Synthesis of Bis-Heteroaryl Piperazine Derivatives as Potential Reverse Transcriptase Inhibitors

Jean Guillaumel, David S. Grierson and Claude Monneret*

Laboratoire de Pharmacochimie, UMR 176 CNRS/IC, Institut Curie,
Section Recherche, 26 rue d'Ulm, F-75248 Paris Cedex 05, France

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Vinylogous analogs of non-nucleoside reverse transcriptase inhibitors belonging to the bis-(heteroaryl)piperazine (BHAP) series were synthesized by coupling a piperazine derivative with (*E*)-propenoyl derivatives of heterocyclic moieties.

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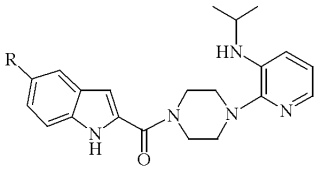
Reverse transcriptase (RT), the virally encoded polymerase of the human immunodeficiency virus (HIV) plays a central role in the life cycle of this virus, orchestrating DNA synthesis from the RNA genome [1]. Nucleoside analogues, including 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxycytidine (ddC), 2',3'-dideoxyinosine (ddI), and 2',3'-dideoxy-3'-thiacytidine (3TC) comprise the first important class of compounds to be developed which inhibit RT. However, the clinical success of such nucleoside analogues is limited by their associated toxicity [2-4], and the emergence of virus strains displaying resistance to these drugs [5,6].

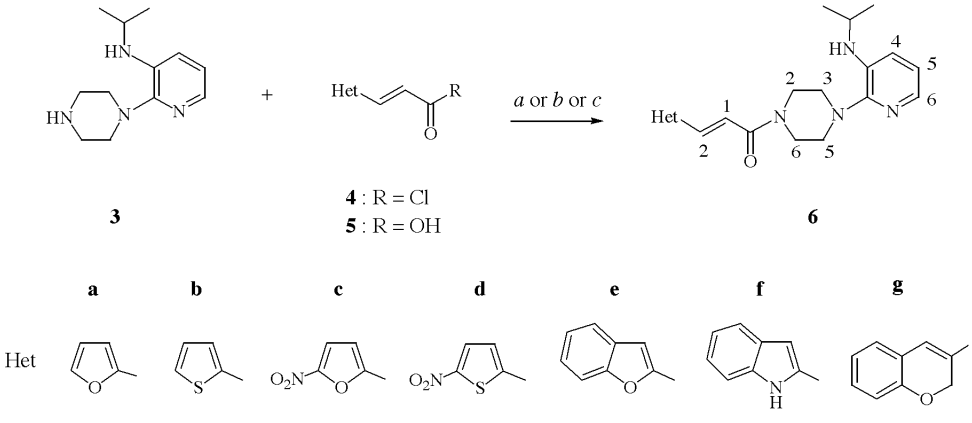


1: R = H
2: R = NH–SO_2–CH_3 (Delavirdine)

A second class of potent structurally diverse non-nucleoside reverse transcriptase inhibitors has been discovered, which block the function of RT through binding in a hydrophobic pocket located near, but distinct from the catalytic site [7,8]. The high specificity of these non-nucleoside inhibitors for HIV-1 RT, combined with their low toxicity, are highly attractive features.

Of the more than 30 different heterocyclic systems which have now been shown to interact and inhibit RT-1 through binding in the hydrophobic pocket, 1-[(*1H*-indol-2-yl)carbonyl]-4-[3-[(1-methylethyl)amino]-2-pyridyl]piperazine or BHAP **1** holds a prominent position [9,10]. Extensive structure-activity studies in this series have established the importance of the 2-(indolylcarbonyl) moiety, the 3-(ethylamino) or 3-(isopropylamino) pyridine substituent, and the 2-pyridine moiety [11]. This effort led to the development of 1-[(5-methanesulfonamido-*1H*-indol-2-yl)carbonyl]-4-[3-[(1-methylethyl)amino]-2-pyridyl]piperazine monomethane sulfonate **2** (Delavirdine mesylate) which was the second non-nucleoside reverse transcriptase inhibitor (NNRTI) approved for use in the treatment of AIDS under the name of Rescriptor™[12].

Scheme 1



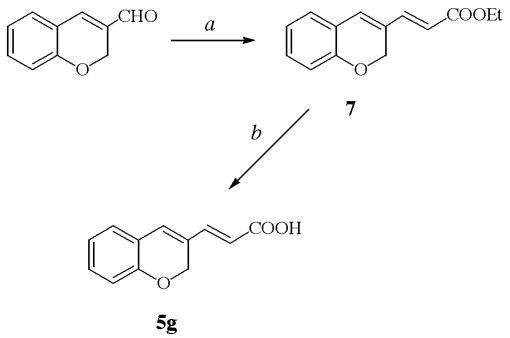
Reaction conditions : *a*, RCOCl, Et_3N, THF; *b*, RCOOH, 1-1'-carbonyldiimidazole, THF; *c*, RCOOH, 4-DMAP, N,N'-dicyclohexylcarbodiimide, CH_2Cl_2.

As part of an ongoing program to identify new non-nucleoside type reverse transcriptase inhibitors, we herein report the synthesis and biological evaluation of a series of new bis-heteroacryloyl piperazines **6a-g** which are vinylogous BHAP analogues. Such a pharmacomodulation has previously been successfully applied in medicinal chemistry as recently illustrated in the field of antitumor agents [13].

To obtain the BHAP analogue **6a**, 1-[3-(1-methylethyl)amino]-2-pyridyl]-piperazine **3** was prepared in five steps from 2-chloro-3-nitropyridine according to Romero *et al*. [11], and then reacted with the (*E*)-propenoyl acid chloride **4a**, in tetrahydrofuran in the presence of triethylamine (procedure I*)*. For compounds **6b-g** the (*E*)-propenoic acids **5b-g** were condensed with piperazine **3** using either 1,1'-carbonyldiimidazole, in tetrahydrofuran at room temperature (procedure II) or *N*,*N*'-dicyclohexylcarbodiimide plus 4-dimethylaminopyridine, in dichloromethane (procedure III) as the condensation agents (Scheme 1). The structure of **6** was unambiguously determined from the ^{1}H nmr, mass spectrometry and microanalytical data. For example, the signals at 6.86 and 7.48 ppm with a coupling constant of 15 Hz for the vinylic protons in **6a** are in agreement with the *E*-configuration.

(*E*)-Propenoyl chloride **4a** and the (*E*)-propenoyl carboxylic acid derivatives **5b-f** were prepared using literature protocols. For 3-(3-chromenyl)-2-propenoic acid **5g** the reported procedure produced a mixture of (*E*) and (*Z*) isomers in a 60:40 ratio [14]. Better *E*-selectivity was obtained using the Wittig reaction between 3-*2H*-chromencarboxaldehyde [15] and (carbethoxymethylene)triphenylphosphorane. In this way, following alkaline deprotection of **7**, compound (*E*)-**5g** was obtained in 57% overall yield after recrystallization from toluene. The *E*-geometry of 3-(3-*2H*-chromenyl)-2-propenoic acid ethyl ester **7** was assigned by the characteristic ^{1}H nmr coupling constants of the olefinic protons (J = 16 Hz).

Scheme 2



Reaction conditions: *a*, (carbethoxymethylene)triphenylphosphorane, toluene; *b*, NaOH, MeOH.

Antiviral Activity.

The seven new bis-(heteroaryl)piperazine analogs **6a-g** were evaluated for their protective effect against the cytopathogenic activity of wild type HIV-1 in CEM/SS and MT4 cells. Despite the fact that certain of these molecules were closely related to BHAP, all compounds were inactive at concentrations up to 10^{-6} μM.

EXPERIMENTAL

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. The ir spectra were obtained on a Perkin-Elmer 1710 spectrophotometer. The ^{1}H nmr spectra were recorded at 300 MHz on a Bruker AC 300 spectrometer. The chemical shift values (ppm) were relative to tetramethylsilane as the internal standard. Coupling constants (J) are given in Hz. Chemical ionization mass spectra (ms: desorption chemical ionization, ammonia, positive ion mode) were recorded on a Nermag R10-10C spectrometer. Microanalyses were performed by the Service Central de Microanalyse du CNRS, Vernaison, France.

Chemistry.

The requisite 1-[3-[(1-methylethyl)amino]-2-pyridyl]piperazine **3** was prepared using the method described by Romero *et al*. [11]. The heteroaryl propenoic acids **5** were synthesized according to literature proceedures. The coupling reactions were achieved using the appropriate protocols (procedures I to III).

(*E*)-3-(3-2*H*-Chromenyl)-2-propenoic acid Ethyl Ester (**7**).

A solution of 3-chromenecarboxaldehyde [15] (0.32 g, 2 mmoles) and commercial (carbethoxymethylene)triphenylphosphorane (1.02 g, 3 mmol) in toluene (25 ml) was heated at reflux for 24 hours. The concentrated solution was purified by chromatography on silica gel (eluent: toluene) to give 0.37 g (80%) of title compound, mp 68-70° (methanol); ^{1}H nmr (deuteriochloroform): δ 1.32 (t, 3H, CH_2-C*H*$_3$), 4.24 (q, 2H, C*H*$_2$-CH_3), 4.97 (s, 2H, H-2), 5.76 (d, J = 16 Hz, 1H, C*H*-COOH), 6.73 (s, 1H, H-4), 6.83 (d, J = 8 Hz, 1H, H-8), 6.90 (m, 1H, H-6), 7.07 (d, J = 8 Hz, 1H, H-5), 7.18 (m, 1H, H-7), 7.38 (d, J = 16 Hz, 1H, C*H*=CH-COOH).

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.25; H, 6.01.

(*E*)-3-(3-2*H*-Chromenyl)-2-propenoic Acid (**5g**).

A suspension of ester **7** (0.35 g, 1.52 mmol) in water (10 ml) and methanol (1 ml) was heated, at 100° for 2 hours, in the presence of sodium hydroxide (0.092 g, 2.3 mmol). The cooled solution was acidified with concentrated hydrochloric acid. The precipitate was filtered and recrystallized from toluene; yield 72%, mp 218°; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 5.00 (s, 2H, H-2), 5.90 (d, J = 16 Hz, 1H, C*H*-COOH), 6.80 (d, J = 8 Hz, 1H, H-8), 6.90 (m, 1H, H-6), 7.00 (s, 1H, H-4), 7.20 (m, 2H, H-5 and H-7), 7.30 (d, J = 16 Hz, 1H, C*H*=CH-COOH), 12.40 (bs, 1H, COOH).

Anal. Calcd. for $C_{12}H_{10}O_3$: C, 71.28; H, 4.98. Found: C, 71.02; H, 4.89.

Procedure I: Coupling Piperazine with Acid Chloride **4** in the Presence of Triethylamine.

1-[3-(2-Furyl)-2-propenoyl]-4-[3[(1-methylethyl)amino]-2-pyridyl]piperazine (**6a**).

To a solution of 3-(2-furyl)-2-propenoyl chloride **4a** (190 mg, 1.21 mmol) (prepared by heating a mixture of the corresponding acid **5a** [16], oxalyl chloride and 2 drops of dimethylformamide in benzene) in tetrahydrofuran was added a solution of **3** (195 mg, 0.89 mmol) and triethylamine (123 mg, 1.21 mmol) in tetrahydrofuran (10 ml). The reaction mixture was stirred at room temperature for 48 hours, and then was diluted with water, and extracted with dichloromethane. The organic phase was washed with water, dried over sodium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (eluent: dichloromethane/methanol: from 99.5/0.5 to 98/2) afforded compound **6a** as a yellow liquid: 230 mg (76%); ^{1}H nmr (deuteriochloroform): δ 1.24 (d, J = 6.5 Hz, 6H, 2 CH_3), 3.10 (bs, 4H, H-3 and H-5 piperazine), 3.55 (m, 1H, C*H*-Me_2), 3.82 (bs, 4H, H-2 and H-6 piperazine), 4.16 (bs, 1H, N*H*-CH-Me_2), 6.46 (m, 1H, H-4 furan), 6.51 (d, J = 3.4 Hz, 1H, H-3 furan), 6.84 (dd, J = 1.4 Hz, 1H, H-4 pyridine), 6.86 (d, J = 15 Hz, 1H, H-1 vinyl), 6.93 (m, 1H, H-5 pyridine), 7.45 (d, J = 1.1 Hz, 1H, H-5 furan), 7.48 (d, J = 15 Hz, 1H, H-2 vinyl), 7.68 (dd, J = 1.4 Hz, J = 4.4 Hz, 1H, H-6 pyridine); ms: m/z 341 $(M + H)^+$.

Anal. Calcd for $C_{19}H_{24}N_4O_2$: C, 67.04; H, 7.11; N, 16.46. Found: C, 66.85; H, 7.28; N, 16.26.

Procedure II: Coupling of Piperazine with Carboxylic Acid using 1,1'-Carbonyldiimidazole.

1-[3-(2-Thienyl)-2-propenoyl]-4-[3-[(1-methylethyl)amino]-2-pyridyl]piperazine (**6b**).

The 3-(2-thienyl)-2-propenoic acid **5b** [17] (190 mg, 1.23 mmol) was added to a solution of 1,1'-carbonyldiimidazole (200 mg, 1.23 mmol) in tetrahydrofuran (10 ml) at room temperature. After being stirred for 2 hours, a solution of 1-[3-[(1-methylethyl)amino]-2-pyridyl]piperazine **3** (246 mg, 1.12 mmol) in tetrahydrofuran (5 ml) was added. The mixture was stirred at room temperature for 24 hours, poured into water, and extracted with dichloromethane. The organic layer was washed with an aqueous solution of sodium bicarbonate, then with water, and dried over sodium sulfate. The residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol: from 99.5/0.5 to 99/1). Compound **6b** was obtained as a yellow liquid, 180 mg (46%); ^{1}H-nmr (deuteriochloroform): δ 1.24 (d, J = 7.6 Hz, 6H, 2 CH_3), 3.10 (bs, 4H, H-3 and H-5 piperazine), 3.57 (m, 1H, C*H*-Me_2), 3.81 (bs, 4H, H-2 and H-6 piperazine), 4.15 (bs, 1H, NH), 6.72 (d, J = 15 Hz, 1H, H-1 vinyl), 6.84 (dd, J = 1 Hz, J = 7.8 Hz, 1H, H-4 pyridine), 6.93 (m, 1H, H-5 pyridine), 7.03 (m, 1H, H-4 thiophene), 7.22 (d, J = 3.5 Hz, 1H, H-3 thiophene), 7.31 (d, J = 5.2 Hz, 1H, H-5 thiophene), 7.67 (dd, J = 1 Hz, J = 4.7 Hz, 1H, H-6 pyridine), 7.82 (d, J = 15 Hz, 1H, H-2 vinyl); ms: m/z 357 $(M + H)^+$.

Anal. Calcd. for $C_{19}H_{24}N_4OS$: C, 64.01; H, 6.79; N, 15.72. Found: C, 63.72; H, 6.99; N, 15.95.

1-[3-(5-Nitro-2-furyl)-2-propenoyl]-4-[3-[(1-methylethyl)-amino]-2-pyridyl]piperazine (**6c**).

This compound was synthesized as **6b** from 3-(5-nitro-2-furyl)-2-propenoic acid **5c** [18]; yield 58%, mp 148-150° (methanol); ^{1}H nmr (deuteriochloroform): δ 1.25 (d, J = 6.3 Hz, 6H, 2 CH_3), 3.13 (m, 4H, H-3 and H-5 piperazine), 3.57 (m, 1H, C*H*-Me_2), 3.87 (m, 4H, H-2 and H-6 piperazine), 4.14 (d, J = 6.9 Hz, 1H, NH), 6.71 (d, J = 3.7 Hz, 1H, H-3 furan), 6.84 (dd, J = 1.1 Hz, J = 8 Hz, 1H, H-4 pyridine), 6.92-6.96 (m, 1H, H-5 pyridine), 7.19 (d, J = 15.2 Hz, 1H, H-1 vinyl), 7.35 (d, J = 3.7 Hz, 1H, H-4 furan), 7.45 (d, J = 15.2 Hz, 1H, H-2 vinyl), 7.67 (dd, J = 1.2 Hz, J = 5 Hz, 1H, H-6 pyridine); ms: m/z 386 $(M + H)^+$.

Anal. Calcd. for $C_{19}H_{23}N_5O_4$: C, 59.22; H, 5.97; N, 18.18. Found: C, 59.13; H, 6.15; N, 18.14.

1-[3-(5-Nitro-2-thienyl)-2-propenoyl]-4-[3-[(1-methylethyl)-amino]-2-pyridyl]piperazine (**6d**).

Starting from 3-(5-nitro-2-thienyl)-2-propenoic acid **5d** [19], compound **6d** was obtained following the same procedure II as above; yield 27%, mp 180-182° (methanol); ir (deuteriochloroform): ν 1642 (C=O); ^{1}H nmr (deuteriochloroform): δ 1.26 (d, 6H, 2 CH_3), 3.13 (d, 4H, H-3 and H-5 piperazine), 3.58 (m, 1H, C*H*-Me_2), 3.83 (d, 4H, H-2 and H-6 piperazine), 4.14 (d, 1H, NH), 6.84 (dd, J = 1.4 Hz, J = 7.9 Hz, 1H, H-4 pyridine), 6.91-6.94 (m, 1H, H-5 pyridine), 6.93 (d, J = 15 Hz, 1H, H-1 vinyl), 7.14 (d, J = 4.2 Hz, 1H, H-3 thiophene), 7.67-7.69 (m, 1H, H-4 thiophene), 7.71 (d, J = 15 Hz, 1H, H-2 vinyl), 7.84 (d, J = 4.4 Hz, 1H, H-6 pyridine); ms: m/z 402 $(M + H)^+$.

Anal. Calcd. for $C_{19}H_{23}N_5O_3S$: C, 56.84; H, 5.72; N, 17.44. Found: C, 56.71; H, 5.82; N, 17.44.

1-[3-(2-Benzofuryl)-2-propenoyl]-4-[3-[(1-methylethyl)amino]-2-pyridyl]piperazine (**6e**).

Compound **6e** was obtained from 3-(2-benzofuryl)-2-propenoic acid **5e** [20] following general procedure II; yield 56%, mp 150-152° (methanol); ^{1}H nmr (deuteriochloroform): δ 1.32 (d, 6H, 2 CH_3), 3.20 (dd, 4H, H-3 and H-5 piperazine), 3.64 (m, 1H, C*H*-Me_2), 3.95 (bs, 4H, H-2 and H-6 piperazine), 4.23 (d, 1H, NH), 6.88-7.00 (m, 2H, H-4 and H-5 pyridine), 6.94 (s, 1H, H-3 benzofuran), 7.17 (d, J = 15 Hz, 1H, H-1 vinyl), 7.28 and 7.39 (2m, 2H, H-5 and H-6 benzofuran), 7.52 (d, J = 8.2 Hz, 1H, H-7 benzofuran), 7.63 (d, J = 7.7 Hz, 1H, H-4 benzofuran), 7.65 (d, J = 15 Hz, 1H, H-2 vinyl), 7.73 (dd, J = 1.3 Hz, J = 4.8 Hz, 1H, H-6 pyridine); ms : m/z 391 $(M + H)^+$.

Anal. Calcd. for $C_{23}H_{26}N_4O_2$: C, 70.75; H, 6.71; N, 14.35. Found: C, 70.46; H, 6.81; N, 14.29.

Procedure III: Coupling with Carboxylic Acid in Presence of 4-Dimethylaminopyridine and *N*,*N*'-Dicyclohexylcarbodiimide.

1-[3-(2-Indolyl)-2-propenoyl]-4-[3-[(1-methylethyl)amino]-2-pyridyl]piperazine (**6f**).

To a solution of **3** (248 mg, 1.13 mmol), indolacrylic acid **5f** [21] (212 mg, 1.13 mmol) and 4-dimethylaminopyridine (137 mg, 1.13 mmol) in dichloromethane (50 ml) was added a solution of *N*,*N*'-dicyclohexylcarbodiimide (348 mg, 1.69 mmol, 1 *M* in dichloromethane). The mixture was refluxed for 18 hours. After evaporation of the solvent, the residue was purified on a silica gel column (eluent: dichloromethane/methanol: from 99.8/0.2 to 99.6/0.4) to afford 260 mg of **6f** (58%), mp 225-227° (methanol); ^{1}H (deuteriochloroform-dimethyl-d_6 sulfoxide): δ 1.24 (d, 6H, 2 CH_3), 3.10 (bs, 4H, H-3 and H-5 piperazine), 3.57 (m, 1H, C*H*-Me_2), 3.85 (bs, 4H, H-2 and H-6 piperazine), 4.15 (d, 1H, NH), 6.76 (s, 1H, H-3 indol), 6.84 (dd, J = 1.4 Hz, J = 7.92 Hz, 1H, H-4 pyridine), 6.89-6.95 (m, 1H, H-5 pyridine), 6.92 (d, J = 15.3 Hz, 1H, H-1 vinyl), 7.08 and 7.21 (2m, 2H, H-5

and H-6 indol), 7.34 (d, J = 8.2 Hz, 1H, H-7 indol), 7.59 (d, J = 7.9 Hz, 1H, H-4 indol), 7.67 (dd, J =1.5 Hz, J = 4.8 Hz, 1H, H-6 pyridine), 7.72 (d, J = 15.3 Hz, 1H, H-2 vinyl).

Anal. Calcd. for $C_{23}H_{27}N_5O$: C, 70.92; H, 6.99; N, 17.98. Found: C, 70.61; H, 7.07; N, 17.90.

1-[3-(3-Chromenyl)-2-propenoyl]-4-[3-[(1-methylethyl)amino]-2-pyridyl] piperazine (**6g**).

This compound was synthesized according to procedure III from 3-(3-chromenyl)-2-propenoic acid **5g**: yield 46%, mp 213-215° (methanol-chloroform); ^{1}H nmr (deuteriochloroform): δ 1.25 (d, 6H, 2 CH_3), 3.11 (bs, 4H, H-3 and H-5 piperazine), 3.56 (m, 1H, C*H*-Me_2), 3.80 (m, 4H, H-2 and H-6 piperazine), 4.15 (m, 1H, NH), 5.00 (s, 1H, H-2 chromene), 6.24 (d, J = 15.4 Hz, 1H, H-1 vinyl), 6.71 (s, 1H, H-4 chromene), 6.86 (m, 2H, H-4 pyridine and H-8 chromene), 6.93 (m, 2H, H-5 pyridine and H-6 chromene), 7.08 (d, J = 7.40 Hz, 1H, H-5 chromene), 7.16 (m, 1H, H-7 chromene), 7.42 (d, J = 15.5 Hz, 1H, H-2 vinyl), 7.68 (dd, J = 1.8 Hz, J = 4.8 Hz, H-6 pyridine).

Anal. Calcd. for $C_{24}H_{28}N_4O_2$: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.97; H, 7.14; N, 13.59.

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