Synthesis of Styrylquinoline Carboxamides for HIV-1 Integrase Inhibitors

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Received July 15, 2006

Key Words : HIV integrase, Inhibitor, Styrylquinoline, 3'-Processing, Strand transfer

AIDS is essentially a viral disease and should be treated by antiretroviral agents.[1] From this standpoint, HIV DNA integration into genomic DNA of the host cell, a crucial step in the life cycle of the virus, constitutes a particularly attractive target for AIDS chemotherapeutics, including potential synergy with currently available HIV reverse transcriptase and protease inhibitors.[2,3]

HIV-1 integrase (IN) catalyzes two distinct reactions: the terminal cleavage at each 3' end of the proviral DNA removing a pair of bases and the strand transfer which results in the joining of each 3' end to 5'-phosphates in the target DNA. Such integration is essential for the production of progeny viruses, and therefore therapeutic agents that can inhibit this process should be effective anti-HIV agents.[4-6] HIV IN has also been recognized as a safe target against HIV because there are no similar enzymes involved in human cellular function.[7] Recently, several aryl 1,3-diketo acids that can inhibit strand transfer reaction of HIV-1 IN have been identified as potent anti-HIV agent.[8] The 1,3-diketo acid moiety has been postulated to be an essential part for the inhibitory activity of HIV-1 IN strand transfer since these part is believed to interact with catalytically important Mg^{2+} in the active site of HIV-1 integration step.[9] Accordingly, the variations of structural features of aryl 1,3-diketo acids have been made leading to 8-hydroxy-1,6-naphthyridine carboxamides **1**, which mimic the metal cation interaction of the 1,3-diketo acid pharmacophore.[10,11] Independently, French scientists from CNRS identified styrylquinoline carboxylic acid **2a** (R = CO_2H, X = CH) as a potent HIV-1 IN inhibitor that can block 3'-processing as well as strand transfer step of HIV-1 IN.[12] We also reported styrylquinazoline ring as a new scaffold for HIV-1 IN inhibitors (for example, **2b**; R = H, X = NH).[13] For styrylquinoline compounds **2a**, the hydroxyl group at C-8 as well as carboxyl group at C-7 of quinoline ring was important on the inhibitory activity against HIV-1 integrase. On the other hand, the free catechol moiety was required in styrylquinazoline compound **2b** for the inhibitory activity against 3'-processing step of HIV-1 IN.

The hybridization of biologically active compounds has been proposed as a promising strategy in the development of new leads for medicinal application. The biological activities of several new hybrids have been found to exceed those of the parent compounds.[14] In this regard, we designed a new structure of compounds by combining structures of 8-hydroxy-1,6-naphthyridine carboxamide **1** and styrylquinoline carboxylic acid **2a** to form a styrylquinoline carboxamides **3**. Thus, we synthesized a new structure of compounds by combining structures of 8-hydroxy-1,6-naphthyridine carboxamide **1** and styrylquinoline carboxylic acid **2a**. Herein, we wish to report the synthesis of styrylquinoline carboxamides **3a-e**, which have free catechol and carboxamide moieties within molecules and their evaluation for HIV-1 IN inhibitory activities.

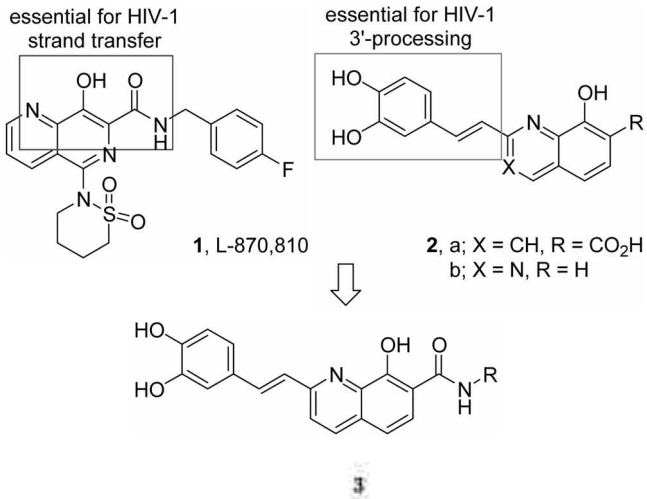
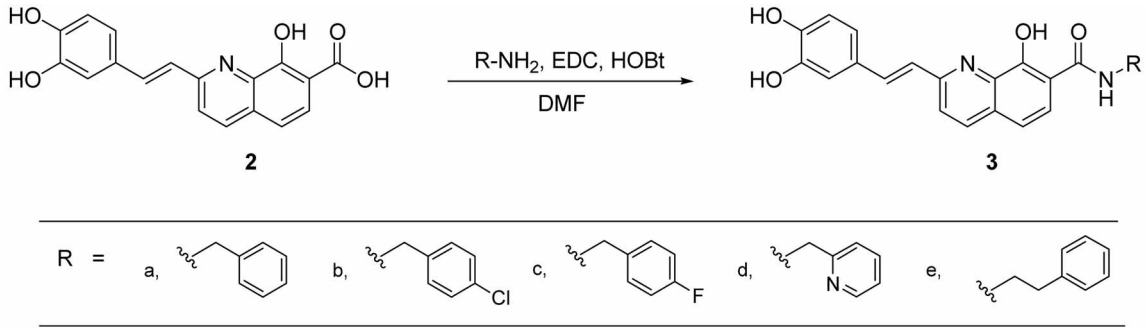


Figure 1. Structures of reported HIV-1 IN inhibitors and new styrylquinoline carboxamides (**3a-e**).

Results and Discussion

Chemistry. The chemistry used to prepare the styrylquinoline carboxamides **3a-e** is illustrated in Scheme 1. The target compounds were synthesized simply by reaction of styrylquinoline carboxylic acid **2a** with various amines using EDC and HOBt as coupling agents. The required starting material **2a** was prepared as described previously



Scheme 1. Synthesis of styrylquinoline carboxamides **3a-e**.

through two-steps sequence: Carboxylation of 8-hydroxyquinaldine under the Kolbe-Schmitt conditions followed by the Perkin condensation of the resulting 8-hydroxyquinaldine-7-carboxylic acid with 3,4-dihydroxybenzaldehyde.[12]

Biological activity. The resulting styrylquinoline carboxamides **3a-e** were assayed *in vitro* for inhibition of 3'-processing[15] and strand transfer[16] steps of HIV-1 IN. To compare the inhibitory activity, the compound **2a** was also assayed as a reference. Unexpectedly, every compound synthesized exhibited no noticeable HIV-1 IN inhibition when tested up to 300 μM while **2a** showed inhibitory activities with IC_{50} values of 72.7 μM for 3'-processing step and 129.0 μM for strand transfer step, respectively. The significant loss of HIV-1 IN inhibitory activities of these compounds compared to **2a** indicates that the increased size of compounds **3a-e** seems not suitable to fit into the catalytic pocket of HIV-1 IN although these compounds have two pharmacophores that can bind with Mg^{2+} of HIV-1 IN within molecules.

In conclusion, styrylquinoline carboxamides **3a-e** were synthesized as new scaffold for HIV-1 IN inhibitors by combining structures of reputed HIV-1 IN inhibitors, 8-hydroxy-1,6-naphthyridine carboxamide **1** and styrylquinoline carboxylic acid **2a**. Although synthesized compounds did not exhibit HIV-1 IN inhibitory activities, these results may be helpful in of design new potent HIV-1 IN inhibitors in future works.

Experimental Section

Chemistry

General: All reactions were carried out under nitrogen atmosphere. Flash column chromatographies were perfomned with Merck Kiesegel 60 Art 9385 (230-400 mesh). All solvents used were purified according to standard procedures. ^{1}H and ^{13}C NMR spectra were recorded on a Gemini Varian-300 (300 and 75 MHz, respectively): chemical shifts are expressed value (ppm) and coupling constants (J) in Hz. The starting material **2** was prepared by the known procedure as described previously.[12]

General procedure for the synthesis of styrylquinoline carboxamides (1a-e). To a solution of (*E*)-8-hydroxy-2-[2-(3,4-dihydroxyphenyl)ethenyl]-7-quinolinecarboxylic acid (**2**, 100 mg, 0.31 mmol) and arylamines (0.33 mmol) in DMF (3 mL) was added *N*-ethyl-*N'*-dimethylaminopropylcarbodiimide hydrochloride (EDC, 65.2 mg, 0.34 mmol) and *N*-hydroxybenzotriazole (HOBt, 44 mg, 0.33 mmol). The mixture was stirred at room temperature for 3 days and then poured into water. The red precipitate was filtered and washed with diethyl ether to provide **3a-e**.

(*E*)-8-Hydroxy-2-[2-(3,4-dihydroxyphenyl)ethenyl]-7-quinoline-benzylcarboxamide (3a). The treatment of **2** (100 mg, 0.31 mmol) with benzylamine (0.036 mL, 0.33 mmol) according to the general procedure provided the desired product **3a** (42 mg, 33%). ^{1}H NMR (DMSO-d_6) δ 9.33 (1H, bs, *NH*), 8.29 (1H, d, J = 8.1 Hz), 8.14 (1H, d J = 9.0 Hz), 8.11 (2H, m), 7.44 (2H, m), 7.23-7.34 (6H, m), 7.08 (1H, d, J = 8.1 Hz), 6.93 (1H, d, J = 8.1 Hz), 4.74 (2H, d, J = 5.4 Hz); ^{13}C NMR (DMSO-d_6) δ 168.5, 156.7, 155.7, 147.6, 146.3, 139.8, 139.5, 137.0, 136.1, 130.0, 129.2, 128.6, 128.1, 127.7, 125.2, 124.6, 122.6, 120.5, 119.5, 117.5, 116.6, 114.6, 113.7, 110.8, 43.4.

(*E*)-8-Hydroxy-2-[2-(3,4-dihydroxyphenyl)ethenyl]-quinoline-7-(4-chlorobenzyl)carboxamide (3b). The treatment of **2** (100 mg, 0.31 mmol) with chlorobenzyl amine (0.04 mL, 0.33 mmol) according to the general procedure provided the desired product **3b** (47 mg, 34%). ^{1}H NMR (DMSO-d_6) δ 9.34 (1H, bs, *NH*), 8.25 (1H, d, J = 8.7 Hz), 8.13 (1H, d, J = 9.0 Hz), 7.91 (2H, m), 7.46 (5H, m), 7.04 (1H, d, J = 8.4 Hz), 6.91 (1H, d, J = 8.4 Hz), 4.67 (2H, d, J = 4.5 Hz); ^{13}C NMR (DMSO-d_6) δ 168.6, 156.6, 155.7, 147.6, 146.3, 139.5, 139.0, 137.0, 136.1, 132.2, 130.0, 129.1, 128.6, 125.2, 122.6, 120.5, 117.5, 116.6, 114.7, 113.7, 42.7.

(*E*)-8-Hydroxy-2-[2-(3,4-dihydroxyphenyl)ethenyl]-quinoline-7-(4-fluorobenzyl)carboxamide (3c). The treatment of **2** (100 mg, 0.31 mmol) with 4-fluorobenzyl amine (0.037 mL, 0.33 mmol) according to the general procedure provided the desired product **3c** (50 mg, 37 %). ^{1}H NMR (DMSO-d_6) δ 9.30 (1H, bs, *NH*), 8.30 (1H, d, J = 8.7 Hz Hz), 7.82-7.96 (3H, m), 7.35-7.48 (3H, m), 7.08-7.22 (4H, m), 7.01 (1H, d, J = 8.4 Hz), 6.83 (1H, d, J = 8.4 Hz), 4.60 (2H, d, J = 2.7 Hz); ^{13}C NMR (DMSO-d_6) δ 168.5, 163.6, 160.4, 156.6, 155.7, 147.6, 146.3, 139.5, 147.0, 136.1, 130.2, 130.1, 130.0, 128.6, 125.2, 122.7, 120.5, 117.5, 116.6, 116.0, 115.7, 114.6, 113.7, 100.2, 42.7.

(*E*)-8-Hydroxy-2-[2-(3,4-dihydroxyphenyl)ethenyl]-quinoline-7-(2-pyridinomethyl)carboxamide (3d). The treatment of **2** (100 mg, 0.31 mmol) with 2-aminomethyl

pyridine (0.034 mL, 0.33 mmol) according to the general procedure provided the desired product **3d** (13 mg, 10%). ^{1}H NMR (DMSO-d_6) δ 9.49 (1H, br s, *NH*), 8.56 (1H, d, J = 3.9 Hz), 8.32 (1H, d, J = 8.7 Hz), 8.25 (1H, d, J = 9.3 Hz), 8.15 (1H, m), 7.99 (1H, d, J = 8.7 Hz), 7.68-7.96 (2H, m), 7.65 (1H, d, J = 16.5 Hz), 7.32-7.48 (2H, m), 7.02-7.13 (2H, m), 7.82 (1H, m), 4.74 (2H, m); ^{13}C NMR (DMSO-d_6) δ 168.1, 164.8, 158.5, 156.0, 149.7, 147.6, 146.3, 141.2, 139.4, 137.6, 137.0, 136.2, 132.2, 129.9, 128.6, 125.0, 123.0, 122.0, 120.5, 117.6, 116.6, 114.7, 114.0, 45.3.

(*E*)-8-Hydroxy-2-[2-(3,4-dihydroxyphenyl)ethenyl]-quinoline-7-phenethylcarboxamide (3e). The treatment of **2** (100 mg, 0.31 mmol) with 2-aminomethyl pyridine phenethylamine (0.037 mL, 0.33 mmol) according to the general procedure provided the desired product **3e** (42 mg, 32%). ^{1}H NMR (DMSO-d_6) δ 8.94 (1H, br s, *NH*), 8.27 (1H, d, J = 8.7 Hz), 7.97 (1H, d, J = 6.6 Hz), 7.82 (1H, d, J = 16.5 Hz), 7.37 (1H, d, J = 8.7 Hz), 7.12-7.42 (6H, m), 7.19 (1H, d, J = 16.5 Hz), 7.05 (1H, d, J = 8.1 Hz), 6.69-6.71 (2H, m), 3.66 (2H, m), 2.95 (2H, t, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6) δ 168.6, 156.8, 155.7, 147.6, 146.3, 140.1, 139.6, 136.9, 136.0, 130.0, 129.4, 129.2, 128.6, 127.0, 125.3, 125.0, 122.6, 120.5, 119.7, 117.5, 116.6, 114.7, 113.5, 110.7, 41.5, 35.7.

Acknowledgement. This research was supported by a grant from Kyung Hee University Research Fund in 2006.

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