Synthesis of Benzothiophene Analogues of Ketoconazole and Itraconazole

Jordi Bolós*, Santiago Gubert, Lluís Anglada, Aurelio Sacristán and José A. Ortiz

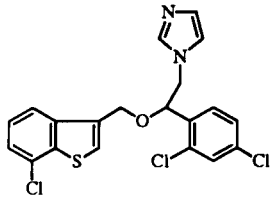
Department of Medicinal Chemistry, Centro de Investigación Grupo Ferrer
Juan de Sada 32, 08028-Barcelona, Spain

Received July 17, 1997

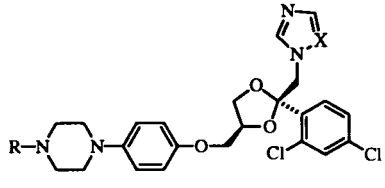
The synthesis of the benzothiophene analogues of the orally active antifungal agents ketoconazole and itraconazole **3a** and **3b** is reported. The key heterocyclic system 3-(1-piperazinyl)benzo[*b*]thiophene is prepared by formation of the enamine between a benzothienone and ethyl 1-piperazinecarboxylate. After elaboration of the respective *N*-substituents, the methoxy group is cleaved with boron tribromide, and *O*-alkylated with the corresponding mesylates.

J. Heterocyclic Chem., **34**, 1709 (1997).

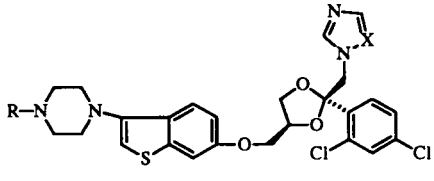
The benzo[*b*]thiophene system is a common feature for a variety of antifungal compounds [1,2]. Among them, sertaconazole (**1**) [1] has been introduced into the market by our laboratory as a potent, wide spectrum topical antifungal. In recent years, there has been an increase in the incidence of systemic mycoses due to immunosuppressive conditions such as AIDS, anticancer chemotherapy and organ transplants. This notwithstanding, relatively few orally active systemic antifungal drugs have received clinical application. Ketoconazole (**2a**) and itraconazole (**2b**), widely used potent oral antifungals, display a phenyl piperazine moiety. In this context, as a part of a program to develop novel antifungal agents, we became interested in potential oral antifungals possessing a 3-(1-piperazinyl)-benzo[*b*]thiophene unit. In this paper, we report the synthesis of the benzothiophene analogues of ketoconazole and itraconazole **3a** and **3b**.



1 Sertaconazole



2a Ketoconazole
2b Itraconazole



3a-b

a X=CH, R=$COCH_3$

b X=N, R=

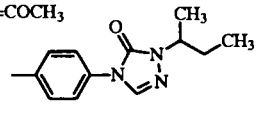


Figure 1

The preparation of the piperazinylbenzothiophene system was achieved by formation of the enamine between 6-methoxybenzothienone (**4**) and ethyl 1-piperazinecarboxylate. This was accomplished by treatment with titanium(IV) chloride as the dehydrating reagent [3]. A modified procedure was employed, which was based on the previous formation of the complex between titanium chloride and an excess of amine [4]. The subsequent deprotection of the carbamate group afforded secondary amine **6**. From this, compound **8**, the precursor of the ketoconazole derivative **3a**, was prepared by *N*-acetylation and ether hydrolysis. Since the piperazinylbenzothiophene unit was susceptible to enamine-like hydrolysis by strongly acidic aqueous media, cleavage of the ether group was performed under anhydrous conditions with boron

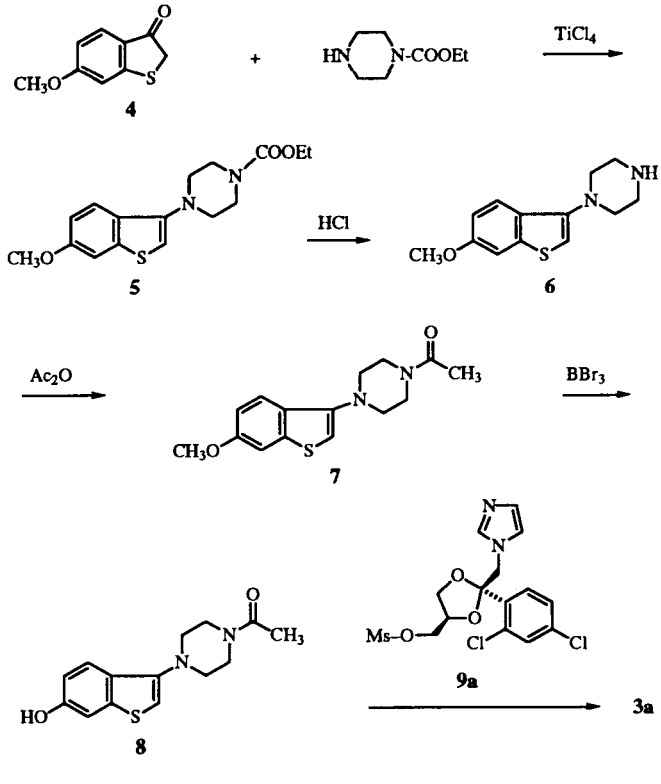


Figure 2

tribromide [5]. Although under the usual conditions [6] cleavage is performed with one third of a mole of boron tribromide and low temperatures, in our case the reaction only succeeded when three moles of the reagent and higher temperatures were used, which can be attributed to an interference with the amine and amide basic groups.

Alternatively, amine **6** was converted to the *p*-nitrophenyl derivative **10** on treatment with 4-chloronitrobenzene. Reduction of the nitro group by catalytic hydrogenation failed, probably because of the presence of the sulfur heterocycle, and reduction with zinc in acidic medium led only to degradation products due to the hydrolysis of the piperazinylbenzothiophene nucleus. A smooth reduction was then achieved by treatment with a solution of titanium(III) chloride in acetic acid [7], affording the amino compound **11** in good yields. Construction of the triazolone ring was performed by a sequence analogous to that described for similar compounds [8]. Thus, amine **11** was treated with phenyl chloroformate, the resulting phenyl carbamate **12** was converted to the semicarbazide **13** on treatment with hydrazine, and closure of the triazolone ring was effected with formamidine acetate in refluxing propanol. Alkylation with 2-bromobutane provided the *sec*-butyl derivative **15**. As in the precedent case, ether hydrolysis was effected with three moles of boron tribromide.

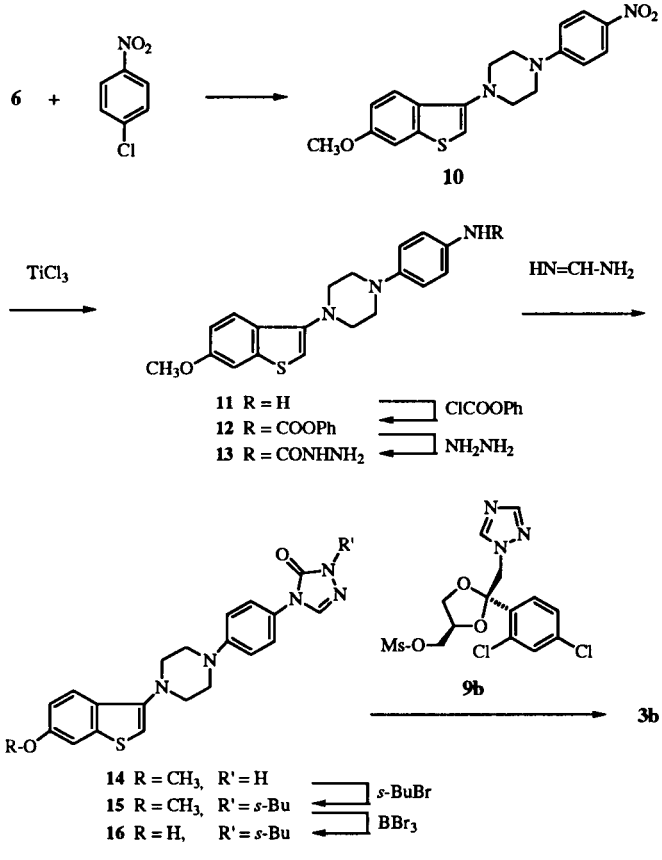


Figure 3

Finally, hydroxy derivatives **8** and **16** were respectively *O*-alkylated with the corresponding sulfonates **9a** [9] and **9b** [10] to afford the benzothiophene analogues of ketoconazole and itraconazole **3a** and **3b**. Interestingly, compound **3b**, which was expected to be a diastereomeric mixture, behave as a single compound, showing no duplicate signals in the ^1H and ^{13}C nmr spectra. A preliminary pharmacological evaluation revealed that compounds **3a** and **3b** were moderately active in several model assays for antifungal compounds [11].

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. Infrared spectra were registered on a Perkin-Elmer 1710 spectrometer as potassium bromide pellets, and only noteworthy absorptions are listed. Nuclear magnetic resonance spectra were recorded on a Varian Gemini 300 spectrometer. Chemical shifts are reported in ppm downfield (δ scale) from tetramethylsilane. Microanalyses were performed on a Perkin-Elmer 2400 elemental analyzer. For column chromatography, silica gel (Merck, 70-230 mesh) was used.

3-[4-(Ethoxycarbonyl)-1-piperazinyl]-6-methoxybenzo[*b*]thiophene (**5**).

To a cooled (-10°) solution of ethyl 1-piperazinecarboxylate (211 g, 1.33 moles) in dry dichloromethane (900 ml) was added dropwise a solution of titanium(IV) chloride (62.6 g, 0.33 moles) in dichloromethane (250 ml). Then, a mixture of 6-methoxy-2,3-dihydrobenzo[*b*]thiophen-3-one (**4**) (60 g, 0.33 mole) and an additional amount of ethyl 1-piperazinecarboxylate (105.5 g, 0.66 mole) in dichloromethane (250 ml) was added at -10°. The resulting solution was gradually heated to boiling, and was stirred under reflux overnight. The solution was cooled and poured into ice-water. The organic layer was washed with 2 *M* hydrochloric acid, and with a saturated solution of sodium bicarbonate. The organic extracts were dried over anhydrous sodium sulfate and vacuum evaporated to afford 83 g of **5** (78%) as an oil, which was used without further purification in the next step. An analytical sample was obtained by column chromatography (chloroform as eluent); ir (potassium bromide): ν 1700, 1245 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.29 (t, J = 7 Hz, 3H, CH_3CH_2), 3.06 (m, 4H, piperazine 2-H and 6-H), 3.69 (m, 4H, piperazine 3-H and 5-H), 3.86 (s, 3H, OCH_3), 4.18 (q, J = 7 Hz, 2H, OCH_2), 6.44 (s, 1H, 2-H), 6.96 (dd, J = 8.7 and 2.1 Hz, 1H, 5-H), 7.21 (d, J = 2.1 Hz, 1H, 7-H), 7.56 (d, J = 8.7 Hz, 1H, 4-H); ^{13}C nmr (deuteriochloroform): δ 14.5 (CH_3CH_2), 43.6 (piperazine 3-C and 5-C), 51.8 (piperazine 2-C and 6-C), 55.2 (OCH_3), 61.2 (OCH_2), 104.6 and 105.1 (5-C and 7-C), 113.5 (2-C), 121.9 (4-C), 127.9 (3a-C), 140.2 (7a-C), 145.6 (3-C), 155.0 (COO), 157.1 (6-C).

Anal. Calcd. for $C_{16}H_{20}N_2O_3S$: C, 59.98; H, 6.29; N, 8.74. Found: C, 59.65; H, 6.40; N, 8.62.

6-Methoxy-3-(1-piperazinyl)benzo[*b*]thiophene, Hydrochloride (**6**).

A solution of **5** (83 g, 0.26 mole) in ethanol (650 ml) and aqueous 3 *M* sodium hydroxide (650 ml) was heated to reflux overnight. Then, the solution was concentrated under vacuum to half its volume, and was extracted with dichloromethane. The organic extracts were washed with brine, dried over anhydrous sodium sulfate, and

evaporated under reduced pressure. The residue was dissolved in absolute ethanol (600 ml), and precipitated by addition of an ethanolic solution of hydrogen chloride. The resulting precipitate was filtered, washed with ethanol, and vacuum dried, to afford 52.6 g (63%) of **6**, mp 279-281°; ir (potassium bromide): ν 1610, 1270, 1055 cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.20-3.40 (m, 8H, piperazine), 3.81 (s, 3H, OCH_3), 6.85 (s, 1H, 2-H), 7.00 (dd, J = 8.8 and 2.3 Hz, 1H, 5-H), 7.50 (d, J = 2.3 Hz, 1H, 7-H), 7.69 (d, J = 8.8 Hz, 1H, 4-H); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 43.0 (piperazine 3-C and 5-C), 48.9 (piperazine 2-C and 6-C), 55.8 (OCH_3), 106.1 and 106.3 (5-C and 7-C), 114.0 (2-C), 122.7 (4-C), 127.7 (3a-C), 140.4 (7a-C), 144.8 (3-C), 157.4 (6-C).

Anal. Calcd. for $C_{13}H_{16}N_2OS$•HCl: C, 54.82; H, 6.02; N, 9.84. Found: C, 55.01; H, 6.24; N, 9.73.

3-(4-Acetyl-1-piperazinyl)-6-methoxybenzo[*b*]thiophene (**7**).

A mixture of **6** (11 g, 38.6 mmoles), acetic anhydride (7.88 g, 77.2 mmoles), sodium acetate (4.75 g, 58 mmoles), and acetic acid (55 ml) was stirred for 4 hours at room temperature. Water was then added, and the mixture was stirred for 30 minutes and extracted twice with chloroform. The organic extracts were washed with saturated solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and evaporated, to afford 9.5 g (85%) of **7**; ir (potassium bromide): ν 1640, 1450, 1250 cm^{-1}; ^1H nmr (deuteriomethanol): δ 2.10 (s, 3H, $COCH_3$), 2.94 (m, 4H, piperazine 2-H and 6-H), 3.61 (t, J = 5 Hz, 2H, piperazine 3-H), 3.71 (t, J = 5 Hz, 2H, piperazine 5-H), 3.80 (s, 3H, OCH_3), 6.51 (s, 1H, 2-H), 6.96 (dd, J = 8.7 and 2.4 Hz, 1H, 5-H), 7.31 (d, J = 2.4 Hz, 1H, 7-H), 7.59 (d, J = 8.7 Hz, 1H, 4-H); ^{13}C nmr (deuteriomethanol): δ 21.2 (CH_3CO), 42.8 (piperazine 3-C), 47.5 (piperazine 5-C), 53.1 and 53.6 (piperazine 2-C and 6-C), 56.0 (OCH_3), 106.2 and 106.5 (5-C and 7-C), 114.7 (2-C), 123.2 (4-C), 129.4 (3a-C), 142.0 (7a-C), 146.9 (3-C), 159.0 (6-C), 171.4 (C=O). An analytical sample was obtained by crystallization from ethyl acetate-diethyl ether, to afford a solid, mp: 148-150°.

Anal. Calcd. for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25; N, 9.65. Found: C, 62.23; H, 6.41; N, 9.29.

3-[4-(4-Nitrophenyl)-1-piperazinyl]-6-methoxybenzo[*b*]thiophene (**10**).

A suspension of **6** (30.2 g, 94 mmoles), 4-chloronitrobenzene (17.3 g, 110 mmoles), and potassium carbonate (15.9 g, 115 mmoles) in dimethyl sulfoxide (125 ml) was slowly heated to 120° and stirred at this temperature for 16 hours. After cooling to room temperature, the reaction mixture was poured dropwise onto 800 ml of ice water. The resulting precipitate was filtered, washed with water and then suspended in methanol with stirring. The product was filtered and vacuum dried at 50° to afford 34 g (98%) of **10**, mp 158-160°; ir (potassium bromide): ν 1600, 1320, 1240 cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.17 (m, 4H, piperazine 2-H and 6-H), 3.69 (m, 4H, piperazine 3-H and 5-H), 3.82 (s, 3H, OCH_3), 6.77 (s, 1H, 2-H), 7.01 (dd, J = 8.7 and 2.1 Hz, 1H, 5-H), 7.11 (d, J = 9.5 Hz, 2H, phenyl 2-H and 6-H), 7.51 (d, J = 2.1 Hz, 1H, 7-H), 7.70 (d, J = 8.7 Hz, 1H, 4-H), 8.10 (d, J = 9.5 Hz, 2H, phenyl 3-H and 5-H).

Anal. Calcd. for $C_{19}H_{19}N_3O_3S$: C, 61.77; H, 5.18; N, 11.37. Found: C, 61.49; H, 5.25; N, 11.14.

3-[4-(4-Aminophenyl)-1-piperazinyl]-6-methoxybenzo[*b*]thiophene (**11**).

To a suspension of **10** (19 g, 15 mmoles) in glacial acetic acid (250 ml) was added a 15% solution of titanium(III) chloride (370 ml, 0.43 mole) and the resulting solution was stirred for 30 minutes. After cooling with ice, the solution was basified with 3 *M* sodium hydroxide (2.5 l). Dichloromethane (1l) was added, and the suspension was filtered. The organic layer was separated, dried over anhydrous sodium sulfate, and evaporated to give 12.3 g (70%) of amine **11**. An analytical sample was obtained by column chromatography (chloroform-methanol 95:5 as eluent), dissolved in ethanol and precipitated by addition of an ethanolic solution of hydrogen chloride, mp 207-210°; ir (potassium bromide): ν 3200-3600, 1500, 1220 cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.22 (m, 4H, piperazine 2-H and 6-H), 3.43 (m, 4H, piperazine 3-H and 5-H), 3.81 (s, 3H, OCH_3), 4.00 (br s, 3H, NH_3^+), 6.80 (s, 1H, 2-H), 7.01 (dd, J = 8.7 and 2.4 Hz, 1H, 5-H), 7.17 (d, J = 9 Hz, 2H, phenyl 2-H and 6-H), 7.24 (d, J = 9 Hz, 2H, phenyl 3-H and 5-H), 7.51 (d, J = 2.4 Hz, 1H, 7-H), 7.69 (d, J = 8.7 Hz, 1H, 4-H).

Anal. Calcd. for $C_{19}H_{21}N_3OS$•HCl: C, 60.71; H, 5.90; N, 11.18; Cl, 9.43; S, 8.53. Found: C, 60.47; H, 6.12; N, 10.95; Cl, 9.10; S, 8.26.

6-Methoxy-3-[[4-(4-phenoxycarbonylamino)phenyl]piperazin-1-yl]benzo[*b*]thiophene (**12**).

To a solution of **11** (12.3 g, 36 mmoles) in chloroform (175 ml) and pyridine (50 ml) was added dropwise over a period of 15 minutes phenyl chloroformate (5.9 g, 38 mmoles). The solution was stirred for 2 hours, and washed with 2-*M* hydrochloric acid and with brine. Evaporation afforded a solid, which was suspended in diethyl ether and filtered to give, after drying, 11.6 g (69%) of carbamate **12**, which was used without further purification; ir (potassium bromide): ν 3350, 1720, 1700, 1600, 1220 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.28 (m, 4H, piperazine 2-H and 6-H), 3.36 (m, 4H, piperazine 3-H and 5-H), 3.87 (s, 3H, OCH_3), 6.49 (s, 1H, 2-H), 6.82 (br s, 1H, NH), 6.98 (d, J = 8.7 Hz, 2H, phenyl), 7.00 (dd, J = 9 and 2.4 Hz, 1H, 5-H), 7.18-7.26 (m, 4H, phenyl), 7.28 (d, J = 2.4 Hz, 1H, 7-H), 7.38 (m, 3H, phenyl), 7.66 (d, J = 9 Hz, 1H, 4-H).

3-[4-[4-(Hydrazinocarbonylamino)phenyl]piperazin-1-yl]-6-methoxybenzo[*b*]thiophene (**13**).

A solution of carbamate **12** (11.5 g, 25 mmoles) and hydrazine hydrate (6.6 g, 132 mmoles) in 50 ml of dioxane was heated to reflux for 2 hours. After cooling, the mixture was poured dropwise on water (300 ml) and the resulting crystals were filtered, washed with water, and dried to give 8.0 g (80%) of **13**, mp: 196-198°; ir (potassium bromide): ν 1670, 1600, 1520, 1230 cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.17 (m, 4H, piperazine 2-H and 6-H), 3.26 (m, 4H, piperazine 3-H and 5-H), 3.82 (s, 3H, OCH_3), 4.32 (br s, 2H, NH_2), 6.74 (s, 1H, 2-H), 6.91 (d, J = 8.7 Hz, 2H, phenyl 2-H and 6-H), 7.00 (dd, J = 8.7 and 2.1 Hz, 1H, 5-H), 7.26 (br s, 1H, NH), 7.39 (d, J = 8.7 Hz, 2H, phenyl 3-H and 5-H), 7.50 (d, J = 2.1 Hz, 1H, 4-H), 7.66 (d, J = 8.7 Hz, 1H, 4-H), 8.41 (br s, 1H, NH); ^{13}C nmr (deuteriochloroform + deuteriomethanol): δ 50.1 and 52.2 (piperazine), 55.5 (OCH_3), 104.5 and 105.4 (5-C and 7-C), 113.5 (4-C), 117.0 (phenyl 2-C and 6-C), 120.8 (phenyl 3-C and 5-C), 122.1 (2-C), 128.2 (3a-C), 130.9 (phenyl 4-C), 140.5 (7a-C), 145.8 (3-C), 147.2 (phenyl 1-C), 157.2 (6-C), 158.3 (C=O).

Anal. Calcd. for $C_{20}H_{24}N_5O_2S$: C, 60.28; H, 6.07; N, 17.57. Found: C, 59.97; H, 6.34; N, 17.28.

6-Methoxy-3-[4-[4-(3-oxo-3,4-dihydro-2*H*-1,2,4-triazol-4-yl)phenyl]piperazin-1-yl]benzo[*b*]thiophene (**14**).

Formamidine acetate (9.3 g, 89 mmoles) and **13** (8.0 g, 20 mmoles) in 1-propanol (400 ml) were stirred and refluxed for

3 hours. The solution was stored in the refrigerator overnight, and the product crystallized. The solid was filtered, washed with propanol, and dried, to afford 5.7 g (70%) of **14**, mp 240-242°; ir (potassium bromide): ν 1700, 1515, 1230 cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.18 (m, 4H, piperazine 2-H and 6-H), 3.39 (m, 4H, piperazine 3-H and 5-H), 3.83 (s, 3H, OCH_3), 6.76 (s, 1H, 2-H), 7.01 (dd, J = 8.7 and 2.1 Hz, 1H, 5-H), 7.11 (d, J = 8.7 Hz, 2H, phenyl 2-H and 6-H), 7.49 (d, J = 8.7 Hz, 2H, phenyl 3-H and 5-H), 7.50 (d, J = 2.1 Hz, 1H, 7-H), 7.68 (d, J = 8.7 Hz, 1H, 4-H), 8.25 (s, 1H, triazolone); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 48.5 and 49.0 (piperazine), 55.4 (OCH_3), 104.7 and 105.4 (5-C and 7-C), 113.6 (4-C), 116.3 (phenyl 2-C and 6-C), 122.0 (2-C), 123.8 (phenyl 3-C and 5-C), 124.7 (phenyl 4-C), 128.1 (3a-C), 136.2 (triazolone CH), 140.5 (7a-C), 145.7 (3-C), 150.6 (phenyl 1-C), 154.0 (C=O), 157.3 (6-C).

Anal. Calcd. for $C_{21}H_{21}N_5O_2S$: C, 61.90; H, 5.19; N, 17.19. Found: C, 62.26; H, 5.24; N, 17.03.

6-Methoxy-3-[4-[4-[2-(1-methylpropyl)-3-oxo-3,4-dihydro-2*H*-1,2,4-triazol-4-yl]phenyl]piperazin-1-yl]benzo[*b*]thiophene (**15**).

To a suspension of potassium hydroxide powder (0.39 g, 6.3 mmoles) and **14** (2.0 g, 4.3 mmoles) in dimethyl sulfoxide (65 ml) was added 2-bromobutane (0.78 g, 5.7 mmoles) and the mixture was stirred for 3 hours, and then poured onto 90 ml of water. The product was extracted with chloroform, washed with brine, and vacuum dried to afford a solid, which was chromatographed on silica with chloroform-methanol (98:2) as the eluent to yield 1.39 g (61%) of **15**, mp 157-160°; ir (potassium bromide): ν 1700, 1510, 1225 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.91 (t, J = 7 Hz, 3H, CH_3CH_2), 1.39 (d, J = 6.6 Hz, 3H, CH_3CH), 1.65-1.95 (m, 2H, CH_2CH_3), 3.27 (m, 4H, piperazine 2-H and 6-H), 3.41 (m, 4H, piperazine 3-H and 5-H), 3.87 (s, 3H, OCH_3), 4.30 (m, 1H, CHMeEt), 6.49 (s, 1H, 2-H), 7.00 (dd, J = 8.7 and 2.1 Hz, 1H, 5-H), 7.04 (d, J = 9Hz, 2H, phenyl 2-H and 6-H), 7.27 (d, J = 2.1 Hz, 1H, 7-H), 7.43 (d, J = 9 Hz, 2H, phenyl 3-H and 5-H), 7.62 (s, 1H, triazolone), 7.65 (d, J = 8.7 Hz, 1H, 4-H).

Anal. Calcd. for $C_{25}H_{29}N_5O_2S$: C, 64.77; H, 6.31; N, 15.11. Found: C, 64.82; H, 6.54; N, 14.97.

3-(4-Acetyl-1-piperazinyl)-6-hydroxybenzo[*b*]thiophene (**8**).

To a cooled solution (-10°) of **7** (1.45 g, 5 mmoles) in dry dichloromethane (100 ml) was added dropwise a 1 *M* solution of boron tribromide (15 ml) in dichloromethane. The solution was stirred for 1 hour at room temperature and then was heated to reflux overnight. The reaction mixture was cooled in an ice bath and then, 5 ml of methanol and 25 ml of 3 *M* sodium hydroxide were added sequentially. The aqueous layer was separated and the organic layer was extracted again with 3 *M* sodium hydroxide. The aqueous extracts were neutralized with hydrochloric acid to *p*H 6-7 and the insoluble residue that appeared was extracted with ethyl acetate, dried over anhydrous sodium sulfate, and vacuum evaporated to afford a gum, which was suspended in diethyl ether and filtered to give 1 g of solid **8** (72%). An analytical sample was obtained by crystallization from ethyl acetate, mp 185-187°; ir (potassium bromide): ν 2500-3500, 1620, 1260 cm^{-1}; ^1H nmr (deuteriomethanol): δ 2.18 (s, 3 H, CH_3), 3.07 (m, 4H, piperazine 2-H and 6-H), 3.68 (t, J = 5 Hz, 2H, piperazine 3-H), 3.85 (t, J = 5 Hz, 2H, piperazine 5-H), 6.40 (s, 1H, 2-H), 6.96 (dd, J = 8.7 and 2.1 Hz, 1 H, 5-H), 7.26 (d, J = 2.1 Hz, 1 H, 6-H), 7.55 (d, J = 8.7 Hz, 1 H, 4-H); ^{13}C nmr (deuteriomethanol): δ 21.3 (CH_3), 41.8 (piperazine 3-C), 46.5 (piperazine 5-C), 52.0 and 52.3 (piperazine 2-C and 6-C), 104.8 and 108.4 (5-C and 7-C), 113.8 (2-C), 122.1 (4-C), 127.8 (3a-C), 140.5 (7a-C), 145.5 (3-C), 154.1 (6-C), 169.4 (C=O).

Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14. Found: C, 60.93; H, 5.51; N, 9.98.

6-Hydroxy-3-[4-[4-[2-(1-methylpropyl)-3-oxo-3,4-dihydro-2*H*-1,2,4-triazol-4-yl]phenyl]piperazin-1-yl]benzo[*b*]thiophene (**16**).

Operating as above, from 1.35 g (2.9 mmoles) of **15** and 8.7 ml of an 1 *M* solution of boron tribromide, **16** (0.86 g, 65%) was obtained, mp 177-180°; ir (potassium bromide): ν 3100-3500, 1690, 1520, 1230 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.92 (t, J = 7.2 Hz, 3H, CH_3CH_2), 1.42 (d, J = 6.6 Hz, 3H, CH_3CH), 1.75-1.95 (m, 2H, CH_2CH_3), 3.20 (m, 4H, piperazine 2-H and 6-H), 3.27 (m, 4H, piperazine 3-H and 5-H), 4.32 (m, 1H, CHMeEt), 6.41 (s, 1H, 2-H), 6.85 (dd, J = 8.7 and 2.1 Hz, 1H, 5-H), 6.91 (d, J = 9Hz, 2H, phenyl 2-H and 6-H), 7.13 (d, J = 2.1 Hz, 1H, 7-H), 7.36 (d, J = 9 Hz, 2H, phenyl 3-H and 5-H), 7.53 (d, J = 8.7 Hz, 1H, 4-H), 7.63 (s, 1H, triazolone); ^{13}C nmr (deuteriochloroform): δ 10.9 (CH_3CH_2), 19.3 (CH_3CH), 28.5 (CH_2CH_3), 48.8 and 52.1 (piperazine), 53.1 (CHMeEt), 104.1 and 108.6 (5-C and 7-C), 113.9 (4-C), 116.2 (phenyl 2-C and 6-C), 122.1 (2-C), 124.3 (phenyl 3-C and 5-C), 125.0 (phenyl 4-C), 127.7 (3a-C), 134.4 (triazole CH), 140.5 (7a-C), 145.9 (3-C), 150.5 (phenyl 1-C), 152.3 (C=O), 154.3 (6-C).

Anal. Calcd. for $C_{24}H_{27}N_5O_2S$: C, 64.12; H, 6.05; N, 15.58. Found: C, 63.90; H, 6.34; N, 15.23.

(±)-*cis*-3-(4-Acetylpiperazin-1-yl)-6-[[2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]benzo[*b*]-thiophene (**3a**).

Sodium hydride 80% dispersion in paraffin (43 mg, 1.45 mmoles), previously washed with hexane, was suspended in dry dimethyl sulfoxide (10 ml) and **8** (400 mg, 1.45 mmoles) was added portionwise. After stirring for 30 minutes, *cis*-[2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl(methyl methanesulfonate (**9a**) [9] (600 mg, 1.47 mmoles) was added and the mixture was heated at 60-70° for 2 hours. Then, it was poured on water, and was extracted with dichloromethane. Evaporation of the organic extracts afforded a solid, which was suspended in diisopropyl ether, filtered, and crystallized from toluene-hexane to afford 500 mg (59%) of **3a**, mp 95-97°; ir (potassium bromide): ν 1640, 1470, 1250, 1230, 1050 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.16 (s, 3H, CH_3), 3.09 (m, 4H, piperazine 2-H and 6-H), 3.39 (dd, J = 9.5 and 7.5 Hz, 1H, dioxolane 5-H), 3.69 (t, J = 5 Hz, 2H, piperazine 3-H), 3.79 (m, 2H, dioxolane 4-CH_2), 3.83 (t, J = 5 Hz, 2H, piperazine 5-H), 3.90 (dd, J = 9.5 and 7.5 Hz, 1H, dioxolane 5-H), 4.39 (m, 1H, dioxolane 4-H), 4.42 and 4.52 (2d, J = 14.7 Hz, 2H, dioxolane 2-CH_2), 6.48 (s, 1H, 2-H), 6.95 (dd, J = 8.7 and 2.1 Hz, 1H, 5-H), 6.98 (br s, 1H, imidazole 5-H), 7.00 (br s, 1H, imidazole 4-H), 7.18 (d, J = 2.1 Hz, 1H, 7-H), 7.27 (dd, J = 8.7 and 2 Hz, phenyl 5-H), 7.48 (d, J = 2 Hz, 1H, phenyl 3-H), 7.54 (br s, 1H, imidazole 2-H), 7.60 (m, 2H, 4-H and phenyl 5-H); ^{13}C nmr (deuteriochloroform): δ 21.5 (CH_3), 41.6 (piperidine 3-C), 46.5 (piperidine 5-C), 51.3 (dioxolane 2-CH_2), 52.2 and 52.5 (piperidine 2-C and 6-C), 67.5 and 67.6 (dioxolane 5-C and 4-CH_2), 74.6 (dioxolane 4-C), 105.6 and 106.9 (5-C and 7-C), 108.0 (dioxolane 2-C), 113.7 (2-C), 121.1 (imidazole 5-C), 122.2 (4-C), 127.1 (phenyl 5-C), 128.4 (imidazole 4-C), 128.7 (3a-C), 129.4 (phenyl 6-C), 131.3 (phenyl 3-C), 132.9 (phenyl 2-C), 134.4 (phenyl

1-C), 135.8 (phenyl 4-C), 138.8 (imidazole 2-C), 140.5 (7a-C), 145.6 (3-C), 156.1 (6-C), 168.9 (C=O).

Anal. Calcd. for $C_{28}H_{28}Cl_2N_4O_4S$: C, 57.24; H, 4.80; N, 9.54; Cl, 12.07; S, 5.46. Found: C, 57.52; H, 4.67; N, 9.20; Cl, 11.82; S, 5.80.

(±)-*cis*-3-[4-[4-[2-(1-Methylpropyl)-3-oxo-3,4-dihydro-2*H*-1,2,4-triazol-4-yl]phenyl]piperazin-1-yl]-6-[[2-(2,4-dichlorophenyl-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]benzo[*b*]thiophene (**3b**).

Operating as above, from 0.9 g (2 mmoles) of **16** and 0.8 g (2 mmoles) of *cis*-[2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl(methyl methanesulfonate (**9b**) [10] was obtained a gum, which was purified by column chromatography on silica (chloroform:methanol 99:1 as eluent) to afford 0.97 (64%) of **3b**, mp 103-106°; ir (potassium bromide): ν 1700, 1520, 1230 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.91 (t, J = 7.2 Hz, 3H, CH_3CH_2), 1.40 (d, J = 6.6 Hz, 3H, CH_3CH), 1.70-2.00 (m, 2H, CH_2CH_3), 3.25 (m, 4H, piperazine 2-H and 6-H), 3.41 (m, 4H, piperazine 3-H and 5-H), 3.62 and 3.80-4.00 (m, 4H, dioxolane 5-H and 4-CH_2), 4.29 (m, 1H, C*H*MeEt), 4.40 (m, 1H, dioxolane 4-H), 4.76 and 4.83 (2d, J = 14.5 Hz, 2H, dioxolane 2-CH_2), 6.51 (s, 1H, 2-H), 6.95 (dd, J = 8.7 and 2.1 Hz, 1H, 5-H), 7.03 (d, J = 9 Hz, 2H, phenyl' 2-H and 6-H), 7.20 (d, J = 2.1 Hz, 1H, 7-H), 7.25 (dd, J = 8.4 and 1.8 Hz, 1H, phenyl 5-H), 7.44 (d, J = 8.7 Hz, 2H, phenyl' 3-H and 5-H), 7.47 (d, J = 2.1 Hz, 1H, phenyl 3-H), 7.58 (d, J = 8.7 Hz, 1H, phenyl 6-H), 7.64 (s, 1H, triazolone), 7.66 (d, J = 9 Hz, 1H, 4-H), 7.90 (s, 1H, triazole 5-H), 8.22 (s, 1H, triazole 3-H); ^{13}C nmr (deuteriochloroform): δ 10.8 (CH_3CH_2), 19.2 (CH_3CH), 28.4 (CH_2CH_3), 49.1 and 52.1 (piperazine), 52.6 (C*H*MeEt), 53.5 (dioxolane 2-CH_2), 67.2 and 67.5 (dioxolane 5-C and 4-CH_2), 74.5 (dioxolane 4-C), 105.1 and 107.5 (5-C and 7-C), 106.7 (dioxolane 2-C), 113.7 (2-C), 116.3 (phenyl' 2-C and 6-C), 123.3 (phenyl' 3-C and 5-C), 122.3 (4-C), 125.7 (phenyl' 4-C), 127.0 (phenyl 5-C), 128.8 (3a-C), 129.4 (phenyl 6-C), 131.2 (phenyl 3-C), 132.9 (phenyl 2-C), 133.7 (triazolone C-H), 135.8 (phenyl 4-C), 140.4 (7a-C), 144.7 (3-C), 145.9 (triazole 5-C), 150.3 and 151.1 (C=O and phenyl' 1-C), 151.8 (triazole 3-C), 155.9 (6-C).

Anal. Calcd. for $C_{37}H_{38}Cl_2N_8O_4S$: C, 58.34; H, 5.03; N, 14.71; Cl, 9.31; S, 4.21. Found: C, 58.12; H, 5.25; N, 14.56; Cl, 9.17; S, 4.11.

Acknowledgement.

We thank Mr. Joan Nieto for accurate experimental work, and Mr. José M. Fernández for the analytical determinations.

REFERENCES AND NOTES

[1a] M. Raga, C. Palacín, J. M. Castelló, J. A. Ortiz, M. R. Cuberes and M. Moreno-Mañas, *Eur J. Med. Chem.*, **21**, 329 (1986); [1b] J. M. Castelló, *Drugs Fut.*, **16**, 213 (1991).

[2a] P. Nussbaumer, G. Petrany and A. Stütz, *J. Med. Chem.*, **34**, 65 (1991); [2b] T. Al Nakib, M. J. Meegan, A. M. Looney and M. L. Burke *J. Chem. Res. (S)*, 170 (1994).

[3] W. A. White and H. Weingarten. *J. Org. Chem.*, **32**, 213 (1967).

[4] R. Carlson, U. Larsson and L. Hansson, *Acta Chem. Scand.*, **46**, 1211 (1992).

[5a] J. F. W. McOmie and M. L. Watts, *Chem. Ind. (London)*, 1658 (1963); [5b] J. F. W. McOmie, M. L. Watts and D. E. West, Tetrahedron, 24, 2289 (1968).

[6] see, for example: J. F. W. McOmie and D. E. West, *Org. Synth., Coll. Vol.* V, 412 (1973).

[7a] Tse-Lok Ho and C. M. Wong, *Synthesis*, **45** (1974); [7b] M. Somei, K. Kato and S. Inoue, *Chem. Pharm. Bull.*, **28**, 2515 (1980).

[8] J. Heeres, L. J. J. Backx and J. Van Cutsem *J. Med. Chem.* **27**, 894 (1984).

[9] J. Heeres, L. J. J. Backx, J. H. Mostmans and J. Van Cutsem *J. Med. Chem.*, **22**, 1003 (1979).

[10] J. Heeres, R. Hendrickx and J. Van Cutsem *J. Med. Chem.*, **26**, 611 (1983).

[11] C. Palacín, unpublished results.