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Synthesis and biological evaluation of naphthyl phenyl ethers (NPEs) as novel nonnucleoside HIV-1 reverse transcriptase inhibitors

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ABSTRACT

A novel series of naphthyl phenyl ether analogues (NPEs) have been synthesized and evaluated for their in vitro activities against HIV in C8166 cells. Most of the compounds exhibited moderate to excellent anti-HIV activities. Among them the most active compound **12o** showed excellent activities against wild-type HIV-1 with an EC_{50} value of 4.60 nM, along with moderate activities against the double mutant strain HIV-1_{IIIB} A17 (K103N+Y181C) and HIV-2 strain ROD with an EC_{50} value of 0.82 and 4.40 μM, respectively. Preliminary structure–activity relationship (SAR) among the newly synthesized NPEs was also investigated.

1. Introduction

Since the benzophenone compound **1** (Fig. 1) was screened out as a weak nonnucleoside reverse transcriptase inhibitor (NNRTI) through high-throughput screening by Glaxo in the middle of 1990s,[1] many benzophenone derivatives, represented by GW678248 (**2**, Fig. 1) and its prodrug GW695634 (**3**, Fig. 1), have been successively found to possess potent activity against both wild-type and mutant virus strains.[2–5] Recently, further development of benzophenones resulted in the discovery of some series of diaryl ether derivatives with excellent anti-HIV activities, such as the compound **4**–**6** (Fig. 1).[6–14]

Our previously long-standing work on NNRTIs has indicated that replacement of the phenyl with a bulky naphthyl in some series such as HEPTs,[15] DABOs,[16] DATAs,[17] and DAPYs[18,19] is beneficial by improving the π–π stacking interactions between inhibitors and amino acid residues Tyr188, Trp229 as well as Tyr181 within the binding pocket of reverse transcriptase (RT). Encouraged by these successful examples, we combined with the structures of compound **2** and **6** and designed a new series of naphthyl phenyl ether analogues (NPEs, **12**, Scheme 1), in which the bulky naphthalene ring is introduced to replace the benzene ring of **2** and **6**. In this paper, we describe the synthesis, biological evaluation of anti-HIV activity and preliminary structure–activity relationship (SAR) of these novel NPEs.

2. Results and discussion

2.1. Chemistry

The synthesis of the target compounds **12a–t** (Table 1) is shown in Scheme 1. Methylation of 2-bromo-4-fluorophenol (**7aa**) or 2-bromo-4-chlorophenol(**7ab**) with iodomethane in the presence of anhydrous potassium carbonate in acetone gave nearly quantitative 2-bromo-4-fluoro-1-methoxybenzene (**8aa**) or 2-bromo-4-chloro-1-methoxybenzene (**8ab**), which was subjected to Ullmann condensation with appropriate substituted naphthols in the presence of CuI/ligand/K_3PO_4 to provide naphthyl phenyl ethers **9a–t** with 11–52% yield. Demethylation of **9a–t** with BBr_3 afforded **10a–t** in high yield of 93–99%. The target compounds **12a–t** were obtained by *O*-alkylation of **10a–t** with known α-bromoacetamide (**11**), which was prepared by condensation of 4-amino-3-methylbenzene sulfonamide and bromoacetyl bromide according to the reported procedure.[2,3] The above-mentioned ligand,

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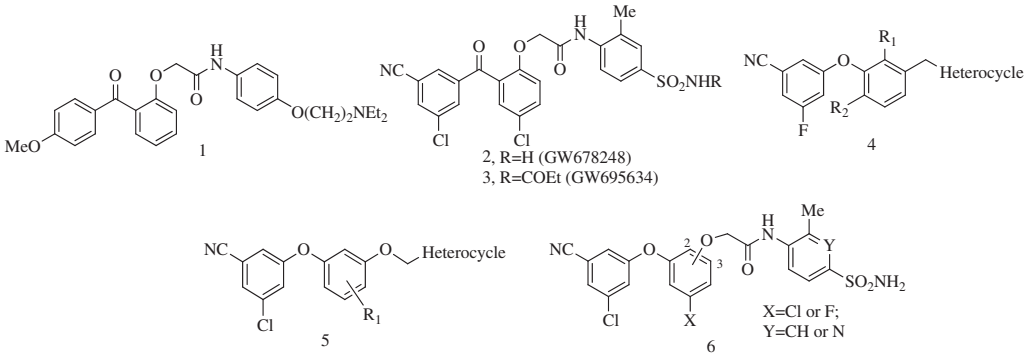
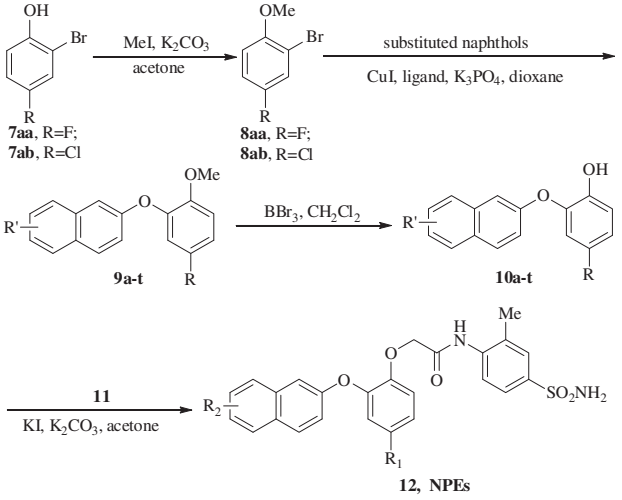


Figure 1. Structures of compounds **1–6**.



Scheme 1. Synthetic route of target compounds **12**.

(*E*)-1-(2-pyridinyl)methylene-2-phenyl hydrazine, was prepared by condensation of 2-pyridine-carboxaldehyde with phenyl hydrazine.[20]

2.2. Biology

The novel NPE derivatives (**12a–t**) were tested for their cytotoxicities and anti-HIV activities in C8166 cells infected by wild-type HIV-1_{IIIB} and the double mutant strains HIV-1_{IIIB} A17 (K103N+Y181C) along with HIV-2 strain ROD according to the previously reported method.[21,22] Zidovudine (AZT) and GW678248 were also tested as reference compounds. The biological evaluation results, expressed as EC_{50}, CC_{50} and SI (selectivity index), are illustrated in Table 1.

All compounds exhibited moderated to excellent activities against wild-type HIV-1_{IIIB} with EC_{50} values ranged from 244.30 to 4.60 nM. The most active compound **12o** showed the outstanding activity against wild-type HIV-1_{IIIB} with an EC_{50} value of 4.60 nM, and moderate activities against the double mutant strain HIV-1_{IIIB} A17 (EC_{50} = 0.82 μM) and HIV-2 ROD (EC_{50} = 4.40 μM). The selectivity index of **12o** against HIV-1 reaches up to 7669.56. The potency of compound **12p** is nearly equipotent to **12o** against both wild-type HIV-1_{IIIB} and the double mutant strain HIV-1_{IIIB} A17, but regretfully its potency against HIV-2 strain ROD is 53-fold weaker than **12o**.

The modifications of NPEs were mainly fixed on 2-naphthyloxy because it seems to be more favorable than 1-naphthyloxy (**12b** > **12a**). The influence of R (fluorine or chlorine) on activities against wild-type HIV-1_{IIIB} seems to be dependent on whether the *C*-3 position was occupied with a substituent. When there is no substituent on the *C*-3 position, the influence of R seems to be ambiguous (**12b** > **12c**, **12k** > **12n**; **12f** ≈ **12j**; **12l** < **12e**). When there is a methyl on the *C*-3 position, the chlorine appears to be superior to fluorine in terms of activities against wild-type HIV-1_{IIIB} (**12s** > **12q**, **12t** > **12g**).

The introduction of methyl and halogen at *C*-1 position in the naphthalene ring of **12b** and **12c** resulted in compounds **12e–f**, **12i,j**, and **12l** with several-fold decrease of activity in inhibiting HIV-1. Similarly, the introduction of chlorine at *C*-1 position in the naphthalene ring of **12g** and **12t** resulted in compounds **12q** and **12s** with both partial loss of activity. Surprisingly, the analogue **12m** with chlorine at *C*-1 position in the naphthalene ring is more potent than nonsubstituted parent compound **12h**. More strikingly, the installation of bromine or chlorine on **12k** (EC_{50} = 38.77) led to significant increase of anti-HIV-1 activity. The resulting two compounds **12o** and **12p** showed the most potent activities against the wild-type HIV-1_{IIIB} with an EC_{50} value of 4.60 and 4.72 nM.

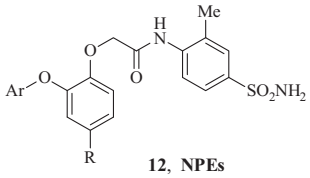
As illustrated in Table 1, the mono-substituted bromine and cyano group at the *C*-6 position in the naphthalene ring appeared to be unfavorable (**12c** > **12n** > **12d**). As far as the modification of **12b** was concerned, the bromine atom at *C*-6 position (**12h**) led to four-fold loss of activity against the wild-type HIV-1_{IIIB}. However, when the cyano group was introduced to the *C*-6 position of **12b** to get **12k**, the activity against the wild-type HIV-1_{IIIB} had no obvious change, but, the SI of **12k** have 6.7-fold increase compared with **12b**. Apparently, simultaneous introduction of cyano group at *C*-6 position and halogen at *C*-1 position in the naphthalene ring are beneficial for improving activities against both wild-type HIV-1 and the double mutant strains HIV-1_{IIIB} A17. In addition, the compound **12r** possessing fluorine at *C*-8 position in the naphthalene showed less activity than **12b**.

Moreover, compounds **12a–t** displayed moderate activity at micromolar level against the double mutant strains HIV-1_{IIIB} A17 with a very narrow range from 3.29 to 0.54 μM. And their anti-HIV-2 activity varies in a wide range from >383.16 to 3.00 μM, that is, satisfactory. Although most of previously discovered NNRTIs are only active against HIV-1 virus and lack of anti-HIV-2 activity,[15–19] that doesn't means they can't serve as HIV-2 inhibitors.[23–25] HIV-1 and HIV-2 reverse transcriptase are similar in structure and functionality, therefore, it is unexpected for some compounds to exhibit both anti-HIV-1 and anti-HIV-2 activities.

2.3. Molecular modeling calculations

Compounds **12o** and **12p**, which displayed the most potent biological activity against wild-type HIV-1 and the double mutant strains HIV-1_{IIIB} A17, were docked into the nonnucleoside binding

Table 1
Biological activities of compounds **12a–t** against HIV in C8166 cells[a]



12, NPEs

Compd.	R	Ar	EC_{50}[b]			CC_{50}[c] (μM)	SI[d]
			HIV-1_{IIIB} (nM)	HIV-1_{IIIB} A17 (μM)	HIV-2 ROD (μM)		
12a	F	1-Naphthyl	137.33	1.68	17.04	33.09	240.25
12b	F	2-Naphthyl	45.49	3.29	96.62	68.55	1506.92
12c	Cl	2-Naphthyl	79.10	1.79	27.26	118.98	1504.17
12d	Cl	6-Br-2-naphthyl	244.30	2.49	20.03	31.33	128.24
12e	Cl	1-Cl-2-naphthyl	169.04	1.73	13.27	40.72	240.89
12f	Cl	1-Br-2-naphthyl	87.90	1.34	136.56	48.05	546.64
12g	F	3-Me-2-naphthyl	140.40	1.09	125.91	66.87	476.28
12h	F	6-Br-2-naphthyl	181.28	1.77	96.01	>357.53	>1972.25
12i	F	1-Me-2-naphthyl	183.47	1.15	26.45	56.05	305.50
12j	F	1-Br-2-naphthyl	85.82	1.59	6.17	39.52	460.50
12k	F	6-CN-2-naphthyl	38.77	1.02	165.97	>395.63	>10201.53
12l	F	1-Cl-2-naphthyl	185.55	3.09	135.63	47.05	253.57
12m	F	1-Cl-6-Br-2-naphthyl	100.06	1.20	11.51	195.13	1950.13
12n	Cl	6-CN-2-naphthyl	116.50	2.33	>383.16	>383.16	>3288.92
12o	F	1-Br-6-CN-2-naphthyl	4.60	0.82	4.40	35.28	7669.56
12p	F	1-Cl-6-CN-2-naphthyl	4.72	0.54	234.82	39.69	8408.90
12q	F	1-Cl-3-Me-2-naphthyl	198.27	1.39	18.84	55.60	280.43
12r	F	8-F-2-naphthyl	92.36	1.45	66.35	170.73	1848.53
12s	Cl	1-Cl-3-Me-2-naphthyl	73.12	1.07	3.00	42.61	582.74
12t	Cl	3-Me-2-naphthyl	58.44	0.76	20.74	76.71	1312.63
GW678248			0.68	0.00138	2.18	>385.82	>567382
AZT			10.59	0.00812	0.1293	5601.71	528975

[a] All data represent mean values at least two separate experiments.
[b] Effective concentration required to protect C8166 cell against the cytopathogenicity of HIV by 50%.[22]
[c] Cytostatic concentration required to reduce C8166 cell proliferation by 50% tested by MTT method.[21]
[d] Selectivity index: ratio CC_{50}/C_{50} (HIV-1_{IIIB}), a higher SI means a more selective compound.

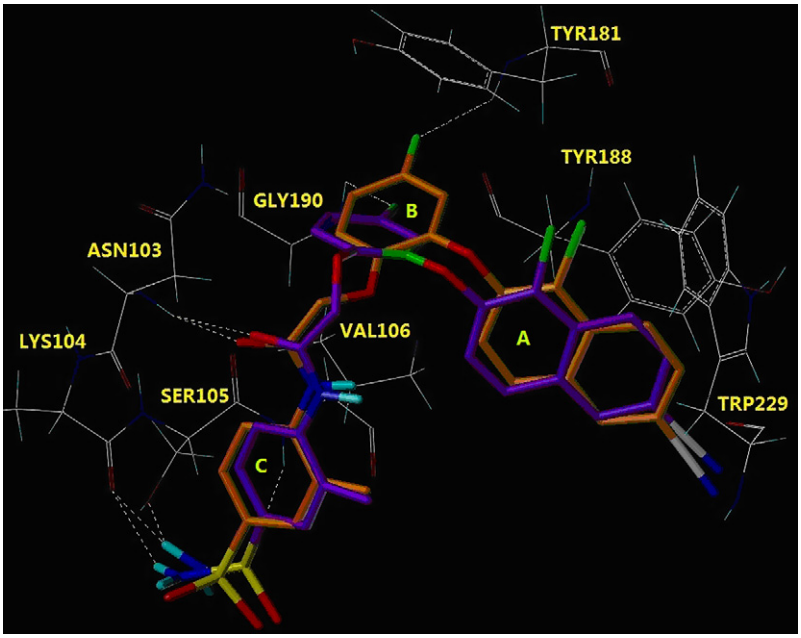


Figure 2. Model of **12o** (orange) and **12p** (purple) docked into the HIV-1 RT nonnucleoside binding site.

site (NNBS) by SURFLEX-DOCK SYBYL-X 1.1 (Fig. 2) to investigate the binding mode of **12o** and **12p** with NNBS of HIV-1 RT. Coordinate of the NNBS was taken from the crystal structure of the RT/GW678248 complex (PDB code: 3DOK)[4] due to the high degree of structural similarity between GW678248 and Compounds **12o** as well as **12p**. The ring A and ring C of them overlap quite well while ring B of them intercross in certain angle. There is strong π–π stacking interactions between the ring A of **12o** and **12p** and amino acid residues Tyr188, Trp229, by contrast, the stacking of **12o** and **12p** with Tyr181 is much weaker. The introduction of cyano group at the *C*-6 position in the naphthalene ring could enhance the interactions of **12o** and **12p** and amino acid residue TRP229, which may account for the high SI of **12o** (7669.56) and **12p** (8408.90).

It has been reported that the presence of the hydrogen bond may be entropically favorable for binding, as it could help to restrain the inhibitor conformation.[4] Although the structure and biological activity against wild-type HIV-1 and the double mutant strains HIV-1_{IIIB} A17 of **12o** and **12p** are both proximal, their hydrogen-bonding interactions with the protein main chain are probably different in some regions. In the case of **12p**, the potential hydrogen bonds involve residues ASN103, LYS104, VAL106 and GLY190, however, for **12o** they involves residues ASN103, LYS104, SER105 and TYR181. Moreover, the fluorine atom in ring B may interact with either TYR181 or GLY190. All these interactions would be in favor of the high binding affinity and increased activity against wild-type and mutant virus strains.

3. Conclusions

In this study, a series of naphthyl phenyl ether analogues have been synthesized and evaluated for their in vitro activity against human immunodeficiency virus. Their preliminary structure–activity relationship was also investigated. Among all the compounds (**12a–t**) examined, **12o** was identified as the most active compound which displayed activity against wild-type HIV-1 with an EC_{50} value of 4.60 nM, along with activities against the double mutant strain HIV-1_{IIIB} A17 (K103N+Y181C) and HIV-2 with an EC_{50} value of 0.82 and 4.40 μM, respectively. And it can serve as the basis for further modification in searching for more effective anti-HIV-1 candidates.

4. Experimental section

4.1. General

Melting points were measured on a SGW X-1 microscopic melting-point apparatus. ^{1}H NMR and ^{13}C NMR spectra on a Bruker AV 400 MHz spectrometer were recorded in DMSO-d_6. Chemical shifts are reported in δ (ppm) units relative to the internal standard tetramethylsilane (TMS). Mass spectra were obtained on a Waters Quattro Micromass instrument using electrospray ionization (ESI) techniques. Elemental analyses were performed on a Carlo Erba 1106 instrument. All chemicals and solvents used were of reagent grade and were purified and dried by standard methods before use. All air-sensitive reactions were run under a nitrogen atmosphere. All the reactions were monitored by TLC on pre-coated silica gel G plates at 254 nM under a UV lamp using ethyl acetate/hexane or dichloromethane/ methanol as eluent. Flash chromatography separations were obtained on silica gel (300–400 mesh).

4.1.1. General procedure for the preparation of 2-bromo-4-fluoro-1-methoxybenzene (8aa) or 2-bromo-4-chloro-1-methoxybenzene (8ab)

To a stirred solution of **7aa** (19.11 g, 0.10 mol) or **7ab** (20.75 g, 0.10 mol) in acetone (150 mL) was added K_2CO_3 (13.80 g, 0.10 mol) and MeI (12.61, 0.10 mol) at room temperature. After the mixture being refluxed for 6 h, the solvent was evaporated under reduced pressure and the residue was poured into H_2O (150 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layer was washed with H_2O (2 × 100 mL) and dried with anhydrous $NaSO_4$. The solvent was evaporated to afford light yellow oil **8aa** (94%) or **8ab** (96%).

4.1.2. General procedure for the preparation of naphthyl phenyl ethers (9a–t)

To a solution of **8aa** or **8ab** (30 mmol) and substituted naphthols(20 mmol) in dioxane (20 mL) was added CuI (0.38 g, 2 mmol), (*E*)-1-(2-pyridinyl)methylene-2-phenyl hydrazine (0.39 g, 2 mmol) and K_3PO_4 (8.49 g, 40 mmol) under N_2 atmosphere. The mixture was stirred and heated to 95–105 °C for 36–48 h. Then the mixture was filtered, and the filter cake was washed with *n*-hexane(4 × 10 mL). The combined filtrate and wash liquor was evaporated to remove solvent under reduced pressure. The residue was purified by column chromatography on silica gel (60–90 °C petroleum ether as eluent) to obtain **9a–t** as pure white solids in the yield of 11–52%.

4.1.3. General procedure for the preparation of 10a–t

The solution of BBr_3 (2.5 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise at −30 °C to a solution of **9a–t** (2 mmol) in CH_2Cl_2 (10 mL). The resulting mixture was stirred for 30 min at the temperature, then stirred for another 12 h under room temperature. The reaction mixture was diluted with CH_2Cl_2 (20 mL), poured slowly into H_2O (30 mL) under stirring conditions. The organic layer was separated, washed subsequently with H_2O (2 × 40 mL) and brine (30 mL), dried with anhydrous $NaSO_4$, and concentrated to give **10a–t** as light yellow solids in high yield (93–99%).

4.1.4. General procedure for the preparation of target compounds 12a–t

K_2CO_3 (276 mg, 2 mmol) and KI (66 mg, 0.4 mmol) was added to a solution of **10a–t** (1 mmol) and *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-bromoacetamide(**11**, 338 mg, 1.1 mmol) in acetone (20 mL). The mixture was heated to reflux for 15 h. After cooling, the mixture was poured into H_2O (50 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layer was washed subsequently with H_2O (2 × 60 mL) and brine (40 mL), dried with anhydrous sodium sulfate, and evaporated to remove solvent to give crude products, which was purified by flash chromatography to afford target compounds **12a–t** as white or light yellow solids.

4.1.4.1. 2-(4-Fluoro-2-(1-naphthyloxy)phenoxy)-*N*-(2-methyl-4-sulfamoylphenyl)acetamide (12a). Yield: 70%; white solid; mp 189.1–190.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.05 (s, 3H, CH_3), 4.84 (s, 2H, OCH2), 6.90–8.22 (m, 15H; Ph, Naph and SO_2NH_2), 9.27 (s, 1H, CONH); ^{13}C NMR (100 MHz, DMSO-d_6)δ (ppm)17.38, 68.46, 108.30 (d, J_{CF} = 25.77 Hz), 110.97 (d, J_{CF} = 22.55 Hz), 111.32, 116.46 (d, J = 9.50 Hz), 121.36, 123.14, 123.49, 123.82, 125.16, 126.12, 126.26, 126.87, 127.61, 127.87, 130.89, 134.51, 138.47, 140.23, 145.81 (d, J_{CF} = 10.69 Hz), 145.97 (d, J_{CF} = 2.94 Hz), 152.36, 156.82 (d, J_{CF} = 239.19 Hz), 166.57; MS(ESI−) *m*/*z* 478.9 $(M-H)^-$; Anal. Calcd for $C_{25}H_{21}FN_2O_5S$: C, 62.49; H, 4.41, F 3.95; N, 5.83; S, 6.67. Found: C, 62.53; H, 4.45; F, 3.91; N, 5.79; S, 6.61.

4.1.4.2. 2-(4-Fluoro-2-(2-naphthyloxy)phenoxy)-*N*-(2-methyl-4-sulfamoylphenyl)acetamide (12b). Yield: 68%; white solid; mp 173.8–174.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.11 (s, 3H, CH_3), 4.80 (s, 2H, OCH2 7.04–7.95 (m, 13H; Ph and Naph), 7.26 (s, 2H, SO_2NH_2), 9.29 (s, 1H, CONH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 17.46, 68.36, 109.11 (d, J_{CF} = 25.00 Hz), 111.29

(d, J_{CF} = 22.90 Hz), 111.73, 116.46 (d, J_{CF} = 9.90 Hz), 118.56, 123.54, 123.78, 124.71, 126.69, 127.04, 127.60, 127.62, 129.65, 130.01, 130.98, 133.86, 138.45, 140.24, 145.09 (d, J_{CF} = 10.79 Hz), 146.32 (d, J_{CF} = 3.07 Hz), 154.77, 156.77 (d, J_{CF} = 239.47 Hz), 166.50; MS(ESI−) *m*/*z* 478.9 $(M-H)^-$; Anal. Calcd for $C_{25}H_{21}FN_2O_5S$: C, 62.49; H, 4.41, F 3.95; N, 5.83; S, 6.67. Found: C, 62.44; H, 4.47; F, 3.89; N, 5.68; S, 6.56.

4.1.4.3. 2-(4-Chloro-2-(2-naphthyloxy)phenoxy)-*N*-(2-methyl-4-sulfamoylphenyl)acetamide (12c). Yield: 63%; white solid; mp 193.6–195.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.13 (s, 3H, CH_3), 4.84 (s, 2H, OCH2), 7.19–7.95 (m, 13H; Ph and Naph), 7.26 (s, 2H, SO_2NH_2), 9.34 (s, 1H, CONH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm)17.49, 67.81, 111.77, 116.52, 118.58, 121.35, 123.58, 123.77, 124.71, 125.00, 125.30, 126.69, 127.04, 127.60, 127.62, 129.64, 130.01, 131.01, 133.86, 138.45, 140.25, 145.14, 148.84, 154.78, 166.31; MS(ESI−) *m*/*z*(%)494.9 (^{35}Cl), 496.9 (^{37}Cl) $(M-H)^-$; Anal. Calcd for $C_{25}H_{21}ClN_2O_5S$: C, 60.42; H, 4.26; Cl, 7.13; N, 5.64; S, 6.45. Found: C, 60.33; H, 4.21; Cl, 7.17; N, 5.66; S, 6.49.

4.1.4.4. 2-(4-Chloro-2-(6-bromo-2-naphthyloxy)phenoxy)-*N*-(2-methyl-4-sulfamoylphenyl)acetamide (12d). Yield: 61%; white solid; mp 229.3–231.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6)δ (ppm) 2.12 (s, 3H, CH_3), 4.83 (s, 2H, OCH2), 7.23–7.94 (m, 12H; Ph and Naph, 7.26 (s, 2H, SO_2NH_2), 9.35 (s, 1H, CONH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 17.54, 67.80, 111.59, 116.55, 117.58, 119.72, 121.75, 123.66, 123.82, 125.37, 125.39, 127.66, 129.32, 129.34, 129.52, 129.62, 130.79, 131.10, 132.52, 138.49, 140.32, 144.68, 148.97, 155.40, 166.33; MS(ESI−) *m*/*z* 572.9 (^{35}Cl+^{79}Br), 574.8 (^{35}Cl+^{81}Br, ^{37}Cl+^{79}Br), 576.8 (^{37}Cl+^{81}Br) $(M-H)^-$; Anal. Calcd for $C_{25}H_{20}BrClN_2O_5S$: C, 52.14; H, 3.50; Br, 13.88; Cl, 6.16; N, 4.86; S, 5.57. Found: C, 52.08; H, 3.53; Br, 13.83; Cl, 6.21; N, 4.82; S, 5.59.

4.1.4.5. 2-(4-Chloro-2-(1-chloro-2-naphthyloxy)phenoxy)-*N*-(2-methyl-4-sulfamoylphenyl)acetamide (12e). Yield: 67%; white solid; mp 217.9–219.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.16 (s, 3H, CH_3), 4.88 (s, 2H, OCH2), 7.02–8.19 (m, 12H; Ph and Naph), 7.26 (s, 2H, SO_2NH_2), 9.38 (s, 1H, CONH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 17.46, 67.95, 116.55, 118.29, 118.48, 119.56, 123.09, 123.48, 123.80, 124.70, 125.35, 125.83, 127.62, 128.21, 128.47, 128.98, 130.70, 130.89, 130.95, 138.45, 140.24, 145.39, 148.03, 149.55, 166.27; MS(ESI−) *m*/*z* 528.9 (^{35}Cl+^{35}Cl), 530.9 (^{35}Cl+^{37}Cl), 533.0 (^{37}Cl+^{37}Cl) $(M-H)^-$; Anal. Calcd for $C_{25}H_{20}Cl_2N_2O_5S$: C, 56.50; H, 3.79; Cl, 13.34; N, 5.27; S, 6.03. Found: C, 56.55; H, 3.81; Cl, 13.28; N, 5.20; S, 6.07.

4.1.4.6. 2-(4-Chloro-2-(1-bromo-2-naphthyloxy)phenoxy)-*N*-(2-methyl-4-sulfamoylphenyl)acetamide (12f). Yield: 59%; white solid; mp 209.5–211.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.16 (s, 3H, CH_3), 4.89 (s, 2H, OCH2), 7.00–8.17 (m, 12H; Ph and Naph), 7.26 (s, 2H, SO_2NH_2), 9.35 (s, 1H, CONH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 17.49, 67.99, 110.36, 116.62, 118.54, 119.54, 123.47, 123.81, 124.67, 125.38, 125.75, 125.83, 127.62, 128.44, 128.50, 129.86, 130.89, 130.93, 132.25, 138.42, 140.24, 145.48, 148.00, 150.99, 166.26; MS(ESI−) *m*/*z* 572.9 (^{35}Cl+^{79}Br), 574.9 (^{35}Cl+^{81}Br, ^{37}Cl+^{79}Br), 576.9 (^{37}Cl+^{81}Br) $(M-H)^-$; Anal. Calcd for $C_{25}H_{20}BrClN_2O_5S$: C, 52.14; H, 3.50; Br, 13.88; Cl, 6.16; N, 4.86; S, 5.57. Found: C, 52.05; H, 3.49; Br, 13.91; Cl, 6.19; N, 4.89; S, 5.54.

4.1.4.7. 2-(4-Fluoro-2-(3-methyl-2-naphthyloxy)phenoxy)-*N*-(2-methyl-4-sulfamoylphenyl)acetamide (12g). Yield: 73%; white solid; mp 162.2–163.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.11 (s, 3H, Ph-CH_3), 2.44 (s, 3H, Naph-CH_3), 4.81 (s, 2H, OCH2), 6.93–7.80 (m, 12H; Ph and Naph), 7.26 (s, 2H, SO_2NH_2), 9.31 (s, 1H, CONH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 16.49, 17.39, 68.57, 108.36 (d, J_{CF} = 25.68 Hz), 110.84 (d, J_{CF} = 22.66 Hz), 111.73, 116.63 (d, J_{CF} = 9.62 Hz), 123.53, 123.81, 124.77, 125.70, 126.75, 126.83, 127.61, 128.26, 129.54, 129.90, 130.95, 132.58, 138.48, 140.25, 145.75 (d, J_{CF} = 10.74 Hz), 145.94 (d, J_{CF} = 2.92 Hz), 156.85 (d, J_{CF} = 239.32 Hz), 166.54; MS(ESI−) *m*/*z* 492.9 $(M-H)^-$, Anal. Calcd for $C_{26}H_{23}FN_2O_5S$: C, 63.15; H, 4.69, F 3.84; N, 5.66; S, 6.48. Found: C, 63.09; H, 4.71; F, 3.88; N, 5.71; S, 6.44.

4.1.4.8. 2-(4-Fluoro-2-(6-bromo-2-naphthyloxy)phenoxy)-*N*-(2-methyl-4-sulfamoylphenyl)acetamide (12h). Yield: 74%; white solid; mp 210.6–212.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.11 (s, 3H, CH_3), 4.80 (s, 2H, OCH2), 7.08–8.17 (m, 12H; Ph and Naph), 7.27 (s, 2H, SO_2NH_2), 9.36 (s, 1H, CONH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 17.53, 68.28, 109.46 (d, *J* = 25.52 Hz), 111.66 (d, *J* = 23.00 Hz), 116.41 (d, *J* = 9.52 Hz), 117.57, 119.71, 123.64, 123.82, 127.66, 129.31, 129.34, 129.51, 129.61, 130.79, 131.09, 132.53, 138.52, 140.30, 144.62 (d, *J* = 10.75 Hz), 146.46 (d, *J* = 2.95 Hz), 156.76 (d, *J* = 239.45 Hz), 166.53; MS(ESI−) *m*/*z* 557.0 (^{79}Br), 558.9 (^{81}Br) $(M-H)^-$; Anal. Calcd for $C_{25}H_{20}BrFN_2O_5S$: C, 53.68; H, 3.60; Br, 14.28, F 3.40; N, 5.01; S, 5.73. Found: C, 53.76; H, 3.64; Br, 14.21; F, 3.37; N, 5.05; S, 5.70.

4.1.4.9. 2-(4-Fluoro-2-(1-methyl-2-naphthyloxy)phenoxy)-*N*-(2-methyl-4-sulfamoylphenyl)acetamide (12i). Yield: 74%; white solid; mp 189.6–191.3 °C;^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.19 (s, 3H, Ph-CH_3), 3.35 (s, 3H, Naph-CH_3), 4.87 (s, 2H, OCH2), 6.53–8.06 (m, 12H; Ph and Naph), 7.27 (s, 2H, SO_2NH_2), 9.43 (s, 1H, CONH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 10.95, 17.41, 68.73, 105.64 (d, *J* = 26.72 Hz), 109.17 (d, *J* = 22.53 Hz), 116.47 (d, *J* = 9.65 Hz), 119.21, 122.71, 123.37, 123.87, 123.96, 124.98, 126.68, 127.64, 128.01, 128.43, 130.54, 130.81, 133.23, 138.54, 140.20, 144.92 (d, *J* = 2.98 Hz), 147.60 (d, *J* = 10.22 Hz), 150.28, 156.89 (d, *J* = 239.13 Hz), 166.69; MS(ESI+) *m*/*z* 495.1 (M+H)+; Anal. Calcd for $C_{26}H_{23}FN_2O_5S$: C, 63.15; H, 4.69, F 3.84; N, 5.66; S, 6.48. Found: C, 63.21; H, 4.72; F, 3.83; N, 5.65; S, 6.46.

4.1.4.10. 2-(4-Fluoro-2-(1-bromo-2-naphthyloxy)phenoxy)-*N*-(2-methyl-4-sulfamoylphenyl)acetamide (12j). Yield: 66%; white solid; mp 188.7–190.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.14 (s, 3H, CH_3), 4.85 (s, 2H, OCH2), 6.87–8.17 (m, 12H; Ph and Naph), 7.29 (s, 2H, SO_2NH_2), 9.32 (s, 1H, CONH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 17.50, 68.56, 107.54 (d, J_{CF} = 26.36 Hz), 110.35, 110.96 (d, J_{CF} = 22.60 Hz), 116.63 (d, J_{CF} = 10.08 Hz), 118.52, 123.50, 123.86, 125.79, 125.87, 127.65, 128.48, 128.55, 129.89, 130.93, 130.97, 132.31, 138.46, 140.26, 145.49 (d, J_{CF} = 2.97 Hz), 145.50 (d, J_{CF} = 10.50 Hz), 151.03, 156.81 (d, J_{CF} = 239.60 Hz), 166.50; MS(ESI−) *m*/*z* 557.0 (^{79}Br), 559.0 (^{81}Br) $(M-H)^-$; Anal. Calcd for $C_{25}H_{20}BrFN_2O_5S$: C, 53.68; H, 3.60; Br, 14.28, F 3.40; N, 5.01; S, 5.73. Found: C, 53.70; H, 3.63; Br, 14.24; F, 3.33; N, 4.98; S, 5.75.

4.1.4.11. 2-(4-Fluoro-2-(6-cyano-2-naphthyloxy)phenoxy)-*N*-(2-methyl-4-sulfamoylphenyl)acetamide (12k). Yield: 61%; light yellow solid; mp 212.5–213.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.08 (s, 3H, CH_3), 4.79 (s, 2H, OCH2), 7.14–8.52 (m, 12H; Ph and Naph), 7.27 (s, 2H, SO_2NH_2), 9.34 (s, 1H, CONH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 17.53, 68.11, 106.76 (d, J_{CF} = 26.60 Hz), 109.98, 110.17 (d, J_{CF} = 24.50 Hz), 110.86, 112.44, 116.27 (d, J_{CF} = 9.4 Hz), 119.35, 120.07, 123.66, 123.80, 127.97, 127.65, 128.33, 128.50, 130.92, 131.07, 134.15, 135.74, 138.50, 140.28, 143.64 (d, J_{CF} = 11.14 Hz), 146.66 (d, J_{CF} = 2.92 Hz), 156.57 (d, J_{CF} = 213.28 Hz), 166.46; MS(ESI−) *m*/*z* 504.0 $(M-H)^-$; Anal.

Calcd for $C_{26}H_{20}FN_3O_5S$: C, 61.77; H, 3.99, F 3.76; N, 8.31; S, 6.34. Found: C, 61.72; H, 3.81; F, 3.79; N, 8.35; S, 6.29.

4.1.4.12. 2-(4-Fluoro-2-(1-chloro-2-naphthyloxy)phenoxy)-*N*-(2-methyl-4-sulfamoylphenyl)acetamide (12l). Yield: 69%; white solid; mp 192.6–194.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.15 (s, 3H, CH_3), 4.85 (s, 2H, OCH2), 6.89–8.18 (m, 12H; Ph and Naph), 7.29 (s, 2H, SO_2NH_2), 9.35 (s, 1H, CONH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 17.49, 68.50, 107.58 (d, J_{CF} = 26.42 Hz), 111.00 (d, J_{CF} = 22.52 Hz), 116.53 (d, J_{CF} = 9.70 Hz), 118.28, 118.48, 123.14, 123.53, 123.87, 125.89, 127.67, 128.27, 128.53, 129.02, 130.76, 130.95, 131.02, 138.50, 140.26, 145.40 (d, J_{CF} = 10.65 Hz), 145.54 (d, J_{CF} = 2.92 Hz), 149.61, 156.79 (d, J_{CF} = 239.59 Hz), 166.53; MS(ESI−) m/z 512.9 (^{35}Cl), 514.9 (^{37}Cl) $(M-H)^-$, Anal. Calcd for $C_{25}H_{20}ClFN_2O_5S$: C, 58.31; H, 3.91; Cl, 6.88, F 3.69; N, 5.44; S, 6.23. Found: C, 58.39; H, 3.87; Cl, 6.79; F, 3.64; N, 5.47; S, 6.19.

4.1.4.13. 2-(4-Fluoro-2-(1-chloro-6-bromo-2-naphthyloxy) phenoxy)-*N*-(2-methyl-4-sulfamoylphenyl)acetamide (12m). Yield: 56%; white solid; mp 198.8–201.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.14 (s, 3H, CH_3), 4.83 (s, 2H, OCH2), 6.96–8.30 (m, 11H; Ph and Naph), 7.28 (s, 2H, SO_2NH_2), 9.37 (s, 1H, CONH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 17.50, 68.40, 108.04 (d, J_{CF} = 25.80 Hz), 111.38 (d, J_{CF} = 22.50 Hz), 116.46 (d, J_{CF} = 9.50 Hz), 118.17, 118.99, 123.58, 123.59, 123.85, 125.50, 127.67, 128.23, 129.78, 130.31, 131.00, 131.11, 131.77, 138.50, 140.28, 144.94 (d, J_{CF} = 10.00 Hz), 145.69 (d, J_{CF} = 2.90 Hz), 150.20, 156.76 (d, J_{CF} = 238.20 Hz), 166.48; MS(ESI−) m/z 590.9 (^{35}Cl+^{79}Br), 592.9 (^{35}Cl+^{81}Br, ^{37}Cl+^{79}Br), 594.9 (^{37}Cl+^{81}Br) $(M-H)^-$; Anal. Calcd for $C_{25}H_{19}BrClFN_2O_5S$: C, 50.56; H, 3.22; Br, 13.46; Cl, 5.97, F 3.20; N, 4.72; S, 5.40. Found: C, 50.64; H, 3.20; Br, 13.42; Cl, 5.90; F, 3.23; N, 4.68; S, 5.38.

4.1.4.14. 2-(4-Chloro-2-(6-cyano-2-naphthyloxy)phenoxy)-*N*-(2-methyl-4-sulfamoylphenyl)acetamide (12n). Yield: 58%; light yellow solid; mp 244.3–246.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.10 (s, 3H, CH_3), 4.83 (s, 2H, OCH2), 7.28–8.09 (m, 12H; Ph and Naph), 7.26 (s, 2H, SO_2NH_2), 9.37 (s, 1H, CONH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 17.52, 67.66, 106.75, 110.82, 119.30, 119.96, 120.11, 122.49, 123.67, 123.76, 123.85, 125.35, 126.99, 127.70, 128.31, 128.49, 130.88, 131.08, 134.21, 135.70, 138.46, 140.29, 143.75, 149.14, 157.62, 166.24; MS(ESI−) m/z 520.0 (^{35}Cl), 521.9 (^{37}Cl) $(M-H)^-$; Anal. Calcd for C26H20ClN3O5S: C, 59.83; H, 3.86; Cl, 6.79; N, 8.05; S, 6.14. Found: C, 59.78; H, 3.90; Cl, 6.76; N, 8.08; S, 6.12

4.1.4.15. 2-(4-Fluro-2-(1-bromo-6-cyano-2-naphthyloxy) phenoxy)-*N*-(2-methyl-4-sulfamoylphenyl)acetamide (12o). Yield: 68%; light yellow solid; mp 221.5–222.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.10 (s, 3H, CH_3), 4.88 (s, 2H, OCH2), 6.89–8.63 (m, 11H; Ph and Naph), 7.26 (s, 2H, SO_2NH_2), 9.34 (s, 1H, CONH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 17.46, 67.59, 103.20 (d, J_{CF} = 27.75 Hz), 107.63, 108.13 (d, J_{CF} = 23.06 Hz), 118.77, 119.16, 122.85 (d, J_{CF} = 10.03 Hz), 123.60, 123.77, 127.00, 127.61, 128.72, 129.18, 130.34, 133.94, 134.80, 138.38, 139.45 (d, J_{CF} = 2.98 Hz), 140.30, 150.63 (d, J_{CF} = 10.77 Hz), 154.00, 154.75, 159.66 (d, J_{CF} = 241.67 Hz), 165.98; MS(ESI−) m/z 581.9 (^{79}Br), 583.8 (^{81}Br) $(M-H)^-$; Anal. Calcd for $C_{26}H_{19}BrFN_3O_5S$: C, 53.43; H, 3.28; Br, 13.67, F 3.25; N, 7.19; S, 5.49. Found: C, 53.37; H, 3.30; Br, 13.62, F 3.28; N, 7.14; S, 5.42.

4.1.4.16. 2-(4-Fluro-2-(1-chloro-6-cyano-2-naphthyloxy) phenoxy)-*N*-(2-methyl-4-sulfamoylphenyl)acetamide (12p). Yield: 73%; light yellow solid; mp 210.8–212.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.11 (s, 3H, CH_3), 4.88 (s, 2H, OCH2), 6.91–8.65 (m, 11H; Ph and Naph), 7.26 (s, 2H, SO_2NH_2), 9.36 (s, 1H, CONH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 17.42, 67.58, 103.17 (d, J_{CF} = 27.81 Hz), 107.65, 108.17 (d, J_{CF} = 23.13 Hz), 116.40, 118.37, 122.85 (d, J_{CF} = 10.73 Hz), 123.59, 123.77, 124.37, 127.62, 128.50, 128.89, 129.48, 130.98, 132.57, 132.57, 138.40, 134.80, 139.30 (d, J_{CF} = 2.74 Hz), 140.29, 150.66 (d, J_{CF} = 10.91 Hz), 152.59, 153.39, 159.68 (d, J_{CF} = 240.26 Hz), 165.97; MS(ESI+) m/z 540.0 (^{35}Cl), 541.9 (^{37}Cl) (M+H)+; Anal. Calcd for $C_{26}H_{19}ClFN_3O_5S$: C, 57.83; H, 3.55; Cl, 6.57, F 3.52; N, 7.78; S, 5.94. Found: C, 57.91; H, 3.53; Cl, 6.50, F 3.55; N, 7.81; S, 5.91

4.1.4.17. 2-(4-Fluro-2-(1-chloro-3-methyl-2-naphthyloxy) phenoxy)-*N*-(2-methyl-4-sulfamoylphenyl)acetamide (12q). Yield: 62%; white solid; mp 190.4–192.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.26 (s, 3H, Ph-CH_3), 2.32 (s, 3H, Naph-CH_3), 4.94 (s, 2H, OCH2), 6.21–8.16 (m, 11H; Ph and Naph), 7.26 (s, 2H, SO_2NH_2), 9.57 (s, 1H, CONH); C13 NMR (100 MHz, DMSO-d_6) δ (ppm) 16.58,17.42,68.98, 101.83 (d, J_{CF} = 27.60 Hz), 108.38 (d, J_{CF} = 20.85 Hz), 116.78 (d, J_{CF} = 9.26 Hz), 122.75, 123.18, 123.44, 123.94, 126.77, 127.33, 127.68, 127.84, 129.19, 129.66, 130.54, 131.02, 131.78, 138.63, 140.13, 143.36 (d, J_{CF} = 2.88 Hz), 146.73, 147.14 (d, J_{CF} = 9.91 Hz), 156.95 (d, J_{CF} = 239.12 Hz), 166.73; MS(ESI−) m/z 527.0 (^{35}Cl), 529.0 (^{37}Cl) $(M-H)^-$, Anal. Calcd for $C_{26}H_{22}ClFN_2O_5S$: C, 59.03; H, 4.19; Cl, 6.70, F 3.59; N, 5.30; S, 6.06. Found: C, 59.08; H, 4.13; Cl, 6.72, F 3.54; N, 5.35; S, 6.09.

4.1.4.18. 2-(4-Fluro-2-(8-fluoro-2-naphthyloxy)phenoxy)-*N*-(2-methyl-4-sulfamoylphenyl)acetamide (12r). Yield: 55%; white solid; mp 190.8–192.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.11 (s, 3H,CH_3), 4.80 (s, 2H, OCH2), 7.12–8.05 (m, 12H; Ph and Naph), 7.26 (s, 2H, SO_2NH_2), δ (ppm) 9.29 (s, 1H, CONH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 17.44, 68.28, 103.48 (d, J_{CF} = 5.30 Hz), 109.69 (d, J_{CF} = 25.45 Hz), 110.48 (d, J_{CF} = 19.19 Hz), 111.88 (d, J_{CF} = 22.64 Hz), 116.46 (d, J_{CF} = 9.57 Hz), 119.59, 123.52 (d, J CF = 16.11 Hz), 123.57, 123.77, 123.89 (d, J_{CF} = 3.57 Hz), 124.53 (d, J_{CF} = 8.08 Hz), 127.60, 130.26 (d, J_{CF} = 2.58 Hz), 130.99, 131.04 (d, J_{CF} = 4.82 Hz), 138.45, 140.26, 144.34 (d, J_{CF} = 10.93 Hz), 146.47 (d, J_{CF} = 3.06 Hz), 155.70, 156.74 (d, J_{CF} = 238.3 Hz), 157.26 (d, J_{CF} = 246.9 Hz), 166.40; MS(ESI−) m/z 497.0 $(M-H)^-$, Anal. Calcd for C25H22F2N2O5S: C, 60.23; H, 4.04, F 7.62; N, 5.62; S, 6.43. Found: C, 60.18; H, 4.12, F 7.57; N, 5.64; S, 6.46.

4.1.4.19. 2-(4-Chloro-2-(1-chloro-3-methyl-2-naphthyloxy) phenoxy)-*N*-(2-methyl-4-sulfamoylphenyl)acetamide (12s). Yield: 65%; white solid; mp 223.6–225.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.28 (s, 3H, Ph-CH_3), 2.31 (s, 3H, Naph-CH_3), 4.99 (s, 2H, OCH2), 6.34–8.15 (m, 11H; Ph and Naph), 7.28 (s, 2H, SO_2NH_2), 9.60 (s, 1H, CONH); C13 NMR (100 MHz, DMSO-d_6) δ (ppm) 16.58, 17.50, 68.34, 113.57, 116.65, 122.45, 122.76, 123.17, 123.46, 123.97, 125.41, 126.83, 127.40, 127.72, 127.88, 129.24, 129.66, 130.59, 131.00, 131.78, 138.66, 140.16, 145.97, 146.73, 146.91, 166.55; MS(ESI+) m/z 545.1 (^{35}Cl+^{35}Cl), 547.0 (^{35}Cl+^{37}Cl), 549.0 (^{37}Cl+^{37}Cl) (M+H)+; Anal. Calcd for $C_{26}H_{22}Cl_2N_2O_5S$: C, 57.25; H, 4.07; Cl, 13.00; N, 5.14; S, 5.88. Found: C, 57.32; H, 4.03; Cl, 13.03; N, 5.09; S, 5.84

4.1.4.20. 2-(4-Chloro-2-(3-methyl-2-naphthyloxy)phenoxy)-*N*-(2-methyl-4-sulfamoylphenyl)acetamide (12t). Yield: 67%; white solid; mp 206.7–208.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.12 (s, 3H, Ph-CH_3), 2.44 (s, 3H, Naph-CH_3), 4.85 (s, 2H, OCH2), 7.08–7.80 (m, 12H; Ph and Naph), 7.27 (s, 2H, SO_2NH_2), 9.35 (s, 1H, CONH); C13 NMR (100 MHz, DMSO-d_6) δ (ppm) 16.51, 17.46, 68.02, 111.84, 116.67, 120.59, 123.59, 123.85, 124.65, 124.83, 125.44, 125.75, 126.78, 126.88, 127.66, 128.32, 129.58, 129.95, 131.02, 132.60, 138.52, 140.29, 145.77, 148.51, 153.96, 166.40; MS(ESI−) m/z 509.0 (^{35}Cl), 511.0 (^{37}Cl) $(M-H)^-$,

Anal. Calcd for $C_{26}H_{23}ClN_2O_5S$: C, 61.11; H, 4.54; Cl, 6.94; N, 5.48; S, 6.28. Found: C, 61.14; H, 4.50; Cl, 6.89; N, 5.46; S, 6.31.

4.2. Anti-HIV activity assays

The novel NPEs derivatives (**12a–t**) were tested for their cytotoxicities and anti-HIV activities against in C8166 cells according to the following method,[21,22] and GW678248 and Zidovudine (AZT) were used as reference compounds.

4.2.1. Cytotoxicity assays

The cytotoxicities of compounds on C8166 cells were assessed by MTT colorimetric assay as described previously.[21]The absorbance at 570 nm/630 nm ($A_{570/630}$) was read in an ELISA reader (Elx800, Bio-Tek Instrument Inc., USA). The minimum cytotoxic concentration that caused the reduction of viable cells by 50% (CC_{50}) was determined from dose response curve.

4.2.2. Syncytium reduction assays

In the presence of 100 μl various concentrations of compounds, C8166 cells (4×10^5/mL) were infected with viruses(HIV-1_{IIIB}; HIV-1_{IIIB} A17, and HIV-2 ROD) at a multiplicity of infection (M.O.I) of 0.06. The final volume per well was 200 μl. AZT was used for drug control. After a 3-day culture at 37 °C, the number of syncytia (multinucleated giant cells) was scored under an inverted microscope; 50% effective concentration to blocking syncytia formation (EC_{50}) was calculated as previous method.[22]

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