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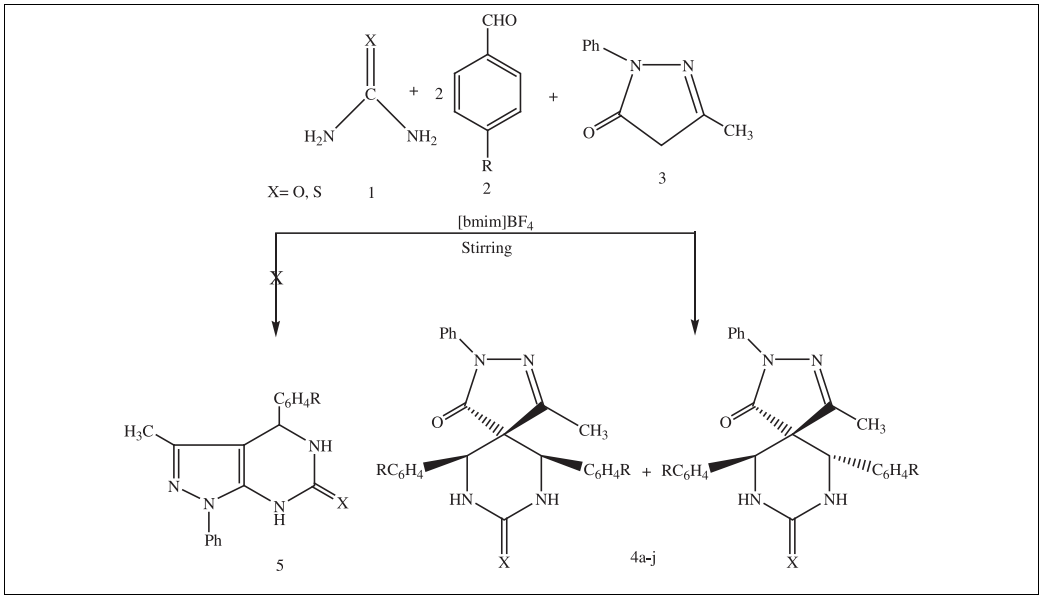

A pseudo four-component reaction of urea or thiourea, diverse aryl aldehydes, and 3-methyl-1-phenyl-2-pyrazolin-5-one in ionic liquids yields novel azaspiro[4.5]decene derivatives. However, the corresponding reaction in volatile organic solvents gives Knoevenagel adduct as a major product with little amount of the title compound. Interestingly, the expected pyrimidine derivative was not formed in any case. The advantageous features of this methodology are the environmentally benign character, operational simplicity, high yield processing, and easy handling without any catalyst. All the compounds were subjected to *in vitro* antimicrobial screening against a panel of pathogenic strains of bacteria and fungi. Some of the compounds were found to be equipotent or more potent than the commercial antibiotics.

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INTRODUCTION

Solvents have a significant impact on environment because of the quantity used in pharmaceutical productions. They typically account for between 80% and 90% of the mass utilization of a batch operation [1]. Consequently, replacing conventional solvents, usually volatile organic compounds, with more environmentally benign media is one of the central tenets of the *Green Chemistry* [2] and a subject of significant academic and commercial interest [3,4]. In the search for alternative solvents, ionic liquids (ILs), especially those based on the imidazolium cation, are emerging as effective solvents for chemical transformations [5]. Many interesting results have been reported, which demonstrate advantages of using ILs as alternative for organic solvents. Especially, one of the most important advantages of ILs is the behavior of solvophobic interactions that generate an internal pressure, which promotes the association of the reagents in a solvent cavity during the activation process, allowing an acceleration of the multicomponent reactions (MCRs) in comparison with the conventional solvents [6].

Organic molecules containing a spiroheterobicyclic moiety exhibiting unique chemical and conformational features are of increasing scientific interest because of their biological properties often associated with the asymmetric spirocarbon atom. They have attracted considerable attention of the synthetic community [7]. The spiroheterobicyclic nucleus, present in a variety of natural and biologically active compounds, is important in the development of new medicinally relevant heterocyclic scaffolds. For example, a new class of marine toxins isolated from shellfish and dinoflagellate, such as pinnatoxins [8] and pteriatoxin [9], exhibits an azaspiro system responsible for the biological activity. Therefore, targeting these types of heterocyclic core has long been an area of intense development and still constitutes an active domain.

Pyrimidine and its derivatives have been recently emerged as important target molecules because of their therapeutic and pharmacological properties such as antiviral [10], analgesic and anti-inflammatory [11], anticancer [12], and antileishmanial [13]. Their remarkable use as calcium channel modulators has also been reported [14]. Pyrimidine framework has been found in natural marine alkaloid batzelladines A and B, the first low molecular weight natural products, which inhibit the binding of HIV gp-120 to CD4 cells, opening a new field towards the development of AIDS therapy [15].

Pyrazolones are also important ingredients in many pharmaceutical preparations. Substituted pyrazolones are reported to possess kinase inhibitory properties, particularly of enzymes that catalyze the phosphorylation of serine and threonine in proteins. Therefore, an inhibitor of these protein kinases can be developed as a drug candidate for treating diseases related to these enzymes, such as rheumatoid arthritis, psoriasis, septic shock, bone loss, cancers, and other proliferative diseases [16].

Integration of pyrimidine as well as pyrazolone moieties in a single molecular framework often remarkably enhances the biocidal profile [17]. However, there appears to be no report on synthesis of spiropyrimidine derivatives containing both the aforementioned moieties together. In view of our interest in green chemical heterocyclic synthesis and our continual work on the synthesis of biodynamic spiroheterocycles [18], we report herein a pseudo four-component reaction of urea, benzaldehyde, and 3-methyl-1-phenyl-2-pyrazolin-5-one to afford a series of novel azaspiro[4.5]decene in ILs.

RESULTS AND DISCUSSION

To establish suitable experimental conditions for the synthesis of azaspiro[4.5]decene system, we tried the model reaction of urea (**1**), benzaldehyde (**2b**), and 3-methyl-1-phenyl-2-pyrazolin-5-one (**3**) in ethanol that was stirred at refluxing temperature for 2 days, but no reaction occurred. When three to four drops of concentrated HCl were added to the reaction mixture, there was an immediate color change from light yellow to reddish yellow. The stirring was continued, till the completion of the reaction (**8h**). Formation of two products were indicated by TLC, wherein the major product corresponds to the Knoevenagel adduct **8b** (62%), whereas the desired spiro compound **4b** was formed in 12% yield (Table 1, entry 1). Replacing ethanol with glacial acetic acid led to the formation of **8b** exclusively, and no reaction was observed when dichloromethane was used as reaction media.

Recent reports have disclosed that MCRs could be promoted in room temperature ionic liquids (RTILs) [19]. Subsequently, we examined the reaction with a series of RTILs. To our delight, [bmim]BF_4 was found to act both as promoter and as reaction media to afford the azaspiro [4.5]decene **4** in excellent yields. The model reaction was also carried out in [bmim]Cl, which gave lower yields. However, [bmim]BF_4 was proved to be the most suitable solvent and catalyst for this transformation giving higher yields (Table 1).

The enhanced reactivity for the synthesis of azaspiro [4.5]decene in the imidazolium IL even in the absence of a catalyst may be attributed to the inherent Brønsted and Lewis acidities of the ring hydrogens H2, H4, and H5 of the imidazolium cation in [bmim]BF_4. Previous studies involving multinuclear NMR spectroscopy and conductivity measurements for the imidazolium ions correlating their acidity characteristics support the aforementioned observations [20].

While investigating the effect of the molar ratios of reagents on the reaction, it was found that 1 equiv each of urea (**1**), aldehyde (**2b**), and 3-methyl-1-phenyl-2-pyrazolin-5-one (**3**) in IL resulted in the formation of intractable mixture of products that could not be separated, although TLC studies indicated the formation of Knoevenagel adduct (**8b**) along with some other products. However, when we conducted the aforementioned reaction by changing the ratio of reactants (1:2:1) in IL, a multifunctionalized azaspiro[4.5]decene (**4b**) was generated with excellent yield (92%). Identification of the products was carried out by spectroscopic methods.

The ^{1}H NMR spectrum of **4b** indicated the formation two diastereomers in a ratio of 6:5. The major isomer exhibited a singlet at δ 2.32 for the 3-CH_3 protons and another singlet at δ 3.62 for the 4-OCH_3 protons. The benzylic protons resonated as a singlet at δ 5.07. The ^{13}C NMR showed a signal at δ 62.5 due to the spirocarbon. The structure of compound **4b** was further

Table 1

Solvent effect on the reaction of urea (10 mmol), anisicaldehyde (20 mmol), and 3-methyl-1-phenyl-2-pyrazolin-5-one (10 mmol).

Entry	Solvent	Catalyst	Temp. (°C)	Time (h)	Isolated yield of products (%)
1	Ethanol	3–4 drops conc. HCl	Refluxing	8	12 (**4b**) + 62 (**8b**)
2	Gl. AcOH		80	10	58 (**8b**)
3	Dichloromethane		Refluxing	18	No reaction
4	[bmim]Cl		60	5	78 (**4b**)
5	[bmim]BF_4		60	4	92 (**4b**)

confirmed by MS, which exhibited a molecular ion peak $(M+H)^+$ at *m/z* 471.

The HMBC spectrum of **4b** conclusively established the azaspiro[4.5]decene structure. The spectra clearly showed the connectivity between benzylic CH appearing at δ 5.06 ppm with C_1 and C_4 carbon atoms resonating at 170.9 and 129.2 ppm, respectively, and spirocarbon C_5 resonating at 62.5 ppm. Thus, the structure of product **4b** was unequivocally established as azaspiro[4.5]decene rather than the expected pyrimidine derivative **5** (Biginelli product). Therefore, the observation of a long-range coupling in the HMBC spectrum seems to be a reliable tool for determination of molecular structure whenever obtaining the single crystal X-ray structure is not possible (Figures 1 and 2).

With these encouraging results in hand, we tuned our interest in exploring the scope of the reaction using various aryl aldehydes having both electron-withdrawing and electron-releasing substituents under the optimized reaction conditions. The results are summarized in Table 2. All aryl aldehydes underwent effective reaction in [bmim]BF_4 regardless of the nature of the substituents on the aryl ring, affording the desired products in moderate to good yields (Table 2). Exceptionally, when *para*-dimethylaminobenzaldehyde was used, the reaction proceeded only up to the Knoevenagel adduct. Schemes 1 and 2

Interestingly, under identical conditions, when cyclic 1,3-dicarbonyl compounds such as dimedone were used as a substrate, instead of 3-methyl-1-phenyl-2-pyrazolin-5-one in the model reaction, 7,7-dimethyl-4-phenyl-4,6,7,8-tetrahydro-1*H*,3*H*-quinazoline-2,5-dione was formed instead of spiroheterobicyclic ring (Scheme 3).

To explore the mechanism for the formation of azaspiro [4.5]decene, we carried out the reaction of the presynthesized Knoevenagel adduct **8** with an additional equivalent of aldehyde and urea, but the reaction did not resulted in the formation of **4** (Scheme 4). Additionally, we have also performed the reaction using acetamide instead of urea and clearly identified an intermediate product **9** obtained from condensation of one molecule of each component by using NMR and MS techniques (Scheme 5).

Thus, the plausible mechanism for the formation of **4** is outlined in Scheme 6. The reaction occurs via initial condensation of aromatic aldehyde **2** with urea **1** to afford the Shiff base **10**, which then undergoes *in situ* addition reaction with 3-methyl-1-phenyl-2-pyrazolin-5-one **3** to yield the intermediate product **11**. Compound **11** further reacted with additional equivalent of aldehydes **2** to allow the formation of the aldimines **12** as a mixture of cis and trans isomers. It is already reported that the anion of 3-methyl-1-phenyl-2-pyrazolin-5-one is an ambident nucleophile, indicating that proton transfer from the enolized pyrazolone to the imine would be facile. Then nucleophilic addition of pyrazolone moiety to the aldimines carbocation affords the azaspiro heterobicyclic rings.

ANTIMICROBIAL ACTIVITY

The results of antifungal activity of azaspiro heterocyclic derivatives **4a–j** against a panel of selected fungi are presented in Table 3 in comparison with those of the reference drugs flucanazole and ketoconazole. All the microbial strains used were of noninvasive species of their genera and thus applicable for analytical work. *Rhizopus stolinifer* and *Fusarium culmorum* are common fungi causing skin diseases, whereas *Aspergillus niger* and *Aspergillus flavus* are known to cause aspergillosis and opportunistic

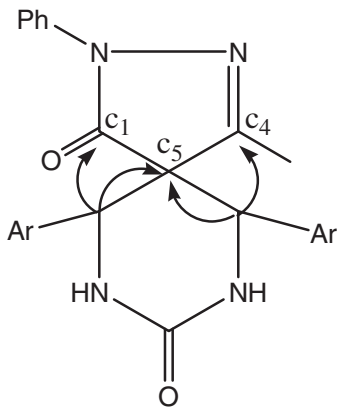


Figure 1. Selected ^1H–^{13}C HMBC correlations of **4b**.

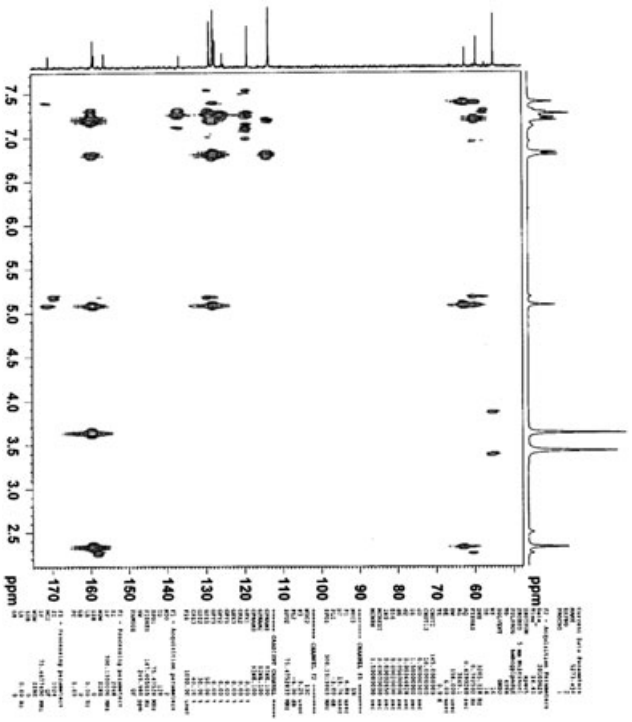


Figure 2. HMBC spectrum for mixture of compound **4b**.

Table 2

Preparation of spiroheterobicyclic rings **4** and pyrimidinones **7** in [bmim]BF_4.

Product	R	X	Time (h)	Yield[a] (%)	Diastereomers ratio[b]	mp (°C)
4a	H	O	4.5	90	64/36	240–242
4b	OCH_3	O	4	92	55/45	236–238
4c	Cl	O	4	88	72/28	216–218
4d	Br	O	4.5	91	78/22	230–232
4e	NO_2	O	5	87	63/37	246–248
4f	OCH_3	S	4.5	90	81/19	232–234
4g	Cl	S	4.5	91	73/27	292–294
4h	Br	S	5	85	68/32	226–228
4i	NO_2	S	5	84	87/13	254–256
4j	F	S	5	92	57/43	244–246
7	H	O	4	86		290–292

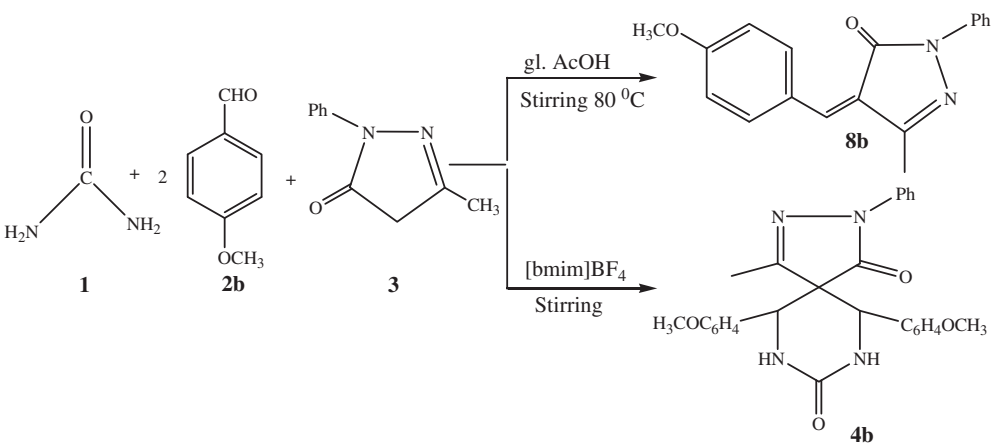
[a]Isolated yields of mixtures after column chromatography.
[b]Determined by ^{1}H NMR spectroscopy.

infections of humans (zygomycosis), respectively. Therefore, we have selected these fungi for the screening work.

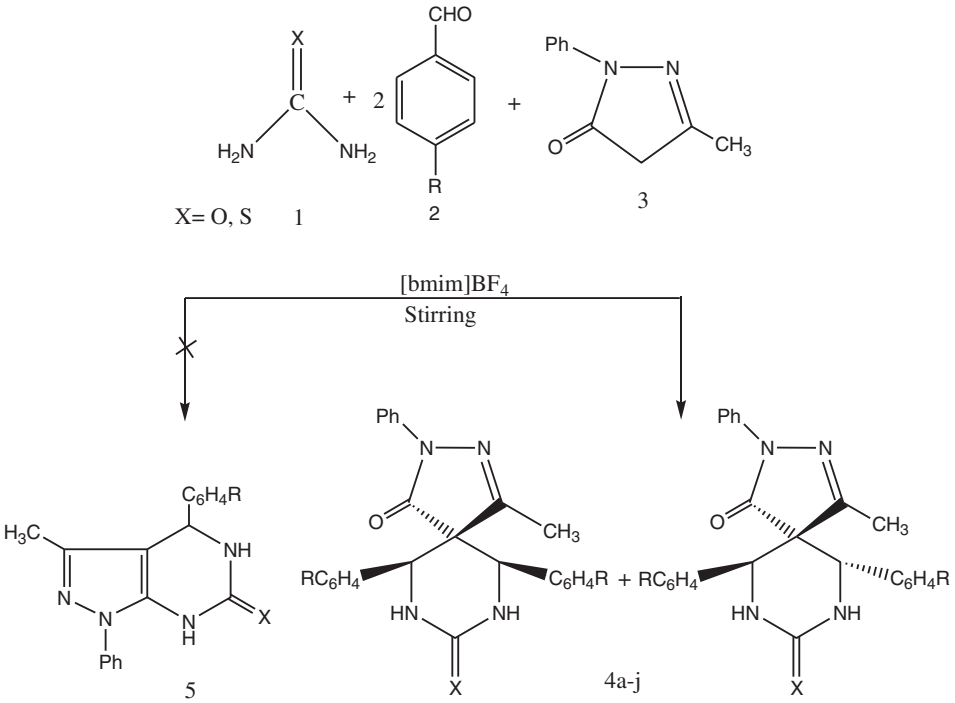
All the compounds tested showed fungistatic activity at 19.6–49.2 μg/mL and fungicidal activity at 37.8–89.6 μg/mL against all the fungi tested. Derivatives **4a–b** exhibited fungistatic effect at 24.8–49.2 μg/mL, and fungicidal activity was observed at 43.3–89.6 μg/mL. Among this group, compound **4b** showed the best antifungal potential against *F. culmorum* and *A. flavus*. Compounds **4c–e** showed almost the same activity, with minimum inhibitory concentration (MIC) at 30.1–39.4 μg/mL and minimum fungicidal concentration (MFC) at 52.8–68.7 μg/mL, whereas compound **4f–i** showed moderate activity in range of MIC at 33.4–49.2 μg/mL and MFC at 56.4–89.3 μg/mL. Compound **4j** exhibited the highest antifungal potential with MIC at 19.6–34.6 μg/mL and MFC at 37.8–60.1 μg /mL. This compound showed the best antifungal effect among all tested. The majority of compounds showed the reasonable activity against *F. culmorum* and *A. flavus*, whereas *A. niger* is the most sensitive species. The most active compound against *A. niger* (MTCC 282) and *R. stolinifer* (MTCC 349) among all tested is **4j**, whereas compound **4b** exhibited the best antifungal potential against *F. culmorum* (MTCC 2591) and *A. flavus* (MTCC 2456) among all tested. Taking into account that most of the compounds exhibited activity better than the reference drugs, they could be promising candidates for antifungal drugs.

In addition, compounds **4a–j** were evaluated for antibacterial activity against a wide number of Gram-positive bacteria, as well as Gram-negative bacteria. The selected bacteria are known to cause human diseases, whereas *Staphylococcus aureus* causes staph-related illness. *Zymomonas mobilis* causes cider sickness and spoilage of beer, *Escherichia coli* causes bloody diarrhea, and *Pseudomonas aeruginosa* causes respiratory system infections, dermatitis, soft tissue infections, bacteremia, and urinary tract infections. Therefore, we have selected these bacteria for the screening process. The antibacterial activity of compounds tested by microdilution method are presented in Table 4. The kind of the exerted antibacterial activity was investigated by determining the minimal bactericidal concentrations (MBCs). The experimental data (second values) presented in Table 4 show that **4a–j** possess bacteriostatic properties, with MBCs being almost twofold higher than the corresponding MICs.

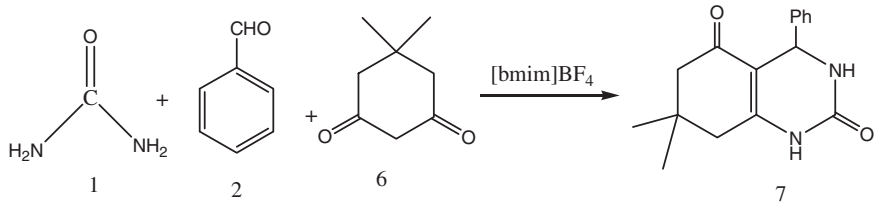
Scheme 1. Model reaction.



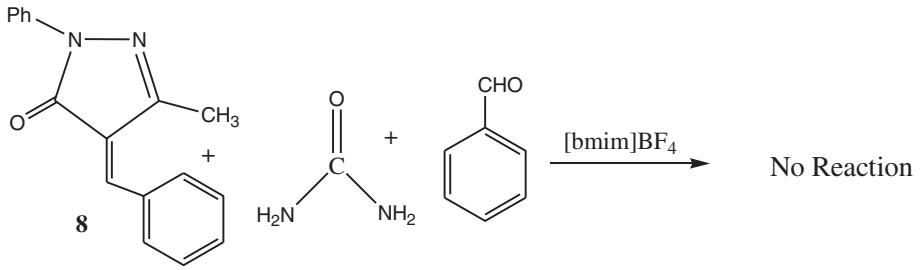
Scheme 2. Synthesis of spiroheterobicyclic rings (**4a–j**) in [bmim]BF_4.



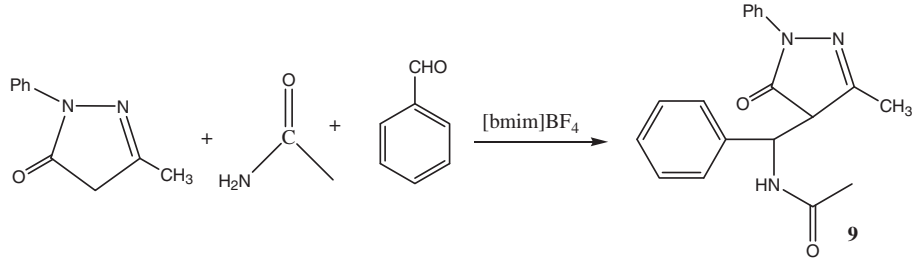
Scheme 3. Synthesis of 7,7-dimethyl-4-phenyl-4,6,7,8-tetrahydroquinazoline-2,5-dione.



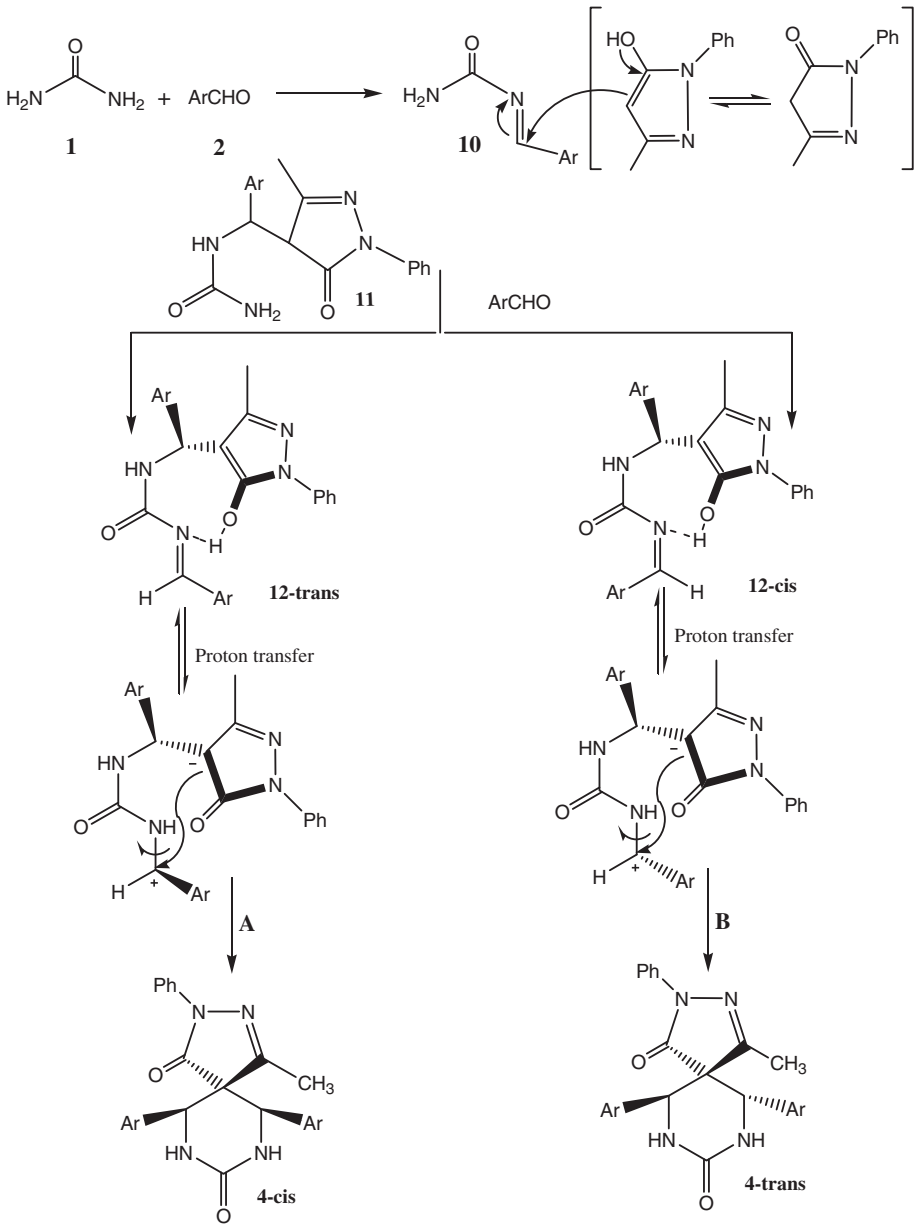
Scheme 4. Reaction of pre-synthesized Knoevenagel adduct **8** with benzaldehyde and urea.



Scheme 5. Reaction of acetamide and benzaldehyde with 3-methyl-1-phenyl-2-pyrazolin-5-one.



Scheme 6. Plausible mechanism for the reaction of urea and aldehyde with 3-methyl-1-phenyl-2-pyrazolin-5-one.



Most of the compounds have shown strong antibacterial activity against all bacterial species. MIC for compounds **4a–j** is at 20.9–48.7 μg/mL and MBC at 37.1–96.8 μg/mL. Compounds **4a–c** showed MIC at 23.6–39.1 μg/mL and MBC at 45.4–76.3 μg/mL, and these compounds were found to be more potent as compared with standard drugs. MIC for compounds **4d–f** is at 28.8–48.1 μg/mL and MBC at 49.3–93.6 μg/mL; these compounds are equipotent against all species. On the other hand, compounds **4g–i** showed moderate activity in range of MIC at 38.8–48.7 μg/mL and MBC at 76.4–96.8 μg/mL. Compound **4j** showed MIC at 20.9–31.1 μg/mL and MBC at 37.1–60.7 μg/mL; it can be seen that **4j** showed the highest antibacterial activity in this series. Most significant inhibitory properties were detected for compound **4j** against *S. aureus* (MTCC 3160) as well as *E. coli* (MTCC 1652), whereas **4b** is the most active compound against *Z. mobilis* (MTCC 88) and *P. aeruginosa* (MTCC 2584) among all tested.

It can be seen that most of the compounds tested for antimicrobial activity showed much better effect than commercial fungicides flucanazole and ketoconazole (MIC 36.3–48.2 μg/mL and MBC 67.4–90.7 μg/mL for flucanazole and MIC 40.0–61.2 μg/mL and MBC 78.0–114.5 μg/mL for ketoconazole) as well as antibiotics ampicillin and streptomycin (MIC 28.8–41.0 μg/mL and MBC 47.6–82.0 μg/mL for ampicillin and MIC 28.8–47.9 μg/mL and MBC 46.9–80.1 μg/mL for streptomycin). Thus, all these

Table 3

Antifungal activity of tested compounds **4a–j** and fungicides (MIC and MFC in μg/mL).

Compound	*Rhizopus stolinifer* (MTCC 349) MIC/MFC	*Fusarium culmorum* (MTCC 2591) MIC/MFC	*Aspergillus niger* (MTCC 282) MIC/MFC	*Aspergillus flavus* (MTCC 2456) MIC/MFC
4a	43.6/85.4	49.2/89.6	32.3/41.4	43.6/88.2
4b	46.2/89.1	**24.8/43.3**	32.1/55.7	**27.8/51.8**
4c	34.1/64.6	31.8/61.2	39.4/66.3	30.3/54.5
4d	30.1/57.3	33.2/59.1	35.2/68.7	31.2/56.1
4e	33.2/52.8	38.4/62.1	35.8/65.2	30.2/48.6
4f	41.2/84.3	48.2/82.2	38.6/63.4	48.1/87.3
4g	38.2/61.4	39.7/81.1	44.3/80.2	37.4/68.2
4h	39.4/71.4	45.8/84.4	49.2/89.3	33.4/56.4
4i	44.7/78.5	44.8/70.1	47.4/80.5	48.2/84.6
4j	**27.8/52.7**	34.6/60.1	**19.6/37.8**	31.2/58.2
Flucanazole	36.3/67.4	48.2/90.7	40.3 / 79.5	36.7/67.9
Ketoconazole	40.1/78.3	40.0/78	61.2/114.5	41.6/95.2

Bold emphasis indicates the highest activity.

Table 4

Antibacterial activity of tested compounds **4a–j** and antibiotics (MIC and MBC in μg/mL).

Compound	*Staphylococcus aureus* (MTCC 3160) MIC/MBC	*Zymomonas mobilis* (MTCC 88) MIC/MBC	*Escherichia coli* (MTCC 1652) MIC/MBC	*Pseudomonas aeruginosa* (MTCC 2584) MIC/MBC
4a	23.6/45.4	32.9/66.3	31.2/60.1	29.4/62.9
4b	26.2/48.7	**26.1/53.7**	32.1/55.7	**29.1/50.2**
4c	28.1/56.4	27.2/54.9	39.1/76.3	30.9/51.8
4d	28.8/49.3	38.9/78.9	39.2/79.8	36.8/71.1
4e	29.8/54.1	40.7/80.1	39.8/80.7	40.9/81.3
4f	29.1/52.3	42.7/82.9	48.1/93.6	38.7/79.6
4g	41.1/78.4	39.3/81.9	42.1/82.9	44.4/88.9
4h	39.9/78.3	41.7/83.6	43.1/81.7	43.3/86.6
4i	41.9/78.8	38.8/76.4	43.9/88.1	48.7/96.8
4j	**20.9/37.1**	31.1/60.7	**22.0/43.5**	30.6/58.9
Ampicillin	28.8/47.6	38.2/79.6	41.0/82.0	38/69.3
Streptomycin	28.8/46.9	41.9/70.2	47.9/80.1	36.9/64.2

Bold emphasis indicates the highest activity.

compounds could be used as lead compounds for new antimicrobial drugs.

Test for antifungal activity. For the antifungal bioassays, four fungi were used: *R. stolinifer* (MTCC 2591), *F. culmorum* (MTCC 349), *A. niger* (MTCC 282), and *A. flavus* (MTCC 2456). The organisms were obtained from the Microbial Type Culture Collection and Gene Bank (MTCC), Institute of Microbial Technology, Chandigarh. The micromycetes were maintained on potato dextrose agar, and the cultures stored at 4°C and subcultured once a month. To investigate the antifungal activity of the extracts, a modified microdilution technique was used [21]. The fungal spores were washed from the surface of agar plates with sterile 0.85% saline containing 0.1% Tween 80 (v/v). The spore suspension was adjusted with sterile saline to a concentration of approximately 1.0×10^7 in a final volume of 100 μL per well. The inocula were stored at 4°C for further use. Dilutions of the inocula were cultured on solid potato dextrose agar to verify the absence of contamination and to check the validity of the inoculum. MIC determinations were performed by a serial dilution technique using 96-well microtiter plates. The compounds investigated were dissolved in DMSO (1 mg/mL) and added in potato dextrose broth medium with inoculum. The microplates were incubated for 72 h at 28°C. The lowest concentrations without visible growth (at the binocular microscope) were defined as MICs.

The MFCs were determined by serial subcultivation of 2 μL into microtiter plates containing 100 μL of broth per well and by further incubation for 72 h at 28°C. The lowest concentration with no visible growth was defined as MFC indicating 99.5% killing of the original inoculum. DMSO was used as a negative control; commercial fungicides, flucanazole and ketoconazole (Sigma, India), were used as positive controls (1–3000 μg/mL). All experiments were performed in duplicate and repeated three times.

Test for antibacterial activity. The Gram-negative bacteria *E. coli* (MTCC 1652), *P. aeruginosa* (MTCC 2584), and *Z. mobilis* (MTCC 88) and the Gram-positive bacteria *S. aureus* (MTCC 3160) were used. The organisms were obtained from the MTCC, Institute of Microbial Technology, Chandigarh. The antibacterial assay was carried out by microdilution method [21] to determine the antibacterial activity of the compounds tested against the human pathogenic bacteria. The bacterial suspensions were adjusted with sterile saline to a concentration of 1.0×10^7 cfu/mL. The inocula were prepared daily and stored at +4°C until use. Dilutions of the inocula were cultured on solid medium to verify the absence of contamination and to check the validity of the inoculum. All experiments were performed in duplicate and repeated three times.

Microdilution test. The MICs and MBCs were determined using 96-well microtiter plates. The bacterial suspension was adjusted with sterile saline to a concentration of 1.0×10^7 cfu/mL. Compounds to be investigated were dissolved in Luria Broth (LB) medium (100 μL) with bacterial inocula (1.0×10^5 cfu/well) to achieve the wanted concentrations (1 mg/mL). The microplates were incubated for 24 h at 48°C. The lowest concentrations without visible growth (at the binocular microscope) were defined as concentrations that completely inhibited bacterial growth (MICs). The MBCs were determined by serial subcultivation of 2 μL into microtiter plates containing 100 μL of broth per well and by further incubation for 72 h. The lowest concentration with no visible growth was defined as the MBC, indicating 99.5% killing of the original inoculum. The optical density of each well was measured at a wavelength of 655 nm by a microplate reader (ENM8602, Perlong, India) and compared with a blank and the positive control. Streptomycin and ampicillin (Himedia lab, India) were used as positive controls (1 mg/mL DMSO). All experiments were performed in duplicate and repeated three times.

In conclusion, we have demonstrated a novel MCR of urea (thiourea), aryl aldehydes, and 3-methyl-1-phenyl-2-pyrazolin-5-one leading to a diverse set of spiropyrimidine heterocycles with excellent yields and no traces of the expected Biginelli product. Particularly, valuable features of this method included the broader substrate scope and operational simplicity as well as increased safety for small-scale high-speed synthesis. In addition, we have successfully combined the advantages of IL, which acts not only as novel reaction media for this transformation but also as a promoter for the reaction. The easy work-up procedures, the absence of a catalyst, and the recyclability of the nonvolatile IL used as the reaction medium make the method amenable for scale-up operations. Furthermore, this series provides new classes of biologically active compound as antimicrobial agents, because most of the compounds screened exhibit superior activity than commercial agents used as reference drugs. They could be promising candidates for antimicrobial drugs.

EXPERIMENTAL

The melting points of all compounds were determined on a Toshniwal apparatus. The purity of compounds was checked on thin layers of silica gel-G coated glass plates and *n*-hexane/ethyl acetate (7:3) as eluent. IR spectra were recorded on a Shimadzu FTIR-8400S spectrophotometer using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 using TMS as an internal standard on a Bruker spectrophotometer at 300 and 75 MHz, respectively. Mass spectra of representative compounds were recorded on JEOL SX-102 spectrometer at 70 eV. Elemental microanalyses were carried out on a Carlo Erba 1108 CHN analyzer.

General procedure for the synthesis of compounds 4a–j. A mixture of aldehyde (20 mmol), 3-methyl-1-phenyl-2-pyrazolin-5-one (10 mmol), and urea (10 mmol) in 1-butyl-3-methylimidazolium tetrafluoroborate (10 mmol) was stirred at 50–60°C for an appropriate time (Table 2). After completion of the reaction, as indicated by TLC, the reaction mixture was washed with diethyl ether (3 × 15 mL). The combined ether extracts were concentrated *in vacuo*, and the resulting product was directly charged on a small silica gel column and eluted with ethyl acetate/*n*-hexane (2:8) to afford the inseparable diastereoisomeric mixture of spiropyrimidines. The remainder of the viscous IL was further washed with ether and recycled in subsequent reactions.

4-Methyl-2,6,10-triphenyl-2,3,7,9-tetraazaspiro[4.5]dec-3-ene-1,8-dione (4a). White crystalline solid; (yield 90%); mp 240–242°C; IR (KBr): ν = 3376, 3212, 3082, 1720, 1696, 1614 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz, mixture-major isomer only): δ 2.32 (s, 3H, CH_3), 5.08 (s, 2H, CH), 6.84–7.33 (m, 15H, ArH), 7.30 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.4, 57.8, 62.7, 113.5, 113.8, 119.1, 119.4, 125.7, 127.4, 128, 128.2, 128.9, 129.0, 132.4, 133.7, 136.7, 161.1, 170.7; MS (*m/z*): 411 $(M+H)^+$. *Anal*. Calcd for $C_{25}H_{22}N_4O_2$: C, 73.15; H, 5.40; N, 13.65. Found: C, 73.39; H, 5.21; N, 13.52.

6,10-Bis-(4-methoxyphenyl)-4-methyl-2-phenyl-2,3,7,9-tetraazaspiro[4.5]dec-3-ene-1,8-dione (4b). White crystalline solid; (yield 92%); mp 236–238°C; IR (KBr): ν = 3360, 3200, 3080, 1718, 1680, 1612 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz, mixture-major isomer only): δ 2.32 (s, 3H, CH_3), 3.62 (s, 6H, OCH_3), 5.07 (s, 2H, CH), 6.75–7.29 (m, 13H, ArH), 7.41 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.3, 55.2, 59.5, 62.5, 113.9, 114.1, 119.2, 119.7, 125.7, 127.6, 128.2, 128.7, 129.2, 129.9, 130.7, 136.7, 151.3, 161.4, 170.9; MS (*m/z*): 471 $(M+H)^+$. *Anal*. Calcd for $C_{27}H_{26}N_4O_4$: C, 68.92; H, 5.57; N, 11.91. Found: C, 68.78; H, 5.41; N, 11.98.

6,10-Bis-(4-chlorophenyl)-4-methyl-2-phenyl-2,3,7,9-tetraazaspiro[4.5]dec-3-ene-1,8-dione (4c). White crystalline solid; (yield 88%); mp 216–2218°C; IR (KBr): ν = 3384, 3228, 3096, 1716, 1694, 1618 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz, mixture-major isomer only): δ 2.33 (s, 3H, CH_3), 5.07 (s, 2H, CH), 6.98–7.52 (m, 13H, ArH), 7.28 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.8, 57.8, 62.6, 113.6, 114.3, 119.4, 120.9, 125.4, 127.9, 128.6, 128.9, 129.1, 130.3, 136.8, 161.9, 170.6; MS (*m/z*): 480 $(M+H)^+$. *Anal*. Calcd for $C_{25}H_{20}$

$Cl_2N_4O_2$: C, 62.64; H, 4.21; N, 11.69. Found: C, 62.78; H, 4.38; N, 11.54.

6,10-Bis-(4-bromophenyl)-4-methyl-2-phenyl-2,3,7,9-tetraazaspiro[4.5]dec-3-ene-1,8-dione (4d). White crystalline solid; (yield 91%); mp 230–232°C; IR (KBr): ν = 3378, 3224, 3092, 1720, 1692, 1612 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz, mixture-major isomer only): δ 2.32 (s, 3H, CH_3), 5.08 (s, 2H, CH), 6.93–7.54 (m, 13H, ArH), 7.30 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.7, 58.1, 62.8, 113.9, 114.8, 120.3, 120.7, 125.4, 127.8, 128.9, 129.0, 130.3, 131.8, 136.7, 161.8, 171.2; MS (*m/z*): 569 $(M+H)^+$. *Anal*. Calcd for $C_{25}H_{20}Br_2N_4O_2$: C, 52.84; H, 3.55; N, 9.86. Found: C, 52.67; H, 3.67; N, 10.02.

4-Methyl-6,10-bis-(4-nitrophenyl)-2-phenyl-2,3,7,9-tetraazaspiro[4.5]dec-3-ene-1,8-dione (4e). White crystalline solid; (yield 87%); mp 246–248°C; IR (KBr): ν = 3394, 3218, 3092, 1724, 1698, 1624 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz, mixture-major isomer only): δ 2.33 (s, 3H, CH_3), 5.18 (s, 2H, CH), 6.94–8.12 (m, 13H, ArH), 7.32 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.9, 58.4, 63.2, 113.5, 114.9, 119.2, 121.3, 125.7, 127.4, 128.9, 129.0, 131.6, 133.1, 142.2, 161.7, 171.8; MS (*m/z*): 501 $(M+H)^+$. *Anal*. Calcd for $C_{25}H_{20}N_6O_6$: C, 60.00; H, 4.03; N, 16.79. Found: C, 60.17; H, 3.97; N, 16.62.

6,10-Bis-(4-methoxyphenyl)-4-methyl-2-phenyl-8-thioxo-2,3,7,9-tetraazaspiro[4.5]dec-3-en-1-one (4f). White crystalline solid; (yield 90%); mp 232–234°C; IR (KBr): ν = 3364, 3202, 3078, 1722, 1684, 1616 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz, mixture-major isomer only): δ 2.33 (s, 3H, CH_3), 3.63 (s, 6H, OCH_3), 5.06 (s, 2H, CH), 6.82–7.28 (m, 13H, ArH), 7.24 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.6, 55.2, 56.1, 62.5, 114.2, 115.8, 119.1, 120.6, 121.7, 126.2, 127.6, 128.1, 128.4, 129.7, 138.3, 152.2, 168.8, 176.6; MS (*m/z*): 487 $(M+H)^+$. *Anal*. Calcd for $C_{27}H_{26}N_4O_3S$: C, 66.65; H, 5.39; N, 11.51. Found: C, 66.78; H, 5.54; N, 11.38.

6,10-Bis-(4-chlorophenyl)-4-methyl-2-phenyl-8-thioxo-2,3,7,9-tetraazaspiro[4.5]dec-3-en-1-one (4g). White crystalline solid; (yield 91%); mp 292–294°C; IR (KBr): ν = 3382, 3220, 3090, 1720, 1692, 1608 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz, mixture-major isomer only): δ 2.32 (s, 3H, CH_3), 5.07 (s, 2H, CH), 6.82–7.58 (m, 13H, ArH), 7.31 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.8, 57.3, 62.6, 114.7, 116.4, 119.8, 120.1, 122.4, 125.7, 127.6, 128.3, 128.9, 129.3, 137.8, 168.9, 176.4; MS (*m/z*): 496 $(M+H)^+$. *Anal*. Calcd for $C_{25}H_{20}Cl_2N_4OS$: C, 60.61; H, 4.07; N, 11.31. Found: C, 60.75; H, 4.23; N, 11.45.

6,10-Bis-(4-bromophenyl)-4-methyl-2-phenyl-8-thioxo-2,3,7,9-tetraazaspiro[4.5]dec-3-en-1-one (4h). White crystalline solid; (yield 91%); mp 226–228°C; IR (KBr): ν = 3376, 3214, 3088, 1718, 1698, 1614 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz, mixture-major isomer only): δ 2.31 (s, 3H, CH_3), 5.07 (s, 2H, CH), 6.91–7.68 (m, 13H, ArH), 7.32 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.7, 57.5, 62.7, 113.9, 116.7, 119.4, 120.6, 122.3, 125.7, 127.2, 128.6, 129.4, 130.1, 138.7, 168.3, 176.9; MS (*m/z*): 585 $(M+H)^+$. *Anal*. Calcd for $C_{25}H_{20}Br_2N_4OS$: C, 51.39; H, 3.45; N, 9.59. Found: C, 51.57; H, 3.28; N, 9.72.

4-Methyl-6,10-bis-(4-nitrophenyl)-2-phenyl-8-thioxo-2,3,7,9-tetraazaspiro[4.5]dec-3-en-1-one (4i). White crystalline solid; (yield 84%); mp 254–256°C; IR (KBr): ν = 3380, 3220, 3094, 1720, 1696, 1622 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz, mixture-major isomer only): δ 2.33 (s, 3H, CH_3), 5.21 (s, 2H, CH), 6.98–8.16 (m, 13H, ArH), 7.33 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 19.2, 57.7, 62.9, 114.8, 116.3, 119.7, 120.4, 121.9, 125.8, 130.3, 132.9, 133.1, 136.2 141.3, 169.1, 176.8; MS (*m/z*): 517 $(M+H)^+$. *Anal*. Calcd for $C_{25}H_{20}N_6O_5S$: C, 58.13; H, 3.90; N, 16.27. Found: C, 58.04; H, 4.07; N, 16.36.

6,10-Bis-(4-fluorophenyl)-4-methyl-2-phenyl-8-thioxo-2,3,7,9-tetraazaspiro[4.5]dec-3-en-1-one (4j). White crystalline solid; (yield 92%); mp 244–246°C; IR (KBr): ν = 3372, 3208, 3084, 1718, 1694, 1610 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz, mixture-major isomer only): δ 2.32 (s, 3H, CH_3), 5.07 (s, 2H, CH), 6.88–7.62 (m, 13H, ArH), 7.33 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.7, 57.5, 62.6, 114.1, 116.3, 118.7, 120.8, 121.9, 125.8, 127.3, 128.9, 128.1, 129.47, 137.8, 168.4, 176.1; MS (*m/z*): 463 $(M+H)^+$. *Anal*. Calcd for $C_{25}H_{20}F_2N_4OS$: C, 64.92; H, 4.36; N, 12.11. Found: C, 64.77; H, 4.22; N, 11.92.

***7,7-Dimethyl-4-phenyl-4,6,7,8-tetrahydro-1H,3H-*quinazoline-2,5-dione (7).** White solid; (yield 76%); mp 290–292°C; IR (KBr): ν = 3320, 3258, 2966, 1710, 1680, 1608 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 0.97(s, 3H, CH_3); 1.10(s, 3H, CH_3); 2.18 (q, *J* = 16.1 Hz, 2H, CH2); 2.39 (q, *J* = 16.8 Hz, 2H, CH2); 5.27 (d, *J* = 2.8 Hz, 1H, CH); 7.32–7.21 (m, 5H, Ar); 7.46 (s, 1H, NH); 9.39 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 27.2, 29.23, 32.7, 50.4, 52.7, 55.3, 108.5, 127.2, 128.1, 128.9, 144.1, 149.3, 175.1, 194.2; MS (*m/z*): 271 $(M+H)^+$. *Anal*. Calcd for C16H18N2O2: C, 71.09; H, 6.71, N, 10.36. Found: C, 71.16, H, 6.69; N 10.33.

4-(4-Methoxy-benzylidene)-5-methyl-2-phenyl-2,4-dihydro-pyrazole-3-one (8b). Brown red solid; (yield 58%); mp 124–126°C; IR (KBr): ν = 3060, 1692, 1620, 1586, 1090, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.35 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.99 (d, *J* = 12.2 Hz, 2H), 7.18 (t, *J* = 12.4 Hz, 1H), 7.34 (s, 1H), 7.41 (t, *J* = 8.4 Hz, 2H), 7.95 (d, *J* = 9.6 Hz, 2H), 8.58 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.3, 57.1, 114.9, 115.7, 120.3, 124.8, 125.6, 127.1, 128.3, 128.9, 130.2, 132.3, 143.7, 152.9, 168.4; MS (*m/z*): 293 $(M+H)^+$. *Anal*. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52, N, 9.58. Found: C, 74.16, H, 5.70; N 9.38.

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