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4,1-Benzoxazepinone Analogues of Efavirenz (Sustiva™) as HIV-1 Reverse Transcriptase Inhibitors

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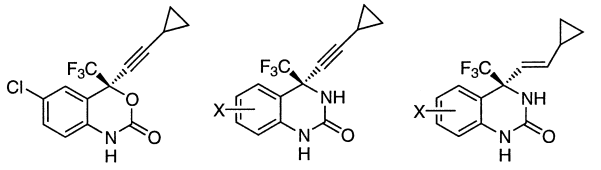
Abstract—A series of 4,1-benzoxazepinone analogues of efavirenz (Sustiva™) as potent NNRTIs has been discovered. The *cis*-3-alkylbenzoxazepinones are more potent then the *trans* isomers and can be synthesized preferentially by a novel stereoselective cyclization. The best compounds are potent orally bioavailable inhibitors of both wild-type HIV-1 and its clinically relevant K103N mutant virus, but are highly protein-bound in human plasma.

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 efficacy 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] Although HIV infection is generally well controlled by efavirenz-containing regimens, a number of patients develop resistance to the drug through a mutation in the viral reverse transcriptase. 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 to determine the effect of varying the aromatic substitution pattern of efavirenz as well as modifying and replacing the acetylenic side chain.[4–6] In addition, other ring systems have been examined. Investigation of the analogous quinazolinones resulted in four compounds (DPC 961, DPC 963, DPC 082, and DPC 083) which are currently under clinical investigation.[7–9] This report describes the synthesis and preclinical evaluation of a new class of efavirenz-related NNRTIs, the 4,1-benzoxazepinones (**1** and **2**).



Efavirenz (Sustiva™) DPC 961 (X = 6-Cl) DPC 963 (X = 5,6-diF) DPC 083 (X = 6-Cl) DPC 082 (X = 5,6-diF)

We synthesized 4,1-benzoxazepinone NNRTIs by a route analogous to the preparation of efavirenz and its analogues.[4,5,10] As has been previously described, treatment of the readily available trityl protected 2-aminotrifluoroacetophenones **3** with lithium acetylides afforded acetylenic alcohols **4** (Scheme 1). Detritylation provided acetylenic amino alcohols **5**, while lithium aluminum hydride reduction of the acetylene followed by deprotection afforded *trans* olefinic aminoalcohols **6**. These amino alcohols, which had previously been converted to efavirenz and its benzoxazine analogues by cyclization with phosgene, were converted to 4,1-benzoxazepinones **1** and **2** by *N*-acylation with 2-bromoacylbromides followed by sodium hydride mediated intramolecular *O*-alkylation. Use of bromoacetyl bromide provided high yields of 3-unsubstituted 4,1-benzoxazepinones while homologous 2-bromoacyl bromides yielded difficult to separate mixtures of two diastereomeric 3-alkyl-4,1-benzoxazepinones.

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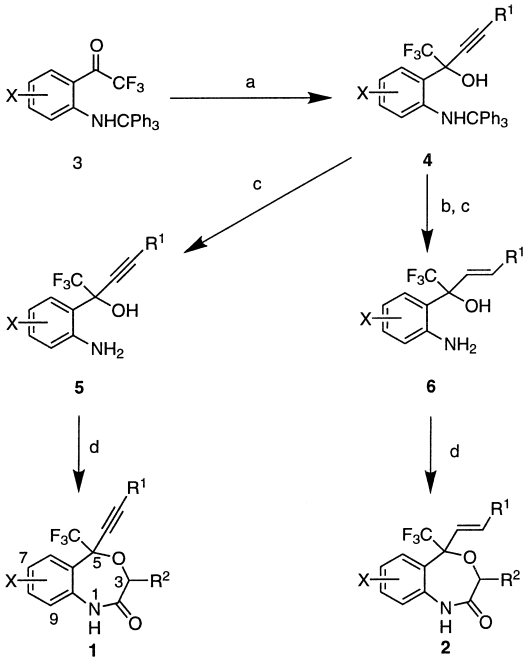
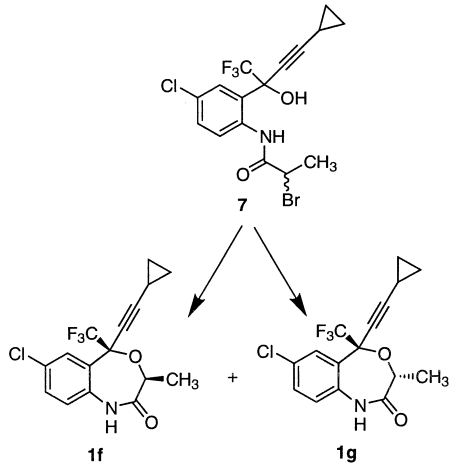
The difficulty in separating the 3-alkyl-4,1-benzoxazepinone diastereomers led us to investigate a stereoselective synthesis. By carefully monitoring the sodium hydride-mediated cyclization reaction depicted in Scheme 2 by TLC and NMR we found that one diastereomeric 2-bromoamide **7** cyclized much faster than the other. If the reaction was not allowed to proceed to completion the more potent benzoxazepinone **1f**, in which the 3-methyl is *cis* to the 5-trifluoromethyl group, formed in preference to the *trans* isomer **1g**. Since this strategy could at best afford a 50% yield of **1f**, we sought reaction conditions which would promote the conversion of both diastereomeric bromoamides **7** into the desired *cis*-benzoxazepinone **1f**. In particular, reaction conditions which caused the two diastereomeric bromoamides to interconvert at a rate faster than the cyclization step could funnel both bromoamide intermediates into the desired *cis* isomer. Such a fast interconversion of haloamides could possibly be effected by tandem S_N2 reactions promoted by the addition of excess bromide or iodide. 2-Bromopropionamide **7** was subjected to a number of such conditions, one of which proved particularly effective in promoting a diastereoselective transformation. Treatment of **7** with cesium carbonate (1.5 equiv) and lithium iodide (2 equiv) in DMF at room temperature afforded a 93:7 ratio of the *cis*-benzoxazepinone **1f** to the *trans*-benzoxazepinone **1g**.[11] The structure of **1f** was confirmed by X-ray crystallography, while the relative stereochemistry of later analogues could be determined by the ^{19}F NMR resonance of the trifluoromethyl group (−79 δ for the *cis*-benzoxazepinones, −74.5 δ for the *trans* in $CDCl_3$). The procedures described above were used to synthesize a number of 3-alkylbenzoxazepinones. The sodium hydride cyclization procedure was initially used to prepare mixtures of the two diastereomeric 3-alkyl-benzoxazepinones, and once the *trans* isomers were found less potent, the cesium carbonate/lithium iodide cyclization conditions were used to prepare stereoselectively the *cis*-4,1-benzoxazepinones (Table 1).



Scheme 1. Reagents and conditions: (a) *n*-BuLi, alkylacetylene, THF, 0 °C, 15 min; (b) LAH, THF, rt, 16 h; (c) concd HCl, MeOH, rt, 30 min; (d) 2-bromoacyl bromide, pyridine, ether, 1 h; (e) NaH, DMF, rt, 3–24 h.

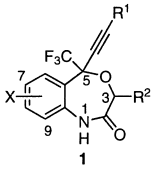


Scheme 2.

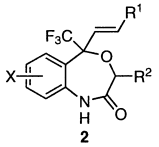
The ability of 4,1-benzoxazepinones to inhibit HIV-1 reverse transcriptase in an in vitro enzyme assay (enzyme IC_{50}) and to inhibit the wild-type RF strain of HIV-1 (wild-type IC_{90}) in a whole cell assay is represented in Table 1. In addition, most compounds were examined for their ability to inhibit a virus containing the clinically relevant K103N mutation (K103N IC_{90}). Aromatic substitutions which had proven optimal in other series were investigated and compounds with potent activity were found in 7-chloro, 7-fluoro, and 6,7-difluoro substituted compounds. Compounds in which the acetylene or olefin side chain was terminally substituted with ethyl, isopropyl, or cyclopropyl groups (**1b**, **1c**, and **1e**) were potent antivirals, however, acetylenes substituted with larger phenyl (**1a**) or 3-furanyl (**1d**) groups resulted in some loss of activity. 3-Unsubstituted benzoxazepinones **1b**, **1c**, **1e**, and **2e** demonstrated potency against wild-type virus, but their ability to inhibit replication of the K103N mutant was poor. When a 3-methyl or 3-ethyl group was introduced *cis* to the trifluoromethyl group, benzoxazepinones with potent antiviral activity against both wild-type and the K103N mutant viruses were obtained. The antiviral potency of **1f**, **2f**, and **2h** is comparable to quinazolinones DPC 961 and DPC 083. The introduction of larger 3-alkyl groups (**1i**, **1j**, and **1k**) resulted in some loss of wild-type activity. When compared to their *cis*-stereoisomers, benzoxazepinones in which the 3-alkyl is *trans* to the trifluoromethyl group suffered loss in wild-type or K103N potency. For example, **1g** exhibited far less potency against the mutant virus than its isomer **1f**.[15]

Two benzoxazepinone NNRTIs, acetylene **1f** and its olefin analogue **2f** were selected for in vivo evaluation. Rhesus monkeys were given either a single oral 10 mg/kg

Table 1. Structure and biological activity of 4,1-benzoxazepinones



1



2

Compound	X	R^1	R^2	Enzyme IC_{50} (nM)[12]	Wild-type IC_{90} (nM)[13]	K103N IC_{90} (nM)[13]
Efavirenz[14]				38	1.9	49
DPC 961[14]				32	2.0	10
DPC 083[14]				23	2.1	27
1a	7-Cl	Phenyl	H	3300	24.3	4100
1b	7-Cl	Ethyl	H	964	9.1	1763
1c	7-Cl	Isopropyl	H	423	9.7	784
1d	7-Cl	3-Furanyl	H	2510	47.5	ND
1e	7-Cl	Cyclopropyl	H	432	9.1	1395
2e	7-Cl	Cyclopropyl	H	108	3.9	362
1f[14]	7-Cl	Cyclopropyl	*cis* Me	82	2.2	29
1g[14]	7-Cl	Cyclopropyl	*trans* Me	249	7.0	1130
1h	7-Cl	Cyclopropyl	*cis* Et	391	8.4	139
1i	7-Cl	Cyclopropyl	*cis* nPr	799	17.2	ND
1j	7-Cl	Cyclopropyl	*cis* iPr	597	20.7	ND
1k	7-Cl	Cyclopropyl	*cis* CH_2CF_3	235	16.8	ND
2f[14]	7-Cl	Cyclopropyl	*cis* Me	46	2.5	35
2h	7-Cl	Cyclopropyl	*cis* Et	185	7.8	13
1l	7-F	Cyclopropyl	*trans* Me	1940	189.4	ND
1m	7-F	Cyclopropyl	*trans* Et	1140	87.4	ND
1n	7-F	Cyclopropyl	*cis* Me	95	5.2	333
1p	7-F	Cyclopropyl	*cis* Et	171	5.3	117
2n	7-F	Cyclopropyl	*cis* Me	129	7.6	118
2p	7-F	Cyclopropyl	*cis* Et	151	2.5	70
1q	6,7-diF	Cyclopropyl	*cis* Me	193	5.8	75
2q	6,7-diF	Cyclopropyl	*cis* Me	173	5.2	81

Table 2. Pharmacokinetic parameters of **1f** and **2f** in rhesus monkeys after a 10 mg/kg po dose

Compd	C_{max} (μM)	T_{max} (h)	AUCT (μM h)	$T_{1/2}$	$C_{24\ h}$ (μM)	*N*
1f	1.67	6	30	N.D.	1.14	1
2f	2.36	11	50.8	16	1.4	3

dose of **1f** or **2f** and the pharmacokinetic results are summarized in Table 2. The total plasma concentration of these drugs at 24 h was sufficient to be considered for development. However, equilibrium dialysis protein binding experiments showed that these compounds were highly protein bound in human serum (>99.7% bound) so that the free fraction of drug at 24 h would be less than the IC_{90} for the K103N mutation.[16] Therefore, these compounds would not be considered viable candidates for development.

We have discovered a new class of non-nucleoside reverse transcriptase inhibitor: the 4,1-benzoxazepinones. The *cis*-3-alkyl-4,1-benzoxazepinones are inhibitors of both wild-type HIV-1 and the clinically significant mutant K103N with potency comparable to efavirenz and the quinazolinone clinical candidates. Two compounds selected for further study (**1f** and **2f**) exhibited favorable pharmacokinetic profiles in rhesus monkeys but were highly protein bound in human plasma.

References and Notes

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11. Experimental procedure for compound **1f**: To a 0 °C solution of **4f** (X = 4-Cl, R^1 = cycPr) (1.54 g, 5.3 mmol) and pyridine (0.527 mL, 6.5 mmol) in anhydrous ether (85 mL) was added 2-bromopropionyl bromide (0.640 mL, 6.1 mmol). After stirring for 30 min, the reaction mixture was washed with water, sat. sodium bicarbonate, and brine, dried over magnesium sulfate and evaporated. The intermediate bromoamide **7** was dissolved in dry DMF (85 mL), lithium iodide (1.48 g, 11.1 mmol) and cesium carbonate (2.7 g, 8.2 mmol) were added, and the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was diluted with water and extracted with ether (3×). The combined extracts were washed with brine, dried and evaporated to a crude product (1.5 g) of a 93:7 mixture of **1f** and **1g**. Crystallization from ethyl acetate/hexane afforded 860 mg (47%) of **1f** as a single diastereomer. Additional material could be obtained by chromatography of the mother liquor.
12. Compounds were assayed for enzyme inhibitory activity (IC_{50}) according to the protocol descibed in ref 7.
13. 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.
14. The data presented for efavirenz, DPC 961, DPC 083, **1f**, **1g**, and **2f** reflect values obtained for a single enantiomer. All other compounds were tested as racemic mixtures. The biological evaluation of each enantiomer of efavirenz, quinazolinones, and 4,1-benzoxazepinones determined that only the *S* enantiomer is active.
15. The lower antiviral potency of the 3-unsubstituted and *trans*-3-alkylbenzoxazepinone compared to the *cis*-3-alkylbenzoxazepinones is not easily explained by comparing the minimum energy conformations of efavirenz, **1f**, and **1g** as determined by X-ray crystallography and molecular modeling studies. While key structural features of efavirenz overlap better with the more potent **1f** than **1g**, these differences are small.
16. Although protein-binding shift assays were routinely run on our compounds, these studies failed to predict the high values determined by the more direct equilibrium dialysis experiments.