Synthesis of a Benzo[5,6]cyclohepta[1,2-*b*]thiophene and Thieno[3,2-*c*]-benzazepine Derivatives

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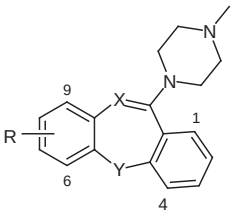
Abstract: A new series of 2-methyl-4-(4-methylpiperazin-1-yl)-10*H*-benzo[5,6]cyclohepta[1,2-*b*]thiophene (**5**) and 2-methyl-4-(4-methylpiperazin-1-yl)thieno[3,2-*c*][1]benzazepine derivatives **6b–f** have been synthesized from 2-methylthiophene and phthalic anhydride. Preparation of the key intermediate 2-methyl-4,5-dihydro-10*H*-benzo[5,6]cyclohepta[1,2-*b*]thiophene-4-one (**12**) and 2-methylthieno[3,2-*c*][1]benzazepine-4(5*H*),10-dione (**16**) were carried out by intramolecular dehydration of the phenylacetic acid **11** and Lewis acid associated cyclization of the isocyanate **14**, respectively.

Key words: cyclization, Curtius rearrangement, antipsychotic agents

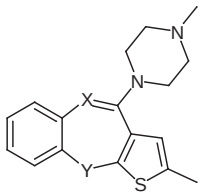
Dibenzodiazepine, dibenzothiazepine and dibenzoxazepine derivatives have desirable antipsychotic activities.[1–4] Investigations into the synthesis of these novel compounds and their biological activities have made exciting progress in the medical field. It is known that a slight modification of this tricycle structure leads to a profound alteration of the activity and toxicity profile. Indeed, clozapine (**1**; X = N, Y = NH, R = 8-Cl, Figure 1) is an atypical neuroleptic agent that very rarely causes extrapyramidal symptoms (EPS) in men, but its therapeutic use has been hampered because of its toxicity (agranulocytosis[5]). On the other hand, clothiapine (**2**; X = N, Y = S, R = 2-Cl) and loxapine (**3**; X = N, Y = O, R = 2-Cl) are potent antipsychotic agents with a strong propensity to induce EPS. Most attempts to develop clinically useful heteroazepine (Y = NH, O, S) have been unsuccessful for thirty years, because of this unexpected toxicity or the unacceptable side effects of these compounds. We speculated that the presence of heteroatoms (X = N, Y = NH, O or S) in these tricyclic compounds may be the origin of their toxicological problems.

It is known that pharmacological activity is maintained even though a benzene ring was replaced by the isostere thiophene ring.[6] Indeed, olanzapine (**4**; X = N, Y = NH, Figure 2), which is a thienobenzodiazepine derivative structurally related to **1**, is an effective antipsychotic agent.[7] Furthermore, the biological activity of azepine **6a** (X = N, Y = CH_2), which is a thienobenzazepine derivative structurally related to **4**, was also reported.[8] As an alternate modification of the olanzapine structure, we designed a benzocycloheptathiophene derivative **5** (X = CH, Y = CH_2), which is a seven-membered carbocyclic analogue of olanzapine, and thienobenzazepine derivatives **6b–f** [X = N, Y = C(O), C = CR_2 or CHR], which are structurally similar to azepine **6a**. In this paper, we describe the synthesis of benzo[5,6]cyclohepta[1,2-*b*]thiophene derivative **5** and thieno[3,2-*c*]benzazepine derivatives **6b–f**.



	X	Y	R
clozapine (**1**)	N	NH	8-Cl
clothiapine (**2**)	N	S	2-Cl
loxapine (**3**)	N	O	2-Cl

Figure 1 The structures of clozapine (**1**), clothiapine (**2**) and loxapine (**3**)



	X	Y
olanzapine (**4**)	N	NH
5	CH	CH_2
6a	N	CH_2
6b	N	C=O
6c	N	$C=CH_2$
6d	N	$C=(CH_3)_2$
6e	N	CH-OH
6f	N	CH-OMe

Figure 2 The structures of olanzapine (**4**), the benzocycloheptathiophene derivative **5** and the thieneobenzazepine derivatives **6a–f**

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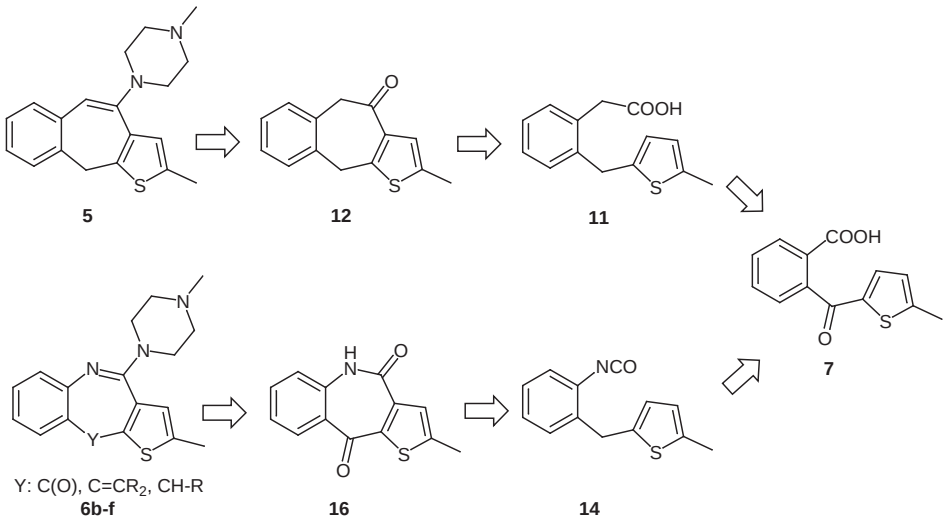
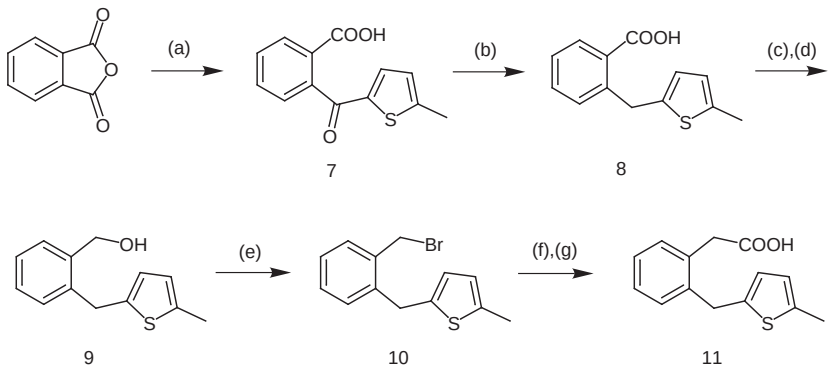


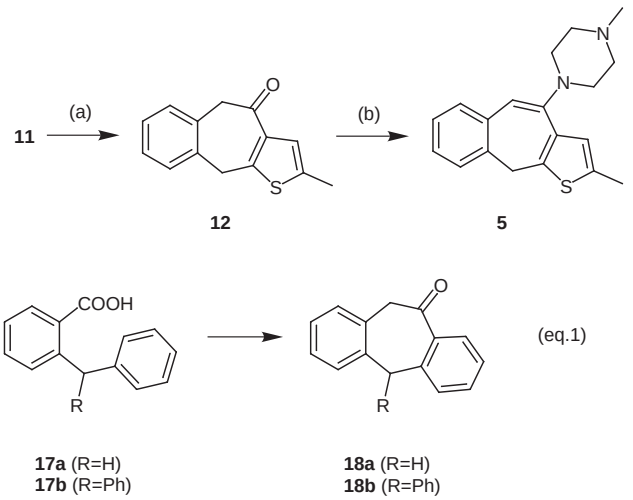
Scheme 1

The retro synthetic pathway for the target molecules **5** and **6b**–**f** is shown in Scheme 1. In the retro synthetic analysis, **5** and **6b**–**f** were considered to be synthesized via the key cyclization reactions of **11** and **14**, respectively. Furthermore, the intermediates **11** and **14** were planned to be derived from a common starting material **7**. The key intermediate **11** was synthesized from phthalic anhydride (Scheme 2). 2-(5-Methyl-2-thenoyl)benzoic acid (**7**) was prepared from 2-methylthiophene and phthalic anhydride according to the method of MacDowell and Wisowaty.[9] Although the preparation of thenylbenzoic acid (**8**) by the reduction of **7** in the presence of triethylsilane (3.1 equiv to **7**) was not successful, reduction of **7** was accomplished by zinc dust in ammonia solution (28–30%, as NH_3) to give **8** in 67% yield. The carboxylic acid **8** was reduced to the corresponding benzyl alcohol **9** (2 steps, 95%) with $LiAlH_4$ via the methyl ester derived from **8**. Bromination of **9** with hydrobromic acid,[10] cyanation of **10** with potassium cyanide in DMF–H_2O, and hydrolysis of the cyanide using HCl–HOAc led to the carboxylic acid **11**. As reported previously,[11] dihydrodibenzocycloheptene derivative **18a** (R = H) was prepared by cyclization of the corresponding 2-benzylbenoic acid (**17a**) in polyphosphoric acid (PPA) (Scheme 3, eq. 1). However, treatment of **11** with PPA resulted in a poor yield of the desired product because of the presence of inseparable byproducts. In addition, an acid chloride prepared from **17b** (R = Ph) resulted in the formation of **18b** (yield: 18%) and the starting material **17b** was recovered.[12] Therefore, phosphorus pentoxide was chosen as the dehydrating agent in this cyclization. Treatment of **11** with phosphorus pentoxide in refluxing toluene formed the corresponding cycloheptathiophene **12** in good yield (65%). Finally, **12** was converted to the desired product **5** by the reaction of 1-methylpiperazine in the presence of titanium(IV) chloride.

The key intermediate **16** of the thieno[3,2-*c*]benzoxazepine derivatives **6b**–**f** were synthesized from 2-(5-methyl-2-thenoyl)benzoic acid (**7**) (Scheme 4). A Curtius rearrangement of acyl azide conducted from active mixed anhydride of carboxylic acid **7** afforded the corresponding keto isocyanate **13**. Liégeois et al.[4] have reported that treatment of 2-[(4-chlorophenyl)thio]nicotinoyl isocyanate, which was prepared from the corresponding acyl azide, in the presence of aluminum chloride in 1,2-dichlo-



Scheme 2 *Reagents and conditions*: (a) 2-methylthiophene, $AlCl_3$, 1,2-dichloroethane, 40 °C; (b) Zn, $CuSO_4$, ammonia solution (28–30%, as NH_3), 70 °C; (c) $SOCl_2$, MeOH, reflux; (d) $LiAlH_4$, THF, r.t.; (e) 48% HBr, reflux (f) KCN, DMF–H_2O, r.t.; (g) concd HCl, HOAc, 55 °C



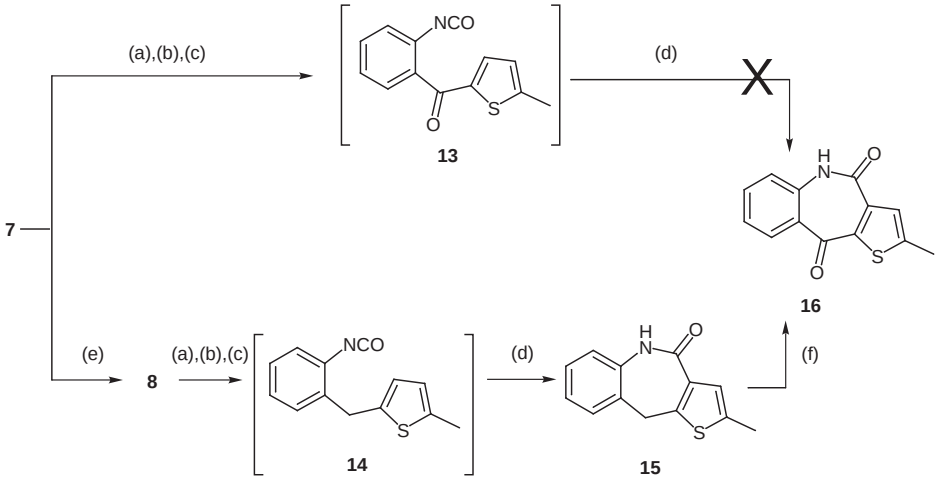
Scheme 3 *Reagents and conditions*: (a) P_2O_5, toluene, reflux; (b) 1-methylpiperazine, $TiCl_4$, benzene, 55 °C

robenzene at 160–170 °C afforded 8-chloro-5*H*-pyrido[2,3-*b*][1,4]benzothiazepine-6-one in 20–30% yield. In a similar manner, the azepine ring system of **16** could be constructed from the isocyanate **13**. However, treatment of **13** with aluminum chloride in 1,2-dichlorobenzene was unsuccessful. As a reason, it seemed likely that the ketone unit of **13** would reduce the neucleophilicity at the 2-thiophenyl position. Next, to increase the neucleophilicity at the 2-thiophenyl position, the cyclization of (2-thenyl)phenyl isocyanate derivative **14** was attempted instead of (2-thenoyl)phenyl isocyanate derivative **13**. Fortunately, a Curtius rearrangement of acyl azide obtained from active mixed anhydride of carboxylic acid **8** followed by treatment with aluminum chloride at 100 °C in 1,2-dichlorobenzene gave azepine **15** in 51% yield. Both the acyl azide and the isocyanate **14** have a similar R_f value on TLC in the Curtius rearrangement (from the acyl azide of **8** to the isocyanate **14**). Therefore, the end of the reaction was judged by the FT-IR spectrum (in neat). The absorption of the acyl azide (CON_3) group and the isocyanate (N=C=O group appeared at 2278 and 2133 cm^{-1}, respectively. As a result, the reaction was completed in 60 minutes at 60 °C. The resulting isocyanate **14** was used in the next reaction without purification to give the lactam **15**. Furthermore, synthesis of the key intermediate **16** was accomplished by oxidation[13] of **15** with potassium permanganate in acetone in 88% yield.

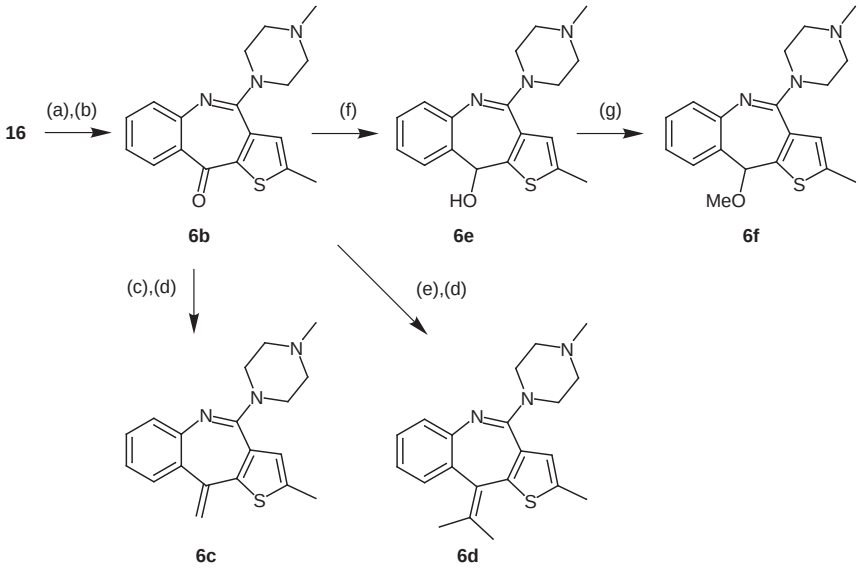
Syntheses of the azepines **6b**–**f** are depicted in Scheme 5. Treatment of **16** with phosphorus oxychloride formed the corresponding imino chloride intermediate, which was converted to the methylpiperazine derivative **6b** (yield: 80%). A Grignard reaction with methylmagnesium bromide on the ketone **6b** followed by dehydration with hydrochloric acid gave exomethylene derivative **6c** in 59% yield. In a similar manner isopropylidene derivative **6d** was synthesized from **6b** (yield: 95%). On the other hand, **6b** was reduced with $NaBH_4$ in THF–MeOH to give the alcohol **6e**, and treatment of **6e** with MeOH in the presence of sulfuric acid resulted in the corresponding methyl ether **6f** (2 steps; 54%).

In conclusion, we have synthesized a new series of 2-methyl-4-(4-methylpiperazin-1-yl)-10*H*-benzo[5,6]cyclohepta[1,2-*b*]thiophene (**5**) and 2-methyl-4-(4-methylpiperazin-1-yl)thieno[3,2-*c*][1]benzazepine derivatives **6b**–**f** from 2-methylthiophene and phthalic anhydride. Compounds **5** and **6b**–**f** have been tested for their neuroleptic activity. The details of the pharmacological properties will be described elsewhere.

Column chromatography was performed using Merck Kieselgel 60. Melting points were obtained on a Büchi 535 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Jeol α400 spectrometer (400 MHz) using TMS as an internal standard. Mass spectra were measured on a Jeol-JMS-DX300 instrument. IR spectra were recorded on a Jasco FT/IR-5300 spectrometer. Element analyses were performed on a Yanako CHN coder MT-5, and



Scheme 4 *Reagents and conditions*: (a) $ClCO_2Et$, Et_3N, acetone, –60 °C; (b) NaN_3, 0 °C; (c) 1,2-dichlorobenzene, 60 °C; (d) $AlCl_3$, 1,2-dichlorobenzene, 100 °C; (e) Zn, $CuSO_4$, ammonia solution (28–30%, as NH_3), 70 °C; (f) $KMnO_4$, acetone, r.t.



Scheme 5 *Reagents and conditions*: (a) $POCl_3$, *N*,*N*-dimethylaniline, reflux; (b) 1-methylpiperazine, reflux; (c) MeMgBr, THF, 5 °C (d) 4 N HCl, dioxane, reflux; (e) isopropylmagnesium chloride, THF, 5 °C; (f) $NaBH_4$, THF–MeOH, r.t.; (g) H_2SO_4, MeOH, reflux

the results indicated by element symbols are within ±0.4% of the calculated values.

2-Methyl-4-(4-methylpiperazin-1-yl)-10*H*-benzo[5,6]cyclohepta[1,2-*b*]thiophene (5)

To a solution of **12** (560 mg, 2.45 mmol) and 1-methylpiperazine (1.13 g, 11.27 mmol) in benzene (18 mL) was added $TiCl_4$ (0.16 mL, 1.47 mmol). The mixture was stirred at 55 °C for 1 h. Aq 2% $NaHCO_3$ (50 mL) was added and the mixture was extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), and evaporated in vacuo. The crude product was purified by column chromatography ($CHCl_3$–MeOH, 5:1) to give **5** as a yellow oil (0.39 g, 51%).

IR (neat): 2939, 1599, 1485, 1448, 1140 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.35 (3 H, s, CH_3), 2.36 (3 H, s, CH_3), 2.55 (4 H, br s, piperazine H), 3.05 (4 H, br s, piperazine H), 3.64 (2 H, s, CH_2), 6.13 (1 H, s, vinyl H), 6.89 (1 H, s, thiophene H), 7.12–7.24 (4 H, m, ArH).

MS: *m*/*z* = 310 (M^+).

Anal. Calcd for $C_{19}H_{22}N_2S·1/4H_2O$: C, 72.45; H, 7.20; N, 8.89. Found: C, 72.40; H, 7.21; N, 8.52.

2-Methyl-4-(4-methylpiperazin-1-yl)thieno[3,2-*c*][1]benzazepine-10-one (6b)

2-Methylthieno[3,2-*c*][1]benzazepine-4(5*H*),10-dione (**16**; 430 mg, 1.77 mmol) was suspended in $POCl_3$ (2.7 mL, 29.1 mmol) and *N*,*N*-dimethylaniline (100 mg, 0.80 mmol) was added. The mixture was stirred under reflux for 1 h. The solvent was completely evaporated azeotropically with toluene under reduced pressure and 1-methylpiperazine (10 mL) was added to the residue. The mixture was stirred under reflux for 2.5 h. The mixture was cooled to r.t. and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography ($CHCl_3$–MeOH, 20:1) to give **6b** (460 mg, 80%) as yellow crystals; mp 166–169 °C (EtOAc–hexane).

IR (KBr): 1572, 1413, 1253, 1140 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.34 (3 H, s, CH_3), 2.54 (4 H, m, piperazine H), 2.55 (3 H, s, CH_3), 3.57 (4 H, m, piperazine H), 6.97 (1 H, s, thiophene H), 7.27 (1 H, dd, *J* = 6.8, 8.3 Hz, ArH), 7.48 (1 H, d, *J* = 8.3 Hz, ArH), 7.55 (1 H, dd, *J* = 6.8, 8.3 Hz, ArH), 8.15 (1 H, d, *J* = 7.8 Hz, ArH).

MS: *m*/*z* = 325 (M^+).

Anal. Calcd for $C_{18}H_{19}N_3OS$: C, 66.43; H, 5.88; N, 12.91. Found: C, 66.08; H, 5.86; N, 12.72.

2-Methyl-10-methylene-4-(4-methylpiperazin-1-yl)thieno[3,2-*c*][1]benzazepine (6c)

To a solution of **6b** (160 mg, 0.49 mmol) in THF (5 mL) was added MeMgBr (3.0 M solution in Et_2O, 2.25 mL) at 5 °C. After stirring at 5 °C for 1.5 h, H_2O was added. The solvent was evaporated off in vacuo and the residue treated with H_2O and $CHCl_3$. The organic layer was dried (Na_2SO_4) and concentrated to give 10-hydroxy-10-methyl-thieno[3,2-*c*][1]benzazepine (170 mg) as a yellow oil. The hydroxybenzazepine derivative, 4 M HCl (6 mL) and HCl (37 wt% in H_2O, 3 mL) in dioxane (5 mL) was heated under reflux for 18 h. The mixture was cooled to r.t. and the mixture was made basic with aq sat. $NaHCO_3$ solution and extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), and evaporated. The crude product was purified by column chromatography ($CHCl_3$–MeOH, 10:1) to give **6c** (94 mg, 59%) as a yellow oil. The free base was converted into the hydrochloride and crystallized from MeOH–EtOAc–diisopropyl ether (IPE); mp 160–165 °C.

IR (KBr): 1614, 1506, 1433 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 2.52 (3 H, s, CH_3), 3.03 (3 H, s, CH_3), 3.40–4.60 (8 H, m, piperazine H), 5.76 (1 H, s, vinyl H), 5.80 (1 H, s, vinyl H), 7.14 (1 H, s, thiophene H), 7.50–7.51 (4 H, m, ArH).

MS: *m*/*z* = 323 (M^+).

Anal. Calcd for $C_{19}H_{21}N_3S·2HCl·3H_2O$: C, 50.66; H, 6.48; N, 9.23. Found: C, 50.25; H, 6.22; N, 8.92.

2-Methyl-10-(1-methylethylidene)-4-(4-methylpiperazin-1-yl)-thieno[3,2-*c*][1]benzazepine (6d)

To a solution of **6b** (470 mg, 1.5 mmol) in THF (10 mL) was added isopropylmagnesium chloride (2.0 M solution in Et_2O, 2.25 mL, 4.50 mmol) at 5 °C. After stirring at 5 °C for 2 h, H_2O was added to the mixture. The solvent was evaporated off in vacuo and the residue was treated with H_2O and EtOAc. The organic layer was dried

(Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was taken in dioxane (18 mL) and HCl (37 wt% in H_2O, 24 mL) and refluxed for 4 h. The mixture was made basic with 1 N NaOH solution and extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), and evaporated. The crude product was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 10:1) to give **6d** (460 mg, 95%) as a yellow oil. The free base converted into the fumarate and crystallized from MeOH–EtOAc–IPE; mp 224–225 °C.

IR (KBr): 2854, 1577, 1410, 1371, 1235, 1161 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.78 (3 H, s, CH_3), 1.91 (3 H, s, CH_3), 2.24 [3 H, s, $(CH_3)_2C$], 2.38 [3 H, s, $(CH_3)_2C$], 3.16–3.60 (10 H, m, piperazine H and CO_2H), 6.60 (2 H, s, fumaric acid CH), 6.80 (1 H, s, thiophene H), 6.95–7.02 (4 H, m, ArH).

MS: *m*/*z* = 351 (M^+).

Anal. Calcd for $C_{21}H_{25}N_3S{\cdot}C_4H_4O_4{\cdot}3/5H_2O$: C, 62.77; H, 6.36; N, 8.78. Found: C, 62.45; H, 6.36; N, 8.38.

10-Hydroxy-2-methyl-4-(4-methylpiperazin-1-yl)thieno[3,2-*c*]-[1]benzazepine (6e)

To a solution of **6b** (170 mg, 0.52 mmol) in THF (10 mL) was added $NaBH_4$ (60 mg, 1.06 mmol) at r.t. After stirring at r.t. for 1 h, MeOH (30 mL) was added to the mixture. The solvent was evaporated off in vacuo and the residue treated with H_2O and EtOAc. The organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography ($CHCl_3$–MeOH, 10:1) to give **6e** (135 mg, 79%) as colorless crystals; mp 161–163 °C (EtOAc–hexane).

IR (KBr): 3061, 1574, 1408, 1248, 1149, 976 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.21 (3 H, s, CH_3), 2.34 (3 H, s, CH_3), 2.49 (4 H, m, piperazine H), 3.46 (4 H, m, piperazine H), 5.28 (1 H, d, *J* 4.4 Hz, CHO), 6.61 (1 H, br d, *J* = 4.4 Hz, OH), 6.64 (1 H, s, thiophene H), 6.92 (1 H, d, *J* = 7.3 Hz, ArH), 7.03 (1 H, dd, *J* = 7.3, 7.4 Hz, ArH), 7.08 (1 H, dd, *J* = 7.3, 7.4 Hz, ArH), 7.42 (1 H, d, *J* = 4.4 Hz, ArH).

MS: *m*/*z* = 327 (M^+).

Anal. Calcd for $C_{18}H_{21}N_3OS{\cdot}1/5H_2O$: C, 65.31; H, 6.52; N, 12.69. Found: C, 65.30; H, 6.56; N, 12.95.

2-Methyl-4-(4-methylpiperazin-1-yl)-10-methoxythieno[3,2-*c*]-[1]benzazepine (6f)

To a solution of **6e** (140 mg, 0.43 mmol) in MeOH (7 mL) was added H_2SO_4 (6 drops) at r.t. The mixture was stirred under reflux for 2 h. It was then cooled to r.t., made basic with aq sat. $NaHCO_3$ solution and extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), and evaporated. The crude product was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 10:1) to give **6f** (100 mg, 68%) as a yellow oil.

IR (KBr): 2934, 1575, 1406, 1290, 1242, 1141 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.25 (3 H, s, CH_3), 2.30 (3 H, s, CH_3), 2.47 (4 H, m, piperazine H), 3.27 (3 H, s, OCH_3), 3.50–3.61 (4 H, m, piperazine H), 4.91 (1 H, s, CHO), 6.45 (1 H, s, thiophene H), 6.89–7.21 (4 H, m, ArH).

MS: *m*/*z* = 341 (M^+).

Anal. Calcd for $C_{19}H_{23}N_3O{\cdot}1/2H_2O$: C, 65.11; H, 6.90; N, 11.99. Found: C, 65.38; H, 6.84; N, 11.86.

2-(5-Methyl-2-thenoyl)benzoic Acid (7)

To a suspension of 2-methylthiophene (49.3 mL, 509.3 mmol) and phthalic anhydride (90.5 g, 611.2 mmol) in 1,2-dichloroethane (500 mL) was added powdered $AlCl_3$ (135.8 g, 1018.6 mmol) at 5°C. After stirring at 40 °C for 2 h, ice water (1 L) was added and the mixture was extracted with EtOAc. The organic extract was washed with brine, dried (Na_2SO_4), and evaporated. Recrystallization from diisopropyl ether gave **7** (120.0 g, 96%) as colorless crystals; mp 124–125 °C (EtOAc–IPE–hexane).

IR (KBr): 2872, 1684, 1630, 1593 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.50 (3 H, s, CH_3), 6.72 (1 H, d, *J* = 3.7 Hz, thiophene H), 7.07 (1 H, d, *J* = 3.7 Hz, thiophene H), 7.44 (1 H, d, *J* = 7.3 Hz, ArH), 7.54 (1 H, ddd, *J* = 1.4, 7.6, 7.8 Hz, ArH), 7.62 (1 H, ddd, *J* = 1.4, 7.6, 7.6 Hz, ArH), 8.06 (1 H, d, *J* = 7.8 Hz, ArH).

MS: *m*/*z* = 325 (M^+).

Anal. Calcd for $C_{13}H_{10}O_3S{\cdot}1/5H_2O$: C, 62.48; H, 4.19. Found: C, 62.67; H, 4.26.

2-(5-Methyl-2-thenyl)benzoic Acid (8)

To a suspension of **7** (40.0 g, 162.4 mmol) and $CuSO_4$ (1.0 g, 6.5 mmol) in NH_4OH (28% NH_3 in H_2O, 1 L) was added zinc powder (106.0 g, 1624 mmol) at r.t. After stirring at 70 °C for 6 h, HCl (35 wt% in H_2O, 120 mL) was added. The mixture was cooled to r.t. and partitioned between EtOAc and H_2O. The organic layer was dried (Na_2SO_4) and evaporated. The obtained residue was recrystallized from EtOAc–hexane to give **8** (15.4 g, 67%) as colorless crystals; mp 130–134 °C (EtOAc–hexane).

IR (KBr): 2878, 1687, 1452, 1412, 1288 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.19 (3 H, s, CH_3), 4.37 (2 H, s, CH_2), 6.32 (1 H, s, thiophene H), 6.44 (1 H, s, thiophene H), 7.13–7.31 (4 H, m, ArH), 7.87 (1 H, s, CO_2H).

MS: *m*/*z* = 232 (M^+).

Anal. Calcd for $C_{13}H_{12}O_2S$: C, 67.22; H, 5.21. Found: C, 67.19; H, 4.99.

2-(5-Methyl-2-thenyl)benzyl Alcohol (9)

To a solution of $SOCl_2$ (7.06 mL, 96.85 mmol) in MeOH (140 mL) was added a solution of **8** (15.0 g, 64.6 mmol) in MeOH (100 mL) and the mixture was stirred under reflux for 6 h. The mixture was cooled to r.t., poured into H_2O (200 mL), and extracted with EtOAc (2 ×). The EtOAc layer was washed with brine, dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 5:1) to give the methyl ester of **9** (12.54 g, 78%) as a yellow oil. To a solution of the methyl ester (3.62 g, 14.7 mmol) in THF (30 mL) was added $LiAlH_4$ (0.56 g, 14.7 mmol) at r.t. and stirred for 3 h. H_2O was added and the mixture was extracted with EtOAc. The organic extract was washed with brine, dried (Na_2SO_4), and evaporated. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 3:1) to give **9** (2.93 g, 95%) as a yellow oil.

IR (KBr): 3333, 1452, 1039 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.33 (3 H, s, CH_3), 4.06 (2 H, s, CH_2), 4.51 (2 H, d, *J* = 5.4 Hz, OCH_2), 5.11 (1 H, t, *J* = 5.4 Hz, OH), 6.57 (2 H, s, thiophene H), 7.15–7.37 (4 H, m, ArH).

MS: *m*/*z* = 218 (M^+).

Anal. Calcd for $C_{13}H_{14}OS$: C, 71.52; H, 6.46. Found: C, 71.22; H, 6.45.

2-(5-Methyl-2-thenyl)benzyl Bromide (10)

The alcohol **9** (2.93 g, 13.4 mmol) was suspended in 48% HBr (9 mL). The mixture was stirred under reflux for 2 h. The mixture was cooled to r.t. and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. Recrystallization from EtOAc–hexane gave **10** (2.84 g, 75%) as brown crystals; mp 38–40 °C (EtOAc–hexane).

IR (KBr): 1491, 1452, 760 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (3 H, s, CH_3), 4.21 (2 H, s, CH_2), 4.50 (2 H, s, CH_2), 6.51 (1 H, s, thiophene H), 6.52 (1 H, s, thiophene H), 7.22–7.33 (4 H, m, ArH).

MS: *m*/*z* = 281 (M^+).

Anal. Calcd for $C_{13}H_{13}BrS$: C, 55.52; H, 4.66. Found: C, 55.49; H, 4.99.

2-(5-Methyl-2-thenyl)phenylacetic Acid (11)

To a solution of **10** (12.94 g, 46.0 mmol) in DMF (60 mL) was added KCN (18 wt% in H_2O, 15 mL). The mixture was stirred at r.t. for 3 h. H_2O (200 mL) was added and the mixture was extracted with EtOAc. The organic extract was washed with brine, dried (Na_2SO_4), and the solvent was removed in vacuo. To a solution of the residue in AcOH (80 mL) was added HCl (37 wt% in H_2O, 50 mL) at r.t., and the mixture was stirred at 95 °C for 4 h. The mixture was stirred at 55 °C for 1 h, poured into H_2O (200 mL) and extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 20:1) to give **11** (7.84 g, 83%) as yellow crystals; mp 60–63 °C (EtOAc–hexane).

IR (KBr): 2916, 1693, 1406, 1238 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (3 H, s, CH_3), 3.66 (2 H, s, CH_2), 4.10 (2 H, s, CH_2), 6.45 (1 H, d, *J* = 3.4 Hz, thiophene H), 6.49 (1 H, d, *J* = 3.4 Hz, thiophene H), 7.22–7.24 (4 H, m, ArH).

MS: *m*/*z* = 246 (M^+).

Anal. Calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73. Found: C, 68.43; H, 5.82.

2-Methyl-4,5-dihydro-10*H*-benzo[5,6]cyclohepta[1,2-*b*]thiophene-4-one (12)

To a solution of **11** (0.5 g, 2.03 mmol) in toluene (5 mL) was added P_2O_5 (1.0 g) and mixture was stirred at 90 °C for 13 h. It was then cooled to r.t. and washed with 1 N NaOH solution. The organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 5:1) to give **12** (0.30 g, 65%) as yellow crystals; mp 118–110 °C (EtOAc–hexane).

IR (KBr): 1664, 1487, 1238 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (3 H, s, CH_3), 4.04 (2 H, s, CH_2), 4.35 (2 H, s, CH_2), 6.99 (1 H, s, thiophene H), 7.16–7.36 (4 H, m, ArH).

MS: *m*/*z* = 228 (M^+).

Anal. Calcd for $C_{14}H_{12}OS$: C, 73.65; H, 5.30. Found: C, 73.68; H, 5.25.

2-Methylthieno[3,2-*c*][1]benzazepine-4(5*H*)-one (15)

To a solution of **8** (5.35 g, 23.0 mmol) and Et_3N (2.68 g, 26.5 mmol) in acetone (110 mL) was added ethyl chloroformate (2.75 g, 25.3 mmol) at –60 °C. The mixture was stirred at –60 °C for 1 h and a solution of NaN_3 (10 wt% in H_2O, 18 mL) was added. The mixture was stirred for 2 h at 0 °C, poured into H_2O, and extracted with $CHCl_3$. The organic extract was washed with brine, dried (Na_2SO_4), and evaporated. A solution of the residue in 1,2-dichlorobenzene (100 mL) was heated for 60 min at 60 °C. After cooling, $AlCl_3$ (7.76 g, 58.2 mmol) was added to the mixture and it was heated for 30 min at 100 °C. The mixture was cooled to r.t., poured into H_2O (200 mL), and extracted with $CHCl_3$ (2 ×) and washed with H_2O. The organic layer was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 5:1) to give **15** as yellow crystals (2.2 g, 51%); mp 214–218 °C (EtOAc–hexane).

IR (KBr): 3178, 3057, 1668, 1496, 1429 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.34 (3 H, s, CH_3), 3.98 (2 H, s, CH_2), 6.93 (1 H, s, thiophene H), 7.06 (1 H, dd, *J* = 7.3, 7.3 Hz, ArH), 7.16 (1 H, d, *J* = 6.8 Hz, ArH), 7.20 (1 H, dd, *J* = 7.3, 7.4 Hz, ArH), 7.27 (1 H, d, *J* = 7.3 Hz, ArH), 10.11 (1 H, br s, NH).

MS: *m*/*z* = 229 (M^+).

Anal. Calcd for $C_{13}H_{11}NOS$: C, 68.10; H, 4.84; N, 6.11. Found: C, 68.09; H, 4.85; N, 6.06.

2-Methylthieno[3,2-*c*][1]benzazepine-4(5*H*),10-dione (16)

To a dispersion of **15** (0.84 g, 3.7 mmol) in acetone (30 mL) was added $KMnO_4$ (1.46 g, 9.25 mmol) at 5 °C. The mixture was stirred at r.t. for 1 h, diluted with H_2O (200 mL), and extracted with EtOAc (2 ×). The organic extract was washed with H_2O, and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the precipitated crystals were collected by filtration and washed with hexane to give **16** (780 mg, 88%) as yellow crystals; mp 220 °C (EtOAc–IPE).

IR (KBr): 3055, 1662, 1618, 1597, 1483, 1332 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.57 (3 H, s, CH_3), 7.29 (1 H, dd, *J* = 6.8, 8.3 Hz, ArH), 7.54 (1 H, s, thiophene H), 7.56 (1 H, d, *J* = 8.3 Hz, ArH), 7.69 (1 H, dd, *J* = 6.8, 7.4 Hz, ArH), 8.21 (1 H, d, *J* = 6.8 Hz, ArH), 11.23 (1 H, br s, NH).

MS: *m*/*z* = 243 (M^+).

Anal. Calcd for $C_{13}H_9NO_2S$: C, 64.18; H, 3.73; N, 5.76. Found: C, 64.21; H, 4.06; N, 5.52.

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