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Synthesis and biological evaluation of new simple indolic non peptidic HIV Protease inhibitors: The effect of different substitution patterns

C. Bonini [a,*], L. Chiummiento [a], N. Di Blasio [a], M. Funicello [a], P. Lupattelli [a], F. Tramutola [a], F. Berti [b], A. Ostric [b], S. Miertus [c,d], V. Frecer [c,e], D.-X. Kong [f,g]

[a] Dipartimento di Scienze, Università degli studi della Basilicata, Viale dell'Ateneo Lucano 10, 85100 Potenza, Italy
[b] Dipartimento di Scienze Chimiche e Farmaceutiche, Università di Trieste, via Giorgieri 1, 34127 Trieste, Italy
[c] International Centre for Applied Research and Sustainable Technology, Bratislava SK-8410, Slovakia
[d] University of SS. Cyril & Methodius, Faculty of Natural Sciences, Trnava, Slovakia
[e] Department of Physical Chemistry of Drugs, Faculty of Pharmacy, Comenius University, Bratislava SK-83232, Slovakia
[f] ICS-UNIDO, Area Science Park, Trieste, Italy
[g] State Key Laboratory of Agricultural Microbiology, Huazhong Agricultural University, Wuhan 430070, China

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ABSTRACT

New structurally simple indolic non peptidic HIV Protease inhibitors were synthesized from (*S*)-glycidol by regioselective methods. Following the concept of targeting the protein backbone, different substitution patterns were introduced onto the common stereodefined isopropanolamine *core* modifying the type of functional group on the indole, the position of the functional group on the indole and the type of the nitrogen containing group (sulfonamides or perhydroisoquinoline), alternatively. The systematic study on in vitro inhibition activity of such compounds confirmed the general beneficial effect of the 5-indolyl substituents in presence of arylsulfonamide moieties, which furnished activities in the micromolar range. Preliminary docking analysis allowed to identify several key features of the binding mode of such compounds to the protease.

1. Introduction

The devastating effect of the AIDS epidemic is still a reality. However, since the highly active antiretroviral therapy (HAART) has been employed to combat the illness, HIV infection has definitely become more manageable.[1] During the last 20 years an unprecedented success has been achieved in discovering anti-HIV drugs as reflected by the fact that there are now more drugs approved for the treatment of HIV than for all other viral infections taken together.

The currently FDA approved anti-HIV drugs can be divided into seven groups: nucleoside reverse transcriptase inhibitors, nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors (PIs), fusion inhibitors, co-receptor inhibitors, and integrase inhibitors.[2] Detailed knowledge of the structure of HIV protease and its substrate has led to the preparation of specific PIs, whose arrival was a pivotal moment in the development of antiretroviral therapy and made possible the dual class triple combination therapy.[3] Despite the already marketed PIs have an evident crucial role into HAART regimen, their clinical utility can be limited by low bioavailability and reduced long-term viral inhibition, with multiple protease resistance mutations being observed. Thus, novel PIs with high potency against the known HIV protease variants have been designed. We recently demonstrated the beneficial effect of a heteroaromatic group in a series of new thienyl ring containing analogues of nelfinavir and saquinavir, which showed to maintain or even increase their activity against either wild type or mutant HIV protease.[4] Recently the concept of targeting the protein backbone in structure-based drug design was introduced. Thus new non-peptidic templates, which can maximize interactions in the HIV-protease active site, particularly with the enzyme backbone atoms, were developed.[5] Both extensive hydrogen bonding and hydrophobic interactions with enzyme subsites can limit the protease ability to acquire drug resistance as the geometry of the catalytic site must be conserved to maintain functionality.[6] This new concept

* Corresponding author. Tel.: +39 0971205495; fax: +39 0971205503.
E-mail address: carloc.bonini@libero.it (C. Bonini).

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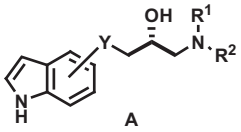


Figure 1.

allowed to design different compounds of very simple structure and to focus the interest more toward their easy synthetic availability and less to structural similarity. Our preliminary investigation showed the beneficial effect of indolyl ring on a simple substituted stereodefined isopropanolamine core.[7] In this respect, with the aim of finding new easily accessible non-peptidic PIs, we started a systematic study on the synthesis and inhibition activity of new indolyl derivatives with general structure **A** (Fig. 1), modifying the following parameters:

(1) Type of functional group on the indole.
(2) Position of the functional group on the indole.
(3) Type of the nitrogen containing group R^1 and R^2 (sulfonamides or PHIQ).

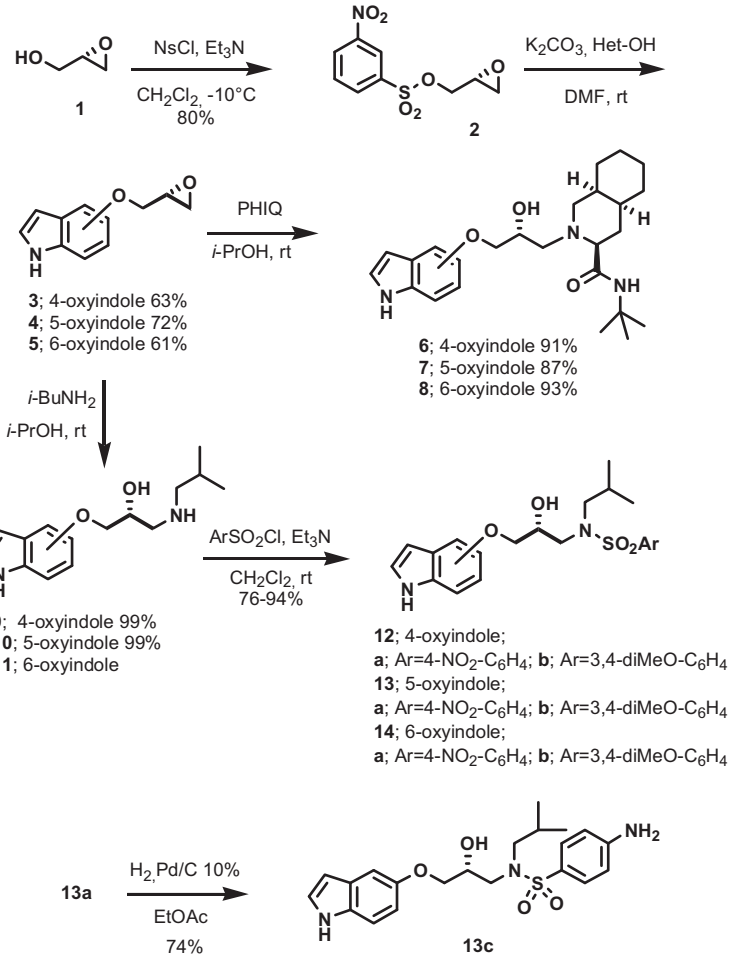
2. Results and discussion

Although the synthetic work can appear tedious at a first sight, we took advantage of the commercially available bidentate electrophile (*S*)-glycidol **1** for the generation of the core (Scheme 1). The glycidol was first activated by the reaction with *m*-nosyl chloride to obtain compound **2**. The subsequent nucleophilic displacement of the nosyl group was performed by the commercially available 4-, 5-, or 6-hydroxyindoles affording the corresponding oxyindoles **3**, **4** and **5** in good yields and mild reaction conditions, without any competitive epoxide ring opening.[8] Each oxyindole represents the common precursor for the preparation of either perhydroisoquinyl- or sulfonamidyl derivatives. Indeed, perhydroisoquinoline (PHIQ) was introduced by direct regioselective oxiranyl ring opening, obtaining the corresponding **6**, **7** and **8** in good yield and as single diastereoisomers (>57% overall yield in 3 steps).

For the preparation of arylsulfonamidyl compounds, the oxiranyl-oxyindoles **3**, **4** and **5** were reacted with isobutylamine, affording the amino-derivatives **9**, **10** and **11** in excellent yield. Starting from this triad, arylsulfonyl fragments with different electronic properties were introduced by employing suitable chlorides, affording compounds **12a**,**b**, **13a**,**b** and **14a**,**b** (>46% overall yield in 4 steps). In particular, electron releasing 3,4-dimethoxyphenyl- and electron withdrawing 4-nitrophenyl groups were introduced to evaluate their potentially different effect on inhibitory activity. Compound **13a** was also transformed into 4-aminophenyl derivative **13c** by Pd-catalyzed hydrogenation.

All these oxyindoles were tested in vitro for anti HIV-PR activity and the results are reported in Table 1.

This systematic study confirms the trend observed in our preliminary results on oxyindoles.[7b] In general 5-oxyindoles show better activity than the 4- and 6-substituted ones and this difference is



Scheme 1.