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
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 benzothien-[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.
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
KBr disc, and wave numbers are reported in cm\(^{-1}\). The \(^1\)H 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 (\(\delta\)) relative to TMS as an internal standard. \(J\) values are given in Hertz.

Microanalyses were carried out on a Fisons EA 1108 analyzer. 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 \(\times\) 25 mL) to afford crude benzothiophene ester 3 (682 mg, 74%) as a pale yellow solid, which was purified by column chromatography (CH\(_2\)Cl\(_2\)) 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 \(v_{\text{max}}\): 3010 (C-H, Ar), 1702 (C=O), 1260 (C-O). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\): 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\(_4\)S:
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$_2$Cl$_2$) to give compound 5 as a bright yellow solid (820 mg, 84% yield), mp 84–85°C; Anal. calcd. for C$_{11}$H$_9$ClO$_3$S: C, 51.47; H, 3.53; S, 12.49. Found: C, 50.54; H, 3.64; S, 12.45%. IR $\nu_{\text{max}}$: 1730 (ArCOCl), 1600 (C=Ar). $^1$HNMR (300 MHz, CDCl$_3$) $\delta$: 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). $^{13}$CNMR (75 MHz, CDCl$_3$): 55.8, 56.1, 104.9, 108.6, 130.6, 130.9, 133.5, 134.8, 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$_2$Cl$_2$) 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$_2$O$_3$S: 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 $\nu_{\text{max}}$: 3032 (C-H Ar), 2931 (C-H Aliph.), 1620 (NHCO), 1484 (C=Ar). $^1$H NMR (CDCl$_3$): $\delta$ 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 \text{ Hz}, \ 7.29 \text{ (t, 2H, 3'-H and 5'-H \( J = 7.8 \text{ Hz} \)}, \ 7.66 \text{ (s, 1H, 3-H)}. \]

\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3\): \delta 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\(_2\)Cl\(_2\) (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\(_2\)O\(_3\)S: 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 \( \nu \text{max}: 3030 \text{ (C-H Ar), 2935 (C-H Aliph), 1626 (C=O), 1510 and 1485 (C=C Ar).} \)

\[ ^{1}H \text{ NMR (CDCl}_3\): d 3.15 \text{ [t, 4H, CON-(CH}_2\text{)2, } J = 5.0 \text{ Hz]}, \ 3.91 \text{ (s, 3H, C-7 OMe), 3.93–3.95 \text{ [m, 7H, (CH}_2\text{)2-N-Ar and C-4 OMe]}, \ 6.68 \text{ (d, 1H, 5-H, } J = 8.4 \text{ Hz}), \ 6.74 \text{ (d, 1H, 6-H, } J = 8.4 \text{ Hz)}, \ 6.87–6.92 \text{ (m, 2H, 2'-H and 6'-H), 6.96–7.02 \text{ (m, 2H, 3'-H and 5'-H), 7.66 (s, 1H, 3-H).} \]

\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3\): d 45.2 (2C), 50.8 (2C), 55.8, 56.1, 104.8, 105.8, 115.7 (d, 2J = 22.1 Hz), 118.7 (d, 2C, 2J = 7.7 Hz), 122.8, 135.6, 130.9 (2C), 147.6 (d, 2J = 2.3 Hz), 149.0, 150.0, 157.7 (d, 2J = 240 Hz), 163.9 (NCO). \]

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

White pale crystals (column chromatographed, CH\(_2\)Cl\(_2\) (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\(_2\)O\(_3\)S: C, 62.63; H, 5.35; N, 6.97; S, 7.63%. Found: C, 62.25; H, 5.20; N, 6.90; S, 7.60%. IR \( \nu \text{max: 3030 (C-H Ar), 2935 (C-H Aliph), 1626 (C=O), 1510 and 1485 (C=C Ar).} \)

\[ ^{1}H \text{ NMR (CDCl}_3\): d 3.14 \text{ [t, 4H, CON-(CH}_2\text{)2, } J = 5.0 \text{ Hz]}, \ 3.91 \text{ (s, 3H, C-7 OMe), 3.95 [m, 7H, (CH}_2\text{)2-N-Ar and C-4 OMe]}, \ 6.68 \text{ (d, 1H, 5-H, } J = 8.4 \text{ Hz}), \ 6.74 \text{ (d, 1H, 6-H, } J = 8.4 \text{ Hz)}, \ 6.87–6.92 \text{ (m, 2H, 2'-H and 6'-H), 6.96–7.02 \text{ (m, 2H, 3'-H and 5'-H), 7.66 (s, 1H, 3-H).} \]

\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3\): d 45.6 (2C), 50.8 (2C), 55.8, 56.1, 104.8, 105.8, 117.7 (d, 2C, 2J = 21.1 Hz), 118.7 (d, 2C, 2J = 7.7 Hz), 122.8, 135.6, 130.9 (2C), 147.6 (d, 2J = 2.3 Hz), 149.0, 150.0, 157.7 (d, 2J = 240 Hz), 163.5 (NCO). \]

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

Yellow crystals (column chromatographed, CH\(_2\)Cl\(_2\) (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\(_3\)O\(_5\)S: C, 58.95; H, 4.91; N, 9.83; S, 7.50. Found: C, 58.66; H, 5.00; N, 9.68; S,
IR v_max: 1625 (C=O), 1598 (NO2 asym.), 1485 (C≡C Ar), 1335 (NO2 sym.), 3.92 (s, 3H, C-7 OMe), 3.96 (s, 3H, C-4 OMe), 3.98 (s, 3H, 3'-H and 5'-H, J = 9.4 Hz), 7.69 (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). 13C NMR (75 MHz, CDC13): 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, CH2Cl2) (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 C20H21N3O3S: C, 62.64; H, 5.52; N, 10.96; S, 8.32. Found: C, 62.39; H, 5.25; N, 10.99; S, 8.52%. IR v_max: 1619 (C=O), 1600 (C≡N), 1483 (C≡C Ar). 1H NMR (300 MHz, CDCl3): δ 3.63 [m, 4H, CON-(CH2)2], 3.83–3.95 [m, 10H, (CH2)2-N-Ar, C-4 OMe and C-7 OMe], 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). 13C NMR (75 MHz, CDCl3): 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-[(4,7-Dimethoxy-1-benzothien-2-yl) carbonyl]piperazin-1-yl pyrimidine (6f)

White crystals (column chromatographed, CH2Cl2) (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 C19H20N4O3S: 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 v_max: 1627 (C=O), 1589 (C≡N), 1546 (C≡C Ar). 1H NMR (300 MHz, CDCl3): δ 3.81–3.98 [m, 14H, CON-(CH2)2, (CH2)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). 13C NMR (75 MHz, CDCl3): 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.

ACKNOWLEDGMENTS

We thank Proyectos Fondecyt 1050890–1050950 and Proyecto Cepedeq—Facultad, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile.
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