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Convenient Synthesis and Biological Activity of 4-Aminomethylene 1-phenylpyrazolidine-3,5-diones

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Abstract. Reaction of (*Z*)-4-((dimethylamino)methylene)-1-phenylpyrazolidine-3,5-dione (**1**) with different nucleophiles is described. Treatment of enaminone **1** with phenylhydrazine led to 3-oxo-*N'*,2-diphenyl-2,3-dihydro-1*H*-pyrazole-4-carbohydrazide **7**. New enaminone derivatives **2–6** and **12–14** were conveniently obtained in high yields via nucleophilic substitution of the dimethylamino group in enaminone **1** when reacted with *o*-aminophenol, *o*-aminothiophenol, ethanolamine, cysteamine hydrochloride, piperidine, morpholine, 2-aminopyridine and glycine. Reaction of enaminone **1** with diaza-nucleophiles, such as hydrazine hydrate, ethylenediamine and *o*-phenylenediamine, afforded the corresponding *bis*-enaminones **9–11**. Anti-inflammatory and antimicrobial activities of some new products were evaluated. Compounds **1, 2, 4, 7, 12a**, and **12b** showed high anti-inflammatory activity compared with indomethacin as the reference, while the highest antimicrobial effect was observed in the case of compound **3**.
Key words: pyrazolidine-3,5-diones, enaminones, nucleophiles, anti-inflammatory activity, antimicrobial activity.

Resumen. Se describe la reacción de (*Z*)- 1-fenil-4-((dimetilamino) metilen)pirazolidin-3,5-diona (**1**) con diferentes nucleófilos. El tratamiento de la enaminona **1** con fenilhidrazina condujo a la *N'*,2-difenil-2,3-dihidro-3-oxo-1*H*-pirazol-4-carbohidrazida **7**. Los nuevos derivados enaminónicos **2–6** y **12–14** se obtuvieron convenientemente en elevados rendimientos vía sustitución nucleofílica del grupo dimetilamino en la enaminona **1** cuando reaccionó con *o*-aminofenol, *o*-aminotiofenol, etanolamina, clorhidrato de cisteamina, piperidina, morfolina, 2-aminopiridina y glicina. La reacción de **1** con diaza-nucleófilos, tales como hidrato de hidrazina, etilendiamina y *o*-fenildiamina, proporcionó las *bis*-enaminonas correspondientes **9-11**. Se evaluó la actividad anti-inflamatoria y antimicrobiana de algunos productos nuevos. Los compuestos **1**, **2**, **4**, **7**, **12a** y **12b** mostraron elevada actividad anti-inflamatoria en comparación a la indometacina como compuesto de referencia, mientras que se observó la más elevada actividad antimicrobiana para el compuesto **3**.
Palabras clave: pirazolidin-3,5-dionas, enaminonas, nucleófilos, actividad anti-inflamatoria, actividad antimicrobiana.

Introduction

The synthesis of β-enaminones has received much attention in recent times due to their chemical and biological activities. It is known that, β-enaminone derivatives are push-pull electron systems which represent versatile synthetic intermediates. These category of compounds showed significant reactivity in a wide variety of nucleophilic and electrophilic substitution [1,2], photochemical [3], reduction and oxidation reactions [4,5]. Also, they have been employed as synthons of a wide variety of biologically and medicinally active compounds [6,7], as well as of pharmaceutical compounds having anti-epileptic [8], antibacterial [9,10], anti-inflammatory [10], anti-convulsant [11], antitumor [12] and anti-parasitic activities [13]. In addition to this wide spectrum of activity, enaminones revealed good stability under simulated physiological pH conditions and low toxicity [14]. On the other hand, *N*-arylpyrazoles possess significant medicinal applications, such as antitumor [15], antiviral [16] and anti-inflammatory agents [17]. Building on above chemical and biological activity of enaminones and *N*-arylpyrazoles, the present work describes new derivatives in which both enaminone moiety and *N*-arylpyrazole nucleus are gathered in one-molecular frame. Thus, the biological activity of these new derivatives were tested in the hope of obtaining novel anti-inflammatory and/or antimicrobial agents.

Results and Discussion

Chemistry

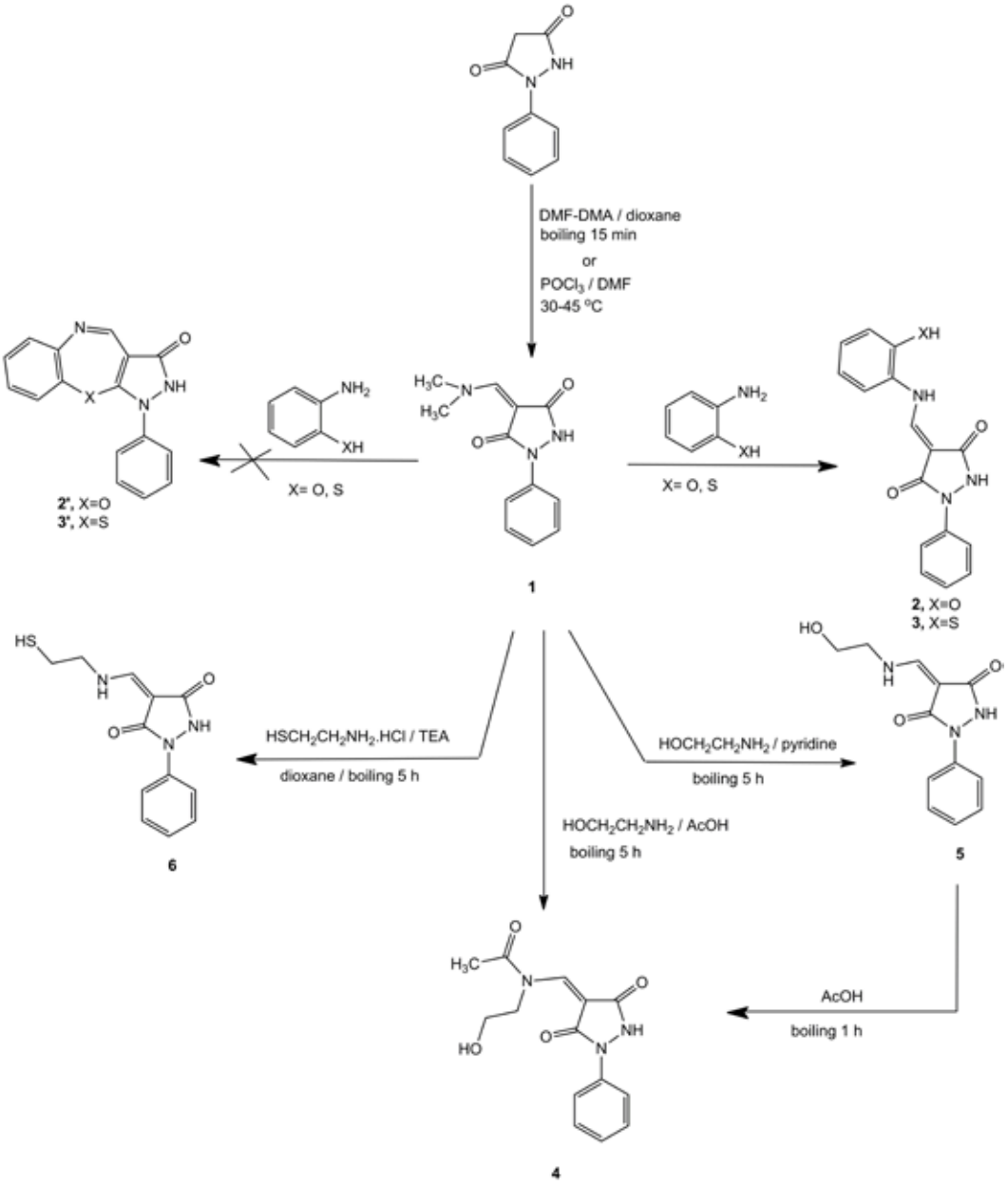
As depicted in Scheme 1, the starting compound; 4-((dimethylamino)methylene)-1-phenylpyrazolidine-3,5-dione (**1**) was obtained via two convenient synthetic routes. Condensation of 1-phenylpyrazolidine-3,5-dione with dimethylformamide-dimethyl acetal (DMF-DMA) in boiling dioxane gave enaminone 1 in 90% yield. When 1-phenylpyrazolidine-3,5-dione was subjected to Vilsmeier-Haack reaction using phosphorus oxychloride and dimethylformamide the same enaminone **1** was afforded in 75% yield. Even when the last route leads to a relatively lower yield, it was economically favored because DMF-DMA is expensive compared to $POCl_3$ and DMF. ^{1}H NMR spectrum of **1** revealed a singlet signal at δ 9.55 assignable to N–H proton, a singlet signal at δ 7.09 due to the olefinic proton, and two singlet signals due to the dimethylamino group at δ 3.35 and 3.72. Mass spectrum revealed the molecular ion (M^+) at m/z 231 as the base peak. IR spectrum showed the existence

of two strong stretching vibrations at ν 1645 and 1695 cm^{-1} due to two carbonyl functions of the pyrazoledione nucleus.

Enaminone **1** was treated with some 1,4-binucleophiles such as *o*-aminophenol and *o*-aminothiophenol. Thus, treatment with *o*-aminophenol, in boiling glacial acetic acid, gave (4*E*)-4-(((2-hydroxyphenyl)amino)methylidene)-1-phenylpyrazolidine-3,5-dione (**2**). Similarly, when *o*-aminothiophenol was reacted with **1**, in boiling dioxane, led to (4*E*)-4-(((2-mercaptophenyl)amino)methylene)-1-phenylpyrazolidine-3,5-dione (**3**). Neither the expected cyclized products pyrazolobenzoxazepinone 2' nor pyrazolobenzothiazepinone 3' were obtained at any ratio (Scheme 1).

The structure of compounds **2** and **3** was established on the basis of their spectral and analytical data. In addition, X-ray single crystal technique was employed to explore the geometry of compound **2** (Fig. 1)[19]. The products were formed via initial addition of the amino group of *o*-aminophenol or *o*-aminothiophenol to the enaminone double bond, followed by elimination of dimethylamine. As shown in Fig. 1, compound **2** has the (*E*)-geometry in which intramolecular cyclocondensation is not allowed. This accounts for the obtained open-chain compounds **2** and **3** but not the cyclized products.

Reaction of enaminone **1** with some aliphatic *bis*-nucleophiles was also studied. Thus, by heating **1** with ethanolamine in



Scheme 1. Synthesis of enaminone 1 and its reactions with *o*-aminophenol, *o*-aminothiophenol, ethanolamine and cysteamine hydrochloride.

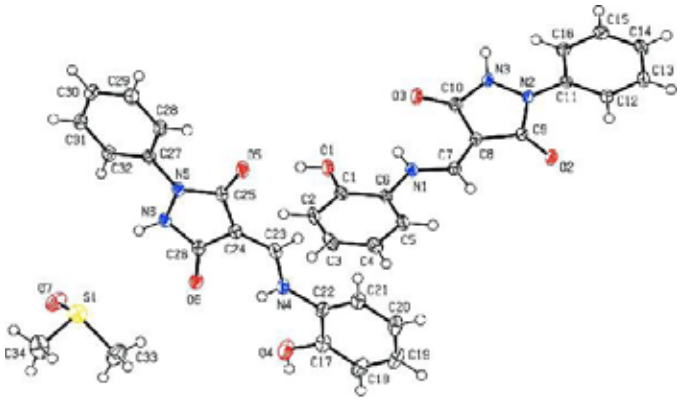


Fig. 1. X-ray molecular structure of compound **2**.

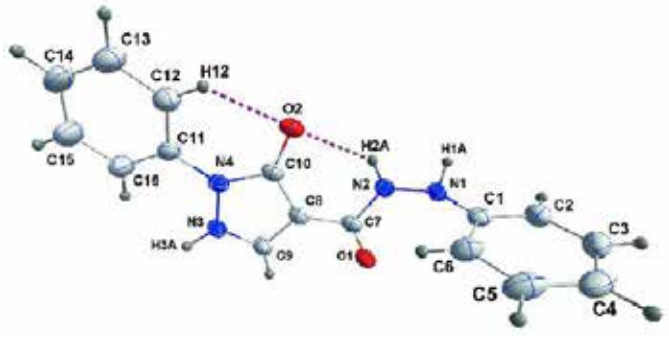
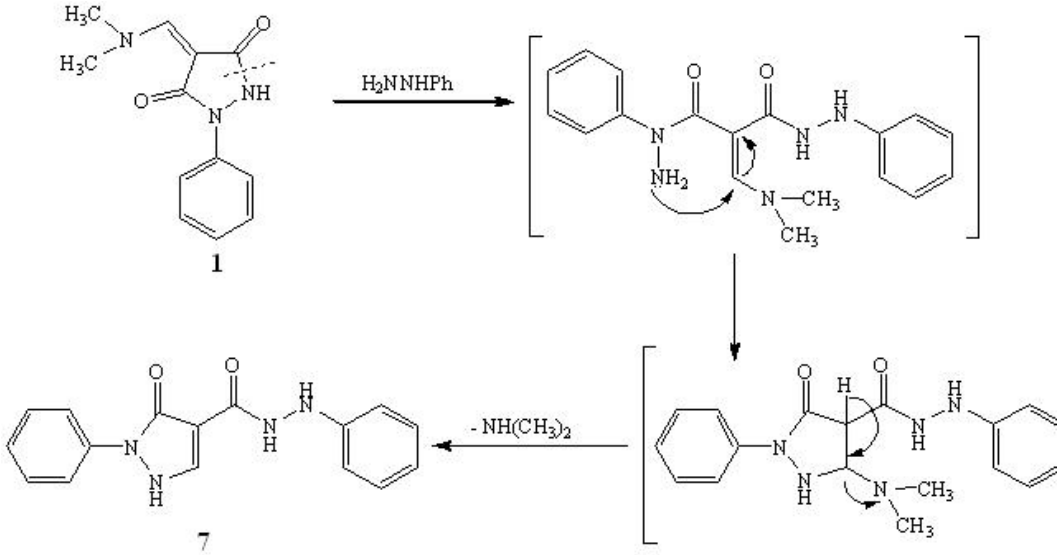


Fig. 2. X-ray molecular structure of compound **7**.

pyridine afforded 4-(((2-hydroxyethyl)amino)methylene)-1-phenylpyrazolidine-3,5-dione (**5**) in 79% yield. Interestingly, during attempts to recrystallize compound **5** from glacial acetic acid, *N*-acetylation took place leading to *N*-[(3,5-dioxo-1-phenylpyrazolidin-4-ylidene)methyl]-*N*-(2-hydroxyethyl)-acetamide (**4**) (Scheme 1). So that the same reaction of enaminone **1** with ethanolamine have been carried out in boiling glacial acetic acid to afford the expected acetamide **4**, in 88% yield (Scheme 1). Obviously, this product was formed via initial *N*-nucleophilic replacement of dimethylamine group, followed by *N*-acetylation. Similarly, when enaminone **1** was reacted with cysteamine hydrochloride in dioxane under reflux in presence of triethylamine, the corresponding 4-(((2-mercaptoethyl) amino)methylene)-1-phenylpyrazolidine-3,5-dione (**6**) was afforded (Scheme 1).

In addition, when enaminone **1** was subjected to react with phenylhydrazine in boiling dioxane, afforded a mixture of 3-oxo-*N'*,2-diphenyl-2,3-dihydro-1*H*-pyrazole-4-carbohydrazide (**7**) in 84% and 1-phenyl-4-((2-phenylhydrazino) methylene) pyrazolidine-3,5-dione (**8**) in 12% (Schemes 2-3). The structure of these products was established on the basis of their spectral and analytical data. X-ray single crystal technique was employed to confirm the structure of compound **7** (Fig. 2)[20]. The suggested reaction mechanism for compound **7** was assumed to be as described in Scheme 2.

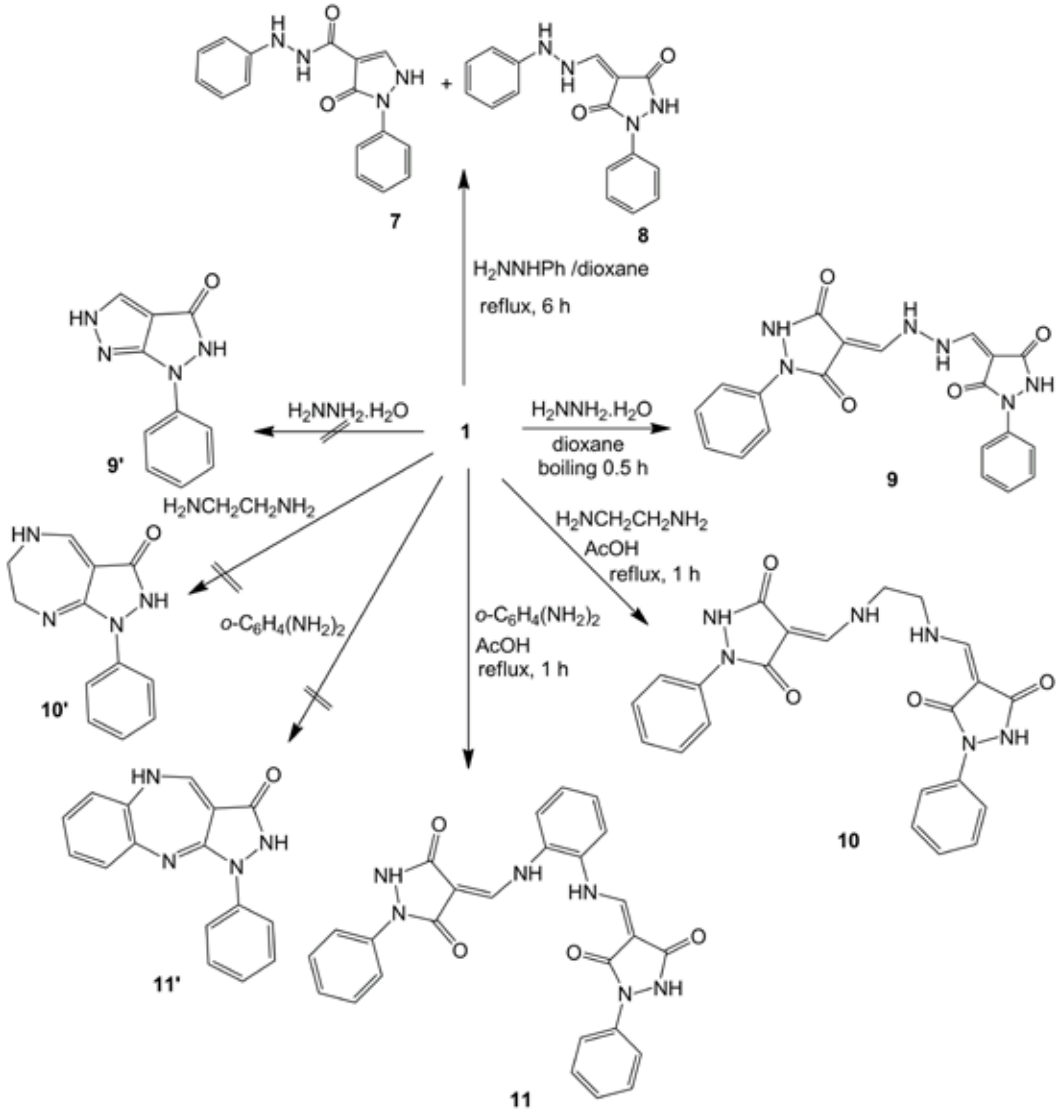
Enaminone **1** was then allowed to react with diamines, such as hydrazine hydrate, ethylenediamine and *o*-phenylenediamine with the hope to obtain pyrazoles with an additional five or seven-membered heterocycles annulated at the [*c*] or [*e*] face or new pyrazoles carbohydrazides as like in the case of compound **7**. Remarkably, the reaction of enaminone **1** with the aforementioned diamines gave neither the open chain enaminones nor cyclized products. Interpretations of analytical and spectral data of the products confirmed that *bis*-enaminones were formed (Scheme 3). Reaction with hydrazine hydrate in boiling dioxane afforded *N,N'*-disubstituted hydrazine derivative **9**, in 89% yield. ^{1}H NMR spectrum (DMSO-d_6) exhibited chemical shifts at δ 9.31 and 7.97 which were exchangeable with deuterium on addition of deuterium oxide and were assigned to N–H



Scheme 2. Reaction of compound **1** with phenylhydrazine to yield compound **7**.

protons. Additionally, a singlet signal at δ 6.7 for two olefinic protons was observed. Elemental microanalysis of product **9**, for C, H, and N elements (within ± 0.4%) supported the proposed molecular formula $C_{20}H_{16}N_6O_4$ (MW 404.37).

The structure of the *N,N'*-disubstituted ethylenediamine **10** was proven on basis of its ^{1}H NMR and ^{13}C NMR, in addition to elemental microanalysis. NMR spectra showed the presence of (N–CH_2–CH_2–N) grouping. A set of singlet signal appeared at δ 3.7 due to four protons of two (N–CH_2), while ^{13}C NMR spectrum showed signals of two aliphatic sp^3-carbons at δ 50 and two olefinic sp^2-carbons at δ 90, in addition to aromatic sp^2-carbons appeared at δ 118–138. ^{1}H NMR spectrum of *N,N'*-disubstituted o-phenylenediamine **11** revealed integration of aromatic protons, in the range of δ 7.1–8.1, corresponding to 14 protons. Mass spectrum as well as C, H, and N microanalysis (within ± 0.4%) strongly supported the proposed molecular formula $C_{26}H_{20}N_6O_4$ (MW 480.47). Quantum mechanics calculations were performed to confirm the structure of the obtained products and validate the spectral analysis data. For this purpose, DFT calculations were carried out for enaminone **1**, diamines and proposed products using hybrid functional B3LYP with polarized basis set 6-311G (d,p) as implemented in Gaussian03 program package [21]. This method is considered as most suitable for organic systems with reasonable computational time [22]. Stability of compounds **9**, **9'**, **10**, **10'**, **11**, and **11'** were evaluated from energetic point of view, more specifically the reaction energies were calculated using the formula (ΔE = EP – ER), where EP is the sum of products energy and ER is the sum of reactants energy. Table 1 lists the calculated reaction energies for all products. According to these values, it is clear that (*bis*-products) **9-11** are more stable than cyclized products **9'-11'**.



Scheme 3. Reactions of enaminone **1** with phenylhydrazine, hydrazine hydrate, ethylenediamine and *o*-phenylenediamine.

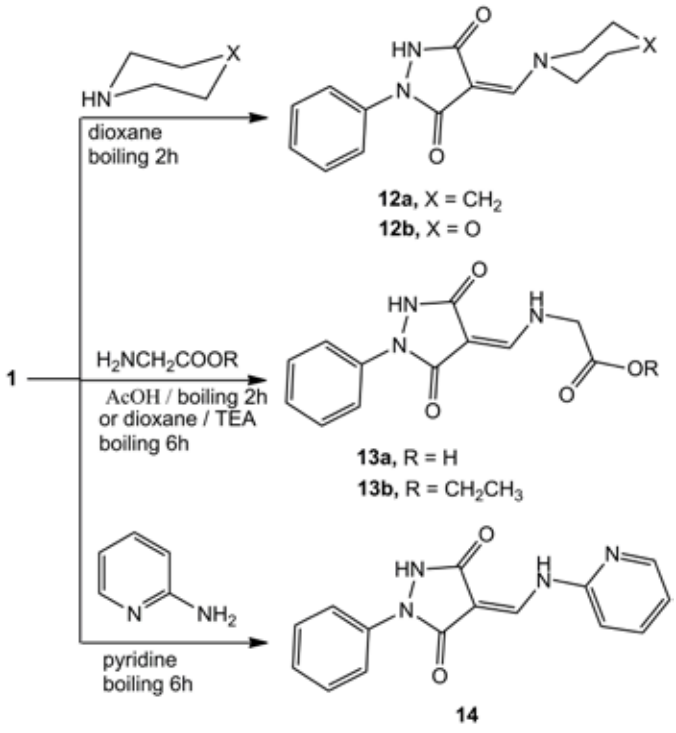
Table 1. The calculated formation energies for 9, 9', 10, 10', 11 and 11' according to the reactions in Scheme 3.

Reaction Energy	Δ E (Kcal/mol)
Compound **9'**	0.92
Compound **9**	-7.34
Compound **10'**	9.33
Compound **10**	-14.62
Compound **11'**	21.07
Compound **11**	-0.92

Reactions of enaminone **1** with some selected primary and secondary amines were carried out to obtain new enaminones of biological interest. Thus, reacting **1** with piperidine and/or morpholine, in boiling dioxane, led to 4-[(1-piperidyl)/(4-morpholinyl)]methylenepyrazolidinediones **12a** and **12b**, in 95-98% yields (Scheme 4). IR of piperidinyl derivative **12a** showed the presence of absorption vibrations for two different (C=O) at ν 1695 and 1648 cm^{-1}. ^1H NMR spectrum exhibited characteristic set of chemical shifts due to *N*-substituted piperidine moiety. This spectrum revealed a multiplet signal at δ ~1.65 due to six protons (CH_2–CH_2–CH_2) and two triplets at δ 3.71 and 4.44 due to four protons (CH_2–N–CH_2). Nevertheless, ^{13}C NMR spectrum of piperidinyl derivative **12a** gave a good evidence for its structure in which the chart showed chemical shift signals at δ 57, 52, 27, 25, and 23 due to sp^3-carbons, due to two (NCH_2) and three (CH_2) methylenes, in addition to a characteristic signal at δ 90 corresponding to sp^2-carbon of enamine. Mass spectrum revealed the molecular ion (M+) as the base peak at *m/z* 271 along with (M^++1) ion *m/z* 272 (relative intensity 19%), which supported the proposed molecular formula. Similarly, the structure of morpholinyl derivative **12b** was evidenced utilizing IR, ^1H NMR, ^{13}C NMR, and mass spectra.

When enaminone **1** was reacted with glycine, in boiling acetic acid, white crystalline product of *N*-substituted glycine derivative **13a** was obtained in 98% yield (Scheme 4). IR spectrum showed presence of both O–H and N–H functional groups appeared as medium broad bands at ν 3433, 3257, and 3150 cm^{-1}, in addition to three strong stretching vibrations at ν 1740, 1690, 1638 cm^{-1} due to (C=O) of the carboxylic acid, and pyrazolidinedione, respectively. ^1H NMR and ^{13}C NMR spectral data of compound **13a** are coincident with the suggested structure. When enaminone **1** was reacted with ethyl glycinate hyrdrochloride, in boiling dioxane in presence of triethyl amine, a yellowish white crystalline product of ethyl (((Z)-(3,5-dioxo-1-phenylpyrazolidin-4-ylidene)methyl)amino)acetate **13b** was obtained in 90% yield (Scheme 4). IR spectra of compounds **13b** showed new absorption bands corresponding to the NH and (C=O)-ester groups at 3296 and 1745 cm^{-1}, respectively. Its ^1H NMR spectrum showed new signals corresponding to the NH glycinate group at 9.32 ppm, $2CH_2$ at 4.32, 4.19-4.14 ppm and CH_3 at 1.22 ppm, respectively. X-ray single crystal technique confirmed the structure of compound **13b** (Fig. 3)[23].

Condensation of enaminone **1** with 2-aminopyridine was attempted in different solvent media and reaction conditions.



Scheme 4. Reaction of enaminone **1** with piperidine, morpholine, glycine, ethyl glycinate hydrochloride and 2-aminopyridine.

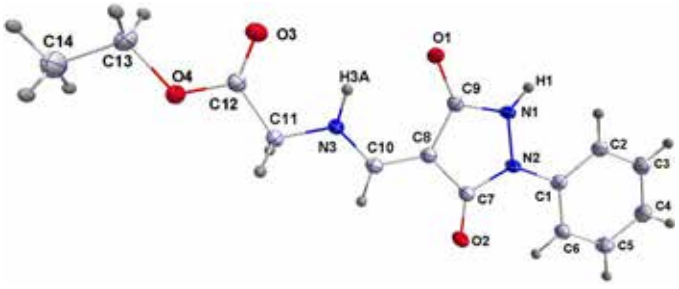


Fig. 3. X-ray molecular structure of compound **13b.**

Thus, when the reaction was carried out in acetic acid or ethanol or DMF low yields were obtained. Interestingly, a high yield (91%) of 4-(2-pyridinylaminomethylene)pyrazolidinedione **14** was achieved when the reaction was carried out in boiling pyridine. The structure of product **14** was evidenced utilizing spectral and analytical data.

Biological Results

Antimicrobial Activity

The newly synthesized products **1, 2, 3, 4, 6, 7, 12a, 12b, 13a** and **13b** were tested for their antimicrobial activities using six bacterial species, namely *Staphylococcus aureus, Bacillus*

Table 2. Antimicrobial activity of compounds **1, 2, 3, 7** and **13a.**

Tested Microorganism	Inhibition zone diameter					
	1	**2**	**3**	**7**	**13a**	**Stand.***
Staphylococcus aureus (+ve) AUMC No. B-54	16	0	12	0	10	24
Bacillus cereus (+ve) AUMC No. B-52	16	11	12	12	0	30
Escherichia coli (-ve) AUMC No. B-53	22	10	11	11	11	25
Micrococcus luteus (+ve) AUMC No. B-112	0	0	13	12	11	23
Pseudomonas aeruginosa (-ve) AUMC No. B-53	0	0	15	12	0	15
Serratia marcescens (-ve) AUMC No. B-55	15	0	12	8	0	34
Candida albicans AUMC No. 1299	0	0	30	20	0	24
Geotrichum candidum AUMC No. 226	0	0	26	20	0	24
Trichophyton rubrum AUMC No. 1804	0	0	42	28	0	36
Fusarium oxyspoum AUMC No. 5119	0	0	40	26	0	25
Scopulariopsis brevicaulis AUMC No. 361	0	0	30	20	0	28
Aspergillus flavus AUMC No. 1276	0	0	15	20 p.i	0	26

***** Chloramphenicol was used as a standard antibacterial agent and clotrimazole was used as a standard antifungal agent.
AUMC:Assuit University Mycological Center
p.i: Partial Inhibition

cereus, Escherichia coli, Micrococcus luteus, Pseudomonas aeruginosa and *Serratia marcescens*, in addition to six species of fungi, namely *Candida albicans, Geotrichum candidum, Trichophyton rubrum, Fusarium oxyspoum, Scopulariopsis brevicaulis* and *Aspergillus flavus*. The organisms were tested against the activity of solutions of 50 mg/mL of each compound and using inhibition zone diameter (IZD) in mm as criterion for the antimicrobial activity. The bactericide chloramphenicol and the fungicide clotrimazole were used as the references to evaluate the potency of the tested compounds under the same conditions. The results, depicted in Table 2, revealed that compounds **3** and **7** exhibited high degree of inhibition against *Pseudomonas aeruginosa, Candida albicans, Geotrichum candidum, Trichophyton rubrum, Fusarium oxyspoum, Scopulariopsis brevicaulis* and *Aspergillus flavusin*, more than the fungicide reference. Compound **1** had high inhibition effect against *Escherichia coli* and *Staphylococcus aureus*. Compounds **1**, **2**, **3**, and **7** also exhibited moderate inhibition effect against *Bacillus cereus*. Compounds **4**, **6**, **12a-b**, and **13b** were reflecting no inhibition of growth against all the tested microorganisms.

Anti-inflammatory Activity

The anti-inflammatory effects of compounds **1**, **2**, **3**, **4**, **6**, **7**, **12a**, **12b**, and **13a** were evaluated by the Kataoka *et al* method [24,25]. Male rats weighing 200-250 g were purchased from animal house of Assuit University. All animals were maintained with a balanced diet and water *ad libitum*, rats were divided into 11 groups, each of three animals. One group left as a control group, 9 groups received the tested compounds and one group received the reference standard. Paw oedema was induced by injecting single dose of Carrageenan that was dissolved in

Table 3. The anti-inflmmatory activity of products **1, 2, 3, 4, 6, 7, 12a, 12b**, **13a** (50 mg/mL) and indomethacin (50 mg/mL).

(I) Treatment Indomethacin	(J) Treatment	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
	treatment **1**	-.03333	.02789	.246	-.0915	.0248
	treatment **2**	-.03333	.02789	.246	-.0915	.0248
	treatment **3**	-.10000*	.02789	.002	-.1582	-.0418
	treatment **4**	.00000	.02789	1.000	-.0582	.0582
	treatment **6**	-.11667*	.02789	.001	-.1748	-.0585
	treatment **7**	.00000	.02789	1.000	-.0582	.0582
	treatment **12a**	.00000	.02789	1.000	-.0582	.0582
	treatment **12b**	-.01667	.02789	.557	-.0748	.0415
	treatment **13a**	-.20000*	.02789	.001	-.2582	-.1418

***** The mean difference is significant at the 0.05 level.

physiological saline solution (500 µl of 1% v/v) in the right paw. The tested compounds (60 mg/kg body weight) were administered. The thickness of the paw was measured after administration of the compounds at 0.5, 1, 2, 3, 4 and 5 h by using micrometer. The effect of the tested compounds and indomethacin, as the reference, was measured before and 0.5, 1, 2, 3, 4 and 5 h after carrageenan injection. Edema inhibition was calculated as a regard to saline control group, as depicted in Table 3 and Fig. 4. The results indicated that:

i. Compounds **1, 2, 4, 7, 12a,** and **12b** showed high anti-inflammatory activity compared with indomethacin.
ii. Compounds **3, 6** and **13a** showed moderate anti-inflammatory activity compared with indomethacin.

Statistical analysis

The results were analyzed by one way analysis of variance (ANOVA) followed by Newman-Keuls Multiple Comparison Test as a post-Test. These analyses were carried out using computer prism program for windows, version 3.0 (Graph pad software, Inc, San Diago CA. USA). The significance difference between groups was accepted at $p < 0.05$, 0.001*, and the data were expressed as mean ± Standard error (SE) after 5 hour as shown in Table 3

Conclusion

It was found that 4-[(dimethylamino)methylene]-1-phenylpyrazolidine-3,5-dione is good precursor for the synthesis of biologically important heterocyclic enaminone derivatives. This compound shows significant chemical reactivity towards different nucleophilic reagents, in which dimethylamino group acts as good leaving group even against low-reactive nucleophiles such as glycine and 2-aminopyridine. Many new enaminone derived from this compound exhibited moderate to high anti-inflammatory and antimicrobial activities.

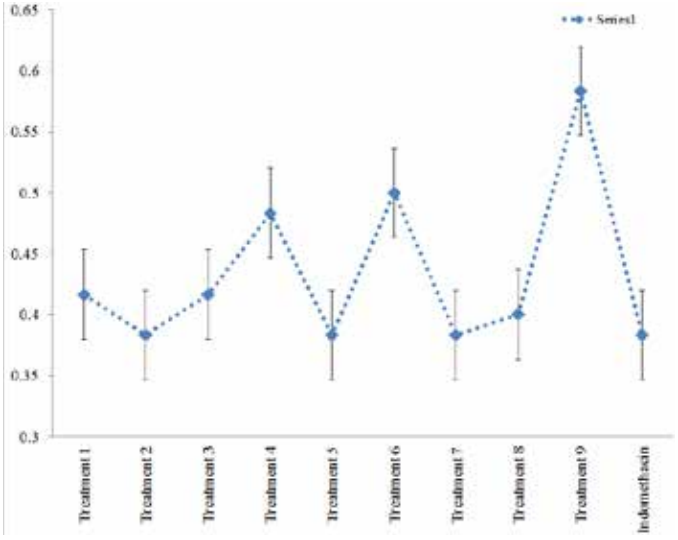


Fig. 4. Anti-inflammatory of the tested compounds and indomethacin.

Experimental Section

General

All melting points were determined on a Melt-Temp-II apparatus and are uncorrected. IR spectra were taken on a Nicolet 710 Fourier Transform (FT) instrument in potassium bromide discs. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker Bio spin AG-400 spectrometer, using DMSO-d_6 as solvent and TMS as an internal reference. Mass spectra were measured on a Shimadzu Qp-2010 plus spectrometer (70 eV). Elemental analyses were carried out at the Microanalytical Center of Cairo University. X-ray was measured on Bruker APEX2; cell refinement: Bruker SAINT; program(s) used to solve structure: SHELXS97; program(s) used to refine structure: SHELXL97; molecular graphics: XSEED. Anti-inflammatory and Antimicrobial activities were evaluated at Faculty of Medicine and Mycological Center, Assuit University, respectively.

4-[(Dimethylamino)methylene]-1-phenylpyrazolidine-3,5-dione (1). Method a. A mixture of 1-phenylpyrazolidine-3,5-dione (1.76 g, 0.01 mol) and dimethylformamide dimethylacetal (DMF-DMA) (1.19 g, 0.01 mol) in anhydrous dioxane (10 mL) was refluxed for 15 min., the solid product was precipitated on hot, collected by filtration and recrystallized from dimethyl sulfoxide to give white crystals, yield 2.08 g, 90%. **Method b.** To phosphorous oxychloride (10 mL, 0.1 mol), in a conical flask with magnetic stirrer, dry dimethylformamide (35 mL) was added drop-wise with stirring at temperature did not exceed 30–35 °C for 30 min. Then a solution of 1-phenylpyrazolidine-3,5-dione (8.8 g, 0.05 mol), in dimethylformamide (15 mL), was drop-wise added with continuous stirring at temperature did not exceed 45 °C. The reaction mixture was left overnight, poured onto crushed ice. The solid product was collected by filtration and recrystallized from dimethylsulfoxide to give white crystals, yield 8.66 g, 75%, m. p. 260–262 °C (248 – 250 °C).[18] IR (KBr) ν: 3118 (N–H), 1695 (C=O), 1645 (C=O) cm^{-1}. ^{1}HNMR (DMSO-d_6) δ: 9.55 (s, 1H, N–H disappeared on addition of D_2O), 7.63–7.37 (m, 5H, H_{arom}), 7.09 (s, 1H, N–CH_{olefin}), 3.72 (s, 3H, N–CH_3), 3.35 (s, 3H, N–CH_3).^{13}CNMR (DMSO-d_6) δ: 169, 167 (CONPh), 166 (CONH), 163, 159.29 (=CH-N), 138 (C), 130 (CH), 123 (CH), 118 (CH), 117 (CH), 92 (C-4), 47 (N-CH_3), 43 (N-CH_3). MS, *m/z* (%) 232 (M^++1, 16), 231 (M^+, 100), 139 (26), 105 (42), 97 (22), 80 (29), 69 (26). Anal. Calcd. for $C_{12}H_{13}N_3O_2$ (231.25): C, 62.33; H, 5.67; N, 18.17. Found: C, 62.40; H, 5.51; N, 17.77.

4-{[(2-Hydroxyphenyl)amino]methylene}-1-phenylpyrazolidine-3,5-dione (2). A mixture of enaminone **1** (0.23 g, 0.001 mol) and *o*-aminophenol (0.11 g, 0.001 mol) in anhydrous acetic acid (15 mL) was refluxed for 1 h. The solid product was precipitated on hot, collected by filtration, washed with

water and recrystallized from dimethyl sulfoxide to give colorless crystals, yield 0.28 g, 97%, m.p. 268–269 °C. IR (KBr) ν: 3414 (OH), 3290 (N–H), 3152 (N–H), 1690 (C=O), 1640 (C=O) cm^{-1}. ^{1}HNMR (DMSO-d_6) δ: 10.70-10.30 (br, 3H, OH+2N–H disappeared on addition of D_2O), 8.56 (s, 1H, CH=), 7.73–6.86 (m, 9H, H_{arom}). ^{13}CNMR (DMSO-d_6) δ: 169, 165 (CONPh), 163 (CONH), 147 (=CH) , 146 (CH), 145 (C), 138 (C), 130 (CH),126 (CH), 120 (CH), 119 (CH), 118 (CH), 116 (CH), 93 (C-4). MS, *m/z* (%) (M^++1, 17), 295 (M^+, 80), 187 (55), 162 (20), 133 (11), 119 (59), 91(36), 80 (100), 64(68). Anal. Calcd. for $C_{16}H_{13}N_3O_3$ (295.29): C, 65.08; H, 4.44; N, 14.23. Found: C, 65.48; H, 4.61; N, 14.03.

4-{[(2-mercaptophenyl)amino]methylene}-1-phenylpyrazolidine-3,5-dione (3). A mixture of enaminone **1** (0.23 g, 0.001 mol) and o-aminothiophenol (0.125 g, 0.001 mol) in anhydrous dioxane (50 mL) was refluxed for 4 h. After cooling, the solid product was collected by filtration and recrystallized from ethanol to give yellow crystals, yield 0.25 g, 80%, m.p. 280 °C. IR (KBr) ν: 3200 (N–H), 1689 (C=O), 1641 (C=O) cm^{-1}. ^{1}HNMR (DMSO-d_6) δ: 9.35 (s, 1H, N–H disappeared on addition of D_2O), 7.94–7.11 (m, 11H, N–H+ H_{arom}+ H_{olefin}). ^{13}CNMR (DMSO-d_6) δ: 169 (CONPh), 166 (CONH), 145 (=CH), 140 (C), 138 (C), 130 (CH), 126 (CH), 119 (CH), 118 (CH), 92 (C-4). Anal. Calcd. for $C_{16}H_{13}N_3O_2S$ (311.36): C, 61.72; H, 4.21; N, 13.50; S, 10.30. Found: C, 61.49; H, 3.91; N, 13.35; S, 10.66.

***N*-[(3,5-Dioxo-1-phenylpyrazolidin-4-ylidene)methyl]-*N*-(2-hydroxyethyl)-acetamide (4).**

Method a. A mixture of enaminone **1** (0.23 g, 0.001 mol) and ethanolamine (0.06 g, 0.001 mol) in anhydrous acetic acid (15 mL) was refluxed for 4 h. After cooling, the reaction mixture was poured onto ice cold water, the solid product was collected by filtration and recrystallized from ethanol. White crystals yield 0.254 g, 88%, m. p. 207–208 °C. IR (KBr) ν: 3428 (OH), 3264 (N–H), 1725 (C=O), 1693 (C=O), 1641 (C=O) cm^{-1}; ^{1}HNMR (DMSO-d_6) δ: 10 (s, 1H, OH disappeared on addition of D_2O), 9.30 (s, 1H, N–H disappeared on addition of D_2O), 7.80–7.10 (m, 6H, H_{arom}+H_{olefin}), 4.19 (s, 2H, CH_2OH), 3.69 (s, 2H, CH_2N), 2.02 (s, 3H, CH_3). ^{13}CNMR (DMSO-d_6) δ: 171 ($COCH_3$), 169, 167 (CONPh), 164 (CONH), 163, 157 (=CH), 138 (C), ~~145~~130 (CH), 123 (CH), 118 (CH), 90 (C-4), 63 (CH_2O), 49 (CH_2N), 21 (CH_3). MS, m/z(%) 290 (M^++1, 7), 289 (M^+, 38), 230 (15), 187 (13), 114 (24), 96(14), 80 (100), 64(42). Anal. Calcd. for $C_{14}H_{15}N_3O_4$ (289.29): C, 58.13; H, 5.23; N, 14.53. Found: C, 57.9; H, 4.86; N, 14.2. **Method b.** Boiling of compound **5** (0.5 g, 0.002) in glacial acetic acid (5 mL) for 1 h gave white crystals of the same compound **4**, 0.526 g, yield 90%.

4-{[(2-Hydroxyethyl)amino]methylene}-1-phenylpyrazolidine-3,5-dione (5). A mixture of enaminone **1** (0.23 g, 0.001 mol) and ethanolamine (0.06 g, 0.001 mol) in anhydrous pyridine (15 mL) was refluxed for 4 h. After cooling, the reaction mixture was concentrated. The solid product was collected by filtration and recrystallized from ethanol to give green crystals, yield 0.195 g, 79%, m.p. 194–196 °C. IR (KBr(ν: 3408 (OH), 3284 (N–H), 1693 (C=O), 1647 (C=O) cm^{-1}. ^{1}HNMR (DMSO-d_6) δ: 10 (s, 1H, OH disappeared on addition of D_2O), 9.37 (s, 1H, N–H disappeared on addition of D_2O), 7.87–7.08 (m, 7H, N–H+ H_{arom}+H_{olefin}), 3.56 (s, 2H, CH_2OH), 3.48 (s, 2H, CH_2N–H). ^{13}CNMR (DMSO-d_6) δ: 169, 167 (CONPh), 164 (CONH), 163, 156 (=CH), 138 (C), 129 (CH), 123 (CH), 118 (CH), 90 (C-4), 60 (CH_2O), 52 (CH_2N). Anal. Calcd. for $C_{12}H_{13}N_3O_3$ (247.25): C, 58.29; H, 5.30; N, 16.99. Found: C, 58.69; H, 5.44; N, 16.62.

4-{[(2-Mercaptoethyl)amino]methylene}-1-phenylpyrazolidine-3,5-dione (6). A mixture of enaminone **1** (0.23 g, 0.001 mol), cysteamine hydrochloride (0.113 g, 0.001 mol) and triethylamine (1.01 g, 0.001 mol) in anhydrous dioxane (50 mL) was refluxed for 4 h. The solid product was precipitated on hot, collected by filtration, washed with water, dried and recrystallized from DMF to give white crystals, yield 0.244 g, 93%, m.p. 285–287 °C. IR (KBr) ν: 3265 (N–H), 1695 (C=O), 1639 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 10.02 (s, 1H, N–H disappeared on addition of D_2O), 9.44 (s, 1H, N–H disappeared on addition of D_2O), 7.89–7.09 (m, 6H, H_{arom}+H_{olefin}), 3.75 (s, 2H, CH_2N–H), 3.05 (s, 2H, CH_2SH), 2.75 (s, 1H, SH). ^{13}CNMR (DMSO-d_6) δ: 169, 167 (CONPh), 164 (CONH), 163, 156 (=CH), 138 (C), 129 (CH), 123 (CH), 118 (CH), 90 (C-4), 49 (CH_2N), 38 (CH_2S). Anal. Calcd. for $C_{12}H_{13}N_3O_2S$ (263.32): C, 54.74; H, 4.98; N, 15.96; S, 12.18. Found: C, 54.9; H, 4.68; N, 15.8; S, 12.46.

1-Phenyl-4-[(2-phenylhydrazino)methylene]pyrazolidine-3,5-dione (8). A mixture of enaminone **1** (0.23 g, 0.001 mol) and phenyl hydrazine (0.108 g, 0.001 mol) in anhydrous dioxane (50 mL) was refluxed for 6 h, small amount of yellow precipitate was formed, filtered on hot, recrystallized from DMF to give yellowish white crystals, yield 0.035 g, 12%, m.p. 270–272 °C. IR (KBr) ν: 3420, 3255, 3150 (3NH), 1700, 1642 (2C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 11.05 (s, 1H, N–H disappeared on addition of D_2O), 10.35, 9.45 (br, 2H, 2NH disappeared on addition of D_2O), 8.44 (s, 1H, =CH), 7.73–7.14 (m, 10H, H_{arom}). ^{13}CNMR (DMSO-d_6) δ: 168 (CONPh), 165 (CONH), 164, 148 (=CH), 147 (C), 130 (C), 129 (CH), 125 (CH), 124 (CH), 118 (CH), 93 (C-4). Anal. Calcd. For $C_{16}H_{14}N_4O_2$ (294.31): C, 65.30; H, 4.79; N, 19.04. Found: C, 65.6; H, 4.63; N, 18.72.

3-Oxo-N',2-diphenyl-2,3-dihydro-1H-pyrazole-4-carbohydrazide (7). The filtrate of the compound **8** was cooled, the solid product was collected by filtration and recrystallized from ethanol, yield 0.246 g, 84%, m. p. 210–211 °C. IR (KBr) ν: 3400, 3252, 3150 (3NH), 1695, 1642 (2C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 11.00, 10.00 (s, 2H, NH disappeared on addition of D_2O), 8.22 (s, 1H, $H_{pyrazole}$), 7.74–6.71 (m, 10H, H_{arom}). ^{13}CNMR (DMSO-d_6) δ: 170 (CONH), 164 (CONPh), 158 (C), 150 (C), 140 (CH-5), 138 (CH), 130 (CH), 128 (CH), 122 (CH), 119 (CH), 112 (CH), 98 (C-4). Anal. Calcd. For $C_{16}H_{14}N_4O_2$ (294.31): C, 65.30; H, 4.79; N, 19.04. Found: C, 65.7; H, 4.75; N, 18.71.

4,4'-[Hydrazine-1,2-diyldimethylylidene]bis(1-phenylpyrazolidine-3,5-dione) (9). A mixture of enaminone **1** (0.23 g, 0.001 mol) and hydrazine hydrate (0.05 g, 0.001 mol) in anhydrous dioxane (50 mL) was refluxed for 30 min, the solid

product was precipitated on hot, collected by filtration and recrystallized from dioxane to give yellow crystals, yield 0.18 g, 89%, m.p. >300 °C. IR (KBr) ν: 3150 (N–H), 1645 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 9.31 (s, 2H, 2N–H disappeared on addition of D_2O), 7.97 (s, 2H, 2N–H disappeared on addition of D_2O), 7.78–6.70 (m, 12H, H_{arom}+H_{olefin}). Anal. Calcd. for $C_{20}H_{16}N_6O_4$ (404.37): C, 59.40%; H, 3.99%; N, 20.78%. Found: C, 59.27; H, 3.75; N, 21.21%.

4,4'-[Ethane-1,2-diylbis(iminomethylylidene)] bis(1-phenylpyrazolidine-3,5-dione) (10). A mixture of enaminone **1** (0.23 g, 0.001 mol) and ethylenediamine (0.06 g, 0.001 mol) in anhydrous acetic acid (15 mL) was refluxed for 2 h, the solid product was precipitated on hot, collected by filtration and recrystallized from dimethylsulfoxide to give white crystals, yield 0.18 g, 90%, m.p.>300 °C. IR (KBr) ν: 3290, 3150 (2N–H), 1695, 1649 (2C=O) cm^{-1}. ^{1}HNMR (DMSO-d_6) δ: 9.60-9.20 (br, 4H, 4N–H disappeared on addition of D_2O), 7.86–7.08 (m, 12H, H_{arom}+H_{olefin}), 3.70 (s, 4H, $2CH_2$). ^{13}CNMR (DMSO-d_6) δ: 164 (CONPh), 163 (CONH), 157 (=CH), 156 (=CH), 138 (C), 129 (CH), 125 (CH), 118 (CH), 90 (C), 50 ($2CH_2$). Anal. Calcd. for $C_{22}H_{20}N_6O_4$ (432.43): C, 61.10%; H, 4.66%; N, 19.43%. Found: C, 61.16; H, 4.35; N, 19.57%.

4,4'-[1,2-Phenylenebis(iminomethylylidene)]-bis(1-phenylpyrazolidine-3,5-dione) (11). A mixture of enaminone **1** (0.23 g, 0.001 mol) and *o*-phenylenediamine (0.108 g, 0.001 mol), in anhydrous acetic acid (15 mL), was refluxed for 1 h. The solid product was precipitated on hot, collected by filtration, washed with water and recrystallized from dimethylsulfoxide to give white crystals, yield 0.204 g, 85%, m.p. 300 °C. IR (KBr) ν: 3149 (N–H), 1644 (C=O) cm^{-1}. ^{1}HNMR (DMSO-d_6) δ: 11.25 (s, 2H, 2N–H disappeared on addition of D_2O), 10.45 (s, 2H, 2N–H disappeared on addition of D_2O), 8.10-7.10 (m, 16H, H_{arom}+H_{olefin}). Anal. Calcd. for $C_{26}H_{20}N_6O_4$ (480.47): C, 64.99%; H, 4.20%; N, 17.49%. Found: C, 65.32; H, 3.98; N, 17.70%.

1-Phenyl-4-(piperidin-1-ylmethylene)pyrazolidine-3,5-dione (12a). A mixture of enaminone **1** (0.23 g, 0.001 mol) and piperidine (0.85 g, 0.001 mol) in anhydrous dioxane (50 mL) was refluxed for 2 h. The solid product was precipitated on hot, collected by filtration and recrystallized from dioxane to give white crystals, yield 0.257 g, 95%, m.p. 245-247 °C. IR (KBr) ν: 3145 (N–H), 1695 (C=O), 1648 (C=O) cm^{-1}. ^{1}HNMR (DMSO-d_6) δ: 9.91 (s, 1H, N–H disappeared on addition of D_2O), 7.63–7.34 (m, 5H, H_{arom}), 7.07 (s, 1H, H_{olefin}), 4.44 (t, 2H, CH_2N), 3.71 (t, 2H, CH_2N), 1.65 (m, 6H, $(CH_2)_3$). ^{13}CNMR (DMSO-d_6) δ: 169, 167 (CONPh), 165 (CONH), 162, 152 (=CH), 138 (C), 129 (CH), 124 (CH), 118 (CH), 90 (C-4), 57 (CH_2), 52 (CH_2), 27 (CH_2), 25 (CH_2), 23 (CH_2). MS, *m/z* (%) 272 (M^++1, 19), 271 (M+, 100), 231 (15), 198 (18), 179 (47), 136(22), 108 (27), 93(17), 83(64), 80(85), 69(15), 64(32), 53(18). Anal. Calcd. for $C_{15}H_{17}N_3O_2$ (271.31): C, 66.40; H, 6.32; N, 15.49. Found: C, 66.09; H, 5.98; N, 15.4.

4-(Morpholin-4-ylmethylene)-1-phenylpyrazolidine-3,5-dione (12b). A mixture of enaminone **1** (0.23 g, 0.001 mol) and morpholine (0.87 g, 0.001 mol) in anhydrous dioxane (50 mL) was refluxed for 2 h. The solid product was precipitated on hot, collected by filtration and recrystallized from DMF. To give white crystals, yield 0.267 g, 98%, m.p. 280-282°C. IR (KBr)ν: 3125 (N–H), 1695 (C=O), 1650 (C=O) cm^{-1}. ^{1}HNMR (DMSO-d_6) δ: 10.10 (s, 1H, N–H disappeared on addition of D_2O), 7.61–7.09 (m, 6H, H_{arom}+H_{olefin}), 4.57 (s, 2H, CH-O), 3.80-3.60 (br, 6H, (CH-O + $2CH_2$-N). ^{13}CNMR (DMSO-d_6) δ: 169, 167 (CONPh), 162 (CONH), 152 (=CH), 138 (C), 129 (CH), 124 (CH), 118 (CH), 89 (C-4), 67 (CH_2), 66 (CH_2), 56 (CH_2), 53 (CH_2); MS, *m/z* (%) 274 (M^++1, 15), 273 (M+, 100), 231 (27), 187 (19), 181 (25), 138(14), 105 (15), 93(17), 85(38), 80(40), 77(38), 64(20), 53(23). Anal. Calcd. for $C_{14}H_{15}N_3O_3$ (273.29): C, 61.53; H, 5.53; N, 15.38. Found: C, 61.2; H, 5.34; N, 15.7.

{[(3,5-Dioxo-1-phenylpyrazolidin-4-ylidene)methyl] amino}acetic acid (13a). A mixture of enaminone **1** (0.23 g, 0.001 mol) and glycine (0.75 g, 0.001 mol) in anhydrous acetic acid (15 mL) was refluxed for 2 h. The solid product was precipitated on hot, collected by filtration, washed with water, dried and recrystallized from dimethylformamide to give white crystals, yield 0.256 g, 98%, m.p. 290–291 °C. IR (KBr) ν: 3433 (O–H), 3257, 3150 (2NH), 1740, 1690, 1638 (3C=O) cm^{-1}. ^{1}HNMR (DMSO-d_6) δ: 11.0 (s, 1H, COOH disappeared on addition of D_2O), 9.35 (s, 1H, N–H disappeared on addition of D_2O), 7.91–7.10 (m, 7H, N–H+ H_{arom}+H_{olefin}), 4.26 (s, 2H, NCH_2CO_2H). ^{13}CNMR (DMSO-d_6) δ: 171 (COOH), 169, 167 (CONPh), 165 (CONH), 164, 163, 157 (=CH), 156, 128 (CH), 124 (CH), 118 (CH), 90 (C-4), 50 (CH_2). Anal. Calcd. for $C_{12}H_{11}N_3O_4$ (261.23): C, 55.17; H, 4.24; N, 16.09. Found: C, 55.1; H, 4.26; N, 15.69.

Ethyl {[(Z)-(3,5-dioxo-1-phenylpyrazolidin-4-ylidene) methyl]amino}acetate (13b). A mixture of enaminone **1** (0.23 g, 0.001 mol), ethyl glycinate hydrochloride (0.139 g, 0.001 mol) and triethylamine (0.101 g, 0.001 mol) in anhydrous dioxane (50 mL) was refluxed for 6 h. The solid product was precipitated on hot, collected by filtration, washed with water, dried and recrystallized from DMSO to give white crystals, yield 0.26 g, 90%, m.p. 216–218 °C. IR (KBr) ν: 3296, 3150 (2NH), 1740, 1693, 1637 (3C=O) cm^{-1}. ^{1}HNMR (DMSO-d_6) δ: 10.15 (s, 1H, NH disappeared on addition of D_2O), 9.35 (s, 1H, N–H disappeared on addition of D_2O), 7.92–7.08 (m, 6H, H_{arom}+H_{olefin}), 4.32 (s, 2H, NCH_2CO_2Et), 4.19-4.14 (q, 2H, CH_2CH_3), 1.24-1.2 (t, 3H, CH_2CH_3). ^{13}CNMR (DMSO-d_6) δ: 170 (COOR), 169, 167 (CONPh), 165 (CONH), 164, 156 (=CH), 155, 138 (C), 129 (CH), 124 (CH), 118 (CH), 90 (C), 62 (OCH_2), 50 (NCH_2), 14 (CH_3). MS, *m/z* (%) 290 (M^++1, 14), 289 (M+, 78), 216 (20), 199 (10), 187 (14), 156(25), 128 (10), 108(17), 93(27), 82(67), 80(100), 77(57), 64(83), 55(26), 53(33). Anal. Calcd. for $C_{14}H_{15}N_3O_4$ (289.29): C, 58.13; H, 5.23; N, 14.53. Found: C, 58.43; H, 5.02; N, 14.19.

1-Phenyl-4-[(pyridin-2-ylamino)methylene]pyrazolidine-3,5-dione (14). A mixture of enaminone **1** (0.23 g, 0.001 mol) and 2-aminopyridine (0.094 g, 0.001 mol) in anhydrous pyridine (15 mL) was refluxed for 4 h. After cooling, the solid product was collected by filtration and recrystallized from pyridine to give yellow crystals, yield 0.254 g, 91%, m. p. 268-270°C. IR (KBr) ν: 3265, 3152 (2N–H), 1690 (C=O), 1650

(C=O) cm^{-1}. ^{1}HNMR (DMSO-d_6) δ: 11.20(s, 1H, N–H disappeared on addition of D_2O), 8.83 (s, 1H, N–H disappeared on addition of D_2O), 8.41(s, 1H, N–H disappeared on addition of D_2O), 7.88–7.13 (m, 10H, H_{arom}+H_{olefin}). Anal. Calcd. for: $C_{15}H_{12}N_4O_2$ (280.28): C, 64.28; H, 4.32; N, 19.99. Found: C, 64.6; H, 4.41; N, 19.7.

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