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

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3-(1-ethoxy-3-oxo-3-phenylpropyle-1-enyl)-2*H*-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 multisubtituted 3-(pyrazol, pyrimidine, pyridine, diazepine, oxazepin, triazol)-2*H*- coumarin-2-one derivatives.

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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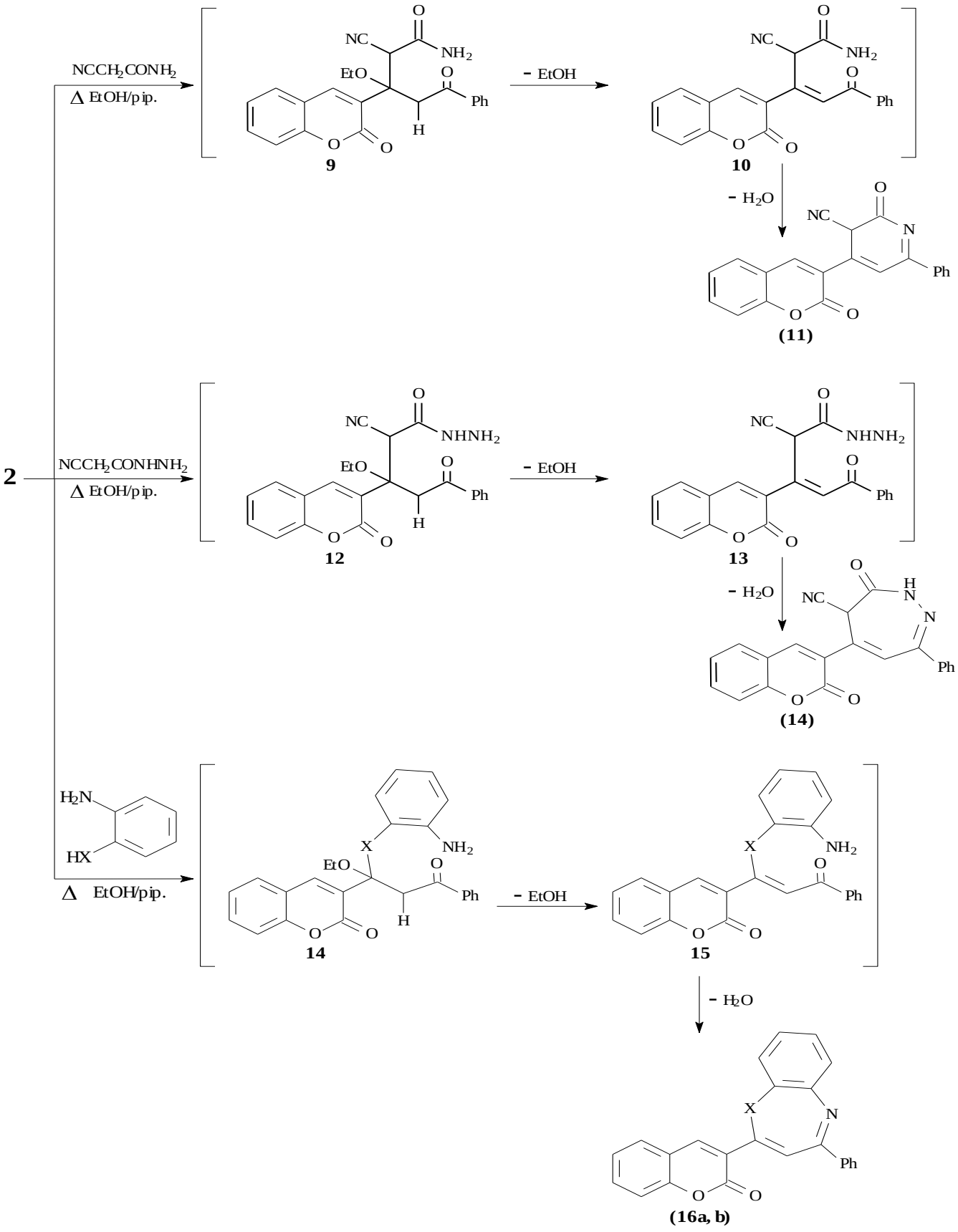
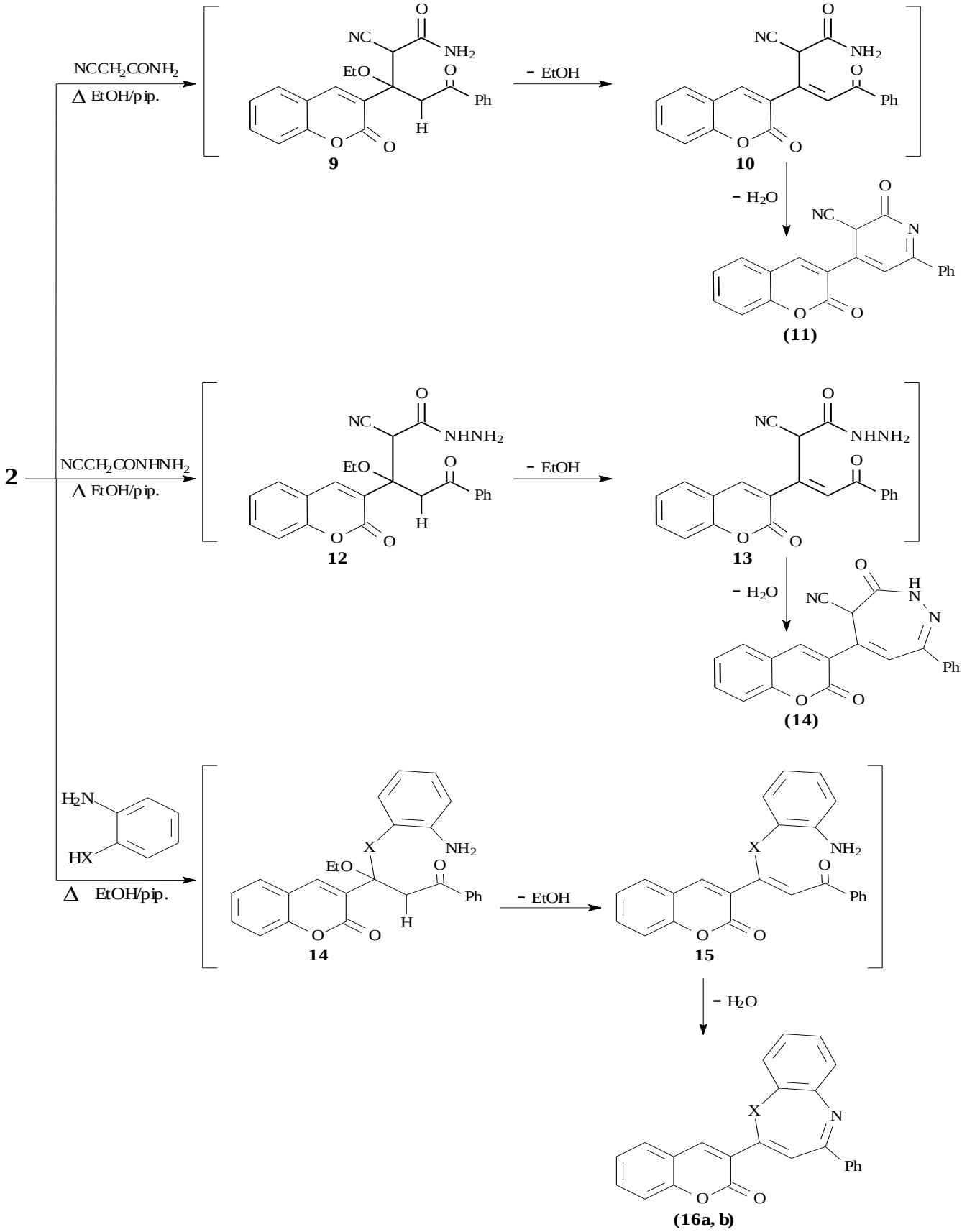
INTRODUCTION

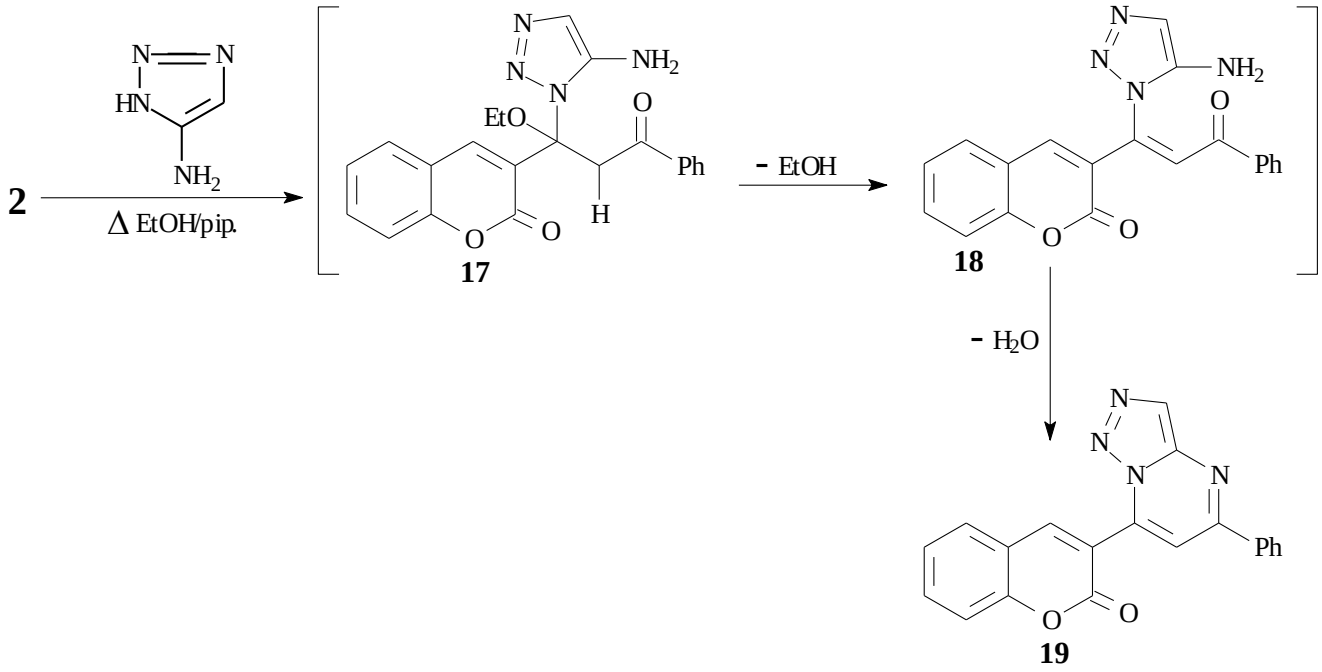
Coumarins are an important class of compounds of both natural and synthetic origin. Many compounds which contain the coumarin moiety exhibit useful and diverse pharmaceutical and biological activities, often depending on the substituents they bear in the parent benzopyran moiety (Musa et al., 2011,Borah 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, but cytotoxic properties as well (Benci et al., 2012).



Scheme 1: Synthesis procedure



Scheme 1: Continue...



Scheme 1: Continue…

As these 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 hypervacualization 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 ν = cm^{-1}) spectra were determined in 1650 FT-9R Instrument (Cairo University). ^1H NMR spectra (δ = 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-2*H*-coumarin-3-carboxylate (1)

To a cold mixture of salicyladehyde (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 ºC and yield was 85% (Suresh et al., 2008).

Synthesis of 3-(1-ethoxy-3-oxo-3-phenylprop-1-enyl)-2*H*-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 filteration, wash with methanol and recrystallized from ethanol. The results are registered in Table (1, 2).

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

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).

Table 1: Characterization of the prepared compounds

Comp. No	Nature of products			Molecular formula (M. Wt)	Analysis %					
					Calculated			Found		
	Colour	Yield %	M.p. ºC		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	$C_{18}H_{12}N_2O_2$ (288.30)	74.99	4.20	9.72	74.97	4.18	9.69
8	White	66.6	215 - 217	$C_{19}H_{12}N_2O_3$ (316.31)	72.15	3.80	8.86	72.14	3.83	8.84
11	Yellow	65	195 - 198	$C_{21}H_{12}N_2O_3$ (340.25)	74.13	3.53	8.23	74.14	3.40	8.20
14	Red	60	250 - 253	$C_{21}H_{13}N_3O_3$ (355.36)	70.98	3.69	11.83	70.95	3.65	11.80
16a	Prawn	68	120 - 122	$C_{24}H_{16}N_2O_2$ (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	$C_{20}H_{12}N_4O_2$ (340.34)	70.58	3.55	16.46	70.68	3.55	16.46

Table 2: IR and ^{1}H 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^{-2}): 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^{+1})
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^{+1}): 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^{+1}): 366
19	1609 (C-N=N-), 1760 (C=O)	7.02-7.72 (m, 11H, Ar-H), 7.75 (s, 1H, triazole) (M^+): 340

Synthesis of 3-(1,2*H*-2-oxo-4-phenypyrimidin-6-yl)-2*H*-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.

REFERENCES

Sinclair, J., Abdullah, A., 2011. Cytotoxic activity of new acetoxycoumarin derivatives in cancer cell lines. Anticancer Research 31, 2017–2022.

Musa, M.A., Badisa, V.L.; Latin., Cooperwood Borah, P., Naidu, P.S., Bhuyan, P.J., 2012. Synthesis of some tetrazole fused pyrido[2,3-c]coumarin derivatives from a one-pot three-component reaction via intramolecular 1,3-dipolar cycloaddition reaction of azide to nitriles. Tetrahedron Letters 53, 5034–5037.

El-Ansary, S.L., Abbas, S.E., Mikhael, A.N., El-Banna, H.A., 1992. Synthesis and biological activity of some new coumarins. Egyptian Pharmaceutical Journal 33, 639–650.

Manfredini, S., Daniele, S., Ferroni, R., Bazzanini, R., Vertuani, S., Hatse, S., Balzarini, J., de Clercq, E., 1997. Rretinoic acid conjugates as potential antitumor agents: synthesis and biological activity of conjugates with Ara-A, Ara-C, 3(2H)-furanone, and aniline mustard moieties. Journal of Medicinal Chemistry 40, 3851–3857.

Wattenberg, L.W., Lam, K.T., Fladmoe, A.V., 1979. Inhibition of chemical carcinogen-induced neoplasia by coumarins and α-angelicalactone. Cancer Research 39, 1651–1654.

Kashman, Y., Gustafson, K.R., fuller, R.W., Cardellina, J.H., McMahon, J.B., Currens, M.J., Buckheit, R.W., Hughes, S.H., Craqq, G.M.,Boyd, M.R., 1992. The calanolides, a novel HIV-inhibitory class of coumarin derivatives from the tropical rainforest tree, Calophyllum lanigerum. Journal of Medicinal Chemistry 35, 2735–2743.

Mckee, T.C., Fuller, R.W., Covington, C.D., Cardellina, J.H., Gulakowski, R.J., Krepps, B.L., McMahon, J.B., Boyd, M.R., 1996. New pyranocoumarins isolated from Calophyllum lanigerum and Calophyllum teysmannii. Journal of Natural Products 59, 754–758.

Anjum, N.F., Aleem, A., Nayeem, N., Asdaq, S.M., 2011. Synthesis and antibacterial activity of substituted 2-phenyl-4-chromones. Der Pharma Chemica 3, 56–62.

De Souza, S.M., Delle Monache, F., Smânia, A., Jr., 2005. Antibacterial activity of coumarins. Z. Naturforsch C 60, 693–700.

Behrami, A., 2014. Antibacterial activity of coumarine derivatives synthesized from 4-chloro-chromen-2-one. The comparison with standard drug. Oriental Journal of Chemistry 30, 1747–1752.

Jung, J., Kim, J., Park, O., 1999. Simple and cost effective syntheses of 4-hydroxycoumarin. Synthetic Communications 29, 3587–3595.

Barker, W.M., Hermodson, M.A., Link, K.P., 1971. 4-Hydroxycoumarins. Synthesis of the metabolites and some other derivatives of warfarin. Journal of Medicinal Chemistry 14, 167–169.

Greaves, M., 2005. Pharmacogenetics in the management of coumarin anticoagulant therapy: The way forward or an expensive diversion. PLOS Medicine 2, 342.

Montagner, C., de Souzaa, S.M., Groposo, C., Delle Monacheb, F., Smania, E.F.A., Smania, A., 2008. Antifungal activity of coumarins. Z. Naturforsch C 63, 21–28.

De Araújo, R.S.A., Guerra, F.Q.S., Lima, E., De Simone, C.A., Tavares, J.F., Scotti, L., Scotti, M.T., De Aquino, T.M., De Moura, R.O., Mendonça, F.J.B., 2013. Synthesis, structure-activity relationships (SAR) and in silico studies of coumarin derivatives with antifungal activity. International Journal of Molecular Sciences 14, 1293–1309.

Mazzone, G., Malaj, N., Galano, A., Russo, N., Toscano, M., 2015. Antioxidant properties of several coumarin–chalcone hybrids from theoretical insights. RSC Advances 5, 565–575.

Raboin, J., Beley, M., Kirsch, G., 2000. Pyridine-fused coumarins: A new class of ligands for ruthenium complexes with enhanced spectral absorption. Tetrahedron Letters 4, 1175–1177.

Karatzas, N.B., 2014. Coumarins, a class of drugs with a unique contribution to medicine: The tale of their discovery. Hellenic Journal of Cardiology 55, 89–91.

Agarwal, R., 2000. Synthesis and biological screening of some novel coumarin derivatives. Biochemical Pharmacology 6, 1042–1051.

Marshall, M.E., Butler, K., Hermansen, D., 1990. Treatment of hormone-refractory stage D carcinoma of prostate with coumarin (1,2-benzopyrone) and cimetidine: A pilot study. Prostate 17, 95–99.

Benci, K., Mandic, L., Suhina, T., Sedic, M., Klobucar, M., Pavelic, S.K., Pavelic, K., Wittine, K., Mintas, M., 2012. Novel coumarin derivatives containing 1,2,4-triazole, 4,5-dicyanoimidazole and purine moieties: Synthesis and evaluation of their cytostatic activity. Molecules 17, 11010–11025.

Marshall, M.E., Kervin, K., Benefield, C., Umerani, A., Albainy-Jenei, S., Zhao, Q., Khazaeli, M.B., 1994. Growth-inhibitory effects of coumarin (1,2-benzopyrone) and 7-hydroxycoumarin on human malignant cell lines in vitro. Journal of Cancer Research and Clinical Oncology 120, S3–S10.

Mohler, J.L., Gomella, L.G., Crawford, E.D., Glode, L.M., Zippe, C.D., Fair, W.R., Marshall, M.E., 1992. Phase II evaluation of coumarin (1,2-benzopyrone) in metastatic prostatic carcinoma. Prostate 20, 123–131.

Thornes, R.D., Daly, L., Lynch, G., Breslin, B., Browne, H., Browne, H.Y., Corrigan, T., Daly, P., Edwards, G., Gaffney, E., 1994. Treatment with coumarin to prevent or delay recurrence of malignant melanoma. Journal of Cancer Research and Clinical Oncology 120, S32–S34.

Marshall, M.E., Butler, K., Fried, A., 1991. Phase I evaluation of coumarin (1,2-benzopyrone) and cimetidine in patients with advanced malignancies. Molecular Biotherapy 3, 170–178.

Mirunalini, S., Deepalakshmi, K., Manimozhi, J., 2014. Antiproliferative effect of coumarin by modulating oxidant/antioxidant status and inducing apoptosis in Hep2 cells. Biomed. Aging and Pathology 4, 131–135.

Suresh, Kh., Veeresh, M., Prashant, A., Mahesh, P., Pradeepkumar, R., Shivalingarao, M., 2008. AHM thippeswamy. European Journal of Medicinal Chemistry 30, 1-7.