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Synthesis and biological evaluation of new series of phthalazinone, pyridazinone, oxadiazole, pyrazolone scaffolds based on coumarin-3-carbohydrazide

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Abstract:

A new series of phthalazinone, pyridazinone, oxadiazole, pyrazolone scaffolds based on coumarin-3-carbohydrazide was efficiently synthesized. Reaction of hydrazine hydrate with 2-oxo-2*H*-chromene carboxylate **(1)** produced the key compound coumarin-3-carbohydrazide **(2),** which used for synthesizing Schiff`s base derivatives **(3a-d)**.

The hydrazide **(2)** was used for efficient synthesis of different scaffolds such as dihydrophthalazine-1,4-Dione **(4a, 4b)**, pyridazinone derivatives **(5)** and **(6)** via treatment with phthalic anhydride and/or tetrabromo phthalic anhydride, maleic anhydride and succinic anhydride, respectively**.** Moreover, Reaction of benzoic acid and/or acetic acid with coumarin-3-carbohydrazide **(2)** in phosphorous oxychloride produced the oxadiazole derivatives **(8a, b)**.

Pyrazolone and pyrazolidinone scaffolds **(9-12)** were obtained in good yields upon reaction of the hydrazide derivative **(2)** with numerous active methylene compounds such as acetylacetone, ethyl cyanoacetate, ethyl acetoacetate, and diethyl malonate.

Evaluation of antimicrobial activity of some of the synthesized compounds towards the selected bacteria and fungi strains in comparison with Gentamicin and ketoconazole as reference drugs revealed that compounds **3d, 6, 8a, 8b, 11, 12 and 14** exhibited promising activity in comparison to the tested standard.

The products structures were assigned and confirmed via their elemental analyses as well as spectral data (IR, MS and ^{1}H NMR).

Keywords: Coumarin-3-carbohydrazide, scaffolds, oxadiazole, pyrazolone, phthalazine, pyridazine, antimicrobial activity.

1. Introduction

Coumarin derivatives are widely distributed in nature and synthetic products, they are known with their broad spectrum of biological properties [1-7]. A variety of products and new heterocyclic systems were synthesized based on the reactivity of these coumarin derivatives towards various nucleophiles. They have shown numerous antimicrobial activities such as anticancer [8-10], antimicrobial [11,12], antibiotic [13], antiproliferative [14], anti-inflammatory [15], anticoagulant [16], antioxidant [17], and antibacterial [18], as well as antiviral activities [19,20], antirheumatic [21], neuroprotective [22] and HIV-inhibitory [23,24].

Also, different coumarins have found applications in perfumery [25], fluorescent indicators [26,27], also as laser dyes, solar energy collectors, nonlinear optical chromophores and fluorescent whiteners [27,28].

Furthermore, 3-substituted coumarins have been reported to be used as precursor and precious building blocks to prepare diversity of heterocyclic systems [29-33]. Thus, incorporation of the hydrazide at the coumarin moiety provides a broad synthetic potential [35].

Herein, we describe an efficient synthetic routes to new series of coumarin derivatives based on coumarin-3-carbohydrazide reactivity and evaluation of their biological activities.

2. Experimental

2.1. Materials

Melting points were measured in open capillaries by the melting point apparatus Gallen kamp and are uncorrected. Elemental analyses as well as IR, ^{1}H NMR and Mass spectra carried out by micro analytical unit at Cairo university and Mansoura university. IR-spectra (KBr disk) were recorded on Ft /IR-Brucker, vector22. ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with TMS as internal reference. Mass spectrometry was done on shimadzu Gcms-QP-1000 Ex mass spectrophotometer at 70 ev, and Carlo Erba-1106 instrument used for performing Elemental analyses.

Thin layer chromatography TLC was carried out on 0.1 mm silica gel 60f254 and used for monitoring all reactions. Biological activities were carried out at Al-Azhar University.

2.2. Methods

Synthesis of ethyl 2-oxo-2H-chromene-3-carboxylate (1) [36].

A mixture of salicyaldehyde (4.13 ml, 0.01 mol), diethylmalonate (6.09 ml, 0.01 mol) in 30 mL ethanol, 0.5 ml pipredine, and 2 drops of glacial CH_3COOH were added, and the reaction mixture refluxed for 4hrs. Then poured on ice/HCl. After filtration of the precipitated solid, washed, dried and recrystallized from ethanol to give compound **(1)**. (*c.f.* Table 1).

Synthesis of 2-oxo-2H-chromene-3-carbohydrazide (2) [35]**.**

Ethyl-2-oxo-2H-chromene-3-carboxylate **1** (2.18 gm, 0.01 mol) treated with hydrazine hydrate (1.0 ml, 0.02 mol) in 30 mL ethanol for 4hrs on water bath. After cooling, the reaction mixture was precipitated, the solid precipitated filtered off. After drying, recrystallized from ethanol to give compound **(2).** (*c.f.* Table 1).

General procedure for synthesis of compounds (3a-d).

A (0.1gm, 0.5mmol) of 2-oxo-2H-chromene-3-carbohydrazide **2** was refluxed with (0.5mmol) of benzaldehyde, 2-hydroxy benzaldehyde, 4-chloro benzaldehyde, and/or 4-hydroxy benzaldehyde, in 30 mL ethanol for 5 hrs. Then, the precipitated solid was filtered off, and recrystallized from a proper solvent to get compounds **(3a-d).**

Synthesis of *N*'-benzylidene-2-oxo-2H-chromene-3-carbohydrazide (3a). (*c.f.* Table 1).

Synthesis of compound *N*'-(2-hydroxybenzylidene)-2-oxo-2H-chromene-3-carbohydrazide (3b). (*c.f.* Table 1).

Synthesis of *N*'-(4-chlorobenzylidene)-2-oxo-2H-chromene-3-carbohydrazide (3c). (*c.f.* Table 1).

Synthesis of *N*'-(4-hydroxybenzylidene)-2-oxo-2H-chromene-3-carbohydrazide (3d). (*c.f.* Table 1).

General procedure for synthesis of compounds (4a,b).

A (0.5g, 0.0025 mol) of compound **2** was refluxed for 4hrs with (0.0025 mol) of phthalic anhydride and/or tetrabromo phthalic anhydride in (20 mL) of benzene in the presence of a catalytic amount of Et_3N. After filtration of the produced solid, washed and crystallized from a proper solvent. (*c.f.* Table 1).

Synthesis of 2-(2-oxo-2H-chromene-3-carbonyl)-2, 3-dihydro phthalazine-1, 4-dione (4a). (*c.f.* Table 1).

Synthesis of 5, 6, 7, 8-tetrabromo-2-(2-oxo-2H-chromene-3-carbonyl)-2, 3-dihydrophthalazine-1, 4-dione (4b). (*c.f.* Table 1).

General procedure for synthesis of compounds (5 and 6).

A mixture of compound **2** (0.5g, 0.0025 mol), maleic anhydride and/or succinic anhydride (0.0025 mol) in n-butanol (30 mL) were refluxed for 5hrs. After that, the solid settled down was filtered off, and recrystallized from a proper solvent.

Synthesis of 1-(2-oxo-2H-chromene-3-carbonyl)-1, 2-dihydropyridazine-3, 6-dione (5). (*c.f.* Table 1).

Synthesis of 1-(2-oxo-2H-chromene-3-carbonyl) tetrahydro pyridazine-3, 6-dione (6). (*c.f.* Table 1).

Synthesis of *N*'-benzoyl-2-oxo-2H-chromene-3-carbohydrazide (7).

To a stirred solution of the benzoyl chloride (0.058 ml, 0.5 mmol) in (40 mL) ethanol, 2-oxo-2H-chromene-3-carbohydrazide **2** (0.1gm, 0.5 mmol) was added. The reaction mixture was refluxed for 5hrs, and the precipitated solid settled down was filtered off, dried and recrystallized from ethanol to give compound **(7)**. (*c.f.* Table 1).

General procedure for synthesis of compounds (8a,b).

2-oxo-2H-chromene-3-carbohydrazide **2** (0.5gm, 0.002 mol) was reacted with acetic acid and/or benzoic acid (0.002 mol) in 15 mL $POCl_3$ and refluxed for about 4 hrs. After cooling, poured on crushed ice, the solid precipitated filtered, washed, and compounds **(8a,b)** were obtained, which recrystallized from proper solvents.

Synthesis of 3-(5-methyl-1, 3, 4-oxadiazole-2-carbonyl)-2H-chromen-2-one (8a). (*c.f.* Table 1).

Synthesis of 3-(5-phenyl-1, 3, 4-oxadiazole-2-carbonyl)-2H-chromen-2-one (8b). (*c.f.* Table 1).

General procedure for synthesis of compounds (9-12).

To a (0.1gm, 0.5 mmol) of 2-oxo-2H-chromene-3-carbohydrazide **2** in ethanol, (0.5 mmol) of the active methylene compounds namely, acetyl acetone, ethyl cyanoacetate, ethyl acetoacetate, and/or diethylmalonate in presence of few drops of piperidine were refluxed for 5-6 hrs, then concentrated. The solid settled, filtered off, recrystallized from proper solvents to obtain the desired products.

Synthesis of 3-(3, 5-dimethyl-1H-pyrazole-1-carbonyl)-2H-chromen-2-one (9). (*c.f.* Table 1).

Synthesis of 5-methyl-2-(2-oxo-2H-chromene-3-carbonyl)-2, 4-dihydro-3H-pyrazol-3-one (10). (*c.f.* Table 1).

Synthesis of 5-amino-2-(2-oxo-2H-chromene-3-carbonyl)-2, 4-dihydro-3H-pyrazol-3-one (11). (*c.f.* Table 1).

Synthesis of 1-(2-oxo-2H-chromene-3-carbonyl) pyrazolidine-3, 5-dione (12). (*c.f.* Table 1).

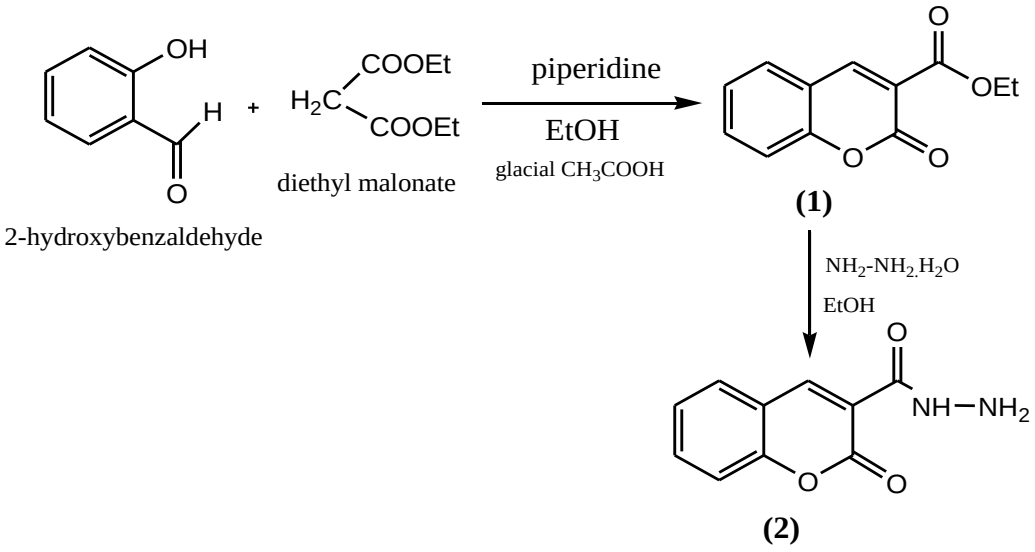
Table (1). Physical data of the synthesized compounds **(1-12).**

Compd. No	M.F. M.wt.	M.p. Colour	Yield (%)	Solvent	Analysis Calc.(Found)% C	H	N
1	**$C_{12}H_{10}O_4$**	90-92	87	Ethanol	66.05	4.62	---
	218.21	White			66.10	4.60	---
2	**$C_{10}H_8N_2O_3$**	206-208	69	Ethanol	58.82	3.95	13.72
	204.19	Yellow			58.87	3.94	13.68

3a	**$C_{17}H_{12}N_2O_3$**	234-236	98	Ethanol	69.86	4.14	9.58
	292.29	Yellow			69.88	4.11	9.51
3b	**$C_{17}H_{12}N_2O_4$**	240-242	80	Methanol	66.23	3.92	9.09
	308.29	Yellow			66.20	3.95	9.05
3c	**$C_{17}H_{11}ClN_2O_3$**	212-214	94	Ethanol	62.49	3.39	8.57
	326.74	Yellow			62.51	3.43	8.39
3d	**$C_{17}H_{12}N_2O_4$**	222-224	66	Ethanol	66.23	3.92	9.09
	308.29	Yellow			66.19	3.98	9.07
4a	**$C_{18}H_{10}N_2O_5$**	200-202	76	Ethanol	64.67	3.02	8.38
	334.29	Yellow			64.70	3.04	8.35
4b	**$C_{18}H_6Br_4N_2O_5$**	208-210	65	Ethanol	33.27	0.93	4.31
	649.87	Pale yellow			33.22	0.91	4.29
5	**$C_{14}H_8N_2O_5$**	208-210	71	Butanol	59.16	2.84	9.86
	284.23	Yellow			59.19	2.80	9.84
6	**$C_{14}H_{10}N_2O_5$**	214-216	89	Butanol	58.75	3.52	9.79
	286.24	Yellow			58.73	3.50	9.76
7	**$C_{17}H_{12}N_2O_4$**	210-212	60	Ethanol	66.23	3.92	9.09
	308.29	Yellow			66.26	3.88	9.05
8a	**$C_{12}H_8N_2O_3$**	218-220	63	Acetic acid	63.16	3.53	12.28
	228.21	Orange			63.13	3.49	12.24
8b	**$C_{17}H_{10}N_2O_3$**	246-248	55	Ethanol	70.34	3.47	9.63
	290.28	Yellow			70.36	3.43	9.60
9	**$C_{15}H_{12}N_2O_3$**	206-208	65	Ethanol	67.16	4.51	10.44
	268.27	Yellow			67.19	4.46	10.41
10	**$C_{14}H_{10}N_2O_4$**	204-206	60	Methanol	62.22	3.73	10.37
	270.24	Yellow			62.26	3.70	10.34
11	**$C_{13}H_9N_3O_4$**	206-208	67	Ethanol	57.57	3.34	15.49
	271.23	Orange			57.52	3.31	15.45
12	**$C_{13}H_8N_2O_5$**	198-200	62	Ethanol	57.36	2.96	10.29
	272.21	yellow			57.32	2.92	10.32

3. Results and discussion:

Chromene-3-carboxylate **(1)** was treated with hydrazine hydrate in refluxed ethanol and afforded the key compound 2-oxo-2H-chromene-3-carbohydrazide **(2))** [35]. **(Scheme 1)**.



Scheme (1) Synthesis of compounds (1,2)

Compound **(2)** structure was deduced from its elemental analyses as well as its IR spectrum which showed disappearance of C=O of ester and appearance of (νC=O amide) at 1680 cm^{-1}, and νNH's at 3332, 3196 cm^{-1}, in addition to other characteristic peaks of the compound.

^{1}H NMR spectrum (DMSO-*d6*) showed signals δ'^{S} ppm at 3.4 (brs, 2H , NH_2), 6.8-8.4 (m, 4H, Ar-H), and 9.00 (s, 1H, NH). Its mass spectrum showed molecular ion peak $M^{\cdot+}$ at 204 (1.97%), and the base peak at 89 (100%), and other fragments, which confirm the structure are given in chart **1**.

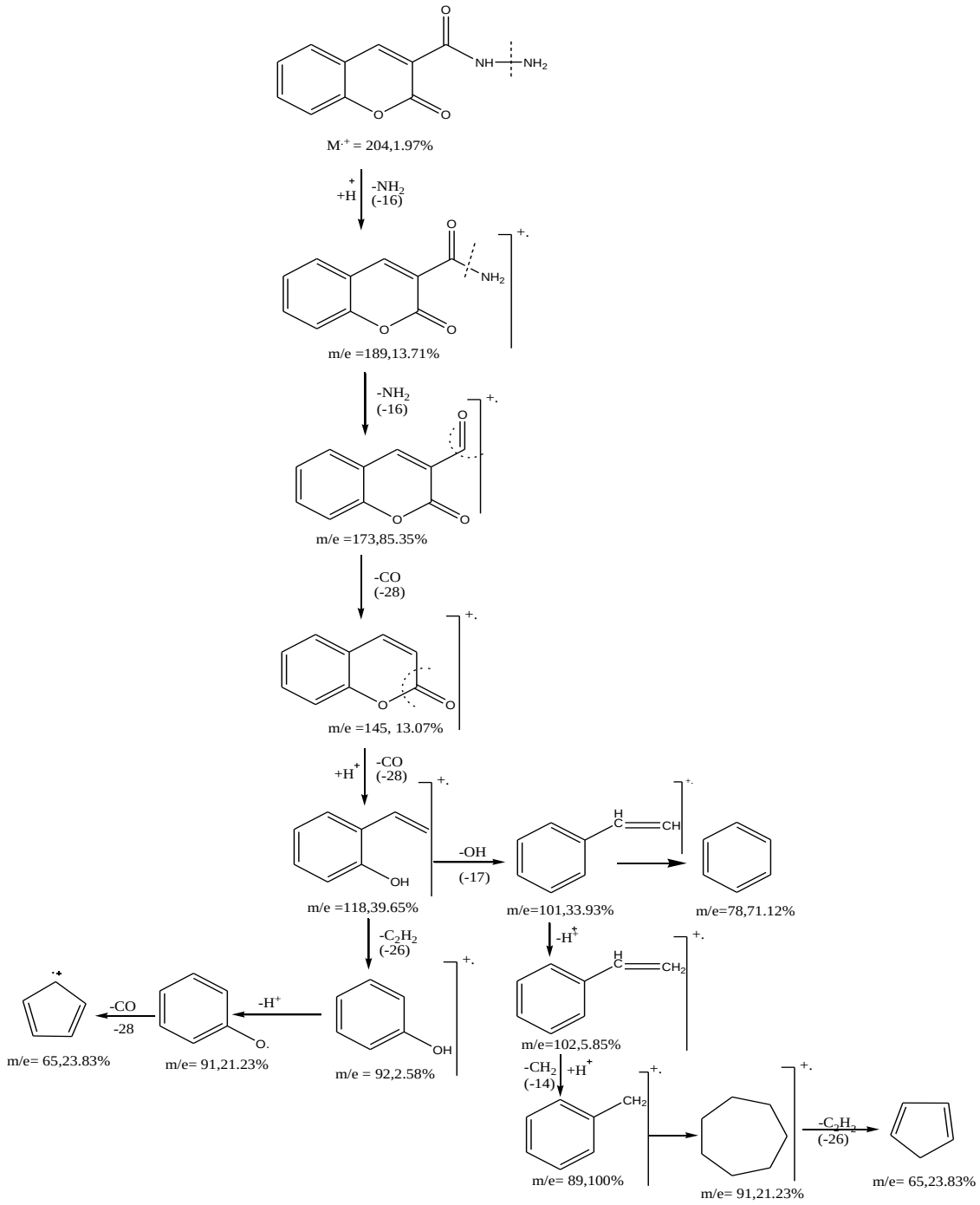
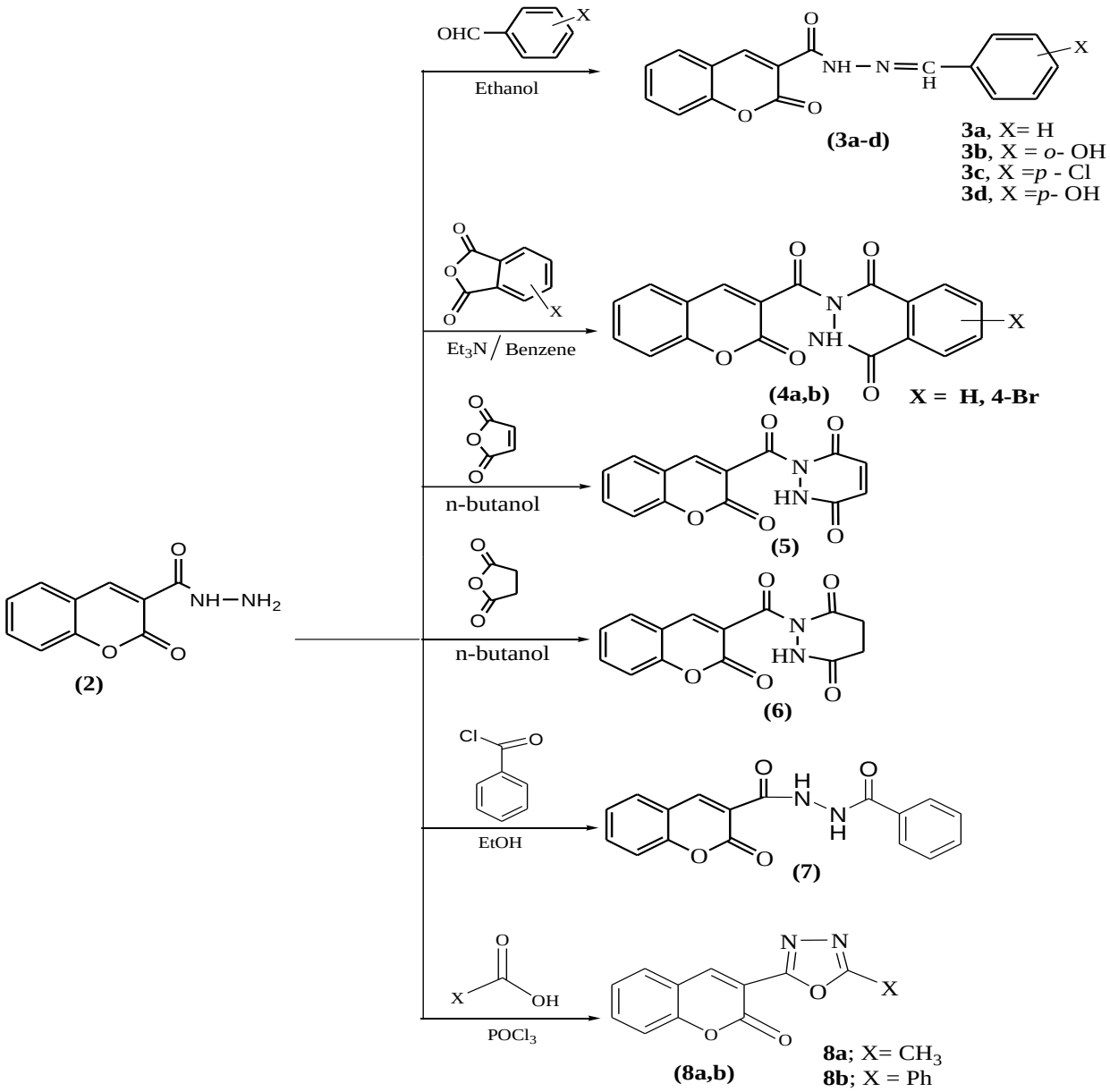


Chart (1) Mass fragmentation pattern of compound **(2)**



Scheme (2) Synthesis of compounds (3-8)

Then, the coumarin hydrazide **(2)** has been checked for alternate synthesis of some other derivatives **(3-8)**. **(Scheme 2).**

The Schiff's base derivatives **(3a-d)** were obtained in good yields when the hydrazide **(2)** was allowed to condense with different aldehydes such as benzaldehyde, salicyaldehyde, 4-chloro benzaldehyde, and/or *p*-hydroxy benzaldehyde, respectively.

The schiff's base derivative **(3a)** was elucidated via its IR spectrum which showed absorption bands at νNH at 3439 cm^{-1}, νCH aromatic at 3076 cm^{-1}, νCH aliphatic at 2922 cm^{-1}, νC=O amide at 1656 cm^{-1}, and νC=N at 1623 cm^{-1} .

While, the structure of compound **(3b)** was deduced from its elemental analyses as well as its IR spectrum which showed νOH at 3280cm^{-1}, νNH at 3189cm^{-1}, νC=O at 1675 cm^{-1}, and νC=N at 1620 cm^{-1}, and ^{1}H NMR spectrum (DMSO-*d6*) showed signals δ'^{S} ppm at 6.9-8.6 (m, 8H, Ar-H), 10.00 (s, 1H, NH) and 11.9 (s, 1H, OH). Mass spectrum of compound **(3b)** showed molecular ion peak $M^{\cdot+}$ at 308 (35.6%), and the base peak at 239 (100%), and other fragments, which confirm the structure are given in chart **2**. Also, IR-spectrum of compound **(3c)** showed νNH at 3204 cm^{-1} and νC=O amide at 1665 cm^{-1}.

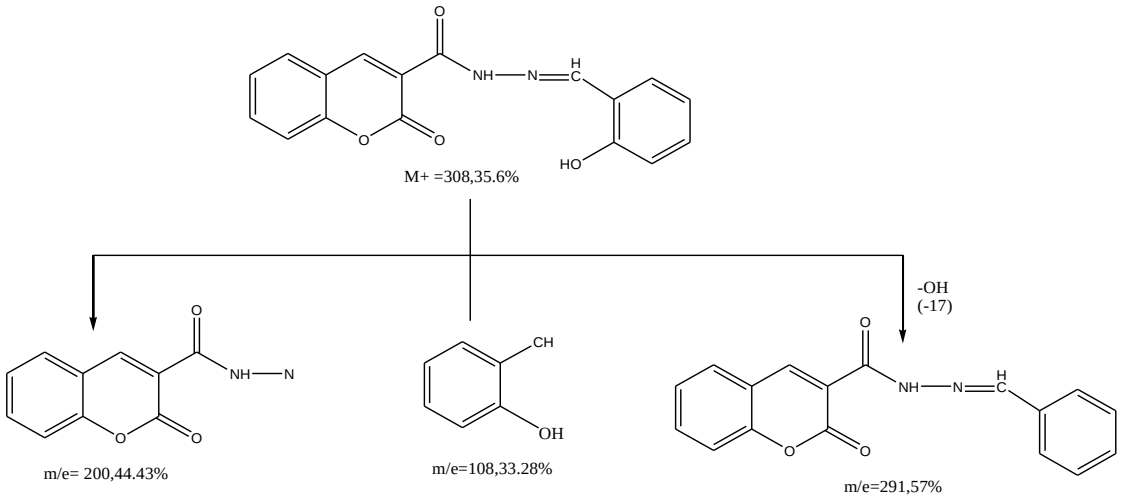


Chart (2) Mass fragmentation pattern of compound **(3b)**

Furthermore, the structure of compound **(3d)** confirmed *via* its IR spectrum which displayed the following absorption peaks at 3198 cm^{-1} (νNH stretching), 1664 cm^{-1} (νC=O amide), and 1613cm^{-1}(νC=N). And ^{1}H NMR spectrum which showed signals at δ'^{S} ppm at 4.6 (s, 1H, CH), 6.8-8.2 (m, Ar-H), 9.0 (s, 1H, NH) and 11.1 (s , 1H , OH).

Because of wide range of biological activity of phthalazinones, its used as a remarkable scaffold in drug discovery [37], which depend on the substituent present. Thus, when the hydrazide **(2)** was treated with phthalic anhydride and/or tetrabromo phthalic anhydride furnished 2-(2-oxo-2H-chromene-3-carbonyl)-2,3-dihydrophthalazine-1,4-Dione **(4a)** and 5, 6, 7, 8-tetrabromo-2-(2-oxo-2H-chromene-3-carbonyl)-2, 3-dihydrophthalazine-1, 4-dione **(4b)**, respectively.

IR-spectrum of **(4a)** showed νNH at 3274 cm^{-1}, in addition to νC=O'^{S} in range of 1765-1668 cm^{-1}, while IR spectrum of compound **(4b)** exhibit absorption bands at νNH at 3329 cm^{-1}, and νC=O'^{S} in range of 1781-1668 cm^{-1} besides the other characteristic peaks of the compound.

Also, in order to demonstrate pyridazine analogous owing to its diverse biological activities [38]. A pyridazinone derivatives **(5)** and **(6)** were efficiently synthesized via treatment of the hydrazide derivative **(2)** with maleic anhydride and/ or succinic anhydride, respectively. IR-spectrum of compound **(5)** showed νNH at 3442 cm^{-1}, in addition to νC=O'^{S} in range of 1765-1698 cm^{-1} and IR-spectrum of **(6)** exhibits νNH at 3443 cm^{-1}, and νC=O'^{S} in range of 1770-1695 cm^{-1} besides the other peaks of the compounds.

Benzoylation of the hydrazide derivative **(2)** was carried out using benzoyl chloride and afforded *N*-benzoyl-2-oxo-2H-Chromne-3-carbohydrazide **(7)** in good yield.

The chemical structure of the carbohydrazide derivative **(7)** was elucidated on the basis of its IR-spectrum which showed νNH at 3445 cm^{-1}, and νC=O's at 1699, 1668 cm^{-1}. ^{1}H NMR spectrum (DMSO-*d6*) showed signals δ'^{S} ppm at 3.9 (s, 1H , CH), 6.8-8.5 (m, 8H, Ar-H), 9.0 (s, 1H, NH $_{exchangeable}$) and 9.8 (s, 1H, NH $_{exchangeable}$).

Also, the reaction of hydrazide **(2)** with acetic acid and/or benzoic acid in $POCl_3$ produced the oxadiazole derivatives **(8a, b)**, respectively.

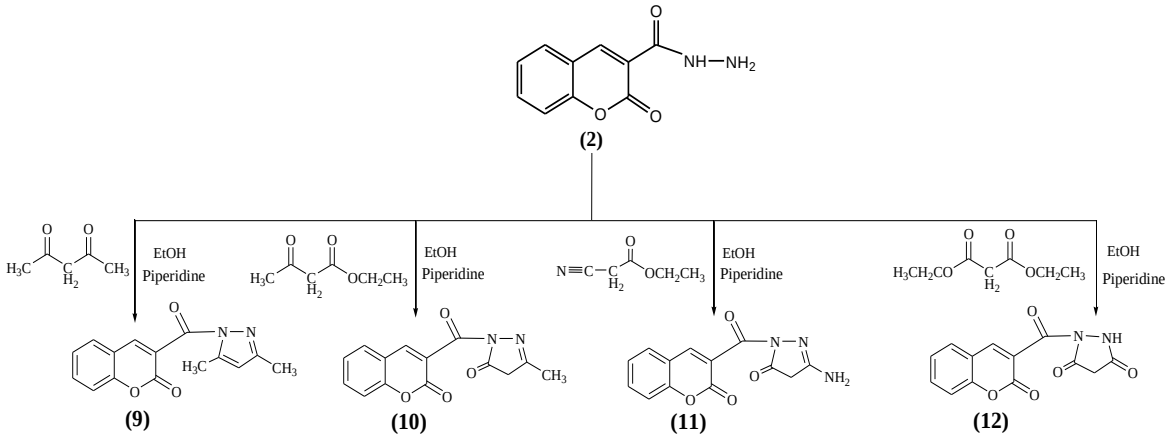
IR-spectrum of compound **(8a)** showed νNH at 3448 cm^{-1}, νC-H aromatic centered at 3048 cm^{-1}, and νC=O at 1768cm^{-1}, while IR-spectrum of compound **(8b)** showed νNH at 3423 cm^{-1}, in addition to νC=O at 1765 cm^{-1}, and νC=N at 1623 cm^{-1}.

On the other hand, pyrazolone and pyrazolidinone scaffolds **(9-12)** were obtained in good yields via reaction of the hydrazide derivative **(2)** with numerous active methylene compounds as acetylacetone, ethyl acetoacetate, ethyl cyanoacetate and diethyl malonate. **Scheme (3)**.

Reaction of the hydrazide derivative **(2)** with the active methylene acetylacetone in ethanol yielded dimethyl pyrazole derivative **(9)**, which deduced based on it is correct elemental analyses as well as it is IR spectrum, which displayed absorption bands at 3422 cm^{-1} due to νNH, 3040 cm^{-1} νCH aromatic, 2922, 2851 cm^{-1} νCH aliphatic, and 1700 cm^{-1} due to νC=O.

Moreover, ethyl acetoacetate reacted with the hydrazide **(2)** in presence of piperidine as a catalyst and afforded 5-methyl-2-(2-oxo-2H-chromene-3-carbonyl)-2, 4-dihydro-3H-pyrazol-3-one **(10)**.

IR-spectrum of compound **(10)** showed νCH aromatic at 3030 cm^{-1}, and νC=O at 1688 cm^{-1}. Its ^{1}H NMR spectrum (DMSO-*d6*) showed signals δ'^{S} ppm at 1.2 (s, 3H, CH_3), 4.0 (s, 2H, 1CH_2), and 6.8-8.6 (m, Ar-H).



Scheme (3) Synthesis of compounds (9-12)

By the same way, 5-amino pyrazolone **(11)** was obtained in good yield upon treatment of the hydrazide derivative **(2)** with ethyl cyanoacetate in the presence of piperidine as a catalyst.

IR-spectrum of compound **(11)** showed νNH at 3429 cm^{-1}, and νC=O's in range of at 1687-1620 cm^{-1} besides the other characteristic peaks of the compound. ^{1}H NMR spectrum of compound **(11)** showed signals δ'S ppm at 3.5ppm (s, 2H, $2CH_2$), 4.0 (S, 2H, $NH_{2\ exchangeable}$), 6.8-8.2ppm (m, Ar-H).

Moreover, the hydrazide derivative **(2)** reacted with diethyl malonate and furnished pyrazolidine-3,5-dione **(12)**, which deduced from its IR-spectrum which showed νNH at 3445 cm^{-1}, and νC=O's in range of at 1765-1675 cm^{-1}. And, mass spectrum showed molecular ion peak $M^{\cdot+}$ at 272 (23.81%), with a base peak at 78 (100%), besides the other fragments, which confirm the structure are given in chart **3**.

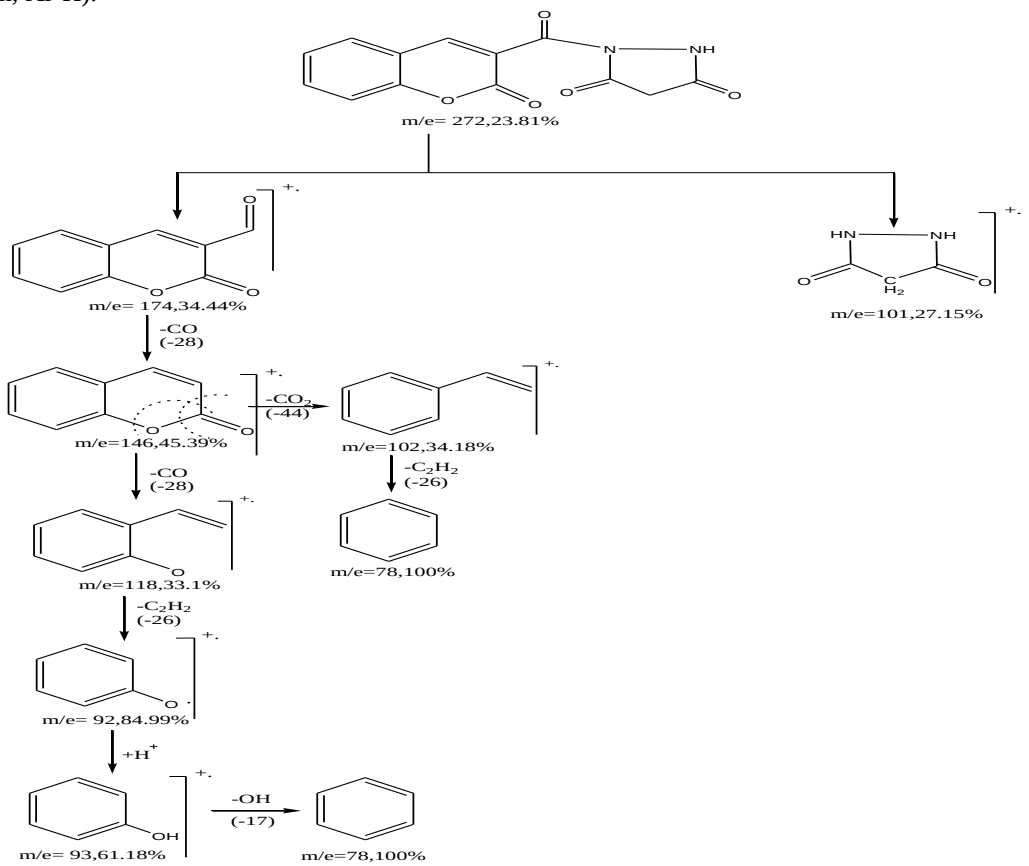


Chart (2) Mass fragmentation pattern of compound **(3b)**

Table (2) Biological activities of some of the synthesized compounds.

Compound No.	Candida albicans	Aspergillus flavus	Staphylococcus aureus	Bacillus subtilis	Escherichia coli	Proteus vulgaris
2	NA	NA	8	NA	NA	NA
3a	NA	NA	10	NA	9	NA
3d	10	NA	14	10	14	NA
5	12	NA	NA	NA	12	NA
6	14	NA	8	NA	10	NA
8a	14	NA	NA	NA	8	NA
8b	10	NA	NA	NA	13	10
11	NA	NA	14	NA	12	10
12	10	NA	22	NA	25	NA
	20	16	24	26	30	25
Control	Ketoconazole		Gentamycin		Gentamycin	

3.2 Antimicrobial Activity

Evaluation of antimicrobial activity of some of the synthesized compounds was demonstrated invitro using the diffusion agar method [6.0 mm, 100µl] [39]. The tested microorganisms were Gram (+) bacteria *Bacillus subtilis* (ATCC 6635) and *Staphylococcus aureus* (ATCC 25923) and Gram (-) bacteria *Proteus vulgaris and Escherichia coli* (ATCC 25922). In addition, fungi *Aspergillus Flavus and* yeast *Candida albicans* (ATCC 10231) were also tested.

The selected microorganisms sensitivity to some of the synthesized compounds was assessed at concentration (10 mg/mL). The results are given in Table **(2)**.

Signals in table **(2)** signify the extent of the zone diameter (r mm) inhibition of either bacterial cells or fungal growth for each tested compound; (NA) no activity.

The results presented in table **(2)** revealed that most of tested compounds exhibited adjustable inhibition effect on the growth of the tested microorganisms. Generally, most of them showed weak activities against Aspergillus flavus and Bacillus subtilis strains.

Also, it was noticed that some of the tested compounds showed promising inhibitory effect against both bacterial and fungal strains in comparison to the key compound coumarin-3-carbohydrazide **(2)**, and the standard drugs ketoconazole, and Gentamycin.

Coumarin derivatives **3d, 8b, 11, and 12** showed moderate activity against both *Streptococcus sp.* and *Escherichia Coli*, while compounds **2, 3a, 15** and **16a** showed low activity towards the tested bacteria strains.

On the other side, compounds **6, 8a,** and **14** showed good antifungal activity towards *Candida albicans* and *Aspergillus Flavus* in comparison with a standard drug ketoconazole.

The antimicrobial activity for some of the synthesized compounds were enhanced by incorporation of pyridazinone, oxadiazole, pyrazolidinone moieties to the coumarin ring.

In conclusion, the antimicrobial activity studies of some of the synthesized compounds led to the fact that some of these derivatives are biologically active against the tested microorganisms, which is compatible with the present study objectives. In general, the synthesized compounds presented lower to moderate activities, and none of these compounds was as or more active than the reference drugs.

4. Conclusion

An efficient synthesis of series of phthalazinone, pyridazinone, oxadiazole, pyrazolone scaffolds was achieved based on coumarin-3-carbohydrazide. Some of the new developed series are potent antimicrobial agents towards Gram (+) bacteria *Bacillus subtilis and Staphylococcus aureus* and Gram (-) bacteria *Escherichia coli and Proteus vulgaris.* In addition to the yeast *Candida albicans* and fungi *Aspergillus Flavus* in comparison with standard drugs. These new lead compounds may be used for development of new promising antimicrobial agents.

5. Acknowledgement

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Conflicts of Interest

Authors declare no conflicts of interest concerning the publication of this paper.

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