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SYNTHESIS OF NOVEL BENZIMIDAZOLE AND BENZOTHIAZOLE DERIVATIVES

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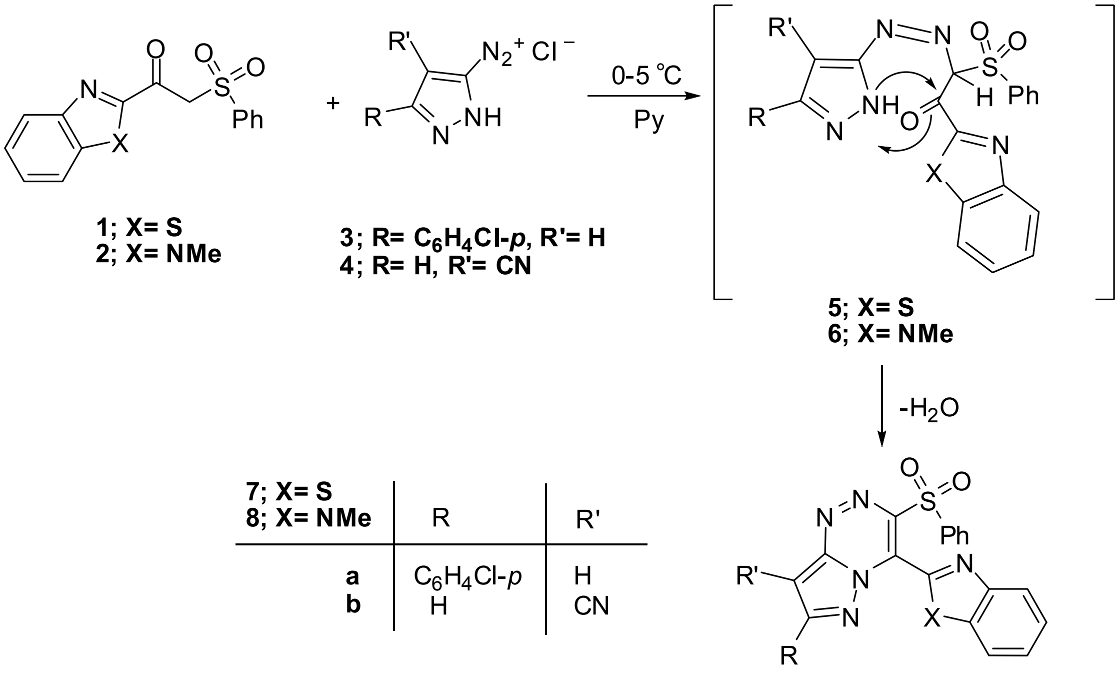
Abstract – 1-(Benzothiazol-2-yl)-2-phenylsulfonyl-1-ethanone (**1**) and 1-(1-methyl-1*H*-benzimidazol-2-yl)-2-(phenylsulfonyl)-1-ethanone (**2**) were used as potential scaffolds for biologically interesting azoloazine derivatives *via* their reaction with the diazonium salts of 5-aminopyrazole, 5-amino[1,2,4]triazole and 2-aminobenzimidazole. Coupling of the *β*-ketosulfones **1** or **2** with diazotized aromatic amines afforded the corresponding arylhydrazone derivatives which have been utilized as versatile building blocks for the synthesis of biologically interesting pyridazine ring systems.

INTRODUCTION

Benzothiazole and benzimidazole ring systems are very important classes of compounds due to their wide spectrum of biological activities. Many of their derivatives are used as antiviral,[1-4] antifungal,[5-8] antitumor[9-12] and antihelminthic agents in veterinary medicinel.[13-15] Some of benzimidazole derivatives are now included in many of commercialized drugs.[16-18] On the other hand, *β*-ketosulfone moiety is readily available from a variety of precursor functionalities and displays a broad range of synthetic versatility.[19,20] These are also important group of intermediates in Michael and Knoevengel reactions.[21] Compounds containing *β*-ketosulfones moiety have attracted considerable attention of synthetic chemists in the past decade.[22] As part of our ongoing research program directed towards the synthesis of a variety of heterocycles for biological evaluation,[23,34] we report here on the synthesis of several heterocyclic ring systems incorporation benzothiazole and benzimidazole moieties starting from the versatile hitherto unreported 1-(benzothiazol-2-yl)-2-phenylsulfonyl-1-ethanone (**1**) and 1-(1-methyl-1*H*-benzimidazol-2-yl)-2-(phenylsulfonyl)-1-ethanone (**2**).

RESULTS AND DISCUSSION

Treatment of each of the 1-(benzothiazol-2-yl)-2-phenylsulfonyl-1-ethanone (**1**) and 1-(1-methyl-1*H*-benzimidazol-2-yl)-2-(phenylsulfonyl)-1-ethanone (**2**) with the diazonium salts of 3-(4-chlorophenyl)-5-amino-1*H*-pyrazole (**3**) and 4-cyano-5-amino-1*H*-pyrazole (**4**) afforded the corresponding non-isolable azo intermediates **5** and **6**, respectively**.** The latter intermediates underwent *in situ* intramolecular cyclization, yielding the corresponding pyrazolo[5,1-*c*][l,2,4]triazine derivatives **7a,b** and **8a,b**, respectively (Scheme 1). The structures of the isolated products **7a,b** and **8a,b** were established on the basis of their elemental analyses and spectral data. For example, the IR spectrum of the compounds **7b** and **8b** revealed, in each case, no bands corresponding to the endocyclic NH group and showed absorption band due to nitrile group near 2233 cm^{-1}. Their mass spectra showed, in each case, a peak corresponding to the molecular ion. Their ^{1}H NMR spectra revealed, in each case, a singlet signal near 8.64 ppm due pyrazole CH proton and a multiplet signal corresponding to aromatic protons in the range 7.20-8.14 ppm.

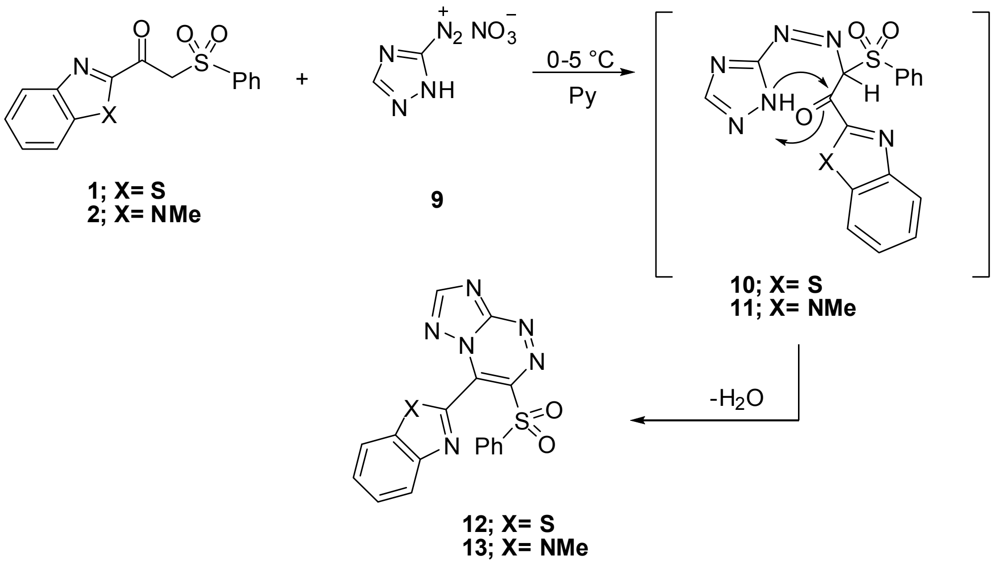


7; X= S 8; X= NMe	R	R'
a	C_6H_4Cl-*p*	H
b	H	CN

Sheme 1

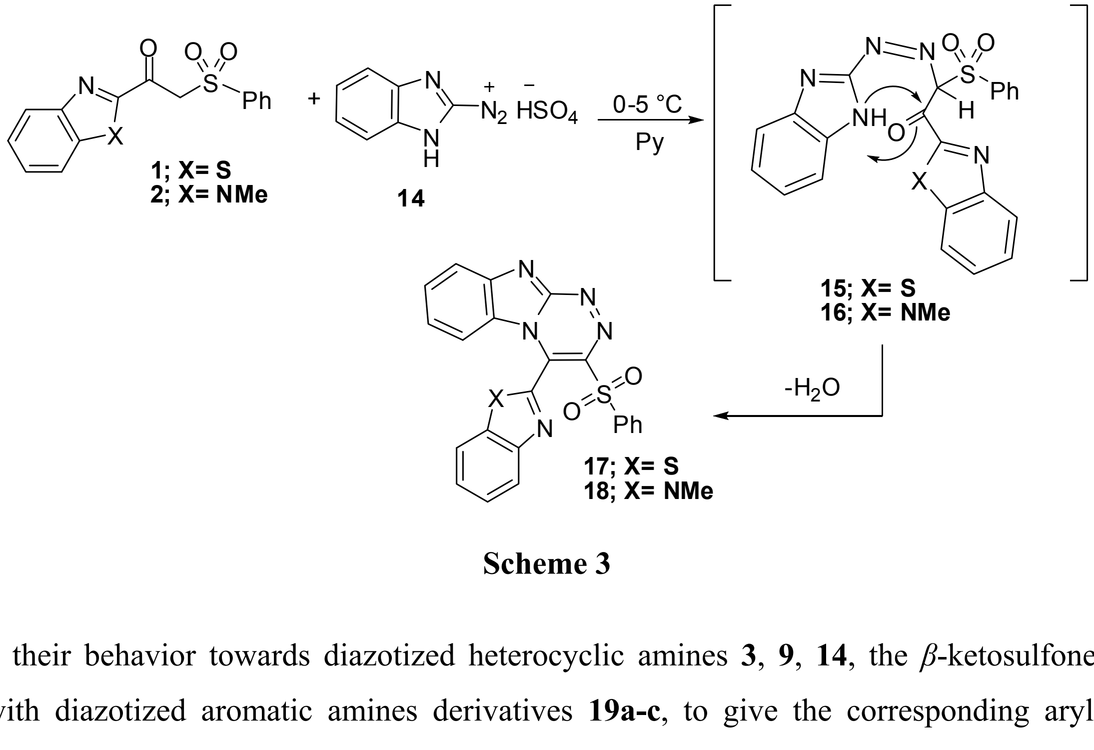
In a similar manner, the *β*-ketosulfones **1** and **2** reacted with the diazonium salts of 5-amino-l,2,4-triazole (**9**) and afforded products identified as 4-(benzothiazol-2-yl)-3-(phenylsulfonyl)-[1,2,4]triazolo[5,1-*c*]-[1,2,4]triazine (**12**) and 4-(1-methylbenzimidazol-2-yl)-3-(phenysulfonyl)-[1,2,4]triazolo[5,1-*c*][1,2,4]-triazine (**13**), respectively (Scheme 2).

The structures of the reaction products **12** and **13** were established on the basis of their elemental analyses and spectral data (see Experimental part).



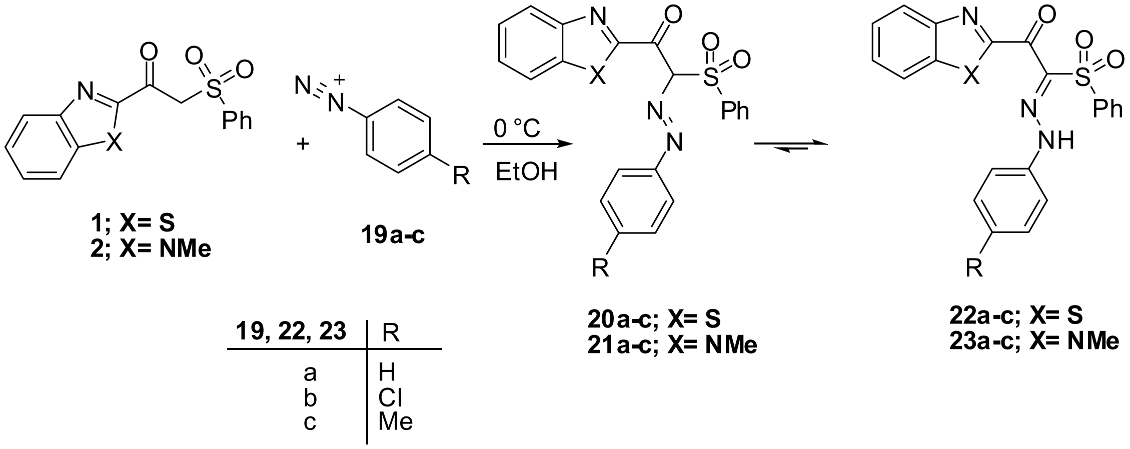
Scheme 2

Also, the *β*-ketosulfones **1** and **2** reacted with the diazonium salt of 2-amino-1*H*-benzimidazole (**14**) to afford the corresponding 4-(benzothiazol-2-yl)-3-(phenylsulfonyl)-1,2,4-triazino[4,3-*a*]benzimidazole (**17**) and 4-(1-methylbenzimidazol-2-yl)-3-(phenylsulfonyl)-1,2,4-triazino[4,3-*a*]benzimidazole (**18**), respectively (Scheme 3). The mass spectra of the reaction products showed, in each case, a peak corresponding to the molecular ion. The ^{1}H NMR spectrum of compound **18**, taken as an example of the prepared compounds revealed a singlet signal at δ 4.02 due to *N*-CH_3 protons and a multiplet signals at δ 7.38-8.16 due to aromatic protons.



Scheme 3

Similar to their behavior towards diazotized heterocyclic amines **3**, **9**, **14**, the *β*-ketosulfones **1** and **2** coupled with diazotized aromatic amines derivatives **19a-c**, to give the corresponding arylhydrazone derivatives **22a-c** and **23a-c**, respectively (Scheme 4). The structures of the compounds **22a-c** and **23a-c** were established on the basis of their elemental analyses and spectral data (see Experimental part).



1; X= S
2; X= NMe

19a-c

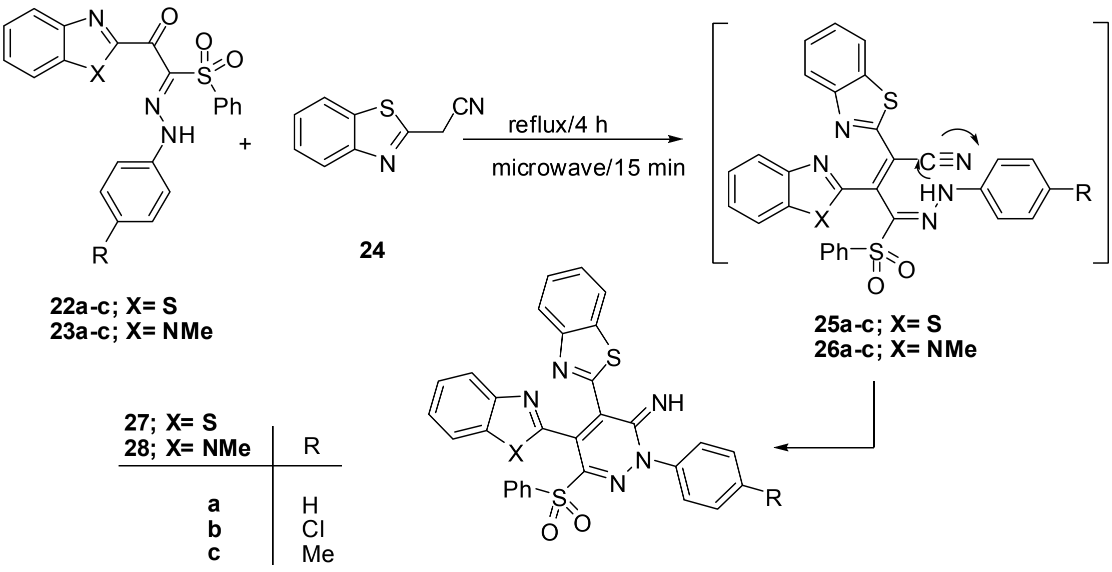
20a-c; X= S
21a-c; X= NMe

22a-c; X= S
23a-c; X= NMe

19, 22, 23	R
a	H
b	Cl
c	Me

Scheme 4

The obtained arylhydrazones **22a-c** and **23a-c** have been utilized as building blocks for the synthesis of biologically interesting pyridazine ring system. Thus, the arylhydrazones **22a-c** and **23a-c** undergo cyclocondensation with 2-cynomethylbenzothiazole (**24**) under both heating in ethanol and under microwave irradiation conditions, to afford the corresponding pyridazine derivatives **27a**-**c** and **28a**-**c**, respectively in almost quantitative yield (Scheme 5). The IR spectra of the obtained compounds revealed, in each case, absorption band near 3332 cm^{-1} due to NH function whereas their ^{1}H NMR spectra revealed, in each case, a singlet signal near 11.88 ppm due NH protons. Other signals appeared at their respective chemical shifts.



22a-c; X= S
23a-c; X= NMe

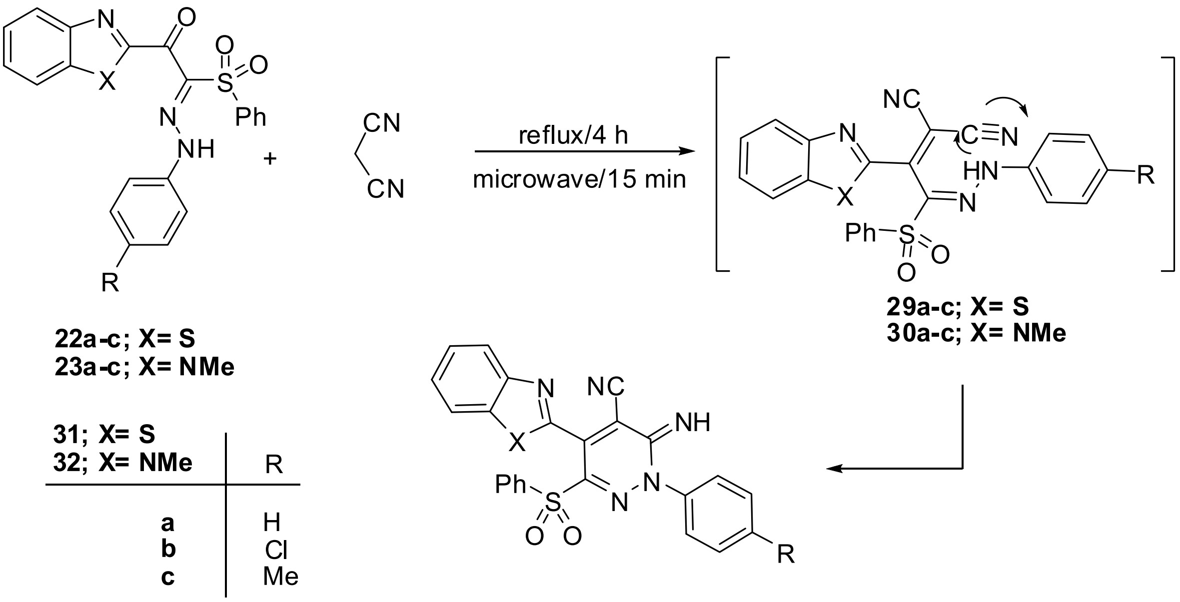
24

25a-c; X= S
26a-c; X= NMe

27; X= S 28; X= NMe	R
a	H
b	Cl
c	Me

Scheme 5

Similarly, condensation of the arylhydrazones **22a-c** and **23a-c** with malononitril afforded the corresponding 1-aryl-4-(benzothiazol-2-yl)-5-(cyano)-1,6-dihydro-6-imino-3-(phenylsulfonyl)pyridazine (**31a-c**) and 1-aryl-4-(1-methylbenzimidazol-2-yl)-5-(cyano)-1,6-dihydro-6-imino-3-(phenylsulfonyl)-pyridazine (**32a-c**), respectively (Scheme 6). The structures of the products **31a-c** and **32a-c** were established on the basis of their elementals analysis and spectral data (see Experimental part).



Scheme 6

EXPERIMENTAL

Melting points were determined in open glass capillaries with a Gallenkamp apparatus. The IR spectra were recorded using KBr disks on a Pye Unicam SP 3-300 or a Shimadzu FTIR 8101 PC IR spectrophotometer. The NMR spectra were recorded with a Varian Mercury VXR-300 NMR spectrometer at 300 and 75 MHz (^{1}H and ^{13}C NMR spectra, respectively) using $CDCl_3$ and DMSO-d_6 as solvents. Chemical shifts were related to that of the solvent. Mass spectra (EI) were obtained at 70 eV with a Shimadzu GCMQP 1000 EX spectrometer. TLC analyses were performed using precoated silica gel 60778 plates (Fluka), and the spots were visualized with UV light at 254 nm. Fluka silica gel 60741 (70–230 mesh) was used for flash column chromatography. Microwave experiments were carried out using a CEM Discover LabMate microwave apparatus (300 W with ChemDriver Software). 2-Bromo-1-(1-methyl-1*H*-benzimidazol-2-yl)ethanone[35] 3-(4-chlorophenyl)-(1*H*)-pyrazole-5-diazonium chloride (**3**),[36] 4-cyano-1*H*-pyrazole-3-diazonium chloride (**4**),[37] 1*H*-1,2,4-triazole-5-diazonium salt (**9**),[37] 1*H*-benzimidazol-2-diazonium salt (**14**),[37] benzothiazole-2-acetonitrile (**24**),[38] 2-bromo-1-benzothiazol-2-yl-ethanone,[39] were prepared following literature procedures.

1-(Benzothiazol-2-yl)-2-phenylsulfonyl-1-ethanone (1). A mixture of 2-bromo-1-benzothiazol-2-yl-ethanone (2.56 g, 10 mmol) and sodium benzenesulfinate (1.64 g 10 mmol), in absolute EtOH (20 mL) was refluxed for 3 h, and then left to cool to rt. The precipitated solid was filtrated off, washed with water and dried. Recrystallization from EtOH afforded the title compound. Yield (79%); mp 142 °C; IR (KBr) ν_{max}/cm^{-1}: 1690 (C=O), 1325, 1160 (SO_2); ^{1}H NMR (DMSO-d_6) δ 5.41 (s, 2H, CH_2), 7.35−8.03 (m, 9H, ArH); ^{13}C NMR (DMSO-d_6) δ 60.45, 121.66, 123.43, 124.60, 128.34, 129.34, 133.56, 136.01, 138.69, 145.47, 155.12, 182.34; MS (*m/z*, %): 317 (M$^+$, 23.7). Anal. Calcd for $C_{15}H_{11}NO_3S_2$ (317.38): C, 56.76; H, 3,49; N, 4.41; S, 20.21%. Found: C, 56.55; H, 3.44; N, 4.49; S, 20.23 %

1-(1-Methyl-1*H*-benzimidazol-2-yl)-2-(phenylsulfonyl)-1-ethanone (2). To a solution of triethylbenzylammonium chloride (TEBAC) (0.2 g) in MeCN (25 mL) was added sodium benzenesulfinate (1.80 g, 12 mmol) and the suspension was stirred at rt for 15 min. To this mixture was added a solution of 2-bromo-1-(1-methyl-1*H*-benzimidazol-2yl)ethanone (2.58 g 10 mmol) in MeCN (20 mL). The progress of the reaction was monitored by TLC till the disappearance of the reactants. After the reaction was complete (about 1h), the mixture was filtered off, and the solid material (NaBr) was washed with MeCN. The washings along with mother liquor were mixed and evaporated under reduced pressure. The residue was taken up in CH_2Cl_2 (50 mL) and washed with water (2 × 10 mL). The organic layer was separated and dried over anhydrous $MgSO_4$ then evaporated under reduced pressure. The residue was crystallized from hexane-benzene (9:1) to afford **2**. Yield (90%), mp 159−161 °C; IR (KBr) ν_{max}/cm^{-1}: 1690 (C=O), 1325 and 1160 (SO_2); ^{1}H NMR (DMSO-d_6) δ 4.03 (s, 3H, NCH_3), 5.41 (s, 2H, CH_2), 7.38−7.95 (m, 9H, ArH); ^{13}C NMR (DMSO-d_6) δ 31.97, 60.45, 111.01, 120.43, 123.31, 128.32, 129.34, 133.56, 134.01, 138.29, 138.41, 140.12, 179.34; MS (*m/z*, %): 314 (M$^+$, 29.2). Anal. Calcd for $C_{16}H_{14}N_2O_3S$ (314.36): C, 61.13; H, 4.49; N, 8.91; S, 10.20%. Found: C, 61.16; H, 4.46; N, 8.93; S, 10.18%.

Reaction of the β-ketosulfones 1 and 2 with diazotized heterocyclic amines.

General procedure:

To a stirred cold solution (ice bath at 0−5 °C) of the appropriate *β*-ketosulphone **1** or **2** (2 mmol), in pyridine (30 mL) was added the appropriate heterocyclic diazonium salt of the heterocyclic amines **3**, **4**, **9** and **14** (2 mmol) portionwise over a period of 30 min. The reaction mixture was stirred for further 3 h at 0−5 °C. The precipitate solid was collected by filtration, washed with water and dried. Recrystallization from DMF/H_2O afforded the corresponding fused ring systems **7a,b, 8a,b, 12**, **13**, **17** and **18**, respectively.

4-(Benzothiazol-2-yl)-7-(4-chlorophenyl)-3-(phenylsulfonyl)pyrazolo[5,1-*c*][1,2,4]triazine (7a): Yield (78%), mp 170−172 °C; IR (KBr) ν_{max}/cm^{-1}: 1597 (C=N); ^{1}H NMR (DMSO-d_6) δ 6.99 (s, 1H, pyrazole-8-CH), 7.42-8.13 (m, 13H, ArH's); MS (*m/z*, %): 503 (M^+, 100%). Anal. Calcd for $C_{24}H_{14}N_5ClO_2S_2$ (503.98): C, 57.20; H, 2.80; N, 13.90; S, 12.72%. Found: C, 57.24; H, 2.83; N, 13.94; S, 12.68%.

4-(Benzothiazol-2-yl)-3-(phenylsulfonyl)pyrazolo[5,1-*c*]-[1,2,4]triazine-8-carbonitrile (7b): Yield (79%), mp 152−154 °C; IR (KBr) ν_{max}/cm^{-1}: 2233 (C≡N); ^{1}H NMR (DMSO- d_6) δ 7.42−8.14 (m, 9H, ArH's), 8.64 (s, 1H, pyrazole-7-CH); MS (*m/z*, %): 418 (M^+,100%); Anal. Calcd for $C_{19}H_{10}N_6O_2S_2$ (418.45): C, 54.54; H, 2.41; N, 20.08; S, 15.33%. Found: C, 54.49; H, 2.40; N, 20.05; S, 15.35 %.

7-(4-Chlorophenyl)-4-(1-methyl-1*H*-benzimidazol-2-yl)-3-(phenylsulfonyl)pyrazolo[5,1-*c*][1,2,4]triazine (8a): Yield (72%), mp 188−189 °C.IR (KBr) ν_{max}/cm^{-1}: 1597 (C=N); ^{1}H NMR (DMSO-d_6) δ 4.02 (s, 3H, NCH_3), 6.89 (s, 1H, pyrazole-8-CH), 7.20−7.89 (m, 13H, ArH's); MS (*m/z*, %): 500 (M^+, 100%); Anal. Calcd for $C_{25}H_{17}N_6ClO_2S$ (500.96): C, 59.94; H, 3.42; N, 16.78; S, 6.40%. Found: C, 59.96; H, 3.39; N, 16.80; S, 6.41%.

4-(1-Methyl-1*H*-benzimidazol-2-yl)-3-(phenylsulfonyl)pyrazolo[5,1-*c*][1,2,4]triazine-8-carbonitrile (8b): Yield (77%), mp 168−170 °C; IR (KBr) ν_{max}/cm^{-1}: 2233 (C≡N); ^{1}H NMR (DMSO-d_6) δ 4.02 (s, 3H, NCH_3), 7.20−8.04 (m, 9H, ArH's), 8.64 (s, 1H, pyrazole-7-CH). MS (*m/z*, %): 415 (M^+, 100%); Anal. Calcd for $C_{20}H_{13}N_7O_2S$ (415.43): C, 57.82; H, 3.15; N, 23.60; S, 7.72%. Found: C, 57.85; H, 3.18; N, 23.62; S, 7.75%.

4-(Benzothiazol-2-yl)-3-(phenylsulfonyl)-[1,2,4]triazolo[5,1-*c*][1,2,4]triazine (12): Yield (72%), mp 205−206 °C; IR (KBr) ν_{max} /cm^{-1}: 1607 (C=N); ^{1}H NMR (DMSO-*d6*) δ 7.43−8.14 (m, 9H, ArH's), 8.57 (s, 1H, triazole-7-CH). ^{13}C NMR (DMSO-*d6*) δ 120.23, 121.53, 124.30, 125.32, 128.10, 129.57, 133.43, 133.02, 136.22, 152.54, 156.04, 156.05,156.63; MS (*m/z, %*): 394 (M^+, 100%); Anal. Calcd for $C_{17}H_{10}N_6O_2S_2$ (394.43): C, 51.77; H, 2.56; N, 21.31; S, 16.26%. Found: C, 51.73; H, 2.59; N, 21.34; S, 16.23%.

4-(1-Methylbenzimidazol-2-yl)-3-(phenysulfonyl)-[1,2,4]-triazolo[5,1-*c*][1,2,4]-triazine (13): Yield (72%), mp 160−162 °C; IR (KBr) ν_{max}/cm^{-1}: 1607 (C=N); ^{1}H NMR (DMSO-d_6) δ 4.02 (s, 3H, NCH_3), 7.20−8.04 (m, 9H, ArH's), 8.47 (s, 1H, triazole-7-CH); ^{13}C NMR (DMSO-d_6) δ 31.97 (NCH_3), 111.67, 121.43, 123.60, 128.10, 129.22, 133.36, 134.01, 136.02, 140.54 (aromatic carbons), 141.11 (C-2 benzimidazole ring), 148.45, 148.57 (-N-CH, triazole ring); MS (*m/z*, %): 391 (M^+, 100%); Anal. Calcd for $C_{18}H_{13}N_7O_2S$ (391.41): C, 55.23; H, 3.35; N, 25.05; S, 8.19%. Found: C, 55.19; H, 3.29; N, 25.09; S, 8.21%.

4-(Benzothiazol-2-yl)-3-(phenylsulfonyl)-[1,2,4]triazino[4,3-*a*]benzimidazole (17): Yield (70%), mp 166−167 °C; IR (KBr) ν_{max}/cm^{-1}: 1607 (C=N). ^{1}H NMR (DMSO-d_6) δ 7.41−8.16 (m, 13H, ArH's); MS (*m/z*, %): 443(M^+, 100%); Anal. Calcd for $C_{22}H_{13}N_5O_2S_2$ (443.50); C, 59.58; H, 2.95; N, 15.79; S, 14.46%. Found: C, 59.53; H, 2.98; N, 15.76; S, 14.42%.

4-(1-Methylbenzimidazol-2-yl)-3(phenylsulfonyl)-1,2,4-triazino[4,3-*a*]benzimidazole (18): Yield (70%), mp 175−176 °C; IR (KBr) ν_{max}/cm^{-1}: 1607 (C=N); ^{1}H NMR (DMSO-d_6) δ 4.02 (s, 3H, NCH_3), 7.38−7.94 (m, 13H, ArH's); MS (*m/z*, %): 440 (M^+, 100%); Anal. Calcd for $C_{23}H_{16}N_6O_2S$ (440.48): C, 62.72; H, 3.66; N, 19.08; S, 7.28%. Found: C, 62.68; H, 3.64; N, 19.12; S, 7.33%.

Reaction of the β-ketosulfones 1 and 2 with arene diazonium chlorides (19a-c). To a stirred solution of the appropriate ketosulfone **1** or **2** (20 mmol), in EtOH (50 mL) was added sodium acetate trihydrate (8 g). After stirring for 10 min, the mixture was cooled to 0 °C then treated with the appropriate arene diazonium salt **19** [prepared by diazotizing the corresponding aromatic amine (20 mmol) in hydrochloric acid (6M, 6 mL) with sodium nitrite solution [(1.4 g, 20 mmol), in H_2O (15 mL)]. The addition of the diazonium salt was carried out with rapid stirring over a period of 30 min. The reaction mixture was stirred for further 2 h at 0 °C, and then left for 6 h at 4 °C in a refrigerator. The resulting solid was collected by filtration, washed thoroughly with water then dried. The crude product was recrystallized from EtOH to afford the corresponding hydrazone derivatives **22a-c** and **23a-c**, respectively.

1-(Benzothiazol-2-yl)-2-(2-phenylhydrazono)-2-(phenylsulfonyl)ethanone (22a): Yield (80%), mp 180−182 °C; IR (KBr) ν_{max}/cm^{-1}: 3215 (NH), 1630 (CO), 1597 (C=N); ^{1}H NMR (DMSO-d_6) δ 7.07−8.33 (m, 14H, ArH's), 11.11 (s, 1H, D_2O-exchangable, NH); ^{13}C NMR (DMSO-d_6) δ 113.05, 120.94, 122.74, 124.35, 125.29, 128.40, 129.20, 129.28, 133.52, 138.27, 139.40, 142.16, 160.25, 162.67, 182.35, 154.21; MS (*m/z*, %): 421 (M^+, 100%); Anal. Calcd for $C_{21}H_{15}N_3O_3S_2$ (421.49): C, 59.84; H, 3.59; N, 9.97; S, 15.21%. Found: C, 59.79; H, 3.62; N, 10.00; S, 15.23%

1-(Benzothiazol-2-yl)-2-(2-(4-chlorophenyl)-hydrazono)-2-(phenylsulfonyl)ethanone (22b): Yield (68%), mp 210−212 °C; IR (KBr) ν_{max}/cm^{-1}: 3243 (NH), 1634 (CO), 1611 (C=N); ^{1}H NMR (DMSO-d_6) δ 7.09−8.14 (m, 13H, ArH's), 11.08 (s, 1H, D_2O-exchangable, NH); ^{13}C NMR (DMSO-d_6) δ 116.39, 119.31, 122.82, 123.41, 125.13, 125.44, 127.93, 128.1, 128.87, 129.36, 133.79, 136.59, 139.74, 140.67, 141.24, 152.46, 181.8; MS (*m/z*, %): 455 (M^+, 100%); Anal. Calcd for $C_{21}H_{14}ClN_3O_3S_2$ (455.94): C, 55.32; H, 3.09; N, 9.22; S, 14.07%. Found: C, 55.30; H, 3.11; N, 9.26; S, 14.05 %.

1-(Benzothiazol-2-yl)-2-(phenylsulfonyl)-2-(2-p-tolylhydrazono)ethanone (22c): Yield (74%), mp 188−190 °C; IR (KBr) ν_{max}/cm^{-1}: 3227 (NH), 1637 (CO), 1601 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.32 (s, 3H, CH_3), 6.48−8.14 (m, 13H, ArH's), 11.10 (s, 1H, D_2O-exchangable, NH); ^{13}C NMR (DMSO-d_6) δ 20.52, 117.58, 123.34, 125.26, 127.41, 127.84, 128.22 128.66, 129.39, 129.96, 133.62, 134.61, 135.9, 136.45, 139.91, 141.15, 152.85, 182.43; MS (*m/z*, %): 435 (M^+, 100%); Anal. Calcd for $C_{22}H_{17}N_3O_3S_2$ (435.52): C, 60.67; H, 3.93; N, 9.65; S, 14.72%. Found: C, 60.71; H, 3.91; N, 9.68; S, 14.74%.

1-(1-Methyl-1*H*-benzimidazol-2-yl)-2-(2-phenylhydrazono)-2-(phenylsulfonyl)ethanone (23a): Yield (74%), mp 204−206 °C; IR (KBr) ν_{max}/cm^{-1}: 3240 (NH), 1648 (CO), 1611 (C=N); ^{1}H NMR (DMSO-d_6) δ

4.02 (s, 3H, NCH_3), 6.79−7.86 (m, 14H, ArH's), 11.02 (s, 1H, D_2O-exchangable, NH). ^{13}C NMR (DMSO-d_6) δ 31.95, 111.67, 114.62, 121.40, 121.43, 123.60, 128.10, 129.11, 129.22, 133.36, 134.01, 137.05, 139.45, 141.11, 142.36, 145.21, 182.34; MS (*m/z*, %): 418 (M^+, 100%); Anal. Calcd for $C_{22}H_{18}N_4O_3S$ (418.47): C, 63.14; H, 4.34; N, 13.39; S, 7.66%. Found: C, 63.12; H, 4.31; N, 13.36; S, 7.70%

2-(2-(4-Chlorophenyl)hydrazono)-1-(1-methyl-1*H*-benzimidazol-2-yl)-2-(phenylsulfonyl)ethanone (23b): Yield (75%), mp 210−212 °C; IR (KBr) ν_{max}/cm^{-1}: 3251 (NH), 1648 (CO), 1612 (C=N); ^1H NMR (DMSO-d_6) δ 4.02 (s, 3H, NCH_3), 7.08−7.83 (m, 13H, ArH's), 11.10 (s, 1H, D_2O-exchangable, NH); ^{13}C NMR (DMSO-d_6) δ 32.13, 111.88, 116.02, 121.61, 124.25, 126.92, 127.05, 128.01, 128.12, 129.25, 129.4, 133.65, 136.97, 137.67, 140.92, 141.46, 145.18, 180.44; MS (*m/z*, %): 452 (M^+, 100%); Anal. Calcd for $C_{22}H_{17}ClN_4O_3S$ (452.91): C, 58.34; H, 3.78; N, 12.37; S, 7.08%. Found: C, 58.32; H, 3.81; N, 12.39; S, 7.05%

1-(1-Methyl-1*H*-benzimidazol-2-yl)-2-(phenylsulfonyl)-2-(2-p-tolylhydrazono)ethanone (23c): Yield (76%), mp 180−182 °C; IR (KBr) ν_{max}/cm^{-1}: 3247 (NH), 1638 (CO), 1611 (C=N); ^1H NMR (DMSO-d_6) δ 2.32 (s, 3H, CH_3), 4.02 (s, 3H, NCH_3), 6.49−7.83 (m, 13H, ArH's), 11.12 (s, 1H, D_2O-exchangable, NH); MS (*m/z*, %): 432 (M^+, 100%); Anal. Calcd for $C_{23}H_{20}N_4O_3S$ (432.49): C, 63.87; H, 4.66; N, 12.95; S, 7.41%. Found: C, 63.83; H, 4.69; N, 12.97; S, 7.45%.

Reactions of the hydrazones 22a-c and 23a-c with (benzothiazol-2-yl)acetonitrile (24) and malononitrile.

(A)-Thermal method

General procedure:

To a solution of the appropriate hydrazone **22** or **23** (10 mmol) and (benzothiazol-2-yl)acetonitrile (**24**) or malononitrile (10 mmol), in EtOH (50 mL), was added few drops of piperdine. The reaction mixture was refluxed for 3-4 h, then poured into ice cold water, and neutralized with dil. HCl. The resulting solid product was collected by filtration washed with EtOH, dried and finally recrystalized from DMF, to afford the corresponding pyridazine derivatives **27a-c**, **28a-c, 31a-c,** and **32a-c**, respectively**.**

(B)-Microwave method (MW)

General procedure:

A mixture of the appropriate hydrazone **22a** or **23a** (1mmol) and (benzothiazol-2-yl)acetonitrile (**24**) or malononitrile (1 mmol) and a catalytic amount of triethylamine was added in a process vial. The vial was capped properly and irradiated under the appropriate condition (17.2 bars, 150 °C) for 15 min. The reaction mixture was left to cool then poured into ice cold water, and neutralized with dil. HCl. The resulting solid product was collected by filtration washed with ethanol, dried and recrystallized from

DMF, to afford the pyridazine derivative **27a**, **28a, 31a** and **32a**, respectively. The isolated products were found to be identical in all respects [mp, mixture mp and spectra] with those obtained by method (**A**) above.

4,5-(Bisbenzothiazol-2-yl)-1,6-dihydro-6-imino-3-(phenylsulfonyl)-1-(phenyl)pyridazine (27a): Yield (MW) 79%; yield (thermally) 70%, mp 258−260 °C; IR (KBr) ν_{max}/cm^{-1}: 3332 (NH), 1620 (C=N); ^{1}H NMR (DMSO-d_6) δ 6.74−8.14 (m, 18H, ArH's), 11.88 (s, 1H, D_2O-exchangable, NH); MS (*m/z*, %): 577 (M$^+$, 100%); Anal. Calcd for $C_{30}H_{19}N_5O_2S_3$ (577.70): C, 62.37; H, 3.32; N, 12.12; S, 16.65%. Found: C, 62.35; H, 3.34; N, 12.08; S, 16.68%

4,5-(Bisbenzothiazol-2-yl)-1,6-dihydro-6-imino-3-(phenylsulfonyl)-1-(4-chlorophenyl)pyridazine (27b): Yield (65%), mp > 300 °C; IR (KBr) ν_{max}/cm^{-1}: 3339 (NH), 1610 (C=N); ^{1}H NMR (DMSO-d_6) δ 6.60−8.14 (m, 17H, ArH's), 11.82 (br. s, 1H, D_2O-exchangable, NH); MS (*m/z*, %): 611 (M$^+$, 100%); Anal. Calcd for $C_{30}H_{18}ClN_5O_2S_3$ (612.14): C, 58.86; H, 2.96; N, 11.44; S, 15.71%. Found: C, 58.83; H, 2.97; N, 11.41; S, 15.75%.

4,5-(Bisbenozthiazol-2-yl)-1,6-dihydro-6-imino-3-(phenylsulfonyl)-1-(4-methylphenyl)pyridazine (27c): Yield (72%), mp > 300 °C; IR (KBr) ν_{max} /cm^{-1}: 3328 (NH), 1598 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.32 (s, 3H, CH_3), 6.42−8.14 (m, 17H, ArH's), 11.80 (s, br, 1H, D_2O-exchangable, NH); MS (*m/z*, %): 591 (M$^+$, 100%); Anal. Calcd for $C_{31}H_{21}N_5O_2S_3$ (591.73): C, 62.92; H, 3.58; N, 11.84; S, 16.26%. Found: C, 62.89; H, 3.61; N, 11.85; S, 16.24%.

5-(Benzothiazol-2-yl)-1,6-dihydro-6-imino-3-(1-methylbenzimidazol-2-yl)-3-(phenylsulphonyl)-1-(phenyl)pyridazine (28a): Yield (MW) 82%; yield (thermally) 75%, mp 258−260 °C; IR (KBr) ν_{max}/cm^{-1}: 3330 (NH), 1645 (CO); ^{1}H NMR (DMSO-d_6) δ 4.02 (s, 3H, NCH_3), 6.67- 8.14 (m, 18H, ArH's), 11.85 (br. s, 1H, D_2O-exchangable, NH); ^{13}C NMR (DMSO-d_6) δ 32.03, 111.43, 113.32, 120.23, 123.25, 123.48, 124.66, 124.9, 125.51, 126.16, 126.4, 127.5, 127.64, 128.48, 128.6, 129.1, 129.32, 129.56, 131.62, 133.83, 134.19, 135.72, 137.88, 140.45, 142.77, 151.46, 157.42; MS (*m/z*, %): 574 (M$^+$, 100%); Anal. Calcd for $C_{31}H_{22}N_6O_2S_2$ (574.68): C, 64.79; H, 3.86; N, 14.62; S, 11.16%. Found: C, 64.75; H, 3.89; N, 14.65; S, 11.14%.

5-(Benzothiazol-2-yl)-1,6-dihydro-6-imino-3-(1-methylbenzimidazol-2-yl)-3-(phenylsulphonyl)-1-(4-chlorophenyl) pyridazine (28b): Yield (68%), mp > 300 °C; IR (KBr) ν_{max}/cm^{-1}: 3341 (NH), 1649 (CO); ^{1}H NMR (DMSO-d_6) δ 4.02 (s, 3H, NCH_3), 6.62−8.14 (m, 17H, ArH's), 11.79 (s, br, 1H, D_2O-exchangable, NH); MS (*m/z*, %): 608 (M$^+$, 100%); Anal. Calcd for $C_{31}H_{21}ClN_6O_2S_2$ (609.12): C, 61.13; H, 3.47; N, 13.80; S, 10.53%. Found: C, 61.10; H, 3.49; N, 13.83; S, 10.51%.

5-(Benzothiazol-2-yl)-1,6-dihydro-6-imino-3-(1-methylbenzimidazol-2-yl)-3-(phenylsulphonyl)-1-(4-methylphenyl) pyridazine (28c): Yield (72%), mp > 300 °C; IR (KBr) ν_{max}/cm^{-1}: 3325 (NH), 1651 (CO); ^{1}H NMR (DMSO-d_6) δ 2.32 (s, 3H, CH_3), 4.02 (s, 3H, NCH_3), 6.43−8.14 (m, 17H, ArH's), 11.75

(s, br, 1H, D_2O-exchangable, NH); MS (*m/z*, %): 588 (M^+, 100%); Anal. Calcd for $C_{32}H_{24}N_6O_2S_2$ (588.70); C, 65.29; H, 4.11; N, 14.28; S, 10.89%. Found: C, 65.25; H, 4.09; N, 14.30; S, 10.85%.

4-(Benzohiazol-2-yl)-5-cyano-1,6-dihydro-6-imino-3-(phenylsulfonyl)-1-(phenyl)pyridazine (31a): Yield (thermally) 75%; yield (MW) 88%, mp 240−242 °C; IR (KBr) ν_{max}/cm^{-1}: 3332 (NH), 2233 (C≡N), 1597 (C=N); ^1H NMR (DMSO-d_6) δ 6.94−8.14 (m, 14H, ArH's), 11.78 (br. s, 1H, D_2O-exchangable, NH). MS (*m/z*, %): 469 (M^+, 100%); Anal. Calcd for $C_{24}H_{15}N_5O_2S_2$ (469.54): C, 61.39; H, 3.22; N, 14.92; S, 13.66%. Found: C, 61.42; H, 3.24; N, 14.88; S, 13.62%.

4-(Benzothiazol-2-yl)-5-cyano-1,6-dihydro-6-imino-3-(phenylsulfonyl)-1-(4-chlorophenyl)pyridazine (31b): Yield (69%), mp > 300 °C; IR (KBr) ν_{max}/cm^{-1}: 3332 (NH), 2233 (C≡N), 1597 (C=N); ^1H NMR (DMSO-d_6) δ 6.64−8.14 (m, 13H, ArH's), 11.88 (s, br, 1H, D_2O-exchangable, NH); ^{13}C NMR (DMSO-d_6) δ 114.88, 123.01, 124.86, 125.41, 126.16, 126.75, 127.54, 128.03, 129.07, 129.46, 129.69, 130.51, 133.33, 133.69, 135.2, 138.48, 140.05, 141.79, 151.06, 156.04; MS (*m/z*, %): 503 (M^+, 100%); Anal. Calcd for $C_{24}H_{14}ClN_5O_2S_2$ (503.98): C, 57.20; H, 2.80; N, 13.90; S, 12.72%. Found: C, 57.23; H, 2.82; N, 13.87; S, 12.74%.

4-(Benzothiazol-2-yl)-5-cyano-1,6-dihydro-6-imino-3-(phenylsulfonyl)-1-(4-methylphenyl)pyridazine (31c): Yield (71%), mp 290−292 °C; IR (KBr) ν_{max}/cm^{-1}: 3352 (NH), 2267 (C≡N), 1593 (C=N); ^1H NMR (DMSO-d_6) δ 2.32 (s, 3H, CH_3), 6.44−8.14 (m, 13H, ArH's), 11.88 (s, br, 1H, D_2O-exchangable, NH); ^{13}C NMR (DMSO-d_6) δ 20.88, 113.37, 123.01, 124.86, 125.45, 126.16, 126.66, 127.41, 127.58, 127.99, 129.53, 129.76, 130.87, 131.51, 133.48, 135.11, 136.07, 137.15, 140.22, 150.9, 156.04; MS (*m/z*, %): 483 (M^+, 100%); Anal. Calcd for $C_{25}H_{17}N_5O_2S_2$ (483.56): C, 62.09; H, 3.54; N, 14.48; S, 13.26%. Found: C, 62.11; H, 3.51; N, 14.52; S, 13.23%.

4-(1-Methylbenzimidazol-2-yl)-5-cyano-1,6-dihydro-6-imino-3-(phenylsulfonyl)-1-(phenyl)-pyridazine (32a: Yield (thermally) 77%; yield (MW) 89%, mp 220−222 °C; IR (KBr) ν_{max}/cm^{-1}: 3332 (NH), 2233 (C≡N), 1597 (C=N); ^1H NMR (DMSO-d_6) δ 4.02 (s, 3H, NCH_3), 6.54−7.92 (m, 14H, ArH's), 11.79 (br. s, 1H, D_2O-exchangable, NH); MS (*m/z*, %): 466 (M^+, 100%); Anal. Calcd for $C_{25}H_{18}N_6O_2S$ (466.51): C, 64.36; H, 3.89; N, 18.01; S, 6.87%. Found: C, 64.41; H, 3.86; N, 18.04; S, 6.89%.

4-(1-Methylbenzimidazol-2-yl)-5-cyano-1,6-dihydro-6-imin-3-(phenylsulfonyl)-1-(4-chlorophenyl)-pyridazine (32b): Yield (74%), mp >300 °C; IR (KBr) ν_{max}/cm^{-1}: 3352 (NH), 2267 (C≡N), 1593 (C=N); ^1H NMR (DMSO-d_6) δ 4.05 (s, 3H, CH_3), 6.59−7.92 (m, 13H, ArH's), 11.82 (br. s, 1H, D_2O-exchangable, NH); MS (*m/z*, %): 500 (M^+, 100%); Anal. Calcd for $C_{25}H_{17}ClN_6O_2S$ (500.96): C, 59.94; H, 3.42; N, 16.78; S, 6.40%. Found: C, 59.90; H, 3.46; N, 16.80; S, 6.36%.

4-(1-Methylbenzimidazol-2-yl)-5-cyano-1,6-dihydro-6-imin-3-(phenylsulfonyl)-1-(4-methylphenyl)-pyridazine (32c): Yield (78%), mp 242−244 °C; IR (KBr) ν_{max}/cm^{-1}: 3352 (NH), 2267 (C≡N), 1593 (C=N); ^1H NMR (DMSO-d_6) δ 2.32 (s, 3H, CH_3), 4.12 (s, 3H, CH_3), 6.40−7.92 (m, 13H, ArH's), 11.81

(br. s, 1H, D_2O-exchangable, NH); MS (*m/z*, %): 480 (M^+, 100%); Anal. Calcd for $C_{26}H_{20}N_6O_2S$ (480.54): C, 64.98; H, 4.20; N, 17.49; S, 6.67%. Found: C, 64.95; H, 4.18; N, 17.51; S, 6.70%.

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