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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME NOVEL HETEROCYCLES AS ANTIPYRINE DERIVATIVES

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Abstract – Novel antipyrine derivatives bearing pyran, pyridopyrimidine, chromene, benzothiazole, indole, pyrazole and pyridazine moieties were synthesized by using 2-cyano-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)acetamide (**1**) as a staring material. The newly synthesized compounds were evaluated for their antimicrobial activities based on inhibition diameter zone against Gram-positive and Gram-negative bacteria.

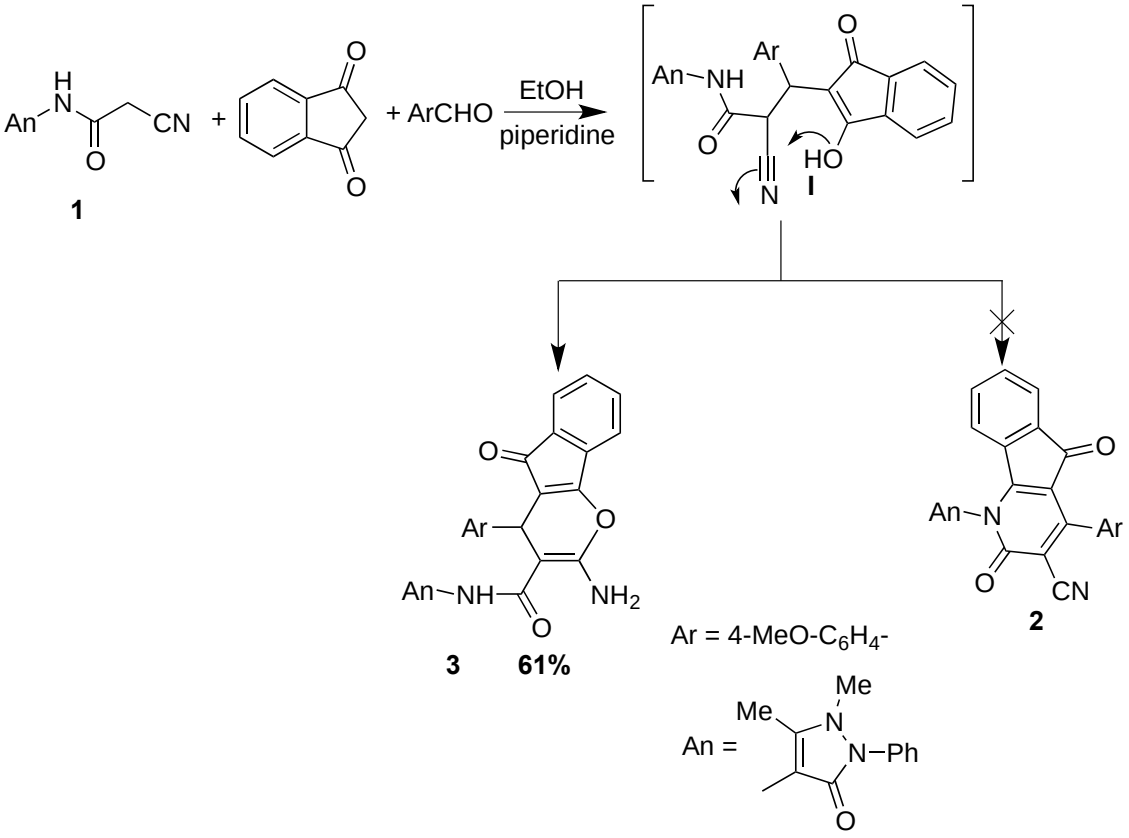
INTRODUCTION

Antipyrine (1,2-dihydro-1,5-dimethyl-2-phenyl-3*H*-pyrazol-3-one) was the chief pyrazolone derivative used in the reducing of inflammation and pain. Antipyrine and amidopyrine derivatives have appealed the attention of many research groups because of their significant activities.[1-5] Antipyrine derivatives possessing a variety of bioactivities such as anticancer activity,[6] antimicrobial,[7,8] anti-inflammatory,[9] analgesic,[10] antiviral,[11] and antioxidant[12] have been reported. The antibacterial activity caught our consideration due to development of antibacterial resistance established by significant pathogens has enlarged in the last decade.[13] After a perusal of the above mentioned data, it was of our interest to synthesis some novel 4-substituted antipyrine derivatives aiming to discover new compounds with promising antimicrobial activity. The possibility and applicability of the use 2-cyanoacetamide derivative **1**[14] as a distinctive precursor for the synthesis of some novel antipyrine derivatives to achieve our objective.

RESULTS AND DISCUSSION

Multicomponent reaction of **1**, 1,3-indandione and 4-anisaldehyde in refluxing ethanol catalyzed by

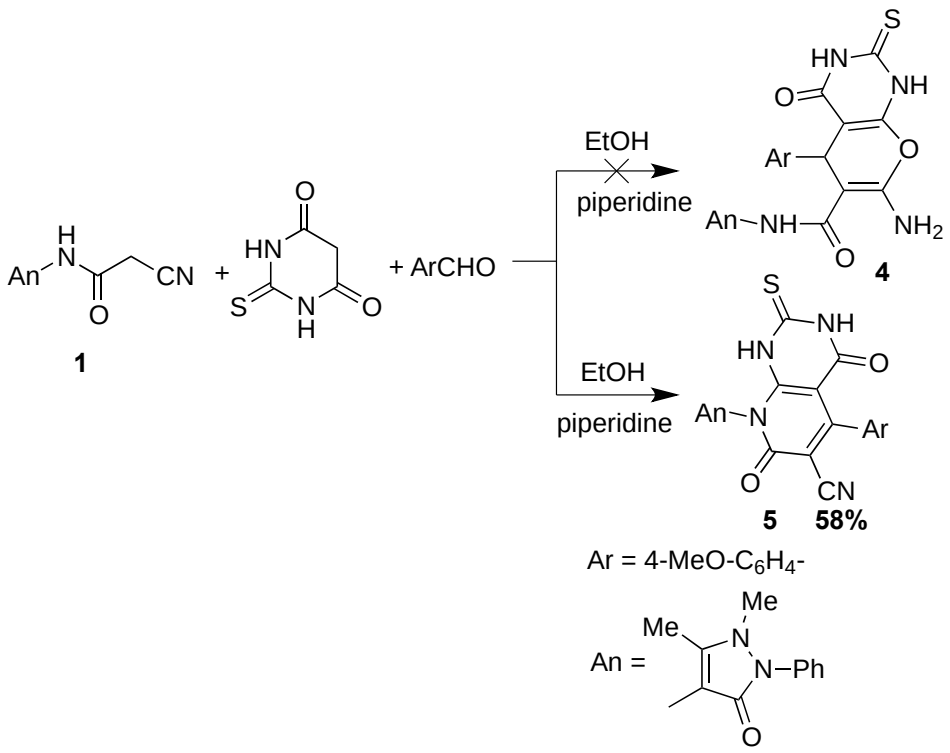
piperidine furnished 4,5-dihydroindeno[1,2-*b*]pyran derivative **3** instead of 2-pyridone derivative **2**[15] (Scheme 1). The assignment of structure **3** was based on its analytical and spectral data. Thus, its IR spectrum disclosed absence of any absorption peak due to nitrile group, which approve that CN group was involved in the cyclization reaction. ^{1}H-NMR spectrum of **3** established its structure by providing singlet signal at δ 6.92 ppm due to NH_2 protons.



Scheme 1

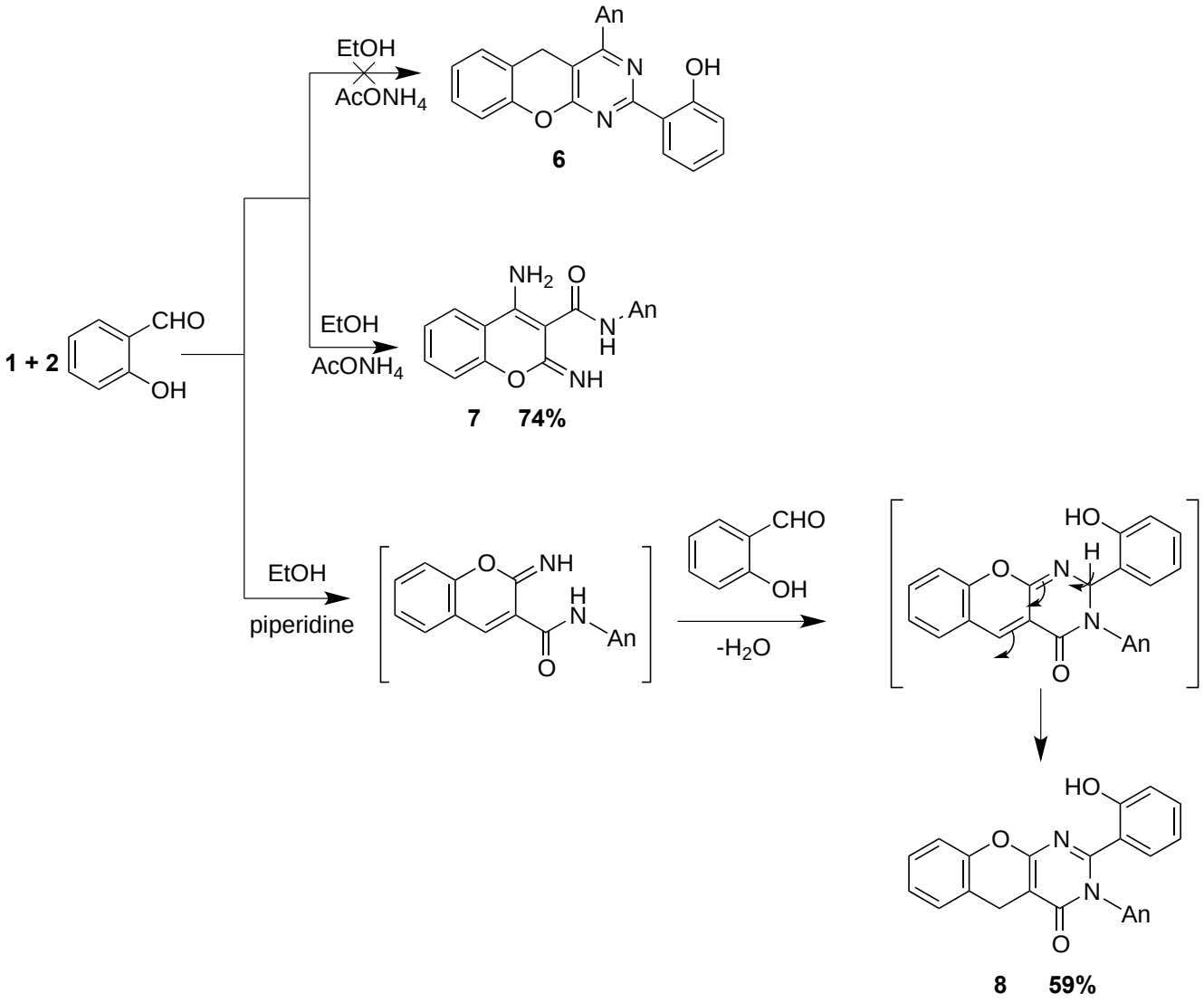
On a different manner, when compound **1** was treated with thiobarbituric acid and 4-anisaldehyde in a similar methodology to the synthesis of compound **3**, it afforded 8-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-5-(4-methoxyphenyl)-4,7-dioxo-2-thioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (**5**) instead of pyranopyrimidine derivative **4** (Scheme 2). The analysis and spectral data of compound **5** was in agreement with its suggested structure. Mass spectrum of **5** revealed molecular ion peak at *m/z* 512 that accord with structure **5** and not structure **4**. In addition, ^{1}H-NMR spectrum of compound **5** revealed two singlet signals (D_2O-exchangeable) at δ 8.57 and 13.24 ppm due to two NH groups. The IR analysis authenticated the results of ^{13}C-NMR by presence of stretching frequency of CN group at 2210 cm^{-1}. The different behavior of cyclization reaction of compound **1** to give pyran derivative **3** or 2-pyridone derivative **5** may be attributed to that the enol

intermediate **I** is stable by conjugation with benzene ring and ketone group so enhance formation of pyran derivative **3** instead of pyridone derivative as obtained in compound **5**.



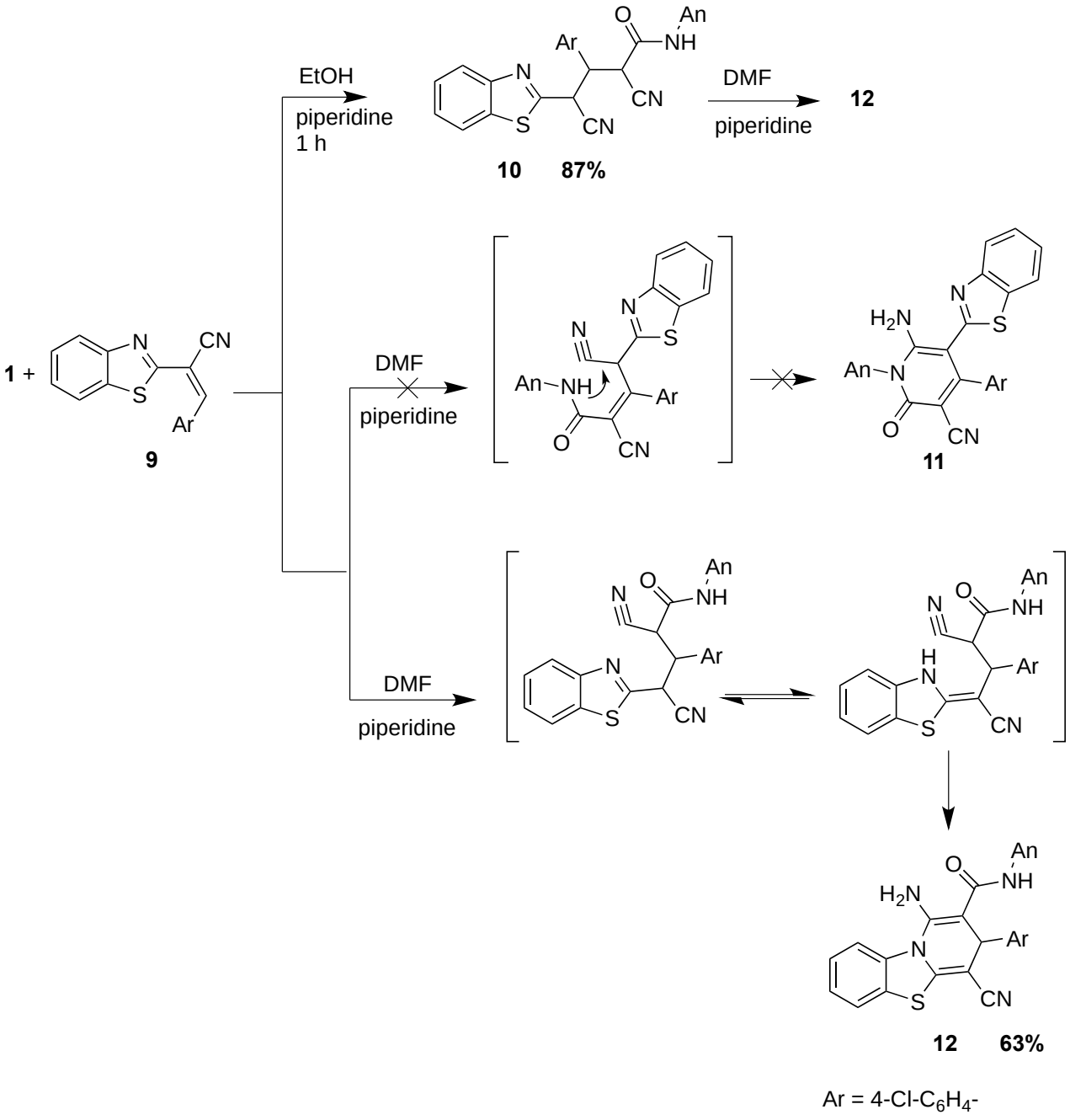
Scheme 2

Treatment of **1** with two moles of salicylaldehyde in refluxing ethanol containing ammonium acetate presented 4-amino-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-imino-2*H*-chromene-3-carboxamide (**7**) other than the expected product **6** according to reported literature[16] (Scheme 3). The anticipated structure of **7** was sustained by its analytical and spectral data. Thus, its mass spectrum provided molecular ion peak at *m/z* 389 that coincided with structure of **7**. Moreover, its ^{1}H-NMR spectrum revealed only nine aromatic protons, which indicated that only one mole of salicylaldehyde was introduced in the reaction. Moreover, ^{1}H-NMR spectrum of **7** displayed three singlet signals (D_2O exchangeable) at δ 6.90, 9.69 and 12.93 ppm corresponding to NH_2 and two NH protons, respectively. On the other hand, when compound **1** was allowed to react with two moles of salicylaldehyde in refluxing ethanol having drops of piperidine, it offered chromeno[2,3-*d*]pyrimidine derivative **8** (Scheme 3). ^{1}H-NMR spectrum of **8** exhibited presence of singlet signal at δ 4.32 ppm due to CH_2 in addition to only one D_2O exchangeable broad singlet signal at δ 6.44 ppm attributed to OH group.



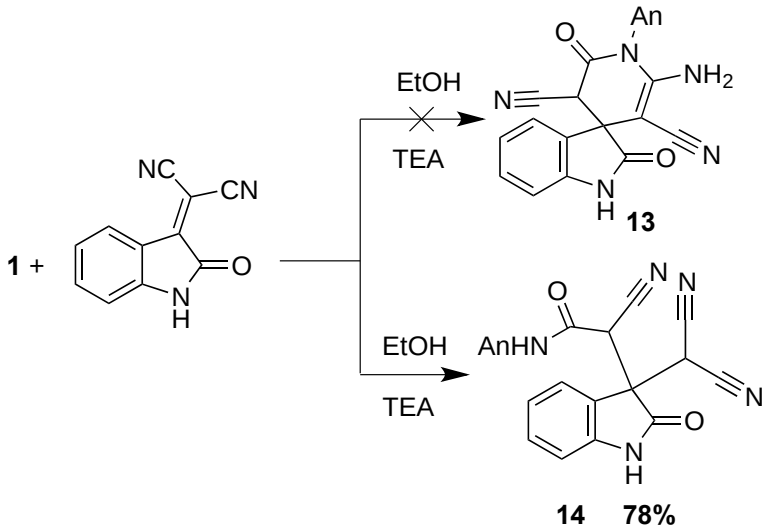
Scheme 3

Interaction of **1** with 2-(benzo[*d*]thiazol-2-yl)-3-(4-chlorophenyl)acrylonitrile[17] (**9**) in refluxing ethanol gave solid isolable product formed on hot within one hour. The formed product was identified as 4-(benzo[*d*]thiazol-2-yl)-3-(4-chlorophenyl)-2,4-dicyano-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1-*H*-pyrazol-4-yl)butanamide (**10**) (Scheme 4) based on its ^{1}H-NMR spectrum, which revealed triplet signal for CH at δ 3.92 ppm and two doublet signals at δ 4.07 and 4.99 ppm attributed to two CH protons. Refluxing a mixture of **1** and **9** in DMF can occur in two mechanistic routes to give either structure **11**[18] or **12**[19] (Scheme 4). Mass spectrum of reaction product revealed molecular ion peak at *m/z* 567 which indicated that cyclization reaction was occurred without loss of any molecules. The structure **11** was excluded based on ^{1}H-NMR spectrum, which revealed a singlet signal at δ 4.76 ppm attributed to CH that settled the structure **12** and not **11**. Compound **12** was obtained also by refluxing a solution of **10** in DMF comprising a catalytic amount of piperidine (Scheme 4).



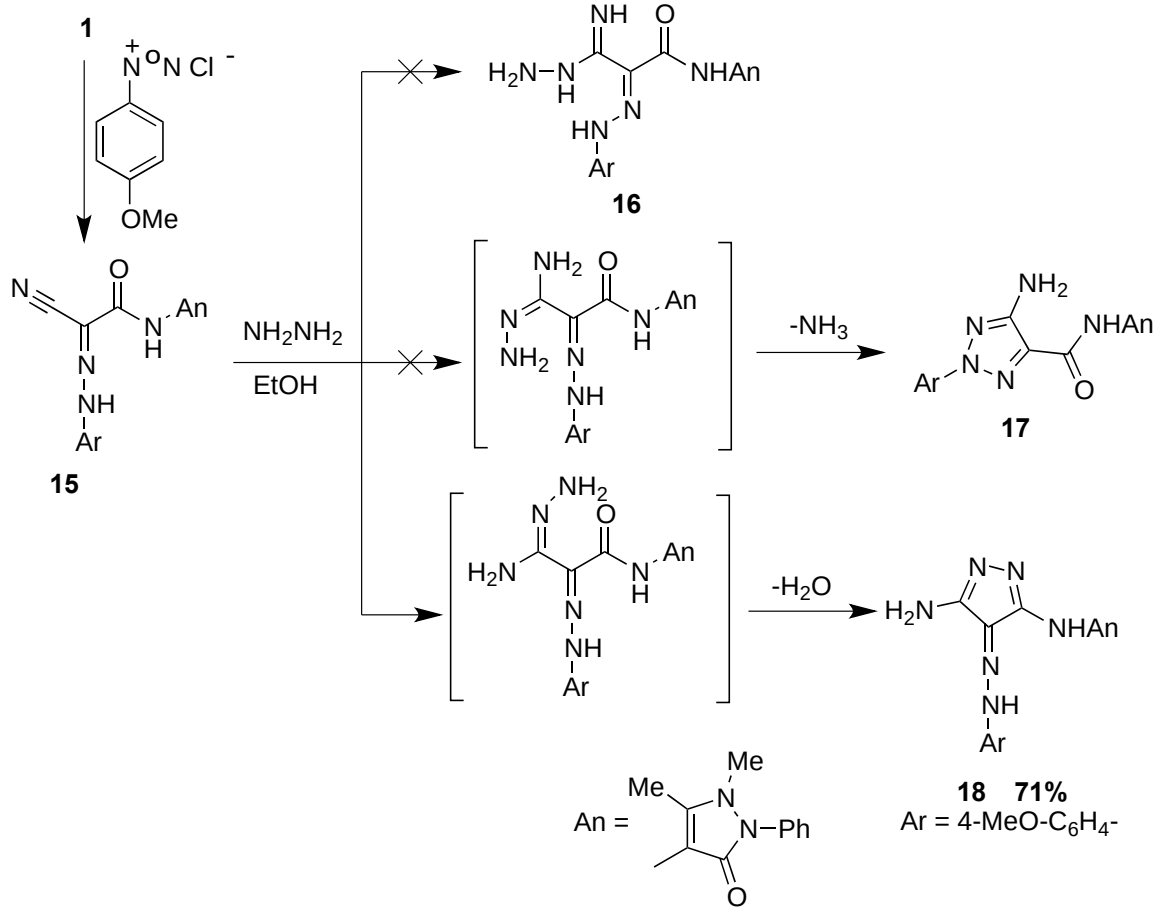
Scheme 4

Attempt to synthesize spiro[indoline-3,4'-pyridine] derivative **13** *via* treatment of **1** with 2-(2-oxoindolin-3-ylidene)malononitrile in refluxing EtOH was failed and instead we obtained 2-cyano-2-(3-(dicyanomethyl)-2-oxoindolin-3-yl)-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)acetamide (**14**) (Scheme 5). The structure assignment of **14** was clearly determined based on its ^{1}H-NMR spectrum, which displayed two singlet signals for two CH groups at δ 5.48 and 5.94 ppm in addition to two singlet signals (D_2O exchangeable) at δ 10.83 and 11.04 ppm attributed to two NH protons.



Scheme 5

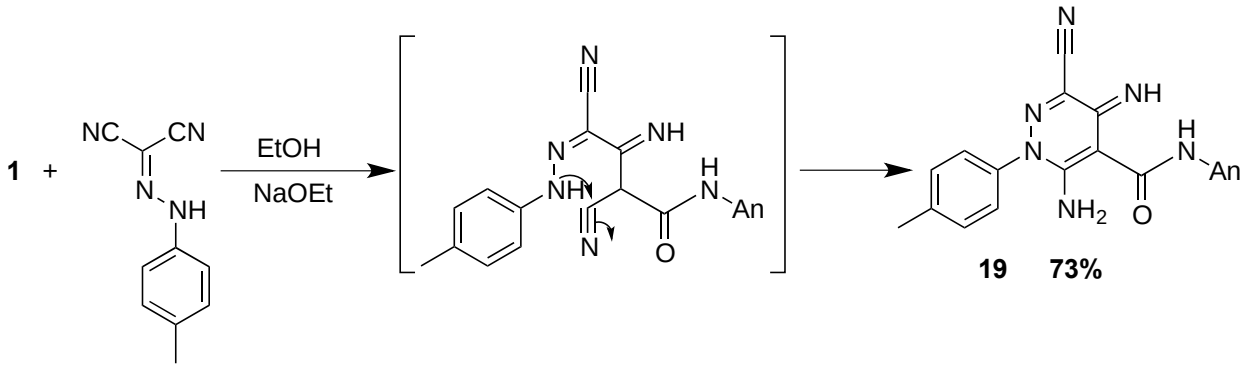
Coupling reaction of **1** with 4-methoxyphenyldiazonium chloride in pyridine furnished 2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)amino)-*N*-(4-methoxyphenyl)-2-oxoacetohydrazonoyl cyanide (**15**)[20] (Scheme 6).



Scheme 6

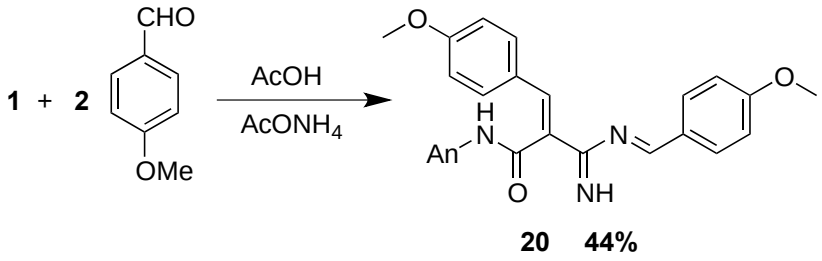
Treatment of compound **15** with hydrazine hydrate in refluxing ethanol generated a single product for which structure **16** or **17**[21] or **18**[22] seemed probable structures (Scheme 6).

Mass spectra of reaction product revealed molecular ion peak at *m/z* 418 that excluded structure **16**. IR and ^{1}H-NMR spectra omitted the structure **17** and approved formation of structure **18** by providing two singlet signals at δ 9.11 and 12.99 ppm due to two NH groups. The reaction of **1** with *N*-*p*-tolylcarbonohydrazonoyl dicyanide in refluxing EtOH containing NaOEt gave the pyridazine derivative **19** (Scheme 7).[23]



Scheme 7

The proposed structure of **19** was in accordance with its elemental and spectral data. Treatment of compound **1** with two moles of 4-anisaldehyde in refluxing glacial acetic acid containing ammonium acetate afforded acrylamide derivative **20** (Scheme 8).



Scheme 8

The structure assignment was based on its analytical and spectral data. Thus, its ^{1}H-NMR spectrum displayed seven singlet signals at δ 2.16, 3.08, 3.85, 8.21, 8.25, 9.51 and 13.76 ppm corresponding to two methyl, two methoxy, vinylic CH, CH=N and two NH groups, respectively. All attempts for obtaining cycloaddition product *via* reaction of **19** with thioglycolic acid or chloroacetyl chloride were failed.

ANTIMICROBIAL ASSAY

The antibacterial activity of the novel synthesized antipyrine derivatives was tested in *vitro* against Gram-positive bacteria (*Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli*) using filter paper disc diffusion method.[24] Ampicillin was used as a reference standard for in *vitro* antibacterial activity. The % activity index was calculated by the formula as under:

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

Antibacterial activity was expressed as inhibition diameter zones in millimeters (mm) of examined antipyrine derivatives was showed in Table 1.

Table 1. Inhibition diameter zone (mm) of the novel synthesized antipyrine derivatives

	Gram (+) bacteria *S. aureus* (mg/mL)		**Gram (-) bacteria *E. coli* (mg/mL)**	
Compound No.	**Diameter of inhibition zone (mm)**	**%Activity index**	**Diameter of inhibition zone (mm)**	**%Activity index**
3	NA	----	NA	----
5	3	13.0	2	8.3
7	17	73.9	16	66.7
8	21	91.3	19	79.2
10	19	82.6	15	62.5
12	22	95.7	21	87.5
14	2	8.7	NA	----
15	15	65.2	13	54.2
18	20	86.9	18	75.0
19	9	39.1	5	20.8
20	NA	----	NA	----
Ampicillin	23	100	24	100

"NA": No Activity

The results depicted in Table 1 exposed that compounds **3** and **20** have no activity against tested Gram-positive and Gram-negative bacteria, while compound **14** was biologically inactive against Gram-negative bacteria. In general, the investigated compounds showed higher activities against Gram-

positive bacteria than Gram-negative bacteria. Compound **12** furnished the best results against Gram-positive and Gram-negative bacteria, in particularly towards Gram-positive bacteria. Compounds **7**, **8**, **10**, **12** and **18** offered the best results against Gram-positive bacteria, while compounds **8**, **12** and **18** presented the greatest activities towards Gram-negative bacteria. Other investigated compounds gave moderate to weak results.

STRUCTURE-ACTIVITY RELATIONSHIP STUDIES

Structure activity relationship for antipyrine derivatives **3**, **5**, **7**, **8**, **10**, **12**, **14**, **15**, **18**, **19** and **20** presented obviously that introducing of chromene (compounds **7** and **8**), benzothiazole (compounds **10** and **12**) or pyrazole moieties as in compound **18** to antipyrine moiety revealed best results against tested bacteria. The good antibacterial results of compounds **7** and **8** that containing chromene moiety were in accordance with reported literature.[8] Introducing fused pyrimidine ring to chromene derivative **8** exhibited good results than chromene derivative **7**. The high antibacterial activities of compounds **10** and **12** may be due to presence of benzothiazole nucleus.[25] In a similar manner, incorporating fused pyridine ring to benzothiazole **12** revealed better results than benzothiazole derivative **10**. Additionally, the good result of **18** agreed with reported literatures which confirmed that incorporating pyrazole moiety to heterocyclic compounds revealed good biological activity.[26]

CONCLUSION

The current work describes the synthesis of novel antipyrine derivatives for antimicrobial assessment with the expectation of discovering novel structure leads serving as good antimicrobial agents.

EXPERIMENTAL

Melting points were measured with a Gallenkamp apparatus are uncorrected. IR spectra were recorded KBr disc on a Mattson 5000 FTIR spectrophotometer at Microanalytical Unit, Faculty of Science, Mansoura University. The ^{1}H-NMR and ^{13}C-NMR spectra were measured on Bruker 500 (125 MHz) in DMSO-d_6 as solvent, using tetramethylsilane (TMS) as an internal standard, and chemical shifts are expressed as δ_{ppm}. Mass spectra were determined on Finnigan Incos 500 (70 eV). Elemental analyses were carried out at the Microanalytical Centre, Faculty of Science, Cairo University, Egypt. All the compounds were checked for their purity on TLC (silica gel, aluminium sheets).

General procedure for the synthesis of 2-amino-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-4-(4-methoxyphenyl)-5-oxo-4,5-dihydroindeno[1,2-*b*]pyran-3-carboxamide (3) and 8-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-5-(4-methoxyphenyl)-4,7-dioxo-2-thioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (5)

A mixture of **1** (1.08 g, 4 mmol), 1,3-dicarbonyl compounds namely 1,3-indandione and thiobarbituric acid (4 mmol) and 4-anisaldehyde (0.48 mL, 4 mmol) in EtOH containing three drops of piperidine was refluxed for 10 h for 1,3-indandione and 18 h for thiobarbituric acid (TLC controlled), and then the reaction mixture was allowed to cool to room temperature. The formed precipitate was filtered off, dried well and recrystallized from EtOH to give compounds **3** and **5**.

2-Amino-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-4-(4-methoxyphenyl)-5-oxo-4,5-dihydroindeno[1,2-*b*]pyran-3-carboxamide (3)

Pale brown powder; yield 61%; mp > 300 °C (EtOH); IR (KBr): ν_{max}/cm^{-1} = 1683, 1718 (2 C=O), 3227 (NH), 3443 and 3451 (NH_2); ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 2.18 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 3.66 (s, 3H, OMe), 4.57 (s, 1H, CH), 6.83 (d, 2H, *J* = 9 Hz, Ar-H), 6.92 (s, 2H, NH_2), 7.29-7.49 (m, 8H, Ar-H), 7.64-7.70 (m, 2H, Ar-H), 8.03 (d, 1H, *J* = 8 Hz, Ar-H), 9.53 (s, 1H, NH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 10.24, 34.25, 35.83, 55.05, 88.34, 103.74, 114.25, 114.42, 121.13, 123.67, 125.27, 125.50, 127.73, 127.87, 129.05, 130.24, 131.91, 132.44, 137.25, 138.33, 139.22, 159.26, 162.94, 165.18, 173.48, 188.29; MS *m/z*: 534 (M^+); Anal. Calcd for $C_{31}H_{26}N_4O_5$ (534.57): C, 69.65; H, 4.90; N, 10.48%. Found: C, 69.69; H, 4.88; N, 10.55%.

8-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-5-(4-methoxyphenyl)-4,7-dioxo-2-thioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (5)

Brown powder; yield 58%; mp 208-209 °C (EtOH); IR (KBr): ν_{max}/cm^{-1} = 1664, 1652 (2C=O), 2210 (CN), 3298 and 3422 (2NH); ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 2.20 (s, 3H, CH_3), 3.09 (s, 3H, CH_3), 3.74 (s, 3H, OMe), 6.82 (d, 2H, *J* = 8 Hz, Ar-H), 7.33-7.54 (m, 7H, Ar-H), 8.57 (s, 1H, NH), 13.24 (s, 1H, NH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 10.46, 35.28, 55.39, 95.26, 106.79, 114.92, 116.88, 118.35, 123.17, 123.68, 124.46, 128.97, 129.68, 131.42, 134.36, 154.58, 157.80, 159.72, 161.93, 167.59, 168.13, 176.38; MS *m/z*: 512 (M^+); Anal. Calcd for $C_{26}H_{20}N_6O_4S$ (512.54): C, 60.93; H, 3.93; N, 16.40%. Found: C, 61.01; H, 3.96; N, 16.44%.

Synthesis of 4-amino-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-imino-2*H*-chromene-3-carboxamide (7)

To a solution of **1** (1.08 g, 4 mmol) dissolved in EtOH (15 mL) containing ammonium acetate (0.3 g, 4 mmol), salicylaldehyde (0.85 mL, 8 mmol) was added. The reaction mixture was heated under reflux for 16 h (TLC controlled). The reaction mixture was left to cool to room temperature, then poured into ice-cold water containing few drops of conc. HCl. The formed precipitate was filtered off, washed with water, dried and recystalized from EtOH to give compound **7** in 74% yield; pale yellow crystal; mp 183-185 °C (EtOH); IR (KBr): ν_{max}/cm^{-1} = 1654, 1633 (2 C=O), 3299, 3324 (2NH), 3386 and 3448 (NH_2); ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 2.39 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 6.90 (s, 2H, NH_2), 7.36-7.55 (m, 9H, Ar-H), 9.69 (s, 1H, NH), 12.93 (s, 1H, NH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 10.19, 35.24,

90.29, 106.09, 110.37, 115.44, 120.78, 122.43, 123.63, 124.11, 129.27, 129.73, 133.25, 134.27, 153.86, 159.75, 160.16, 161.14, 163.57; MS *m/z*: 389 (M^+); Anal. Calcd for $C_{21}H_{19}N_5O_3$ (389.42): C, 64.77; H, 4.92; N, 17.98%. Found: C, 64.68; H, 4.90; N, 17.99%.

Synthesis of 3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-(2-hydroxyphenyl)-3,5-dihydro-4*H*-chromeno[2,3-*d*]pyrimidin-4-one (8)

A mixture of **1** (1.08 g, 4 mmol) and salicylaldehyde (0.85 mL, 8 mmol) in 15 mL EtOH containing 3 drops of piperidine was refluxed for 12 h (the reaction progress was monitored by TLC). Upon completion, the reaction mixture poured into crushed ice containing few drops of conc. HCl. The solid product was collected by filtration, washed with water for several times, dried and recrystallized from EtOH to give compound **8** in 59% yield; yellow crystal; mp 293-294 ºC (EtOH); IR (KBr): ν_{max}/cm^{-1} = 1629, 1688 (2 C=O), 3458 (OH); ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 2.09 (s, 3H, CH_3), 2.93 (s, 3H, CH_3), 4.32 (s, 2H, CH_2), 6.44 (brs, 1H, OH), 6.71-6.76 (m, 2H, Ar-H), 7.03 (d, 1H, *J* = 8 Hz, Ar-H), 7.11 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.22-7.25 (m, 2H, Ar-H), 7.29 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.33 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.49-7.55 (m, 3H, Ar-H), 7.72 (d, 1H, *J* = 6 Hz, Ar-H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 10.48, 29.47, 35.27, 103.47, 104.88, 112.78, 117.04, 117.49, 118.11, 120.96, 122.15, 122.83, 123.46, 124.85, 127.19, 128.66, 129.51, 131.29, 133.47, 134.15, 142.67, 155.92, 156.27, 160.49, 161.59, 162.88; MS *m/z*: 478 (M^+); Anal. Calcd for $C_{28}H_{22}N_4O_4$ (478.51): C, 70.28; H, 4.63; N, 11.71%. Found: C, 70.23; H, 4.66; N, 11.80%.

Synthesis of 4-(benzo[*d*]thiazol-2-yl)-3-(4-chlorophenyl)-2,4-dicyano-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)butanamide (10)

To a mixture of **1** (1.08 g, 4 mmol) and 2-(benzo[*d*]thiazol-2-yl)-3-(4-chlorophenyl)acrylonitrile (1.18 g, 4 mmol) in 20 mL EtOH, three drops of piperidine was added. The reaction mixture was refluxed for 1 h. The precipitated solid product formed on hot was filtered off, dried and recrystallized from EtOH-DMF to give compound **10** in 87% yield; white crystal; mp 249-250 ºC (EtOH-DMF); IR (KBr): ν_{max}/cm^{-1} = 1696 (C=O), 2234, 2257 (two CN), 3448 (NH); ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 2.03 (s, 3H, CH_3), 3.18 (s, 3H, CH_3), 3.92 (t, 1H, *J* = 12.5 Hz, CH), 4.07 (d, 1H, *J* = 12.5 Hz, CH), 4.99 (d, 1H, *J* = 12 Hz, CH), 7.28-7.55 (m, 13H, Ar-H), 9.41 (s, 1H, NH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 10.37, 30.57, 33.49, 35.16, 36.42, 105.76, 117.24, 118.63, 120.42, 120.89, 122.16, 123.62, 124.08, 125.66, 127.33, 128.45, 129.61, 132.62, 133.48, 133.93, 137.81, 147.77, 153.79, 161.22, 167.35, 170.86; MS *m/z*: 567 (M^+); Anal. Calcd for $C_{30}H_{23}ClN_6O_2S$ (567.06): C, 63.54; H, 4.09; N, 14.82%. Found: C, 63.60; H, 4.14; N, 14.88%.

Synthesis of 1-amino-3-(4-chlorophenyl)-4-cyano-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-3*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-2-carboxamide (12)

To a mixture of **1** (1.08 g, 4 mmol) and 2-(benzo[*d*]thiazol-2-yl)-3-(4-chlorophenyl)acrylonitrile (1.18 g,

4 mmol) in 10 mL DMF, three drops of piperidine was added. The reaction mixture was refluxed for 9 h (TLC controlled). Upon competition, the reaction mixture was left to cool and then poured on crushed ice containing drops of conc. HCl. The formed precipitate was filtered off, washed for several times with water, dried and recrystallized from EtOH-DMF to give compound **12** in 63% yield; brown powder; mp 195-196 °C (EtOH-DMF); IR (KBr): ν_{max}/cm^{-1} = 1652 (C=O), 2206 (CN), 3338 (NH), 3426, 3447 (NH_2); ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 2.03 (s, 3H, CH_3), 3.14 (s, 3H, CH_3), 4.76 (s, 1H, CH), 6.68 (s, 2H, NH_2), 7.37-7.58 (m, 13H, Ar-H), 9.12 (s, 1H, NH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 10.26, 35.72, 41.59, 71.37, 91.68, 105.22, 117.99, 120.23, 121.47, 122.38, 122.86, 123.46, 124.39, 125.79, 127.88, 129.62, 130.46, 132.15, 133.37, 134.27, 143.54, 147.08, 160.36, 161.87, 163.14, 169.22; MS *m/z*: 567 (M^+); Anal. Calcd for $C_{30}H_{23}ClN_6O_2S$ (567.06): C, 63.54; H, 4.09; N, 14.82%. Found: C, 63.56; H, 4.05; N, 14.79%.

Synthesis of 2-cyano-2-(3-(dicyanomethyl)-2-oxoindolin-3-yl)-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)acetamide (14)

A mixture of **1** (1.08 g, 4 mmol) and 2-(2-oxoindolin-3-ylidene)malononitrile (0.78 g, 4 mmol) in 15 mL EtOH containing 3 drops of TEA was refluxed for 16 h (the reaction progress was monitored by TLC). The solid precipitate that formed on cooling to room temperature was filtered off, dried and recystalized from EtOH to give compound **14** in 78% yield; yellow powder; mp > 300 °C (EtOH); IR (KBr): ν_{max}/cm^{-1} = 1631, 1689, 1714 (3 C=O), 2190, 2272 (two CN), 3322, 3452 (2 NH); ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 2.18 (s, 3H, CH_3), 3.22 (s, 3H, CH_3), 5.48 (s, 1H, CH), 5.94 (s, 1H, CH), 6.91-6.94 (m, 1H, Ar-H), 7.08-7.11 (m, 2H, Ar-H), 7.21-7.41 (m, 3H, Ar-H), 7.51-7.56 (m, 2H, Ar-H), 7.75 (d, 1H, *J* = 7.5, Ar-H), 10.83 (s, 1H, NH), 11.04 (s, 1H, NH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 10.92, 23.48, 35.39, 37.11, 49.24, 105.42, 114.89, 116.28, 117.59, 121.73, 123.49, 123.96, 124.55, 127.34, 129.51, 134.12, 134.67, 136.92, 144.26, 161.28, 172.56, 181.19; MS *m/z*: 465 (M^+); Anal. Calcd for $C_{25}H_{19}N_7O_3$ (465.47): C, 64.51; H, 4.11; N, 21.06%. Found: C, 64.47; H, 4.10; N, 21.02%.

Synthesis of 4-((5-amino-4-(2-(4-methoxyphenyl)hydrazineylidene)-4*H*-pyrazol-3-yl)amino)-2,5-dimethyl-1-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (18)

To a solution of 2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)amino)-*N*-(4-methoxyphenyl)-2-oxoacetohydrazonoyl cyanide (0.8 g, 2 mmol) in 15 mL EtOH, hydrazine hydrate (0.1 mL, 2 mmol) was added. The reaction mixture was refluxed for 2 h. The solid precipitate formed on cooling solution to room temperature was filtered off, dried and recrystallized from EtOH to give compound **18** in 71% yield; brown powder; mp 133-135 °C (EtOH); IR (KBr): ν_{max}/cm^{-1} = 1629 (C=O), 3299 and 3316 (2 NH) 3409, 3430 (NH_2); ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 2.12 (s, 3H, CH_3), 3.08 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.62 (s, 2H, NH_2), 6.93 (d, 2H, *J* = 8 Hz, Ar-H), 7.34-7.58 (m, 7H, Ar-H), 9.11 (s, 1H, NH), 12.99 (s, 1H, NH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 10.48,

34.81, 55.19, 107.20, 113.56, 116.33, 123.29, 126.34, 128.11, 128.77, 129.65, 136.57, 139.04, 151.28, 151.33, 153.67, 162.18; MS *m/z*: 418 (M^+); Anal. Calcd for $C_{21}H_{22}N_8O_2$ (418.46): C, 60.28; H, 5.30; N, 26.78%. Found: C, 60.23; H, 5.31; N, 26.83%.

Synthesis of 3-amino-6-cyano-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-5-imino-2-(*p*-tolyl)-2,5-dihydropyridazine-4-carboxamide (19)

A mixture of **1** (1.08 g, 4 mmol) and *N*-*p*-tolylcarbonohydrazonoyl dicyanide (0.73 g, 4 mmol) in 15 mL absolute EtOH containing 4 mmol NaOEt was heated under reflux for 12 h (TLC control). The formed precipitate was filtered off, dried and recrystallized from EtOH to give compound **19** in 73% yield; brown powder; mp 183-184 ºC (EtOH); IR (KBr): ν_{max}/cm^{-1} = 1697 (C=O), 2222 (CN), 3181, 3201 (2NH), 3224, 3451 (NH_2); ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 2.18 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 6.57 (s, 2H, NH_2), 7.29-7.53 (m, 9H, Ar-H), 9.31 (s, 1H, NH), 9.66 (s, 1H, NH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 10.69, 20.94, 35.29, 86.29, 105.44, 117.37, 120.88, 122.31, 123.51, 127.59, 129.64, 131.88, 133.68, 134.26, 144.20, 148.84, 155.39, 158.10, 161.47, 164.86; MS *m/z*: 454 (M^+); Anal. Calcd for $C_{24}H_{22}N_8O_2$ (454.49): C, 63.43; H, 4.88; N, 24.66%. Found: C, 63.42; H, 4.93; N, 24.70%.

Synthesis of *N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-(*N*-(4-methoxybenzylidene)carbamimidoyl)-3-(4-methoxyphenyl)acrylamide (20)

To a solution of **1** (1.08 g, 4 mmol) in glacial acetic acid (10 mL), 4-anisaldehyde (0.97 mL, 8 mmol) and ammonium acetate (0.3 g, 4 mmol) were added. The reaction mixture was heated under reflux for 19 h (TLC controlled). The reaction mixture was left to cool at room temperature, then poured onto ice-cold water. The formed precipitate was filtered off, washed for several times with water, dried and recrystallized from EtOH-DMF to give compound **20** in 44% yield; brown crystal; mp 162-163 ºC (EtOH-DMF); IR (KBr): ν_{max}/cm^{-1} = 1669 (C=O), 3393, 3480 (2 NH); ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 2.16 (s, 3H, CH_3), 3.08 (s, 3H, CH_3), 3.85 (s, 6H, two MeO), 7.13-7.16 (m, 4H, Ar-H), 7.31-7.36 (m, 3H, Ar-H), 7.49-7.52 (m, 2H, Ar-H), 7.98 (d, 2H, *J* = 7.5 Hz, Ar-H), 8.04 (d, 2H, *J* = 9 Hz, Ar-H), 8.21 (s, 1H, CH=N), 8.25 (s, 1H, CH=N), 9.51 (s, 1H, NH), 13.76 (s, 1H, NH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 10.58, 35.34, 55.73, 105.27, 116.38, 118.76, 122.48, 123.51, 125.84, 127.08, 129.66, 130.56, 130.73, 133.85, 134.95, 144.39, 158.66, 159.21, 161.48, 163.59, 164.21, 164.95; MS *m/z*: 523 (M^+); Anal. Calcd for $C_{30}H_{29}N_5O_4$ (523.59): C, 68.82; H, 5.58; N, 13.38%. Found: C, 68.86; H, 5.54; N, 13.32%.

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