Poster Session I: Retrovirus Infections

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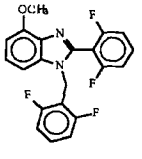
4-ALKOXY-SUBSTITUTED 1-BENZYL-2-PHENYL-BENZIMIDAZOLES AS NNRTIS: SYNTHESIS AND BIOLOGICAL ACTIVITY

G. Pürstinger[#], M. Witvrouw[$], C. Pannecouque[$], J. Balzarini[$], E. De Clercq[$]

[$]Rega Institute for Medical Research, Minderbroedersstraat 10, B-3000 Leuven, Belgium, [#]Institut für Pharmazeutische Chemie, Universität Innsbruck, Innrain 52a, A-6020 Innsbruck, Austria

1-(2,6-Difluorobenzyl)-2-(2,6-Difluorophenyl)-4-methoxybenzimidazole (1) has been described as a potent NNRTI with an IC_{50} of 0.06 μg/ml [1]. We have synthesized a series of analogues (**A**) and evaluated it for its anti-HIV activity.



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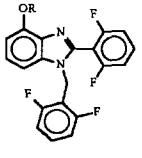

A

R=Me,Et,Pr,i-Pr,Allyl, Ph,Bz,H

Several of the synthesized compounds showed anti-HIV-1 activity. The highest activity was found for the 4-allyl analogue with an IC_{50} of 0.09 μg/ml and a selectivity index of 149. The synthesis and the biological data will be presented.

[1] C. Michejda, M. Morningstar and T. Roth; WO 98/37072

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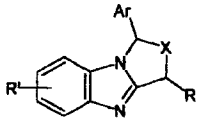
Synthesis and metabolic study of 1*H*,3*H*-oxazolo[3,4-a]benzimidazoles, a new class of non-nucleoside HIV-1 RT inhibitors.

A. Chimirri,[1] E. De Clercq,[2] A.M. Monforte,[3] P. Monforte,[1] C. Pannecouque,[2] A. Rao,[1] M. Witvrouw,[2] M. Zappalà[1]

[1]*Dipartimento Farmaco-Chimico, Università di Messina, Italy*
[2]*Rega Institute for Medical Research, Leuven, Belgium*
[3]*Dipartimento di Scienze Farmacobiologiche, Università di Catanzaro "Magna Græcia", Italy*

The approved chemotherapeutic agents for the treatment of HIV-1 infections are enzyme inhibitors which interfere with critical steps in the HIV-replication cycle. In particular targeting the virally encoded reverse transcriptase (RT) has proved to be a successful strategy in the development of drugs used to treat HIV-1 infections and AIDS. We have previously reported (1-2) that some 1*H*,3*H*-thiazolo[3,4-a]benzimidazole derivatives (TBZs) are potent and selective non-nucleoside HIV-1 RT inhibitors (NNRTIs). The key structural requirements for an efficient RT inhibition were identified by SAR and molecular modeling studies (3). Pharmacokinetic studies demonstrated that the therapeutic utility of TBZs may be hampered by metabolic oxidation of the sulfur atom to the less active sulfone and sulfoxide derivatives. In order to obtain more stable and effective NNRTIs, a series of 1*H*,3*H*-oxazolo[3,4-a]benzimidazoles (OBZs) was synthesized and evaluated as anti-HIV agents both against wild-type and a variety of mutant strains. HPLC assays, carried out for a comparative determination of OBZs, TBZs and their metabolites in biological fluids, will also be presented.



X = S, TBZs
X = O, OBZs

1) P. Monforte *et al.*, *U.S. Patent*, 5,217,984 (1993). 2.a) A. Chimirri *et al.*, *Antiviral Chem. Chemother.* **8**, 363 (1997); b) *ibid.* **9**, 431 (1998); c) *ibid.* **10**, 211 (1999). 3) M.L. Barreca *et al.*, *Bioorg. Med. Chem.* **7**, 2283 (1999).