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SYNTHESIS AND BIOLOGICAL STUDIES OF SOME NEW PYRAZOLE, DIHYDROPYRIDINETHIONE, PYRIMIDINE, THIOPHENE AND 4*H*-PYRAN DERIVATIVES

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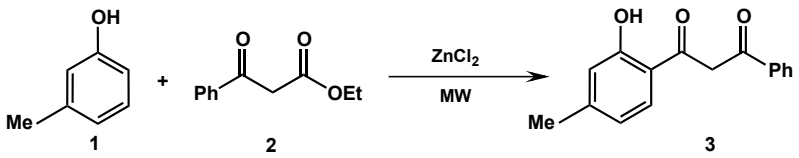
Abstract - This study aims to synthesis of 1-(2-hydroxy-4-methylphenyl)-3-phenylpropane-1,3-dione **3** in a quantitative yield from the reaction of ethyl benzoylacetate and *m*-cresol using a microwave in the absence of solvents. Phenylpropane-1,3-dione derivative **3** was used as the key synthetic intermediate for the synthesis of many derivatives in this study. A new pyrazole **12**, pyrimidine **15**, thiophene **37**, 4*H*-pyrane **51** and pyridine derivatives **8**, **28**, **34**, **41** and **46** were synthesized through different chemical reactions. The structures of the newly synthesized compounds were confirmed based on analytical and spectral data. The compounds were evaluated for both their *in vitro* antibacterial and antifungal activities. The compounds showed varying degree of antimicrobial activity.

In recent years, heterocyclic compounds represent an important class of biologically active molecules. Specifically, those containing pyrazoles, cyanopyridines, pyrimidinethiones, pyrans and pyridazine nucles. Many pyrazole derivatives are known to exhibit a wide range of biological properties such as anti-cancer,[1] anti-viral,[2] anti-inflammatory,[3] anti-microbial,[4] analgesic and anti-platelet,[5,6] anti-depressant,[7]and anticonvulsant.[8] Cyanopyridine derivatives occupy a unique position in medicinal chemistry because of their association with anti-convulasnt,[9] anti-cancer[10] and anti-soriasis activities.[11] Pyrimidinethiones have been found to possess anti-tubercular.[12] Pyran and fused 4*H*-pyran derivatives are very important class of heterocycles due to their biological and pharmacological activities which exhibit anti-microbial activity,[13,14] anti-oxidant,[15] inhibition of influenza virus sialidases,[16] mutagenic activity,[17]

anti-viral[18] and anti-cancer.[19] Finally, pyridazine ring is a nucleus of a many of drugs available in the market like cadralazine (anti-hypertensive), minaprine (anti-depressant), hydralazine (smooth muscle relaxant), and pipofezine (tricyclic anti-depressant).[20,21] In this article, and in continution to our research for chemistry developments,[22,23] the aim of the present work was to synthesize new pyrazole, pyridine, pyran, and pyrimidine derivatives by using 1-(2-hydroxy-4-methylphenyl)-3-phenylpropane-1,3-dione as the key starting material. Moreover, anti-microbial evaluations of newly synthesized products werealso investigated. In general, the novel synthesized compounds showed a good antimicrobial activity against the previously mentioned microorganisms.

Recently, there has been a growing interest in the use of microwave technology for organic synthesis. The reactions under microwave irradiation take place in a few minutes and no solvent is required,[24,25] hence we report here the use of microwave irradiation for the solvent free synthesis of 1-(2-hydroxy-4-methylphenyl)-3-phenylpropane-1,3-dione **3** in a quantitative yield (92%) from the reaction of ethyl benzoylacetate with *m*-cresol in the presence of zinc chloride.[26,27] The structure of compound **3** was assigned from the elemental analyses and spectral data. The IR spectrum of **3** showed charactersitic bands at 3446 (OH), 3097 (CH-arom), 2920 (CH-aliph), 1749, 1626 (2C=O) cm^{-1}. Its ^{1}H-NMR spectrum in $CDCl_3$ revealed the presence of a singlet signal at δ 1.60 ppm corresponding to Me protons, a singlet signal at δ4.00 ppm corresponding to CH_2 protons, a multiplet signals at δ 6.46-7.93 ppm corresponding to aromatic protons and a singlet signal at δ 15.97 ppm corresponding to OH. Its mass spectrum showed a molecular ion peak at *m/z* 256 (M^++2) in agreement with its molecular formula $C_{16}H_{14}O_3$ as shown in Scheme 1.

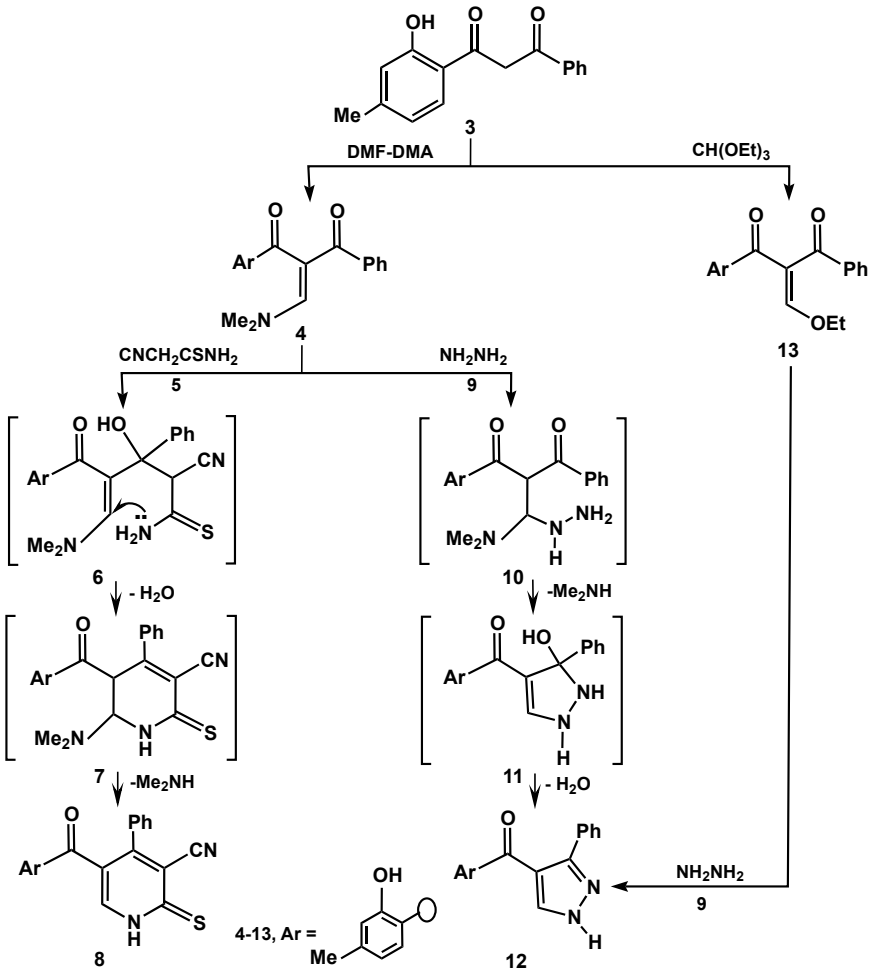


Scheme 1

Further confirmation of structure **3** was obtained through its reactivity towards some chemical reagents. Thus, when compound **3** was refluxed with dimethylformamide dimethyl acetal (DMF-DMA) in dioxane 2-((dimethylamino)methylene)-1-(2-hydroxy-4-methylphenyl)-3-phenylpropane-1,3-dione **4** was obtained. The structure of **4** was elucidated on the basis of analytical and spectral data. The ^{1}H-NMR spectrum exhibited the signals at δ 3.73 ppm for NMe_2 and a singlet signal at δ 5.88 ppm for olefinic proton. Also, the mass spectrum of compound **4** is in agreement with the proposed structure, which showed a molecular ion peak at *m/z* 311 (M^++2) in agreement with its molecular formula $C_{19}H_{19}NO_3$.

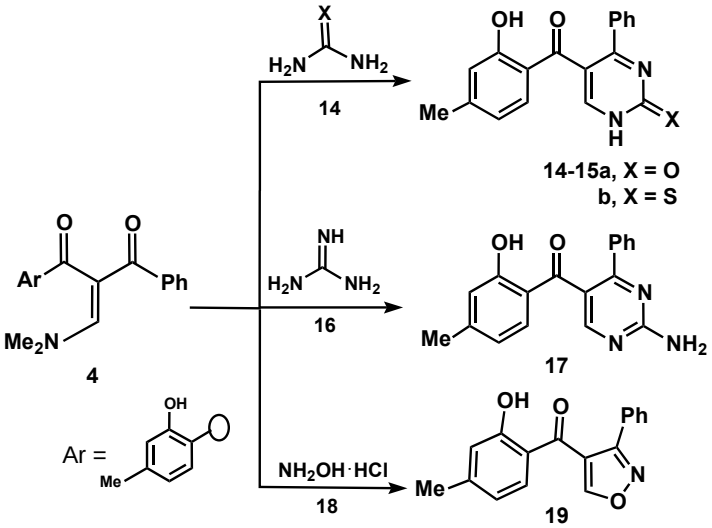
Compound **4** is used as starting material for preparation of several heterocycles. Thus, when a mixture of **4**, cyanothioacetamide **5** and sodium ethoxide was refluxed in ethanol for 24 h, a product with molecular formula $C_{20}H_{14}N_2O_2S$ was formed. This was considered to be the dihydropyridinethione **8**.

Formation of **8** from cyanothioacetamide and compound **4** is suggested to be proceeded via condensation and followed by subsequent cyclization with an elimination of dimethylamine to give dihydropyridinethione (Scheme 2). The structure of **8** was confirmed from ^{1}H-NMR which showed a singlet signal at δ 1.33 ppm corresponding to methyl protons, a singlet signal appeared at δ 5.68 ppm corresponding to CH-pyridine, a multiplet signals at δ 6.89-8.01 ppm corresponding to the aromatic protons and a singlet signal at δ 11.30 ppm corresponding to NH. Whereas, the phenolic OH appeared at δ 12.40 ppm. The mass spectrum showed a very intense molecular ion peak at *m/z* 348 (M^++2). Furthermore, hydrazinolysis of **4** afforded the pyrazole derivative **12** in a quantitative yield via the intermediates **10**, **11**. The structure of **12** was further chemically confirmed from the treatment of **13** (prepared from reaction of **3** and triethoxymethane in acetic anhydride) with hydrazine hydrate at reflux for 12 h as shown in Scheme 2.[26]



Scheme 2

In addition to this, the behavior of **4** towards some nitrogen nucleophiles was also investigated. Thus, reaction of **4** with urea **14a** or thiourea **14b** in ethanolic sodium ethoxide for about 24 h afforded 5-(2-hydroxy-4-methylbenzoyl)-4-phenylpyrimidin-2(1*H*)-one **15a** and 5-(2-hydroxy-4-methylbenzoyl)-4-phenylpyrimidin-2(1*H*)-thione **15b**, respectively. The molecular structure of compound **15** was established by analytical and spectral data. The IR spectrum of **15a** revealed the presence of a band at 3417 cm^{-1} corresponding to OH group, a band at 3379 cm^{-1} corresponding to NH group and a band at 1700 cm^{-1} corresponding to CO group. The ^{1}H-NMR spectrum of the **15a** showed a singlet signal at δ 1.65 ppm corresponding to methyl group, a singlet signal at δ 5.50 ppm related to CH-pyrimidine, a multiplet signals at δ 7.24-7.88 ppm corresponding to aromatic protons, a singlet signal at δ8.51 ppm corresponding to NH, and a singlet signal at δ 10.15 ppm corresponding to phenolic OH. Similarly, guanidine hydrochloride **16** was reacted with **4** to afford 2-amino-4-phenylpyrimidin-5-yl)(2-hydroxy-4-methylphenyl)methanone **17** (Scheme 3). In a similar way, hydroxylamine hydrochloride **18** was reacted with **4** in refluxing ethanol containing sodium acetate to afford (2-hydroxy-4-methylphenyl)(3-phenylisoxazol-4-yl)methanone **19** (Scheme 3). The ^{1}H-NMR spectrum of **19** revealed the absence of a signal corresponding to the *N*,*N*-dimethylamino protons at instead a signal at δ 6.52 ppm corresponding to CH-isoxazole was appeared.[28]



Scheme 3

The behavior of phenylpropane-1,3-dione **3** towards the same nucleophiles was investigated. Thus, when phenylpropane-1,3-dione **3** was reacted with hydroxylamine hydrochloride in refluxing ethanol containing anhydrous sodium acetate a cyclic product **20** was obtained. Trials to cyclize **20** failed even using different conditions. In contrast, the reaction of hydrazine hydrate and phenylhydrazine with **3** in refluxing ethanol afforded phenylpyrazole derivatives **21a**,**b**. The elemental analyses and spectral data of

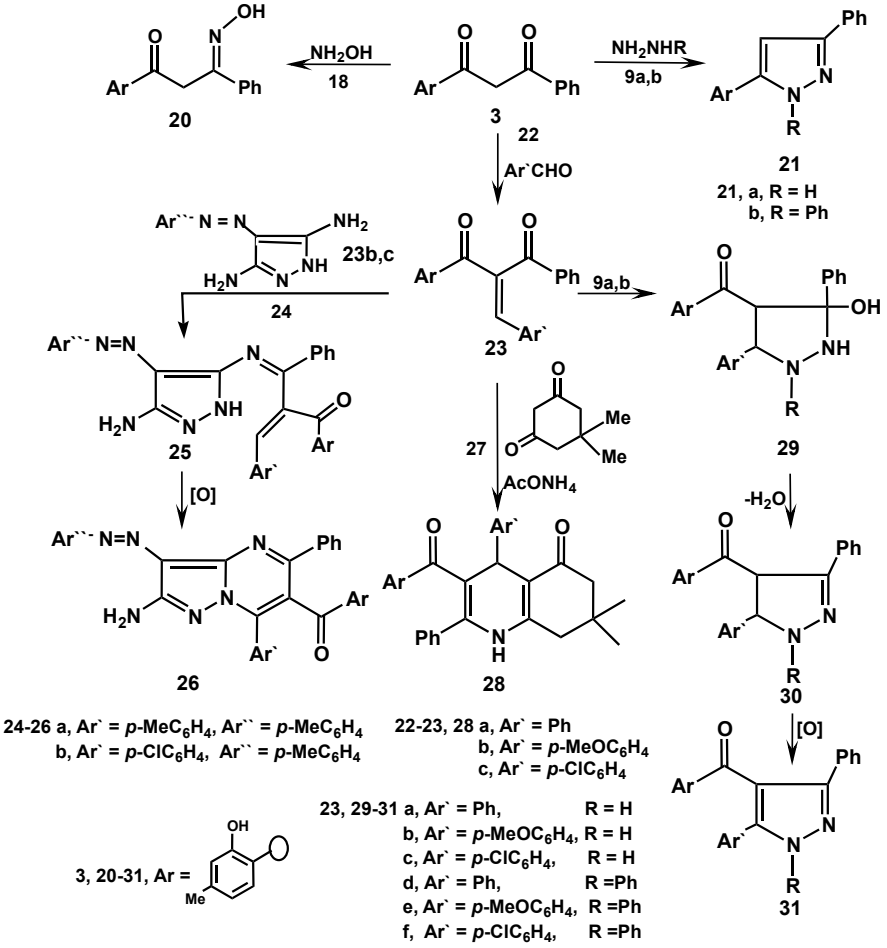
pyrazoles **21a**,**b** confirmed the proposed structures and agreed with the reference[29] (Scheme 4). The IR spectrum of **21a** showed the absence of the bands corresponding to carbonyl function. ^{1}H-NMR revealed the presence of a signal at δ 1.22 ppm corresponding to methyl protons, a signal at δ6.58 ppm corresponding to 4*H*-pyrazole, a multiplet signals at δ 7.27-7.76 ppm corresponding to the aromatic and NH protons and hump at δ 12.20 ppm corresponding to phenolic OH. Treatment of phenylpropane-1,3-dione **3** with aryl aldehydes **22a-c** led to the condensation and the products **23a-c** were obtained in a quantitative yield as illustrated in Scheme 4.

The behavior of **23** towards heterocyclic amines was also investigated. Thus, treatment of **23b**,**c** with aminopyrazole **24** in refluxing ethanol in the presence of catalytic amount of piperidine afforded pyrazolopyrimidines **26a**,**b** via the intermediate **25**. Formation of **26a** from aminopyrazole and **23b** is believed to be formed via initial condensation and subsequent cyclization (Scheme 4). Structures of pyrazolopyrimidines **26a**,**b** were established using their elemental and spectral data. For example, the ^{1}H-NMR spectrum of **26a** revealed the presence of two signals at δ 1.55 and δ 1.58 ppm corresponding to two methyl groups, and a signal at δ 3.90 corresponding to methoxy group. The mass spectrum of **26a** is in accordance with the proposed structure.

Compounds **23a-c** were used in many chemical transformations to prepare unique heterocyclic compounds. Thus, the reaction of dimedone **27** with compounds **23a-c** and ammonium acetate in the absence of solvent afforded the corresponding compounds **28a-c**[30-32]as shown in Scheme 4. Confirmation of the structures of **28a-c** were based on their elemental and spectral data. The IR spectrum of **28a** revealed the presence of a band at 3394 cm^{-1} corresponding to OH group, a band at 3271 cm^{-1} corresponding to NH group and a band at 1680-1620 cm^{-1} corresponding to 2CO group. The ^{1}H-NMR spectrum of **28a** revealed the presence of a signals at δ 0.99, 1.01, 1.23 ppm corresponding to three methyl groups and the two methylene groups of dimedone appeared as two doublet of doublets at δ 1.96-2.19 ppm and δ 2.30-2.42 ppm. The pyridine ring proton appeared at δ 4.81 ppm. The aromatic protons appeared at δ 6.56-8.12 ppm and the NH group appeared at δ 9.28 ppm. Whereas, the OH group appeared at δ 10.80 ppm. The mass spectrum of **28a** is in accordance with the proposed structure. Thus, it revealed a molecular ion peak at 465 (M^++2) and a number of fragments corresponding to the proposed structure.

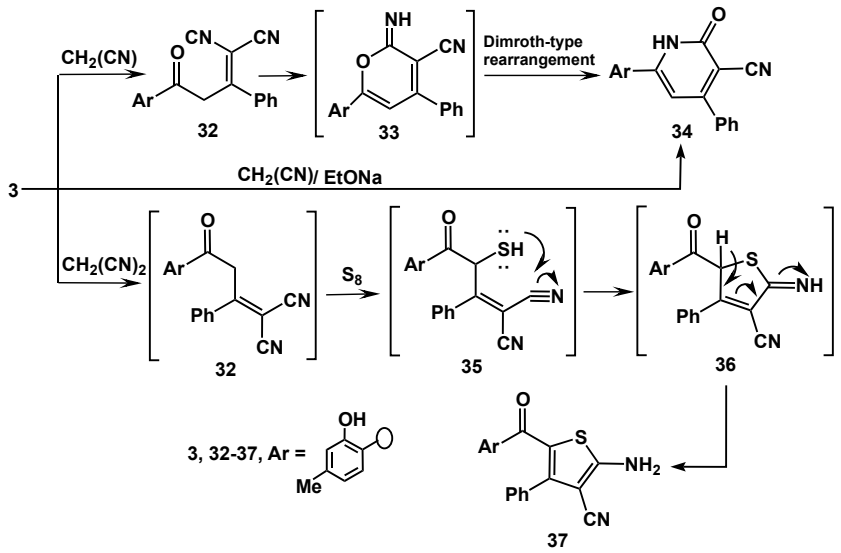
In addition to this, the pyrazole derivatives **31a-f** were prepared from the reaction of 1,3-diketone **23** with hydrazine hydrate and phenylhydrazine in refluxing ethanol[26,33] (Scheme 4). Structural elucidation was done using different spectroscopic techniques. IR spectrum of **31a** revealed the presence of a band at 3402 cm^{-1} corresponding to OH group, a band at 3143 cm^{-1} corresponding to NH group, and a band at 1624 cm^{-1} corresponding to CO group. The ^{1}H-NMR of **31a** revealed the presence of a signals at δ1.08

ppm corresponding to methyl group and a multiplet signals at δ6.41-7.83 ppm related to the aromatic protons. Whereas, the NH and phenolic OH were observed at δ8.40 ppm and at δ12.30 ppm, respectively.



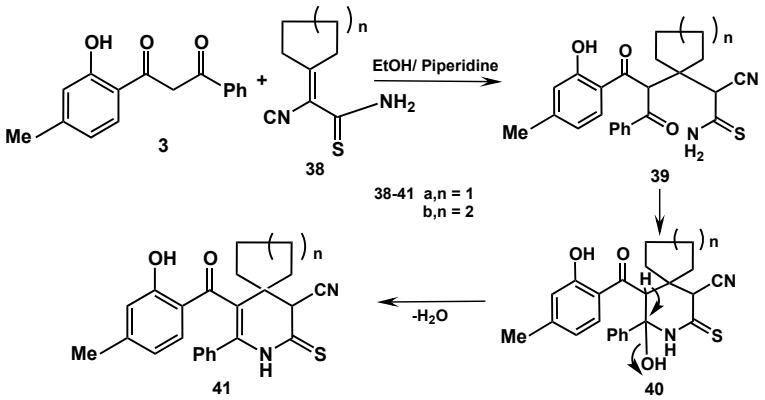
Scheme 4

Furthermore, malononitrile was allowed to react with 1,3-diketone **3** in ethanol containing catalytic amount of piperidine to give a compound **32**. Trials to cyclize 2-(3-(2-hydroxy-4-methylphenyl)-3-oxo-1-phenylpropylidene)malononitrile **32** to 1,2-dihydropyridine derivative **34** succeeded in refluxing ethanolic/piperidine. In addition, compound **34** was obtained in a quantitative yield in one step by reflux an equimolar amount of **3** and malononitrile in the presence of sodium ethoxide.[34] Establishing structure **34** was based on its elemental analyses and spectral data. The IR spectrum of **34** revealed an absorption band at 2190 cm^{-1} corresponding to CN group and a band at 1625 cm^{-1}corresponding to carbonyl group. Its mass spectrum is in accordance with the proposed structure. Thus, it revealed a molecular ion peak at 302 (M^+) and a number of fragments corresponding to the proposed structure (Scheme 5). On the other hand, the synthetic activity of phenolic β-diketone **3** towards active methylene reagents was also investigated. Thus, when a mixture of phenolic β-diketone **3**, malononitrile and elemental sulfur were allowed to react in ethanol containing catalytic amount of piperidine 2-amino-5-(2-hydroxy-4-methylbenzoyl)-4-phenylthiophene-3-carbonitrile **37** was obtained in good yield and its structure was determined based on its elemental analyses and spectral data[26] (Scheme 5).



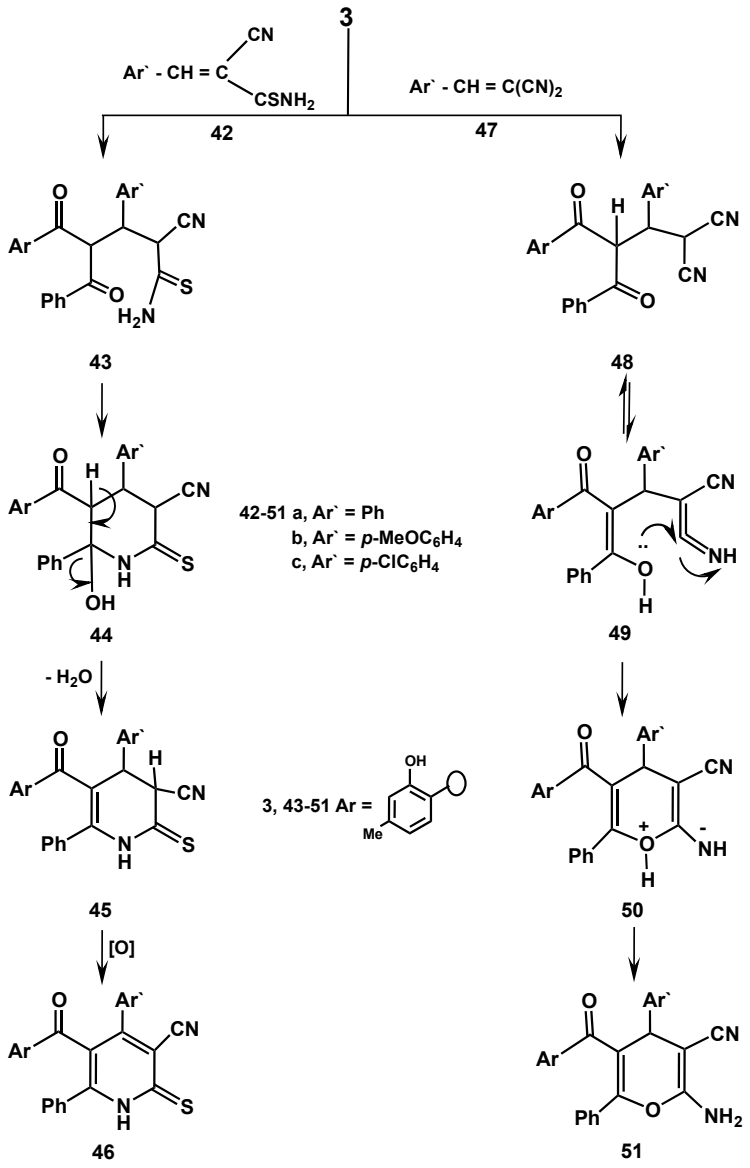
Scheme 5

Cyclocondensation of **3** with 2-cyano-2-cyclopentylideneethanethioamide **38a** or 2-cyano-2-cyclohexylideneethanethioamide **38b** afforded the non-isolable intermediates **39, 40** through an intramolecular cyclization and tautomerization to 10-(2-hydroxy-4-methylbenzoyl)-9-phenyl-7-thioxo-8-azaspiro[4,5]dec-9-ene-6-carbonitrile **41a** and 5-(2-hydroxy-4-methylbenzoyl)-4-phenyl-2-thioxo-3-azaspiro[5,5]undec-4-ene-1-carbonitrile **41b**, respectively. The structure of the former product **41a** was confirmed via its elemental analyses and spectral data. Thus, the infrared spectrum of compound **41a** revealed absorption bands at 3444, 3394, 3055, 2927, 2206, 1666 cm^{-1} for hydroxyl, amino, aromatic and aliphaticcyano and carbonyl function groups, respectively. The ^{1}H-NMR spectrum of compound **41a** showed the following signals at δ 1.23 (s, 3H, CH_3), 1.55-1.61 (m, 4H, $2CH_2$), 2.73-2.89 (m, 4H, $2CH_2$), 3.00 (s, 1H, CH), 7.24-7.95 (m, 9H, aromatic H and NH), and 10.22 (s, 1H, OH). Also, its mass spectrum showed a molecular ion peak at *m/z* 404 (M^{+}+2) and a number of fragments which agrees with the proposed structure[35] (Scheme 6).



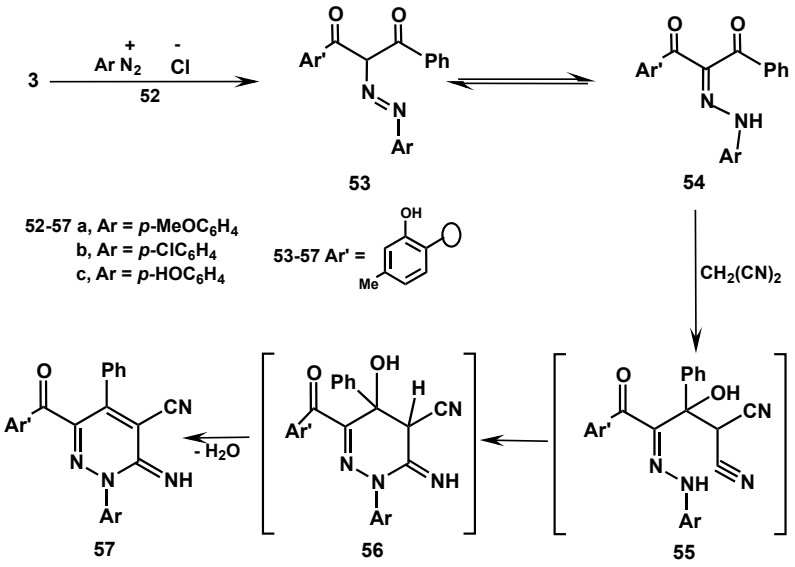
Scheme 6

Reactions of compound **3** with some electrophilic reagents under alkaline conditions were also investigated. Thus, the active methylene group in 1-(2-hydroxy-4-methylphenyl)-3-phenylpropane-1,3-dione **3** was utilized to synthesize novel 1,2-dihydropyridine-3-carbonitrile derivatives **46a-c** and 4*H*-pyran-3-carbonitrile derivatives **51a-c** through its reactions with some electrophilic reagents. Thus, the 1,2-dihydropyridine-3-carbonitrile derivatives **46a-c** were obtained in a quantitative yield from the reaction of **3** with arylidenecyanothioacetamide **42a-c** in ethanol / TEA. Compounds **46a-c** were confirmed on the basis of their spectroscopic analyses. Thus, the IR spectrum of compound **46a** as example revealed the presence of a characteristic bands for amino and cyano functional groups. The ^{1}H-NMR spectrum of **46a** in DMSO-d_6 revealed the absence of methylene moiety. The structure of compound **46a** was further supported by its mass spectrum which revealed a molecular ion peak at *m/z* 424 (M^{+}+2) corresponding to $C_{26}H_{18}N_2O_2S$. Moreover, 4*H*-pyran-3-carbonitriles **51a-c** were synthesized in excellent yields upon treatment of **3** with arylidenemalononitriles **47a-c** in the presence of a catalytic amount of piperidine. The structures of compounds **51a-c** were established based on analytical and spectral data. Thus, the IR spectrum of compound **51a** as example showed an absorption band at 2191 cm^{-1} due to the CN group. The ^{1}H-NMR spectrum of **51a** in DMSO-d_6 revealed a signal at δ 4.19 ppm, which could be attributed to 4*H*-pyran. Moreover, its mass spectrum exhibited a molecular ion peak at *m/z* 408 (M^{+}) corresponding to $C_{26}H_{20}N_2O_3$. 4*H*-Pyran-3-carbonitrile derivatives **51a-c** were assumed to be formed by Michael type addition of the active methylene group in β-diketone **3** to the activated double bond in arylidenemalononitrile derivatives **47a-c** via the non-isolable intermediates **48-50** followed byan intramolecular cyclization to give **51a-c**[26,36] (Scheme 7).



Scheme 7

Compound **3** could be readily coupled with aromatic diazonium salts to yield the corresponding aryl-hydrazone derivatives **54a-c**. The structure of **54** was established through microanalysis, IR, ^{1}H-NMR and mass spectral data and its chemical reactivity to active methylene compound was then attempted. So, fusion of compounds **54a-c** with malononitrile over melting point without solvent in presence of ammonium acetate afforded 3-imino-5-phenyl-2,3-dihydropyridazine-4-carbonitrile derivatives **57a-c** in quantitative yields. The structures of **57a-c** were established through elemental analyses and spectral data. The IR spectrum of **57a** as example showed the following bands at 3304 (OH), 3253 (NH), 3057 (CH-arom), 2927 (CH-aliph), 2210 (CN), and 1622 (CO) cm^{-1}. Its ^{1}H-NMR spectrum in DMSO-d_6 exhibited signals at δ 1.04 ppm for Me, δ 3.82 ppm for OMe, δ 6.59-8.12 ppm for 12H-aromatic, δ 9.24 ppm for NH and δ12.30 ppm for the phenolic OH. Moreover, the mass spectrum of **57a** showed a molecular ion peak at *m/z* 436 (M^+) corresponding to the molecular formula $C_{26}H_{20}N_4O_3$ [37] (Scheme 8).



Scheme 8

ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES

The antibacterial activity of the synthesized compounds was tested against bacterial species ***Escherichia coli, Bacillus megaterium & Bacillus subtilis*** and the antifungal activity was tested also against fungal species ***Fusarium proliferatum, Trichoderma harzianum & Aspergillus niger***. Each compound was dissolved in DMF, and about 100 µL of each compound will be pipetted and poured into the wells existed in nutrient agar plates (peptone 5.00, sodium chloride 5.00, beef extract 1.50, yeast extract 1.50, agar 15.00 all in gm/L, final pH at 25 °C; 7.4±0.2) or Czapek's agar plates for fungi (sucrose 30.00, sodium nitrate 2.00, dipotassium phosphate 1.00, magnesium sulphate 0.50, potassium chloride 0.50, ferrous sulphate 0.01, agar 15.00, all in gm/L, final pH at 25 °C; 7.3±0.2), seeded with ***E. coli, B. megaterium & B. subtilis, F. proliferatum, T. harzianum & A. niger***, respectively.

For determining minimum inhibitory concentration (MIC), serial dilutions of tested compounds (µg/mL) as well as reference antibiotics were prepared using 10% DMF solution. Paper discs of Whatman filter paper were prepared with standard size (8 mm), were cut and sterilized in an autoclave. The paper discs soaked in the desired compound solution, were placed aseptically by forceps, in the petri dishes containing agar media and microbial species.

The petri dishes were incubated at 37 ^{o}C and the inhibition zones were recorded after 24 h of incubation in case of bacteria and after 5-7 days in case of fungi. Each treatment was replicated three times.[38,39] The antibacterial activity of a common standard antibiotic ***Ampicillin*** and antifungal ***Clotrimazole*** was also recorded using the same procedure as above at the same concentration and solvents. The % activity index for the complex was calculated by the following formula:

$$\% \text{ Activity Index} = \frac{\text{Zone of inhibition by test compound (diameter)}}{\text{Zone of inhibition by standard (diameter)}} \times 100$$

The newly synthesized compounds and their derivatives have been screened for antibacterial activity against Gram negative bacteria ***E. col*i** and Gram positive bacteria ***B. megaterium & B. subtilis***, and antifungal activity against ***F. proliferatum, T. harzianum& A. niger***, by the cup (wells)-plate method and agar diffusion disc method for determining MIC (Minimum Inhibitory Concentration). ***Ampicillin*** and ***Clotrimazole*** were used as standards for comparison of antibacterial and antifungal activities, respectively.

Our study illustrated that most of tested compounds were active against most of microbes used. The results of antimicrobial and antifungal activities and MIC are illustrated in **Tables (1.2).** We recorded that, compounds; **31c** and **19** have strong antimicrobial activity (antifungal & antibacterial) against all tested bacteria and fungi. On the other hand, we found that compounds; **37**, **19**, **12** and **41b** had antibacterial activity rather than antifungal activity against tested microbes, so they are effective as antibacterial agents. We noticed that compounds; **20**, **23c**, **37**, **19**, and **23b** were more effective against tested fungi than others, So, their antifungal activities can be evaluated for application against detrimental fungi.

The biological activity of compounds; **31c**, **20**, **23c**, **19**, **37**, **12**, **41b**, **23b**, **23a**, **31f**, **28c**, **31b**, **54b**, **28a**, **54a**, **51c**, **46c**, **4** and **31d** were observed for all tested bacteria and fungi, therefore, they could be used as broad spectrum antimicrobial agents, and could be considered as promising broad spectrum antibiotics.

From our study, it is obvious that most tested compounds have antibacterial activity rather than antifungal activity. Compound **31c** has the lowest values of MIC for all tested microorganisms.

Moderate antimicrobial activity against Gram positive, Gram negative bacteria and fungi was observed from the highest values of MIC, and these compounds are, **23a**, **57c**, and **41a** for bacteria, while **31e**, **31d**, **4**, **21a** and **46c**for fungi. These compounds exhibited high concentrations of MIC as compared with standard antimicrobial agents used.

Table 1 . Antibacterial and antifungal activities of synthesized compounds

	Escherichia coli		*Bacillus megaterium*		*Bacillus subtilis*		*Fusariumpr oliferatum*		*Trichoderma harzianum*		*Aspergillus niger*	
	Inhibition Zone (mm)	% Activity Index	Inhibition Zone (mm)	% Activity Index	Inhibition Zone (mm)	% Activity Index	Inhibition Zone (mm)	% Activity Index	Inhibition Zone (mm)	% Activity Index	Inhibition Zone (mm)	% Activity Index
3	15	65.22	15	65.22	12	52.17	15	68.18	15	68.18	NA	NA
51a	15	65.22	15	65.22	NA	NA	12	54.55	NA	NA	NA	NA
51c	12	52.17	15	65.22	15	65.22	12	54.55	10	45.45	12	54.55
51b	15	65.22	15	65.22	NA	NA	12	54.55	12	54.55	12	54.55
21b	15	65.22	20	86.96	20	86.96	10	45.45	NA	NA	NA	NA
21a	20	86.96	15	65.22	15	65.22	NA	NA	15	68.18	10	45.45
32	15	65.22	15	65.22	15	65.22	15	68.18	NA	NA	15	68.18
13	15	65.22	10	43.48	15	65.22	15	68.18	NA	NA	15	68.18
54c	NA	NA	15	65.22	NA	NA	12	54.55	NA	NA	NA	NA
54b	15	65.22	20	86.96	15	65.22	12	54.55	12	54.55	12	54.55
54a	15	65.22	12	52.17	20	86.96	15	68.18	10	45.45	12	54.55
12	20	86.96	20	86.96	20	86.96	12	54.55	15	68.18	10	45.45
57c	10	43.48	10	43.48	NA	NA	12	54.55	15	68.18	NA	NA
57b	15	65.22	15	65.22	NA	NA	12	54.55	15	68.18	NA	NA
57a	15	65.22	12	52.17	NA	NA	NA	NA	20	90.91	10	45.45
34	20	86.96	15	65.22	20	86.96	12	54.55	12	54.55	12	54.55
8	15	65.22	15	65.22	15	65.22	NA	NA	20	90.91	10	45.45
46a	15	65.22	15	65.22	NA	0.00	12	54.55	NA	0.00	12	54.55
46c	15	65.22	20	86.96	20	86.96	10	45.45	15	68.18	10	45.45
46b	15	65.22	15	65.22	20	86.96	NA	NA	15	68.18	15	68.18
37	20	86.96	20	86.96	20	86.96	12	54.55	20	90.91	20	90.91
15a	15	65.22	15	65.22	12	52.17	12	54.55	15	68.18	NA	NA
15b	12	52.17	NA	0.00	15	65.22	NA	NA	15	68.18	15	68.18
17	20	86.96	15	65.22	15	65.22	15	68.18	NA	NA	15	68.18
19	20	86.96	20	86.96	20	86.96	20	90.91	20	90.91	15	68.18
23c	12	52.17	20	86.96	20	86.96	15	68.18	20	90.91	20	90.91
23b	20	86.96	20	86.96	15	65.22	20	90.91	20	90.91	15	68.18
23a	10	43.48	20	86.96	20	86.96	15	68.18	20	90.91	15	68.18
41a	15	65.22	10	43.48	10	43.48	NA	NA	NA	NA	12	54.55
41b	20	86.96	20	86.96	15	65.22	15	68.18	15	68.18	NA	NA
28c	15	65.22	15	65.22	12	52.17	20	90.91	15	68.18	12	54.55
28b	20	86.96	12	52.17	15	65.22	12	54.55	NA	0.00	12	54.55
28a	15	65.22	20	86.96	20	86.96	15	68.18	10	45.45	12	54.55
31c	20	86.96	20	86.96	20	86.96	20	90.91	20	90.91	20	90.91
31b	20	86.96	12	52.17	15	65.22	10	45.45	15	68.18	12	54.55

31a	15	65.22	20	86.96	20	86.96	NA	NA	15	68.18	12	54.55
31f	15	65.22	20	86.96	20	86.96	20	90.91	15	68.18	12	54.55
20	15	65.22	15	65.22	15	65.22	20	90.91	20	90.91	20	90.91
31e	15	65.22	12	52.17	15	65.22	10	45.45	10	45.45	NA	NA
31d	15	65.22	20	86.96	20	86.96	10	45.45	10	45.45	10	45.45
26b	12	52.17	23	100.0	NA	NA	NA	NA	12	54.55	NA	NA
26a	10	43.48	23	100.0	NA	NA	12	54.55	NA	NA	NA	NA
4	20	86.96	15	65.22	12	52.17	15	68.18	10	45.45	10	45.45
Ampicillin	23	100.0	23	100.0	23	100.0	-	-	-	-	-	-
Clotrimazole	-	-	-	-	-	-	22	100.0	22	100.0	22	100.0

Table 2 . Minimum inhibitory concentrations (MIC) for tested compounds

Compounds	Minimum Inhibitory Concentration (MIC) of the synthesized compounds (µg/mL)					
	Escherichia coli	***Bacillus subtilis***	***Bacillus megaterium***	***Fusariumpr oliferatum***	***Trichoderm aharzianum***	***Aspergillus niger***
3	35	35	75	35	35	NA
51a	35	35	NA	75	NA	NA
51c	75	35	35	75	125	75
51b	35	35	NA	75	75	75
21b	35	15	15	125	NA	NA
21a	15	35	35	NA	35	125
32	35	35	35	35	NA	35
13	35	125	35	35	NA	35
54c	NA	35	NA	75	NA	NA
54b	35	15	35	75	75	75
54a	35	75	15	35	125	75
12	15	15	15	75	35	125
57c	125	125	NA	75	35	NA
57b	35	35	NA	75	35	NA
57a	35	75	NA	NA	15	125
34	15	35	15	75	75	75
8	35	35	35	NA	15	125
46a	35	35	NA	75	NA	75

46c	35	15	15	125	35	125
46b	35	35	15	NA	35	35
37	15	15	15	75	15	15
15a	35	35	75	75	35	NA
15b	75	NA	35	NA	35	35
17	15	35	35	35	NA	35
19	15	15	15	15	15	35
23c	75	15	15	35	15	15
23b	15	15	35	15	15	35
23a	125	15	15	35	15	35
41a	35	125	125	NA	NA	75
41b	15	15	35	35	35	NA
28c	35	35	75	15	35	75
28b	15	75	35	75	NA	75
28a	35	15	15	35	125	75
31c	15	15	15	15	15	15
31b	15	75	35	125	35	75
31a	35	15	15	NA	35	75
31f	35	15	15	15	35	75
20	35	35	15	15	15	35
20	35	35	35	15	15	15
31e	35	75	35	125	125	NA
31d	35	15	15	125	125	125
4	15	35	75	35	125	125
Ampicillin	12	12	12	-	-	-
Clotrimazole	-	-	-	12	12	12

Abbreviations: NA; No activity.

Structure – activity relationship: By analyzing the previous results, it is noted that the substitutes do not play a clear role in the biological activity. However, in most of the results it was observed that the compounds that contain electron-withdrawing groups have a higher biological activity than the compounds that contain electron-donating groups and that the biological activity depends on the formation of the new fused rings and the type of strains chosen from bacteria and fungi.

CONCLUSION

In this work, m-cresol in the presence of zinc chloride reacted with ethyl benzoylacetate to afford1-(2-hydroxy-4-methylphenyl)-3-phenylpropane-1,3-dione **3**. The reactivity of 1,3-diketone **3** was

investigated as a versatile and readily accessible building block for the synthesis of new heterocycles through its reaction with different reagents. The investigation of antifungal and antibacterial screening data revealed that some of the tested compounds show moderate to low activities

EXPERIMENTAL

The melting points, the elemental analyses and the spectral data were recorded as reported in references.[26]

Preparation of 1-(2-hydroxy-4-methylphenyl)-3-phenylpropane-1,3-dione (3): A mixture of *m*-cresol **1** (0.01 mol), ethyl benzoylacetate **2** (0.01 mol) and zinc chloride (5mg) was exposed to microwave irradiation (microwave assisted synthesis was performed on a CEM Microwave synthesizer, the irradiation power was 200W as the maximum level of irradiation and a maximum level of internal vessel pressure at 250 Psi for about 5 min), and the reaction mixture was allowed to reach room temperature, then diluted with EtOH with stirring and the solid product that formed, was filtrated off and crystallized from EtOH to give **3** (92%) as yellow crystals; mp 160-162 ^{o}C; IR (KBr) ν cm^{-1} 3446 (OH), 3097 (CH-arom), 2920 (CH-aliph), 1749, 1626 (2C=O) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.60 (s, 3H, CH_3), 4.00 (s, 2H, CH_2), 6.46-7.93 (m, 8H, aromatic H), 15.97 (s, 1H, OH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 23.6, 54.2, 117.6, 120.1, 123.4, 124.2, 127.5, 127.5, 127.7, 127.7, 134.1, 135.6, 142.2, 160.2, 192.3, 202.3; MS: *m/z* 256 (M^{+}+2). Anal. Calcd for $C_{16}H_{14}O_3$ (254): C, 75.57; H, 5.55; O, 18.88%. Found: C, 75.59; H, 5.58%.

Preparation of 2-((dimethylamino)methylene)-1-(2-hydroxy-4-methylphenyl)-3-phenylpropane-1,3-dione (4): A mixture of **3** (0.01 mol) and DMF-DMA (0.01 mol) in dioxane (30 mL) was heated under reflux for 6 h. The reaction mixture was allowed to cool. The separated solid was filtered off, washed with EtOH and crystallized from EtOH to give **4** (77%) as pale yellow crystals; mp 173-175 ^{o}C; IR (KBr) ν cm^{-1} 3447 (OH), 3098 (CH-arom), 2965-2857 (CH-aliph), 1739, 1626 (2CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6)δ 1.66 (s, 3H, CH_3), 3.73 (s, 6H, $N(CH_3)_2$), 5.88 (s, 1H, CH-olefinic), 6.46-7.93 (m, 8H, aromatic H), 15.97 (s, 1H, OH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 24.1, 44.3, 44.3, 116, 118.9, 119.7, 124.1, 127.6, 127.6, 128.8, 128.8, 132.5, 133.6, 138.3, 146.6, 160.2, 163.1, 193.4, 193.4; MS: *m/z* 311 (M^{+}+2). Anal. Calcd for $C_{19}H_{19}NO_3$ (309): C, 73.77; H, 6.19; N, 4.53 %. Found: C, 73.79; H, 6.21; N, 4.55%.

Preparation of 5-(2-hydroxy-4-methylbenzoyl)-4-phenyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (8): A mixture of **4** (0.01 mol) and cyanothioacetamide (0.01 mol) in presence of sodium ethoxide (Na, 20% in EtOH, 30 mL) was heated under reflux for 24 h. The solution was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered off, washed with water and crystallized from EtOH to give **8** (76%) as yellow crystals; mp 238-240 ^{o}C; IR (KBr) ν cm^{-1} 3449 (OH), 3374 (NH), 3061 (CH-arom), 2928 (CH-aliph), 2216 (CN), 1681 (CO) cm^{-1}; ^{1}H-NMR (400

MHz, DMSO-d_6) δ 1.33 (s, 3H, CH_3), 5.68 (s, 1H, CH-pyridine), 6.89-8.01 (m, 8H, aromatic H), 11.30 (s, 1H, NH), 12.40 (s, 1H, OH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 23.6, 103.5, 116.7, 118.3, 118.9, 119.3, 121.1, 126.8, 127.5, 127.5, 127.8, 127.8, 130.6, 133.3, 143.6, 146.3, 160.7, 160.8, 173.5, 190.8; MS: *m/z* 348 (M^++2). Anal. Calcd for $C_{20}H_{14}N_2O_2S$ (346): C, 69.35; H, 4.07; N, 8.09%. Found: C, 69.37 H, 4.09; N, 8.11%.

Preparation of (2-hydroxy-4-methylphenyl)(3-phenyl-1*H*-pyrazol-4-yl)methanone (12):

Method (A): A mixture of **4** (0.5 g) and hydrazine hydrate (10 mL) was heated under reflux for 12 h. The reaction mixture was allowed to cool and poured into crushed ice. The separated solid was filtered off, washed with water and crystallized from EtOH to give **12** (90%).

Method (B): A mixture of **13** (0.5 g) and hydrazine hydrate (10 mL) was heated under reflux for 12 h. The reaction mixture was allowed to cool and poured into crushed ice. The separated solid was filtered off, washed with water and crystallized from EtOH to give **12** (91%) as white crystals; mp 281-283 ºC; IR (KBr) ν cm^{-1} 3393 (OH), 3210 (NH), 3064 (CH-arom), 2902 (CH-aliph), 1680 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.23 (s, 3H, CH_3), 6.55 (s, 1H, CH-pyrazole), 7.27-7.76 (m, 8H, aromatic H), 12.01 (hump, 1H, NH), 12.36 (hump, 1H, OH); MS: *m/z* 278 (M^+). Anal. Calcd for $C_{17}H_{14}N_2O_2$ (278): C, 73.37; H, 5.07; N, 10.07%. Found: C, 73.39; H, 5.09; N, 10.09%.

Preparation of 2-(ethoxymethylene)-1-(2-hydroxy-4-methylphenyl)-3-phenylpropane-1,3-dione (13): A mixture of **3** (0.01 mol) and triethoxymethane (3 mL) in acetic anhydride (10 mL) was heated under reflux for 12 h. The reaction mixture was allowed to cool. The separated solid was filtered off, washed with EtOH and crystallized from EtOH to give **13** (86%) as pale yellow crystals; mp 150-152 ºC; IR (KBr) ν cm^{-1} 3448 (OH), 3097 (CH-arom), 2988-2859 (CH-aliph), 1725, 1626 (2CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.11 (t, J = 8 *Hz*, 3H, CH_3), 1.90 (s, 3H, CH_3), 4.37 (q, J = 4 *Hz*, 2H, CH_2), 6.88 (s, 1H, CH-olefinic), 7.36-8.05 (m, 8H, aromatic H), 15.50 (s, 1H, OH); MS: *m/z* 310 (M^+). Anal. Calcd for $C_{19}H_{18}O_4$ (310): C, 73.53; H, 5.85; O, 20.62%. Found: C, 73.55; H, 5.87%.

General procedure for preparation of compounds (15a,b and 17): A mixture of **4** (0.01 mol) and urea (0.01 mol), thiourea (0.01 mol) or guanidine hydrochloride (0.01 mol), in presence of sodium ethoxide (Na, 20% in EtOH, 30 mL) was heated under reflux for 24 h. The solutions were allowed to cool and poured into crushed ice then acidified with HCl. The separated solids were filtered off, washed with water and crystallized from the proper solvent to give **15a,b** and **17**.

5-(2-Hydroxy-4-methylbenzoyl)-4-phenylpyrimidin-2(1*H*)-one (15a): It was obtained as beige crystals from DMF; yield (79%); mp >300 ºC; IR (KBr) ν cm^{-1} 3417 (OH), 3379 (NH), 3059 (CH-arom), 2978 (CH-aliph), 1700 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.65 (s, 3H, CH_3), 5.50 (s, 1H, CH-pyrimidine), 7.24-7.88 (m, 8H, aromatic H), 8.51 (s, 1H, NH), 10.15 (s, 1H, OH); ^{13}C-NMR (100

MHz, DMSO-d_6) δ 23.8, 118.2, 118.6, 118.8, 121.4, 127.5, 127.5, 128.1, 128.1, 129.8, 131.6, 132.3, 138.3, 143.8, 153.6, 162.1, 166.2, 192.1; MS: *m/z* 308 (M^++2). Anal. Calcd for $C_{18}H_{14}N_2O_3$ (306): C, 70.58; H, 4.61; N, 9.15%. Found: C, 70.60; H, 4.63; N, 9.17%.

5-(2-Hydroxy-4-methylbenzoyl)-4-phenylpyrimidine-2(1*H*)-thione (15b): It was obtained as yellow crystals from DMF; yield (79%); mp >300 ºC; IR (KBr) ν cm^{-1} 3444 (OH), 3421 (NH), 3059 (CH-arom), 2927 (CH-aliph), 1700 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.63 (s, 3H, CH_3), 5.70 (s, 1H, CH-pyrimidine), 7.24-8.20 (m, 9H, aromatic H and NH), 10.15 (s, 1H, OH); MS: *m/z* 324 (M^++2). Anal. Calcd for $C_{18}H_{14}N_2O_2S$ (322): C, 67.06; H, 4.38; N, 8.69%. Found: C, 67.08; H, 4.40; N, 8.71%.

(2-Amino-4-phenylpyrimidin-5-yl)(2-hydroxy-4-methylphenyl)methanone (17): It was obtained as yellow crystals from EtOH; yield (71%); mp 150-152 ºC; IR (KBr) ν cm^{-1} 3479 (OH), 3444, 3421 (NH_2), 3050 (CH-arom), 2974 (CH-aliph), 1624 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.37 (s, 3H, CH_3), 5.72 (s, 1H, CH-pyrimidine), 6.48 (s, 2H, NH_2), 7.23-8.04 (m, 8H, aromatic H), 10.15 (s, 1H, OH); MS: *m/z* 305 (M^+). Anal. Calcd for $C_{18}H_{15}N_3O_2$ (305): C, 70.81; H, 4.95; N, 13.76 %. Found: C, 70.83; H, 4.97; N, 13.78 %.

Preparation of (2-hydroxy-4-methylphenyl)(3-phenylisoxazol-4-yl)methanone (19): A mixture of **4** (0.01 mol), hydroxylamine hydrochloride in EtOH (30 mL) containing anhydrous sodium acetate (1 g) was heated under reflux for 24 h. The reaction mixture was allowed to cool and poured into cold water (60 mL). The separated solid was filtered off and crystallized from EtOH to give **19** (71%) as brown crystals; mp 150-152 ºC; IR (KBr) ν cm^{-1} 3406 (OH), 3032 (CH-arom), 2916 (CH-aliph), 1674 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.91 (s, 3H, CH_3), 6.52 (s, 1H, CH-isoxazole), 7.03-8.11 (m, 8H, aromatic H), 12.00 (hump, 1H, OH); MS: *m/z* 279 (M^+). Anal. Calcd for $C_{17}H_{13}NO_3$ (279): C, 73.11; H, 4.69; N, 5.02%. Found: C, 73.13; H, 4.71; N, 5.05%.

Preparation of 1-(2-hydroxy-4-methylphenyl)-3-(hydroxyimino)-3-phenylpropan-1-one (20): A mixture of **3** (0.01 mol), hydroxylamine hydrochloride in EtOH (30 mL) containing anhydrous sodium acetate (1 g) was heated under reflux for 15 h. The reaction mixture was allowed to cool and poured into cold water (60 mL). The separated solid was filtered off and crystallized from EtOH to give **20** (80%) as beige crystals; mp 132-134 ºC; IR (KBr) ν cm^{-1} 3417 (OH), 3059 (CH-arom), 2920 (CH-aliph), 1732 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.09 (s, 3H, CH_3), 4.33 (s, 2H, CH_2), 5.73 (s, 1H, OH-oxime), 6.45-7.88 (m, 8H, aromatic H), 12.94 (hump, 1H, OH); MS: *m/z* 269 (M^+). Anal. Calcd for $C_{16}H_{15}NO_3$ (269): C, 71.36; H, 5.61; N, 5.20%. Found: C, 71.38; H, 5.64; N, 5.23%.

General procedure for preparation of compounds 21a, b: A mixture of **3** (0.01 mol) and hydrazine hydrate or phenylhydrazine (0.01 mol) in EtOH (30 mL) was heated under reflux for 12 h. The reaction mixture was allowed to cool and poured into crushed ice. The separated solid was filtered off, washed

with water and crystallized from the proper solvent to give **21a**,**b**.

5-Methyl-2-(3-phenyl-1*H*-pyrazol-5-yl)phenol (21a): It was obtained as white crystals from EtOH; yield (74%); mp 268-270 °C; IR (KBr) ν cm^{-1} 3400 (OH), 3180 (NH), 3045 (CH-arom), 2939 (CH-aliph) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.22 (s, 3H, CH_3), 6.58 (s, 1H, CH-pyrazole), 7.27-7.76 (m, 9H, aromatic H and NH), 12.20 (hump, 1H, OH); MS: *m/z* 250 (M^+). Anal. Calcd for $C_{16}H_{14}N_2O$ (250): C, 76.78; H, 5.64; N, 11.19 %. Found: C, 76.80; H, 5.66; N, 11.21 %.

2-(1,3-Diphenyl-1*H*-pyrazol-5-yl)-5-methylphenol (21b): It was obtained as yellow crystals from EtOH; yield (83%); mp 178-180 °C; IR (KBr) ν cm^{-1} 3448 (OH), 3058 (CH-arom), 2930 (CH-aliph) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.30 (s, 3H, CH_3), 7.03 (s, 1H, CH-pyrazole), 7.11-7.90 (m, 13H, aromatic H), 12.20 (hump, 1H, OH); MS: *m/z* 326 (M^+). Anal. Calcd for $C_{22}H_{18}N_2O$ (326): C, 80.96; H, 5.56; N, 8.58%. Found: C, 80.98; H, 5.58; N, 8.60%.

General procedure for preparation of compounds (23a-c): A mixture of compound **3** (0.01 mol), appropriate aryl aldehydes **22a-c** (0.01 mol) in EtOH (30 mL) with catalytic amount of piperidine was heated under reflux for 3 h. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered off, washed with water and crystallized from the proper solvent to give **23a-c**.

2-Benzylidene-1-(2-hydroxy-4-methylphenyl)-3-phenylpropane-1,3-dione (23a): It was obtained as beige crystals from EtOH; yield (72%); mp 150-152 °C; IR (KBr) ν cm^{-1} 3444 (OH), 3097 (CH-arom), 2927 (CH-aliph), 1739, 1627 (2CO) cm^{-1};^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.56 (s, 3H, CH_3), 6.86 (s, 1H, CH-olefinic), 7.31-7.91 (m, 13H, aromatic H), 10.02 (s, 1H, OH); MS: *m/z* 342 (M^+). Anal. Calcd for $C_{23}H_{18}O_3$ (342): C, 80.68; H, 5.30; O, 14.02%. Found: C, 80.70; H, 5.32%.

1-(2-Hydroxy-4-methylphenyl)-2-(4-methoxybenzylidene)-3-phenylpropane-1,3-dione (23b): It was obtained as beige crystals from EtOH; yield (78%); mp 150-152 °C; IR (KBr) ν cm^{-1}3444 (OH), 3097 (CH-arom), 2931 (CH-aliph), 1739, 1627 (2CO); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.64 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.65 (s, 1H, CH-olefinic), 6.88-7.89 (m, 12H, aromatic H), 9.90 (s, 1H, OH); MS: *m/z* 372 (M^+). Anal. Calcd for $C_{24}H_{20}O_4$ (372): C, 77.40; H, 5.41; O, 17.18%. Found: C, 77.42; H, 5.43%.

2-(4-Chlorobenzylidene-1-(2-hydroxy-4-methylphenyl)-3-phenylpropane-1,3-dione (23c): It was obtained as yellow crystals from EtOH; yield (73%); mp 150-152 °C; IR (KBr) ν cm^{-1} 3400 (OH), 3097 (CH-arom), 2930 (CH-aliph), 1739, 1627 (2CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.23 (s, 3H, CH_3), 6.87 (s, 1H, CH-olefinic), 7.40-7.95 (m, 12H, aromatic H), 10.01 (s, 1H, OH); MS: *m/z* 378 (M^++2). Anal. Calcd for $C_{23}H_{17}ClO_3$ (376): C, 73.31; H, 4.55; O, 12.74%. Found: C, 73.33; H, 4.57%.

General procedure for preparation of compounds (26a, b): A mixture of **23b**, **c** (0.01 mol), 4-(*p*-tolyldiazenyl)-1*H*-pyrazole-3,5-diamine **24** in EtOH (30 mL) with catalytic amount of piperidine

was heated under reflux for 24 h. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered off, washed with water and crystallized from the proper solvent to give **26a,b**.

(2-Amino-7-(4-methoxyphenyl)-5-phenyl-3-(*p*-tolyldiazenyl)pyrazolo[1,5-*a*]pyrimidin-6-yl)(2-hydroxy-4-methylphenyl)methanone (26a): It was obtained as orange crystals from EtOH; yield (79%); mp 210-212 ^{o}C; IR (KBr) ν cm^{-1} 3445 (OH), 3422, 3400 (NH_2), 3061 (CH-arom), 2930 (CH-aliph), 1678 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.55 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 7.12-7.89 (m, 18H, aromatic H and NH_2), 9.87(s, 1H, OH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 23.6, 23.7, 57.1, 98, 114.3, 118.6, 118.7, 118.7, 122.3, 124.4, 126.1, 126.5, 126.5, 126.7, 127.6, 127.6, 127.6, 127.9, 128.9, 128.9, 129.1, 129.1, 129.2, 129.2, 130.8, 134.2, 139.1, 146.1, 156.2, 162.6, 166.1, 168.3, 168.5, 198.3; MS: *m/z* 568 (M^+). Anal. Calcd for $C_{34}H_{28}N_6O_3$ (568): C, 71.82; H, 4.96; N, 14.78 %. Found: C, 71.84; H, 4.99; N, 14.81%.

(2-Amino-7-(4-chlorophenyl)-5-phenyl-3-(*p*-tolyldiazenyl)pyrazolo[1,5-*a*]pyrimidin-6-yl)(2-hydroxy-4-methylphenyl)methanone (26b): It was obtained as brown crystals from EtOH; yield (74%); mp 237-239 ^{o}C; IR (KBr) ν cm^{-1}3421 (OH), 3394, 3309 (NH_2), 3059 (CH-arom), 2935 (CH-aliph), 1612 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.76 (s, 3H, CH_3), 1.90 (s, 3H, CH_3), 6.59 (s, 2H, NH_2), 6.83-8.14 (m, 16H, aromatic H), 9.87 (s, 1H, OH); MS: *m/z* 574 (M^++2). Anal. Calcd for $C_{33}H_{25}ClN_6O_2$ (572): C, 69.17; H, 4.40; N, 14.67%. Found: C, 69.19; H, 4.43; N, 14.70%.

General procedure for preparation of compounds (28a-c): A mixture of **23a- c** (0.01 mol), dimedone **27** (0.01 mol) and ammonium acetate (2 g) was fused for 30 min. The reaction mixture was allowed to cool, then triturated with EtOH. The separated solid was filtered off, washed with water and crystallized from the proper solvent to give **28a-c**.

3-(2-Hydroxy-4-methylbenzoyl)-7,7-dimethyl-2,4-diphenyl-4,6,7,8-tetrahydroquinolin-5(*1H*)-one (28a): It was obtained as yellow crystals from EtOH; yield (86%); mp 150-152 ^{o}C; IR (KBr) ν cm^{-1} 3394 (OH), 3271 (NH), 3059 (CH-arom), 2954-2870 (CH-aliph), 1680-1620 (2CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 0.99 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.96-2.19 (2d, 2H, CH_2), 2.30-2.42 (2d, 2H, CH_2), 4.81 (s, 1H, 4H-pyridine), 6.56-8.12 (m, 13H, aromatic H), 9.28 (s, 1H, NH), 10.80 (hump, 1H, OH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 23.6, 26.3, 26.3, 33.7, 42.1, 42.3, 51.6, 103.7, 110.8, 118.5, 118.8, 121.1, 126.2, 126.6, 126.6, 126.9, 127.3. 127.3, 127.6, 127.8, 127.8, 128.5, 130.2, 135.1, 142.8, 144.6, 145.2, 151.2, 160.6, 193.5, 203.2; MS: *m/z* 465 (M^++2). Anal. Calcd for $C_{31}H_{29}NO_3$ (463): C, 80.32; H, 6.31; N, 3.02%. Found: C, 80.34; H, 6.34; N, 3.05%.

3-(2-Hydroxy-4-methylbenzoyl)-4-(4-methoxyphenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydro-quinolin-5(*1H*)-one (28b): It was obtained as yellow crystals from EtOH; yield (80%); mp 156-158 ^{o}C;

IR (KBr) ν cm^{-1} 3390 (OH), 3271 (NH), 3062 (CH-arom), 2954-2835 (CH-aliph), 1686, 1624 (2CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.23 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.96-2.13 (2d, 2H, CH_2), 2.30-2.40 (2d, 2H, CH_2), 3.85 (s, 3H, OCH_3), 4.50 (s,1H, 4H-pyridine), 6.53-8.32 (m, 12H, aromatic H), 9.20 (s, 1H, NH), 11.39 (s, 1H, OH); MS: *m/z* 493 (M^+). Anal. Calcd for $C_{32}H_{31}NO_4$ (493): C, 77.87; H, 6.33; N, 2.84%. Found: C, 77.89; H, 6.35; N, 2.86%.

4-(4-Chlorophenyl)-3-(2-hydroxy-4-methylbenzoyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydro-quinolin-5(*1H*)-one (28c): It was obtained as pale yellow crystals from EtOH; yield (83%); mp 190-192 ºC; IR (KBr) ν cm^{-1} 3394 (OH), 3282 (NH), 3062 (CH-arom), 2958-2870 (CH-aliph), 1685, 1643 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 0.86 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 2.16-2.30 (2d, 2H, CH_2), 2.34-2.47(2d, 2H, CH_2), 4.78 (s,1H, 4H-pyridine), 6.59-8.12 (m, 12H, aromatic H), 9.33 (s, 1H, NH), 12.23 (s, 1H, OH); MS: *m/z* 499 (M^++2). Anal. Calcd for $C_{31}H_{28}ClNO_3$ (497): C, 74.76; H, 5.67; N, 2.81%. Found: C, 74.78; H, 5.69; N, 2.83%.

General procedure for preparation of compounds (31a-f): A mixture of **23a-c** (0.01 mol) and hydrazine hydrate or phenylhydrazine (0.01 mol) in EtOH (30 mL) was heated under reflux for 12 h. The reaction mixture was allowed to cool and poured into crushed ice. The separated solid was filtered off, washed with water and crystallized from the proper solvent to give **31a-f**.

(3,5-Diphenyl-1*H*-pyrazol-4-yl)(2-hydroxy-4-methylphenyl)methanone (31a): It was obtained as reddish brown crystals from dioxane; yield (83%); mp 252-254 ºC; IR (KBr) ν cm^{-1} 3402 (OH), 3143 (NH), 3051 (CH-arom), 2939 (CH-aliph), 1624 (C=O) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.08 (s, 3H, CH_3), 6.41-7.83 (m, 13H, aromatic H), 8.40 (s, 1H, NH), 12.30 (hump, 1H, OH); MS: *m/z* 356 (M^++2). Anal. Calcd for $C_{23}H_{18}N_2O_2$ (354): C, 77.95; H, 5.12; N, 7.90%. Found: C, 77.97; H, 5.15; N, 7.92%.

(2-Hydroxy-4-methylphenyl)(5-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazol-4-yl)methanone (31b): It was obtained as brown crystals from EtOH; yield (86%); mp 244-246 ºC; IR (KBr) ν cm^{-1} 3402 (OH), 3143 (NH), 3051 (CH-arom), 2935-2908 (CH-aliph), 1624 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ1.08 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.58-7.77 (m, 12H, aromatic H), 8.40 (s, 1H, NH), 12.30 (hump, 1H, OH); MS: *m/z* 386 (M^++2). Anal. Calcd for $C_{24}H_{20}N_2O_3$ (384): C, 74.98; H, 5.24; N, 7.29%. Found: C, 74.99; H, 5.26; N, 7.30 %.

(5-(4-Chlorophenyl)-3-phenyl-1*H*-pyrazol-4-yl)(2-hydroxy-4-methylphenyl)methanone (31c): It was obtained as white crystals from EtOH; yield (84%); mp 230-232 ºC; IR (KBr) ν cm^{-1}3405 (OH), 3197 (NH), 3062 (CH-arom), 2966 (CH-aliph), 1626 (C=O) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.08 (s, 3H, CH_3), 6.35-7.72 (m, 12H, aromatic H), 10.75 (s, 1H, NH), 15.90 (hump, 1H, OH); MS: *m/z* 390 (M^++2). Anal. Calcd for $C_{23}H_{17}ClN_2O_2$ (388): C, 71.04; H, 4.41; N, 7.20%. Found: C, 71.07; H, 4.43; N,

7.23%.

(2-Hydroxy-4-methylphenyl)(1,3,5-triphenyl-1*H*-pyrazol-4-yl)methanone (31d): It was obtained as beige crystals from EtOH; yield (81%); mp 160-162 ^{o}C; IR (KBr) ν cm^{-1} 3394 (OH), 3059 (CH-arom), 2927 (CH-aliph), 1712 (C=O) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ 1.56 (s, 3H, CH_3), 7.12-7.95 (m, 18H, aromatic H), 11.60 (s, 1H, OH); MS: *m/z* 430 (M^+). Anal. Calcd for $C_{29}H_{22}N_2O_2$ (430): C, 80.91; H, 5.15; N, 6.51%. Found: C, 80.93; H, 5.17; N, 6.53%.

(2-Hydroxy-4-methylphenyl)(5-(4-methoxyphenyl)-1,3-diphenyl-1*H*-pyrazol-4-yl)methanone (31e): It was obtained as gray crystals from EtOH; yield (80%); mp 180-182 ^{o}C; IR (KBr) ν cm^{-1} 3250 (OH), 3059 (CH-arom), 2927 (CH-aliph), 1708 (C=O) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ 1.64 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 7.11-7.94 (m, 17H, aromatic H), 11.60 (s, 1H, OH); MS: *m/z* 460 (M^+). Anal. Calcd for $C_{30}H_{24}N_2O_3$ (460): C, 78.24; H, 5.25; N, 6.08%. Found: C, 78.26; H, 5.27; N, 6.11%.

(3-(4-Chlorophenyl)-1,5-diphenyl-1*H*-pyrazol-4-yl)(2-hydroxy-4-methylphenyl)methanone (31f): It was obtained as beige crystals from EtOH; yield (80%); mp 175-177 ^{o}C; IR (KBr) ν cm^{-1} 3248 (OH), 3055 (CH-arom), 2935 (CH-aliph), 1708 (C=O) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ 1.32 (s, 3H, CH_3), 6.61-7.95 (m, 17H, aromatic H), 12.80 (s, 1H, OH); MS: *m/z* 466 (M^++2). Anal. Calcd for $C_{29}H_{21}ClN_2O_2$ (464): C, 74.91; H, 4.55; N, 6.03%. Found: C, 74.93; H, 4.57; N, 6.07%.

Preparation of 2-(3-(2-hydroxy-4-methylphenyl)-3-oxo-1-phenylpropylidene)malononitrile (32): A mixture of **3** (0.01 mol), malononitrile (0.01 mol) in EtOH (30 mL) containing catalytic amount of piperidine was heated under reflux for 12 h. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered off, washed with water and crystallized from EtOH to give **32** (69%) as olive crystals; mp 162-164 ^{o}C; IR (KBr) ν cm^{-1} 3444 (OH), 3099 (CH-arom), 2935 (CH-aliph), 2206-2200 (2CN), 1739 (C=O) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ 1,64 (s, 3H, CH_3), 4.19 (s, 2H, CH_2), 6.24-8.06 (m, 8H, aromatic H), 12.93 (hump, 1H, OH); MS: *m/z* 303 (M^++1). Anal. Calcd for $C_{19}H_{14}N_2O_2$ (302): C, 75.48; H, 4.67; N, 9.27%. Found: C, 75.50; H, 4.70; N, 9.30%.

Preparation of 6-(2-hydroxy-4-methylphenyl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (34): Method (A): A mixture of **3** (0.01 mol), malononitrile (0.01 mol) in EtOH (30 mL) containing catalytic amount of piperidine was heated under reflux for 24 h. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered off, washed with water and crystallized from EtOH to give **34** (55%).

Method (B): A mixture of **3** (0.01 mol), malononitrile (0.01 mol) in EtOH (30 mL) in the presence of NaOEt (2.3 mg) was heated under reflux for 12 h. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered off, washed with water and

crystallized from EtOH to give **34** (72%) as pale beige crystals; mp 163-165 ºC; IR (KBr) ν cm^{-1} 3444 (OH), 3247 (NH), 3099 (CH-arom), 2924 (CH-aliph), 2190 (CN), 1625 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.22 (s, 3H, CH_3), 5.37 (s, 1H, CH-pyridine), 6.90-8.06 (m, 9H, aromatic H and NH), 13.00 (hump, 1H, OH); MS: *m/z*302 (M^+). Anal. Calcd for $C_{19}H_{14}N_2O_2$ (302): C, 75.48; H, 4.67; N, 9.27%. Found: C, 75.50; H, 4.70; N, 9.30%.

Preparation of 2-amino-5-(2-hydroxy-4-methylbenzoyl)-4-phenylthiophene-3-carbonitrile (37): Equimolar amounts of **3** (0.01 mol), malononitrile and elemental sulfur (0.01 mol) in EtOH (30 mL) containing catalytic amount of piperidine were refluxed for 15 h, poured onto cold water (30 mL) and acidified with HCl (pH=3). The solid product thus formed was filtered off and crystallized from EtOH to give **37** (80%) as brown crystals; mp 130-132 ºC; IR (KBr) ν cm^{-1} 3421 (OH), 3329, 3201 (NH_2), 3097 (CH-arom), 2935 (CH-aliph), 2210 (CN), 1739 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.23 (s, 3H, CH_3), 6.87 (s, 2H, NH_2), 7.47-7.89 (m, 8H, aromatic H), 12.23 (s, 1H, OH); MS: *m/z*336 (M^++2). Anal. Calcd for $C_{19}H_{14}N_2O_2S$ (334): C, 68.24; H, 4.22; N, 8.38%. Found: C, 68.25; H, 4.24; N, 8.40%.

General procedure for preparation of compounds (41a,b): A mixture of **3** (0.01 mol) and 2-cyano-2-cyclopentylidenethanethioamide **38a** (0.01 mol) or 2-cyano-2-cyclohexylidenethanethioamide **38b** (0.01 mol) in EtOH (30 mL) containing catalytic amount of piperidine was heated under reflux for 24 h. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered off, washed with water and crystallized from the proper solvent to give **41a**,**b**.

10-(2-Hydroxy-4-methylbenzoyl)-9-phenyl-7-thioxo-8-azaspiro[4,5]dec-9-ene-6-carbonitrile (41a): It was obtained as brown crystals from EtOH; yield (74%); mp 180-182 ºC; IR (KBr) ν cm^{-1} 3444 (OH), 3394 (NH), 3055 (CH-arom), 2927-2854 (CH-aliph), 2206 (CN), 1666 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.23 (s, 3H, CH_3), 1.55-1.61 (m, 4H, $2CH_2$), 2.73-2.89 (m, 4H, $2CH_2$), 3.00 (s, 1H, CH), 7.24-7.95 (m, 9H, aromatic H and NH), 10.22 (s, 1H, OH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 23.2, 26.6, 26.6, 26.6, 26.6, 27.8. 48.9, 113.2, 118.6, 118.6, 118.8, 124.3, 125.2, 126.8, 127.2, 127.5, 127.7, 132.1, 138.1, 144.8, 155.2, 160.2, 193.1, 205.6; MS: *m/z* 404 (M^++2). Anal. Calcd for $C_{24}H_{22}N_2O_2S$ (402): C, 71.62; H, 5.51; N, 6.96%. Found: C, 71.64; H, 5.53; N, 6.98%.

5-(2-Hydroxy-4-methylbenzoyl)-4-phenyl-2-thioxo-3-azaspiro[5,5]undec-4-ene-1-carbonitrile (41b): It was obtained as brown crystals from DMF; yield (87%); mp 310-312 ºC; IR (KBr) ν cm^{-1} 3394 (OH), 3336 (NH), 3055 (CH-arom), 2927-2854 (CH-aliph), 2202 (CN), 1620 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.23 (s, 3H, CH_3), 1.56-2.13 (m, 6H, $3CH_2$), 2.58-2.67 (m, 4H, $2CH_2$), 3.00 (s, 1H, CH), 7.44-7.90 (m, 9H, aromatic H, and NH), 10.20 (s, 1H, OH); MS: *m/z*418 (M^++2). Anal. Calcd for $C_{25}H_{24}N_2O_2S$ (416): C, 72.09; H, 5.81; N, 6.73%. Found: C, 72.11; H, 5.83; N, 6.75%.

General procedure for preparation of compounds (46a-c): A mixture of **3** (0.01 mol) and

arylidenecyanothioacetamide**42a-c** (0.01 mol) in EtOH (30 mL) containing catalytic amount of TEA was heated under reflux for 12 h. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered off, washed with water and crystallized from the proper solvent to give **46a-c**.

5-(2-Hydroxy-4-methylbenzoyl)-4,6-diphenyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (46a): It was obtained as orange crystals from EtOH; yield (78%); mp 147-149 ^{o}C; IR (KBr) ν cm^{-1} 3447 (OH), 3387 (NH), 3099 (CH-arom), 2935 (CH-aliph), 2201 (CN), 1740 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.30 (s, 3H, CH_3), 6.91-7.90 (m, 13H, aromatic H), 10.30 (s, 1H, NH), 12.99 (hump, 1H, OH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 23.5, 107.2, 109.6, 118.4, 118.6, 118.6, 123.2, 126.8, 126.9, 127.2, 127.2, 127.5, 127.5, 127.5, 127.5, 127.7, 127.7, 132.6, 133.6, 135.2, 146.3, 158.6, 163.7, 164.8, 173.1, 194.2; MS: *m/z* 424 (M^{+}+2). Anal. Calcd for $C_{26}H_{18}N_2O_2S$ (422): C, 73.91; H, 4.29; N, 6.63%. Found: C, 73.93; H, 4.31; N, 6.65%.

5-(2-Hydroxy-4-methylbenzoyl)-4-(4-methoxyphenyl)-6-phenyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (46b): It was obtained as orange crystals from EtOH; yield (82%); mp 150-152 ^{o}C; IR (KBr) ν cm^{-1} 3323 (OH), 3207 (NH), 3099 (CH-arom), 2927 (CH-aliph), 2204 (CN), 1741 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.23 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.90-7.90 (m, 12H, aromatic H), 9.90 (s, 1H, NH), 13.01 (hump, 1H, OH); MS: *m/z* 454 (M^{+}+2). Anal. Calcd for $C_{27}H_{20}N_2O_3S$ (452): C, 71.66; H, 4.45; N, 6.19%. Found: C, 71.68; H, 4.47; N, 6.21%.

4-(4-Chlorophenyl)-5-(2-hydroxy-4-methylbenzoyl)-6-phenyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (46c): It was obtained as orange crystals from EtOH; yield (88%); mp 136-138 ^{o}C; IR (KBr) ν cm^{-1} 3448 (OH), 3420 (NH), 3099 (CH-arom), 2934 (CH-aliph), 2198 (CN), 1739 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.30 (s, 3H, CH_3), 6.90-7.95 (m, 12H, aromatic H), 10.30 (s, 1H, NH), 13.04 (hump, 1H, OH); MS: *m/z* 458 (M^{+}+2). Anal. Calcd for $C_{26}H_{17}ClN_2O_2S$ (456): C, 68.34; H, 3.75; N, 6.13%. Found: C, 68.36; H, 3.77; N, 6.15%.

General procedure for preparation of compounds (51a-c): A mixture of **3** (0.01 mol) and arylidenemalononitriles **47a-c** (0.01 mol) in EtOH (30 mL) containing catalytic amount of piperidine was heated under reflux for 12 h. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered off, washed with water and crystallized from the proper solvent to give **51a-c**.

2-Amino-5-(2-hydroxy-4-methylbenzoyl)-4,6-diphenyl-*4H*-pyran-3-carbonitrile (51a): It was obtained as olive crystals from EtOH; yield (82%); mp 160-162 ^{o}C; IR (KBr) ν cm^{-1} 3450 (OH), 3390, 3336 (NH_2), 3099 (CH-arom), 2937 (CH-aliph), 2191 (CN), 1741 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.64 (s, 3H, CH_3), 4.19 (s, 1H, 4H-pyrane), 6.84 (s, 2H, NH_2), 7.44-7.89 (m, 13H, aromatic

H), 15.94 (s, 1H, OH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 23.2, 44.7, 62.1, 116.8, 118.3, 118.5, 118.7, 124.6, 124.7, 126.8, 126.8, 126.8, 126.8, 126.8, 127.5, 127.5, 127.5, 127.5, 131.2, 134, 147.1, 147.3, 153.2, 163.2, 165.1, 194.3; MS: *m/z* 408 (M^+). Anal. Calcd for $C_{26}H_{20}N_2O_3$ (408):C, 76.45; H, 4.94; N, 6.86%. Found: C, 76.47; H, 4.96; N, 6.89%.

2-Amino-5-(2-hydroxy-4-methylbenzoyl)-4-(4-methoxyphenyl)-6-phenyl-4*H*-pyran-3-carbonitrile (51b): It was obtained as green crystals from EtOH; yield (70%); mp 160-162 ºC; IR (KBr) ν cm^{-1}3446 (OH), 3435, 3338 (NH_2), 3099 (CH-arom), 2935 (CH-aliph), 2202 (CN), 1739 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.64 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 4.50 (s, 1H, 4H-pyrane), 6.10 (s, 2H, NH_2), 6.93-8.40 (m, 12H, aromatic H), 15.94 (s, 1H, OH); MS: *m/z* 440 (M^++2). Anal. Calcd. for $C_{27}H_{22}N_2O_4$ (438): C, 73.96; H, 5.06; N, 6.39%. Found: C, 73.98; H, 5.10; N, 6.41%.

2-Amino-4-(4-chlorophenyl)-5-(2-hydroxy-4-methylbenzoyl)-6-phenyl-4*H*-pyran-3-carbonitrile (51c): It was obtained as brown crystals from EtOH; yield (84%); mp 162-164 ºC; IR (KBr) ν cm^{-1} 3444 (OH), 3390, 3334 (NH_2), 3099 (CH-arom), 2935 (CH-aliph), 2191 (CN), 1741 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.65 (s, 3H, CH_3), 4.43 (s, 1H, 4H-pyrane), 6.89 (s, 2H, NH_2), 7.12-7.88 (m, 12H, aromatic H), 15.94 (s, 1H, OH); MS: *m/z* 444 (M^++2). Anal. Calcd for $C_{26}H_{19}ClN_2O_3$ (442): C, 70.51; H, 4.32; N, 6.33%. Found: C, 70.53; H, 4.35; N, 6.35%.

General procedure for preparation of compounds (54a-c): A cold suspension of aryldiazonium salts **52a-c** (0.002 mol) (prepared from 0.002 mol of aromatic amine with the appropriate quantities of sodium nitrite and hydrochloric acid) was gradually added to a cold solution (0-5 ºC) of **3** (0.002 mol) in EtOH (50 mL) containing anhydrous sodium acetate (2 g) with continuous stirring for 1 h. The resulting reaction product was filtered off, washed with water and crystallized from the proper solvent to give compounds **54a-c**.

1-(2-Hydroxy-4-methylphenyl)-2-(2-(4-methoxyphenyl)hydrazono)-3-phenylpropane-1,3-dione (54a): It was obtained as green crystals from EtOH; yield (81%); mp 160-162 ºC; IR (KBr) ν cm^{-1} 3447 (OH), 3421 (NH), 3096 (CH-arom), 2968 (CH-aliph), 1739, 1626 (2CO) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 6.68-7.94 (m, 13H, aromatic H and NH), 15.97 (s, 1H, OH); MS: *m/z* 388 (M^+). Anal. Calcd for $C_{23}H_{20}N_2O_4$ (388): C, 71.12; H, 5.19; N, 7.21%. Found: C, 71.14; H, 5.22; N, 7.23%.

2-(2-(4-Chlorophenyl)hydrazono)-1-(2-hydroxy-4-methylphenyl)-3-phenylpropane-1,3-dione (54b): It was obtained as yelllow crystals from EtOH; yield (77%); mp 160-162 ºC; IR (KBr) ν cm^{-1} 3445 (OH), 3400 (NH), 3096 (CH-arom), 2970 (CH-aliph), 1739, 1626 (2CO) cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.28 (s, 3H, CH_3), 6.54-7.93 (m, 13H, aromatic H and NH), 15.97 (s, 1H, OH); MS: *m/z* 394 (M^++2). Anal. Calcd for $C_{22}H_{17}ClN_2O_3$ (392): C, 67.26; H, 4.36; N, 7.13%. Found: C, 67.28; H, 4.38; N, 7.16%.

1-(2-Hydroxy-4-methylphenyl)-2-(2-(4-hydroxyphenyl)hydrazono)-3-phenylpropane-1,3-dione (54c) : It was obtained as olive crystals from EtOH; yield (71%); mp 162-164 ºC; IR (KBr) ν cm^{-1}3445 (OH), 3400 (NH), 3096 (CH-arom), 2969 (CH-aliph), 1739, 1626 (2CO) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 3H, CH_3), 6.68-7.94 (m, 14H, aromatic H , NH and OH), 15.97 (s, 1H, OH); MS: *m/z* 376 (M^++2). Anal. Calcd for $C_{22}H_{18}N_2O_4$ (374): C, 70.58; H, 4.85; N, 7.48%. Found: C, 70.60; H, 4.87 N, 7.50%.

General procedure for preparation of compounds (57a-c): A mixture of compounds **54a-c** (0.001 mole), ammonium acetate (2 g) and malononitrile (0.001 mol) was fused for 10 min. The solid precipitate so formed was treated with EtOH and filtered out and crystallized from the proper solvent to give **57a-c**.

6-(2-Hydroxy-4-methylbenzoyl)-3-imino-2-(4-methoxyphenyl)-5-phenyl-2,3-dihydropyridazine-4-carbonitrile (57a): It was obtained as brown crystals from EtOH; yield (79%); mp 230-232 ºC; IR (KBr) ν cm^{-1} 3304 (OH), 3253 (NH), 3057 (CH-arom), 2927 (CH-aliph), 2210 (CN), 1622 (CO) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.04 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 6.59-8.12 (m, 12H, aromatic H), 9.24 (s, 1H, NH), 12.30 (s, 1H, OH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 23.7, 57.7, 117.3, 117.3, 118.5, 118.7, 118.7, 120.1, 120.1, 120.2, 125.1, 126.6, 127.5, 127.5, 127.8, 127.8, 133.2, 133.4, 134.2, 147.5, 152.3, 157.3, 159.2, 159.8, 160.8, 190.1; MS: *m/z* 436 (M^+). Anal. Calcd for $C_{26}H_{20}N_4O_3$ (436): C, 71.55; H, 4.62; N, 12.84%. Found: C, 71.57; H, 4.64; N, 12.86%.

2-(4-Chlorophenyl)-6-(2-hydroxy-4-methylbenzoyl)-3-imino-5-phenyl-2,3-dihydropyridazine-4-carbonitrile (57b): It was obtained as brown crystals from EtOH; yield (79%); mp 258-260 ºC; IR (KBr) ν cm^{-1} 3447 (OH), 3421 (NH), 3063 (CH-arom), 2931 (CH-aliph), 2208 (CN), 1626 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.76 (s, 3H, CH_3), 6.41-8.12 (m, 12H, aromatic H), 12.15 (hump, 1H, NH), 12.37 (hump, 1H, OH); MS: *m/z* 442 (M^++2). Anal. Calcd for $C_{25}H_{17}ClN_4O_2$ (440): C, 68.11; H, 3.89 N, 12.71%. Found: C, 68.13; H, 3.91; N, 12.74%.

6-(2-Hydroxy-4-methylbenzoyl)-2-(4-hydroxyphenyl)-3-imino-5-phenyl-2,3-dihydropyridazine-4-carbonitrile (57c): It was obtained as brown crystals from EtOH; yield (79%); mp 272-274 ºC; IR (KBr) ν cm^{-1} 3446 (OH), 3421 (NH), 3061 (CH-arom), 2933 (CH-aliph), 2209 (CN), 1683 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.76 (s, 3H, CH_3), 6.53-7.88 (m, 12H, aromatic H), 9.96 (s, 1H, NH), 11.39 (s, 1H, OH), 12.22 (s, 1H, OH); MS: *m/z* 422 (M^+). Anal. Calcd for $C_{25}H_{18}N_4O_3$ (422). Calcd: C, 71.08; H, 4.29; N, 13.26%. Found: C, 71.11; H, 4.31; N, 13.28%.

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