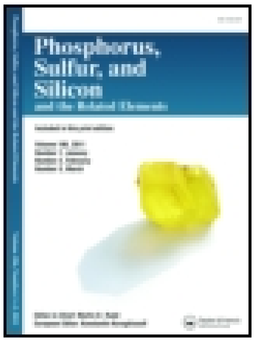

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SYNTHESIS OF NEW 8-METHOXY-4-METHYL-3-(N-[2'-AMINO-(1',3',4')THIA/OXA-DIAZOL-5'-YL]-SUBSTITUTED METHYL)-AMINO THIOCOUMARINS

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SYNTHESIS OF NEW 8-METHOXY-4-METHYL-3-(N-[2′-AMINO-(1′,3′,4′)THIA/OXA-DIAZOL-5′-YL]-SUBSTITUTED METHYL)-AMINO THIOCOUMARINS

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*8-Methoxy-4-methyl-3-(N-[2′-amino-(1′, 3′,4′)thia/oxa-diazol-5′-yl] substituted methyl)-amino thiocoumarins **6(a–f)** and **7(a–f)**, were synthesized by using the unreported 8-methoxy-4-methyl-3-[N-(2′-oxo-2′-methoxy-1′-substituted ethan-1′-yl) amino thiocoumarins as key intermediates.*

Keywords: Aminoacids; amino thia/oxa-diazoles; 8-methoxy-4-methyl-thiocoumarin

INTRODUCTION

Many derivatives of coumarins, such as EM 800, are known to be Chromone prodrugs,[1] which are useful as orally active nonsteroidal antiestrogens[2] and antitumor agents.[3] Tazarotene, a substituted benzothiopyran, is used for clinical evaluation of psoriasis.[4,5] Tertatol is another substituted benzothiopyran that is widely used against hypertension.[6,7]

Inspired by these observations, and in continuation of our program of synthesizing sulfur heterocycles,[8] we designed the synthesis of a series of a new 8-methoxy-4-methyl-3-(N-[2′-amino-(1′,3′,4′)thia/oxa-diazol-5′-yl]-substituted methyl)-amino thiocoumarins **6**(**a–f**) and **7**(**a–f**) starting from 6-methoxy-2-acetyl thiophenol.

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RESULTS AND DISCUSSION

6-Methoxy-2-acetyl thiophenol **1** was prepared by acetylating 6-methoxy thiophenol with acetyl chloride in anhydrous $AlCl_3$ by using dry DCM as solvent. The acetyl compound **1** was later reacted with chloroacetyl chloride by refluxing in dry acetone containing anhydrous potassium carbonate in order to convert it into the corresponding acetyl thio compounds **2**. Upon further treatment with substituted amino acid esters **3**(**a–e**) in presence of dry acetone containing anhydrous potassium carbonate, componds **2** produced a series of 2-acetyl-6-methoxy-1-[S-(1′oxo-3′-aza-4-substituted-5′-oxo-5′-methoxy-pent-1′–yl]-thiophenols **4**(**a–e**). These esters, when treated with NaOMe in dry methanol, in turn furnished the desired 8-methoxy-4-methyl-3-[N-(2′-oxo-2′-methoxy-1′-substituted ethan-1′-yl)]-amino thiocoumarins **5**(**a–e**).

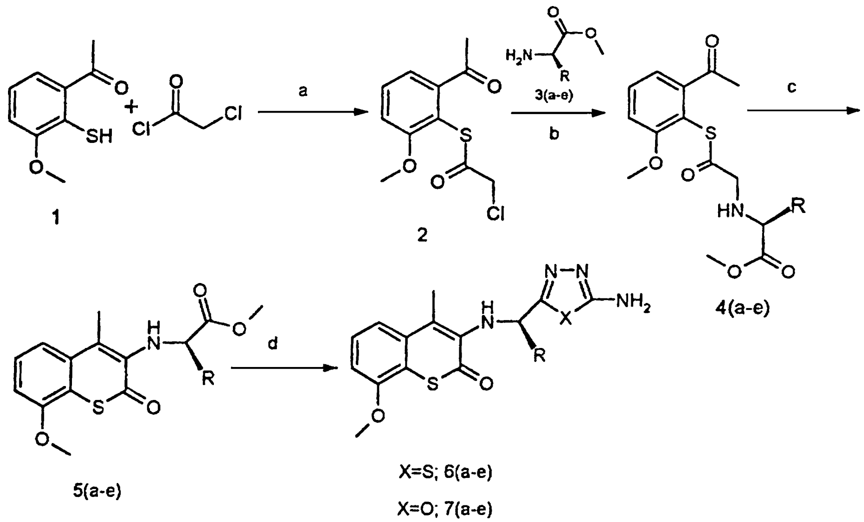
The esters **5**(**a–e**), upon reaction with thiosemicarbazide and semicarbazide, produced a series of required thia/oxa diazole derivatives **6**(**a–e**) and **7**(**a–e**), respectively, as shown in Scheme 1.

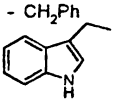
By using methyl proline ester **3f** in the place of the aminoacid esters, and by carrying out same sequence of reactions b, c, and d, we got another set products, 4f, 5f, 6f, and 7f, respectively, which are not shown in the above scheme.

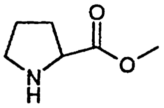
The structures of the compounds synthesized were established on the basis of analytical and spectral data (Tables I–III). In the IR spectrum of compound **4b**, vibration bands at 3180 cm^{-1} and 1710 cm^{-1} correspond to (CH_3CO) group. The ^1H NMR of the same compound contains signals at 2.3 δ (d, 3H, CH_3), 4.46 δ (s, 2H, CH_2), 4.18 δ (q, 1H, CH), 3.74 δ (s, 3H, OMe), 4.28 δ (d, 3H, —CO—OCH3), 6.88–7.42 δ (m, 3H, Ar—H). In case of compound **5b**, the signal for $—CH_2$ is absent. The absence of this signal indicated in the participation of $—CH_2$ in the cyclization to give rise to the thiocoumarin heterocycles. The mass spectrum of **5b** contains molecular ion peak of m/z 306. The ^1H NMR spectra of the compounds **6**(**a–f**) and **7**(**a–f**) show the absence of amino acid methyl ester (—COOMe) group.

EXPERIMENTAL

All melting points were uncorrected. The elementary analysis was carried out by CARRLO ERBA STUMENTOZOINE, Itali model, 1108, and IR spectra (cm^{-1}) were recorded on a PERKINE Elmer-282 instrument. The ^1H NMR spectra were recorded on a Varian 300 MHz spectrometer using tetra methyl silane as an internal standard. Chemical shift values



3(a-e)	R
a	- H
b	- CH_3
c	- CH_2Ph
d	
e	p-hydroxy benzyl



3f

SCHEME 1 a) Anhydrous K_2CO_3: acetone, reflux; b) anhydrous K_2CO_3, acetone; c) NaOMe, Methanol, reflux; d) NH_2–NH–CX–NH_2, ethanol, stirred at rt.

are expressed upon δ scale. Mass spectra were scanned on a Jeol-Jms-300 spectrometer at 70 eV. The purity of the compound was monitored by TLC performed on a silica gel plates (Merck) using ethylecetate and petroleum ether.

2-Acetyl-6-methoxy-S-chloroacetyl Thiophenol 2

To a suspension of 2-acetyl-6-methoxy thiophenol **1** (1.82 g, 0.01 mol) and anhydrous potassium carbonate (2.7 g, 0.02 mol) in dry acetone (20 ml), chloro acetylchloride (1.13 g, 0.01 mol) was added. The resulting mixture was refluxed with stirring for 6 h. The progress of the reaction was monitored by TLC. The reaction mixture was cooled, filtered,

TABLE I Physical Properties and Analytical Data (Calc./Found%) of the Compounds **4**(**a–f**), **5**(**a–f**), **6**(**a–f**), and **7**(**a–f**)

Comp.	Mol. formula	m.p. (°C)	C	H	N	O	S
4a	$C_{14}H_{17}NO_5S$	123–125	54.01/ 53.94	5.50/ 5.45	4.50/ 4.46	25.69/ 26.54	10.30/ 10.32
4b	$C_{15}H_{19}NO_5S$	131–133	55.37/ 55.35	5.89/ 5.84	4.30/ 4.26	24.30/ 24.23	9.85/ 9.80
4c	$C_{21}H_{23}NO_5S$	142–144	62.83/ 62.78	5.77/ 5.72	3.49/ 3.45	19.93/ 19.90	7.99/ 8.01
4d	$C_{23}H_{24}N_2O_5S$	155–157	62.71/ 62.68	5.49/ 5.42	6.36/ 6.34	18.16/ 18.12	7.28/ 7.26
4e	$C_{21}H_{23}NO_6S$	163–165	60.42/ 60.39	5.55/ 5.52	3.36/ 3.34	22.99/ 22.94	7.68/ 7.62
4f	$C_{17}H_{21}NO_5S$	114–116	56.96/ 56.92	5.68/ 5.64	4.15/ 4.10	23.71/ 23.67	9.50/ 9.52
5a	$C_{14}H_{15}NO_4S$	162–164	57.32/ 57.30	5.15/ 5.11	4.77/ 4.72	21.82/ 21.78	10.93/ 10.90
5b	$C_{15}H_{17}NO_4S$	174–176	58.62/ 58.58	5.57/ 5.52	4.56/ 4.50	20.82/ 20.79	10.43/ 10.40
5c	$C_{21}H_{21}NO_4S$	183–185	65.78/ 65.72	5.52/ 5.49	3.65/ 3.63	16.69/ 16.65	8.36/ 8.32
5d	$C_{23}H_{22}N_2O_4S$	202–204	65.39/ 65.34	5.25/ 5.23	6.63/ 6.60	15.16/ 15.12	7.59/ 7.52
5e	$C_{21}H_{21}NO_5S$	158–160	63.14/ 63.10	5.30/ 5.26	3.51/ 3.48	20.03/ 19.92	8.03/ 8.08
5f	$C_{17}H_{19}NO_4S$	152–154	61.24/ 61.20	5.74/ 5.71	4.20/ 4.18	19.19/ 19.14	9.62/ 9.58
6a	$C_{14}H_{14}N_4O_2S_2$	192–194	50.28/ 50.24	4.22/ 4.20	16.75/ 16.72	9.57/ 9.51	19.18/ 19.15
6b	$C_{15}H_{16}N_4O_2S_2$	204–206	51.71/ 51.67	4.63/ 4.60	16.08/ 16.02	9.18/ 9.15	18.40/ 18.42
6c	$C_{21}H_{20}N_4O_2S_2$	218–220	59.41/ 59.38	4.75/ 4.72	13.20/ 13.16	7.54/ 7.50	15.11/ 15.08
6d	$C_{23}H_{21}N_5O_2S_2$	242–244	59.59/ 59.55	4.57/ 4.52	15.11/ 15.08	6.90/ 6.87	13.83/ 13.78
6e	$C_{21}H_{20}N_4O_3S_2$	185–187	57.25/ 57.22	4.58/ 4.55	12.72/ 12.68	10.90/ 10.86	14.56/ 14.54
6f	$C_{17}H_{18}N_4O_2S_2$	166–168	54.53/ 54.50	4.84/ 4.78	14.96/ 14.92	8.54/ 8.50	17.12/ 17.08
7a	$C_{14}H_{14}N_4O_3S$	172–174	52.82/ 52.80	4.43/ 4.38	17.60/ 17.57	15.08/ 15.02	10.07/ 10.04
7b	$C_{15}H_{16}N_4O_3S$	189–191	54.20/ 54.17	4.85/ 4.82	16.86/ 16.82	14.44/ 14.41	9.65/ 9.61
7c	$C_{21}H_{20}N_4O_3S$	242–246	61.75/ 61.71	4.64/ 4.60	13.72/ 13.68	13.72/ 13.69	7.85/ 7.82
7d	$C_{23}H_{21}N_5O_3S$	235–237	61.73/ 61.70	4.73/ 4.69	15.65/ 15.61	10.73/ 10.70	7.16/ 7.11
7e	$C_{21}H_{20}N_4O_4S_2$	209–211	59.42/ 59.40	4.75/ 4.73	13.20/ 13.17	15.08/ 15.02	7.55/ 7.51
7f	$C_{17}H_{18}N_4O_3S$	194–196	56.97/ 56.92	5.06/ 5.02	15.63/ 15.60	13.39/ 13.34	8.95/ 8.91

TABLE II IR and ^{1}H NMR Spectral Data of the Compounds **5**(**a–f**)

Comp.	IR (cm^{-1})	m/z (M^{+1})	^{1}H NMR (δ ppm)
5a	1680 (–S–C=O), 1710 (CO),3240(NH)	292	2.22 (s, 3H, CH_3), 3.62 (s, 3H, OCH_3), 3.90 (s, 3H, CO–OCH_3), 4.20 (s, 2H, CH_2), 6.96–7.40 (m, 3H, Ar–H), 12.16 (s, 1H, NH)
5b	1680 (–S–C=O), 1705 (–CO), 3254 (–NH)	306	1.34 (d, 3H, CH_3), 2.59 (s, 3H, CH_3), 4.30 (q, 1H, CH), 6.88–7.42 (m, 3H, Ar–H), 12.38 (s, 1H, NH)
5c	1690 (–S–C=O), 1710 (–CO), 3242 (NH)	382	2.32 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 4.12 (s, 3H, CO–OCH_3), 4.14 (t, 1H, CH), 4.32 (d, 2H, CH_2), 6.90–7.46 (m, 8H, Ar–H)
5d	1692 (–S–C=O), 1704 (CO), 3320 (NH)	421	2.12 (s, 3H, CH_3), 3.3 (d, 2H, CH_2), 3.64 (s, 3H, OCH_3), 4.26 (s, 3H, –CO–OCH_3), 4.36 (t, 1H, CH), 5.20 (s, 1H, Indole-H), 6.92–7.52, (m, 7H, Ar–H), 12.12 (s, 1H, NH)
5e	1694 (–S–C=O), 1705 (CO), 3140 (NH), 3520 (–OH)	408	2.34 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 4.00 (s, 1H, CH), 4.26 (s, 3H, CO–OCH_3), 3.32 (d, 2H, CH_2), 6.94–7.42 (m, 7H, Ar–H), 10.42 (s, 1H, OH), 12.14 (s, 1H, NH)
5f	1690 (–S–C=O), 1704 (–CO)	332	2.10–2.18 (m, 6H, $(CH_2)_3$), 2.36 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 4.12 (t, 1H, CH), 4.30 (s, 3H, CO–OCH_3), 7.12 (m, 3H, Ar–H), 12.14 (s, 1H, NH)

the inorganic residue was washed with acetone, and the solvent was removed on a rotavapor. By the addition of water to the residue, the title compound was obtained as an oil, which was purified by column chromatography (EtOAc/petroleum ether 1:9). Yield, 70–74%.

2-Acetyl-6-methoxy-1-[S-(1′-oxo-3′-aza-4′-substituted-5′-oxo-5′-methoxy-pent -1′-yl]-thiophenols 4(a–e) and 4f

A mixture of **3**(**a–f**) (0.01 mol), 2-Acetyl-6-methoxy-S-chloroacetyl thiophenol 2 (0.01 mol), and anhydrous K_2CO_3 (2.7 g; 0.02 mol) in 25 ml of dry acetone was refluxed with stirring for 8 h. The progress of the reaction was monitored by TLC. The reaction mixture was cooled, filtered, the inorganic residue was washed with acetone, and the solvent was removed on a rotavapor. The addition of water to the residue gave the title compounds as precipitates, which were collected by filtration. They were washed with water and crystallized from ethanol. Yield, 60–72%.

TABLE III IR and ^{1}H NMR Spectral Data of the Compounds **6**(**a–f**) and **7**(**a–f**)

Comp.	IR cm^{-1}	(m/z) M^{+1}	^{1}H NMR(δ ppm)
6a	1680 (C=O), 3242 (NH), 3415 (NH_2)	333	2.32 (s, 3H, CH_3), 2.48 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3), 7.30–7.36 (m, 3H, Ar—H) 9.8 (s, 2H, NH_2), 12.2 (s, 1H, NH)
6b	1684 (C=O), 3140 (NH), 3412 (NH_2)	347	2.14 (d, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.42 (q, 1H, CH), 3.84 (s, 3H, OCH_3), 7.32–7.38 (m, 3H, Ar—H), 9.6 (s, 2H, NH_2), 12.8 (s, 1H, NH)
6c	1682 (C=O), 3142 (NH), 3416 (NH_2)	425	2.30 (s, 3H, CH_3), 2.54 (t, 1H, CH), 3.14 (d, 2H, CH_2), 3.84 (s, 3H, OCH_3), 7.34–7.36 (m, 8H, Ar—H), 9.6 (s, 2H, NH_2), 12.1 (s, 1H, NH)
6d	1690 (C=O), 3145 (indole-NH), 3244 (NH), 3418 (NH_2)	462	2.32 (s, 3H, CH_3), 2.58 (t, 1H, CH), (d, 2H, CH_2), 3.42 3.86 (s, 3H, OCH_3), 4.68 (s, 1H, CH), 5.12 (s, 1H, indole—H), 6.94–7.42 (m, 7H, Ar—H), 9.4 (s, 2H, NH_2), 11.4 (s, 1H, NH)
6e	1692 (C=O), 3140 (NH), 3412 (NH_2), 3560 (—OH)	441	2.36 (s, 3H, CH_3), 2.48 (t, 1H, CH), 3.40 (d, 2H, CH_2), 3.86 (s, 3H, OCH_3), 6.92–7.40 (m, 7H, Ar—H), 9.4 (s, 2H, NH_2), 10.8 (s, 1H, OH), 12.6 (s, 1H, NH)
6f	1690 (C=O), 3412 (NH_2)	375	2.10 (t, 1H, CH), 2.22–2.26 (complex multiplet pattern, 6H, $(CH_2)_3$), 2.32 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.92–7.24 (m, 3H, Ar—H), 2.42 (s, 2H, NH_2)
7a	1682 (C=O), 3180 (NH), 3412 (NH_2)	303	2.30 (s, 3H, CH_3), 2.54 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 7.34–7.92 (m, 3H, Ar—H), 9.92 (s, 2H, NH_2), 12.42 (s, 1H, NH)
7b	1688 (C=O), 3142 (NH), 3414 (NH_2)	333	2.10 (d, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.48 (q, 2H, CH_2), 8.88 (s, 3H, OCH_3), 7.52–7.58 (m, 3H, Ar—H), 9.6 (s, 2H, NH_2), 12.24 (s, 1H, NH)
7c	1686 (C=O), 3240 (NH), 3412 (NH_2)	409	2.33 (s, 3H, CH_3), 2.52 (t, 1H, CH), 3.12 (d, 2H, CH_2), 3.86 (s, 3H, OCH_3), 6.92–7.38 (m, 8H, Ar—H), 9.72 (s, 2H, NH_2), 12.51 (s, 1H, NH)
7d	1692 (C=O), 3182 (NH), 3415 (NH_2)	446	2.32 (s, 3H, CH_3), 2.56 (t, 1H, CH), 3.46 (d, 2H, CH_2), 3.86 (s, 3H, OCH_3), 5.62 (s, 1H, indole-H), 6.92–7.30 (m, 7H, Ar—H), 9.4 (s, 2H, NH_2), 12.3 (s, 1H, NH)
7e	1688 (C=O), 3240 (NH), 3412 (NH_2), 3540 (—OH)	423	2.46 (t, 1H, CH), 2.48 (s, 3H, CH_3), 3.46 (d, 2H, CH_2), 3.88 (s, 3H, OCH_3), 6.94–7.42 (m, 7H, Ar—H), 9.7 (s, 2H, NH_2), 10.6 (s, 1H, OH), 12.3 (s, 1H, NH)
7f	1690 (C=O), 3415 (NH_2)	357	2.10 (t, 1H, CH), 2.26–2.32 (complex multiplet pattern, 6H, $(CH_2)_3$), 2.34 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 6.92–7.32 (m, 3H, Ar—H), 9.8 (s, 2H, NH_2)

8-Methoxy-4-methyl-3-[N-(2′-oxo-2′-methoxy-1′-substituted Ethan-1′-yl)]-amino Thiocoumarins 5(a–e) and 5f

To a stirred solution of **4**(**a–f**) (0.001 mol) in dry methanol (15 ml) was added dropwise a solution of sodium methoxide (0.01 mol) in methanol (5 ml). The reaction mixture was refluxed for 3 h followed by removal of methanol under reduced pressure. The resultant precipitate was obtained by addition of water. The residue was filtered, washed with water, dried, and crystallized from ethanol. Yield, 58–64%.

8-Methoxy-4-methyl-3-(N-[2′-amino-(1′,3′,4′)thia/oxa-diazol-5′-yl]-substituted methyl)-amino Thiocoumarins 6(a–f) and 7(a–f)

A mixture of **5**(**a–f**) (0.001 mol) and thiosemicarbazide or semicarbazide (0.001 mol) in dry ethanol (20 ml) was stirred at room temperature for 5 h. The reaction mixture was poured into ice-cold water. The precipitated solids were collected and recrystallized from chloroform. Yield, 56–60%.

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