Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 1729–1731

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis and Evaluation of Quinoxalinones as HIV-1 Reverse Transcriptase Inhibitors

Mona Patel,* Robert J. McHugh, Jr., Beverly C. Cordova, Ronald M. Klabe, Susan Erickson-Viitanen, George L. Trainor and James D. Rodgers

DuPont Pharmaceuticals Company, Experimental Station, E500/4803, PO Box 80500, Wilmington, DE 19880-0500, USA

Received 18 April 2000; accepted 31 May 2000

Abstract—A series of 3,3-disubstituted quinoxalinones was prepared and evaluated as HIV-1 reverse transcriptase inhibitors. The *N*-allyl (**6b** and **6f**), *N*-cyclopropylmethyl (**6a**, **6g**, **6h**, and **6k**) and *N*-carboalkoxy (**6m**–**6y**) substituted compounds displayed activity comparable or better than Efavirenz and GW420867X.

Non-nucleoside HIV-1 reverse transcriptase inhibitors (NNRTIs) play an integral role in combination therapy for the treatment of AIDS. Efavirenz,[1] a potent NNRTI, is an essential component of a very effective combination therapy when administered with AZT and 3TC. However, as with all current HIV therapies, the development of drug-resistant strains of the virus is of major concern. In our attempts to find second generation analogues that may effectively treat NNRTI therapy failures, we prepared hybrid compounds containing structural features from both Efavirenz and the Glaxo Wellcome clinical candidate GW420867X.[2] The hybrids synthesized combine the quaternary carbon bearing the trifluoromethyl and cyclopropylacetylene groups of Efavirenz with the quinoxaline core of GW420867X (Fig. 1).

Chemistry

Commercially available *ortho*-phenylenediamines (**1**) were treated with hexafluoropropylene oxide (HFPO) under basic conditions to provide the corresponding quinoxalinones (**2**).[3] 4-Substituted phenylenediamines gave mixtures of 6- and 7-substituted quinoxalinones, which were separated via chromatography. Protection of **2** with SEM-Cl (DIPEA, DMF) provided the *N*-SEM protected compounds (**3**). Addition of lithium cyclopropylacetylide to imines (**3**) resulted in the formation of 3,3-disubstituted quinoxalinones (**4**) in good yields. Introduction of a variety of substitutents at the *N*-4 position either by (a) alkylation with alkyl halides (*t*BuOK, THF) or (b) acylation or sulfonylation (*n*BuLi, THF/chloroformates/acid chlorides/sulfonyl chlorides) provided the fully substituted quinoxalinones (**5**). Removal of the SEM protecting group by treatment with boron trifluoride in dichloromethane provided quinoxalinones (**6**) in moderate yields as shown in Scheme 1.[4]

To improve upon the overall yield so as to facilitate the scale up of (**6m**) for pharmacokinetic studies, an alternate route for the preparation of (**6m**) was developed (Scheme 2). Quinoxalinone (**2**) was converted to quinoxaline (**7**)

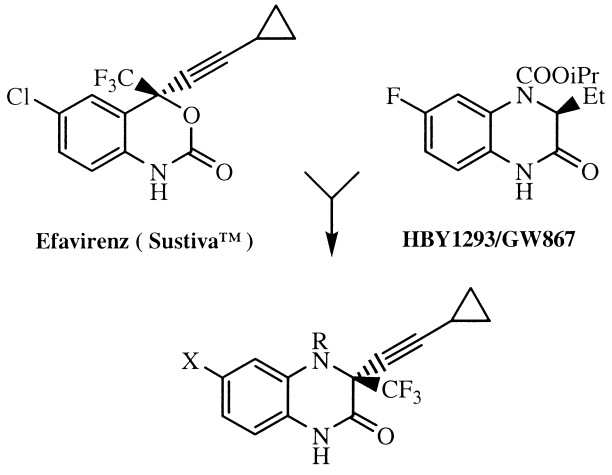


Figure 1.

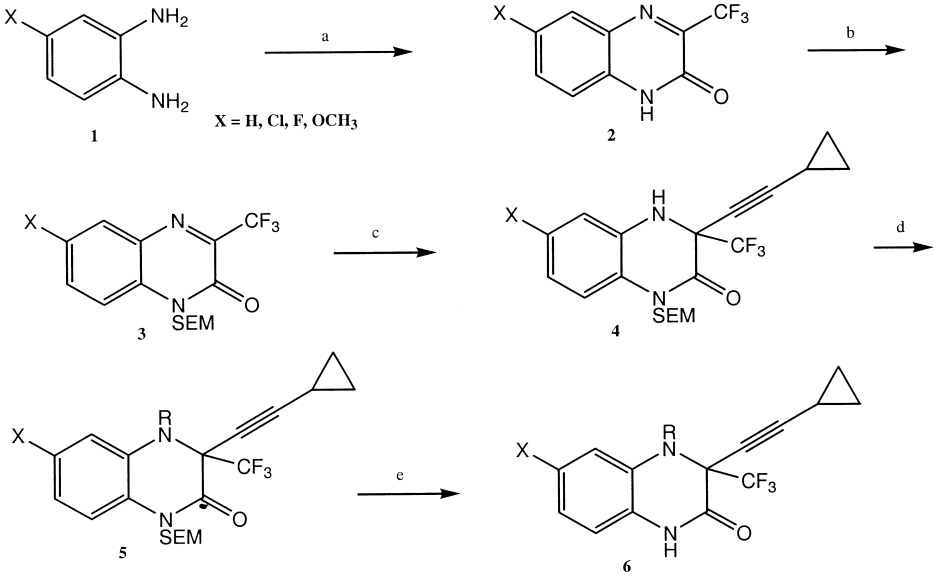
*Corresponding author. Tel.: +1-302-695-1233; fax: +1-302-695-8344; e-mail: mona.patel@dupontpharma.com

0960-894X/00/$ - see front matter
PII: S0960-894X(00)00321-8

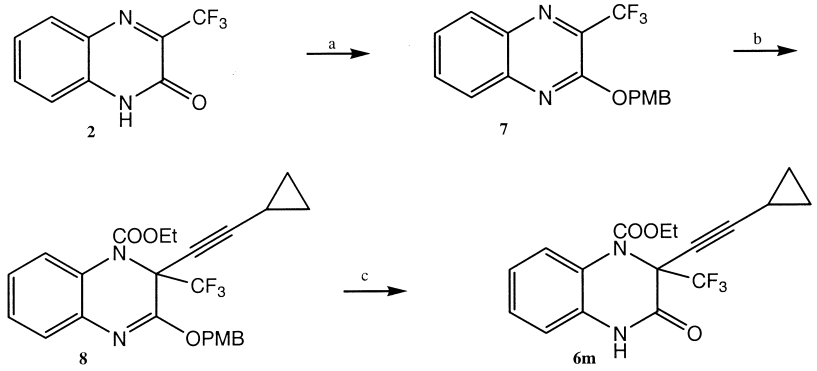
by treatment with silver carbonate and *p*-methoxybenzyl chloride. Quinoxaline (**7**) was treated with lithium cyclopropylacetylide and the resulting anion was quenched with ethyl chloroformate to provide the fully substituted quinoxaline (**8**) in good yield. Removal of the PMB protecting group was carried out under acidic conditions, providing **6m** in a substantially improved overall yield of 27% versus 1.5% by the earlier route (Scheme 2).[4]

Results and Discussion

A variety of alkyl groups were introduced at the *N*-4 position of quinoxalinones to provide compounds **6a**–**6l**. This substitution pattern resulted in compounds comparable in activity in both the enzyme inhibition and whole cell antiviral assays to GW420867X. Next, we introduced acyl groups at the *N*-4 position of the quinoxalinones. Carbamates (**6m**–**6o** and **6r**–**6y**) were the most potent compounds prepared in this series. Compounds **6w**–**6y** were of special interest as they bore the 6-F susbtitution present in GW420867X and were more potent in the cell based assay. Amides (**6z**, **6aa**, and **6bb**) bearing isopropyl, cyclopropyl and phenyl groups were prepared. Groups larger than isobutyl were not tolerated as side chains in both the carbamate (**6p** and **6q**) and amide (**6bb**) series. Derivatisation of the *N*-4 position to a sulfonamide (**6cc**–**6ee**) was clearly detrimental to antiviral activity. Substitutions at the C-6 position of the quinoxalinones (X = Cl, F, OMe) did not appear to influence the potency of the compound. Although the 6-F and 6-Cl substituted carbamates (**6t**–**6y**) were very potent compounds, they were highly protein bound resulting in a 33- to 50-fold loss in IC_{90} values in the protein binding shift assay,[5] and therefore were not considered for pharmacokinetic studies. Comparatively, 6-H substituted carbamate (**6m**) showed low protein binding (18-fold loss in IC_{90} value) and a good resistance profile (K103N = 30 nM; L100I = 75 nM), and was selected for pharmacokinetic studies. Compound **6m** was resolved by chiral HPLC and the

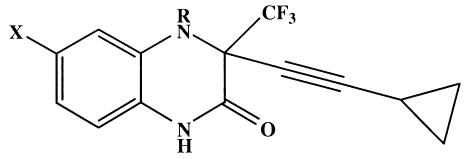


Scheme 1. Reagents and conditions: (a) HFPO, $NaHCO_3$, ether, 25 °C, 3 h, 15–90%; (b) SEMCl, DIPEA, DMF, 25 °C, 14 h, 13–90%; (c) *n*BuLi, cyclopropylacetylene, THF, −78 °C to 25 °C, 0.3 h, 45–92%; (d) RX, *t*BuOK, DMF, 25 °C, 14 h, 21–70%; or $ClCO_2R$, *n*BuLi, THF, −78 °C to 25 °C, 1 h, 34–92%; or ClCOR, *n*BuLi, THF, −78 °C to 25 °C, 1 h, 60–69%; or $ClSO_2R$, *n*BuLi, THF, −78 °C to 25 °C, 1 h, 16–34%; (e) $BF_3 \cdot Et_2O$, DCM, 0 °C to 25 °C, 1.5 h; 15% NaOH, MeOH, 25 °C, 0.6 h, 3–87%.



Scheme 2. Reagents and conditions: (a) PMBCl, Ag_2CO_3, DMF, 25 °C, 14 h, 46%; (b) *n*BuLi, cyclopropylacetylene, THF, −78 °C to 25 °C, 1 h; NaI, 25 °C, 0.6 h; $ClCO_2Et$, THF, 25 °C, 0.6 h, 85%; (c) HCl in ether, 25 °C, 0.6 h, 70%.

Table 1. Antiviral activity of 3,3-disubstituted quinoxalinones



Compound	X	R	IC_{50} (nM)[6a]	IC_{90} (nM)[6b]
Efavirenz[7]	—	—	48	2
GW620867X[7]	—	—	179	11
6a	H	Cyclopropylmethyl	253	17
6b	H	Allyl	601	22
6c	H	Benzyl	1818	21
6d	H	Propargyl	1807	53
6e	H	Cyclopropylethyl	340	32
6f	F	Allyl	124	21
6g	F	Cyclopropylmethyl	263	23
6h	Cl	Cyclopropylmethyl	329	27
6i	Cl	Isobutyl	404	52
6j	Cl	Allyl	650	85
6k	OMe	Cyclopropylmethyl	109	19
6l	OMe	Allyl	123	29
6m	H	COOEt	118	9
6n	H	COO*i*Pr	108	15
6o	H	$COOC(CH_2)Me$	169	11
6p	H	COO*i*Bu	1142	158
6q	H	COO*n*Bu	672	105
6r	H	$COOCH_2CHCH_2$	147	30
6s	H	COOMe	504	44
6t	Cl	COOEt	127	11
6u	Cl	COO*i*Pr	160	19
6v	Cl	$COOC(CH_2)Me$	315	15
6w	F	COOEt	121	8
6x	F	COO*i*Pr	130	9
6y	F	$COOC(CH_2)Me$	183	8
6z	H	CYcyclopropylmethyl	127	11
6aa	H	CI*i*Pr	160	19
6bb	H	COPh	>5000	>1000
6cc	H	SO_2Et	>5000	>1000
6dd	H	$SO2_iPr$	>5000	>1000
6ee	H	SO_2nPr	>5000	>1000

active enantiomer **6m*** (IC_{50} = 45 nM; IC_{90} = 4.8 nM) was subjected to oral pharmacokinetic studies in rhesus monkeys. Unfortunately, poor bioavailability of **6m***, was observed and no further studies have been planned.

In summary, although we were able to prepare potent compounds bearing trifluoromethyl and cyclopropylacetylene groups at the C-3 carbon of quinoxalinones, high protein binding (**6t**–**6y**) and a poor pharmacokinetic profile (**6m***) precluded further development of this class of compounds (Table 1).

References and Notes

1. (a) Young, S. D.; Britcher, S. F.; Tran, L. O.; Payne, L. S.; Lumma, W. C.; Lyle, T. A.; Huff, J. R. et al., *Antimicrob. Agents Chemother*. **1995**, *39*, 2602. (b) Patel, M.; Ko, S. S.; McHugh, R. J.; Markwalder, J. A.; Srivastava, A. S.; Cordova, B. C.; Klabe, R. M.; Erickson-Viitanen, S.; Trainor, G. L.; Seitz, S. P. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 2805. (c) Patel, M.; McHugh, R. J.; Cordova, B. C.; Klabe, R. M.; Erickson-Viitanen, S.; Trainor, G. L.; Ko, S. S. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 3221.

2. Kleim, J.-P.; Bender, R.; Billhardt, U. M.; Meischner, C.; Reiss, G.; Rosner, M.; Winkler, I.; Paessens, A. *Antimicrob. Agents Chemother*. **1993**, *37*, 1659.

3. Ishikawa, N.; Sasaki, S. *Bull. Chem. Soc. Jpn*. **1977**, *50*, 2164.

4. All compounds provided satisfactory spectral data (^1H NMR, ^{19}F NMR, CIMS/ESIMS, and HRMS/peak match) and were homogeneous by TLC.

5. The protein binding shift assay is a measure of the increase in IC_{90} values due to the binding of the compound to human serum proteins (HSA and AAG) in plasma, resulting in lower free drug concentrations.

6. (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.

7. The data presented for Efavirenz and HBY1293/GW867 reflect values determined for a single enantiomer, whereas the data shown for **6a**–**6ee** are that of racemic mixtures. The biological evaluation of each enantiomer of Efavirenz and other quinoxalinones had determined that only the *S* enantiomer was active.