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SYNTHESIS OF SOME COUMARIN-ETHYLIDENEAMINO-2-THIOXOIMIDAZOLIN-4-ONE DERIVATIVES

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ABSTRACT

The synthesis of some coumarin derivatives was aimed at creating a new molecular frame work. Seven of coumarin derivatives have been synthesized by reacting of 3-acetyl-2H-chromen-2-one with thiosemicarbazide followed by cyclization with ethyl chloroacetate then reacted with acetic anhydride, 4-chlorobenzaldehyde and diethylamine to yield other compounds All these compounds were characterized by physical and spectral data.

KEYWORDS: Coumarin, chloroacetate, thiosemicarbazide, diethylamine.

1. INTRODUCTION

There are a number of reports that natural and synthetic Coumarin derivatives possess antioxidant activity.[1-3] The aim is done because synthetic Coumarin itself posse's versatile pharmacological and biological activities like antimicrobial, anti-inflammatory, anti HIV, anticoagulant, anticancer, antihypertensive, hypoglycemic and antileshmanial activities so on.[4-6] however, their natural abundance in plants is very low and the purification processes are complex. Therefore, various methods have been developed for the total synthesis of coumarins,[7-9] including the Perkin,[10] Pechmann,[11] and Knoevenagel reaction is the one that have been adopted in this research.[12] we synthesized some Coumarin heterocyclic derivatives by condensation of 2-(1-(2-oxo-2H-chromen-3 yl)ethylidene)hydrazine carbothio amide with ethylchoroacetate. The aim of this work was the synthesis of coumarin compounds with potential antioxidant activity.

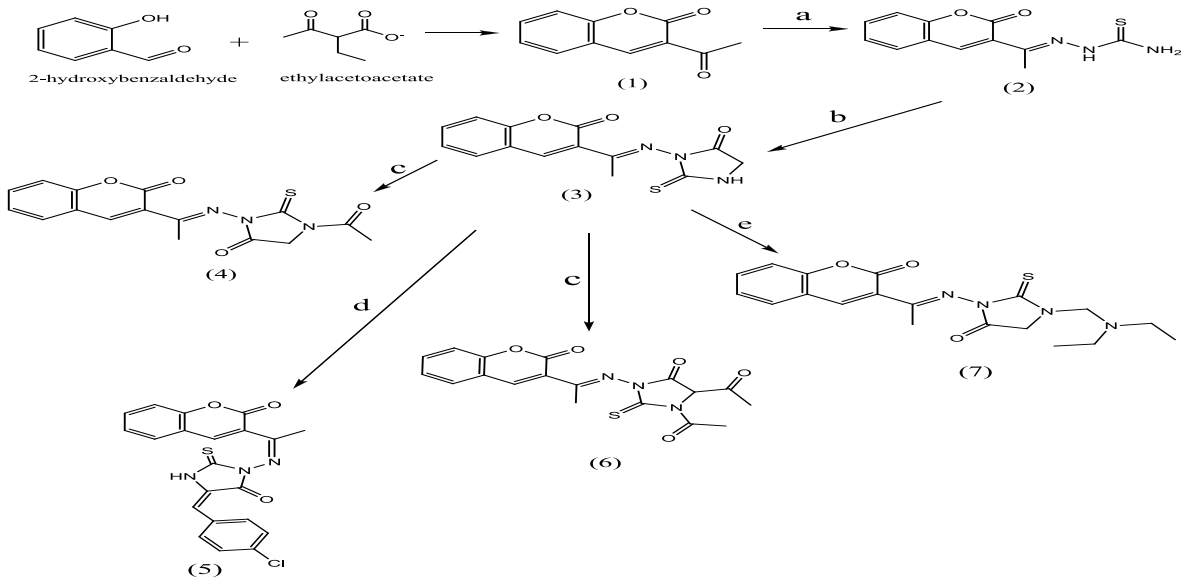
2. Experimental Section

All the chemicals and solvents used were of synthetic grade obtained from Sd Fine chemicals Ltd., (Mumbai, India), E. Merck. Completion of the reactions was monitored from time to time by analytical thin layer chromatography (TLC) using E-Merck silica gel 60 F254 0.25 mm precoated aluminium plates.

Melting points were determined on open capillary tubes in ANALAB melting point apparatus and were uncorrected. All the IR spectra were recorded on SCHIMADZU FT-IR spectrophotometer by using 1 % potassium bromide discs. NMR data of the compounds were recorded on Ultra Shield 300MHz, Bruker, Switzerland, at University of Tahran.

In the present scheme, the angular coumarins were synthesized by in following steps.

1. Cyclization of coumarin with ethylchoroacetate.
2. Condensation of compound 3 with different reagents. Finally, these synthesized compounds are planned to screen for antioxidant studies.



Reagents and Conditions: *a= Hydrazinecarbothioamide; b= Ethylchoroacetate; c=Acetic anhydride; d= 4-chloro benzaldehyde; e=Diethyl amine.*

Step 1: Synthesis of *3-acetyl-2H-chromen-2-one* (1)
Salicylaldehyde (3.05g ,0.025mol) and ethyl acetoacetate (3.25g ,0.025 mol) was mixed, stirred and cooled .To this mixture 10 mL of piperidine was added with shaking .The mixture was kept in refrigerator for 2 hrs. , after that a yellow solid was obtained, then was recrystallized from ethanol.[13]

Step2: Synthesis of *(E)-2-(1-(2-oxo-2H-chromen-3 yl)ethylidene) hydrazinecarbothioamide* (2*)*

Was previously prepared by refluxing 3-acetyl-2*H*-chromen-2-one (**1**) and thiosemicarbazide in absolute ethanol in the presence of catalytic amounts of HCl.[14]

Step 3: Synthesis of *(E)-3-(1-(2-oxo-2H-chromen-3-yl)ethylideneamino)-2-thioxoimidazolidin-4-one* (3)
A mixture of (compound 2) (0.01mol) and ethyl chloroacetate (0.01mol) in ethanol (50 ml) in presence of anhydrous sodium acetate (0.03mol) was heated under reflux for 4 hr. After cooling to room temperature, the reaction mixture was poured into ice water. The resulting solid was filtered off, washed with hot water, dried and recrystallized from appropriate solvent.[15]

Step 4: Synthesis of (E)-1-acetyl-3-(1-(2-oxo-2H-chromen-3-yl) ethylideneamino)-2-thioxoimidazolidin-4-one (4)
A solution of (compound 3) (0.01 mol) in acetic anhydride (25 mL) was heated under reflux for 2 h, then cooled and the resulting solid was collected by filtration, dried and purified by crystallization from benzene to give compound (4).[16]

Step 5: Synthesis of (E)-5-(4-chlorobenzylidene)-3-((Z)-1-(2-oxo-2H-chromen-3-yl) ethylideneamino)-2-thioxoimidazolidin-4-one (5)
A mixture of (compound 3) (0.01mol), appropriate aromatic aldehydes (4-chlorobenzaldehyde) (0.01mol) and triethylamine (1 ml) was heated at 120-125 ^{o}C for 1hr without solvent. The reaction mixture was then left to cool at room temperature and acidified with dilute hydrochloric acid (2%). The crude product was filtered off, washed with water, dried and purified by recrystallization from the suitable solvent to give compounds (5).[15]

Step 6: Synthesis of (E)-1,1'-(4-oxo-3-(1-(2-oxo-2H-chromen-3-yl)ethylideneamino)-2-thioxoimidazolidine-1,5-diyl)diethanone (6)
A mixture of (compound 3) (0.01 mol) and fused sodium acetate (0.02 mol) in acetic anhydride (25 mL) was heated under reflux for 3 h, then cooled and poured into ice-water. The resulting solid was filtered off, washed with water, dried and purified by crystallization from benzene.[16]

Step 7: Synthesis of (E)-1-((diethylamino) methyl)-3-(1-(2-oxo-2H-chromen-3-yl)ethylideneamino)-2-thioxoimidazolidin-4-one (7)
To a solution of **(**compound 3) (0.01 mol) soluble in 50 mL ethanol was added, a mixture of secondary amines (0.01 mol) (diethylamine) and aqueous formaldehyde 37% (1.25 mL) dissolved in 10 mL ethanol, drop wise throw 30 min, then stirred at room temperature for 3 h. Finally refrigerated for 48 h to form crystals. The solid formed was filtered off and crystallized from ethanol to give compound (7) as pale yellow crystals.[16]

3. RESULTS AND DISCUSSION

The compounds were synthesized according to the scheme and interpreted by Physical, chemical and analytical data as shown in Table-1 and Table-2.

Table 1: Physical data of synthesis compounds.

Compound No.	Molecular formula	Molecular weight (g/mol)	Colour	Yield (%)	Melting point (°C)
1	$C_{11}H_8O_3$	188.18	Light orange	80	119-121
2	$C_{12}H_{11}N_3O_2S$	261.30	Yellow	65	190-192
3	$C_{14}H_{11}N_3O_3S$	301.32	Dark yellow	45	271-273
4	$C_{16}H_{13}N_3O_4S$	343.36	Dark brown	55	280-282
5	$C_{21}H_{14}ClN_3O_3S$	423.87	Light brown	60	206-209
6	$C_{18}H_{15}N_3O_5S$	385.39	White	50	174-177
7	$C_{19}H_{22}N_4O_3S$	386.47	Milky	45	254-256

Table 2: Spectral data of synthesis compounds.

Compounds No.	IR (cm^{-1})	^{1}H-NMR (δ, ppm)
1	1675 (C=O, lactone); 1750 (C=O, ester)	2.26(s,3H,CH_3); 8.41 (s, 1H: CH); 7.42-7.63(m,4H, Ar-H)
2	1678 (C=O, lactone); 3238.5, 3155.65 (NH_2); 3387.1 (NH**)**; 623(S-C)	8.53 (s, 2H; NH_2) ; 7.0(s,1H,NH);2.07(s,3H,CH_3); 7.54 (s, 1H: CH); 7.42-7.63(m,4H, Ar-H)
3	1616.4 (C=O, lactone); 1595.1(C=O); 3205.8 (NH**)**; 625(S-C)	2.07 (s,3H,CH_3)7.43(s,1H,NH);4.16(s,3H,CH_3); 7.45 (s, 1H: CH); 7.42-7.63(m,4H, Ar-H)
4	1679 (C=O, lactone); 1745 (C=O, ester)**;** 1690 (C=O)	2.04 (s.3H,CH_3);2.07(s,3H,CH_3); 4.34 (s, 1H: CH); 7.40-7.62(m,4H, Ar-H)
5	1689.7(C=O, lactone); 1743.7(C=O); 3211.59 (NH); 688.6(S-C)	2.34 (s.3H,CH_3); 7.34(s,1H,CH); 4.34 (s, 1H: CH); 7.41-7.84(m,4H, Ar-H) ; 7.44-7.68(m,4H, Ar-H); 2.0(s,1H,NH)
6	1622.19 (C=O, lactone); 1759.1, 1708.9 (2C=O, ester)**;** 1695.4 (C=O)	2.31 (s.3H,CH_3);2.04(s,3H,CH_3); 2.07 (s, 3H: CH_3); 7.54 (s, 1H: CH); 7.42-7.80(m,4H, Ar-H)
7	1630.5(C=O, lactone); 1690.1(C=O); 622(S-C)	4.37 (s.2H,CH_2); 1.02(t,3H,CH_3); 2.07 (s, 3H: CH_3); 7.46(s, 1H: CH); 7.40-7.79(m,4H, Ar-H)

4. CONCLUSION

A new series of coumarin derivatives were synthesized, and structurally elucidated using IR, ^{1}H NMR starting from the compound 3-(1-(2-oxo-2H-chromen-3-yl)ethylideneamino)-2thioxoimidazolidin--4-one (3) was synthesized by combining 2-(1-(2-oxo-2H-chromen-3 yl)ethylidene)hydrazinecarbothioamide (2) with ethyl chloroacetate in ethanol in presence of anhydrous sodium acetate.

REFERENCE

1. Al-Amiery AA, Al-Majedy YK, Kadhum AAH, Mohamad AB Hydrogen Peroxide Scavenging Activity of Novel Coumarins Synthesized Using Different Approaches. PloS one, 2015; 10(7): e0132175.
2. Al-Amiery AA, Al-Majedy YK, Kadhum AAH, Mohamad AB Novel macromolecules derived from coumarin: synthesis and antioxidant activity. Scientific Reports, 2015; 5: 11825.
3. Al-Majedy YK, Al-Duhaidahawi DL, Al-Azawi KF, Kadhum AAH, Al-Amiery AA, Mohamad AB. Coumarins as Potential Antioxidant Agents Complemented with Suggested Mechanisms and Approved by Molecular Modeling Studies. Molecules, 2016; 11-1(2): 21.
4. Balaji P.N. and Sai Sree vani. J. Chem. Pharm. Res., 2010; 2(4): 754-758
5. P.M. Gurubasavaraja Swamy and Y.S. Agasimundin. Acta Pharmaceutica Sciencia, 50: 197-202.
6. Gummudavelly Sandeep and Y Sri Ranganath. Asian J. Research Chem, 2009; 2(1).
7. Chen, W.A. Convenient total synthesis of isofraxidin, a natural coumarin. *Indian J. Chem. Sect. B Org. Chem. Incl. Med. Chem*, 1996; *35*, 1085–1087.
8. Demyttenaere, J.; Syngel, K.V.; Markusse, A.P.; Vervisch, S.; Debenedetti, S.; de Kimpe, N. Synthesis of 6-methoxy-4*H*-1-benzopyran-7-ol, a character donating component of the fragrance of *Wisteria sinensis*. *Tetrahedron* 2002, *58*, 2163–2166.
9. Crosby, D.G. Improved synthesis of scopoletin. *J. Org. Chem.* 1961, *26*, 1215–1217.
10. Hauer, H.; Ritter, T.; Grotemeier, G. An improved and large scale synthesis of the natural coumarin scopoletin. *Arch. Pharm.* 1995, *328*, 737–738.

11. Hao, S.; Zong, G.; Wei, Y.; Meng, Z. Synthesis and pesticidal activity of 6,7-dimethoxy coumarin. *J. Qingdao Agric. Univ.* 2007, *24*, 241–244.
12. Zhang, S.; Ma, J.; Chen, S.; Li, H.; Xin, J. Improved synthesis techniques of 6,7-dimethoxy coumarin. *J. Hebei Univ. Sci. Technol*, 2007; *28*; 24–28.
13. Nadeem Siddiqi, Faiz Arshad and Suroor Khan, "Synthesis of some new coumarin incorporated thiazolyl symicarbazones as anticonvulsants ", *Pharm. Soci*., 2009; 66(2).
14. Chimenti, F.; Bolasco, A.; Secci, D.; Chimenti, P.; Granese, A.; Carradori, S.; Yáñez, M.; Orallo, F.; Ortuso, F.; Alcaro, S. Investigations on the 2-thiazolylhydrazyne scaffold: Synthesis and molecular modeling of selective human monoamine oxidase inhibitors. *Bioorg. Med. Chem*, 2010; *18*: 5715–5723.
15. Roaa Majid Abdul-Amir Hamid." Synthesis of New beta-lactam, 2-thioxoimidazolidin-4-one and Imidazole-5-one Derivatives from thiosemicarbazide and Their Biological Activity Study",*Ibn Al-Haitham Jour. for Pure & Appl. Sci.*, 2017; 30(2).
16. Heba A. Elhady, Refat El‐Sayed and Hamedah S. Al‐nathali, "Design, synthesis and evaluation of anticancer activity of novel 2‐thioxoimidazolidin‐4‐one derivatives bearing pyrazole, triazole and benzoxazole moieties",*Elhady et al. Chemistry Central Journal*, 2018; 12: 51.