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New indolic non-peptidic HIV protease inhibitors from (*S*)-glycidol: synthesis and preliminary biological activity

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Dedicated to Professor Carlo Bonini on the occasion of his 60th birthday

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ABSTRACT

A series of non-peptidic HIV protease inhibitors were synthesized starting from the same optically active precursor, (*S*)-glycidol. The substrate was easily converted into different indolic sulfonamides or amines by regioselective reactions. The preliminary inhibitory activity was evaluated.

1. Introduction

Acquired immunodeficiency syndrome (AIDS) represents one of the most important problems in medicine and the interest in developing inhibitors targeting the different steps in the life cycle of the virus is still significant. More recent therapies for AIDS[1,2] are essentially directed against important enzymes that regulate the HIV vital life cycle: reverse transcriptase (RT), aspartyl protease (PR)[3] and more recently integrase (IN).[4] In particular, the early recognition of the central role of HIV protease in viral maturation has made it an important target for the treatment of HIV/AIDS.

Since Saquinavir, the first protease inhibitor (PI), appeared on the market, a number of PIs have been introduced in the regimens of highly active antiretroviral therapy (HAART). Nevertheless, the first generation anti-protease therapeutics have shown several drawbacks. These include: (1) severe side effects and drug toxicity; (2) higher therapeutic doses and low bioavailability due to 'peptide-like' character; (3) costly synthesis, which leads to high treatment cost; (4) rapid emergence of drug resistance. To alleviate these problems, great interest has been directed to design and synthesize new inhibitors with a non-peptidic skeleton. As recently reported,[5] all inhibitors tailored after substrate-based peptide of an enzyme are referred to as peptidomimetics and show a structure where aminoacidic residues are numbered starting from the scissile peptidic bond, such as $P_n \ldots P_2–P_1–P_{1'}–P_{2'} \ldots P_{n'}$. All the commercially available drugs against HIV protease are peptidomimetics, but Tipranavir,[6] a recently approved drug, possesses a non-peptidomimetic structure.

The need to overcome viral resistance and to have a simpler synthetic sequence prompted us to investigate new non-peptidic compounds with simplified structure, bearing the central isopropanolamine unit found in the commercially available peptidic drugs and in some non-peptidic ones such as Darunavir.[7] In our continuing investigation on new inhibitors bearing heteroarylic groups,[8] the attention was focused on some reported structures[9] in which the presence of the indole ring, mimicking the aminoindane group of Indinavir, seems to be important for the activity.

In a first synthetic approach various aspects can be considered: (1) in drugs such as Saquinavir and Nelfinavir a perhydroisoquinoline (PHIQ) residue appears important[10] as $P_{2'}$ ligand for a good interaction at the $S_{2'}$ subsite of the protease; (2) in most of the commercially available anti-HIV PR drugs and in other compounds with good inhibitory activity an isopropanolamine core is present with *R* configuration of the hydroxyl function; (3) some non-peptidic inhibitors, such as Darunavir, possess the arylsulfonamide moiety.

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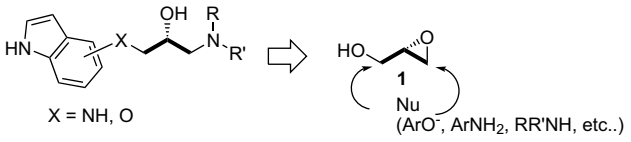
On the basis of the previous considerations, we designed a series of new indolic compounds as potential HIV PIs starting from the commercially available (*S*)-glycidol, fundamental in generation of the core. At one end of this central structure we hypothesized to link a suitable indolic derivative by changing functionality and/or its position on the heterocyclic ring, while at the other end we considered the introduction of PHIQ or an arylsulfonamide moiety (Scheme 1).

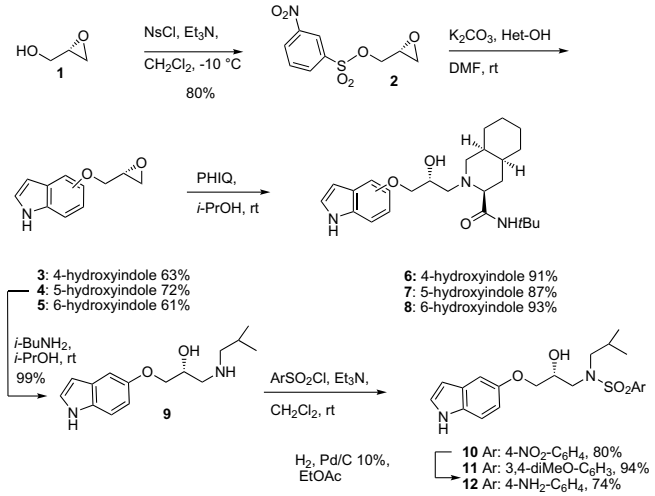


Scheme 1.

By this synthetic approach the influence of both the type and the position of the substituent on the indole ring can be tested using the commercial 4-, 5- and 6-hydroxyindole and 4- and 5-aminoindole, largely used in many drugs synthesis,[11] as starting material.

2. Results and discussion

Glycidol offers two potential sites of electrophilic reactivity so we can realize a first displacement and then ring opening, or we can invert the reaction sequence. In a preliminary consideration both routes were possible even if the direct displacement of the activated hydroxyl function by 4- or 5-aminoindole seemed more difficult due to the decreased nucleophilicity of the heteroaromatic amino group. After preliminary attempts by using different nucleophiles, it was clear that two different approaches should be followed depending on the type of functionality present on the heterocyclic ring: in fact, the activation of glycidol by a nosyl group was fundamental with hydroxyindoles since it allowed a regioselective displacement without epoxide opening (Scheme 2), as reported by Sharpless and co-workers.[12]



Scheme 2. Preparation of compounds **6**–**8** and **10**–**12**.

Hence, (*S*)-glycidol was treated with *m*-nosyl chloride to obtain compound **2** in 80% yield: the subsequent displacement of the nosyl group by suitable hydroxyindoles was performed affording the corresponding **3**, **4** and **5** in good yields and in mild reaction conditions. At last, epoxide ring opening was easily realized to give the desired final products.

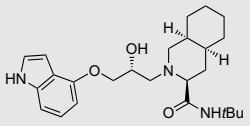
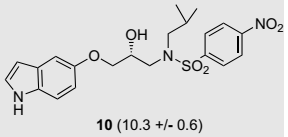
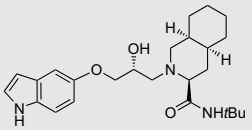
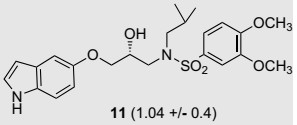
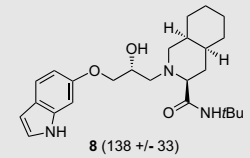
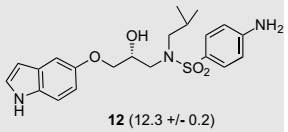
In particular, when we opened the epoxide ring with the chiral amine PHIQ the final products **6**, **7** and **8** were obtained in excellent chemical yields and as single diastereomers.

For the preparation of indolic inhibitors with an arylsulfonamidic moiety, we then decided to use only epoxide **4** in reaction with isobutylamine to afford compound **9** in excellent yield.[13,14] This compound was then transformed into **10**, **11** and **12** in high yields by reacting with suitable arylsulfonyl chlorides.

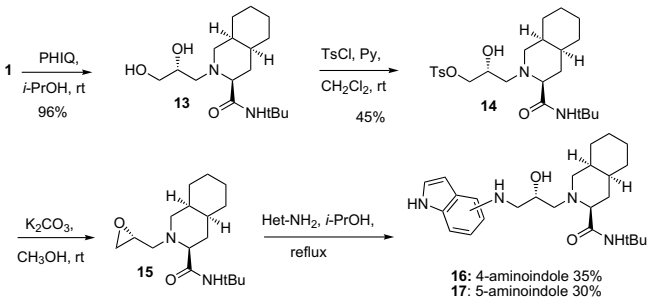
It is noteworthy that we could differentiate the final target molecule by introducing arylsulfonic residues with different electronic properties in order to evaluate their possible effect on inhibitory activity.

These six compounds were tested for anti-HIV PR activity and their biological results are reported in Table 1. From these preliminary biological results, it appeared clear that the 5-indolic derivatives possess better activity than the 4- and 6-indolic ones (Table 1, entries 1–3). Moreover, comparison of the results to compounds **10**–**12** (Table 1, entries 4–6) showed that electron donating properties of the arylsulfonamide ring could have some effects on inhibition.

Table 1
IC_{50} values for compounds **6**–**8** and **10**–**12**

Entry	Compound IC_{50} (μM)	Entry	Compound IC_{50} (μM)
1	 **6** (23.7 +/- 7)	4	 **10** (10.3 +/- 0.6)
2	 **7** (14 +/- 0.2)	5	 **11** (1.04 +/- 0.4)
3	 **8** (138 +/- 33)	6	 **12** (12.3 +/- 0.2)

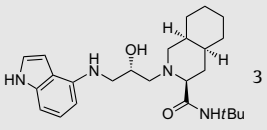
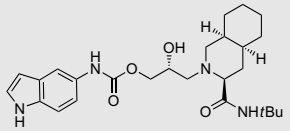
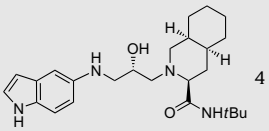
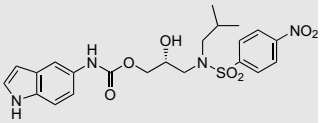
With the aim to explore the effect of different functionality on the indole ring we considered using 4- or 5-aminoindole. In this case a different synthetic approach must be followed: in fact, PHIQ was firstly introduced by epoxide ring opening of compound **1**. Then, diol **13** was selectively activated on the primary hydroxyl function in moderate yields and subsequently transformed into the new epoxide **15**. Finally 4- or 5-aminoindole was introduced under mild reaction conditions with acceptable chemical yields (Scheme 3).



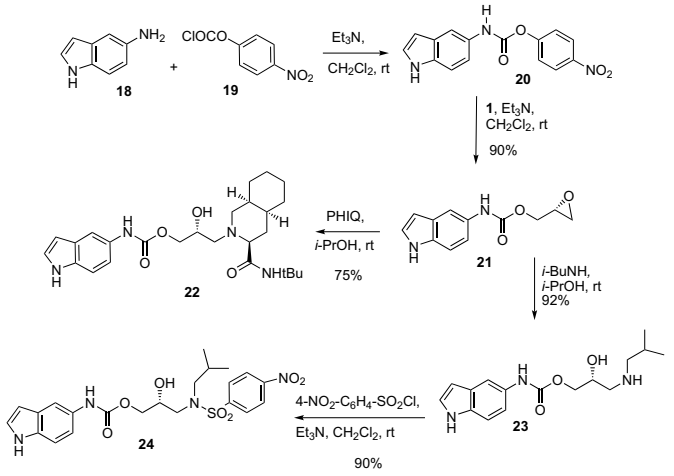
Scheme 3. Preparation of compounds **16** and **17**.

Biological assays were performed on these two new compounds (Table 2, entries 1 and 2), but the results were unsatisfactory and prompted us to consider other compounds. Hence, the amino group on the 5-position of indole was transformed into a carbamate function and readily introduced into our inhibitor structure as the P_2 ligand.

Table 2
IC_{50} for compounds **16**, **17**, **22** and **24**

Entry	Compound IC_{50} (μM)	Entry	Compound IC_{50} (μM)
1	 **16** (157 +/- 12)	3	 **22**(606)[15]
2	 **17** (176 +/- 2)	4	 **24** (2.4 +/- 0.7)

Two parent compounds (**22** and **24**) bearing PHIQ or arylsulfonamide as the $P_{2'}$ unit were synthesized in good to excellent yields, according to literature conditions reported for similar structures[16] (Scheme 4).



Scheme 4. Preparation of compounds **22** and **24**.

The values of HIV PR inhibitory activity are shown in Table 2 (entries 3 and 4): the obtained results appear difficult to explain. In fact while compound **22** shows the worst value of the biological activity, structure **24** shows an improvement of IC_{50} with respect to the structures **16** and **17** (see Table 2): in our opinion, the simple substitution of the PHIQ with sulfonamidic group is unable to rationalize such data.

The results of inhibitory assays led us to make further considerations: in particular it is clear that the 5-hydroxyindolic inhibitors are the most active with both the PHIQ residue and with the arylsulfonamidic one as the $P_{2'}$ unit.

On the other hand, the aminoindolic structures show generally low activity, but transformation of the amino group into a carbamate function gave an improvement in IC_{50} value when a sulfonamidic framework is present, but a lowering with a PHIQ residue.

3. Conclusion

Ten new indolic non-peptidic inhibitors were prepared starting from (*S*)-glycidol in two different synthetic approaches. For the synthesis of compounds **6**, **7** and **8** a suitable activation of the primary hydroxyl function by nosyl chloride was necessary to obtain the final products in only three steps and with 46%, 50% and 45% overall yields, respectively. Indeed, the preparation of compounds **16** and **17**, according to the second strategy, needed an additional step of reaction due to the necessity to control the regioselectivity in the epoxide ring opening (overall yields were 15 and 13%, respectively).

Moreover better biological activity resulted when an arylsulfonamide moiety was introduced in the $P_{2'}$ position.

Work is in progress in attempting to enlarge this series of non-peptidic HIV PIs in order to improve the biological activity and to evaluate the structure–activity relationships through a theoretical approach.

4. Experimental

4.1. General

Column chromatography was carried out on Merck silica gel (0.063–0.200 mm particle size) by progressive elution with opportune solvent mixtures. ^1H and ^{13}C NMR spectra were normally carried out in $CDCl_3$ solutions on a VARIAN INOVA 500. Mass spectra were obtained with a Hewlett–Packard 5971 mass-selective detector on a Hewlett–Packard 5890 gas chromatograph [(OV-1 capillary column between 70 and 250 °C (20 °C min^{-1})]. The optical purity was evaluated by using a polarimeter JASCO Mod Dip-370. Dichloromethane was dried by distillation over anhydrous $CaCl_2$ in inert atmosphere. Dry dimethylformamide was commercially available. Compound **2** was prepared according to the literature[12] starting from the commercially available (*S*)-(−)-glycidol.

4.2. Nosyl displacement with hydroxyindoles: general procedure

K_2CO_3 (0.1433, 1.04 mmol) was added to a stirred solution of hydroxyindole (0.0461 g, 0.35 mmol) in dry DMF (4 mL) at room temperature under argon atmosphere; after 1 h a DMF solution (3 mL) of compound **2** (0.0815 g, 0.31 mmol) was added and the mixture was stirred overnight. After above 14 h (TLC control, $CHCl_3$/CH_3OH 99:1) the reaction mixture was quenched by adding ammonium chloride (saturated aqueous solution), then was extracted with diethyl ether and the organic layer washed with brine. After drying over Na_2SO_4, the organic layer was concentrated under vacuo and the crude was purified by column chromatography on silica gel (eluent: CH_2Cl_2/EtOAc 99:1).

*4.2.1. (−)-4-[((R)-Oxiran-2-yl)methoxy]-1H-indole (**3**)*

Compound **3** was isolated as a brown thick oil (0.0375 g, 63%). $[\alpha]_D^{20}$ −6.4 (*c* 1.6, $CHCl_3$); R_f 0.5 (CH_2Cl_2/EtOAc 99:1); δ_H (500 MHz, $CDCl_3$) 8.25 (1H, s), 7.14–7.05 (3H, m), 6.71 (1H, t, *J* 2.5), 6.55 (1H, d, *J* 8.0), 4.38 (1H, dd, *J* 3.0 and 11.0), 4.17 (1H, dd, *J* 6.0 and 11.0), 3.49–3.47 (1H, m), 2.96 (1H, t, *J* 5.0), 2.85 (1H, dd, *J* 2.5 and 5.0); δ_C (125 MHz, $CDCl_3$) 152.1, 133.2, 127.1, 120.5, 117.6, 112.3, 103.4, 102.7, 70.5, 50.9, 44.3. MS (EI) *m*/*z*: 189 (M^+) (100), 132 (63), 104 (50). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86%. Found: C, 69.85; H, 5.84.

*4.2.2. (−)-5-[((R)-Oxiran-2-yl)methoxy]-1H-indole (**4**)*

Compound **4** was isolated as a brown thick oil (0.0450 g, 72%). $[\alpha]_D^{20}$ −2.2 (*c* 1.2, $CHCl_3$); R_f 0.5 (CH_2Cl_2/EtOAc 99:1); δ_H (500 MHz, $CDCl_3$) 8.16 (1H, s), 7.31–7.14 (3H, m), 6.92 (1H, dd, *J* 1.5 and 8.5), 6.5 (1H, s), 4.27 (1H, dd, *J* 3.5 and 12.0), 4.04 (1H, dd, *J* 6 and 11.0), 3.43–3.42 (1H, m), 2.942 (1H, t, *J* 4.5), 2.81 (1H, dd, *J* 3.0 and 5.5); δ_C (125 MHz, $CDCl_3$) 153.0, 131.2, 128.1, 125.0, 112.8, 111.7, 103.8, 102.3, 69.6, 50.4, 44.9; MS (EI) *m*/*z*: 189 (M^+) (100), 132 (80), 104 (54). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86%. Found: C, 69.82; H, 5.87.

*4.2.3. (−)-6-[((R)-Oxiran-2-yl)methoxy]-1H-indole (**5**)*

Compound **5** was isolated as a yellow solid (0.0357 g, 61%). Mp 105 °C; $[\alpha]_D^{20}$ −3.4 (*c* 1, $CHCl_3$); R_f 0.4 (CH_2Cl_2/EtOAc 99:1); δ_H (500 MHz, $CDCl_3$) 8.15 (1H, s), 7.54 (1H, d, *J* 11.0), 7.09 (1H, s), 6.85 (2H, d, *J* 6.5), 6.50 (1H, d, *J* 1.0), 4.24 (1H, dd, *J* 1.5 and 13.5), 3.96 (1H, dd, *J* 7.0 and 14.0), 3.39 (1H, m), 2.93–2.78 (2H, m); δ_C (125 MHz, $CDCl_3$) 155.1, 136.3, 123.4, 122.5, 121.2, 110.2, 102.2, 95.9, 69.3, 50.3, 44.7; MS (EI) *m*/*z*: 189 (M^+) (100), 132 (80), 104 (54). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86%. Found: C, 69.82; H, 5.87.

4.3. Ring opening of the oxyranylmethoxy-1*H*-indole with PHIQ: general procedure

PHIQ (0.0433 g, 0.18 mmol) was added to a stirred solution of suitable epoxide (0.0314 g, 0.15 mmol) in *i*-PrOH (2 mL) at room temperature. After above 20 h the solvent was removed under reduced pressure and the crude purified by column chromatography on silica gel ($CHCl_3$/CH_3OH 95:5).

*4.3.1. (−)-(3S,4aS,8aS)-2-[(R)-3-(1H-Indol-4-yloxy)-2-hydroxypropyl]-N-tert-butyl-decahydroisoquinoline-3-carboxamide (**6**)*

Compound **6** was isolated as a pink solid (0.0613 g, 91%); mp 85 °C; $[\alpha]_D^{20}$ −61.2 (*c* 1.5, $CHCl_3$); R_f 0.4 ($CHCl_3$/CH_3OH 95:5); δ_H (500 MHz, $CDCl_3$) 8.51 (1H, s), 7.14–7.06 (3H, m), 6.65 (1H, d, *J* 2.5), 6.53 (1H, d, *J* 7.5), 6.25 (1H, s, NH), 4.42 (1H, d, *J* 9.0), 4.07 (1H, t, *J* 8.0), 3.12 (1H, s, OH), 2.99 (1H, d, *J* 7.5), 2.78 (1H, d, *J* 8.0), 2.66 (1H, d, *J* 8.0), 2.44 (1H, d, *J* 7.5), 2.31 (1H, d, *J* 8.0), 1.92–1.39 (9H, m), 1.34 (9H, s), 1.28–1.16 (4H, m); δ_C (125 MHz, $CDCl_3$) 171.5, 152.1, 137.3, 122.8, 122.5, 118.6, 105.1, 100.7, 99.5, 70.4, 68.2, 59.5, 58.4, 50.6, 35.7, 33.1, 30.8, 30.6, 28.6, 26.1, 25.7, 20.4. IR (cm^{-1}) 3311, 2925, 1652, 1365. Anal. Calcd for $C_{25}H_{37}N_3O_3$: C, 70.22; H, 8.72%. Found: C, 70.20; H, 8.73.

*4.3.2. (−)-(3S,4aS,8aS)-2-[(R)-3-(1H-Indol-5-yloxy)-2-hydroxypropyl]-N-tert-butyl-decahydroisoquinoline-3-carboxamide (**7**)*

Compound **7** was isolated as a yellow thick oil (0.0632 g, 87%); $[\alpha]_D^{20}$ −70.3 (*c* 2, $CHCl_3$); R_f 0.4 ($CHCl_3$/CH_3OH 95:5); δ_H (500 MHz, $CDCl_3$) 8.45 (1H, s), 7.29 (1H, t, *J* 9.0), 7.21 (1H, t, *J* 2.5), 7.11 (1H, d, *J* 2.5), 6.87 (1H, dd, *J* 2.5 and 9.0), 6.47 (1H, t, *J* 2.5), 6.29 (1H, s, NH), 4.19 (1H, s, OH), 4.11 (1H, dd, *J* 4.0 and 9.5), 3.95 (1H, dd, *J* 7.0 and 9.0), 3.01–2.22 (5H, m), 1.91–139 (10H, m), 1.35 (9H, s), 1.22–1.18 (3H, m); δ_C (125 MHz, $CDCl_3$) 173.9, 152.9, 131.3, 128.2, 125.1, 112.6, 111.8, 103.7, 102.7, 71.2, 70.3, 68.3, 59.4, 58.6, 50.7, 35.7, 35.7, 33.1, 30.8, 30.6, 29.6, 28.6, 26.1, 25.7, 20.5. IR (cm^{-1}) 3311, 2925, 1652, 1365. Anal. Calcd for $C_{25}H_{37}N_3O_3$: C, 70.22; H, 8.72%. Found: C, 70.19; H, 8.76.

*4.3.3. (−)-(3S,4aS,8aS)-2-[(R)-3-(1H-Indol-6-yloxy)-2-hydroxypropyl]-N-tert-butyl-decahydroisoquinoline-3-carboxamide (**8**)*

Compound **8** was isolated as a brown thick oil (0.0633 g, 93%); $[\alpha]_D^{20}$ −66.0 (*c* 1.3, CH_3OH); R_f 0.6 ($CHCl_3$/CH_3OH 95:5); δ_H (500 MHz, $CDCl_3$) 8.53 (1H, s), 7.51 (1H, d, *J* 8.5), 7.21 (1H, t, *J* 2.5), 6.90 (1H, d, *J* 2.0), 6.79 (1H, dd, *J* 2.5 and 9.0), 6.48 (1H, t, *J* 2.0), 6.24 (1H, s, NH), 4.16 (1H, t, *J* 5.0), 4.08 (1H, dd, *J* 4.5 and 9.0), 3.95 (1H, dd, *J* 6.5 and 9.5), 2.95 (1H, dd, *J* 2.0 and 11.5), 2.76–2.64 (2H, m), 2.4 (1H, dd, *J* 5.0 and 13.5), 2.28 (1H, dd, *J* 3.0 and 12.0), 1.92–1.40 (11H, m), 1.37 (9H, s), 1.34–1.21 (3H, m); δ_C (125 MHz, $CDCl_3$) 174.0, 155.0, 136.4, 123.4, 122.5, 121.1, 110.1, 102.1, 95.9, 70.9, 70.2, 68.3, 59.5, 58.5, 50.7, 35.7, 33.1, 30.8, 30.6, 28.6, 26.1, 25.7, 20.5. IR (cm^{-1}) 3311, 2925, 1652, 1365. Anal. Calcd for $C_{25}H_{37}N_3O_3$: C, 70.22; H, 8.72%. Found: C, 70.20; H, 8.71.

4.4. (+)-(*R*)-1-(1*H*-Indol-5-yloxy)-3-(isobutylamino)-propan-2-ol (9)

i-BuNH_2 (1.12 g, 1.48 mmol) was added to a stirred solution of compound **4** (0.287 g, 1.38 mmol) in *i*-PrOH (30 mL) at room temperature for 26 h. Then solvent was removed under reduced pressure and the crude was purified by column chromatography on silica gel ($CHCl_3$/CH_3OH 9:1) affording compound **9** as a colourless thick oil (0.358 g, 99%). $[\alpha]_D^{20}$ +6.5 (*c* 1.3, CH_3OH); R_f 0.5 ($CHCl_3$/CH_3OH 9:1); δ_H (500 MHz, $CDCl_3$) 8.66 (1H, s), 7.25–7.10 (3H, m), 6.85 (1H, dd, *J* 1.5 and 8.5), 6.45 (1H, s), 4.22–4.18 (1H, m), 4.02–3.97 (2H, m), 3.72–3.68 (2H, m), 2.87 (2H, d, *J* 7.0), 1.85–1.80 (1H, m), 0.94 (3H, d, *J* 3.5), 0.93 (3H, d, *J* 3.5); δ_C (125 MHz, $CDCl_3$) 152.9, 131.2, 128.2, 125.1, 112.4, 111.7, 103.6, 101.9, 71.3, 67.9, 57.4, 51.8, 27.7, 20.4. IR (cm^{-1}) 3402, 3313, 3050, 2958, 1455, 1159. Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45%. Found: C, 68.69; H, 8.43.

4.5. Synthesis of arylsulfonamides starting from compound 9: general procedure

Dry triethylamine (0.14 mL, 1.01 mmol) and the opportune arylsulfonyl chloride (0.93 mmol) were added to a solution of stirred compound **9** (0.206 g, 0.78 mmol) in dry CH_2Cl_2 (40 mL) at room temperature under argon atmosphere. After about 24 h (TLC control in $CHCl_3$/CH_3OH 99:1) the reaction mixture was quenched by adding a 5% solution of H_2SO_4 and extracted by CH_2Cl_2. The organic layer was washed with a $NaHCO_3$ (saturated aqueous solution) and brine, then it was dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography on silica gel ($CHCl_3$/CH_3OH 99:1).

*4.5.1. (+)-(R)-N-[3-(1H-Indol-5-yloxy)-2-hydroxypropyl]-N-isobutyl-4-nitrobenzenesulfonamide (**10**)*

Compound **10** was isolated as a yellow solid (0.279 g, 80%). Mp 135 °C; $[\alpha]_D^{20}$ +18.0 (*c* 0.8, $CHCl_3$); R_f 0.7 ($CHCl_3$/CH_3OH 99:1); δ_H (500 MHz, $CDCl_3$) 8.29 (1H, d, *J* 8.5), 8.16 (1H, s), 7.99 (2H, d, *J* 8.5), 7.27 (1H, d, *J* 7.0), 7.20 (1H, d, *J* 2.5), 7.07 (1H, s), 6.80 (1H, dd, *J* 1.5 and 8.5), 6.47 (1H, s), 4.22–4.18 (1H, m), 4.00–3.99 (2H, m), 3.42–3.38 (2H, m), 3.09–3.05 (2H, m), 2.86 (2H, d, *J* 4.5), 2.01–1.98 (1H, m), 0.92 (3H, d, *J* 2.5), 0.90 (3H, d, *J* 2.5); δ_C (125 MHz, $CDCl_3$) 152.6, 149.9, 145.1, 131.3, 128.5, 128.3, 124.0, 112.3, 111.8, 103.8, 102.4, 70.2, 68.8, 57.4, 51.8, 26.7, 19.9. IR (cm^{-1}) 3417, 3102, 2961, 1529, 1349, 1159. Anal. Calcd for $C_{21}H_{25}N_3O_6S$: C, 56.36; H, 5.63%. Found: C, 56.38; H, 5.61.

*4.5.2. (+)-(R)-N-[3-(1H-Indol-5-yloxy)-2-hydroxypropyl]-N-isobutyl-3,4-dimethoxybenzenesulfonamide (**11**)*

Compound **11** was isolated as a white solid (0.34 g, 94%). Mp 118 °C; $[\alpha]_D^{20}$ +4.1 (*c* 1.6, $CHCl_3$); R_f 0.6 ($CHCl_3$/CH_3OH 99:1); δ_H (500 MHz, $CDCl_3$) 8.14 (1H, s), 7.45 (1H, dd, *J* 1.5 and 8.0), 7.29–7.26 (2H, m), 7.19 (1H, d, *J* 2.5), 7.09 (1H, s), 6.93 (1H, d, *J* 8.5), 6.83 (1H, dd, *J* 2.0 and 8.5), 6.47 (1H, t, *J* 1.0), 4.26–4.22 (1H, m), 4.06–3.99 (2H, m), 3.93 (3H, s), 3.91 (3H, s), 3.33–3.21 (2H, m), 3.04–2.92 (2H, m), 1.98–1.96 (1H, m), 0.94 (3H, d, *J* 8.5), 0.90 (3H, d, *J* 8.5); δ_C (125 MHz, $CDCl_3$) 152.8, 152.6, 149.1, 131.3, 130.5, 128.3, 125.1, 121.3, 112.4, 111.7, 110.6, 109.9, 103.7, 102.4, 70.3, 69.2, 58.3, 56.2, 56.0, 52.7, 27.0, 20.0. IR (cm^{-1}) 3390, 2954, 1509, 1262, 1137. Anal. Calcd for $C_{22}H_{30}N_2O_6S$: C, 59.72; H, 6.54%. Found: C, 59.70; H, 6.51.

4.6. (+)-(*R*)-4-Amino-*N*-[3-(1*H*-indol-5-yloxy)-2-hydroxypropyl]-*N*-isobutyl-benzenesulfonamide (12)

Compound **15** (0.1041 g, 0.23 mmol) was added to a suspension of 10% Pd/C (14 mg) in ethyl acetate (20 mL) under hydrogen atmosphere. After 28 h the reaction mixture was filtered on a plate of Celite, concentrated under vacuo and purified by column chromatography on silica gel ($CHCl_3$/CH_3OH 95:5) to afford compound **12** as a violet thick oil (0.071 g, 74%). $[\alpha]_D^{20}$ +12.0 (*c* 1, CH_3OH); R_f 0.3 ($CHCl_3$/CH_3OH 95:5); δ_H (500 MHz, CD_3OD) 7.64 (2H, d, *J* 9.0), 7.26 (1H, d, *J* 8.5), 7.18 (1H, d, *J* 3.0), 7.06 (1H, d, *J* 2.5), 6.99 (1H, d, *J* 9.0), 6.79 (1H, dd, *J* 2.0 and 9.0), 6.36 (1H, d, *J* 2.5), 4.18–4.14 (1H, m), 4.00

(1H, dd, *J* 4.0 and 10.0), 3.94 (1H, dd, *J* 5.0 and 9.5), 3.42 (1H, dd, *J* 4.5 and 15.0), 3.11 (1H, dd, *J* 7.0 and 14.5), 2.96 (1H, dd, *J* 7.5 and 13.5), 2.88 (1H, dd, *J* 7.5 and 13.5), 2.01–1.97 (1H, m), 0.93 (3H, d, *J* 3.0), 0.91 (3H, d, *J* 3.0); δ_C (125 MHz, CD_3OD) 157.1, 154.1, 133.1, 129.8, 126.2, 114.5, 113.2, 112.9, 112.7, 104.4, 102.2, 71.9, 70.3, 59.1, 53.1, 28.0, 20.5. IR (cm^{-1}) 3465, 3312, 3065, 2954, 1509, 1262, 1137. Anal. Calcd for $C_{21}H_{27}N_3O_4S$: C, 60.41; H, 6.52%. Found: C, 60.39; H, 6.53.

4.7. (−)-(3*S*,4a*S*,8a*S*)-*N*-*tert*-Butyl-2-[(*R*)-2,3-dihydroxypropyl]decahydroisoquinoline-3-carboxamide (13)

PHIQ (1.1442 g, 4.8 mmol) was added to a stirred solution of (*S*)-(−)-glicydol **1** (0.2922 g, 4 mmol) in *i*-PrOH (45 mL), at room temperature for about 34 h until complete disappearance of epoxide (TLC control, EtOAc). Evaporation of the solvent and crystallization (EtOAc/hexane) afforded compound **13** (1.2 g, 96%) as a white solid. Mp 166–168 °C; $[\alpha]_D^{20}$ −142.0 (*c* 1, $CHCl_3$); R_f 0.4 (EtOAc); δ_H (500 MHz, $CDCl_3$) 6.04 (1H, s), 3.83 (2H, d, *J* 9.0), 3.63 (1H, dd, *J* 4.0 and 11.5), 2.82 (1H, d, *J* 11.0), 2.58 (1H, d, *J* 10.0), 2.52 (1H, dd, *J* 9.5 and 12.5), 2.24 (2H, dt, *J* 4.5 and 12.5), 1.97–1.59 (4H, m), 1.53–1.32 (6H, m), 1.30 (9H, s), 1.28–1.20 (2H, m); δ_C (125 MHz, $CDCl_3$) 174.0, 70.2, 68.7, 64.7, 59.1, 58.2, 51.2, 35.8, 33.3, 30.8, 30.8, 28.6, 26.1, 25.5, 20.3. IR (cm^{-1}) 3400, 2954, 1680, 1429, 1262, 1137. Anal. Calcd for $C_{17}H_{32}N_2O_3$: C, 65.35; H, 10.32%. Found: C, 65.32; H, 10.34.

4.8. (−)-(*R*)-3-[(3*S*,4a*S*,8a*S*)-3-(*tert*-Butylcarbamoyl)-octahydroisoquinolin-2(1*H*)-yl]-2-hydroxypropyl 4-methylbenzenesulfonate (14)

Dry pyridine (0.284 mL, 3.49 mmol) and tosyl chloride (0.666 g, 3.49 mmol) were added to a stirred solution of compound **13** (0.992 g, 3.17 mmol) in dry CH_2Cl_2 (43 mL) at room temperature. The mixture was stirred in argon atmosphere for 20 h, then it was washed with diluted hydrochloric acid (0.1 M, 20 mL), with a saturated aqueous solution of $NaHCO_3$ and finally with brine. The organic layer was dried and evaporated under reduced pressure to leave a crude purified by crystallization (Et_2O/hexane). Compound **14** was obtained as a pink solid (0.666 g, 45%). Mp 110–111 °C; $[\alpha]_D^{20}$ −34.0 (*c* 1.14, $CHCl_3$); R_f 0.5 (petroleum ether/EtOAc 1:1); δ_H (500 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.5), 7.34 (2H, d, *J* 8.0), 5.97 (1H, s), 4.57–4.43 (2H, m), 4.09 (1H, dd, *J* 8.0 and 12.5), 3.94 (1H, t, *J* 9.5), 3.86 (1H, dd, *J* 9.0 and 12.0), 2.43 (3H, s), 2.78–2.53 (3H, m), 2.29–2.15 (3H, m), 1.84–1.35 (6H, m), 1.30 (9H, s), 1.28–1.15 (4H, m); δ_C (125 MHz, $CDCl_3$) 167.5, 144.9, 132.4, 129.8, 127.9, 71.9, 69.9, 67.1, 57.6, 51.9, 50.8, 35.6, 32.9, 31.5, 30.5, 28.5, 26.0, 25.3, 21.5, 21.2. Anal. Calcd for $C_{24}H_{38}N_2O_5S$: C, 61.77; H, 8.21%. Found: C, 61.73; H, 8.24.

4.9. (3*S*,4a*S*,8a*S*)-*N*-*tert*-Butyl-2-[(*R*)-oxiran-2-yl methyl]decahydroisoquinoline-3-carboxamide (15)

Potassium carbonate was added to a stirred solution of compound **14** (0.208 g, 0.45 mmol) in methanol (26 mL) at room temperature. After disappearance of the starting material, the reaction was quenched by adding ammonium chloride (saturated aqueous solution), then extracted with diethyl ether and washed with brine. The combined extracts were dried over Na_2SO_4 and evaporated under reduced pressure to give the crude **15** (0.107 g): this compound was used in subsequent reaction without any purification. R_f 0.6 (petroleum ether/EtOAc 3:2); δ_H (500 MHz, $CDCl_3$) 6.61 (1H, s), 3.01–2.57 (8H, m), 1.75–1.46 (10H, m), 1.30 (9H, s).

4.10. Ring opening of epoxide 15: general procedure

Aminoindole (0.0285 g, 0.22 mmol) was added to a stirred solution of the crude epoxide **15** (0.0534 g, 0.18 mmol) in *i*-PrOH (3 mL). The mixture was heated at reflux temperature until disappearance of epoxide (about 10 h, TLC control, $CHCl_3/CH_3OH$ 9:1). After cooling the solvent was removed under reduced pressure and the crude was purified by column chromatography on silica gel (eluent: $CHCl_3/CH_3OH$ 9:1).

4.10.1. (−)-(3*S*,4a*S*,8a*S*)-2-[(*S*)-3-(1*H*-Indol-4-ylamino)-2-hydroxypropyl]-*N*-tert-butyl-decahydroisoquinoline-3-carboxamide (*16*)

Compound **16** was isolated as a violet thick oil (0.0334 g, 35% from compound **14**). $[\alpha]_D^{20}$ −96.4 (*c* 1.4, $CHCl_3$); R_f 0.3 ($CHCl_3/CH_3OH$ 9:1); δ_H (500 MHz, $CDCl_3$) 8.68 (1H, s), 7.10 (1H, t, *J* 2.5), 7.01 (1H, t, *J* 7.5), 6.87 (1H, d, *J* 8.0), 6.46–6.36 (3H, m), 3.84–2.57 (7H, m), 2.15 (1H, dd, *J* 3.0 and 11.5), 1.99 (1H, d, *J* 12.0), 1.88–1.41 (9H, m), 1.36 (9H, s), 1.33–1.24 (4H, m); δ_C (125 MHz, $CDCl_3$) 173.7, 139.1, 136.8, 122.8, 122.5, 117.3, 103.9, 102.3, 98.4, 69.7, 65.7, 64.6, 58.1, 57.8, 50.8, 35.7, 33.1, 30.8, 30.7, 28.5, 26.2, 25.4, 20.1. IR (cm^{-1}) 3286, 3100, 2944, 1659, 1368, 1262, 1140. Anal. Calcd for $C_{25}H_{38}N_4O_2$: C, 70.39; H, 8.98%. Found: C, 70.41; H, 8.95.

4.10.2. (−)-(3*S*,4a*S*,8a*S*)-2-[(*S*)-3-(1*H*-Indol-5-ylamino)-2-hydroxypropyl]-*N*-tert-butyl-decahydroisoquinoline-3-carboxamide (*17*)

Compound **17** was isolated as a violet solid (0.029 g, 30% from compound **14**). Mp 128 °C; $[\alpha]_D^{20}$ −87.3 (*c* 1.1, $CHCl_3$); R_f 0.3 ($CHCl_3/CH_3OH$ 9:1); δ_H (500 MHz, $CDCl_3$) 8.24 (1H, s), 7.18 (1H, d, *J* 8.5), 7.11 (1H, d, *J* 3.0), 6.94 (1H, s), 6.66–6.64 (1H, m), 6.35 (1H, s), 6.04 (1H, s), 3.81–3.62 (3H, m), 3.81–3.37 (7H, m), 2.77 (1H, d, *J* 11.0), 2.55–2.47 (2H, m), 2.21–2.15 (2H, m), 1.92–1.37 (5H, m), 1.35 (9H, s), 1.34–1.20 (2H, m); δ_C (125 MHz, $CDCl_3$) 174.1, 139.2, 130.7, 128.7, 124.7, 112.8, 111.5, 105.5, 101.3, 70.2, 65.6, 64.7, 59.1, 58.2, 51.1, 35.7, 33.2, 30.8, 30.7, 28.6, 26.1, 25.5, 20.2. IR (cm^{-1}) 3281, 3090, 2950, 1642, 1388, 1256, 1123. Anal. Calcd for $C_{25}H_{38}N_4O_2$: C, 70.39; H, 8.98%. Found: C, 70.37; H, 8.96.

4.11. 4-Nitrophenyl 1*H*-indol-5-ylcarbamate (20)

Dry triethylamine (0.54 mL, 3.9 mmol) and compound **18** (0.7860 g, 3.9 mmol) were added to a stirred solution of **19** (0.396 g, 3 mmol) in dry CH_2Cl_2 (30 mL) at room temperature and in argon atmosphere. After 2 h a TLC control (CH_2Cl_2/EtOAc 99:1) showed the disappearance of **19** and the reaction was quenched by adding water (15 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under vacuo affording compound **20** (0.862 g, 97%) as a yellow solid. This compound was used as crude for the following reaction. R_f 0.6 (CH_2Cl_2/EtOAc 99:1).

4.12. (+)-(*R*)-Oxiran-2-ylmethyl 1*H*-indol-5-ylcarbamate (21)

Dry triethylamine (0.7 mL, 5 mmol) and *S*-glycidol **1** (0.279 g, 3.8 mmol) were added to a stirred solution of compound **20** (0.8621 g, 2.9 mmol) in dry CH_2Cl_2 (30 mL) at room temperature and under argon atmosphere. After the disappearance of glycidol **1** (about 10 h by TLC control, CH_2Cl_2/EtOAc 8:2) the mixture was diluted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under vacuo. The crude was purified by column chromatography (CH_2Cl_2/EtOAc 8:2) affording compound **21** as a yellow solid (0.606 g, 90%). Mp 109 °C; $[\alpha]_D^{20}$ +7.0 (*c* 1, $CHCl_3$); R_f 0.3 (CH_2Cl_2/EtOAc 8:2); δ_H (500 MHz, $CDCl_3$) 8.18 (1H s), 7.69 (1H, s), 7.33–7.13 (3H, m), 6.70 (1H, s), 6.51 (1H, d, *J* 2.5), 4.56 (1H, dd, *J* 3.0 and 12.5), 4.01 (1H, dd, *J* 5.5 and 11.0), 3.30–2.71 (3H, m); δ_C (125 MHz, $CDCl_3$) 153.7, 133.0, 130.0, 128.1, 125.3, 115.7, 111.3, 111.1, 102.7, 65.5, 49.8, 44.7. Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21%. Found: C, 62.09; H, 5.24.

4.13. (−)-(*R*)-3-[(3*S*,4a*S*,8a*S*)-3-(*tert*-Butylcarbamoyl)-octahydroisoquinolin-2(1*H*)-yl]-2-hydroxypropyl - 1*H*-indol-5-ylcarbamate (22)

PHIQ (0.040 g, 0.19 mmol) was added to a stirred solution of compound **21** (0.030 g, 0.13 mmol) in *i*-PrOH (5 mL) at room temperature. After about 28 h the mixture was concentrated in vacuo and the crude was purified by column chromatography ($CHCl_3$/CH_3OH 9:1) affording compound **22** as a brown powder (0.046 g, 75%). Mp 139 °C; $[\alpha]_D^{20}$ +42.0 (*c* 1.2, CH_3OH); R_f 0.6 ($CHCl_3$/CH_3OH 9:1); δ_H (500 MHz, $CDCl_3$) 8.31 (1H, s), 7.68 (1H, s), 7.31 (1H, d, *J* 9.0), 7.21 (1H, t, *J* 2.5), 7.11 (1H, d, *J* 8.0), 6.85 (1H, br s), 6.47 (1H, t, *J* 2.5), 6.50 (1H, s), 6.16 (1H, s), 4.39 (1H, d, *J* 8.0), 4.08–4.12 (2H, m), 2.92 (1H, d, *J* 11.5), 2.63 (1H, t, *J* 5.0), 2.28 (2H, t, *J* 12.0), 2.22–1.39 (11H, m), 1.35 (9H, s), 1.22–1.18 (3H, m); δ_C (125 MHz, $CDCl_3$) 173.7, 154.4, 133.1, 130.0, 129.7, 128.1, 125.2, 115.7, 111.3, 102.6, 70.1, 68.1, 59.4, 58.8, 50.8, 35.7, 33.0, 31.9, 30.7, 30.6, 29.7, 29.3, 28.7, 26.1, 25.7, 20.6. IR (cm^{-1}) 3410, 3280, 3046, 2939, 1730, 1642, 1308, 1245, 1128. Anal. Calcd for $C_{26}H_{38}N_4O_4$: C, 66.36; H, 8.14%. Found: C, 66.39; H, 7.15.

4.14. (+)-(*R*)-2-Hydroxy-3-(isobutylamino)propyl 1*H*-indol-5-ylcarbamate (23)

i-$BuNH_2$ (0.3 mL, 2.9 mmol) was added to a stirred solution of compound **21** (0.24 g, 0.96 mmol) in *i*-PrOH (24 mL) at room temperature. After 34 h the solvent was evaporated in vacuo affording product **23** (0.270 g, 92%) as a yellow thick oil. $[\alpha]_D^{20}$ +4.9 (*c* 1.4, CH_3OH); R_f 0.6 ($CHCl_3$/CH_3OH 7:3); δ_H (500 MHz, $CDCl_3$) 8.45 (1H, s), 7.66 (1H, s), 7.27–7.04 (3H, m), 6.46 (1H, s), 4.28–4.25 (1H, m), 4.13–3.94 (2H, m), 2.75–2.41 (4H, m), 1.75–1.70 (1H, m), 0.91 (3H, d, *J* 3.0), 0.89 (3H, d, *J* 3.0); δ_C (125 MHz, $CDCl_3$) 154.4, 133.0, 130.1, 128.0, 125.3, 125.1, 115.5, 111.3, 102.6, 67.9, 67.2, 57.6, 51.3, 28.3, 20.5. IR (cm^{-1}) 3316, 2958, 1704, 1557, 1481, 1237, 1063. Anal. Calcd for $C_{16}H_{23}N_3O_3$: C, 62.93; H, 7.59%. Found: C, 62.89; H, 7.55.

4.15. (+)-(*R*)-2-Hydroxy-3-(*N*-isobutyl-4-nitrophenylsulfonamido)propyl 1*H*-indol-5-ylcarbamate (24)

Dry triethylamine (0.04 mL, 0.3 mmol) and 4-nitrobenzene-1-sulfonyl chloride (0.059 g, 0.3 mmol) were added to a stirred solution of compound **23** (0.075 g, 0.23 mmol) in dry CH_2Cl_2 at room temperature under argon atmosphere. After 26 h the reaction was quenched by adding 5% H_2SO_4 solution. Hence the mixture was extracted with CH_2Cl_2 and the organic layer washed with a saturated aqueous solution of $NaHCO_3$ and brine. After drying over Na_2SO_4 the solvent was evaporated in vacuo. The crude was purified by column chromatography on silica gel ($CHCl_3$/CH_3OH 9:1) affording compound **24** as a yellow thick oil (0.10 g, 90%). $[\alpha]_D^{20}$ +8.8 (*c* 0.8, $CHCl_3$); R_f 0.6 ($CHCl_3$/CH_3OH 99:1); δ_H (500 MHz, $CDCl_3$) 8.38 (1H, s), 8.24 (2H, br s), 7.95 (2H, br s), 7.63 (1H, s), 7.28–7.00 (4H, m), 6.46 (1H, s), 4.27 (1H, dd, *J* 5.0 and 11.5), 4.18–4.09 (2H, m), 3.27–3.01 (4H, m), 1.95–1.91 (1H, m), 0.92 (3H, d, *J* 3.0), 0.89 (3H, d, *J* 3.0); δ_C (125 MHz, $CDCl_3$) 154.2, 149.9, 144.8, 133.1, 129.8, 128.6, 128.4, 128.1, 125.5, 124.3, 115.6, 111.5, 102.4, 68.8, 66.8, 57.4, 51.6, 26.8, 19.9. IR (cm^{-1}) 3410, 3071, 2957, 1709, 1535, 1346, 1161. Anal. Calcd for $C_{22}H_{26}N_4O_7S$: C, 53.87; H, 5.34%. Found: C, 53.82; H, 5.36.

4.16. Protease inhibition assay

Biological assays were performed measuring the increase in the fluorescence due to the Abz-NF*-6 (K_m=37±8 μM; V_{max}=690 ±90 nmol min^{-1} (mg protease)$^{-1}$; K_{cat}=0.29±0.03 S^{-1}; K_{cat}/K_m=7.8±0.3 mM^{-1}) substrate's hydrolysis by a commercially available HIV-PR, at a λ_{exc} and at a λ_{em} of 325 nm and 420 nm, respectively; 114 μL of the fluorogenic substrate (with a concentration of 53 μM, obtained diluting 10 μL of a stock solution containing 10 mg mL^{-1} of substrate in DMSO with 1.99 mL of pH 5.5 MES buffer) were put in a thermostated cuvette (25 °C) with 75 μL of MES buffer (containing 100 mM 2-[*N*-morpholino]ethansulfonic acid (MES)/NaOH, pH 5.5; 400 mM NaCl; 1 mM ethylendiaminotetracetic acid (EDTA); 1 mM dithiotreitol (DTT)), obtaining a final concentration of 30 μM and starting measuring the fluorescence. After 1.5 min the HIV-PR was added (11 μL of a solution obtained diluting 1:100, with a MES/BSA buffer, a stock solution of 0.4 mg mL^{-1} of HIV-PR in a 10 mM sodium phosphate pH=6.5, 1 mM EDTA/10% glycerol/0.05% mercaptoethanol/50–100 mM NaCl), obtaining an enzymatic concentration of 10 nm. The increase in the fluorescence was then measured; after 1 min the inhibitor containing solution was added (2 μL) and the fluorescence measured for other additional 10 min. For each inhibitor, a stock solution in DMSO was prepared by weight, then diluted it with DMSO or MES buffer. The amount of the inhibition was evaluated comparing the initial rates, extrapolated from the linear parts of the curves obtained plotting fluorescence versus time, of the catalyzed reaction in the presence of different inhibitor's concentration. IC_{50} values were obtained simply plotting the different slopes versus inhibitor's concentrations (expressed using a logarithmical scale) and interpolating the value corresponding to the 50% of inhibition.

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