REGIOSELECTIVE CYCLOCONDENSATION REACTIONS LEADING TO PHENOLIC PYRAZOLES

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الخلاصـة :

تم تعريض بيتا-داي كيتونز I(a-d) الفينولي لتفاعل تكثيفي متكرر بوجود فينيل هيدرازين وتحت ظروف تفاعل مختلفة وذلك للحصول على شبيهات II(a-d) و IV(a-d) ، والتي تحققنا من تركيبها باستخدام التقنية المطيافيِّة .

وكذلك قمنا يتقييم درجة السُّمية وأثر هذه المواد كمضادات فيروسية .

ABSTRACT

Phenolic β-diketones **I(a–d)** were subjected to cyclocondensation reaction with phenylhydrazine under different reaction conditions to give regioisomers **II(a–d)** and **IV(a–d)**, the structure of which was confirmed by spectroscopic techniques. The cytotoxicity and antiviral activity of these compounds were also assessed.

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INTRODUCTION

Pyrazoles are important because of their potential for biological activity [1]. Both traditional and new synthetic methods are used to prepare new materials for medicine, agriculture, and for other studies [2]. Phenolic pyrazoles have been synthesized by cyclocondensation of β-diketones [3], chalcones [4], or flavones [5] with hydrazine derivatives. With unsymmetrical diketones, isomeric pyrazoles can theoretically arise and sometimes both can be isolated from the reaction mixture. Several attempts have been made to devise methods for the selective synthesis of one of the two possible isomeric pyrazoles through the use of functional derivatives of β-dicarbonyl compounds. Among these derivatives, acetals [6, 7] of β-ketoaldehydes, enol ethers, enol esters, and enamines were more prominent. More recently, the cyclocondensation of trifluoro-β-diketones [8], have been reported to give the regioselective products. Some reports on cyclocondensation of phenolic β-diketones have appeared in the literature but the regiospecificity of the reactions have not been discussed. Moreover the spectroscopic data reported is insufficient to prove the structure of the products [3].

In the present work, the β-diketones **I(a–d)** [9] were subjected to the cyclocondensation reaction with phenylhydrazine, leading to regioselective formation of isomers **II(a–d)** and **IV(a–d)** under acidic and neutral conditions respectively (Figure 1). Under acidic conditions the flavones **III** were isolated as the major side product. The preparation spectroscopy and cytotoxic/antiviral activity of these isomeric pyrazoles is also reported here.

RESULTS AND DISCUSSION

The two regioisomeric pyrazoles, 1-phenyl-3-(4′-substituted phenyl)-5(2′-hydroxyphenyl) pyrazoles **II(a–d)** and 1-phenyl-3(2′-hydroxyphenyl)-5(4′-substituted phenyl) pyrazoles **IV(a–d)** obtained under different reaction conditions were isolated and purified chromatographically. The percent yields of these compounds are given in Table 1.

β-Diketones **I(a–d)** exhibit intramolecular hydrogen bonding which makes C-1 of the 1,3-dione the most electrophilic center in the molecule. The monosubstituted nitrogen of phenylhydrazine, being the more nucleophilic in neutral medium, will link itself to the more electrophilic C-1 center to give the isolated isomer, **IV(a–d)**, Figure 2.
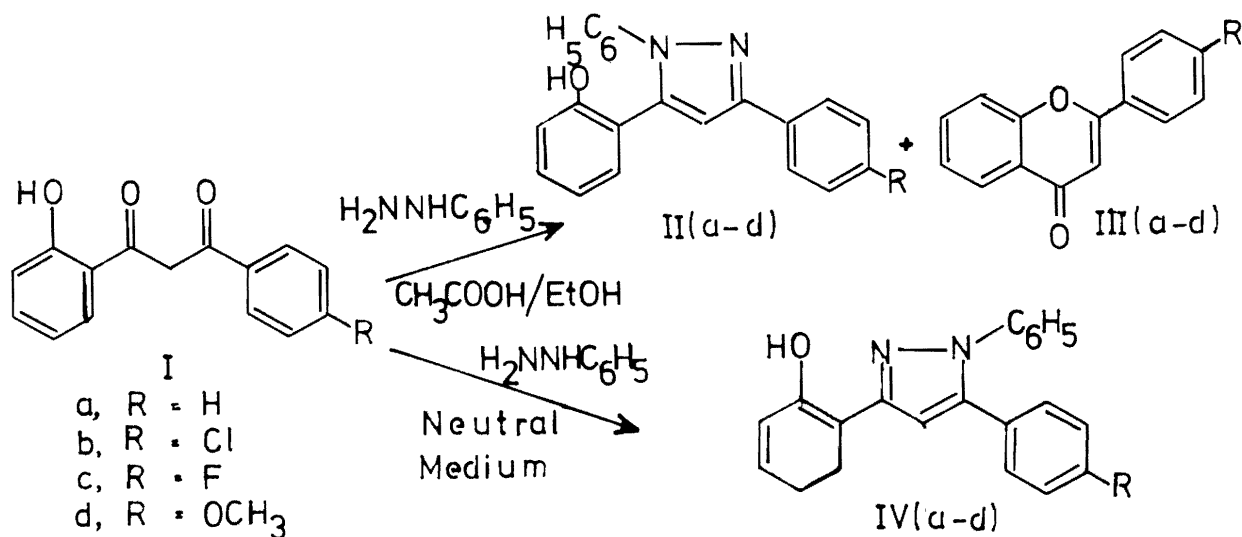

Figure 1.

In acidic medium, the more basic nitrogen of phenylhydrazine gets protonated easily with acetic acid leaving the substituted nitrogen as the only nucleophilic site to react with the most electrophilic C-1 carbon, Figure 3.

The UV spectra of these isomeric pyrazoles showed two maxima at 295.4–375.8 nm and 256.2–280 nm due to $\pi \to \pi^*$ and $n \to \pi^*$ transitions, which is in accordance with the values reported in the literature [2]. The IR spectra of compounds **II(a–d)** showed OH absorption at 3238–3178 cm^{-1} while in compounds **IV(a–d)** these have been shifted towards the lower frequency region 3178–3028 cm^{-1}, indicating the presence of intramolecular hydrogen bonding with unsubstituted nitrogen of pyrazole ring. ^{1}H-NMR spectra of the regioisomers confirmed these results. In compounds **II(a–d)** the phenolic protons resonated at high field in the region of 5.4–5.46 ppm and were exchangeable with D_2O while the phenolic protons of **IV(a–d)** appeared down field in the region of 10.69–10.88 ppm.

Although the sp^3-hybridized nitrogen (having less s-character) is theoretically expected to give stronger H-bonding than sp^2-hybridized nitrogen in **IV(a–d)**, nevertheless the experimental results are the other way round. Molecular models have revealed that in **II(a–d)** the sp^3-orbital of N bearing a lone pair of electrons is not in the plane of the benzene ring having phenolic OH, thus reducing the possibility of H-bonding. Moreover the upfield appearance of phenolic protons of **II(a–d)** may be attributed to lack of H-bonding and/or anisotropic shielding of phenolic protons by the benzene ring at the nearest nitrogen.
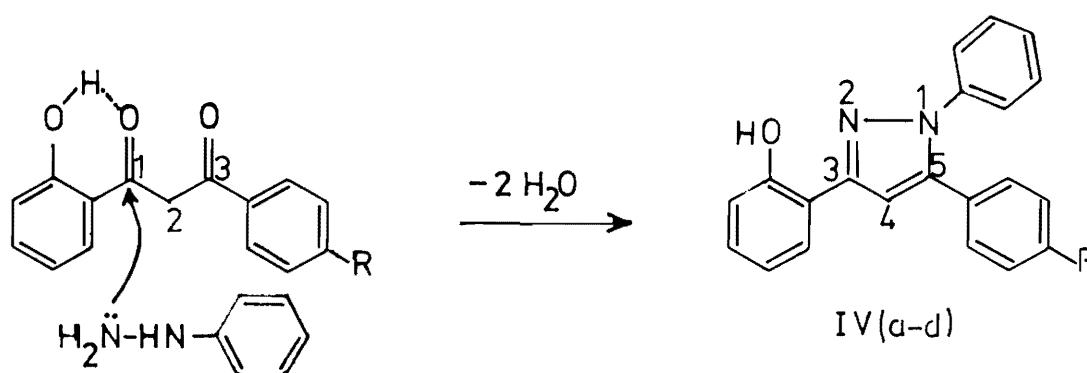

Figure 2.

Table 1. Percent Yield of Different Products under Different Reaction Conditions.

No.	Compound	Conditions used	% yield of regioisomer II	% yield of regioisomer IV	% yield of flavone III
1	**IIa**	Acidic	76.6	4.93	9.3
2	**IIb**	Acidic	64.3	3.31	8.5
3	**IIc**	Acidic	49.6	5.18	9.1
4	**IId**	Acidic	43.2	5.33	8.3
5	**IVa**	Neutral	8.78	71.2	–
6	**IVb**	Neutral	9.4	74.1	–
7	**IVc**	Neutral	7.39	67.8	–
8	**IVd**	Neutral	10.2	65	–

In order to establish the spatial proximity of the *N*-phenyl substituent and 3/5 substituent on the pyrazole ring, an nOe difference experiment for the compound **IVa** was carried out (Figure 4).

All the protons showed their resonance in the aromatic region. The C-2″ and C-6″ protons appeared as a multiplet alongwith other aromatic protons, hence could not be irradiated specifically. However the irradiation of C-6″ protons at δ 7.62 resulted in 13.8% and 18% nOe at δ 6.94 (C-5″H) and at δ 6.86(C-4 H) respectively. No nOe interactions were observed with the *N*-substituted phenyl ring, confirming the spatial proximity of the *N*-substituted phenyl ring and the *o*-hydroxy phenyl ring at 1 and 3 positions respectively.
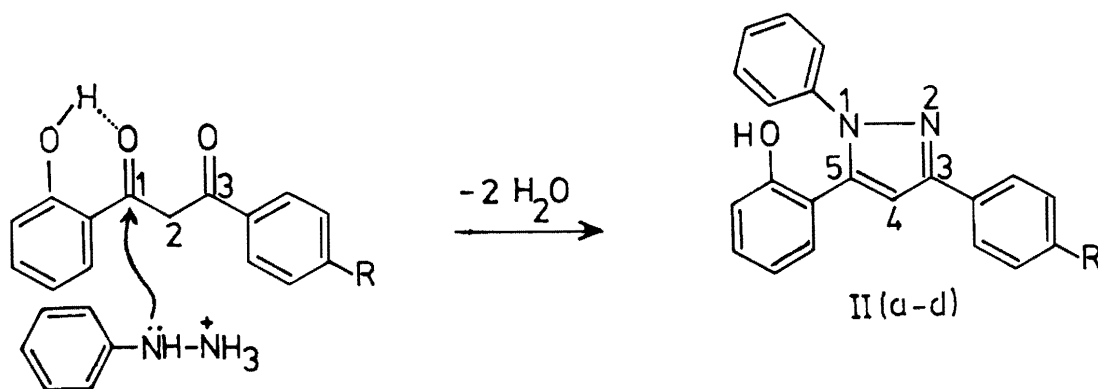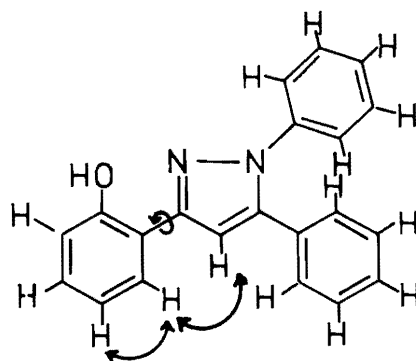

Figure 3.

Figure 4.

The base peak in the EI mass spectra was the molecular ion peak. The general fragmentation pattern of these mass spectra gave very little information about the structure of these regioisomers. The last point in favor of the structure of these isomers is the formation of co-ordination complexes of **IV(a–d)** with transition metals and the inability of compounds **II(a–d)** to make these complexes [10].

All the regioisomeric pyrazoles were assessed for cytotoxicity and antiviral activity on mouse embryo cell culture infected with Herpes simplex Type 1 and Type 2. The results are tabulated in Table 2. The regioisomers **IV(a–d)** were more toxic than **II(a–d)**. The fluoro-derivatives showed greater cytotoxicity than corresponding chloro-derivatives. All these compounds showed no antiviral activity.

EXPERIMENTAL

Melting points are uncorrected and determined on Gallenkamp digital melting point apparatus. IR spectra in KBr were recorded on a Hitachi 270-50 Infrared spectrophotometer. UV spectra were recorded on a Shimadzu Model 265 FS/FW spectrophotometer. For NMR and Mass spectra Jeol Model JNM FX 900 and Varian Mat CH-5 were used respectively. NMR spectra of the compounds were taken in $CDCl_3$/using TMS as internal standard. Phenolic β-diketones **I(a–d)** were prepared according to the reported method [9].

General Procedure of Cyclocondensation in Acidic Medium

Phenolic β-diketone I (0.01 moles) was dissolved in ethanol (15 ml). Glacial acetic acid (5 ml) and phenylhydrazine were added and the mixture was refluxed for about 4–5 hours. Solvent was removed under reduced pressure. The oily mixture obtained was applied to a dry silica gel column, using chloroform as eluant. Regioisomers **IV(a–d)** were eluted first, followed by the other regioisomers **II(a–d)**. Flavones **III(a–d)** were the last eluted from the column.

Table 2. Cytotoxicity and Antiviral Activity of Compounds II(a–d) and IV(a–d).

| No. | Compound | R | X | Cytotoxicity/Antiviral activity* |
				0.05 µg/ml		0.5 µg/ml		5 µg/ml		50 µg/ml		500 µg/ml	
1	**IIa**	C_6H_5	H	Ø	Ø	Ø	Ø	Ø	Ø	X	Ø	XXXX	Ø
2	**IIb**	C_6H_5	Cl	Ø	Ø	Ø	Ø	Ø	Ø	X	Ø	XXXX	Ø
3	**IIc**	C_6H_5	F	Ø	Ø	Ø	Ø	X	Ø	XX	Ø	XXXX	Ø
4	**IId**	C_6H_5	OCH_3	Ø	Ø	Ø	Ø	Ø	Ø	X	Ø	XXXX	Ø
5	**IVa**	C_6H_5	H	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø
6	**IVb**	C_6H_5	Cl	Ø	Ø	Ø	Ø	Ø	Ø	X	Ø	XX	Ø
7	**IVc**	C_6H_5	F	XX	Ø	XX	Ø	XX	Ø	XX	Ø	XX	Ø
8	**IVd**	C_6H_5	OCH_3	XX	Ø	XX	Ø	XX	Ø	XX	Ø	XX	Ø

*	% inhibition of cell growth/ % reduction of plaque cell	Cytotoxicity/ cytopathic effect(CPE)
Ø	No Inhibition	Nil
X	25%	weak
XX	50%	medium
XXX	75%	strong
XXXX	100%	Very strong

1,3-Diphenyl-5(2'hydroxyphenyl) pyrazole (IIa)

m.p. 163–164.5°C; Yield 76.6%.

IR (v_{max}, KBr, cm^{-1}): 3958, 3892, 3742, 3550, 3304, 3238, 3166, 3052, 2962, 2746, 2710, 2590, 2560, 2476, 2344, 2206, 2164, 1944, 1902, 1881, 1827, 1782, 1746, 1641, 1593, 1548, 1521, 1491, 1455, 1434, 1413, 1356, 1290, 1221, 1176, 1155, 1110, 1071, 1026, 957, 744, 675, 600.

UV [λ_{max} (ε)nm]: 305(5640), 275(5520).

^{1}H-NMR (CDCl$_3$)(δ_H): 5.46(s, 1H, OH) 6.73, (m, 1H, Ar-H), 6.74(s, 1H, pyrazole C-4 H), 6.8(d, 1H, J = 8.1 Hz, Ar), 6.9(d, 1H, J = 7.7, Ar-H), 7.13–7.34(m, 9H, Ar-H), 7.81(d, 2H, J = 7.4 Hz, Ar-H).

^{13}C-NMR (CDCl$_3$) (δ_C): 154.55(C-2‴), 153.55(C-5), 140.90(C-1′), 140.01(C-3), 133.78(C-1″), 131.97(C-4‴), 131.76(C-6‴), 129.91(C-2′ and C-6′), 129.75(C-3″ and C-5″), 129.26(C-4″), 128.40(C-5‴), 126.90(C-3′ and C-5′), 125.30(C-2″ and C-6″), 121.59(C-4′), 118.20(C-3‴), 117.11(C-1‴), 106.97(C-4).

MS m/z (%): 312(M$^{+\cdot}$, 100), 311(36), 295(6.5), 284(4.9), 283(3), 267(0.8), 235(0.8), 207(11.9), 207(4), 192(6.6), 181(8), 180(29), 178(8), 165(5), 133(3), 127(2), 104(8), 91(17), 78(6.5), 77(42), 64(7).

1-Phenyl-3(4-chlorophenyl)-5(2-hydroxyphenyl) pyrazole (IIb)

m.p. 179.8–183.1°C; Yield 64.3%.

IR (v_{max}, KBr, cm^{-1}): 3238, 3064, 1599, 1548, 1500, 1455, 1434, 1398, 1350, 1293, 1251, 1230, 1158, 1113, 1089, 1068, 1041, 1014, 975, 957, 912, 840, 828, 819, 807, 756, 693, 663, 600, 516, 501, 474, 423, 297.

UV [λ_{max} (ε) nm]: 305(5600), 280(5540).

^{1}H-NMR (CDCl$_3$) (δ_H): 5.39(s, 1H, OH) 6.77(s, 1H, py-H), 6.8(m, 1H, Ar), 6.87(t, 1H, Ar), 6.96(t, 1H, Ar), 7.14–7.35(m, 8H, Ar), 7.55(dd, 1H, Ar, J = 7.9 Hz), 7.77(d, 1H, Ar, J=8.4 Hz).

^{13}C-NMR (CDCl$_3$) (δ_C): 157.33(C-2″), 153.21(C-5), 143.89(C-1′), 140.21(C-3), 136.02(C-4″), 131.14(C-3″ and C-5″), 130.71(C-4‴), 129.96(C-2′ and C-6′), 129.94(C-3′ and C-5′), 129.34(C-1″), 129.03(C-6‴), 127.49(C-5‴), 126.02(C-2″ and C-6″), 121.72(C-4′), 118.22(C-3‴), 116.99(C-1‴), 106.85(C-4).

MS m/z (%): 346(100), 345(24), 329(2), 318(0.5), 317(1), 311(0.5), 283(1), 254(0.9), 241(1), 233(1), 214(6), 190(2), 181(2), 173(8), 165(2), 155(4), 127(2), 104(2), 91(17), 78(5), 77(33).

1-Phenyl-3(4-fluorophenyl)-5(2-hydroxyphenyl) pyrazole (IIc)

m.p. 214–216.3°C; Yield 49.6 %.

IR (v_{max}, KBr, cm^{-1}): 3232, 3060, 1953, 1881, 1662, 1611, 1593, 1554, 1527, 1503, 1458, 1437, 1401, 1356, 1317, 1296, 1257, 1218, 1155, 1113, 1098, 1068, 1044, 1023, 975, 960, 942, 915, 843, 831, 810, 756, 717, 693, 666, 600, 537, 519, 483, 434, 378, 348, 303.

UV [λ_{max} (ε) nm]: 300(5580), 274(5540).

^{1}H-NMR, (CD$_3$OD) (δ_H): 5.4(s, 1H, OH), 6.87(s, 1H, py H), 6.89–7.1(m, 4H, ArH), 7.08–7.38(m, 8H, Ar H), 7.59(dd, 1H, Ar, J = 8.1).

^{13}C-NMR, (CD$_3$OD) (δ_C): 163.8(C-4″), 161.5(C-2‴), 155.8(C-5), 151.77(C-1′), 142.91(C-3), 140.02(C-1″), 130.72(C-4‴), 130.16(C-2′ and C-6′), 129.04(C-6‴), 128.75(C-3′ and C-′5), 127.83(C-5‴), 126.49(C-2″ and C-6″), 125.11(C-3″ and C-5″), 118.99(C-4′), 117.52(C-3‴), 116.9(C-1‴), 106.5(C-4).

MS m/z (%): 330(M$^{+\cdot}$, 100), 329(26), 313(2), 302(1), 301(1.5), 285(0.2), 198(4), 196(1.5), 181(1), 180(2), 165(4), 152(0.9), 122(0.8), 91(4.2), 77(8).

1-Phenyl-3(4-methoxyphenyl)5(2-hydroxyphenyl) pyrazole (IId)

m.p. 183.7–186.2°C; Yield 43.2%.

IR (v_{max}, KBr, cm^{-1}): 3178, 3064, 2938, 2842, 2722, 2044, 1980, 1953, 1884, 1797, 1614, 1557, 1530, 1503, 1461, 1437, 1362, 1293, 1254, 1203, 1176, 1158, 1116, 1074, 1026, 978, 960, 939, 912, 879, 834, 804, 759, 690, 663, 612, 600, 549, 534, 513, 483, 444.

UV [λ_{max} (ε) nm]: 305(5580), 275(5520).

^{1}H-NMR (Acetone-d$_6$) (δ_H): 3.75(s, 3H, - OCH$_3$), 5.44(s, 1H, OH) 6.81(s, 1H, py-H), 6.82(t, 1H, Ar), 6.87(t, 1H, Ar), 6.90(dt, 1H, Ar), 7.05(dd, 1H, Ar, J=8.1, 1.2 Hz), 7.18–7.38(m, 8H, Ar), 7.62(dd, 1H, Ar).

^{13}C-NMR (CDCl$_3$) (δ_C): 158.73(C-4″), 156.12(C-2‴), 152.11(C-5), 143.39(C-1′), 139.77(C-3), 130.20(C-2′ and C-6′), 129.15(C-3′ and C-5′), 129.04(C-4‴), 127.60(C-6″), 126.59(C-5‴), 124.78(C-2″ and C-6″), 122.78(C-1″), 119.9(C-4′), 118.07(C-3‴), 117.01(C-1‴), 114.31(C-3″ and C-5″), 106.8(C-4), 55.34(–OCH$_3$).

MS m/z (%): 342(M$^+$, 100), 341(18), 327(18), 325(3), 314(1), 313(1), 299(5), 237(1), 224(2.8), 210(14), 208(6), 181(3), 180(8), 170(6), 165(5), 140(6.4), 127(2.8), 104(4), 91(6.8), 78(3), 77(25.8).

General Procedure for the Cyclocondensation Reaction of Phenylhydrazine with 1,3 Diketone I(a–d) in Neutral Conditions

1(2′-Hydroxyphenyl)-3(4′-substituted phenyl) propane-1,3 dione (0.01 mole) was dissolved in ethanol (15 ml). Phenylhydrazine (0.01 mole) was added and the mixture was refluxed for about 5-6 hours. Solvent was removed under reduced pressure. The mixture obtained was purified by the procedure given previously in the presence of acid.

1-Phenyl-3(2′-hydroxyphenyl)-5(phenyl pyrazole (IVa)

m.p. 114–115°C; Yield 71.2%.

IR (v_{max}, KBr, cm^{-1}): 3178, 3064, 1959, 1887, 1806, 1632, 1581, 1548, 1500, 1488, 1446, 1419, 1392, 1365, 1317, 1299, 1272, 1248, 1206, 1155, 1119, 1059, 1035, 1023, 960, 945, 915, 825, 795, 759, 723, 693, 663, 597, 558, 528, 471.

UV [λ_{max} (ε) nm]: 299(5539), 256.2(5510).

^{1}H-NMR, (CDCl$_3$) (δ_H): 6.58(s, 1H, py-H), 6.69(t, 1H, Ar), 6.92(d, 1H, Ar, J = 8.2 Hz), 7.10–7.16(m, 11H, Ar), 7.46(dd, 1H, Ar, J = 7.7 Hz, 1.2 Hz), 10.73(1H, OH).

^{13}C-NMR (CDCl$_3$) (δ_C): 157.47(C-2″), 153.17(C-3), 145.13(C-1′), 140.51(C-5), 130.94(C-1‴), 130.65(C-4″), 130.11(C-2′ and C-6′), 129.96(C-3‴ and C-5‴), 129.88(C-6″), 129.72(C-3′) and C-5′), 128.83(C-4‴), 127.62(C-5″), 126.1(C-2‴ and C-6‴), 120.40(C-4′), 118.24(C-3″), 117.25(C-1″), 104.92(C-4).

MS m/z (%): 312(M$^+$, 100), 311(58.7), 295(5.5), 284(6.4), 283(7.3), 255(1.8), 217(4.5), 208(7.3), 192(11.9), 190(4.5), 181(11.9), 180(61.46), 178(11.90), 164(11.9), 156(11.9), 152(8.2), 147(25.68), 133(5.5), 104(8.25), 92(1.8), 91(19.26), 89(11.99), 78(8.25), 77(98.1), 76(7.3), 64(11.9), 51(37.6).

1-Phenyl-3(2′-hydroxyphenyl)-5(4′-chlorophenyl) pyrazole (IVb)

m.p. 138.5–139°C; Yield 74.1%.

IR (v_{max}, KBr, cm^{-1}): 3958, 3922, 3892, 3712, 3634, 3556, 3040, 2968, 1881, 1620, 1584, 1485, 1446, 1365, 1293, 1278, 1242, 1152, 1083, 1014, 978, 804, 741, 681, 597, 492.

UV [λ_{max} (ε) nm]: 297.4(5607), 259.8(5638).

^{1}H-NMR (CDCl$_3$) (δ_H): 6.77(s, 1H, Py-H), 6.86(t, 1H, Ar), 6.99(d, 1H, Ar, J = 8.2 Hz), 7.11–7.29(m, 10H, Ar), 7.55(d, 1H, Ar, J = 7.7 Hz), 10.69(s, 1H, OH).

^{13}C-NMR (CDCl$_3$) (δ_C): 157.38(2″-C), 153.22(C-3), 143.88(C-1′), 140.22(C-5), 136.02(C-4‴), 131.16(C-3‴ and C-5‴), 130.74(C-4″), 130.23(C-2′ and C-6′), 129.99(C-3′ and C-5′), 129.33(C-1‴), 129.05(C-6″), 127.55(C-5″), 126.02(C-2‴ and C-6‴), 120.40(C-4′), 118.25(C-3″), 117.02(C-1″), 104.95(C-4).

MS *m/z* (%): 346(M$^{+\cdot}$,100), 345(48.3), 329(6.4), 318(6.7), 317(1.8), 269(0.9), 268(0.9), 240(1.5), 227(15.3), 214(41.5), 212(6.2), 193(15.3), 186(1.3), 181(13.7), 150(11.9), 133(5.4), 116(6.6), 105(1), 91(23.9), 77(88.5), 76(8).

1-Phenyl-3(2′-hydroxyphenyl)5(4′-fluorophenyl) pyrazole (IVc)

m.p. 133–133.5°C; Yield 67.8%.

1R (ν_{max}, KBr, cm^{-1}): 3970, 3880, 3814, 3766, 3724, 3592, 3436, 3352, 3178, 2638, 2536, 2464, 2266, 2200, 2158, 2068, 1965, 1896, 1581, 1482, 1446, 1383, 1359, 1290, 1224, 1155, 1059, 970, 945, 804, 756, 710, 642, 585, 519, 495, 468.

UV [λ_{max} (ε) nm]: 297.4(5607), 259.8(5638).

^{1}H-NMR (CDCl$_3$) (δ_H): 6.85(s, 1H, Py-H), 6.9–7.15(m, 4H, Ar H), 7.2–7.4(m, 8H, Ar H), 7.64(dd, 1H, Ar, *J* = 7.76, 1.6 Hz), 10.82(1H, OH).

^{13}C-NMR. (CDCl$_3$) (δ_C): 164.9(C-4‴), 160.93(C-2″), 156.2(C-3), 151.98(C-1′), 142.97(C-5), 139.19(C-1‴), 130.7(C-2′ and C-6′), 130.84(C-4″), 129.65(C-6″), 129.13(C-3′ and C-5′), 127.92(C-5″), 126.51(C-2‴ and C-6‴), 125.003(C-3‴ and C-5‴), 119.39(C-4′), 117.26(C-3″), 116.1(C-1″), 104.59(C-4).

Mass *m/z* (%): 330(M$^{+\cdot}$, 100), 329(22.9), 313(4.5), 302(2.1), 301(8.2), 253(1), 252(1), 224(0.9), 211(21.8), 198(52), 196(19), 193(21.8), 170(0.9), 181(0.9), 134(1.8), 133(0.9), 116(2.6), 105(3), 91(18.1), 77(60), 76(1.3).

1-Phenyl-3(2′-hydroxyphenyl),-5(4′-methoxyphenyl) pyrazole (IVd)

m.p. 95–97°C; Yield 65%.

1R (ν_{max}, KBr, cm^{-1}): 3790, 3670, 3490, 3424, 3028, 2830, 2530, 2152, 2056, 1977, 1893, 1584, 1488, 1440, 1395, 1362, 1242, 1173, 1113, 1065, 1020, 975, 825, 789, 744, 678, 594, 522.

UV [λ_{max} (ε) nm]: 375.8(5663), 258.4(5604).

^{1}H-NMR (CDCl$_3$) (δ_H): 3.81(s, 3H, –OCH), 6.82(s, 1H, py-H), 6.85(t, 1H, Ar), 6.87(t, 1H, Ar), 6.94(dt, 1H, Ar), 7.04(dd, 1H, Ar, *J* = 8.3, 1.1 Hz) 7.18–7.38(m, 8H, Ar), 7.63(dd, 1H, Ar, *J* = 7.76, 1.59 Hz), 10.88(s, 1H, OH).

^{13}C-NMR (CDCl$_3$) (δ_C): 159.34(C-4‴), 156.20(C-2″), 152.11 (C-3), 144.51(C-1′), 140.02(C-5), 130.202(C-2′ and C-6′), 129.47(C-4″), 129.05(C-3′ and C-5′), 127.65(C-6″), 126.48 (C-5″), 124.9(C-2‴ and C-6‴), 122.20(C-1‴), 119.3(C-4′), 117.19(C-3″), 116.9(C-1″) 114.085(C-3‴ and C-5‴), 104.092(C-4), 55.318(-OCH).

MS *m/z* (%): 342(M$^{+\cdot}$, 100), 314(13.7), 327(19), 325(8.2), 314(1.9), 313(3.6), 265(.9), 264(0.9), 236(1.5), 223(18.4), 210(68), 208(0.9), 193(18.4), 182(2.5), 181(3.6), 136(6.4), 133(6.7), 116(1.3), 105(1.5), 91(15.6), 77(79.4), 76(6.6).

Cytotoxicity and Antiviral Activity

The mouse embryo cell cultures were infected with Herpes simplex Type 1 and Type 2. The test substances were dissolved in 2.5% DMSO in water and diluted to different concentrations (0.05 µg/ml–500 µg/ml). The Herpes infected cell cultures were treated with different concentrations of test substance and incubated for 3-days, after which the cell cultures were studied for cytotoxic and cytopathic effects.

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