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Anti HIV-1 agents 5: Synthesis and anti-HIV-1 activity of some *N*-arylsulfonyl-3-acetylindoles in vitro

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ABSTRACT

In continuation of our program aimed at the discovery and development of compounds with superior anti-human immunodeficiency virus type 1 (HIV-1) activity, 21*N*-arylsulfonyl-3-acetylindole analogs (**2a**–**u**) were synthesized and preliminarily evaluated as HIV-1 inhibitors in vitro. Among of all the analogs, several compounds exhibited significant anti-HIV-1 activity, especially *N*-phenylsulfonyl-3-acetyl-6-methylindole (**2j**) and *N*-(*p*-ethyl)phenylsulfonyl-3-acetyl-6-methylindole (**2n**) showed the most potent anti-HIV-1 activity with EC_{50} values of 0.36 and 0.13 μg/mL, and TI values of >555.55 and 791.85, respectively. It demonstrated that introduction of the acetyl group at the 3-position of *N*-arylsulfonyl-6-methylindoles could generally lead to the more potent analogs.

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] Therefore, the rapid worldwide spread of AIDS has prompted an intense research effort to discover compounds that could effectively inhibit HIV. In the past two decades, 25 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] Consequently, it is imperative that the design and development of new, selective and safe drugs for the treatment of HIV-1.[4,5]

Recently, a series of *N*-arylsulfonylindole derivatives showed the selective affinity on the human serotonin 5-HT_6 receptor,[6–8] and especially some single *N*-arylsulfonylindoles (**1**, Fig. 1) displayed potent anti-HIV-1 activity.[9] Meanwhile, much attention has been paid in recent years to the chemistry of 3-acetylindole derivatives, because some compounds derived from 3-acetylindoles exhibited the diverse biological activities, for example, anticancer activity[10,11] and antiinflammatory activity.[12] Inspired by these previous observations, and as part of our continuing studies on the indoles as anti-HIV-1 agents, in this Letter we synthesized some *N*-arylsulfonyl-3-acetylindole analogs (**2a**–**u**, Fig. 1) by introduction of the acetyl group at the 3-position of *N*-arylsulfonylindoles, and wanted to investigate whether the anti-HIV-1 activity of the target compounds **2a**–**u** could be improved to some extent.

As outlined in Scheme 1, a series of *N*-arylsulfonyl-3-acetylindole analogs (**2a**–**u**) were synthesized from the commercially available indoles. Firstly, indoles reacted with arylsulfonyl chlorides in the presence of sodium hydroxide (NaOH) and triethylbenzylammonium chloride (TEBA) at room temperature to give *N*-arylsulfonylindoles (**1a**–**u**),[13] which were used directly for the next step reaction without further purification. Subsequently, treatment of **1a**–**u** with acetic anhydride by a regioselective Friedel–Crafts acylation reaction led to *N*-arylsulfonyl-3-acetylindoles (**2a**–**u**) in 51–89% yields,[14] which were well characterized by ^{1}H NMR, MS, and mp (see Supplementary data).

Target compounds **2a**–**u** were evaluated for their inhibitory activity against HIV-1 replication in acutely infected C8166 cells in vitro according to the previously described method,[9,15] and AZT was used as a positive control. In the meantime, in order to investigate the influence of 3-acetyl group of **2a**–**u** on the anti-HIV-1 activity, intermediates **1a**–**u** without 3-acetyl group were also tested for their anti-HIV-1 activity. The assay results of compounds **1a**–**u** and **2a**–**u** are presented in Table 1. Among of all the target compounds, **2c**, **2j–l**, and **2n–o** exhibited the significant

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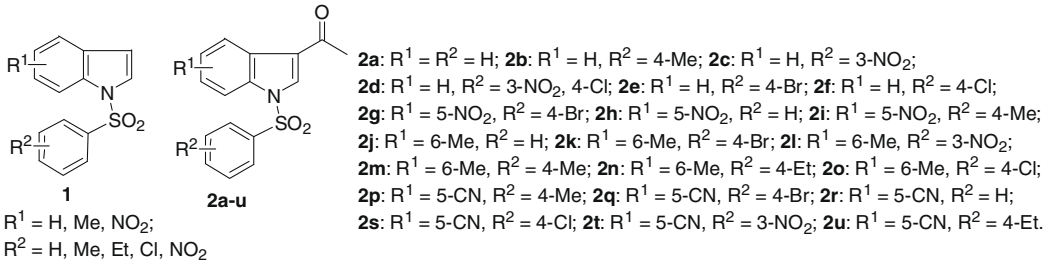
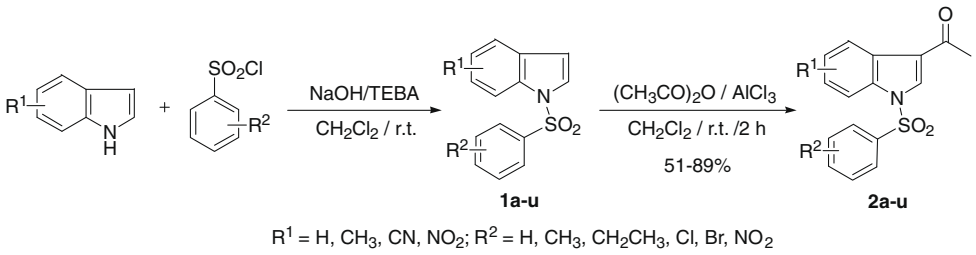


Figure 1.



Scheme 1. The synthetic route of compounds **2a–u**.

anti-HIV-1 activity with EC_{50} values of 2.12, 0.36, 4.29, 1.02, 0.13, and 5.54 μg/mL, and TI values of 77.43, >555.55, >46.62, 122.5, 791.85, and 31.72, respectively. Most noteworthy, *N*-phenylsulfonyl-3-acetyl-6-methylindole (**2j**) and *N*-(*p*-ethyl)phenylsulfonyl-3-acetyl-6-methylindole (**2n**) showed the most potent anti-HIV-1 activity with EC_{50} values of 0.36 and 0.13 μg/mL, and TI values of >555.55 and 791.85, respectively.

Table 1
Anti-HIV-1 activity of *N*-arylsulfonylindoles **1a–u** and *N*-arylsulfonyl-3-acetylindoles **2a–u** in vitro[a]

Compounds	CC_{50}[b](μg/mL)	EC_{50}[c](μg/mL)	TI[d]
1a[e]/**2a**	47.14/30.27	0.93/2.68	50.68/11.29
1b[e]/**2b**	>200/23.72	13.38/31.13	>14.94/0.76
1c[e]/**2c**	>200/164.26	0.74/2.12	>270.27/77.43
1d/**2d**	2.79/3.21	0.38/3.43	7.34/0.94
1e/**2e**	>200/53.31	20.42/80.78	>9.79/0.66
1f[e]/**2f**	>182.71/31.18	12.33/88.29	>14.81/0.35
1g/**2g**	>163.86/70.44	62.72/54.51	>2.61/1.29
1h/**2h**	>145.64/>200	4.81/45.83	>30.27/>4.36
1i[e]/**2i**	>175.77/>200	26.31/>200	>6.68/1
1j/**2j**	28.73/>200	0.89/0.36	32.10/>555.55
1k/**2k**	23.61/>200	13.84/4.29	1.71/>46.62
1l[e]/**2l**	141.38/124.95	0.26/1.02	543.78/122.5
1m[e]/**2m**	78.04/>200	3.00/13.83	26.01/>14.46
1n/**2n**	78.63/102.94	8.14/0.13	9.66/791.85
1o/**2o**	17.41/175.78	0.72/5.54	24.18/31.72
1p/**2p**	>200/147.11	63.46/76.89	>3.15/1.91
1q/**2q**	>200/>200	69.44/>200	>2.88/1
1r/**2r**	>200/66.15	3.23/57.53	>61.92/1.21
1s/**2s**	>200/65.15	49.59/54.4	>4.03/1.19
1t/**2t**	>187.02/60.12	40.37/15.47	>4.63/3.88
1u/**2u**	136.52/112.92	4.16/30.5	32.82/3.70
AZT[f]	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] In vitro therapeutic index (CC_{50} value/EC_{50} value).
[e] The results were from Ref. 9.
[f] AZT was used as a positive control.

Meanwhile, preliminary structure–activity relationships (SAR) showed the following interesting characteristics: (1) In general, the *N*-arylsulfonyl-3-acetyl-6-methylindole analogs (**2j–o**) showed the more potent anti-HIV-1 activity than *N*-arylsulfonyl-3-acetylindole analogs (**2a–f**, except **2c**), *N*-arylsulfonyl-3-acetyl-5-nitroindole analogs (**2g–i**), and *N*-arylsulfonyl-3-acetyl-5-cyanoindole analogs (**2p–u**). (2) Among of *N*-arylsulfonyl-3-acetylindoles (**2a–f**), *N*-(3-nitrobenzene)sulfonyl-3-acetylindole (**2c**) exhibited the most potent anti-HIV-1 activity, but when the chloro or the bromo atom was introduced on the phenyl ring of **2c** or **2a**, the anti-HIV-1 activities of the corresponding compounds were reduced sharply (**2c** vs **2d**; **2a** vs **2e** and **2f**). (3) Generally, when the electron-withdrawing group (such as nitro or cyano group) was introduced on the indolyl ring of *N*-arylsulfonyl-3-acetylindoles, the anti-HIV-1 activities of the corresponding compounds were less potent than those of *N*-arylsulfonyl-3-acetyl-6-methylindoles (e.g., **2h** and **2r** vs **2j**; **2g** and **2q** vs **2k**; **2i** and **2p** vs **2m**). (4) When introduction of the acetyl group at the 3-position of *N*-arylsulfonyl-6-methylindoles (**1j–o**), the corresponding *N*-arylsulfonyl-3-acetyl-6-methylindole analogs (**2j–o**, except **2l** and **2m**) usually displayed the more potent anti-HIV-1 activity. For example, the EC_{50} and TI values of **1j**, **1k**, **1n**, and **1o** were 0.89/13.84/8.14/0.72 μg/mL, and 32.10/1.71/9.66/24.18, respectively; while the EC_{50} and TI values of **2j**, **2k**, **2n**, and **2o** were 0.36/4.29/0.13/5.54 μg/mL, and >555.55/>46.62/791.85/31.72, respectively. Especially the TI value of **2n** was more than 80 times of that of **1n**.

In conclusion, 21*N*-arylsulfonyl-3-acetylindole analogs (**2a–u**) were synthesized and preliminarily evaluated as HIV-1 inhibitors in vitro. Among of all the analogs, compounds **2c**, **2j–l**, and **2n–o** exhibited the potent anti-HIV-1 activity, especially *N*-phenylsulfonyl-3-acetyl-6-methylindole (**2j**) and *N*-(*p*-ethyl)phenylsulfonyl-3-acetyl-6-methylindole (**2n**) showed the most potent anti-HIV-1 activity with EC_{50} values of 0.36 and 0.13 μg/mL, and TI values of >555.55 and 791.85, respectively. It demonstrated that introduction of the acetyl group at the 3-position of *N*-arylsulfonyl-6-methylindoles could generally lead to the more potent analogs. Therefore, some new analogs are being prepared starting from 6-methylindole as the lead compound in our laboratory, and the research results will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.04.132.

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