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Article

Synthesis and *in vitro* anti-HIV-1 evaluation of some *N*-arylsulfonyl-3-formylindoles

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As our ongoing work on research of anti-HIV-1 inhibitors, fifteen *N*-arylsulfonyl-3-formylindoles (**3a-o**) were designed and prepared through two step synthetic route. Firstly, 3-formylindoles (**2a-c**) were synthesized via the Vilsmeier-Haack reaction. Subsequently, treatment of **2a-c** with the appropriate arylsulfonyl chlorides led to the corresponding target compounds in excellent yields. All analogues were also preliminary evaluated *in vitro* for their inhibitory activity against HIV-1 replication. Among of all the reported analogues, three compounds **3c**, **3g** and **3i** displayed significant anti-HIV-1 activity, with EC_{50} values of 9.57, 11.04 and 5.02 μM, and TI values of 31.89, 13.79 and 81.69, respectively. *N*-*m*-nitrophenylsulfonyl-3-formylindole (**3c**) and *N*-*m*-nitrophenylsulfonyl-6-methyl-3-formylindole (**3i**) especially exhibited the best promising anti-HIV-1 activity. In addition, it demonstrated that insertion of a methyl group at the C-6 position of the indolyl ring and a nitro group at the meta position of the arylsulfonyl ring, as in compound **3i**, resulted in both low cytotoxicity (CC_{50} = 410.41 μM) and good antiviral activity.

Keywords: *N*-Arylsulfonyl-3-formylindole/synthesis. Human immunodeficiency virus type-1/inhibitor.

INTRODUCTION

Acquired immune deficiency syndrome (AIDS) is usually caused by human immunodeficiency virus type 1 (HIV-1) infection and pandemic continues to be a global problem for public health (Faria *et al*., 2014; Piot, Quinn, 2013; Sampériz *et al*., 2014). According to Joint United Nations Programme on AIDS (*UNAIDS*)-2015 report, it is estimated that, approximately 36.9 million people (2.6 million of them were children) were living with HIV infection, and 1.2 millions died due to the infected with HIV and related diseases in the year 2014 (Chander *et al*., 2016; Global HIV and AIDS Statistics, 2015).

The reverse transcriptase (RT) of the HIV-1 plays a pivotal role in the viral replication process, which makes it a crucial target for anti-HIV-1 inhibitors research (Jonckheere, Anné, De Clercq, 2000; Yisma *et al*., 2014). In spite of numerous RT inhibitors (including the nucleotide RT inhibitors (NRTIs) and non-nucleotide RT inhibitors (NNRTIs) have been discovered and developed, like other anti-HIV-1 inhibitors, effectiveness of currently approved NRTIs and NNRTIs have been hampered because of their severe side effects and the aggravation of viral variants resistant to HIV-1 drug (Boone, 2006; De Clercq, 2002; Sluis-Cremer, Wainberg, Schinazi, 2015; Yu *et al*., 2011). To circumvent this challenge, there is an urgent require to develop new, efficacy, selective and safe HIV-1 inhibitors having significant potency against drug-resistant RT viral strains and less toxicity still remains a high priority for medical research (Huang *et al*., 2007; Polanski *et al*., 2006; Safakish *et al*., 2017).

To the best of our knowledge, *N*-arylsulfonylindoles or *N*-arylsulfonyl-3-acylindoles are excellent candidates for the study of serotonin 5-HT_6 receptor (Pullagurla *et al*., 2005; Russell *et al*., 2001; Tsai *et al*., 2000) or anti-HIV-1 inhibitors (Che *et al*., 2016; Fan *et al*., 2009; Ran *et al*., 2010), and especially some *N*-arylsulfonyl-3-acetylindoles showed potent anti-HIV-1 activity. The general structural formula of *N*-arylsulfonylindoles and *N*-arylsulfonyl-3-acylindoles (Figure 1) is shown as a formula **I-III**. Nevertheless, no attention has been paid to the anti-HIV-1 activity of the *N*-arylsulfonyl-3-formylindoles. Inspired by

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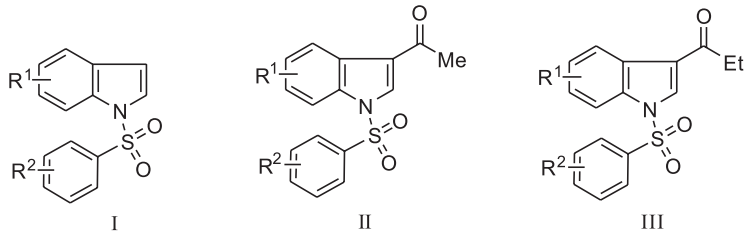


FIGURE 1 - Chemical structure of *N*-arylsulfonylindoles (**I**), *N*-arylsulfonyl-3-acetylindoles (**II**) and *N*-arylsulfonyl-3-propionylindoles (**III**).

these previous observations, and the aim in our program is to discover and develop novel compounds with potent biological activity (Che *et al*., 2013a; Che *et al*., 2015; Che *et al*., 2013b), we report here the results of the synthesis and anti-HIV-1 activity of 15 *N*-arylsulfonyl-3-formylindole derivatives. Furthermore, an investigation of preliminary structure activity relationship (SAR) was also discussed in detail.

RESULTS AND DISCUSSION

Chemistry

N-arylsulfonyl-3-formylindoles **3a-o** (Figure 2) were prepared using two step synthetic route, reaction conditions used for the synthesis of fifteen target compounds are outlined in Scheme 1. Firstly, treatment of commercially available indoles (**1a-c**) with *N*, *N*-dimethylformamide (DMF) solution in phosphorus oxychloride ($POCl_3$) provided an iminium intermediate, which followed by basic hydrolysis with 30% aqueous sodium hydroxide (NaOH) afforded 3-formylindoles (**2a-c**) (Ge, Wu, Xue, 2006). Secondly, introduction of the arylsulfonyl moieties were performed by reacting **2a-c** with the appropriate arylsulfonyl chlorides in the presence of potassium carbonate (K_2CO_3) to produce the corresponding target compounds (**3a-o**) in excellent yields (Abid, Teixeira, Torok, 2007). Compounds **2a-c**, **3a-e**, **3g-j**, **3l** and **3n** were known compounds and characterized by comparison of the data as described in our previous paper (Che *et al*., 2013b).

Biological activities

Purified and characterized 3-formylindoles (**2a-c**) and *N*-arylsulfonyl-3-formylindoles (**3a-o**) were screened *in vitro* for their inhibitory activity against HIV-1 replication in acutely infected C8166 cells, and 3′-azido-

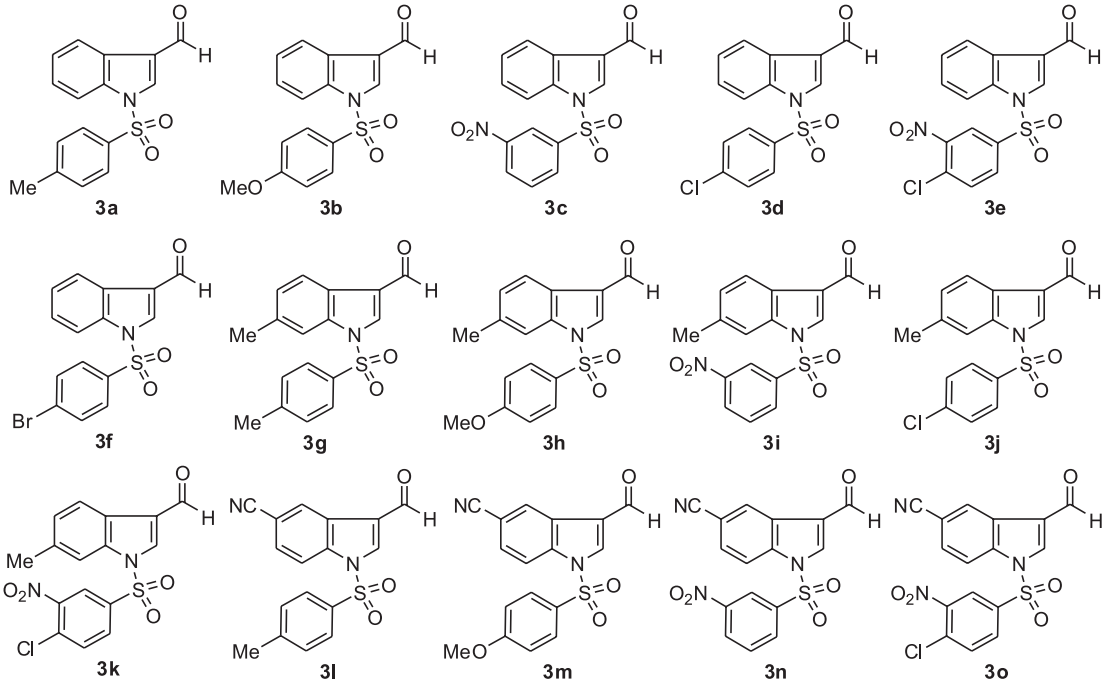
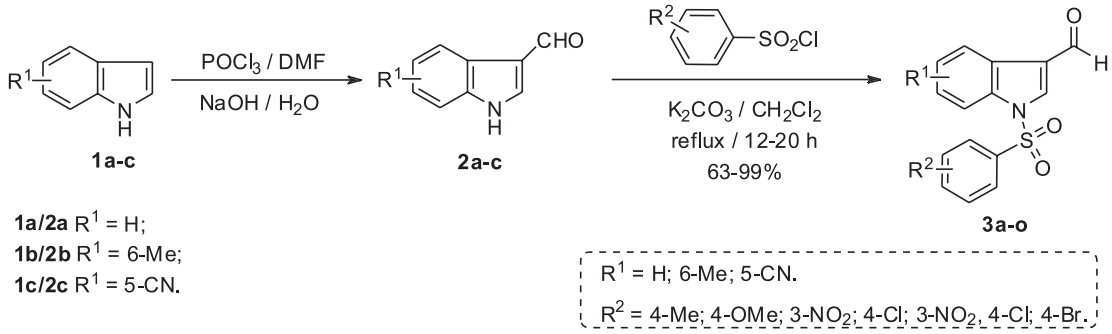


FIGURE 2 - Chemical structures of *N*-arylsulfonyl-3-formylindoles **3a-o**.



SCHEME 1 - Synthetic route for the preparation of 3-formylindoles (**2a-c**) and *N*-arylsulfonyl-3-formylindoles **3a-o**.

3′-deoxythymidine (AZT) was used as a positive control (see Table I). The results of anti-HIV-1 activity detection revealed that, out of 15 screened *N*-arylsulfonyl-3-formylindoles, one (**3i**) displayed the most significant (effective concentration causing 50% inhibition of syncytia formation (EC_{50}) values of 5.02 μM, therapeutic index (TI) values of 81.69), two (**3c** and **3g**) showed moderate (EC_{50} values of 9.57 and 11.04 μM, TI values of 31.89 and 13.79, respectively), while the rest of tested compounds exhibited relatively weak HIV-1 inhibitory activity (EC_{50} values of 11.70 to 46.67 μM, except **3e**, the EC_{50} values of 7.90 μM, and TI values of 0.59 to 9.89).

Consequently, based upon the above investigation, when the arylsulfonyl moieties were introduced on the 1-position of the indole′s ring, the anti-HIV-1 activity of the corresponding compounds were significantly increased (**2a** *vs* **3a-f**; **2b** *vs* **3g-k**; **2c** *vs* **3l-o**). For example, the EC_{50} value of **2a** (EC_{50} = 454.19 μM) was close to 21 times of that of **3c** (EC_{50} = 9.57 μM), the TI value of **3c** (TI = 31.89) was more than 16 times of that of **2a** (TI = 1.96); the EC_{50} value of **2b** (EC_{50} = 428.50 μM) was more than 39 times of that of **3i** (EC_{50} = 5.02 μM), the TI value of **3i** (TI = 81.69) was close to 134 times of that of **2b** (TI = 0.61); the EC_{50} value of **2c** (EC_{50} = 480.35 μM) was more than 6 times of that of **3n** (EC_{50} = 37.63 μM), the TI value of **3n** (TI = 8.94) was more than 9 times of that of **2c** (TI = 0.97).

In order to elucidate the HIV-1 inhibitory activity of **3a-o** on a molecular level as well as to disclose structural features critical for their activity, an investigation of preliminary structure activity relationship (SAR) was determined in detail, which revealed that the electronic effect of various substituted on *N*-arylsulfonyl-3-formylindoles were related to HIV-1 inhibitory activity. In general, (1) Introducing an electron-withdrawing group (such as a nitro group) on the arylsulfonyl ring, could result in the more potent compound than the corresponding one having an electron-donating group (such as a methyl or methoxyl group) (**3c** *vs* **3a** and **3b**; **3i** *vs* **3g** and **3h**; **3n** *vs* **3l** and **3m**). For example, the EC_{50} and TI values of **3c**, **3a** and **3b** were 9.57, 13.66, 11.70 μM, and 31.89, 7.18, 3.72, respectively; that is, the TI value of **3c** was more than 8 times of that of **3b** and was more than 4 times of that of **3a**. The EC_{50} and TI values of **3i**, **3g** and **3h** were 5.02, 11.04, 41.99 μM, and 81.69, 13.79, 4.68, respectively; that is, the

TABLE I - Anti-HIV-1 activity of *n*-arylsulfonyl-3-formylindoles **3a-o** *in vitro*[a]

Compounds	CC_{50}[b] (μM)	EC_{50}[c] (μM)	TI[d]
2a	889.79	454.19	1.96
3a	98.15	13.66	7.18
3b	43.48	11.70	3.72
3c	305.04	9.57	31.89
3d	308.04	31.15	9.89
3e	12.12	7.90	1.53
3f	80.67	11.23	7.18
2b	260.89	428.50	0.61
3g	152.22	11.04	13.79
3h	196.62	41.99	4.68
3i	410.41	5.02	81.69
3j	77.02	11.62	6.63
3k	13.31	9.13	1.46
2c	465.54	480.35	0.97
3l	194.51	39.93	4.87
3m	151.37	32.88	4.60
3n	336.51	37.63	8.94
3o	27.40	46.67	0.59
AZT[e]	4263.82	0.01212	351688.27

[a]Values are means of two separate experiments (the values exhibited standard deviation (SD) less than ±5% from mean). [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]In vitro therapeutic index (CC_{50} value / EC_{50} value). [e]AZT was used as a positive control.

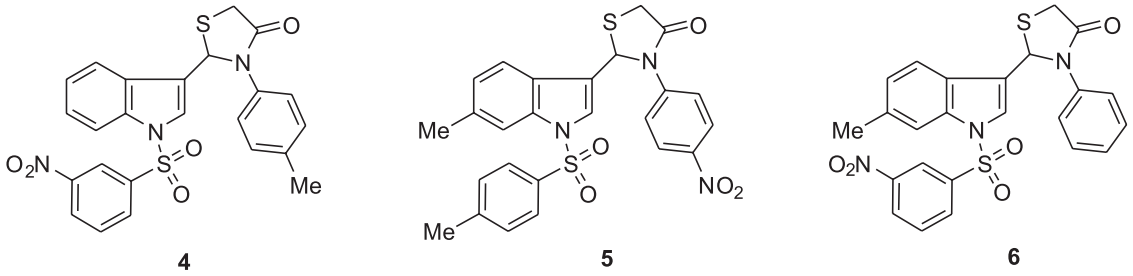


FIGURE 3 - Chemical structure of 2-(*N*-*m*-nitrophenylsulfonylindol-3-yl)-3-*p*-methylphenyl-1,3-thiazolidin-4-ones (**4**), 2-(*N*-*p*-methylphenylsulfonyl-6-methylindol-3-yl)-3-*p*-nitrophenyl-1,3-thiazolidin-4-ones (**5**) and 2-(*N*-*m*-nitrophenylsulfonyl-6-methylindol-3-yl)-3-phenyl-1,3-thiazolidin-4-ones (**6**).

TI value of **3i** was more than 17 times of that of **3h** and was close to 6 times of that of **3g**. The EC_{50} and TI values of **3n**, **3l** and **3m** were 37.63, 39.93, 32.88 μM, and 8.94, 4.87, 4.60, respectively; that is, the TI value of **3n** was nearly 2 times of that of **3m** and was close to 2 times of that of **3l**. (2) Interestingly, variations at the C-4 position of the arylsulfonyl ring outbalance to anti-HIV-1 activities for the corresponding compounds (**3a** *vs* **3b**; **3g** *vs* **3h**; **3l** *vs* **3m**; **3d** *vs* **3f**). For example, 4-methyl was more significant for the anti-HIV-1 activities than 4-ethyl; 4-chloro was more essential for the anti-HIV-1 activities than 4-bromo. The EC_{50} and TI values of **3a**, **3b**, **3g**, **3h**, **3l**, **3m**, **3d** and **3f** were 13.66, 11.70, 11.04, 41.99, 39.93, 32.88, 31.15 and 11.23 μM, and 7.18, 3.72, 13.79, 4.68, 4.87, 4.60, 9.89 and 7.18, respectively. (3) In contrast, when two electron-withdrawing groups (such as nitro and chloro groups) were introduced on the arylsulfonyl ring, the anti-HIV-1 activities of the corresponding compounds were decreased sharply as compared with those containing one electron-withdrawing group (**3e** *vs* **3c** and **3d**; **3k** *vs* **3i** and **3j**; **3o** *vs* **3n**). For example, the EC_{50} and TI values of **3e**, **3k** and **3o** were 7.90, 9.13, 46.67 μM, and 1.53, 1.46, 0.59, respectively; that is, the TI value of **3c** was more than 20 times of that of **3e**; the TI value of **3d** was more than 6 times of that of **3e**; the TI value of **3i** was close to 56 times of that of **3k**; the TI value of **3j** was more than 4 times of that of **3k**; the TI value of **3n** was more than 15 times of that of **3o**. (4) When a methyl group was introduced at the C-6 position of the indolyl ring, the anti-HIV-1activities of the corresponding compounds were more pronounced than those of the compounds carrying a hydrogen group or a cyano group (TI = 13.79 for **3g** *vs* TI = 7.18 for **3a** and TI = 4.87 for **3l**; TI = 4.68 for **3h** *vs* TI = 3.72 for **3b** and TI = 4.60 for **3m**; TI = 81.69 for **3i** *vs* TI = 31.89 for **3c** and TI = 8.94 for **3n**). (5) In the meantime, it is noteworthy that insertion of a methyl group at the C-6 position of the indolyl ring and a nitro group at the meta position of the arylsulfonyl ring, as in compound **3i**, resulted in both low cytotoxicity (cytotoxic concentration causing 50% reduction in total C8166 cell number (CC_{50}) = 410.41 μM) and high antiviral activity (TI = 81.69).

It is noteworthy that introduction of the formyl group at the 3-position of *N*-arylsulfonylindoles could generally lead to the more potent compounds (e.g., **3c**, **3g** and **3i**) relative to those containing 1,3-thiazolidin-4-ones group (e.g., **4**, **5** and **6**, Figure 3). The EC_{50} and TI values of three compounds of containing 1,3-thiazolidin-4-ones group at the 3-position of *N*-arylsulfonylindoles were 172.04, 93.46, 47.21 μM, and >2.36, >4.20, >8.58, respectively; that is, the EC_{50} value of **4** was close to 27 times of that of **3c**, the EC_{50} value of **5** was close to 14 times of that of **3g**, the EC_{50} value of **6** was more than 13 times of that of **3i** (Yang *et al*., 2012). Therefore, further chemical modifications should be deliberately manipulated so as to exploit more potent inhibitors.

EXPERIMENTAL SECTION

General information

Unless specified otherwise, all solvents and reagents were commercially available or purified by standard techniques before use. All reactions were monitored by thin-layer chromatography (TLC) on silica gel plates using silica gel 60 GF_{254} (Qingdao Haiyang Chemical Co., Ltd.). Yields were recorded by purification, and preparative thin-layer chromatography (PTLC) was performed with silica gel plates. Melting points were determined using digital melting-point apparatus (Beijing Tech Instrument Co., Ltd.). Nuclear magnetic resonance spectra (NMR) were recorded on a Bruker Avance DMX 500 MHz instrument (Bruker Daltonik, Bremen, Germany) in $CDCl_3$ or DMSO-d_6 (^{1}H at 500 MHz and ^{13}C at 125 MHz) using tetramethylsilane (TMS) as the internal standard. Electrospray iontrap mass spectrometry (ESI-TRAP-MSn) was performed on a Bruker ESI-TRAP Esquire 3000 plus mass spectrometry instrument (Bruker Daltonics, San Diego, California, USA). The purities of

the target compounds were determined by reverse phase high-performanceliquid chromatography (RP-HPLC) recorded on a Shimadzu LC-15C liquid chromatograph [SPD-15C UV-Vis spectrophotometric detector (190-700 nm); Shimadzu, Kyoto, Japan] using a Hypersil ODS C_{18} column (5 μm, 4.6 × 150 mm) as the stationary phase.

Preparation of *N*-arylsulfonyl-3-formylindoles (3a-o)

A mixture of DMF (5 mL) and $POCl_3$ (0.5 mL) was stirred at 0 °C for 10 min. A solution of indoles (**1a-c**, 5 mmol) in 2 mL DMF was added dropwise to the former mixture. After the addition, the mixture was stirred at 35 °C for 1 h, then 100 mL water was added, followed by the addition of 30% aqueous NaOH to adjust the pH value to 8-9. The mixture was refluxed for 1 h. On cooling, the solution was poured into ice water, and the precipitated product was collected, washed by water, and then washed with a certain amount of petroleum ether until it was pure, monitored by TLC. The pure compounds were dried in vacuum drying chamber to afford 3-formylindoles **2a-c** in excellent yields. Subsequently, a solution of **2a-c** (1 mmol), substituted arylsulfonyl chlorides (2 mmol), and K_2CO_3 (3 mmol) in dry acetone/dichloromethane (10 mL) was refluxed for 12-20 h, till the completion of the reaction as monitored by TLC. The reaction mixture was filtered, and the filtrate was merged, the crude product was purified by PTLC (petroleum ether/ethyl acetate, 1/1) to obtain pure compounds **3a-o** in 63-99% yields, and its purity was >95% as measured with RP-HPLC. The typical spectral data of compounds **3f**, **3k**, **3m** and **3o** were as follows.

N-*p*-Bromophenylsulfonyl-3-formylindole (Weng *et al*., 2007) ***3f***: Tan solid, Yield = 63%, m.p. 145-147 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.10 (s, 1H), 8.27 (d, J = 7.5 Hz, 1H), 8.19 (s, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.80-7.82 (m, 2H), 7.63-7.65 (m, 2H), 7.37-7.44 (m, 2H). MS (ESI-TRAP-MSn), *m/z* (%): 364 ([M+H]$^+$, 100).

N-*m*-Nitro-*p*-chlorophenylsulfonyl-6-methyl-3-formylindole ***3k***: Yellow solid, Yield = 73%, m.p. 153-155 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.08 (s, 1H), 8.48 (d, J = 2.0 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H), 8.11 (s, 1H), 8.02-8.04 (m, 1H), 7.71-7.73 (m, 2H), 7.25 (dd, J = 8.0 Hz, 0.5 Hz, 1H), 2.52 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 186.4, 148.1, 137.5, 136.1, 135.7, 133.0, 131.6, 130.7, 128.3, 125.5, 124.3, 122.7, 119.2, 113.2, 21.5. MS (ESI-TRAP-MSn), *m/z* (%): 377 ([M–H]$^-$, 100).

N-*p*-Methoxylphenylsulfonyl-5-cyano-3-formylindole ***3m***: White solid, Yield = 88%, m.p. 238-240 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.09 (s, 1H), 9.06 (s, 1H), 8.50 (s, 1H), 8.18 (d, J = 9.0 Hz, 1H), 8.13 (d, J = 9.0 Hz, 2H), 7.89 (dd, J = 9.0 Hz, 1.5 Hz, 1H), 7.18 (d, J = 9.0 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 199.1, 186.1, 147.5, 139.3, 135.2, 132.1, 130.4, 129.0, 127.5, 125.4, 120.7, 118.3, 114.7, 107.4, 56.3. MS (ESI-TRAP-MSn), *m/z* (%): 339 ([M–H]$^-$, 100).

N-*m*-Nitro-*p*-chlorophenylsulfonyl-5-cyano-3-formylindole ***3o***: Yellow solid, Yield = 76%, m.p. 228-230 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.10 (s, 1H), 9.09 (s, 1H), 8.92 (d, J = 2.0 Hz, 1H), 8.48-8.50 (m, 2H), 8.24 (d, J = 9.0 Hz, 1H), 8.09 (d, J = 9.0 Hz, 1H), 7.91 (dd, J = 8.5 Hz, 1.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 199.1, 186.2, 148.0, 140.1, 136.1, 132.5, 130.3, 129.7, 127.9, 125.4, 119.9, 118.8, 115.1, 107.7. MS (ESI-TRAP-MSn), *m/z* (%): 388 ([M–H]$^-$, 100).

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, UK. C8166 was maintainedin RPMI-1640 supplemented with 10% heat-inactivated newborn calf serum (Gibco). The cells used in all experiments were in log-phasegrowth. 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 3-formylindoles (**2a-c**) and *N*-arylsulfonyl-3-formylindoles (**3a-o**) on C8166 cells was assessed by MTT method as described previously. Briefly, cells were seeded on 96-well microtiter plate in the absence or presence of various concentrations of *N*-arylsulfonyl-3-formylindoles 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 μL of 50% *N*, *N*-dimethylformamide (DMF)-20% SDS was added. After the formazan was dissolved completely, the plates were read on a Bio-TekElx800 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 μL various concentrations of *N*-arylsulfonyl-3-formylindoles, C8166 cells (4 × 10^5/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 μL. 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}.

CONCLUSIONS

In conclusion, fifteen *N*-arylsulfonyl-3-formylindoles (**3a-o**) were prepared and preliminarily evaluated as HIV-1 inhibitors *in vitro*. Especially, *N*-*m*-nitrophenylsulfonyl-3-formylindole (**3c**) and *N*-*m*-nitrophenylsulfonyl-6-methyl-3-formylindole (**3i**) displayed moderate anti-HIV-1 activity with EC_{50} values of 9.57 and 5.02 μM, and TI values of 31.89 and 81.69, respectively. In addition, it demonstrated that introduction of the methyl group at the C-6 position of the indolyl ring and the nitro group at the meta position of the phenylsulfonyl ring were two certainly important functional groups for **3i** being significant anti-HIV-1 activity.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

The authors have reported no conflict of interest.

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