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Synthesis and Evaluation of Novel Quinolinones as HIV-1 Reverse Transcriptase Inhibitors

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Abstract—A series of 4,4-disubstituted quinolinones was prepared and evaluated as HIV-1 reverse transcriptase inhibitors. The C-3 substituted compound **9h** displayed improved antiviral activity against clinically significant single (K103N) and double (K103N/L100I) mutant viruses. © 2001 DuPont Pharmaceuticals Company. Published by Elsevier Science Ltd. All rights reserved.

Human immunodeficiency virus type -1 (HIV-1) is the causative agent for the transmission and development of the acquired immunodeficiency syndrome (AIDS).[1] Current therapies target two sites of intervention in the replication cycle of the virus. These sites are the inhibition of (a) HIV protease and (b) HIV reverse transcriptase. Reverse transcriptase inhibitors are of two types: nucleoside reverse transcriptase inhibitors (NRTIs) such as AZT, 3TC, and DDI, and non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as nevirapine, delavirdine and efavirenz.[2] Non-nucleoside reverse transcriptase inhibitors play a vital role in combination therapy for the treatment of AIDS. Efavirenz (Fig. 1),[3] a potent NNRTI, is a significant component of a very effective (protease sparing) regimen when coadministered with AZT and 3TC. One of the difficulties encountered during antiretroviral therapy has been the emergence of resistant mutant viral forms. A subset of patients for reasons of poor compliance, partial pre-existing resistance or poor bioavailability often develops resistant viral strains. This situation is compounded by the selection of some resistance mutations which confer cross-class resistance such as single mutation K103N and double mutation K103N/L100I. Herein we describe a series of novel 4,4-disubstituted quinolinones that were discovered as part of our continuing effort directed towards the development of second generation NNRTIs possessing an improved resistance profile.

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Synthesis of the parent quinolinone is shown in Scheme 1. Readily available 4-chloro-2-trifluoroacetylaniline **1** (an intermediate in the synthesis of efavirenz)[3] was acylated with bromoacetyl bromide in tetrahydrofuran to provide **2** in quantitative yield. Due to the unstable nature of this compound, it was used as is without further purification. Treatment of **2** with two equivalents of the sodium salt of benzenesulfinic acid resulted in the initial displacement of the halogen followed by deprotonation and ring closure to provide bicyclic compound **3** in good yield. Introduction of the double bond through an acylation–elimination pathway was accomplished by treatment of **3** with acetic anhydride and DMAP in dichloromethane, resulting in sulfone **4**. Nucleophilic addition of lithium cyclopropylacetylide to sulfone **4** followed by reductive desulfurization with aluminum amalgam provided quinolinone **5** in good overall yield (Scheme 1).[4]

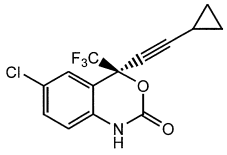

Figure 1. Efavirenz (Sustiva™).

In order to introduce functionality at the C-3 position, we had to first prepare the SEM protected quinolinone using SEMCl, DIPEA in dichloromethane. Treatment of the SEM protected quinolinone with LDA and tosyl azide[5] in tetrahydrofuran provided azido quinolinone **6**

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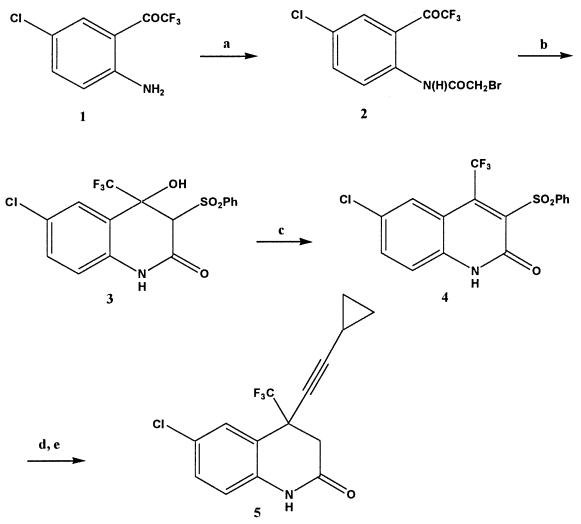
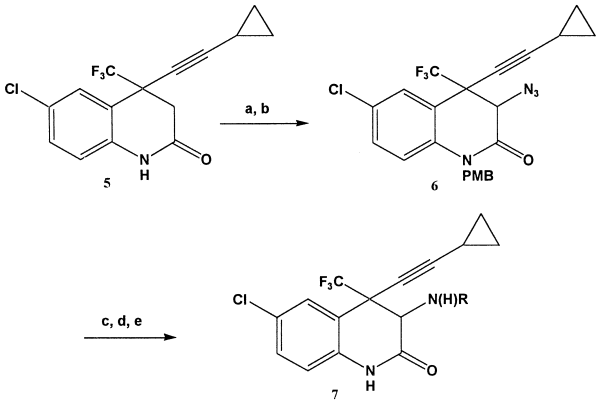
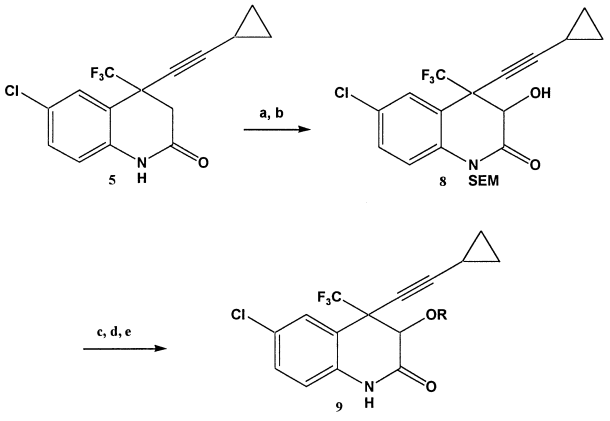


Scheme 1. (a) $BrCOCH_2Br$, K_2CO_3, THF, 25 °C, 3 h, quantitative; (b) $NaSO_2Ph$, DMF, 25 °C, 18 h, 89%; (c) Ac_2O, DMAP, DCM, 25 °C, 18 h, 94%; (d) *n*BuLi, cyclopropylacetylene, THF, −78 °C to 25 °C, 1 h, 75%; (e) Al/Hg, EtOH, reflux, 1 h, 77%.



Scheme 2. (a) PMBCl, K_2CO_3, DMF, 25 °C, 14 h, 74%; (b) LDA, TsN_3, THF, 0 °C to 25 °C, 1 h, 93%; (c) $SnCl_2{\cdot}H_2O$, MeOH/THF (1:1), 25 °C, 3 h, 83%; (d) BuBr, K_2CO_3, DMF, 25 °C, 14 h, 50%; or Ac_2O, pyridine, DCM, 25 °C, 3 h, 74%; or $ClCO_2Me$, K_2CO_3, THF, 25 °C, 2 h, 67%; (e) CAN, $MeCN/H_2O$ (9:1), 25 °C, 0.5 h, 45–84%.



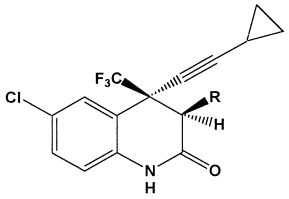
Scheme 3. (a) SEMCl, NaH, THF, 25 °C, 14 h, 39%; (b) LDA, MoOPH, THF, 0–25 °C, 14 h, 68%; (c) RX, NaH, DMF, 25 °C, 14 h, 18–73%; (d) nBu_3P, NH_4OH/THF (1:1), 25 °C, 14 h, 16–55%; (e) TFA/DCM (1:1), 25 °C, 0.3 h; 15% aq NaOH/MeOH (1:1), 25 °C, 0.1 h, 12–61%.

in good yield. Reduction of the azide to the corresponding amine followed by either alkylation or acylation and removal of the SEM protecting group provided compounds **7a–c** as a 1:1 mixture of diastereomers (Scheme 2).[4] The diastereomers were separated by column chromatography and the relative stereochemistry assigned on the basis of NOE experiments prior to antiviral evaluation.

In a comparable manner, the introduction of a hydroxy group at the C-3 position was carried out by the treatment of SEM protected quinolinone with LDA and MoOPH[6] in tetrahydrofuran to provide quinolinone **8** in good yield. Alkylation of the hydroxy group in quinolinone **8** resulted in compounds **9a–o** as a 1:1 mixture of diastereomers (Scheme 3).[4] As in the C-3 amino substituted series, the diastereomers were separated by column chromatography prior to antiviral evaluation.

The results of the enzyme inhibition and the antiinfectivity assays have been summarized in Table 1. The parent quinolinone **5** showed good activity in the antiviral assays. However, the activity against single mutations (K103N and L100I) was rather poor. In an attempt to improve upon the resistance profile, we introduced substitutions at the C-3 position. As seen in Table 1, introduction of a nitrogen containing group at the C-3 position was detrimental to antiviral activity. As a series, the 3-alkoxy substituted quinolinones (**9a–o**) were more potent in both the enzyme inhibition and whole cell based assays than the C-3 amino substituted compounds. The *O*-alkyl substituted compounds (**9b–d**)

Table 1. Antiviral activity of quinolinones



Compound	R	IC_{50} (nM)[7a]	IC_{50} (nM)[7b]
Efavirenz[a]	—	48	2
5	H	130	14
7a	N(H)Bn	>2000	218
7b	$N(H)CO_2Me$	>2000	212
7c	N(H)Ac	>2000	917
9a	OH	>2000	637
9b	*O*-3,3-Dimethylallyl	>2000	>1000
9c	*O*-Cyclopropylmethyl	1434	130
9d	*O*-*n*-Propyl	1051	62
9e	OBn	440	71
9f	*O*-2-Pyridylmethyl	1572	140
9g	*O*-3-Pyridylmethyl	438	20
9h	*O*-4-Pyridylmethyl	129	19
9i	*O*-2-Fluorobenzyl	1296	140
9j	*O*-3-Fluorobenzyl	1776	201
9k	*O*-4-Fluorobenzyl	899	112
9l	*O*-2-Aminobenzyl	1019	115
9m	*O*-3-Aminobenzyl	1455	138
9n	*O*-4-Aminobenzyl	412	21
9o	*O*-3-Fluoro-4-aminobenzyl	241	26

[a]Denotes single enantiomer.

Table 2. Resistance profile of **9h**

Compound	K103N IC_{90} (nM)	L100I IC_{90} (nM)	K103N/L100II C_{90} (nM)
Efavirenz[a]	64 (±24)[b]	77 (±18)[b]	7300 (±5000)[b]
5	1770	992	nd
9h	50	23	4830
9n	1082	49	3848

nd = not determined.
[a]Denotes single enantiomer.
[b]Values are means of two experiments, standard deviation is given in parentheses.

were unimpressive as antivirals. The introduction of aryloxy substitutions at the C-3 position improved the antiviral activity profile. Of particular interest were the pyridylmethyl (**9f–h**) and the aminobenzyl (**9m–o**) substituted compounds for they exhibit low nanomolar activity in the whole cell assay. The most potent compound **9h** was selected for further testing against resistant mutant strains (Table 2).

Although the activity of **9h** as a racemic mixture against wild type is 5-fold worse than efavirenz, the activity against the two important singles (K103N and L100I) was improved. Unfortunately, there was no significant improvement against the K103N/L100I double mutation (Table 2).

In summary, we have described the preparation and evaluation of quinolinones as novel non-nucleoside reverse transcriptase inhibitors. Although compound **9h** showed an improved resistance profile as compared to efavirenz against single mutations, there was not enough improvement against the K103N/L100I double mutation to warrant further investigation.

References and Notes

1. Levy, J. A. *Microbiol. Rev*. **1993**, *57*, 183.
2. (a) Jonckheere, H.; Anné, J.; De Clercq, E. *Med. Res. Rev*. **2000**, *20*, 129. (b) Hajos, G.; Riedl, Z.; Molnar, J.; Szabo, D. *Drugs Future* **2000**, *25*, 47.
3. Young, S. D.; Britcher, S. F.; Tran, L. O.; Payne, L. S.; Lumma, W. C.; Lyle, T. A.; Huff, J. R.; Andersen, P. S.; Olsen, D. B.; Carroll, S. S.; Pettibone, D. J.; O'Brien, J. A.; Ball, R. G.; Balani, S. K.; Lin, J. H.; Chen, I-W.; Scheif, W. A.; Sardana, V. V.; Long, W. J.; Brynes, V. W.; Emini, E. A. *Antimicrob. Agents Chemother*. **1995**, *39*, 2602.
4. All compounds provided satisfactory spectral data (^{1}H NMR, ^{19}F NMR, CI-MS/ESI-MS, and HR-MS/peak match) and were homogeneous by TLC.
5. Tosyl azide was prepared as follows: To a solution of tosyl chloride (20 g, 105 mmol) in water (40 mL) at room temperature was added sodium azide (8.6 g, 132 mmol) and the resulting reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was diluted with water (500 mL) and extracted with ether (3×100 mL). The combined ether extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to provide 19.73 g of tosyl azide (20.63 g theoretical, 96% yield). Tosyl azide can be purchased from Esprit Chemical Company, Sarasota, FL, USA.
6. For the preparation of MoOPH see: Vedejs, E.; Larsen, S. In *Organic Syntheses*; Freeman, J. P., Ed.; John Wiley & Sons: New York, 1990; Coll. Vol. 7, pp 277–282.
7. (a) All compounds were assayed for enzyme inhibitory activity (IC_{50}) according to the protocol described in: Sardana, V. V.; Emini, E. A.; Gotlib, L.; Graham, D. J.; Lineberger, D. W.; Long, D. W.; Schlabach, A. J.; Wolfgang, J. A.; Condra, J. H. *J. Biol. Chem*. **1992**, *267*, 17526, using a template primer poly (rA) oligo $(dT)_{12-18}$. (b) All compounds were assayed for whole cell based antiviral activity (IC_{90}) according to the protocol described in: Bacheler, L. T.; Paul, M.; Jadhav, P. K.; Otto, M.; Miller, J. *Antiviral Chem. Chemother*. **1994**, *5*, 111.