# Anti Human Immunodeficiency Virus Type 1 (HIV-1) Agents 4. Discovery of 5,5′-(*p*-Phenylenebisazo)-8-hydroxyquinoline Sulfonates as New HIV-1 Inhibitors *in Vitro*

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**To search for compounds with superior anti-human immunodeficiency virus type 1 (HIV-1) activity, ten 5,5′-(*p*-phenylenebisazo)-8-hydroxyquinoline sulfonates (4a—j) were synthesized and preliminarily evaluated as HIV-1 inhibitors *in vitro* for the first time. Some compounds demonstrated anti-HIV-1 activity, especially 5,5′-(*p*-phenylenebisazo)-8-hydroxyquinoline *p*-ethylbenzenesulfonate (4g) and 5,5′-(*p*-phenylenebisazo)-8-hydroxyquinoline *p*-chlorobenzenesulfonate (4i) showed the more potent anti-HIV-1 activity with 50% effective concentration ($EC_{50}$) values of 2.59 and 4.01 μg/ml, and therapeutic index (TI) values of 31.77 and 24.51, respectively.**

**Key words** 8-hydroxyquinoline; sulfonate; acquired immune-deficiency syndrome; human immunodeficiency virus-1; inhibitor

Since the first case of acquired immunodeficiency syndrome (AIDS) was reported in 1981, the human immunodeficiency virus (HIV)/AIDS has always been a global health threat and the leading cause of deaths.[1)] In the past two decades, twenty-five drugs, including nucleoside/nucleotide viral reverse transcriptase (RT) inhibitors (NRTIs), non-nucleoside RT inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (INIs) and fusion (or entry) inhibitors (FIs), were approved for clinical use in the world.[2)] However, these drugs have only limited or transient clinical benefit due to their severe side effects and the emergence of viral variants resistant to HIV-1 inhibitors.[3—5)] Currently, the design and development of new, selective and safe HIV-1 inhibitors is therefore highly desirable in the world. Recently, some 8-hydroxyquinolinyl azo derivatives have been used as corrosion inhibitors for mild steel,[6)] ligands,[7)] and probes for monitoring of enzymatic activity and heavy metal ions.[8,9)] To the best of our knowledge, however, little attention has been paid to the anti-HIV-1 activity of the single 8-hydroxyquinolinyl azo derivatives. In our previous paper, some single *N*-arylsulfonylindoles,[10)] benzyl phenyl ethers[11)] and dibenzofurans[12)] were found to demonstrate the significant anti-HIV-1 activity *in vitro*. As a consequence, these encouraging results prompted us to further study the anti-HIV-1 activity of other single compounds, and in continuation of our program aimed at the discovery and development of bioactive molecules, herein we report the synthesis and anti-HIV-1 activity of some 5,5′-(*p*-phenylenebisazo)-8-hydroxyquinoline sulfonates.

## Results and Discussion

A series of novel 5,5′-(*p*-phenylenebisazo)-8-hydroxyquinoline sulfonates **4a**—**j** (Fig. 1) were synthesized as shown in Chart 1. Firstly, 1,4-benzenediamine (**1**) reacted with $NaNO_2$ and HCl at 0—5 °C to give benzidine diazonium chloride (**2**), which then reacted with 8-quinolinol to yield 5,5′-(*p*-phenylenebisazo)-8-hydroxyquinoline (**3**). Finally, ten 5,5′-(*p*-phenylenebisazo)-8-hydroxyquinoline sulfonates (**4a**—**j**) were obtained by reaction of **3** with the corresponding sulfonyl chlorides in the presence of triethylamine. The structures of the compounds were well characterized by $^1$H-NMR, MS, IR, and mp.

Subsequently, all the target compounds **4a**—**j** and **3** were evaluated for inhibitory activity against HIV-1 replication in acutely infected C8166 cells *in vitro* and 3′-azido-3′-deoxythymidine (AZT) was used as a positive control. The assay results of compounds **4a**—**j** and **3** were presented in Table 1. Among these compounds, **3**, **4f**, **4g**, and **4i** demonstrated significant anti-HIV-1 activity with 50% effective concentration ($EC_{50}$) values of 0.45, 3.51, 2.59, and 4.01 μg/ml, and therapeutic index (TI) values of 18.91, 17.55, 31.77, and 24.51, respectively. Especially compound **4g** exhibited the most potent and promising anti-HIV-1 activity (TI=31.77). However, **4a**, **4e**, **4h**, and **4j** showed the lower TI values less than 5.

Meanwhile, some preliminary structure–activity relationships (SAR) of **4a**—**j** and **3** were also observed. Once the methylsulfonyl or benzenesulfonyl group was introduced on the 8-position of **3** (TI=18.91), the corresponding TI values of **4a** and **4e** were sharply reduced to 3.25 and 2.21, respectively. But when the ethyl group or the chloro atom was introduced at 4′-position on the phenyl ring of **4a**, the corresponding compounds exhibited the more potent anti-HIV-1 activity (**4g** and **4i** *vs.* **4a**). For example, the TI values of **4g** and **4i** were 31.77 and 24.51, respectively, and the $EC_{50}$ values of **4g** and **4i** were 2.59 and 4.01 μg/ml, respectively; while the $EC_{50}$ and TI values of **4a** were 14.36 μg/ml and 3.25, respectively. That is, the TI value of **4g** was more than 9 times of that of **4a**, while the $EC_{50}$ value of **4g** was significantly decreased more than 5 times compared with **4a**. Interestingly, when the *p*-methyl group of **4c** was substituted by the *p*-ethyl group to give **4g**, the $EC_{50}$ value of **4g** was reduced from 13.40 (**4c**) to 2.59 μg/ml, while the TI value of **4g** was increased from 6.24 (**4c**) to 31.77, *i.e.*, the TI value of **4g** was nearly 5 times of that of **4c**. When the *p*-bromo atom of **4d** was substituted by the *p*-chloro atom to give **4i**, the $EC_{50}$ value of **4i** was reduced from 17.11 (**4d**) to 4.01 μg/ml,

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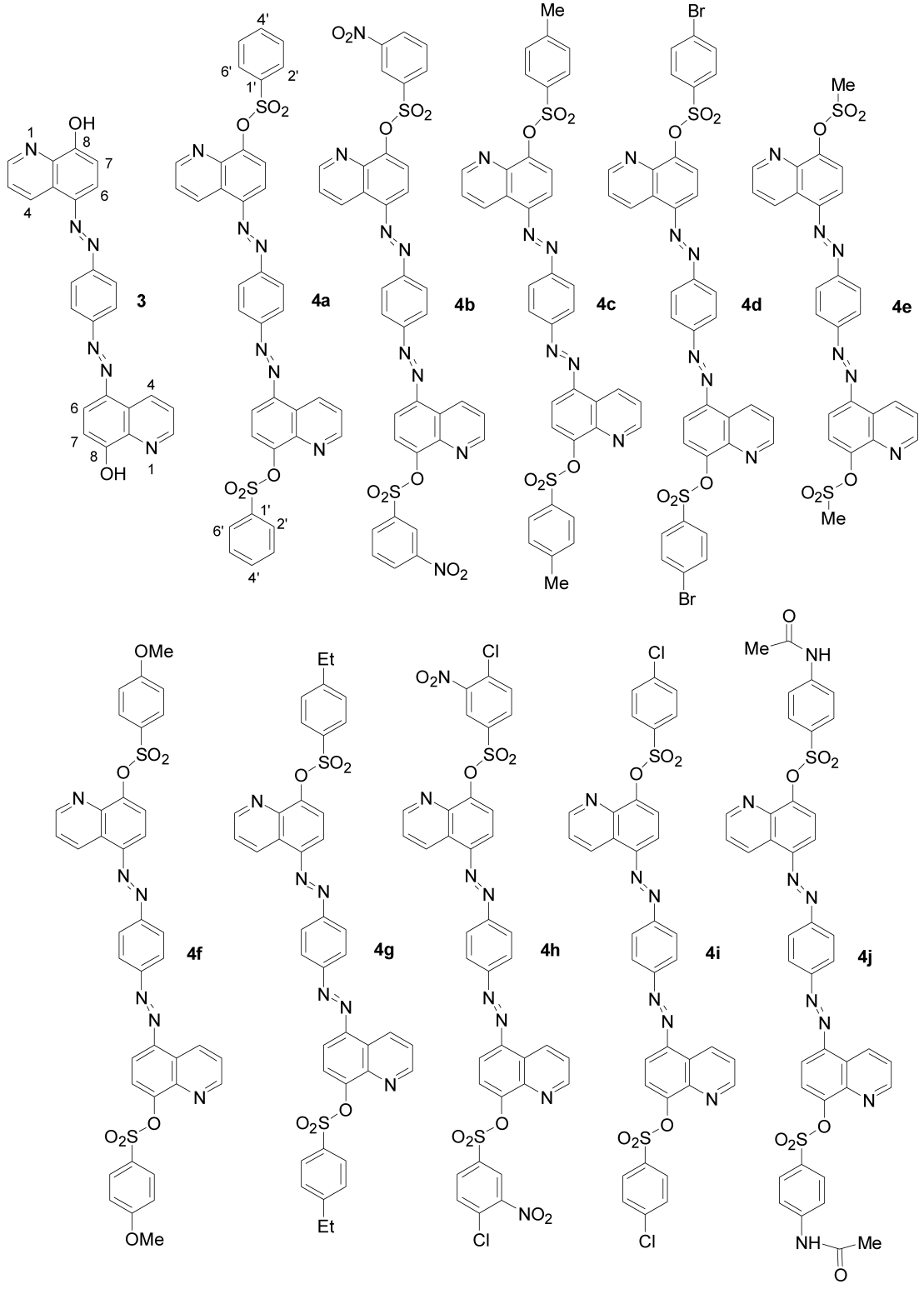


Fig. 1. Chemical Structures of **3** and **4a**—**j**

while the TI value of **4i** was increased from 5.96 (**4d**) to 24.51. Moreover, when the nitro group was introduced at the *meta* position on the phenyl ring of **4i** to give **4h**, the TI value of **4h** was decreased from 24.51 (**4i**) to 4.88, and the 50% cytotoxic concentration ($CC_{50}$) values of **4h** was sharply reduced from 98.31 (**4i**) to 13.41, *i.e.*, the cytotoxicity of **4h** against C8166 cells was more than 7 times of that of **4i**.

## Conclusion

In summary, ten novel 5,5′-(*p*-phenylenebisazo)-8-hydroxyquinoline sulfonates (**4a**—**j**) were synthesized and preliminarily evaluated as HIV-1 inhibitors *in vitro* for the first time. Some compounds demonstrated anti-HIV-1 activity, especially 5,5′-(*p*-phenylenebisazo)-8-hydroxyquinoline *p*-ethylbenzenesulfonate (**4g**) and 5,5′-(*p*-phenylenebisazo)-8-hydroxyquinoline *p*-chlorobenzenesulfonate (**4i**) exhibited the more

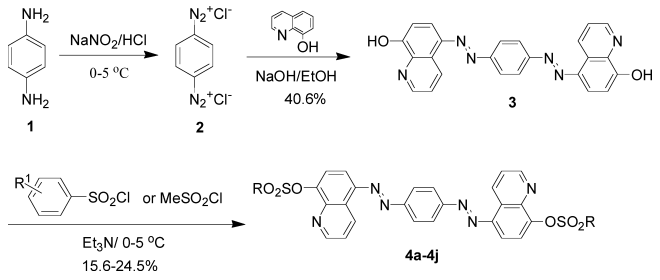


Chart 1. The Synthetic Route of 5,5′-(*p*-Phenylenebisazo)-8-hydroxyquinoline Sulfonates **4a**—**j**

Table 1. Anti-HIV-1 Activity of 5,5′-(*p*-Phenylenebisazo)-8-hydroxyquinoline Sulfonates (**4a**—**j**) *in Vitro*[a)]

| Compounds | $CC_{50}$[b)] ($\mu$g/ml) | $EC_{50}$[c)] ($\mu$g/ml) | TI[d)] |
|---|---|---|---|
| **3** | 8.51 | 0.45 | 18.91 |
| **4a** | 47.56 | 14.63 | 3.25 |
| **4b** | 40.36 | 4.03 | 10.02 |
| **4c** | 83.66 | 13.40 | 6.24 |
| **4d** | 102.02 | 17.11 | 5.96 |
| **4e** | 7.55 | 3.41 | 2.21 |
| **4f** | 61.62 | 3.51 | 17.55 |
| **4g** | 82.29 | 2.59 | 31.77 |
| **4h** | 13.14 | 2.69 | 4.88 |
| **4i** | 98.31 | 4.01 | 24.51 |
| **4j** | 37.69 | 19.73 | 1.91 |
| AZT[e)] | 1139.47 | 0.00324 | 352688.27 |

*a*) Values are means of two separate experiments; *b*) $CC_{50}$ (50% cytotoxic concentration), concentration of drug that causes 50% reduction in total C8166 cell number; *c*) $EC_{50}$ (50% effective concentration), concentration of drug that reduces syncytia formation by 50%; *d*) therapeutic index (TI) is a ratio of the $CC_{50}$ value/$EC_{50}$ value; *e*) AZT was used as a positive control.

potent anti-HIV-1 activity with $EC_{50}$ values of 2.59 and 4.01 $\mu$g/ml, and TI values of 31.77 and 24.51, respectively. Moreover, the preliminary SAR showed that the ethyl group or the chloro atom at 4′-position on the phenyl ring of 5,5′-(*p*-phenylenebisazo)-8-hydroxyquinoline benzenesulfonate was very important for possessing potent anti-HIV-1 activity. It will pave the way for further optimal structural modifications of the 8-hydroxyquinolinyl azo derivatives as HIV-1 inhibitors.

## Experimental

All the solvents were of analytical grade and the reagents were used as purchased. Thin-layer chromatography (TLC) and preparative thin-layer chromatography (PTLC) were performed with silica gel plates using silica gel 60 $GF_{254}$ (Qingdao Haiyang Chemical Co., Ltd., China). Melting points were determined on a digital melting-point apparatus and were uncorrected. Infrared spectra (IR) were recorded on a Thermo Nicolet Nexus FTIR-8700 spectrometer (Thermo Nicolet, U.S.A.). $^1$H-NMR spectra were recorded on a Bruker Avance DMX 300 MHz instrument (Bruker, Swiss) using TMS as internal standard and $CDCl_3$ as solvent. Electrospray iontrap mass spectra (electrospray ionization (ESI)-TRAP-MS) were recorded on a Bruker ESI-TRAP Esquire 3000 (Bruker, Swiss) plus mass spectrometry instrument.

**General Procedure for the Synthesis of 5,5′-(*p*-Phenylenebisazo)-8-hydroxyquinoline Sulfonates 4a—j** To a solution of 1,4-benzenediamine (**1**, 30 mmol) in distilled water (15 ml) at 0 °C, HCl (12 mol/l, 15 ml) was added dropwise, followed by a solution of $NaNO_2$ (65.9 mmol) in distilled water (15 ml), and the temperature of the reaction mixture was kept at 0—5 °C. After stirring for 20 min, a solution of benzidine diazonium chloride (**2**) was prepared. Subsequently, the solution of **2** was added dropwise to a mixture of 8-hydroxyquinoline (60 mmol), NaOH (60 mmol) and ethanol (30 ml) at 0—5 °C, and the mixture was stirred until a lot of brown precipitate was produced, which was filtered, washed with distilled water, and purified by recrystallization to give 5.12 g 5,5′-(*p*-phenylenebisazo)-8-hydroxyquinoline **3** as a brown solid in a 40.6% yield, mp 195—197 °C (lit.,[13)] 200 °C). Finally, to a suspended solution of **3** (0.5 mmol) in dichloromethane (15 ml) at 0 °C, sulfonyl chlorides (1.2 mmol) and triethylamine (1.5 mmol) were added in sequence. After adding, the above mixture was stirred for 36 h at room temperature, and the solvent was evaporated under reduced pressure to give the residue, which was seperated by preparative thin-layer chromatography (PTLC) and purified by recrystallization from cyclohexane to give the pure products **4a**—**j**.

**4a**: Yield: 21.6%, red solid, mp 123—125 °C; IR (KBr) cm$^{-1}$: 3060, 1586, 1493, 1449, 1357; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 9.23 (d, $J$=8.4 Hz, 2H, H-2), 8.88 (d, $J$=3.0 Hz, 2H, H-4), 7.95—8.03 (m, 6H, H-3, H-2′, H-6′), 7.90 (d, $J$=8.4 Hz, 2H, H-6), 7.72 (d, $J$=8.4 Hz, 2H, H-7), 7.55-7.64 (m, 6H, H-4′, Ar-H), 7.48 (t, $J$=8.0 Hz, 4H, H-3′, H-5′); MS (ESI-TRAP) *m*/*z*: 390 [(M+DMSO+2H)$^+$/2, 100].

**4b**: Yield: 19.6%, salmon solid, mp 177—178 °C; IR (KBr) cm$^{-1}$: 3044, 3015, 1609, 1497, 1473, 1369; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 9.22 (d, $J$=8.4 Hz, 2H, H-2), 9.11 (s, 2H, H-2′), 8.81 (s, 2H, H-4), 8.46 (d, $J$=8.0 Hz, 2H, H-4′), 8.37 (d, $J$=8.0 Hz, 2H, H-6′), 8.02 (d, $J$=7.2 Hz, 2H, H-3), 7.93 (d, $J$=8.4 Hz, 2H, H-6), 7.83 (d, $J$=8.4 Hz, 2H, H-7), 7.70 (t, $J$=8.0 Hz, 2H, H-5′), 7.55 (s, 4H, Ar-H); MS (ESI-TRAP) *m*/*z*: 435 [(M+DMSO+2H)$^+$/2, 100].

**4c**: Yield: 17.2%, salmon solid, mp 142—144 °C; IR (KBr) cm$^{-1}$: 3052, 2917, 2844, 1595, 1496, 1375; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 9.22 (d, $J$=8.4 Hz, 2H, H-2), 8.92 (s, 2H, H-4), 8.02 (d, $J$=6.0 Hz, 2H, H-3), 7.87—7.91 (m, 6H, H-6, H-2′, H-6′), 7.69 (d, $J$=8.4 Hz, 2H, H-7), 7.55 (s, 4H, Ar-H), 7.28 (d, $J$=7.8 Hz, 4H, H-3′, H-5′), 2.41 (s, 6H, $CH_3$); MS (ESI-TRAP) *m*/*z*: 404 [(M+DMSO+2H)$^+$/2, 100].

**4d**: Yield: 15.6%, salmon solid, mp 145—147 °C; IR (KBr) cm$^{-1}$: 3083, 2924, 2844, 1573, 1496, 1379; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 9.24 (d, $J$=7.8 Hz, 2H, H-2), 8.88 (s, 2H, H-4), 8.04 (s, 2H, H-3), 7.87—7.92 (m, 6H, H-6, H-2′, H-6′), 7.76 (d, $J$=8.4 Hz, 2H, H-7), 7.56—7.63 (8H, Ar-H, H-3′, H-5′); MS (ESI-TRAP) *m*/*z*: 469 [(M+DMSO+2H)$^+$/2, 100].

**4e**: Yield: 24.5%, red solid, mp 170—172 °C; IR (KBr) cm$^{-1}$: 2925, 2844, 1628, 1543, 1367; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 9.32 (d, $J$=8.4 Hz, 2H, H-2), 9.07 (s, 2H, H-4), 8.04 (d, $J$=6.3 Hz, 2H, H-3), 7.95 (d, $J$=8.4 Hz, 2H, H-6), 7.82 (d, $J$=8.4 Hz, 2H, H-7), 7.57 (s, 4H, Ar-H), 3.52 (s, 6H, $CH_3$); MS (ESI-TRAP) *m*/*z*: 328 [(M+DMSO+2H)$^+$/2, 100].

**4f**: Yield: 18.3%, red solid, mp 116—118 °C; IR (KBr) cm$^{-1}$: 2917, 2842, 1594, 1496, 1376; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 9.24 (d, $J$=8.4 Hz, 2H, H-2), 8.93 (s, 2H, H-4), 8.02 (d, $J$=6.0 Hz, 2H, H-3), 7.88—7.96 (m, 6H, H-6, H-2′, H-6′), 7.73 (d, $J$=8.4 Hz, 2H, H-7), 7.57 (s, 4H, Ar-H) ,6.92 (d, $J$=7.2 Hz, 4H, H-3′, H-5′), 3.85 (s, 6H, $OCH_3$); MS (ESI-TRAP) *m*/*z*: 420 [(M+DMSO+2H)$^+$/2, 100].

**4g**: Yield: 16.1%, red solid, mp 117—119 °C; IR (KBr) cm$^{-1}$: 3055, 2969, 2925, 2849, 1593, 1493, 1469, 1372; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 9.24 (d, $J$=8.4 Hz, 2H, H-2), 8.91 (s, 2H, H-4), 8.02 (d, $J$=7.5 Hz, 2H, H-3), 7.88—7.93 (m, 6H, H-6, H-2′, H-6′), 7.72 (d, $J$=8.4 Hz, 2H, H-7), 7.56 (s, 4H, Ar-H), 7.29 (d, $J$=7.8 Hz, 4H, H-3′, H-5′), 2.70 (m, 4H, $\underline{CH_2}CH_3$), 1.23 (m, 6H, $CH_2\underline{CH_3}$); MS (ESI-TRAP) *m*/*z*: 418 [(M+DMSO+2H)$^+$/2, 100].

**4h**: Yield: 20.5%, red solid, mp 112—115 °C; IR (KBr) cm$^{-1}$: 3095, 1593, 1536, 1497, 1347; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 9.26 (d, $J$=8.4 Hz, 2H, H-2), 8.86 (s, 2H, H-4), 8.75 (s, 2H, H-2′), 8.15 (d, $J$=8.4 Hz, 2H, H-3), 8.03 (d, $J$=7.8 Hz, 2H, H-6′), 7.95 (d, $J$=8.4 Hz, 2H, H-6), 7.86 (d, $J$=8.4 Hz, 2H, H-7), 7.67 (d, $J$=8.4 Hz, 2H, H-5′), 7.58 (s, 4H, Ar-H); MS (ESI-TRAP) *m*/*z*: 469 [(M+DMSO+2H)$^+$/2, 100].

**4i**: Yield: 16.2%, salmon solid, mp 118—120 °C; IR (KBr) cm$^{-1}$: 3095, 1586, 1496, 1379; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 9.23 (d, $J$=8.0 Hz, 2H, H-2), 8.86 (s, 2H, H-4), 8.04 (s, 2H, H-3), 7.89—7.95 (m, 6H, H-6, H-2′, H-6′), 7.75 (d, $J$=8.4 Hz, 2H, H-7), 7.56 (s, 4H, Ar-H), 7.45 (d, $J$=6.3 Hz, 4H, H-3′, H-5′); MS (ESI-TRAP) *m*/*z*: 424 [(M+DMSO+2H)$^+$/2, 100].

**4j**: Yield: 17.8%, salmon solid, mp 205—207 °C; IR (KBr) cm$^{-1}$: 3104, 2917, 2844, 1678, 1591, 1497, 1376; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 9.26 (d, $J$=8.4 Hz, 2H, H-2), 8.91 (s, 2H, H-4), 8.02 (d, $J$=6.3 Hz, 2H, H-3), 7.89—7.92 (m, 6H, H-6, H-2′, H-6′), 7.75—7.81 (m, 4H, H-7, NH), 7.64 (d, $J$=7.5 Hz, 4H, H-3′, H-5′), 7.56 (s, 4H, Ar-H), 2.20 (s, 6H, $CH_3$); MS (ESI-TRAP) *m*/*z*: 447 [(M+DMSO+2H)$^+$/2, 100].

**Anti-HIV-1 Activity Assay.[10)] Cells and Virus** Cell line (C8166) and the laboratory-derived virus (HIV-$1_{IIIB}$) were obtained from MRC, AIDS Reagent Project, U.K. C8166 was maintained in RPMI-1640 supplemented with 10% heat-inactivated newborn calf serum (Gibco). The cells used in all experiments were in log-phase growth. The 50% HIV-$1_{IIIB}$ tissue culture infectious dose ($TCID_{50}$) in C8166 cells was determined and calculated by the Reed and Muench method. Virus stocks were stored in small aliquots at −70 °C.

**MTT-Based Cytotoxicity Assay** Cellular toxicity of compounds **3** and **4a**—**j** on C8166 cells was assessed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method as described previously. Briefly, cells were seeded on 96-well microtiter plate in the absence or presence of various concentrations of compounds in triplicate and incubated at 37 °C in a humid atmosphere of 5% $CO_2$ for 3 d. The supernatants were discarded and MTT reagent (5 mg/ml in PBS) was added to each wells, then incubated for 4 h, 100 $\mu$l of 50% *N*,*N*-dimethylformamide (DMF)–20% sodium dodecyl sulfate (SDS) was added. After the formazan was dissolved completely, the plates were read on a Bio-Tek Elx 800 enzyme-linked immunosorbent assay (ELISA) reader at 595/630 nm. The cytotoxic concentration that caused the reduction of viable C8166 cells by 50% ($CC_{50}$) was determined from dose-response curve.

**Syncytia Assay** In the presence of 100 $\mu$l various concentrations of compounds, C8166 cells ($4\times10^5$/ml) were infected with virus HIV-$1_{IIIB}$ at a multiplicity of infection (M.O.I.) of 0.06. The final volume per well was 200 $\mu$l. Control assays were performed without the testing compounds in HIV-$1_{IIIB}$ infected and uninfected cultures. After 3 d of culture, the cytopathic effect (CPE) was measured by counting the number of syncytia. Percentage inhibition of syncytia formation was calculated and 50% effective concentration ($EC_{50}$) was calculated. AZT (Sigma) was used as a positive control. Therapeutic index (TI)=$CC_{50}/EC_{50}$.

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