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Synthesis and Studying of The Biological Activity of Some New Coumarin-3-Carboxylic Acid Heterocyclic Derivatives

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Abstract

This study includes the synthesis of a few different coumarin-3-carboxylic acid derivatives of 1,2,3-triazole and triazoline as a starting material. The first step involves the formation of compound (a) in absolute ethanol through the reaction of coumarin-3-carboxylic acid to thiosemicarbazide. Then compound (a) reacts with chloroacetyl chloride in the presence of triethylamine for compound forming (b). Azide derivative compound (c) was prepared with sodium azide in DMF by compound reaction (b). The heterocyclic compounds 1,2,3-triazole and triazoline derivatives (Mch1, Mch2, d, e , and f) were prepared with some unsaturated compounds such as propergyl bromide, cinnamic acid, and maleic anhydride in DMF from the reaction of compound (c). All compounds were identified by FT-IR, 1H-NMR spectrum, and C.H.N.S elemental analysis. The heterocyclic compounds were tested as an antibacterial activity with certain microorganism types. They showed good antimicrobial activity towards the investigated specific microorganisms.

Keywords: Coumarin, Heterocyclic compounds, 1,2,3-Triazole, Antimicrobial activity;

1. Introduction

Coumarin, of artificial and natural origin, is a broad family of cyclic heterocyclic compounds that contain a benzo-a-pyrone group. Coumarin is widely distributed on plants. Where coumarin was first found in tonka bean (Dipteryx odorata Wild) and extensively investigated in both the pharmaceutical and biochemical fields [1,2], The highest levels of coumarin are present in fruit plants, followed by leaves and roots. Some essential coumarin members have been isolated from microbial sources such as comercmicin and novobiosin from aflatoxins and streptomyces as opposed to forms of Aspergillus [3], Coumarin (such as bilberry and cloudberry), green tea and other foods such as dandelionare also present in fruits [4]. Among the many classes of natural compounds coumarins have made a name for themselves. In 2008, Larsen and colleagues [5] found that certain essential oils contain high levels of coumarin, notably in lavender oil and peppermint oil (20 mg / kg), cinnamon bark oil (7000 mg / kg), cinnamon leaf oil (40,600 mg / kg), and cassia leaf oil (up to 83,300 mg / kg). Found in Artemisia scoparia over the past decades, Coumarin has attracted strong scientific interest due to its wide range of pharmacological activities that act as antidiabetic [6], antiviral [7], anti-inflammatory [8], act as antagonists of adenosine receptors [9] and many of the synthetic and naturally occurring coumarin derivatives have already been reported for their anti-cancer age. A series of compounds of coumarin derivatives were prepared in this lab, and their antibacterial activity was investigated using two types of bacteria, Gram-positive and Gram-negative.

2. Experimental Part

Fluke, Sigma Aldrich, BDH, and Merck Chemicals Companies provided all of the chemicals. Melting points were measured using an Electro-Thermal Melting point Unit, UK. FT-IR spectra were generated using Fourier infrarot transformation Bruker ALPHA FT-IR, College of Science; some spectra were captured by KBr disk infrarot spectrophotometer Shimadzu FT-IR-8400S, Faculty of Pharmacy, University of Kufa. The Bruker spectrometer which operates at (500MHZ) with (DMSO.-d6) registered 1H-NMR. Measurements were carried out at the

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Faculty of Science, Tehran University, Iran. The elemental analysis was documented by the use of E.A.G.E.R.-100, Carlo Erba, Italy. Measurements were carried out at the Faculty of Science, Tehran University, Iran. Thin layer chromatography (TLC) was conducted on aluminum plates and covered with a film of silica gel; iodine vapor was used to detect compounds.

2.1. Synthesis and Methods

Synthesis of 3-(5-amino-1,3,4-thiadiazole-2yl)-2H-chromen-2-one (a) [15]: A mixture of thiosemicarbazide (0.01 mol) with aryl-replaced carboxylic acid (0.01 mol) and a concentrated 5 ml sulfuric acid in (50 ml) absolute ethanol was refluxed for (5 hrs) below 80 oC. The substance that resulted was transferred to the beaker and poured on crushed ice. The seperated solid was filtered, cold water cleaned, and ethanol recrystallized. Using TLC the reaction progress was tracked. yield reaction (81 %), m.p. (176-179 oC), and Rf (0.69) (benzene: methanol, 4:1). The prepared compound is yellow solid powder.

Synthesis of 2-chloro-N-(5-(2-oxo-2H-chromen-3-yl)-1,3,4-thiadiazol-2-yl)acetamide (b)[16,17]: A mixture of thiadiazole (0.01 mol) with triethylamine (1.5 ml) as a solvent in DMF, chloro acetyl chloride (0.01 mol) has been applied in style-wise fall. At room temperature, the reaction mixture was stirred for (4 hours) and the precipitate obtained was filtered at the end of the reaction, washed with ethanol, then dried and recrystallized. Using TLC the reaction progress was tracked. Yield reaction (78 %), m.p (210-212 oC), and Rf (0.7) (benzene: methanol, 4:1), The prepared compound is pale yellow solid powder.

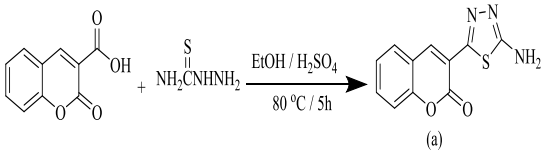
Synthesis of 2-azido-N-(5- (2-oxo-2H-chromen-3-yl)-1,3,4-thiadiazole-2-yl)acetamide (c) [16]: In (10 ml) of (DMF) the sodium azide (0.01 mol) was applied to the compound solution (b) (0.01 mol). The reaction mixture was refluxed by continuous stirring for (7 hrs) at (90 oC). It evaporated the solvent, precipitated and purified the brown substance, washed well by diethyl ether and then recrystallized into ethanol. Using TLC the reaction progress was tracked. Yield reaction (75 %), m.p. (142-145 oC), and Rf (0.68) (benzene: methanol, 4:1) The prepared compound is brown solid powder.

Synthesis of chalcone derivatives (Ch1,Ch2) General procedure [16]: A mixture of (0.01 mol) 4-amino acetophenone with (0.01 mol) aromatic aldehyde was dissolved in ethanol (35 ml), then added to the mixture the aqueous solution of (NaOH 40 per cent). A blend of reactions was kept at room temperature overnight. The obtained precipitate was then filtered, washed with diethyl ether and recrystallized with ethanol. Then the reaction was completed through a note TLC, all the prepared compounds are solid powder.

Synthesis of triazole derivatives (Mch1-Mch2, d,e, and f) General procedure [18,19]**:** Compound (c) (0.01 mol) was dissolved in N,N-dimethylformamide (DMF) (50 ml), were added α,β-unsaturated compound (0.01 mol) to the solution. the reaction mixture was stirred under heat within refluxed at (100 ^{o}C) for (18 hrs). then removing the solvent and the residue was washed with diethyl ether and recrystallized from ethanol. Then the reaction was completed through a follow it by TLC, all the prepared compounds are solid powder**.**

3. Results and discussion

Coumarin-3-carboxylic acid is the starting material for this research in which the reaction of thiose micarbazide in the presence of a small concentrate of sulfuric acid as a catalytic in absolute alcohol ethanol (Scheme 1) has been converted to the compound (a).



Scheme 1. Synthesis compound (a)

The prepared compound (a) was characterized by a sodium fusion test and the results were positive and this good evidence of the compound 's composition was identified by using FT-IR spectroscopy by disappearing bond of (C=O) stretching vibrations at (1734 cm^{-1}) and disappearing a broad bond of (O-H) stretching vibration at (3451 cm^{-1}) and appearing bond of (NH_2) group at (3350 cm^{-1}), appearing (C=C) stretching vibration for the aromatic ring at (1559 cm^{-1}), appearing (C=O) stretching vibration in (1671 cm^{-1}), appearing (C=N) stretching vibration at (1600 cm^{-1}), appearing (C-H) for the aromatic ring at (3054 cm^{-1}) while appearing (C-O) and (C-S) at (1206 cm^{-1}), (1122 cm^{-1}) respectively. Were also identified by using **^{1}H-NMR** spectrum (δ ppm), showed figure **(1)** for compound **(a)** using (DMSO-d6) as a solvent, and give

the following signals: (7.3) for (2H) $(=C\text{-}NH_2)_{\text{-1,3,4-thiadiazole}}$ (7.50-7.95) for H Aromatic (8.13) for (1H) $(C\text{-}CH{=}C)_{\text{5,6-dihydro-2H-pyran-2-one}}$

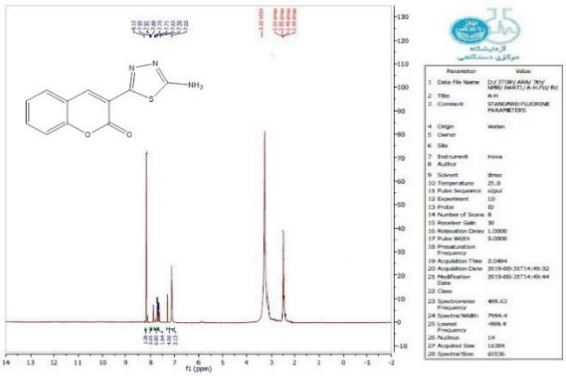
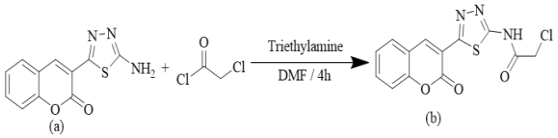


Figure 1. ^{1}H-NMR spectrum of the compound (a)

Whereas, compound (b) was synthesized by a reaction of compound (a) with chloroacetyl chloride and triethylamine in DMF, **(Scheme 2).**



Scheme 2. Synthesis compound (b)

Compound (b) was identified by using FT-IR spectroscopy by disappearing bond of (NH_2) group at (3350 cm^{-1}) and appearing bond (NH) stretching vibration at (3206 cm^{-1}) [20], appearing of (C=O) stretching vibrations of amide at (1698 cm^{-1}) and appearing of (C-Cl) group at (755 cm^{-1}), also identified by using **^{1}H-NMR** spectrum (δ ppm), showed figure **(2)** for compound **(b)** using (DMSO-d6) as a solvent, and give the following signals: (4.27) for (2H) $(O{=}C\text{-}CH_2\text{-}Cl)_{\text{-carbonyl}}$ (7.62-7.69) for (1H) $(CH)_{\text{benzene}}$ (7.96) for (1H) $(C\text{-}CH{=}C)_{\text{5,6-.dihydro-2H-pyran-2-one}}$ (12.54) for (1H) $(=C\text{-}NH\text{-}C{=}O)_{\text{-1,3,4-thiadiazole}}$

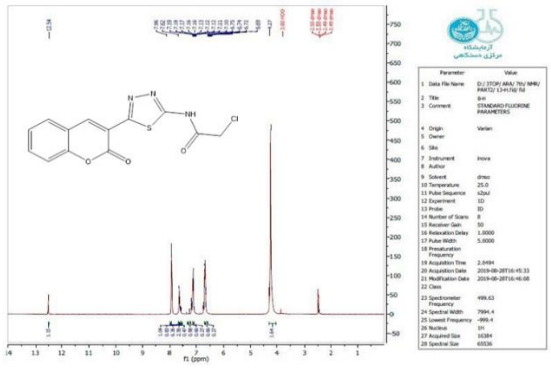
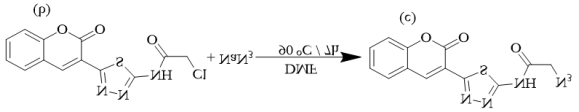


Figure 2. ^{1}H-NMR spectrum of the (b)

Compound (c) was synthesized by a reaction of compound (b) with sodium azide in DMF as solvent **(Scheme 3).**



Scheme 3. Synthesis compound (c)

Compound (c) was identified by using FT-IR spectroscopy by appearing bond of $(-N_3)$ stretching vibration at (2118 cm^{-1}) [21] and disappearing bond of (C-Cl) group at (755 cm^{-1}). Were also identified by using **^{1}H-NMR** spectrum (δ ppm), showed figure **(3)** for compound **(c)** using (DMSO-d6) as a solvent, and give the following signals: (2.07) for (2H) $(O{=}C\text{-}CH_2\text{-}N3)_{\text{-carbonyl}}$ (6.69-7.88) for (1H) $(CH)_{\text{benzene}}$ (8.14) for (1H) $(C\text{-}CH{=}C)_{\text{5,6-.dihydro-2H-pyran-2-one}}$ (12.36) for (1H) $(=C\text{-}NH\text{-}C{=}O)_{\text{-1,3,4-thiadiazole}}$.

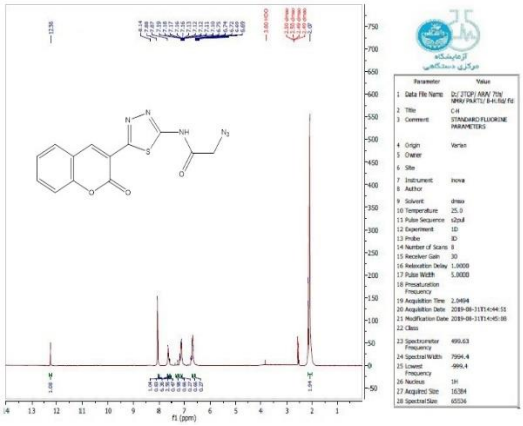
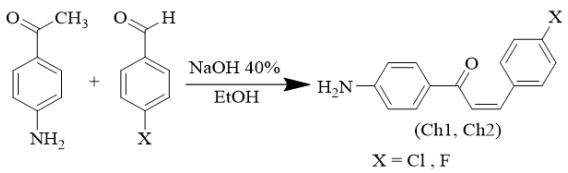


Figure 3. ^{1}H-NMR spectrum of the compound (c)

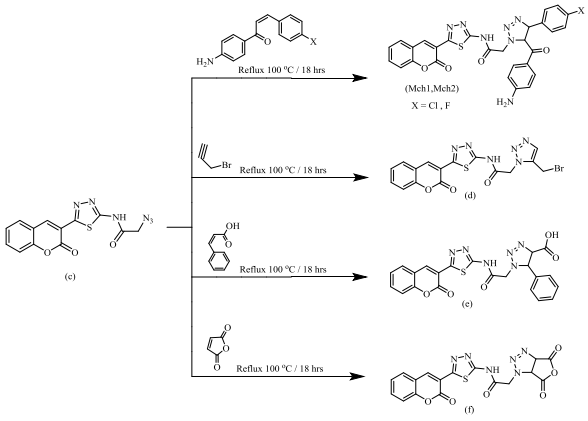
Chalcones (Ch1-Ch2) was synthesized by using the reaction of Claisen Schmidt condensation 4-amino acetophenone with aromatic benzaldehyde different by the presence of base-catalyzed in ethanol, **(Scheme 4).**



Scheme 4. Synthesis chalcones (Ch1-Ch2)

Chalcones compounds (Ch1-Ch2) were identified by using FT-IR spectroscopy appearing vibrations of $(-NH_2)$ group at the range between (3336-3334 cm^{-1}), appearing of (C-H) stretching vibrations for the

aromatic ring at the range between (3046-3036cm^{-1}) appearing of (C=O) vibrations of the carbonyl group at the range between (1645-1621cm^{-1}), appearing bond vibrations (C=C) aliphatic at the range between (1590-1589cm^{-1}), appearing vibrations of (C=C) for the aromatic ring at the range between (1557-1535cm^{-1}), all these absorptions are good evidence of preparation chalcones.



Scheme 5. Synthesis heterocyclic compounds (Mch1-Mch2, d, e, and f)

Comp No.	Calculated / found			
	C %	H %	N %	S %
Mch1	57.39 56.11	3.44 2.78	16.73 14.68	5.47 4.90
d	42.97 40.84	2.48 1.96	18.79 16.88	7.17 6.03

The prepared compounds (Mch1-Mch2, d, e, and f) were identified by using FT-IR spectroscopy by disappearing bond of (-N_3) stretching vibration at (2118 cm^{-1})

Also identified by using **^{1}H-NMR** spectrum (δ ppm), showed figure **[4]** for compound **(Mch1)** using (DMSO-d6) as a solvent, and gives the following signals:

(3.41) for (2H) (O=C-CH_2-N)$_{\text{-1,2,3-triazole}}$ (4.33) for (1H) (-N-CH-C)$_{\text{triazole}}$ (5.42) for (2H) (NH_2-Ph)$_{\text{-benzene}}$ (5.57) for (1H) (=N-CH-Ph)$_{\text{triazole}}$ (6.56-7.93) for (1H) (CH)$_{\text{benzene}}$ (8.14) for (1H) (C-CH=C)$_{\text{5,6-dihydro-2H-pyran-2-one}}$ (12.49) for (1H) (=C-NH-C=O)$_{\text{-1,3,4-thiadiazole}}$

^{1}H-NMR spectrum (δ ppm), showed figure **(5)** for compound **(Mch2)**using (DMSO-d6) as a solvent, and gived the following signals:

(3.41) for (2H) (O=C-CH_2-N)$_{\text{-1,2,3-triazole}}$ (4.32) for (1H) (-N-CH-C)$_{\text{triazole}}$ (5.58) for (2H) (NH_2-Ph)$_{\text{-benzene}}$ (5.88) for (1H) (=N-CH-Ph)$_{\text{triazole}}$ (6.12-7.91) for (1H) (CH)$_{\text{benzene}}$ (7.93) for (1H) (C-CH=C)$_{\text{5,6-dihydro-2H-pyran-2-one}}$ (12.36) for (1H) (=C-NH-C=O)$_{\text{-1,3,4-thiadiazole}}$

^{1}H-NMR spectrum (δ ppm), showed figure **(6)** for compound **(d)** using (DMSO-d6) as a solvent, and gived the following signals:

(4.66) for (2H) (=C-CH_2-Br)$_{\text{-1,2,3-triazole}}$ (5.60) for (2H) (O=C-CH_2-N)$_{\text{-1,2,3-triazole}}$ (6.79) for (1H) (C=CH-N)$_{\text{triazole}}$ (7.03-7.95) for (1H) (CH)$_{\text{benzene}}$ (8.13) for (1H) (C-CH=C)$_{\text{5,6-dihydro-2H-pyran-2-one}}$ (12.19) for (1H) (=C-NH-C=O)$_{\text{-1,3,4-thiadiazole}}$

^{1}H-NMR spectrum (δ ppm), showed figure **(7)** for compound **(e)** using (DMSO-d6) as a solvent, and gived the following signals:

(2.11) for (1H) (=N-CH-C=O)$_{\text{triazole}}$ (3.44) for (2H) (O=C-CH_2-N)$_{\text{-1,2,3-triazole}}$ (4.09) for (1H) (N-CH-Ph)$_{\text{triazole}}$ (7.37-7.57) for (1H) (CH)$_{\text{benzene}}$ (8.10) for (1H) (C-CH=C)$_{\text{5,6-dihydro-2H-pyran-2-one}}$ (12.36) for (1H) (=C-NH-C=O)$_{\text{-1,3,4-thiadiazole}}$ (12.53) for (1H) (OH-C=O)$_{\text{-1,2,3-triazole}}$

^{1}H-NMR spectrum (δ ppm), showed figure **(8)** for compound **(f)** using (DMSO-d6) as a solvent, and gived the following signals:

(3.05) for (1H) (=N-CH-C=O)$_{\text{triazole}}$ (3.45) for (2H) (O=C-CH_2-N)$_{\text{-1,2,3-triazole}}$ (4.1) for (1H) (-N-CH-C=O)$_{\text{triazole}}$ (6.75-7.63) for (1H) (CH)$_{\text{benzene}}$ (8.05) for (1H) (C-CH=C)$_{\text{5,6-dihydro-2H-pyran-2-one}}$ (12.63) for (1H) (=C-NH-C=O)$_{\text{-1,3,4-thiadiazole}}$

Table (1) C.H.N.S Elemental Analysis of compound (Mch1,d)

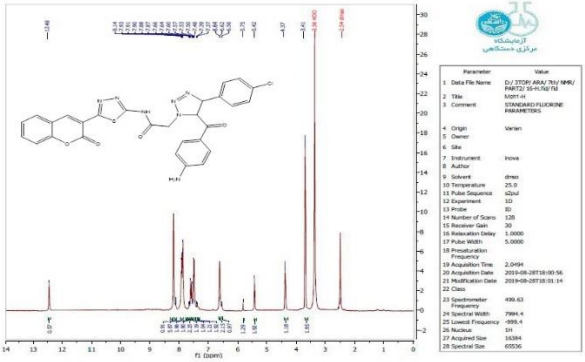


Figure 4. ^{1}H-NMR spectrum of compound (Mch1)

4. Biological Activity [22]

For antibacterial activity against Staphylococcus the prepared compounds (Mch1, d , and e) were examined. Aureus (positive gram), and Escherichia. Coli (Gram-negative) by method of well-diffusion in the Mueller-Hinton agar medium, where

the compounds were displayed against S. Aurores and E. The coli were measured at (30 mg) and after (24 hrs) for the inhibition zone around each disk; the test results in Table (7).

Table (2) Antibacterial activity of some prepared compounds

Comp. No	The diameter of the inhibition zone (mm)	
	S. aureus **(Gram-positive)**	***E. coli*** **(Gram-negative)**
Mch1	19	22
d	28	17
e	24	27

5. Conclusions

A series of coumarin-based triazoles compounds were synthesized in this paper, and their antibacterial activity against S was evaluated. Aurores and E. Coli. Coli. Both prepared compounds had relatively and stable high melting points by resonance, this is yet another proof of the quality of stable compounds. The results of the following measurements FT-IR, ^{1}H-NMR spectroscopy, element analysis C.H.N.S and TLC data, it gave clear evidence for the formation of the prepared compounds. Some prepared compounds showed high inhibition activity against two types of Staphylococcus aureus (Gram-positive) and Escherichia coli (Gram-negative) bacteria, and gave good test results to compounds.

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