SYNTHESIS AND ANTI-MICROBIAL ACTIVITY OF THIAZOLE SUBSTITUTED COUMARINS

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Abstract:

A series of some innovative 7-((4-substituted thiazol-2-yl) methoxy)-4-methyl-2H-chromen-2-one **(4a-d) & (6a-b)** were synthesized starting from ethyl 2-(4-methyl-2-oxo-2H-chromone-7-yloxy)acetate **(1a).** Reaction of compound **(1a)** with aqueous ammonia yielded 2-(4-methyl-2-oxo-2H-chromomen-7-yloxy)acetamide **(2a).** Compound **(2a)** on reaction with P_2S_5 in dioxane gave 2-(4-methyl-2-oxo-2H-chromomen-7yloxy) ethanethioamide **(3a).** Reaction of **(3a)** with different substituted phenacylbromide/ dichloroacetone afforded **(4a-d) & (5a).** Condensation of **(5a)** with different secondary amines gave desired compounds **(6a-b).** The newly synthesized compounds are characterized by IR, ^{1}H NMR and mass spectral studies. These synthesized compounds were also screened for their antibacterial and antifungal activities.

Key words: 2-(4-methyl-2-oxo-2H-chromomen-7yloxy)ethanethioamide; 2,4-disubtituted thiazoles; anti-microbial activity.

Introduction:

Thiazoles and their derivatives are found to be associated with various biological activities such as antibacterial, antifungal and anti-inflammatory activitives[1-4] and some are known to possess biological activities[5-10]. Further coumarin substituted thiazole derivatives are of great importance for their physiological, photodynamic and bacteriostatic activities[11-13]. 7-Hydroxycoumarin is known for its antibiotic and antifungal bactivities[14-15]. Some coumarin analogs were highly fluorescent in nature and are used as laser dyes[6]. In addition to being used in the pharmaceutical industry, thiazoles also find wide application in the dye and photographic industries. A survey of the literature reveals that introduction of either coumarin or thiazole nucleus into different heterocycles have yielded many biologically active compounds endowed with a wide spectrum of pharmacological activity[16-17]. It has been well established that the presence 7-hydroxy-4-methyl-coumarin moiety is an important structural feature of a wide variety of synthetic drugs[18-20]. Encouraged by the above molecules containing 7-hydroxy-4-methyl-coumarin moiety at position 2 and substituted methyl/aryl group at position 4 of the thiazole ring, it is desirable to modify the nucleus with the hope that the resulting compounds may exhibit promising biological properties. The present study describes the synthesis of hitherto novel coumarin substituted thiazole derivatives **4a-d & 6a-b** and evaluation of their invitro antibacterial and antifungal activity against pathogenic strains.

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Experimental:

All the reagents were obtained commercially and used with further purification. The melting points were determined on an open capillary method and are uncorrected; IR spectra were recorded on a Perkin-Elmer Spectrum ONE FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a AMX-400 AV III Solids NMR. The chemical shifts were expressed in the ppm (δ scale) downfield from TMS. Mass spectra were recorded on a LCMS-2010A Data Report-Shimadzu and elemental analysis on a Flash EA 1112 Series CHNS Report Thermo Finnigan. Silica gel Merck (60-120 mesh) and DC-Alufoline 60 F254 were normally used for column and TLC Chromatography respectively.

Synthesis of ethyl 2- (4- methyl-2-oxo-2H-Chromen-7-yloxy) acetate (1a)

To an equimolar mixture of 7-hydroxy- 4- methyl coumarin (**1**) (0.01 mole) and ethylchloroacetate (0.01 mole) added anhydrous potassium carbonate (6 g) and anhydrous acetone (25 ml). The reaction mixture was refluxed for 10-12 hrs. The reaction product was filtered and the filtrate evaporated to dryness. The residue crystallized from ethanol to yield the desired compound (**1a**). Yield: 92 %. m.p. 90-92^{0}C. IR: 2977 aromatic CH and 1753 C=O cm^{-1}. ^{1}H NMR: δ 7.5-6.8 (m, 4H, ArH), 4.6 (s, 2H, OCH_2), 4.6 (q, 3H, CH_3), 2.1 (s, 3H, CH_3), 1.4 (t, 2H, CH_2). Elemental analysis: Calcd for $C_{14}H_{14}O_5$: C, 64.12: H, 5.38. Found: C, 64.10; H, 5.35.

Synthesis of 2-(4- methyl- 2-oxo - 2H - chromen-7-yloxy) acetamide (2a)

A mixture of ethyl 2-(4- methyl-2-oxo-2H-chromen-7-yloxy) acetate (**1a**) (1 mole) and 20 ml aqueous ammonia (20%) was stirred for 12-14 hrs at room temperature with purging of ammonia gas. The progress of the reaction was monitored by TLC. The white solid product separated was filtered, dried and recrystallized from ethanol gave (**2a**). Yield: 64%. m.p. 200-202^{0}C. IR: 3160 NH_2 and 1657 C=O cm^{-1}. ^{1}H NMR: δ 7.7-6.7 (m, 4H, ArH), 6.2 (s, 2H, NH_2), 4.5 (s, 2H, OCH_2), 2.1 (s, 3H, CH_3). Elemental analysis: Calcd for $C_{12}H_{11}NO_4$: C, 61.80: H, 4.75; N, 6.01. Found: C, 61.78; H, 4.73; N, 6.00.

Synthesis of 2-(4- methyl-2-oxo-2H-Chromen-7- yl oxy) ethanethioamide (3a):

To a Solution of 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetamide (**2a**) (1 mole) in 25 ml of dioxane, phosphorous pentasulfide (2 mole) was added slowly at 10-12^0 C over a period of 2 hrs with constant stirring. The reaction mixture was heated to 40^{0}C for 2-3 hrs. It was then poured into ice cold water. The precipitated yellow solid was filtered, washed with water, dried and recrystallized from ethyl acetate furnished (**3a**). Yield: 92%. m.p. 170-172^{0}C. IR: 3393 NH_2 and 1698 C=O cm^{-1}. ^{1}H NMR: δ 7.9-6.8 (m, 4H, ArH), 5.8 (s, 2H, NH_2), 4.7 (s, 2H, OCH_2), 2.3 (s, 3H, CH_3). Mass: m/z=249 (M^+, 80%), 234 (100%) and 176 (70%). Elemental analysis: Calcd for $C_{12}H_{11}NO_3$: C, 57.82: H, 4.45; N, 5.62. Found: C, 57.80; H, 4.41; N, 5.60.

Synthesis of 7- ((4-phenyl thiazol-2-yl) methoxy)-4 -methyl-2H -chromen- 2- one (4a-d):

An Equimolar mixture of 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) ethanethioamide (**3a**) (1 mole) and substituted phenacylbromides (1 mole) was dissolved in 20 ml of absolute ethanol. The reaction mixture was refluxed for 8 hrs on a steam bath and left overnight at room temperature. The solid obtained was filtered, washed with ethanol and purified by recrystallization from ethanol.

4a: Yield: 58%. m.p. 222-225^{0}C. IR: 3069 aromatic CH and 1681 C=O cm^{-1}. ^{1}H NMR: δ 7.6-6.7 (m, 9H, ArH), 6.2 (s, 1H, thiazole CH), 4.5 (s, 2H, OCH_2), 2.1 (s, 3H, CH_3). Mass: m/z=349 (M^+, 30%), 266 (12%), and 234 (100%). Elemental analysis: Calcd for $C_{20}H_{15}NO_3S$: C, 68.75: H, 4.33; N, 4.01. Found: C, 68.71; H, 4.30; N, 4.00.

4b: Yield: 64%. m.p. 150-151^{0}C. ^{1}H NMR: δ 7.9-6.5 (m, 9H, ArH), 6.0 (s, 1H, thiazole CH), 5.0 (s, 2H, OCH_2), 2.1 (s, 6H, 2 CH_3). Mass: m/z=363 (M^+, 1000%), 279 (5%), and 97 (50%). Elemental analysis:
Calcd for $C_{21}H_{17}NO_3S$: C, 69.40: H, 4.71; N, 3.85. Found: C, 69.36; H, 4.68; N, 3.83.

4c: Yield: 54%. m.p. 158-160^{0}C. ^{1}H NMR: δ 7.9-6.8(m, 9H, ArH), 6.3 (s, 1H, thiazole CH), 5.1 (s, 2H, OCH_2), 2.1 (s, 3H, CH_3). **4d:** Yield: 64%. m.p. 215-217^{0}C. ^{1}H NMR: δ 9.2 (s, 1H, OH), 7.9-6.8 (m, 9H, ArH), 6.1 (s, 1H, thiazole CH), 5.2 (s, 2H, OCH_2), 2.3 (s, 3H, CH_3).

Synthesis of 7-((4-(chloromethyl) thiazol-2-yl) methoxy)-4-methyl-2H-chromen-2-one (5a):

To a clear solution of 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) ethanethioamide (**3a**) (1 mol) in ethanol (15 ml) 1,3-dichloroacetone (1.2 mol) was added slowly over a period of 1 hr with stirring. The mixture was then refluxed for 3 hrs and then left over night at room temperature. The solid separated was filtered, washed with ethanol and recrystalized with ethanol gave (**5a**). Yield: 61%. m.p. 225-227^{0}C. IR: 3090 aromatic CH and 1678 C=O cm^{-1}. ^{1}H NMR: δ 7.4-6.9 (m, 9H, ArH), 6.67 (s, 1H, thiazole CH), 5.13 (s, 2H, OCH_2), 4.64 (s, 2H, CH_2), 1.9 (s, 3H, CH_3). Elemental analysis: Calcd for $C_{15}H_{12}ClNO_3S$: C, 55.99: H, 3.76; N, 4.35. Found: C, 55.96; H, 3.72; N, 4.32.

Synthesis of 7-((4-((amine-1-yl) methyl) thiazol-2-yl) methoxy)-4-methyl-2H-chromen-2-one (6a,b):

A mixture of compound 7-((4-(chloromethyl) thiazol-2-yl) methoxy)-4-methyl-2H-chromen-2-one (1 mole) (**5a**), secondary amines (1.2 mole) and super dry ethanol (20 ml) was heated under reflux for 3-4 hrs. The reaction mass was left overnight at RT and the solid obtained was filtered, washed with cold ethanol, dried and recrystallized from ethanol furnished (**6a,b**). **6a** Yield: 63%. m.p. 210-212^{0}C. IR: 3236 NH and 1660 C=O cm^{-1}. ^{1}H NMR: δ 7.2-6.7 (m, 5H, ArH), 6.6 (s, 1H, thiazole CH), 5.5 (s, 1H, piperizine NH), 5.24 (s, 2H, OCH_2), 4.1 (s, 2H, CH_2), 2.8 (m, 8H, piperizine CH_2). Elemental analysis: Calcd for $C_{19}H_{21}N_3O_3S$: C, 61.44: H, 5.70; N, 11.31. Found: C, 61.41; H, 5.67; N, 11.28.

Result and discussion:

The reaction sequence employed for the synthesis of title compounds is shown in scheme-1. The key intermediate, ethyl 2-(4- methyl-2-oxo-2H-Chromen-7-yloxy)acetate (**1a**) was prepared by reacting ethyl chloroacetate with 7-hydroxy-4-methyl-coumarin (**1**) in boiling acetone in presence of potassium carbonate. Further, the compound (**1a**) was readily converted in to 2-(4- methyl-2-oxo-2H-chromen-7-yl-oxy)acetamide (**2a**) by treating with aq.ammonia. The acetamide (**2a**) on reaction with phosphorous pentasulfide in dioxane at 50^{0}C yielded 2- (4- methyl-2-oxo-2H-Chromen- 7-yl-oxy)ethanethioamide (**3a**), which on condensation with substituted phenacyl bromides in alcoholic media at reflux temperature afforded 7 - ((4 - phenyl thiazol - 2-yl)methoxy)-4 -methyl-2H -chromen- 2- one (**4a-d**) in 53-64% yield (Table -1). On the other hand, reaction of (**3a**) with alcoholic 1, 3-dichloroacetone gave 7-((4-(chloromethyl) thiozaol-2-yl) methoxy)-4-methyl-2H-chromon-2-one under reflux furnished (**5a**) in 50% yield. The compound (**5a**) was finally reacted with secondary amines to furnish the title compounds 7-((-4-phenylthiazol-2-yl)methoxy)-4-methyl-2*H*-chromen-2-one (**6a-b**) in 57-60% yield. All the synthesized compounds were characterized by IR, ^{1}H NMR and Mass spectral data and elemental analysis data.

Anti-microbial activity:

Antimicrobial activities of synthesized compounds have been tested for their antibacterial activity against *Klebsiella, E.coli* and *S.aureus* and antifungal activity against *A.niger, A.flamp* and *A.terrus* by cup-plate method. Ciprofloxin, Gentamycin and Fluconazole were used as standards for antibacterial and antifungal activities respectively. The compounds were tested at the concentration of 1000μg/ml in DMF for both antibacterial and antifungal activity. The zone of inhibition after 24 hrs of incubation at 37^{0}c, in case of antibacterial activity and 72 hrs in case of antifungal activity was compared with that of standards. The results are tabulated in the table-2.

In anti-bacterial activity compounds **2a** to **6a** were highly active against *klebsiella*, **4a,4b** and **5a** were showed good activity against *E.coli & S.aureus* and remaining compounds were moderate activity against all the organisms.

In anti-fungal activity compounds **4a** and **4c**were good active against *A.niger*, compounds **4a,4c,4d,5a,6a** and **6b** were highly active against *A.flamp*, compounds **2a** to **6a** highly active against *A.terrus* and remaining compounds were showed moderate active against all the organisms.

Table - 1; Physical data of synthesized compounds

Sl. No.	Compound Code	Molecular Formula	Melting Point (^{0}C)	Percentage (%)Yield
1	1 a	$C_{14}H_{14}O_5$	90 - 95^0 c	91
2	2 a	$C_{12}H_{11}O_4N$	200 - 205^0 c	64
3	3 a	$C_{12}H_{11}O_3NS$	170 - 175^0 c	92
4	4a	$C_{22}H_{18}O_4NS$	220 - 225^0 c	57
5	4b	$C_{23}H_{20}O_4NS$	150-151^0	64
6	4c	$C_{22}H_{17}O_4ClNS$	158-160^0	53
7	4d	$C_{22}H_{18}O_5NS$	215-217^0	63
8	5a	$C_{15}H_{12}ClNO_3S$	225-227^{0}C	64
9	6a	$C_{19}H_{21}N_3O_3S$	210-212^{0}C	60
10	6b	$C_{20}H_{22}N_2O_3S$	187-189^{0}C	57

Table- 2: Anti-microbial activity of the synthesized compounds

Compounds	Concc-^{n} (µg/ml) in DMF	* Zone of inhibition in mm					
		Antibacterial activity			Antifungal activity		
		Klebsiella	*E.coli*	*S. aureus*	*A.niger*	*A.flamp*	*A.terrus*
1a	1000	12	08	06	08	08	08
2a	1000	16	11	06	08	10	14
3a	1000	13	08	08	08	08	18
4a	1000	16	16	11	13	12	14
4b	1000	14	13	12	08	10	14
4c	1000	16	08	08	12	18	18
4d	1000	16	11	08	10	18	18
5a	1000	14	12	10	10	16	17
6a	1000	12	11	09	11	14	14
6b	1000	11	10	08	10	12	13
Control	DMF	06	06	06	06	06	06
Standard	Ciprofloxin	12	11	10	-	-	-
Standard	Gentamycin	18	16	10	-	-	-
Standard	Fluconazole	-	-	-	13	12	13

*Diameter of well (bore size) - 6 mm,

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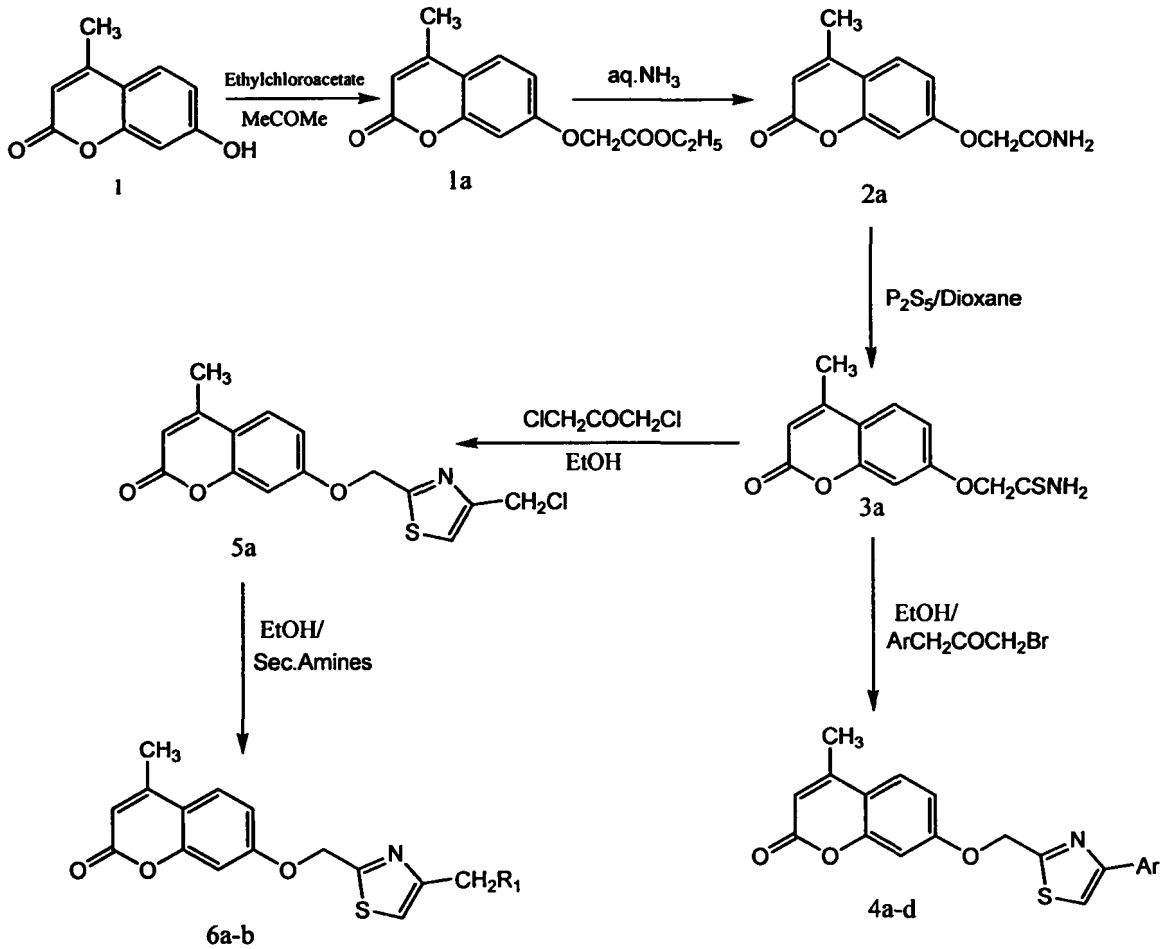
Received on December 1,2008.

scheme-1



R_1
6a-Piperazine
6b-piperidine

Ar
4a- C_6H_5
4b- $C_6H_4CH_3(p)$
4c- C_6H_4Cl (p)
4d- C_6H_4OH (p)