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Synthesis and Reactions of Some New Heterocyclic Carbohydrazides and Related Compounds as Potential Anticancer Agents

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Abstract: Acylation of 3-hydrazino-5,6-diphenyl-1,2,4-triazine (**2**) and hydrazine hydrate (**7**) with 4-aryl-1,3,7-triphenyl-8-oxa-1,2,6-triazaspiro[4.4]nona-2,6-dien-9-ones **5a,b** gave the corresponding heterocyclic carbohydrazides **6a,b** and **8a,b** respectively. Conversion of compounds **8a,b** into the versatile carbohydrazide derivatives **9a-g**, **10**, **13** and the related oxadiazoles **11, 12a,b** was undertaken. A primary *in vitro* test of compound **8a** (concentration 10^{-4} M) showed activity against leukemia cell lines (CCRF-CEM, K-256, MOLT-4, PRMI-8226, SR).

Keywords: Synthesis, Pyrazoles, 2-Pyrazolines, Carbohydrazides.

Introduction

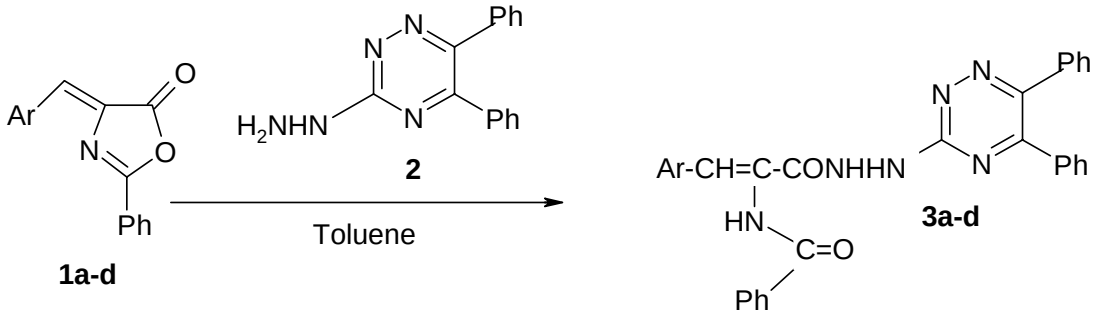
Hydrazides and related compounds have been described as useful building blocks for the assembly of various heterocyclic rings [1]. A large number of aliphatic, alicyclic, aromatic and heterocyclic carbohydrazides, their derivatives and related compounds are reported to present a plethora of biological activities [2-15]. Thus, different carbohydrazides were found to be useful as medicaments especially in the treatment of inflammatory and autoimmune diseases, osteoarthritis, respiratory

diseases, tumors, cachexia, cardiovascular diseases, fever, hemorrhage and sepsis [11]. Carbohydrazides and related compounds exhibited antifungal [2], antiviral [14], bacteriostatic [2,7,9,14], antiparasite [2,10], antituberculous [3-6], psychotropic [2], and insecticidal [15] activities. Some heterocyclic carbohydrazides are useful as antifertility agents in rats and pigeons [13]. Other carbohydrazides were reported to be components of deodorant compositions that can be used for removal of offensive odor components [16]. The 1,3,4-oxadiazoles have been reported to be biologically versatile compounds having bactericidal, fungicidal, analgesic, antiproteolytic, hypoglycemic, tranquilizing and CNS depressant properties [2]. All these facts encouraged us to synthesize some new 2-pyrazolin-3-carbohydrazides **8a,b**, their derivatives **9a-g**, **10**, **13** and some related oxadiazoles **11**, **12a,b** in anticipation of expected interesting biological activities.

Results and discussion

Acylation of 3-hydrazino-5,6-diphenyl-1,2,4-triazine (**2**) with 4-arylidene-2-phenyl-oxazol-5(4H)-ones (**1a-d**) has been previously reported [17] to give the corresponding N-(5,6-diphenyl-1,2,4-triazin-3-yl)-carbohydrazides **3a-d** (Scheme1).

Scheme 1

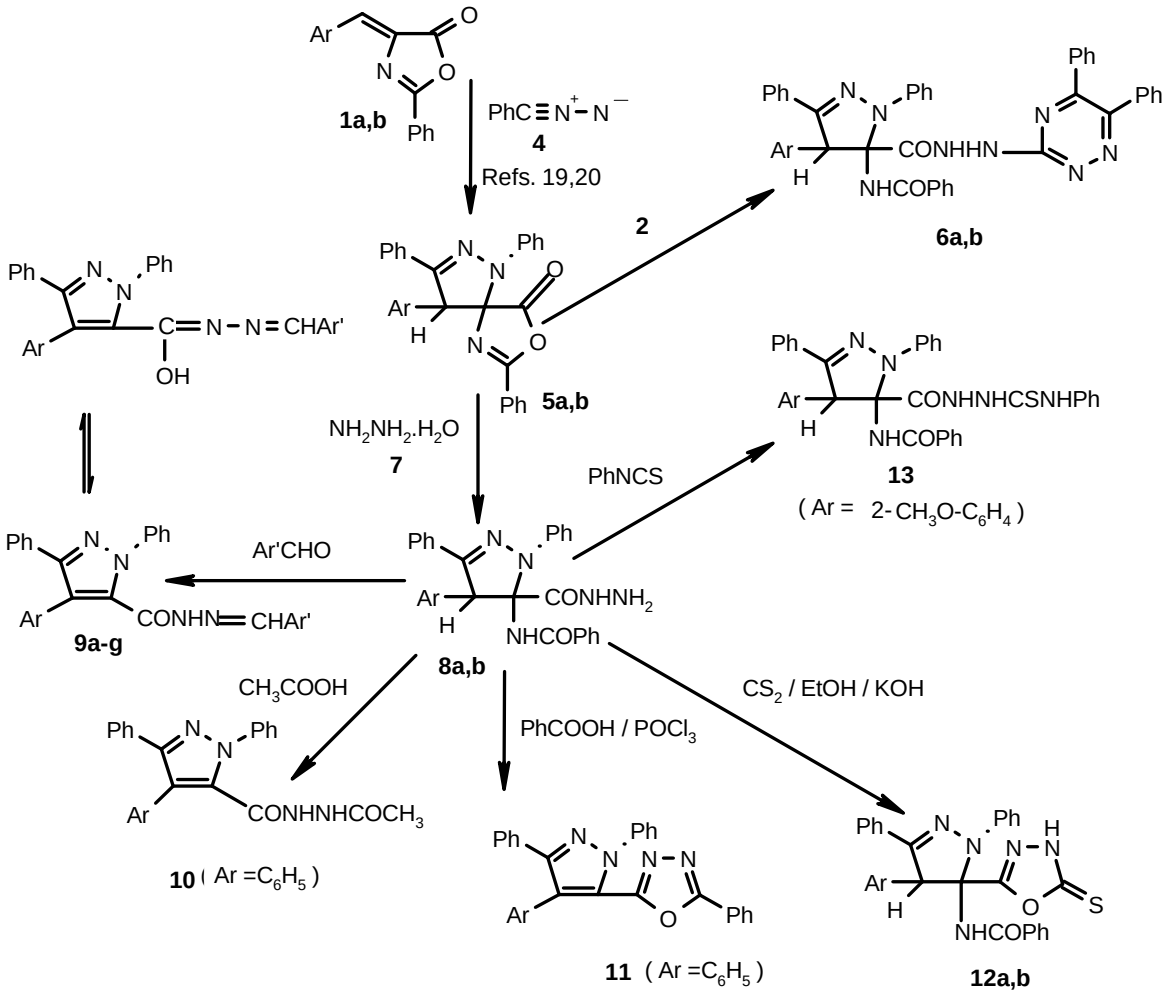


1,3	Ar
a	C_6H_5
b	2-$CH_3OC_6H_4$
c	4-$CH_3OC_6H_4$
d	3,4-$(CH_3O)_2C_6H_3$

We have now studied the acylation of both compound **2** and hydrazine hydrate (**7**) with the 4-aryl-1,3,7-triphenyl-8-oxa-1,2,6-triazaspiro[4.4]nona-2,6-dien-9-ones **5a,b**. Some chemical transformations leading to new functionalities have also been achieved (Scheme 2). For example, acylation of 3-hydrazino-5,6-diphenyl-1,2,4-triazine (**2**) with the spiro compounds **5a,b** [19,20] gave the corresponding novel N-(5,6-diphenyl-1,2,4-triazin-3-yl)-1,3-diphenyl-4-aryl-5-benzoylamino-2-pyrazolin-5-carbohydrazides **6a,b**. The structure of compounds **6a,b** was assigned based on analytical and spectral data. Thus, the IR spectra of these compounds showed bands at 3405-3396, 3277-3267

(NH stretching), 3063-3059, 3038-3028 (aromatic CH stretching), 1709 (hydrazide C=O stretching), 1685-1682 (amide C=O stretching), 1627 (C=N stretching) and 1601-1597 cm^{-1} (aromatic C=C stretching).

Scheme 2



9	Ar	Ar'
a	C_6H_5	C_6H_5
b	C_6H_5	2-(OH)-C_6H_4
c	C_6H_5	4-CH_3-C_6H_4
d	C_6H_5	4-CH_3O-C_6H_4
e	2-CH_3O-C_6H_4	C_6H_5
f	2-CH_3O-C_6H_4	2-(OH)-C_6H_4
g	2-CH_3O-C_6H_4	4-$CH_3OC_6H_4$

1,5,6,8,12	Ar
a	C_6H_5
b	2-CH_3O-C_6H_4

Also, the ^{1}H-NMR spectra of compounds **6a,b** revealed signals at δ 11.31-10.28 (2s, hydrazide NHNH), 7.97-7.72 (s, amide NH), 7.61-6.50 (m, ArH's), 5.87-5.64 (s, pyrazolinyl CH). Moreover, the ^{13}C-NMR of compounds **6a,b** showed signals consistent with their structures (cf. Experimental). Similarly, acylation of hydrazine hydrate (**7**) with the spiro compounds **5a,b** afforded the corresponding 4-aryl-5-benzoylamino-1,3-diphenyl-2-pyrazoline-5-carbohydrazides **8a,b**. The structure of compounds **8a,b** was established chemically and spectroscopically. Thus, the ^{1}H-NMR spectra of these compounds not only showed the presence of the pyrazolinyl proton at δ 5.59-5.32, but also revealed the presence of NH_2 protons at δ 4.61-4.54 [s, 2H (exchangeable)]. The mass spectra of compounds **8a,b**, also gave their correct parent ion peaks at m/z 475 (M^+, 1.3%), and 505 (M^+, 0.4%), respectively.

Condensation of compounds **8a,b** with aryl aldehydes and/or acetylation of compound **8a** with acetic acid was found to proceed concurrently with the elimination of a benzamide molecule to give the corresponding N-arylidene and/or N-acetoxy-4-aryl-1,3-diphenyl-pyrazole-5-carbohydrazides **9a-g** and/or **10** respectively. The structures of these compounds were inferred from their analytical and spectral data. Thus, the IR spectra of compounds **9a-g** showed only one carbonyl function (hydrazide C=O) at 1722-1670 cm^{-1} and that of compound **10** showed a carbonyl function at 1672 cm^{-1}(hydrazide C=O overlapped with acetyl C=O). The ^{1}H-NMR spectra of **9a-g** and **10** not only showed the absence of both the pyrazolinyl proton at δ 5.59-5.32 and the NH_2 protons at δ 4.61-4.54, but also the presence of the N=CH in compounds **9a-g** (δ 8.30-7.65) and the acetyl protons of compound **10** (δ 1.86). The IR spectra of compounds **9a-g** as well as their ^{1}H-NMR spectra (relative proton integration ratio) showed the presence of both hydrazide (25-63.3%) and hydrazole (36.7-75%) tautomeric structures. The mass spectra of compounds **9a,c** gave their correct parent ion peaks at m/z 442 (M^+, 13.7%) and 456 (M^+, 12%), respectively.

Treatment of compound **8a** with benzoic acid and phosphorous oxychloride was found to proceed via concurrent cyclocondensation and elimination of a benzamide molecule to give the 5-phenyl-2-(1,3,4-triphenylpyrazol-5-yl)-1,3,4-oxadiazole (**11**). The mass spectrum of compound **11** showed its correct parent ion peak at m/z 440 (M^+, 49.9%).

Compounds **8a,b** reacted with carbon disulfide in ethanolic KOH to yield the corresponding 2-(4-aryl-1,3-diphenyl-5-benzoylamino-2-pyrazolin-5-yl)-1,3,4-oxadiazole-5(4H)-thiones (**12a,b**). The absence of the characteristic weak S-H stretching bands at 2600-2550 and the appearance of the strong C=S stretching bands at 1069-1064 cm^{-1} in the IR spectra of compounds **12a,b** confirmed their thione form and excluded the tautomeric thiol structure. The IR spectra of compounds **12a,b** showed also bands at 1199-1019 cm^{-1} (=C-O-C= stretching). The ^{1}H-NMR spectra revealed the presence of the NH oxadiazolyl proton at δ 14.60-14.52 and the CH pyrazolinyl proton at δ 6.32-5.90.

Reaction of compound **8b** with phenyl isothiocyanate gave N-(N-phenylthiocarbamoyl)-5-benzoylamino-1,3-diphenyl-4-(2-methoxyphenyl)-2-pyrazolin-5-carbohydrazide (**13**). Elemental and spectral data are consistent with the structure assigned to this compound (cf. Experimental).

Biological Evaluation

A primary *in vitro* test of compound **8a** (concentration 10^{-4} M) showed activity against Leukemia cell lines (CCRF-CEM, K-562, MOLT-4, PRMI-8226, SR). Further investigation is in progress.

Experimental

General

All melting points are uncorrected. IR spectra (KBr disks) were recorded on a Perkin-Elmer 1430 spectrometer. The abbreviations str. and bend. are used to indicate stretching and bending bands, respectively . ^{1}H-NMR and ^{13}C-NMR were measured with a Varian GEMINI 200 spectrometer (200 MHz for ^{1}H-NMR; 50MHz for ^{13}C-NMR). The abbreviation exch. is used to indicate exchangeable protons. Mass spectra were recorded on a GCMS - QP 1000 EX (70EV) spectrometer. Elemental analyses were carried out at the Microanalytical Center, Cairo University. Anticancer screening of compound **8a** was carried out at the National Cancer Institute – National Institutes of Health, Bethesda, Maryland, United States of America. The starting materials 3-hydrazino-5,6-diphenyl-1,2,4-triazine (**2**) [18] and 4-aryl-1,3,7-triphenyl-8-oxa-1,2,6-triazaspiro-[4.4]nona-2,6-dien-9-ones **5a,b** [19,20] were prepared as reported.

General procedure for the preparation of N-(5,6-diphenyl-1,2,4-triazin-3-yl)-4-aryl-5-benzoylamino-1,3-diphenyl-2-pyrazoline-5-carbohydrazides (**6a,b**).

Each of compounds **5a,b** (1 mmol) was added to a solution of compound **2** (1 mmol) in toluene (10 mL). The reaction mixture was then heated under reflux for $1^{1}/_{2}$ hour, concentrated, and diluted with petroleum ether (bp. 40-60 ºC). After decantation, the residue obtained was boiled in ethanol (5 mL), filtered, and cooled. The formed precipitate was collected by filtration and recrystallized from ethanol giving colorless crystals of **6a,b**.

N-(5,6-Diphenyl-1,2,4-triazin-3-yl)-5-benzoylamino-1,3,4-triphenyl-2-pyrazoline-5-carbohydrazide (**6a**). Using the general procedure, **5a** gave **6a** (73%); mp. 218-219ºC; IR (cm^{-1}): 3405, 3277 (NH str.), 3063, 3038 (aromatic CH str.), 2922, 2866, 2855 (pyrazolinyl aliphatic CH str.), 1709 (hydrazide C=O str.), 1685 (amide C=O str.), 1627 (C=N str.), 1601 (aromatic C=C str.), 1505, 1480 (NH bend.), 1365, 1312, 1283, 1251 (C-N str.), 762, 697 (aromatic CH bend.); ^{1}H-NMR (DMSO-d_6) δ 11.31, 10.31 [2s, 2H (exch.), hydrazide NHNH], 7.72 [s, 1H (exch.), amide NH], 7.57-6.82 (m, 30H, ArH's), 5.64 (s, 1H, pyrazolinyl CH); ^{13}C-NMR (DMSO-d_6) δ 171.5, 164.8 (C=O), 157, 152, 146.5, 142.5 (C=N), 136.2, 134.6, 132.2, 131.5 (aromatic C), 130.5, 129.5, 129.4, 128.7, 128.6, 128.5, 128.2, 127.6, 127.3, 127.2, 127.0. 126.2 (aromatic CH), 81.6 (pyrazolinyl C), 63.5 (pyrazolinyl CH); Anal. for $C_{44}H_{34}N_8O_2$ Calcd.: C, 74.77; H, 4.85; N, 15.85. Found: C, 74.60; H, 5.00, N, 15.70.

N-(5,6-Diphenyl-1,2,4-triazin-3-yl)-5-benzoylamino-1,3-diphenyl-4-(2-methoxyphenyl)-2-pyrazoline-5-carbohydrazide (**6b**). Using the general procedure, **5b** gave **6b** (41%); mp. 210-212ºC; IR (cm^{-1}): 3396, 3267 (NH str.), 3059, 3028 (aromatic CH str.), 2964, 2932, 2883, 2833 (OCH_3 and pyrazolinyl aliphatic CH str.), 3059, 3028, 2997 (aromatic CH str.), 1709 (hydrazide C=O str.), 1682 (amide C=O str.), 1597(aromatic C=C str.), 1495, 1473, 1445 (NH bend.), 1358, 1331, 1290, 1252 (C-N str.), 1067, 1028 (C-O str. of OCH_3), 762, 692 (aromatic CH bend.); ^{1}H-NMR (DMSO-d_6) δ 11.23, 10.28 [2 brs, 2H (exch.), hydrazide NHNH], 7.97 [s, 1H (exch.), amide NH] 7.61-6.50 (m, 29H, ArH's), 5.87 (s, 1H, pyrazolinyl CH), 3.60 (s, 3H, OCH_3); ^{13}C-NMR (DMSO-d_6) δ 171.64, 164.30, (C=O), 157.28, 146.84, 142.78, 136.41 (C=N), 135.95, 134.76, 132.74, 132.49, 132.45, 132.41, 131.46 (aromatic C), 130.54, 129.70. 129.31, 129.20, 128.74, 128.64, 128.40, 128.29, 126.86, 126.08, 125.89, 121.68, 120.33, 115.15, 115.09, 114.99 (aromatic CH), 110.04 (pyrazolinyl C), 80.55 (pyrazolinyl CH), 55.04 (OCH_3); Anal. for $C_{45}H_{36}N_8O_3$ Calcd.: C, 73.35; H, 4.92; N, 15.21. Found: C, 73.50; H, 5.00; N, 15.40.

General procedure for the preparation of 4-aryl-5-benzoylamino-1,3-diphenyl-2-pyrazoline-5-carbohydrazides (**8a,b**)**.** To a suspension of each of compounds **5a,b** (1 mmol) in methanol (20 mL) was added 80% hydrazine hydrate (0.5 mL). While the reaction mixture of compound **8a** was shaken for ten minutes at room temperature, that of compound **8b** was heated under reflux for one hour. The reaction mixtures of each compound were then left overnight at room temperature. The colorless precipitate formed was collected by filtration and recrystallized from methanol to give colorless crystals of **8a,b.**

5-Benzoylamino-1,3,4-triphenyl-2-pyrazoline-5-carbohydrazide **(8a**). Using the general procedure, **5a** gave **8a** (73%); mp. 214-215ºC; IR (cm^{-1}): 3400, 3325 (NH, NH_2 str.), 3065, 3034 (aromatic CH str.), 2930 (pyrazolinyl CH str.), 1669 (C=O str.), 1625 (C=N str.), 1601 (aromatic C=C str.), 1503, 1480 (NH bend.), 1374, 1321, 1280, 1243 (C-N str.), 750, 696 (aromatic CH bend.); ^{1}H-NMR (DMSO-d_6) δ 10.05 [s, 1H (exch.), hydrazide NH], 8.07 [s, 1H (exch.), amide NH], 7.60-6.86 (m, 20H, ArH's), 5.32 (s, 1H, pyrazolinyl CH), 4.54[s, 2H (exch.), NH_2]; MS m/z 475 (M^+, 1.3%); Anal. for $C_{29}H_{25}N_5O_2$ Calcd.: C, 73.24; H, 5.30; N, 14.73. Found: C, 73.20; H, 5.25; N, 14.60.

5-Benzoylamino-1,3-diphenyl-4-(2-methoxyphenyl)-2-pyrazoline-5-carbohydrazide (**8b**). Using the general procedure, **5b** gave **8b** (74%); mp. 230ºC; IR (cm^{-1}): 3384, 3334,3284 (NH, NH_2 str.), 3061, 3025 (aromatic CH str.), 2954, 2942, 2901, 2835 (OCH_3 and pyrazolinyl aliphatic CH str.), 1684 (hydrazide C=O str.), 1672 (amide C=O str.), 1636 (C=N str.), 1604 (aromatic C=C str.), 1497, 1475 (NH bend.), 1375, 1294, 1250 (C-N str.), 1167, 1028 (C-O str. of OCH_3), 750, 692 (aromatic CH bend.); ^{1}H-NMR (DMSO-d_6) δ 10.25 [s, 1H (exch.), hydrazide NH], 8.18 [s, 1H (exch.), amide NH], 7.56-6.49 (m, 19H, ArH's), 5.59 (s, 1H, pyrazolinyl CH), 4.61[s, 2H (exch.), NH_2], 3.82 (s, 3H, OCH_3); MS m/z 505 (M^+, 0.4%); Anal. for $C_{30}H_{27}N_5O_3$ Calcd.: C, 71.27; H, 5.38; N, 13.85. Found: C, 71.30; H, 5.50; N, 14.00.

N-Arylidene-4-aryl-1,3-diphenylpyrazole-5-carbohydrazides (**9a-g**).

General Procedure A: To a solution of each of compounds **8a,b** (1 mmol) in either acetic acid (12 mL) or n-butanol (20 mL) was added the appropriate aryl aldehyde (1 mmol) and the reaction mixture was then heated under reflux for a time as shown as in Table 1. The crystalline colorless precipitates of compounds **9a-d,f** were collected by filtration, washed with methanol, and recrystallized from the appropriate solvent. Pure **9e,g** were obtained from their reaction mixtures via dilution with water, collection of the formed precipitate by filtration, and recrystallization from the appropriate solvent.

Table 1

9	Reaction Solvent	Reflux Time	Recrystallization Solvent
a	n-Butanol	3 hours	EtOH
b	Acetic acid	20 minutes	n-Butanol
c	Acetic acid	$1^1/_2$ hour	Acetic acid
d	Acetic acid	$1^1/_2$ hour	Acetic acid
e	Acetic acid	2 hours	Ethanol
f	Acetic acid	$1^1/_4$ hour	Ethanol
g	Acetic acid	2 hours	Ethanol

General Procedure B: To compound **8a** (1 mmol) was added 4-methylbenzaldehyde (1 mmol) and 3 drops of piperidene. The reaction mixture was then heated (oil bath) at 120 ºC till complete dissolution which was followed by an immediate resolidification. The reaction mixture was allowed to cool to room temperature, diluted with methanol, and the formed colorless crystalline product was collected by filtration and recrystallized from ethanol giving colorless crystals of **9c**, identical with the product **9c** obtained from general procedure A (mp. and mixed mp. as well as analytical and spectral data).

N-Benzylidene-1,3,4-triphenylpyrazole-5-carbohydrazide (**9a**). Using general procedure A, **8a** gave **9a** (34%); mp. 229-230ºC; IR (cm^{-1}): 3584-3291 (OH str. of hydrazole tautomer), 3213 (NH str.), 3066, 3028 (aromatic CH str.), 1674 (hydrazide C=O str.) 1655 (C=N str.), 1597 (aromatic C=C str.), 1556, 1500 (NH bend.), 1365, 1313, 1275, 1246 (C-N str.), 760, 692 (aromatic CH bend.); ^{1}H-NMR ($CDCl_3$) δ 10.03, 8.43 [2brs,1H (exch.), hydrazide (53.7%) - hydrazole (46.3%) tautomeric proton], 7.73-7.07 (m, 21H, ArH's, N=CH); Ms m/z 442 (M^+, 13.7%); Anal. for $C_{29}H_{22}N_4O$ Calcd.: C, 78.71; H, 5.01; N, 12.66. Found: C, 78.80; H, 5.20; N, 12.80.

N-(2-Hydroxybenzylidene)-1,3,4-triphenylpyrazole-5-carbohydrazide (**9b**). Using general procedure A, **8a** gave **9b** (88%); mp.283-285ºC; IR (cm^{-1}): 3200-2500 (OH str.), 3178 (NH str.), 3055, 3007 (aromatic CH str.), 1722 (hydrazide C=O str.), 1651(C=N str.), 1601 (aromatic C=C str.), 1545, 1499 (NH bend.), 1367, 1331, 1313, 1292, 1277, 1250, 1186, 1184, 1149 [C-N, C-O (phenolic) str.], 758,

692 (aromatic CH bend.); ^{1}H-NMR (DMSO-d_6) δ 12.36 [s, 1H (exch.), 2-(O<u>H</u>)-C_6H_4] 10.70, 9.96 [2s, 1H (exch.), hydrazide (63.3%) - hydrazole (36.7%) tautomeric proton], 8.30 (s, 1H, N=CH), 7.72-6.73 (m, 19H, ArH's); Anal. for $C_{29}H_{22}N_4O_2$ Calcd.: C, 75.97; H, 4.83; N, 12.22. Found: C, 76.00; H, 4.76; N, 12.00.

N-(4-Methylbenzylidene)-1,3,4-triphenylpyrazole-5-carbohydrazide (**9c**). Using the general procedures A and/or B, **8a** gave **9c** (67%) and / or (70%), respectively; mp. 222-223ºC; IR (cm^{-1}): 3342-2400 (OH str. of hydrazole tautomer), 3197 (NH str.), 3052, 3000 (aromatic CH str.), 2947, 2919 (CH str. of CH_3), 1672 (hydrazide C=O str.) 1653 (C=N str.), 1603 (aromatic C=C str.), 1564, 1500 (NH bend.), 1372, 1335, 1322, 1311, 1292, 1279, 1256, 1211-1027 [C-O (of hydrazole tautomer), C-N str.], 765,757, 702, 684 (aromatic CH bend.); ^{1}H-NMR ($CDCl_3$) δ 10.45, 8.50 [2s, 1H (exch.), hydrazide (61.0%) - hydrazole (39.0%) tautomeric proton], 7.65-7.08 (m, 20H, ArH's, N=CH), 2.33 (s, 3H, CH_3); MS m/z 456 (M^+, 12.0%); Anal. for $C_{30}H_{24}N_4O$ Calcd.: C, 78.92; H, 5.30; N, 12.27. Found: C, 78.90; H, 5.40; N, 12.40.

N-(4-Methoxybenzylidene)-1,3,4-triphenylpyrazole-5-carbohydrazide (**9d**). Using general procedure A, **8a** gave **9d** (83%); mp. 245-247ºC; IR (cm^{-1}): 3713-2555 (OH str.of hydrazole tautomer), 3194 (NH str.), 3055, 3006 (aromatic CH str.), 2967, 2927, 2838 (CH str. of OCH_3), 1673 (hydrazide C=O str.), 1651 (C=N str.), 1604 (aromatic C=C str.), 1565, 1506 (NH bend.), 1369, 1306, 1251, 1172-1028 [C-O, C-N str.), 762,701 (aromatic CH bend.); ^{1}H-NMR ($CDCl_3$) δ 9.93, 8.40 [2s, 1H (exch.), hydrazide (52.2%) - hydrazole (47.8%) tautomeric proton], 7.69-6.83 (m, 20H, ArH's, N=CH), 3.84 (s, 3H, OCH_3); Anal. for $C_{30}H_{24}N_4O_2$ Calcd.: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.40; H, 5.08; N, 12.00.

N-Benzylidene-1,3-diphenyl-4-(2-methoxyphenyl)-pyrazole-5-carbohydrazide (**9e**). Using general procedure A, **8b** gave **9e** (80%); mp. 175-176ºC; IR (cm^{-1}): 3200-2500 (OH str. of hydrazole tautomer), 3196 (NH str.), 3067 (aromatic CH str.), 2987, 2930, 2856 (CH str. of OCH_3), 1670 (hydrazide C=O str.) 1651 (C=N str.), 1612, 1595 (aromatic C=C str.), 1556, 1499 (NH bend.), 1364, 1273,1242-1074 (C-O, C-N str.), 760, 700, 692 (aromatic CH bend.); ^{1}H-NMR ($CDCl_3$) δ 9.83, 9.43 [2s, 1H (exch.), hydrazide (27.8%) - hydrazole (72.2%) tautomeric proton], 7.72-6.95 (m, 20H, ArH's, N=CH), 3.85 (s, 3H, OCH_3); Anal. for $C_{30}H_{24}N_4O_2$ Calcd.: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.40; H, 5.10; N, 11.60.

N-(2-Hydroxybenzylidene)-1,3-diphenyl-4-(2-methoxyphenyl)-pyrazole-5-carbohydrazide (**9f**). Using general procedure A, **8b** gave **9f** (81%); mp. 207-208ºC; ^{1}H-NMR ($CDCl_3$): δ 10.69 [s, 1H (exch.), OH], 9.37 [s, 1H (exch.), NH], 7.89 (s, 1H, N=CH), 7.67-6.84 (m, 18H, ArH's), 3.84 (s, 3H, OCH_3); Anal. for $C_{30}H_{24}N_4O_3$ Calcd.: C, 73.75; H, 4.95; N, 11.47. Found: C, 73.80; H, 5.00; N, 11.62.

N-(4-Methoxybenzylidene)-1,3-diphenyl-4-(2-methoxyphenyl)-pyrazole-5-carbohydrazide (**9g**). Using general procedure A, **8b** gave **9g** (85%); mp. 178-180ºC; IR (cm^{-1}): 3645-3266 (OH str. of hydrazole

tautomer), 3175 (NH str.), 3068, 3005 (aromatic CH str.), 2962, 2933, 2902, 2837(CH str. of OCH_3), 1685 (hydrazide C=O str.) 1650 (C=N str.), 1603 (aromatic C=C str.), 1547, 1509 (NH bend.), 1366, 1307,1254 , 1170-1026 (C-O, C-N str.) 758, 694 (aromatic CH bend.); ^{1}H-NMR ($CDCl_3$): δ 9.74, 9.34 [2s,1H (exch.), hydrazide (25.0%) - hydrazole (75.0%) tautomeric proton], 7.72-6.86 (m, 19H, ArH's, N=CH), 3.83(s, 6H, OCH_3); Anal. for $C_{31}H_{26}N_4O_3$ Calcd.: C, 74.08; H, 5.21; N, 11.15. Found: C, 74.12; H, 5.10; N, 11.60.

N-Acetyl-1,3,4-triphenylpyrazole-5-carbohydrazide (**10**). To compound **8a** (1 mmol) was added acetic acid (15 mL) and the reaction mixture was heated under reflux for $1^1/_4$ hour. After cooling, the reaction mixture was poured onto water and the formed precipitate was collected by filtration and recrystallized from ethanol as colorless crystals of **10** (83%); mp. 237-238ºC; IR (cm^{-1}): 3194 (NH str.), 3055, 3009 (aromatic CH str.), 2968, 2914, 2839 (CH str. of CH_3), 1672 (C=O str.), 1651 (C=N str.), 1605 (aromatic C=C str.), 1564, 1512, 1500 (NH bend.), 1371, 1306, 1279, 1250 (C-N str.), 772, 768, 704, 690 (aromatic CH bend.); ^{1}H-NMR (DMSO-d_6): δ 10.76, 9.98 [2s, 2H (exch.), hydrazide NHNH], 7.97-7.26 (m, 15H, ArH's), 1.85 (s, 3H, $C\underline{H}_3CO$); Anal. for $C_{24}H_{20}N_4O_2$ Calcd.: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.80; H, 5.10; N, 14.50.

2-(1,3,4-Triphenylpyrazol-5-yl)-5-phenyl-1,3,4-oxadiazole (**11**). A mixture of compound **8a** (1 mmol), benzoic acid (1 mmol), and phosphororus oxychloride (1 mmol) was heated under reflux for $1^1/_2$ hour. After cooling to room temperature, the reaction mixture was poured onto crushed ice, stirred, decanted and diluted with water. The residue obtained after a second decantation was boiled with methanol. The solidified residue obtained on cooling was collected by filtration and recrystallized from N,N-dimethylformamide as colorless crystals of **11** (23%); mp.185ºC; ^{1}H-NMR (DMSO-d_6): δ 7.69-7.34 (m, ArH's); MS m/z 440 (M^+, 49.9); Anal. for $C_{29}H_{20}N_4O$ Calcd.: C, 79.07; H, 4.57; N, 12.72. Found: C, 79.10; H, 4.62; N, 12.69.

General procedure for the preparation of 2-(4-Aryl-5-benzoylamino-1,3-diphenyl-2-pyrazolin-5-yl)-1,3,4-oxadiazole-5(4H)-thiones (**12a,b**). To a solution containing 95% ethanol (5 mL) and potassium hydroxide (1 mmol, dissolved in the least amount of water), were added compounds **8a,b** (1 mmol) followed by carbon disulfide (1.5 mmol). The reaction mixture was heated under reflux for 3 hours till all the evolution of hydrogen sulfide ceased. After decantation, the supernatant solution was evaporated, diluted with water (while a milky solution was obtained), and acidified with hydrochloric acid containing ice. The reaction mixture was allowed to stand at room temperature for 15 minutes, filtered, and the solid obtained was washed well with water and dried at room temperature. The crude products were then recrystallized from ethanol as colorless crystals of **12a,b**.

2-(5-Benzoylamino-1,3,4-triphenyl-2-pyrazolin-5-yl)-1,3,4-oxadiazole-5(4H)-thione (**12a**). Using the general procedure, **8a** gave **12a** (81%); mp. 236-237ºC; IR (cm^{-1}): 3421, 3157 (NH str.), 3063, 3030 (aromatic CH str.), 2945, 2926, 2852 (pyrazolinyl CH str.), 1683 (amide C=O str.), 1600 (aromatic

C=C str.), 1507, 1489, 1469 (NH bend.), 1331, 1286, 1255 (C-N str.), 1199, 1153,1019 (=C-O-C= str.), 1064 (C=S str.), 761, 649 (aromatic CH bend.); ^{1}H-NMR (DMSO-d_6): δ 14.60 [brs, 1H (exch.), oxadiazolyl NH], 9.85 [s, 1H (exch.), amide NH], 7.83-7.10 (m, 20H, ArH's), 5.90 (s, 1H, pyrazolinyl CH); Anal. for $C_{30}H_{23}N_5O_2S$ Calcd.: C, 69.61; H, 4.48; N, 13.53; S,6.19. Found: C, 69.50; H, 4.50; N, 13.59; S, 6.15.

2-[5-Benzoylamino-1,3,-diphenyl-4-(2-methoxyphenyl)-2-pyrazolin-5-yl]-1,3,4-oxadiazole-5(4H)-thione (**12b**). Using the general procedure, **8b** gave **12b** (81%); mp. 140ºC; IR ((cm^{-1}): 3375, 3139 (NH str.), 3067 (aromatic CH str.), 2938, 2836 (OCH_3 and pyrazolinyl aliphatic CH str.), 1682 (amide C=O str.), 1602 (aromatic C=C str.), 1498, 1470, 1446 (NH bend.), 1343, 1328, 1293, 1253 (C-N str.), 1190, 1149, 1106, 1027 (=C-O-C= str., C-O str. of OCH_3), 1069 (C=S str.), 759, 699 (aromatic CH bend.); ^{1}H-NMR (DMSO-d_6): δ 14.52 [brs, 1H (exch.), oxadiazolyl NH], 9.69 [s, 1H (exch.), amide NH], 7.78-6.78 (m,19H, ArH's), 6.32 (s, 1H, pyrazolinyl CH), 3.85 (s, 3H, OCH_3); Anal. for $C_{31}H_{25}N_5O_3S$ Calcd.: C, 67.99; H, 4.60; N, 12.79; S,5.85. Found: C, 68.12 H, 4.62; N, 12.69; S,5.82.

N-(N-Phenylthiocarbamoyl)-5-benzoylamino-1,3-diphenyl-4-(2-methoxyphenyl)-2-pyrazoline-5-carbo-hydrazide (**13**). To a suspension of **8b** (1 mmol) in absolute ethanol (25 mL) was added phenyl isothiocyanate (1.01 mmol), and the mixture was heated under reflux for $2^1/_2$ hours (all materials went into solution after 45 minutes of heating under reflux). The reaction mixture was concentrated, allowed to cool, and upon scratching, the product precipitated as colorless crystals. The crude product was collected by filtration and recrystallized from ethanol as colorless crystals of **13** (75%) mp.145-146ºC; IR (cm^{-1}): 3371, 3327, 3150, 3110 (NH str.), 3059,3029 (aromatic CH str.), 2964, 2923, 2880, 2842 (OCH_3 and pyrazolinyl aliphatic CH str.), 1718 (hydrazide C=O str.), 1678 (amide C=O str.), 1651, 1625 (C=N str.), 1599 (aromatic C=C str.), 1543,1497, 1473, 1442 (NH bend.), 1380, 1357, 1320, 1291, 1252 (C-N str.), 1210-1025 (C-O str.), 1070 (C=S str.), 758, 692 (aromatic CH bend.); ^{1}H-NMR (DMSO-d_6): δ 10.79, 9.92, 9.34, 9.15 [3s, 1brs, 4H (exch.), 4NH], 7.80-6.55 (m, 24H, ArH's), 6.23 (s, 1H, pyrazolinyl CH), 3.76 (s, 3H, OCH_3); Anal. for $C_{37}H_{32}N_6O_3S$ Calcd.: C, 69.35; H, 5.03; N, 13.11; S, 5.04. Found: C, 69.1, H, 5.30; N, 13.00; S, 5.10

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