Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 5, No. 5, pp. 491-496, 1995

0960-894X/95 $9.50+0.00

0960-894X(95)00059-3

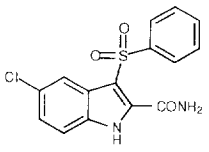
2-HETEROCYCLIC INDOLE-3-SULFONES AS INHIBITORS OF HIV-1 REVERSE TRANSCRIPTASE

Steven D. Young*+, Muriel C. Amblard%+, Susan F. Britcher+, Vanessa E. Grey,+ Lee O. Tran+, William C. Lumma+, Joel R. Huff+, William A. Schleif^, Emilio E. Emini^, Julie A. O'Brien~ and Douglas J. Pettibone~

Departments of Medicinal Chemistry+, Antiviral Research^, and Pharmacology~
Merck Research Laboratories, West Point, Pennsylvania 19486 USA

Abstract: A variety of 2-heterocycle substituted 3-phenysulfonyl-5-chloroindoles were investigated as replacements for the 2-carboxamide functionality of the potent HIV-1 reverse transcriptase inhibitor L-737,126. The 2-carboxamide series of compounds typified by L-737,126 have poor solubility. Replacement of the carboxamide moiety with a variety of heterocycles results in a series of potent enzyme inhibitors with equivalent *ex vivo* antiviral activity and improved physicochemical properties.

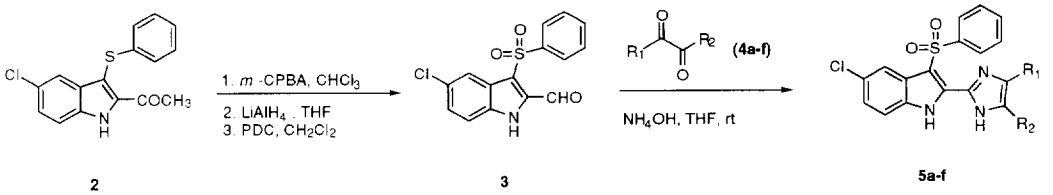
The non-nucleoside inhibitors (NNI's) of HIV-1 reverse transcriptase (RT) have been studied extensively in the laboratory and clinic as antiviral agents for the treatment of AIDS.[1] At least twelve structurally distinct classes of NNI's have been identified.[2] Compounds from four of these classes entered clinical trials in the early 1990's, where antiviral activity in humans was demonstrated. Unfortunately, rapid emergence of resistant strains of HIV-1 forced researchers to abandon monotherapy with these first generation compounds.[3] In searching for NNI's with both improved potency against resistant mutants and pharmacokinetic profile, Williams and co-workers identified L-737,126 (**1**) as a potent NNI of wild type HIV-1 reverse transcriptase with activity against certain RT's from clinically relevant resistant mutant viruses.[4] Modest oral bioavailability of this compound in animals was attributed to its poor solubility. Compound **1** is a neutral, highly crystalline substance with a melting point of 252-253°C. We felt the 2-carboxamide was, at least in part, responsible for the insoluble nature of **1**, having the ability to form strong intermolecular hydrogen bonds in a crystal lattice. Therefore an important design feature of any replacements for the carboxamide was the ability of the amide surrogate to form water soluble salts with pharmaceutically acceptable acids. In this letter we report the preparation and structure-activity relationships of several carboxamide replacements for the L-737,126 series based on bioisosteric basic heterocycles.

L-737,126 (1) 

%Current address: Centre CNRS-INSERM de Pharmacologie-Endocrinologie, Rue de la Cardonille, 34094 Montpellier, Cedex 5, France

Synthesis: Preparation of the 2-(imidazol-2-yl)indoles **5a-f** are shown in Scheme I. Aldehyde **3** was prepared from the known[4] ester **2** in three steps by oxidation of the sulfide then reduction of the ester to the alcohol and reoxidation with pyridinium dichromate. This aldehyde was condensed with the appropriate α-dicarbonyl compound **4a-f** in the presence of NH_4OH to give the desired imidazoles **5a-f**. Yields for this condensation were modest, ranging from 22% for glyoxal (**4a**) to 62% for 2,3-butanedione (**4c**).

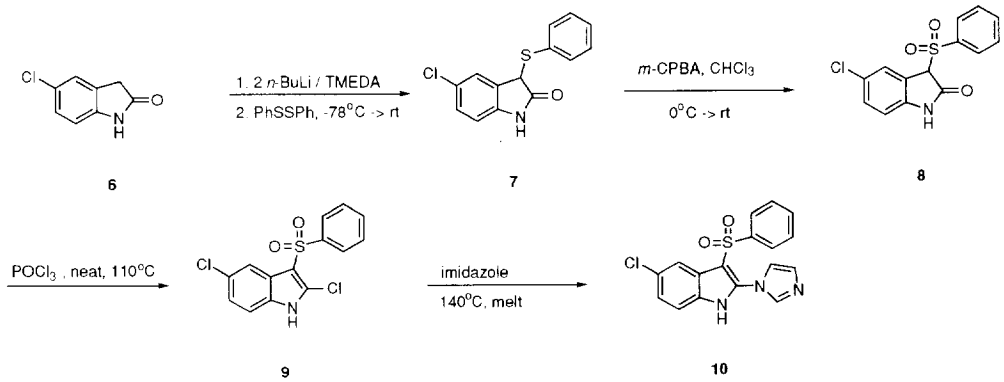
Scheme I



2 **3** **5a-f**

The 2-(imidazol-1-yl)indole **10** required a four step synthesis from commercially available 5-chloro-2-oxindole **6** (Scheme II).[5] Oxindole **6** was metallated with *n*-butyllithium in the presence of TMEDA according to the procedure of Kende and the dianion was phenylthioated with diphenyldisulfide.[6] The resulting 3-phenylthio-5-chloro-2-oxindole **7** was oxidized with *m*-CPBA to sulfone **8** then chlorinated with neat $POCl_3$ to give 2,5-dichloro-3-phenylsulfonylindole **9**. Heating a mixture of **9** and excess imidazole at 140°C for 6h gave **10** in good yield.

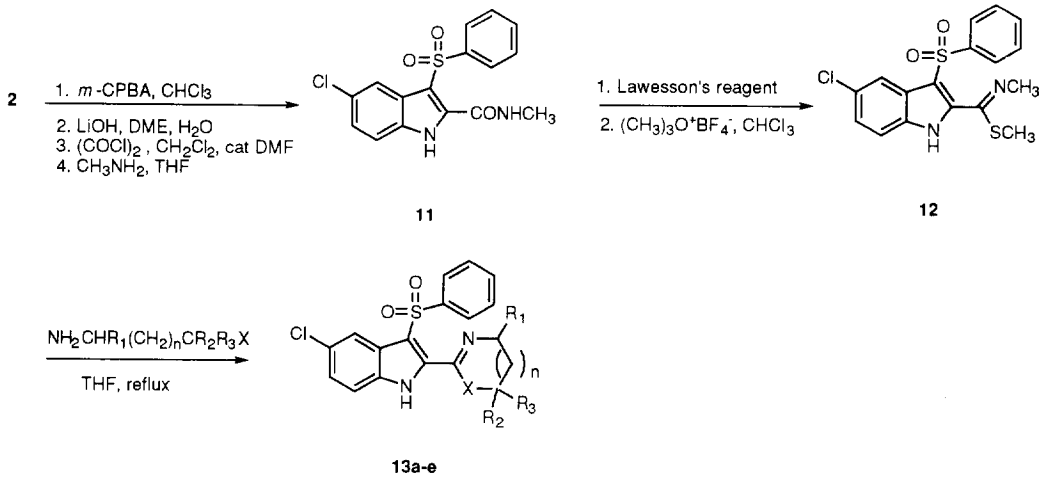
Scheme II



6 **7** **8** **9** **10**

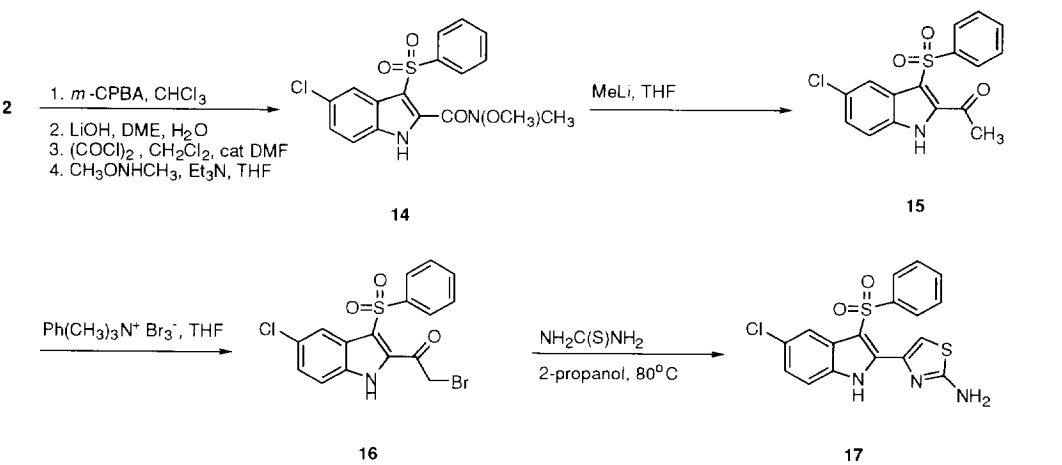
Syntheses of the more basic imidazolidines **13a-d** and thiazolidine **13e** are shown in Scheme III. Sulfide **2** was oxidized to the sulfone and the ester was converted into the N-methylamide **11** via the acid chloride. Amide **11** was then converted to the thioamide with Lawesson's reagent which was in turn methylated with Meerwein's salt to give iminothioether **12.** Reaction of **12** with a variety acyclic and cyclic 1,2 or 1,3-diamines in refluxing THF provided imidazolidines **13a-d,** and reaction with 2-aminoethanethiol gave thiazolidine **13e.**

Scheme III



Preparation of 2-aminothiazole derivative **17** also begins with the known ester **2** (Scheme IV). In a manner similar to the preparation of methylamide **11**, Weinreb amide **14** was prepared from the acid chloride with N,O-dimethylhydroxylamine. Addition of methyllithium to **14** gave the methyl ketone **15** which was α-brominated with phenyltrimethylammonium tribromide in 58% yield. Other brominating agents such as pyridinium bromide perbromide were less effective, leading to significant amounts of the dibromide. The resulting bromomethyl ketone **16** was treated with thiourea in 2-propanol at 80°C whereupon the 2-aminothiazole **17** precipitated as the HBr salt.

Scheme IV



Results and Discussion: The compounds were assayed for inhibition of HIV-1 RT activity using a poly·rC-oligo·dG template primer combination under assay conditions described previously.[7] Antiviral activity in cell culture was determined in MT4 cells using the IIIb strain of HIV-1. The extent of infection was determined by p24 core antigen ELISA 72h after addition of drug to a culture infected to a 0.01 MOI 24h prior to addition of drug.[8] Enzyme inhibitory and *ex vivo* antiviral activity data for the 5-chloro-3-phenylsulfonyl-2-(imdazol-2-yl)indoles **5a-f** is shown in Table I.

Table I

Inhibition of HIV-1 RT and Antiviral Activity of Imidazoles 5a-f

Compound	R_1	R_2	mp	$IC_{50}(\mu M)$	$CIC_{95}(\mu M)$
5a	H	H	>270°C	0.0035	0.002
5b	H	CH_3	225-227°C	0.0047	0.012
5c	CH_3	CH_3	220-221°C	0.0051	0.012
5d	CH_3	$CH_2CH_2CH_3$	216-218°C	0.0094	0.050
5e	CH_2CH_3	CH_2CH_3	234-236°C	0.0100	0.050
5f		$-CH_2CH_2CH_2CH_2-$	>250°C	0.0081	0.050

The 2-(imidazol-2-yl)indoles in Table I were the most effective mimics of L-737,126 (**1**), with the unsubstituted imidazole derivative **5a** being equipotent to **1** in both the enzymatic inhibition and antiviral assays. Substitution of the ring with aliphatic groups results in less potent inhibitors, with the larger substituents causing the most diminution in activity. Table II shows a similar effect in the imidazolidine and thiazolidine series with larger substituents affecting the potency in a negative manner. Clearly, expansion of the imidazolidine ring of **13b** to the analogous tetrahydropyrimidine **13c** dramatically reduces activity. This result is suggestive of significant conformational differences between **13b** and **13c**. The larger six-membered tetrahydropyrimidine is no longer capable of co-planarity with the indole, which may be required for activity. The antiviral activity was not determined for compounds **13a-e.**

Table II

Inhibition of HIV-1 Reverse Transcriptase for Azolidines 13a-e

Compound	n	X	R_1	R_2	R_3	mp (°C)	$IC_{50}(\mu M)$
13a	0	S	H	H	H	115-117°	0.0166
13b	0	NH	H	H	H	236-238°	0.0065
13c	1	NH	H	H	H	249-251°	2.288
13d	0	NH	H	CH_3	CH_3	249-251°	0.050
13e	0	NH	$-(CH_2)_4-$*		H	>250°	0.029

* *trans* ring junction.

The 2-(imidazol-1-yl)indole **10** was also a very weak inhibitor of the enzyme (Table III). Two explanations are possible. First, this compound lacks any potential to donate a hydrogen from the imidazole to the enzyme in a hydrogen bond situation, making it an unacceptable amide mimic. Second, the electron rich imidazole nitrogen unfavorably alters the electronics of the 3-sulfonylindole system, reducing the acidity of the indole NH proton. The 2-amino-5-thiazole **17** has RT inhibitory activity, although it is ten-fold weaker than the best imidazole **5a**. It is capable of forming a hydrogen bond although not in an optimal fashion. This analog did not show antiviral activity at concentrations of 200 nM and less.

Table III

Activity of Imidazole 10 and Aminothiazole 17

Compound	mp	$IC_{50}(\mu M)$	$CIC_{95}(\mu M)$
10	237-238°C	2.385	n.d.*
17	267-270°C (HBr salt)	0.020	>0.200

*n.d.: not determined

In searching for anti-HIV agents with the broadest possible spectrum of activity, we tested selected compounds for their ability to inhibit reverse transcriptases derived from clinically relevant mutant viruses. Significant resistance to two NNI's in the clinic is attributed to the mutations at position 103 (K->N) and 181 (Y->C), both singly and together.[9] It has been reported that replacement of amino acid residues 176-190 in HIV-2 RT with the same region from HIV-1 RT results in a chimeric enzyme that is susceptible to inhibition by NNI's.[10] Therefore, in some ways HIV-2 may be viewed as the ultimate resistant mutant, as there are no reported NNI's that inhibit the RT from this virus. The activity of our 2-heterocyclic-3-phenylsulfonylindole's against these mutant RT's including RT from HIV-2 is shown in Table IV.

Table IV

Inhibitory Activity Against Mutant HIV Reverse Transcriptases

Compound	$IC_{50}(\mu M)$ K103N	$IC_{50}(\mu M)$ K103N/Y181C	$IC_{50}(\mu M)$ HIV-2 RT
5a	0.023	1.07	>300
5b	0.009	n.d.*	>300
5c	0.022	>30	>300
5d	0.210	n.d.	>300
13a	1.250	n.d.	>300
13b	0.358	n.d.	>300
17	0.222	n.d.	>300

* n.d.: not determined

The three most potent imidazole derivatives **5a-c** were also the most potent inhibitors of the K103N mutant, a trend also seen with amide **1**. Although **5a** and **5c** have similar activity against the single mutant K103N, **5c** is a significantly weaker inhibitor the double mutant K103N / Y181C. All compounds tested were inactive against RT from HIV-2.

Our objective of finding a water soluble analog of amide **1** was marginally successful as the HCl salt of imidazole derivative **5a** has an aqueous solubility of 0.5 $\mu g\ mL^{-1}$ which, while small, is 50X greater than amide **1**. In this investigation incremental improvements in activity were made against resistant RT mutants, i.e., compound **5b** is 11X more potent than **1** against the K103N enzyme. However, without still greater enhancements to the spectrum of activity against resistant mutants, the clinical utility and development of NNRTI's is in question.

References and Notes:

1. (a) DeClerq, E. *AIDS Res. Hum. Retroviruses* **1992**, *8(2)*, 119; (b) Saunders, J.; Storer, R. *Drug News Perspect.* **1992**, *5(3)*, 153.
2. Young, S. D. *Perspect. Drug Discovery Design*, **1993**, *1*, 181.
3. (a) 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; (b) Boyer, P. L.; Currens, M. J.; McMahon, J. B.; Boyd, M. R.; Hughes, S. H. *J. Virol.* **1993**, *67*, 2412; (c) Poppe, S. M.; Dueweke, T. J.; Pushkarskaya, T.; Stevenson, M.; Chen, I. S. Y.; Tarpley W. G. *J. Cell Biol.* **1993**, *N17E*, 4; (d) Mellors, J. W.; Im, G-J.; Tramontano, E.; Winkler, S. R.; Medina, D. J.; Dutschman, G. E.; Bazmi, H. Z.; Piras, G.; Gonzalez, C. J.; Cheng, Y-C. *Mol. Pharmacol.* **1993**,*43*, 11.
4. Williams, T. M.; Ciccarone, T. M.; MacTough, S. C.; Rooney, C. S.; Balani, S. K.; Condra, J. H.; Emini, E. A.; Goldman, M. E.; Greenlee, W. J.; Kauffman, L. R.; O'Brien, J. A.; Sardana, V. V.; Schleif, W. A.; Theoharides, A. D.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 1291.
5. (a) Quallich, G. J.; Morrissey, P. M. *Synthesis* **1993**, 51; (b) Available from Aldrich Chemical Co. Inc.
6. Kende, A. S.; Hodges, J. C. *Synth. Commun.* **1982**, *12(1)*, 1.
7. Goldman, M. E.; Nunberg, J. H.; O'Brien, J. A.; Quintero, J. C.; Schleif, W. A.; Freund, K. F.; Gaul, S. L.; Saari, W. S.; Wai, J. S.; Hoffman, J. M.; Anderson, P. S.; Hupe, D. J.; Emini, E. A.; Stern, A. M. *Proc. Natl. Acad. Sci, U.S.A.* **1991**, *88*, 6863.
8. Vacca, J. P.; Dorsey, B. D.; Schleif, W. A.; Levin, R. B.; McDaniel, S. L.; Darke, P. L.; Zugay, J.; Quintero, J. C.; Blahy, M.; Roth, E.; Sardana, V. V.; Schlabach, A. J.; Graham, P. I.; Condra, J. H.; Gotlib, L.; Holloway, M. K.; Lin, J.; Chen, I.-W.; Vastag, K.; Ostovic, D.; Anderson, P. S.; Emini, E. A.; Huff, J. R. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 4096.
9. Tong, L.; Cardozo, M.; Jones, P-J.; Adams, J. *Bioorg. Med. Chem. Lett.* **1993**, *3(4)*, 721.
10. Shih, C-K.; Rose, J. M.; Hansen, G. L.; Wu, J. C.; Bacolla, A.; Griffin, J. A. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 9878.

(*Received in USA* 6 *December* 1994; *accepted* 23 *January* 1995)