



Simple synthesis of some new heterocyclic derivatives incorporation coumarin -2-one moiety

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ABSTRACT

3-(1-ethoxy-3-oxo-3-phenylpropyle-1-enyl)-2H-coumarin-2-one (**2**), had been synthesized and reacted with some selected reagents such as hydrazine hydrate, urea, cyanoacetamide, cyanoacetohydrazide, orthophenylene diamine, ortho-aminophenol and 5-aminotriazole in ethanol piperidine solution to afford new multisubstituted 3-(pyrazol, pyrimidine, pyridine, diazepine, oxazepin, triazol)-2H- coumarin-2-one derivatives.

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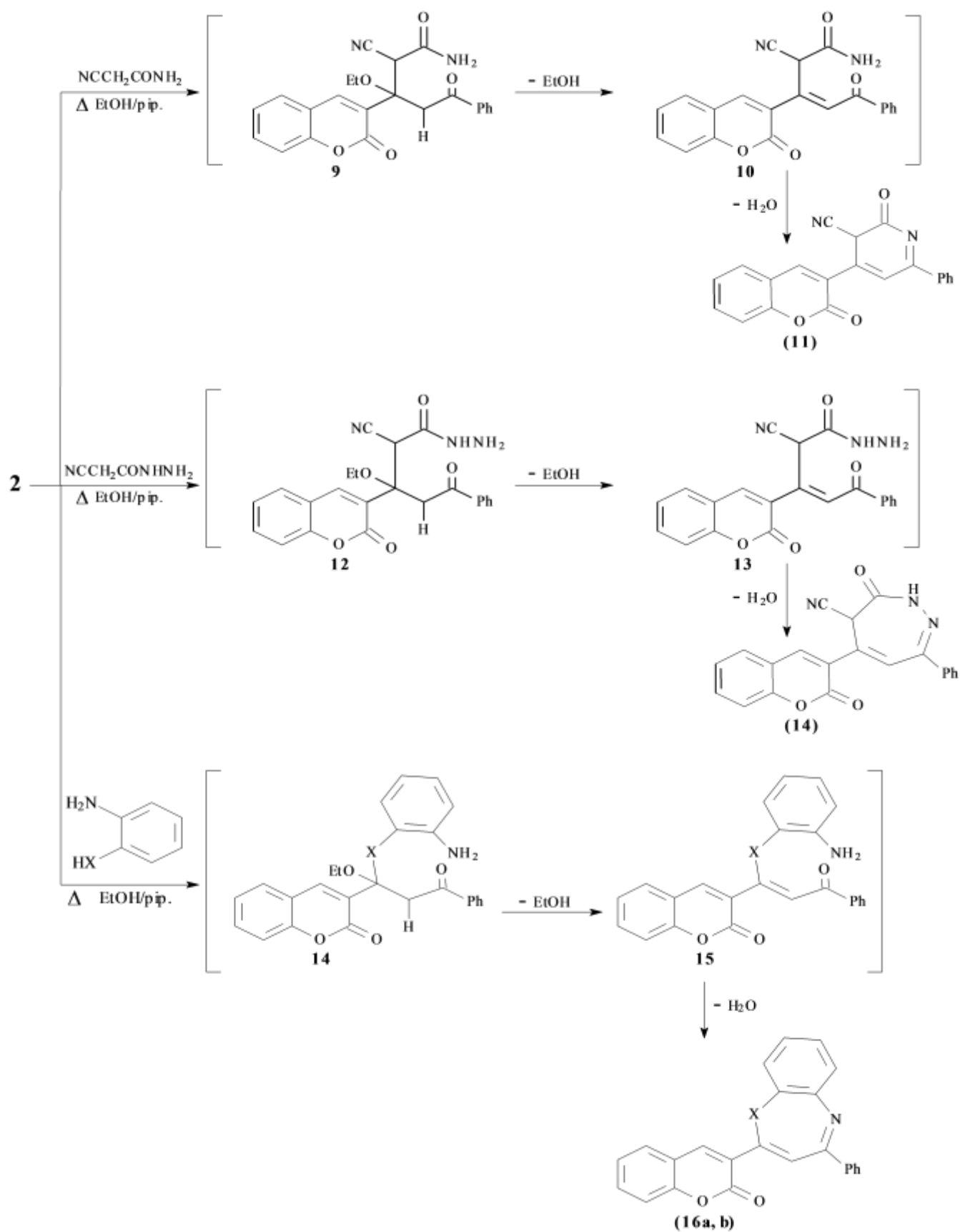
Capsule Summary: New multisubstituted 3-(pyrazole, pyrimidine, pyridine, diazepine, oxazepine, triazole)-2H-coumarin-2-one derivatives have been prepared and their structures are determined by IR spectra and 1H NMR spectra.

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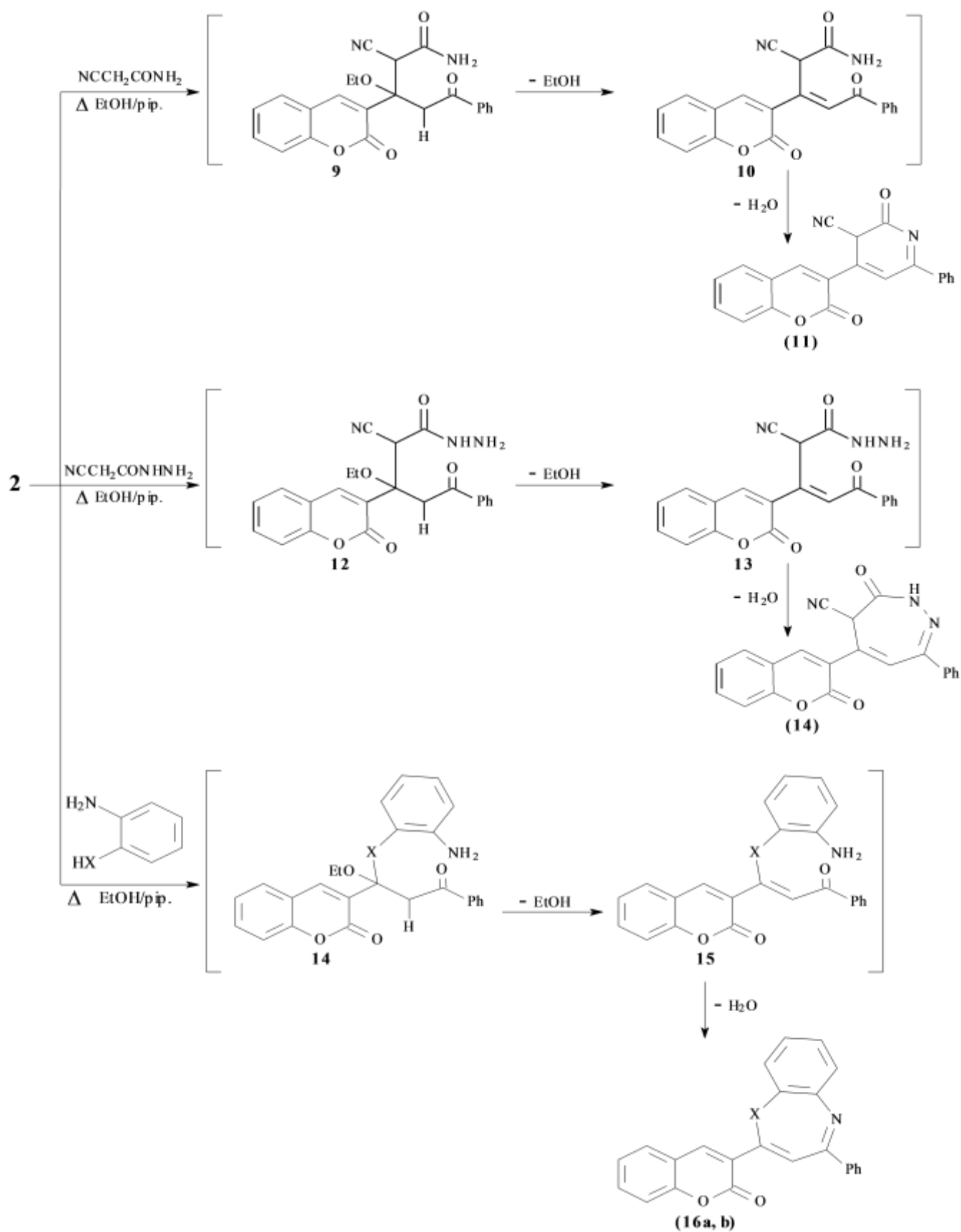
INTRODUCTION

Coumarins are an important class of compounds of both natural and synthetic origin. Many compounds which contain the coumarin moiety exhibit useful and diverse pharmaceutical and biological activities, often depending on the substituents they bear in the parent benzopyran moiety (Musa et al., 2011, Borah et al., 2012) and, there has been a growing interest in their synthesis (EL-Ansary et al., 1992). Some of these coumarin derivatives have been found useful in photochemotherapy, antitumor (Manfredini et al., 1997), anti -HIV therapy (Wattenberg et al., 1979; Kashman et al.,

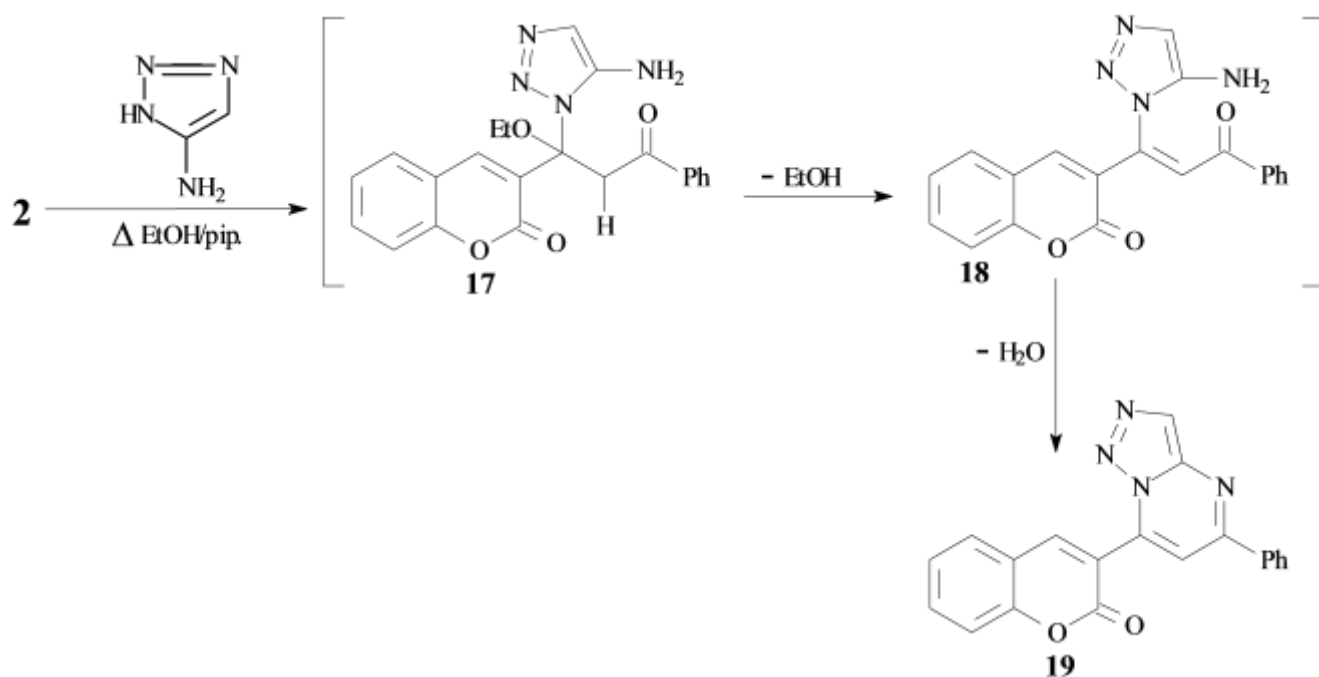
1992) as CNS-stimulants (Mckee et al., 1996), antibacterial (Anjum et al., 2011; De Souza et al., 2005; Behrami, 2014) anticoagulants (Jung and Park, 1999; Barker et al., 1971; Greaves 2005), antifungal (Montagner, 2008; De Araujo et al., 2013), antioxidant (Mazzone et al., 2015) agents and as dyes (Raboin et al., 2000) (all references in text need correction, use et al form instead of number). Natural, semi-synthetic and synthetic coumarins are useful substances in drug research (Karatzas, 2014). Coumarins can be used not only to treat cancer, but to treat the side effects caused by radiotherapy (Agarwal, 2000; Marshall et al., 1990). Coumarin Benciderivatives can possess not only cytostatic,



Scheme 1: Synthesis procedure



Scheme 1: Continue.....



Scheme 1: Continue.....

but cytotoxic properties as well (Benci et al., 2012) as they can inhibit growth in human cancer cell lines (Mohler et al., 1992) such as A549 (lung), ACHN (renal), H727 (lung), MCF7 (breast) and HL-60 (leukemia) and in some clinical trials they exhibited anti-inoliferative activity in prostate cancer (Mohler et al., 1992) malignant melanoma [Thornes et al., 1994] and renal cell carcinoma (Marshall et al., 1991). Coumarin itself also exhibited cytotoxic effects against Hep2 cells (human epithelial type 2) in a dose dependent manner and showed some typical characteristics of apoptosis with loss of membrane microvilli, cytoplasmic hypervacuolization and nuclear fragmentation (Mirunalini et al., 2014). In present investigation, new multisubstituted 3-(pyrazole, pyrimidine, pyridine, diazepine, oxazepine, triazole)-2H-coumarin-2-one derivatives have been prepared and their structures are determined by IR spectra and ^1H NMR spectra.

Material and methods

All melting points are measured using Galenkamp melting point apparatus and are uncorrected. Elemental analysis was carried out at Microanalytical Center of Cairo University. IR (KBr pellets $\nu = \text{cm}^{-1}$) spectra were determined in 1650 FT-9R Instrument (Cairo University). ^1H NMR spectra ($\delta = \text{ppm}$) were accomplished using 300 MHz NMR spectrometer and

mass spectroscopy were recorded on GCMS-QP-1000 EX spectrometer (Cairo University).

Synthesis of ethyl-2-oxo-2H-coumarin-3-carboxylate (1):

To a cold mixture of salicylaldehyde (2 mmol) and diethyl malonate (2 mmol), 2 ml of piperidine was added by rapid stirring. After 20 min. the solid separated was filtered off subsequently washed with ethanol and was recrystallized from water: ethanol (2 : 8), Mp = 128 °C and yield was 85% (Suresh et al., 2008).

Synthesis of 3-(1-ethoxy-3-oxo-3-phenylprop-1-enyl)-2H-coumarin-2-one (2):

A Compound 1 (0.44 g, 2 mmol) was dissolved in solution containing (30 ml) ethanol with acetophenone (0.24 ml, 2 mmol) in presence of piperidine (0.1 ml) as catalyst was refluxed for 5 hours, the reaction mixture was evaporated under reduced pressure, the resulting product was triturated with methanol and the resulting product was collected by filtration, wash with methanol and recrystallized from ethanol. The results are registered in Table (1, 2).

Synthesis of 3-(3-phenyl-1H-pyrazol-5-yl)-2H-coumarin-2-one (5):

Table 1: Characterization of the prepared compounds

Comp. No	Nature of products			Molecular formula (M. Wt)	Analysis %					
	Colour	Yield %	M.p. °C		Calculated			Found		
					C	H	N	C	H	N
2	White	64	110 - 112	C ₂₀ H ₁₆ O ₄ (320.34)	74.88	5.03	-	74.99	4.90	-
5	Yellow	62	126-130	C ₁₈ H ₁₂ N ₂ O ₂ (288.30)	74.99	4.20	9.72	74.97	4.18	9.69
8	White	66.6	215 - 217	C ₁₉ H ₁₂ N ₂ O ₃ (316.31)	72.15	3.80	8.86	72.14	3.83	8.84
11	Yellow	65	195 - 198	C ₂₁ H ₁₂ N ₂ O ₃ (340.25)	74.13	3.53	8.23	74.14	3.40	8.20
14	Red	60	250 - 253	C ₂₁ H ₁₃ N ₃ O ₃ (355.36)	70.98	3.69	11.83	70.95	3.65	11.80
16a	Prawn	68	120 - 122	C ₂₄ H ₁₆ N ₂ O ₂ (364.40)	79.10	4.44	7.69	79.11	4.42	7.68
16b	Red	62	220 - 223	C ₂₄ H ₁₅ NO ₃ (365.39)	78.89	4.14	3.83	78.87	4.12	3.80
19	White	63	143-145	C ₂₀ H ₁₂ N ₄ O ₂ (340.34)	70.58	3.55	16.46	70.68	3.55	16.46

Table 2: IR and ¹H NMR (Mass) Spectral Data of the Prepared Compounds.

Comp. No	IR Spectrum (KBr, Cm ⁻¹)	¹ H NMR Spectrum (DMSO, δ);& (Mass data)
2	1689-1707 (C=O).	1.22 (t, 3H, CH ₃), 4.01(q, 2H, CH ₂), 6.08 (s, 1H, CH), 7.02-7.81 (m, 10H, Ar-H). (M ⁺): 318.
5	1689 (C=O), 3282 (NH).	6.50 (s, 1H, pyrazol), 7.02-7.72 (m, 10H, Ar-H), 13.70 (s, 1H, NH). Ms: m/z at 289 (M ⁺).
8	1689-1707 (C=O), 3220 (N-H).	4.60 (s, 1H, CH), 8.02 (s, 1H, NH), 7.3-7.6 (m, 10H, Ar-H). (M ⁺): 316.
11	1685 (C=O), 2207 (C≡N).	4.04 (s, 1H, CH), 5.2 (s, 1H, CH), 7.02-7.6 (m, 10H, Ar-H). (M ⁺): 341.
14	1689-1700 (C=O), 2208 (C≡N), 3200 (N-H).	4.12 (s, 1H, CH), 5.22 (s, 1H, CH), 7.01 (s, 1H, NH), 7.02-7.60 (m, 10H, Ar-H). (M ⁺): 355.
16a	3242 (NH).	4.0 (s, 1H, NH), 4.30 (s, 1H, heterocyclic nuclei), 6.50-7.62 (m, 14H, Ar-H). (M ⁺): 364.
16b	1302 (C-O).	4.4 (s, 1H, heterocyclic nuclei), 7.02-7.62 (m, 14H, Ar-H). (M ⁺): 366.
19	1609 (C-N=N-), 1760 (C=O)	7.02-7.72 (m, 11H, Ar-H), 7.75 (s, 1H, triazole). (M ⁺): 340.

A compound (2) (0.64 g, 2 mmol), was dissolved in solution containing hydrazine hydrate (0.1 ml, 2 mmol) and ethanol (30 ml) in presence of piperidine (0.1 ml) as catalyst and refluxed for 5 hours, the reaction mixture was evaporated under reduced pressure, the residue was triturated with methanol and the resulting product was collected by

filtration, washed with methanol and crystallized from dioxane. The results are registered in Table (1, 2).

Synthesis of 3-(1,2H-2-oxo-4-phenypyrimidin-6-yl)-2H-coumarin-2-one (8):

A mixture of **2** (0.64 g, 2 mmol), urea (0.12 g, 2 mmol) in ethanol (30 ml) containing piperidine (0.1 ml) was refluxed for 5 hours, the reaction mixture was evaporated under reduced pressure, the residue was triturated with methanol and the resulting product was collected by filtration, washed with methanol and crystallized from ethanol. The results are registered in Table (1, 2).

Synthesis of 3-(2,3*H*-3-cyano-2-oxo-6-phenylpyridine-4-yl)-2*H*-coumarin-2-one (**11**):

A mixture of **2** (0.64 g, 2 mmol), cyanoacetamide (0.17 g, 2 mmol) in ethanol (30 ml) containing piperidine (0.1 ml) was refluxed for 5 hours, the reaction mixture was evaporated under reduced pressure, the residue was triturated with methanol and the resulting product was collected by filtration, washed with methanol and crystallized from ethanol. The results are registered in Table (1, 2).

Synthesis of 3-(2,3,4*H*-4-cyano-3-oxo-7-phenyl-1,2-diazepine-5-yl)-2*H*-coumarin-2-one (**14**):

A mixture of **2** (0.64 g, 2 mmol), cyanoacetahydrazide (0.20 g, 2 mmol) in ethanol (30 ml) containing piperidine (0.1 mol) was refluxed for 5 hours, the reaction mixture was evaporated under reduced pressure, the residue was triturated with ethanol. The resulting product was collected by filtration, washed with ethanol and crystallized from ethanol. The results are registered in Table (1, 2).

General procedure for preparation of compounds (**16a**, **b**):

A mixture of **2** (0.64 g, 2 mmol), orthophenylenediamine (0.22 g, 2 mmol) or orthoaminophenol (0.22 g, 2 mmol) in ethanol (30 ml) containing piperidine (0.1 ml) was refluxed for 8 hours, the reaction mixture was evaporated under reduced pressure, the residue was triturated with ethanol and the resulting product was collected by filtration, washed with ethanol and crystallized from ethanol. The results are registered in Table (1, 2).

Synthesis of 3-(triazolo[1,2-*a*]pyrimidine-4-phenyl-6-yl)-2*H*-coumarin-2-one (**19**)

A mixture of **2** (0.64 g, 2 mmol), 5-aminotriazole (0.09 g, 2 mmol) in ethanol (30 ml) containing piperidine (0.1 ml) was refluxed for 6 hours, the reaction mixture was evaporated under reduced pressure, the residue was triturated with ice/water and the resulting product was collected by filtration, washed with ice/water and crystallized from . The results are registered in Table (1, 2).

RESULTS AND DISCUSSION

We herein report a simple approach to the synthesis of new multisubstituted five, six and seven heterocyclic compounds derivatives by reaction of 3-(1-ethoxy-3-oxo-3-phenylprop-1-enyl)-2*H*-coumarin-2-one (**2**) with some readily available reagents. The formation of compound (**2**) may proceed via condensation reaction of the methyl group of acetophenone with carbonyl group of compound (**1**) in refluxing ethanol containing a catalytic amount of piperidine. The Ms of compound (**2**) showed m/z at 318 (M^{+2}).

Compound (**2**) consider a good and available starting material for synthesis of new functionalized heterocyclic compound by reaction with the amine function group of some selected reagents yielding new compounds **5**, **8**, **11**, **14**, **16_{a,b}**, **19** which were established based on analytical and spectral analysis which showed the absence of ethoxy group (ex. Experimental section).

CONCLUSIONS

This research describe the synthesis and spectral characterization of some new multisubstituted (pyrazole, pyrimidine, pyridine, diazepine, oxazepine, triazole)-2*H*-coumarin-2-one derivatives.

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