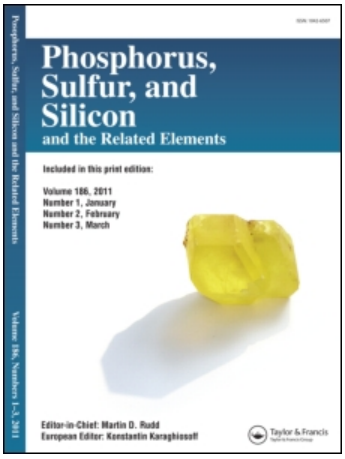

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Synthesis and Analgesic Activities of Some 2-(Benzazolylacetyl)amino-3-ethoxycarbonylthiophene Derivatives

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In this study, some 2-[2-(benzazole-2-thioxy)acetylamino]-3-ethoxycarbonylthiophene and 2-[2-(benzazole-1-yl)acetylamino]-3-ethoxycarbonylthiophene compounds were obtained by the reaction of 2-chloroacetylamino-3-ethoxycarbonylthiophene derivatives and a suitable benzazole-2-thione or benzimidazole derivatives. Analgesic activities of the compounds were tested by using tail-flick and tail-immersion methods. It is reported that some of the compounds showed remarkable analgesic activities.

Keywords Analgesic activity; benzazole; thiophene

INTRODUCTION

The role of thiophene derivatives in the design and synthesis of pharmacologically important molecules has grown enormously since 1950.[1,2] The electron-rich properties as well as the slightly smaller steric volume of thiophene, as compared with benzene, may play an important role in fitting the necessary biological agents of this type, which have been prepared based upon active benzene derivatives.

It is well known that, 2-aminothiophenes and their substituted acyl derivatives **I** show analgesic and anti-inflammatory activities.[1–8]

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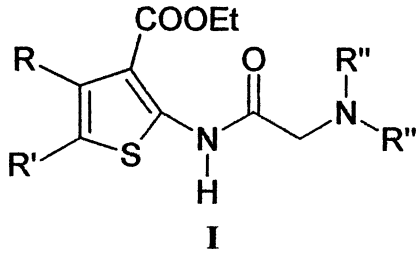


I

FORMULA 1

It was reported that some of the compounds were superior to some widespread analgesics such as acetylsalicylic acid, phenylbutazone, aminopyrine and indomethacin. In light of the above findings, we aimed to synthesize some 2-(2-benzazolylthio/1-benzimidazolyl-acetyl)amino-3-ethoxycarbonylthiophene derivatives and investigate their analgesic activities.

EXPERIMENTAL

Chemistry

Melting points were determined by using an Electrothermal 9100 digital melting point apparatus and were uncorrected. Spectroscopic data were recorded on the following instruments; FTIR, Schimadzu 8400S spectrophotometer, and ^{1}H-NMR, Bruker DPX 400 NMR spectrometer in DMSO-d_6. Analyses for C, H, and N was within 0.4% of the theoretical values.

2-Amino-3-ethoxycarbonylthiophenes, **1**,[9] benzazole-2-thione, **3**,[10] and benzimidazole, **5**, derivatives[11] were prepared according to the literature methods. 2-Chloroacetylamino-3-ethoxycarbonylthiophene derivatives, **2**, were obtained by reacting the appropriate 2-amino-3-ethoxycarbonylthiophene derivatives with chloroacetyl chloride in the presence of triethylamine in THF, in a common procedure.[9] Some characteristics of the synthesized compounds were given in Table I.

General Method for the Preparation of 2-[2-(Benzazole-2-thioxy)acetylamino]-3-ethoxycarbonyl-4,5-alkylsubstituted thiophene and 2-[2-(Benzazol-1-yl)acetylamino]-3-ethoxycarbonyl-4,5-alkylsubstituted thiophene derivatives, 4 and 6

A mixture of **2** (5 mmol), an appropriate **3** or **5** (5 mmol) and potassium carbonate (6 mmol) in acetone (100 mL) was refluxed. In the case

TABLE I Some Characteristics of the Compounds

Comp.	R R′	R″	X	m.p. (°C)	Yield (%)	Mol. Formula
4a	$-(CH_2)_3-$	H	NH	205	72	$C_{19}H_{19}N_3O_3S_2$
4b	$-(CH_2)_4-$	H	NH	159	75	$C_{20}H_{21}N_3O_3S_2$
4c	$-(CH_2)_4-$	CH_3	NH	164	82	$C_{21}H_{23}N_3O_3S_2$
4d	$-(CH_2)_4-$	Cl	NH	193	82	$C_{20}H_{20}ClN_3O_3S_2$
4e	$-(CH_2)_4-$	NO_2	NH	229	87	$C_{20}H_{20}N_4O_5S_2$
4f	$-(CH_2)_5-$	H	NH	167	77	$C_{21}H_{23}N_3O_3S_2$
4g	$-(CH_2)_4-$	H	O	113	81	$C_{20}H_{22}N_2O_4S_2$
4h	$-(CH_2)_4-$	CH_3	O	121	73	$C_{21}H_{24}N_2O_4S_2$
4i	$-(CH_2)_4-$	Cl	O	129	84	$C_{20}H_{21}ClN_2O_4S_2$
4j	$-(CH_2)_4-$	H	S	140	75	$C_{20}H_{22}N_2O_3S_3$
6a	$-(CH_2)_4-$	H	—	176	65	$C_{20}H_{21}N_3O_3S$
6b	$-(CH_2)_4-$	Cl	—	173	67	$C_{20}H_{20}ClN_3O_3S$

of the compounds **4**, the reflux time is 2 h and in the case of the compounds **6**, the reflux time is 12 h. The solvent was evaporated at low temperature. The residue was washed with water and then ethanol. The raw product was recrystallized from ethanol.

4a IR(KBr)ν_{max}(cm^{-1}): 3170(N–H), 1664(C=O), 1561–1477(C=N, C=C). ^{1}H-NMR(400 MHz)(DMSO-d_6) δ (ppm): 1.25(3H, t, J: 7.08 Hz $OCH_2\underline{CH_3}$), 2.26–2.31(2H, m, $-CH_2-$), 2.75–2.80(4H, m, two $-CH_2-$), 4.23(2H, q, J: 7.01 Hz, $O\underline{CH_2}CH_3$), 4.32(2H, s, CO–CH_2–S), 7.11–7.14(2H, m, Benzimidazole-$C_{5,6}$–H), 7.45–7.50(2H, m, Benzimidazole-$C_{4,7}$–H), 11.70(1H, bs, N–H), 12.70(1H, bs, N–H).

4b IR(KBr)ν_{max}(cm^{-1}): 3170(N–H), 1664(C=O), 1561–1477(C=N, C=C). ^{1}H-NMR(400 MHz) (DMSO-d_6) δ (ppm): 1.35(3H, t, J: 8.1 Hz $OCH_2\underline{CH_3}$), 1.7–1.85(4H, m, Tetrahydrobenzothiophene-$C_{5,6}$–H), 2.6–2.7(2H, m, Tetrahydrobenzothiophene-C_7–H), 2.8–2.88(2H, m, Tetrahydrobenzothiophene-C_4–H), 4.24(2H, q, J: 7.08 Hz, $O\underline{CH_2}CH_3$), 4.31(2H, s, CO–CH_2–S), 7.2–7.3(2H, m, Benzimidazole-$C_{5,6}$–H), 7.4–7.48(1H, m, Benzimidazole-C_7–H), 7.65–7.7(1H, m, Benzimidazole-C_4–H), 11.70(1H, bs, N–H), 12.70(1H, bs, N–H).

4f IR(KBr)ν_{max}(cm^{-1}): 3170(N–H), 1664(C=O), 1561–1477(C=N, C=C). ^{1}H-NMR(400 MHz)(DMSO-d_6) δ (ppm): 1.25(3H, t, J: 7.08 Hz, $OCH_2\underline{CH_3}$), 1.48–1.6(4H m, two $-CH_2-$), 1.74–1.82(2H, m, $-CH_2-$), 2.57–2.7(2H, m, $-CH_2-$), 2.9–2.95(2H, m, $-CH_2-$), 4.25(2H, q, J: 7.1 Hz, $O\underline{CH_2}CH_3$), 4.29(2H, s, CO–CH_2–S), 7.10–7.14(2H, m, Benzimidazole-$C_{5,6}$–H), 7.45–7.50(2H, m, Benzimidazole-$C_{4,7}$–H), 11.70(1H, bs, N–H), 12.80(1H, bs, N–H).

4g IR(KBr)ν_{max}(cm^{-1}): 3170(N–H), 1664(C=O), 1561–1477(C=N, C=C). ^{1}H-NMR(400 MHz) (DMSO-d_6) δ (ppm): 1.26 (3H, t, J: 7.07 Hz $OCH_2\underline{CH_3}$), 1.65–1.75(4H, m, Tetrahydrobenzothiophene-$C_{5,6}$–H),

2.55–2.60(2H, m, Tetrahydrobenzothiophene-C_7—H), 2.65–2.70(2H, m, Tetrahydrobenzothiophene-C_4—H), 4.24(2H, q, J: 7.1 Hz, O$\underline{CH_2}CH_3$), 4.31(2H, s, CO—CH_2—S), 7.31–7.36(2H, m, Benzoxazole-$C_{5.6}$—H), 7.63–7.76(1H, m, Benzoxazole-$C_{4,7}$—H), 11.68(1H, bs, N—H).

4h IR(KBr)ν_{max} (cm^{-1}): 3170(N—H), 1664(C=O), 1561–1477(C=N, C=C). ^{1}H-NMR(400 MHz) (DMSO-d_6) δ (ppm): 1.27 (3H, t, J: 7.09 Hz $OCH_2\underline{CH_3}$), 1.68–1.76(4H, m, Tetrahydrobenzothiophene-$C_{5,6}$—H), 2.55–2.60(2H, m, Tetrahydrobenzothiophene-C_7—H), 2.65–2.70(2H, m, Tetrahydrobenzothiophene-C_4—H), 4.25(2H, q, J: 7.11 Hz, O$\underline{CH_2}CH_3$), 4.42(2H, s, CO—CH_2–S), 7.14(1H, dd, J: 2.85 Hz, J: 8.35 Hz, Benzoxazole-C_6—H), 7.44 (1H, d, J: 0.66 Hz, Benzoxazole-C_4—H), 7.52(1H, d, J: 8.33 Hz, Benzoxazole-C_7—H), 11.67(1H, bs, N—H).

4j IR(KBr)ν_{max}(cm^{-1}): 3170(N—H), 1664(C=O), 1561–1477(C=N, C=C). ^{1}H-NMR(400 MHz) (DMSO-d_6) δ (ppm): 1.27 (3H, t, J: 7.09 Hz $OCH_2\underline{CH_3}$), 1.6–1.75(4H, m, Tetrahydrobenzothiophene-$C_{5,6}$—H), 2.55–2.65(2H, m, Tetrahydrobenzothiophene-C_7—H), 2.65–2.75(2H, m, Tetrahydrobenzothiophene-C_4—H), 4.26(2H, q, J: 7.1 Hz, O$\underline{CH_2}CH_3$), 4.46(2H, s, CO—CH_2—S), 7.35–7.39(1H, m, Benzothiazole-C_5—H), 7.45–7.49(1H, m, Benzothiazole-C_6—H), 7.88(1H, d, J: 8.0 Hz, Benzothiazole-C_7—H), 8.03(1H, d, J: 8.01 Hz, Benzothiazole-C_4—H), 11.71(1H, bs, N—H).

6a IR(KBr)ν_{max}(cm^{-1}): 3238(N—H), 1664(C=O), 1535–1494(C=N, C=C). ^{1}H-NMR(400 MHz) (DMSO-d_6) δ (ppm): 1.27(3H, t, J: 7.1 Hz $OCH_2\underline{CH_3}$), 1.7–1.82(2H, m, Tetrahydrobenzothiophene-$C_{5,6}$—H), 2.6–2.65(2H, m, Tetrahydrobenzothiophene-C_7—H), 2.68–2.75(2H, m, Tetrahydrobenzothiophene-C_4—H), 4.16(2H, q, J: 7.08 Hz, O$\underline{CH_2}CH_3$), 5.03(2H, s, CO—CH_2-S), 7.22–7.3(2H, m, Benzimidazole-$C_{5.6}$—H), 7.38–7.4(1H, m, Benzimidazole-C_7—H), 7.7–7.85(1H, m, Benzimidazole-C_4—H), 8.04(1H, s, Benzimidazole-C_2—H), 11.42(1H, s, NH).

6b IR(KBr)ν_{max}(cm^{-1}): 3238(N—H), 1664(C=O), 1535–1494(C=N, C=C). ^{1}H-NMR(400 MHz) (DMSO-d_6) δ (ppm): 1.27–1.32(3H, m, $OCH_2\underline{CH_3}$), 1.68–1.8 (2H, m, Tetrahydrobenzothiophene-$C_{5,6}$—H), 2.55–2.6 (2H, m, Tetrahydrobenzothiophene-C_7—H), 2.62–2.75 (2H, m, Tetrahydrobenzothiophene-C_4—H), 4.21–4.28(2H, m, O$\underline{CH_2}CH_3$), 5.49, 5.50(2H, two s, CO—CH_2—S), 7.24–7.32(1H, m, Benzimidazole-C_4—H), 7.61–7.80(2H, m, Benzimidazole-$C_{7,8}$—H), 8.31, 8.34(1H, two s, Benzimidazole-C_2—H), 11.20, 11.21(1H, two s, NH).

Pharmacology

Swiss albino mice of either sex were used for *in vivo* tail-clip and tail immersion (52.5°C hot water) analgesic tests.[12,13] Mice were assigned to groups of five animals each. Morphine sulfate (10 mg/kg) and

TABLE II Effects of the Compounds on Tail-Clip Response in Mice. A: Morphine sulfate, B: Acetylsalisylic Acid. Values are Expressed as Mean ± S.E.M. of Five Mice in Each Group ($^{*}p \leq 0.01$ and $^{**}p \leq 0.05$)

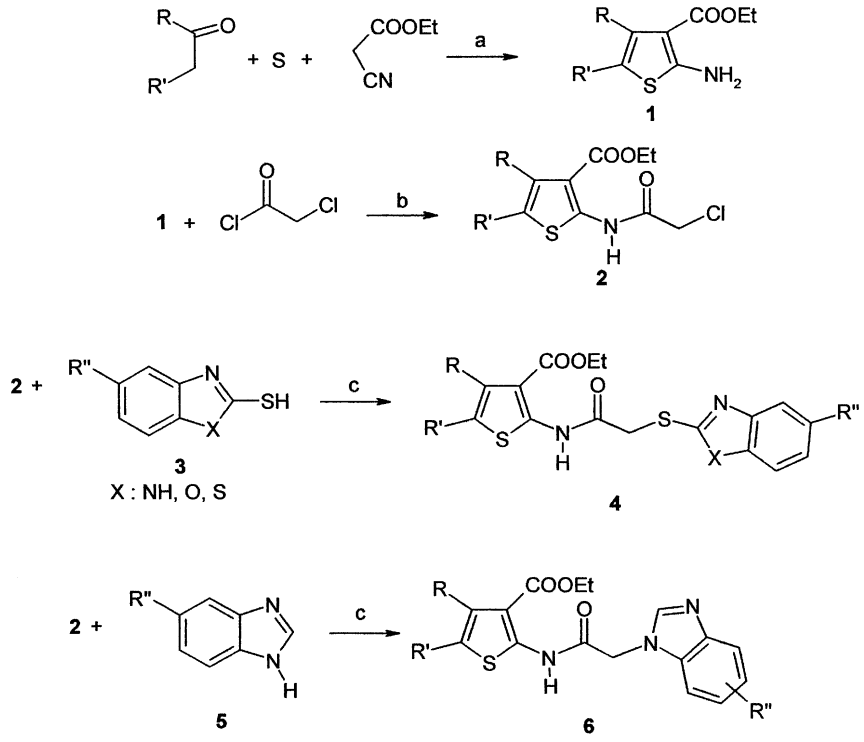
Comp.	Dose (mg/kg) (i.p.)	Reaction Time (sec.)	% Analgesia Tail-Clip
A	10	14.37 ± 0.62	95.38
B	100	14.34 ± 0.66	95.15
4a	100	13.15 ± 0.7**	86.01
4b	100	6.98 ± 2.05	38.00
4c	100	1.30 ± 0.19	0.11
4d	100	11.52 ± 1.56	74.49
4e	100	12.62 ± 0.56*	82.86
4f	100	11.70 ± 0.66**	76.40
4g	100	4.21 ± 2.71	24.50
4h	100	12.84 ± 0.15*	84.40
4i	100	4.29 ± 0.86	19.83
4j	100	11.68 ± 0.42*	74.77
6a	100	1.54 ± 0.29	1.07
6b	100	25 ± 0.07	1.51

acetylsalisylic acid (100 mg/kg) were used as the reference analgesic agent. Test latencies (in seconds) were assessed 30 min after the administration of compounds. To avoid irreversible damage in tail structures of mice, a maximum latency of 15 s. was imposed, if no response was observed within that time. Percent analgesia was calculated by following formula (% analgesia = {(postdrug latency)-(predrug latency)/(cutoff time)-(predrug latency)} × 100). Results expressed as mean SEM, and student's *t*-test was used to assess statistical significances. Test results are given in Tables II and III.

RESULTS AND DISCUSSION

Chemistry

The synthesis of the title 2-[2-(Benzazole-2-thioxy)acetylamino]-3-ethoxycarbonylthiophene and 2-[2-(benzazole-1-yl)acetylamino]-3-ethoxycarbonylthiophene derivatives, **4** and **6**, were accomplished in accordance with the sequence of reactions depicted in Scheme 1. The starting compounds, 2-amino-3-ethoxycarbonyl-4,5-alkylsubstituted thiophenes **1**, were prepared according to Gewald's Method[6] by the reaction of an appropriate cycloalkanone and ethyl cyanoacetate in the presence of sulphur and morpholine as a base catalyst in ethanol. 2-Chloroacetylamino-3-ethoxycarbonylthiophene



SCHEME 1 (a) EtOH/Morpholine, (b) Et_3N/THF, and (c) K_2CO_3/Acetone.

derivatives **2** were obtained by reacting the appropriate 2-amino-3-ethoxycarbonylthiophene derivatives with chloroacetyl chloride in the presence of triethylamine in THF in a common procedure.[9] The resulting compounds **4** and **6** were prepared by reacting an appropriate **2** and a benzazole-2-thione **3** or a benzimidazole **5** in the presence of potassium carbonate in acetone.

The structures of the obtained compounds were elucidated by using the spectral data. In the IR spectra, the characteristic amid N—H and C=O stretching bands were observed at 3200–3100 and 1665 cm^{-1}, respectively. In the NMR spectra, methylene protons of acetyl residue, which are common in all compounds, were observed at about 4.1–4.2 ppm in case of the compounds **4** and 5 ppm in case of the compounds **6**. Because of the tautomeric equilibrium from N—H in the ring of benzimidazole, the compound **6b**, which synthesized using 5(6)-chlorobenzimidazole as starting material, is a mixture of two structural isomers arising 5- and/or 6-chlorobenzimidazolyl residues. Thus, proton

TABLE III Effects of the Compounds on Tail-Immersion Response in Mice. A: Morphine Sulfate, B: Acetylsalisylic Acid. Values are Expressed as Mean ± S.E.M. of Five Mice in Each Group

Comp.	Dose (mg/kg) (i.p.)	Reaction Time (sec.)	% Analgesia Tail-immersion
A	10	10.99 ± 1.84	50.7
B	100	6.19 ± 1.41	21.9
4a	100	3.31 ± 0.71	7.3
4b	100	3.89 ± 0.87	5.8
4c	100	2.34 ± 0.67	0.1
4d	100	3.73 ± 0.29	9.6
4e	100	4.97 ± 0.98	19
4f	100	2.79 ± 0.74	6.2
4g	100	5.39 ± 2	3
4h	100	2.54 ± 0.38	6.73
4i	100	3.70 ± 0.72	6.9
4j	100	4.08 ± 0.89	3
6a	100	3.28 ± 0.40	2.3
6b	100	5.66 ± 2.12	12.2

signals in the NMR spectra were observed as overlaped. The peaks expected singlets were obtained as two singlets. However, the integral values of the peaks, belonging to the similar protons in each isomer, were in accordance. The other protons were obtained as multiplets as expected.

Pharmacology

Analgesic activities of the compounds were tested by using "tail-flick" and "tail-immersion" methods. The analgesic activity in each group is shown in Tables II and III. As control analgesic agents, morphine sulfate (10 mg/kg) and acetylsalisylic acid (100 mg/kg) were used and in tail clip method 95.38% and 95.15% and in tail immersion method 50.7% and 21.9% analgesic activity were observed, respectively.

In tail clip method, among the compounds tested **2a, 2e**, and **2h** showed remarkable activity in regard to the effects of morphine sulfate and acetylsalisylic acid. The activity obtained is quite close to the activity observed for both morphine sulfate and acetylsalisylic acid. The other notable compounds **2d, 2f**, and **2j** showed about 75% activity. It is noticeable that the effective compounds are carrying sulfanyl-bridged benzazole residue. However, the compounds **6a** and **6b** which are directly attached to benzimidazole residues do not show any analgesic activity.

The higher activity levels mentioned above were not observed in the tail-immersion experiments. Thus, it could be said that the compounds exhibited potent analgesic activity against physical stimuli, and they were found as potent as acetylsalisylic acid (ip. 100 mg/kg).

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