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# Synthesis and biological evaluation of (±)-benzhydrol derivatives as potent non-nucleoside HIV-1 reverse transcriptase inhibitors

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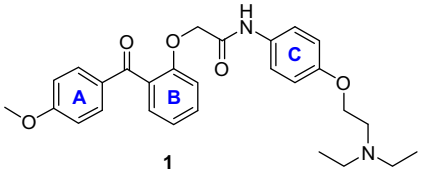
ABSTRACT

A series of (±)-benzhydrol derivatives featuring the essential sulfonamide group at the *para* position on the C-ring were synthesized and evaluated for the potential anti-HIV activity in C8166 cells. Most of these analogues demonstrated low concentration inhibitory activity with $EC_{50}$ values less than 1 μM against the wild-type HIV-1. In particular, compound **7h** was identified as the highest active inhibitor of wild-type HIV-1 with an $EC_{50}$ value of 0.12 μM and selectivity index value of 312.73. Furthermore, some of them also exhibited moderate activity against the double mutant strain $A_{17}$ (K103N + Y181C) with $EC_{50}$ values lower than 5 μM. In addition, the binding modes with RT and the preliminary structure–activity relationships of these derivatives were also explored for further chemical modifications.



## 1. Introduction

As novel non-nucleoside reverse transcriptase inhibitors (NNRTIs),[1–5] benzophenone derivatives (BPs, Fig. 1), originated in a high-throughput screening in 1995,[6] have attracted considerable attention due to their excellent activity against most current clinically relevant HIV-1 mutants.[7–14] Hitherto, lots of constructive work for optimizing the initial benzophenone **1**, have led to discover several highly potent compounds against both wild-type and mutant HIV-1 viruses, such as **2** (GW45119[9]), **3** (GW678248[10,11]) and its prodrug **4** (GW695634[11]). Previous studies on the structure modifications of BPs have shown that the carbonyl group between the A- and B-rings was essential for maintaining high anti-HIV activity,[7,12] so little attention has been paid on this keto template in the following studies. Considering that the flexibility of benzhydrol derivatives might be more adaptive to bind with HIV-1 RT, herein, we reduced the carbonyl to hydroxy group and afforded a series of (±)-benzhydrol derivatives (**7a–t**) bearing the sulfonamide group at the *para* position on the C-ring, which pointed directly into the exterior water through a rather small window in the protein surface and played an important role in the capacity to inhibit HIV-1 replication.[12] Furthermore, all of these analogues evaluated the activity against the wild-type HIV-1 virus and the double mutant strain $A_{17}$ (K103N + Y181C).




**2**, $R^1$ = F, $R^2$ = $CF_3$, $R^3$ = H (GW4511)
**3**, $R^1$ = Cl, $R^2$ = CN, $R^3$ = H (GW678248)
**4**, $R^1$ = Cl, $R^2$ = CN, $R^3$ = propionyl (GW695634)

**Figure 1.** Structures of potent benzophenones.

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In addition, the preliminary structure–activity relationships (SARs) and the binding modes with RT of these analogues were also investigated in this manuscript.

## 2. Results and discussion

### 2.1. Chemistry

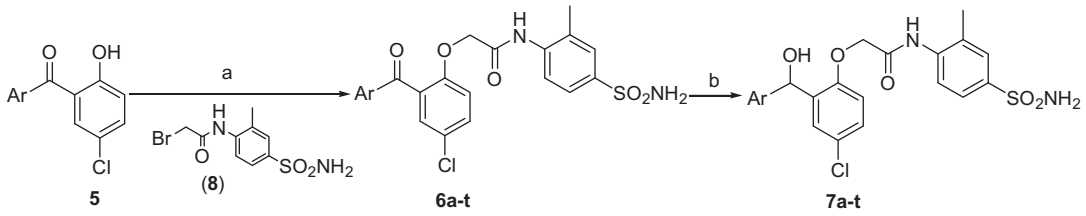
The synthesis of the target compounds **7a**–**t** is shown in Scheme 1. As reported previously,[9,11] the starting material 5-chloro-2-hydroxyphenyl phenylmethanone (**5**) were obtained from 4-chloroanisole by Friedel–Crafts acylation with substituted benzoyl chloride. The following alkylation with *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-bromoacetamide (**8**) formed the benzophenone intermediates **6a**–**t**, respectively. Finally, reduction of **6a**–**t** in the presence of $NaBH_4$ at 50 °C for 2 h in MeOH solution conveniently afforded the desired (±)-benzhydrol derivatives **7a**–**t** in 73–93% yield.

### 2.2. Biological activity

All synthesized compounds were tested in their capacity to inhibit the replication of wild-type HIV-1 strain $III_B$ and the double mutant strain $A_{17}$ (K103N + Y181C) in C8166 cells, in parallel with cytotoxic activity. For comparasion, the FDA-approved drug zidovudine (AZT) and the lead compound GW678248 were also tested as reference drugs according to the same procedure.[15,16] 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 shown in Table 1.

Apparently, most of the (±)-benzhydrol derivatives were potent against the wild-type HIV-1 virus within less than 1 μM concentration. Among these active inhibitors, compound **7h** exhibited the highest potency with an $EC_{50}$ value of 0.12 μM and selectivity index value of 312.73. In addition, all the newly synthesized compounds were also evaluated in the activity against the double mutant strain $A_{17}$ (K103N + Y181C) to explore the capacity of these analogues to inhibit the drug-resistant virus. However, as seen from the test results, except for analogue **7h** ($EC_{50}$ = 4.34 μM) and **7l** ($EC_{50}$ = 2.08 μM), most of them almost lost the potency against this double mutated virus.

In terms of the SARs, it seemed that the changes in the A-ring did prove to have a less influence on the potency of the analogues. For example, mono-substituted analogues **7b**–**h** were not superior to **7a** without any substituents on the A-ring, furthermore, comparing with mono-substituted analogues, addition of another substituent at different position (**7i**–**r**) was also not effective to improve anti-HIV activity. While for the **7s** and **7t**, which were substituted by 1-naphthyl and 2-naphthyl on the A-ring, respectively, the activity was almost similar to that of phenyl analogues. Although all of these compounds showed little difference in the potency against wild-type HIV-1 virus, in fact, for the series of




**Scheme 1.** Synthesis of (±)-benzhydrol analogues **7a**–**t**. Reagents and conditions: (a) *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-bromoacetamide (**8**), $K_2CO_3$, KI, acetone, 2 h, 50 °C, 53–72%; (b) $KBH_4$, MeOH, 50 °C, 2 h, 73–93%.

**Table 1**
Anti-HIV activity and cytotoxicity of compounds **7a–t** in C8166 cells

| Compd | Ar | $EC_{50}$[a] (μM) | | $CC_{50}$[c] (μM) | SI[d] |
|---|---|---|---|---|---|
| | | $III_B$ | $A_{17}$[b] | | |
| **7a** | Ph | 1.12 ± 0.59 | 16.46 | 33.40 ± 0.79 | 29.92 |
| **7b** | 2-Me-Ph | 1.21 ± 0.46 | 20.83 | 33.92 ± 4.65 | 27.97 |
| **7c** | 3-Me-Ph | 0.48 ± 0.35 | 9.70 | 33.15 ± 5.57 | 69.05 |
| **7d** | 4-Me-Ph | 0.65 ± 0.3 | 13.38 | 38.70 ± 0.27 | 59.30 |
| **7e** | 2-Cl-Ph | 1.30 ± 0.38 | 20.35 | 31.98 ± 2.80 | 24.58 |
| **7f** | 3-Cl-Ph | 0.72 ± 0.24 | 12.98 | 33.25 ± 4.51 | 46.40 |
| **7g** | 3-F-Ph | 0.48 ± 0.21 | 6.61 | 37.64 ± 2.89 | 78.54 |
| **7h** | 3-$NO_2$-Ph | 0.12 ± 0.05 | 4.34 | 36.85 ± 4.31 | 312.73 |
| **7i** | 2,3-DiMe-Ph | 9.02 | 216.49 | 217.78 | 24.14 |
| **7j** | 2,4-DiMe-Ph | 4.27 | 40.44 | 26.35 | 6.18 |
| **7k** | 2,5-DiMe-Ph | 0.81 ± 0.31 | 14.33 | 35.52 ± 2.55 | 43.70 |
| **7l** | 3,5-DiMe-Ph | 0.18 ± 0.07 | 2.08 | 29.36 ± 1.39 | 165.97 |
| **7m** | 2,4-DiCl-Ph | 2.92 ± 0.61 | 33.59 | 39.89 ± 0.12 | 13.67 |
| **7n** | 2,5-DiCl-Ph | 1.06 ± 0.07 | 9.58 | 36.17 ± 2.53 | 34.19 |
| **7o** | 3,4-DiCl-Ph | 2.15 ± 0.53 | 31.59 | 24.04 ± 0.24 | 11.20 |
| **7p** | 3,5-DiCl-Ph | 1.06 ± 0.42 | 9.45 | 13.12 ± 1.55 | 12.40 |
| **7q** | 3,5-Cl,Br-Ph | 0.54 ± 0.18 | 7.79 | 22.92 ± 4.37 | 42.39 |
| **7r** | 3,5-Cl,CN-Ph | 0.39 ± 0.25 | 6.84 | 31.58 ± 3.21 | 80.75 |
| **7s** | 1-Naphthyl | 0.39 ± 0.25 | 8.47 | 31.13 ± 0.03 | 80.14 |
| **7t** | 2-Naphthyl | 1.09 ± 0.61 | 10.70 | 15.66 ± 0.57 | 14.30 |
| GW678248 | | 0.00069 ± 0.00043 | 0.0014 ± 0.0001 | >386.8 | >563380.2 |
| AZT | | 0.0128 ± 0.00312 | 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. Data represent the mean of at least two separate experiments.
[b] $A_{17}$: HIV-1 mutated strain bearing both K103N and Y181C mutations. Data represent one experiment.
[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 $III_B$).

mono-substituted compounds **7b**–**h**, obviously, placement of a small group at the *meta* position (**7c**) was more favourable than that at the *ortho* (**7b**) or the *para* (**7d**) position. Furthermore, introduction of electron withdrawing substituent at *meta* position (**7h**) was also very tolerable. In the case of the di-substituents (**7i**–**r**), such as cyan and chloro (**7r**), dimethyl (**7p**) at di-*meta* position, strong capacity to inhibit the wild-type HIV-1 virus was displayed.

### 2.3. Molecular modelling analysis

In order to explore the binding modes of the (±)-benzhydrol derivatives with HIV-1 RT, molecular simulation was carried out by docking two most potent compounds **7h** and **7l** into the non-nucleoside binding site (NNBS) of HIV-1 RT (PDB code: 3DOK),[12] for comparasion, lead compound GW678248 was simulated, too. On the basis of the protocols,[17,18] illustrated in detail in Section 3, the simulations were performed using the Base-builder program and Flex-dock program interfaced with SYBYL-X 1.2.[19–22] The default SYBYL-X 1.2 parameters were used.

As shown in Figure 2, GW678248 formed several well-known interactions with RT: (i) the van der Waals interactions between the cyano group at *meta*-position of the A-ring and the amino acid residue Trp229; (ii) the H-bond interactions were formed by the NH group that links the B- and C-rings with Asn103, the NH of the sulfonamide group with Lys104 and the oxygen atom of the sulfonamide group with Val106; (iii) the $\pi$–$\pi$ interactions were formed by the A-ring with Tyr188 and B-ring with Tyr181. However, the binding sites of the analogue **7h** with enzyme were greatly different from that of GW678248. Almost, **7h** reached out of the binding pocket and lost the interactions with the key mutant amide acid Tyr181, Tyr188 and Trp229. Meanwhile, although the docked conformation of **7l** was superimposed well onto that of GW678248, the strong H-bond between NH group of analogue **7l** and Asn103 of RT disappeared completely, which was important for BPs to maintain high potency against wild-type HIV-1 virus and mutant HIV-1 virus. In summary, all these docking results were in accordance with the anti-HIV activity data.

### 2.4. Conclusion

In the present paper, we synthesized a series of (±)-benzhydrol derivatives bearing the important substitution of sulfonamide group at the *para* position on the C-ring, and evaluated their activity against HIV in C8166 cells. It was found that most of the analogues demonstrated inhibitory activity in low micromolar concentration with $EC_{50}$ values less than 1 μM against wild-type HIV-1. Furthermore, some of them also exhibited moderate potency against the double mutant HIV-1 strain $A_{17}$ (K103N + Y181C) at the concentration lower than 5 μM. In addition, we also built the molecular modes to analyse the interactions between the analogues and RT. In the view of the preliminary studies on the molecular simulations and the SARs of these derivatives, it was indicated that both the keto and sulfonamide groups were essential for BPs to maintain strong capacity to inhibit HIV-1 replication.

## 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 are reported in $\delta$ (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 and N were within ±0.4% of the theoretical values. TLC analyses were run on Silica Gel 60 F254 plates (Merck) using a variety of solvent systems and a fluorescent indicator for visualization. Spots were visualized under 254 nm UV illumination. Flash chromatography separations were obtained on silica gel (300–400 mesh) using EtOAc/hexane as eluents.

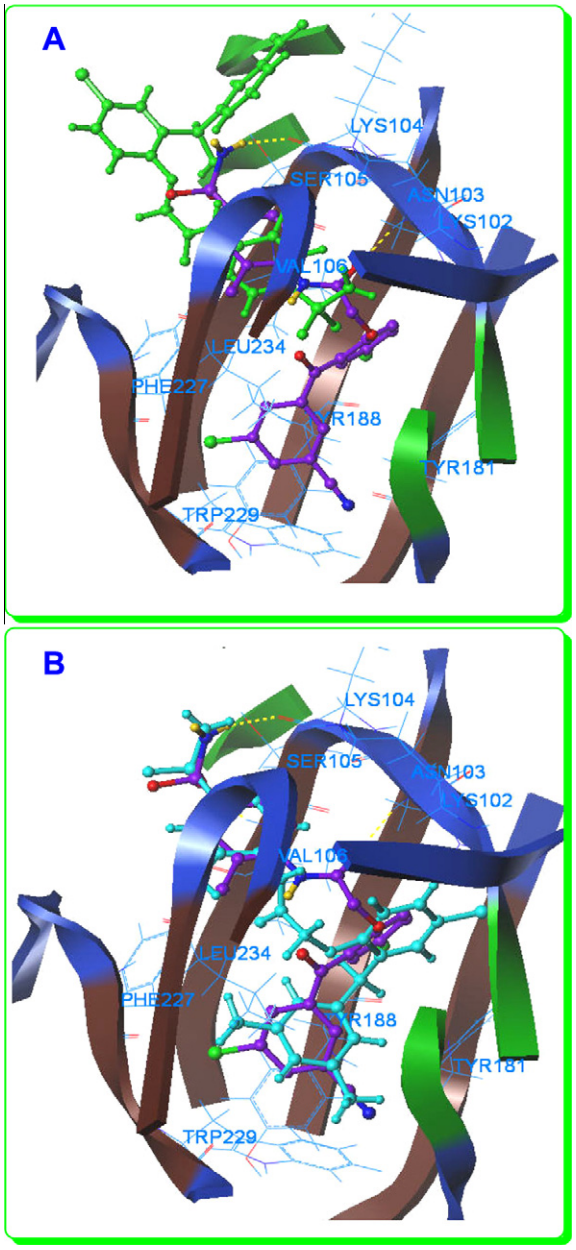



**Figure 2.** (A) Superimposition of the docked conformations of GW678248 (purple) and **7h** (green); (B) superimposition of the docked conformations of GW678248 (purple) and **7l** (cyan).

### 3.2. General procedure for the synthesis of 7a–t[7]

Sodium borohydride (0.19 g, 5.00 mmol) was added to a solution of **6a–t** (5.00 mmol) in THF (50 mL) at 0 °C. The mixture was slowly warmed to reflux and stirred for 1 h, and then the reaction

mixture was poured into water (30 mL) and extracted twice with EtOAc (2 × 30 mL). The combined organic layers were washed with 2 N HC1, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude product which was crystallized from acetonitrile to give **7a**–**t** as white solids in yield of 73–93%.

#### 3.2.1. (±)-*N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(hydroxyphenylmethyl)phenoxyl]acetamide (7a)

Yield 91.7%; mp 185.3–186.4 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.25 (s, 3H, C$H_3$), 4.74–4.85 (m, 2H, C$H_2$), 6.00 (d, 1H, $J$ = 4.4 Hz, O$H$), 6.15 (d, 1H, $J$ = 4.0 Hz, C$H$), 7.31 (s, 2H, N$H_2$), 7.00–7.75 (m, 11H, Ph$H$), 9.59 (s, 1H, N$H$); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 17.8, 67.9, 68.1, 114.0, 123.8, 124.4, 125.2, 126.4 (2C), 126.6, 126.9, 127.6, 127.7, 127.9, 128.0 (2C), 131.8, 136.2, 138.6, 140.5, 144.4, 153.1, 166.6; MS (ESI$^-$) $m/z$ 459 [M−H]$^-$; Anal. Calcd for $C_{22}H_{21}ClN_2O_5S$: C, 57.33; H, 4.59; Cl, 7.69; N, 6.08; S, 6.96. Found: C, 57.30; H, 4.58; Cl, 7.70; N, 6.10; S, 6.98.

#### 3.2.2. (±)-*N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[hydroxyl(2-methylphenyl)methyl]phenoxyl}acetamide (7b)

Yield 93.2%; mp 195.5–196.4 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.23 (s, 3H, C$H_3$), 2.29 (s, 3H, C$H_3$), 4.72–4.86 (m, 2H, C$H_2$), 5.85 (d, 1H, $J$ = 4.8 Hz, O$H$), 6.29 (d, 1H, $J$ = 4.8 Hz, C$H$), 7.32 (s, 2H, N$H_2$), 7.06–7.72 (m, 10H, Ph$H$), 9.49 (s, 1H, N$H$); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 17.8, 18.9, 65.4, 67.8, 114.2, 123.8, 124.5, 125.2, 125.7, 128.6, 127.0, 127.4, 127.8, 127.9, 130.1, 131.9, 135.3, 136.3, 138.6, 140.8, 141.6, 153.7, 166.7; MS (ESI$^-$) $m/z$ 473 [M−H]$^-$; Anal. Calcd for $C_{23}H_{23}ClN_2O_5S$: C, 58.16; H, 4.88; Cl, 7.46; N, 5.90; S, 6.75. Found: C, 58.15; H, 4.90; Cl, 7.45; N, 5.89; S, 6.73.

#### 3.2.3. (±)-*N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[hydroxyl(3-methylphenyl)methyl]phenoxyl}acetamide (7c)

Yield 90.5%; mp 193.4–194.7 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.24 (s, 3H, C$H_3$), 2.25 (s, 3H, C$H_3$), 4.73–4.85 (m, 2H, C$H_2$), 5.95 (s, 1H, O$H$), 6.10 (s, 1H, C$H$), 7.31 (s, 2H, N$H_2$), 6.99–7.74 (m, 10H, Ph$H$), 9.54 (s, 1H, N$H$); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 17.8, 21.1, 67.6, 68.1, 114.0, 123.5, 123.8, 124.4, 125.2, 126.6, 127.0, 127.5, 127.6, 127.7, 127.9, 131.8, 136.3, 137.0, 138.6, 140.6, 144.3, 153.0, 166.6; MS (ESI$^-$) $m/z$ 473 [M−H]$^-$; Anal. Calcd for $C_{23}H_{23}ClN_2O_5S$: C, 58.16; H, 4.88; Cl, 7.46; N, 5.90; S, 6.75. Found: C, 58.15; H, 4.89; Cl, 7.45; N, 5.90; S, 6.75.

#### 3.2.4. (±)-*N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[hydroxyl(4-methylphenyl)methyl]phenoxyl}acetamide (7d)

Yield 92.1%; mp 190.4–191.7 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.23 (s, 3H, C$H_3$), 2.25 (s, 3H, C$H_3$), 4.73–4.85 (m, 2H, C$H_2$), 5.93(d, 1H, $J$ = 4.4 Hz, O$H$), 6.09 (d, 1H, $J$ = 4.4 Hz, C$H$),7.31 (s, 2H, N$H_2$), 7.00–7.73 (m, 10H, Ph$H$), 9.59 (s, 1H, N$H$); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 17.8, 20.9, 67.6, 67.9, 114.0, 123.8, 124.4, 125.1, 126.4, 126.6, 127.4, 127.7, 128.5 (2C), 131.8, 135.9, 136.4 (2C), 138.8, 140.6, 141.4, 153.0, 166.6; MS (ESI$^-$) $m/z$ 473 [M−H]$^-$; Anal. Calcd for $C_{23}H_{23}ClN_2O_5S$: C, 58.16; H, 4.88; Cl, 7.46; N, 5.90; S, 6.75. Found: C, 58.15; H, 4.90; Cl, 7.48; N, 5.93; S, 6.74.

#### 3.2.5. (±)-*N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[hydroxyl(2-chlorphenyl)methyl]phenoxyl}acetamide (7e)

Yield 88.4%; mp 173.7–174.8 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.25 (s, 3H, C$H_3$), 4.75–4.89 (m, 2H, C$H_2$), 6.16 (s, 1H, O$H$), 6.41 (s, 1H, C$H$), 7.38 (s, 2H, N$H_2$), 7.08–7.75 (m, 10H, Ph$H$), 9.53 (s, 1H, N$H$); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 18.2, 66.1, 68.4, 114.9, 124.3, 124.8, 125.6, 127.6, 127.8, 128.2, 128.7, 129.2, 129.4, 129.7, 132.2, 134.4, 134.7, 139.0, 141.0, 141.2, 154.4, 166.2; MS (ESI$^-$) $m/z$ 493 [M−H]$^-$; Anal. Calcd for $C_{22}H_{20}Cl_2N_2O_5S$: C, 53.34; H, 4.07; Cl, 14.31; N, 5.65; S, 6.47. Found: C, 53.32; H, 4.05; C, 14.32; N, 5.63; S, 6.49.

#### 3.2.6. (±)-*N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[hydroxyl(3-chlorphenyl)methyl]phenoxyl}acetamide (7f)

Yield 87.1%; mp 181.1–182.5 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.25 (s, 3H, C$H_3$), 4.73–4.85 (m, 2H, C$H_2$), 5.94 (d, 1H, $J$ = 4.4 Hz, O$H$), 6.10 (d, 1H, $J$ = 4.4 Hz, C$H$), 7.31 (s, 2H, N$H_2$), 7.00–7.74 (m, 10H, Ph$H$), 9.56 (s, 1H, N$H$); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 17.8, 67.6, 68.1, 114.0, 123.5, 123.8, 124.4, 125.2, 126.6, 127.0, 127.5 (2C, 127.48, 127.50), 127.7, 127.9, 131.8, 136.3, 137.0, 138.6, 140.5, 144.3, 153.0, 166.6; MS (ESI$^-$) $m/z$ 493 [M−H]$^-$; Anal. Calcd for $C_{22}H_{20}Cl_2N_2O_5S$: C, 53.34; H, 4.07; Cl, 14.31; N, 5.65; S, 6.47. Found: C, 53.33; H, 4.04; C, 14.32; N, 5.66; S, 6.45.

#### 3.2.7. (±)-*N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[hydroxyl(3-fluorophenyl)methyl]phenoxyl}acetamide (7g)

Yield 85.4%; mp 157.8–158.9 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.27 (s, 3H, C$H_3$), 4.78–4.88 (m, 2H, C$H_2$), 6.15 (m, 2H, O$H$, C$H$), 7.31 (s, 2H, N$H_2$), 6.98–7.74 (m, 10H, Ph$H$), 9.64 (s, 1H, N$H$); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 17.8, 67.4, 67.6, 113.0 ($J_{C\text{-}F}$ = 22.2 Hz), 113.6 ($J_{C\text{-}F}$ = 20.4 Hz), 114.1, 122.3 ($J_{C\text{-}F}$ = 2.8 Hz), 123.8, 124.4, 125.3, 126.6, 127.7, 127.8, 129.9 ($J_{C\text{-}F}$ = 4.0 Hz), 131.8, 135.6, 138.6, 140.6, 147.5 ($J_{C\text{-}F}$ = 7.1 Hz), 153.0, 162.0 ($J_{C\text{-}F}$ = 241.1 Hz), 166.6; MS (ESI$^-$) $m/z$ 477 [M−H]$^-$; Anal. Calcd for $C_{22}H_{20}ClFN_2O_5S$: C, 55.17; H, 4.21; Cl, 7.40; F, 3.97; N, 5.85; S, 6.70. Found: C, 55.15; H, 4.20; Cl, 7.43; F, 3.95; N, 5.82; S, 6.73.

#### 3.2.8. (±)-*N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[hydroxyl(3-nitrophenyl)methyl]phenoxyl}acetamide (7h)

Yield 78.9%; mp 189.9–190.7 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.28 (s, 3H, C$H_3$), 4.81–4.90 (m, 2H, C$H_2$), 6.29 (s, 1H, C$H$), 6.44 (s, 1H, O$H$), 7.73 (s, 2H, N$H_2$), 7.04–8.30 (m, 10H, Ph$H$), 9.80 (s, 1H, N$H$); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 18.0, 67.5, 67.6, 114.2, 120.9, 122.0, 123.9, 124.6, 125.4, 126.6, 127.8, 128.2, 129.7, 132.1, 133.3, 136.1, 138.8, 140.6, 146.7, 147.8, 153.1, 166.7; MS (ESI$^-$) $m/z$ 504 [M−H]$^-$; Anal. Calcd for $C_{22}H_{20}ClN_3O_7S$: C, 52.23; H, 3.98; Cl, 7.01; N, 8.31; S, 6.34. Found: C, 52.20; H, 3.95; Cl, 7.06; N, 8.34; S, 6.31.

#### 3.2.9. (±)-*N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[hydroxyl(2,3-dimethylphenyl)methyl]phenoxyl}acetamide (7i)

Yield 91.7%; mp 173.4–174.3 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.15 (s, 3H, C$H_3$), 2.18 (s, 3H, C$H_3$), 2.23 (s, 3H, C$H_3$), 4.75–4.89 (m, 2H, C$H_2$), 5.83 (s, 1H, O$H$), 6.33 (s, 1H, C$H$), 7.33 (s, 2H, N$H_2$), 7.01–7.71 (m, 9H, Ph$H$), 9.65 (s, 1H, N$H$); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 14.5, 17.9, 20.2, 65.5, 67.7, 114.1, 123.7, 123.8, 124.4, 124.6, 125.0 (2C), 127.4, 127.7 (2C), 128.6, 133.8, 136.6, 138.2, 138.6, 140.6, 141.5, 153.6, 166.8; MS (ESI$^-$) $m/z$ 487 [M−H]$^-$; Anal. Calcd for $C_{24}H_{25}ClN_2O_5S$: C, 58.95; H, 5.15; Cl, 7.25; N, 5.73; S, 6.56. Found: C, 58.92; H, 5.16; Cl, 7.27; N, 5.75; S, 6.54.

#### 3.2.10. (±)-*N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[hydroxyl(2,4-dimethylhenyl)methyl]phenoxyl}acetamide (7j)

Yield 89.9%; mp 185.4–186.3 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.21 (s, 6H, 2C$H_3$), 2.25 (s, 3H, C$H_3$), 4.72–4.85 (m, 2H, C$H_2$), 5.78 (s, 1H, O$H$), 6.32 (s, 1H, C$H$), 7.27 (s, 2H, N$H_2$), 6.92–7.70 (m, 9H, Ph$H$), 9.45 (s, 1H, N$H$); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 17.8, 18.8, 20.6, 65.2, 67.7, 114.0, 123.8, 124.5, 125.1, 126.2, 126.6, 127.3, 127.7 (2C), 130.8, 132.0, 135.1, 135.5, 135.9, 138.6, 138.7, 140.6, 153.6, 166.7; MS (ESI$^-$) $m/z$ 487 [M−H]$^-$; Anal. Calcd for $C_{24}H_{25}ClN_2O_5S$: C, 58.95; H, 5.15; Cl, 7.25; N, 5.73; S, 6.56. Found: C, 58.92; H, 5.17; Cl, 7.23; N, 5.70; S, 6.57.

#### 3.2.11. (±)-*N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[hydroxyl(2,5-dimethylphenyl)methyl]phenoxyl}acetamide (7k)

Yield 92.2%; mp 190.4–191.9 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.22 (s, 9H, 3C$H_3$), 4.72–4.85 (m, 2H, C$H_2$), 5.79 (d, 1H, $J$ = 4.8 Hz,

O*H*), 6.23 (d, 1H, *J* = 4.8 Hz, C*H*), 7.31 (s, 2H, N$H_2$), 6.93–7.70 (m, 9H, Ph*H*), 9.44 (s, 1H, N*H*); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 17.7, 18.4, 20.9, 65.4, 67.7, 114.1, 123.8, 124.4, 125.1, 127.1, 127.3, 127.6, 127.7, 127.8, 130.0, 131.8, 132.1, 134.4, 135.3, 138.5, 140.6, 141.4, 153.6, 167.0; MS (ESI$^-$) *m/z* 487 [M−H]$^-$; Anal. Calcd for $C_{24}H_{25}ClN_2O_5S$: C, 58.95; H, 5.15; Cl, 7.25; N, 5.73; S, 6.56. Found: C, 58.98; H, 5.17; Cl, 7.22; N, 5.71; S, 6.58.

### 3.2.12. (±)-*N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[hydroxyl(3,5-dimethylphenyl)methyl]phenoxyl}acetamide (7l)

Yield 93.1%; mp 198.9–199.7 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.19 (s, 6H, 2C$H_3$), 2.24 (s, 3H, C$H_3$), 4.72–4.84 (m, 2H, C$H_2$), 5.89 (d, 1H, *J* = 4.4 Hz, O*H*), 6.05 (d, 1H, *J* = 3.6 Hz, C*H*), 7.30 (s, 2H, N$H_2$), 6.81–7.73 (m, 9H, Ph*H*), 9.49 (s, 1H, N*H*); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 17.7, 21.0 (2C), 67.6, 68.1, 114.1, 123.8, 124.2 (2C), 124.4, 125.2, 126.7, 127.5, 127.7, 128.3, 131.8, 136.3, 136.9 (2C), 138.6, 140.6, 144.2, 153.0, 166.6; MS (ESI$^-$) *m/z* 487 [M−H]$^-$; Anal. Calcd for $C_{24}H_{25}ClN_2O_5S$: C, 58.95; H, 5.15; Cl, 7.25; N, 5.73; S, 6.56. Found: C, 58.96; H, 5.14; Cl, 7.23; N, 5.74; S, 6.53.

### 3.2.13. (±)-*N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[hydroxyl(2,4-dichlorophenyl)methyl]phenoxyl}acetamide (7m)

Yield 81.4%; mp 154.4–155.3 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.29 (s, 3H, C$H_3$), 4.54–4.73 (m, 2H, C$H_2$), 5.36 (s, 1H, C*H*), 5.56 (br, 1H, O*H*), 7.35 (s, 2H, N$H_2$), 6.94–7.74 (m, 9H, Ph*H*), 9.49 (s, 1H, N*H*); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 17.8, 59.8, 65.3, 114.4, 123.8, 124.3, 125.1, 127.2, 127.4, 127.8, 128.3, 128.7, 130.2, 131.6, 132.5, 133.0, 133.8, 138.6, 140.0, 140.5, 153.8, 166.6; MS (ESI$^-$) *m/z* 527 [M−H]$^-$; Anal. Calcd for $C_{22}H_{19}Cl_3N_2O_5S$: C, 49.87; H, 3.61; Cl, 20.07; N, 5.29; S, 6.05. Found: C, 49.90; H, 3.60; Cl, 20.05; N, 5.30; S, 6.03.

### 3.2.14. (±)-*N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[hydroxyl(2,5-dichlorphenyl)methyl]phenoxyl}acetamide (7n)

Yield 80.7%; mp 199.5–200.7 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.26 (s, 3H, C$H_3$), 4.77–4.89 (m, 2H, C$H_2$), 6.34 (m, 2H, C*H*, O*H*), 7.31 (s, 2H, N$H_2$), 7.08–7.78 (m, 9H, Ph*H*), 9.58 (s, 1H, N*H*); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 17.8, 65.6, 67.9, 114.5, 123.8, 124.3, 125.1, 127.2, 127.7, 128.3, 128.5, 128.8, 130.6, 131.0, 131.6, 131.8, 133.4, 138.6, 140.5, 143.1, 153.9, 166.6; MS (ESI$^-$) *m/z* 527 [M−H]$^-$; Anal. Calcd for $C_{22}H_{19}Cl_3N_2O_5S$: C, 49.87; H, 3.61; Cl, 20.07; N, 5.29; S, 6.05. Found: C, 49.86; H, 3.60; Cl, 20.05; N, 5.27; S, 6.07.

### 3.2.15. (±)-*N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[hydroxyl(3,4-dichlorophenyl)methyl]phenoxyl}acetamide (7o)

Yield 79.8%; mp 201.3–202.5 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.28 (s, 3H, C$H_3$), 4.80–4.89 (m, 2H, C$H_2$), 6.15 (s, 1H, C*H*), 6.27 (s, 1H, O*H*), 7.52 (s, 2H, N$H_2$), 7.02–7.76 (m, 9H, Ph*H*), 9.67 (s, 1H, N*H*); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 17.9, 67.2, 67.6, 114.1, 123.9, 124.6, 125.4, 126.6, 126.8, 127.8, 128.1, 128.4, 129.5, 130.3, 130.8, 131.9, 135.1, 138.7, 140.6, 145.6, 153.0, 166.6; MS (ESI$^-$) *m/z* 527 [M−H]$^-$; Anal. Calcd for $C_{22}H_{19}Cl_3N_2O_5S$: C, 49.87; H, 3.61; Cl, 20.07; N, 5.29; S, 6.05. Found: C, 49.85; H, 3.60; Cl, 20.08; N, 5.30; S, 6.04.

### 3.2.16. (±)-*N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[hydroxyl(3,5-dichlorophenyl)methyl]phenoxyl}acetamide (7p)

Yield 77.1%; mp 198.7–199.8 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.27 (s, 3H, C$H_3$), 4.81–4.85 (m, 2H, C$H_2$), 6.14 (d, 1H, *J* = 4.4 Hz, O*H*), 6.30 (d, 1H, *J* = 4.4 Hz, C*H*), 7.30 (s, 2H, N$H_2$), 7.02–7.75 (m, 9H, Ph*H*), 9.68 (s, 1H, N*H*); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 17.8, 67.1, 67.5, 114.1, 123.7, 124.4, 125.1 (2C), 125.3, 126.4, 126.5, 127.9, 128.1, 131.8, 133.8 (2C), 134.7, 138.6, 140.5, 148.7, 152.9, 166.5; MS (ESI$^-$) *m/z* 527 [M−H]$^-$; Anal. Calcd for $C_{22}H_{19}Cl_3N_2O_5S$: C, 49.87; H, 3.61; Cl, 20.07; N, 5.29; S, 6.05. Found: C, 49.85; H, 3.60; Cl, 20.05; N, 5.30; S, 6.07.

### 3.2.17. (±)-*N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[hydroxyl(3-chloro-5-bromophenyl)methyl]phenoxyl}acetamide (7q)

Yield 75.6%; mp 138.8–139.7 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.29 (s, 3H, C$H_3$), 4.85–4.86 (m, 2H, C$H_2$), 6.16 (s, H, O*H*), 6.34 (s, H, C*H*), 7.32 (s, 2H, N$H_2$), 7.03–7.76 (m, 9H, Ph*H*), 9.72 (s, 1H, N*H*); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 18.0, 67.2, 67.6, 114.2, 122.0, 123.9, 124.6, 125.4, 125.5, 126.6, 127.8, 128.0, 128.2, 129.3, 132.0, 134.0, 134.8, 138.7, 140.6, 148.9, 153.0, 166.6; MS (ESI$^-$) *m/z* 570 [M−H]$^-$; Anal. Calcd for $C_{22}H_{19}BrCl_2N_2O_5S$: C, 46.01; H, 3.33; Br, 13.91; Cl, 12.35; N, 4.88; S, 5.58. Found: C, 46.02; H, 3.35; Br, 13.93; Cl, 12.36; N, 4.86; S, 5.56.

### 3.2.18. (±)-*N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[hydroxyl(3-chloro-5-cyanophenyl)methyl]phenoxyl}acetamide (7r)

Yield 73.8%; mp 169.4–170.5 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.30 (s, 3H, C$H_3$), 4.84–4.88 (m, 2H, C$H_2$), 6.19 (s, H, C*H*), 6.41 (s, H, O*H*), 7.32 (s, 2H, N$H_2$), 7.02–7.89 (m, 9H, Ph*H*), 9.73 (s, 1H, N*H*); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 17.9, 67.1, 67.4, 112.3, 114.0, 117.6, 123.8, 124.5, 125.4, 126.5, 127.8, 128.3, 128.9, 130.3, 131.2, 132.9, 133.8, 134.5, 138.7, 140.6, 148.3, 152.9, 166.6; MS (ESI$^-$) *m/z* 518 [M−H]$^-$; Anal. Calcd for $C_{23}H_{19}BrCl_2N_3O_5S$: C, 53.08; H, 3.68; Cl, 13.63; N, 8.07; S, 6.16. Found: C, 53.06; H, 3.66; Cl, 13.65; N, 8.06; S, 6.14.

### 3.2.19. (±)-*N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[hydroxyl(1-naphyl phenyl)methyl]phenoxyl}acetamide (7s)

Yield 85.4%; mp 228.1–229.5 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.18 (s, 3H, C$H_3$), 4.81–4.94 (m, 2H, C$H_2$), 6.10 (d, 1H, *J* = 5.6 Hz, C*H*), 7.33 (s, 2H, N$H_2$), 6.91–8.23 (m, 13H, Ph*H*), 9.52 (s, 1H, N*H*); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 17.7, 66.0, 67.7, 114.3, 123.8, 123.9, 124.0, 124.4, 125.1, 125.3, 125.6, 126.0, 127.7 (3C, 127.67, 127.70, 127.74), 128.0, 128.5, 130.4, 131.8, 133.3, 135.3, 138.5, 139.3, 140.6, 153.5, 166.6; MS (ESI$^-$) *m/z* 509 [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, 61.09; H, 4.56; Cl, 6.96; N, 5.46; S, 6.27.

### 3.2.20. (±)-*N*-[4-(Aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[hydroxyl(2-naphylphenyl)methyl]phenoxyl}acetamide (7t)

Yield 79.6%; mp 225.3–226.4 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.24 (s, 3H, C$H_3$), 4.78–4.88 (m, 2H, C$H_2$), 6.17 (d, 1H, *J* = 4.4 Hz, C*H*), 6.34 (d, 1H, *J* = 4.4 Hz, O*H*), 7.36 (s, 2H, N$H_2$), 7.03–7.98 (m, 13H, Ph*H*), 9.59 (s, 1H, N*H*); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 17.8, 67.7, 68.3, 114.1, 123.8, 124.4, 124.7, 125.1, 125.3, 125.7, 126.1, 126.8, 127.5, 127.6, 127.7 (2C), 127.8, 131.8, 132.2, 132.8, 136.0, 138.6, 140.6, 141.8, 153.2, 166.7; MS (ESI$^-$) *m/z* 509 [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, 61.10; H, 4.51; Cl, 6.91; N, 5.50; S, 6.26.

## 3.3. Anti-HIV activity

### 3.3.1. Cytotoxicity assay

The cytotoxicity of compounds on C8166 cells were assessed by MTT colorimetric assay as described previously.[15] 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 the dose response curve.

### 3.3.2. Syncytium reduction assay

In the presence of 100 μL of various concentrations of compounds, C8166 cells ($4 \times 10^5$/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.[16]

### 3.4. Molecular simulation

Molecular modelling was carried out with the tripos molecular modelling packages Sybyl-X 1.2.[17,18] All the molecules for docking were built by using the standard bond lengths and angles from the Sybyl-X 1.2/base Builder, and then were relaxed by performing a 2000-step minimization with maximum derivative being set to 0.1 kcal $mol^{-1}$ $Å^{-1}$. Molecular dynamics simulation at a high temperature of 1000 K was then carried out to efficiently cross the energy barriers and sample local minima. Three hundred snapshots were collected at a rate of 1 ps/snapshot for post processing analysis, and the 300 collected snapshots were further minimized with the steepest descent and followed by the conjugate gradient methods until the maximum derivative was less than 0.001 kcal $mol^{-1}$ $Å^{-1}$. Subsequently, the protein was prepared by removing water, ligand and other useless small molecules from the complex of HIV-1 RT with GW678248 (PDB code: 3DOK).[16] After being added hydrogen on the protein, a flexible docking method with the tripos FLEXDOCK program was used to simulate the interactions between inhibitors and RT. During flexible docking, a RT binding pocket was firstly defined to cover all residues within 4 Å of the ligand, and all of the single bonds of residue side chains inside the defined RT binding pocket were regarded as rotatable or flexible bonds, and the ligand was allowed to rotate on all single bonds and move flexibly within the tentative binding pocket. The atomic charges were recalculated by using the Kollman all-atom approach for the protein and the Gasteiger–Hückel approach for the ligand. The binding interaction energy was calculated to include van der Waals, electrostatic, and torsional energy terms defined in the tripos force field. The structure optimization was performed for 20,000-generations using a genetic algorithm, and only the best-scoring ligand-protein complexes were kept for analyses.[19–22]

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