Microwave-enhanced Efficient Synthesis of Some Polyfunctional Pyridazines

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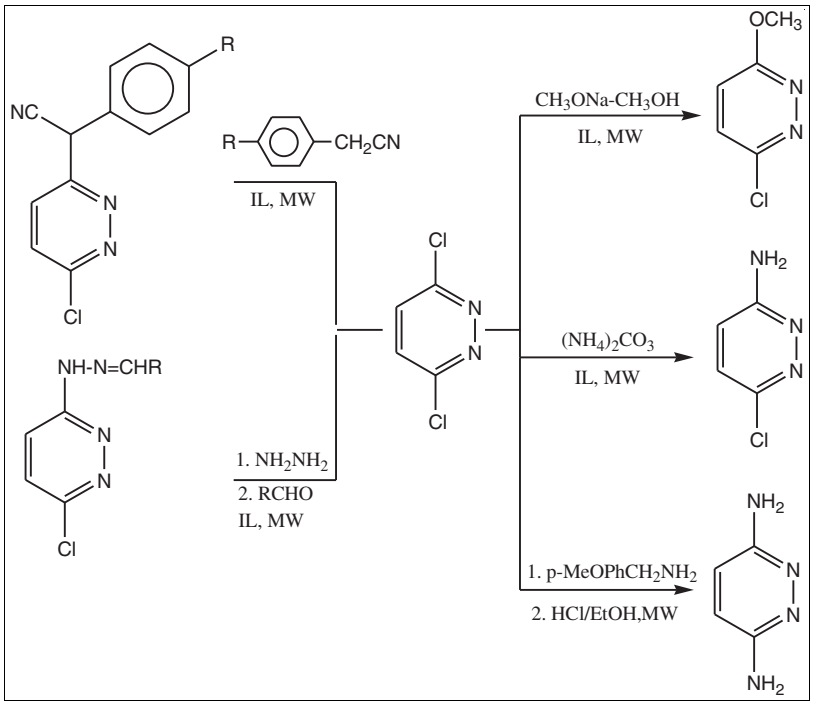

Microwave-enhanced highly efficient protocol for the synthesis of polyfunctional pyridazines beginning from 3,6-dichloropyridazine in environmentally benign ionic liquids have been developed. The products obtained were 3-amino-6-chloropyridazine, 3,6-diaminopyridazine, and 3-chloro-6-methoxypyridazine. These derivatives were then be converted to a variety of polyfunctional pyridazine derivatives. The ionic liquids used were 1-*n*-butyl-3-methylimidazolium hydroxide/tetrafluoroborate/hexafluorophosphate and 1,3-di-*n*-butylimidazolium hydroxide. This powerful strategy is less time-consuming green methodology. The ionic liquid employed may be recovered and recycled.

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INTRODUCTION

Pyridazines and its myriad derivatives [1–7] continue to attract significant attention in pharmaceutical industry in the quest to search new drugs because of its wide spectrum applications as pharmacologically important compounds, viz. antimicrobial [8], analgesic [9], anticancer [10], antitubercular [11], cyclooxygenase (COX) inhibitor [12], antidiabetic [13], antiviral [14], and so on. 3-Aminopyridazines, for example, minaprine (cantor) is used as an antidepressant drug, which act as a short-acting monoamine oxidase inhibitor [15]. Various 3-aminopyridazines have been intelligently exploited as extended analogs of γ-aminobutyric acid (GABA), which act as competitive $GABA_A$ receptor antagonists [16]. Specifically, gabazine (SR-95531) has demonstrated high specificity [17,18] and potency towards $GABA_A$ and $GABA_C$ receptors [19,20].

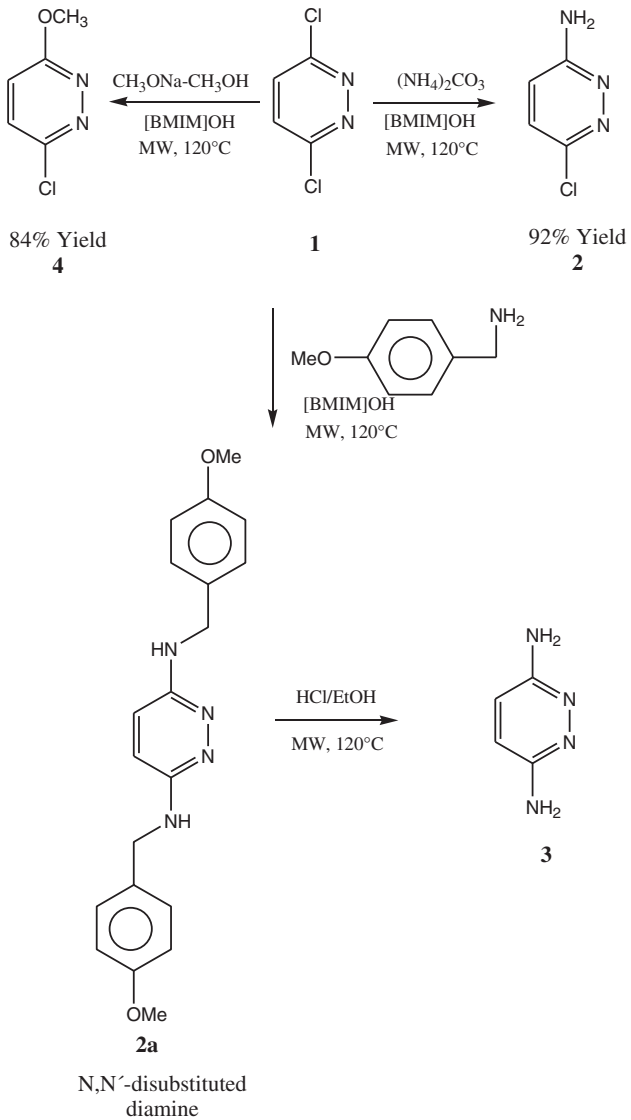
The discovery of pyridazomycin [21], a new antifungal antibiotic from *Streptomyces violaceoniger*, and Zarzissine [22], a new cytotoxic guanidine alkaloid isolated from Mediterranean sponge *Anchinoe paupertas*, both containing this heteroatom scaffold, is expected to stimulate even broader interest in 1,2-diazanine chemistry.

General synthetic approaches for construction of 3-amino-6-aryl pyridazines involve synthesis of pyridazinone core, on the basis of the condensation of 1,4-dicarbonyl compounds in the presence of hydrazine [23,24], Chlorination of pyridazinones [15,17], with phosphorus oxotrichloride followed by amidation using ammonia/hydrazine [17]. Moreover, there are also a few reports of palladium-catalyzed Suzuki cross coupling reactions [25] on 3-amino-6-chloropyridazine moieties. Recently, Attanasi *et al*. [26] have presented a novel synthesis of diversely functionalized pyridazines from

4-chloro-1,2-di-aza-1,3-butadienes by Michael-type addition of active methylene compounds.

A solvent-free microwave-assisted synthesis of polyfunctional pyridazine derivatives (Scheme 1) has been reported from ethyl-5-cyano-1,6-dihydro-4-methyl-6-oxo-(4-X-phenyl)-pyridazine-3-carboxylate, which was synthesized from ethylcyano acetate and corresponding hydrazones [27]. Synthesis of some new pyridazines have been published from 3,6-dichloropyridazine with hydrazine/arylmethylcyanide in dimethyl sulfoxide and sodium hydroxide [28]. Most recently, Chebib *et al*. have presented a microwave-assisted synthesis of 2,3,6-trisubstituted pyridazines using potassium carbonate base, which has been extended to synthesize gabazine (SR-95531) [1].

Scheme 1. Synthesis of pyridazine derivatives.



Except few, [1,21] most of the aforementioned approaches to the synthesis of diversified pyridazines have several disadvantages, for example, harsh reaction conditions, a number of steps, inconvenient operations, limited availability of substances, use of toxic chemicals, lack of atom economy, and poor yields. Inspired by the wide spectrum applications of pyridazine nuclei and our continuous interest in developing an efficient ecofriendly procedure [29], we herein report, for the first time, a convenient microwave-assisted synthesis of polyfunctional pyridazines in ionic liquids, viz. [BMIM]OH, [BMIM]BF_4, [BMIM]PF_6, and [DBIM]OH, starting from 3,6-dichloro-1,2-pyridazines.

RESULTS AND DISCUSSION

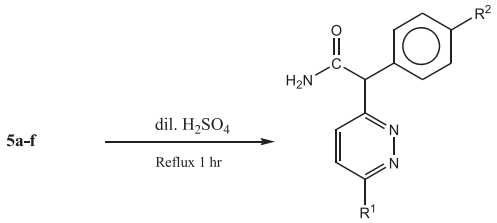
In our strategy, we have first targeted the synthesis of 3-amino-6-chloropyridazine **2**, 3,6-diaminopyridazine **3**, and 3-chloro-6-methoxypyridazine **4** by irradiating 3, 6-dichloropyridazine **1** in 1-*n*-butyl-3-methylimidazolium hydroxide/tetrafluoroborate/hexafluorophosphate [BMIM]OH/BF_4/PF_6 1,3-di-*n*-butylimidazolium hydroxide [DBIM]OH as mentioned in the succeeding text.

We have carried out the reaction of 3,6-dichloropyridazine **1** with ammonium carbonate in [BMIM]OH, [BMIM]BF_4, [BMIM]PF_6, [DBIM]OH and obtained 3-amino-6-chloropyridazine in 92%, 10%, 60%, and 70% yield, respectively. Also, the reaction of compound **1** with 4-methoxybenzylamine followed by hydrolysis with hydrogen chloride in ethanol by irradiating microwave radiations afforded 3,6-diaminopyridazine in 85%, 15%, 70%, and 60% yield in [BMIM][OH], [BMIM]BF_4, [BMIM]PF_6, and [DBIM]OH, respectively. Compound **1** when exposed to microwave irradiation in [BMIM]OH containing sodium methoxide-methanol afforded 3-chloro-6-methoxypyridazine in 84% yield. These observations suggest that [BMIM]OH is a better ionic liquid for derivatization. The reaction was monitored on silica gel $^{60}F_{254}$ aluminum sheet in pet. ether (60–80°C) ethyl acetate (9.5:0.5), and the reaction was completed in 10 min.

Compound **1/4** and substituted benzylcyanide in [BMIM]OH, when subjected to microwave irradiation at 120°C, yielded compound **5a–c/5d–f** in good yield (Scheme 2; Table 1). Also, compounds **5a–c** when treated with 4-benzylpiperidine, 4-phenylpiperazine, pyrrolidine, and morpholine under microwave irradiation in [BMIM]OH afforded compounds **6a–h** in good yield (Scheme 2; Table 1).

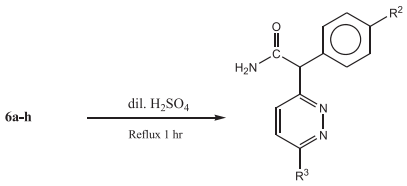
In another approach, compound **1/4** was reacted with hydrazine in [BMIM]OH under microwave irradiation and yielded compounds **7a–b** in good yield. The later compound, when mixed with R^4-CHO ($R^4 = C_6H_5$, $MeOC_6H_4$) and irradiated with microwave, resulted compounds **8a–d** quantitatively (Scheme 3, Table 1).

Compounds **5a–f** and **6a–h** upon hydrolysis in the presence of dilute sulfuric acid gave products **9a–f** and **10a–h** respectively, in quantitatively yield.



9a-f

Compd.	9a		9b		9c		9d		9e		9f	
Substituent	R_1	R_2	R_1	R_2	R_1	R_2	R_1	R_2	R_1	R_2	R_1	R_2
	Cl	OMe	Cl	Me	Cl	Cl	OMe	OMe	OMe	Me	OMe	Cl
Yield (%)	78		76		70		77		78		78	



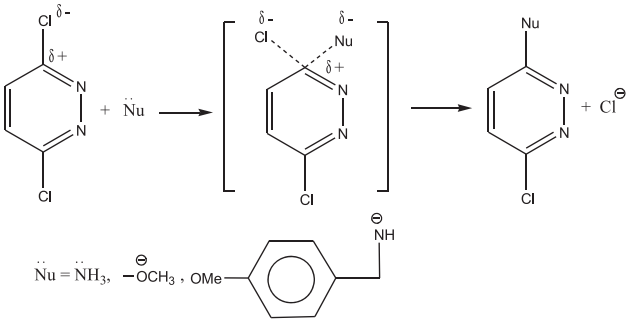
10a-h

Compd	10a	10b	10c	10d	10e	10f	10g	10h
Substituents	R_2 = Cl, R_3 = Bn	R_2 = Cl, R_3 = Ph	R_2 = Cl, R_3 = pyrrolidin-1-yl	R_2 = Cl, R_3 = morpholin-4-yl	R_2 = OMe, R_3 = morpholin-4-yl	R_2 = OMe, R_3 = Bn	R_2 = Me, R_3 = Bn	R_2 = Me, R_3 = Ph
Yield (%)	90	88	85	86	85	87	85	84

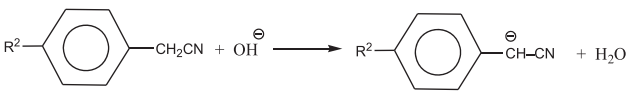
We have then synthesized 3-amino-6-phenylpyridazine **12** by microwave irradiation of 3-chloro-6-phenylpyridazine **11** in [BMIM]OH containing ammonium carbonate. The product **12** was obtained in 80% yield and characterized by IR and ^{1}H NMR spectroscopy. Next, we attempted the derivatization of compound **12** with substituted phenylisocyanate/phenylisothiocyanate in [BMIM]OH under microwave irradiation and obtained the compounds **13a–f** (Scheme 4) in good yield.

Compound **12** upon reaction with substituted benzenesulfonyl chloride in [BMIM]OH under microwave irradiation in the presence of acid scavenger, for example, butylamine afforded corresponding sulfonamide derivatives of pyridazine **14a–c** (Scheme 5) in 84–90% yield.

Role of [BMIM]OH in the synthesis of pyridazine derivatives. [BMIM]OH, used as an ionic liquid catalyst in the synthesis of pyridazine derivatives, seems to act as a nucleophilic solvent of which the OH– ion enhances the nucleophilic ability of the generated nucleophiles. The generated nucleophiles, viz. ammonia, methoxide ion, and *p*-methoxy phenyl methyl azanide anion under microwave activation appears to attack the C-Cl bond of pyridazine **1** via SNAr mechanism yielding corresponding derivatives **2**, **2a**, and **4**, respectively, as shown next (Scheme 1).

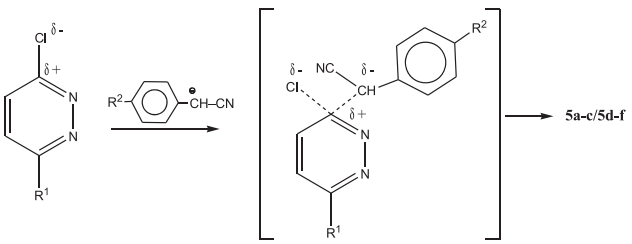


In the conversion of compound **1/4** to **5a–c/5d–f**, the nucleophilic OH- (from [BMIM]OH) abstracts hydrogen of the active methylene compound to yield a nem carbanion as given (Scheme 2).



This carbanion attacks the pyridazine **1/4** to yield **5a–c** and **5d–f** quantitatively.

A tentative mechanism of the reaction process may be presented next.



The conversion of compounds **1/4** and **11** to compounds **7a–b** and **12**, respectively, is also expected to follow the mechanism described earlier. The aforementioned hypothesis is in consonance with the earlier report [30]. The exact mechanism of the reaction, however, needs a detailed investigation.

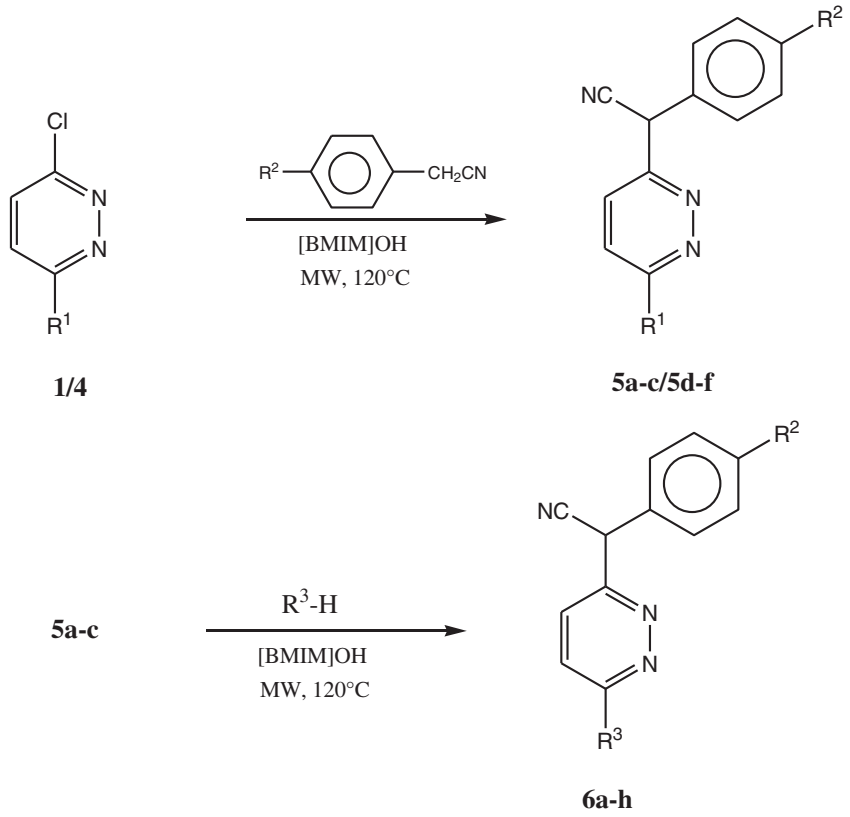
The ionic liquid [BMIM]OH was recovered by keeping the ionic liquid at 80 ± 2°C under pressure (2 mm of Hg) for 2 h. The recovered ionic liquid was recycled for the derivatization of compounds **2**, **4**, and **6a**, and the products obtained in three recycles are presented in Table 2.

These data suggest that the corresponding pyridazines are obtained in good yield with the loss of 10 ± 12% yield in three recycles (Table 2) and thus making this methodology economical.

CONCLUSION

We have successfully developed an efficient and versatile protocol for the synthesis of substituted pyridazines in ionic liquids under microwave irradiation. The methodology is clean and economically viable.

Scheme 2. Synthesis of pyridazine derivatives under microwave irradiation.



EXPERIMENTAL

General details. Melting points of all the synthesized compounds were determined in an open capillary tube and are uncorrected. IR spectra were recorded on a SHIMADZU FTIR spectrometer (Tokyo, Japan) using potassium bromide pellets. ^{1}H NMR spectra were recorded on a JEOL AL-300 MHz NMR spectrometer (Tokyo, Japan) in $CDCl_3$ using TMS as an internal standard (chemical shift in δ ppm). ^{13}C NMR spectra were recorded on a JEOL AL-75 MHz NMR spectrometer in $CDCl_3$ using TMS as an internal standard. The purity of each product was checked by TLC using silica gel $^{60}F_{254}$ aluminum sheet as adsorbent, and visualization was accomplished by iodine/UV light. The microwave irradiation was effected using the CEM Discover Benchmate single-mode microwave synthesis system with infrared temperature probe and adjustable 0–300 W output power using safe pressure regulation 10-mL pressurized vials with "snap-on" cap. All the chemicals were purchased from Sigma-Aldrich Co. and were used without further purification.

General procedure for the synthesis of 3-amino-6-chloropyridazine 2. 3,6-Dichloropyridazine **1** (0.74 g, 0.005 M) was added to ammonium carbonate (0.52 g, 0.0055 M) in ionic liquid [BMIM]OH. The resulting mixture was subjected to microwave irradiation at 120°C for 10 min. After cooling, the product was extracted by diethyl ether, and the solvent was removed by distillation, and the product was crystallized by 2-propanol. Yellowish white solid, yield 92%, mp 230–232°C; ^{1}H NMR (DMSO-d_6): δ 7.33 (d, J = 9.2 Hz, 1H), 6.80 (d, J = 9.2 Hz, 1H), 6.59 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 160.77, 144.95, 129.40, 118.02; *Anal.* Calcd for $C_4H_4ClN_3$: C, 43.62, H, 5.50, N, 50.88. Found: C, 43.50, H, 5.35, N, 50.68.

General procedure for the synthesis of 3,6-diaminopyridazine 3. 3,6-Dichloropyridazine **1** (0.74 g, 0.005 M) was added to 4-methoxybenzylamine (0.68 g, 0.005 M) in ionic liquid [BMIM]OH. The reaction mixture was subjected to microwave irradiation for 10 min at 120°C. After cooling, the product was extracted with diethyl ether, and the solvent was removed by distillation. The product was recrystallized with ethanol. The product **3** was dissolved in ethanol (2 mL) and concentrated hydrogen chloride (4 mL), and the resulting mixture was subjected to microwave irradiation. The product was extracted with diethyl ether and recrystallized with ethanol.

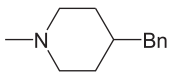
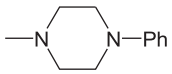
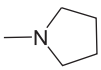
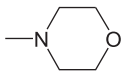
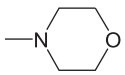
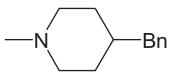
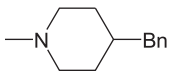
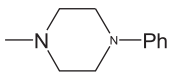
The characteristic data of compound **3** are presented next: Yellow solid, mp 224–226°C; ^{1}H NMR (DMSO-d_6) : δ 5.38 (s, 4H), 6.60 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 154.6, 117.8; *Anal.* Calcd for $C_4H_6N_4$; C, 43.6, H, 5.49, N, 50.9, Found: C, 43.4, H, 5.32, N, 50.4.

General procedure for the synthesis of compounds 5a–f. The pyridazine derivatives **4a–b** (0.005 M) were dissolved in [BMIM]OH (5 mL), and appropriate substituted acetonitriles (0.005 M) were added. The reaction mixture was subjected to microwave irradiation for 10 min at 120°C. After completing the reaction, the product was extracted with ethylacetate (3 × 10 mL), and the solvent was removed by distillation under reduced pressure (10 mmHg) at 60°C. Compounds **5a–f** were recrystallized from methanol.

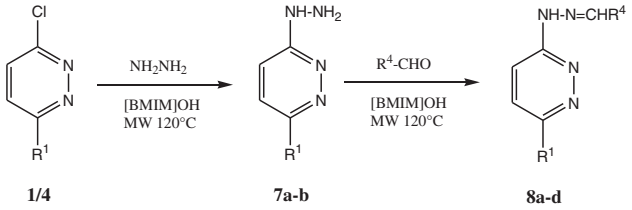
The characteristic properties of the compounds **5a–f** are given next:

Table 1

Synthesis of substituted pyridazines in [BMIM]OH under microwave irradiation.

Compound	R^1	R^2	R^3	R^4	Time (min)	*T* (°C)	Conversion (%)
5a	Cl	OMe	—	—	10	120	85
5b	Cl	Me	—	—	10	120	82
5c	Cl	Cl	—	—	10	120	85
5d	OMe	OMe	—	—	10	120	85
5e	OMe	Me	—	—	10	120	83
5f	OMe	Cl	—	—	10	120	84
6a	—	Cl		—	10	120	85
6b	—	Cl		—	10	120	83
6c	—	Cl		—	10	120	85
6d	—	Cl		—	10	120	90
6e	—	OMe		—	10	120	84
6f	—	OMe		—	10	120	80
6g	—	Me		—	10	120	83
6h	—	Me		—	10	120	85
7a	Cl	—	—	—	10	120	75
7b	OMe	—	—	—	10	120	75
8a	Cl	—	—	C_6H_5	10	120	77
8b	Cl	—	—	$MeOC_6H_4$	10	120	78
8c	OMe	—	—	C_6H_5	10	120	78
8d	OMe	—	—	$MeOC_6H_4$	10	120	80

Scheme 3. Synthesis of pyridazine derivatives of hydrazine and benzylidenehydrazines.



1/4 **7a-b** **8a-d**

2-(6′-Chloropyridazin-3-yl)-2-(4″-methoxyphenyl)acetonitrile 5a. White solid; mp 130–133°C; ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H), 5.62 (s, 1H), 6.90 (s, 1H), 6.95 (s, 1H), 7.36 (s, 1H), 7.40 (s, 1H), 7.54 (s, 2H); IR (KBr) ν_{max} 3040, 2925, 2251, 1610, 1512, 1453, 1178, 1150, 1027, 821 cm^{-1}; *Anal*. Calcd for $C_{13}H_{10}ClON_3$: C, 60.12, H, 3.88, N, 16.18; Found C, 59.90, H, 3.85, N, 16.13.

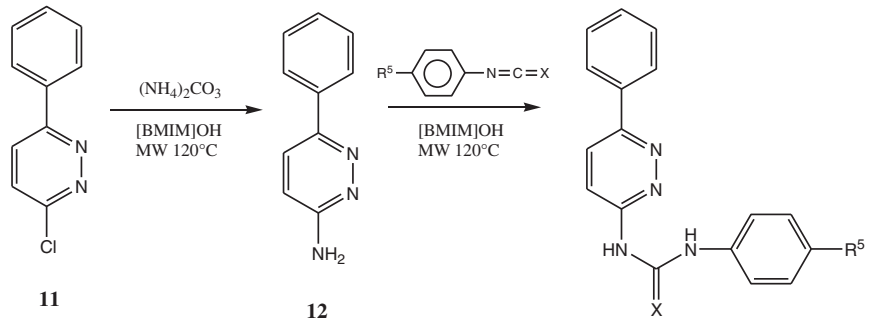
2-(6′-Chloropyridazin-3-yl)-2-(4″-methylphenyl)acetonitrile 5b. White solid; mp 129–131°C; ^{1}H NMR ($CDCl_3$) δ 1.80 (s, 3H), 5.60 (s, 1H), 7.40 (s, 4H), 7.60 (s, 2H); IR (KBr) ν_{max} 3057, 2935, 2250, 1570, 1490, 1412, 1149, 1066, 862, 697 cm^{-1}; *Anal*. Calcd for $C_{13}H_{10}ClN_3$: C, 60.07, H, 4.13, N, 17.24; Found C, 60.01, H, 4.04, N, 17.16.

2-(4′-Chlorophenyl)-2-(6″-chloropyridazin-3-yl)acetonitrile 5c. White solid, mp 144–145°C; ^{1}H NMR ($CDCl_3$) δ 5.64 (s, 1H), 7.40 (s, 4H), 7.56 (s, 2H); IR (KBr) ν_{max} 3057, 2935, 2250, 1410, 1149, 1066, 862, 967 cm^{-1}; *Anal*. Calcd for $C_{12}H_7Cl_2N_3$; C, 54.57, H, 2.67, N, 15.91; Found C, 54.43, H, 2.65, N, 15.88.

2-(4′-Methoxyphenyl)-2-(6″-methoxypyridazin-3-yl)acetonitrile 5d. White solid; mp 136–138°C, ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 3H), 3.82 (s, 3H), 5.25 (s , 1H), 6.90 (s, 1H), 6.95 (s , 1H), 7.35 (s, 1H), 7.40 (s, 1H), 7.54 (s, 2H); IR (KBr) ν_{max} 3041, 293, 2255, 1610, 1512, 1409, 1250, 1027, 821 cm^{-1}. *Anal*. Calcd for $C_{14}H_{13}O_2N_3$: C, 65.87, H, 5.13, N, 16.46; Found: C, 65.79, H, 5.08, N, 16.39.

2-(6′-Methoxypyridazin-3-yl)-2-(4″-methylphenyl)acetonitrile 5e. White solid; mp 120–123°C; ^{1}H NMR ($CDCl_3$) δ 1.2 (s, 3H), 3.80 (s, 3H), 5.55 (s, 1H), 7.36 (m, 4H), 7.65 (s, 2H); IR (KBr) ν_{max}

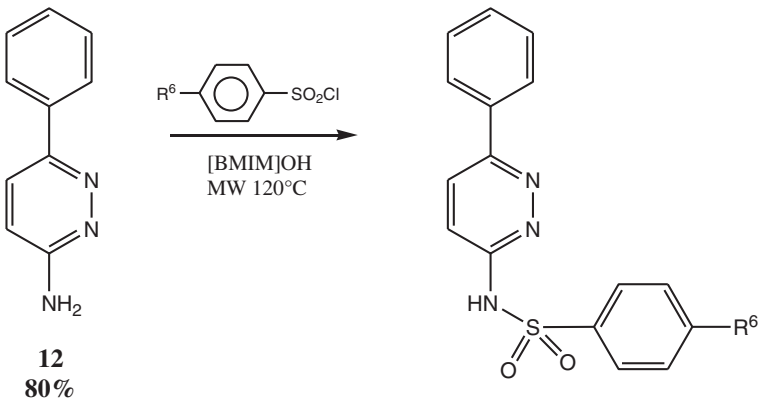
Scheme 4. Synthesis of pyridazine derivatives of urea and thiourea under microwave irradiation.



11 **12** **13a-f**

Compound	13a	13b	13c	13d	13e	13f
X	O	O	O	S	S	S
R	H	Cl	CH_3	H	Cl	CH_3
Yield (%)	75	70	68	62	65	70

Scheme 5. Synthesis of pyridazine derivative of sulfonamide.



12
80%

14a-c

R^6 = H, Cl, CH_3

Table 2

Recyclability studies of [BMIM]OH for pyridazines.

Compound	No. of cycles	% yield of pyridazines
2	0	92
2	1	88
2	2	85
2	3	80
4	0	84
4	1	82
4	2	79
4	3	74
6a	0	90
6a	1	87
6a	2	83
6a	3	80

3057, 2980, 2935, 2257, 1410, 1412, 1152, 1097, 824 cm^{-1}; *Anal.* Calcd for $C_{14}H_{13}ON_3$: C, 70.27, H, 5.47, N, 17.56; Found C, 70.18, H, 5.39, N, 17.48.

2-(4′-Chlorophenyl)-2-(6″-methoxypyridazin-3-yl)acetonitrile 5f. White solid, mp 127–130°C; ^{1}H NMR ($CDCl_3$) δ 3.56 (s, 3H), 5.40 (s, 1H), 7.46 (s, 4H), 7.55 (s, 2H); IR (KBr) ν_{max} 3057, 2990, 2935, 2250, 1570, 1490, 1412, 1152, 1097, 824 cm^{-1} *Anal.* Calcd for $C_{13}H_{10}OClN_3$: C, 60.12, H, 3.88, N, 16.18, Found: C, 60.05, H, 3.76, N, 16.08.

General procedure for the synthesis of compounds 6a–h. Compounds **5a–c** (0.005 M) were dissolved in ionic liquid with 4-phenylpiperazine/4-benzylpiperidine/pyrrolidine/morpholine (0.005 M). The reaction mixture was irradiated with microwave for 10 min at 120°C. After cooling, the product was extracted from chloroform. The removal of solvent by distillation yielded the desired products **6a–h**, and recrystallization was accomplished by ethanol. The characteristic data of these compounds are given next.

2-[6′-(4″-Benzylpiperidin-1-yl)pyridazin-3-yl]-2-(4‴-chlorophenyl) acetonitrile 6a. White solid, mp 175–177°C; ^{1}H NMR ($CDCl_3$) δ 1.35 (m, 2H), 1.80 (m, 3H), 2.55 (m, 2H), 2.90 (m, 2H), 4.40 (d, J = 11.7 Hz, 2H), 5.47 (s, 1H), 6.89 (d, J = 9.5 Hz, 1H), 7.10–7.51 (m, 10H); IR (KBr) ν_{max} 3061, 2915, 2853, 2253, 1590, 1541, 1492, 1445, 1257, 1095, 753, 704 cm^{-1}; *Anal.* Calcd for $C_{24}H_{23}ClN_4$: C, 71.54, H, 5.75, N, 13.91; Found C, 71.72, H, 5.73, N, 13.87.

2-(4′-Chlorophenyl)-2-[6″-(4‴-phenylpiperazin-1-yl)pyridazin-3-yl]acetonitrile 6b. White solid, mp 142–146°C; ^{1}H NMR ($CDCl_3$) δ 3.60 (m, 4H), 3.90 (s, 4H), 5.50 (s, 1H), 6.98 (d, J = 9.3 Hz, 1H), 7.02–7.45 (m , 10H); IR (KBr) ν_{max} 3060, 2245, 1599, 1495, 1444, 1236, 948, 845, 756, 697 cm^{-1}; *Anal.* Calcd for $C_{22}H_{20}ClN_5$: C, 67.77, H, 5.17, N, 17.96; Found C, 67.67, H, 5.08, N, 17.86.

2-(4′-Chlorophenyl)-2-[6″-(pyrrolidin-1-yl)pyridazin-3-yl] acetonitrile 6c. White solid, mp 178–180°C; ^{1}H NMR ($CDCl_3$) δ 2.10 (m, 4H), 3.55 (m, 4H), 5.51 (s, 1H), 7.10–7.35 (m, 6H); IR (KBr) ν_{max} 3035, 2919, 2864, 2240, 1594, 1542, 1475, 1450, 1025, 740, 700 cm^{-1}; *Anal*. Calcd for $C_{16}H_{15}ClN_4$: C, 64.32, H, 5.06, N, 18.75; Found C, 64.26, H, 4.96, N, 18.65.

2-(4′-Chlorophenyl)-2-(6″-Morpholinopyridazin-3-yl)acetonitrile 6d. White solid, mp 103–105°C; ^{1}H NMR ($CDCl_3$) δ 3.65 (m, 4H), 3.84 (m, 4H), 5.54 (s, 1H), 6.90 (d, J = 9.5 Hz, 1H), 7.15–7.50 (m, 5H); IR (KBr) ν_{max} 3055, 2920, 2854, 2250, 1595, 1444, 1236, 948, 843, 827 cm^{-1}; *Anal*. Calcd for $C_{16}H_{15}ClON_4$: C, 61.05, H, 4.80, N, 17.80; Found C, 60.85, H, 4.77, N, 17.75.

2-(4-Methoxyphenyl)-2-(6-morpholinopyridazin-3-yl)acetonitrile 6e. White solid, mp 114–116°C; ^{1}H NMR ($CDCl_3$) 3.85 (m, 4H), 3.95 (m, 7H), 5.50 (s, 1H), 6.90–7.45 (m , 6H); IR (KBr) ν_{max} 3065, 2960, 2850, 2250, 1605, 1510, 1446, 1235, 1177, 1119, 1030, 930, 830 cm^{-1}; *Anal*. Calcd for $C_{17}H_{18}O_2N_4$: C, 65.79, H, 5.85, N, 18.05; Found C, 65.67, H, 5.80, N, 17.99.

2-[6-(4′-Benzylpiperidin-1-yl)pyridazin-3-yl]-2-(4″-methoxyphenyl)acetonitrile 6f. White solid, mp 155–157°C; ^{1}H NMR ($CDCl_3$) δ 1.28 (m, 2H), 1.75 (m, 3H), 2.62 (m, 2H), 3.85 (s, 3H), 4.45 (d, J = 13.0 Hz, 2H), 5.50 (s, 1H), 6.20–6.60 (m, 5H), 7.10–7.45 (m, 6H); IR (KBr) ν_{max} 3065, 2920, 2840, 2249, 1590, 1510, 1440, 1257, 1175, 1035, 752, 705 cm^{-1}; *Anal*. Calcd for $C_{25}H_{26}ON_4$: C, 78.50, H, 6.85, N, 14.64; Found C, 78.42, H, 6.76, N, 14.57.

2-[6′-(4″-Benzylpiperidin-1-yl)pyridazin-3-yl]-2-(4‴-methylphenyl)acetonitrile 6g. White solid; mp 150–152°C; ^{1}H NMR ($CDCl_3$) δ 1.30 (m, 2H), 1.50 (s, 3H), 1.72 (m, 3H), 2.60 (m, 2H), 2.90 (m, 2H), 440 (d, J = 13.0 Hz, 2H), 5.48 (s, 1H), 6.20–6.90 (m, 5H), 7.15–7.40 (m, 6H); IR (KBr) ν_{max} 3062, 2917, 2838, 2249, 1591, 1511, 1444, 1257, 1177, 1033, 752, 704 cm^{-1}; *Anal*. Calcd for $C_{25}H_{26}N_4$: C, 78.50, H, 6.85, N, 14.64; Found C, 78.42, H, 6.76, N, 14.57.

2-(4′-Methylphenyl)-2-[6″-(4‴-phenylpiperazin-1-yl)pyridazin-3-yl]acetonitrile 6h. White solid; mp 120–122°C; ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 3H), 3.25 (m, 4H), 3.85 (m, 4H), 5.48 (s, 1H), 680–7.25 (m, 1H); IR (KBr) ν_{max} 3065, 2960, 2240, 1595, 1510, 1142, 1255, 1030, 984, 755 cm^{-1}; *Anal*. Calcd for $C_{23}H_{23}N_5$: C, 74.77, H, 6.27, N, 18.95; Found C, 74.68, H, 6.23, N, 18.89.

General procedure for the synthesis of 7a–b. Compound **1/4** (0.005 M) were dissolved in [BMIM]OH (5 mL), and hydrazine (0.005 M) was added. The mixture was subjected to microwave irradiation for 10 min at 120°C. The product was extracted with ethyl acetate (3 × 10 mL), and removal of solvent by distillation under reduced pressure (10 mmHg) at 60°C yielded the desire product **7a–b**. The product was recrystallized from ethanol/2-propanol. The characteristic data of compounds **7a** and **7b** are given next.

(6-Chloro-pyridazine-3-yl)hydrazine 7a. White solid, mp 122–126°C; ^{1}H NMR (DMSO-d_6) δ 4.42 (bs, 2H), 7.10 (d, J = 9.4 Hz, 1H), 7.40 (dd, J = 9.4 Hz, 1H); 8.20 (bs, 1H,); IR (KBr) ν_{max} 3250, 3030, 2925, 1595, 1450, 1154, 833, 641 cm^{-1}; *Anal*. Calcd for $C_4H_5ClN_4$: C, 33.23, 3.49, N, 38.76; Found: C, 33.17, H, 3.57, N, 38.66.

(6-Methoxy-pyridazine-3-yl)hydrazine 7b. White solid; mp 130–133°C; ^{1}H NMR (DMSO-d_6) δ 3.65 (s, 3H), 4.40 (bs, 2H) 7.10 (d, J = 9.4 Hz, 1H), 7.40 (d, J = 9.4 Hz, 1H); 8.20 (bs, 1H); IR (KBr) ν_{max} 3255, 3030, 2980, 2925, 1600, 1452, 1154, 833, 641 cm^{-1}; *Anal*. Calcd for $C_5H_8ON_4$: C, 42.85, H, 5.75, N, 39.98; Found: C, 42.80, H, 5.70, N, 39.92.

General procedure for the synthesis of 8a–d. Compound **7a/7b** (0.02 M) was dissolved in [BMIM]OH (5 mL), and appropriate aldehyde (0.025 M) was added to it. The reaction

mixture was irradiated for 10 min at 120°C. The product was extracted by ethylacetate (3 × 10 mL), and the solvent was removed by distillation under reduced pressure (10 mm Hg) at 60°C to give products **8a–d**. The product was recrystallized from 2-propanol.

3-[2′(Benzylidenehydrazinyl)-6-chloropyridazine 8a. White solid; mp 254–256°C; ^{1}H NMR (DMSO-d_6) δ 7.54–7.70 (m, 7H), 8.14 (s, 1H), 11.72 (s, 1H); IR (KBr) ν_{max} 3024, 2921, 2847, 1614, 1593, 1530, 1413, 1064, 751, 687 cm^{-1}; *Anal*. Calcd for $C_{11}H_9ClN_4$: C, 56.78, H, 3.90, N, 20.48; Found: C, 56.63, H, 3.87, N, 24.01.

3-[2′-(4″-Methoxybenzylidene)hydrazinyl]-6-chloropyridazine 8b. White solid, mp 260–263°C; ^{1}H NMR (DMSO-d_6) δ 3.50 (s, 3H), 7.40–7.72 (m, 6H), 8.0 (s, 1H), 11.68 (s, 1H); IR (KBr) ν_{max} 3028, 2995, 2950, 2847, 1614, 1582, 1530, 1440, 1135, 751, 687 cm^{-1}; *Anal*. Calcd for $C_{12}H_{11}OClN_4$: C, 54.86, H, 4.22, N, 21.32; Found : C, 54.77, H, 4.17, N, 21.24.

3-(2-Benzylidenehydrazinyl)-6-methoxypyridazine 8c. White solid; mp 260–263°C; ^{1}H NMR (DMSO-d_6) δ 3.68 (s, 3H), 7.30–7.66 (m, 7H) 8.15 (s, 1H), 11.50 (s, 1H): IR (KBr) ν_{max} 3024, 2985, 2921, 2847, 1614, 1593, 1545, 1145, 1135, 687 cm^{-1}; *Anal*. Calcd for $C_{12}H_{12}ON_4$: C, 63.14, 5.29, N, 24.54; Found: C, 63.05, H, 5.23, N, 24.47.

3-[2′(4″-Methoxybenzylidene)hydrazinyl]-6-methoxypyridazine 8d. White solid; mp 265–267°C; ^{1}H NMR (DMSO-d_6) δ 3.50 (s, 3H), 3.65 (s, 3H), 7.37–7.67 (m, 6H), 8.10 (s, 1H), 11.68 (s, 1H); IR (KBr) ν_{max} 3028, 2990, 2950, 2847, 1614, 1582, 1530, 1440, 1135, 751, 687 cm^{-1}; *Anal*. Calcd for $C_{13}H_{14}ON_4$: C, 60.45, 5.46, N, 21.96; Found: C, 60.38, H, 5.43, N, 21.88.

General procedure for the synthesis of 9a–f and 10a–h. Compounds **5a–f/6a–h** were dissolved in concentrated sulfuric acid (5 mL), and then, reaction mixture was refluxed for 1 h. The products **9a–f/10a–h** were extracted with ethyl acetate (3 × 10 mL). The solvent was removed by distillation under reduced pressure (10 mmHg) at 60°C, and the product was recrystallized by 2-propanol. The physicochemical characteristics of some important compounds are present next:

2-(4′-Methoxyphenyl)-2-(6′-methoxypyridazin-3-yl)acetamide 9d. White solid; mp 78–80°C; ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H), 3.90 (s, 3H), 5.40 (s, 1H), 7.30–7.65 (m, 6H), 7.66–7.85 (m, 2H); IR (KBr) ν_{max} 3325, 3205, 2995, 1669, 1624, 1410, 1152, 702 cm^{-1}; *Anal*. Calcd for $C_{14}H_{15}O_3N_3$: C, 61.52, H, 5.54, N, 15.37, Found: C, 61.48, H, 5.49, N, 15.33.

2-(6′-Methoxypyridazin-3-yl)-2-(4″-methylphenyl)acetamide 9e. White solid; mp 218–220°C; ^{1}H NMR ($CDCl_3$) δ 1.72 (s, 3H), 3.75 (s, 3H), 5.45 (s, 1H), 6.70–7.30 (m, 6H), 7.65–7.90 (m, 2H); IR (KBr) ν_{max} 3365, 3195, 2975, 1628, 1480, 1420, 1150, 820, 650 cm^{-1}; *Anal*. Calcd for $C_{14}H_{15}O_2N_3$: C, 65.34, H, 5.88, N, 16.33; Found: C, 65.29, H, 5.82, N, 16.29.

2-(4′-Chlorophenyl)-2-(6″-methoxypyridazin-3-yl)-acetamide 9f. White solid; mp 220–222°C, ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 5.38 (s, 1H), 7.30–7.66 (m, 6H), 7.70–7.90 (m, 2H); IR (KBr) ν_{max} 3365, 3193, 2970, 1628, 1487, 1415, 1158, 820, 648 cm^{-1}; *Anal*. Calcd for $C_{13}H_{12}O_2Cl\ N_3$: C, 56.22, H, 4.41, N, 15.13; Found: C, 56.18, H, 4.38, N, 15.08.

2-[6′-(4″-Benzylpiperidin-1-yl)pyridazin-3-yl]-2-(4‴-methoxyphenyl) acetamide 10f. White solid; mp 243–245°C; ^{1}H NMR ($CDCl_3$) δ 1.25 (m, 2H), 1.60 (m, 3H), 2.50 (m, 2H), 2.90 (m, 2H), 3.40 (bs, 2H), 3.72 (s, 3H), 4.25 (d J = 12.8 Hz, 2H), 5.07 (s, 1H) 6.75–785 (m, 11H); IR (KBr) ν_{max} 3425, 3196, 2995, 2920, 2851, 1679, 1650, 1600, 1495, 1450, 1180, 1032, 010, 621 cm^{-1}; *Anal*. Calcd for $C_{25}H_{28}O_2N_4$: C, 72.09, H, 6.78, N, 13.45; Found: C, 71.95, H, 6.75, N, 13.41.

2-[6′-(4″-Benzylpiperidin-1-yl)pyridazin-3-yl]-2-(4‴-methylphenyl)acetamide 10g. White solid; mp 214–217°C; ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 2H), 1.70 (s, 3H), 1.82 (s, 3H), 2.50 (m, 2H), 3.20 (m, 2H), 3.40 (bs, 2H), 4.22 (d, J = 9.2 Hz, 2H,), 5.20 (s, 1H), 7.09–8.00 (m, 11H); IR (KBr) ν_{max} 3412, 3215, 2995, 2920, 1684, 1640, 1580, 1216, 1174, 1121, 1034, 690, 605 cm^{-1}; *Anal*. Calcd for $C_{25}H_{28}O\ N_4$: C, 74.97, H, 7.04, N, 13.98; Found : C, 74.91, H, 6.99, N, 13.94.

2-[4′-Methylphenyl]-2-[6″-(4‴-phenylpiperazin-1-yl)pyridazin-3-yl]acetamide 10h. White solid; mp 100–122°C; ^{1}H NMR ($CDCl_3$) δ 1.80 (s, 3H), 3.55 (s, 4H), 3.80 (s, 4H), 5.10 (s, 1H), 5.84 (bs, 1H), 6.75–7.55 (m, 12H); IR (KBr) ν_{max} 3375, 3185, 2847, 1678, 1597, 1492, 1445, 1386, 1231, 759 cm^{-1}; *Anal*. Calcd for $C_{23}H_{25}ON_5$: C, 71.29, H, 6.50, N, 18.07; Found: C, 71.22, H, 6.44, N, 18.02.

General procedure for the synthesis of 13a–f. The appropriate isocyanate/isothiocyanate (0.003 M) and compound **12** (0.003 M) were added to [BMIM]OH (5 mL). The resulting mixture was subjected to microwave irradiation for 10 min at 120°C. The compound was extracted by ethylacetate (3 × 10 mL) under reduced pressure (10 mmHg) at 60°C to give products **13a–f**. The product was crystallized with dilute acetic acid (5 mL).

***N*-Phenyl-*N*′-(6-phenylpyridazin-3-yl)urea 13a**. Creamy solid, mp 305°C; ^{1}H NMR (DMSO-d_6) δ 9.83 (s, 1H), 9.76 (s, 1H), 8.22 (d, J = 9.2 Hz, 1H), 7.95 (d, J = 9.2 Hz, 1H), 8.04–8.12 (m, 3H), 7.50–7.58 (m, 3 H), 7.34 (d, J = 7.6 Hz, 1H × 2), 7.03 (d, J = 7.6 Hz, 1H × 2); *Anal*. Calcd for $C_{17}H_{14}ON_4$: C, 70.33, H, 4.86, N, 19.30; Found: C, 70.25, H, 4.81, N, 19.17.

***N*-(4-Chlorophenyl)-*N*′-(6-phenylpyridazin-3-yl)urea 13b**. White solid, mp 300°C; ^{1}H NMR (DMSO-d_6) δ 9.87 (s, 1H), 9.85 (s, 1H), 8.24 (d, J = 9.2 Hz, 1H), 7.95 (d, J = 9.2 Hz, 1H), 8.06–8.12 (m, 3H), 7.48–7.55 (m, 2H), 7.35 (d, J = 8.8 Hz, 2H × 2); *Anal*. Calcd for $C_{17}H_{13}ClN_4O$: C, 62.87, H, 4.03, N, 17.25; Found : C, 63.60, H, 3.96, N, 17.20.

***N*-(4-Methylphenyl)-*N*′-(6-phenylpyridazin-3-yl)urea 13c**. White solid, mp 285°C; ^{1}H NMR (DMSO-d_6) δ 9.81 (s, 1H), 9.72 (s, 1H), 8.20 (d, J = 9.2 Hz, 1H), 8.05–8.10 (m, 2H), 7.50–7.58 (m, 4H), 7.40 (d, J = 8 Hz, 2H), 7.15 (d, J = 8 Hz, 2H), 2.26 (s, 3H); *Anal*. Calcd for $C_{18}H_{16}N_4O$: C, 71.04, H, 5.30, N, 18.41; Found: C, 70.95, H, 5.17, N, 18.23.

***N*-Phenyl-*N*′-(6-phenylpyridazin-3-yl)thiourea 13d**. White solid; mp 200°C; ^{1}H NMR (DMSO-d_6) δ 13.50 (s, 1H), 11.20 (s, 1H), 8.31 (d, J = 9.6 Hz, 1H), 8.10 (d, J = 6.4 Hz, 2H), 7.50–7.70 (m, 6H), 7.45 (t, J = 8 Hz, 2H), 7.25 (t, J = 8 Hz, 1H); *Anal*. Calcd for $C_{17}H_{14}N_4S$: C, 66.64, H, 4.61, N, 18.29, S, 10.47; Found : C, 66.60, H, 4.55, N, 18.15; S, 10.30.

***N*-(4-Chlorophenyl)-*N*′-(6-phenylpyridazin-3-yl)thiourea 13e**. White solid, mp 200°C; ^{1}H NMR (DMSO-d_6) δ 13.50 (s, 1H), 8.32 (d, J = 9.6 Hz, 1H), 8.10 (d, J = 6.4 Hz, 2H), 7.52–7.70 (m, 9H); *Anal*. Calcd for $C_{17}H_{13}ClN_4S$: C, 59.91, H, 3.84, N, 16.44, S, 9.41; Found : C, 59.80, H, 3.75, N, 16.30; s, 9.42.

***N*-(4-Methylphenyl)-*N*′-(6-phenylpyridazin-3-yl)thiourea 13f**. White solid, mp 198°C; ^{1}H NMR (DMSO-d_6) δ 13.45 (s, 1H), 8.33 (d, J = 9.2 Hz, 1H), 8.06 (d, J = 6.4 Hz, 2H), 7.70 (d, J = 9.6 Hz, 1H), 7.50–7.60 (m, 6H), 7.25 (d, J = 8 Hz, 2H), 2.35 (s, 3H): *Anal*. Calcd for $C_{18}H_{16}N_4S$: C, 67.47, H, 5.08, N, 17.49, S, 10.01; Found : C, 67.40, H, 4.92, N, 17.52; S, 9.95.

General procedure for the synthesis of 14a–c. Substituted benzenesulfonyl chloride (0.005 M) and compound **12** (0.005 M)

was take in [BMIM]OH (5 mL). The resulting mixture was subjected to microwave irradiation for 10 min at 120°C. The product was extracted with ethyl acetate (3 × 10 mL). The solvent was removed under reduced pressure (10 mmHg) at 60°C, and product **14a–c** was recrystallized from 2-propanol. The characteristic data of compounds **14a–c** are presented next.

***N*-(6-Phenylpyridazin-3-yl)benzenesulfonamide 14a**. Solid; yield 92%; mp 204°C; ^{1}H NMR (DMSO-d_6) δ 8.25 (d, J = 10 Hz, 1H), 7.50–7.80 (m, 12H); *Anal*. Calcd for $C_{16}H_{13}N_3O_2S$: C, 61.72, H, 4.21, N, 13.50, S, 10.30; Found : C, 61.62, H, 4.5, N, 13.30; S, 10.15.

4-Chloro-*N*-(6-phenylpyridazin-3-yl)benzenesulfonamide 14b. Solid; yield 95%; mp 210°C; ^{1}H NMR (DMSO-d_6) δ 8.32 (d, J = 10 Hz, 1H), 7.55–7.75 (11H, m); *Anal*. Calcd for $C_{16}H_{12}ClN_3O_2S$: C, 55.57, H, 3.50; N, 12.15; S, 9.27; Found: C, 55.45; H, 3.30; N, 12.22; S, 9.20.

4-Methyl-*N*-(6-phenylpyridazin-3-yl)benzenesulfonamide 14c. Solid; yield 85%; mp 194°C; ^{1}H NMR (DMSO-d_6) δ 8.28 (d, J = 10 Hz, 1H), 7.55–7.80 (m, 9H); 7.33 (d, J = 8 Hz, 1H × 2), 2.35 (s, 3H), *Anal*. Calcd for $C_{16}H_{15}N_3O_2S$: C, 62.75, H, 4.65; N, 12.91; S, 9.85; Found: C, 62.50; H, 4.62; N, 12.75; S, 9.80.

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