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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis, and *in vitro* evaluation of cytotoxic activity of new substituted 1,4-benzoquinones and hydroquinones

Ibrahim Chaaban · El-Sayeda El-Khawass · Mona Mahran · Ola El-Sayed · Hassan El-Saidi · Hassan Aboul-Enen

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Abstract A new series of *p*-benzoquinones, hydroquinones, and quinol dimethyl ethers substituted by a pyrazole ring either directly or after an oxoethyl linker was synthesized and screened for *in vitro* cytotoxic activity. Compounds **8d, f, g, i,** and **9c, f,** and **13c** exhibited broad-spectrum activity (GI_{50} MG-MID values 9.27–14.72 μM). With regard to sensitivity, compounds **8f** and **9c, f** have proved to possess a remarkable activity against leukemia tumor cell lines (GI_{50} = 3.43–5.03 μM). Indeed, compound **13c** showed the highest activity profile against individual leukemia subpanel cell line SR (GI_{50} = 0.91 μM).

Keywords 1,4-Benzoquinone · Cytotoxic agents · Hydroquinone · Pyrazole · Pyrazolidendione · Quinol dimethyl ether

Introduction

Quinones as well as hydroquinones represent an important class of compounds with diverse pharmacological activities. Among the most important biological activities reported are anticancer (Radeke *et al.*, 1997; Rozek *et al.*, 2001; Stahl *et al.*, 2001; Afrasiabi *et al.*, 2005; Ward *et al.*, 2005; Hasinoff and Begleiter, 2006), antimicrobial (Chabaan *et al.*, 1984a,b, 1989; Kaneshiro *et al.*, 2000; Habib and Mahran, 2004; Tapia *et al.*, 2004), antiviral (Urbam and Capon, 1996; Iwashima *et al.*, 2005), and anti-inflammatory (Ospina *et al.*, 2001) activities. Mitomycins comprise a group of substituted indoloquinone antibiotics with potent antitumor

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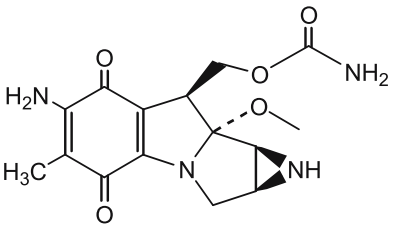
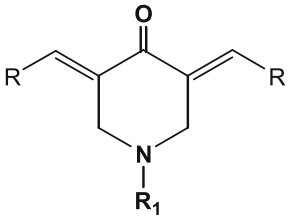
activity (Iyer and Szyblaski, 1963; Misra *et al.*, 1977). These compounds act as bifunctional alkylating agents that add across both strands of the DNA double helix leading to cancer cell death (Iyer and Szyblaski, 1963). Reduction of benzoquinone ring of mitomycins to the corresponding hydroquinone ring was proved to be an essential step for attaining the biological activity (Schwartz *et al.*, 1963). Moreover, evidence was provided indicating that the carbamoyl group and the aziridine ring of mitomycin C (Fig. 1) are not essential for its activity (Iyer and Szyblaski, 1963). In view of these facts, the pharmacophoric groups of the structural backbone of mitomycin could be simplified to a combined β-aminoketone and a cyclic α,β-unsaturated ketone. These two parts were previously combined into one chemical structure in the design of several piperidone derivatives (El-Subbagh *et al.*, 2000) (Fig. 1) as anticancer agents. These analogs were synthesized to fulfill such structural requirements and proved to be very promising cytotoxic agents (IC_{50} values < 10 μM). Those compounds were shown to possess a higher affinity for the thiol rather than the amino or the hydroxyl function of the nucleic acids, thus decreasing host toxicity.



1

Mitomycin C



2

Piperidone derivatives
R = aryl or heteroaryl
R_1 = alkyl

Fig. 1

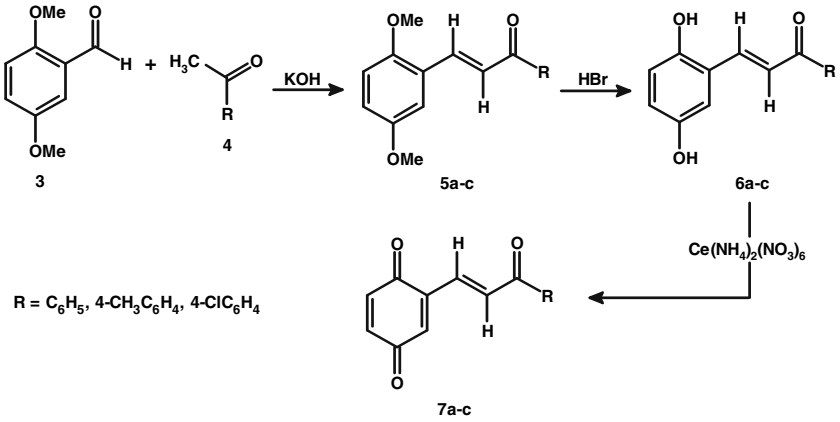
Based on the aforementioned rationale, a new series of 1,4-benzoquinones and hydroquinones was designed, synthesized, and screened for anticancer activity. The proposed compounds were designed to include both the α,β-unsaturated ketone and/or the β-aminoketone moieties in their structures.

Results and Discussion

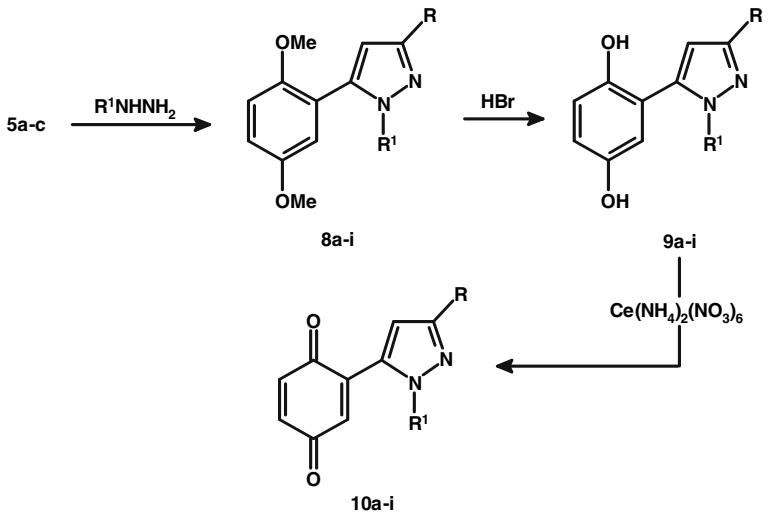
Chemistry

The starting material 1-aryl-3-(2,5-dimethoxyphenyl) propenones **5a–c** were synthesized via Claisen–Schmidt condensation (Wattanasin and Murrphy, 1980) (Scheme 1). The prepared quinol dimethylethers **5a–c** were demethylated with 48%

hydrobromic acid (Borgman *et al.*, 1973) to yield the dihydroxy chalcones **6a–c**. Subsequent oxidation of the dihydric phenolic compounds **6a–c** to the corresponding *p*-benzoquinones **7a–c** was carried out using ceric ammonium nitrate in aqueous acetonitrile (Ho *et al.*, 1972). The target pyrazole derivatives **8a–i** (Scheme 2) were obtained through cyclocondensation of the α,β-unsaturated ketones **5a–c** with the selected 4-substituted phenylhydrazine hydrochlorides in boiling glacial acetic acid containing an equimolar amount of anhydrous sodium acetate. Similarly, demethylation of **8a–i** by boiling with 48% hydrobromic acid yielded the corresponding hydroquinones **9a–i**, which on treatment with ceric ammonium nitrate in aqueous acetonitrile yielded the corresponding quinones **10a–i**.



Scheme 1

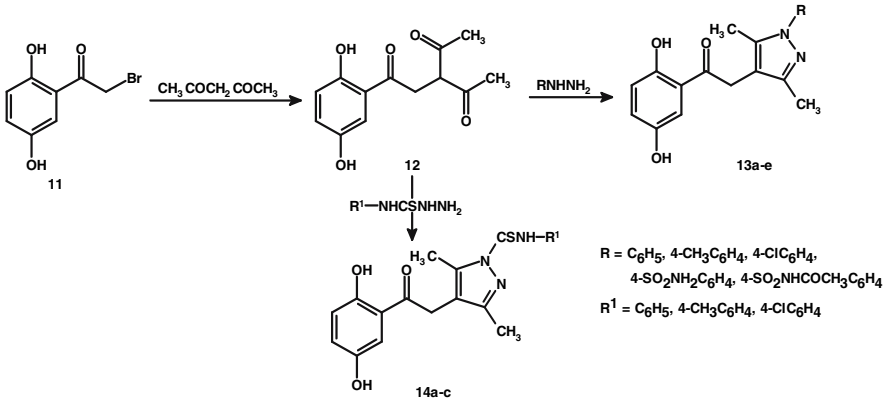


R = C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_6H_4

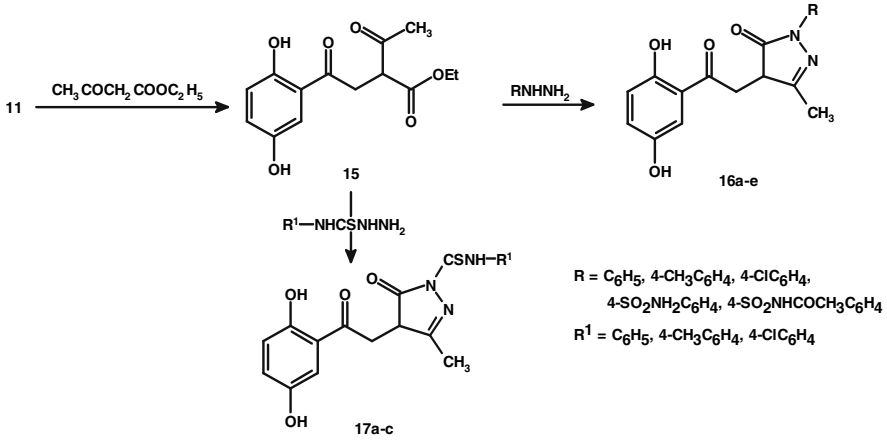
R^1 = C_6H_5, 4-$SO_2NH_2C_6H_4$, 4-$SO_2NHCOCH_3C_6H_4$

Scheme 2

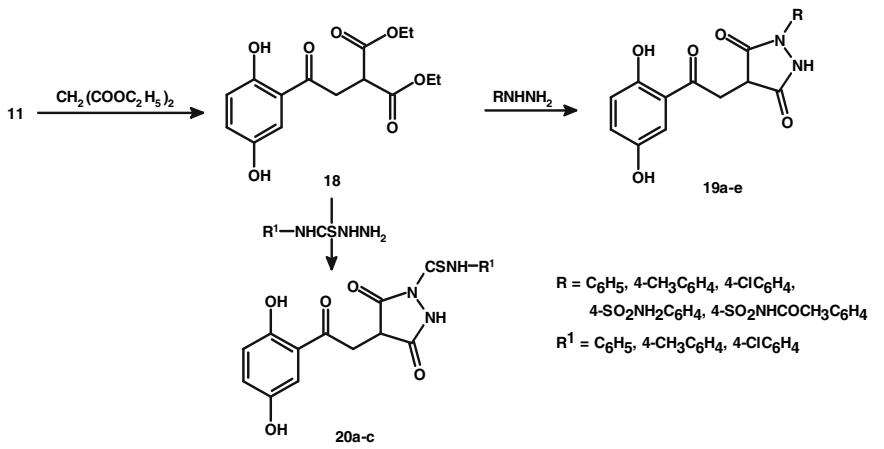
The starting material, 2,5-dihydroxyphenacylbromide **11,** was prepared according to a reported method (King and Ostrum, 1964). Heating a solution of acetylacetone, ethyl acetoacetate, or diethyl malonate in absolute ethanol with metallic sodium and an equimolar amount of 2,5-dihydroxyphenacyl bromide **11** gave the expected 3-(2,5-dihydroxyphenacyl)pentane-2,4-dione **12**, ethyl 2-(2,5-dihydroxyphenacyl)-3-oxobutanoate **15** and diethyl 2-(2,5-dihydroxyphenacyl) propanedioate **18**, respectively (Schemes 3, 4, and 5). Cyclocondensation of the prepared 1,3-dicarbonyl compounds **12, 15,** and **18** with the selected 4-substituted phenylhydrazine hydrochloride in the presence of anhydrous sodium acetate (Mong *et al.*, 1991) yielded the target substituted pyrazole, pyrazoline, and pyrazolidinedione derivatives **13, 16,** and **19**, respectively. On the other hand, reaction of the aforementioned 1,3-diketone with some selected 4-arylthiosemicarbazides in glacial acetic acid and anhydrous sodium acetate (Farghaly *et al.*, 1981) yielded the corresponding *N*-arylthiocarbamoylpyrazoles **14, 17,** and **20**.



Scheme 3



Scheme 4



Scheme 5

Attempts to oxidize the dihydroxy compounds, i.e., 1-aryl and 1-(*N*-arylthiocarbamoyl)-4-(2,5-dihydroxyphenacyl)-3,5-dimethylpyrazoles **13** and **14**, 1-aryl and 1-(*N*-arylthiocarbamoyl)- 4-(2,5-dihydroxyphenacyl)-3-methyl-4, 5-dihydropyrazolin-5-ones **16** and **17** or 1-aryl and 1-(*N*-arylthiocarbamoyl)-4-(2,5-dihydroxyphenacyl) pyrazolidine-3,5-diones **19** and **20,** were all unsuccessful. Many procedures were tried using different oxidizing agents and reaction conditions, including silver oxide, mercuric oxide, ceric ammonium nitrate, ferric chloride, and potassium permanganate. It was presumed that these series of compounds would exhibit clear strong intramolecular hydrogen bonding due to the presence of a carbonyl group in the ortho position to the hydroxyl group, which would create a system that can capture metals, giving stable six-membered ring water-soluble colored chelates. Thus, such compounds would undergo chelate formation reactions with the oxidizing metals rather than undergoing the expected oxidation reactions. To examine this assumption, solutions of dihydroxy derivatives **13a, 14a, 16a, 17a, 19a,** or **20a** in dimethylformamide (DMF) were treated with 5% aqueous solutions of $CuSO_4$, $CoSO_4$, or $NiSO_4$ yielded colored chelates The recorded λ_{max} for the chelates and blank experiments are listed in Table 1. The results obtained proved the formation of stable chelates between the aforementioned derivatives and the different metals used, thus accounting for the difficulty faced in oxidizing the dihydroxy compounds to their corresponding quinones.

Biological results

The in *vitro* antitumor evaluation of the tested compounds revealed that compounds **8d, f, g, i, 9c, f,** and **13c** exhibited a significantly high activity (GI_{50} = 9.27–14.72 μM; Table 2), with mild cytotoxicity (LC_{50} = 48.76–79.16 μM; Table 3). Compounds **8c, 9a, i, 10c, f, 16c,** and **19c** showed moderate activity (GI_{50} = 23.03–36.31 μM; Table 2). However, compounds **9d, g,** and **10e, g** possessed a weak activity (GI_{50} = 53.19–90.06 μM; Table 2). Among all tested compounds, **9c**

Table 1

Comp. no.	λ_{max} (in nm)		
	Cu^{2+} (505[b])	Co^{2+} (510[b])	Ni^{2+} (720[b])
13a	593 (351[a])	673 (351[a])	670 (351[a])
14a	598 (342[a])	675 (342[a])	673 (342[a])
16a	596 (351[a])	576 (351[a])	671 (351[a])
17a	594 (355[a])	574 (355[a])	675 (355[a])
19a	609 (351[a])	673 (351[a])	679 (351[a])
20a	615 (353[a])	674 (353[a])	677 (353[a])

[a] Blank of the compound in DMF–water

[b] Blank of the metal ion in DMF–water

showed the highest activity (GI_{50} = 9.27 μM) with a weak cytotoxic activity (LC_{50} = 76.14 μM, Table 3). Moreover, compound **13c** proved to be effective against individual leukemia subpanel cell lines SR (GI_{50} = 0.91 μM; results are not shown), whereas compound **8g** possessed a high activity against colon subpanel tumor cell lines (GI_{50} = 3.74 μM; Table 2), and compound **8i** exhibited growth inhibition (GI_{50}) potency against prostate cancer subpanel tumor cell lines at 3.61 μM (Table 2). With regard to selectivity, compounds **8c, g,** and **i,** i.e., the 1,3-diaryl-5-(2,5-dimethoxyphenyl) pyrazoles, possessed a moderate selectivity against various tumor cell lines (Table 2). Compound **8c** was selective against leukemia subpanel tumor cell lines (selectivity ratio of 3.03), compound **8g** was selective against colon subpanel tumor cell lines (selectivity ratio of 3.21), while compound **8i** showed selectivity against prostate subpanel tumor cell lines (selectivity ratio of 4.07).

The attempts to rationalize the structural variations of the synthesized compounds and the obtained antitumor data facilitated the deduction of the following general considerations. Direct attachment of the pyrazole moiety to the dihydroxyphenyl ring is required for optimal activity. This argument is based on the reported anticancer activity for the pyrazole ring (Abdou *et al.*, 2004). The introduction of sulfamoyl or an *N*-acetylsulfamoyl group at position 4 of the phenyl ring at the N^1 of the pyrazole ring resulted in the highest potency within the quinol dimethyl ether derivatives, whereas a chlorine atom at position 4 of the phenyl ring at C_3 of the pyrazole ring resulted in the highest potency within the hydroquinone and quinone series. However, the observed weak activity of the quinone derivatives as compared to hydroquinones or quinol dimethyl ethers was unexpected, because those quinones comprise both pharmacophores the α,β-unsaturated ketone and the β-aminoketone that are believed to be essential for the sought for activity. However, the evidence provided by Schwartz *et al.* (1963) demonstrated that reduction of the benzoquinone ring of mitomycins to the corresponding hydroquinone was an essential step for attaining the biological activity.

In the case of the second series of compounds that comprise a hydroquinone moiety connected to the pyrazole counterpart through an oxoethyl linker, it was

Table 2 Median growth inhibitory concentrations GI_{50} (μM) of *in vitro* subpanel tumor cell lines and GI_{50} (μM) full panel mean-graph midpoints (MG-MID)

Comp. no.	Subpanel tumor cell lines [a]									Full-panel GI_{50}
	I	II	III	IV	V	VI	**VII**	VIII	IX	MG-MID[b]
8c	11.11	40.63	25.17	29.23	34.93	49.00	34.89	60.45	17.68	33.67
	(3.03)[c]	(0.83)	(1.34)	(1.15)	(0.96)	(0.69)	(0.96)	(0.55)	(1.92)	
8d	6.94	31.38	11.92	14.96	15.33	13.60	12.95	13.90	12.28	12.80
	(1.84)	(0.95)	(1.07)	(0.85)	(0.83)	(0.94)	(0.98)	(0.92)	(1.04)	
8f	4.44	10.87	0.95	16.20	12.85	16.95	13.52	7.86	11.49	11.01
	(2.47)	(1.01)	(2.22)	(0.67)	(0.85)	(0.64)	(0.81)	(1.40)	(0.95)	
8g	7.40	15.26	3.74	18.10	15.41	13.27	13.34	11.99	9.70	12.02
	(1.62)	(0.79)	(3.21)	(0.66)	(0.78)	(0.90)	(0.90)	(1.00)	(1.24)	
8i	7.45	17.72	8.18	19.35	10.68	23.39	17.72	3.61	25.45	14.72
	(1.97)	(0.83)	(1.79)	(0.76)	(1.37)	(0.65)	(0.83)	(4.07)	(0.57)	
9a	35.70	26.86	28.51	18.62	22.57	37.65	22.58	16.70	17.05	25.13
	(0.70)	(0.93)	(0.88)	(1.35)	(1.11)	(0.67)	(1.11)	(1.50)	(1.47)	
9c	3.43	6.85	5.75	17.90	8.79	8.01	8.86	14.64	9.25	9.27
	(2.70)	(1.35)	(1.61)	(0.52)	(1.05)	(1.15)	(1.04)	(0.63)	(1.00)	
9d	49.57	88.92	75.68	86.60	61.88	81.32	88.07	77.60	83.87	77.05
	(1.55)	(0.86)	(1.02)	(0.89)	(1.25)	(0.95)	(0.87)	(0.99)	(0.92)	
9f	5.03	12.98	15.07	17.83	14.58	14.68	11.99	13.43	16.66	13.58
	(2.69)	(1.04)	(0.90)	(0.76)	(0.93)	(0.92)	(1.13)	(1.01)	(0.81)	
9g	93.63	93.88	78.63	90.40	84.77	100	78.06	100	91.31	90.06
	(0.96)	(0.96)	(1.14)	(0.99)	(1.06)	(0.90)	(1.15)	(0.90)	(0.98)	
9i	37.35	36.19	37.60	38.46	36.16	44.62	23.46	17.65	55.30	36.31
	(0.97)	(1.00)	(0.96)	(0.94)	(1.00)	(0.81)	(1.54)	(2.05)	(0.65)	
10c	27.80	53.47	42.38	65.35	69.37	67.27	55.57	36.50	51.46	25.43
	(0.91)	(1.01)	(1.00)	(0.98)	(0.95)	(0.79)	(1.14)	(1.18)	(1.11)	
10e	37.38	53.47	42.38	65.35	69.37	67.37	55.57	36.50	51.46	53.19
	(1.42)	(0.99)	(1.25)	(0.81)	(0.76)	(0.79)	(0.95)	(1.45)	(1.03)	
10f	31.75	23.90	17.55	23.73	26.66	26.50	23.05	21.55	21.86	24.05
	(0.75)	(1.00)	(1.37)	(1.01)	(0.90)	(0.90)	(1.04)	(1.11)	(1.10)	
10g	57.80	100	78.35	100	92.02	100	89.97	100	78.53	88.51
	(1.53)	(0.88)	(1.12)	(0.88)	(0.96)	(0.88)	(0.98)	(0.88)	(1.12)	
13c	7.71	12.01	11.18	11.31	13.08	14.05	12.03	12.39	11.37	11.68
	(1.52)	(0.97)	(1.04)	(1.03)	(0.89)	(0.83)	(0.97)	(0.94)	(1.02)	

obvious that the best activity was obtained when the substituent R for the N^1 of the pyrazole ring is a 4-bromophenyl group. Changing the substituent R with a phenyl, a *p*-tolyl, or a *p*-sulfamoylphenyl group resulted in a dramatic loss of activity. Interestingly, methyl groups attached to the pyrazole ring result in a higher activity, as shown in the order of activity of compounds: **13c > 16c > 19c**. This might be

Table 2 Continued

Comp. no.	Subpanel tumor cell lines [a]									Full-panel GI_{50}
	I	II	III	IV	V	VI	**VII**	VIII	IX	MG-MID[b]
16c	7.75	38.21	35.96	25.84	28.01	34.20	39.77	42.20	19.14	30.12
	(3.89)	(0.79)	(0.84)	(1.16)	(1.08)	(0.88)	(0.76)	(0.71)	(1.57)	
19c	34.13	21.68	17.68	18.83	22.02	26.22	23.73	22.65	16.09	23.03
	(0.67)	(1.06)	(1.28)	(1.22)	(1.05)	(0.88)	(0.83)	(1.02)	(1.43)	

[a] I, Leukemia; H, non-small cell lung cancer; III, colon cancer; IV, CNS cancer; V, melanoma; VI, ovarian cancer; VII, renal cancer; VIII, prostate cancer; IX, breast cancer

[b] GI_{50} (μM) full-panel mean-graph midpoints (MG-MID) = the average sensitivity of all cell lines toward the test agent

[c] Selectivity ratio of the nine tumor cell lines toward the active compounds

Table 3 Median total growth inhibitory concentrations (TGI, μM) of *in vitro* subpanel tumor cell lines, TGI (μM) full panel mean-graph mid-points (MG-MID) and LC_{50} (μM) full panel mean-graph midpoints (MG-MID)

Comp no.	Subpanel tumor cell lines[a]									Full panel TGI
	I	II	III	IV	V	VI	VII	VIII	XI	MG-MID[b]
8c	78.15	100	82.80	84.33	70.00	85.15	77.44	100	78.56	84.04 (99.82)[c]
8d	68.53	40.67	27.50	31.10	40.84	43.70	29.75	28.75	32.93	38.19 (73.02)
8f	52.14	44.32	38.37	37.20	36.72	50.77	39.50	20.80	33.96	39.35 (74.68)
8g	53.44	49.75	18.19	42.56	36.16	50.73	37.65	28.75	44.51	40.19 (77.06)
8i	50.14	52.58	35.99	49.97	28.66	67.07	53.18	21.90	70.16	47.74 (79.16)
9a	100	63.65	77.40	71.17	63.91	75.25	67.27	100	75.68	77.14 (91.28)
9c	49.72	33.21	16.82	34.63	32.46	60.35	32.02	30.70	41.05	36.77 (76.14)
9d	100	100	100	100	92.00	98.15	99.31	100	96.00	98.38 (100)
9f	61.41	39.05	43.07	35.46	38.90	50.85	35.40	29.80	54.45	43.15 (76.61)
9g	100	100	100	100	100	100	100	100	100	100 (100)
9i	92.63	73.72	66.55	93.86	60.06	81.22	59.80	38.75	82.13	72.08 (91.16)
10c	87.13	70.12	69.67	55.80	55.36	81.67	53.28	66.35	69.26	67.62 (95.61)
10e	94.04	100	88.83	100	97.27	100	86.78	100	95.46	95.82 (99.23)
10f	84.58	71.07	37.40	53.00	52.66	65.67	50.16	71.85	62.63	61.00 (92.28)
10g	91.23	100	100	100	100	100	100	100	100	95.32 (100)
13c	46.58	32.92	42.08	29.80	31.38	42.40	36.70	47.30	36.30	38.38 (48.76)
16c	35.81	48.55	45.46	45.96	42.57	50.00	46.15	50.00	38.18	44.67 (49.57)
19c	50.00	48.36	43.33	40.50	42.44	44.34	46.92	50.00	40.91	45.21 (49.87)

[a] I, Leukemia; II, non-small cell lung cancer; III, colon cancer; IV, CNS cancer; V, melanoma; VI, ovarian cancer; VII, renal cancer; VIII, prostate cancer; IX, breast cancer

[b] GI_{50} (μM) full-panel mean-graph mid-points (MG-MID) = The average sensitivity of all cell lines toward the test agent

[c] LC_{50} (μM) full-panel mean-graph midpoint (MG-MID) are shown in parentheses

attributed to the increase in lipid solubility that may facilitate absorption and penetration of the compound to the target active site of its action.

Conclusion

In this study, compounds **9c**, i.e., the 3-(4-chlorophenyl)-5-(2,5-dihydroxyphenyl)-1-phenylpyrazole and **13c**, i.e., the 1-(4-bromophenyl)-4-(2,5-dihydroxyphenacyl)-3,5-dimethylpyrazole, exhibited remarkable antitumor activity against leukemia subpanel tumor cell lines. These two compounds could be considered as useful templates or leads for future development and further derivation or structural variation to obtain more potent selective and less toxic antitumor agents.

Experimental Procedures

Biological methods

For the past decade, the Development Therapeutic Program (DTP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), Bethesda, MD, has used an *in vitro* model consisting of 60 human tumor cell lines as a primary anticancer screening (Paul *et al.*, 1989; Monks *et al.*, 1991; Grever *et al.*, 1992; Acton *et al.*, 1994; Boyd and Paull, 1995). Out of the newly synthesized pyrazole derivatives in the present work, 29 compounds **(5c, 8c, d, f, g, i, 9a, c, d, f, g, i, 10c, d, g, h, i, 13a–d, 16a–d, 19a–d)** were selected by the National Cancer Institute (NCI) for the *in vitro* disease–oriented human cells screening panel assay to investigate their antitumor activities.

Primary anticancer assay (3-cell line/one dose assay). The three-cell line one-dose assay has been in use by DTP for several years for evaluation of the combinatorial libraries and has proved to be an effective prescreen. The inclusion of this assay in the decision-making process will allow for more detailed evaluation of agents that have exhibited some level of ability to inhibit the growth of human tumor cells in culture. In this assay, a panel of three cell lines consisting of **MCF-7** (breast), **NCI-H460** (lung), and **SF-268** (CNS) was used. Each cell line was seeded and preincubated on a microtiter plate. Test agents were then added at a single concentration dose and the culture was incubated for additional 48 h. End points were determined with Alamar blue, and the results for each test agent were reported as the percent of growth of treated cells compared to untreated control cells. Compounds that reduced the growth of any of the cell lines up to 32% or less (negative numbers indicate cell kill) were then evaluated for their anticancer activity (over a 5-log dose range) using an extended panel of 60 cell lines. Eighteen compounds **(8c, d, f, g, i, 9a, c, d, f, g, i, 10c, e,f, g, 13c, 16c, 19c)** showed promising activity and reduced the growth of lung, breast, and/or CNS cell lines to <32%. The active compounds have been

automatically scheduled for evaluation against full panel 60 human cell lines (Grever *et al.*, 1992).

Full-panel anticancer assay (60-cell lines/five dose assay). The NCI's *in vitro* full-panel antitumor screen consisting of 60 cell lines derived from nine tumor subpanels, including leukemia, non-small-cell lung, colon, CNS, melanoma, ovarian, renal, prostate, and breast cancer cell lines were incubated with five concentrations (0.01–100 μM) for each compound and were used to create log concentration–% growth inhibition curves (Paull *et al.*, 1989; Monks *et al.*, 1991; Grever *et al.*, 1992; Acton *et al.*, 1994; Boyd and Paull, 1995). Cell viability and growth were then estimated using the sulforhodamine B (SRB) protein assay. Sulforhodamine B is a bright pink anionic dye that, in dilute acetic acid, binds electrostatically to the basic amino acids. This reagent gives the best combination of stain intensity, signal-to-noise ratio and linearity with cell number. Three responses parameters—GI_{50}, TGI, and LC_{50}—were calculated for each cell line. GI_{50} value (median growth inhibitory concentration) corresponds to the concentration of the compound that causes 50% decrease in net cell growth. TGI value (total growth inhibitory concentration; cytostatic activity) corresponds to the concentration of the compound that results in total growth inhibition. LC_{50} value (mean lethal concentration; cytotoxic activity) is the concentration of the compound causing 50% loss of initial cells at the end of the incubation period (48 hours). Subpanel or full panel mean-graph midpoint values (MG-MID) are the average of individual real and default GI_{50}, TGI, and LC_{50} values of all cell lines in the subpanel or the full panel, respectively. The ratio obtained by dividing the compound full-panel MG-MID (μM) by its individual MG-MID (μM) is considered as a measure of compound selectivity (Boyd and Paull, 1995). Ratios between 3 and 6 referred to moderate selectivity; ratios greater than 6 indicated high selectivity toward the corresponding cell line.

The median growth inhibitory concentrations (GI_{50}, μM) of *in vitro* subpanel tumor cell lines and GI_{50} (μM) full-panel mean-graph midpoints (MG-MID) are listed in Table 2. The median total growth inhibitory concentrations (TGI, μM) of *in vitro* subpanel tumor cell lines TGI (μM), full-panel mean-graph midpoints (MG-MID), and LC_{50} (μM) full-panel mean-graph midpoints (MG-MID) are recorded in Table 3.

The selectivity ratios of the active compounds toward the nine tumor cell lines are shown in Table 2.

Chemistry

General

Melting points were determined in open glass capillaries on a Griffin melting point apparatus and are all uncorrected. Infrared spectra (IR) were recorded, for KBr discs, on a Perkin Elmer 1430 Infrared spectrophotometer. Nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) was scanned on a Jeol-NMR 400 MHZ spectrophotometer and are reported as δ values (ppm) relative to tetramethylsilane

(TMS) as internal standard. The type of signal is indicated by one of the following letters: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet. Mass spectra were run on a Finnigan mass spectrometer model SSQ/700 (70 ev). Microanalyses were performed on Perkin Elmer 2400 elemental analyzer, at King Faisal Specialist Hospital and Research Center, Saudi Arabia. The absorption spectra of the formed colored chelates were recorded on Shimadzu U.V–Vis. recording spectrophotometer U.V–160A. Reactions were monitored via thin-layer chromatography (TLC) on silica gel (60 GF254, Merck), using glass plates, and the spots were visualized by exposure to iodine vapor or UV lamp at λ_{254} nm for few seconds.

General procedure for the preparation of 1-aryl-3-(2,5-dimethoxyphenyl) propenones **(5a–c)**

A solution of 2,5-dimethoxybenzaldehyde **3** (1.66 g, 10 mmol) in absolute ethanol (10 ml) was added to a well stirred solution of an equimolar amount of 4-substituted acetophenones (10 mmol) in 4% ethanolic sodium hydroxide (10 ml). Stirring was continued for 24 h at room temperature. The formed yellow crystalline product was filtered, washed with cold ethanol, dried in a vacuum desiccator and finally recrystallized.

3-(2,5-Dimethoxyphenyl)-1-phenylpropenone **(5a)**

Reagents: acetophenone (1.2 g, 10 mmol). *Crystallization*: dioxane. Yellow crystals (2.51 g, 94%), mp 118 °C. IR (KBr, cm^{-1}): 1663, 1603, 1266, 1053. Anal. % ($C_{17}H_{16}O_3$) C, H, calcd. 76.10, 6.01, found, 76.09, 6.00.

3-(2,5-Dimethoxyphenyl)-1-*p*-tolylpropenone **(5b)**

Reagents: 4-methylacetophenone (1.34 g, 10 mmol). *Crystallization*: dioxane. Yellow crystals (2.76 g, 98%), mp 122°C. IR (KBr, cm^{-1}): 1658, 1598, 1255, 1050. ^{1}H-NMR (DMSO-d_6, 400MHz): 2.42 (s, 3H), 3.80, 3.85 (two s, each 3H), 6.86 (d, 1H, J = 8.80Hz,), 6.92 (dd, 1H, J = 8.80, 2.92 Hz), 7.15 (d, 1H, J = 2.92 Hz), 7.28 (d, 2H , J = 8.08 Hz), 7.57 (d, 1H, J = 16.12 Hz), 7.92 (d, 2H, J = 8.08 Hz), 8.06 (d, 1H, J = 16.16 Hz). Anal. % ($C_{18}H_{18}O_3$) C, H, calcd. 76.57, 6.43, found, 76.57, 6.42.

1-(4-Chlorophenyl)-3-(2,5-dimethoxyphenyl)propenone **(5c)**

Reagents: 4-chloroacetophenone (1.54 g, 10 mmol). *Crystallization*: dioxane. Yellow crystals (2.9 g, 96%), mp 57°C, with decomposition. IR (KBr, cm^{-1}): 1653, 1590, 1226, 1042. ^{1}H-NMR ($CDCl_3$, 400 MHz): 3.79, 3.84 (two s, each 3H), 6.85 (d, 1H, J = 8.8 Hz), 6.92 (dd, 1H, J = 8.80, 2.92 Hz), 7.13 (d, 1H, J = 2.92 Hz), 7.45 (d, 2H, J = 11.00 Hz), 7.51 (d, 1H, J = 16.12 Hz), 7.92 (d, 2H, J = 11.00 Hz), 8.05 (d, 1H, J = 16.12 Hz). Anal. % ($C_{17}H_{15}ClO_3$) C, H, calcd. 67.44, 4.99, found, 67.43, 4.98.

General procedure for the preparation of 1-aryl-3-(2,5-dihydroxyphenyl) propenones **(6a–c)**

Under anhydrous condition, a mixture of 1-aryl-3-(2,5-dimethoxyphenyl)propenones 5a–c (1.0 mmol) and hydrobromic acid 48% (9 ml) was kept for 20 h at a temperature of 90°C via an oil bath. The excess hydrobromic acid was removed under reduced pressure and the formed dark residue was recrystallized.

3-(2,5-Dihydroxyphenyl)-1-phenylpropenone **(6a)**

Reagents: compound **5a** (0.27 g, 1.0 mmol) *Crystallization*: 90% aqueous ethanol. Brown solid (0.17 g, 70%), mp 186°C, with decomposition. IR (KBr, cm^{-1}): 3375-2980, 1625, 1537. Anal. % ($C_{15}H_{12}O_3$) C,H, calcd. 74.99, 5.03, found, 74.97, 5.03.

3-(2,5-Dihydroxyphenyl)-1-*p*-tolylpropenone **(6b)**

Reagents: compound **5b** (0.28 g, 1.0 mmol). *Crystallization*: 90% aqueous ethanol. Dark brown crystals (0.18 g, 72%), mp 223°C. IR (KBr, cm^{-1}): 3250–2900, 1612, 1520. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.42(s, 3H), 6.86 (d, 1H, J = 8.80 Hz), 6.92 (dd, 1H, J = 8.80, 2.92 Hz), 7.15 (d, 1H, J = 2.92 Hz), 7.28 (d, 2H, J = 8.08 Hz), 7.93 (d, 2H, J = 8.08 Hz), 7.57 (d, 1H, J = 16.12 Hz), 8.05 (d, 1H, J = 16.16 Hz), 9.33, 9.71 (two s, each 1H, D_2O-exch). Anal. % ($C_{16}H_{14}O_3$) C, H, calcd. 75.58, 5.55, found, 75.57, 5.54.

3-(2,5-Dihydroxyphenyl)-1-(4-chlorophenyl)propenone **(6c)**

Reagents: compound **5c** (0.3 g, 1.0 mmol). *Crystallization*: 90% aqueous ethanol. Dark brown solid (0.178 g, 66%), melting with decomposition at 254°C. IR (KBr, cm^{-1}): 3250–2870, 1612, 1516. ^{1}H-NMR (DMSO-d_6, 400 MHz): 6.85 (d, 1H, J = 8.80 Hz), 6.92 (dd, 1H, J = 8.80, 2.92 Hz), 7.13 (d, 1H, J = 2.92 Hz), 7.45 (d, 2H, J = 11.00 Hz), 7.93 (d, 2H, J = 11.00 Hz), 7.51 (d, 1H, J = 16.12 Hz), 8.05 (d, 1H, J = 16.12Hz), 9.23, 9.73 (two s, each 1H, two D_2O-exch.). Anal. % ($C_{15}H_{11}ClO_3$), C,H, calcd. 65.59, 4.04, found 65.58, 4.03.

General procedure for the preparation of 2-(3-aryl-3-oxopropenyl)-1,4-benzoquinones **(7a–c)**

A cold solution of ceric ammonium nitrate (2.74 g, 5 mmol) in (1:1) aqueous acetonitrile (40 ml) was gradually added to a cooled and vigorously stirred solution of 1-aryl-3-(2,5-dihydroxy-phenyl)propenones **6a–c** (1.0 mmol) dissolved in a mixture of acetonitrile (28 ml) and water (12 ml) over a period of 30 min. Cooling and stirring were continued for another further hour. The reaction mixture was allowed to attain room temperature, diluted with water (40 ml), and then extracted five times each with 20 ml portions of dichloromethane. The combined dichloromethane extracts were washed with an equal volume of water and dried over

anhydrous sodium sulfate, and the solvent was removed under diminished pressure. The crude dark brown precipitate was recrystallized.

2-(3-Oxo-3-phenylpropenyl)-1,4-benzoquinone **(7a)**

Reagents: 3-(2,5-dihydroxyphenyl)-1-phenylpropenone **6a** (0.24 g, 1.0 mmol) *Crystallization*: 10% aqueous DMF. Brown solid (0.17 g, 71%), mp 260°C, with decomposition. IR (KBr, cm^{-1}): 1725, 1637, 1525. Anal. % ($C_{15}H_{10}O_3$), C,H, calcd. 75.62, 4.23, found, 75.61, 4.22.

2-(3-oxo–ptolylpropenyl)-1,4-benzoquinone **(7b)**

Reagents: compound **6b** (0.25 g, 1.0 mmol). *Crystallization*: 10% aqueous DMF. Brown solid (0.16 g, 63%), mp >360°C. IR (KBr, cm^{-1}): 1720, 1635, 1522. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.42(s, 3H), 6.85 (d, 1H, J = 8.80 Hz), 6.92 (dd, 1H, J = 8.80, 2.92 Hz), 7.15 (d,1H, J = 2.92 Hz), 7.28 (d, 2H , J = 8.08 Hz), 7.56 (d, 1H, J = 8.80 Hz), 7.92 (d, 2H, J = 8.08 Hz), 8.07 (d, 1H, J = 8.80 Hz). Anal. % ($C_{16}H_{12}O_3$) C, H, calcd. 76.18, 4.79, found, 76.17, 4.77.

2-[3-(4-Chlorophenyl)-3-oxopropenyl]-1,4-benzoquinone **(7c)**

Reagents: compound **6c** (0.27 g, 1.0 mmol). *Crystallization*: 10% aqueous DMF. Brown solid (0.16 g, 59%), mp >360°C. IR (KBr, cm^{-1}): 1718, 1635, 1512. ^{1}H-NMR (DMSO-d_6, 400 MHz): 6.86 (d, 1H, J = 8.80 Hz), 6.93 (dd, 1H, J = 8.80, 2.92 Hz), 7.13 (d,1H, J = 2.92 Hz), 7.44 (d, 2H , J = 8.08 Hz), 7.51(d, 1H, J = 16.12 Hz), 7.92 (d, 2H, J = 8.08 Hz), 8.05 (d, 1H, J = 16.12 Hz). Anal. % ($C_{15}H_9ClO_3$) C, H, calcd. 66.07, 3.33, found, 66.06, 3.33.

General procedure for the preparation of 1,3-diaryl-5-(2,5-dimethoxyphenyl)pyrazoles **(8a–i)**

A mixture of 1-aryl-3-(2,5-dimethoxyphenyl)propenone **5a–c** (1.0 mmol) and the appropriate 4-substituted phenylhydrazine hydrochloride (1.05 mmol) or the selected 4-hydrazino-*N*-substituted benzenesulfonamide hydrochlorides (1.05 mmol) in glacial acetic acid (20 ml) containing an equimolar amount of anhydrous sodium acetate (0.086 g, 1.05 mmol) was heated under reflux for 12 h. The reaction mixture was concentrated, cooled and poured with stirring onto cold water (30 ml). The yellow precipitate formed was filtered, washed with water, air-dried, and finally recrystallized.

1,3-Diphenyl-5-(2,5-dimethoxyphenyl)pyrazole **(8a)**

Reagents: compound **5a** (0.27 g, 1.0 mmol) and phenylhydrazine hydrochloride (0.15 g, 1.05 mmol). *Crystallization*: chloroform–ethanol mixture (3:1). Yellow solid (0.25 g, 70%), mp 159°C. IR (KBr, cm^{-1}): 1598, 1500, 1215, 1048. Anal. % ($C_{23}H_{20}N_2O_2$) C, H, N, calcd. 77.51, 5.66, 7.86, found, 77.50, 5.63, 7.85.

5-(2,5-Dimethoxyphenyl)-3-(*p*-tolyl)-1-phenylpyrazole **(8b)**

Reagents: compound **5b** (0.28 g, 1.0 mmol) and *p*-tolylhydrazine hydrochloride, (0.17 g, 1.05 mmol). *Crystallization*: chloroform–ethanol mixture (3:1). Yellow solid (0.24 g, 65%), mp 172°C. IR (KBr, cm^{-1}): 1595, 1498, 1214, 1046. Anal. % ($C_{24}H_{22}N_2O_2$) C, H, N calcd. 77.81, 5.99, 7.56, found, 77.79, 5.89, 7.55.

3-(4-Chlorophenyl)-5-(2,5-dimethoxyphenyl)-1-phenylpyrazole **(8c)**

Reagents: compound **5c** (0.30 g, 1.0 mmol) and 4-chlorophenylhydrazine hydrochloride, (0.187 g, 1.05 mmol). *Crystallization*: chloroform–ethanol mixture (3:1). Yellow solid (0.27 g, 69%), mp 185°C. IR (KBr, cm^{-1}): 1593, 1499, 1214, 1045. ^{1}H-NMR (DMSO-d_6, 400 MHz): 3.81, 3.89 (two s, each 3H), 7.08 (dd, 1H, J = 9.52, 2.92 Hz), 7.25 (s, 1H), 7.20 (d, 1H, J = 9.52 Hz), 7.29 (d, 1H, J = 2.92 Hz), 7.41–7.43 (m, 3H), 7.52 (d, 2H, J = 11.76 Hz), 7.65 (d, 2H, J = 11.76 Hz), 7.74 (d, 2H, J = 11.00 Hz). Anal. ($C_{23}H_{19}ClN_2O_2$) C, H, N, calcd. 70.68, 4.90, 7.17, found, 70.66, 4.89, 7.17.

4-[5-(2,5-Dimethoxyphenyl)-3-phenylpyrazol-1-yl]benzenesulfonamide **(8d)**

Reagents: compound **5a** (0.27 g, 1.0 mmol) with 4-hydrazinobenzenesulfonamide hydrochloride, (0.234 g, 1.05 mmol). *Crystallization*: chloroform–ethanol mixture (3:1). Yellow solid (0.28 g, 64%), mp 140°C. IR (KBr, cm^{-1}): 3490, 1616, 1601, 1496, 1337, 1224, 1097, 1178. ^{1}H-NMR (DMSO-d_6, 400 MHz): 3.80, 3.85 (two s, each 3H), 4.65 (s, 2H, D_2O- exch), 6.86 (d, 1H, J = 8.80 Hz), 6.93 (dd, 1H, J = 8.80, 2.92 Hz), 7.15 (d, 1H, J = 2.92 Hz), 7.25(s, 1H), 7.48–7.50 (m, 3H), 7.56 (d, 2H, J = 16.12 Hz), 7.99 (d, 2H, J = 8.80 Hz), 8.05 (d, 2H, J = 16.12 Hz). Anal. % ($C_{23}H_{21}N_3O_4S$) C, H, N, calcd. 63.43, 4.86, 9.65, found, 63.39, 4.84, 9.63.

4-[5-(2,5-Dimethoxyphenyl)-3-*p*-tolylpyrazol-1-yl]benzenesulfonamide **(8e)**

Reagents: compound **5b** (0.28 g, 1.0 mmol) with 4-hydrazinobenzenesulfonamide hydrochloride, (0.234 g, 1.05 mmol). *Crystallization*: chloroform–ethanol mixture (3:1). Yellow solid (0.87 g, 64%), mp 168°C. IR (KBr, cm^{-1}): 3488, 1616, 1600, 1497, 1330, 1220, 1176, 1088. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.41 (s, 3H), 3.80, 3.84 (two s, each 3H), 4.46 (s, 2H, D_2O exch), 6.85 (d, 1H, J = 8.80 Hz), 6.93 (dd, 1H, J = 8.80, 2.92 Hz), 7.13 (d, 1H, J = 2.92 Hz), 7.25 (s, 1H), 7.44 (d, 2H, J = 11.00 Hz), 7.51 (d, 2H, J = 16.12 Hz), 7.92 (d, 2H, J = 11.00 Hz), 8.04 (d, 2H, J = 16.12 Hz). Anal. % ($C_{24}H_{23}N_3O_4S$) C, H, N, calcd. 64.13, 5.16, 9.35, found, 64.09, 5.13, 9.32.

4-[3-(4-Chlorophenyl)-5-(2,5-dimethoxyphenyl)pyrazol-1-yl]benzenesulfonamide **(8f)**

Reagents: compound **5c** (0.30 g, 1.0 mmol) with 4-hydrazinobenzenesulfonamide hydrochloride, (0.234 g, 1.05 mmol). *Crystallization*: chloroform–ethanol mixture

(3:1). Yellow solid (0.32 g, 68%), mp. 182°C. IR (KBr, cm^{-1}): 3489, 1616, 1598, 1496, 1328, 1224, 1175, 1086. ^{1}H-NMR (DMSO-d_6, 400 MHz): 3.80, 3.89 (two s, each 3H), 4.22 (s, 2H, D_2O exch.), 6.86 (d, 1H, J = 9.56 Hz), 6.93 (dd, 1H, J = 9.56, 2.92 Hz), 7.13 (d, 1H, J = 2.92 Hz), 7.25 (s, 1H), 7.45 (d, 2H, J = 8.80 Hz), 7.52 (d, 2H, J = 16.16 Hz), 7.94 (d, 2H, J = 8.80 Hz), 8.06 (d, 2H, J = 16.16 Hz). Anal. % ($C_{23}H_{20}ClN_3O_4S$) C, H, N, calcd. 58.78, 4.29, 8.94, found, 58.72, 4.19, 8.90.

N-Acetyl-4-[5-(2,5-dimethoxyphenyl)-3-phenylpyrazol-1-yl]benzenesulfonamide **(8g)**

Reagents: compound **5a** (0.27 g, 1.0 mmol) and *N*-acetyl-4-hydrazinobenzenesulfonamide hydrochloride, (0.28 g, 1.05 mmol). *Crystallization*: chloroform–ethanol mixture (3:1). Yellow solid (0.3 g, 63%), mp 158°C. IR (KBr, cm^{-1}): 3495, 1615, 1597, 1488, 1321, 1218, 1175, 1085. ^{1}H-NMR (DMSO-d_6, 400 MHz): 3.79, 3.83 (two s, each 3H), 2.32 (s, 3H), 6.86 (d, 1H, J = 8.80 Hz), 6.92 (dd, 1H, J = 8.80, 2.92 Hz), 7.15 (d, 1H, J = 2.92 Hz), 7.25 (s, 1H), 7.48–7.50 (m, 3H), 7.57 (d, 2H, J = 16.12 Hz), 7.99 (d, 2H, J = 8.80 Hz), 8.06 (d, 2H, J = 16.16 Hz), 10.25 (s, 1H, D_2O-exch.). Anal. % ($C_{25}H_{23}N_3O_5S$) C, H, N, calcd. 62.88, 4.85, 8.80, found, 62.79, 4.78, 8.78.

N-Acetyl-4-[5-(2,5-dimethoxyphenyl)-3-*p*-tolylpyrazol-1-yl]benzenesulfonamide **(8h)**

Reagents: compound **5b** (0.28 g, 1.0 mmol) and *N*-acetyl-4-hydrazinobenzenesulfonamide hydrochloride, (0.28 g, 1.05 mmol). *Crystallization*: chloroform–ethanol mixture (3:1). Yellow solid (0.39 g, 79%), mp 190°C. IR (KBr, cm^{-1}): 3490, 1616, 1598, 1486, 1322, 1219, 1175, 1089. ^{1}H-NMR (DMSO-d_6, 400 MHz): 1.99 (s, 3H), 3.80, 3.84 (two s, each 3H), 2.35 (s, 3H), 7.06 (d, 1H, J = 8.80 Hz), 7.14 (dd, 1H, J = 8.80, 2.92 Hz), 7.25 (s, 1H), 7.33 (d, 1H, J = 2.92 Hz), 7.64 (d, 2H, J = 8.80 Hz), 7.88 (d, 2H, J = 16.00 Hz), 8.05 (d, 2H, J = 16.00 Hz), 8.17 (d, 2H, J = 8.80 Hz), 10.11 (s, 1H, D_2O-exch.). Anal. % ($C_{26}H_{25}N_3O_5S$) C, H, N, calcd. 63.53, 5.13, 8.55, found, 63.48, 5.07, 8.53.

N-Acetyl-4-[3-(4-chlorophenyl)-5-(2,5-dimethoxyphenyl)pyrazol-1-yl]benzenesulfon-amide **(8i)**

Reagents: compound **5c** (0.30 g, 1.0 mmol) with *N*-acetyl-4-hydrazinobenzenesulfonamide hydrochloride, (0.28 g, 1.05 mmol). *Crystallization*: chloroform–ethanol mixture (3:1). Yellow solid (0.38 g, 74%), mp 206°C. IR (KBr, cm^{-1}): 3497, 1616, 1595, 1489, 1335, 1228, 1180, 1092. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.42 (s, 3H), 3.81, 3.85 (two s, each 3H), 6.85 (d, 1H, J = 8.80 Hz), 6.92 (dd, 1H, J = 8.80, 2.92 Hz), 7.15 (d, 1H, J = 2.92 Hz), 7.25 (s, 1H), 7.28 (d, 2H, J = 8.80 Hz), 7.57 (d, 2H, J = 15.40 Hz), 7.92 (d, 2H, J = 8.80 Hz), 8.06 (d, 2H, J = 15.40 Hz), 10.01 (s, 1H, D_2O-exch.). Anal. % ($C_{25}H_{22}ClN_3O_5S$) C, H, N, calcd. 58.65, 4.33, 8.21, found, 58.58, 4.26, 8.19.

General procedure for the preparation of 1,3-diaryl-5-(2,5-dihydroxyphenyl)pyrazoles **(9a–i)**

Under anhydrous condition, a mixture of the appropriate 1,3-diaryl-5-(2,5-dimethoxyphenyl) pyrazoles **8a–i** (1.0 mmol) and 48% hydrobromic acid (9 ml) was heated for 4 h, keeping the temperature between 120 and 125°C with an oil bath. The reaction mixture was allowed to cool and poured with stirring onto cold water. The brown precipitate formed was filtered, air-dried, and finally recrystallized.

5-(2,5-Dihydroxyphenyl)-1,3-diphenylpyrazole **(9a)**

Reagents: compound **8a** (0.356 g, 1.0 mmol). *Crystallization*: chloroform–ethanol mixture (3:1). Brown solid (0.246 g, 75%), mp 180°C. IR (KBr, cm^{-1}): 3414–3190, 1615, 1505. Anal. % ($C_{21}H_{16}N_2O_2$) C, H, N, calcd. 76.81, 4.91, 8.53, found, 76.80, 4.90, 8.53.

5-(2,5-Dihydroxyphenyl)-3-(*p*-tolyl)-1-phenylpyrazole **(9b)**

Reagents: compound **8b** (0.37 g, 1.0 mmol). *Crystallization*: 10% aqueous DMF. Brown solid (0.26 g, 76%), mp 289°C. IR (KBr, cm^{-1}): 3420–3112, 1600, 1500. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.19 (s, 3H), 6.88 (d, 1H, J = 8.80 Hz), 6.93 (dd, 1H, J = 8.80, 2.92 Hz), 7.16 (d, 1H, J = 2.92 Hz), 7.27 (s, 1H), 7.45–7.49 (m, 3H), 7.57 (d, 2H, J = 16.00 Hz), 7.92 (d, 2H, J = 8.08 Hz), 8.05 (d, 2H, J = 16.00 Hz), 9.17, 9.6 (two s, each 1H, two D_2O-exch.). Anal. % ($C_{22}H_{18}N_2O_2$) C, H, N, calcd. 77.17, 5.30, 8.18, found, 77.15, 5.28, 8.18.

3-(4-Chlorophenyl)-5-(2,5-dihydroxyphenyl)-1-phenylpyrazole **(9c)**

Reagents: compound **8c** (0.39 g, 1.0 mmol). *Crystallization*: 10% aqueous DMF. Brown solid (0.29 g, 80%), mp >360°C. IR (KBr, cm^{-1}): 3425–3100, 1598, 1493. ^{1}H-NMR (DMSO-d_6, 400 MHz): 6.08 (dd, 1H, J = 9.52, 2.92 Hz), 7.19 (d, 1H, J = 9.52 Hz), 7.25 (s, 1H), 7.29 (d, 1H, J = 2.92 Hz), 7.42–7.44 (m, 3H), 7.52 (d, 2H, J = 11.76 Hz), 7.66 (d, 2H, J = 11.76 Hz), 7.75 (d, 2H, J = 11.00 Hz), 9.20, 9.63 (two s, each 1H, two D_2O-exch.). Anal. % ($C_{21}H_{15}ClN_2O_2$) C, H, N, calcd. 69.52, 4.17, 7.72, found, 69.50, 4.15, 7.71.

4-[5-(2,5-Dihydroxyphenyl)-3-phenylpyrazol-1-yl]benzenesulfonamide **(9d)**

Reagents: compound **8d** (0.435 g, 1.0 mmol). *Crystallization*: 10% aqueous DMF. Brown solid (0.33 g, 87%), mp 290°C. IR (KBr, cm^{-1}): 3409–3239 (several bands), 1640, 1593, 1499, 1215, 1188. ^{1}H-NMR (DMSO-d_6, 400 MHz): 4.67 (s, 2H, D_2O exch), 6.84 (d, 1H, J = 8.80 Hz), 6.93 (dd, 1H, J = 8.80, 2.92 Hz), 7.15 (d, 1H, J = 2.92 Hz), 7.26 (s, 1H), 7.48–7.51 (m, 3H), 7.57 (d, 2H, J = 16.12 Hz), 7.99 (d, 2H, J = 8.80 Hz), 8.06 (d, 2H, J = 16.12 Hz), 9.17, 9.63 (two s, each 1H, two D_2O-exch.). Anal. % ($C_{21}H_{17}N_3O_4S$) C, H, N, calcd. 61.91, 4.21, 10.31, found, 61.88, 4.19, 10.28.

4-[5-(2,5-Dihydroxyphenyl)-3-*p*-tolylpyrazol-1-yl]benzenesulfonamide **(9e)**

Reagents: compound **8e** (0.45 g, 1.0 mmol). *Crystallization*: chloroform–ethanol mixture (3:1). Brown solid (0.33 g, 78%), mp > 360°C. IR (KBr, cm^{-1}): 3420–3230 (several bands), 1635, 1590, 1497, 1215, 1165. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.41 (s, 3H), 4.46 (s, 2H, D_2O exch), 6.86 (d, 1H, J = 8.80 Hz), 6.92 (dd, 1H, J = 8.80, 2.92 Hz), 7.14 (d, 1H, J = 2.92 Hz), 7.28 (s, 1H), 7.44 (d, 2H, J = 11.00 Hz), 7.51 (d, 2H, J = 16.12 Hz), 7.92 (d, 2H, J = 11.00 Hz), 8.04 (d, 2H, J = 16.12 Hz), 9.17, 9.63 (two s, each 1H, two D_2O-exch.). Anal. % ($C_{22}H_{19}N_3O_4S$) C, H, N, calcd. 62.69, 4.54, 9.97, found, 62.65, 4.52, 9.95.

4-[3-(4-Chlorophenyl)-5-(2,5-dihydroxyphenyl)pyrazol-1-yl]benzenesulfonamide **(9f)**

Reagents: compound **8f** (0.47 g, 1.0 mmol). *Crystallization*: 10% aqueous DMF. Dark brown solid (0.322 g, 73%), mp >360°C. IR (KBr, cm^{-1}): 3465–3230 (several bands), 1605, 1590, 1491, 1219, 1128. ^{1}H-NMR (DMSO-d_6, 400 MHz): 4.36 (s, 2H, D_2O exch.), 6.86 (d, 1H, J = 9.56 Hz), 6.93 (dd, 1H, J = 9.56, 2.92 Hz), 7.13 (d, 1H, J = 2.92 Hz), 7.25 (s, 1H), 7.45 (d, 2H, J = 8.80 Hz), 7.50 (d, 2H, J = 16.16 Hz), 7.92 (d, 2H, J = 8.80 Hz), 8.05 (d, 2H, J = 16.16 Hz), 9.23, 9.73(two s, each 1H, two D_2O-exch.). Anal. % ($C_{21}H_{16}Cl\ N_3\ O_4S$) C, H, N, calcd. 57.08, 3.65, 9.51, found, 57.06, 3.62, 9.49.

N-Acetyl-4-[5-(2,5-dihydroxyphenyl)-3-phenylpyrazol-1-yl]benzenesulfonamide **(9g)**

Reagents: compound **8g** (0.477 g, 1.0 mmol). *Crystallization*: 10% aqueous DMF. Brown solid (0.32 g, 71%), mp >360°C. IR (KBr, cm^{-1}): 3400–3250, 1687, 1600, 1500, 1487, 1250, 1153. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.33 (s, 3H), 6.86 (d, 1H, J = 8.80 Hz), 6.93 (dd, 1H, J = 8.80, 2.92 Hz), 7.15 (d, 1H, J = 2.92 Hz), 7.25 (s, 1H), 7.48–7.50 (m, 3 H), 7.57 (d, 2H, J = 16.12 Hz), 7.99 (d, 2H, J = 8.80 Hz), 8.06 (d, 2H, J = 16.12 Hz), 9.17, 9.36, 10.25 (three s, each 1H, two D_2O-exch.). Anal. % ($C_{23}H_{19}\ N_3O_5S$) C, H, N, calcd. 61.46, 4.26, 9.35, found, 61.46, 4.25, 9.33.

N-Acetyl-4-[5-(2,5-dihydroxyphenyl)-3-(4-methylphenyl)pyrazol-1-yl]benzene sulfonamide **(9h)**

Reagents: compound **8h** (0.491 g, 1.0 mmol). *Crystallization*: 10% aqueous DMF. Brown solid (0.34 g, 73%), mp >360°C. IR (KBr, cm^{-1}): 3400–3280, 1670, 1598, 1498, 1455, 1245, 1138. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.05 (s, 3H), 2.43 (s, 3H), 7.08 (dd, 1H, J = 9.52, 2.92 Hz), 7.19 (d, 1H, J = 9.52 Hz), 7.30 (d, 2H, J = 16.00 Hz), 7.35 (s, 1H), 7.44 (d, 2H, J = 16.00 Hz), 7.52 (d, 2H, J = 11.76 Hz), 7.65 (d, 2H, J = 11.76 Hz), 7.73 (d, 1H, J = 2.92 Hz), 9.02, 9.65, 10.43(three s, each 1H, two D_2O-exch.). Anal.% ($C_{24}H_{21}N_3O_5S$) C, H, N, calcd. 62.19, 4.57, 9.07, found, 62.09, 4.55, 9.06.

N-Acetyl-4-[3-(4-chlorophenyl)-5-(2,5-dihydroxyphenyl)pyrazol-1-yl]benzene-sulfonamide **(9i)**

Reagents: compound **8i** (0.51 g, 1.0 mmol). *Crystallization*: 10% aqueous DMF. Brown solid (0.37 g, 77%), mp >360°C. IR (KBr, cm^{-1}): 3400–3286, 1678, 1594, 1490, 1459, 1243, 1137. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.42 (s, 3H), 6.88 (d, 1H, J = 8.76 Hz), 6.94 (dd, 1H, J = 8.76, 2.92 Hz), 7.15 (d, 1H, J = 2.92 Hz), 7.21 (s, 1H), 7.28 (d, 2H, J = 8.80 Hz), 7.57 (d, 2H, J = 15.20 Hz), 7.92 (d, 2H, J = 8.80 Hz), 8.07 (d, 2H, J = 15.2 Hz), 9.17, 9.63, 10.35 (three s, each 1H, two D_2O-exch.). Anal. % ($C_{23}H_{18}ClN_3O_5S$) C, H, N, calcd. 57.09, 3.75, 8.68, found, 57.07, 3.69, 8.67.

General procedure for the preparation of 1,3-(diaryl)-5-(1,4-benzo-quinonyl) pyrazoles **(10a–i)**

To a solution of the appropriate 1,3-diaryl-5-(2,5-dihydroxyphenyl)pyrazoles **9a–i** (1.0 mmol) dissolved in a mixture of acetonitrile (28 ml) and water (6 ml), a cooled solution of ceric ammonium nitrate (2.74 g, 5 mmol) in a mixture of acetonitrile (20 ml) and water (20 ml) was slowly added with vigorous stirring over a period of 30 min. During addition, the reaction mixture was kept in an ice water bath whereupon the violet crystalline product separated out. Compound was filtered, washed with ether, and finally recrystallized.

5-(1,4-Benzoquinonyl)-1,3-diphenylpyrazole **(10a)**

Reagents: compound **9a** (0.328 g, 1.0 mmol). *Crystallization*: DMF/water (5:1). Violet solid (0.22 g, 67%), mp >360°C. IR (KBr, cm^{-1}): 1712, 1612, 1512. Anal. % ($C_{21}H_{14}N_2O_2$) C, H, N, calcd. 77.29, 4.32, 8.58, found, 77.26, 4.28, 8.54.

5-(1,4-Benzoquinonyl)-3-(*p*-tolyl)-1-phenylpyrazole **(10b)**

Reagents: compound **9b** (0.342 g, 1.0 mmol). *Crystallization*: 10% aqueous DMF. Violet solid (0.22 g, 65%), mp >360°C. IR (KBr, cm^{-1}): 1710, 1612, 1500. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.19 (s, 3H), 6.86 (d, 1H, J = 8.80 Hz), 6.92 (dd, 1H, J = 8.80, 2.92 Hz), 7.15 (d, 1H, J = 2.92 Hz), 7.27 (s, 1H), 7.46–7.49 (m, 3H), 7.57 (d, 2H, J = 16.12 Hz), 7.93 (d, 2H, J = 8.08 Hz), 8.06 (d, 2H, J = 16.12 Hz). Anal. % ($C_{22}H_{16}N_2O_2$) C, H, N, calcd. 77.63, 4.74, 8.23, found, 77.60, 4.71, 8.20.

5-(1,4-Benzoquinonyl)-3-(4-Chlorophenyl)-1-phenylpyrazole **(10c)**

Reagents: compound **9c** (0.362 g, 1.0 mmol). *Crystallization*: 10% aqueous DMF. Violet solid (0.25 g, 69%), mp >360°C. IR (KBr, cm^{-1}): 1706, 1609, 1498. Anal. % ($C_{21}H_{13}ClN_2O_2$) C, H, N, calcd. 69.91, 3.63, 7.76, found, 69.88, 3.59, 7.75.

4-[5-(1,4-Benzoquinonyl)-3-phenylpyrazol-1-yl]benzenesulfonamide **(10d)**

Reagents: compound **9d** (0.407 g, 1.0 mmol). *Crystallization*: 10% aqueous DMF. Violet solid (0.235 g, 58%), mp 321°C with decomposition. IR (KBr, cm^{-1}): 3250, 1728, 1593, 1500, 1450, 1250, 1162. ^{1}H-NMR (DMSO-d_6, 400 MHz): 4.67 (s, 2H, D_2O exch.), 6.63 (d, 1H, J = 9.52 Hz), 6.93 (dd, 1H, J = 9.52, 2.92 Hz), 7.15 (d, 1H, J = 2.92 Hz), 7.26 (s, 1H), 7.48–7.50 (m, 3H), 7.56 (d, 2H, J = 16.12 Hz), 7.99 (d, 2H, J = 8.80 Hz), 8.06 (d, 2H, J = 16.12 Hz). Anal. % ($C_{21}H_{15}N_3O_4S$) C, H, N, calcd. 62.21, 3.73, 10.36, found, 62.18, 3.70, 10.35.

4-[5-(1,4-Benzoquinonyl)-3-*p*-tolyl-pyrazol-1-yl]benzenesulfonamide **(10e)**

Reagents: compound **9e** (0.421 g, 1.0 mmol). *Crystallization*: 10% aqueous DMF. Violet solid (0.26 g, 62%), mp >360°C. IR (KBr, cm^{-1}): 3250, 1725, 1593, 1498, 1448, 1250, 1158. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.41 (s, 3H), 4.60 (s, 2H, D_2O exch.), 7.08 (dd, 1H, J = 9.56, 2.92 Hz), 7.19 (d, 1H, J = 9.56 Hz), 7.24 (s, 1H), 7.34 (d, 2H, J = 11.96 Hz), 7.42 (d, 2H, J = 11.96 Hz), 7.52 (d, 2H, J = 11.76 Hz), 7.65 (d, 2H, J = 11.76 Hz), 7.73 (d, 1H, J = 2.92 Hz). Anal. % ($C_{22}H_{17}N_3O_4S$) C, H, N, calcd. 63.00, 4.09, 10.02, found, 62.97, 4.06, 10.00.

4-[5-(1,4-Benzoquinonyl)-3-(4-chlorophenyl)pyrazol-1-yl]benzenesulfonamide **(10f)**

Reagents: compound **9f** (0.442 g, 1.0 mmol). *Crystallization*: DMF–water (5:1). violet solid (0.26 g, 59%), mp 340°C with decomposition. IR (KBr, cm^{-1}): 3255, 1709, 1594, 1495, 1445, 1241, 1148. ^{1}H-NMR (DMSO-d_6, 400 MHz): 4.45 (s, 2H, D_2O exch.), 6.85 (d, 1H, J = 8.80 Hz), 6.96 (dd, 1H, J = 8.80, 2.92 Hz), 7.14 (d, 1H, J = 2.92 Hz), 7.22 (s, 1H), 7.33 (d, 2H, J = 15.40 Hz), 7.51 (d, 2H, J = 15.40 Hz), 7.79 (d, 2H, J = 9.52 Hz), 7.90 (d, 2H, J = 9.52 Hz). Anal. % ($C_{21}H_{14}ClN_3O_4S$) C, H, N, calcd. 57.34, 3.21, 9.55, found, 57.29, 3.18, 9.54.

N-Acetyl-4-[5-(1,4-benzoquinonyl)-3-phenylpyrazol-1-yl]benzenesulfonamide **(10g)**

Reagents: compound **9g** (0.449 g, 1.0 mmol). *Crystallization*: 10% aqueous DMF. Violet solid (0.26 g, 58%), mp >360°C. IR (KBr, cm^{-1}): 3375, 1731, 1662, 1584, 1496, 1437, 1250, 1175. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.32 (s, 3H), 6.86 (d, 1H, J = 8.80 Hz), 6.93 (dd, 1H, J = 8.80, 2.92 Hz), 7.15 (d, 1H, J = 2.92 Hz), 7.27 (s, 1H), 7.48–7.50 (m, 3H), 7.56 (d, 2H, J = 16.12 Hz), 7.99 (d, 2H, J = 8.80 Hz), 8.05 (d, 2H, J = 16.12 Hz), 10.26 (s, 1H, D_2O-exch.). Anal. % ($C_{23}H_{17}N_3O_5S$) C, H, N, calcd. 61.74, 3.83, 9.39, found, 61.70, 3.79, 9.38.

N-Acetyl-4-[5-(1,4-benzoquinonyl)-3-(*p*-tolyl)pyrazol-1-yl]benzenesulfonamide **(10h)**

Reagents: compound **9h** (0.463 g, 1.0 mmol). *Crystallization*: DMF–water (5:1). Violet solid (0.30 g, 65%), mp >360°C. IR (KBr, cm^{-1}): 3370, 1730, 1660, 1580, 1495, 1430, 1245, 1170. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.06 (s, 3H),

2.44 (s, 3H), 7.08 (dd, 1H, J = 9.52, 2.92 Hz), 7.20 (d, 1H, J = 9.52 Hz), 7.30 (d, 2H, J = 16.00 Hz), 7.35 (s, 1H), 7.45 (d, 2H, J = 16.00 Hz), 7.52 (d, 2H, J = 11.76 Hz), 7.67 (d, 2H, J = 11.76 Hz), 7.73 (d, 1H, J = 2.92 Hz), 10.35 (s, 1H, D_2O-exch.). Anal. % ($C_{24}H_{19}N_3O_5S$) C, H, N, calcd. 62.46, 4.15, 9.11, found, 62.39, 4.11, 9.09.

N-Acetyl-4-[5-(1,4-benzoquinonyl)-3-(4-chlorophenyl))pyrazol-1-yl]benzene-sulfonamide **(10i)**

Reagents: compound **9i** (0.483 g, 1.0 mmol). *Crystallization*: DMF–water (5:1). Violet solid (0.30 g, 62%), mp >360°C. IR (KBr, cm^{-1}): 3368, 1725, 1662, 1588, 1493, 1446, 1240, 1173. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.45 (s, 3H), 6.88 (d, 1H, J = 8.76 Hz), 6.94 (dd, 1H, J = 8.76, 2.92 Hz), 7.15 (d, 1H, J = 2.92 Hz), 7.21 (s, 1H), 7.28 (d, 2H, J = 8.08 Hz), 7.57 (d, 2H, J = 15.24 Hz), 7.93 (d, 2H, J = 8.80 Hz), 8.07 (d, 2H, J = 15.24 Hz), 10.35(s, 1H, D_2O-exch.). Anal. % ($C_{23}H_{16}ClN_3O_5S$) C, H, N, calcd. 57.32, 3.35, 8.72, found, 57.31, 3.32, 8.68.

3-(2,5-Dihydroxyphenacyl)pentane-2,4-dione **(12)**

To a well stirred solution of acetyl acetone (1.0 g, 10 mmol) in absolute ethanol (10 ml) was added (0.23 g, 10 mmol) of metallic sodium. The reaction mixture was stirred for 1 h under anhydrous condition until sodium was completely dissolved. A solution of 2,5-dihdroxyphenacylbromide 11 (2.31 g, 10 mmol) in absolute ethanol (20 ml) was then added to the previously prepared solution and the reaction mixture was stirred while heating under reflux for 16 h. The formed dark brown precipitate was filtered, washed with diethyl ether, and recrystallized from ethanol to yield 12 (1.92 g, 77%): mp >360°C. IR (KBr, cm^{-1}): 3425, 1625. . ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.39 (s, 6H), 3.56 (s, 1/2H, D_2O-exch.), 5.08 (s, 1/2H), 5.33 (s, 2H), 7.09 (dd, 1H, J = 9.56, 3.86 Hz), 7.19 (d, 1H, J = 9.56 Hz), 7.54 (d, 1H, J = 3.86 Hz), 9.19, 9.63 (two s, each 1H, D_2O-exch.). Anal. % ($C_{13}H_{14}O_5$) C, H, calcd, 62.39, 5.64, found, 62.38, 5.62.

Compounds 14 and 19 were prepared via the same procedure.

Ethyl 2-(2,5-dihydroxyphenacyl)-3-oxobutanoate **(15)**

Reagents: ethylacetoacetate (1.30 g, 10 mmol) and compound 11 (2.31 g, 10 mmol), reaction time: 18 hours. *Crystallization*: ethanol. Brown solid (2.24 g, 80%), mp > 360°C. IR(KBr, cm^{-1}): 3425, 1700, 1612, 1225. ^{1}H-NMR (DMSO-d_6, 400 MHz): 1.28 (t, 3H, J = 7.00 Hz), 2.39 (s, 3H), 3.50 (s, 1/2H, D_2O-exch.), 4.06 (q, 2H J = 7.00 Hz), 5.08 (s, 1/2H), 5.33 (s, 2H), 7.08 (dd, 1H, J = 9.56, 3.86 Hz), 7.19 (d, 1H, J = 9.56 Hz), 7.54 (d,1H, J = 3.80 Hz), 9.19, 9.63 (two s, each 1H, D_2O-exch.). Anal. % ($C_{14}H_{16}O_6$) C, H, calcd. 60.00, 5.75, found, 59.99, 5.74.

Diethyl 2-(2,5-dihydroxyphenacyl)propanedioate **(18)**

Reagents: diethyl malonate (1.60 g, 10 mmol) and compound 11 (2.31 g, 10 mmol). *Crystallization*: Brown solid (2.45 g, 79%), reaction time: 22 h, mp >360°C. IR (KBr, cm^{-1}): 3412, 1703, 1609, 1275. ^{1}H-NMR (DMSO-d_6, 400 MHz): 1.28 (t, 6H, J = 7.00 Hz), 3.56 (s, 1/2H, D_2O-exch.), 4.06 (q, 4H, J = 7.00 Hz), 5.08 (s, ½ H), 5.33 (s, 2H), 7.09 (dd, 1H, J = 9.56, 3.86 Hz), 7.19 (d, 1H, J = 9.56 Hz), 7.54 (d, 1H, J = 3.86 Hz), 9.19, 9.63 (two s, each 1H, D_2O-exch.). Anal. % ($C_{15}H_{18}O_7$) C, H, calcd. 58.06, 5.85, found, 58.06, 5.82.

General procedure for the preparation of 1-aryl-4-(2,5-dihyroxyphenacyl)-3,5-dimethylpyrazoles **(13a–e)**

A solution of substituted arylhydrazine hydrochloride (1.05 mmol) in absolute ethanol (10 ml) was gradually added to a solution of compound **12** (0.25 g, 1.0 mmol) in absolute ethanol (10 ml) containing few drops of glacial acetic acid and an equimolar amount of anhydrous sodium acetate (0.123 g, 1.05 mmol). The reaction mixture was stirred while heating under reflux for 18 h and set aside for an overnight at room temperature. The formed brown precipitate was filtered, washed several times with cold water, dried, and finally recrystallized.

4-(2,5-Dihyroxyphenacyl)-1-pheyl-3,5-dimethylpyrazole **(13a)**

Reagents: phenylhydrazine hydrochloride (0.15 g, 1.05 mmol). *Crystallization*: 10% aqueous ethanol. Brown solid (0.19 g, 59%), melting with decomposition at 224°C. IR (KBr, cm^{-1}): 3425–2800, 1606, 1584, 1525. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.08, 2.20 (two s, each 3H), 5.20 (s, 2H), 6.85 (d, 1H, J = 8.8Hz), 6.95 (dd, 1H, J = 8.80, 3.68 Hz), 7.24 (d, 1H, J = 3.68 Hz), 7.36–7.41 (m, 3H), 7.66 (d, 2H, J = 8.08 Hz), 9.17, 9.53 (two s, each 1H, D_2O-exch.). Anal. % ($C_{19}H_{18}N_2O_3$) C, H, N, calcd. 70.79, 5.63, 8.69, found, 70.76, 5.62, 8.68.

4-(2,5-Dihyroxyphenacyl)-1-(*p*-tolyl)-3,5-dimethylpyrazole **(13b)**

Reagents: *p*-tolylhydrazine hydrochloride (0.166 g, 1.05 mmol). *Crystallization*: 10% aqueous ethanol. Brown crystals (0.19 g, 57%), melting with decomposition at 260°C. IR (KBr, cm^{-1}): 3450–2875, 1662, 1575, 1512. ^{1}H- NMR (DMSO-d_6, 400 MHz): 2.08, 2.20 (two s, each 3H), 2.40 (s, 3H), 5.30 (s, 2H), 7.08 (dd, 1H, J = 9.56, 2.92 Hz), 7.19 (d, 1H, J = 9.56 Hz), 7.53 (d, 2H, J = 11.76 Hz), 7.65 (d, 2H, J = 11.76 Hz), 7.73 (d, 1H, J = 2.92 Hz), 9.20, 9.36 (two s, each 1H, D_2O-exch.). Anal. % ($C_{20}H_{20}N_2O_3$) C, H, N, calcd, 71.41, 5.99, 8.33, found, 71.40, 5.97, 8.32.

1-(4-Bromophenyl)-4-(2,5-dihyroxyphenacyl)-3,5-dimethylpyrazole **(13c)**

Reagents: 4-bromophenylhydrazine hydrochloride (0.234 g, 1.05 mmol). *Crystallization*: 10% aqueous DMF. Brown crystals (0.24 g, 60%), mp > 360°C. IR (KBr, cm^{-1}): 3412–2800, 1650, 1575, 1512. ^{1}H-NMR (DMSO-d_6, 400MHz): 1.80, 1.94

(two s, each 3H), 5.20 (s, 2H), 6.99 (dd, 1H, J = 8.08, 2.92 Hz), 7.07 (d, 2H, J = 8.80 Hz), 7.18 (d, 1H, J = 2.92 Hz), 7.31 (d, 1H, J = 8.08 Hz), 7.44 (d, 2H, J = 8.08 Hz), 9.30, 9.63 (two s, each 1H, D_2O-exch.). Anal. % ($C_{19}H_{17}BrN_2O_3$) C, H, N, calcd. 56.87, 4.27, 6.98, found, 56.84, 4.25, 6.96.

4-(2,5-Dihydroxyphenacyl)-1-(4-sulfamoylphenyl)-3,5-dimethylpyrazole **(13d)**

Reagents: 4-hydrazinobenzenesulfonamide hydrochloride (0.234 g, 1.05 mmol). *Crystallization*: 10% aqueous DMF. Brown crystals (0.25 g, 62%), mp > 360°C. IR (KBr, cm^{-1}): 3550–2805, 1600, 1556, 1525, 1481, 1250, 1162. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.09, 2.21 (two s, each 3H), 4.00 (s, 2H, D_2O-exch.), 5.20 (s, 2H), 7.08 (dd, 1H, J = 9.52, 2.92 Hz), 7.19 (d, 1H, J = 9.52 Hz), 7.53 (d, 2H, J = 11.76 Hz), 7.65 (d, 2H, J = 11.76 Hz), 7.73 (d, 1H, J = 2.92 Hz), 9.17, 9.53 (two s, each 1H, D_2O-exch.). Anal. % ($C_{19}H_{19}N_3O_5S$) C, H, N, calcd. 56.85, 4.77, 10.47, found, 56.83, 4.77, 10.47.

1-[4-(*N*-acetylsulfamoyl)phenyl]-4-(2,5-dihydroxyphenacyl)-3,5-dimethylpyrazole **(13e)**

Reagents: 4-(*N*-acetylsulfamoyl)phenylhydrazine hydrochloride (0.278 g, 1.05 mmol). *Crystallization*: 10% aqueous DMF. Brown solid (0.28 g, 63%), mp > 360°C. IR (KBr, cm^{-1}): 3480–2820, 1650, 1602, 1555, 1520, 1480, 1255, 1160. Anal. % ($C_{21}H_{21}N_3O_6S$) C, H, N, calcd. 56.88, 4.77, 9.48, found, 56.84, 4.74, 9.45.

General procedure for the preparation of 1-(*N*-arylthiocarbamoyl)-4-(2,5-dihydroxyphenacyl)-3,5-dimethylpyrazoles **(14a–c)**

A solution of selected 4-arylthiosemicarbazides (1.0 mmol) in glacial acetic acid (20 ml) was gradually added with stirring over a period of 30 minutes to a boiling solution of an equimolar amount of compound **12** (0.25 g, 1.0 mmol) in glacial acetic acid (20 ml) containing an equimolar amount of anhydrous sodium acetate (0.082 g, 1.0 mmol). The reaction mixture was stirred while heating under reflux for 24 h and then left for an overnight at room temperature. The formed dark precipitate was filtered, washed several times with water, dried, and finally recrystallized.

4-(2,5-Dihydroxyphenacyl)-1-(*N*-phenylthiocarbamoyl)-3,5-dimethylpyrazole **(14a)**

Reagents: phenylthiosemicarbazide (0.167 g, 1.0 mmol). *Crystallization*: 10% aqueous DMF. Dark brown crystals (0.19 g, 50%), mp > 360°C. IR (KBr, cm^{-1}): 3525–2775, 1656, 1618, 1575, 1515, 1478, 1262, 1112, 984. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.10, 2.18 (two s, each 3H), 5.21 (s, 2H), 6.71 (dd, 1H, J = 8.80, 2.96 Hz), 6.78 (d, 1H, J = 8.80 Hz), 7.00 (s, 1H), 7.22–7.25 (m, 3H), 7.48 (d, 2H, J = 10.28 Hz), 9.07, 9.37, 9.93 (three s, each 1H, D_2O-exch.). Anal. % ($C_{20}H_{19}N_3O_3S$) C, H, N, calcd. 62.98, 5.02, 11.02, found, 62.96, 5.01, 11.02.

4-(2,5-Dihydroxyphenacyl)-1-[*N*-(p-tolyl)thiocarbamoyl]-3,5-dimethyl-pyrazole **(14b)**

Reagents: *p*-tolylthiosemicarbazide (0.18 g, 1.0 mmol). *Crystallization*: 10% aqueous DMF. Brown solid (0.217 g, 55%), mp > 360°C. IR (KBr, cm^{-1}): 3425–2650, 1687, 1637, 1598, 1543, 1500, 1262, 1118, 987. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.10, 2.18 (two s, each 3H), 2.65(s, 3H), 5.21 (s, 2H), 6.91–7.68 (m, 7H), 9.07, 9.27, 9.93 (three s, each 1H, D_2O-exch.). Anal. % ($C_{21}H_{21}N_3O_3S$) C, H, N, calcd. 63.78, 5.35, 10.62, found, 63.78, 5.33, 10.60.

1-[*N*-(4-Bromophenyl)thiocarbamoyl]-4-(2,5-dihydroxyphenacyl)-3,5-dimethyl-pyrazole **(14c)**

Reagents: 4-bromophenylthiosemicarbazide (0.246 g, 1.0 mmol). *Crystallization*: 10% aqueous DMF. Black solid (0.26 g, 57%), mp > 360°C. IR (KBr, cm^{-1}): 3487–2975, 1662, 1625, 1587, 1525, 1487, 1287, 1109, 1287. Anal. % ($C_{20}H_{18}BrN_3O_3S$) C, H, N, calcd. 52.18, 3.94, 9.13, found, 52.16, 3.92, 9.13.

General procedure for the preparation of 1-aryl-4-(2,5-dihydroxy-phenacyl)-3-methyl-4,5-dihydropyrazol-5-ones **(16a–e)**

A solution of substituted phenylhydrazine hydrochloride (1.05 mmol) in absolute ethanol (10 ml) was gradually added over a period of 30 min to a well stirred solution of compound **15** (0.28 g, 1.0 mmol) in a mixture of 20 ml of absolute ethanol–glacial acetic acid (1:1) containing an equimolar amount of anhydrous sodium acetate (0.123 g). The reaction mixture was stirred while heating under reflux for 14 h and then concentrated under diminished pressure. The formed brown precipitate was filtered, washed several times with water, dried, and finally recrystallized.

4-(2,5-Dihydroxyphenacyl)-3-methyl-1-phenyl-4,5-dihydropyrazol-5-one **(16a)**

Reagents: phenylhydrazine hydrochloride (0.15 g, 1.05 mmol). *Crystallization*: 10% aqueous DMF. Brown solid (0.194 g, 60%), mp > 360 °C. IR (KBr, cm^{-1}): 3450–2650, 1648, 1562,1503. Anal. % ($C_{18}H_{16}N_2O_4$) C, H, N, calcd. 66.66, 4.97, 8.64, found, 66.64, 4.95, 8.62.

4-(2,5-Dihydroxyphenacyl)-3-methyl-1-*p*-tolyl-4,5-dihydropyrazol-5-one **(16b)**

Reagents: *p*-tolylhydrazine hydrochloride (0.166 g, 1.05 mmol). *Crystallization*: dioxane/ water (3:1). Brown solid (0.20 g, 59%), mp > 360°C. IR (KBr, cm^{-1}): 3475–2825, 1662, 1584, 1518. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.07 (s, 3H), 2.21 (s, 3H), 3.55 (s, 1/2H, D_2O-exch.), 4.91 (s, 1/2H), 5.15 (s, 2H), 6.65 (dd, 1H, J = 8.08, 2.92 Hz), 6.69 (d, 1H, J = 8.08 Hz), 6.90(d, 1H, J = 2.92 Hz), 7.00 (d, 2H, J = 8.80 Hz), 7.43 (d, 2H, J = 8.80 Hz), 9.15, 9.44 (two s, each 1H, two D_2O-exch.). Anal. % ($C_{19}H_{18}N_2O_4$) C, H, N, calcd. 67.45, 5.36, 8.28, found, 67.40, 5.36, 8.26.

1-(4-Bromophenyl)-4-(2,5-dihydroxyphenacyl)-3-methyl-4,5-dihydropyrazol-5-one **(16c)**

Reagents: 4-bromophenylhydrazine hydrochloride (0.234 g, 1.05 mmol). *Crystallization*: 10% aqueous DMF. Brown solid (0.27 g, 67%), mp > 360°C. IR (KBr, cm^{-1}): 3450–2720, 1648, 1573, 1511. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.07 (s, 3H), 3.55 (s, ½ H, D_2O-exch.), 4.94 (s, ½ H), 5.15 (s, 2H), 6.78 (s, 1H), 6.83 (dd, 1H, J = 8.80, 2.96 Hz), 6.99 (d, 1H, J = 8.80 Hz), 7.49 (d, 2H, J = 8.80 Hz), 7.75 (d, 2H, J = 8.80 Hz), 9.15, 9.44 (two s, each 1H, two D_2O-exch.). Anal. % ($C_{18}H_{15}BrN_2O_4$) C, H, N, calcd. 53.62, 3.75, 6.95, found,53.62, 3.70, 6.94.

4-(2,5-Dihydroxyphenacyl)-3-methyl-1-(4-sulfamoylphenyl)-4,5-dihydropyrazol-5-one **(16d)**

Reagents: 4-sulfamoylphenylhydrazine hydrochloride (0.234 g, 1.05 mmol). *Crystallization*: 10% aqueous DMF. Brown solid (0.282 g, 70%), mp > 360°C. IR (KBr, cm^{-1}): 3500–2950, 1600, 1550, 1525, 1487, 1268, 1175. Anal. % ($C_{18}H_{17}N_3O_6S$) C, H, N, calcd. 53.59, 4.25, 10.42, found, 53.57, 4.21, 10.41.

1-[4-(*N*-acetylsulfamoyl)phenyl]-4-(2,5-dihydroxyphenacyl)-3-methyl-4,5-dihydro-pyrazol-5-one **(16e)**

Reagents: 4-(*N*-acetylsulfamoyl)phenylhydrazine hydrochloride (0.278 g, 1.05 mmol).

Crystallization: 10% aqueous DMF. Brown solid (0.315 g, 71%), mp > 360°C. IR (KBr, cm^{-1}): 3589–2880, 1650, 1600, 1554, 1524, 1488, 1275, 1170. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.07 (s, 3H), 2.19 (s, 3H), 3.55 (s, 1/2H, D_2O-exch.), 4.94 (s, 1/2H), 5.15 (s, 2H), 7.08 (dd, 1H, J = 9.56, 2.92 Hz), 7.19 (d,1H, J = 9.56 Hz), 7.53 (d, 2H, J = 11.76 Hz), 7.65 (d, 2H, J = 11.76 Hz), 7.73 (d, 1H, J = 2.92 Hz), 9.15, 9.44, 10.04 (three s, each 1H, D_2O-exch.). Anal. % ($C_{20}H_{19}N_3O_7S$) C, H, N, calcd. 53.93, 4.30, 9.43, found, 53.91, 4.28, 9.43.

General procedure for the preparation of 1-(*N*-arylthiocarbamoyl)-4-(2,5-dihydroxyphenacyl)-3-methyl-3,4-dihydropyrazol-5-ones **(17a–c)**

A solution of selected 4-arylthiosemicarbazide (1.00 mmol) in glacial acetic acid was gradually added over a period of 30 min to a boiling well stirred solution of an equimolar amount of compound 15 (0.28 g, 1.00 mmol) in glacial acetic acid (20 ml) containing two drops of conc. sulfuric acid. The reaction mixture was heated under reflux for 19 h, after which the excess solvent was evaporated under diminished pressure. The formed sticky mass was triturated five times with 10-ml portions of petroleum ether (60–8$\mathring{0}$C) and then the formed solid was filtered, dried, and finally recrystallized.

4-(2,5-Dihydroxyphenacyl)-3-methyl-1-(*N*-phenylthiocarbamoyl)-3,4-dihydropyrazol-5-one **(17a)**

Reagents: phenylthiosemicarbazide (0.167 g, 1.0 mmol). *Crystallization*: DMSO–water (9:1). Dark brown crystals (0.23 g, 60%), mp > 360°C. IR (KBr, cm^{-1}): 3325–2750, 1675, 1625, 1587, 1525, 1484, 1284, 1112, 998. Anal. % ($C_{19}H_{17}N_3O_4S$) C, H, N, calcd. 59.52, 4.47, 10.96, found, 59.50, 4.44, 10.96.

4-(2,5-Dihydroxyphenacyl)-3-methyl-1-[*N*-(*p*-tolyl)thiocarbamoyl]-3,4-dihydropyrazol-5-one **(17b)**

Reagents: *p*-tolylthiosemicarbazide (0.181 g, 1.00 mmol). *Crystallization*: 10% aqueous DMF. Brown solid (0.25 g, 63%), mp > 360°C. IR (KBr, cm^{-1}): 3575–2975, 1662, 1625, 1587, 1518, 1481, 1275, 1112.5, 993. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.07 (s, 3H), 2.21 (s, 3H), 3.55 (s, 1/2H, D_2O-exch.), 4.94 (s, 1/2H), 5.15 (s, 2H), 6.93 (d, 2H, J = 12.44 Hz), 6.98 (dd, 1H, J = 8.80, 2.92 Hz), 7.01 (d, 1H, J = 8.80 Hz), 7.38 (d, 2H, J = 12.44 Hz), 7.79 (d, 1H, J = 2.92 Hz), 9.15, 9.44, 10.07 (three s, each 1H, D_2O-exch.). Anal. % ($C_{20}H_{19}N_3O_4S$) C, H, N, calcd. 60.44, 4.82, 10.57, found, 60.42, 4.80, 10.56.

1-[*N*-(4-Bromophenyl)thiocarbamoyl]-4-(2,5-dihydroxyphenacyl)-3-methyl-3,4-dihydropyrazol-5-one **(17c)**

Reagents: 4-bromophenylthiosemicarbazide (0.246 g, 1.00 mmol). *Crystallization*: 10% aqueous DMSO. Brown solid (0.29 g, 63%), mp > 360°C. IR (KBr, cm^{-1}): 3400–2800, 1675, 1612, 1553, 1506, 1287, 1112, 987. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.00 (s, 3H), 3.56 (s, 1/2H, D_2O-exch.), 5.04 (s, 1/2H,), 5.19 (s, 2H), 7.10 (d, 2H, J = 8.08 Hz), 7.30 (d, 1H, J = 8.80 Hz), 7.35 (s, 1H), 7.43 (d, 2H, J = 8.08 Hz), 7.51 (d, 1H, J = 8.80 Hz), 9.01, 9.14, 9.71 (three s, each 1H, D_2O-exch.). Anal. % ($C_{19}H_{16}BrN_3O_4S$) C, H, N, calcd. 49.36, 3.49, 9.09, found, 49.35, 3.48, 9.08.

General procedure for the preparation of 2-aryl-4-(2,5-dihydroxy-phenacyl)-pyrazolidine-3,5-diones **(19a–e)**

A solution of 4-substituted phenylhydrazine hydrochloride (1.05 mmol) in dry dioxane (10 ml) was gradually added with stirring over a period of 30 min to a solution of compound 18 (0.31g, 1.0 mmol) in dry dioxane (10 ml) containing an equimolar amount of anhydrous sodium acetate (0.123 g). The reaction mixture was stirred while heating under reflux for 18 h, after which it was allowed to attain room temperature. The formed precipitate was filtered, washed with water, dried, and finally recrystallized.

4-(2,5-Dihydroxyphenacyl)-2-phenylpyrazolidine-3,5-dione **(19a)**

Reagents: phenylhydrazine hydrochloride (0.15 g, 1.05 mmol). *Crystallization*: ethanol. Dark brown solid (0.185 g, 57%), melting with decomposition at

290–291°C. IR (KBr, cm^{-1}): 3700–2675, 1662, 1575, 1500. ^{1}H-NMR (DMSO-d_6, 400 MHz): 3.59 (s, ½ H, D_2O-exch.), 4.90 (s, ½ H), 5.15 (s, 2H), 6.74 (dd, 1H, J = 8.80, 2.96 Hz), 7.78(d, 1 H, J = 8.80 Hz), 7.00(s, 1H), 7.22–7.25 (m, 3H), 7.48 (d, 2H, J = 10.28 Hz), 9.19, 9.59, 11.28 (three s, each 1H, D_2O-exch.). Anal. % ($C_{17}H_{14}N_2O_5$) C, H, N, calcd. 62.58, 4.32, 8.58, found, 62.57, 4.30, 8.58.

4-(2,5-Dihydroxyphenacyl)-2-(*p*-tolyl)pyrazolidine-3,5-dione **(19b)**

Reagents: *p*-tolylhydrazine hydrochloride (0.166 g, 1.05 mmol). *Crystallization*: 10% aqueous DMF. Dark brown solid (0.20 g, 59%), melting with decomposition at 320–321°C. IR (KBr, cm^{-1}): 3425–2650, 1675, 1581, 1512. Anal. % ($C_{18}H_{16}N_2O_5$) C, H, N, calcd. 63.53, 4.74, 8.23, found, 63.52, 4.72, 8.20.

2-(4-Bromophenyl)-4-(2,5-dihydroxyphenacyl)pyrazolidine-3,5-dione **(19c)**

Reagents: 4-bromophenylhydrazine hydrochloride (0.234 g, 1.05 mmol). *Crystallization*: 10% aqueous DMF. Dark brown solid (0.263 g, 65%), mp >360°C. IR (KBr, cm^{-1}): 3450–2675, 1675, 1575, 1500. ^{1}H-NMR (DMSO-d_6, 400 MHz): 3.59 (s, ½ H, D_2O-exch.), 4.90 (s, ½ H), 5.15 (s, 2H), 6.80 (d, 2H, J = 8.80 Hz), 6.90 (s, 1H), 6.98 (d, 1H, J = 2.92 Hz), 7.01 (d, 1H, J = 2.92 Hz), 7.19 (d, 2H, J = 8.80 Hz), 9.19, 9.59, 11.28 (three s, each 1H, D_2O-exch.). Anal. % ($C_{17}H_{13}BrN_2O_5$) C, H, N, calcd. 50.39, 3.23, 6.91, found, 50.38, 3.22, 6.90.

4-(2,5-Dihydroxyphenacyl)-2-(4-sulfamoylphenyl)pyrazolidine-3,5-dione **(19d)**

Reagents: 4-sulfamoylphenylhydrazine hydrochloride (0.234 g, 1.05 mmol). *Crystallization*: 10% aqueous DMF. Dark brown solid (0.27 g, 67%), mp >360°C. IR (KBr, cm^{-1}): 3525–2998, 1600, 1525, 1484, 1243, 1146. Anal. % ($C_{17}H_{15}N_3O_7S$) C, H, N, calcd. 50.37, 3.73, 10.37, found, 50.36, 3.73, 10.36.

2-[4-(*N*-acetylsulfamoyl)phenyl]-4-(2,5-dihydroxyphenacyl)pyrazolidine-3,5-dione **(19e)**

Reagents: *N*-acetylsulfamoylphenylhydrazine hydrochloride (0.278 g, 1.05 mmol). *Crystallization*: 10% aqueous DMF. Dark brown solid (0.31 g, 69%), mp >360°C. IR (KBr, cm^{-1}): 3575–2980, 1650, 1619, 1550, 1495, 1247, 1146. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.10 (s, 3H), 3.59 (s, ½ H, D_2O-exch.), 4.85 (s, ½ H), 5.15 (s, 2H), 7.09 (dd, 1H, J = 9.52, 3.68 Hz), 7.20 (d, 1H, J = 9.52 Hz), 7.54 (d, 2H, J = 11.76), 7.66 (d, 2H, J = 11.76 Hz), 7.73 (d, 1H, J = 3.68 Hz), 9.20, 9.59, 10.05, 11.20 (four s, each 1H, D_2O-exch.). Anal. % ($C_{19}H_{17}N_3O_8S$) C, H, N, calcd. 51.01, 3.83, 9.39, found, 51.00, 3.81, 9.39.

General procedure for the preparation of 2-(*N*-arylthiocarbamoyl-4-(2,5-dihydroxyphenacyl)-pyrazolidine-3,5-diones **(20a–c)**

A mixture of compound **18** (1.0 mmol) and selected 4-arylthiosemicarbazide (1.0 mmol) was fused at 140°C in an oil bath for 4 h, whereupon the reaction mixture melted and then solidified The formed crude mass was allowed to attain the room temperature and then recrystallized.

4-(2,5-Dihydroxyphenacyl)-2-(*N*-phenylthiocarbamoyl)pyrazolidine-3,5-dione **(20a)**

Reagents: phenylthiosemicarbazide (0.167 g, 1.0 mmol). *Crystallization*: DMF–water (6:1). Dark brown solid (0.30 g, 78%), mp > 360 °C. IR (KBr, cm^{-1}): 3400–2675, 1675, 1587, 1550, 1475, 1287, 1125, 993. Anal. % ($C_{18}H_{15}N_3O_5S$) C, H, N, calcd. 56.10, 3.92, 10.90, found, 56.10, 3.90, 10.90.

4-(2,5-Dihydroxyphenacyl)-2-[*N*-(*p*-tolyl)thiocarbamoyl]pyrazolidine-3,5-dione **(20b)**

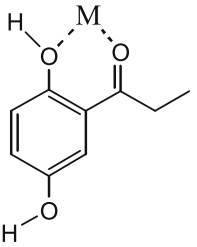
Reagents: *p*-tolylthiosemicarbazide (0.181 g, 1.0 mmol). *Crystallization*: 15% aqueous DMF. Dark brown solid (0.31 g, 83%), mp > 360°C. IR (KBr, cm^{-1}): 3400–2750, 1687, 1606, 1550, 1500, 1268, 1112, 987. ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.40 (s, 3H), 3.59 (s, ½ H, D_2O-exch.), 4.90 (s, ½ H), 5.15 (s, 2H), 7.08 (dd, 1H, J = 9.52, 3.68 Hz), 7.19 (d, 1H, J = 9.52 Hz), 7.53 (d, 2H, J = 11.76 Hz), 7.65 (d, 2H, J = 11.76 Hz), 7.73 (d, 1H, J = 3.68 Hz), 9.20, 9.59, 10.30, 11.28 (four s, each 1H, D_2O-exch.). Anal. % ($C_{19}H_{17}N_3O_5S$) C, H, N, calcd. 57.13, 4.29, 10.52, found, 57.13, 4.27, 10.50.

2-[*N*-(4-Bromophenyl)thiocarbamoyl]-4-(2,5-dihydroxyphenacyl)pyrazolidine-3,5-dione **(20c)**

Reagents: 4-bromophenylthiosemicarbazide (0.246 g, 1.0 mmol). *Crystallization*: 15% aqueous DMF. Dark brown solid (0.4 g, 86%), mp > 360°C. IR (KBr, cm^{-1}): 3450–2980, 1662, 1587, 1525, 1484, 1265, 1112, 981. ^{1}H-NMR (DMSO-d_6, 400 MHz): 3.59 (s, ½ H, D_2O-exch.), 4.90 (s, ½ H), 5.15 (s, 2H), 6.95–7.68 (m, 7H), 9.20, 9.52, 10.40, 11.25 (four s, each 1H, D_2O-exch.). Anal. % ($C_{18}H_{14}BrN_3O_5S$) C, H, N, calcd. 46.57, 3.04, 9.05 , found, 46.54, 2.03, 9.05.

Formation of colored metal chelates of compounds; **13a, 14a, 16a, 17a, 19a,** and **20a** with Cu^{2+}, Co^{2+} and Ni^{2+}

A solution of 1-aryl and 1-(*N*-arylthiosemicarbamoyl)-4-(2,5-dihydroxyphenacyl)-3,5-dimethyl-pyrazole; **13a** and **14a,** 1-aryl and 1-(*N*-arylthiosemicarbamoyl)-3-methyl-4,5-dihydro-pyrazol-5-one; **16a** and **17a** or 1-aryl and 1-(*N*-arylthiosemicarbamoyl)-4-(2,5-dihydroxyphenacyl) pyrazolidine-3,5-dione; 19a and 20a (1 mmol) in DMF (7 ml) was treated with 5% aqueous solution (5 ml) of $CuSO_4$,



M = Cu^{+2}, Co^{+2}or Ni^{+2}.

$CoSO_4$ and $NiSO_4$. The corresponding blank experiments were carried out simultaneously. The formed colored chelates; were light blue for Cu^{2+}, purple for Co^{2+} and bluish violet for Ni^{2+}. The reported λ_{max} for the chelates and for the blank experiments are listed in Table 1.

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