# Anti Human Immunodeficiency Virus-1 (HIV-1) Agents 3. Synthesis and *in Vitro* Anti-HIV-1 Activity of Some *N*-Arylsulfonylindoles

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**In order to find compounds with superior anti human immunodeficiency virus type 1 (HIV-1) activity, twelve simple *N*-arylsulfonylindoles (3a—l) were synthesized and preliminarily evaluated as HIV-1 inhibitors *in vitro* for the first time. Several compounds demonstrated significant anti-HIV-1 activity, especially *N*-(3-nitrobenzene)sulfonyl-6-methylindole (3h) and *N*-(3-nitrobenzene)sulfonylindole (3i) showed the highest anti-HIV-1 activity with $EC_{50}$ values of 0.26 and 0.74 $\mu$g/ml, and TI values of 543.78 and >270.27, respectively.**

**Key words** *N*-arylsulfonylindole; human immunodeficiency virus type 1; inhibitor

According to World Health Organization (WHO)/Joint United Nations Programme on human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) (UNAIDS) estimates published in December 2007, 33.2 million people are living with HIV, 2.5 million people have been newly infected in 2007, and 2.1 million died from AIDS in 2007.[1)] Consequently, the rapid worldwide spread of AIDS has prompted an intense research effort to discover compounds that can effectively inhibit HIV. 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 inhibitor 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)] Therefore, the development of new, selective and safe HIV-1 inhibitors still remains a high priority for medical research.[4—8)] Although a series of *N*-arylsulfonylindole derivatives were found to be potent and selective ligands for the human serotonin 5-$HT_6$ receptor,[9—11)] to the best of our knowledge, little attention has been paid to the anti-HIV-1 activity of the single *N*-arylsulfonylindoles. In our previous paper, we have synthesized some single *N*-arylindoles and benzyl phenyl ethers evaluated as HIV-1 inhibitors, and found some compounds demonstrated significant anti-HIV-1 activity.[12,13)] In continuation of our program aimed at the discovery and development of bioactive molecules,[12—18)] herein we report the synthesis and anti-HIV-1 activity of some single *N*-arylsulfonylindoles bearing various functional groups. Furthermore, the preliminary structure–activity relationships (SARs) were also discussed.

## Results and Discussion

**Synthesis of *N*-Arylsulfonylindoles 3a—l** *N*-Arylsulfonylindoles **3a**—**l** (Fig. 1) were synthesized as shown in Chart 1. Arylsulfonyl chlorides (**1**) reacted with indoles (**2**) in the presence of NaOH and triethylbenzylammonium chloride (TEBA) under ultrasonic irradiation at 40 °C, and compounds **3a**—**l** were obtained in 83—99% yields and identified by satisfactory $^1$H-NMR and mass spectra.

**Anti-HIV-1 Activity of *N*-Arylsulfonylindoles 3a—l** Compounds **3a**—**l** were evaluated *in vitro* for their inhibitory activity against HIV-1 replication in acutely infected C8166 cells. 3′-Azido-3′-deoxythymidine (AZT) was used as a positive control. As shown in Table 1, among the tested com-

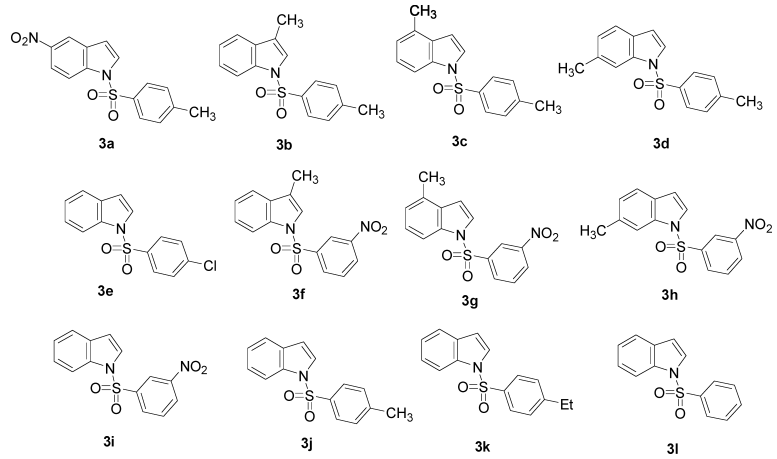


Fig. 1. Structures of Different *N*-Arylsulfonylindoles **3a**—**l**

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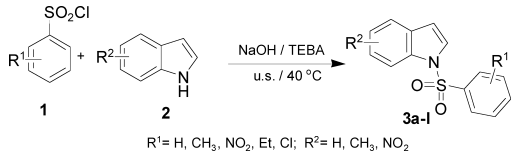


Chart 1. The Synthetic Route of *N*-Arylsulfonylindoles **3a**—**l**

Table 1. Anti-HIV-1 Activity of *N*-Arylsulfonylindoles (**3a**—**l**) *in Vitro*[a)]

| Compounds | $CC_{50}$[b)] ($\mu$g/ml) | $EC_{50}$[c)] ($\mu$g/ml) | TI[d)] |
|---|---|---|---|
| **3a** | >175.77 | 26.31 | >6.68 |
| **3b** | >200 | 11.38 | >17.57 |
| **3c** | >200 | 24.73 | >8.08 |
| **3d** | 78.04 | 3.00 | 26.01 |
| **3e** | >182.71 | 12.33 | >14.81 |
| **3f** | 125.87 | 1.03 | 121.61 |
| **3g** | >200 | 1.69 | >118.34 |
| **3h** | 141.38 | 0.26 | 543.78 |
| **3i** | >200 | 0.74 | >270.27 |
| **3j** | >200 | 13.38 | >14.94 |
| **3k** | 100.91 | 5.31 | 19.05 |
| **3l** | 47.14 | 0.93 | 50.68 |
| AZT[e)] | 1307.39 | 0.0024 | 544745.83 |

*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.

pounds, **3d**, **3f**, **3g**, **3h**, **3i** and **3l** exhibited the more potent anti-HIV-1 activity with $EC_{50}$ values of 3.00, 1.03, 1.69, 0.26, 0.74 and 0.93 $\mu$g/ml, and therapeutic index (TI) values of 26.01, 121.61, >118.34, 543.78, >270.27 and 50.68, respectively. Especially **3h** and **3i** showed the highest anti-HIV-1 activity with $EC_{50}$ values of 0.26 and 0.74 $\mu$g/ml, and TI values of 543.78 and >270.27, respectively. Interestingly, the anti-HIV-1 activities of many *N*-arylsulfonylindoles were more potent than those of our previously reported *N*-arylindoles and benzyl phenyl ethers. For example, the TI value of **3h** was more than 22 times of that of *N*-(2-nitrophenyl)indole (TI=24.61), which exhibited the highest anti-HIV-1 activity of eight synthesized *N*-arylindoles, while the $EC_{50}$ value of **3h** was significantly decreased 30 times compared with *N*-(2-nitrophenyl)indole ($EC_{50}$=7.88 $\mu$g/ml).[12)] Similarly, the TI value of **3h** was nearly 30 times of that of 4-nitrobenzyl phenyl ether (TI=18.32), which exhibited the highest anti-HIV-1 activity of ten synthesized benzyl phenyl ethers, while the $EC_{50}$ value of **3h** was significantly decreased 23 times compared with 4-nitrobenzyl phenyl ether ($EC_{50}$=5.96 $\mu$g/ml).[13)]

As it can be seen in Table 1, it was possible to draw some structure–activity relationships from the comparative study. Firstly, it was shown that the electronic effect of substituted groups on the *N*-arylsulfonylindoles was related to anti-HIV-1 activity. For example, the $EC_{50}$ and TI values of **3b** and **3f** were 11.38/1.03 $\mu$g/ml, and >17.57/121.61, respectively; the $EC_{50}$ and TI values of **3c** and **3g** were 24.73/1.69 $\mu$g/ml, and >8.08/>118.34, respectively; the $EC_{50}$ and TI values of **3d** and **3h** were 3.00/0.26 $\mu$g/ml, and 26.01/543.78, respectively. Accordingly, the TI value of **3f** was nearly 7 times of that of **3b**; the TI value of **3g** was more than 14 times of that of **3c**; the TI value of **3h** was nearly 21 times of that of **3d**. That is, introducing electron-withdrawing group (*e.g.*, nitro group) on the benzenesulfonyl ring, would give compound possessing more potent anti-HIV-1 activity than the corresponding one having electron-donating group (*e.g.*, methyl group) (**3f** *vs.* **3b**; **3g** *vs.* **3c**; **3h** *vs.* **3d**). The same results were also found on **3i** (having nitro group on the benzenesulfonyl ring), and **3j** or **3k** (having methyl or ethyl group on the benzenesulfonyl ring), for example, the TI values of **3i**, **3j** and **3k** were >270.27, >14.94, and 19.05, respectively. On the contrary, when the electron-withdrawing group (*e.g.*, nitro group) was introduced on the indole's ring of **3j** to give **3a**, the anti-HIV-1 activity of which was decreased as compared with **3j**. For example, the $EC_{50}$ and TI values of **3a** and **3j** were 26.31/13.38 $\mu$g/ml, and >6.68/>14.94, respectively. While the electron-donating group (*e.g.*, methyl group) introduced on the 6-position of the indole's ring of **3j** to give more potent compound **3d** (TI>14.94 for **3j** *vs.* TI=26.01 for **3d**).

In the meantime, it was found that the position of methyl group on the indole's ring was very important to anti-HIV-1 activity of the corresponding compound. (1) When the methyl group was introduced on the 3- or 6-position of the indole's ring of **3j** to yield more potent compounds **3b** and **3d**, the corresponding $EC_{50}$ and TI values of which were 11.38/3.00 $\mu$g/ml, and >17.57/26.01, respectively; however, when the methyl group was introduced on the 4-position of the indole's ring of **3j** to yield less potent compound **3c** (TI>14.94 for **3j** *vs.* TI>8.08 for **3c**). (2) When the methyl group was introduced on the 3- or 4-position of the indole's ring of **3i**, the corresponding compound **3f** or **3g** showed the less potent anti-HIV-1 activity than **3i** (TI>270.27 for **3i** *vs.* TI=121.61 for **3f** or TI>118.34 for **3g**); but when the methyl group was introduced on the 6-position of the indole's ring of **3i**, the corresponding compound **3h** showed the more potent anti-HIV-1 activity than **3i**, for example, the $EC_{50}$ and TI values of **3i** and **3h** were 0.74/0.26 $\mu$g/ml, and >270.27/543.78, respectively.

Consequently, based upon the above investigation, the nitro group on the benzenesulfonyl ring and the methyl group on the 6-position of the indole's ring certainly were two important functional groups for **3h** being good HIV-1 inhibitory activity. Additionally, in order to find more potent molecules containing these kind structures, the mechanisms of the anti-HIV-1 function of these compounds need to be studied further.

## Conclusion

In conclusion, twelve simple *N*-arylsulfonylindoles were synthesized and preliminarily evaluated as HIV-1 inhibitors *in vitro*. Six compounds **3d**, **3f**, **3g**, **3h**, **3i** and **3l** demonstrated significant anti-HIV-1 activity. Especially compounds **3h** and **3i** showed the highest anti-HIV-1 activity with $EC_{50}$ values of 0.26 and 0.74 $\mu$g/ml, and TI values of 543.78 and >270.27, respectively.

### Experimental

**General** 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.). Melting points were determined on a digital melting-point apparatus and were uncorrected. $^1$H-NMR spectra were recorded on a Bruker Avance DMX 400 MHz instrument using TMS as internal standard and $CDCl_3$ as solvent. EI-MS was carried out with Thermo DSQ GC/MS instrument. Sonication was performed in

Ningbo SB-5200DT ultrasonic cleaner with the frequency of 40 kHz and an output power of 200 W.

**General Procedure for the Synthesis of *N*-Arylsulfonylindoles 3a—l** The mixture of arylsulfonyl chlorides (**1**, 0.55 mmol), indoles (**2**, 0.5 mmol), NaOH (0.875 mmol), and triethylbenzylammonium chloride (TEBA, 0.05 mmol) in dichloromethane (2 ml) in 25 ml round-bottomed flask was reacted under ultrasonic irradiation at 40 °C. When the reaction was complete according to TLC analysis, the reaction mixture was filtered, and the filtrate was concentrated *in vacuo* and purified by PTLC to give the pure *N*-arylsulfonylindoles.

*N*-Tosyl-5-nitroindole **3a**: 142.0 mg, 90% yield, white solid, mp 156—157 °C; $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 2.37 (3H, s), 6.80 (1H, d, $J$=3.6 Hz), 7.26 (2H, m), 7.73 (1H, d, $J$=3.6 Hz), 7.78 (2H, d, $J$=8.0 Hz), 8.07 (1H, d, $J$=9.2 Hz), 8.19 (1H, dd, $J$=2.4 Hz, $J$=8.8 Hz), 8.46 (1H, d, $J$=2.0 Hz); EI-MS $m/z$: 316 ($M^+$, 30).

*N*-Tosyl-3-methylindole **3b**: 141.4 mg, 99% yield, white solid, mp 102—104 °C (lit.,[19] 112—114 °C); $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 2.23 (3H, s), 2.32 (3H, s), 7.18 (5H, m), 7.43 (1H, d, $J$=7.2 Hz), 7.73 (2H, d, $J$=8.4 Hz), 7.97 (1H, d, $J$=8.0 Hz); EI-MS $m/z$: 285 ($M^+$, 42).

*N*-Tosyl-4-methylindole **3c**: 121.3 mg, 85% yield, white solid, mp 99—101 °C (lit.,[20] 107—108 °C); $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 2.23 (3H, s), 2.46 (3H, s), 6.67 (1H, d, $J$=4.0 Hz), 7.00 (1H, d, $J$=7.2 Hz), 7.19 (3H, m), 7.55 (1H, d, $J$=3.6 Hz), 7.75 (2H, d, $J$=8.0 Hz), 7.80 (1H, d, $J$=8.4 Hz); EI-MS $m/z$: 285 ($M^+$, 53).

*N*-Tosyl-6-methylindole **3d**: 118.5 mg, 83% yield, white solid, mp 95—96 °C (lit.,[20] syrup); $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 2.23 (3H, s), 2.46 (3H, s), 6.58 (1H, d, $J$=3.6 Hz), 7.03 (1H, d, $J$=8.0 Hz), 7.19 (2H, d, $J$=8.4 Hz), 7.37 (1H, d, $J$=8.0 Hz), 7.47 (1H, d, $J$=3.6 Hz), 7.74 (2H, d, $J$=8.4 Hz), 7.79 (1H, s); EI-MS $m/z$: 285 ($M^+$, 49).

*N*-(4-Chlorobenzene)sulfonylindole **3e**: 142.9 mg, 98% yield, white solid, mp 106—107 °C (lit.,[21] 78.5—79.9 °C); $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 6.67 (1H, d, $J$=3.6 Hz), 7.22 (1H, m), 7.30 (1H, t, $J$=7.6 Hz), 7.38 (2H, d, $J$=8.4 Hz), 7.53 (2H, m), 7.79 (2H, d, $J$=8.4 Hz), 7.96 (1H, d, $J$=8.4 Hz); EI-MS $m/z$: 291 ($M^+$, 40), 293 ($M^+$, 15).

*N*-(3-Nitrobenzene)sulfonyl-3-methylindole **3f**: 151.9 mg, 97% yield, orange solid, mp 139—140 °C; $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 2.25 (3H, s), 7.25 (2H, m), 7.34 (1H, t, $J$=8.0 Hz), 7.45 (1H, d, $J$=8.0 Hz), 7.61 (1H, t, $J$=7.6 Hz), 7.98 (1H, d, $J$=8.40 Hz), 8.14 (1H, d, $J$=7.2 Hz), 8.34 (1H, m), 8.69 (1H, s); EI-MS $m/z$: 316 ($M^+$, 23).

*N*-(3-Nitrobenzene)sulfonyl-4-methylindole **3g**: 147.2 mg, 93% yield, yellow solid, mp 114—116 °C; $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 2.46 (3H, s), 6.75 (1H, d, $J$=3.6 Hz), 7.05 (1H, d, $J$=7.2 Hz), 7.23 (1H, t, $J$=8.0 Hz), 7.55 (1H, d, $J$=3.6 Hz), 7.63 (1H, t, $J$=8.0 Hz), 7.82 (1H, d, $J$=8.4 Hz), 8.16 (1H, d, $J$=7.6 Hz), 8.35 (1H, d, $J$=8.0 Hz), 8.70 (1H, s); EI-MS $m/z$: 316 ($M^+$, 33).

*N*-(3-Nitrobenzene)sulfonyl-6-methylindole **3h**: 139.3 mg, 88% yield, yellow solid, mp 104—107 °C; $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 2.49 (3H, s), 6.66 (1H, d, $J$=4.0 Hz), 7.08 (1H, d, $J$=8.4 Hz), 7.40 (1H, d, $J$=7.6 Hz), 7.47 (1H, d, $J$=3.6 Hz), 7.63 (1H, t, $J$=8.0 Hz), 7.81 (1H, s), 8.15 (1H, d, $J$=7.6 Hz), 8.36 (1H, d, $J$=8.0 Hz), 8.71 (1H, s); EI-MS $m/z$: 316 ($M^+$, 29).

*N*-(3-Nitrobenzene)sulfonylindole **3i**: 135.6 mg, 89% yield, yellow solid, mp 127—128 °C (lit.,[22] mp not given); $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 6.72 (1H, d, $J$=3.6 Hz), 7.25 (1H, m), 7.34 (1H, t, $J$=8.0 Hz), 7.53 (2H, m), 7.64 (1H, t, $J$=8.4 Hz), 7.99 (1 H, d, $J$=8.4 Hz), 8.17 (1 H, d, $J$=8.0 Hz), 8.36 (1H, dd, $J$=0.8 Hz, $J$=8.0 Hz), 8.71 (1H, s); EI-MS $m/z$: 302 ($M^+$, 33).

*N*-Tosylindole **3j**: 129.9 mg, 96% yield, white solid, mp 83—84 °C (lit.,[23] 87—88 °C); $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 2.33 (3H, s), 6.65 (1H, d, $J$=4.8 Hz), 7.20 (4H, m), 7.51 (1H, d, $J$=10 Hz), 7.56 (1H, d, $J$=4.4 Hz), 7.75 (2H, d, $J$=10.8 Hz), 7.97 (1H, d, $J$=10.8 Hz); EI-MS $m/z$: 271 ($M^+$, 100).

*N*-(4-Ethylbenzene)sulfonylindole **3k**: 139.0 mg, 97% yield, colourless liquid; $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 1.15 (3H, t, $J$=7.2 Hz), 2.60 (2H, q, $J$=7.2 Hz), 6.53 (1H, d, $J$=3.6 Hz), 7.20 (4H, m), 7.52 (1H, d, $J$=8.0 Hz), 7.56 (1H, d, $J$=3.6 Hz), 7.78 (2H, d, $J$=8.4 Hz), 7.99 (1H, d, $J$=8.4 Hz); EI-MS $m/z$: 285 ($M^+$, 69).

*N*-Benzenesulfonylindole **3l**: 125.3 mg, 97% yield, white solid, mp 78—79 °C (lit.,[24] 78—79 °C); $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$: 6.66 (1H, d, $J$=2.8 Hz), 7.21 (1H, d, $J$=7.6 Hz), 7.29 (1H, d, $J$=8.4 Hz), 7.40 (2H, d, $J$=7.6 Hz), 7.50 (2H, d, $J$=8.0 Hz), 7.56 (1H, d, $J$=3.6 Hz), 7.87 (2H, d, $J$=8.0 Hz), 7.99 (1H, dd, $J$=4.0 Hz, $J$=8.4 Hz); EI-MS $m/z$: 257 ($M^+$, 85).

**Anti-HIV-1 Activity Assay. 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.[25]

**MTT-Based Cytotoxicity Assay** Cellular toxicity of compounds **3a**—**l** on C8166 cells was assessed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method as described previously.[26] 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 well, then incubated for 4 h, 100 $\mu$l of 50% *N*,*N*-dimethylformamide (DMF)–20% SDS was added. After the formazan was dissolved completely, the plates were read on a Bio-Tek Elx 800 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)=$CC_{50}/EC_{50}$.[27]

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