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Design, synthesis and biological evaluation of GPR55 agonists

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Abstract

GPR55, a G protein-coupled receptor, is an attractive target to alleviate inflammatory and neuropathic pain and treat osteoporosis and cancer. Identifying a potent and selective ligand will aid to further establish the specific physiological roles and pharmacology of the receptor. Towards this goal, a targeted library of 22 compounds was synthesized in a modular fashion to obtain structure-activity relationship information. The general route consisted of coupling a variety of *p*-aminophenyl sulfonamides to isothiocyanates to form acylthioureas. For the synthesis of a known naphthyl ethyl alcohol motif, route modification led to a shorter and more efficient process. The 22 analogues were analyzed for their ability to serve as agonists at GPR55 and valuable information for both ends of the molecule was ascertained.

Graphical abstract

Keywords

GPR55; Homology model; Thiourea; β -Arrestin recruitment assay; Cancer

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at xxxxx.

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1. Introduction

GPR55 is a membrane-bound G protein-coupled receptor (GPCR) that is highly expressed in the brain, particularly in the hypothalamus, olfactory bulb, and striatum.^{1–2} It is also found in other organs and tissues such as bone marrow,³ neutrophils⁴ and the spleen.⁵ It has been established so far that GPR55 is a potential target for treating pain,⁶ osteoporosis³ and cancer.⁷ In adjuvant-induced inflammation and partial nerve ligation pain models, GPR55 knockout mice developed neither inflammatory nor neuropathic mechanical hyperplasia.⁶ The receptor-deprived mice also revealed a role of GPR55 in regulating osteoclasts' number and function based on the finding that the number of inactive osteoclasts was higher compared to wild type mice.³ A recent study revealed high expression of GPR55 in myenteric colonic neurons and the involvement of the receptor in colonic motility.⁸ The role of GPR55 in cancer proliferation has been recently well-established to be proliferative rather than anti-proliferative.⁷ It was not only detected in various cancer cell lines such as breast, brain, skin⁷, and prostate⁹ but also discovered in a number of clinical isolates from cancer patients.⁷ Furthermore, it has been shown that GPR55 activation stimulates angiogenesis¹⁰ and metastasis,⁹ which explains the correlation of GPR55 expression with cancer aggressiveness.

Initial *in vitro* screening identified GPR55 as a cannabinoid receptor due to similarities with cannabinoid receptors CB₁ and CB₂.¹¹ Yet the various cannabinoid ligands exert different pharmacology when bound to GPR55. AM251 for instance, which is antagonist, strongly activates GPR55.¹² Another example is the CB₁ and CB₂ agonist CP55940¹³ which acts as an antagonist when bound to GPR55. In addition, the results obtained for the same ligand tested may vary depending on the assay employed and the cell type.^{14–16}

L- α -lysophosphatidylinositol (LPI, **1**; Figure 1) is the endogenous agonist of GPR55, but not the best candidate to be labeled for studying the receptor due to its lack of selectivity for GPR55. The need for a selective and potent ligand prompted high-throughput screening which was conducted by the Sanford-Burnham screening center. Out of approximately 290,000 different compounds tested, three chemically distinct compounds, namely CID1792197 (**2**),^{17–18} CID1172084 (**3**), and CID2440433 (**4**), were identified as potent agonists of GPR55 with EC₅₀'s of 0.11, 0.16 and 0.26 μ M, respectively.¹⁹ In addition to the moderate potency of these ligands is their selectivity for GPR55 over other cannabinoid receptors, > 30 μ M activity of CB₁, CB₂ and the closely related atypical cannabinoid receptor GPR35, which renders them as appropriate leads to develop probes for studying GPR55.¹⁷

For the study described herein, it was decided to explore analogues of CID1792197 (**2**). There are a variety of reasons for this decision. First, the synthetic approach, described hereafter, is modular in nature to rapidly enable the independent modification of either end of the molecule. Second, there was not many commercially available derivatives of this molecule that explored modifications that we desired. Third, it was envisioned that synthetic derivatives of compound **2** could remove the α , β -unsaturated amide, which could serve as an indiscriminate Michael acceptor with diverse off-target activities. Finally, this compound was a selective GPR55 agonist with no activity at CB₁, CB₂, or GPR35.¹⁷

2. Results and discussion

CID1792197 (**2**) was the scaffold chosen for further lead development due to synthetic feasibility to obtain analogues. Modifications of the lead (**2**) were targeted at the two termini in order to increase activity as a selective GPR55 agonist, enhance solubility, and eliminate the Michael acceptor functionality. In order to synthesize analogues that explored the role that each end of the molecule plays with respect to the overall activity of the analogue, a retrosynthesis was designed to be modular in nature (Scheme 1). By doing so, each end of the analogue could be independently modified and the total number of steps to analogues would be fewer. It was envisioned that the two parts of the molecule could be coupled by reacting an acylisothiocyanate with an amine to generate the acylthiourea moiety of the analogues (**6**). The acylisothiocyanates could be synthesized from carboxylic acids **5**. The anilines (**7**) could be prepared by substituting the chloride in *p*-nitrophenyl sulfonyl chloride with the proper amine (**8**),²⁰ followed by catalytic hydrogenation of the nitro group.²¹ Many, but not all, of the carboxylic acids (**5**) and amines (**8**) were commercially available and the remainder were synthesized as described herein.

2.1. Preparation of amine precursors **8**

Six of the amine precursors were commercially available (**8f–8k**), and the remaining structures (**8a–8e**) were synthesized through reductive amination (Scheme 2).²² As such, aniline was reacted with the different aldehydes **9a–9e** to give the corresponding imine which was reduced into the target secondary amines (**8a–8e**) using NaHB₄.²² In the case of isonicotinaldehyde (**9a**) and 5-(hydroxymethyl)furan-2-carbaldehyde (**9b**), the resulting imines (**9a** and **9b**) were purified. For secondary amines **8c–8e**, the imine intermediates were reacted with the reducing agent without being isolated.

2.2. Synthesis of *p*-aminobenzene sulfonamides **7**

Upon the availability of the primary or secondary amines (**8a–8k**), they were reacted with *p*-nitrophenyl sulfonyl chloride in basic conditions to give corresponding *p*-nitrophenyl sulfonamides **11a–11k** (Scheme 3).²⁰ Hydrogenation using Pd/C and an atmosphere of hydrogen reduced the nitro group into an amine and yield anilines **7a–7k**. In addition to these eleven sulfonamides, sulfisoxazole (**7l**) was purchased and used in the subsequent synthetic route.

2.3. Preparation of aryl carboxylic acids **5**

Three of the desired carboxylic acids (**5v–5x**) were commercially available and the 6-hydroxymethyl and 6-hydroxyethyl 2-naphthoic acids (**5y** and **5z**) required synthetic routes (Scheme 4). The naphthoic acid derivatives were prepared in lab starting with commercially available methyl 6-bromo-2-naphthoate (**12**). Attempts to reduce ester **12** to the corresponding aldehyde (**14**) using DIBAL-H²³ in a one pot reaction were not successful despite the efforts of maintaining the temperature of the mixture at –78 °C throughout the entire reaction time. The only product observed following quenching the reaction at various times, even before the ester was fully consumed, was alcohol **13**. Thus, the number of equivalents of DIBAL-H used was increased to ensure full conversion. Alternatively, this reaction was also examined using flow chemistry. It was previously determined that aryl

esters were especially difficult to reduce to the aldehyde,^{24–25} but using high flow rates (50 mL/min), cold temperatures (–78 °C), and short reaction times (0.037 sec), we were able to obtain a moderate yield of the aldehyde (**14**) directly, although with some over-reduction to the alcohol (**13**). For simplicity, it was decided to fully convert ester **12** to alcohol **13** and then oxidize it to the aldehyde. For an alternate analogue, alcohol **13** was protected as a silyl ether to generate bromide **17**.

Alcohol **13** was oxidized using MnO₂ in CHCl₃ to give the corresponding aldehyde **14**.²⁶ The low yields for this benzylic oxidation reaction, in particular when scaling up the reaction, benefitted from the use of the alternative Swern oxidation conditions. The use of DMSO and oxalyl chloride followed by Et₃N significantly enhanced the yields of oxidizing alcohol **13** to aldehyde **14**. A Wittig reaction, using methyltriphenylphosphonium iodide, was conducted to prepare 2-bromo-6-vinylnaphthalene **15**.²⁷ Hydroboration and oxidation of **15** gave the anti-Markovnikov alcohol **16**.²⁸ Protection of the alcohol was done using TBSCl in basic conditions²⁹ to generate bromide **18**. Conversion of the aryl bromide of silyl ether **18** into the corresponding carboxylic acid (**5z**) was achieved by lithium-halogen exchange using *n*-butyl lithium followed by purging the mixture with CO₂ gas.³⁰ Structurally similar precursor **17** was also converted to the carboxylic acid (**5y**) to investigate the effect of the side chain length on activity.

The synthetic route described in Scheme 4 was successful in obtaining compounds for examination, however, the inefficiency and number of reactions led to a reexamination of the route, especially for acid **5z**. It was envisioned that the bromide could be converted into an organometallic species, which could in turn open ethylene oxide to access the same acid (**5z**) in a more straightforward fashion. Initial attempts using metal-halogen exchange and opening of ethylene oxide in the presence of Lewis acids were not successful. Fortunately, a milder procedure, recently reported by Weix and coworkers, using nickel-catalysis produced the desired acid in 66% yield which generates the protected silyl ether (**5z**) after facile silylation and saponification. This modification of the route using chemistry developed by Weix and coworkers shortened the synthesis of acid **5z** from 6 steps to 2 steps and increased the overall yield from under 10% to more than 40%.

2.4. Synthesis of completed analogues 6

The commercially available carboxylic acids (**5v–5x**) and synthesized naphthoic acid derivatives (**5y** and **5z**) were converted into the more active acyl chlorides by refluxing with thionyl chloride (Scheme 5). The resultant acyl chlorides were converted without isolation into the isothiocyanate intermediates using potassium thiocyanate.³¹ The unpurified intermediates were further reacted with the *p*-amino sulfonamides (**7a–7l**) to give the target analogues (**6**).²¹ In order to be systematic, all of the amines were combined with acid **5v** since this was present in the parent system (**2**). These analogues (**6av–6lv**) determined the role of the sulfonamide section of the molecule. To explore the role of the carboxylate section, all of the acids were coupled to amine **7f** since the groups on this amine are present in the parent molecule (**2**). Analogues **6fv–6fz** therefore show the role that the carboxylate plays for activity. Based on the activities of these compounds (*vide infra*), the best two

carboxylic acids (**5x** and **5z**) were coupled to the best sulfonamides (**7a**, **7b**, **7e**, and **7g**) to generate analogues **6ax**, **6bx**, **6ex**, **6gx**, **6bz**, and **6gz**.

2.5. GPR55 agonist activities

The synthesized final compounds (**6**) were tested for activation of GPR55 using a β -arrestin assay. The parent compound was previously tested in two other assays, MAPK and PKC translocation, but the β -arrestin assay was chosen since it was most active in that assay.¹⁷ The β -arrestin assay was run using CHO-K1 cells stably expressing GPR55, fused with a β -galactosidase enzyme fragment, and β -arrestin fused to an N-terminal deletion mutant of β -galactosidase (DiscoverX) in the PathHunter® β -arrestin assay as previously published.³² Activation of GPR55 induces β -arrestin recruitment, forcing complementation of the two β -galactosidase enzyme fragments. Levels of this active enzyme are a direct result of GPR55 activation and are quantitated using chemiluminescent PathHunter® detection reagents containing the β -galactoside substrate. The chemiluminescence signal was measured using a Perkin Elmer Envision plate reader for 1 second. Ligand readings were subtracted by their corresponding vehicle reading and analyzed in GraphPad Prism. Agonist activity was evaluated along with LPI-induced receptor activation. All data was analyzed using GraphPad Prism version 5.0 (GraphPad, San Diego, CA) to obtain EC₅₀ values summarized in Figures 2 and 3.

The synthesized parent ligand activity was slightly lower (0.3 μ M) in comparison to the reported activity (0.11 μ M), but in a similar range. For analogues having the 2-methoxyphenyl acryloyl moiety (**6av**-**6lv**), it is crucial to have an aromatic phenyl ring as one of the substituents of the sulfonamide's nitrogen; removing the phenyl ring diminished the activity (**6jv**, **6kv**, and **6lv**). Even replacing the phenyl group with another aromatic bioisostere; namely 3, 4-dimethylisoxazole of analogue **6lv** led to the same result as when removing the ring. Although, the aforementioned substituent leads to solubility enhancement, the change of distribution and overall electron density of the isoxazole π -system relative to the phenyl counterpart may play a major contributing factor to disturbing *pi-pi* stacking in the binding pocket of the receptor.

Among the synthesized analogues possessing the 2-methoxyphenyl acryloyl moiety, compounds **6av**, **6bv**, **6ev**, and **6gv** were selected for further exploration since they were accessible and had good activities (EC₅₀ 0.5 μ M). With respect to the different carboxylates, it was decided to continue studying analogues **6fx** and **6fz** since they had the more potent activities.

For the second generation analogues (Figure 3), it was determined that the quinoline-based analogues (**6ax**, **6bx**, **6ex**, and **6gx**) had similar or slightly improved potency. Unfortunately, the second generation analogues utilizing the hydroxyethylnaphthyl group (**6bz** and **6gz**) were both less active. Although the second generation analogues did not receive a significant activity boost by modifying both ends of the analogue, they still provide valuable information. First, five different analogues containing the 7-quinoline moiety were synthesized and all of them are relatively active. While this is also true for the 2-methoxyphenyl acryloyl moiety of the parent compound, the quinoline ring removes the Michael acceptor of the parent system, making the compounds much more attractive as leads

and tools in biochemical systems. Another conclusion from the second generation analogues is that the presence of hydroxyl groups on both ends of the analogue was not beneficial.

3. Conclusion

Utilizing a modular synthesis, 22 unique compounds were synthesized. These included 12 different sulfonamide substitutions, five different acyl groups attached to the thiourea, and six hybrid analogues where both sections were modified. The activities of the compounds indicated both beneficial and detrimental interactions. For example, the potential and optimal positions of hydroxyl groups for hydrogen bonding to the receptor (analogues **6bv**, **6cv**, **6dv**, **6ev**, **6gv**, **6jv**, **6kv**, **6fy**, **6fz**, **6bx**, **6ex**, **6gx**, **6bz**, and **6gz**) and the position of aromatic nitrogen atoms (**6av**, **6iv**, **6lv**, **6fw**, **6fx**, **6ax**, **6bx**, **6ex**, and **gx**) on either end of the ligand were analyzed. These data serve as a springboard for the design of even more potent and selective ligands to serve as agonists at GPR55.

4. Experimental

4.1. General experimental procedures

Unless otherwise stated, all reactions were carried out under an atmosphere of dry nitrogen in oven-dried glassware. Indicated reaction temperatures refer to those of the reaction bath, while room temperature (rt) is noted as 25 °C. All solvents and reagents were obtained from commercial sources and were used as received. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 precoated plates (0.25 mm) from Merck. Visualization was accomplished by irradiation under a 254 nm UV lamp. Silicycle silica gel 230–400 (particle size 40–63 µm) mesh was used for all flash column chromatography. If needed, products were purified by reverse phase chromatography, which was performed using a Varian purification system employing a Phenomenex Gemini-NX, (5 µm, C18, 110A, AX, 250 × 21.20 mm). The mobile phase was a mixture of acetonitrile and H₂O containing 0.1% formic acid. ¹H NMR spectra were recorded on a Jeol ECA 500 MHz spectrometer or a Jeol ECS 400 MHz spectrometer in the solvent indicated. All ¹H NMR experiments were run at 17 °C except for DMSO-d₆ solvent that was run at 25 °C. Chemical shifts are reported in δ units, parts per million (ppm) downfield of TMS, and were measured relative to the signals for chloroform (7.26 ppm), methanol (3.31 ppm), acetone (2.05 ppm) and dimethyl sulfoxide (2.50 ppm). All ¹³C NMR spectra were reported in ppm relative to the signals for chloroform (77 ppm), methanol (49 ppm), acetone (29.8 ppm) and dimethyl sulfoxide (39.5 ppm) with ¹H decoupled observation. Data for ¹H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, oct = octet, m = multiplet), integration and coupling constant (Hz), whereas ¹³C NMR analyses were reported in terms of chemical shift and number of equivalent carbons if more than one. ¹H and ¹³C NMR spectra for new all new compounds are included in the Supporting Information. High resolution mass spectrometry data (HRMS) were performed on a Thermo Fisher Scientific UPLC/LTQ Orbitrap XL system.

4.2. Synthesis of secondary amines (8a–8e)

4.2.1. Two-step synthesis of secondary amines (8a–8b)

Step 1: Synthesis of imines **10a–10b**.³³ Aniline (1 equiv.) and the aldehyde **9a–9b** (1 equiv.) were dissolved in dry ethanol (0.5 M) and the resulting mixture heated under reflux for 3 hrs. The solution was cooled to room temperature and the solvent removed under reduced pressure. Purification of the product was done via recrystallization using an appropriate mixture of solvents where enough volume of the more polar solvent was added to dissolve the crude mixture and the less polar solvent was added until reaching the saturation point.

Step 2: Reduction of Imines **10a–10b**.²² To a solution of the imine (**10a–10b**, 1 equiv.) in MeOH (0.5 M) was added NaBH₄ (5 equiv.) portion-wise and the mixture stirred for 24 hours at room temperature. The solution was acidified to a pH of 3 using HCl (50 % v/v) followed by increasing the pH to 9 using NaOH (2 M). The product was extracted using dichloromethane. The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure. Purification of the product was accomplished using flash column chromatography or via recrystallization using an appropriate mixture of solvents where enough volume of the more polar solvent was added to dissolve the crude mixture and the less polar solvent was added until reaching the saturation point.

4.2.1.1. (E)-N-Phenyl-1-(pyridin-4-yl)methanimine (10a): The crude product was recrystallized using a mixture of ethyl acetate and hexane. Yield (0.936 g, 28%). ¹H NMR matched that previously reported.²² ¹H NMR (500 MHz, acetone-d₆): δ 8.73 (dd, *J* = 1.7, 4.3 Hz, 2H; Ar-H), 8.64 (s, 1H; CH), 7.84 (dd, *J* = 1.7, 4.3 Hz, 2H; Ar-H), 7.42 (dd, *J* = 1.7, 6.6 Hz, 2 H; Ar-H), 7.26–7.30 (m, 3H; Ar-H).

4.2.1.2. (E)-(5-((Phenylimino)methyl)furan-2-yl)methanol (10b): The crude product was recrystallized using a mixture of dichloromethane and hexane. Yield (0.47 g, 56%). ¹H NMR (500 MHz, acetone-d₆): δ 8.33 (s, 1H, N=CH), 7.37 (m, 2H; Ar-H), 7.20 (m, 3H; Ar-H), 7.00 (d, *J* = 3.3 Hz, Ar-H), 6.48 (d, *J* = 3.4 Hz, Ar-H), 4.61 (s, 1H, O-CH₂), 4.60 (s, 1H, O-CH₂). ¹³C NMR (125 MHz, acetone-d₆): δ 159.3, 152.0, 147.9, 129.2 (2C), 125.9 (2C), 120.9 (2C), 117.3, 109.3, 56.6. HRMS (ESI, *m/z*): Calculated for C₁₂H₁₂NO₂ [M + H]⁺ 202.0863; found 202.0855 (3.7 ppm).

4.2.1.3. N-(Pyridin-4-ylmethyl)aniline (8a): The crude product was recrystallized using a mixture of dichloromethane and hexane. Yield (0.786 g, 52%). ¹H NMR matched that previously reported.²² ¹H NMR (500 MHz, acetone-d₆): δ 8.46 (dd, *J* = 1.7, 4.6 Hz, 2H; Ar-H), 7.33 (dd, *J* = 1.7, 4.6 Hz, 2H; Ar-H), 7.04 (dd, *J* = 1.7, 6.6 Hz, 2H; Ar-H), 6.54–6.59 (m, 3H; Ar-H), 4.39 (d, *J* = 5.7 Hz, 2H, CH₂).

4.2.1.4. (5-((Phenylamino)methyl)furan-2-yl)methanol (8b): The crude product was purified using flash column chromatography over silica gel. It eluted with ethyl acetate and hexane (0.2:1, v/v). Yield (0.514 g, 72%). ¹H NMR (500 MHz, acetone-d₆): δ 7.07 (dd, *J* = 7.2, 8.6 Hz, 2H, Ar-H), 6.68 (dd, *J* = 1.2, 8.6 Hz, 2H, Ar-H), 6.58 (d, *J* = 7.2 Hz, Ar-H), 6.16 (d, *J* = 3.2 Hz, 1H, Fu-H), 6.15 (d, *J* = 3.2 Hz, 1H, Fu-H), 5.28 (bs, 1H; N-H), 4.44 (d, *J* = 5.7 Hz, 2H; O-CH₂), 4.25 (d, *J* = 5.7 Hz, 2H; N-CH₂), 4.21 (t, *J* = 6.0 Hz, 1H; O-H). ¹³C

NMR (125 MHz, acetone- d_6): δ 154.8, 153.0, 148.6, 128.9 (2C), 116.8, 112.7 (2C), 107.6, 107.4, 56.5, 40.7. **HRMS** (ESI, m/z): Calculated for $C_{12}H_{14}NO_2$ $[M + H]^+$ 204.1019; found 204.1014 (2.5 ppm).

4.2.2. One-step synthesis of secondary amines (8c–8e)—Aniline 1.20 (1 equiv.) and the aldehyde **9c–9e** (1 equiv.) were dissolved in dry ethanol (0.8 M) and the resulting mixture heated under reflux for 3 hrs. The solution was cooled to room temperature, $NaBH_4$ (5 equiv.) was added portion-wise and the mixture stirred for an hour. The solution was diluted with H_2O and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude product was accomplished via recrystallization using an appropriate mixture of solvents where enough volume of the more polar solvent was added to dissolve the crude mixture and the less polar solvent was added until reaching the saturation point.

4.2.2.1. 2-((Phenylamino)methyl)phenol (8c): The crude product was via recrystallization using a mixture of ethyl acetate and hexane. Yield (0.359 g, 96%). 1H NMR matched that previously reported.³⁴ **1H NMR** (400 MHz, $CDCl_3$): δ 8.44 (bs, 1H; O-H), 7.26-7.20 (m, 3H; Ar-H), 7.16 (d, J = 6.9 Hz, 1H; Ar-H), 6.94-6.84 (m, 5H; Ar-H), 4.41 (s, 2H, N- CH_2), 3.95 (bs, 1H; N-H).

4.2.2.2. 3-((Phenylamino)methyl)phenol (8d): The crude product was purified via recrystallization using a mixture of ethyl acetate and hexane. Yield (0.116 g, 36%). 1H NMR matched that previously reported.³⁵ **1H NMR** (400 MHz, CD_3OD): δ 7.08 (t, J = 7.8 Hz, 1H; Ar-H), 7.03 (t, J = 8.0 Hz, 2H; Ar-H), 8.24 (m, 2H; Ar-H), 6.62-6.53 (m, 4H; Ar-H), 4.20 (s, 2H, N- CH_2).

4.2.2.3. 4-((Phenylamino)methyl)phenol (8e): The crude product was purified via recrystallization using a mixture of ethyl acetate and hexane. Yield (110 mg, 34%). 1H NMR matched that previously reported.³⁶ **1H NMR** (500 MHz, $CDCl_3$): δ 7.24 (d, J = 8.6 Hz, 2H; Ar-H), 7.17 (dd, J = 7.5, 8.6 Hz, 2H, Ar-H), 6.80 (d, J = 8.6 Hz, 2H; Ar-H), 6.72 (t, J = 7.5 Hz, 1H; Ar-H), 6.63 (d, J = 8.6 Hz, 2H; Ar-H), 4.24 (s, 2H; N- CH_2).

4.3. General procedure for the synthesis of *p*-nitro sulfonamides (11a–11k)

A suspension of *p*-nitrobenzenesulfonyl chloride (1.1 equiv.), in CH_2Cl_2 (0.6 M), was added to a solution of the amine (**8a–8k**, 1 equiv.) and pyridine (2 equiv.) in CH_2Cl_2 (0.9 M) and the mixture stirred for 24 hours. The solution was diluted with CH_2Cl_2 and quenched with 1M HCl and washed with 10% $NaHCO_3$. The organic layer was dried and the solvent evaporated. Purification was done via flash column chromatography or recrystallization using an appropriate solvent or a mixture of solvents where enough volume of the more polar solvent was added to dissolve the crude mixture and the less polar solvent was added until reaching the saturation point.

4.3.1. 4-Nitro-N-phenyl-N-(pyridin-4-ylmethyl)benzenesulfonamide (11a)—The crude product was purified via recrystallization using ethyl acetate. Yield (0.193 g, 38%). **1H NMR** (500 MHz, acetone- d_6): δ 8.45 (d, J = 6.3 Hz, 2H; Ar-H), 8.43 (d, J = 9.2 Hz, 2H; Ar-

H), 7.94 (d, $J = 8.6$ Hz, 2H; Ar-H), δ 7.31 (d, $J = 6.3$ Hz, 2H; Ar-H), 7.29-7.25 (m, 3H, Ar-H), 7.17-7.15 (m, 2H, Ar-H), 4.96 (s, 2H, N-CH₂). **¹³C NMR** (125 MHz, acetone-d₆): δ 150.6, 149.9 (2C), 145.3, 143.7, 138.5, 129.3 (2C), 129.2 (2C), 128.8 (2C), 128.4, 124.5 (2C), 123.0 (2C), 53.6. **HRMS** (ESI, m/z): Calculated for C₁₈H₁₆N₃O₄S [M + H]⁺ 370.0856; found 370.0844 (3.3 ppm).

4.3.2. *N*-((5-(Hydroxymethyl)furan-2-yl)methyl)-4-nitro-*N*-phenylbenzenesulfonamide (11b)—The crude product was purified via

recrystallization using a mixture of ethyl acetate in hexane. Yield (9.3 mg, 5%). **¹H NMR** (500 MHz, acetone-d₆): δ 8.38 (dd, $J = 2.3, 8.6$ Hz, 2H; Ar-H), 7.89 (dd, $J = 2.3, 8.6$ Hz, 2H, Ar-H), 7.31-7.26 (m, 3H; Ar-H), 7.05 (dd, $J = 2.3, 8.0$ Hz, 2H; Ar-H), 6.06 (d, $J = 2.9$ Hz, 1H; Fu-H), 6.03 (d, $J = 2.9$ Hz, 1H; Fu-H), 4.88 (s, 2H; N-CH₂), 4.36 (d, $J = 5.7$ Hz, 2H; N-CH₂), 4.21 (t, $J = 5.7$ Hz, 1H; O-H). **¹³C NMR** (125 MHz, acetone-d₆): δ 156.1, 150.3, 148.6, 144.7, 138.7, 129.3 (2C), 129.2 (2C), 129.1 (4C), 128.5, 124.3 (2C), 110.7, 107.5, 56.3, 48.2. **HRMS** (ESI, m/z): Calculated for C₁₈H₁₇N₂O₆S [M + H]⁺ 389.0802; found 389.0794 (2.0 ppm).

4.3.3. *N*-(2-Hydroxybenzyl)-4-nitro-*N*-phenylbenzenesulfonamide (11c)—The crude product was purified via recrystallization using a mixture of ethyl acetate and hexane. Yield (175 mg, 91%). **¹H NMR** (400 MHz, CDCl₃): δ 8.35 (d, $J = 8.7$ Hz, 2H; Ar-H), 7.88 (d, $J = 8.7$ Hz, 2H; Ar-H), 7.32-7.24 (m, 3H; Ar-H), δ 7.15 (dt, $J_d = 1.8$ Hz, $J_t = 7.3$ Hz, 1H; Ar-H), 6.95 (dd, $J = 1.8, 8.0$ Hz, 2H; Ar-H), 6.72 (dt, $J_t = 1.8$ Hz, $J_d = 7.8$ Hz, 1H; Ar-H), 6.68 (t, $J = 7.8$ Hz, 1H; Ar-H), 4.76 (s, 2H; N-CH₂). **¹³C NMR** (100 MHz, CDCl₃): δ 155.8, 151.1, 145.0, 139.7, 130.8, 129.9 (2C), 129.7 (2C), 129.6 (2C), 129.6, 128.8, 125.1, 122.7, 120.3, 115.9, 49.9. **HRMS** (ESI, m/z): Calculated for C₁₉H₁₇N₂O₅S [M + H]⁺ 385.0853; found 385.0845 (2.0 ppm).

4.3.4. *N*-(3-Hydroxybenzyl)-4-nitro-*N*-phenylbenzenesulfonamide (11d)—The crude product was purified via recrystallization using a mixture of ethyl acetate and hexane. Yield (260 mg, 67%). **¹H NMR** (500 MHz, DMSO-d₆) δ 9.35 (bs, 1H; Ar-OH), 8.38 (d, $J = 8.6$ Hz, 2H; Ar-H), 7.87 (d, $J = 8.6$ Hz, 2H; Ar-H), 7.27-7.21 (m, 3H; Ar-H), 7.05 (d, $J = 7.5$ Hz, 2H; Ar-H), 7.00 (dd, $J = 7.5, 8.0$ Hz, 1H; Ar-H), 6.68 (s, 1H; Ar-H), 6.60 (d, $J = 7.5$ Hz, 1H; Ar-H), 6.56 (d, $J = 8.0$ Hz, 1H; Ar-H), 4.73 (s, 2H; N-CH₂). **¹³C NMR** (125 MHz, DMSO-d₆) δ 157.9, 150.5, 143.8, 138.6, 137.7, 129.9, 129.6 (2C), 129.5 (2C), 129.1 (2C), 128.6, 125.2 (2C), 119.2, 115.4, 115.1, 54.4. **HRMS** (ESI, m/z): calculated for C₁₉H₁₇N₂O₅S [M + H]⁺ 385.0853; found 385.0843 (2.5 ppm).

4.3.5. *N*-(4-Hydroxybenzyl)-4-nitro-*N*-phenylbenzenesulfonamide (11e)—The crude product was purified via flash column chromatography using ethyl acetate in hexane (0.2:1 % v/v). Yield (106 mg, 45%). **¹H NMR** (500 MHz, CD₃OD): δ 8.38 (d, $J = 9.2$ Hz, 2H; Ar-H), 7.86 (d, $J = 9.2$ Hz, 2H; Ar-H), 7.22-7.21 (m, 3H; Ar-H), 6.99 (d, $J = 8.6$ Hz, 2H; Ar-H), 6.95-6.93 (m, 2H; Ar-H), 6.59 (d, $J = 8.6$ Hz, 2H; Ar-H), 4.71 (s, 2H; N-CH₂). **¹³C NMR** (125 MHz, CD₃OD) δ 156.9, 150.3, 144.3, 138.3, 129.9 (2C), 129.1 (2C), 128.8 (2C), 128.7 (2C), 128.0, 126.3, 124.0 (2C), 114.8 (2C), 54.3. **HRMS** (ESI, m/z): Calculated for C₁₉H₁₇N₂O₅S [M + H]⁺ 385.0853; found 385.0845 (2.0 ppm).

4.3.6. *N*-Methyl-4-nitro-*N*-phenylbenzenesulfonamide (11f)—The crude product was purified via recrystallization using a mixture of ethyl acetate and hexane. Yield (0.677 g, 26%). ¹H NMR matched that previously reported.³⁷ ¹H NMR (500 MHz, acetone-d₆): δ 8.39 (d, *J* = 8.6 Hz, 2H; Ar-H), 7.80 (d, *J* = 8.6 Hz, 2H; Ar-H), 7.35-7.29 (m, 3H; Ar-H), 7.14 (d, *J* = 8.0 Hz, 2H; Ar-H), 3.25 (s, 3H; N-CH₃).

4.3.7. *N*-(2-Hydroxyethyl)-4-nitro-*N*-phenylbenzenesulfonamide (11g)—The crude product was purified via recrystallization using ethyl acetate. Yield (0.147 g, 10%). ¹H NMR (500 MHz, acetone-d₆): δ 8.38 (dd, *J* = 2.3, 9.2 Hz, 2H; Ar-H), 7.88 (d, *J* = 9.2 Hz, 2H; Ar-H), 7.35-7.32 (m, 3H; Ar-H), 7.14 (dd, *J* = 2.3, 6.9 Hz, 2H; Ar-H), 3.91 (t, *J* = 5.7 Hz, 1H; O-H), 3.77 (t, *J* = 6.3 Hz, 2H; N-CH₂), 3.54 (q, *J* = 5.7 Hz, 2H; O-CH₂). ¹³C NMR (125 MHz, acetone-d₆): δ 150.3, 144.4, 139.1, 129.3 (2C), 129.2 (2C), 129.1 (2C), 128.4 (2C), 124.3, 59.4, 53.6. HRMS (ESI, *m/z*): Calculated for C₁₄H₁₅N₂O₅S [M + H]⁺ 323.0696; found 323.0691 (1.6 ppm).

4.3.8. 4-Nitro-*N*-phenylbenzenesulfonamide (11h)—The crude product was purified via recrystallization was done using ethyl acetate. Yield (68 mg, 5%). ¹H NMR matched that previously reported.³⁷ ¹H NMR (500 MHz, acetone-d₆): δ 9.29 (s, 1H; NH), 8.35 (dd, *J* = 2.3, 8.6 Hz, 2H; Ar-H), 8.02 (dd, *J* = 2.3, 8.6 Hz, 2H; Ar-H), 7.28-7.24 (m, 2H; Ar-H), 7.21-7.19 (m, 2H; Ar-H), 7.12 (tt, *J* = 1.2, 7.5 Hz, 1H; Ar-H).

4.3.9. *N*-Methyl-4-nitro-*N*-(pyridin-4-yl)benzenesulfonamide (11i)—The crude product was purified via flash column chromatography. It eluted with ethyl acetate and hexane (0.75:1, v/v). Yield (0.366 g, 34%). ¹H NMR (500 MHz, acetone-d₆): δ 8.49 (dd, *J* = 1.7, 4.6 Hz, 2H; Ar-H), 8.40 (dd, *J* = 2.3, 9.2 Hz, 2H; Ar-H), 7.90 (dd, *J* = 2.3, 9.2 Hz, 2H; Ar-H), 7.27 (dd, *J* = 1.7, 4.6 Hz, 2H; Ar-H), 3.34 (s, 3H; N-CH₃). ¹³C NMR (125 MHz, acetone-d₆): δ 150.8 (2C), 148.3, 141.93, 141.92, 129.1 (2C), 124.6 (2C), 118.6 (2C), 36.5. HRMS (ESI, *m/z*): Calculated for C₁₂H₁₂N₃O₄S [M + H]⁺ 294.0543; found 294.0539 (1.4 ppm).

4.3.10. *N*-(2-Hydroxyethyl)-4-nitrobenzenesulfonamide (11j)—The crude product was purified via recrystallization using a mixture of ethyl acetate and hexane. Yield (658 mg, 54%). ¹H NMR (500 MHz, CD₃OD): δ 8.39 (d, *J* = 8.6 Hz, 2H; Ar-H), 8.08 (d, *J* = 8.6 Hz, 2H; Ar-H), 3.52 (t, *J* = 5.7 Hz, 2H; O-CH₂), 3.00 (t, *J* = 5.7 Hz, 2H; N-CH₂). ¹³C NMR (125 MHz, CD₃OD) δ 150.0, 146.6, 128.1 (2C), 124.1 (2C), 60.5, 45.0. HRMS (ESI, *m/z*): Calculated for C₈H₁₁N₂O₅S [M + H]⁺ 247.0383; found 247.0379 (1.7 ppm).

4.3.11. *N*-(2, 3-Dihydroxypropyl)-4-nitrobenzenesulfonamide (11k)—The crude product was purified via flash column chromatography over silica gel. It eluted using 70% ethyl acetate in hexane. Yield (69 mg, 45%). ¹H NMR matched that previously reported.³⁸ ¹H NMR (500 MHz, CD₃OD): δ 8.39 (d, *J* = 8.6 Hz, 2H; Ar-H), 8.08 (d, *J* = 8.6 Hz, 2H; Ar-H), 3.60 (p, *J* = 5.2 Hz, 1H; O-CH) 3.47-3.41 (m, 2H; O-CH₂), 3.07 (dd, *J* = 5.2, 13.2 Hz, 1H; N-CH₂), 2.86 (dd, *J* = 6.9, 13.2 Hz, 1H; N-CH₂).

4.4. General procedure for the synthesis of *p*-amino sulfonamides (7a–7k)

Nitro-substituted benzenesulfonamides **7a–7k** were dissolved in MeOH (0.1 M) and hydrogenated (1 bar-H₂) over 50% w/w palladium on charcoal. The reaction mixture stirred at ambient temperature for 1–5 hr, filtered through a pad of Celite®, and the solvent was evaporated under reduced pressure. Purification was done via flash column chromatography or recrystallized using an appropriate solvent or mixture of solvents where enough volume of the more polar solvent was added to dissolve the crude mixture and the less polar solvent was added until reaching the saturation point.³⁹

4.4.1. 4-Amino-*N*-phenyl-*N*-(pyridin-4-ylmethyl)benzenesulfonamide (7a)—The crude product was purified via recrystallization using ethyl acetate. Yield (71 mg, 32%). **¹H NMR** (500 MHz, acetone-*d*₆): δ 8.42 (dd, *J* = 1.7, 4.6 Hz, 2H; Ar-H), 7.32–7.30 (m, 4H; Ar-H), 7.24–7.20 (m, 2H; Ar-H), 7.19–7.16 (m, 1H; Ar-H), 7.16–7.12 (m, *J* = 2H; Ar-H), 6.71 (dd, *J* = 2.3, 8.6 Hz, 2H; Ar-H), 5.62 (bs, 1H; N-H₂), 4.81 (s, 2H; N-CH₂). **¹³C NMR** (125 MHz, acetone-*d*₆): δ 153.2, 149.8 (2C), 146.3, 139.9, 129.8 (2C), 128.7 (2C), 128.6 (2C), 127.5, 124.0, 123.1 (2C), 113.1, 52.8. **HRMS** (ESI, *m/z*): calculated for C₁₈H₁₈N₃O₂S [M + H]⁺ 340.1114; found 340.1104 (3.0 ppm).

4.4.2. 4-Amino-*N*-((5-(hydroxymethyl)furan-2-yl)methyl)-*N*-phenylbenzenesulfonamide (7b)—The crude product was purified via flash column chromatography. It eluted using ethyl acetate in hexane (0.4:1 % v/v). Yield (253 mg, 50%). **¹H NMR** (400 MHz, CDCl₃): δ 7.37 (d, *J* = 8.7 Hz, 2H; Ar-H), 7.25–7.22 (m, 3H; Ar-H), 7.02–6.99 (m, 2H; Ar-H), δ 6.60 (d, *J* = 8.7 Hz, 2H; Ar-H), 6.07 (d, *J* = 3.2 Hz, 1H; Ar-H), 5.99 (d, *J* = 3.2 Hz, 1H; Ar-H), 4.69 (s, 2H; O-CH₂), 4.44 (s, 2H; N-CH₂). **¹³C NMR** (125 MHz, acetone-*d*₆): δ 155.5, 153.0, 149.4, 139.8, 129.8 (2C), 128.9 (2C), 128.6 (2C), 127.6, 124.6, 113.1 (2C), 110.0, 107.6, 56.4, 47.4. **HRMS** (ESI, *m/z*): Calculated for C₁₈H₁₉N₂O₄S [M + H]⁺ 359.1060; found 359.1056 (1.1 ppm).

4.4.3. 4-Amino-*N*-(2-hydroxybenzyl)-*N*-phenylbenzenesulfonamide (7c)—The crude product was purified via flash column chromatography using 30% ethyl acetate in hexane. Yield (70 mg, 76%). **¹H NMR** (400 MHz, CD₃OD) δ 7.27 (d, *J* = 8.7 Hz, 2H; Ar-H), 7.19–7.13 (m, 4H; Ar-H), 7.02 (dd, *J* = 1.8, 7.8 Hz, 2H; Ar-H), 6.93 (dt, *J_d* = 1.8 Hz, *J_t* = 7.8 Hz, 2H; Ar-H), 6.66–6.59 (m, 4H; Ar-H), 4.72 (s, 2H; N-CH₂). **¹³C NMR** (100 MHz, Acetonitrile-*d*₃) δ: 155.0, 152.8, 139.6, 130.2, 129.8 (2C), 129.0, 128.7 (2C), 128.6 (2C), 127.7, 124.1, 122.2, 119.8, 115.4, 113.2 (2C), 49.0. **HRMS** (ESI, *m/z*): Calculated for C₁₉H₁₉N₂O₃S [M + H]⁺ 355.1111; found 355.1102 (2.5 ppm).

4.4.4. 4-Amino-*N*-(3-hydroxybenzyl)-*N*-phenylbenzenesulfonamide (7d)—The crude product was purified flash column chromatography using 30% ethyl acetate in hexane. Yield (63 mg, 68%). **¹H NMR** (400 MHz, CD₃OD): δ 7.27 (d, *J* = 8.7 Hz, 2H; Ar-H), 7.19–7.13 (m, 3H; Ar-H), 7.00–6.94 (m, 3H; Ar-H), 6.69 (s, 1H; Ar-H), 6.63 (m, 3H; Ar-H), 6.55 (dd, *J* = 1.8, 7.8 Hz, 1H; Ar-H), 4.6 (s, 1H; N-CH₂). **¹³C NMR** (125 MHz, CD₃OD): δ 157.1, 153.2, 139.5, 138.0, 129.5 (2C), 128.9 (2C), 128.9 (2C), 128.3, 127.3, 123.8, 119.4, 115.0, 114.0, 112.9, 53.9. **HRMS** (ESI, *m/z*): Calculated for C₁₉H₁₉N₂O₃S [M + H]⁺ 355.1111; found 355.1096 (4.2 ppm).

4.4.5. 4-Amino-*N*-(4-hydroxybenzyl)-*N*-phenylbenzenesulfonamide (7e)—The crude product was purified via flash column chromatography using 30% ethyl acetate in hexane. Yield (35.5 mg, 47%). ¹H NMR (400 MHz, Acetonitrile-*d*₆): δ 7.29 (d, *J* = 8.7 Hz, 2H; Ar-H), 7.22-7.15 (m, 3H; Ar-H), 7.02-6.97 (m, 4H; Ar-H), 6.83 (s, 1H; Ar-OH), 6.64 (d, *J* = 8.7 Hz, 2H; Ar-H), 6.60 (d, *J* = 8.2 Hz, 2H; Ar-H), 4.85 (bs, 2H; Ar-NH₂), 4.57 (s, 2H; N-CH₂). ¹³C NMR (100 MHz, Acetonitrile-*d*₃): δ 156.3, 152.6, 139.6, 129.9 (2C), 129.7 (2C), 129.0 (2C), 128.6 (2C), 127.7, 127.5, 124.7, 115.0 (2C), 113.2 (2C), 53.3. HRMS (ESI, *m/z*): Calculated for C₁₉H₁₉N₂O₃S [M + H]⁺ 355.1111; found 355.1108 (0.8 ppm).

4.4.6. 4-Amino-*N*-methyl-*N*-phenylbenzenesulfonamide (7f)—The crude product was purified via recrystallization using MeOH. Yield (210 mg, 12%). ¹H NMR matched that previously reported.³⁷ ¹H NMR (500 MHz, acetone-*d*₆) δ 7.29 (d, *J* = 7.5 Hz, 1H; Ar-H), 7.27 (d, *J* = 6.9 Hz, 1H; Ar-H), 7.23-7.20 (m, 1H, Ar-H), 7.16 (d, *J* = 8.6 Hz, 2H; Ar-H), 7.12 (dd, *J* = 1.7, 7.5 Hz, 2H; Ar-H), 6.65 (d, *J* = 8.6 Hz, 2H; Ar-H), 5.53 (bs, 1H; N-H₂), 3.08 (s, 3H, N-CH₃).

4.4.7. 4-Amino-*N*-(2-hydroxyethyl)-*N*-phenylbenzenesulfonamide (7g)—The crude product was purified via recrystallization using a mixture of ethyl acetate and hexane. Yield (236 mg, 52%). ¹H NMR (400 MHz, CDCl₃): δ 8.01 (d, *J* = 8.7 Hz, 2H; Ar-H), 7.79 (d, *J* = 8.7 Hz, 2H; Ar-H), 7.35-7.34 (m, 3H; Ar-H), 7.11-7.09 (m, 2H; Ar-H), 3.77 (t, *J* = 5.5 Hz, 2H; O-CH₂), 3.69 (t, *J* = 5.5 Hz, 2H; O-CH₂). ¹³C NMR (100 MHz, CDCl₃): 154.3, 140.6, 139.0, 129.6 (2C), 129.02 (2C), 129.00 (2C), 128.7, 123.6 (2C), 60.5, 53.8. HRMS (ESI, *m/z*): Calculated for C₁₄H₁₆N₂O₃S [M + H]⁺ 293.0954; found 293.0946 (2.9 ppm).

4.4.8. 4-Amino-*N*-phenylbenzenesulfonamide (7h)—The crude product was purified via recrystallization using methanol. Yield (82 mg, 18%). ¹H NMR matched that previously reported.³⁷ ¹H NMR (500 MHz, acetone-*d*₆): δ 8.63 (bs, 1H; Ar-NH₂), 7.44 (dd, *J* = 2.3, 8.6 Hz, 2H; Ar-H), 7.21-7.16 (m, 4H; Ar-H), 6.99 (tt, *J* = 1.7, 6.9 Hz, 1H; Ar-H), 6.62 (dd, *J* = 2.3, 8.6, 2H; Ar-H), 5.45 (bs, 1H; SO₂-NH).

4.4.9. 4-Amino-*N*-methyl-*N*-(pyridin-4-yl)benzenesulfonamide (7i)—The product was isolated without the need for further purification. Yield (0.107 g, 73%). ¹H NMR (500 MHz, acetone-*d*₆): δ 8.42 (dd, *J* = 1.7, 4.6 Hz, 2H; Ar-H), 7.29 (d, *J* = 2.3, 8.6 Hz, 2H; Ar-H), 7.25 (dd, *J* = 1.7, 4.6 Hz, 2H; Ar-H), 6.66 (d, *J* = 1.7, 8.6 Hz, 2H; Ar-H), 5.65 (d, *J* = 6.3 Hz, 1H; N-H₂), 3.20 (s, 3H; N-CH₃). ¹³C NMR (125 MHz, acetone-*d*₆): δ 153.5, 150.2 (2C), 149.3, 129.5 (2C), 122.5, 117.4 (2C), 113.1, 113.0, 113.0 (2C), 35.7. HRMS (ESI, *m/z*): Calculated for C₁₂H₁₄N₃O₂S [M + H]⁺ 264.0801; found 264.0794 (2.7 ppm).

4.4.10. 4-Amino-*N*-(2-hydroxyethyl)benzenesulfonamide (7j)—The crude product was purified via recrystallization using a mixture of ethyl acetate in hexane. Yield (118 mg, 34%). ¹H NMR (500 MHz, CD₃OD) δ: δ 7.51 (d, *J* = 8.6 Hz, 2H; Ar-H), 6.68 (d, *J* = 8.6 Hz, 2H; Ar-H), 3.51 (t, *J* = 5.7 Hz, 2H; O-CH₂), 2.87 (t, *J* = 5.7 Hz, 2H; N-CH₂). ¹³C NMR (125 MHz, CD₃OD): δ 152.8, 128.6 (2C), 125.9, 113.1 (2C), 60.5, 44.8. HRMS (ESI, *m/z*): Calculated for C₈H₁₃N₂O₃S [M + H]⁺ 217.0641; found 217.0637 (2.0 ppm).

4.4.11. 4-Amino-*N*-(2,3-dihydroxypropyl)benzenesulfonamide (7k)—The crude product was purified via flash column chromatography using 100% ethyl acetate. Yield (47 mg, 92%). ¹H NMR matched that previously reported.³⁸ ¹H NMR (500 MHz, CD₃OD): δ 7.51 (d, *J* = 8.6 Hz, 2H; Ar-H), 6.68 (d, *J* = 8.6 Hz, 2H; Ar-H), 3.62 (p, *J* = 5.2 Hz, 1H; CHO), 3.48 (dd, *J* = 4.6, 11.5 Hz, 1H; O-CH₂), 3.43 (dd, *J* = 4.6, 11.5 Hz, 1H; O-CH₂), 2.91 (dd, *J* = 5.2, 13.2 Hz, 1H; N-CH₂), 2.74 (dd, *J* = 5.2, 13.2 Hz, 1H; N-CH₂).

4.5. Synthesis of 6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-naphthoic acid (5y) and 6-(2-(((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-naphthoic acid (5z)

4.5.1. (6-Bromonaphthalen-2-yl)methanol (13)²³—Methyl 6-bromo-2-naphthoate (12) (1.5 g, 5.66 mmol) was dissolved in anhydrous THF and cooled to −40 °C in CH₃CN/dry ice bath. DIBAL-H (17 mL, 17 mmol) was added drop wise and the mixture left stirring at ambient temperature for 8 hours. The mixture was then quenched using a saturated solution of NH₄Cl (15 mL) followed by extraction with CH₃Cl (100 mL × 2). The organic layers were combined, extracted with H₂O (100 mL × 1), dried using anhydrous Na₂SO₄ and the solvent evaporated. Yield (1.194 g, 90%). ¹H NMR matched that previously reported.⁴⁰ ¹H NMR (500 MHz, acetone-*d*₆) δ 8.07 (d, *J* = 1.7 Hz, 1H; Ar-H), 7.84-7.79 (m, 3H; Ar-H), 7.57-7.52 (m, 2H; Ar-H), 4.77 (s, 2H; O-CH₂), 4.85 (bs, 1H; O-H).

4.5.2. 6-Bromo-2-naphthaldehyde (14)⁴¹—DMSO (2.9 mL, 41.2 mmol) was added dropwise to a solution of oxalyl chloride (1.77 mL, 20.58 mmol) in CH₂Cl₂ (65 mL) at −78 °C. A solution of (6-bromonaphthalen-2-yl)methanol (13) (1.22 g, 5.14 mmol) in CH₂Cl₂ (12 mL) was then added dropwise and the mixture stirred for 15 minutes. Triethylamine (12.9 mL, 0.926 mmol) was then added to mixture dropwise followed by H₂O (5 mL) after 15 minutes. The mixture was diluted with EtOAc (100 mL) and extracted with 20 KHSO₃ (100 mL × 2) and brine (100 mL). The organic layer was dried and condensed under reduced pressure. Yield (724 mg, 60%). ¹H NMR matched that previously reported.⁴² ¹H NMR (500 MHz, acetone-*d*₆): δ 10.16 (s, 1H; O=CH), 8.52 (s, 1H; Ar-H), 8.24 (d, *J* = 2.3 Hz, 1H; Ar-H), 8.08 (d, *J* = 8.6 Hz, 1H; Ar-H), 8.02 (d, *J* = 8.6 Hz, 1H; Ar-H), 7.96 (dd, *J* = 1.2, 8.6 Hz, 1H; Ar-H), 7.74 (dd, *J* = 1.7, 8.6 Hz, 1H; Ar-H).

4.5.3. Synthesis of 13 and 14 using flow chemistry—Following related reports,^{24–25} solutions of methyl 6-bromo-2-naphthoate in toluene (12; 0.1 M) and DIBAL-H in toluene (0.3 M) were added via inhouse built syringe pumps⁴³ into 0.04 inch internal diameter tubing at a rate of 25 mL/min. Each solution was precooled to −78 °C before mixing by submerging 1.6 feet of steel tubing into a dry ice/acetone bath. The solutions were mixed by meeting at a T-joint and the reactor length was 1.5 inches long (0.04 inch internal diameter PFA tubing) before being mixed at a different T-joint with saturated aqueous ammonium chloride. The retention time between mixing of the reagents and quenching of the reaction for the combined flow rate of 50 mL/min was 37 milliseconds. The solutions were washed with diethyl ether to extract the organic material and concentrated under reduced pressure. The conversion of ester 12 and yields of alcohol 13 and aldehyde 14 were determined by both NMR and GC/MS. A variety of flow rates, reactor lengths, temperatures, and concentrations were screened, with the optimal conditions described above giving 93% conversion of ester 12, 35% yield of alcohol 13, and 57% yield of aldehyde 14 (average of

six experiments). The NMR data for the compounds matched those described earlier in this experimental section.

4.5.4. 2-Bromo-6-vinylnaphthalene (15)²⁷—Sodium hydride (0.299 g, 12.46 mmol) was added to a suspension of 6-bromo-2-naphthaldehyde (**14**) (0.586 g, 2.49 mmol) and triphenylphosphonium iodide (1.61 g, 3.99 mmol) in anhydrous THF (30 mL) and the mixture stirred for 25 hours. The mixture was diluted with CHCl₃ (30 mL) and extracted with brine (100 mL × 3). The organic layer was dried using anhydrous Na₂SO₄ and condensed under reduced pressure. The solid residue was purified via flash column chromatography (5% Ethyl acetate/Hexane) to afford the desired product. Yield (377 mg, 65%). ¹H NMR matched that previously reported.⁴⁴ ¹H NMR (400 MHz, CDCl₃): δ 7.95 (d, *J* = 1.8 Hz, 1H; Ar-H), 7.70-7.63 (m, 4H; Ar-H), 7.52 (dd, *J* = 2.3, 8.7 Hz, 1H; Ar-H), 6.84 (dd, *J* = 11.0, 17.9 Hz, 1H; Ar-CH=C), 5.86 (d, *J* = 17.9 Hz, 1H; C=CH₂), 5.36 (d, *J* = 11.0 Hz, 1H; C=CH₂).

4.5.5. 2-(6-Bromonaphthalen-2-yl)ethan-1-ol (16)²⁸—2-Bromo-6-vinylnaphthalene (**15**) (200 mg, 0.858 mmol) was added to a cooled solution of BH₃.THF (0.64 mL, 0.64 mmol) in anhydrous THF (4 mL) and the mixture stirred for 2 hours at ambient temperature. NaOH (3M, 0.52 mL) followed by 30% H₂O₂ (0.17 mL) were added and the mixture stirred for additional 2 hours. The mixture was then diluted with EtOAc (20 mL), extracted with H₂O and brine (20 mL × 2), dried over anhydrous Na₂SO₄ and condensed under reduced pressure. The solid residue was purified via flash column chromatography (0–60% EtOAc/Hexane) to afford the desired product. Yield (98 mg, 46%). ¹H NMR matched that previously reported.⁴⁰ ¹H NMR (500 MHz, CDCl₃): δ 7.97 (d, *J* = 1.8 Hz, 1H; Ar-H), 7.70 (d, *J* = 8.6 Hz, 1H; Ar-H), 7.65 (d, *J* = 8.7 Hz, 1H; Ar-H), 7.64 (s, 1H; Ar-H), 7.52 (dd, *J* = 2.3, 8.6 Hz, 1H; Ar-H), 7.38 (dd, *J* = 1.7, 8.6 Hz, 1H; Ar-H), 3.94 (t, *J* = 6.3 Hz, 2H; O-CH₂), 3.00 (t, *J* = 6.3 Hz, 2H; Ar-CH₂).

4.5.6. ((6-bromonaphthalen-2-yl)methoxy)(tert-butyl)dimethylsilane (17)²⁹—*tert*-Butyldimethylsilyl chloride (100 mg, 0.42 mmol), 4-dimethylaminopyridine (12.9 mg, 0.11 mmol), and trimethylamine (0.22 mL, 0.55 mmol) were added to a solution of 2-(6-bromonaphthalen-2-yl)methanol (**13**, 100 mg, 0.42 mmol) in CH₂Cl₂ (5 mL) and stirred at room temperature for 25 hours. The mixture was then diluted with CH₂Cl₂ (10 mL), extracted with a saturated solution of NH₄Cl (15 mL × 2). The organic layer was dried using anhydrous sodium sulfate and condensed under reduced pressure. The solid residue was purified via flash column chromatography (0–5% EtOAc/Hexane) to afford the desired product. Yield (125 mg, 84%). ¹H NMR matched that previously reported.⁴⁵ ¹H NMR (500 MHz, CDCl₃): δ 7.97 (s, 1H; Ar-H), 7.74 (s, 1H; Ar-H), 7.70 (t, *J* = 8.2 Hz, 2H; Ar-H), 7.52 (dd, *J* = 1.8, 8.7 Hz, 1H; Ar-H), 7.44 (d, *J* = 8.2 Hz, 1H; Ar-H), 4.87 (s, 2H; O-CH₂), 0.97 (s, 9H; Si-C(CH₃)₃), 0.13 (s, 6H; Si(CH₃)₂). ¹³C NMR (100 MHz, CDCl₃) δ 139.6, 133.8, 129.8, 129.6, 129.4, 127.1, 126.0, 125.7, 124.3, 119.43, 65.0, 26.1, 18.6, –5.1.

4.5.7. (2-(6-Bromonaphthalen-2-yl)ethoxy)(tert-butyl)dimethylsilane (18)²⁹—*tert*-butyldimethylsilyl chloride (57.6 mg, 0.38 mmol), 4-dimethylaminopyridine (9.7 mg, 0.08 mmol), and trimethylamine (58 μL, 0.414 mmol) were added to a solution of 2-(6-

bromonaphthalen-2-yl)ethanol **16** (80.0 mg, 0.32 mmol) in CH₂Cl₂ (4 mL) and stirred at room temperature for 25 hours. The mixture was then diluted with CH₂Cl₂ (10 mL), extracted with a saturated solution of NH₄Cl (15 mLx2). The organic layer was dried using anhydrous sodium sulfate and condensed under reduced pressure. The solid residue was purified via flash column chromatography (0–5% EtOAc/Hexane) to afford the desired product. Yield (62 mg, 53%). ¹H NMR matched that previously reported.⁴⁶ **¹H NMR** (500 MHz, CDCl₃): δ 7.96 (d, *J*=1.7 Hz, 1H; Ar-H), 7.67 (d, *J*= 8.6 Hz, 1H; Ar-H), 7.64 (d, *J*= 8.6 Hz, 1H; Ar-H), 7.62 (s, 1H; Ar-H), 7.51 (dd, *J*= 2.3, 8.6 Hz, 1H; Ar-H), 7.37 (dd, *J*= 1.7, 8.6 Hz, 1H; Ar-H), 3.87 (t, *J*= 6.9 Hz, 2H; O-CH₂), 2.96 (t, *J*= 6.9 Hz, 2H; Ar-CH₂), 0.85 (s, 9H, Si-C(CH₃)₃), –0.05 (s, 6H; Si(CH₃)₂).

4.5.8. 6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-naphthoic acid (5y)³⁰—A solution of (2-(6-Bromonaphthalen-2-yl)methoxy)(*tert*-butyldimethylsilane (**17**) (100 mg, 0.29 mmol) in anhydrous THF (10 mL) was cooled to –78 °C was added dropwise to a previously cooled *n*-butyllithium (0.12 mL, 0.30 mmol) and the mixture stirred for 3 hours. The mixture was purged with CO₂ gas at –78 °C for half an hour then allowed to warm to room temperature. The mixture was then acidified with 1 M HCl, extracted with ethyl acetate (20 mL × 2) and the organic layer dried over anhydrous Na₂SO₄ and condensed under reduced pressure. Purification was done via flash column chromatography using 20% ethyl acetate in hexane. Yield (17.0 mg, 19%). ¹H NMR matched that previously reported.⁴⁷ **¹H NMR** (500 MHz, CDCl₃): δ 8.67 (bs, 1H; Ar-H), 8.10 (dd, *J*= 1.7, 8.6 Hz, 1H; Ar-H), 7.94 (d, *J*= 8.6 Hz, 1H; Ar-H), 7.89 (d, *J*= 8.6 Hz, 1H; Ar-H), 7.84 (s, 1H; Ar-H), 7.50 (dd, *J*= 1.2, 8.6 Hz, 1H; Ar-H), 4.93 (s, 2H; O-CH₂), 0.98 (s, 9H, Si-C(CH₃)₃), 0.14 (s, 6H; Si(CH₃)₂).

4.5.9. 6-(2-(((*tert*-butyldimethylsilyl)oxy)ethyl)-2-naphthoic acid (5z)³⁰—A solution of (2-(6-Bromonaphthalen-2-yl)ethoxy)(*tert*-butyldimethylsilane (**18**) (61.9 mg, 0.17 mmol) in anhydrous THF (4 mL) was cooled to –40 °C was added dropwise to a previously cooled *n*-butyllithium (0.25 mL, 0.25 mmol) and the mixture stirred for 3 hours. The mixture was purged with CO₂ gas at –40 °C for half an hour then allowed to warm to room temperature. The mixture was then acidified with 1 M HCl, extracted with brine (20 mL × 2) and the organic layer dried over anhydrous Na₂SO₄ and condensed under reduced pressure. Purification was done via flash column chromatography using 50% v/v ethyl acetate in hexane. Yield (29.7 mg, 53%). **¹H NMR** (500 MHz, CDCl₃): δ 8.67 (bs, 1H; Ar-H), 8.09 (dd, *J*= 1.7, 8.6 Hz, 1H; Ar-H), 7.90 (d, *J*= 8.6 Hz, 1H; Ar-H), 7.84 (d, *J*= 8.6 Hz, 1H; Ar-H), 7.72 (s, 1H; Ar-H), 7.45 (dd, *J*= 1.7, 8.6 Hz, 1H; Ar-H), 3.91 (t, *J*= 6.9 Hz, 2H; O-CH₂), 3.01 (t, *J*= 6.9 Hz, 2H; Ar-CH₂), 1.25 (s, 9H, Si-C(CH₃)₃), 0.86 (s, 6H; Si(CH₃)₂). **¹³C NMR** (100 MHz, CD₃OD): δ 169.3, 139.9, 135.7, 131.4, 130.4, 128.7, 128.5, 127.9, 127.3, 127.2, 125.2, 63.9, 39.3, 25.0, –6.7. **HRMS** (ESI, *m/z*): Calculated for C₁₉H₂₇O₃Si [M + H]⁺ 331.1724; found 331.1720 (1.2 ppm).

4.5.10. 6-Bromo-2-naphthoic acid (S1)⁴⁸—Potassium hydroxide (127 mg, 2.26 mmol) was added to a suspension of methyl 6-bromo-2-naphthoate (200 mg, 0.75 mmol) in methanol (50 mL) and the mixture heated at 50 °C for 48 hours. The solvent was evaporated and the residue diluted with water (30 mL), acidified with HCl (1M) and the extracted with

ethyl acetate (30 mL $\times$ 2). The combined organic layers were dried with anhydrous magnesium sulfate and the solvent evaporated under reduced pressure. The crude product was purified via recrystallization using ethyl acetate to give the product as white crystals (105 mg, yield 56%). ^1H NMR matched that previously reported.⁴⁸ ^1H NMR (400 MHz, CD_3OD): δ 8.58 (s, 1H; Ar-H), 8.14 (s, 1H; Ar-H), 8.06 (dd, J = 1.8, 8.7 Hz, 1H; Ar-H), 7.92 (d, J = 8.7 Hz, 1H; Ar-H), 7.87 (d, J = 8.7 Hz, 1H; Ar-H), 7.64 (dd, J = 1.8, 8.7 Hz, 1H; Ar-H).

4.5.11. Methyl 6-(2-Hydroxyethyl)-2-naphthoate (S2)—Methyl 6-bromo-2-naphthoate (1.0 g, 3.8 mmol), triethylamine hydrochloride (523 mg, 3.80 mmol), zinc dust (497 mg, 7.60 mmol), nickel(II) bromide (83 mg, 0.38 mmol), 2,2'-bipyridyl (59 mg, 0.38 mmol), and sodium iodide (140 mg, 0.95 mmol) were added to flask inside a glove box. 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (20 mL), pyridine (0.06 mL, 0.8 mmol), and ethylene oxide (2.0 mL, 5.1 mmol) were all added to the flask inside a hood. The mixture stirred for 24 hours at room temperature. The mixture was poured into 300 mL of 0.1 M pH 8 phosphate buffer, and then extracted with diethyl ether. The organic layers were combined, washed with brine, and dried over MgSO_4 . Purification was done via flash column chromatography using 20% ethyl acetate in hexane to give the product as a white solid (575.8 mg, yield 66%). ^1H NMR (500 MHz, CDCl_3): δ 8.48 (s, 1H), 7.96 (dd, J = 8.6, 1.15 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.61 (s, 1H), 7.34 (dd, J = 8.6, 1.72 Hz, 1H), 3.91 (s, 3H), 3.88 (t, J = 6.6 Hz, 2H), 2.96 (t, J = 6.6 Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 167.5, 139.3, 135.7, 131.2, 130.9, 129.6, 128.4, 127.8, 127.4, 126.8, 125.4, 63.3, 52.3, 39.5. HRMS (ESI, m/z): Calculated for $\text{C}_{14}\text{H}_{15}\text{O}_3$ $[\text{M} + \text{H}]^+$ 231.1021; found 231.1019 (0.87 ppm).

4.5.12. 6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-naphthoic acid (5z)—*tert*-Butyldimethylsilyl chloride (79 mg, 0.52 mmol) was added to a CH_2Cl_2 solution (5.0 mL) of imidazole (59.2 mg, 0.87 mmol) and 4-dimethylaminopyridine (5 mg, 0.04 mmol). The reaction mixture was stirred at room temperature for 10 min and methyl 6-(2-hydroxyethyl)-2-naphthoate (100 mg, 0.43 mmol) in CH_2Cl_2 (1.0 mL) was slowly added. The reaction was allowed to stir at ambient temperature for 24 hours. Upon completion, the reaction mixture was washed with water (5.0 mL $\times$ 3) and the organic layer was dried and concentrated under reduced pressure. The residue was purified by column chromatography using 10% ethyl acetate in hexane to obtain the desired product (115 mg, 71% yield). ^1H NMR (500 MHz, acetone- d_6): δ 8.56 (s, 1H; Ar-H), 8.01 – 7.96 (m, 2H; Ar-H), 7.90 (d, J = 8.6 Hz, 1H; Ar-H), 7.80 (s, 1H; Ar-H), 7.52 (dd, J = 8.4, 1.7 Hz, 1H; Ar-H), 3.92 (t, J = 6.6 Hz, 2H; OCH_2) 3.91 (s, 3H; O-CH_3), 2.98 (t, J = 6.6 Hz, 2H; Ar- CH_2), 0.82 (s, 9H; $\text{Si-C(CH}_3)_3$), -0.07 (s, 6H; $\text{Si(CH}_3)_2$). This TBS-protected derivative (100 mg, 0.29 mmol) was then dissolved in THF (6.0 mL) and water (3.0 mL). LiOH (52 mg, 2.14 mmol) was added and the mixture was stirred at 50 $^\circ\text{C}$ for 24 hr. After that time, THF was removed under reduced pressure and the resultant aqueous solution was washed with CH_2Cl_2 (3.0 mL $\times$ 3), acidified with HCl (2N), and extracted with ethyl acetate (10 mL $\times$ 2). The desired product was isolated after removal of solvent under reduced pressure (88% yield). NMR data for this compound matched that for **5z** prepared by the previous method.

4.6. General procedure for the synthesis of thiourea compounds (6)

The carboxylic acid (**5**, 1 equiv.) was refluxed with thionyl chloride (120 equiv.) and the mixture heated under reflux for 3 hours. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was further dried via high vacuum and used in the proceeding reaction without further purification. KSCN (1–2 equiv.) was added to the solution of crude acyl chloride in anhydrous acetonitrile (0.5 M) and the reaction was allowed to stir for 4 hours at room temperature. The solid KCl was removed through filtration and the aniline (**7**, 1 equiv.), dissolved in acetonitrile (0.1 M), was added drop wise to the filtrate and the mixture stirred for 24 hours.³¹ The product either precipitated and needed no further purification, recrystallized using the appropriate mixture of solvents or purified via flash column chromatography or preparative HPLC.

4.6.1. (*E*)-3-(2-Methoxyphenyl)-*N*-((4-(*N*-phenyl-*N*-(pyridin-4-ylmethyl)sulfamoyl)phenyl)carbamoithioyl)acrylamide (6av**)**—The product precipitated as a yellow solid. Yield (16.5 mg, 28%). ¹H NMR (500 MHz, CDCl₃): δ 8.69 (s, 1H, N-H), 8.53 (d, *J* = 6.0 Hz, 2H; Ar-H), 8.07 (d, *J* = 15.5 Hz, 1H; Ar-CH=C), 8.00 (d, *J* = 8.6 Hz, 2H; Ar-H), 7.64 (d, *J* = 8.6 Hz, 2H; Ar-H), 7.59 (dd, *J* = 1.7, 8.0 Hz, 2H; Ar-H), 7.43 (dt, *J*_t = 1.7, *J*_d = 8.0 Hz, 1H; Ar-H), 7.38 (d, *J* = 4.0 Hz, 2H; Ar-H), 7.28–7.26 (m, 3H; Ar-H), 7.04–7.00 (m, 3H; Ar-H), 6.97 (d, *J* = 8.0 Hz, 1H; Ar-H), 6.66 (d, *J* = 15.5 Hz, 1H; CH=CO), 4.80 (s, 2H; N-CH₂), 3.95 (s, 3H; O-CH₃). ¹³C NMR (125 MHz, CDCl₃): δ 178.4, 166.7, 159.3, 149.5, 146.1, 143.6, 142.1, 138.6, 134.9, 132.9, 130.9, 129.4 (2C), 128.7 (2C), 128.5, 123.4, 123.1 (2C), 122.4, 121.0, 118.6, 11.5, 55.7, 53.9. HRMS (ESI, *m/z*): Calculated for C₂₉H₂₇N₄O₄S₂ [M + H]⁺ 559.1396; found 559.1446.

4.6.2. (*E*)-*N*-((4-(*N*-((5-(Hydroxymethyl)furan-2-yl)methyl)-*N*-phenylsulfamoyl)phenyl)carbamoithioyl)-3-(2-methoxyphenyl)acrylamide (6bv**)**—The product precipitated as a yellow solid. Yield (98 mg, 61%). ¹H NMR (500 MHz, acetone-*d*₆): δ 8.14 (d, *J* = 15.8 Hz, 1 H; Ar-CH=C), 8.08 (d, *J* = 8.9 Hz, 2H; Ar-H), 7.66 (d, *J* = 8.6 Hz, 2H; Ar-H), 7.62 (dd, *J* = 1.7, 7.7 Hz, 2H; Ar-H), 7.45 (dt, *J*_t = 1.7, *J*_d = 7.7 Hz, 1H; Ar-H), 7.28–7.25 (m, 3H; Ar-H), 7.19 (d, *J* = 15.5 Hz, 1H; C=CHCO), 7.11 (d, *J* = 8.6 Hz, 1H; Ar-H), 7.07–7.05 (m, 2H; Ar-H), 7.01 (t, *J* = 7.5 Hz, 1H; Ar-H), 6.05 (d, *J* = 3.2 Hz, 1H; Fu-H), 6.02 (d, *J* = 3.2 Hz, 1H; Fu-H), 4.84 (s, 2H; O-CH₂), 4.39 (s, 2H; N-CH₂), 3.94 (s, 3H; O-CH₃). ¹³C NMR (125 MHz, acetone-*d*₆): δ 179.2, 167.3, 159.0, 155.9, 149.0, 142.3, 141.4 (2C), 139.2, 135.7, 132.6, 129.5, 129.1 (2C), 128.9 (2C), 128.5 (2C), 128.0, 122.8 (2C), 120.9, 119.5, 111.7, 110.3, 107.4, 56.4, 55.3, 47.8. HRMS (ESI, *m/z*): Calculated for C₂₉H₂₈N₃O₆S₂ [M + H]⁺ 578.1414; found 578.1395 (3.3 ppm).

4.6.3. (*E*)-*N*-((4-(*N*-(2-Hydroxybenzyl)-*N*-phenylsulfamoyl)phenyl)carbamoithioyl)-3-(2-methoxyphenyl)acrylamide (6cv**)**—The product precipitated as a yellow solid. Yield (39 mg, 48%). ¹H NMR (400 MHz, CDCl₃): δ 8.62 (s, 1H, N-H), 8.07 (d, *J* = 15.6 Hz, 1H; Ar-CH=C), 8.03 (d, *J* = 8.7 Hz, 2H; Ar-H), 7.73 (d, *J* = 8.7 Hz, 2H; Ar-H), 7.50 (d, *J* = 8.0 Hz, 1H; Ar-H), 7.43 (t, *J* = 8.0 Hz, 1H; Ar-H), 7.27 (d, *J* = 2.3 Hz, 2H; Ar-H), 7.17–7.12 (m, 1H; Ar-H), 7.02 (d, *J* = 7.8 Hz, 1H; Ar-H), 6.99–6.96 (m, 3H; Ar-H), 6.90 (d, *J* = 7.3 Hz, 2H; Ar-H), 6.65 (d, *J* = 15.6 Hz, 1H; CH=CO), 6.63 (d, *J* = 4.6 Hz, 2H; Ar-H), 4.71 (s, 2H; N-CH₂), 3.95 (s, 3H; O-CH₃). ¹³C

NMR (100 MHz, acetone- d_6): δ 179.2, 167.3, 159.0, 155.0, 142.4, 141.4, 139.5, 135.3, 132.6, 129.9, 129.5, 128.8 (2C), 128.7 (2C), 128.6, 128.5 (2C), 127.6, 122.9 (2C), 122.9, 122.4, 119.5, 119.5, 115.2, 111.7, 55.3, 48.7. **HRMS** (ESI, m/z): Calculated for $C_{30}H_{28}N_3O_5S_2$ $[M + H]^+$ 574.1465; found 574.1449 (2.8 ppm).

4.6.4. (E)-N-((4-(N-(3-Hydroxybenzyl)-N-phenylsulfamoyl)phenyl)carbamothioyl)-3-(2-methoxyphenyl)acrylamide (6dv)

—The product precipitated as a yellow solid. Yield (32 mg, 44%). **1H NMR** (400 MHz, $CDCl_3$): δ 8.62 (s, 1H, N-H), 8.06 (d, J = 15.6 Hz, 1H; Ar-CH=C), 7.97 (d, J = 8.7 Hz, 2H; Ar-H), 7.67 (d, J = 8.7 Hz, 2H; Ar-H), 7.50 (dd, J = 1.8, 8.0 Hz, 1H; Ar-H), 7.43 (t, J = 8.0 Hz, 1H; Ar-H), 7.22 (dd, J = 1.8, 5.0 Hz, 2H; Ar-H), 7.07 (t, J = 7.8 Hz, 1H; Ar-H), 7.03-6.96 (m, 4H; Ar-H), 6.75-6.72 (m, 2H; Ar-H), 6.67-6.65 (m, 1H; Ar-H), 6.64 (d, J = 15.6 Hz, 1H; CH=CO), 4.70 (s, 1H; O-H), 4.68 (s, 2H; N-CH₂), 3.94 (s, 3H; O-CH₃). **^{13}C NMR** (100 MHz, acetone- d_6): δ 179.2, 167.3, 159.0, 157.5, 142.4, 141.4, 139.3, 138.2, 135.4, 132.6, 129.5, 129.4, 128.9 (2C), 128.8 (2C), 128.4 (2C), 127.7, 122.9 (2C), 122.8, 120.9, 119.5, 119.4, 115.2, 114.5, 111.7, 55.3, 54.1. **HRMS** (ESI, m/z): Calculated for $C_{30}H_{28}N_3O_5S_2$ $[M + H]^+$ 574.1465; found 574.1438 (4.7 ppm).

4.6.5. (E)-N-((4-(N-(4-Hydroxybenzyl)-N-phenylsulfamoyl)phenyl)carbamothioyl)-3-(2-methoxyphenyl)acrylamide (6ev)

—The product precipitated as a yellow solid. Yield (104 mg, 54%). **1H NMR** (400 MHz, DMSO- d_6): δ 11.76 (s, 1H; N-H), 9.31 (s, 1H; N-H), 7.99 (d, J = 8.70 Hz, 2H; Ar-H), 7.94 (d, J = 16.0 Hz, 1H; Ar-CH=C), 7.63 (d, J = 8.7 Hz, 2H; Ar-H), 7.54 (dd, J = 1.4, 7.8 Hz, 1H; Ar-H), 7.44 (dd, J = 7.3, 7.8 Hz, 1H; Ar-H), 7.23-7.09 (m, 6H; Ar-H), 7.03 (d, J = 7.3 Hz, 1H; Ar-H), 6.99-6.95 (m, 5H; Ar-H), 6.56 (d, J = 8.2 Hz, 2H; Ar-H), 4.64 (s, 2H; N-CH₂), 3.87 (s, 3H; O-CH₃). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 178.1, 167.3, 142.3, 141.6, 141.4, 135.9, 133.7, 131.8, 129.8, 129.5, 129.1 (2C), 129.0, 128.8 (2C), 128.2, 127.6, 126.8 (2C), 125.1, 123.3, 122.9 (2C), 65.0, 38.3. **HRMS** (ESI, m/z): Calculated for $C_{30}H_{28}N_3O_5S_2$ $[M + H]^+$ 574.1465; found 574.1452 (2.2 ppm).

4.6.6. (E)-3-(2-Methoxyphenyl)-N-((4-(N-methyl-N-phenylsulfamoyl)phenyl)carbamothioyl)acrylamide (6fv)

—The product precipitated as a yellow solid. Yield (25 mg, 46%). **1H NMR** (500 MHz, acetone- d_6): δ 8.05 (d, J = 15.5 Hz, 1 H, Ar-CH=), 7.95 (d, J = 8.6, 2H, Ar-H), 7.56 (d, J = 8.6, 2H, Ar-H), 7.49 (dd, J = 1.7, 8.0 Hz, 1H, Ar-H), 7.42 (dd, J = 1.7, 8.0 Hz, 1H, Ar-H), 7.30 (m, 3H, Ar-H), 7.12 (s, 1 H, Ar-H), 7.10 (d, J = 7.5 Hz, 1 H, Ar-H), 7.00 (t, J = 7.5 Hz, 1 H, Ar-H), 6.96 (d, J = 8.6 Hz, 1 H, Ar-H), 6.66 (d, J = 15.5 Hz, 1 H, C=CHCO), 3.19 (s, 3H; N-CH₃), 3.94 (s, 3H; O-CH₃). **^{13}C NMR** (125 MHz, DMSO- d_6): δ 179.4, 167.4, 158.9, 142.6, 141.6, 140.8, 133.3, 133.1, 129.8, 129.5 (2C), 128.8 (2C), 127.8, 126.8 (2C), 123.9 (2C), 122.9, 121.4, 120.5, 112.5, 56.2, 38.5. **HRMS** (ESI, m/z): Calculated for $C_{24}H_{24}N_3O_4S_2$ $[M + H]^+$ 482.1203; found 482.1184 (3.9 ppm).

4.6.7. (E)-N-((4-(N-(2-Hydroxyethyl)-N-phenylsulfamoyl)phenyl)carbamothioyl)-3-(2-methoxyphenyl)acrylamide (6gv)

—The product precipitated as a yellow solid. Yield (58%). **1H NMR** (500 MHz, acetone-

d₆): δ 10.54 (s, 1H; N-H), 8.13 (d, J = 15.8 Hz, 1H; Ar-CH=C), 8.08 (d, J = 8.6 Hz, 2H; Ar-H), 7.64-7.61 (m, 3H; Ar-H), 7.44 (d, J = 7.7 Hz, 1H; Ar-H), 7.35-7.29 (m, 3H; Ar-H), 7.19 (d, J = 15.8 Hz, 1H; CH=CO), 7.14-7.10 (m, 3H; Ar-H), 7.01 (t, J = 7.5 Hz, 1H; Ar-H), 3.94 (s, 3H; O-CH₃), 3.83 (t, J = 5.7 Hz, 1H; OH), 3.73 (t, J = 6.3 Hz, 2H, N-CH₂), 3.54 (q, J = 6.0 Hz, 2H; O-CH₂). **¹³C NMR** (125 MHz, acetone-d₆) δ 179.2, 167.3, 159.0, 142.3, 141.3, 139.9, 135.5, 132.6, 129.5, 129.1 (2C), 129.0 (2C), 128.4 (2C), 127.9, 122.8 (2C), 120.9 (2C), 119.5, 111.7 (2C), 59.6, 55.3, 53.2. **HRMS** (ESI, m/z): Calculated for C₂₅H₂₆N₃O₅S₂ [M + H]⁺ 512.1308; found 512.1287 (4.2 ppm).

4.6.8. (*E*)-3-(2-Methoxyphenyl)-*N*-((4-(*N*-phenylsulfamoyl)phenyl)carbamothioyl)acrylamide (6hv)—

The product precipitated as a yellow solid. Yield (21 mg, 38%). **¹H NMR** (500 MHz, acetone-d₆) δ 8.10 (d, J = 15.8 Hz, 1H; Ar-CH=C), 8.02 (d, J = 8.6 Hz, 2H; Ar-H), 7.80 (d, J = 8.6 Hz, 2H; Ar-H), 7.59 (dd, J = 1.7, 7.7 Hz, 2H; Ar-H), 7.42 (d, J = 8.1 Hz, 1H; Ar-H), 7.25-7.20 (m, 3H; Ar-H), 7.15 (d, J = 15.8 Hz, 1H; CH=CO), 7.08 (d, J = 8.1 Hz, 1H; Ar-H), 7.07-7.03 (m, 2H; Ar-H), 7.01 (t, J = 7.5 Hz, 1H; Ar-H), 3.91 (s, 3H; O-CH₃). **¹³C NMR** (125 MHz, acetone-d₆) δ 179.2, 167.2, 159.0, 142.3, 141.3, 137.9, 136.7, 132.6, 129.5, 129.2 (2C), 127.9 (2C), 124.6, 122.9 (2C), 122.8, 120.9 (2C), 119.5, 111.7 (2C), 55.3. **HRMS** (ESI, m/z): Calculated for C₂₃H₂₂N₃O₄S₂ [M + H]⁺ 468.1046; found 468.1028 (3.9 ppm).

4.6.9. (*E*)-3-(2-Methoxyphenyl)-*N*-((4-(*N*-methyl-*N*-(pyridin-4-yl)sulfamoyl)phenyl)carbamothioyl)acrylamide (6iv)—

Purification was done via recrystallization using methanol. Yield (12 mg, 15%). **¹H NMR** (500 MHz, CDCl₃) δ 8.78 (s, 1H; N-H), 8.53 (dd, J = 1.7, 4.6 Hz, 2H; Ar-H), 8.06 (d, J = 15.8 Hz, 1H; Ar-CH=C), 7.97 (d, J = 8.9 Hz, 2H; Ar-H), 7.60 (d, J = 8.6 Hz, 2H; Ar-H), 7.49 (dd, J = 1.7, 7.5 Hz, 1H; Ar-H), 7.43 (dd, J = 1.7, 7.7 Hz, 1H; Ar-H), 7.18 (dd, J = 1.7, 4.7 Hz, 2H; Ar-H), 7.00 (t, J = 7.5 Hz, 1H; Ar-H), 6.96 (d, 8.6 Hz, 1H; Ar-H), 6.65 (d, J = 15.8 Hz, 1H; C=CH-CO), 3.93 (s, 3H; N-CH₃). **¹³C NMR** (125 MHz, CDCl₃) δ 178.5, 166.8, 159.2, 150.7 (2C), 148.8, 143.5, 142.4, 133.2, 132.9, 130.9, 128.4 (2C), 123.1 (2C), 122.4, 121.0, 118.6, 118.3 (2C), 111.4, 55.7, 36.7. **HRMS** (ESI, m/z): Calculated for C₂₃H₂₃N₄O₄S₂ [M + H]⁺ 483.1155; found 483.1134 (4.4 ppm).

4.6.10. (*E*)-*N*-((4-(*N*-(2-Hydroxyethyl)sulfamoyl)phenyl)carbamothioyl)-3-(2-methoxyphenyl)acrylamide (6jv)—

The product was isolated after column chromatography using 5% methanol in CH₂Cl₂. Yield (20.0 mg, 19% yield). **¹H NMR** (500 MHz, DMSO-d₆) δ 12.95 (s, 1H; N-H), 11.70 (s, 1H; N-H), 7.95-7.92 (m, 3H; Ar-H), 7.79 (d, J = 9.2 Hz, 2H; Ar-H), 7.59 (t, J = 6.1 Hz, 1H; Ar-H), 7.54 (dd, J = 1.5, 7.6 Hz, 1H; Ar-H), 7.43 (dt, J_d = 1.5, J_t = 7.6 Hz, 1H; Ar-H), 7.13 (d, J = 16.1 Hz, 1H; Ar-CH=C), 7.10 (d, J = 7.6 Hz, 1H; Ar-H), 7.02 (t, J = 7.6 Hz, 1H; Ar-H), 4.66 (t, J = 6.1 Hz, 1H; O-H), 3.87 (s, 3H; O-CH₃), 3.35 (q, J = 6.1 Hz, 2H; O-CH₂), 2.78 (q, J = 6.1 Hz, 2H; N-CH₂). **¹³C NMR** (125 MHz, DMSO-d₆) δ 179.7, 167.4, 158.9, 141.7, 140.7, 138.0, 133.0, 129.8, 127.7 (2C), 124.6 (2C), 122.8, 121.5, 120.6, 112.4, 60.5, 56.2, 45.6. **HRMS** (ESI, m/z): Calculated for C₁₉H₂₂N₃O₅S₂ [M + H]⁺ 436.0995; found 574.1452 (1.7 ppm).

4.6.11. (*E*)-*N*-((4-(*N*-(2,3-Dihydroxypropyl)sulfamoyl)phenyl)carbamothioyl)-3-(2-methoxyphenyl)acrylamide (6kv)—The product precipitated as a yellow solid. Yield (77 mg, 59%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.95 (s, 1H; N-H), 11.73 (s, 1H; N-H), 7.95-7.91 (m, 3H; Ar-CH=C and Ar-H), 7.78 (d, *J* = 8.7 Hz, 2H; Ar-H), 7.58-7.52 (m, 2H; Ar-H), 7.43 (t, *J* = 7.3 Hz, 2H; Ar-H), 7.13 (d, *J* = 15.6 Hz, 1H; C=CH), 7.10 (d, *J* = 8.7 Hz, 1H; Ar-H), 7.01 (t, *J* = 7.3 Hz, 1H; Ar-H), 4.77 (d, *J* = 5.0 Hz, 1H; O-H), 4.53 (t, *J* = 6.0 Hz, 1H; O-H), 3.86 (s, 3H; O-CH₃), 3.43 (dq, *J*_d = 6.9, *J*_q = 5.5 Hz, 1H; O-CH), 3.23 (m, 2H; O-CH₂), 2.85 (m, 1H; N-CH₂), 2.57 (m, 1H; N-CH₂). ¹³C NMR (125 MHz, DMSO-*d*₆): δ 179.6, 167.4, 158.9, 141.7, 140.8, 138.0, 133.1, 129.9, 127.8 (2C), 124.5 (2C), 122.8, 121.4, 120.5, 112.5, 70.9, 64.0, 56.2, 46.6. HRMS (ESI, *m/z*): Calculated for C₂₀H₂₄N₃O₆S₂ [M + H]⁺ 466.1101; found 466.1088 (2.8 ppm).

4.6.12. (*E*)-*N*-((4-(*N*-(3,4-Dimethylisoxazol-5-yl)sulfamoyl)phenyl)carbamothioyl)-3-(2-methoxyphenyl)acrylamide (6lv)—The product precipitated as a pure yellow solid. Yield (63%). ¹H NMR (400 MHz, CDCl₃): δ 8.69 (s, 1H; N-H), 8.05 (d, *J* = 15.6 Hz, 1H; Ar-CH=C), 8.02 (d, *J* = 8.7 Hz, 2H; Ar-H), 7.83 (d, *J* = 8.7 Hz, 2H; Ar-H), 7.49 (d, *J* = 7.6 Hz, 1H; Ar-H), 7.42 (dt, *J*_d = 1.4, *J*_t = 8.0 Hz, 1H; Ar-H), 7.00 (t, *J* = 7.3 Hz, 1H; Ar-H), 6.96 (d, *J* = 8.4 Hz, 1H; Ar-H), 6.65 (d, *J* = 15.6 Hz, 1H; C=CHCO), 6.63 (bs, 1H; SO₂N-H), 3.93 (s, 3H; O-CH₃), 2.19 (s, 3H; Ar-CH₃), 1.92 (s, 3H; Ar-CH₃). ¹³C NMR (125 MHz, CDCl₃): δ 179.4, 167.2, 161.6, 159.0, 155.4, 142.8, 141.4, 137.0, 132.6, 129.5, 127.9, 123.3, 123.2, 122.8, 120.9, 119.5, 11.7, 106.5, 55.3, 9.9, 5.7. HRMS (ESI, *m/z*): Calculated for C₂₂H₂₃N₄O₅S₂ [M + H]⁺ 487.1104; found 487.1088 (3.4 ppm).

4.6.13. *N*-((4-(*N*-methyl-*N*-phenylsulfamoyl)phenyl)carbamothioyl)quinoline-3-carboxamide (6fw)—The product precipitated as a pure yellow solid. Yield (59 mg, 65%). ¹H NMR (500 MHz, acetone-*d*₆): δ 9.40 (d, *J* = 2.3 Hz, 1H; Ar-H), 9.23 (s, 1H; Ar-H), 8.26 (d, *J* = 8.6 Hz, 1H; Ar-H), 8.22 (d, *J* = 8.0 Hz, 1H; Ar-H), 8.10 (dd, *J* = 6.3, 8.6 Hz, 2H; Ar-H), 8.01 (d, *J* = 7.7 Hz, 1H; Ar-H), 7.80 (d, *J* = 7.5 Hz, 1H; Ar-H), 7.59 (d, *J* = 8.9 Hz, 2H; Ar-H), 7.35-7.27 (m, 3H; Ar-H), 7.15 (dd, *J* = 1.7, 8.3 Hz, 2H; Ar-H), 3.22 (s, 3H; N-CH₃). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 179.6, 167.4, 149.6, 149.5, 142.7, 141.6, 138.6, 133.5, 132.8, 130.2, 129.5 (2C), 129.3, 128.8 (2C), 128.3, 127.8, 126.8 (2C), 126.5, 125.6, 124.3 (2C), 38.5. HRMS (ESI, *m/z*): calculated for C₂₄H₂₁N₄O₃S₂ [M + H]⁺ 477.1050; found 477.1030 (4.1 ppm).

4.6.14. *N*-((4-(*N*-Methyl-*N*-phenylsulfamoyl)phenyl)carbamothioyl)quinoline-7-carboxamide (6fx)—Purification was done via recrystallization using a mixture of chloroform and hexane. Yield (8.0 mg, 11%). ¹H NMR (500 MHz, acetone-*d*₆): δ 9.02 (dd, *J* = 1.7, 4.0 Hz, 1H; Ar-H), 8.76 (s, 1H; Ar-H), 8.44 (dd, *J* = 1.2, 8.6 Hz, 1H; Ar-H), 8.14 (s, 2H), 8.11 (d, *J* = 8.6 Hz, 2H; Ar-H), 7.66 (dd, *J* = 4.0, 8.6 Hz, 1H; Ar-H), 7.59 (d, *J* = 8.9 Hz, 2H; Ar-H), 7.35-7.27 (m, 3H; Ar-H), 7.15 (d, *J* = 8.0 Hz, 2H; Ar-H), 3.22 (s, 3H; N-CH₃). ¹³C NMR (125 MHz, acetone-*d*₆): δ 179.0, 168.2, 152.1, 147.4, 142.4, 141.8, 135.9, 133.7, 132.8, 130.9, 130.7, 129.0, 128.9 (2C), 128.6 (2C), 127.3, 126.6 (2C), 124.8, 123.6, 123.2, 37.7. HRMS (ESI, *m/z*): Calculated for C₂₄H₂₁N₄O₃S₂ [M + H]⁺ 477.1050; found 477.1030 (4.1 ppm).

4.6.15. 6-(Hydroxymethyl)-*N*-((4-(*N*-methyl-*N*-phenylsulfamoyl)phenyl)carbamothioyl)-2-naphthamide (6fy)—The product precipitated as a yellow solid. Yield (13.25 mg, 48%). ¹H NMR (500 MHz, CDCl₃): δ 9.26 (s, 1H; N-H), 8.40 (s, 1H; Ar-H), 7.98-7.92 (m, 4H; Ar-H), 7.87 (dd, *J* = 1.4, 8.7 Hz, 1H; Ar-H), 7.57 (d, *J* = 8.7 Hz, 2H; Ar-H), 7.51 (dd, *J* = 1.8, 8.2 Hz, 1H; Ar-H), 7.33-7.27 (m, 3H; Ar-H), 7.10 (dd, *J* = 1.8, 6.9 Hz, 2H; Ar-H), 3.99 (t, *J* = 6.4 Hz, 2H; O-CH₂), 3.19 (s, 3H; N-CH₃), 3.08 (t, *J* = 6.4 Hz, 2H; Ar-CH₂). ¹³C NMR (100 MHz, CDCl₃): δ 178.1, 167.3, 141.7, 141.4, 140.5, 136.0, 133.8, 131.3, 129.7, 129.4, 129.2, 129.1 (2C), 129.0, 128.9 (2C), 127.7, 127.6, 126.8 (2C), 123.2, 123.0 (2C), 63.3, 39.5, 38.3. HRMS (ESI, *m/z*): Calculated for C₂₆H₂₄N₃O₄S₂ [M + H]⁺ 506.1203; found 506.1186 (3.3 ppm).

4.6.16. 6-(2-Hydroxyethyl)-*N*-((4-(*N*-methyl-*N*-phenylsulfamoyl)phenyl)carbamothioyl)-2-naphthamide (6fz)—The residue was purified by preparative HPLC using a Phenomenex Gemini-NX column C18 (250 × 21.20 mm, 110 Å, 5 μm spherical particle size). The column was perfused at a flow rate of 21.24 mL/min with a linear gradient from 60% (CH₃CN-H₂O) to 80% over 15 min. The compound eluted at 12.5 min. Yield (7.4 mg, 6%). ¹H NMR (500 MHz, CDCl₃): δ 9.26 (s, 1H; N-H), 8.40 (s, 1H; Ar-H), 7.98-7.92 (m, 4H; Ar-H), 7.87 (dd, *J* = 1.4, 8.7 Hz, 1H; Ar-H), 7.57 (d, *J* = 8.7 Hz, 2H; Ar-H), 7.51 (dd, *J* = 1.8, 8.2 Hz, 1H; Ar-H), 7.33-7.27 (m, 3H; Ar-H), 7.10 (dd, *J* = 1.8, 6.9 Hz, 2H; Ar-H), 3.99 (t, *J* = 6.4 Hz, 2H; O-CH₂), 3.19 (s, 3H; N-CH₃), 3.08 (t, *J* = 6.4 Hz, 2H; Ar-CH₂). ¹³C NMR (100 MHz, CDCl₃): δ 178.1, 167.3, 141.7, 141.4, 140.5, 136.0, 133.8, 131.3, 129.7, 129.4, 129.2, 129.1 (2C), 129.0, 128.9 (2C), 127.7, 127.6, 126.8 (2C), 123.2, 123.0 (2C), 63.3, 39.5, 38.3. HRMS (ESI, *m/z*): Calculated for C₂₇H₂₆N₃O₄S₂ [M + H]⁺ 520.1359; found 520.1339 (3.9 ppm).

4.6.17. *N*-((4-(*N*-phenyl-*N*-(Pyridin-4-ylmethyl)sulfamoyl)phenyl)carbamothioyl)quinoline-7-carboxamide (6ax)—The product precipitated as a yellow solid. Yield (80 mg, 63%). ¹H NMR (500 MHz, DMSO-*d*₆): δ 12.74 (s, 1H; N-H), 12.02 (s, 1H; N-H), 9.02 (dd, 1.5, 4.6 Hz, 1H; Ar-H), 8.65 (s, 1H; Ar-H), 8.46 (d, *J* = 8.4 Hz, 1H; Ar-H), 8.43 (d, *J* = 6.1 Hz, 2H; Ar-H), 8.12 (d, *J* = 8.4 Hz, 1H; Ar-H), 8.05 (d, *J* = 8.4 Hz, 3H; Ar-H), 7.69-7.65 (m, 3H; Ar-H), 7.29 (d, *J* = 5.4 Hz, 2H; Ar-H), 7.26 (d, *J* = 7.6 Hz, 2H; Ar-H), 7.23-7.20 (m, 1H; Ar-H), 7.11 (d, *J* = 6.9 Hz, 2H; Ar-H), 4.87 (s, 2H; N-CH₂). ¹³C NMR (125 MHz, DMSO-*d*₆): δ 179.6, 168.3, 152.5 (2C), 150.1 (2C), 147.1, 146.2, 142.9, 139.1, 136.5, 134.7, 133.4, 131.1, 130.8, 129.6 (2C), 129.1, 128.8 (2C), 128.7 (2C), 128.5, 125.7, 124.4, 124.1, 123.4 (2C), 53.2. HRMS (ESI, *m/z*): Calculated for C₂₉H₂₄N₅O₃S₂ [M + H]⁺ 554.1315; found 554.1298 (3.1 ppm).

4.6.18. *N*-((4-(*N*-((5-(Hydroxymethyl)furan-2-yl)methyl)-*N*-phenylsulfamoyl)phenyl)carbamothioyl)quinoline-7-carboxamide (6bx)—The product precipitated as yellow solid. Yield (45 mg, 34%). ¹H NMR (500 MHz, DMSO-*d*₆): δ 12.04 (s, 1H; N-H), 9.02 (dd, *J* = 1.4, 4.1 Hz, 1H; Ar-H), 8.64 (s, 1H; Ar-H), 8.46 (d, *J* = 8.2 Hz, 1H; Ar-H), 8.11 (d, *J* = 8.7 Hz, 1H; Ar-H), 8.04 (dd, *J* = 1.7, 8.7 Hz, 1H; Ar-H), 7.99 (d, *J* = 8.7 Hz, 2H; Ar-H), 7.66 (dd, *J* = 4.1, 8.2 Hz, 1H; Ar-H), 7.62 (d, *J* = 8.7 Hz, 2H; Ar-H), 7.27-7.25 (m, 3H; Ar-H), 7.00 (dd, *J* = 2.3, 7.8 Hz, 2H; Ar-H), 6.04 (d, *J* = 3.2 Hz, 1H; Fur-H), 6.00 (d, *J* = 3.2 Hz, 1H; Fur-H), 5.17 (t, *J* = 6.0 Hz, 1H; O-H), 4.78 (s, 2H; N-CH₂),

4.24 (d, J = 6.0, 2H; O-CH₂). **¹³C NMR** (125 MHz, DMSO-*d*₆): δ 179.6, 168.2, 156.1, 152.1, 148.8, 142.7, 139.0, 137.4, 135.4, 133.7, 130.8, 130.4, 129.4 (2C), 129.2, 129.1 (2C), 128.7 (2C), 128.7 (2C), 128.5, 126.0, 124.3, 124.1, 110.8, 108.0, 56.1, 48.0. **HRMS** (ESI, *m/z*): Calculated for C₂₉H₂₅N₄O₅S₂ [*M* + *H*]⁺ 573.1261; found 573.1243 (3.1 ppm).

4.6.19. *N*-((4-(*N*-(4-Hydroxybenzyl)-*N*-

phenylsulfamoyl)phenyl)carbamothioyl)quinoline-7-carboxamide (6ex)—The product precipitated as a yellow solid. Yield (42.5 mg, 29%). **¹H NMR** (400 MHz, DMSO-*d*₆): δ 12.73 (s, 1H; N-H), 12.04 (s, 1H; N-H), 9.13 (bs, 1H; O-H), 9.03 (dd, J = 1.8, 4.1 Hz, 1H; Ar-H), 8.65 (s, 1H; Ar-H), 8.48 (d, J = 7.8 Hz, 1H; Ar-H), 8.12 (d, J = 8.2 Hz, 1H; Ar-H), 8.07-8.01 (m, 3H; Ar-H), 7.69-7.64 (m, 3H; Ar-H), 7.24-7.16 (m, 3H; Ar-H), 6.99-6.96 (m, 4H; Ar-H), 6.56 (d, J = 8.2 Hz, 2H; Ar-H), 4.65 (s, 2H, N-CH₂). **¹³C NMR** (125 MHz, DMSO-*d*₆): δ 179.5, 157.4, 152.2, 147.1, 142.6, 139.1, 136.7, 135.5, 133.4, 131.1, 130.8, 130.1 (2C), 129.3 (2C), 129.1 (2C), 128.6 (2C), 128.2, 126.6, 125.7, 124.4 (2C), 124.0, 115.6, 53.8. **HRMS** (ESI, *m/z*): Calculated for C₃₀H₂₅N₄O₄S₂ [*M* + *H*]⁺ 569.1312; found 569.1295 (2.9 ppm).

4.6.20. *N*-((4-(*N*-(2-Hydroxyethyl)-*N*-

phenylsulfamoyl)phenyl)carbamothioyl)quinoline-7-carboxamide (6gx)—The product precipitated as a yellow solid. Yield (24.3 mg, 55%). **¹H NMR** (500 MHz, CDCl₃): δ 9.42 (s, 1H; N-H), 9.07 (dd, J = 1.7, 4.0 Hz, 1H; Ar-H), 8.68 (s, 1H; Ar-H), 8.27 (dd, J = 1.2, 8.6 Hz, 1H; Ar-H), 8.05-8.02 (m, 2H; Ar-H), 8.00 (d, J = 9.2 Hz, 2H; Ar-H), 7.66 (d, J = 9.2 Hz, 2H; Ar-H), 7.59 (dd, J = 4.0, 8.0 Hz, 1H; Ar-H), 7.37-7.32 (m, 3H; Ar-H), 7.11-7.09 (m, 2H; Ar-H), 3.75 (m, 2H; O-CH₂), 3.68 (m, 2H; N-CH₂). **¹³C NMR** (125 MHz, CDCl₃): δ 177.9, 166.7, 152.4, 147.4, 141.7, 139.3, 136.1, 135.4, 132.0, 131.2, 120.0, 129.6, 129.5 (2C), 129.0 (2C), 128.7 (2C), 128.6, 124.1, 123.8, 123.2 (2C), 60.5, 53.7. **HRMS** (ESI, *m/z*): Calculated for C₂₅H₂₃N₄O₄S₂ [*M* + *H*]⁺ 507.1155; found 507.1145 (2.0 ppm).

4.6.21. 6-(2-hydroxyethyl)-*N*-((4-(*N*-((5-(hydroxymethyl)furan-2-yl) methyl)-*N*-phenylsulfamoyl)phenyl)carbamothioyl)-2-naphthamide (6bz)—The product was

purified by column chromatography (40% EtOAc: hexane) and then recrystallized using acetone and hexane. Yield (5.4 mg, 3%). **¹H NMR** (500 MHz DMSO-*d*₆): δ 12.86 (s, 1H; N-H), 11.86 (s, 1H, N-H), 8.7 (s, 1H, Ar-H), 8.13 – 7.94 (m, 5H; Ar-H), 7.92 (s, 1H; Ar-H), 7.67 (d, J = 8.7 Hz, 2H; Ar-H), 7.61 (dd, J = 8.6, 1.6 Hz, 1H; Ar-H), 7.34 – 7.24 (m, 3H, Ar-H), 7.04 (dd, J = 7.9, 2.0 Hz, 2H), 6.08 (d, J = 3.0 Hz, 1H; Ar-H), 6.04 (d, J = 3.0 Hz, 1H; Ar-H), 5.17 (t, J = 5.8 Hz, 1H; OH), 4.82 (s, 2H), 4.28 (d, J = 5.8 Hz, 2H; CH₂OH), 4.00 (t, J = 6.9 Hz, 2H), 3.26 (t, J = 6.9 Hz, 2H). **¹³C NMR** (100 DMSO-*d*₆): δ 179.7, 168.7, 156.1, 148.8, 142.7, 141.3, 138.9, 135.7, 135.2, 130.8, 130.5, 129.7, 129.6, 129.4 (2C), 129.1 (2C), 128.8, 128.7 (2C), 128.5, 128.2, 127.4, 125.0, 124.3 (2C), 110.8, 108.0, 65.5, 62.3, 56.1, 47.9. **HRMS** (ESI, *m/z*): Calculated for C₃₂H₂₉N₃O₆S₂ [*M* + *H*]⁺ 616.1576; found 616.1559 (2.8 ppm).

4.6.22. 6-(2-hydroxyethyl)-*N*-((4-(*N*-(2-hydroxyethyl)-*N*-phenylsulfamoyl)phenyl)carbamothioyl)-2-naphthamide (6gz)—The residue was purified by

preparative HPLC using a Phenomenex Gemini-NX column C18 (250 × 21.20 mm, 110 Å, 5

μm spherical particle size). The column was perfused at a flow rate of 21.24 mL/min with a linear gradient from 60% (CH₃CN-H₂O) to 80% over 15 min. The compound eluted at 14.96 min. Yield (6.1 mg, 9%). ¹H NMR (500 MHz, Chloroform-d) δ 9.27 (s, 1H), 8.41 (d, *J* = 1.4 Hz, 1H; Ar-H), 8.01 (d, *J* = 8.8 Hz, 2H; Ar-H), 7.96 (dd, *J* = 8.4, 6.3 Hz, 2H; Ar-H), 7.90 (dd, *J* = 8.7, 1.9 Hz, 1H; Ar-H), 7.79 (br. s, 1H, Ar-H), 7.66 (d, *J* = 8.8 Hz, 2H; Ar-H), 7.54 (dd, *J* = 8.4, 1.7 Hz, 1H; Ar-H), 7.38 – 7.32 (m, 4H; Ar-H), 7.12 – 7.08 (m, 2H; Ar-H), 4.01 (t, *J* = 6.5 Hz, 2H), 3.74 (t, *J* = 5.3 Hz, 2H), 3.70 – 3.64 (m, 4H), 3.25 – 3.18 (m, 3H), 3.10 (t, *J* = 6.4 Hz, 5H), 1.44 (dt, *J* = 14.8, 7.4 Hz, 4H), 1.01 (t, *J* = 7.3 Hz, 5H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 179.7, 168.7, 142.6, 139.6 (2C), 135.5, 135.3, 131.1, 130.5, 130.02, 129.6 (2C), 129.2, 129.2 (2C), 129.0, 128.5, 128.4 (2C), 128.3, 127.8, 125.3, 124.3 (2C), 59.2, 53.3, 45.7, 38.8. HRMS (ESI, *m/z*): Calculated for C₂₈H₂₇N₃O₅S₂ [M + Na]⁺ 572.12898; found 572.12733 (2.9 ppm).

4.7. Analysis of GPR55 agonist activity

Agonist activity was evaluated using DiscoverX PathHunter® Complementation technology. CHO-K1 cells stably expressing GPR55 (fused to a β-galactosidase enzyme fragment), and β-arrestin (fused to an N-terminal deletion β-galactosidase mutant), were grown in selection media and were passaged up to 10 times according to manufacturer protocols. In the presence of agonist and PathHunter® detection reagents containing β-galactosidase substrate, a chemiluminescent signal is generated due to the forced complementation of the GPR55 fused β-galactosidase fragment and the β-arrestin fused N-terminal deletion mutant fragment of β-galactosidase. In this complementation assay, a chemiluminescent signal arises due to a 1:1 interaction between the GPR55- β-galactosidase enzyme fragment and the mutant β-galactosidase-β-arrestin fragment in the presence of substrate at room temperature. The cells were licensed from DiscoverX (Fremont, CA), catalog # 93-0245C2. The beta arrestin reporter sequence is proprietary. Assays were conducted according to the manufacturer's instructions using concentrations of ligands ranging from 0.5 nM to 30 μM. The chemiluminescence signal was measured using a Perkin Elmer Envision plate reader for 1 second. Experiments were run in triplicate and repeated at a minimum of 3 times. Ligand readings, expressed as relative luminescence units, were subtracted from corresponding vehicle readings and analyzed in GraphPad Prism version 5.0 (GraphPad, San Diego, CA) to obtain EC₅₀ values (Figures 2 and 3). LPI was used as the positive control and vehicle served as the negative control.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Chemical structures of LPI (1), CID1792197 (2), CID1172084 (3) and CID2440433 (4).

Figure 2.
 EC_{50} Activities of First Generation GPR55 Agonists. Confidence intervals included parenthetically for compounds with EC_{50} values less than 1 micromolar.

Figure 3.
EC₅₀ Activities of Second Generation GPR55 Agonists. Confidence intervals included parenthetically for compounds with EC₅₀ values less than 1 micromolar.

Scheme 1.
Retrosynthetic scheme of GPR55 Agonists

Scheme 2.

Synthetic scheme for synthesis of alkylphenyl amines **8a–8e**. Reagents and conditions: (a) aniline, ethanol, 80 °C (28–56%); (b) i) NaBH₄, MeOH ii) HCl (52–72%); (c) i) ethanol, 80 °C ii) NaBH₄, MeOH iii) HCl (34–96%).

Scheme 3.

Synthesis of *p*-nitro and *p*-amino benzene sulfonamides. Reagents and conditions: (a) *p*-nitrophenyl sulfonyl chloride, pyridine, CH₂Cl₂ (5–91%); (b) Pd/C, H₂, MeOH (12–92%).

Scheme 4.

Synthesis of naphthoic acid derivatives. Reagents and conditions: (a) DIBAL-H (3 equiv.), THF, -40°C - rt, 8 hr (90% yield of **20**); (b) DIBAL-H (3 equiv.), -78°C , toluene, 0.03 sec (in flow; 95% yield of a 1:1.6 mixture of **13** and **14**); (c) MnO_2 , CHCl_3 (47%); (d) 1) oxalyl chloride, DMSO; 2) Et_3N (60%); (e) $\text{Ph}_3\text{PCH}_3\text{I}$, NaH, THF (65%); (f) 1) $\text{BH}_3\text{-THF}$, THF; 2) NaOH, H_2O_2 (77%); (g) TBSCl, DMAP, Et_3N (53% of **17**); (h) TBSCl, DMAP, Et_3N (84% of **18**); (i) 1) $n\text{BuLi}$, THF; 2) CO_2 ; 3) H_3O^+ (19% for **5y**; 42% for **5z**); (j) Et_3NHCl , Zn, NiBr_2 , bipy, NaI, DMPU, pyridine, ethylene oxide (66%); (k) TBSCl, imidazole, DMAP (5 mol %), CH_2Cl_2 ; then LiOH(aq) /THF, 50°C (62% yield of **5z**).

- 6av** R¹=Ph, R²=CH₂(4-pyridinyl), R³=2-(2'-methoxy)phenyl acrylyl
6bv R¹=Ph, R²=CH₂((5-CH₂OH)-2-furyl), R³=2-(2'-methoxy)phenyl acrylyl
6cv R¹=Ph, R²=CH₂(2-phenol), R³=2-(2'-methoxy)phenyl acrylyl
6dv R¹=Ph, R²=CH₂(3-phenol), R³=2-(2'-methoxy)phenyl acrylyl
6ev R¹=Ph, R²=CH₂(4-phenol), R³=2-(2'-methoxy)phenyl acrylyl
6fv R¹=Ph, R²=CH₃, R³=2-(2'-methoxy)phenylacrylyl
6gv R¹=Ph, R²=CH₂CH₂OH, R³=2-(2'-methoxy)phenyl acrylyl
6hv R¹=Ph, R²=H, R³=2-(2'-methoxy)phenyl acrylyl
6iv R¹=4-pyridinyl, R²=CH₃, R³=2-(2'-methoxy)phenyl acrylyl
6jv R¹=H, R²=CH₂CH₂OH, R³=2-(2'-methoxy)phenyl acrylyl
6kv R¹=H, R²=CH₂CHOHCH₂OH, R³=2-(2'-methoxy)phenyl acrylyl
6lv R¹=H, R²=3,4,-dimethylisoxazoyl, R³=2-(2'-methoxy)phenyl acrylyl
6fw R¹=Ph, R²=CH₃, R³=3-quinolinyl
6fx R¹=Ph, R²=CH₃, R³=7-quinolinyl
6fy R¹=Ph, R²=CH₃, R³=6-(2-hydroxymethyl)-2-naphthoyl
6fz R¹=Ph, R²=CH₃, R³=6-(2-hydroxyethyl)-2-naphthoyl
6ax R¹=Ph, R²=CH₂(4-pyridinyl), R³=7-quinolinyl
6bx R¹=Ph, R²=CH₂((5-CH₂OH)-2-furyl), R³=7-quinolinyl
6ex R¹=Ph, R²=CH₂(4-phenol), R³=7-quinolinyl
6gx R¹=Ph, R²=CH₂CH₂OH, R³=7-quinolinyl
6bz R¹=Ph, R²=CH₂((5-CH₂OH)-2-furyl), R³=6-(2-hydroxyethyl)-2-naphthoyl
6gz R¹=Ph, R²=CH₂CH₂OH, R³=6-(2-hydroxyethyl)-2-naphthoyl

Scheme 5.

Synthesis of analogues **6**. Reagents and conditions: (a) SOCl₂, 80 °C, 3 hrs; (b) i) KSCN, CH₃CN, -10 °C -r.t., 3 hrs; ii) **7a-7l**, 24 hrs (6-65%).