Pergamon

Bioorganic & Medicinal Chemistry Letters 11 (2001) 1177–1179

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis and Evaluation of Efavirenz (Sustiva™) Analogues as HIV-1 Reverse Transcriptase Inhibitors: Replacement of the Cyclopropylacetylene Side Chain

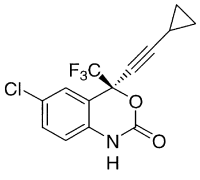
Anthony J. Cocuzza,* Dennis R. Chidester, Beverly C. Cordova, Susan Jeffrey, Rodney L. Parsons, Lee T. Bacheler, Susan Erickson-Viitanen, George L. Trainor and Soo S. Ko

DuPont Pharmaceuticals Company, Experimental Station, E336/141, PO Box 80336, Wilmington, DE 19880-0336, USA

Received 16 January 2001; accepted 5 March 2001

Abstract—Two series of efavirenz analogues have been developed: one in which the cyclopropane ring has been replaced by small heterocycles and another in which the entire acetylenic side chain has been replaced by alkyloxy groups. Several members of both series show equivalent potency to efavirenz against both wild-type virus and the key K103N mutant.

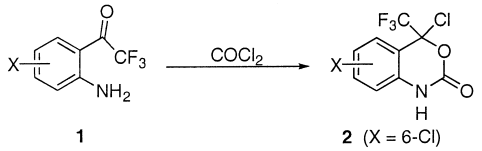
Effective therapy for the treatment of HIV-1 infection and AIDS requires a combination of antiviral drugs. Currently, the standard of care for antiretroviral naïve patients is efavirenz or an HIV protease inhibitor and two nucleoside reverse transcriptase inhibitors. Efavirenz,[1] a non-nucleoside reverse transcriptase inhibitor (NNRTI), has demonstrated clinical activity in both antiretroviral naïve and experienced patients and may also provide an option of a protease-sparing regimen when used with two nucleoside reverse transcriptase (RT) inhibitors.[2]



Efavirenz (Sustiva™)

Although HIV infection is generally well controlled by efavirenz-containing regimens, a number of patients develop resistence to the drug. In these patients, the K103N mutation is present in over 90% of the RT sequences examined.[3] In an effort to develop a second-generation drug with improved activity against K103N and other resistant mutants, an SAR investigation was launched. While earlier reports from our laboratory[4,5] described the effect of varying the aromatic substitution pattern of efavirenz, herein we describe the effect of modifying and replacing the acetylenic side chain.

We first examined the preparation of analogues of efavirenz in which the cyclopropane ring was replaced with a five- or six-membered heterocycle. The synthesis of these compounds was greatly facilitated by the availability of 4-chlorobenzoxazinones (**2**–**4**) which are prepared in high yield by treatment of 2-aminotrifluoroacetophenones **1**[4] with phosgene in toluene solution at 110 °C (Scheme 1).[6] These stable crystalline intermediates react with a variety of nucleophiles through an elimination–addition pathway. For example, reaction of **2** with 2 equiv of the lithium salt of 2-pyridylacetylene in THF at 0 °C afforded **7**. In most



1

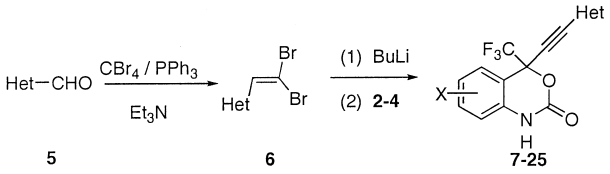
2 (X = 6-Cl)
3 (X = 6-F)
4 (X = 5,6-diF)

Scheme 1.

*Corresponding author. Fax: +1-302-695-6670; e-mail: anthony.j.cocuzza@dupontpharma.com

0960-894X/01/$ - see front matter
PII: S0960-894X(01)00192-5

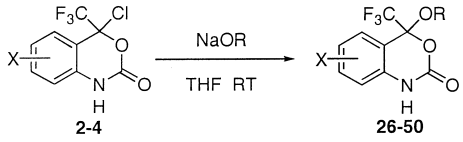
cases, the heterocyclic acetylenes are not commercially available, however the corresponding carboxaldehydes **5** are (Scheme 2). Using the Weinreb[7] modification of the Corey–Fuchs[8] procedure, treatment of **5** with carbon tetrabromide/triphenylphosphine/triethylamine yielded the dibromo-olefins **6** which form the corresponding lithium acetylides in situ when treated with 2 equiv of *n*-butyllithium. Reaction of the acetylides with 4-chlorobenzoxazinones **2**–**4** afforded the target compounds.[9] In addition to the 6-chlorobenzoxazinones **7**–**13**, we also chose to prepare the 6-fluoro- (**14**–**19**) and 5,6-difluoro- (**20**–**25**) analogues, since these aromatic ring substituents proved optimal in earlier SAR studies.[4]



Scheme 2.

Table 1 summarizes the antiviral activity of **7**–**25** against both wild-type and K103N mutant viruses.[10] It can be seen that, with the exception of 4-pyridyl, all the heterocycles employed can effectively replace the cyclopropane ring of efavirenz to give analogues that retain potent activity against wild-type HIV-1. Selected compounds were also tested against the K103N virus. While a number of these exhibited activity comparable to efavirenz against this key mutant, none displayed the significant increase in potency we sought.

Simple room temperature treatment of 4-chlorobenzoxazinones **2**–**4** with sodium alkoxides in THF afforded 4-alkoxybenzoxazinones **26**–**50**, compounds that would otherwise be very difficult to obtain (Scheme 3). In contrast to other ketals, **26**–**50** are very stable to acidic conditions. The presence of the trifluoromethyl group markedly destabilizes the developing positive charge at C-4 which would necessarily arise during acid hydrolysis. In fact when 4-(butyloxy)benzoxazinone **28** was treated with 1 N aq HCl at room temperature, no reaction could be detected by HPLC or NMR even after 48 h. Thus, 4-alkyloxy-4-(trifluoromethyl)benzoxazinones would be expected to survive the acidic conditions present in the GI tract and consequently may exhibit oral bioavailability. Since any alcohol that forms a stable sodium salt can be introduced into the 4-position of a 4-(trifluoromethyl)-benzoxazinone, a much greater variety of side chains could be examined than in previous SAR investigations.



Scheme 3.

Inspection of the first eight entries of Table 2 reveals that optimal side-chain length is four or five and that larger substituents result in decreased potency. Inclusion of a terminal cyclopropyl group (**30** and **31**) as is present in efavirenz does not improve activity against wild-type virus. However, introduction of unsaturation, either a double or triple bond (e.g., **34**–**38**, **45**, and **48**) provides the most active compounds, while incorporation of electronegative groups (Cl, F, CN, OMe) (**40**–**44**) results in a marked reduction in potency. The optimal side chain is dimethallyloxy, and the three compounds (**37**, **45**, and **48**) which incorporate this side chain in this series are the most potent against both wild-type and K103N virus.

Table 1. Antiviral activity of heterocyclic analogues of efavirenz

Compound	X	Het	Wild-type IC_{90} (nM)[a]	K103N IC_{90} (nM)
Efavirenz[b]	6-Cl	Cyclopropyl	1.70	64.0
7	6-Cl	2-Pyridyl	5.39	1105.8
8	6-Cl	3-Pyridyl	3.97	144.6
9	6-Cl	4-Pyridyl	102.10	—
10	6-Cl	2-Furanyl	3.80	152.2
11	6-Cl	3-Furanyl	3.80	321.9
12	6-Cl	3-Thienyl	4.47	106.2
13	6-Cl	5-Thiazolyl	6.69	—
14	6-F	2-Pyridyl	12.19	—
15	6-F	3-Pyridyl	2.56	329.3
16	6-F	2-Furanyl	2.58	—
17	6-F	3-Furanyl	2.52	369.0
18	6-F	2-Thienyl	2.93	—
19	6-F	3-Thienyl	2.55	193.0
20	5,6-diF	2-Pyridyl	6.78	—
21	5,6-diF	3-Pyridyl	2.23	59.3
22	5,6-diF	2-Furanyl	3.79	—
23	5,6-diF	3-Furanyl	3.21	279.7
24	5,6-diF	2-Thienyl	2.23	155.9
25	5,6-diF	3-Thienyl	2.34	139.2

[a]All compounds were assayed for whole cell antiviral activity according to the protocol described in ref 10.
[b]The data presented for efavirenz reflect values determined for a single enantiomer, whereas the data shown for all other compounds are for racemic mixtures. The biological evaluation of efavirenz and other benzoxazinones had determined that only one enantiomer was active.

Table 2. Antiviral activity of 4-alkyloxybenzoxazinones[a]

Compound	X	R	Wild-Type IC_{90} (nM)	K103N IC_{90} (nM)
Efavirenz			1.70	64.0
26	6-Cl	CH_2CH_3	18.26	
27	6-Cl	$CH_2CH_2CH_3$	5.81	
28	6-Cl	$CH_2CH_2CH_2CH_3$	10.19	989
29	6-Cl	$CH_2CH_2CH(CH_3)_2$	10.07	286
30	6-Cl	CH_2cycPr	7.70	
31	6-Cl	CH_2CH2cycPr	8.04	
32	6-Cl	CH_2Ph	17.89	
33	6-Cl	CH_2CH_2Ph	166.80	
34	6-Cl	$CH_2CH=CH_2$	3.90	
35	6-Cl	$CH_2CH=CHCH_3$ (*cis*)	4.35	237
36	6-Cl	$CH_2CH=CHCH_3$ (*trans*)	5.60	404
37	6-Cl	$CH_2CH=C(CH_3)_2$	2.68	83
38	6-Cl	$CH_2C\equiv CCH_3$	3.13	310
39	6-Cl	$CH_2CH_2CH=CH_2$	13.68	
40	6-Cl	$CH_2CH=CCl_2$	9.50	242
41	6-Cl	$CH_2CH_2OCH_3$	61.41	
42	6-Cl	CH_2CH_2CN	>1500	
43	6-Cl	CH_2(3-pyridyl)	75.27	
44	6-Cl	$CH_2CF_2CF_3$	650.60	
45	6-F	$CH_2CH=C(CH_3)_2$	2.98	107
46	6-F	$CH_2CH=CHCH_3$ (*trans*)	8.85	1148
47	6-F	$CH_2CH=CCl_2$	11.94	
48	5,6-diF	$CH_2CH=C(CH_3)_2$	1.54	65
49	5,6-diF	$CH_2CH=CH_2$	6.47	1617
50	5,6-diF	$CH_2CH=CCl_2$	6.35	183

[a]See notes to Table 1.

In summary, we have demonstrated that the potent activity of efavirenz against wild-type HIV-1 can be retained despite significant modification of its side chain. The cyclopropane ring can be replaced with a variety of small heterocyclic rings, and the entire cyclopropylacetylene group can be replaced by an alkoxy side chain containing either a double or triple bond. While a number of these analogues displayed potency equivalent to efavirenz against K103N virus, no compound demonstrated the increased activity required for development of a second-generation compound.

References and Notes

1. Young, S. D.; Britcher, S. F.; Tran, L. O.; Payne, L. S.; Lumma, W. C.; Lyle, T. A.; Huff, J. R.; Anderson, 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.
2. Panel on Clinical Practices for the Treatment of HIV Infection. *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents*. 28 January 2000; http://www.hivatis.org
3. Bacheler, L.; Weislow, O.; Snyder, S.; Hanna, G.; D'Aquila, R.; the SUSTIVA Resistance Study Team. *Abstract*, presented at the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA, 24–27 September 1998.
4. 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.
5. 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.
6. For a complete description of the synthesis and reactions of **2**, see: Parsons, R. L.; Fortunak, J. M. *Tetrahedron Lett*. submitted for publication.
7. McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem*. **1993**, *58*, 4823.
8. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett*. **1972**, *36*, 3769.
9. The following is a representative synthetic procedure: To a −20 °C solution of 1,1-dibromo-2-(2-furanyl)ethylene (**6**, 4.0 mmol) in THF (20 mL) was added dropwise *n*-butyllithium (8.0 mmol) in THF (5 mL). This solution was allowed to warm to 0 °C over 30 min and then cooled to −50 °C. After **2** (1.5 mmol) was added in a single portion, the reaction mixture was stirred at −50 to −35 °C for 30 min and then the reaction was quenched by the addition of aqueous ammonium chloride. Extraction of the aqueous layer with ethyl acetate followed by flash chromatography on silica gel (hexane/ethyl acetate 3:1) afforded **10** (mp 170–171 °C) in 53% yield.
10. Bacheler, L. T.; Paul, M.; Jadhav, P. K.; Otto, M.; Miller, J. *Antiviral. Chem. Chemother*. **1994**, *5*, 111.