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Synthesis and biological activity of naphthyl-substituted (B-ring) benzophenone derivatives as novel non-nucleoside HIV-1 reverse transcriptase inhibitors

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ABSTRACT

A novel series of benzophenone derivatives with B-ring substituted by naphthyl ring has been synthesized and evaluated as non-nucleoside HIV-1 reverse transcriptase inhibitors. Most of these compounds showed good to moderate activity against wild-type HIV-1 and mutated viruses. In particular, the analogue **10i** demonstrated the most potent activity against wild-type HIV-1 with an EC_{50} value of 4.8 nM, and with a high selectivity index up to 10347.9, it also proved to be active against the HIV-1 double mutant strain A_{17} (K103N+Y181C) with an EC_{50} value of 2.1 μM. In addition, the molecular modeling study was used to explore the major interactions between the potent inhibitors with the HIV-1 RT. The investigation of the structure–activity relationships may serve as an important lead for the further optimization.

1. Introduction

Since their first discovery in the early 1990s, non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been shown to be a key component of highly active anti-retroviral therapy (HAART).[1–4] To date, four NNRTIs have been approved for clinical use (**1**–**4**, Fig. 1): nevirapine (**1**, NVP),[5] delavirdine (**2**, DLV),[6] efavirenz (**3**, EFE)[7] and etravirine (**4**, ETV).[8,9] In spite of the achievements of combination therapy in reducing the deaths from AIDS, the emergence of resistance to current anti-HIV drugs in clinical use means that further entities with broadened spectrum of activity are required in order to allow continued suppression of the viral infection.[10,11]

As novel NNRTIs, benzophenone derivatives (BPs, Fig. 2), such as **6** (GW4511[12]) and 7 (GW678248[13,14]), which were derived from **5** (GF128590[15]) showed a greatly improved profile of activity against both wild-type and clinically relevant NNRTI-resistant mutant strains of HIV-1. Recent crystallographic studies of HIV-1 RT in complexes with **5** and **6** have indicated that it was possible to

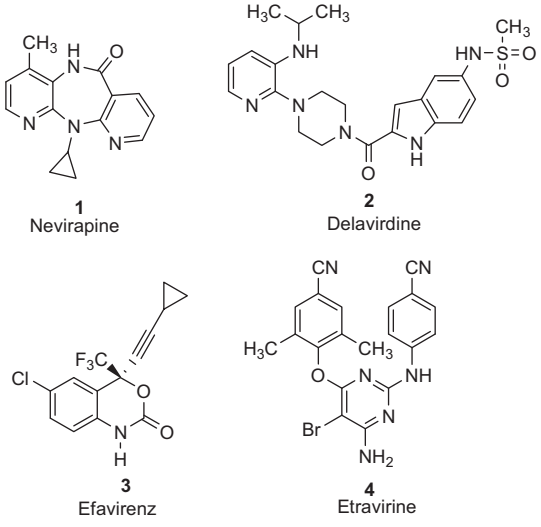

Figure 1. Structures of currently marketed NNRTIs.

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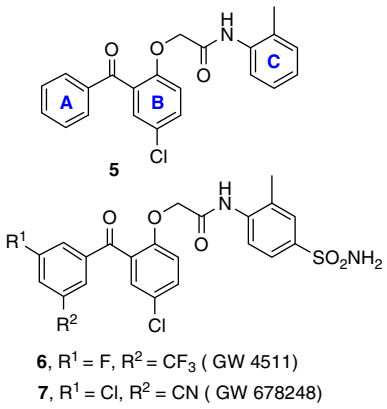


Figure 2. Structures of potent benzophenones.

introduce further substituents on the B-ring of the benzophenone template, such increase in bulk will result in strong interactions with Leu100, Val106 and Tyr188, and thus the tighter packing with the binding pocket of RT gave high level inhibitions.[16] On this basis, we replaced B-ring with the bulky naphthyl moiety and synthesized a series of naphthyl-substituted (B-ring) benzophenone derivatives 1**0a**–**y** for their potential anti-HIV activity. Additionally, the preliminary structure–activity relationships (SARs) and molecular modeling study of these compounds are also described in this manuscript.

2. Results and discussion

2.1. Chemistry

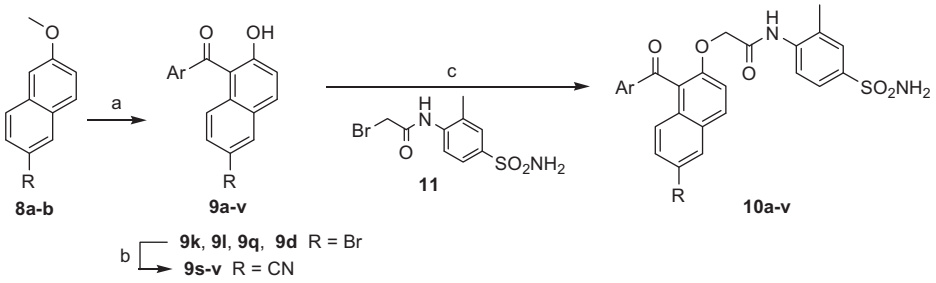
The synthesis of target compounds **10a**–**v** is shown in Scheme 1. Starting from 6-substituted-2-methoxynaphthalene (**8a**–**b**), the 2-benzoyl-1-naphthol (**9a**–**r**) were prepared by Friedel–Crafts acylation[17,18] with aryl chloride in the presence of catalytic aluminium chloride, which conveniently removed the methoxy group to release the naphthol for the subsequent alkylation step. The cyanation[13] of **9k**, **9l**, **9q** and **9d** with CuCN at 160 °C for 8 h in anhydrous DMF gave the corresponding 6-cyano intermediates **9s**–**v** in 32–43% yield, respectively. Subsequent alkylation of **9a**–**v** with **11**[13] yielded the desired analogues **10a**–**v** in a slightly convergent route (Scheme 1).

2.2. Biological activity

The biological activity of naphthyl-substituted (B-ring) benzophenone analogues **10a**–**v** against wild-type HIV-1 strain in C8166 cells are summarized in Table 1.[19,20] Lead compound GW678248 and the FDA-approved drug, zidovudine (AZT) were also evaluated as reference compounds. The activity data are interpreted in CC_{50} values (cytotoxicity), EC_{50} (anti-HIV activity) and SI (selectivity, given by the CC_{50}/EC_{50} ratio).

As seen from the results in Table 1, clearly, the analogues **10a**–**i**, without any substitutions at the C-6 position on the naphthyl ring, were much more potent against wild-type HIV-1 virus than that with C-6-bromo (**10j**–**r**) or cyano (**10s**–**v**) substitution. Generally, most of the compounds **10a**–**i** were highly potent, with the EC_{50} values ranging from 4.8 nM (**10i**) to 608.9 ± 112.6 nM (**10g**) and selectivity index (SI) values ranging from 54.2 (**10g**) to 10347.9 (**10i**). In particular, compound **10d** (EC_{50} = 7.8 ± 3.3 nM) and **10i** (EC_{50} = 4.8 nM) exhibited more anti-HIV-1 potency than zidovudine, whereas less than the leading compound GW678248. Apparently, the sharp decline in biological activity of the derivatives **10j**–**v** indicated that the introduction of a bromo or cyano group in the naphthyl ring of the title molecules resulted the bulky or electron-withdrawing group at the C-6 position, which may only weakly improve the π–π stacking interaction between inhibitors and amino acid residues with Leu100, Val106 and Tyr188 within the binding pocket of RT.

To investigate the potential SAR of these compounds, the impact on the potency by moving a small substituent around the A-ring was further explored. Clearly, placement of a methyl group



10	Ar	R	10	Ar	R	10	Ar	R
a	Ph	H	**i**	3,5-Cl,CN-Ph	H	**q**	3,4-Me_2-Ph	Br
b	3-Me-Ph	H	**j**	Ph	Br	**r**	3,5-Cl,Br-Ph	Br
c	3-Cl-Ph	H	**k**	3-Me-Ph	Br	**s**	3-Me-Ph	CN
d	3,5-Me_2-Ph	H	**l**	3-Cl-Ph	Br	**t**	3-Cl-Ph	CN
e	2,5-Me_2-Ph	H	**m**	3-F-Ph	Br	**u**	3,4-Me_2-Ph	CN
f	2,4-Me_2-Ph	H	**n**	3,5-Me_2-Ph	Br	**v**	3,5-Me_2-Ph	CN
g	3,4-Me_2-Ph	H	**o**	2,4-Me_2-Ph	Br			
h	3,5-Cl,Br-Ph	H	**p**	2,5-Me_2-Ph	Br			

Scheme 1. Synthesis of naphthyl-substituted (B-ring) benzophenone analogues**10a**–**v**. Reagents and conditions: (a) $AlCl_3$, ArCOCl, CS_2, reflux, 2 h, 50–76%; (b) CuCN, DMF, 160 °C, 32–43%; (c) K_2CO_3, NaI, *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-bromoacetamide (**11**), acetone, 2 h, 50 °C, 57–67%.

Table 1
Biological activity of compounds **10a–v** against HIV-1 in C8166 cells

Compd	EC_{50}[a]		CC_{50}[c] (μM)	SI[d]
	III_B (nM)	A_{17}[b] (μM)		
10a	52.7 ± 22.0	9.6	33.8 ± 4.7	641.8
10b	13.5	2.4	40.4 ± 0.5	2992.0
10c	33.8 ± 9.3	9.5	37.4 ± 0.8	1106.5
10d	7.8 ± 3.3	8.4	39.1 ± 2.1	5038.4
10e	11.6	7.6	47.5	4093.5
10f	139.3 ± 33.8	7.9	25.5 ± 7.2	183.1
10g	608.9 ± 112.6	12.3	33.0 ± 2.0	54.2
10h	27.1	7.5	36.6 ± 12.6	1348.9
10i	4.8	2.1	49.4 ± 0.8	10347.9
10j	4607.7	25.8	29.2 ± 12.5	6.3
10k	2299.8 ± 563.3	3.4	6.8 ± 0.3	2.9
10l	1672.1 ± 348.9	3.9	6.8 ± 0.2	4.1
10m	9170.3	9.7	31.0 ± 6.3	2.7
10n	4419.8	7.8	24.5 ± 5.1	7.0
10o	23605.3 ± 2196.4	33.1	61.4 ± 23.3	2.6
10p	2644.1 ± 949.7	20.7	14.0 ± 2.2	5.3
10q	31946.1 ± 9353.8	28.2	85.2 ± 27.4	2.7
10r	7573.8	10.2	28.5 ± 15.1	3.8
10s	790.6 ± 140.0	10.4	15.2 ± 3.0	19.2
10t	2046.0 ± 341.8	20.6	>374.5	>183.1
10u	86348.3 ± 2456.0	97.3	>379.1	>4.4
10v	1777.9 ± 226.2	16.3	128.1 ± 17.6	72.0
GW678248	0.69 ± 0.43	0.0014 ± 0.0001	>386.8	>563380.2
AZT	12.82 ± 3.12	0.023	5401.4 ± 345.5	422068.8

[a] EC_{50}: effective concentration of compound required to protect the cell against viral cytopathogenicity by 50% in C8166 cells.
[b] A_{17}: HIV-1 mutated strain bearing both K103N and Y181C mutations.
[c] CC_{50}: cytotoxic concentration of compound that reduces the normal uninfected C8166 cell viability by 50%.
[d] SI: selectivity index: ratio CC_{50}/EC_{50}(HIV-1 III_B).

Table 2
Biological activity of compounds **10b–e**, **10i**, **10j**, **10m**, **10n** and **10r** against HIV-2 ROD in C8166 cells

Compd	EC_{50}[a] (μM)	CC_{50}[b] (μM)	SI[c]
10b	28.3	40.4 ± 0.5	0.7
10c	34.5	37.4 ± 0.8	0.9
10d	45.4	39.1 ± 2.1	1.2
10e	30.3	47.5 ± 0.03	0.6
10i	23.6	49.4 ± 0.8	0.5
10j	27.7	29.2 ± 12.5	0.9
10m	6.0	24.5 ± 5.1	0.2
10n	29.8	31.0 ± 6.3	1.0
10r	11.1	28.5 ± 15.1	0.4
GW678248	2.1	>386.8	>176.7
AZT	39.0	5201.1	133354.1

[a] EC_{50}: effective concentration of compound required to protect the cell against viral cytopathogenicity by 50% in C8166 cells.
[b] CC_{50}: cytotoxic concentration of compound that reduces the normal uninfected C8166 cell viability by 50%.
[c] SI: selectivity index: ratio CC_{50}/EC_{50}.

at *meta*-position was more favorable than that with hydrogen or chloro at the same position. Nevertheless, for the dimethyl substituent at different positions, the activity was vastly different, with the EC_{50} values ranging from 7.8 ± 3.3 nM (**10d**, 3,5-dimethyl-substituted) to 608.9 ± 112.6 nM (**10g**, 3,4-dimethyl-substituted). Although addition of another methyl group (**10d**) at the second *meta*-position on the A-ring did prove to be beneficial, it was 1.6-fold less potent than the chloro, cyano di-substituted analogue **10i** (EC_{50} = 4.8 nM, SI = 10347.9). In fact, in the case of the analogues **10a–i**, a polar aprotic and sterically small *meta*-substituent, such as cyano, would reach into the hydrophobic region adjacent to the side chains of Tyr181 and Tyr188, and thus favoured to enchance the interactions with HIV-1 RT.

In addition, all of the synthesized compounds (**10a–v**) were tested the anti-HIV activity against the double mutant strain A_{17} (103N+181C) and the moderate inhibitory activity with EC_{50} values

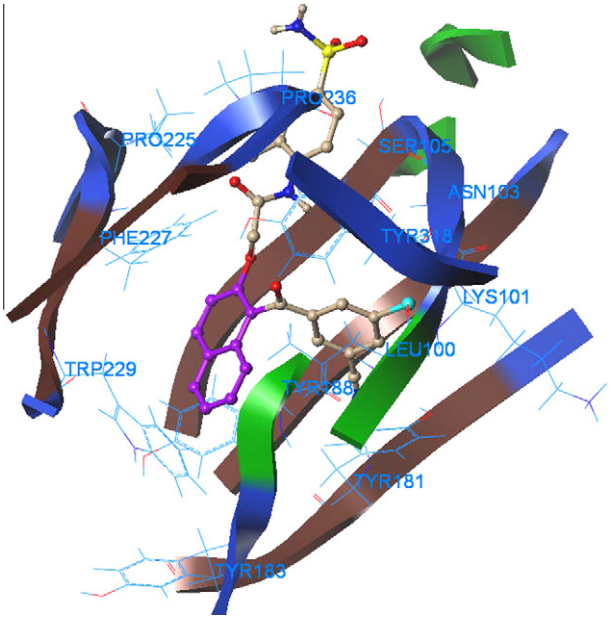


Figure 3. Binding model of **10i** with HIV-1 RT (PDB code: 3DOK).[16]

ranging from 2.1 μM to 97.3 μM were obtained (Table 1). Furthermore, some analogues (**10b–e**, **10i**, **10j**, **10m**, **10n** and **10r**) were also evaluated the potency against the HIV-2 ROD virus (Table 2). Unfortunately, these naphthyl-substituted derivatives almost only exhibited mediocre inhibitory activity against HIV-2 with EC_{50} values in a range from 6.0 μM to 45.4 μM.

2.3. Molecular modeling analysis

To understand how our newly synthesized compounds interact with the reverse transcriptase, a modeling study was carried out

using the program FLEX-DOCK SYBYL-X 1.2 (the default SYBYL-X 1.2 parameters were used).[21] The most potent compound **10i** was chosen to be docked into non-nucleoside inhibitor binding pocket (NNIBP) of HIV-1 RT. As shown in Figure 3, apparently, the naphthyl ring enhances the π–π interactions with amino acid residues Tyr188, Trp229 and Phe227. In addition, there is also a strong π–π interactions between the phenyl (A-ring) and the amino acid residues Tyr181 and Leu100. Moreover, the cyano substituent of A-ring makes a hydrogen bond with the NH group of Tyr181. All these interactions support our initial design, however, the low sensitivity of the title compounds to the drug-resistant strain (K103+Y181) may due to the lack of effective interaction with the key mutant amino acid Asn103, which plays an important role in generating drug-resistance of HIV.

2.4. Conclusion

In the present study, a series of BP derivatives with B-ring substituted by the naphthyl ring were discovered as potent NNRTIs, and their preliminary SARs have been established via chemical modifications. The newly synthesized derivatives **10a**–**i** exhibited excellent potency against HIV-1 wild-type virus, in particular, compound **10i** displayed the best activity with an EC_{50} value of 4.8 nM and selective index value of 10347.9. Also, compound **10i** showed good potency against the double mutant strain A_{17} (K103N+Y181C) with EC_{50} value of 2.1 μM. Furthermore, the binding model of **10i** with RT was also simulated and indicated that the naphthyl ring enchanced the π–π interactions with RT as initial design. Overall, this compound may serve as the basis for further modification in searching for more potent candidates for anti-HIV chemotherapy.

3. Experimental section

3.1. Chemistry

All chemicals used were purchased from commercial sources, were of analytical grade and were used without further purification. Melting points were measured on a SGW X-1 microscopic melting-point apparatus and were uncorrected. Mass spectra were obtained on a Waters Quattro Micromass instrument using electrospray ionization (ESI) techniques. ^{1}H NMR and ^{13}C NMR spectra on a Brucker AV 400 MHz spectrometer were recorded in DMSO-d_6. Chemical shifts were reported in δ (ppm) units relative to the internal standard tetramethylsilane (TMS). Elemental analyses were performed on a Carlo Erba 1106 instrument and the results of elemental analyses for C, H, Cl, Br, F and N were within ±0.4% of the theoretical values. Flash chromatography separations were obtained on Silica gel (300–400 mesh) using EtOAc/hexane as eluents.

3.2. General procedure for the synthesis of 9a–r[17,18].

Anhydrous $AlCl_3$ (1.85 g, 13.90 mmol) was added to a solution of 2-methoxynaphthalene **10a**–**b** (6.32 mmol) and substituted benzoyl chloride (7.51 mmol) in CS_2 (30 mL), carefully holding the temperature under 5 °C. After completion, the mixture was heated to reflux and stirred for additional 2 h. Then the reaction mixture was poured to a beaker containing ice water (45 mL) and concd HCl (15 mL), and stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with dichloromethane three times. The organic layers were combined, dried with anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography using hexane/EtOAc (20:1) to afford **9a–r** as a light yellow solid.

3.3. General procedure for the synthesis of 9s–v[13]

To a solution of **9k**, **9l**, **9q**, **9d** (21.00 mmol) in DMF (20 mL), copper cyanide (3.76, 42.00 mmol) was added and the resulting mixture was heated to 160 °C and stirred for 2 h. The mixture was then cooled, and water was added. The resulting solid was filtered and washed with EtOAc. The filtrate was dried over $MgSO_4$ and concentrated in vacuo. Column chromatography on silica gel using hexane/EtOAc (15:1) gave **9s–v** as a light yellow solid in 32–43% yield.

3.4. General procedure for the synthesis of 10a–v

A mixture of **9a**–**v** (10.00 mmol), **11** (3.06 g, 10.00 mmol), NaI (0.15 g, 1.00 mmol) and K_2CO_3 (4.97 g, 36.00 mmol) in acetone (20 mL) was warmed to reflux for 2 h. The reaction mixture was then poured into water (30 mL) and extracted twice with 30 mL of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to give crude product. Purification by flash chromatography using hexane/EtOAc (10:1) gave **10a**–**v**.

3.4.1. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-(1-benzoyl-2-naphenoxy)acetamide (10a)

Yield 66.9%; white solid, mp 181.2–182.1 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.16 (s, 3H, CH_3), 4.92 (s, 2H, CH_2), 7.28 (s, 2H, NH_2), 7.38–8.16 (m, 14H, Ph*H*, Naph*H*), 9.26 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 17.5, 67.8, 114.6, 122.3, 122.4, 123.4, 123.5, 123.8, 124.4, 127.6, 128.3, 128.7, 129.0 (2C), 129.2 (2C), 130.8, 130.9, 131.3, 134.0, 137.1, 138.4, 140.2, 152.3, 168.4, 196.9; MS (ESI$^-$) *m/z* 473 [M−H]$^-$; Anal. Calcd for $C_{26}H_{22}N_2O_5S$: C 65.81, H 4.67, N 5.90, S 6.76. Found: C 65.79, H 4.65, N 5.93, S 6.78.

3.4.2. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[1-(3-methylbenzoyl)-2-naphenoxy]acetamide (10b)

Yield 65.4%; white solid, mp 200.2–201.3 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.16 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 4.92 (s, 2H, CH_2), 7.29 (s, 2H, NH_2), 7.35–8.15 (m, 13, Ph*H*, Naph*H*), 9.22(s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 17.5, 20.8, 67.8, 114.6, 122.6, 123.5, 123.6, 123.8, 124.5, 126.8, 127.9, 128.4, 128.7, 128.9, 129.4, 130.9, 131.3, 134.8, 137.3, 138.5, 140.3, 152.3, 166.5, 196.8; MS (ESI$^-$) *m/z* 487 [M−H]$^-$; Anal. Calcd for $C_{27}H_{24}N_2O_5S$: C 66.38, H 4.95, N 5.73, S 6.56. Found: C 66.37, H 4.98, N 5.74, S 6.55.

3.4.3. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[1-(3-chlorobenzoyl)-2-naphenoxy]acetamide (10c)

Yield 65.4%; white solid, mp 180.1–181.2 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.19 (s, 3H, CH_3), 4.94 (s, 2H, CH_2), 7.29 (s, 2H, NH_2), 7.39–8.17 (m, 13, Ph*H*, Naph*H*), 9.38(s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 17.6, 67.6, 114.5, 121.4, 123.3, 123.7, 123.8, 124.6, 127.7, 127.9, 128.1, 128.5 (2C), 128.7, 130.8, 131.0, 131.1, 131.8, 133.7, 134.0, 138.6, 139.1, 140.3, 152.7, 166.5, 195.5; MS (ESI$^-$) *m/z* 507 [M−H]$^-$; Anal. Calcd for $C_{26}H_{21}ClN_2O_5S$: C 61.35, H 4.16, Cl 6.97, N 5.50, S 6.30. Found: C 61.33, H 4.17, Cl 6.98, N 5.52, S 6.29.

3.4.4. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[1-(3,5-dimethylbenzoyl)-2-naphenoxy]acetamide (10d)

Yield 58.9%; white solid, mp 191.3–192.4 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.16 (s, 3H, CH_3), 2.24 (s, 6H, 2CH_3), 4.93 (s, 2H, CH_2), 7.28 (s, 2H, NH_2), 7.26–8.14 (m, 12H, Ph*H*, Naph*H*), 9.16 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 17.4, 20.6 (2C), 67.8, 114.6, 122.7, 123.5, 123.8, 124.4, 126.9 (2C), 127.6 (3C), 128.3, 128.7, 130.8, 130.9, 131.1, 136.4, 137.4, 138.2 (2C), 138.4, 140.2, 152.2, 166.4, 196.8; MS (ESI$^-$) *m/z* 501 [M−H]$^-$; Anal. Calcd for $C_{28}H_{26}N_2O_5S$: C 66.91, H 5.21, N 5.57, S 6.38. Found: C 66.89, H 5.20, N 5.57, S 6.40.

3.4.5. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[1-(2,5-dimethylbenzoyl)-2-naphenoxy]acetamide (10e)

Yield 63.5%; white solid, mp 199.9–200.8 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.10 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 4.88 (s, 2H, CH_2), 7.25 (s, 2H, NH_2), 7.25–8.13 (m, 12H, Ph*H*, Naph*H*), 9.26(s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 17.6, 20.3, 20.9, 67.9, 114.8, 123.4, 123.7, 123.8, 124.4 (2C), 127.6, 127.7, 128.4, 128.7, 130.8, 131.1, 131.3, 131.9, 132.0, 133.2, 135.2, 135.7, 137.1, 138.5, 140.3, 152.3, 166.5, 198.9; MS (ESI$^-$) *m/z* 502 [M−H]$^-$; Anal. Calcd for $C_{28}H_{26}N_2O_5S$: C 66.91, H 5.21, N 5.57, S 6.38. Found: C 66.90, H 5.20, N 5.59, S 6.39.

3.4.6. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[1-(2,4-dimethylbenzoyl)-2-naphenoxy]acetamide (10f)

Yield 64.8%; white solid, mp 197.4–198.5 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.08 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 4.81 (s, 2H, CH_2), 7.30 (s, 2H, NH_2), 7.03–8.13 (m, 12H, Ph*H*, Naph*H*), 9.15(s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 16.2, 17.5, 20.0, 68.1, 115.0, 123.4, 123.7, 123.8, 124.5, 124.8, 125.4, 127.7, 127.8, 128.4, 128.7, 128.8, 130.9, 131.2, 131.5, 133.9, 136.7, 138.2, 138.4, 138.7, 140.4, 152.6, 166.4, 199.4; MS (ESI$^-$) *m/z* 502 [M−H]$^-$; Anal. Calcd for $C_{28}H_{26}N_2O_5S$: C 66.91, H 5.21, N 5.57, S 6.38. Found: C 66.93, H 5.23, N 5.56, S 6.37.

3.4.7. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[1-(3,4-dimethylbenzoyl)-2-naphenoxy]acetamide (10g)

Yield 67.1%; white solid, mp 209.8–210.7 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.15 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 4.88 (s, 2H, CH_2), 7.29 (s, 2H, NH_2), 6.96–8.11 (m, 12H, Ph*H*, Naph*H*), 9.17(s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 17.5, 21.0, 21.5, 67.9, 114.8, 123.5, 123.7, 123.8, 124.4, 124.5, 126.7, 127.6, 127.7, 128.3, 128.7, 130.8, 131.0, 131.1, 132.5, 132.8, 134.2, 138.5, 139.2, 140.3, 143.1, 152.0, 166.5, 198.2; MS (ESI$^-$) *m/z* 502 [M−H]$^-$; Anal. Calcd for $C_{28}H_{26}N_2O_5S$: C 66.91, H 5.21, N 5.57, S 6.38. Found: C 66.89, H 5.20, N 5.59, S 6.37.

3.4.8. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[1-(3-chloro-5-bromobenzoyl)-2-naphenoxy]acetamide (10h)

Yield 57.9%; light yellow solid, mp 242.3–243.3 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.21 (s, 3H, CH_3), 4.97 (s, 2H, CH_2), 7.27 (s, 2H, NH_2), 7.43–8.19 (m, 12H, Ph*H*, Naph*H*), 9.46 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 17.7, 67.4, 114.3, 120.3, 123.0, 123.1, 123.7 (2C), 124.5, 127.6, 127.9, 128.0, 128.4, 128.6, 130.4, 130.8, 131.0, 132.1, 135.1, 135.7, 138.5, 140.2, 140.3, 153.0, 166.3, 194.2; MS (ESI$^-$) *m/z* 586 [M−H]$^-$; Anal. Calcd for $C_{26}H_{20}BrN_2O_5S$: C 53.12, H 3.43, Cl 6.03, Br 13.59, N 4.77, S 5.45. Found: C 53.10, H 3.45, Cl 6.02, Br 13.57, N 4.78, S 5.44.

3.4.9. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[1-(3-chloro-5-cyanobenzoyl)-2-naphenoxy]acetamide (10i)

Yield 58.6%; off-white solid, mp 223.4–224.5 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.23 (s, 3H, CH_3), 4.99 (s, 2H, CH_2), 7.29 (s, 2H, NH_2), 7.44–8.31 (m, 12H, Ph*H*, Naph*H*), 9.62 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 17.8, 67.2, 114.1, 114.2, 116.8, 119.9, 123.2, 123.7, 123.8, 124.6, 127.7, 128.1, 128.5, 128.7, 130.8, 131.2, 131.9, 132.4, 133.0, 134.9, 136.5, 138.6, 139.6, 140.2, 153.4, 166.5, 194.0; MS (ESI$^-$) *m/z* 532 [M−H]$^-$; Anal. Calcd for $C_{27}H_{20}ClN_3O_5S$: C 60.73, H 3.78, N 7.57, S 6.00. Found: C 60.72, H 3.79, N 7.55, S 6.01.

3.4.10. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-(6-bromo-1-benzoyl-2-naphenoxy)acetamide (10j)

Yield 60.3%; light yellow solid, mp 213.3–214.5 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.17 (s, 3H, CH_3), 4.94 (s, 2H, CH_2), 7.28 (s, 2H, NH_2), 7.31–8.30 (m, 13H, Ph*H*, Naph*H*), 9.30 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 17.6, 67.9, 115.8, 117.3, 122.3, 123.6, 123.8, 125.6, 127.5, 129.0, 129.3 (2C), 129.4 (2C), 129.8, 130.2, 130.6 (2C), 131.0, 134.2, 137.0, 138.5, 140.2, 152.8, 166.3, 196.1; MS (ESI$^-$) *m/z* 552 [M−H]$^-$; Anal. Calcd for $C_{26}H_{21}BrN_2O_5S$: C 56.43, H 3.82, Br 14.44, N 5.06, S 5.79. Found: C 56.44, H 3.83, Br 14.46, N 5.04, S 5.80.

3.4.11. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[6-bromo-1-(3-methylbenzoyl)-2-naphenoxy]acetamide (10k)

Yield 59.5%; white solid, mp 207.7–208.9 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.17 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 4.94 (s, 2H, CH_2), 7.28 (s, 2H, NH_2), 7.31–8.29 (m, 12H, Ph*H*, Naph*H*), 9.25 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 17.5, 20.8, 67.8, 115.8, 117.3, 122.5, 123.5, 123.8, 125.6, 126.8, 127.6, 128.9, 129.4, 129.5, 129.8, 130.1, 130.4, 130.5, 130.9, 134.8, 137.0, 138.4, 138.5, 140.2, 152.7, 166.3, 196.2; MS (ESI$^-$) *m/z* 567 [M−H]$^-$; Anal. Calcd for $C_{27}H_{23}N_2O_5S$: C 57.15, H 4.09, N 4.94, Br 14.08, S 5.65. Found: C 57.13, H 4.11, N 4.96, Br 14.09, S 5.64.

3.4.12. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[6-bromo-1-(3-chlorobenzoyl)-2-naphenoxy]acetamide (10l)

Yield 61.2%; white solid, mp 199.5–200.4 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.19 (s, 3H, CH_3), 4.96 (s, 2H, CH_2), 7.28 (s, 2H, NH_2), 7.35–8.30 (m, 12H, Ph*H*, Naph*H*), 9.41 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 17.6, 67.5, 115.7, 117.4, 121.3, 123.7 (2C), 123.8, 125.5, 127.7, 128.2, 128.5, 129.4, 129.8, 130.2, 130.7, 131.0, 131.1, 133.8, 134.0, 138.5, 138.8, 140.3, 153.2, 166.3, 194.9; MS (ESI$^-$) *m/z* 586 [M−H]$^-$; Anal. Calcd for $C_{26}H_{20}ClBrN_2O_5S$: C 53.12, H 3.43, N 4.77, Cl 6.03, Br 13.59, S 5.45. Found: C 53.10, H 3.44, N 4.78, Cl 6.02, Br 13.60, S 5.46.

3.4.13. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[6-bromo-1-(3-fluorobenzoyl)-2-naphenoxy]acetamide (10m)

Yield 57.5%; white solid, mp 258.8–259.5 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.19 (s, 3H, CH_3), 4.95 (s, 2H, CH_2), 7.28 (s, 2H, NH_2), 7.34–8.29 (m, 12H, Ph*H*, Naph*H*), 9.40 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 17.6, 67.6, 115.2 (J_{CF} = 22.1 Hz), 115.7, 117.4, 121.1 (J_{CF} = 21.1 Hz), 121.6, 123.8 (2C), 125.5, 125.8 (J_{CF} = 2.2 Hz), 127.7, 129.4, 129.9, 130.3, 130.8, 131.0, 131.2, 131.3 (J_{CF} = 7.4 Hz),, 138.5, 139.3 (J_{CF} = 6.1 Hz), 140.3, 153.1, 162.4 (J_{CF} = 243.9 Hz), 166.4, 195.1 (J_{CF} = 2.1 Hz); MS (ESI$^-$) *m/z* 569 [M−H]$^-$; Anal. Calcd for $C_{26}H_{20}BrFN_2O_5S$: C 54.65, H 3.53, Br 13.98, F 3.32, N 4.90, S 5.61. Found: C 54.63, H 3.54, Br 13.99, F 3.30, N 4.91, S 5.60.

3.4.14. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[6-bromo-1-(3,5-dimethylbenzoyl)-2-naphenoxy]acetamide (10n)

Yield 57.9%; white solid, mp 207.7–208.6 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.16 (s, 3H, CH_3), 2.34 (s, 6H, 2CH_3), 4.92 (s, 2H, CH_2), 7.30 (s, 2H, NH_2), 7.28–8.14 (m, 11H, Ph*H*, Naph*H*), 9.17 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 17.4, 20.6 (2C), 67.8, 114.6, 122.7, 123.4, 124.4, 126.9 (2C), 127.6 (3C), 128.3, 128.7, 130.8, 130.9, 131.1, 135.4, 136.7, 137.4, 138.2 (2C), 138.4, 140.2, 152.2, 166.4, 196.8; MS (ESI$^-$) *m/z* 580 [M−H]$^-$; Anal. Calcd for $C_{28}H_{25}BrN_2O_6S$: C 57.84, H 4.33, N 4.82, S, Br 13.74. Found: C 57.83, H 4.35, N 4.80, S, Br 13.73.

3.4.15. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[6-bromo-1-(2,4-dimethylbenzoyl)-2-naphenoxy]acetamide (10o)

Yield 63.7%; white solid, mp 209.8–210.5 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.16 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 4.90 (s, 2H, CH_2), 7.28 (s, 2H, NH_2), 6.97–8.27 (m, 11H, Ph*H*, Naph*H*), 9.19 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 17.5, 21.0, 21.5, 67.8, 116.0, 117.3, 123.7, 123.8, 124.5, 125.7, 126.7, 127.6, 129.4, 129.9, 130.1, 130.3, 130.5, 131.0, 132.5, 132.9, 134.0, 138.4, 139.3, 140.3, 143.2, 152.5, 166.3, 197.5; MS (ESI$^-$) *m/z* 580 [M−H]$^-$; Anal. Calcd for $C_{28}H_{25}BrN_2O_5S$: C 57.84, H 4.33, N 4.82, Br 13.74, S 5.51. Found: C 57.85, H 4.34, N 4.80, Br 13.72, S 5.50.

3.4.16. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[6-bromo-1-(2,5-dimethylbenzoyl)-2-naphenoxy]acetamide (10p)

Yield 65.8%; white solid, mp 205.5–206.3 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.17 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 4.83 (s, 2H, CH_2), 7.31 (s, 2H, NH_2), 7.05–8.29 (m, 11H, Ph*H*, Naph*H*), 9.18 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 16.3, 17.6, 20.0, 68.0, 116.3, 117.4, 123.8 (2C), 124.8, 125.4, 125.7, 127.7, 128.7, 129.5, 130.0, 130.2, 130.7, 130.8, 131.2, 133.8, 136.8, 138.2, 138.4, 138.5, 140.4, 153.0, 166.3, 198.7; MS (ESI$^-$) *m/z* 580 [M−H]$^-$; Anal. Calcd for $C_{28}H_{25}BrN_2O_5S$: C 57.84, H 4.33, N 4.82, Br 13.74, S 5.51. Found: C 57.86, H 4.34, N 4.80, Br 13.73, S 5.50.

3.4.17. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[6-bromo-1-(3,4-dimethylbenzoyl)-2-naphenoxy]acetamide (10q)

Yield 63.7%; white solid, mp 210.4–211.9 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.10 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 4.88 (s, 2H, CH_2), 7.25 (s, 2H, NH_2), 7.28–8.27 (m, 11H, Ph*H*, Naph*H*), 9.27 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 17.6, 20.3, 20.9, 67.8, 116.1, 117.3, 123.8 (2C), 124.4, 125.7, 127.7, 129.4, 129.9, 130.2, 130.6 (2C, 130.55, 130.62), 131.1, 132.0 (2C, 132.00, 132.03), 133.3, 135.3, 135.8, 136.8, 138.5, 140.3, 152.8, 166.4, 198.2; MS (ESI$^-$) *m/z* 580 [M−H]$^-$; Anal. Calcd for $C_{28}H_{25}BrN_2O_5S$: C 57.84, H 4.33, N 4.82, Br 13.74, S 5.51. Found: C 57.83, H 4.32, N 4.81, Br 13.72, S 5.52.

3.4.18. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[6-bromo-1-(3-chloro-5-bromobenzoyl)-2-naphenoxy]acetamide (10r)

Yield 59.1%; white solid, mp 227.3–228.2 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.22 (s, 3H, CH_3), 4.98 (s, 2H, CH_2), 7.27 (s, 2H, NH_2), 7.40–8.30 (m, 11H, Ph*H*, Naph*H*), 9.48 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 17.7, 67.3, 115.6, 117.4, 120.4, 123.1, 123.7(2C), 125.4, 127.6, 128.0, 129.3, 129.8, 130.2, 130.4, 130.8, 131.1, 131.4, 135.1, 135.9, 138.5, 140.1, 140.2, 153.5, 166.2, 193.7; MS (ESI$^-$) *m/z* 666 [M−H]$^-$; Anal. Calcd for $C_{26}H_{19}Br_2N_2O_5S$: C 46.83, H 2.87, Cl 5.32, Br 23.97, N 4.20, S 4.81. Found: C 46.80, H 2.88, Cl 5.35, Br 23.96, N 4.22, S 4.80.

3.4.19. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[6-cyano-1-(3-methylbenzoyl)-2-naphenoxy]acetamide (10s)

Yield 56.9%; off-white solid, mp 228.9–230.8 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.18 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 5.00 (s, 2H, CH_2), 7.27 (s, 2H, NH_2), 7.35–8.29 (m, 12H, Ph*H*, Naph*H*), 9.35 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 17.7, 20.8, 67.5, 106.7, 116.3, 119.1, 122.6, 123.8, 123.9, 124.9, 125.8, 126.9, 127.6, 127.8, 128.1, 129.1, 129.5, 129.6, 130.6, 132.3, 132.6, 135.0, 135.1, 137.0, 138.6, 138.7, 156.0, 166.3, 196.0; MS (ESI$^-$) *m/z* 513 [M−H]$^-$; Anal. Calcd for $C_{29}H_{23}N_3O_5S$: C 65.48, H 4.51, N 8.18, S 6.24. Found: C 65.51, H 4.50, N 8.18, S 6.25.

3.4.20. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[6-cyano-1-(3-chlorobenzoyl)-2-naphenoxy]acetamide (10t)

Yield 57.1%; off-white solid, mp 184.7–185.5 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.21 (s, 3H, CH_3), 5.03 (s, 2H, CH_2), 7.28 (s, 2H, NH_2), 7.52–8.65 (m, 12H, Ph*H*, Naph*H*), 9.48 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 17.7, 67.3, 106.7, 116.1, 119.0, 121.3, 123.7 (2C), 124.6, 127.4, 127.9, 128.1, 128.2, 128.5, 131.0, 131.1, 132.4, 132.6, 133.9, 134.0, 134.9, 138.5, 138.6, 140.3, 156.3, 166.1, 194.6; MS (ESI$^-$) *m/z* 533 [M−H]$^-$; Anal. Calcd for $C_{27}H_{20}ClN_3O_5S$: C 60.73, Cl 6.64, H 3.78, N 7.87, S 6.00. Found: C 60.72, Cl 6.65, H 3.79, N 7.88, S 6.01.

3.4.21. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[6-cyano-1-(3,4-dimethylbenzoyl)-2-naphenoxy]acetamide (10u)

Yield 56.2%; off-white solid, mp 220.7–221.9 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.17 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 4.91 (s, 2H, CH_2), 7.28 (s, 2H, NH_2), 7.04–8.63 (m, 11H, Ph*H*, Naph*H*), 9.24 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 16.2, 17.6, 20.0, 67.8, 106.6, 116.5, 119.0, 123.8 (2C), 124.6, 124.8, 125.4, 127.4, 127.9, 128.1, 128.8, 131.2, 132.3, 132.4, 133.9, 134.9, 136.9, 138.1, 138.3, 138.4, 140.4, 156.1, 166.0, 198.3; MS (ESI$^-$) *m/z* 527 [M−H]$^-$; Anal. Calcd for $C_{29}H_{25}N_3O_5S$: C 66.02, H 4.78, N 7.96, S 6.08. Found: C 66.01, H 4.79, N 7.95, S 6.06.

3.4.22. *N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[6-cyano-1-(3,5-dimethylbenzoyl)-2-naphenoxy]acetamide (10v)

Yield 58.2%; off-white solid, mp 258.7–259.5 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.16 (s, 3H, CH_3), 2.24 (s, 6H, 2CH_3), 5.01 (s, 2H, CH_2), 7.28 (s, 2H, NH_2), 7.28–8.64 (m, 11H, Ph*H*, Naph*H*), 9.30 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ: 17.6, 20.6 (2C), 67.4, 106.6, 116.2, 119.0, 122.6, 123.5, 123.8, 124.8, 127.0 (2C), 127.4, 127.8, 127.9, 130.9, 132.0, 132.1, 134.9, 135.7, 137.0, 138.3, 138.4 (2C), 140.2, 154.9, 166.1, 195.9; MS (ESI$^-$) *m/z* 526 [M−H]$^-$; Anal. Calcd for $C_{29}H_{25}N_3O_5S$: C 66.02, H 4.78, N 7.96, S 6.08. Found: C 66.00, H 4.10, N 7.97, S 6.09.

3.5. Anti-HIV activity

3.5.1. Cytotoxicity assay

The cytotoxicities of compounds on C8166 cells were assessed by MTT colorimetric assay as described previously.[19] The absorbance at 570 nm/630 nm ($A_{570/630}$) was read in an ELISA reader (Elx1000, 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.

3.5.2. Syncytium reduction assay

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_{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 and GW678248 were used for drug control. After 3 days of culture, the number of syncytia (multinucleated giant cells) was scored under an inverted microscope; 50% effective concentration to blocking syncytia formation (EC_{50}) was calculated.[20]

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