Synthesis of 2-Benzothienyl Carbonyl 4-Arylpiperazines as Novel Delavirdine Analogs

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Abstract: A novel series of 2-benzothienyl carbonyl arylpiperazines (**6a**–**f**) was synthesized as potential HIV nonnucleoside reverse transcriptase inhibitors (NNRTIs). Preparation of the derivatives was performed by reacting benzo[*b*]thiophene carbonyl chloride (**5**) with a series of substituted 4-arylpiperazines.

Keywords: arylpiperazines, benzothiophene, delavirdine, HIV-1 reverse transcriptase inhibitors

INTRODUCTION

Heteroaryl amides bearing an arylpiperazine moiety are interesting frameworks utilized in antipsychotic drugs and HIV nonnucleoside reverse transcriptase inhibitors (NNRTIs), such as delavirdine (Fig. 1).[1–6] As a retrovirus, HIV is distinguished by the presence of a viral reverse transcriptase (RT), an enzyme responsible for the synthesis of DNA from the viral RNA genome. This

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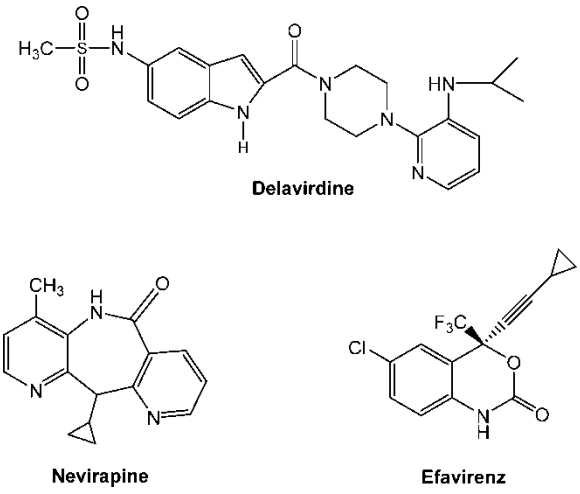


Figure 1.

enzyme is one of the most important antiviral targets in the chemotherapy of acquired immunodeficiency syndrome (AIDS). Reverse transcriptase inhibitors of HIV-1 have successfully been used in combination with HIV-1 protease inhibitors as a treatment regimen termed highly active antiretroviral therapy (HAART),[7,8] in which efavirenz, nevirapine, and delavirdine are the NNRTIs agents currently used.

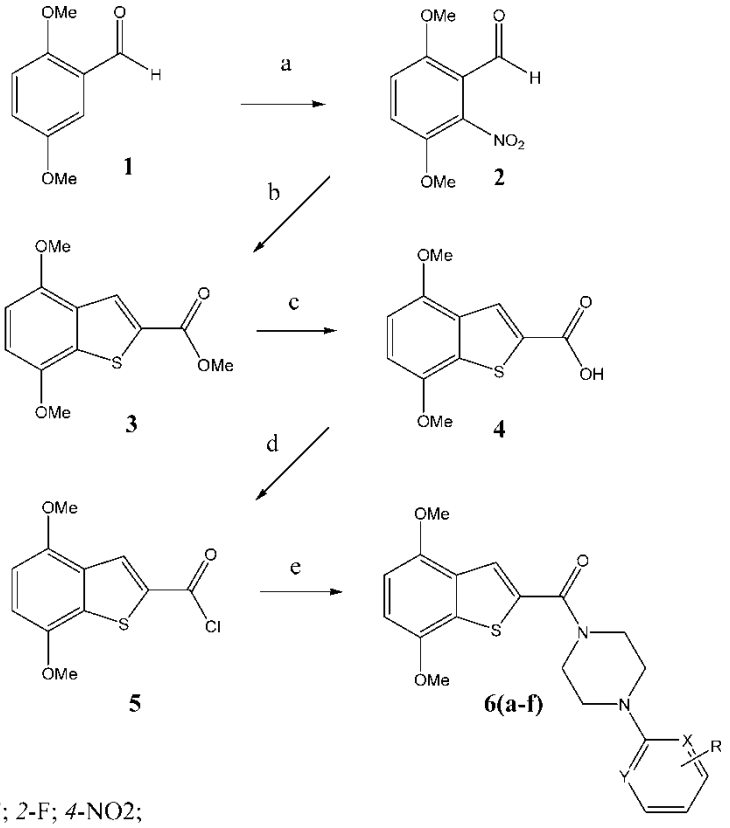
A major drawback with AIDS drugs is the rapid development of resistance;[9] thus, continued efforts need to be focused on the synthesis of new compounds with enhanced activity or metabolic stability. In 2001, Pinna and coworkers[10] reported the synthesis and pharmacological evaluation of a series of arylpyrrol piperazines as delavirdine analogs in acutely infected MT4 cells.

Although a number of synthetic approaches to molecules with potential NNRTI activity have been reported,[11–13] the preparation of arylpiperazinil benzo[*b*]thiophene derivatives as potential anti-HIV-1 agents has not yet been investigated to the best of our knowledge.

The present study describes the synthesis of a series of 1-[(4,7-dimethoxy-1-benzothien-2-yl)carbonyl]-4-arylpiperazines **6**(**a**–**f**) structurally related to the NNRTI delavirdine.

RESULTS AND DISCUSSION

The synthesis of 2-benzothienyl arylpiperazines **6**(**a**–**f**) is outlined in Scheme 1. Treatment of the starting 2,5-dimethoxy benzaldehyde (**1**) with nitric acid in glacial acetic acid gave the corresponding nitro compound, (**2**),[14] which reacted with methyl thioglycolate in basic medium at 65–70°C to provide the benzo[*b*]thiophene ester (**3**)[15] in 74% crude yield.



R= H, *4*-F; *2*-F; *4*-NO2;
X=N; Y=CH ; R=H
X=N; Y=N ; R=H

Scheme 1. Reagents and conditions: a) HNO_3/HOAc; b) methyl thioglycolate/K_2CO_3/DMF, 65–70°C, 4 h, c) KOH-CH_3OH, 3 h, rt, H_3O^+; d) $SOCl_2$, reflux 3 h; e) substituted 4-arylpiperazines, dry pyridine/anhydrous THF/N_2 atmosphere.

The ester (**3**) was subsequently hydrolyzed at room temperature in a methanolic potassium hydroxide solution to afford the heteroaromatic carboxylic acid derivative (**4**) in 82% yield. The aroylchloride (**5**) was obtained by reaction of acid (**4**) with thionyl chloride under reflux conditions to provide a yellow solid, which was purified and subsequently treated under an inert atmosphere with different 4-arylpiperazines to afford the expected benzothiophene carboxamides in good yield (Table 1).

EXPERIMENTAL

Melting points were determined on a hot-stage apparatus and are uncorrected. The IR spectra were recorded on a FT-IR Bruker IFS 55 spectrophotometer for

Table 1. Products, mp, and yields

Compound	R	mp(°C)	Yield (%)
6-a	H; X,Y=CH	151–152	83
6-b	4-F; X,Y=CH	119–120	87
6-c	2-F; X,Y=CH	143–144	65
6-d	4-NO_2; X,Y=CH	192–193	81
6-e	H; X=N, Y=CH	155–156	87
6-f	H; X,Y=N	150–151	89

KBr disc, and wave numbers are reported in cm^{-1}. The ^1H NMR and ^{13}C NMR measurements were performed on a Bruker DRX-300 spectrometer (300 and 75 MHz) in deuteriochloroform, or DMSO-d_6. Chemical shifts were recorded in ppm (δ) relative to TMS as an internal standard. *J* values are given in Hertz. Microanalyses were carried out on a Fisons EA 1108 analizer. Silica-gel 60 (Merck, 70–230 mesh) and DC-alufolien 60 F_{254} were normally used for column chromatography and thin-layer chromatography (TLC) respectively.

4,7-Dimethoxy-2-methoxycarbonyl-benzo[*b*]thiophene (3)

To a solution of nitrobenzaldehyde **2** (774 mg, 3.7 mmol) in DMF (10 mL), anhydrous K_2CO_3 (507 mg, 3.7 mmol) and methylthioglycolate (0.34 mL, 3.7 mmol) were added. The suspension was stirred at 70°C for 4 h, then poured onto crushed ice, and vigorously stirred for 15 min. The resultant precipitate was filtered off and washed with water (3 × 25 mL) to afford crude benzothiophene ester **3** (682 mg, 74%) as a pale yellow solid, which was purified by column chromatography (CH_2Cl_2) to afford pure benzothiophene ester **3** (623 mg, 67.4%), mp 124–125°C. Anal. calcd. for $C_{12}H_{12}O_4$ S: C, 57.13; H, 4.80; S, 12.69. Found: C, 56.78; H, 4.90; S, 12.52%. IR ν_{max}: 3010 (C-H, Ar), 1702 (C=O), 1260 (C-O). ^1H NMR (300 MHz, $CDCl_3$) δ: 3.91 (s, 3H, OCH_3), 3.93 (s, 3H, Ar-OCH_3), 3.94 (s, 3H, Ar-OCH_3), 6.66 (d, 1H, 5-H, $J = 8.5$ Hz), 6.76 (d, 1H, 6-H, $J = 8.5$ Hz), 8.2 (s, 1H, 3-H). ^{13}C NMR (75 MHz, $CDCl_3$): 52.4, 55.8, 56.0, 104.6, 106.8, 128.0, 131.1, 132.4, 132.9, 148.4, 150.5, 163.2.

4,7-Dimethoxy-benzo[*b*]thiophene-2-carboxylic Acid (4)

A solution of the methyl ester **3** (800 mg, 3.17 mmol) in potassium hydroxide 0.5 N:ethanol (1:1 v/v) (60 mL) was stirred at room temperature for 3 h. The mixture was then concentrated in vacuo and acidified with HCl (c) at 0°C. The resulting precipitate was filtered off, washed with a small amount of cold water, and dried to provide a yellow pale solid **5** (620 mg, 82%), which was used without further purification, Mp 129–130°C. Anal. calcd. for $C_{11}H_{10}O_4S$:

C, 55.45; H, 4.23; S, 13.46. Found: C, 55.45; H, 4.50; S, 13.21%. IR ν_{max}: (cm^{-1}): 3650–2800 (O-H), 1670 (C═O), 1529 (C═C Ar). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.91 (s, 3H, OCH_3), 3.94 (s, 3H, Ar-OCH_3), 6.86 (d, 1H, 5-H, $J = 8.5$ Hz), 6.95 (d, 1H, 6-H, $J = 8.5$ Hz), 8.24 (s, 1H, 3-H), 12.7 (s, 1H, COOH). ^{13}CNMR (75 MHz, $CDCl_3$): 56.2, 56.4, 105.9, 107.3, 122.6, 130.7, 131.4, 135.4, 148.3, 150.0, 171.6.

4,7-Dimethoxy-benzo[*b*]thiophene-2-carbonyl Chloride (5)

A solution of carboxylic acid **4** (910 mg, 3.8 mmol) in thionyl chloride (50 mL) was heated under reflux for 4 h. Once the reaction proceeded, the excess of the thionyl chloride was removed under reduced pressure, and the crude residue immediately chromatographed on a silica-gel column (CH_2Cl_2) to give compound **5** as a bright yellow solid (820 mg, 84% yield), mp 84–85°C; Anal. calcd. for $C_{11}H_9ClO_3S$: C, 51.47; H, 3.53; S, 12.49. Found: C, 50.54; H, 3.64; S, 12.45%. IR ν_{max}: 1730 (ArCOCl), 1600 (C═C Ar). ^{1}HNMR (300 MHz, $CDCl_3$) δ: 3.93 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.68 (d, 1H, 5-H, $J = 8.5$ Hz), 6.84 (d, 1H, 6-H, $J = 8.5$ Hz), 8.38 (s, 1H, 3-H). ^{13}C NMR (75 MHz, $CDCl_3$): 55.8, 56.1, 104.9, 108.6, 130.6, 133.5, 134.8, 135.5, 148.0, 151.1, 161.1.

General Procedure for Preparation of the [(4,7-Dimethoxy-1-benzothien-2-yl) carbonyl]-4-arylpiperazines (6a–f): Compound (6a) as a Model

[(4,7-Dimethoxy-1-benzothien-2-yl)carbonyl]-4-phenylpiperazine (6a)

Aroyl chloride **5** (277 mg, 1.08 mmol) in dry THF (20 mL) was slowly added to a stirred solution at 0°C of 1-phenylpiperazine (175 mg, 1.08 mmol) and dry pyridine (85 mg, 1.08 mmol) in dry THF (50 mL) under a nitrogen atmosphere. The mixture was maintained with stirring for 3 h at room temperature and then diluted with water (100 mL). The solution was extracted with ethyl acetate (3×50 mL), and the organic layers were dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by silica-gel column chromatography (CH_2Cl_2) to give benzothiophene carboxamide **6a** (345 mg, 83.4%) as a yellow pale solid, mp 156–157°C (EtOH). Anal. calcd. for $C_{21}H_{22}N_2O_3S$: C, 65.95; H, 5.80; N, 7.32; S, 8.38. Found: C, 65.83; H, 5.91; N, 7.19; S, 8.15%; IR ν_{max}: 3032 (C-H Ar), 2931 (C-H Aliph.), 1620 (NHCO), 1484 (C═C Ar). ^{1}H NMR ($CDCl_3$): δ 3.25 [t, 4H, CON-$(CH_2)_2$, $J = 5.0$ Hz], 3.91–3.95 [m, 10H, $(CH_2)_2$-N-Ph and C-4 Ar OMe, C-7 Ar OMe], 6.68 (d, 1H, 5-H, $J = 8.4$ Hz), 6.74 (d, 1H, 6-H, $J = 8.4$ Hz), 6.90 (d, 1H, 4′-H, $J = 7.4$ Hz), 6.95 (d, 2H, 2′-H and 6′-H,

$J = 8.4$ Hz), 7.29 (t, 2H, 3′-H and 5′-H $J = 7.8$ Hz), 7.66 (s,1H, 3-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 46.1 (2C), 49.8 (2C), 55.8, 56.0, 104.8, 105.8, 116.8 (2C), 120.7, 122.8, 129.3 (2C), 130.9 (2C), 135.7, 148.5, 150, 151, 163.9.

[(4,7-Dimethoxy-1-benzothien-2-yl) carbonyl]-4-(4-fluorophenyl)piperazine (6b)

White pale crystals (column chromatographed, CH_2Cl_2) (325 mg, 87.3%). Prepared from **5** (238 mg, 0.93 mmol) and 4-(4-fluorophenyl)piperazine (167 mg, 0.93 mmol), mp 119–120°C (ethanol/petroleum benzin 5:1). Anal. calcd. for $C_{21}H_{21}FN_2O_3S$: C, 62.98; H, 5.29; F, 4.74; N, 7.00; S 7.99. Found: C, 62.25; H, 5.20; N, 6.90; S, 7.60%. IR ν_{max}: 3030 (C-H Ar), 2935 (C-H Aliph), 1626 (C═O), 1510 and 1485 (C═C Ar). ^{1}H NMR ($CDCl_3$): δ 3.15 [t, 4H, CON-$(CH_2)_2$, $J = 5.0$ Hz,], 3.91 (s, 3H, C-7 OMe), 3.93–3.95 [m, 7H, $(CH_2)_2$-N-Ar and C-4 OMe], 6.68 (d, 1 H, 5-H, $J = 8.4$ Hz), 6.74 (d, 1H, 6-H, $J = 8.4$ Hz), 6.87–6.92 (m, 2H, 2′-H and 6′-H), 6.96–7.02 (m, 2H, 3′-H and 5′-H), 7.66 (s, 1H, 3-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 45.2 (2C), 50.8 (2C), 55.8, 56.1, 104.8, 105.8, 115.7 (d, 2C, $^2J = 22.1$ Hz), 118.7 (d, 2C, $^3J = 7.7$ Hz), 122.8, 135.6, 130.9 (2C), 147.6.0 (d, $^4J = 2.3$ Hz), 149.0, 150.0, 157.7 (d, $^1J = 240$ Hz), 163.9 (NCO).

[(4,7-Dimethoxy-1-benzothien-2-yl) carbonyl]-4-(2-fluorophenyl)piperazine (6c)

White pale crystals (column chromatographed, CH_2Cl_2) (176 mg, 65%). Prepared from **5** (200 mg, 0.78 mmol) and 4-(2-fluorophenyl)piperazine (141 mg, 0.78 mmol), mp 156–157°C (ethanol). Anal. calcd. for $C_{21}H_{21}FN_2O_3S$: C, 62.98; H, 5.29; F, 4.74; N, 7.00; S, 7.99. Found: C, 62.63; H, 5.35; N, 6.97; S, 7.63%. IR ν_{max}: 3030 (C-H Ar), 2935, (C-H Aliph.), 1626 (C═O), 1510 and 1485 (C═C Ar). ^{1}H NMR ($CDCl_3$): δ 3.14 [t, 4H, CON-$(CH_2)_2$, $J = 5.0$ Hz], 3.91 (s, 3H, C-7 OMe), 3.95 [m, 7H, $(CH_2)_2$-N-Ar and C-4 OMe], 6.68 (d, 1H, 5-H, $J = 8.4$ Hz), 6.73 (d, 1H, 6-H, $J = 8.4$ Hz), 6.92–7.05 (m, 2H, 2′-H and 6′-H), 7.03–7.08 (m, 2H, 3′-H and 5′-H), 7.66 (s, 1H, 3-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 45.6 (2C), 49.8 (2C), 54.7, 55.0, 103.8, 104.8, 115.3 (d, $^2J = 21$ Hz), 118.3 (d, $^{2'}J = 2.6$ Hz), 121.7, 122.2 (d, $^3J = 8.0$ Hz), 123.6 (d, $^4J = 3.6$ Hz), 129.8, 129.9, 134.7, 138.5 (d, $^{2'}J = 3.6$ Hz), 147.5, 148.9, 154.8 (d, $^1J = 246$ Hz), 162.9.

[(4,7-Dimethoxy-1-benzothien-2-yl) carbonyl]-4-(4-nitrophenyl)piperazine (6d)

Yellow crystals (column chromatographed, CH_2Cl_2) (233 mg, 81%). Prepared from **5** (186 mg, 0.73 mmol) and 4-(4-nitrophenyl)piperazine (152 mg, 0.73 mmol), mp 192–193°C (ethanol). Anal. calcd. for $C_{21}H_{21}N_3O_5S$: C, 58.95; H, 4.91; N, 9.83; S, 7.50. Found: C, 58.66; H, 5.00; N, 9.68; S,

7.46%. IR ν_{max}: 1625 (C═O), 1598 (NO_2 asym.), 1485 (C═C Ar), 1335 (NO_2 sym.). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.53 [t, 4H, CON-$(CH_2)_2$, $J = 5.1$ Hz], 3.92 (s, 3H, C-7 OMe), 3.96 (s, 3H, C-4 OMe), 3.98 [t, 4H, $(CH_2)_2$-N-Ar, $J = 5.1$ Hz], 6.69 (d, 1H, 5-H, $J = 8.5$ Hz), 6.76 (d, 1H, 6-H, $J = 8.5$ Hz), 6.83 (d, 2H, 2′-H and 6′-H, $J = 9.4$ Hz), 7.69 (s, 1H, 3-H), 8.15 (d, 2H, 3′-H and 5′-H, $J = 9.4$ Hz). ^{13}CNMR (75 MHz, $CDCl_3$): δ 44.6 (2C), 47.6 (2C), 56.3, 56.6, 105.4, 106.6, 113.5 (2C), 123.8, 126.5 (2C), 131.4, 131.5, 135.8, 139.7, 149.0, 150.5, 154.9, 164.6.

[(4,7-Dimethoxy-1-benzothien-2-il) carbonil]-4-(2-pyridinil)piperazine (6e)

White crystals (column chromatographed, CH_2Cl_2) (264 mg, 87%). Prepared from **5** (225 mg, 0.88 mmol) and 4-(2-pyridinyl)piperazine (337 mg, 0.88 mmol), mp 156–157°C. (ethanol). Anal. calcd. for $C_{20}H_{21}N_3O_3S$: C, 62.64; H, 5.52; N, 10.96; S, 8.36. Found: C, 62.39; H, 5.25; N, 10.99; S, 8.52%. IR ν_{max}: 1619 (C═O), 1600 (C═N), 1483 (C═C Ar). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.63 [m, 4H, CON-$(CH_2)_2$], 3.83–3.95 [m, 10H, $(CH_2)_2$-N-Ar, C-4 OMe and C-7 OMe], 6.65–6.67 (m, 4 H, 5-H, 6-H and 4′-H, 6′-H), 7.51 (td, 1H, 5′-H, $Jo = 8.3$ Hz, $Jm = 2.3$ Hz), 7.67 (s, 1H, 3-H), 8.21 (d,1H, 3′-H, $J = 3.9$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 43.5 (2C), 46.1 (2C), 56.5, 56.8, 105.5, 106.5, 108.1, 114.8, 123.6, 131.5, 131.6, 136.5, 138.5, 148.8, 149.2, 150.7, 159.8, 164.8.

2-{4-[(4,7-dimethoxy-1-benzothien-2-yl) carbonyl]piperazin-1-yl} pyrimidine (6f)

White crystals (column chromatographed, CH_2Cl_2) (205 mg, 89%). Prepared from **5** (154 mg, 0.60 mmol) and 2-(piperazin-1-yl) pyrimidine (98.5 mg, 0.60 mmol), mp 150–151°C. (ethanol). Anal. calcd. for $C_{19}H_{20}N_4O_3S$: C, 59.36; H, 5.24; N, 14.57; S, 8.34. Found: C, 58.65; H, 5.25; N, 14.21; S, 8.17%. IR ν_{max}: 1627 (C═O), 1589 (C═N), 1546 (C═C Ar). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81–3.98 [m, 14H, CON-$(CH_2)_2$, $(CH_2)_2$-N-Ar, C-4 OMe and C-7 OMe], 6.57 (m,1H, 4′-H), 6.69 (d, 1H, 5-H, $J = 8.4$ Hz), 6.74 (d, 1H, 6-H, $J = 8.4$ Hz), 7.67 (s, 1H, 3-H), 8.34 (d, 2H, 3′-H and 5′-H, $J = 4.7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 42.8 (2C), 48.7 (2C), 55.7, 56.0, 104.7, 105.7, 110.6, 122.8, 130.8 (2C), 135.7, 148.4, 149.9, 156.8 (2C), 161.5, 164.1.

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