtained as a yellow solid (320 mg, 43.0%). R_f = 0.50 (TLC, EtOAc/hexane [1:2]); mp 149−151 °C. ^{1}H NMR, (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.23−8.20 (m, 2H), 7.79−7.72 (m, 2H), 7.64 (d, J = 4.1 Hz, 1H), 7.01 (d, J = 4.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.99, 161.21, 145.85, 139.77, 134.53, 134.47, 133.10, 132.78, 131.60, 129.58, 128.25, 127.24, 127.00, 104.99. LC-MS (ESI+) 761.89 $(2M + NH_4)^+$. HRMS (ESI+) m/z calculated for $C_{14}H_8Cl_2NO_3S_2$ $(M + H)^+$ 371.9317, found 371.9324.

*N-(3-Chloro-4-oxonaphthalen-1(4H)-ylidene)-4′-trifluoromethyl-biphenyl-4-sulfonamide (**13l**).* This compound was prepared using the procedure described for **13a** except using 4′-trifluoromethylbiphenyl-4-sulfonamide (603 mg, 2 mmol), $TiCl_4$ (2 mL, 1 M solution in DCM), TEA (0.615 mL, 4.4 mmol), and THF (15 mL) as the solvent. The title compound was obtained as a yellow solid (794 mg, 83.4%); mp 190.4−191.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.21 (dd, J = 7.6, 1.2 Hz, 1H), 8.18−8.16 (m, 2H), 8.17 (d, J = 8.6 Hz, 1H), 7.81 (d, J = 8.6 Hz, 2H), 7.78−7.72 (m, 5H), 7.68 (td, J = 7.6, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.12, 161.41, 145.50, 145.20, 142.93, 140.04, 134.36, 134.22, 133.05, 131.61, 130.95 (q, J = 32.5 Hz), 129.92, 128.42, 128.26, 128.16, 128.01, 127.09, 126.30 (q, J = 3.7 Hz), 124.23 (d, J = 270.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.01 (s). LC-MS (ESI+) 493.05 $(M + NH_4)^+$. HRMS (ESI+) m/z calculated for $C_{23}H_{14}ClF_3NO_3S$ $(M + H)^+$ 476.0330, found 476.0325.

*N-(3-Chloro-4-oxonaphthalen-1(4H)-ylidene)-5-(phenylsulfonyl)-thiophene-2-sulfonamide (**13m**).* This compound was prepared using the procedure described for **13a** except using 5-(phenylsulfonyl)-thiophene-2-sulfonamide (341 mg, 1.2 mmol), $TiCl_4$ (1.1 mL, 1 M solution in DCM), TEA (0.345 mL, 2.5 mmol), and THF (10 mL) as the solvent. The title compound was obtained as a yellow solid (272 mg, 50.7%); mp 165.3 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.22−8.19 (m, 2H), 8.06−8.01(m, 2H), 7.79−7.76 (m, 2H), 7.73 (d, J = 4.0 Hz, 1H), 7.68−7.64 (m, 2H), 7.60−7.56 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.41, 150.49, 148.23, 146.44, 140.75, 134.85, 134.73, 134.52, 132.52, 132.46, 132.34, 131.59, 129.98, 129.70, 128.40, 128.00, 127.40, 104.99. Elemental analysis for **13m**: Calculated: C, 50.26; H, 2.53; N, 2.93. Found: C, 50.53; H, 2.85; N, 2.68.

*N-(3-Chloro-4-oxonaphthalen-1(4H)-ylidene)-1-(phenylsulfonyl)-1H-pyrrole-3-sulfonamide (**13n**).* This compound was prepared using the procedure described for **13a** except using 1-(phenylsulfonyl)-1H-pyrrole-3-sulfonamide (390 mg, 1.4 mmol), $TiCl_4$ (1.4 mL, 1 M solution in DCM), TEA (0.42 mL, 3 mmol), and THF (10 mL) as the solvent. The title compound was obtained as a yellow solid (444 mg, 70.7%); mp 127.5−131.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.20−8.16 (m, 2H), 7.97−7.95 (m, 2H), 7.85 (dd, J = 2.4, 1.6 Hz, 1H), 7.76−7.68 (m, 3H), 7.60 (t, J = 7.6 Hz, 2H), 7.27 (dd, J = 3.4, 2.4 Hz, 1H), 6.74 (dd, J = 3.4, 1.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.11, 161.01, 145.34, 137.75, 135.29, 134.41, 134.21, 132.97, 131.58, 130.18, 129.76, 128.88, 128.13, 127.71, 127.11, 124.19, 122.43, 111.92. LC-MS (ESI+) 461.00 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{20}H_{14}ClN_2O_5S_2$ $(M + H)^+$ 461.0027, found 461.0024.

*N-(3-Chloro-4-oxonaphthalen-1(4H)-ylidene)naphthalene-1-sulfonamide (**13o**, intermediate for compound compound **34**).* This compound was prepared using the procedure described for **13a** except using naphthalene-1-sulfonamide (415 mg, 2 mmol), $TiCl_4$ (2 mL, 1 M solution in DCM), TEA (0.615 mL, 4.4 mmol), and THF (15 mL) as the solvent. The title compound was obtained as an orange−red solid (0.653 mg, 85.5%) R_f = 0.67 (TLC, EtOAc/hexane [1:2]); mp 185.6 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.67 (dd, J = 8.8, 0.8 Hz, 1H), 8.44 (dd, J = 7.4, 1.6 Hz, 1H), 8.21−8.17 (m, 2H), 8.00 (appdt, J = 7.9, 1.9 Hz, 2H), 7.72−7.62 (m, 4H), 7.59 (td, J = 8.0, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.20, 161.53, 145.34, 135.61, 135.51, 134.47, 134.41, 134.08, 133.21, 131.61, 130.28, 129.32, 129.22, 128.78, 128.64, 128.08, 127.29, 127.14, 125.41, 124.44. LC-MS (ESI+) 382 $(M + H)^+$, 399.06 $(M + NH_4)^+$. HRMS (ESI+) m/z calculated for $C_{20}H_{13}ClNO_3S$ $(M + H)^+$ 382.0299, found 382.0300.

*4-Chloro-N-(3-chloro-4-oxonaphthalen-1(4H)-ylidene)-benzenesulfonamide (**13p**).* This compound was prepared using the procedure described for **13a** except using 4-chlorobenzenesulfonamide (383 mg, 2 mmol), $TiCl_4$ (2 mL, 1 M solution in DCM), TEA (0.615 mL, 4.4 mmol), and THF (15 mL) as the solvent. The title compound was obtained as a yellow solid (399 mg, 54.5%). R_f = 0.60 (TLC, EtOAc/hexane [1:2]); mp 138−140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.21 (dd, J = 7.6, 1.6 Hz, 1H), 8.12 (dd, J = 7.6, 1.2 Hz, 1H), 8.01 (d, J = 8.7 Hz, 2H), 7.75 (td, J = 8.8,1.2, Hz, 1H), 7.68 (td, J = 7.6, 1.6 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.07, 161.51, 145.59, 140.47, 138.99, 134.41, 134.30, 132.93, 131.58, 129.88, 129.72, 129.17, 128.18, 127.07. LC-MS (ESI+) 383.00 $(M + NH_4)^+$. HRMS (ESI+) m/z calculated for $C_{16}H_{10}Cl_2NO_3S$ $(M + H)^+$ 365.9753, found 365.9763.

*3,4-Dichloro-N-(3-chloro-4-oxonaphthalen-1(4H)-ylidene)-benzenesulfonamide (**13q**).* This compound was prepared using the procedure described for **13a** except using 3,4-dichlorobenzenesulfonamide (452 mg, 2 mmol), $TiCl_4$ (2 mL, 1 M solution in DCM), TEA (0.615 mL, 4.4 mmol), and THF (15 mL) as the solvent. The title compound was obtained as a yellow solid (622 mg, 77.6%). R_f = 0.41 (TLC, EtOAc/hexane [1:2]); mp 140.2−141.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.22 (dd, J = 7.7, 1.4 Hz, 1H), 8.16 (d, J = 2.2 Hz, 1H), 8.12 (dd, J = 8.0, 1.6 Hz, 1H), 7.90 (dd, J = 8.4, 2.2 Hz, 1H), 7.77 (td, J = 7.2, 1.2 Hz, 1H), 7.72−7.68 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.97, 162.00, 145.89, 140.15, 138.81, 134.49, 134.10, 132.75, 131.57, 131.47, 129.90, 129.68, 128.27, 127.14, 126.73. LC-MS (ESI+) 817.90 $(2M + NH_4)^+$. HRMS (ESI+) m/z calculated for $C_{16}H_9Cl_3NO_3S$ $(M + H)^+$ 399.9363, found 399.9375.

*N-(3-Chloro-4-oxonaphthalen-1(4H)-ylidene)-benzenesulfonamide (**13r**).* This compound was prepared using the procedure described for **13a** except using phenylsulfonamide (314 mg, 2 mmol), $TiCl_4$ (2 mL, 1 M solution in DCM), TEA (0.615 mL, 4.4 mmol), and THF (15 mL) as the solvent. The title compound was obtained as a yellow solid (508 mg, 76.6%). R_f = 0.31 (TLC, EtOAc/hexane [1:4]); mp 184.8−186.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.20 (dd, J = 7.6, 1.2 Hz, 1H), 8.15 (d, J = 7.6 Hz, 1H), 8.09 (d, J = 7.2 Hz, 2H), 7.74 (td, J = 7.2, 1.2 Hz, 1H), 7.71−7.66 (m, 2H), 7.62 (t, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.18, 161.22, 145.33, 140.49, 134.36, 134.14, 133.81, 133.08, 131.57, 129.93, 129.40, 128.09, 127.68, 127.09. LC-MS (ESI+) 349.03 $(M + NH_4)^+$. HRMS (ESI+) m/z calculated for $C_{16}H_{11}ClNO_3S$ $(M + H)^+$ 332.0143, found 332.0145.

*2-(1-Oxo-4-(thiophen-2-ylsulfonylimino)-1,4-dihydronaphthalen-2-ylthio)acetic Acid (**14a**).* The **13a** (188 mg, 0.56 mmol) was dissolved in THF (5 mL), and THF solution containing pyridine (0.56 mL, 0.5 M)was added, followed by THF solution containing 2-mercaptoglycolic acid (0.56 mL, 0.5 M). Additional pyridine (0.56 mL, 0.5 M in THF) and 2-mercaptoglycolic acid (0.56 mL, 0.5 M in THF) were added to the mixture. The mixture was stirred at room temperature for 30 min, and 2,3-dichloro-5,6-dicyanobenzoquinone (114 mg, 0.5 mmol) was added and stirred at room temperature overnight (12 h). The insoluble solid obtained was filtered, and the filtrate was concentrated. The crude residue was first purified via preparative TLC (2.5% CH_3OH in DCM) and then using SiO_2 column chromatography (CH_3OH/CH_3COOH/DCM [1.5:0.5:100]) to afford a yellow solid as the desired pure product **14a** (20 mg, 9.2%) and a mixture of desired product and reduced product (80.9 mg, 36.9%). R_f = 0.33 (TLC, CH_3OH/DCM [1:20]);

mp 131.7 °C (dec.). ^{1}H NMR (400 MHz, CD_3CN) δ 8.21−8.19 (m, 1H), 8.12−8.10 (m, 1H), 7.92−7.90 (m, 2H), 7.87 (dd, J = 3.8, 1.3 Hz, 1H), 7.80−7.78 (m, 2H), 7.24 (dd, J = 4.8, 3.6 Hz, 1H), 3.88 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.77, 168.99, 160.11, 153.94, 141.97, 134.37, 133.54, 133.34, 133.22 132.94, 131.78, 127.59, 127.43, 127.17, 120.53, 33.90. LC-MS (ESI−) 391.97 $(M - H)^-$. HRMS (ESI−) m/z calculated for $C_{16}H_{10}NO_5S_3$ $(M - H)^-$ 391.9727, found 391.9729.

*N-(3-(1-Methyl-1H-tetrazol-5-ylthio)-4-oxonaphthalen-1(4H)-ylidene)thiophene-2-sulfonamide (**14b**).* The **13a** (36 mg, 0.1 mmol) was dissolved in THF (3 mL), and 1-methyl-tetrazole-5-thiol (11.7 mg, 0.1 mol) was added. The reaction mixture was stirred at rt for 2 h and concentrated. The residue was dissolved in DCM and triturated with hexane. The precipitate obtained was filtered and washed with DCM/hexane (1:1, 2 mL × 3) to afford the title compound as an orange−red solid (29 mg, 68.9%). R_f = 0.80 (TLC, EtOAc/hexane [7:3]); mp 172 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26−8.24 (m, 1H), 8.17−8.15 (m, 1H), 8.01 (s, 1H), 7.78 (d, J = 3.8 Hz, 1H), 7.76−7.72 (m, 3H), 7.15 (dd, J = 5.2, 4.4 Hz, 1H), 4.21 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.28, 160.98, 149.29, 147.61, 140.87, 136.15, 135.46, 134.90, 134.26, 133.33, 132.00, 128.82, 127.64, 127.15, 122.73, 35.38. LC-MS (ESI+) 418.01 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{16}H_{12}N_5O_3S_3$ $(M + H)^+$ 418.0097, found 418.0099.

*N-(3-(1H-1,2,4-Triazol-5-ylthio)-4-oxonaphthalen-1(4H)-ylidene)-thiophene-2-sulfonamide (**14c**).* This compound was prepared using the procedure described for **14b** except using 3-mercapto-1,2,4-triazole (10 mg, 0.1 mmol). The title compound **14c** was obtained as an orange−red solid (39 mg, 96.5%). R_f = 0.33 (TLC, EtOAc/hexane [1:1]); mp 197 °C (dec.). HPLC 95% (R_t = 4.08 min, 55% CH_3CN in 0.1% TFA water 20 min). ^{1}H NMR (400 MHz, CD_3CN), δ 8.63 (s, 1H), 8.19−8.17 (m, 1H), 8.15−8.14 (m, 1H), 7.90−7.88 (m, 1H), 7.81−7.79 (m, 3H), 7.75−7.74 (m, 1H), 7.22−7.19 (m,1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.55, 160.03, 152.17, 150.60, 146.29, 134.58, 134.15, 133.49, 132.73, 132.23, 130.92, 127.58, 126.46, 125.92, 120.99, 117.56. LC-MS (ESI+) 402.99 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{16}H_{11}N_4O_3S_3$ $(M + H)^+$ 402.9988, found 402.9989.

*2-(1-Hydroxy-4-(thiophene-2-sulfonamido)naphthalen-2-ylthio)-acetic Acid (**15a**).* The (*E*)-*N*-(3-chloro-4-oxonaphthalen-1(4*H*)-ylidene)thiophene-2-sulfonamide (**13 a**) (34 mg, 0.1 mmol) was dissolved in THF (2 mL) and a THF solution was added containing thioglycolic acid (0.1 mL, 1 M in THF) followed by pyridine (1 equiv, 0.2 mL, 0.5 M in THF). The mixture was stirred at rt for 10 min, and the solvent was removed using a rotary evaporator. The orange−red residue obtained was redissolved in ethyl acetate (50 mL). The mixture was transferred to a separation funnel and washed with $NaHSO_4$ (0.5 M solution, 10 mL × 2) to remove pyridine. The sodium hydrosulfite solid (5 equiv, 87 mg, 0.5 mmol) was added followed by water (10 mL). The mixture was shaken until the organic phase turned colorless. The organic phase was separated and washed with water (10 mL × 2) and brine (10 mL), dried (Na_2SO_4), and filtered. The filtrate was concentrated. The solid obtained was suspended in DCM/hexane (1:1, ∼5 mL), filtered, and the product was washed with DCM (1 mL × 3) to afford title compound as an off-white solid (25 mg, 63.6%). The analytical data obtained for compound **15a** are identical to that obtained for **11a**.

*N-(4-Hydroxy-3-(1-methyl-1H-tetrazol-5-ylthio)naphthalen-1-yl)-thiophene-2-sulfonamide (**15b**).* **14b** (13 mg, 0.031 mmol) was dissolved in ethyl acetate (50 mL), and sodium hydrosulfite (27 mg, 0.156 mmol) was added followed by water (10 mL). The mixture was shaken in a separating funnel until the yellow organic phase turned colorless. The organic phase was washed with water (10 mL × 3) and brine (10 mL), dried (Na_2SO_4), and concentrated. The residue obtained was dissolved in DCM (3 mL) and triturated with hexane (3 mL). The precipitate was washed with DCM/hexane (1:1, 1 mL × 3) and dried under vacuum to afford the title compound **15b** as a white solid (13 mg, 99%). R_f = 0.44 (TLC, EtOAc/hexane [1:1]); mp 130 °C (dec.). HPLC 93% (R_t = 8.1 min, 40% CH_3CN in 0.1% TFA water 40 min). ^{1}H NMR (400 MHz, CD_3CN) δ 8.28 (dd, J = 6.4, 2.8 Hz, 1H), 8.14 (br s, 1H, disappeared on D_2O shake), 7.98 (dd, J = 6.8, 3.5 Hz, 1H), 7.94 (br s, 1H, disappeared on D_2O shake), 7.65 (dd, J = 4.8, 1.2 Hz, 1H), 7.61 (dd, J = 6.5, 3.4 Hz, 2H), 7.38 (dd, J = 4.0, 1.2 Hz, 1H), 7.16 (s, 1H), 6.99 (dd, J = 4.8, 3.6 Hz, 1H), 4.00 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.04, 152.73, 140.64, 133.86, 133.07, 132.82, 129.49, 128.42, 128.23, 127.00, 126.30, 125.42, 124.16, 123.42, 107.44, 34.73. LC-MS (ESI+) 420.02 $(M + H)^+$, 442.00 $(M + Na)^+$. HRMS (ESI+) m/z calculated for $C_{16}H_{14}N_5O_3S_3$ $(M + H)^+$ 420.0253, found 420.0240.

*N-(3-(1H-1,2,4-Triazol-5-ylthio)-4-hydroxynaphthalen-1-yl)-thiophene-2-sulfonamide (**15c**).* This compound was prepared using the procedure described for **15b** using **14c** (20 mg, 0.05 mmol) and sodium hydrosulfite (43 mg, 0.25 mmol) to afford the title compound as a white solid (20 mg, 100%). R_f = 0.40 (TLC, EtOAc/hexane [1:1]); mp 180 °C (dec.). HPLC 92% (R_t = 5.4 min, 40% CH_3CN in 0.1% TFA water 40 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (br s, 1H), 10.05 (s, 1H), 8.61 (br s, 1H), 8.16 (d, J = 7.6 Hz, 1H), 7.89 (d, J = 7.4 Hz, 1H), 7.81 (d, J = 4.2 Hz, 1H), 7.48 (brt, J = 7.2 Hz, 2H), 7.28 (d, J = 2.5 Hz, 1H), 6.99 (brt, J = 4.2 Hz, 1H), 6.90 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 140.86, 133.68, 133.00, 132.93, 129.47, 128.16, 126.66, 126.60, 126.28, 124.90, 124.04, 123.14, 104.99. LC-MS (ESI−) 403.00 $(M - H)^-$. HRMS (ESI−) m/z calculated for $C_{16}H_{11}N_4O_3S_3$ $(M - H)^-$ 402.9999, found 402.9989.

*N-(3-(1H-Tetrazol-5-ylthio)-4-hydroxynaphthalen-1-yl)-thiophene-2-sulfonamide (**15d**).* **13a** (34 mg, 0.1 mmol) and 1*H*-tetrazole-5-thiol (10 mg, 0.1 mmol) were dissolved in EtOH/DCM (2 mL, 1:1) and stirred at rt for 2 h. The reaction mixture was diluted with EtOAc (20 mL), and $Na_2S_2O_4$ (0.5 mmol in 5 mL of water) was added. The mixture was shaken in a separation funnel until the color of the organic phase turned colorless (from bright yellow). The organic phase was separated and washed with water (5 mL) and brine (5 mL) and dried (Na_2SO_4). The organic phase was filtered and concentrated, and the residue was slurred in DCM (5 mL). The solid obtained was washed with DCM (1 mL × 2) and dried to afford the title compound **15d** (28 mg, 69.9%, via 2 steps) as an off-white solid; mp 186.6 °C (dec.). HPLC 99% (R_t = 9.5 min, 35% CH_3CN in 0.1% TFA water 30 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.63 (br s, 1H), 10.14 (s, 1H), 8.25−8.23 (m, 1H), 7.96−7.94 (m, 1H), 7.82 (d, J = 4.8 Hz, 1H), 7.56−7.54 (m, 2H), 7.32 (d, J = 3.6 Hz, 1H), 6.97 (t, J = 4.0 Hz, 1H), 6.92 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.80, 140.56, 133.81, 133.17, 133.13, 130.21, 128.41, 128.13, 126.87, 126.47, 125.29, 124.16, 123.57. LC-MS (ESI+) 406.01 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{15}H_{12}N_5O_3S_3$ $(M + H)^+$ 406.0097, found 406.0075.

*N-(3-(1H-Tetrazol-5-ylthio)-4-hydroxynaphthalen-1-yl)biphenyl-4-sulfonamide (**15e**).* This compound was prepared using the procedure described for **15d** except using **13b** (41 mg, 0.1 mmol) to afford the title compound **15e** (32 mg, 67.4%, via 2 steps) as a white solid; mp 158.8 °C (dec.). HPLC 94% (R_t = 7.8 min, 50% CH_3CN in 0.1% TFA water 30 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 8.24−8.22 (m, 1H), 8.02−8.00 (m, 1H), 7.72−7.63 (m, 6H), 7.55−7.53 (m, 2H), 7.51−7.47 (m, 2H), 7.45−7.40 (m, 1H), 6.87 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.63, 144.81, 139.08, 138.97, 133.08, 129.95, 129.77, 129.20, 128.34, 128.20, 127.78, 127.70, 126.86, 126.51, 125.58, 124.39, 123.55. LC-MS (ESI+) 476.09 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{23}H_{18}N_5O_3S_2$ $(M + H)^+$ 476.0846, found 476.0842.

*N-(3-(1H-Tetrazol-5-ylthio)-4-hydroxynaphthalen-1-yl)-5-phenyl-thiophene-2-sulfonamide (**15f**).* This compound was prepared using the procedure described for **15d** except using **13c** (41 mg, 0.1 mmol), to afford the title compound **15f** (34 mg, 70.1%, via 2 steps) as an off-white solid; mp 167.9 °C (dec.). HPLC 98% (R_t = 7.7 min, 50% CH_3CN in 0.1% TFA water, 30 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.65 (br s, 1H), 10.23 (s, 1H), 8.26−8.24 (m, 1H), 8.02−7.90 (m, 1H), 7.60 (dd, J = 8.1, 2.4 Hz, 2H), 7.56−7.54 (m, 2H), 7.46−7.39 (m, 3H), 7.33 (d, J = 3.9 Hz, 1H), 7.29 (d, J = 3.9 Hz, 1H), 7.04 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.95, 150.37, 139.01, 134.22, 133.17, 132.73, 130.38, 130.01, 129.84, 128.47, 126.90, 126.59, 126.49, 125.21, 124.41, 124.17, 123.61. LC-MS (ESI+) 482.04 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{21}H_{16}N_5O_3S_3$ $(M + H)^+$ 482.0410, found 482.0415

*N-(3-(1H-Tetrazol-5-ylthio)-4-hydroxynaphthalen-1-yl)-5-(pyridin-2-yl)thiophene-2-sulfonamide (**15g**).* This compound was

prepared using the procedure described for **15d** except using **13g** (42 mg, 0.1 mmol), to afford the title compound **15g** (40 mg, 84.8%, via 2 steps) as an off-white solid; mp 163.2 °C (dec.). HPLC 96% (R_t = 7.9 min, 40% CH_3CN in 0.1% TFA water, 30 min). ^1H NMR (400 MHz, DMSO-d_6) δ 10.63 (br s, 1H), 10.29 (s, 1H), 8.53 (app. d, J = 4.6 Hz, 1H), 8.23 (dd, J = 6.8, 3.6 Hz, 1H), 7.98 (dd, J = 6.5, 3.2 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.87 (td, J = 7.8, 1.6 Hz, 1H), 7.60 (d, J = 4.0 Hz, 1H), 7.54−7.50 (m, 2H), 7.37−7.34 (m, 1H), 7.28 (d, J = 4.0 Hz, 1H), 7.05 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.87, 151.23, 150.88, 150.31, 141.44, 138.20, 134.06, 133.03, 130.29, 128.48, 126.90, 126.47, 125.26, 125.17, 124.51, 124.09, 123.62, 120.02, 106.90. LC-MS (ESI+) 483.04 (M + H)$^+$. HRMS (ESI+) m/z calculated for $C_{20}H_{15}N_6O_3S_3$ (M + H)$^+$ 483.0362, found 483.0348.

*N-(3-(1H-Tetrazol-5-ylthio)-4-hydroxynaphthalen-1-yl)-4-cyclohexylbenzenesulfonamide (**15h**).* This compound was prepared using the procedure described for **15d** except using **13h** (41 mg, 0.1 mmol) to afford the title compound **15h** (22 mg, 46.3%, via 2 steps) as an off-white solid; mp 169.2 °C (dec.). HPLC 99% (R_t = 14.5 min, 50% CH_3CN in 0.1% TFA water, 40 min). ^1H NMR (400 MHz, DMSO-d_6) δ 10.64 (br s, 1H), 9.79 (s, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.54−7.49 (m, 2H), 7.46 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 6.71 (s, 1H), 1.76−1.64 (m, 5H), 1.34−1.17 (m, 5H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.83, 153.32, 137.35, 133.29, 130.33, 128.27, 127.80, 127.72, 126.77, 126.46, 125.63, 124.42, 123.53, 44.19, 34.12, 26.82, 26.11. LC-MS (ESI−) 480.11 (M −H)$^-$. HRMS (ESI+) m/z calculated for $C_{23}H_{24}N_5O_3S_2$ (M + H)$^+$ 482.1315, found 482.1318

*N-(3-(1H-Tetrazol-5-ylthio)-4-hydroxynaphthalen-1-yl)-4′-methoxybiphenyl-4-sulfonamide (**15i**).* This compound was prepared using the procedure described for **15d** except using **13i** (44 mg, 0.1 mmol) to afford the title compound **15i** (42 mg, 82.0%, via 2 steps) as a white solid; mp 156.8 °C (dec.). HPLC 93% (R_t = 12.0 min, 45% CH_3CN in 0.1% TFA water, 40 min). ^1H NMR (400 MHz, DMSO-d_6) δ 10.61 (br s, 1H), 9.95 (s, 1H), 8.24−8.21 (m, 1H), 8.02−7.99 (m, 1H), 7.68−7.59 (m, 4H), 7.55−7.52 (m, 2H), 7.03 (d, J = 9.2 Hz, 2H), 6.87 (s, 1H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.39, 154.61, 144.43, 138.15, 133.08, 131.26, 129.91, 128.90, 128.34, 128.18, 127.04, 126.86, 126.50, 125.64, 124.40, 123.55, 115.20, 106.77, 55.95. LC-MS (ESI+) 506.10 (M + H)$^+$. HRMS (ESI+) m/z calculated for $C_{24}H_{20}N_5O_4S_2$ (M + H)$^+$ 506.0951, found 506.0936.

*N-(3-(1H-Tetrazol-5-ylthio)-4-hydroxynaphthalen-1-yl)-4′-fluorobiphenyl-4-sulfonamide (**15j**).* This compound was prepared using the procedure described for **15d** except using **13f** (43 mg, 0.1 mmol) to afford the title compound **15j** (40 mg, 81.8%, via 2 steps) as a white solid; mp 168.1 °C (dec.). HPLC 95% (R_t = 13.7 min, 45% CH_3CN in 0.1% TFA water 30 min). ^1H NMR (400 MHz, DMSO-d_6) δ 10.56 (br s, 1H), 9.99 (s, 1H), 8.24−8.22 (m, 1H), 8.02−8.00 (m, 1H), 7.71−7.64 (m, 6H), 7.55−7.52 (m, 2H), 7.32 (t, J = 8.9 Hz, 2H), 6.85(s, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ −114.25 (m). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.13 (d, J = 245 Hz), 154.57, 143.72, 138.96, 135.57, 133.05, 129.85, 129.84 (d, J = 8 Hz), 128.35, 128.21, 127.74, 126.88, 126.51, 125.57, 124.39, 123.54, 116.63 (d, J = 21 Hz), 106.90. LC-MS (ESI+) 494.07 (M + H)$^+$. HRMS (ESI+) m/z calculated for $C_{23}H_{17}FN_5O_3S_2$ (M + H)$^+$ 494.0751, found 494.0739.

*N-(3-(1H-Tetrazol-5-ylthio)-4-hydroxynaphthalen-1-yl)-4-phenoxybenzenesulfonamide (**15k**).* This compound was prepared using the procedure described for **15d** except using **13d** (42 mg, 0.1 mmol) to afford the title compound **15k** (22 mg, 45.1%, via 2 steps) as a white solid; mp 172.5 °C (dec.). HPLC 99% (R_t = 8.2 min, 50% CH_3CN in 0.1% TFA water 30 min). ^1H NMR (400 MHz, DMSO-d_6) δ 10.58 (br s, 1H, disappeared on D_2O shake), 9.88 (s, 1H, disappeared on D_2O shake), 8.22−8.20 (m, 1H), 7.94−7.92 (m, 1H), 7.53 (d, J = 8.8 Hz, 4H), 7.41 (t, J = 7.6 Hz, 2H), 7.21 (t, J = 7.2 Hz, 1H), 6.98 (d, J = 7.6 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.83 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.03, 155.79, 154.58, 134.15, 133.06, 130.99, 130.21, 130.09, 128.30, 126.81, 126.48, 125.57, 125.36, 124.35, 123.54, 120.31, 118.45, 106.87. LC-MS (ESI+) 492.07 (M + H)$^+$. HRMS (ESI+) m/z calculated for $C_{23}H_{18}N_5O_4S_2$ (M + H)$^+$ 492.0795, found 492.0805

*N-(3-(1H-Tetrazol-5-ylthio)-4-hydroxynaphthalen-1-yl)-naphthalene-2-sulfonamide (**15l**).* This compound was prepared using the procedure described for **15d** except **13e** (38 mg, 0.1 mmol) to afford the title compound **15l** (29 mg, 64.9%, via 2 steps) as a gray solid; mp 173.6 °C (dec.). HPLC 98% (R_t = 5.4 min, 50% CH_3CN in 0.1% TFA water 30 min). ^1H NMR (400 MHz, DMSO-d_6) δ 10.54 (br s, 1H), 10.06 (s, 1H), 8.19−8.16 (m, 2H), 7.99−7.93 (m, 4H), 7.70 (dd, J = 8.6, 1.5 Hz, 1H), 7.63 (t, J = 7.2 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.49−7.43 (m, 2H), 6.88 (s, 1H). LC-MS (ESI+) 450.07 (M + H)$^+$. ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.69, 137.30, 134.78, 133.03, 132.10, 130.08, 129.79, 129.77, 129.46, 128.54, 128.43, 128.32, 128.16, 126.82, 126.44, 125.49, 124.29, 123.55, 123.10, 104.99. LC-MS (ESI+) 450.07 (M + H)$^+$. HRMS (ESI+) m/z calculated for $C_{21}H_{16}N_5O_3S_2$ (M + H)$^+$ 450.0689, found 450.0702.

*N-(3-(1H-Tetrazol-5-ylthio)-4-hydroxynaphthalen-1-yl)-4-pentylbenzenesulfonamide (**15m**).* This compound was prepared using the procedure described for **15d** except using **13j** (40 mg, 0.1 mmol) to afford the title compound **15m** (39 mg, 83.6%, via 2 steps) as a gray solid; mp 155.6 °C (dec.). HPLC 99% (R_t = 15.3 min, 50% CH_3CN in 0.1% TFA water 40 min). ^1H NMR (400 MHz, DMSO-d_6) δ 10.53 (br s, 1H), 9.80 (s, 1H), 8.21−8.19 (m, 1H), 7.96−7.94 (m, 1H), 7.56−7.49 (m, 2H), 7.48 (d, J = 8.3 Hz, 2H), 7.16 (d, J = 8.3 Hz, 2H), 6.76 (s, 1H), 2.54 (t, J = 7.5 Hz, 2H), 1.50 (p, J = 7.5 Hz, 2H), 1.30−1.23 (m, 2H), 1.18−1.11 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.75, 148.33, 137.34, 133.23, 130.26, 129.40, 128.27, 127.62, 126.76, 126.47, 125.63, 124.42, 123.53, 106.51, 35.43, 31.24, 30.77, 22.55, 14.56. LC-MS (ESI+) 470.13 (M + H)$^+$. HRMS (ESI+) m/z calculated for $C_{22}H_{24}N_5O_3S_2$ (M + H)$^+$ 470.1315, found 470.1310.

*2-(4-(5-Chlorothiophene-2-sulfonamido)-1-hydroxynaphthalen-2-ylthio)acetic Acid (**15n**).* This compound was prepared using the procedure described for **15a** using **13k** (52 mg, 0.14 mmol) and a solution of thioglycolic acid (0.14 mL, 1 M solution in THF). The title compound **15n** (32 mg, 54%) was obtained as a white solid; mp 143−145 °C. HPLC 95% (R_t = 17.1 min, 40% CH_3CN in 0.1% TFA water, 40 min). ^1H NMR (400 MHz, DMSO-d_6) δ 12.77 (br s, 1H), 10.30 (s, 1H), 9.96 (br s, 1H), 8.14 (d, J = 7.7 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.50−7.43 (m, 2H), 7.22 (d, J = 4.1 Hz, 1H), 7.12−7.11 (m, 2H), 3.55 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.78, 153.29, 139.27, 135.68, 132.92, 131.87, 130.16, 128.59, 127.59, 126.59, 125.76, 124.15, 123.69, 123.18, 113.74, 37.42. LC-MS (ESI−) 427.94 (M − H)$^-$. HRMS (ESI+) m/z calculated for $C_{16}H_{12}ClNO_5S_3Na$ (M + Na)$^+$ 451.9458, found 451.9468.

*2-(4-(Biphenyl-4-ylsulfonamido)-1-hydroxynaphthalen-2-ylthio)-acetic Acid (**15o**).* This compound was prepared using the procedure described for **15a** using **13b** (50 mg, 0.12 mmol) and a solution of thioglycolic acid (0.12 mL, 1 M solution in THF). The title compound **15o** (19 mg, 40%) was obtained as a gray solid; mp 170 °C (dec.). HPLC 97% (R_t = 10.44 min, 50% CH_3CN in 0.1% TFA water 20 min). ^1H NMR (400 MHz, DMSO-d_6) δ 12.78 (br s, 1H), 9.95 (s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.68−7.65 (m, 4H), 7.548−7.39 (m, 5H), 7.00 (s, 1H), 5.73 (br s, 1H), 3.46 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.73, 152.91, 144.78, 139.23, 139.14, 131.89, 129.77, 129.17, 128.25, 127.87, 127.71, 127.28, 126.41, 125.79, 124.79, 124.13, 123.09, 113.72, 37.44. LC-MS (ESI+) 464.07 (M + H)$^+$. HRMS (ESI−) m/z calculated for $C_{24}H_{18}NO_5S_2$ (M − H)$^-$ 464.0632, found 464.0638.

*tert-Butyl 2-(4-(thiophene-2-sulfonamido)naphthalen-1-yloxy)-acetate (**16a**).* The compound **3** (61 mg, 0.2 mmol) was dissolved in DMF (1 mL) and added *tert*-butyl bromoacetate (0.060 mL, 0.4 mmol), followed by DBU (0.4 mL, 1 M solution in NMP) and catalytic amount of KI. The reaction mixture was heated using a microwave reactor at 90 °C for 20 min. The TLC analysis (EtOAc/hexane [1:2]) showed the presence of starting material. To drive the reaction to completion, additional *tert*-butyl bromoacetate (13.5 equiv, 0.4 mL, 2.7 mmol) was added, and the reaction was continued at 90 °C for further 30 min. The resulting mixture was diluted with ethyl acetate (40 mL) and washed with $NaHSO_4$ (10 mL × 2, 0.5 M), water (10 mL × 6) and brine (10 mL). The organic phase was dried (Na_2SO_4) and concentrated. The solid obtained was purified via SiO_2

chromatography (hexane/EtOAc, gradient elution) to afford **16a** (43 mg, 51.3%) as a gray solid. R_f = 0.27 (TLC, EtOAc/hexane [1:2]); mp 128.6 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 7.6 Hz, 1H), 7.80 (dd, J = 7.6, 1.2 Hz, 1H), 7.61 (dd, J = 4.8, 1.2 Hz, 1H), 7.56 (dd, J = 3.6, 1.2 Hz, 1H), 7.46−7.36 (m, 2H), 7.16 (d, J = 8.4 Hz, 1H), 6.99 (dd, J = 5.0, 3.8 Hz, 1H), 6.31 (d, J = 8.4 Hz, 1H), 3.92 (s, 2H), 1.52 (s, 9H). LC-MS (ESI+) 420.09 (M + H)$^+$. HRMS (ESI+) m/z calculated for $C_{20}H_{22}NO_5S_2$ (M + H)$^+$ 420.0934, found 420.0932.

*Methyl 4-(4-(Thiophene-2-sulfonamido)naphthalen-1-yloxy)-butanoate (**16b**).* This compound was synthesized according to the procedure described for **16a** except using 15 equiv of ethyl bromobutanoate (0.44 mL, 3 mmol), and the reaction mixture was heated using a microwave reactor at 90 °C for 30 min. The TLC analysis indicated presence of starting material, and additional 30 min at 90 °C was required to complete the reaction. The crude solid **16b** was purified (SiO_2 chromatography, hexane/EtOAc gradient elution) to afford **16b** (43 mg, 51.3%) as a brown oil. The baseline impurities were still observed after SiO_2 purification. This product was used in the next step without further purification. R_f = 0.36 (TLC, EtOAc/hexane = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.80 (m, 1H), 7.78−7.75 (m, 1H), 7.62 (dd, J = 5.2, 1.6 Hz, 1H), 7.58 (dd, J = 4.0, 1.2 Hz, 1H), 7.42−7.36 (m, 2H), 7.13 (d, J = 8.4 Hz, 1H), 7.00 (dd, J = 4.8, 4.0 Hz, 1H), 6.44 (d, J = 8.4 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.31 (t, J = 6.7 Hz, 2H), 2.52 (t, J = 6.8 Hz, 2H), 2.11 (p, J = 6.7 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H).

*2-(4-(Thiophene-2-sulfonamido)naphthalen-1-yloxy)acetic Acid (**17a**).* The **16a** was dissolved in dioxane (1 mL) and added conc HCl (1 mL, 32%). The mixture was stirred at room temperature for 1 h (TLC analysis EtOAc/hexane [1:2] indicated completion of the reaction) and concentrated. The residue was suspended in DCM/hexane (1:1, 2 mL) and left in a refrigerator (overnight). The precipitate was collected by filtration and washed with DCM/hexane (1:1, 3 mL), affording **17a** (21.4 mg, 82.3%) as a gray solid. R_f = 0.33 (TLC, CH_3OH/DCM [1:20]); mp 148.9 °C (dec.). HPLC 98% (R_t = 6.19 min, 50% CH_3CN in 0.1% TFA water 20 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.64 (br s, 1H), 8.14−8.13 (m, 1H), 8.11 (dd, J = 5.2, 1.4 Hz, 1H), 7.78 (dd, J = 3.8, 1.4 Hz, 1H), 7.66−7.63 (m, 1H), 7.46−7.43 (m, 2H), 7.19 (dd, J = 4.8, 3.6 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 6.80 (br s, 1H), 6.23 (d, J = 8.4 Hz, 1H), 3.96 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.94, 143.97, 137.63, 136.87, 135.95, 134.32, 129.07, 127.88, 127.43, 125.75, 123.72, 122.55, 121.54, 120.25, 101.97, 45.39. LC-MS (ESI−) 362.01 (M − H)$^-$.; HRMS (ESI−) m/z calculated for $C_{16}H_{12}NO_5S_2$ (M − H)$^-$ 362.0162, found 362.0174.

*4-(4-(Thiophene-2-sulfonamido)naphthalen-1-yloxy)butanoic Acid (**17b**).* This compound was synthesized using the procedure described for **17a** except using **16b** (43 mg, 0.1 mmol), dioxane (2 mL), and conc HCl (4 mL, 32%). The required product **17b** (23 mg, 56.6%) was obtained as a brown greasy solid. R_f = 0.09 (TLC, CH_3OH/DCM [1:20]). HPLC 97% (R_t = 7.43 min, 50% CH_3CN in 0.1% TFA water 20 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (br s, 1H), 8.18−8.15 (m, 1H), 8.10 (dd, J = 4.8, 1.2 Hz, 1H), 7.77 (dd, J = 2.8, 0.8 Hz, 1H), 7.64−7.62 (m, 1H), 7.42−7.40 (m, 2H), 7.18 (t, J = 4.0 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.42−6.39 (m, 2H), 3.20−3.17 (m, 2H), 2.36 (t, J = 7.2 Hz, 2H), 1.92−1.85 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.19, 144.40, 137.55, 136.84, 135.46, 134.32, 129.02, 127.94, 127.30, 125.42, 123.75, 122.75, 121.45, 120.37, 101.52, 43.20, 32.04, 24.05. LC-MS (ESI−) 390.05 (M − H)$^-$. HRMS (ESI−) m/z calculated for $C_{18}H_{16}NO_5S_2$ (M − H)$^-$ 390.0475, found 390.0476.

*O-4-Nitronaphthalen-1-yl Dimethylcarbamothioate (**19**).* The 4-nitro-1-naphthol (378 mg, 2 mmol) was dissolved in NMP (2 mL) and added K_2CO_3 (276 mg, 2 mmol). The mixture was heated to 50 °C and a solution of *N*,*N*-dimethylthiocarbamoyl chloride (260 mg, 2.1 mmol) was added in NMP (1 mL) dropwise over 5 min. The resulting solution was stirred at 50 °C for 2 h and quenched with water (30 mL) at 50 °C. The brown precipitate obtained was filtered and washed with water and dried to obtain intermediate **19** (496 mg, 89.8%) as a dark-brown solid. R_f = 0.40 (TLC, EtOAc/hexane [1:2]); mp 110.4 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 8.8 Hz, 1H), 8.33 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.77−7.72 (m, 1H), 7.66−7.62 (m, 1H), 7.30 (d, J = 8.4 Hz, 1H), 3.53 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.71, 154.44, 144.13, 130.11, 128.49, 127.95, 126.84, 124.77, 123.93, 122.62, 118.66, 43.77, 39.35. LC-MS (ESI+) 277.07 (M + H)$^+$. HRMS (ESI+) m/z calculated for $C_{13}H_{13}N_2O_3S$ (M + H)$^+$ 277.0641, found 277.0637.

*S-4-Nitronaphthalen-1-yl Dimethylcarbamothioate (**20**).* The intermediate **19** (276 mg, 1 mmol) was dissolved in NMP (2 mL), and the solution was heated to 180 °C in a microwave reactor for 20 min. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with water and brine. The organic phase was dried (Na_2SO_4), concentrated, and the crude product obtained was purified using chromatography (10 g silica gel, hexane/EtOAc gradient elution) to afford compound **20** as a brown solid (198 mg, 71.5%). R_f = 0.38 (TLC, EtOAc/hexane [1:2]); mp 91.2 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50−8.46 (m, 2H), 8.13 (d, J = 7.9 Hz, 1H), 7.87 (d, J = 7.9 Hz, 2H), 7.77−7.64 (m, 1H), 3.24 (s, 3H), 3.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.00, 148.27, 136.12, 134.33, 134.22, 129.61, 128.46, 126.75, 125.69, 123.66, 122.83, 37.41. LC-MS (ESI+) 277.07 (M + H)$^+$. HRMS (ESI+) m/z calculated for $C_{13}H_{13}N_2O_3S$ (M + H)$^+$ 277.0641, found 277.0642.

*2-(4-Nitronaphthalen-1-ylthio)acetic Acid (**21**).* The intermediate **20** (97 mg, 0.35 mmol) was suspended in methanol (1 mL) under argon atmosphere and added KOH (1.4 mL, 1 M solution in CH_3OH). The reaction mixture was stirred at room temperature for 12 h, affording a homogeneous solution. The *tert*-butyl bromoacetate (0.103 mL, 0.7 mmol) was added, and stirring was continued for 12 h. The reaction mixture was concentrated, and the residue was dissolved in water and acidified (pH = 1−2) using solid $NaHSO_4$. The yellow precipitate obtained was filtered, washed with water, and air-dried to obtain a yellow solid, (79 mg, 85.6%, via 2 steps). R_f = 0.18 (TLC, CH_3OH/DCM/HOAc [1:20:0.1]); mp 144.9 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 8.8 Hz, 1H), 8.40 (d, J = 8.8 Hz, 1H), 8.18 (d, J = 8.1 Hz, 1H), 7.77−7.73 (m, 1H), 7.69−7.65 (m, 1H), 7.52 (d, J = 8.4 Hz, 1H), 3.91 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.63, 144.42, 143.51, 131.71, 129.92, 127.67, 125.31, 124.74, 124.16, 124.00, 121.35, 35.19. LC-MS (ESI−) 218.03 (M − H−CO_2)$^-$. HRMS (ESI−) m/z calculated for $C_{12}H_8NO_4S$ (M − H)$^-$ 262.0179, found 262.0179.

*2-(4-Aminonaphthalen-1-ylthio)acetic Acid (**22**).* The intermediate **21** (70 mg, 0.27 mmol) was dissolved in methanol (50 mL) and the solution was passed through the H-cube hydrogenator (10% Pd−C cat. cartridge, 1.0 mL/min., 25 °C, 40 bar) to obtain a slightly brown color solution. The solution was concentrated to dryness to afford the required product **22** (70 mg, 100%) as a gray solid. R_f = 0.40 (TLC, CH_3OH/DCM [1:10]); mp 138.9 °C (dec.). ^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.59 (d, J = 8.0, 1H), 7.55−7.51 (m, 1H), 7.46−7.42 (m, 1H), 6.71 (d, J = 7.6 Hz, 1H), 3.42 (s, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 172.73, 146.04, 135.53, 135.20, 126.58, 125.77, 124.47, 124.40, 122.33, 117.42, 108.43, 38.58. LC-MS (ESI−) 188.05 (M − H−CO_2)$^-$. HRMS (ESI−) m/z calculated for $C_{12}H_{10}NO_2S$ (M − H)$^-$ 232.0438, found 232.0435.

*2-(4-(Thiophene-2-sulfonamido)naphthalen-1-ylthio)acetic Acid (**23**).* The compound **22** (33 mg, 0.14 mmol) was dissolved in THF (1 mL), and pyridine (0.28 mL, 0.5 M solution in THF) was added at 0 °C, followed by water (0.5 mL). Thiophene-2-sulfonyl chloride (26 mg in 1 mL THF) was added dropwise, followed by additional pyridine (0.28 mL 0.5 M solution in THF). The resulting solution was stirred vigorously at 0 °C and slowly warmed to room temperature. After 4 h, the organic phase was removed and the aqueous portion was diluted with water (10 mL) and acidified (pH = 2−3) at 0 °C using $NaHSO_4$ solution (0.5 M). The mixture was extracted with ethyl acetate. The organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The crude product obtained was purified using chromatography (SiO_2, DCM/CH_3OH [20:1]) to afford **23** (31 mg, 58.4%) as a gray solid. R_f = 0.17 (TLC, CH_3OH/DCM/HOAc [1:20:0.1]); mp 159.8 °C (dec.). HPLC 99% (R_t = 4.43 min, 50% CH_3CN in 0.1% TFA water 20 min). ^{1}H NMR (400 MHz, CD_3CN) δ 8.36 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.68 (dd, J = 4.8, 1.3 Hz, 1H), 7.64−7.60 (m, 1H), 7.57−7.51 (m, 2H), 7.43 (dd, J = 3.6,

1.2 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.04 (dd, J = 5.2, 4.0 Hz, 1H), 3.78 (s, 2H). LC-MS (ESI−) 378.00 $(M - H)^-$. HRMS (ESI−) m/z calculated for $C_{16}H_{12}NO_4S_3$ $(M - H)^-$ 377.9934, found 377.9937.

*2-(1-Hydroxy-4-(thiophene-2-sulfonamido)naphthalen-2-ylthio)-benzoic Acid (**24**).* This compound was prepared using the procedure described for **15a** except using thiosalicylic acid (15 mg, 0.1 mmol). The title compound **24** (19 mg, 99%) was obtained as a white solid; mp 215 °C (dec.). HPLC 91% (R_t = 18.9 min, 40% CH_3CN in 0.1% TFA water, 40 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.15 (br s, 1H), 10.09 (s, 1H), 8.19 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 7.6 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 4.8 Hz, 1H), 7.58−7.50 (m, 2H), 7.34−7.31 (m, 2H), 7.17 (t, 7.2 Hz, 1H), 6.91 (s, 2H), 6.47 (d, J = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.15, 156.08, 141.87, 140.39, 133.88, 133.34, 133.21, 133.17, 132.65, 131.78, 128.38, 128.17, 126.70, 126.58, 126.18, 125.15, 125.06, 124.21, 123.69, 109.66, 104.98. LC-MS (ESI+) 475.05 $(M + NH_4)^+$. HRMS (ESI+) m/z calculated for $C_{21}H_{15}NO_5S_3Na$ $(M + Na)^+$ 480.0005, found 479.9992.

*N-(3-(1H-1,2,4-Triazol-3-ylthio)-4-hydroxynaphthalen-1-yl)-3,4-dichlorobenzenesulfonamide (**25**).* This compound was prepared using the procedure described for **15d** except using **13b** (82 mg, 0.2 mmol) and 1*H*-1,2,4-triazole-3-thiol (24 mg, 0.24 mmol). The title compound **25** (23 mg, 91.3%, via 2 steps) was obtained as a white solid. HPLC 98% (R_t = 21.0 min, 40% CH_3CN in 0.1% TFA water, 40 min); mp 154.8 °C (dec.). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (br s, 1H), 9.95 (s, 1H), 8.55 (br s, 1H), 8.145 (d, J = 7.6 Hz, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.68−7.58 (m, 4H), 7.50−7.39 (m, 5H), 6.94 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.68, 144.69, 139.25, 139.08, 132.05, 129.79, 129.39, 129.18, 128.11, 127.77, 127.70, 127.59, 126.58, 126.30, 125.15, 124.15, 123.19. LC-MS (ESI+) 475.09 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{24}H_{19}N_4O_3S_2$ $(M + H)^+$ 475.0893, found 475.0898.

*N-(3-(1H-1,2,4-Triazol-3-ylthio)-4-hydroxynaphthalen-1-yl)-5-phenylthiophene-2-sulfonamide (**26**).* This compound was prepared using the procedure described for **15d** except using **13c** (83 mg, 0.2 mmol) and 1*H*-1,2,4-triazole-3-thiol (20 mg, 0.2 mmol). The title compound **26** (12 mg, 43.0%, via 2 steps) was obtained as a gray solid; mp 172.9 °C (dec.). HPLC 95% (R_t = 20.1 min, 40% CH_3CN in 0.1% TFA water, 40 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (br s, 2H), 8.52 (br s, 1H), 8.17 (d, J = 8.8 Hz, 1H), 7.94 (d, J = 8.8 Hz, 1H), 7.62 (appd, J = 7.2 Hz, 2H), 7.50−7.39 (m, 6H), 7.29 (d, J = 4.0 Hz, 1H), 7.04 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.94, 150.22, 139.29, 134.02, 132.78, 132.25, 130.04, 129.82, 129.73, 127.73, 126.66, 126.58, 126.31, 124.83, 124.48, 124.03, 123.23, 111.15. LC-MS (ESI+) 481.05 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{22}H_{17}N_4O_3S_3$ $(M + H)^+$ 481.0457, found 481.0456.

*N-(3-(1H-1,2,4-Triazol-3-ylthio)-4-hydroxynaphthalen-1-yl)-4′-fluorobiphenyl-4-sulfonamide (**27**).* This compound was prepared using the procedure described for **15d** except using **13f** (85 mg, 0.2 mmol) and 1*H*-1,2,4-triazole-3-thiol (20 mg, 0.2 mmol). The title compound **27** (29 mg, 38.1%, via 2 steps) was obtained as an off-white solid; mp 194.1 °C (dec.). HPLC 97% (R_t = 24.2 min, 40% CH_3CN in 0.1% TFA water, 40 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.51 (br s, 1H), 8.13 (d, J = 7.6 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.70−7.67 (m, 4H), 7.61 (d, J = 8.6 Hz, 2H), 7.45−7.42 (m, 2H), 7.30 (t, J = 8.8 Hz, 2H), 6.88 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.12 (d, J = 244.3 Hz), 145.75, 143.61, 139.26, 135.56, 129.84 (d, J = 8.3 Hz), 128.12, 127.72, 127.54, 126.56, 126.29, 125.04, 124.14, 123.18, 116.64 (d, J = 21.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.28 (m). LC-MS (ESI+) 493.09 $(M + H)^+$.

*N-(3-(1H-1,2,4-Triazol-3-ylthio)-4-hydroxynaphthalen-1-yl)-4-cyclohexylbenzenesulfonamide (**28**).* This compound was prepared using the procedure described for **15d** except using **13h** (83 mg, 0.2 mmol) and 1*H*-1,2,4-triazole-3-thiol (20 mg, 0.2 mmol). The title compound **28** (40 mg, 68.0%, via 2 steps) was obtained as an off-white solid; mp 154.7 °C (dec.). HPLC 95% (R_t = 14.6 min, 50% CH_3CN in 0.1% TFA water 40 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.18 (br s, 1H), 9.77 (s, 1H), 8.59 (br s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.48−7.39 (m, 4H), 7.24 (d, J = 8.4, 2H), 6.84 (br s, 1H), 1.76−1.67 (m, 5H), 1.35−1.30 (m, 5H), 1.25−1.20 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.21, 137.76, 132.17, 129.70, 127.86, 127.57, 127.48, 126.48, 126.25, 125.23, 124.13, 123.16, 44.22, 34.18, 26.83, 26.12. LC-MS (ESI+) 481.15 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{24}H_{25}N_4O_3S_2$ $(M + H)^+$ 481.1363, found 481.1371.

*N-(3-(1H-1,2,4-Triazol-3-ylthio)-4-hydroxynaphthalen-1-yl)-4-phenoxybenzenesulfonamide (**29**).* This compound was prepared using the procedure described for **15d** except using **13d** (78 mg, 0.2 mmol) and 1*H*-1,2,4-triazole-3-thiol (20 mg, 0.2 mmol). The title compound **29** (36 mg, 56.5%, via 2 steps) was obtained as an off-white solid; mp 176.1 °C (dec.). HPLC 99% (R_t = 23.2 min, 40% CH_3CN in 0.1% TFA water, 40 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (br s, 1H, disappeared on D_2O shake), 9.78 (s, 1H, disappeared on D_2O shake), 8.53 (br s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.46−7.35 (m, 4H), 7.18−7.14 (m, 1H), 6.95 (appd, J = 7.7 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.82 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.92, 155.92, 152.67, 134.42, 132.11, 130.99, 130.01, 129.74, 127.56, 126.53, 126.29, 125.28, 125.13, 124.15, 123.18, 120.23, 118.60, 104.99. LC-MS (ESI+) 491.09 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{24}H_{19}N_4O_4S_2$ $(M + H)^+$ 491.0842, found 491.0847.

*N-(3-(1H-1,2,4-Triazol-3-ylthio)-4-hydroxynaphthalen-1-yl)-4′-(trifluoromethyl)biphenyl-4-sulfonamide (**30**).* This compound was prepared using the procedure described for **15d** except using **13l** (95 mg, 0.2 mmol) and 1*H*-1,2,4-triazole-3-thiol (20 mg, 0.2 mmol). The title compound **30** (31 mg, 79.2%, via 2 steps) was obtained as an off-white solid; mp 193.8 °C (dec.). HPLC 95% (R_t = 13.7 min, 50% CH_3CN in 0.1% TFA water, 40 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.18 (br s, 1H), 9.97 (s, 1H), 8.48 (br s, 1H), 8.12 (d, J = 7.9 Hz, 1H), 7.90−7.79 (m, 5H), 7.76 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8 Hz, 2H), 7.44−7.41 (m 2H), 6.86 (s, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ −61.44 (s). LC-MS (ESI+) 543.08 $(M + H)^+$. HRMS (ESI + ve) m/z calculated for $C_{25}H_{18}F_3N_4O_3S_2$ $(M + H)^+$ 543.0767, found 543.0781.

*N-(3-(1H-1,2,4-Triazol-3-ylthio)-4-hydroxynaphthalen-1-yl)-5-(phenylsulfonyl)thiophene-2-sulfonamide (**31**).* This compound was prepared using the procedure described for **15d** except using *N*-(3-chloro-4-oxonaphthalen-1(4*H*)-ylidene)-5-(phenylsulfonyl)thiophene-2-sulfonamide (**13m**) (96 mg, 0.2 mmol) and 1*H*-1,2,4-triazole-3-thiol (20 mg, 0.2 mmol). The title compound **31** (36 mg, 68.9%, via 2 steps) was obtained as an off-white solid; mp 153.3 °C (dec.). HPLC 98% (R_t = 11.5 min, 40% CH_3CN in 0.1% TFA water 40 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H), 10.33 (br s, 1H), 8.46 (br s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 7.6 Hz, 2H), 7.74 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 4.0 Hz, 1H), 7.64 (t, J = 7.6 Hz, 3H), 7.40 (t, J = 7.2 Hz, 1H), 7.29 (d, J = 4.4 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 6.99 (s, 1H), approximately 5% baseline impurity was observed. ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.26, 148.25, 147.60, 145.27, 140.93, 140.66, 135.23, 134.43, 133.19, 131.81, 130.76, 130.38, 127.87, 127.70, 126.71, 126.21, 123.81, 123.32, 123.24. LC-MS (ESI+) 545.00 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{22}H_{17}N_4O_5S_4$ $(M + H)^+$ 545.0076, found 545.0096.

*N-(3-(1H-1,2,4-Triazol-3-ylthio)-4-hydroxynaphthalen-1-yl)-1-(phenylsulfonyl)-1H-pyrrole-3-sulfonamide (**32**).* This compound was prepared using the procedure described for **15d** except using *N*-(3-chloro-4-oxonaphthalen-1(4*H*)-ylidene)-1-(phenylsulfonyl)-1*H*-pyrrole-3-sulfonamide (**13n**) (92 mg, 0.2 mmol) and 1*H*-1,2,4-triazole-3-thiol (20 mg, 0.2 mmol). The title compound **32** (34 mg, 75.2%, via 2 steps) was obtained as an off-white solid; mp 157.1 °C (dec.). HPLC 99.8% (R_t = 9.8 min, 50% CH_3CN in 0.1% TFA water 40 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (br s, 1H), 9.81 (s, 1H), 8.47 (br s, 1H), 8.11 (d, J = 8.3 Hz, 1H), 7.92 (d, J = 7.5 Hz, 2H), 7.81 (d, J = 8.5 Hz, 1H), 7.75 (t, J = 7.5 Hz, 1H), 7.59 (t, J = 7.9 Hz, 2H), 7.53−7.52 (m, 1H), 7.44−7.36 (m, 3H), 7.30 (t, J = 7.3 Hz, 1H), 6.79 (s, 1H), 6.36 (dd, J = 3.3, 1.6 Hz, 1H), approximately 5% baseline impurity was observed. ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.01, 152.65, 137.54, 136.00, 131.87, 130.77, 129.37, 128.83, 127.84, 127.80, 127.44, 126.53, 126.21, 124.98, 123.99, 123.43, 123.21, 123.17, 112.26. LC-MS (ESI+) 528.05 $(M + H)^+$. HRMS (ESI+) m/z calculated for $C_{22}H_{18}N_5O_5S_3$ $(M + H)^+$ 528.0465, found 528.0476.

*N-(3-(1H-1,2,4-Triazol-3-ylthio)-4-hydroxynaphthalen-1-yl)-3,4-dichlorobenzenesulfonamide (**33**).* This compound was prepared

using the procedure described for **15d** except using **13e** (76 mg, 0.2 mmol) and 1*H*-1,2,4-triazole-3-thiol (20 mg, 0.2 mmol). The title compound **33** (71 mg, 78.9%, 2 steps) was obtained as a white solid; mp 183.2 °C (dec.). HPLC 99.9% (R_t = 21.9 min, 35% CH_3CN in 0.1% TFA water 40 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (br s, 1H), 8.30 (br s, 1H), 8.17 (appd, J = 1.3 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 8.00−7.93 (m, 5H), 7.70−7.63 (m, 2H), 7.59 (appt, J = 7.6 Hz, 1H), 7.45−7.37 (m, 2H), 6.87 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 137.61, 134.79, 132.15, 132.03, 129.85, 129.79, 129.41, 129.23, 128.45, 128.37, 128.15, 127.50, 126.55, 126.28, 125.13, 124.18, 123.12, 123.06. LC-MS (ESI+) 449.08 (M + H)$^+$. HRMS (ESI+) m/z calculated for $C_{22}H_{17}N_4O_3S_2$ (M + H)$^+$ 449.0737, found 449.0746.

*N-(3-(1H-1,2,4-Triazol-3-ylthio)-4-hydroxynaphthalen-1-yl)-naphthalene-1-sulfonamide (**34**).* This compound was prepared according to the procedure for **15d** using *N*-(3-chloro-4-oxonaphthalen-1(4*H*)-ylidene)naphthalene-1-sulfonamide (**13o**) (76 mg, 0.2 mmol) and 1*H*-1,2,4-triazole-3-thiol (20 mg, 0.2 mmol). The title compound **34** (29 mg, 74.5%, via 2 steps) was obtained as a white solid; mp 158.1 °C (dec.). HPLC 98% (R_t = 10.6 min, 40% CH_3CN in 0.1% TFA water, 40 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 10.10 (br s, 1H), 8.73 (d, J = 8.4 Hz, 1H), 8.50 (br s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 7.6 Hz, 1H), 7.83−7.782 (m, 2H), 7.69−7.61 (m, 2H), 7.44−7.38 (m, 2H), 7.26 (t, J = 7.2 Hz, 1H), 6.74 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.14, 135.53, 134.70, 134.34, 131.79, 130.06, 129.64, 128.88, 128.49, 128.24, 127.46, 127.27, 126.50, 126.16, 125.33, 124.96, 123.88, 123.04. LC-MS (ESI+) 449.08 (M + H)$^+$. HRMS (ESI+) m/z calculated for $C_{22}H_{17}N_4O_3S_2$ (M + H)$^+$ 449.0737, found 449.0741.

*N-(3-(1H-Tetrazol-5-ylthio)-4-hydroxynaphthalen-1-yl)-4-chlorobenzenesulfonamide (**35**).* This compound was prepared using the procedure described for **15d** using 4-chloro-*N*-(3-chloro-4-oxonaphthalen-1(4*H*)-ylidene)benzenesulfonamide (**13p**) (37 mg, 0.1 mmol) and 1*H*-tetrazole-5-thiol (10 mg, 0.1 mmol). The title compound **35** (35 mg, 81.6%, via 2 steps) was obtained as an off-white solid; mp 180.9 °C (dec.). HPLC 98% (R_t = 11.0 min, 40% CH_3CN in 0.1% TFA water, 30 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (br s, 1H), 10.06 (s, 1H), 8.323−8.20 (m, 1H), 7.94−7.91 (m, 1H), 7.57 (d, J = 8.8 Hz, 2H), 7.55−7.52 (m, 2H), 7.45 (d, J = 8.8 Hz, 2H), 6.83 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.72, 138.99, 138.27, 132.96, 130.12, 129.78, 129.44, 128.41, 126.93, 126.50, 125.23, 124.24, 123.60, 106.88. LC-MS (ESI+) 434.01 (M + H)$^+$. HRMS (ESI+) m/z calculated for $C_{17}H_{13}ClN_5O_3S_2$ (M + H)$^+$ 434.0143, found 434.0129.

*N-(3-(1H-Tetrazol-5-ylthio)-4-hydroxynaphthalen-1-yl)-3,4-dichlorobenzenesulfonamide (**36**).* This compound was prepared using the procedure for **15d** using 3,4-dichloro-*N*-(3-chloro-4-oxonaphthalen-1(4*H*)-ylidene)benzenesulfonamide (**13q**) (40 mg, 0.1 mmol) and 1*H*-tetrazole-5-thiol (10 mg, 0.1 mmol). The title compound **36** (40 mg, 84.8%, via 2 steps) was obtained as a white solid; mp 174.4 °C (dec.). HPLC 97% (R_t = 10.1 min, 45% CH_3CN in 0.1% TFA water, 40 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.64 (br s, 1H), 10.18 (s, 1H), 8.24−8.22 (m, 1H), 7.94−7.92 (m, 1H), 7.75 (appd, J = 2.0 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.56−7.54 (m, 2H), 7.51 (dd, J = 8.4, 1.6 Hz, 1H), 6.85 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.80, 140.35, 136.54, 132.95, 132.65, 132.07, 130.17, 129.21, 128.46, 127.63, 127.00, 126.55, 124.86, 124.15, 123.63, 107.07.; LC-MS (ESI+) 467.98 (M + H)$^+$. HRMS (ESI+) m/z calculated for $C_{17}H_{12}Cl_2N_5O_3S_2$ (M + H)$^+$ 467.9753, found 467.9752.

*N-(3-(1H-Tetrazol-5-ylthio)-4-hydroxynaphthalen-1-yl)-benzenesulfonamide (**37**).* This compound was prepared using the procedure described for **15d** using *N*-(3-chloro-4-oxonaphthalen-1(4*H*)-ylidene)benzenesulfonamide (**13r**) (32 mg, 0.1 mmol) and 1*H*-tetrazole-5-thiol (10 mg, 0.1 mmol). The title compound **37** (32 mg, 78.9%, via 2 steps) was obtained as a white solid; mp 154.8 °C (dec.). HPLC 92% (R_t = 6.5 min, 40% CH_3CN in 0.1% TFA water 30 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (br s, 1H), 9.94 (s, 1H), 8.21−8.19 (m, 1H), 7.95−7.92 (m, 1H), 7.59−7.56 (m, 2H), 7.54−7.48 (m, 3H), 7.39 (t, J = 8.0 Hz, 2H), 6.79 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.57, 140.16, 133.33, 133.03, 129.97, 129.60, 128.31, 127.48, 126.83, 126.47, 125.53, 124.32, 123.52, 106.87. LC-MS (ESI+) 400.06 (M + H)$^+$. HRMS (ESI+) m/z calculated for $C_{17}H_{14}N_5O_3S_2$ (M + H)$^+$ 400.0526, found 400.0529.

*N-(3-(1H-Tetrazol-5-ylthio)-4-hydroxynaphthalen-1-yl)-5-chlorothiophene-2-sulfonamide (**38**).* This compound was prepared using the procedure described for **15d** using **13k** (37 mg, 0.1 mmol) and 1*H*-tetrazole-5-thiol (10 mg, 0.1 mmol). The title compound **38** (36 mg, 81.6%, via 2 steps) was obtained as a gray solid; mp 159.4 °C (dec.). HPLC 96% (R_t = 6.9 min, 45% CH_3CN in 0.1% TFA water, 40 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.68 (br s, 1H), 10.32 (s, 1H), 8.25−8.23 (m, 1H), 7.95−7.93 (m, 1H), 7.57−7.55 (m, 2H), 7.20 (d, J = 4.0 Hz, 1H), 7.04 (d, J = 4.0 Hz, 1H), 6.98 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.92, 138.97, 135.76, 133.03, 133.00, 130.29, 128.54, 128.45, 126.97, 126.50, 124.88, 124.02, 123.65, 107.13. LC-MS (ESI+) 439.96 (M + H)$^+$. HRMS (ESI+) m/z calculated for $C_{15}H_{11}ClN_5O_3S_3$ (M + H)$^+$ 439.9707, found 439.9707.

*N-(3-(1H-Tetrazol-5-ylthio)-4-hydroxynaphthalen-1-yl)-4′-(trifluoromethyl)biphenyl-4-sulfonamide (**39**).* This compound was prepared using the procedure described for **15d** using **13l** (48 mg, 0.1 mmol) and 1*H*-tetrazole-5-thiol (10 mg, 0.1 mmol). The title compound **39** (41 mg, 76.1%, via 2 steps) was obtained as a white solid; mp 168 °C (dec.). HPLC 99% (R_t = 14.6 min, 50% CH_3CN in 0.1% TFA water 30 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (br s, 1H), 10.04 (s, 1H), 8.23−8.20 (m, 1H), 8.00−7.97 (m, 1H), 7.88−7.82 (m, 4H), 7.77 (d, J = 8.6 Hz, 2H), 7.69 (d, J = 8.6 Hz, 2H), 7.54−7.51 (m, 2H), 6.83 (s, 1H). LC-MS (ESI+) 544.08 (M + H)$^+$. HRMS (ESI+) m/z calculated for $C_{24}H_{17}F_3N_5O_3S_2$ (M + H)$^+$ 544.0719, found 544.0704.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Supporting analytical data; ^{1}H NMR, ^{13}C NMR, LCMS, and HPLC for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS USED

CT-L, chymotrypsin like; T-L, trypsin like; SAR, structure−activity relationship; PGPH, postglutamylpeptidase hydrolysis; DCM, dichloromethane; THF, terahydrofuran; DMF, dimethylformamide; DBU, diazabicycloundecene; DMSO, dimethylsulfoxide; TFA, trifluoroacetic acid; DMEM, Dulbecco's Modified Eagle Medium; RPMI1640, Roswell Park Memorial Institute-1640

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