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# Computer-Assisted Design, Synthesis and Biological Evaluation of Novel Pyrrolyl Heteroaryl Sulfones Targeted at HIV-1 Reverse Transcriptase as Non-Nucleoside Inhibitors

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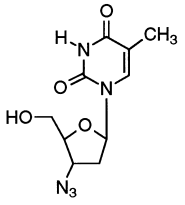
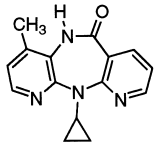
**Abstract**—Three pyrrolyl heteroaryl sulfones (ethyl 1-[(1*H*-benzimidazol-2(3*H*)one-5-yl)sulfonyl]-1*H*-pyrrole-2-carboxylate, ethyl 1-[(1*H*-benzimidazol-5(6)-yl)sulfonyl]-1*H*-pyrrole-2-carboxylate and ethyl 1-[(1*H*-benzotriazol-5(6)-yl)sulfonyl]-1*H*-pyrrole-2-carboxylate) were designed as novel HIV-1 reverse transcriptase non-nucleoside inhibitors using structure-based computational methods. Although these compounds were inactive in the cell-based assay, they inhibited the target enzyme with micromolar potency ($IC_{50}$s = 2 μM, 3 μM and 9 μM, respectively). 

## Introduction

Reverse transcriptase (RT) is a key enzyme in the half life of the human immuno-deficiency virus (HIV) which catalyzes the conversion of RNA retroviral genome into proviral DNA.[1,2] RT inhibitors can be classified into two categories: nucleoside and non-nucleoside compounds, their prototypes being zidovudine (**1**)[3] and nevirapine (**2**),[4] respectively, both currently employed in the treatment of AIDS.[5] The former are converted intracellularly into triphosphates derivatives and act as DNA chain-terminating analogues of the natural deoxy-nucleoside triphosphates; the latter directly inhibit RT, non-competitively, upon binding to an allosteric site located approximately 10 Å from the polymerase catalytic site.[6] While nucleoside inhibitors block RT of either type-1 and type-2 viruses (HIV-1 and HIV-2), non-nucleoside compounds inhibit selectively RT from HIV-1.



**1** ( zidovudine)



**2** (nevirapine)

In 1996 we described pyrrolyl aryl sulfones (PASs) as a new class of RT non-nucleoside inhibitors.[7] The most potent inhibitor of that series, compound **3** ($EC_{50}$ = 0.14 μM, $IC_{50}$ = 0.4 μM and SI > 1429), was more recently taken as a lead for a computer-assisted optimization project.[9] Using the three-dimensional structure of RT co-crystallized with the α-APA derivative R95845,[8] we developed a model of RT/**3** complex (Fig. 1) which guided the design of novel PASs with improved inhibitory activity.[9] Among the new inhibitors synthesized and tested, compound **4** was the most active with $EC_{50}$ = 0.045 μM, $IC_{50}$ = 0.05 μM and SI = 5333. Compared with the lead **3**, these values represented a 3- and 8-fold

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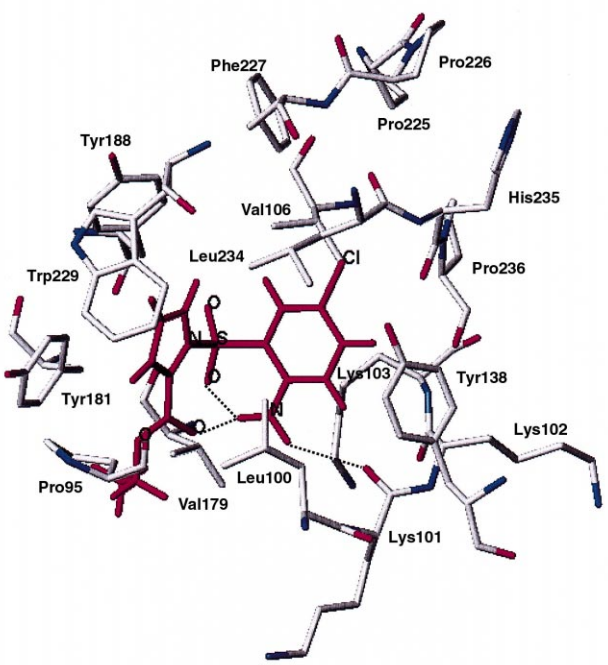



**Figure 1.** Compound **3** docked into the RT binding site of non-nucleoside inhibitors. Only a subset of residues closest to the ligand is displayed for the sake of clarity.

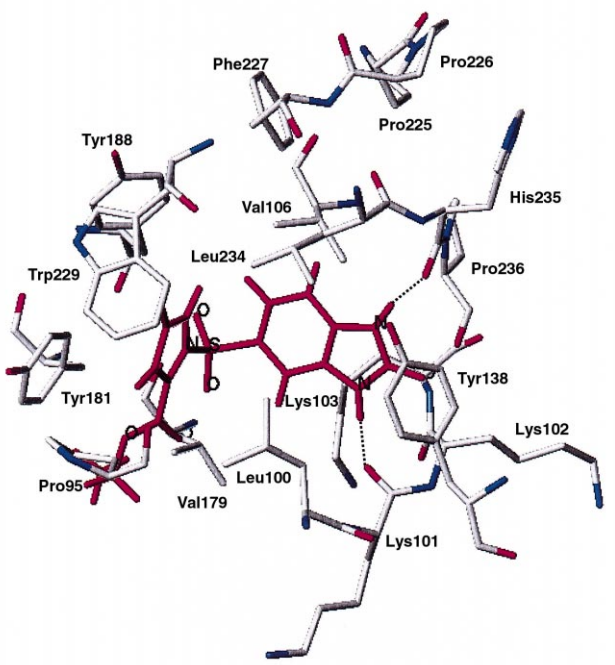
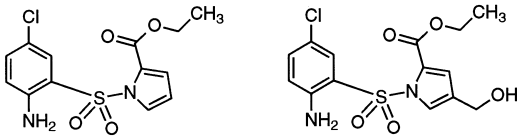



**Figure 2.** Theoretical model of the RT/**5** complex. Two hydrogen bonds are hypothesized to occur betwen the ureidic NH groups of the docked molecule and the carbonyl oxygens of Lys101 and His235. Only a subset of residues of the non-nucleoside binding site closest to the ligand is displayed.

improvement of the in vitro antiviral and RT inhibitory activity, respectively, together with the highest selectivity achieved in the PAS series.



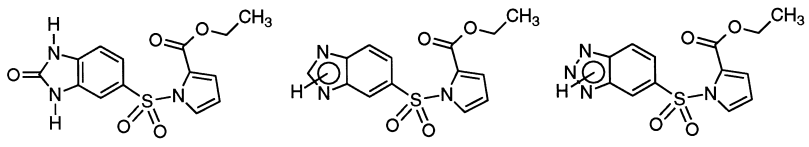

**3** **4**

As a further development of our strucuture-based design strategy we sought novel leads targeted at the HIV-1 RT as non-nucleoside inhibitors structurally related to compound **3**. This problem was approached by replacing the pharmacophoric *p*-chloroaniline moiety, common to all potent PAS derivatives, with a heteroaromatic system containing at least one hydrogen bond donor group for the Lys101 carbonyl. According to our theoretical model of RT/PAS interaction, a hydrogen bond between the $NH_2$ of **3** and the Lys101 oxygen (Fig. 1) was in fact mandatory for high inhibitory activity.[9]

The docking of the *o*-phenylenurea derivative **5** (Fig. 2) brought out the possibility to retain the NH···O=C (Lys101) hydrogen bond and to engage an additional hydrogen bond with the His235 carbonyl. Both hydrogen bonds were expected to occur via the two ureidic NH groups. The benzimidazole and benzotriazole derivatives **6** and **7** were also proposed for synthesis and biological testing. We reasoned that these compounds might 'choose' the energetically most favorable hydrogen bond between those feasible with Lys101 and His235 carbonyls by simply switching from one tautomeric form to another (see Fig. 3).

## Chemistry

The synthetic routes for the novel pyrrolyl heteroaryl sulfones **5**, **6** and **7** are shown in Scheme 1. Ethyl 1-[(4-fluoro-3-nitrophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (**8**) was prepared by adding a suspension of the potassium salt of ethyl 1*H*-pyrrole-2-carboxylate[10] to a solution of 4-fluoro-3-nitrobenzenesulfonyl chloride.[11] Treatment of **8** with an excess of aqueous ammonium hydroxide at room temperature furnished ethyl 1-[(4-amino-3-nitrophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (**9**) which was reduced to the diamino derivative **10** with powdered iron in glacial acetic acid. Compound **10** was transformed into ethyl 1-[(1*H*-benzimidazol-2(3*H*)one-5-yl) sulfonyl]-1*H*-pyrrole-2-carboxylate (**5**) by reaction with bis(trichloromethyl) carbonate (triphosgene)[12] in the presence of triethylamine, into ethyl 1-[(1*H*-benzimidazol-5(6)-yl)sulfonyl]-1*H*-pyrrole-2-carboxylate (**6**) by heating




**5** **6** **7**

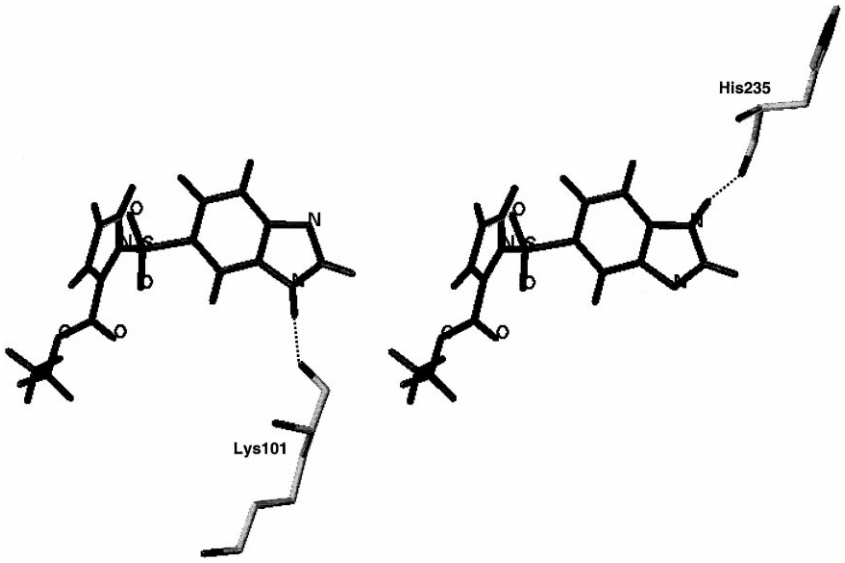
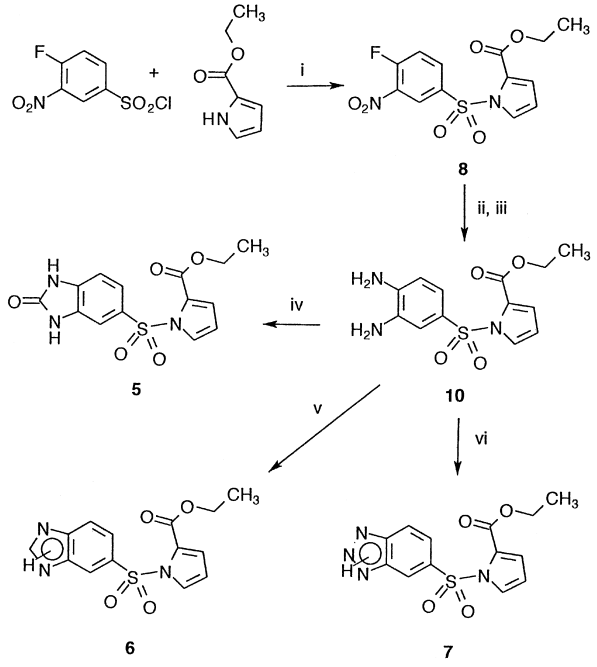



**Figure 3.** Theoretical model of the RT/**6** complex. Two tautomeric forms of the benzimidazole derivative **6** were considered differing in the position of the NH group. This latter donates a hydrogen bond to the carbonyl oxygen of Lys101 (tautomer on the left) or His235 (tautomer on the right). Only residues Lys101 and His 235 of the non-nucleoside binding site are displayed.




**Scheme 1.** Reagents and reaction conditions: (i) *t*-BuOK 18-C-6, THF, r.t., 3.5 h; (ii) 30% $NH_4OH$, dioxane, r.t., 30 min.; (iii) Fe, $CH_3COOH$, 60 °C, 2 h; (iv) $CO(OCCl_3)_2$, $(C_2H_5)_3N$, r.t., 24 h; (v) HCOOH, 100 °C, 2 h; (vi) $NaNO_2$, $CH_3COOH$, r.t., 1 h.

with formic acid, and into ethyl 1-[(1*H*-benzotriazol-5(6)-yl)sulfonyl]-1*H*-pyrrole-2-carboxylate (**7**) by reacting with sodium nitrite in aqueous acetic acid.

## Results and Discussion

Table 1 summarizes the results of the biological evaluations of compounds **5**–**7**, expressed as $CC_{50}$ (cytotoxicity), $EC_{50}$ (antiproliferative activity), SI (selectivity index) and $IC_{50}$ (inhibitory activity against wild type recombinant RT) values. Data relative to nevirapine and **3** are also reported as references.

**Table 1.** Cytotoxicity, anti-HIV-1 activity in MT-4 cells, selectivity index and RT inhibitory activity values[a]

| Compound | $CC_{50}$[b] | $EC_{50}$[c] | SI[d] | $IC_{50}$[e] |
|---|---|---|---|---|
| **5** | 160 | 21 | 7.6 | 2 |
| **6** | 40 | >40 | — | 3 |
| **7** | 200 | >2000 | — | 9 |
| **3** | >200 | 0.14 | >1429 | 0.4 |
| Nevirapine | >200 | 0.35 | >571 | 0.6 |

[a]Data represent mean values for three separate experiments.Variation among triplicate samples was less than 15%.
[b]Dose (μM) required to reduce the viability of mock-infected cells by 50% as determined by the MTT method.
[c]Dose (μM) required to achieve 50% protection of MT-4 cells from HIV-1 induced cytopathicity as determined by the MTT method.
[d]Selectivity index expressed as $CC_{50}/EC_{50}$ ratio.
[e]Dose (μM) required to inhibit the HIV-1 RT activity by 50%.

The compounds designed as potential anti-RT new leads were found devoid of activity in the cell-based assay but moderately active when tested against the enzyme ($IC_{50}$s = 2 μM, 3 μM and 9 μM, respectively). The lower potency of **5**–**7**, compared with **3**, might depend on intramolecular hydrogen bonds stabilizing the RT-bound conformation of **3** which are absent in **5**–**7**. Particularly, the docked conformation of **3** features two hydrogen bonds donated by the $NH_2$ group to sulfone and ester oxygens (see Fig. 1). Additional reasons for the relatively low activity of the novel inhibitors might be the missing chlorine which makes van der Waals interactions in the RT/**3** complex and the partial negative charge of the non protonated nitrogen of **6** and **7** facing the negative electrostatic potential of the Lys101 or His235 carbonyl. In designing the new ligands, it was actually hoped that the favorable effects of the hydrogen bonds attributed to the virtual RT/inhibitor complexes (Figs 2 and 3) could counterbalance the above mentioned unfavorable

factors. To sum up, our structure-based design approach afforded novel HIV-1 RT non-nucleoside inhibitors characterized by micromolar potency.

## Experimental

### Chemical procedures

Melting points (mp) were determined on a Büchi 510 apparatus and are uncorrected. Infrared spectra (IR) were run on a Perkin–Elmer 1310 spectrophotometer and on a Jasco FT/DR-200 diffuse reflectance spectrophotometer. Band position and absorption ranges are given in $cm^{-1}$. Proton nuclear magnetic resonance ($^1H$ NMR) spectra were recorded on Bruker AM-200 (200 MHz) and Varian Gemini (200 MHz) FT spectrometers in the indicated solvent. Chemical shifts are expressed in δ units (ppm) from tetramethylsilane. Column chromatographies were packed with alumina Merck (70–230 mesh) and silica gel Merck (70–230 mesh). Aluminum oxide TLC cards Fluka (aluminum oxide precoated aluminum cards with fluorescent indicator at 254 nM) and silica gel TLC cards Fluka (silica gel precoated aluminum cards with fluorescent indicator at 254 nM) were used for thin-layer chromatography (TLC). Developed plates were visualized by spectroline ENF 260C/F UV apparatus. Organic solutions were dried over anhydrous sodium sulfate. Concentration and evaporation of the solvent after reaction or extraction was carried out on a rotary evaporator Büchi Rotavapor operating at reduced pressure. Elemental analyses were performed by laboratories of Dr. M. Zancato, Dipartimento di Scienze Farmaceutiche, University of Padova (Italy). Analytical results were within ±0.4% of the theoretical values. Ethyl 1*H*-pyrrole-2-carboxylate[10] and 4-fluoro-3-nitrobenzenesulfonyl chloride[11] were prepared according to the literature.

**Ethyl 1-[(4-fluoro-3-nitrophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8).** To a stirred mixture of potassium *tert*-butoxide (1.34 g, 0.012 mol) and 18-crown-6 (0.28 g, 0.0011 mol) in anhydrous THF (21 mL) was added dropwise a solution of ethyl 1*H*-pyrrole-2-carboxylate (1.39 g, 0.010 mol) in the same solvent (21 mL). Stirring was maintained for 15 min. The suspension of potassium salt was cooled to 0 °C and added by small portions to a solution of 4-fluoro-3-nitrobenzenesulfonyl chloride (2.57 g, 0.010 mol) in anhydrous THF (21 mL). Reaction was stirred at room temperature for 3.5 h, then concentrated to a small volume and extracted with ethyl acetate. Organic extracts were washed with brine and dried. Removal of the solvent gave a residue which was purified on silica gel column chromatography (dichloromethane). First fractions gave traces of 4-fluoro-3-nitrobenzenesulfonyl chloride. Second fractions afforded **8** (2.2 g, 65%); thick oil. $^1H$ NMR ($CDCl_3$): δ 1.29 (t, $J=7.1$ Hz, 3H, COO $CH_2CH_3$), 4.21 (q, $J=7.1$ Hz, 2H, $COOCH_2CH_3$), 6.38 (3 line m, 1H, H4-pyrrole), 7.08 (dd, $J=1.4$ and 3.6 Hz, 1H, H3-pyrrole), 7.49 (t, $J=9.3$ Hz, 1H, H5-benzene), 7.71 (unresolved dd, 1H, H5-pyrrole), 8.32–8.43 (8 line m, 1H, H6-benzene), 8.69 ppm (dd, $J=2.5$ and 6.8 Hz, 1H, H2-benzene). IR (Nujol): ν 1710 $cm^{-1}$ (CO). Anal. $C_{13}H_{11}FN_2O_6S$ (342.29), C, H, N, F, S. Further elution with the same solvent furnished ethyl 1-{[4-(2-ethoxycarbonyl-1*H*-pyrrole-1-yl)-3 - nitrophenyl]sulfonyl} - 1*H* - pyrrole-2-carboxylate (0.14 g, 3%); mp 92–94 °C (toluene/cyclohexane). $^1H$ NMR ($CDCl_3$): δ 1.18 and 1.30 (two t, $J=7.0$ Hz, 6H, $COOCH_2CH_3$), 4.11 and 4.23 (two q, $J=7.0$ Hz, 4H, $COOCH_2CH_3$), 6.35–6.47 (m, 2H, pyrrole), 6.91 (m, 1H, pyrrole), 7.06–7.18 (m, 2H, pyrrole), 7.59 (d, $J=8.3$ Hz, 1H, H5-benzene), 7.72 (m, 1H, pyrrole), 8.39 (dd, $J=2.1$ and 8.3 Hz, 1H, H6-benzene), 8.64 ppm (d, $J=2.1$ Hz, 1H, H2-benzene). IR (Nujol): ν 1700 and 1720 $cm^{-1}$ (CO). Anal. $C_{20}H_{19}N_3O_8S$ (461.44), C, H, N, S.

**Ethyl 1-[(4-amino-3-nitrophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (9).** A solution of **8** (1.00 g, 0.0029 mol) in dioxane (10 mL) was treated at room temperature under stirring with 30% ammonium hydroxide (7.7 mL) for 30 min. Water and ethyl acetate were added by shaking. The organic layer was separated, washed with brine and dried. Removal of the solvent furnished satisfactory pure **9** (0.9 g, 91%); mp 129–130 °C (toluene/ligroin). $^1H$ NMR ($CDCl_3$): δ 1.29 (t, $J=7.2$ Hz, 3H, COO $CH_2CH_3$), 4.19 (q, $J=7.2$ Hz, 2H, $COOCH_2CH_3$), 6.30 (m, 1H, pyrrole), 6.59 (broad s, 2H, $NH_2$, disappeared on treatment with $D_2O$), 6.88 (d, $J=9.1$ Hz, 1H, H5-benzene), 7.04 (m, 1H, pyrrole), 7.68 (m, 1H, pyrrole), 8.00 (dd, $J=2.3$ and 9.1 Hz, 1H, H6-benzene), 8.79 ppm (d, $J=2.3$ Hz, 1H, H2-benzene). IR (Nujol): ν 1690 (CO), 3300 and 3440 $cm^{-1}$ ($NH_2$). Anal. $C_{13}H_{13}N_3O_6S$ (339.32), C, H, N, S.

**Ethyl 1-[(3,4-diaminophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (10).** A stirred solution of **9** (1.70 g, 0.005 mol) in glacial acetic acid (21 mL) was treated portionwise with iron powder (1.5 g) while heating at 60 °C under stirring. Reaction mixture was maintained at 60 °C for 2 h, then evaporated to dryness. The residue was mixed with ice water and extracted with ethyl acetate. The organic layers were collected, washed with brine and dried. Removal of the solvent gave a residue which was purified by column chromatography (silica gel/ethyl acetate) to yield **10** (1.0 g, 65%), mp 155–156 °C (toluene). $^1H$ NMR (DMSO-$d_6$): δ 1.20 (t, $J=7.0$ Hz, 3H, COO $CH_2CH_3$), 4.16 (q, $J=7.0$ Hz, 2H, $COOCH_2CH_3$), 4.97 (broad s, 2H, $NH_2PhNH_2$, disappeared on treatment with $D_2O$), 5.65 (broad s, 2H, $NH_2PhNH_2$, disappeared on treatment with $D_2O$), 6.34 (3 line m, 1H, H4-pyrrole), 6.57 (d, $J=8.4$ Hz, 1H, H5-benzene), 6.98 (dd, $J=1.5$ and 3.6 Hz, 1H, H3-pyrrole), 7.02 (d, J = 2.2 Hz, 1H, H2-benzene), 7.10 (dd, $J=2.0$ and 8.4 Hz, 1H, H6-benzene), 7.61 ppm (m, 1H, H5-pyrrole). IR (Nujol): ν 1705 (CO), 3270, 3350, 3420 and 3450 $cm^{-1}$ ($NH_2$). Anal. $C_{13}H_{15}N_3O_4S$ (309.34), C, H, N, S.

**Ethyl 1-[(1*H*-benzimidazol-2(3*H*)one-5-yl)sulfonyl]-1*H*-pyrrole-2-carboxylate (5).** Bis(trichloromethyl) carbonate (triphosgene) (0.15 g, 0.0005 mol) in dichloromethane (10 mL) was dropped into a solution of **10** (0.31 g, 0.0010 mol) and triethylamine (0.12 g, 0.0012 mol) in the same solvent (30 mL). Reaction was stirred at room temperature for 24 h, then diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated to dryness. The

crude residue was purified on silica gel column (ethyl acetate) to yield **5** (0.31 g, 92%); mp >237–238 °C (ethanol). $^1$H NMR (DMSO-$d_6$): δ 1.19 (t, $J$ = 7.0 Hz, 3H, COO $CH_2CH_3$), 4.15 (q, $J$ = 7.0 Hz, 2H, $COOCH_2CH_3$), 6.43 (3 line m, 1H, H4-pyrrole), 7.04 (dd, $J$ = 2.0 and 3.4 Hz, 1H, H3-pyrrole), 7.14 (d, $J$ = 8.3 Hz, 1H, H5-benzene), 7.52 (u, 1H, H2-benzene), 7.64 (dd, $J$ = 1.9 and 8.3 Hz, 1H, H6-benzene), 7.82 (dd, $J$ = 2.0 and 3.1 Hz, 1H, H5-pyrrole), 11.11 and 11.31 ppm (two broad s, 2H, NHCONH, disappeared on treatment with $D_2O$). $^{13}$C NMR (DMSO-$d_6$): δ 14.00 ($COOCH_2CH_3$), 60.52 (COO $CH_2CH_3$), 107.91, 108.37, 110.73, 121.83, 122.68, 124.43, 129.04, 129.29 and 134.62 (aromatic C), 155.23 and 158.28 (COOEt and NHCONH). FT-IR: ν 1713 and 1731 cm$^{-1}$ (CO). Anal. $C_{14}H_{13}N_3O_5S$ (335.33), C, H, N, S.

**Ethyl 1-[(1*H*-benzimidazol-5(6)-yl)sulfonyl]-1*H*-pyrrole-2-carboxylate (6).** A mixture of **10** (1.00 g, 0.0032 mol) and formic acid (98–100%, 0.21 mL) was heated at 100 °C for 2 h. After cooling the mixture was made alkaline with 10% aqueous NaOH and shaken with ethyl acetate. The organic layer was washed with brine and dried. Removal of the solvent furnished the crude product which was passed through a silica gel column (ethyl acetate) to yield **6** (1.0 g, 98%); mp 139–140 °C (toluene). $^1$H NMR (DMSO-$d_6$): δ 1.17 (t, $J$ = 7.1 Hz, 3H, $COOCH_2CH_3$), 4.14 (q, $J$ = 7.1 Hz, 2H, $COOCH_2CH_3$), 6.45 (m, 1H), 7.06 (m, 1H), 7.82 (m, 2H), 7.90 (m, 1H), 8.36 (broad, 1H), 8.55 (broad, 1H), 13.07 (broad s, 1H, NH, disappeared on treatment with $D_2O$). IR (Nujol): ν 1720 cm$^{-1}$ (CO). Anal. $C_{14}H_{13}N_3O_4S$ (319.33), C, H, N, S.

**Ethyl 1-[(1*H*-benzotriazol-5(6)-yl)sulfonyl]-1*H*-pyrrole-2-carboxylate (7).** An aqueous solution of sodium nitrite (0.45 g, 0.0066 mol, 1.5 mL) was added in one portion to a water cooled solution of **10** (1.86 g, 0.0060 mol) in 50% aqueous acetic acid (100 mL). The reaction was stirred for 1 h, then mixture was poured on crushed ice while stirring for some minutes. The solid which formed was filtered, washed with water and dried. Crude product was passed through a silica gel column (ethyl/acetate) to afford **7** (1.5 g, 78%); mp 130–131 °C (toluene/cyclohexane). $^1$H NMR ($CDCl_3$): δ 1.22 (t, $J$ = 7.1 Hz, 3H, $COOCH_2CH_3$), 4.15 (q, $J$ = 7.1 Hz, 2H, $COOCH_2CH_3$), 6.38 (3 line m, 1H, H4-pyrrole), 7.10 (dd, $J$ = 1.8 and 3.7 Hz, 1H, H3-pyrrole), 7.79 (dd, $J$ = 1.8 and 3.1 Hz, 1H, H5-pyrrole), 7.96 (m, 2H, benzene), 8.77 ppm (m, 1H, benzene). IR (Nujol): ν 1700 (CO), 3320 cm$^{-1}$ (NH). Anal. $C_{13}H_{12}N_4O_4S$ (320.32), C, H, N, S.

## Biological evaluations

Activity of the compounds against HIV-1 multiplication in acutely infected cells was based on the inhibition of virus-induced cytopathicity in MT-4 and C8166 cells, respectively. According to a previously reported procedure,[7] the number of viable cells was determined by the 3-(4,5 - dimethylthiazol - 2 - yl) - 2,5 - diphenyltetrazolium bromide (MTT) method. Cytotoxicity of the compounds was evaluated in parallel with their antiviral activity. It was based on the viability of mock-infected cells, as monitored by the MTT method. Anti-RT assays were performed as described in a previous paper.[7]

## Molecular modeling

Molecular modeling studies were performed using the SYBYL[13] software package running on a Silicon Graphics R10000 workstation. Intramolecular and intermolecular energies were calculated using the molecular mechanics Tripos force field[14] including the electrostatic contribution. Atom centered partial charges were calculated according to the Gasteiger–Hückel method.[15,16] Geometry optimizations were realized with the SYBYL/MAXIMIN2 minimizer by applying the BFGS algorithm[17] and setting a root-mean-square gradient of the forces acting on each atom at 0.05 kcal/mol Å as a convergence criterion. Model building and docking of **3** into the RT binding site of non-nucleoside inhibitors (extracted from the RT/R90385 complex solved at 2.4 Å resolution[8]) are detailed in a previous paper.[9] Complexes of compounds **5**–**7** with RT were constructed starting from the docked conformation of **3** and submitted to geometry-optimization.

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