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Synthesis and Evaluation of Antidepressant and Sedative Activities of Some Benzo[*B*] thiophenes

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THE COUPLING reaction of 2-diazo-3-cyano-4,5,6,7-tetrahydrobenzo [b] thiophene (2) with the 2-aminoprop-1-ene-1,1,3-tricarbonitrile (3) gave the hydrazone derivative (4). Compound 4 underwent ready cyclization to give the pyridazine derivative (5). The reaction of 4 with hydrazines gave pyrazole derivatives (6a,b). On the other hand, the reaction of 4 with active methylene reagents gave the pyridazine derivatives (7a,b). The latter products were cyclized into the pyrido [3,2-c] pyrimidine derivatives 8a and 8b, respectively. The reaction of 4 with phenylisothiocyanate gave the 1,2,4-triazine derivative (9). The antidepressant and sedative activities of the newly synthesized products were measured.

Keywords: Benzo [*b*] thiophenes, Pyridazines, Pyrazoles, Antidepressant, and Sedative activity.

Benzo[*b*]thiophenes represent many naturally occurring and designed molecules responsible for a diverse range of biological responses [1–6]. Recently, subtituted benzothiophenes have also found application in liquid crystal displays [7] . The substituted benzo[*b*]thiophene systems [8] are often present in biologically active compounds and many examples of biological activities found for small molecules based on the benzo[*b*]thiophene moiety can be referred. Namely, they can be inhibitors of herpes simplex virus type I (HSV-1) replication, antimitotics, inhibitors of cysteine and serine proteases (importantly, thrombin), opioid receptor analgesics, and 5-HT6 antagonists, making this a very attractive structure for medicinal chemists [9] . Its potential has, actually, already been materialized through the development of marketed drugs, like the anti-asthma drug zileuton [10] and raloxifene, a non-hormonal drug showing estrogen agonist effects on the bone and the cardiovascular system and estrogen antagonist effects on endometrial and breast tissue [11] . Moreover, benzo[b]thiophenes are also a structural part of the commercial imidazole antifungal agent sertaconazole, an antimycotic with applications in dermatology and gynecology [12] . This pompted us to synthesize and identify new compounds derived from benzo[b]thiophenes and screen them for antidepressant and sedative activities.

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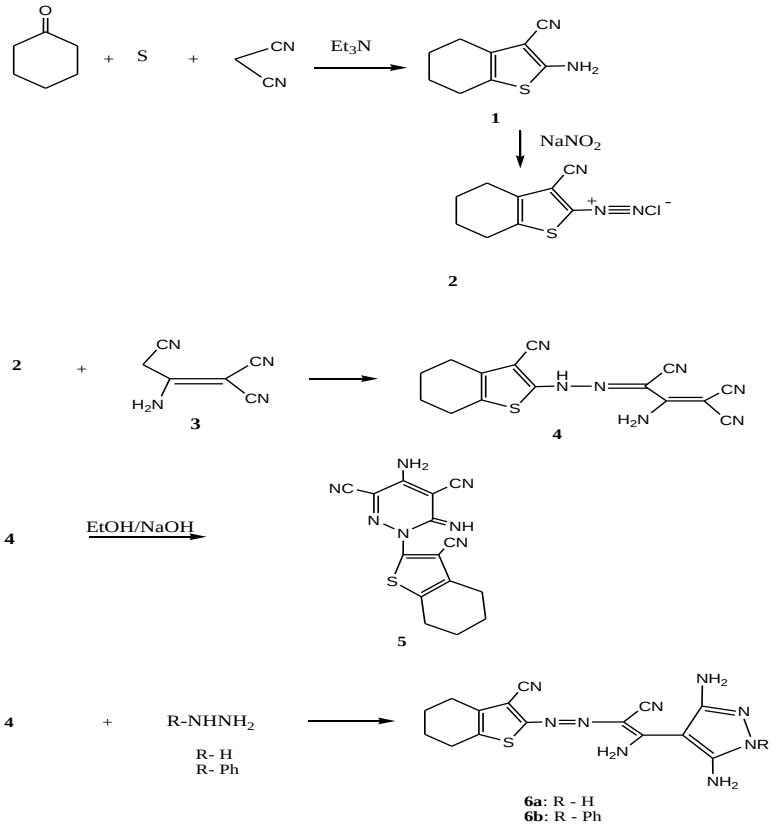
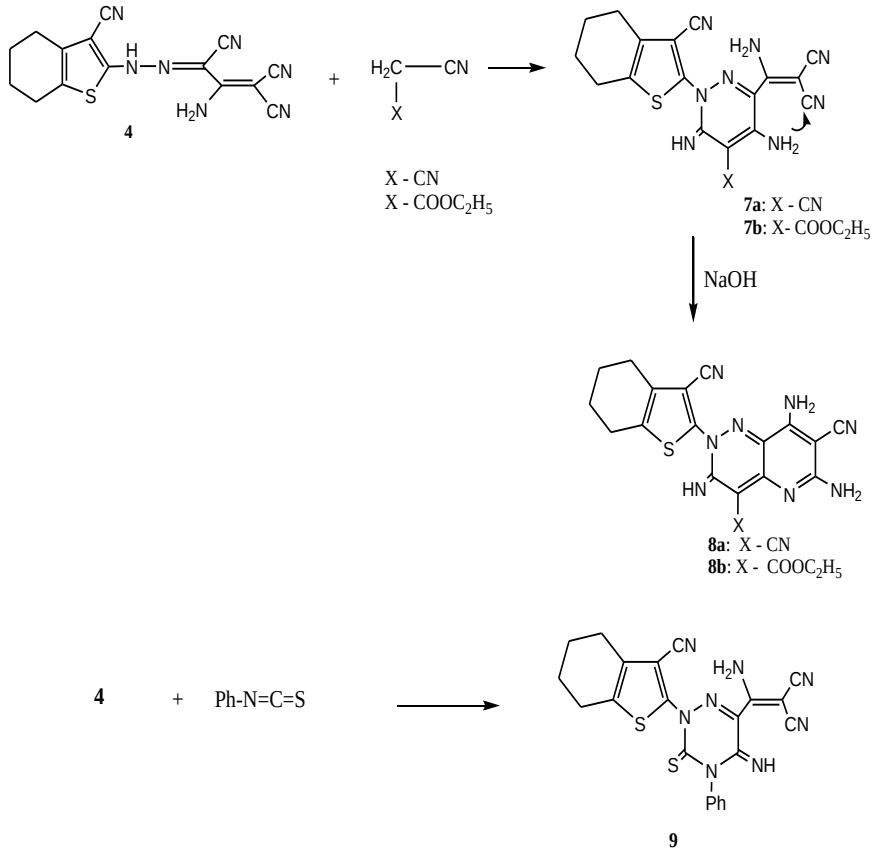
Experimental

Synthetic methods, analytical and spectral data

Melting points were determined on an electrothermal apparatus (Büchi 535, Switzerland) in an open capillary tube and are uncorrected. Elemental analyses were determined on a Yanaco CHN Corder elemental analyzer (Kyoto, Japan). IR spectra expressed in (υ,cm^{-1}) were recorded in KBr pellets on a PA-9721 IR spectrophotometer (Shimadzu, Japan). ^{1}H NMR spectra were obtained on a Jeol 300 MHz (Japan) spectrometer in DMSO-d_6 as solvent, using TMS as internal reference and chemical shifts (δ) are expressed in ppm. Mass spectra were recorded on Kratos (75e-v) Ms equipment (Germany). Synthetic pathways are presented in Schemes 1&2. Physico-chemical and spectral data for the synthesized compounds are given in Tables 1 and 2. The antidepressant and sedative activity of the tested are given in Tables 3 and 4. All compounds produced in this work are novel and their synthetic pathways are also novel. The 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene 1 and the 2-aminoprop-1-ene-1,1,3-tricarbonitrile (3) were synthesized according to literature procedures [13, 14], respectively. All compounds produced in this work are novel, except compounds 1 and 3, and their synthetic pathways are also novel.



Scheme 1 .



Scheme 2 .

4,5,6,7-Tetrahydrobenzo[b]thiophene-2(2-aminoprop-1-ene-1,1,3-tricarbonitrile -3 -yl)-3-carbonitrile (4)

Sodium nitrite (0.8 g, 0.012 mol) was slowly added to the of sulfuric acid (5 ml, 98%) at 0 °C then the resulting solution was stirred for 1 hr at 60 °C, followed by cooling to below 5 °C to form the intermediate nitrosyl sulfuric acid solution. 2-Amino-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene (1.78 g, 0.01 mol) was dissolved in acetic acid/propionic acid mixture (12 mL, 5:1) and slowly added into the cooled nitrosyl sulphuric acid solution. The resulting mixture was stirred for 1 hr at 0 °C to give the diazonium salt solution 2. The latter was then added slowly into a solution of the 2-aminoprop-1-ene-1,1,3-tricarbonitrile 3 (1.32 g, 0.01 mol) in ethanol (50 ml) containing sodium hydroxide solution (10 ml, 10 %). The reaction solution was stirred for 2 hr under 5 °C. The resulting mixture was left in the refrigerate overnight. Then the formed product was filtered off and washed several times with water, dried and recrystallized from methanol to give compound 4.

4-Amino-1-(3-cyano-4,5,6,7- tetrahydrobenzo [b] thiophen-2-yl)-1,6- dihydro-6-iminopyridazine-3,5-dicarbonitrile (5)

A solution of compound 4 (3.21 g, 0.01 mol) in ethanol (40 ml) containing sodium hydroxide (1.0 g) was heated under reflux for 6 hr then left to cool. The solid product formed upon pouring onto ice/water containing few drops of hydrochloric acid (till pH 6) was collected by filtration and recrystallized to give compound 5.

4,5,6,7-Tetrahydrobenzo[b]thiophene-2-(α-azo-β-amino-β–3,5-diaminopyrazol-4-yl)-3-carbonitrile (6a) and 4,5,6,7-Tetrahydrobenzo[b]thiophene-2-(α-azo-β-amino-3,5-diaminopyrazol-4-yl)-3-carbonitrile (6b)

General procedure

To a solution of compound 4 (1.6 g, 0.005 mol) in 1,4-dioxane (25 ml), either hydrazine hydrate (0.25 g, 0.005 mol) or phenylhydrazine (0.51 g, 0.005 mol) was added. The reaction mixture, in each case, was heated under reflux for 4 hr, and then poured onto ice/water mixture containing few drops of hydrochloric acid. The solid product formed was collected by filtration and recrystallized from methanol to give either compound 6a or 6b.

5-Amino -6- (1-amino-2,2-dicyanovinyl)-2-(3-cyano-4,5,6,7-tetrahydrobenzo[b]-thiophen-2-yl)-2,3-dihydro-3-iminopyridazine-4-carbonitrile (7a) and 5-Amino-6-(1-amino-2,2-dicyanovinyl)-2-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-2,3-dihydro-4-ethoxycarbonyl-3-imino-pyridazine (7b)

To a solution of compound 4 (3.21 g, 0.01 mol) in DMF (30 ml) containing triethylamine (1.01 g, 1.4 ml, 0.01 mol) and either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 1.07 ml, 0.01 mol) was added. The resulting reaction mixture was heated under reflux for 3 hr then poured onto ice/water mixture containing hydrochloric acid to get a solution with pH 5. The formed solid product in each case was collected by filtration and recrystallized from 1,4-dioxane to give 7a and from ethanol to give 7b.

6,8-Diamino-2-(3-cyano-4,5,6,7-tetrahydrobenzo [b]thiophen-2-yl)-2,3-dihydro-3-iminopyrido[3,2-c]pyridazine -4,7-dicarbonitrile (8a) and ethyl 6,8-diamino-7-cyano -2- (3-cyano -4,5,6,7- tetrahydrobenzo[b]thiophen-2-yl)-2,3-dihydro-3-iminopyrido[3,2-c]pyridazine-4-carboxylate (8b)

General procedure

To a suspension of either 7a (3.87 g, 0.01 mol) or 7b (4.34 g, 0.01 mol) in sodium ethoxide (0.01 mol) [prepared by dissolving sodium metal (0.23 g, 0.01 mol) in absolute ethanol (15 ml)] was heated in a boiling water bath for 6 hr. The reaction mixture, after reaching room temperature, was poured onto ice/water containing hydrochloric acid (till pH 6) and the formed solid product was collected by filtration. Recrystallization from 1,4-dioxane gave compound 8a and from ethanol gave compound 8b.

4,5,6,7- Tetrahydro - 2- [6-(α-cyano-β-amino-β-yl-acrylonitrilo) -4,5-dihydro-5-imino -4- phenyl -3- thioxo -1,2,4- triazin-2-(3H)-yl)benzo [b] thiophene-3-carbonitrile (9)

To a solution of compound 4 (1.6 g, 0.005 mol) in DMF (30 ml) containing triethylamine (0.5 g, 0.7 ml, 0.005 mol) phenylisothiocyanate (0.68 g, 0.6 ml, 0.005 mol) was added. The resulting reaction mixture was heated under reflux for 3 hr then cooled and poured onto ice/water mixture. The formed solid product was collected by filtration and recrystallized from methanol to give compound 9.

Pharmacological evaluation

Animals

Swiss albino mice of either sex each with 20-25 g of body weight, aged 6-8 weeks, were supplied by the Animal House at National Research Centre, Giza, Egypt for which were approved by the Institutional Ethical Committee. Animals were maintained under 12/12 hr light/dark cycle at 20 ± 2 ^{o}C and fed with standard laboratory diet and water *ad libitum*. In accordance with the recommendations for the proper care and use of laboratory animals (NIH publication No. 85–23, revised 1985) groups of 6 mice for group were used in all experiments.

Screening for antidepressant activity

Porsolt's forced-swimming test. Each mouse was placed individually in a glass cylinder (diameter 12 cm, height 24 cm) filled with water at a height of 12 cm. Water temperature was maintained at 22–23 °C. The animal was forced to swim for 6 min and the duration of immobility was measured. The mouse was considered as immobile when it stopped struggling and moved only to remain floating in the water, keeping its head above water. The floating time, which was the measure of despair (21), was recorded 60 min after treatment with each drug (15 or 30 mg kg^{-1}, *i.p.*), saline or imipramine (15 mg kg^{-1}, *i.p.*). Tested compounds was dissolved using few drops of Tween 80 and further dilutions were done to obtain the necessary doses. During our measurements, the tested compounds were dissolved using few drops of Tween 80 and further dilution was done using saline to get the necessary doses. The negative control is the vehicle solution (Tween 80 in saline).

Screening for sedative effect

Mice were observed in a commercially available motor activity apparatus (Ugo Basel, Italy) in which locomotor and exploratory activity could be monitored. In these experiments, each mouse was intraperitoneally injected with the reference drug at 30 mg kg^{-1} and 30 min later was placed in the activity monitor in which activity was monitored for 6 min.

Statistics

Data are presented as mean ± SEM. Data were analysed by ANOVA followed by Duncan and multiple group comparison test.

Results and Discussion

Chemistry

The 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*] thiophene (1) was obtained via the reaction of cyclohexanone with elemental sulfur and malononitrile in the presence of triethylamine [13]. The reaction of compound 1 with sodium nitrite in the presence of sulpuric acid forms the 2-diazo derivative 2. Coupling of compound 2 with 2-aminoprop-1-ene-1,1,3-tricarbonitrile (3) [14] to give the hydrazone derivative 4. Structure of the latter product was based on analytical and spectroscopic data. The ^{1}H NMR spectrum of compound 4 showed the presence of two multiplets at δ 1.62-1.63 and 2.50-2.58 ppm corresponding to four CH_2 groups, a singlet at δ 2.88 ppm (D_2O exchangeable) for NH_2 group and a singlet at δ 7.31 ppm corresponding to an NH group. Compound 4 underwent ready cyclisation when heated under reflux in ethanolic sodium hydroxide solution to give the pyridazine derivative 5. On the other hand, the reaction of compound 4 with either hydrazine hydrate or phenylhydrazine resulted in formation of pyrazole derivatives 6a and 6b, respectively. Analytical and spectroscopic data of compounds 6a and 6b are in agreement with the proposed structures (Tables 1 and 2).

TABLE 1. Physico-chemical data for synthesized compounds .

Compd No.	Yield (%)	M.p. (^{o}C)	Mol. formula (M_r)	Found/calcd (%)			
				C	H	N	S
4	74	>300	$C_{15}H_{11}N_7S$ (321.36)	56.06 56.42	3.45 3.66	30.51 30.43	9.98 10.07
5	68	220-225	$C_{15}H_{11}N_7S$ (321.36)	56.06 55.85	3.45 3.33	30.51 30.27	9.98 9. 71
6a	70	198-201	$C_{15}H_{15}N_9S$ (353.40)	50.98 51.22	4.28 4.30	35.67 35.39	9.07 8.79
6b	66	236-239	$C_{21}H_{19}N_9S$ (429.50)	58.73 58.63	4.46 4.71	29.35 29.77	7.47 7.41
7a	82	132-134	$C_{18}H_{13}N_9S$ (387.42)	55.80 56.13	3.38 3.27	32.54 32.79	8.28 8.09
7b	55	180-182	$C_{20}H_{18}N_8O_2S$ (434.47)	55.29 55.00	4.18 3.96	25.79 25.48	7.38 7.06
8a	77	174-177	$C_{18}H_{13}N_9S$ (387.42)	55.80 55.68	3.38 4.14	32.54 32.55	8.28 8.05
8b	62	189-193	$C_{20}H_{18}N_8O_2S$ (434.47)	55.29 55.12	4.18 4.48	25.79 25.65	7.38 7.18
9	77	231-234	$C_{22}H_{16}N_8S_2$ (456.55)	57.89 57.91	3.53 3.67	24.54 24.31	14.05 13.89

TABLE 2. Spectral data of newly synthesized products .

Compd No.	(IR υ,cm^{-1})	^{1}H NMR (δ ppm) (DMSO-d_6)	MS (m/e) (M^+)
4	3460-3322 (NH_2, NH), 2987, 2866 (CH_2), 2227, 2222, 2220 (3 CN), 1630 (C=C), 1580 (C=N)	1.62-1.63, 2.50-2.58 (2m, 4H, 4CH_2), 2.88 (s, 2H, NH_2), 7.31 (s, 1H, NH)	321
5	3478-3336 (NH_2, NH), 2983, 2875 (CH_2), 2225, 2220 (2 CN), 1633 (C=C), 1582 (C=N)	1.60-1.64, 2.48-2.59 (2m, 4H, 4CH_2), 2.93 (s, 2H, NH_2), 8.74 (s, 1H, NH)	321
6a	3488-3328 (3NH_2, NH), 2980, 2878 (CH_2), 2227, 2222 (2 CN), 1636 (C=C), 1580 (C=N)	1.62-1.66, 2.45-2.62 (2m, 4H, 4CH_2), 3.08, 4.88, 5.21 (3s, 6H, 3NH_2), 8.20 (s, 1H, NH)	353
6b	3521-3348 (2NH_2, NH), 3056 (CH aromatic), 2982, 2879 (CH_2), 2229, 2223 (2 CN), 1637 (C=C), 1582 (C=N)	1.64-1.67, 2.46-2.65 (2m, 4H, 4CH_2), 3.24, 4.89, 5.24 (3s, 6H, 3NH_2)	429
7a	3497-3326 (2NH_2, NH), 3059 (CH aromatic), 2980, 2881 (CH_2), 2228, 2227-2223 (4 CN), 1634 (C=C), 1580 (C=N)	1.60-1.84, 2.51-2.56 (2m, 4H, 4CH_2), 2.87, 2.94 (2s, 4H, 2NH_2), 8.13 (s, 1H, NH)	387
7b	3469-3329 (2NH_2, NH), 3066 (CH aromatic), 2987, 2888 (CH_3, CH_2), 2228, 2227, 2223 (3 CN), 1636 (C=C), 1577 (C=N)	1.36 (t, 3H, J = 6.89 Hz, CH_3), 1.60-1.85, 2.51-2.60 (2m, 4H, 4CH_2), 4.22 (q, 2H, J = 6.89 Hz, CH_2), 2.88, 2.97 (2s, 4H, 2NH_2), 8.11 (s, 1H, NH)	434
8a	3433-3322 (2NH_2, NH), 3055 (CH aromatic), 2966, 2891 (CH_2), 2229, 2225, 2220 (3 CN), 1670 (exocyclic C=N), 1620 (C=C)	1.61-1.75, 2.50-2.58 (2m, 4H, 4CH_2), 2.86, 2.90 (2s, 4H, 2NH_2), 8.11 (s, 1H, NH)	387
8b	3469-3329 (2NH_2, NH), 3066 (CH aromatic), 2987, 2888 (CH_3, CH_2), 2228, 2227, 2223 (3 CN), 1634 (C=C), 1581 (C=N)	1.33 (t, 3H, J = 6.44 Hz, CH_3), 1.61-1.83, 2.50-2.62 (2m, 4H, 4CH_2), 4.24 (q, 2H, J = 6.44 Hz, CH_2), 2.82, 2.93 (2s, 4H, 2NH_2), 8.19 (s, 1H, NH)	434
9	3471-3325 (NH_2, NH), 3060 (CH aromatic), 2227-2223 (3 CN), 1636 (C=C), 1580 (C=N)	1.60-1.68, 2.52-2.60 (2m, 4H, 4CH_2), 2.83, 2.85 (2s, 4H, 2NH_2), 7.28-7.44 (m, 5H, C_6H_5), 8.10 (s, 1H, NH)	456

The reaction of compound 4 with either malononitrile or ethyl cyanoacetate gave in each case a single product with molecular formulae $C_{18}H_{13}N_9S$ and $C_{20}H_{18}N_8O_2S$, respectively. The pyridazine derivatives 7a and b, respectively, were considered for the reaction products. The structures of the latter products were based on the basis of spectroscopic data obtained. Therefore, the ^{1}H NMR spectrum of 7a showed the presence of two multiplets at δ 1.60-1.84 and 2.51-

2.56 ppm for the four CH_2 groups, two singlets (D_2O exchangeable) at δ 2.78, 2.94 corresponding to two NH_2 groups and a singlet at δ 8.13 ppm for an NH group. Compounds 7a,b were readily cyclised when treated with sodium ethoxide in boiling water bath giving the pyrido[3,2-c]pyridazine derivatives 8a and 8b, respectively. Cyclization of 7a,b into 8a,b took place via Michael addition of the pyridazin-4-amino into the CN group which goes in parallel to the reported literature [15, 16].

Treatment of compound 3 with phenylisothiocyanate in the presence of triethylamine gave the 1,2,4-triazine derivative 9. Structure of compound 9 was established on the basis of analytical and spectroscopic data (Tables 1 & 2). In this work we succeeded to synthesis different classes of heterocyclic compounds attached to 4,5,6,7-tetrahydrobenzo[*b*]thiophene such compounds were obtained from compound 4 through the coupling reaction of the diazonium salt 2 with 2-aminoprop-1-ene-1,1,3-tricarbonitrile (3) .

Pharmacology

In the present work, the activity of the novel synthesized thiourea tetrahydrobenzo[*b*]thiophene derivatives 4, 5, 6a, 6b, 7a, 8b and 9 as antidepressant and sedative agents was investigated.

Screening for antidepressant activity

After 60 min of *i.p.* administration some compounds (4, 5 and 6b) showed mild, non-significant antidepressant activity at high doses and were active, compared with the control group, using saline as negative control. The rest of compounds failed to display antidepressant properties in the swimming test (Table 3).

TABLE 3. Effect of tested compounds on the duration of immobility in Porsolt's forced- swimming test .

Treatment	Duration of immobility (s)[a]
Saline	289.9 ± 7.1
Imipramine (15 mg kg^{-1})	237.0 ± 14.0[b]
4 (15 mg kg^{-1})	266.8 ± 10.4
4 (30 mg kg^{-1})	258.5 ± 15.8
5 (15 mg kg^{-1})	272.42 ± 12.4
5 (30 mg kg^{-1})	266.1 ± 14.3
6a (15 mg kg^{-1})	271.7 ± 11.0
6a (30 mg kg^{-1})	266.7 ± 13.6
7a (15 mg kg^{-1})	282.8 ± 10.8
7a (30 mg kg^{-1})	272.3 ± 12.6
8b (15 mg kg^{-1})	282.9 ± 15.5
8b (30 mg kg^{-1})	308.0 ± 10.4
9 (15 mg kg^{-1})	280.9 ± 12.6
9 (30 mg kg^{-1})	302.0 ± 10.8

[a] Mean± SEM (n = 6).

[b] Significant difference *vs.* saline-treated control group ($p < 0.05$).

Screening for sedative activity

From Table 3, it is obvious that none of the investigated compounds showed any significant antidepressant effect, namely each of them showed the effect lower than that of imipramine. On the other hand, the data from Table 4 showed that compounds 4, 6a, 6b and 7a have no sedative effect and each of them showed such effect lower than indomethacin.

All tested compounds at the two doses (15 or 30 $mgkg^{-1}$), significantly reduced the number of abdominal writhes induced by i.p. injection of acetic acid in mice (Table 4). Compound 7a (the 3-cyanopyridazine derivative) was the most potent in this respect, inhibiting the number of abdominal writhes by 98.8 %, at high doses (30 mg kg^{-1}), compared with the saline as control negative group and the reference drug indomethacine. Meanwhile, compounds 6a (the pyrazole derivative), 6b (1-phenylpyrazole derivative) at high doses inhibited the number of abdominal writhes by 68.4 and 62.8, respectively. Compounds 8b (the pyrido[3,2-c]pyridazine derivative) and 9 (the 1,2,4-triazine-3-thione), at low and high doses, showed higher sedative activities which are higher than indomethacin.

TABLE 4. Inhibition of abdominal constrictions caused by injection of acetic acid[a].

Compound	Number	inhibition (%)
Saline	92.8 ± 8.0	
Indomethacin (20 mg kg^{-1})	50.3 ± 5.4[c]	45.8
Compound 4 (15 mg kg^{-1})	40.8 ± 2.0[c]	40.7
Compound 4 (30 mg kg^{-1})	20.5 ± 0.21[c]	58.3
Compound 6a (15 mg kg^{-1})	32.2 ± 6.5[c]	62.2
Compound 6a (30 mg kg^{-1})	24.8 ± 8.2[c]	68.4
Compound 6b (15 mg kg^{-1})	30.5 ± 6.0[c]	62.8
Compound 6b (30 mg kg^{-1})	24.5 ± 4.2[c]	55.2
Compound 7a (15 mg kg^{-1})	48.2 ± 2.0[c]	42.1
Compound 7a (30 mg kg^{-1})	26.8 ± 3.2[c]	98.8
Compound 8b (15 mg kg^{-1})	68.7 ± 5.9	36.6
Compound 8b (30 mg kg^{-1})	44.3 ± 6.2[c]	30.3
Compound 9 (15 mg kg^{-1})	76.7 ± 2.6	28.6
Compound 9 (30 mg kg^{-1})	53.3 ± 2.0[c]	32.3

[a] Mean± SEM (n = 6)

[c] Significant difference vs. saline-treated control group ($p < 0.05$).

From the structure–activity relationship viewpoint, the (3-cyano-4,5,6,7-tetrahydrobenzo[*b*]-thiophen-2-yl)-2,3-dihydro-3-iminopyridazine derivative 7a has the strongest antidepressant and sadative activity which is more than indomethacine. Introducing pyridazine moiety at position two of the tetrahydrobenzo[*b*]thiophene decreased these activities in the rest of compounds like 5, 7b, 8a and 8b. Moreover, compound 9 with the 1,2,3-triazine-2-thione has the lowest antidepressant and analgesic activities which is lower than imipramine and indomethacine.

Conclusions

In this study an efficient synthesis of novel benzo[*b*]thiophene derivatives derived from the 2-amino-3-cyano-4,5,6,7- tetrahydrobenzo[*b*] thiophene (2) is described. The novel synthesized thiophene derivatives 6a (4,5,6,7-Tetrahydrobenzo [b] thiophene-2- (α-azo-β-amino- β–3,5- diaminopyrazol-4-yl)-3- carbonitrile), 6b (4,5,6,7-Tetrahydrobenzo [b] thiophene-2- (α-azo-β-amino-3,5- diaminopyrazol-4-yl) -3-carbonitrile), 7a (5-Amino-6-(1-amino-2,2 dicyanovinyl)- 2-(3-cyano-4,5,6,7- tetrahydrobenzo [b] -thiophen-2-yl) -2,3-dihydro -3-iminopyridazine -4- carbonitrile), 8b (ethyl 6,8-diamino-7-cyano-2-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-2,3- dihydro-3-iminopyrido [3,2-c] pyridazine-4-carboxylate) and 9 (4,5,6,7-Tetrahydro-2-[6-(α-cyano-β-amino-β-yl-acrylonitrilo) -4,5- dihydro-5-imino-4-phenyl-3-thioxo-1,2,4-triazin-2-(3H)-yl) benzo [b] thiophene-3-carbonitrile) showed mild antidepressant and sedative activity with various intensities. However, compound 7a has the strongest sedative activity, while compound 8 showed the lowest activities. The work described in this article showed the synthesis of novel heterocyclic compounds 4 (4,5,6,7-Tetrahydrobenzo[b]thiophene-2(2-aminoprop-1-ene-1,1,3-tricarbonitrile-3-yl) -3-carbonitrile), 5 (4-Amino-1- (3-cyano-4,5,6,7-tetrahydrobenzo [b] thiophen-2-yl) -1,6-dihydro-6- iminopyridazine-3,5-dicarbonitrile), 6a,b, 7a,b, 8a,b and 9 each containing two different heterocyclic rings, except compound 4 (with only one heterocyclic ring) and some of them showed high sedative activities.

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تحضير وتقييم مشتقات البنزو ثيوفين كمضادات للاكتئاب ومسكنات للألام

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يتناول هذا البحث استخدامات مشتقات البنزو ثيوفين لتحضير مشتقات البيريديزين والبيرازول وتقييم هذه المركبات كمضادات للاكتئاب ومسكنات . فبتفاعل ملح الدبزونيم ٢ مع مركب ثنائى المالونونيتريل ٣ أعطى مشتق الأزو ٤. المركب ٤ تم أستخدامه تجاه العديد من الكواشف الكيميائية ليعطى مشتقات البيريديزين والبيرازول والثيوفين بعض من المركبات الناتجة تم اعادة حولقته ليعطى مركبات عضوية حلقية ملتحمة وبدراسة درجة نشاط المركبات الناتجة كمضادات للاكتئاب ومسكنات اثبتت الدراسة أن معظم المركبات ذات درجة نشاط عالية.