Full Paper

Rapid and Efficient Synthesis of 4-Substituted Pyrazol-5-one under Microwave Irradiation in Solvent-Free Conditions

Magdy A.-H. Zahran[1], Farag A-A. El-Essawy[1], Salah M. Yassin[1], Tarek A-R. Salem[2], and Nader M. Boshta[1]

[1] Organic Chemistry Laboratory, Department of Chemistry, Faculty of Science, Menoufiya University, Egypt
[2] Department of Molecular Biology, Genetic Engineering & Biotechnology Institute, Menoufiya University, Egypt

New heterocyclic compounds containing pyrazol-5-one coupled with benzimidazole, benzothiazole, benzoxazole, quinoline, naphthyridin, and pyrazole were synthesized. Comparative investigations to synthesize these interesting classes of heterocyclic compounds through conventional heating or under microwave-irradiation conditions were presented. Synthesized compounds **1a**, **2a**, **4k**, **3a, c**, **5a, b**, **6b**, **7a, b, d**, **8a**, and **9a** were evaluated for their antitumor activity. Some of these compounds exhibited promising antitumor activity.

Keywords: Antitumor / Benzazoles / Microwave / Pyrazolone / Quinoline

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Introduction

Heterocycles, containing the pyrazolone nucleus, have attracted much attention due to their interesting biological activities [1 – 12]. The synthesis of a large number of heterocycles introducing pyrazolone nucleus functionalities led to very interesting and useful antitumorally [13], antibacterially [8], and agrochemically active products [14, 15]. Similarly, many pyrazole derivatives are associated with antifungal [8], antipyretic [10], and anti-inflammatory properties [9]. Pyrazolone-imines (Schiff's bases), have been used in different reaction sequences for the synthesis of heterocyclic systems such as isoquinolines [16], cyclopentaquinoline, and pyranoquinoline [17].

The utility of solvent-free microwave-assisted organic synthesis (MAOS) is a new and quickly growing area in synthetic organic chemistry [18]. This synthetic technique is somewhat reliant on the empirical observation compared to conventional heating methods. In many cases, reactions that normally require many hours under thermal conditions can be completed within several minutes or even seconds in a microwave oven.

The objective of the presented paper is to investigate and compare between the conventional heating and microwave-irradiation conditions to synthesize pyrazol-5-one coupled with benzimidazole, benzothiazole, benzoxazole, quinoline, naphthyridin, and pyrazole and investigating the antitumor activity of the obtained products.

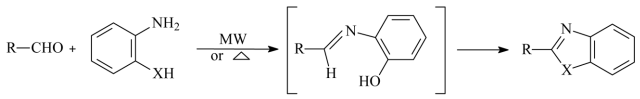
Results and discussion

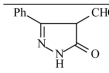
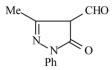
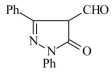
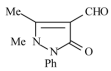
Chemistry

Recently, in order to verify the criteria of rate enhancement, higher chemical yield, greater selectivity, and ease manipulation a great interest has been focused on "dry media" synthesis under microwave (MW) irradiation [19]. Thus, the formyl-pyrazolone derivatives **1a – d** were allowed to react with aromatic amine derivatives in ethanol at reflux for 5 – 12 h, resulting in the formation of pyrazolyl benzimidazole **2a, d, g, j**, pyrazolyl benzothiazole **2b, e, h, k,** and pyrazolyl benzoxazole **2f, i, l** in a good yield (Scheme 1). The compounds **2a – l** were also synthe-

Correspondence: Magdy Abdel-Hamed Zahran, Organic Chemistry Laboratory, Department of Chemistry, Faculty of Science, Menoufiya University, Egypt.
E-mail: magdyzahran@yahoo.com
Fax: +20 2241-59770

Abbreviations: microwave (MW); microwave-assisted organic synthesis (MAOS); Ehrlich ascites carcinoma (EAC); tumor volume (TV)



Starting materials	X	Product
	NH	**2a**
	S	**2b**
	O	**2c**
1a		
	NH	**2d**
	S	**2e**
	O	**2f**
1b		
	NH	**2g**
	S	**2h**
	O	**2i**
1c		
	NH	**2j**
	S	**2k**
	O	**2l**
1d		

Scheme 1. Synthesis route of compounds **2a, b, d – l.**

sized in excellent yield with shorter reaction times and under MW irradiation in solvent-free conditions. Pyrazolone derivatives **1a – d**, the appropriate aromatic amine, and a catalytic amount of DMSO (acting as oxidizing agent) were supported on silica gel and submitted to MW irradiation for 5 – 30 min. to yield the oxidative cyclisation products pyrazolylbenzimidazole **2a, d, g, j,** pyrazolyl benzothiazole **2b, e, h, k,** and pyrazolyl benzoxazole **2f, i, l** (Table 1).

The structure of compounds **2a – d** were evidenced by the disappearance of the formyl proton in ^{1}H-NMR spectrum and appearance of multiplet at δ 6.7 – 7.3 ppm due to new aromatic protons of the aromatic amine moieties.

The reaction of the pyrazolone derivative **1a** with *o*-aminophenol either conventionally or under MW-irradiation condition yielded the corresponding Schiff's base **2c**, which under the oxidative cyclisation reaction resists cyclisation. Applying a long reaction time either under microwave or conventional heating does not lead to oxidative cyclisation reaction. The reason for this abstention is unknown but might be referred to stereo factors explained on the basis of the formation of **2c** in a different isomeric form. In addition, the isolated compound **2c** gives a positive $FeCl_3$ test which confirms the presence of the phenolic OH. The structure of compound **2c** was elucidated by ^{1}H-NMR spectrum which showed the appearance of singlet at δ 10.38 ppm due to the (CH=N) proton and the appearance of a singlet at δ 4.10 ppm due to an OH proton; the microanalysis data confirm the structure of **2c** as well.

Table 1. Comparative study of the microwave (MW) and thermal reactions (Δ) with the melting points (Mp.) of the compounds **2a – l**, **3a – c**, **4a**, **b**, and **7a**, **b**.

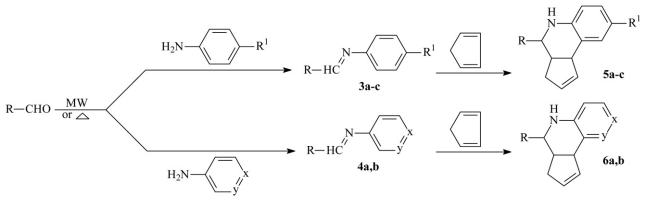
Product	Time (MW)	Time (Δ)	Yield (%) (MW)	Yield (%) (Δ)	Mp. (°C)
2a	5 min	7 h	85%	79%	270 – 271
2b	17 min	7 h	66%	64%	284 – 286
2c	20 min	9 h	73%	55%	229 – 230
2d	15 min	9 h	87%	72%	180
2e	20 min	11 h	75%	65%	198 – 200
2f	15min	8 h	89%	74%	230
2g	15 min	5 h	91%	82%	205 – 207
2h	30 min	9 h	63%	58%	220 – 222
2i	15 min	7 h	88%	77%	255 – 257
2j	25 min	8 h	92%	78%	278 – 280[a)]
2k	20 min	6 h	82%	71%	221 – 223[a)]
2l	30 min	12 h	68%	62%	189 – 190
3a	25 min	10 h	94%	83%	243
3b	20 min	8 h	98%	85%	288
3c	25 min	13 h	95%	79%	225 – 227
4a	35 min	15 h	81%	86%	196 – 198
4b	35 min	13 h	77%	81%	183
7a	15 min	16 h	62%	46%	296 – 298
7b	15 min	9 h	59%	51%	318 – 320
7c	20 min	28 h	72%	81%	146
7d	15 min	15 h	82%	86%	230

[a)] The reported melting points of derivatives **2j**, **k** were in complete accordance with the obtained products [29, 30].

Quinolines are an important class of biologically active compounds, since many quinoline derivatives have proven to posses antimalarial and anti-inflammatory properties [20 – 23]. Imino Diels – Alder reaction of imines with electron-rich dienophiles to give simple quinoline derivatives has been reported [24] and this reaction is found to be catalyzed by triethylamine (TEA) [25], BF_3-Et_2O [26], and $GdCl_3$ [27].

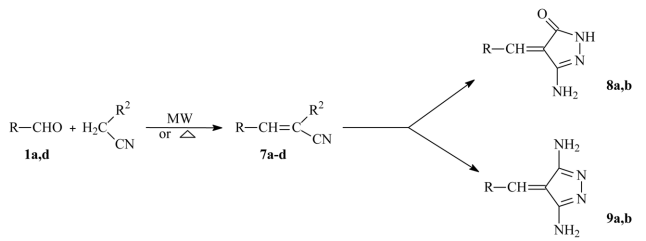
The synthesis of quinoline and naphthyridin coupled with pyrazolone involving the Imino Diels – Alder cycloaddition reaction were described. Thus, pyrazolyl imines **3a – c, 4a, b** were prepared from the reaction of the 4-formyl-5-pyrazolone **1a** with aromatic and heteroaromatic amines, respectively, either in refluxing ethanol or under MW-irradiation condition. The formation of compounds **3a – c, 4a, b** were followed by the disappearance of a singlet for the aldehydic proton in ^{1}H-NMR spectra, appearance of singlet at δ 8.40 – 8.75 ppm due to the (CH=N) proton and two doublets at δ 7.5 – 7.75 and 7.6 – 8.4 ppm (J = 8.6 Hz) due to new aromatic protons for **3a – c** while the pyridine protons appeared as multiplet at δ 8.00 – 8.5 ppm for **4a, b**.

The reaction of pyrazolylimines **3a – c, 4a, b**, cyclopentadiene in acetonitrile and a few drops of trimethylsilyltriflate (TMS triflate) afforded the cycloadducts **5a – c, 6a, b** (Scheme 2). These compounds were evidenced by the



Compound N°	R^1	X	Y
3a	Cl	----	----
3b	NO_2	----	----
3c	OCH_3	----	----
4a	----	N	CH
4b	----	CH	N
5a	Cl	----	----
5b	NO_2	----	----
5c	OCH_3	----	----
6a	----	N	CH
6b	----	CH	N

Scheme 2. Synthesis route of compounds **3a – c**, **4a**, **b**, **5a – c**, and **6a**, **b**.



Start	(R^2)	Product	Final Product
1a	COOEt	**7a**	**8a**
1a	CN	**7b**	**9a**
1d	COOEt	**7c**	**8b**
1d	CN	**7d**	**9b**

Scheme 3. Synthesis route of compounds **7a – d**, **8a**, **b**, and **9a**, **b**.

disappearance of the (CH=N) proton in ^{1}H-NMR spectrum and appearance of multiplet at δ 1.23 – 1.30, 4.23 – 4.55 and at 5.6 – 7.10 ppm, which are typically for the cyclopenta-quinoline system. The microanalysis data confirmed the structures **5a – c, 6a, b**.

The comparative investigation for both reaction conditions leads to the conclusion that the MW irradiation, as expected, provides higher chemical yield, shorter reaction time, and easier manipulation compared to conventional heating methods.

Finally, α-cyanoacrylic ester **7a, c** and malononitrile derivatives **7b, 7d** have been prepared by condensation of ethylcyanoacetate and malononitrile with the pyrazolone derivatives **1a**, **d**, respectively, either at reflux in ethanol or under MW irradiation conditions. Treatment of **7a, b** and **7c, d** with excess of hydrazine hydrate at refluxing in ethanol afforded the pyrazolylmethylen-pyrazole derivatives **8a, b** and **9a, b**, respectively (Scheme 3).

The cyclization of **7a, b** and **7c, d** to furnish the pyrazolylmethylen-pyrazole derivatives **8a, b** and **9a, b** were evidenced by the disappearance of singlet for aldehydic proton in ^{1}H-NMR spectra, appearance of singlet at δ 5.9 – 6.3 ppm due to NH_2 proton, appearance of singlet at δ 8.16 – 8.60 ppm due to (CH=C) proton and appearance of singlet at δ 11.4 – 11.45 ppm due to NH proton. The ^{1}H-NMR spectra of **8a, b** showed disappearance of the ethoxy group. IR spectra for **8a, b** and **9a, b** showed disappearance of the nitrile absorption bands and the appearance of the NH and NH_2 absorption bands.

Conclusion

Results given in (Table 2) shows various effects of the tested compounds on the viability of EAC *in vitro*. The maximal cytotoxic effect was obtained when cells were treated with compound **5b**. Compared to thalidomide [35], compounds **9a**, **5a**, and **5b** show a higher cytotoxic effect.

Table 2. Cytotoxic activity of compounds **1a**, **2a**, **k**, **3a**, **c**, **5a**, **b**, **6b**, **7a**, **b**, **d**, **8a**, and **9a** on EAC *in vitro*[a].

N°	**1a**	**2a**	**2k**	**3a**	**3c**	**5a**	**5b**	**6b**	**7a**	**7b**	**7d**	**8a**	**9a**	**Control**	**Thalidomide**
Live	46	40	42	42	40	21	15	44	45	40	45	42	27	50	28
Dead	4	10	8	8	10	29	35	6	5	10	5	8	23	0	22
%	8	20	16	16	20	58	70	12	10	20	10	16	46	0	44

[a] The concentration for all tested compounds were 1 mM/well.

Table 3. Effect of compounds **1a**, **2a**, **k**, **3a**, **c**; **5a**, **b**, **6b**, **7a**, **b**, **d**, **8a**, and **9a** on solid tumor volume.

N°	**1a**	**2a**	**2k**	**3a**	**3c**	**5a**	**5b**	**6b**	**7a**	**7b**	**7d**	**8a**	**9a**	**Control**	**Thalidomide**
volume (mm^3)	182	176	202	186	166	75	65	143	151	181	189	171	89	260	122

In *in-vivo* experiments as shown in (Table 3), all tested compounds caused a significant reduction of tumor size when compared to the control group. The maximal reduction was obtained in tumor-bearing mice which were treated with compounds **9a**, **5a**, and **5b**. These compounds caused a significant reduction in tumor size also when compared to thalidomide.

Experimental

General

The title compounds were synthesized both conventionally and with MW irradiation. The syntheses of the compounds were carried out by using a domestic microwave oven (Whirl Pool-TALENT). The synthesized product and each reaction either conventionally or by MW irradiation were monitored on Merck silica gel 60 F254 plates (type E; Merck, Darmstadt, Germany) and spots were located by UV light. All ^{1}H-NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer (Varian Inc., Palo Alto, CA, USA) from Cairo University. Chemical shifts are reported in parts per million (ppm) relative to the respective solvent or tetramethylsilane (TMS) and standard abbreviations were used (a = apparent; b = broad; s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet). Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyser in the microanalysis laboratory at Cairo University. IR spectra were recorded (KBr) on a Pye-Unicam Sp-883 or Perkin-Elmer spectrophotometer (Pye Unicam Ltd. Cambridge, England; Perkin Elmer, Beaconsfield, UK), Microanalytical Laboratory, Faculty of Science, Cairo University. MS spectra were run on GC MS-QP 1000 EX Mass Spectrometer (Shimadzu, Tokyo, Japan), Microanalytical Laboratory, Faculty of Science, Cairo University. Melting points were recorded on Stuart scientific melting point apparatus (Stuart Scientific, Stone, Staffordshire, UK) and are uncorrected. Solvents were dried by standard methods and distilled prior to use. The required starting materials, **1a – d**, were prepared by adopting the earlier reported procedures [28].

General synthetic procedure for *2a – l*

Microwave irradiation conditions

To a mixture of pyrazolon-4-carbaldehyde **1a – d** (1.25 mmol), 0.3 mL of DMSO, and 0.75 g of silica gel, a solution of the appropriate aromatic amine derivatives (1.25 mmol) in methylene chloride (5 mL) was added. Then, the solvent was evaporated and irradiated in a microwave oven at 350 W for the appropriate time (Table 1). The product was extracted with methanol, filtered off, the filtrate concentrated, and the final product was separated in pure form.

Conventional heating method

To a mixture of pyrazolon-4-carbaldehyde **1a – d** (1.25 mmol) and 0.3 mL of DMSO, a solution of the appropriate aromatic amine derivatives (1.25 mmol) in absolute ethanol (5 mL) was added. The reaction mixture was refluxed for the appropriate time (Table 1). The solvent was evaporated to dryness and the residue was triturated with water, then allowed to stand under stirring until a precipitate formed.

*4-(1H-Benzimidazol-2-yl)-5-phenyl-2,4-dihydro-3H-pyrazol-3-one **2a***

Yellowish green crystals (methanol); IR (KBr): 3372, 3206 (NH), 1657 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 6.68 – 7.75 (m, 9H, H_{arom}), 8.377 (s, 1H, CH of pyrazole), 11.52 (s, 2H, 2 NH); MS (EI) m/z (%) =277 [M+1] (95), 173 (28), 119 (53), 54 (100). $C_{16}H_{12}N_4O$ (276.29). Anal. Calcd.: C; 69.55, H; 4.38, N; 20.28. Found: C; 69.70, H; 4.40, N; 20.76%

*4-(1,3-Benzothiazol-2-yl)-5-phenyl-2,4-dihydro-3H-pyrazol-3-one **2b***

Greenish yellow crystals (methanol); IR (KBr): 3269 (NH), 1653 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 7.00 – 7.77 (m, 9H, H_{arom}), 8.41 (s, 1H, CH of pyrazole), 11.52 (s, 1H, NH); MS (EI) m/z (%) = 293 [M$^+$] (48), 236 (29), 135 (100). $C_{16}H_{11}N_3OS$ (293.34). Anal. Calcd.: C; 65.51, H; 3.78, N; 14.32. Found: C; 65.40, H; 3.80, N; 14.25%.

*4-{[(2-Hydroxyphenyl)imino]methyl}-5-phenyl-2,4-dihydro-3H-pyrazol-3-one **2c***

Yellow crystals (methanol); IR (KBr): 3231 (NH), 1654 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 4.10 (bs, 1H, OH), 6.84 – 7.77 (m, 9H, H_{arom}), 8.51 (s, 1H, CH of pyrazole), 10.38 (s, 1H, HC=N), 11.48 (s, 1H, NH); MS (EI) m/z (%) = 279 [M+1] (100), 171 (81), 120 (34), 77 (24). $C_{16}H_{13}N_3O_2$ (279.29). Anal. Calcd.: C; 68.81, H; 4.69, N; 15.05 . Found: C; 68.85, H; 5.0, N; 14.86%.

*4-(1H-Benzimidazol-2-yl)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one **2d***

Yellow crystals (methanol); IR (KBr): 3381 (NH), 1670 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 2.48 (s, 3H, CH_3), 6.71 – 8.00 (m, 9H, H_{arom}), 8.44 (s, 1H, CH of pyrazole), 11.40 (s, 1H, NH); MS (EI) m/z (%) = 291 [M+1] (1.2), 178 (15), 149 (100). $C_{17}H_{14}N_4O$ (290.319). Anal. Calcd.: C; 70.33, H; 4.86, N; 19.3. Found: C; 70.09, H; 5.50, N; 19.27%.

*4-(1,3-Benzothiazol-2-yl)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one **2e***

Yellow crystals (methanol); IR (KBr): 1664 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 2.48 (s, 3H, CH_3), 7.02-7.96 (m, 9H, H_{arom}), 8.38 (s, 1H, CH of pyrazole), MS (EI) m/z (%) =308 [M$^+$] (98), 204 (12), 171 (100). $C_{17}H_{13}N_3OS$ (307.371). Anal. Calcd.: C; 66.43, H; 4.26, N; 13.67. Found: C; 66.23, H; 4.14, N; 13.38%.

*4-(1,3-Benzoxazol-2-yl)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one **2f***

Yellow crystals (methanol); IR (KBr): 1669 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 2.49 (s, 3H, CH_3), 7.41 – 8.52 (m, 9H, H_{arom}), 8.75 (s, 1H, CH of pyrazole). $C_{17}H_{13}N_3O_2$ (291.304). Anal. Calcd.: C; 70.09, H; 4.50, N; 14.42. Found: C; 69.82, H; 5.02, N; 15.18%.

*4-(1H-Benzimidazol-2-yl)-2,5-diphenyl-2,4-dihydro-3H-pyrazol-3-one **2g***

Yellowish green crystals (methanol); IR (KBr): 3391 (NH), 1664 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 6.68 – 8.10 (m, 14H, H_{arom}), 8.44 (s, 1H, CH of pyrazole), 11.80 (s, 1H, NH); MS (EI) m/z (%) =353 [M$^+$] (100), 313 (25), 129 (53). $C_{22}H_{16}N_4O$ (353.389).

Anal. Calcd.: C; 74.98, H; 4.58, N; 15.90. Found: C; 75.16, H; 5.29, N; 15.43%.

4-(1,3-Benzothiazol-2-yl)-2,5-diphenyl-2,4-dihydro-3H-pyrazol-3-one ***2h***

Yellow crystals (methanol); IR (KBr): 1663 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 7.02 – 8.03 (m, 14H, H_{arom}), 8.36 (s, 1H, CH of pyrazole); MS (EI) m/z (%) = 369 [M^+] (9), 353 (27), 236 (59), 124 (100). $C_{22}H_{15}N_3OS$ (369.44). Anal. Calcd.: C; 71.52, H; 4.09, N; 11.37. Found: C; 72.01, H; 4.12, N; 11.52%.

4-(1,3-Benzoxazol-2-yl)-2,5-diphenyl-2,4-dihydro-3H-pyrazol-3-one ***2i***

Yellow crystals (methanol); IR (KBr): 1659 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 6.85 – 8.08 (m, 14H, H_{arom}), 8.62 (s, 1H, CH of pyrazole). $C_{22}H_{15}N_3O_2$ (353.374). Anal. Calcd.: C; 74.78, H; 4.28, N; 11.89. Found: C; 75.32, H; 5.37, N; 11.76%.

4-(1H-Benzaimidazol-2-yl)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one ***2j***

Yellowish green crystals (ethanol); IR (KBr): 3322 (NH), 1638 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 2.87 (s, 3H, CH_3), 3.368 (s, 3H, NCH_3), 7.09 – 7.60 (m, 9H, H_{arom}), 11.93 (s, 1H, NH); MS (EI) m/z (%) = 304 [M^+] (100), 212 (17), 171 (12). $C_{18}H_{16}N_4O$ (304.34). Anal. Calcd.: C; 71.04, H; 5.3, N; 18.4. Found: C; 69.29, H; 5.55, N; 18.45%.

4-(1,3-Benzothiazol-2-yl)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one ***2k***

Yellow crystals (ethanol); IR (KBr): 1656 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 2.92 (s, 3H, CH_3), 3.38 (s, 3H, NCH_3), 7.3 – 8.04 (m, 9H, H_{arom}); MS (EI) m/z (%) =321 [M^+] (100), 229 (50), 160 (26). $C_{18}H_{15}N_3OS$ (321.39). Anal. Calcd.: C; 67.27, H; 4.7, N; 13.07. Found: C; 67.26, H; 4.7, N; 13.30%.

4-(1,3-Benzoxazol-2-yl)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one ***2l***

Green crystals (ethanol); IR (KBr): 1654 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 2.92 (s, 3H, CH_3), 3.38 (s, 3H, NCH_3), 7.00 – 8.1 (m, 9H, H_{arom}); MS (EI) m/z (%) = 305 [M^+] (22), 304 (100). $C_{18}H_{15}N_3O_2$ (305.33). Anal. Calcd.: C; 70.8, H; 4.95, N; 13.76. Found: C; 69.10, H; 5.53, N; 13.74%.

General synthetic procedure for *3a – c, 4a, b*

Microwave irradiation conditions

To a solution of **1a** (0.188 g, 1 mmol) in ethanol (10 mL), the appropriate aromatic or heteroaromatic amine derivatives (1 mmol) and silica gel (1 g) was added and the mixture was stirred for 10 min. Then ethanol was evaporated *in vacuo* and the resulting precipitate was irradiated in a microwave oven at 350 W for the appropriate time (Table 1). After irradiation, the product was extracted with methanol, filtered off, the filtrate concentrated, and the final product was separated in pure form.

Conventional heating method

A mixture of **1a** (0.19 g, 1 mmol) and the appropriate aromatic or heteroaromatic amine derivatives (1 mmol) in ethanol (15 mL) was refluxed for the appropriate time (Table 1). After cooling, the product was precipitated, filtered off, and recrystallized from the appropriate solvent.

4-{[(4-Chlorophenyl)imino]methyl}-5-phenyl-2,4-dihydro-3H-pyrazol-3-one ***3a***

Yellow crystals (ethanol); IR (KBr): 3132 (NH), 1668 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 7.40 – 7.49 (m, 5H, Ph), 7.50 (s, 1H, CH of pyrazole), 7.54 (d, 2H, J = 8.7 Hz, H_{arom}), 7.76 (d, 2H, J = 7.5 Hz, H_{arom}), 8.46 (s, 1H, HC=N), 11.58 (s, 1H, NH); MS (EI) m/z (%) = 299 [M+2] (29), 297 [M^+] (86), 240 (5), 204 (11), 171 (100). $C_{16}H_{12}N_3OCl$ (297.73) Anal. Calcd.: C; 64.54, H; 4.06, N; 14.11. Found: C; 64.80, H; 4.24, N; 14.41%.

4-{[(4-Nitrophenyl)imino]methyl}-5-phenyl-2,4-dihydro-3H-pyrazol-3-one ***3b***

Yellow crystals (methanol); IR (KBr): 3140 (NH), 1668 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 7.46 – 7.73 (m, 5H, Ph), 7.76 (s, 1H, CH of pyrazole), 7.78 (d, 2H, J = 7.8 Hz, H_{arom}), 8.26 (d, 2H, J = 9 Hz, H_{arom}), 8.57 (s, 1H, HC=N), 11.7 (s, 1H, NH). $C_{16}H_{12}N_4O_3$ (308.29). Anal. Calcd.: C; 62.33, H; 3.92, N; 18.17. Found: C; 62.12, H; 4.1, N; 17.97%.

4-{[(4-Methoxyphenyl)imino]methyl}-5-phenyl-2,4-dihydro-3H-pyrazol-3-one ***3c***

Green crystals (ethanol); IR (KBr): 3141 (NH), 1666 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 3.75 (s, 3H, OCH_3), 6.95 – 7.42 (m, 5H, Ph), 7.43 (s, 1H, CH of pyrazole), 7.45 (d, 2H, J = 9 Hz H_{arom}), 7.73 (d, 2H, J = 9.3 Hz, H_{arom}), 8.42 (s, 1H, HC=N), 11.5 (s, 1H, NH); MS (EI) m/z (%) = 293 [M^+] (100), 171 (36), 77 (92). $C_{17}H_{15}N_3O_2$ (293.32). Anal. Calcd.: C; 69.61, H; 5.15, N; 14.33. Found: C; 69.24, H; 5.15, N; 14.12%.

5-Phenyl-4-[(pyridine-4-ylimino)methyl]-2,4-dihydro-3H-pyrazol-3-one ***4a***

Orange crystals (ethanol); IR (KBr): 3282 (NH), 1716 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 7.44 – 7.75 (m, 5H, Ph), 7.80 (s, 1H, CH of pyrazole), 8.00 – 8.52 (m, 4H, CH of pyridine), 8.70 (s, 1H, HC=N), 11.6 (s, 1H, NH); MS (EI) m/z (%) = 264 [M^+] (21), 263 (100), 171 (42). $C_{15}H_{12}N_4O$ (264.28). Anal. Calcd.: C; 68.17, H; 4.58, N; 21.20. Found: C; 68.60, H; 4.10, N; 20.96%.

5-Phenyl-4-[(pyridine-3-ylimino)methyl]-2,4-dihydro-3H-pyrazol-3-one ***4b***

Yellow crystals (ethanol); IR (KBr): 3283 (NH), 1715 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 7.44 – 7.76 (m, 5H, Ph), 7.78 (s, 1H, CH of pyrazole), 7.97 – 8.52 (m, 4H, CH pyridine), 8.75 (s, 1H, HC=N), 11.6 (s, 1H, NH). $C_{15}H_{12}N_4O$ (264.28). Anal. Calcd.: C; 68.17, H; 4.58, N; 21.20. Found: C; 68.20, H; 4.20, N; 21.42%.

General synthetic procedure for *5a – c, 6a, b*

To a suspension of the imine derivatives **3a – c, 4a, b** (1 mmol) in dry acetonitrile (10 mL), 3 – 4 drops of TMS triflate, cyclopentadiene (2 mmol) were added, the reaction mixture was stirred overnight at room temperature. A saturated $NaHCO_3$ solution (10 mL) was added to the reaction mixture and the organic layer was extracted with ethyl acetate. The combined organic layer was washed 3 × 50 mL water, dried over anhydrous $CaCl_2$, filtered, and the solvent was evaporated *in vacuo*. The residue was purified

by column chromatography, eluting with chloroform-ethylacetate (9 : 1) to afford the cycloadduct products **5a – c, 6a, b**.

4-(8-Chloro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-5-phenyl-2,4-dihydro-3H-pyrazol-3-one ***5a***

Green crystals, Yield 40%, Mp. 132-133°C ; IR (KBr): 3260 (NH), 1675 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$), (δ ppm): 1.30 (m, 2H, CH_2 of cyclopentene), 4.23 (m, 4H, CH of cyclopentene, quinoline), 6.62 (m, 1H, HC=C of cyclopentene), 7.1 (m, 1H, C=CH of cyclopentene), 7.30 – 7.73 (m, 8H, H_{arom}), 8.10 (s, 1H, CH of pyrazole); MS (EI) m/z (%) = 363 [M^+] (1.4), 251 (2.5), 167 (15), 149 (100). $C_{21}H_{18}N_3OCl$ (363.84). Anal. Calcd.: C; 69.32, H; 4.99, N; 11.55. Found: C; 69.14, H; 5.13, N; 11.47%.

4-(8-Nitro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-5-phenyl-2,4-dihydro-3H-pyrazol-3-one ***5b***

Yellowish green crystals; Yield 48%, Mp. 168 – 170°C; IR (KBr): 3480 (NH), 3360 (NH), 1632 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$), (δ ppm): 1.27 (m, 2H, CH_2 of cyclopentene), 4.35 (m, 4H, CH of cyclopentene, quinoline), 6.65 (m, 2H, HC=CH of cyclopentene), 7.3 – 8.07 (m, 8H, H_{arom}), 8.10 (s, 1H, CH of pyrazole); MS (EI) m/z (%) = 374 [M^+] (8), 138 (42), 108 (81), 65 (100). $C_{21}H_{18}N_4O_3$ (374.39). Anal. Calcd.: C; 67.37, H; 4.85, N; 14.96. Found: C; 67.20, H; 4.70, N; 14.91%.

4-(8-Methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-5-phenyl-2,4-dihydro-3H-pyrazol-3-one ***5c***

Yellowish green crystals; Yield 41%, Mp. 151 – 153°C; IR (KBr): 3254 (NH), 1673 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 1.28 (m, 2H, CH_2 of cyclopentene), 3.61 (s, 3H, OCH_3), 4.55 (m, 4H, CH of cyclopentene, quinoline), 6.50 (m, 1H, HC=C of cyclopentene), 6.65 (m, 1H, C=CH of cyclopentene), 6.96 – 7.3 (m, 8H, H_{arom}), 7.70 (s, 1H, CH of pyrazole); MS (EI) m/z (%) = 360 [M+1] (13), 313 (34), 149 (43), 57 (100). $C_{22}H_{21}N_3O_2$ (359.42). Anal. Calcd.: C; 73.52, H; 5.89, N; 11.69. Found: C; 73.80, H; 5.76, N; 11.68%.

5-Phenyl-4-(6,6a,7,9a-tetrahydro-5H-cyclopenta[c]-1,6-naphthyridin-6-yl)-2,4-dihydro-3H-pyrazol-3-one ***6a***

Yellow crystals; Yield 43%, Mp. 173 – 174°C; IR (KBr): 3415 (NH), 1615 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$), (δ ppm): 1.25 (m, 2H, CH_2 of cyclopentene), 4.23 (m, 4H, CH of cyclopentene, naphthyridine), 5.67 (m, 2H, HC=CH of cyclopentene), 7.27 – 7.55 (m, 8H, H_{arom}), 7.69 (s, 1H, CH of pyrazole). $C_{20}H_{18}N_4O$ (330.38). Anal. Calcd.: C; 72.71, H; 5.49, N; 16.96. Found: C; 72.60, H; 5.00, N; 16.99%.

5-Phenyl-4-(6,6a,7,9a-tetrahydro-5H-cyclopenta[c]-1,5-naphthyridin-6-yl)-2,4-dihydro-3H-pyrazol-3-one ***6b***

Yellow crystals; Yield 36%, Mp. 142 – 144°C; IR (KBr): 3419 (NH), 1617 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 1.23 (m, 2H, CH_2 of cyclopentene), 4.54 (m, 4H, CH of cyclopentene, naphthyridine), 5.65 (m, 2H, HC=CH of cyclopentene), 7.39 – 7.90 (m, 8H, H_{arom}), 8.16 (s, 1H, CH of pyrazole), 9.76 (s, 1H, NH); MS (EI) m/z (%) = 330 [M^+] (100), 77 (45). $C_{20}H_{18}N_4O$ (330.38). Anal. Calcd.: C; 72.71, H; 5.49, N; 16.96. Found: C; 71.97, H; 5.8, N; 16.97%.

General synthetic procedure for *7a – d*

Microwave irradiation conditions

To a mixture of pyrazolon-4-carbaldehyde **1a, d** (1 mmol), few drops of glacial acetic acid (5-6 drops), silica gel (0.75 g) and a solution of ethylcyanoacetate, malononitrile, respectively (1 mmol), were added; the solvent was evaporated and then irradiated in a microwave oven at 350 W for the appropriate time (Table 1). After irradiation, the product was dissolved in methanol, filtered off, the filtrate concentrated, and the final product was separated in pure form.

Conventional heating method

To a mixture of pyrazolon-4-carbaldehyde **1a, d** (1 mmol) and a solution of ethylcyanoacetate, malononitrile, respectively (1 mmol), in ethanol (15 mL) and few drops of glacial acetic acid (5 – 6 drops) were added. The reaction mixture was refluxed for the appropriate time (Table 1). After cooling, the product was filtered off and recrystallized from the appropriate solvent.

Ethyl-2-cyano-3-(5-oxo-3-phenyl-4,5-dihydro-1H-pyrazol-4-yl)acrylate ***7a***

Yellow crystals (ethanol); IR (KBr): 3238 (NH), 2209 (CN), 1759 (C=O), 1681 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 1.29 (t, 3H, J = 7.05 Hz, CH_3-CH_2-), 4.26 (q, 2H, J_1 = 7.2 Hz J_2 = 14.1 Hz, CH_3-CH_2-), 7.57 – 7.82 (m, 5H, Ph), 7.85 (s, 1H, CH of pyrazole), 8.73 (s, 1H, HC=C), 14.1 (s, 1H, NH); MS (EI) m/z (%) = 284 [M^+] (100), 239 (87), 77 (31). $C_{15}H_{13}N_3O_3$ (283.28). Anal. Calcd.: C; 63.60, H; 4.63, N; 14.83. Found: C; 63.88, H; 4.45, N; 14.53%.

[(5-Oxo-3-phenyl-4,5-dihydro-1H-pyrazol-4-yl)methylene]malononitrile ***7b***

Yellow crystals (ethanol); IR (KBr): 3181 (NH), 2219 (CN), 1714 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 7.28 – 7.60 (m, 5H, Ph), 7.67 (s, 1H, CH of pyrazole), 8.61 (s, 1H, HC=C), 13.1 (s, 1H, NH); MS (EI) m/z (%) = 237 [M+1] (20), 186 (71), 77 (100). $C_{13}H_8N_4O$ (236.22). Anal. Calcd.: C; 66.1, H; 3.41, N; 23.72. Found: C; 66.12, H; 4.26, N; 23.42%.

Ethyl-2-cyano-3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)acrylate ***7c***

Yellow crystals (ethanol); IR (KBr): 2213 (CN), 1708 (C=O), 1679 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 1.27 (t, 3H, J = 7.05 Hz, CH_3-CH_2-), 2.51 (s, 3H, CH_3), 3.39 (s, 3H, -NCH_3), 4.24 (q, 2H, J_1 = 6.9 Hz, J_2 = 14.1 Hz, CH_3-CH_2-), 7.35 – 7.56 (m, 5H, Ph), 7.91 (s, 1H, HC=C); MS (EI) m/z (%) = 311 [M^+] (89), 239 (38), 56 (100). $C_{17}H_{17}N_3O_3$ (311.33). Anal. Calcd.: C; 65.58, H; 5.5, N; 13.5. Found: C; 65.28, H; 5.91, N; 13.37%.

[(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)methylene]malononitrile ***7d***

Yellow crystals (ethanol); IR (KBr): 2213 (CN), 1684 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 2.51 (s, 3H, CH_3), 3.39 (s, 3H, -NCH_3), 7.35 – 7.59 (m, 5H, Ph), 7.81 (s, 1H, HC=C); MS (EI) m/z (%) = 264 [M^+] (100), 172 (71), 56 (52). $C_{15}H_{12}N_4O$ (264.28). Anal. Calcd.: C; 68.17, H; 4.58, N; 21.20. Found: C; 68.25, H; 4.66, N; 21.53%.

General synthetic procedure for *8a, b* and *9a, b*

Hydrazine hydrate (7 mL) in absolute ethanol (15 mL) was added to ylidene derivatives **7a – d** (1 mmol). The reaction mixture was refluxed for the appropriate time, cooled and poured into ice-cold water. The separated products were filtered off, dried, and purified by column chromatography using the appropriate eluent.

*5-Amino-4-[(3-oxo-5-phenyl-2,4-dihydro-3H-pyrazol-4-yl)methylene]-2,4-dihydro-3H-pyrazol-3-one **8a***

White crystals (chloroform-ethylacetate 7 : 3); Yield 49%, Mp. 346 – 348°C; IR (KBr): 3436 (NH_2), 3314 (NH), 1732 (C=O), 1654 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 5.9 (s, 2H, NH_2), 7.18 – 7.29 (m, 5H, Ph), 7.32 (s, 1H, CH of pyrazole), 8.29 (s, 1H, HC=C), 11.4 (bs, 1H, NH); MS (EI) m/z (%) = 269 [M^+] (6), 160 (65), 115 (100). $C_{13}H_{11}N_5O_2$ (269.26). Anal. Calcd.: C; 57.99, H; 4.10, N; 26.01. Found: C; 58.15, H; 4.3, N; 26.12%.

*4-[(3-Amino-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene)methyl]-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one **8b***

Yellow crystals (chloroform-ethylacetate 7 : 3); Yield 58%, Mp. 240 – 242°C; IR (KBr): 3429 (NH_2), 3224 (NH), 1773 (C=O), 1695 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$), (δ ppm): 2.73 (s, 3H, CH_3), 3.27 (s, 3H, NCH_3), 5.89 (s, 2H, NH_2), 7.27 – 7.5 (m, 5H, Ph), 8.62 (s, 1H, HC=C); MS (EI) m/z (%) = 297 [M^+] (5), 83 (42), 55 (100). $C_{15}H_{15}N_5O_2$ (297.312). Anal. Calcd.: C; 60.60, H; 5.09, N; 23.56. Found: C; 60.50, H; 4.00, N; 23.49%.

*4-[(3,5-Diamino-1,5-dihydro-4H-pyrazol-4-ylidene)-methyl]-5-phenyl-2,4-dihydro-3H-pyrazol-3-one **9a***

Yellow crystals (chloroform-ethylacetate 9 : 1); Yield 37%, Mp. 334 – 336°C; IR (KBr): 3435 (NH_2), 3254 (NH), 1649 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 6.36 (s, 2H, NH_2), 6.75 (s, 2H, NH_2), 7.18 – 7.34 (m, 5H, Ph), 7.46 (s, 1H, CH of pyrazole), 8.16 (s, 1H, HC=C) 11.45 (bs, 1H, NH); MS (EI) m/z (%) = 271 [M^+] (10), 149 (40), 57 (100). $C_{13}H_{14}N_6O$ (270.290). Anal. Calcd.: C; 57.77, H; 5.22, N; 31.09. Found: C; 57.61, H; 4.98, N; 30.82%.

*4-[(3,5-Diamino-1,5-dihydro-4H-pyrazol-4-ylidene)methyl]-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one **9b***

Brownish yellow crystals (chloroform-ethylacetate 8 : 2), Yield 49%, Mp. 247 – 248°C; IR (KBr): 3413 (NH_2), 3213 (NH), 1728 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), (δ ppm): 2.67 (s, 3H, CH_3), 3.4 (s, 3H, NCH_3), 5.82 (s, 2H, NH_2), 7.34 – 7.57 (m, 5H, Ph), 8.35 (s, 1H, HC=C); MS (EI) m/z (%) = 298 [M^+] (19), 217 (44), 149 (22), 56 (100). $C_{15}H_{18}N_6O$ (298.343). Anal. Calcd.: C; 60.39, H; 6.08, N; 28.17. Found: C; 60.20, H; 5.90, N; 27.95%.

Biological evaluation

Experimental animals and cell line

Female Swiss Albino mice eight weeks of age and of 24 ± 2 g weight were raised at the experimental animal house of the Genetic Engineering and Biotechnology Institute, Menoufiya University. The animals were maintained in an environment controlled for temperature, humidity, and light. They were fed a commercial mouse chow and tap water. Ehrlich ascites carcinoma (EAC) was initially supplied by the National Cancer Institute, Cairo University, and maintained in the peritoneal of female Swiss Albino mice through serial intraperitoneal (i.p.) injection of 2×10^6 cells/mL saline at seven-days intervals.

Tested compounds

All compounds and thalidomide were freshly dissolved in DMSO vehicle, which is composed of 70% DMSO and 30% physiological saline to yield a final concentration 50 mM. All solutions were kept at 4°C in the dark.

In vitro cytotoxicity assay

EAC cells were collected from the mice peritoneal under complete sterile conditions. Cell viability was checked by using trypan blue staining [31]. Cells were washed twice in RPMI media and resuspended in complete RPMI-1640 media (10% FBS + 5% streptomycin/penicillin). An amount of 0.1 mL of cells (2×10^6/mL) was titrated into 96-wells plates. Tested compounds were added to the EAC cells in triplet with final concentration of 1mM. Then, plate was incubated at 37°C for 24 h at 5% CO_2 incubator. The viability of EAC cells was checked to evaluate the cytotoxic activity of compounds [32].

In-vivo antitumor activity of tested compounds

A model of solid Ehrlich carcinoma was used for *in-vivo* experiments, where 2×10^5 EAC cells were implanted subcutaneously (s.c.) into the right thigh of the lower limb of mice [33]. A palpable solid tumor mass developed within 10 – 12 days.

Mice were divided into: Group I (n = 5): mice were s.c. injected with 2×10^5 EAC cells; Group II (n = 5): mice were orally administrated with DMSO vehicle for ten days started at 24 h after the implantation of EAC cells and served as the DMSO control group; Group III (n = 5): mice were orally administrated with 25 mM of thalidomide by gastric intubations for ten days started at 24 h after the implantation of EAC cells; Groups IV to XVI [16] (n = 5 for each group): mice were orally administrated with 10 mM of tested compounds by gastric incubations for ten days started at 24 h after the implantation of EAC cells.

The solid tumor volume (TV) was measured at the end of experiment after 15 days from EAC implantation [34]. The following formula was used to calculate the tumor volume:

$$TV(mm^3) = 4\pi(A/2)^2 \times (B/2)$$

Where: A is minor tumor axis, B is major tumor axis, p = 22/7

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