Available online at www.sciencedirect.com
ScienceDirect
Chinese Chemical Letters 20 (2009) 789–792
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

Synthesis of 6-sulfamoyl-4-oxoquinoline-3-carboxylic acid derivatives as integrase antagonists with anti-HIV activity

Zai Gang Luo, Cheng Chu Zeng, Lei Fu Yang, Hong Qiu He, Cun Xin Wang, Li Ming Hu *

College of Life Science and Bioengineering, Beijing University of Technology, Beijing 100124, China

Received 17 November 2008

Abstract

A series of novel 6-sulfamoyl-4-oxoquinoline-3-carboxylic acids derivatives have been synthesized and screened for HIV integrase inhibition activity. Their structures were confirmed by ESI-MS, ^{1}H NMR and ^{13}C NMR.

Keywords: Quinoline; Integrase; Anti-HIV-1 activity

As a kind of HIV-1 integrase inhibitors, quinolone derivatives were taken great interest in due to their extremely versatile nature, easily synthesized at low cost on a large scale and well-known biochemical properties [1,2]. The first quinolone-based structure GS-9137 [3] with very strong antiretroviral properties was proven to be a highly selective integrase inhibitor.

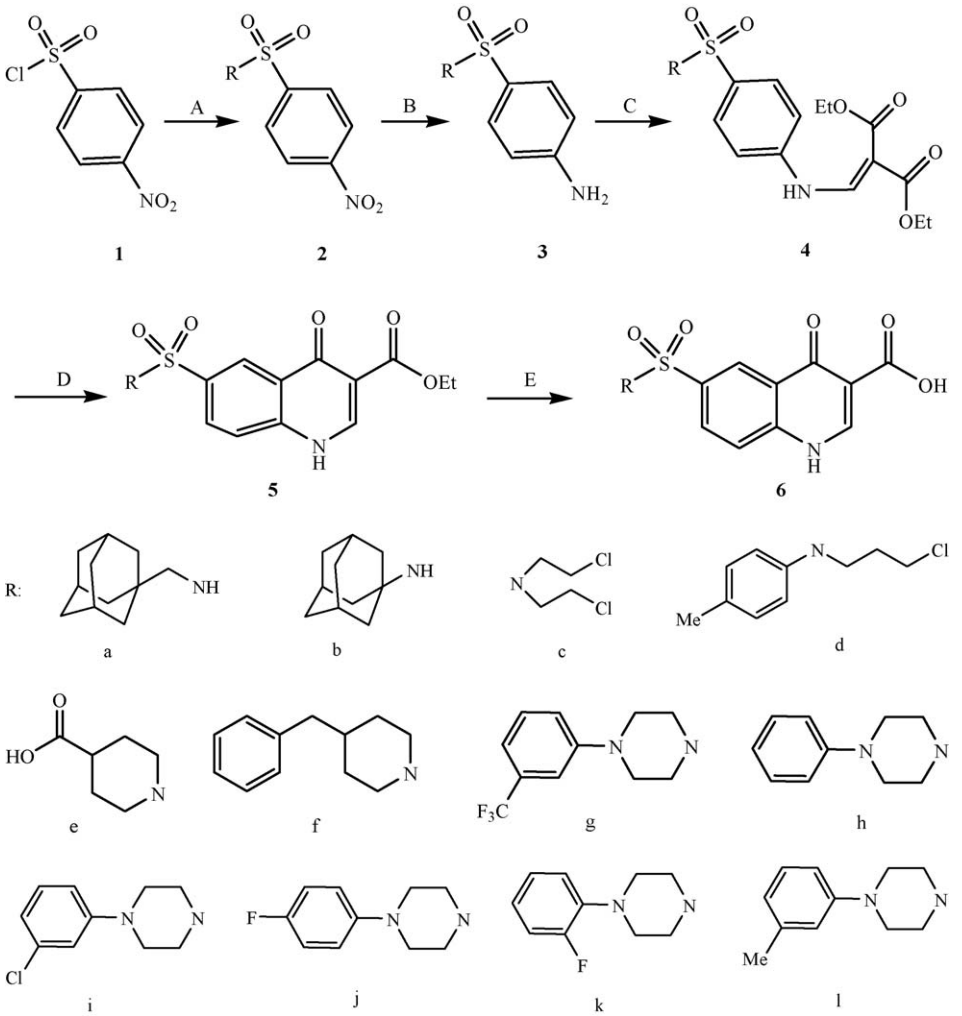
The viral enzyme integrase (IN), along with HIV-1 reverse transcriptase and HIV-1 protease, is an essential enzyme for retroviral replication and represents an important target for interrupting the viral replication cycle [4]. IN is an attractive target because it has no counterpart in mammalian cells, therefore, IN inhibitors should have high selectivity and low toxicity [5]. Quinolone-3-carboxylic acid was assumed a new pharmacophore for designing of new generation HIV-1 IN inhibitors [6]. We envisage that pharmacophore perception is an ideal approach for discovering a new generation IN inhibitors. In this study we synthesize 6-sulfamoyl-4- oxoquinoline-3-carboxylic acids **6a–l** (Scheme 1).

The Gould–Jacob cyclization reaction [7] is one of the main methods to form the core structure of quinolone 3-carboxylic acids. 6-sulfamoyl-4-oxoquinoline-3-carboxylic acid derivatives were prepared starting from the commercially available 4-nitrobenzene sulfonyl chloride **1** in five steps [8,9]. We initially thought that the key cyclization reaction would be preformed difficultly on the relatively electronic-deficient **4** along with the larger sulfamoyl groups, while the quinolone **5** was facile to be synthesized.

Straightforward sulfonamide formation was obtained 4-nitrobenzene sulfonamide **2**, then reduction of **2** was carried out under standard conditions with $SnCl_2{\cdot}2H_2O$ and delivered 4-aminobenzene sulfonamide **3**. Condensation of **3** with ethoxymethylenemalonate diethyl ester yielded aminomethylenemalonate **4**. The compound **4** was converted

* Corresponding author.
E-mail address: huliming@bjut.edu.cn (L.M. Hu).

1001-8417/$ – see front matter
doi:10.1016/j.cclet.2009.03.014



Scheme 1. Reagents and conditions: (A) substituted amines (or substituted piperdine and piperazine), EtN_3/CH_2Cl_2, 81–96%; (B) $SnCl_2{\cdot}2H_2O$, EtOAc, reflux, 4 h, 62–86%; C) diethyl ethoxymethylenemalonate, 1,4-dioxane, reflux, 3.5 h, 62–91%; (D) cat. *p*-chlorobenzoic acid, Ph_2O, 250 °C, ~0.5 h, 45–69%; (E) NaOH, H_2O/EtOH, reflux, 1 h, 10% H_2SO_4, 63–90%.

to quinolone **5** in Ph_2O containing catalytic *p*-chlorobenzoic acid. Building upon the literatures, we found that the typical reaction time for optimal yields for this series transformation should be within 30 min. The unimaginable byproducts will come into being under too higher temperature beyond half hour. Also, we found the catalyst *p*-chlorobenzoic acid did limited effects to shorten the reaction time and improve the yields. Finally, quinolone **5** was hydrolyzed using sodium hydroxide in the mixed solution of EtOH/H_2O, after acidification with 10% H_2SO_4, a small collection of 6-sulfamoyl-4-oxoquinoline-3-carboxylic acids **6** was prepared. The structure of the compounds **6a–l** was confirmed by ^1H NMR, ^{13}C NMR and ESI-MS [10].

HIV-1 integrase strand transfer activity assay was carried out to test the inhibition effectiveness of our compounds as described previously[11] with some minor modifications. Compounds diluted in DMSO were pre-incubated with 800 ng integrase at 37 °C in the reaction buffer in the absence of Mn^{2+} for 10 min. Subsequently, 1.5 pmol donor DNA and 9 pmol target DNA were added and the reaction was initiated by the addition of 10 mmol/L Mn^{2+} into the final reaction volume. The reactions were carried out at 37 °C for 1 h and subsequent detection procedure was applied to detect the assay signals. Integrase inhibitor, L-708906, was used as the control compound (positive control), whereas no compound but only DMSO in the reaction mixture was set as the drug-free control (negative control). The inhibition percentages of 6-sulfamoyl-4- oxoquinoline-3-carboxylic acids **6a–l** were calculated based on the positive and

Table 1
HIV integrase inhibition activity of 6-sulfamoyl-4-oxoquinoline-3-carboxylic acids.

Compound no.	Inhibitory rate % (1 mmol/L)	Compound no.	Inhibitory rate % (1 mmol/L)
6a	99.93	**6h**	78.80
6b	90.93	**6i**	76.59
6c	99.97	**6j**	89.58
6d	74.51	**6k**	73.90
6e	55.88	**6l**	66.79
6f	73.53	L-708906 (25 μmol/L)	100
6g	73.16	control	0

negative controls (Table 1). The data revealed that all compounds showed to inhibit HIV integrase activities at the concentration of 1 mmol/L. Especially the compounds **6a** and **6c** show almost completely inhibitory activity against integrase.

In conclusion, we have synthesized a series of novel 6-sulfamoyl-4-oxoquinoline-3-carboxylic acids derivatives and screened for anti-HIV-1 activities against integrase. The structures of compounds **6a–l** were confirmed by ^{1}H NMR, ^{13}C NMR and ESI-MS. **6a** and **6c** showed inhibitory activity against HIV integrase, further studies directed towards the efficient quinolone 3-carboxylic acid pharmacophore are under investigation and will be reported in due course.

Acknowledgments

The authors gratefully thank the financial supports of the National Basic Research Program (No. 2009CB930200) and the Fund from Beijing City Education Committee (No. KM200610005029) and Funding Project for Academic Human Resources Development in Institutions of Higher Learning Under the Jurisdiction of Beijing Municipality.

References

[1] O. Tabarrini, S. Massari, D. Daelemans, et al. J. Med. Chem. 51 (2008) 5454.
[2] V. Cecchetti, C. Parolin, S. Moro, et al. J. Med. Chem. 43 (2000) 3799.
[3] M. Sato, T. Motomura, H. Aramaki, et al. J. Med. Chem. 49 (2006) 1506.
[4] Y. Pommier, A.A. Johnson, C. Marchand, Nat. Rev. Drug Discov. 4 (2005) 236.
[5] E.E. Boros, B.A. Johns, E.P. Garvey, et al. Bioorg. Med. Chem. Lett. 16 (2006) 5668.
[6] R. Dayam, L.Q. Al-Mawsawi, Z. Zawahir, et al. J. Med. Chem. 51 (2008) 1136.
[7] R. Gould, W. Jacob, J. Am. Chem. Soc. 61 (1939) 2890.
[8] General procedure for the preparation of **3**: 4-nitrobenzene sulfonamide **2** were dissolved in EtOAc (50–100 mL) and $SnCl_2{\cdot}2H_2O$ (1.125 g per mmol nitro compound) was added. The mixture was heated under reflux for 4 h. Then, $NaHCO_3$ solution was added until pH 7–8 was reached and the organic layer was separated. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. Then, the solvent was removed in vacuo to obtain the crude products. General procedure for the preparation of **4**: a mixture of diethyl ethoxymethylenemalonate (46 mmol) and 4-aminobenzene sulfonamide 3 (46 mmol) in 1,4-dioxane solution (25 mL) was refluxed for 3.5 h until the reaction was finished (monitor by thin lay chromatography). Then the solvent was removed under reduced pressure and the residue was recrystallized from Petroleum ether to obtain the pure products. General procedure for the preparation of **5**: phenyl ether (40 mL) was heated under stirring at 250 °C containing catalytic p-chlorobenzoic acid. The aminomethylenemalonate **4** (10 mmol) was slowly added, and the resulting mixture was remained the temperature at 250 °C for 0.5 h. After the mixture was cooled at room temperature, the resulting precipitate was collected by filtration, washed with petroleum ether, and recrystallized from DMF to provide quinolone **5**. General procedure for the preparation of **6**: quinolone **5** (1 mmol) was dissolved in the mixed solution of $EtOH/H_2O$ (25 mL) and NaOH (1.1 mmol) was added. The mixture was refluxed for 1 h. Removal of the solvents under reduced pressure and acidification with 10% H_2SO_4 gave a solid, which was washed with water, dichloromethane and dried. The resulting quinoline-3-carboxylic acid **6** was recrystallized from the appropriate solvent.
[9] Y.F. Suen, L. Robins, B.X. Yang, A.S. Verkman, Bioorg. Med. Chem. Lett. 16 (2006) 537.
[10] Selected data of title compounds: **6a**: Yellow powder, yield 71%, mp: 284–286 °C, ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 1.40-1.66 (m, 12H, -CH_2-adamantane), 1.91 (s, 3H, CH-adamantane), 2.40 (d, 2H, J = 6.8 Hz, CH_2- Adamantane), 7.74 (t, 1H, J = 3.4 Hz, $NHSO_2$), 8.00 (d, 1H, J = 8.8 Hz, H7), 8.21 (dd, 1H, J = 2.0 and 8.8 Hz, H8), 8.67 (d, 1H, J = 2.0 Hz, H5), 8.98 (s, 1H, H2), 13.66 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 178.62, 166.27, 147.03, 141.74, 138.68, 131.36, 124.59, 121.73, 109.13, 54.78, 36.86, 33.32, 28.06. MS (ESI) *m/z*: 417 $[M + H]^+$, 439 $[M + Na]^+$. **6b**: white powder, yield 72%, mp > 290 °C, ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 1.45–1.70 (m, 12H, CH_2-adamantane), 1.92 (s, 3H, CH-adamantane), 7.83 (t, 1H, $NHSO_2$), 7.99 (d, 1H, J = 8.8 Hz, H7), 8.25 (dd, 1H, J = 2.0 and 8.8 Hz, H8), 8.73 (d,

1H, J = 2.0 Hz, H5), 8.97 (s, 1H, H2), 13.65 (s, 1H, NH), 14.87 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 178.62, 166.29, 146.94, 142.79, 141.48, 131.20, 124.56, 124.04, 121.51, 109.11, 54.55, 42.93, 35.89, 29.29. **6e**: White powder, yield 76%, mp>290 °C, ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 1.56 (m, 2H, CH_2), 1.90 (m, 2H, CH_2), 2.25 (m, 1H, CH), 2.46 (m, 2H, CH_2), 3.54 (m, 2H, CH_2), 8.03 (d, 1H, J = 8.8 Hz, H7), 8.17 (dd, 1H, J = 2.4 and 8.8 Hz, H8), 8.54 (d, 1H, J = 2.0 Hz, H5), 9.03 (s, 1H, H2), 12.30 (s, 1H, COOH), 13.71 (s, 1H, NH), 14.77 (s, 1H, COOH). MS (ESI) *m/z*: 379 $[M-H]^-$, 759 $[2M-H]^-$. 6 h: White powder, yield 83%, mp: 265–268 °C, ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.08 (m, 4H, CH_2), 3.23 (m, 4H, CH_2), 6.80 (m, 1H, H-Ar), 6.89 (m, 2H, H-Ar), 7.18 (m, 2H, H-Ar), 8.05 (d, 1H, J = 8.4 Hz, H7), 8.20 (dd, 1H, J = 2.0 and 8.8 Hz, H8), 8.58 (d, 1H, J = 2.0 Hz, H5), 9.03 (s, 1H, H2), 13.71 (s, 1H, NH), 14.75 (s, 1H, COOH). MS (ESI) *m/z*: 412 $[M-H]^-$, 825 $[2M-H]^-$.

[11] H.Q. He, X.H. Ma, B. Liu, et al. Acta Pharmacol. Sin. 29 (2008) 397.