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SYNTHESIS AND EVALUATION OF BENZOXAZINONES AS HIV-1 REVERSE TRANSCRIPTASE INHIBITORS. ANALOGS OF EFAVIRENZ (SUSTIVA™)

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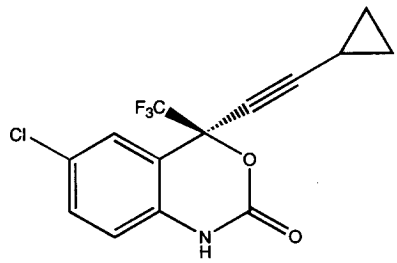
Abstract: Two series of benzoxazinones differing in the aromatic substitution pattern were prepared and evaluated as HIV-1 reverse transcriptase inhibitors. The 5-fluoro (**5a–d**) and 6-nitro (**5e–h**) substituted compounds displayed activity comparable or better than Efavirenz, the lead structure of the series.

Non nucleoside HIV-1 reverse transcriptase inhibitors (NNRTIs) play an important role in combination therapy for the treatment of AIDS. Although Efavirenz together with other antivirals form an effective combination therapy, in a small fraction of the patient population the virus develops resistance to the drug. In pursuit of a better resistance profile for a second generation series, we sought to first optimize the SAR of the substituents on the aromatic ring in terms of reverse transcriptase inhibition and whole cell antiviral activity. Methodology developed for the synthesis of Efavirenz included a crucial ortho-directed metallation step for the introduction of the trifluoromethyl ketone group onto the phenyl ring.[1] Several substitution patterns have been prepared using both this methodology and its modifications.[2] An alternate route had to be developed as the established synthesis was not desirable for the preparation of the 6-fluoro and 5-nitro substituted amino ketones. The SAR resulting from these compounds are summarized here.



Efavirenz (SUSTIVA™)

Chemistry

Commercially available 5-fluoro and 6-nitroanthranilic acids (**1**) were converted to their corresponding Weinreb amides, followed by trityl protection of the amine moiety to give compounds (**2**). Reduction of the

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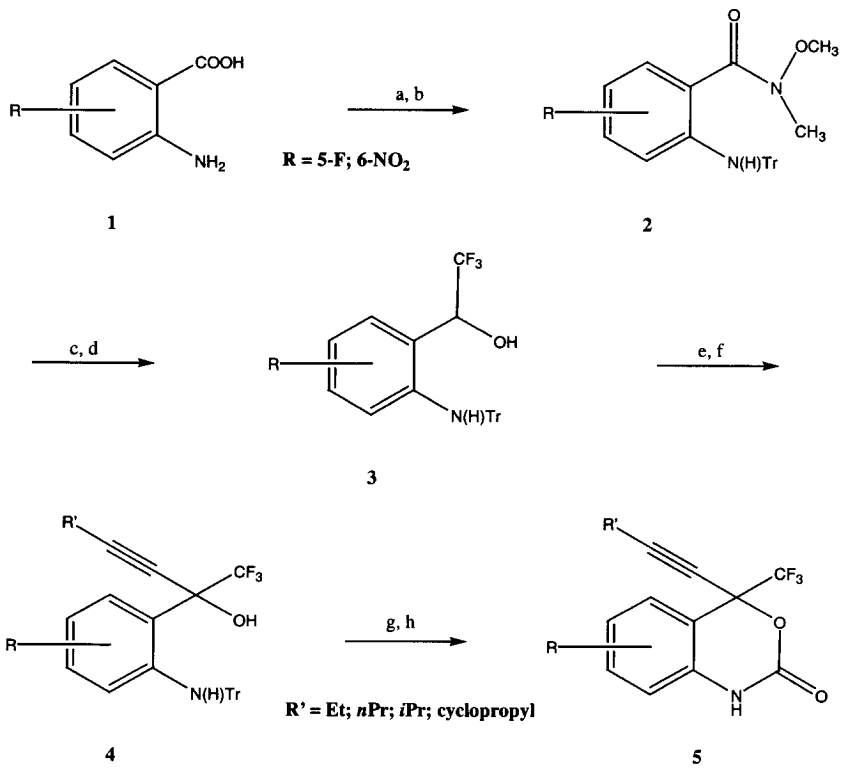
Weinreb amides with lithium aluminum hydride[3] followed by the addition of trifluoromethyl anion (generated in situ by the addition of tetrabutylammonium fluoride to a solution of trifluoromethyltrimethylsilane in tetrahydrofuran) resulted in the formation of the secondary alcohols (**3**) in good yields.[4] Manganese (IV) oxide oxidation of these secondary alcohols to the corresponding amino ketones was followed by treatment with a variety of substituted lithium acetylides in tetrahydrofuran to provide the tertiary alcohols (**4**) in good yields.[5] Detritylation using hydrochloric acid in methanol followed by ring closure with phosgene and Hunig's base in toluene provided benzoxazinones (**5**) (Scheme 1).

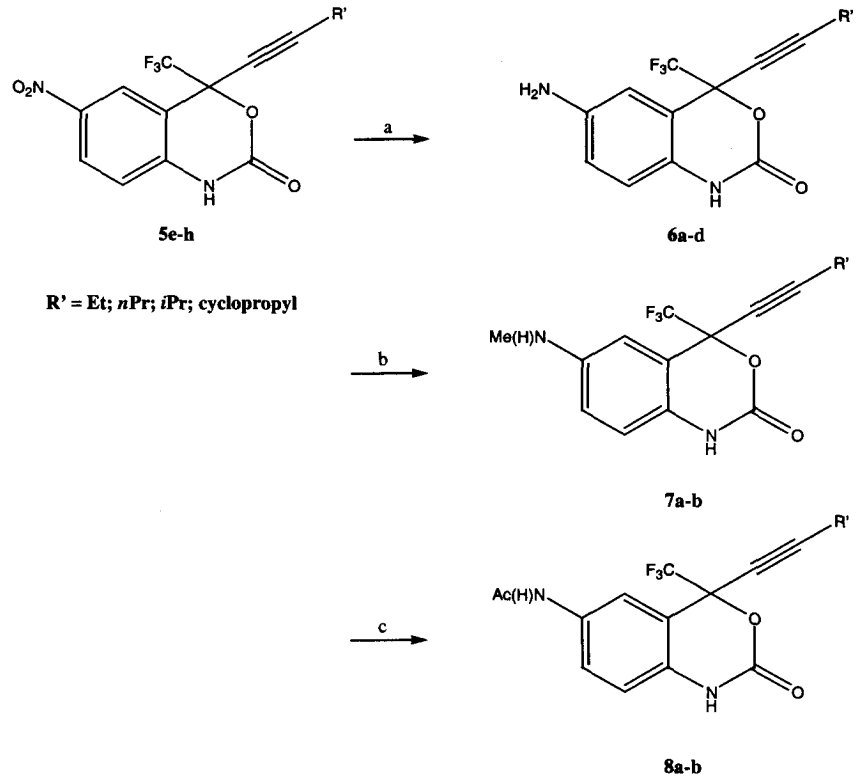
Scheme 1[6]



Reagents and conditions: (a) $HN(OCH_3)CH_3$.HCl, TEA, EDCI, ACN, 25 °C, 14 h, 73–75%; (b) TrBr, DIPEA, DCM, 25 °C, 3 h, 84–93%; (c) LAH, THF, -78 to 25 °C, 1 h, 81–93%; (d) CF_3TMS, TBAF, THF, 0 °C, 73–77%; (e) MnO_2, DCM, 25 °C, 9 h, 75–79%; (f) RC≡CH, nBuLi, THF, 0 °C, 0.5 h, 48–97%; (g) 12 *N* HCl, MeOH, 25 °C, 0.5 h, 21–29%; (h) Phosgene, DIPEA, toluene, 0 °C, 1 h, 34–95%.

Reduction of the nitro group was accomplished using iron powder and 12 *N* HCl in methanol to provide 6-amino benzoxazinones (**6a–d**) in moderate yields. Derivatisation of the 6-aminobenzoxazinones was attempted as illustrated in Scheme 2. *N*-Alkylation was carried out using *N*-hydroxymethylbenzotriazole and sodium borohydride in tetrahydrofuran to give the *N*-methyl compounds (**7a–b**). Conversion of the amine functionality to the corresponding *N*-acetyl compounds (**8a–b**) was carried out by treatment with acetic anhydride in ethyl acetate.

Scheme 2 [6]



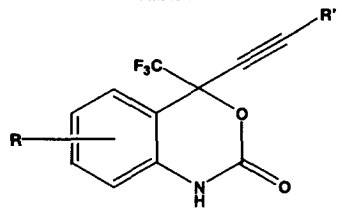
Reagents and conditions: (a) Fe powder, 12 *N* HCl, MeOH, 25 °C, 0.3 h, 41–61%; (b) $NaBH_4$, THF, *N*-Hydroxymethylbenzotriazole, reflux, 3 h , 8–13%; (c) Ac_2O, EtOAc, 25 °C, 1 h, 65–77%.

Results and Discussion

Several 5-fluoro substituted benzoxazinones (**5a–d**) have been prepared. As a series, the 6-nitro substituted benzoxazinones (**5e–h**) were more potent than the corresponding 5-fluoro substituted compounds. Compound **5e** was especially significant, for it possessed subnanomolar activity in the whole cell assay. Reduction of the 6-nitro substituted series provided the 6-amino substituted benzoxazinones (**6a–d**). Conversion to the 6-amino moiety was not well tolerated and the compounds (**6a–d**) lost several fold in both the enzyme inhibition assay as well as the cell based assay. To further explore the SAR of this series, we decided to substitute the amine functionality. *N*-Methylation of the 6-aminobenzoxazinones resulted in compounds (**7a–b**). They show a modest improvement in antiviral activity as compared to the 6-amino series. Acetylation of the 6-amino functionality resulted in compounds (**8a–b**). Clearly, this derivatisation was detrimental to antiviral activity.

In summary, an alternate route for the preparation of benzoxazinones has been established. We have discovered that both the 5-fluoro (**5a–d**) and 6-nitro (**5e–h**) substituted benzoxazinones have activity comparable or better than Efavirenz, and as a result, will be considered for incorporation in the second generation series.

Table 1



Compound	R	R'	IC_{50} (nM)[7a]	IC_{90} (nM)[7b]
Efavirenz[8]	6-Cl	cyclopropyl	48	2.03
5a	5-F	cyclopropyl	78	4.34
5b	5-F	ethyl	127	4.18
5c	5-F	n-propyl	156	5.64
5d	5-F	isopropyl	102	6.64
5e	6-NO_2	cyclopropyl	209	0.83
5f	6-NO_2	ethyl	276	2.23
5g	6-NO_2	n-propyl	304	4.57
5h	6-NO_2	isopropyl	199	3.35
6a	6-NH_2	cyclopropyl	802	20.59
6b	6-NH_2	ethyl	1894	45.74
6c	6-NH_2	n-propyl	1506	33.53
6d	6-NH_2	isopropyl	896	27.49
7a	6-N(H)CH_3	cyclopropyl	608	9.02
7b	6-N(H)CH_3	isopropyl	473	10.25
8a	6-N(H)Ac	cyclopropyl	>2000	295.60
8b	6-N(H)Ac	isopropyl	>2000	499.56

References and Notes

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

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, W. J.; Schlabach, A. J.; Wolfgang, J. A.; Condra, J. H. *J. Biol. Chem.* **1992**, *267*, 17526 using a template primer poly (rA) oligo $(dT)_{12\text{-}18}$. (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. Chemo.* **1994**, *5*, 111.

8. The data presented for Efavirenz reflects values determined for a single enantiomer, whereas the data shown for **5a–8b** are that of racemic mixtures. The biological evaluation of each enantiomer of Efavirenz and other benzoxazinones had determined that only the *S* enantiomer was active.