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Design, synthesis and *in vitro* antitumor evaluation of novel diaryl urea derivatives bearing sulfonamide moiety

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A novel series of diaryl urea derivatives bearing sulfonamide moiety have been designed and synthesized. Their *in vitro* antitumor effect against human cancer cell lines MX-1, A375, HepG2, Ketr3 and HT-29 was screened and evaluated by the standard MTT assay with sorafenib as the positive control. Some of the compounds showed significant inhibitory activity against multiple cell lines compared to sorafenib. In particular, 2,6-dimethyl-4-{6-[3-(4-chloro-3-(trifluoromethyl)phenyl)urea]naphthalene-2-yl}sulfonyl morpholine (**10d**) was found to be the most potent against A375, HepG2 and Ketr3 with IC_{50} values of 0.65–0.97 μmol/L, which were 5–20-fold more potent than sorafenib. Compound **10d** emerged as a valuable lead for further optimization.

diaryl urea derivatives, sulfonamide, sorafenib, antitumor activity

1 Introduction

Sorafenib, a diaryl urea small molecule inhibitor of several kinases involved in tumor proliferation and tumor angiogenesis including Raf, VEGFR and PDGFR [1], was approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced renal cell carcinoma (RCC) [1] and unresectable hepatocellular carcinoma (HCC) [2] in 2005 and 2007 respectively. Due to its advantage of multi-mechanism, broad-spectrum anticancer activity and good tolerability in combination trials, there remains great interest in designing and developing novel diaryl urea compounds with more potent antitumor activity [3–8].

The crystal structure of sorafenib in complex with B-raf (PDB:1UWH) served as a surrogate for structure-based optimization [9]. It has been shown that the urea moiety is highly conservative (fragment B) shared by most type 2 kinase inhibitors. The substituted phenyl ring (fragment A) contributes mainly to the kinase selectivity of sorafenib, the phenyl ring between the urea moiety and the ether bond interacts with kinase through hydrophobic interaction (fragment C), and the *N*-methyl-4-picolinamide (fragment D) binds to the hinge region of kinase which is highly mobile [10, 11]. This motif (frogment D) has been targeted in the design of most kinase inhibitors. A lot of research has been focused on the structural modification of *N*-methyl-4-picolinamide moiety in the sorafenib scaffold in order to enhance the antitumor activity, especially against melanoma, and to improve the physiological property [8, 12–16].

Not only were the sulfonamide derivatives known for their antibacterial activity, but they also emerged as an important class of anticancer agents which interact with a wide range of different cellular targets [17, 18]. The sulfonamide moiety has attracted our considerable attention as a new hinge-binding group instead of *N*-methyl-4-picolinamide (fragment D) in terms of novelty, and chemical modification accessibility.

Our initial effort was to design novel diphenyl urea derivatives containing the sulfonamide moiety (**4a–i**) based on the structural modification of sorafenib, with the aim to obtain more potent antitumor agents. Literature research re-

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vealed that the replacement of phenyl ring (fragment C) with a large naphthyl ring could bring favorable hydrophobic binding interaction [4, 11]. Therefore, the benefit of the naphthyl system prompted us to design a series of phenyl-naphthyl urea derivatives (**10a–i**), not only to improve the antitumor activity but also to understand the effect of the molecular size on the activity by comparison with the diphenyl urea series. Finally, the amino group as part of the sulfonamide moiety was selected from α-methylbenzylamine, cyclic alkyl amine including *N*- or *O*- containing heterocyclic amine in order to evaluate their impact on activity.

Herein, we report the discovery of a new series of diaryl urea derivatives containing the sulfonamide moiety (Figure 1) based on the structural features of sorafenib with the intent of improving the antitumor activity. All target compounds were evaluated for their *in vitro* antitumor activity against five cancer cell lines, including human breast cancer (MX-1), human melanoma cancer (A375), human liver cancer (HepG2), human kidney cancer (Ketr3) and human colon cancer (HT-29) cell lines, using the standard 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.

2 Results and discussion

2.1 Chemistry

The synthesis of diphenyl urea sulfonamide derivatives **4a–i** was outlined in Scheme 1. Condensation of 4-nitro-benzenesulfonyl chloride (**1**) with corresponding amines in the presence of triethylamine, followed by catalytic hydrogenation with 10% Pd/C to give **3a–c** in the yields of 83%–92%. Finally, condensation of **3a–c** with corresponding aryl isocyanates afforded the desired diphenyl urea derivatives **4a–i** [19].

The synthesis of phenyl-naphthyl urea sulfonamide derivatives **10a–i** was outlined in Scheme 2. Protection of 6-aminonaphthalene-2-sulfonic acid (**5**) by benzyl chloroformate (Cbz-Cl) in the presence of sodium carbonate gave *N*-Cbz protected compounds (**6**), then sulfonic acid was transferred to sulfonyl chloride (**7**) in the presence of thionyl chloride, followed by condensation with corresponding amine in the presence of triethylamine to obtain compounds **8a–c**. Then Cbz group of the amines **8a–c** was removed by catalytic hydrogenation with 10% Pd/C to give **9a–c**. Finally, condensation of **9a–c** with corresponding aryl isocyanates afforded the desired phenyl-naphthyl urea derivatives **10a–i**. The chemical structures of the compounds were confirmed by ^{1}H NMR, ^{13}C NMR and HR-MS and the results were presented in the experimental section.

2.2 Biological evaluation

The *in vitro* inhibitory activity of target compounds **4a–i**, **10a–i** against MX-1, A375, HepG2, Ketr3 and HT-29 cell lines was evaluated by MTT-based assay with sorafenib as

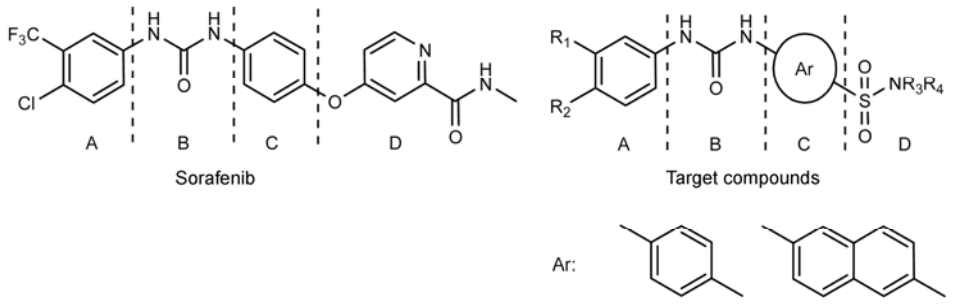
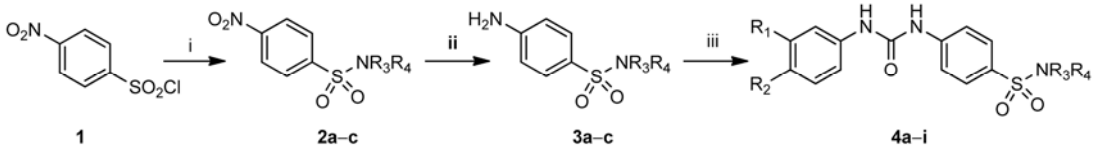


Figure 1 Structures of sorafenib and diaryl urea derivatives bearing sulfonamide moiety.



2a, 3a: NR_3R_4 = cyclobutylamino

2b, 3b: NR_3R_4 = (+/-)-1-phenylethylamino

2c, 3c: NR_3R_4 = 4-methylpiperidyl

4a: R_1 = CF_3, R_2 = Cl, NR_3R_4 = cyclobutylamino

4b: R_1 = CF_3, R_2 = H, NR_3R_4=cyclobutylamino

4c: R_1 = H, R_2 = OCH_3, NR_3R_4 = cyclobutylamino

4d: R_1 = CF_3, R_2 = Cl, NR_3R_4 = (+/-)-1-phenylethylamino

4e: R_1 = H, R_2 = CF_3, NR_3R_4 = (+/-)-1-phenylethylamino

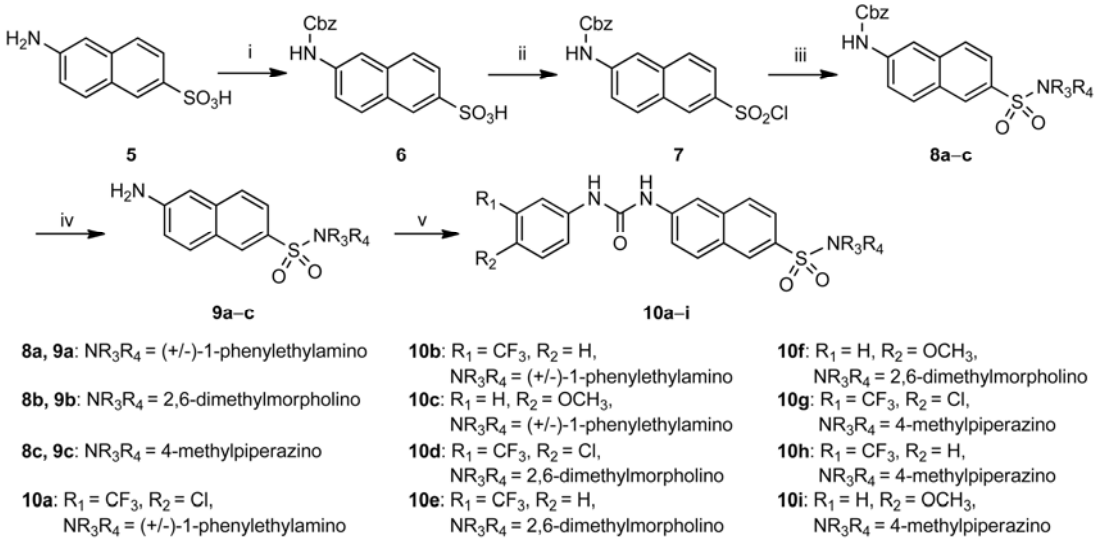
4f: R_1 = H, R_2 = OCH_3, NR_3R_4 = (+/-)-1-phenylethylamino

4g: R_1 = CF_3, R_2 = Cl, NR_3R_4 = 4-methylpiperidyl

4h: R_1 = CF_3, R_2 = H, NR_3R_4 = 4-methylpiperidyl

4i: R_1 = H, R_2 = OCH_3, NR_3R_4 = 4-methylpiperidyl

Scheme 1 Synthesis of compounds **4a–i**. Reagents and conditions: i) NHR_3R_4, Et_3N/THF; ii) H_2, 10% Pd/C, THF/MeOH; iii) ArNCO, anhydrous THF.



Scheme 2 Synthesis of compounds **10a–i**. Reagents and conditions: i) Cbz-Cl, Na_2CO_3, THF/H_2O; ii) $SOCl_2$, DMF; iii) NHR_3R_4, Et_3N, CH_2Cl_2; iv) H_2, 10% Pd/C, THF/MeOH; v) ArNCO, anhydrous THF.

the positive control. The 50% inhibitory concentration (IC_{50}) was defined as the concentration that reduced the absorbance of the untreated wells by 50% compared to the vehicle in the MTT assay.

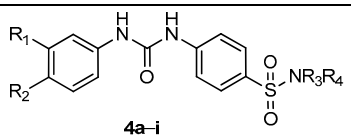
As shown in Table 1, compounds **4a**, **4d** and **4g** with the same distal phenyl ring substituents 3-CF_3-4-Cl exhibited similar potency (IC_{50} 3.15–22.8 μmol/L) versus sorafenib (IC_{50} 5.52–14.4 μmol/L) against MX-1, A375, HepG2 and Ketr3 cell lines, except HT-29 cell line. Interestingly, the electron-withdrawing group CF_3 of the distal phenyl A ring in position 4 led to more potent inhibitors than that in position 3, as exemplified by compound **4e** versus compounds **4b** and **4h** [4]. On the other hand, compounds with electron-donating group OCH_3 on the 4-position in the phenyl ring (**4c**, **4f** and **4i**) lost antitumor activity against five cell lines completely with IC_{50} values over 50 μmol/L. Moreover, sulfonamides with a large substituent on nitrogen, such as **4d** with α-methylbenzyl and **4g** with 4-methylpi- peridine displayed significantly improved activity compared to **4a** containing the cyclobutyl group.

The preliminary promising results of diphenyl urea sulfonamide derivatives prompted us to investigate the impact of modification on the fragment C using the naphathyl to replace the phenyl (**10a–i**). In addition, several heterocyclic alkyls containing N or O such as 2,6-dimethylmorpholine and 4-methylpiperazine were introduced into sulfonamide moiety to enhance the inhibitory activity [13]. The effect of substituents on the distal phenyl ring was also explored. Not surprisingly, a methoxy group on fragment A (**10c**, **10f**, **10i**) drastically decreased the activity (IC_{50} > 50 μmol/L), similar to that in the diphenyl urea system. Bearing an electron-withdrawing group on fragment A, compounds with α-methylbenzyl sulfonamide moiety (**10a**, **10b**) displayed similar activity compared to the phenyl counterparts (**4d**, **4e**). Interestingly we were pleased to find that compounds with 2,6-dimethylmorpholine sulfonamide moiety (**10d, 10e**) showed significantly improved activity against A375, HepG2 and Ketr3 cell lines with IC_{50} values around or below 1 micromolar. It indicates that 2,6-dimethylmorpholine could be a preferred group when choosing sulfonamide moiety in the further structure modification. Furthermore, the trend that the replacement of phenyl ring C with naphathyl system may benefit the antitumor activity, was consistent with the previous structure-activity relationships (SAR) results generated from sorafenib and its analogues [11]. It was worth noting that compound **10d** demonstrated significant activity against A375, HepG2 and Ketr3, which was 5–20-fold more potent than sorafenib, and thereby could become a valuable lead for further optimization. In addition, the SAR of phenyl-naphthyl urea sulfonamide derivatives needs further investigation.

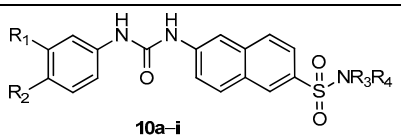
3 Conclusion

In summary, a series of novel scaffold, diaryl urea derivatives bearing sulfonamide moiety (**4a–i**, **10a–i**) have been synthesized based on the structural features of sorafenib and their anti-proliferative activity was evaluated against human cancer cell lines MX-1, A375, HepG2, Ketr3 and HT-29. The most potential compound **10d** in the 2,6-naphthyl series with a large polar sulfonamide fragment exhibited improved activity against A375, HepG2 and Ketr3 cell lines compared to the reference compound sorafenib. Compound **10d** could become a valuable lead for further optimization. These results suggest that development of diaryl urea sulfonamide scaffold is a very promising approach leading to more potent antitumor agents. The SAR of phenyl-naphthyl urea sulfonamide derivatives will be investigated in due course.

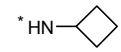
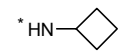
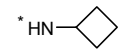
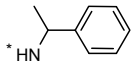
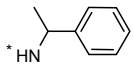
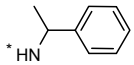
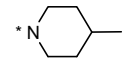
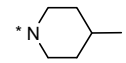
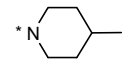
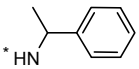
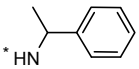
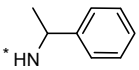
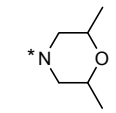
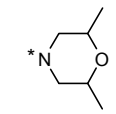
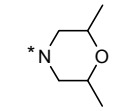
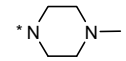
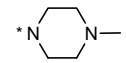
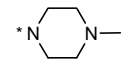
Table 1 Structures and inhibitory activity of target compounds against MX-1, A375, HepG2, Ketr3 and HT-29 cancer cell lines *in vitro*



4a–i



10a–i

Compd.	R_1	R_2	NR_3R_4	IC_{50} (μmol/L)				
				MX-1	A375	HepG2	Ketre3	HT-29
4a	CF_3	Cl		22.8	15.2	12.5	15.3	23.5
4b	CF_3	H		>50	12.1	12.6	>50	>50
4c	H	OCH_3		>50	>50	>50	>50	>50
4d	CF_3	Cl		14.4	10.8	7.48	7.21	22.9
4e	H	CF_3		>50	13.4	23.0	11.6	21.9
4f	H	OCH_3		>50	>50	>50	>50	>50
4g	CF_3	Cl		11.1	11.5	13.5	3.15	11.1
4h	CF_3	H		>50	>50	>50	>50	24.9
4i	H	OCH_3		>50	>50	>50	>50	>50
10a	CF_3	Cl		13.6	12.5	10.3	13.5	13.7
10b	CF_3	H		12.8	12.3	12.5	9.44	12.9
10c	H	OCH_3		>50	>50	>50	>50	>50
10d	CF_3	Cl		9.31	0.97	0.85	0.65	9.01
10e	CF_3	H		21.4	4.45	4.71	4.60	21.6
10f	H	OCH_3		>50	>50	>50	>50	>50
10g	CF_3	Cl		14.1	13.7	16.8	>50	17.0
10h	CF_3	H		14.0	17.1	17.3	23.2	25.6
10i	H	OCH_3		>50	>50	>50	>50	>50
Sorafenib				12.1	5.52	14.4	12.6	2.72

4 Experimental

4.1 Materials and apparatus

Melting points were determined with a Yanaco MP-J3 micro melting point apparatus and were uncorrected. The NMR spectra were obtained on Mercury-300, 400 MHz spectrometers (300 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) with tetramethylsilane (TMS) as the internal standard. High-resolution mass spectra (HR-MS) were taken in electrospray ionization (ESI) mode on an Agilent 1100 se-

ries LC/MSD mass spectrometer. All reagents and solvents were purchased from commercial sources unless otherwise indicated. Anhydrous THF was distilled from Na/benzophenone under a N_2 atmosphere. TLC was carried out on silica gel plates (GF_{254}) with visualization of components by UV light (254 nm). Column chromatography was carried out on silica gel (200-300 mesh).

4.2 General procedures

*N-Cyclobutyl-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)urea] phenyl}sulfonamide (**4a**)*

To a solution of cyclobutylamine (1.70 mL, 20 mmol) in THF (20 mL) and Et_3N (4 mL, 25 mmol) was added 4-nitrobenzenesulfonylchloride (**1**) (5.54 g, 25 mmol) in THF (20 mL) by dropwise under argon protection at 0 °C. Then the reaction mixture was stirred at room temperature for 2 h. The mixture was poured into water, and extracted with EtOAc, then the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel column chromatography (Petroleum ether/EtOAc (*v*/*v*) = 2:1) under reduced pressure to give 4.84 g **2a** as an off-white solid with a yield of 94.4%.

To a solution of **2a** (4.84 g, 18.9 mmol) in THF (25 mL) was added a mixture of 10% Pd/C (0.48 g) in methanol (2 mL), hydrogenated under medium pressure for 4 h. Then the mixture was filtered and concentrated. The residue was washed with hexane to give 4.21 g **3a** as an off-white solid with a yield of 98.4%.

To a solution of **3a** (1.0 eq.) in anhydrous THF (5 mL) was added 4-chloro-3-(trifluoromethyl)phenyl isocyanate (1.1 eq.) in anhydrous THF (5 mL) by dropwise under argon protection at 0 °C. Then the mixture was stirred for about 20 h at room temperature. The mixture was concentrated *in vacuo* and the residue was recrystallized in MeOH to give 0.17 g of **4a** as a white solid with a yield of 54.8%. Mp: 229–231 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.97 (s, 2 H, NHCONH), 8.11 (s, 1 H, ArH), 7.78 (d, 1 H, J = 8.7 Hz, SO_2NH), 7.65 (m, 6 H, ArH), 3.58 (m, 1 H, NHCH), 1.87–1.39 (m, 6 H, $CH_2CH_2CH_2$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 152.15, 142.83, 138.95, 134.41, 132.03 (2 C), 127.64, 126.56 (2 C), 123.31 (2 C), 122.70 (q, J = 30.0 Hz), 117.96 (2 C), 117.01, 47.52, 30.52 (2 C), 14.49; HR-MS (ESI-TOF$^+$): *m/z* [M + H]$^+$ calcd for $C_{18}H_{18}ClF_3N_3O_3S$: 448.0704; found: 448.0691.

*N-Cyclobutyl-{4-[3-(3-(trifluoromethyl)phenyl)urea]phenyl} sulfonamide (**4b**)*

Compound **4b** was prepared from **1** in a manner similar to that described for compound **4a** with a yield of 63.0%. Mp: 211–212 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.26 (s, 1 H, NHCONH), 9.21 (s, 1 H, NHCONH), 8.01 (s, 1 H, SO_2NH), 7.78 (d, 1 H, J = 8.7 Hz, ArH), 7.68 (d, 2 H, J = 9.3 Hz, ArH), 7.62 (d, 2 H, J = 9 Hz, ArH), 7.53 (m, 2 H, ArH), 7.33 (d, 1 H, J = 7.8 Hz, ArH), 3.58 (m, 1 H, NHCH), 1.87–1.46 (m, 6 H, $CH_2CH_2CH_2$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 152.23, 142.98, 140.17, 134.26, 129.96 (2 C), 129.69, 127.65 (2 C), 122.08 (q, J = 30.7 Hz), 118.45, 117.84 (2 C), 114.38, 47.53, 30.54 (2 C), 14.50; HR-MS (ESI-TOF$^+$): *m/z* [M + H]$^+$ calcd for $C_{18}H_{19}F_3N_3O_3S$: 414.1094; found: 414.1097.

*N-Cyclobutyl-{4-[3-(4-methoxyphenyl)urea]phenyl}sulfonamide (**4c**)*

Compound **4c** was prepared from **1** in a manner similar to that described for compound **4a** with a yield of 67.3%. Mp: 214–215 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.00 (s, 1 H, NHCONH), 8.59 (s, 1 H, NHCONH), 7.75 (d, 1 H, J = 9 Hz, SO_2NH), 7.65 (d, 2 H, J = 8.4 Hz, ArH), 7.58 (d, 2 H, J = 8.7 Hz, ArH), 7.35 (d, 2 H, J = 8.7 Hz, ArH), 6.87 (d, 2 H, J = 9 Hz, ArH), 3.71 (s, 3 H, OCH_3), 3.58 (m, 1 H, NHCH), 1.87–1.46 (m, 6 H, $CH_2CH_2CH_2$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 154.74, 152.29, 143.30, 135.58, 133.90, 127.65 (2 C), 120.30, 120.23, 117.54 (2 C), 115.43, 115.21, 55.16, 47.52, 30.53 (2 C), 14.50; HR-MS (ESI-TOF$^+$): *m/z* [M + H]$^+$ calcd for $C_{18}H_{22}N_3O_4S$: 376.1326; found: 376.1317.

*N-[(+/–)-1-Phenylethyl]-{4-[3-(4-chloro-3-(trifluoromethyl) phenyl)urea]phenyl}sulfonamide (**4d**)*

To a solution of (+/–)-1-phenylethylamine (2.82 mL, 22 mmoL) in THF (20 mL) and Et_3N (4.16 mL, 30 mmoL) was added 4-nitrobenzenesulfonylchloride (**1**) (4.44 g, 20 mmol) in THF (20 mL) by dropwise under argon protection at 0 °C. Then the reaction mixture was stirred at room temperature for 3 h. The mixture was poured into water, and extracted with EtOAc, then the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was washed with petroleum ether to give 5.89 g **2b** as a light yellow solid with a yield of 96.1%.

To a solution of **2b** (5.85 g, 19.1 mmol) in THF (20 mL) was added a mixture of 10% Pd/C (0.57 g) in methanol (2 mL), hydrogenated under medium pressure for 4 h. Then the mixture was filtered and concentrated. The residue was washed with petroleum ether to give 5.09 g **3b** as a white solid with a yield of 96.4%.

To a solution of **3b** (1.0 eq.) in anhydrous THF (5 mL) was added 4-chloro-3-(trifluoromethyl)phenyl isocyanate (1.1 eq.) in anhydrous THF (5 mL) by dropwise under argon protection at 0 °C. Then the mixture was stirred for about 20 h at room temperature. The mixture was concentrated *in vacuo* and purified by silica gel column chromatography (Petroleum ether/THF (*v*/*v*) = 3:2) to give 0.25g **4d** as a white solid with a yield of 71.7%. Mp: 226–227 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.25 (s, 1 H, NHCONH), 9.21 (s, 1 H, NHCONH), 8.11 (s, 1 H, ArH), 8.04 (d, 1 H, J = 8.1 Hz, SO_2NH), 7.66–7.51 (m, 6 H, ArH), 7.21–7.12 (m, 5 H, ArH), 4.33 (m, 1 H, NHCHCH$_3$), 1.18 (d, 3 H, J = 6.6 Hz,

CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 152.12, 143.56, 142.59, 138.96, 134.38, 132.02, 128.04 (2 C), 127.59 (2 C), 126.87 (2 C), 126.67 (2 C), 126.57, 126.01 (2 C), 122.89 (q, J = 82.2 Hz), 117.74 (2 C), 52.69, 23.46; HR-MS (ESI-TOF$^+$): *m/z* [M + H]$^+$ calcd for $C_{22}H_{20}ClF_3N_3O_3S$: 498.0861; found: 498.0863.

*N-[(+/−)-1-Phenylethyl]-{4-[3-(4-(trifluoromethyl)phenyl) urea]phenyl}sulfonamide (**4e**)*

Compound **4e** was prepared from **1** in a manner similar to that described for compound **4d** with a yield of 81.0%. Mp: 226–228 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.20 (s, 1 H, NHCONH), 9.17 (s, 1 H, NHCONH), 8.04 (d, 1 H, J = 7.8 Hz, SO_2NH), 7.65 (m, 4 H, ArH), 7.60 (d, 2 H, J = 9 Hz, ArH), 7.53 (d, 2 H, J = 8.7 Hz, ArH), 7.21–7.12 (m, 5 H, ArH), 4.31 (m, 1 H, NHCHCH$_3$), 1.18 (d, 3 H, J = 6.9 Hz, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 151.99, 143.57, 143.06, 142.68, 134.29, 128.05 (2 C), 127.62 (2 C), 126.67, 126.12, 126.08 (2 C), 126.01 (2 C), 122.65 (q, J = 82.2 Hz), 118.09 (2 C), 117.61 (2 C), 52.69, 23.46; HR-MS (ESI-TOF$^+$): *m/z* [M + H]$^+$ calcd for $C_{22}H_{21}F_3N_3O_3S$: 464.1250; found: 464.1247.

*N-[(+/–)-1-Phenylethyl]-{4-[3-(4-methoxyphenyl)urea]phenyl} sulfonamide (**4f**)*

Compound **4f** was prepared from **1** in a manner similar to that described for compound **4d** with a yield of 75.0%. Mp: 217–218 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.95 (s, 1 H, NHCONH), 8.57 (s, 1 H, NHCONH), 8.00 (d, 1 H, J = 8.1 Hz, SO_2NH), 7.58 (d, 2 H, J = 8.7 Hz, ArH), 7.50 (d, 2 H, J = 9 Hz, ArH), 7.35 (d, 2 H, J = 8.7 Hz, ArH), 7.21–7.13 (m, 5 H, ArH), 6.87 (d, 2 H, J = 9.3 Hz, ArH), 4.29 (m, 1 H, NHCHCH$_3$), 3.71 (s, 3 H, OCH_3), 1.18 (d, 3 H, J = 6.9 Hz, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 154.71, 152.32, 143.63, 143.29, 133.60, 132.22, 128.04 (2 C), 127.59 (2 C), 126.66, 126.01 (2 C), 120.26 (2 C), 117.18 (2 C), 114.00 (2 C), 55.16, 52.65, 23.45; MS (ESI-TOF$^+$): *m/z* [M + H]$^+$ calcd for $C_{22}H_{24}N_3O_4S$: 426.1482; found: 426.1485.

*4-Methyl-1-{4-[3-(4-chloro-3-(trifluoromethyl)phenyl)urea] phenyl}sulfonyl piperidine (**4g**)*

To a solution of 4-methylpiperidine (0.60 mL, 5 mmol) in THF (20 mL) and Et_3N (0.77 mL, 5.5 mmol) was added 4-nitrobenzenesulfonylchloride (**1**) (1.15g, 5.2 mmol) in THF (20 mL) by dropwise under argon protection at 0 °C. Then the reaction mixture was stirred at room temperature for 2 h. The mixture was poured into water, and extracted with EtOAc, then the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel column chromatography (Petroleum ether/THF (*v*/*v*) = 3:2) to give 1.20 g **2c** as a yellow solid with a yield of 84.4%.

To a solution of **2c** (1.12 g, 3.9 mmol) in THF (25 mL) was added a mixture of 10% Pd/C (0.11 g) in methanol (2 mL), hydrogenated under medium pressure for 4 h. Then the mixture was filtered and concentrated. The residue was washed with hexane to give 0.98 g **3c** as an off-white solid with a yield of 98.9%.

To a solution of **3c** (1.0 eq.) in anhydrous THF (5 mL) was added 4-chloro-3-(trifluoromethyl)phenyl isocyanate (1.1 eq.) in anhydrous THF (5 mL) by dropwise under argon protection at 0 °C. Then the mixture was stirred for about 20 h at room temperature. The mixture was concentrated *in vacuo* and purified by silica gel column chromatography (Petroleum ether/EtOAc (*v*/*v*) = 2:1) to give 0.14 g **4g** as a light yellow solid with a yield of 49.1%. Mp: 179–181 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.35 (s, 1 H, NHCONH), 9.29 (s, 1 H, NHCONH), 8.10 (s, 1 H, ArH), 7.70–7.62 (m, 6 H, ArH), 3.56 (d, 2 H, J = 11.4 Hz, NCH_2), 2.15 (t, 2 H, J = 11.4 Hz, NCH_2), 1.63 (d, 2 H, J = 11.7 Hz, CH$\underline{CH_2}$), 1.24 (brs, ^{1}H, $\underline{CH}CH_3$), 1.11 (m, 2 H, CH$\underline{CH_2}$), 0.84 (d, 3 H, J = 6.3 Hz, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 152.13, 143.52, 138.90, 132.04, 128.70 (2 C), 128.15, 126.87, 126.57, 123.06 (q, J = 118.7 Hz), 118.08 (2 C), 117.07, 117.02, 46.04 (2 C), 32.81 (2 C), 29.29, 21.28; HR-MS (ESI-TOF$^+$): *m/z* [M + H]$^+$ calcd for $C_{20}H_{22}ClF_3N_3O_3S$: 476.1017; found: 476.1015.

*4-Methyl-1-{4-[3-(3-(trifluoromethyl)phenyl)urea]phenyl} sulfonyl piperidine (**4h**)*

Compound **4h** was prepared from **1** in a manner similar to that described for compound **4g** with a yield of 31.3%. Mp: 175–176 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.32 (s, 1 H, NHCONH), 9.20 (s, 1 H, NHCONH), 8.01 (s, 1 H, ArH), 7.69 (d, 2 H, J = 9 Hz, ArH), 7.63 (d, 2 H, J = 9.3 Hz, ArH), 7.54 (m, 2 H, ArH), 7.34 (d, 1 H, J = 7.8 Hz, ArH), 3.56 (d, 2 H, J = 11.4 Hz, NCH_2), 2.16 (t, 2 H, J = 10.5 Hz, NCH_2), 1.63 (d, 2 H, J = 10.8 Hz, CH$\underline{CH_2}$), 1.27 (brs, ^{1}H, $\underline{CH}CH_3$), 1.14 (m, 2 H, CH$\underline{CH_2}$), 0.84 (d, 3 H, J = 6.3 Hz, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 152.21, 143.67, 140.13, 129.96, 128.70 (2 C), 127.98 (2 C), 122.12 (q, J = 82.7 Hz), 118.52 (2 C), 117.94 (2 C), 114.40, 46.04 (2 C), 32.81 (2 C), 29.28, 21.29; HR-MS (ESI-TOF$^+$): *m/z* [M + H]$^+$ calcd for $C_{20}H_{23}F_3N_3O_3S$: 442.1407; found: 442.1403.

*4-Methyl-1-{4-[3-(4-methoxyphenyl)urea]phenyl}sulfonyl piperidine (**4i**)*

Compound **4i** was prepared from **1** in a manner similar to that described for compound **4g** with a yield of 73.4%. Mp: 189–190 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.08 (s, 1 H, NHCONH), 8.60 (s, 1 H, NHCONH), 7.65 (d, 2 H, J = 8.7 Hz, ArH), 7.60 (d, 2 H, J = 9 Hz, ArH), 7.35 (d, 2 H, J = 8.4 Hz, ArH), 6.87 (d, 2 H, J = 9 Hz, ArH), 3.71 (s, 3 H, OCH_3), 3.55 (d, 2 H, J = 11.7 Hz, NCH_2), 2.15 (t, 2 H, J = 12.3 Hz, NCH_2), 1.63 (d, 2 H, J = 12 Hz, CH$\underline{CH_2}$), 1.27 (m, 1 H, $\underline{CH}CH_3$), 1.11 (m, 2 H, CH$\underline{CH_2}$), 0.84 (d, 3 H, J = 6.3 Hz, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 154.76, 152.30, 144.19, 132.14, 128.70 (2 C), 127.33, 120.32 (2 C), 117.48

(2 C), 114.00 (2 C), 55.16, 46.04 (2 C), 32.81 (2 C), 29.29, 21.30; HR-MS (ESI-TOF$^+$): *m/z* [M + H]$^+$ calcd for $C_{20}H_{26}N_3O_4S$: 404.1639; found: 404.1638.

*N-[(+/−)-1-Phenylethyl]-{6-[3-(4-chloro-3-(trifluoromethyl) phenyl)urea]naphthalene-2-yl}sulfonamide (**10a**)*

To an aqueous solution of 6-aminonaphthalene-2-sulfonic acid (**5**) (2.23 g, 10 mmol) and sodium carbonate (2.12 g, 20 mmol) was added THF (20 mL), then benzyl chloroformate (Cbz-Cl) (1.57 mL, 11 mmol) was added by dropwise at 40°C. The mixture was stirred at room temperature for 2 h then concentrated under reduced pressure, acidized with 1N HCl, filtered and washed with water to give 2.95 g compound **6** as a white solid with a yield of 82.4%.

To a solution of **6** (1.79 g, 5 mmol) in DMF (20 mL) was added thionyl chloride (0.54 mL, 7.5 mmol), stirred at room temperature for 4 h. The mixture was poured into ice-water, extracted with dichloromethane, then the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was resolved in dichloromethane with triethylamine (1.4 mL, 10 mmol) then added (+/−)-1-phenylethylamine (0.65 mL, 5 mmol) by dropwise at 0 °C. The mixture was stirred at room temperature for 6 h then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH/Et_3N (*v/v/v*) = 100:10:1) to give 1.66 g **8a** as a white solid with a yield of 72.1%.

To a solution of **8a** (0.46 g, 1 mmol) in THF (15 mL) was added a mixture of 10% Pd/C (0.05 g) in methanol (2 mL), hydrogenated under atmosphere for 4 h. Then the mixture was filtered and concentrated under reduced pressure to give 0.32 g **9a** as an off-white solid with a yield of 98.1%.

To a solution of **9a** (1.0 eq.) in anhydrous THF (3 mL) was added 4-chloro-3-(trifluoromethyl)phenyl isocyanate (1.1 eq.) in anhydrous THF (5 mL) by dropwise under argon protection at 0 °C. Then the mixture was stirred for about 20 h at room temperature. The mixture was concentrated *in vacuo* and purified by silica gel column chromatography (petroleum ether/EtOAc (*v/v*) = 1:1) to give 0.10 g **10a** as a white solid with a yield of 95.4%. Mp: 228–229 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.32 (s, 1 H, NHCONH), 9.26 (s, 1 H, NHCONH), 8.24–8.20 (m, 3 H, ArH), 8.17 (d, ^{1}H, *J* = 7.9 Hz, SO_2NH), 7.98 (d, 1 H, *J* = 9 Hz, ArH), 7.88 (d, 1 H, *J* = 9 Hz, ArH), 7.68–7.56 (m, 4 H, ArH), 7.20–7.02 (m, 5 H, ArH), 4.37 (m, 1 H, NHCH), 1.18 (d, 3 H, *J* = 7.2 Hz, CH_3); HR-MS (ESI-TOF$^+$): *m/z* [M + H]$^+$ calcd for $C_{26}H_{22}ClF_3N_3O_3S$: 548.1017; found: 548.0990.

*N-[(+/−)-1-Phenylethyl]-{6-[3-(3-(trifluoromethyl)phenyl) urea]naphthalen-2-yl}sulfonamide (**10b**)*

Compound **10b** was prepared from **5** in a manner similar to that described for compound **10a** with a yield of 93.5%. Mp: 175–178 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.19 (s, 2 H, NHCONH), 8.22–8.18 (m, 3 H, ArH), 8.08 (s, 1 H, SO_2NH), 7.97 (d, 1 H, *J* = 9 Hz, ArH), 7.88 (d, 1 H, *J* = 8.7 Hz, ArH), 7.66–7.50 (m, 4 H, ArH), 7.34 (d, 1 H, *J* = 7.8 Hz, ArH), 7.20–7.02 (m, 5 H, ArH), 4.38 (m, 1 H, NHCH), 1.18 (d, 3 H, *J* = 6.6 Hz, CH_3); HR-MS (ESI-TOF$^+$): *m/z* [M + H]$^+$ calcd for $C_{26}H_{23}F_3N_3O_3S$: 514.1407; found: 514.1390.

*N-[(+/-)-1-Phenylethyl]-{6-[3-(4-methoxyphenyl)urea]naphthalen-2-yl}sulfonamide (**10c**)*

Compound **10c** was prepared from **5** in a manner similar to that described for compound **10a** with a yield of 63.2%. Mp: 207–209 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.99 (s, 1 H, NHCONH), 8.62 (s, 1 H, NHCONH), 8.19 (d, 1 H, *J* = 8.1 Hz, SO_2NH), 8.15 (s, 2 H, ArH), 7.94 (d, 1 H, *J* = 9 Hz, ArH), 7.84 (d, 1 H, *J* = 8.7 Hz, ArH), 7.63 (d, 1 H, *J* = 8.4 Hz, ArH), 7.56 (d, 1 H, *J* = 7.8 Hz, ArH), 7.39 (d, 2 H, *J* = 8.7 Hz, ArH), 7.20–7.02 (m, 5 H, ArH), 6.88 (d, 2 H, *J* = 8.7 Hz, ArH), 4.37 (m, 1 H, NHCH), 3.72 (s, 3 H, OCH_3), 1.18 (d, 3 H, *J* = 6.9 Hz, CH_3); HR-MS (ESI-TOF$^+$): *m/z* [M + H]$^+$ calcd for $C_{26}H_{26}N_3O_4S$: 476.1639; found: 476.1624.

*2,6-Dimethyl-4-{6-[3-(4-chloro-3-(trifluoromethyl)phenyl) urea]naphthalen-2-yl}sulfonyl morpholine (**10d**)*

To a solution of **6** (1.79 g, 5 mmol) in DMF (20 mL) was added thionyl chloride (0.54 mL, 7.5 mmol), stirred at room temperature for 4 h. The mixture was poured into ice-water, extracted with dichloromethane, then the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was resolved in dichloromethane with triethylamine (0.7 mL, 5 mmol) then added 2,6-dimethylmorpholine (0.62 mL, 5 mmol) by dropwise at 0 °C. The mixture was stirred at room temperature for 4 h then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH/Et_3N (*v/v/v*) = 50:5:1) to give 0.89 g **8b** as a white solid with a yield of 39.2%.

To a solution of **8b** (0.90 g, 2 mmol) in THF (20 mL) was added a mixture of 10% Pd/C (0.09 g) in methanol (2 mL), hydrogenated under atmosphere for 6 h. Then the mixture was filtered and concentrated under reduced pressure to give 0.64 g **9b** as an off-white solid with a yield of 99.3%.

To a solution of **9b** (1.0 eq.) in anhydrous THF (3 mL) was added 4-chloro-3-(trifluoromethyl)phenyl isocyanate (1.1 eq.) in anhydrous THF (5 mL) by dropwise under argon protection at 0 °C. Then the mixture was stirred for about 20 h at room temperature. The mixture was concentrated *in vacuo* and purified by silica gel column chromatography (petroleum ether/THF (*v/v*) = 1:1) to give 0.11 g **10d** as an off-white solid with a yield of 82.2%. Mp: 90–92 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.34 (d, 2 H, *J* = 3.3 Hz, NHCONH), 8.32 (d, 2 H, *J* = 7.5 Hz, ArH), 8.17 (brs, 1 H, ArH), 8.13 (brs, 1 H, ArH), 8.04 (d, 1 H, *J* = 9 Hz, ArH), 7.65 (m, 4 H, ArH), 4.03–3.55 (m, 3 H, $CHCH_2$), 2.64 (m,

1 H, CHCH$_3$), 1.88 (m, 2 H, NCH$_2$), 1.13–1.01 (m, 6 H, CH$_3$); HR-MS (ESI-TOF$^+$): *m/z* [M + H]$^+$ calcd for $C_{24}H_{24}ClF_3N_3O_4S$: 542.1123; found: 542.1097.

*2, 6-Dimethyl-4-{6-[3-(3-(trifluoromethyl)phenyl)urea]naphthalen-2-yl}sulfonyl morpholine (**10e**)*

Compound **10e** was prepared from **5** in a manner similar to that described for compound **10d** with a yield of 73.7%. Mp: 108–110 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.28 (s, 1 H, NHCONH), 9.23 (s, 1 H, NHCONH), 8.31 (brs, 2 H, ArH), 8.14 (d, 1 H, *J* = 8 Hz, ArH), 8.08 (s, 1 H, ArH), 8.04 (d, 1 H, *J* = 9 Hz, ArH), 7.68–7.51 (m, 4 H, ArH), 7.34 (d, 1 H, *J* = 7.5 Hz, ArH), 4.00–3.55 (m, 3 H, CHCH$_2$), 2.98–2.59 (m, 1 H, CHCH$_3$), 1.88 (m, 2 H, NCH$_2$), 1.13–1.02 (m, 6 H, CH$_3$); HR-MS (ESI-TOF$^+$): *m/z* [M + H]$^+$ calcd for $C_{24}H_{25}F_3N_3O_4S$: 508.1512; found: 508.1485.

*2, 6-Dimethyl-4-{6-[3-(4-methoxyphenyl)urea]naphthalene-2-yl}sulfonyl morpholine (**10f**)*

Compound **10f** was prepared from **5** in a manner similar to that described for compound **10d** with a yield of 88.9%. Mp: 232–234 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.31 (s, 1 H, NHCONH), 9.82 (s, 1 H, NHCONH), 8.28 (br, 2 H, ArH), 8.08 (m, 1 H, ArH), 7.98 (d, 1 H, *J* = 9.3 Hz, ArH), 7.65 (m, 2 H, ArH), 7.43 (d, 2 H, *J* = 8.7 Hz, ArH), 6.87 (d, 2 H, *J* = 8.4 Hz, ArH), 3.98 (brs, 1 H, CHCH$_3$), 3.72 (s, 3 H, OCH$_3$), 3.56 (m, 2 H, NCH$_2$), 2.99–2.64 (m, 1 H, CHCH$_3$), 1.92 (m, 2 H, NCH$_2$), 1.14–1.02 (m, 6 H, CH$_3$); HR-MS (ESI-TOF$^+$): *m/z* [M + H]$^+$ calcd for $C_{24}H_{28}N_3O_5S$: 470.1744; found: 470.1723.

*1-Methyl-4-{6-[3-(4-chloro-3-(trifluoromethyl)phenyl)urea] naphthalen-2-yl} sulfonyl piperazine (**10g**).*

To a solution of **6** (0.54 g, 1.5 mmol) in DMF (10 mL) was added thionyl chloride (0.36 mL, 5 mmol), stirred at room temperature for 4 h. The mixture was poured into ice-water, extracted with dichloromethane, then the organic layer was washed with brine, dried over MgSO$_4$, filtered and concentrated. The residue was resolved in dichloromethane with triethylamine (0.21 mL, 1.7 mmol) and then added 1-methylpiperazine (0.25 mL, 2.3 mmol) by dropwise at 0 °C. The mixture was stirred at room temperature for 4 h then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH$_2$Cl$_2$/MeOH (*v*/*v*) = 50:1) to give 0.52 g **8c** as a white solid with a yield of 78.9%.

To a solution of **8c** (0.52 g, 1.2 mmol) in THF (20 mL) was added a mixture of 10% Pd/C (0.05 g) in methanol (2 mL), hydrogenated under atmosphere for 5 h. Then the mixture was filtered and concentrated under reduced pressure to give 0.36 g **9c** as an off-white solid with a yield of 98.4%.

To a solution of **9c** (1.0 eq.) in anhydrous THF (3 mL) was added 4-chloro-3-(trifluoromethyl)phenyl isocyanate (1.1 eq.) in anhydrous THF (5 mL) by dropwise under argon protection at 0 °C. Then the mixture was stirred for about 20 h at room temperature. The mixture was concentrated *in vacuo* and purified by silica gel column chromatography (CH$_2$Cl$_2$/MeOH (*v*/*v*) = 50:1) to give 0.10 g **10g** as an off-white solid with a yield of 65.2%. Mp: 208–210 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.34 (s, 1 H, NHCONH), 9.32 (s, 1 H, NHCONH), 8.29 (d, 2 H, *J* = 8.1 Hz, ArH), 8.17 (brs, 1 H, ArH), 8.13 (d, 1 H, *J* = 9 Hz, ArH), 8.04 (d, 1 H, *J* = 9 Hz, ArH), 7.67–7.64 (m, 4 H, ArH), 2.93 (brs, 4 H, CH$_2$N(SO$_2$)CH$_2$), 2.34 (brs, 4 H, CH$_2$N(CH$_3$)CH$_2$), 2.11 (s, 3 H, CH$_3$); HR-MS (ESI-TOF$^+$): *m/z* [M+H]$^+$ calcd for $C_{23}H_{23}ClF_3N_4O_3S$: 527.1126; found: 527.1130.

*1-Methyl-4-{6-[3-(3-(trifluoromethyl)phenyl)urea]naphthalen-2-yl} sulfonyl piperazine (**10h**)*

Compound **10h** was prepared from **5** in a manner similar to that described for compound **10g** with a yield of 30.4%. Mp: 98–101 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.46 (s, 2 H, NHCONH), 8.30 (s, 2 H, ArH), 8.14–8.02 (m, 3 H, ArH), 7.67–7.53 (m, 4 H, ArH), 7.33 (d, 1 H, *J* = 6.9 Hz, ArH), 2.94 (brs, 4 H, CH$_2$N(SO$_2$)CH$_2$), 2.39 (brs, 4 H, CH$_2$N(CH$_3$)CH$_2$), 2.14 (s, 3 H, CH$_3$); HR-MS (ESI-TOF$^+$): *m/z* [M + H]$^+$ calcd for $C_{23}H_{24}F_3N_4O_3S$: 493.1516; found: 493.1524.

*1-Methyl-4-{6-[3-(4-methoxyphenyl)urea]naphthalen-2-yl} sulfonyl piperazine (**10i**)*

Compound **10i** was prepared from **5** in a manner similar to that described for compound **10g** with a yield of 13.2%. Mp: 210–212 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.07 (s, 1 H, NHCONH), 8.66 (s, 1 H, NHCONH), 8.28 (s, 1 H, ArH), 8.24 (s, 1 H, ArH), 8.10 (d, 1 H, *J* = 9 Hz, ArH), 7.99 (d, 1 H, *J* = 8.7 Hz, ArH), 7.65–7.61 (m, 2 H, ArH), 7.39 (d, 2 H, *J* = 8.7 Hz, ArH), 6.88 (d, 2 H, *J* = 9 Hz, ArH), 3.72 (s, 3 H, OCH$_3$), 2.93 (brs, 4 H, CH$_2$N(SO$_2$)CH$_2$), 2.34 (brs, 4 H, CH$_2$N(CH$_3$)CH$_2$), 2.11 (s, 3 H, CH$_3$); HR-MS (ESI-TOF$^+$): *m/z* [M + H]$^+$ calcd for $C_{23}H_{27}N_4O_4S$: 455.1748; found: 455.1746.

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