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Environmentally benign synthesis of unsymmetrical bis-1,2,4-triazolopyridazines using iodobenzene diacetate as an oxidant

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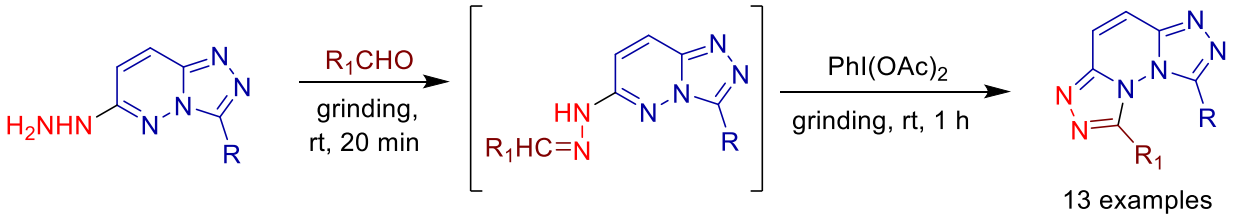
Abstract

The 1,2,4-triazole nucleus is a key structural motif found in numerous drugs and functional molecules with broad applications across medicinal chemistry, materials science, and coordination chemistry. Iodobenzene diacetate is a pivotal hypervalent iodine reagent valued for its mild and selective oxidative capabilities in organic synthesis. This study reports an efficient synthesis of unsymmetrical bis-1,2,4-triazolo[4,3-*b*][3',4'-*f*]pyridazines *via* iodobenzene diacetate-mediated oxidative cyclization of *in situ* generated 6-arylidenehydrazino-3-aryl-1,2,4-triazolo[4,3-*b*]pyridazines under grinding conditions at room temperature. The compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry and elemental analyses. The present environmentally benign and sustainable protocol offers several advantages such as broad substrate scope, high yields, mild reaction conditions, operational simplicity and short reaction time.



Keywords: 6-Hydrazino-1,2,4-triazolo[4,3-*b*]pyridazine; 6-Arylidenehydrazino-3-aryl-1,2,4-triazolo[4,3-*b*]pyridazine; Bis-1,2,4-triazolo-[4,3-*b*][3',4'-*f*]pyridazines; Iodobenzene diacetate.

Introduction

1,2,4-Triazoles are important heterocyclic scaffolds having relevance in the pharmaceutical industry, material science and agriculture.[1,2,3,4] The first triazole compound, fluconazole, featuring two triazole rings, is a first-line antifungal drug (Fig. 1). Itraconazole and Posaconazole are commonly used antifungal drugs having bis-triazole units in their structure. Vorozole is a bis-triazole derivative used to treat advanced breast cancer in postmenopausal patients.[5] 1,2,4-Triazoles offer interesting chemical and biological applications. Many 1,2,4-triazoles, including bis-triazoles, are interesting as ligands in coordination chemistry and building blocks for metal-organic frameworks.[6,7,8] Their applications in corrosion inhibitors,[9,10] sensors,[11] and organocatalysis[12] have also been reported. Some heterocyclic ring fused bis-triazolo derivatives have demonstrated notable pharmacological activities. In particular, 3,6-bis(aryl)bis([1,2,4]triazolo)[3,4-*a*:4',3'-*c*]phthalazines (**I**) displayed promising antimicrobial activities against several bacterial and fungal strains.[13] Bis([1,2,4]triazolo)[4,3-*a*:4',3'-*c*]quinazoline derivatives were designed and synthesized to have anticancer properties through DNA intercalation.[14] Previously, we have reported that a series of 1-aryl-4-methyl-1,2,4-triazolo[4,3-*b*]quinoxalines[15] are effective in photocleaving DNA, and the study was further extended to the synthesis of 3,10-disubtituted-bis-1,2,4-triazolo[4,3-*a*][3',4'-*c*]quinoxalines.[16]

Pyridazine is a heteroaromatic compound containing a six-membered ring with two adjacent nitrogen atoms. Pyridazine scaffold has significance in crop protection,[17] medicinal chemistry,[18] supramolecular and coordination chemistry[19] and the design of new π-conjugated organic compounds.[20] 1,2,4-Triazolo[4,3-*b*]pyridazine, in particular, has utility in the construction of high-energy materials[21,22]. The 1,2,4-triazoles fused with a pyridazine ring have been reported to exhibit diverse biological activities, including antimicrobial,[23] antitubulin,[24] anticancer,[25] antidiabetic,[26] anticonvulsant,[27] anxiolytic[28] and anti-inflammatory[29] activities besides being inhibitors of c-Met kinase,[30] tankyrase,[31] and pan-phosphodiesterase (PDE) inhibitors.[32] (*S*)-6-(1-(6-(1-Methyl-1*H*-pyrazol-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)ethyl)quinoline (**II**) not only exhibited high inhibitory effects against c-Met kinase, but also showed inhibitory effects against tumor growth in GTL-16 xenograft tumor model and pan-PDE family.[32] Quite recently, we reported the anticancer potential of [1,2,4]triazolo[4,3-*b*]pyridazines against three human cancer cell lines—SB-ALL, NALM-6 and MCF-7. Among them, 6-chloro-3-(1*H*-indole-3'-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine (**III**) was the most potent with IC_{50} values ranging from 1.14 to 3.55 μM and was shown to induce apoptosis in NALM-6 cells *via* caspase 3/7 activation.[33]

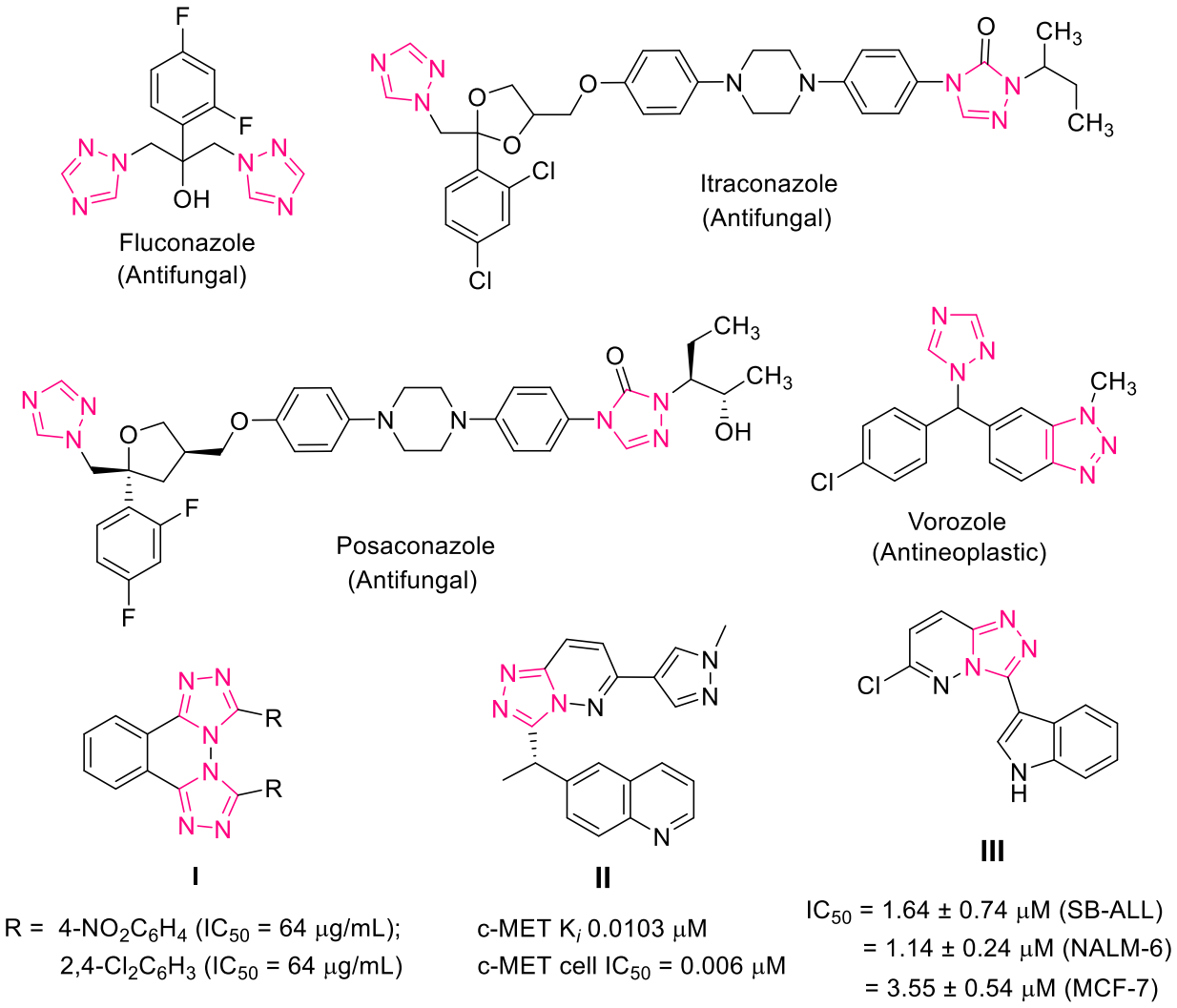


Figure 1. Bis-triazole-based commercial drugs and representative bioactive molecules comprising 1,2,4-triazolo fused heterocycles.

In view of the above interesting results on biologically active 1,2,4-triazoles fused with a pyridazine ring, it was envisioned to extend our work to the synthesis of unsymmetrical bis-1,2,4-triazolopyridazines. The synthesis of unsymmetrical bis-triazolo[4,3-b]pyridazines is significant for several reasons, as different substituents on each triazole ring enable structure–activity relationship (SAR) exploration, selective binding to molecular targets, and tunable physicochemical properties such as solubility, lipophilicity, electronic characteristics, and photophysical behavior. Classical methods to synthesize bis-1,2,4-triazolopyridazines are mainly based on cyclization of 6-arylidenehydrazino-3-aryl-1,2,4-triazolo[4,3-*b*]pyridazine into bis-1,2,4-triazolo-[4,3-*b*][3',4'-*f*]pyridazine upon treatment with Br_2/AcOH or lead tetracetate,[34] or Me_4NBr/oxone®,[35] thereby constructing the second triazole ring. Other protocols involve Br_2/AcOH or lead tetraacetate[34] catalyzed oxidative cyclization of 3,6-bis-(arylidenehydrazino)pyridazines and the reaction of 3,6-dichloropyridazine with two equivalents of acid hydrazides,[36] thereby constructing both triazole rings simultaneously. Furthermore, most of these methods raise significant environmental concerns due to the use of toxic metal catalysts, expensive reagents, harsh reaction conditions, high temperatures, tedious workups, and prolonged reaction times. In this context, the development of environmentally benign protocols for oxidative cyclization under metal-free conditions holds great significance for chemical and pharmaceutical research. In recent years, hypervalent iodine reagents have attracted considerable attention as selective and

environmentally benign oxidants in synthetic transformations owing to their ready accessibility, high stability, reactivity similar to that of transition metals and ease of handling.[37] Iodobenzene diacetate (IBD), a hypervalent iodine(III) reagent, is a greener and safer oxidant that exhibits reactivity pattern similar to heavy metal oxidants. In addition to its mild and selective oxidizing properties, iodobenzene obtained as a byproduct in IBD-mediated transformation can be reused. Therefore, extensive efforts have focused on the use of IBD as an oxidizing agent, and great success has been achieved in modern organic synthesis.[38,39]

In view of the above literature facts, and as a part of our continuous endeavour toward the synthesis of biologically active compounds using hypervalent iodine reagents[40,41,42,43,44], the present work describes the synthesis of a new series of unsymmetrical bis-1,2,4-triazolo-[4,3-*b*][3',4'-*f*]pyridazines *via* oxidative cyclization of hydrazone precursors using iodobenzene diacetate. Cytotoxic activity of the synthesized compounds was also evaluated using MTT assay.

Results and Discussion

Chemistry

Several studies have demonstrated that the hydrazone moiety present at α-position of nitrogen heterocycle undergoes oxidation with hypervalent iodine reagents such as IBD[1],[13] and phenyliodine(III) bis(trifluoroacetate) (PIFA)[45,46] under conventional solution-phase conditions to afford fused triazoloheterocycles *via* intramolecular cyclization (Fig. 2). A key principle of green chemistry is the use of non-toxic reagents and solvent-free conditions to promote sustainability and minimize environmental impact. In this context, we envisaged to explore environmentally benign synthesis of bis-1,2,4-triazolopyridazines through oxidation of hydrazones with IBD under solvent-free condition.

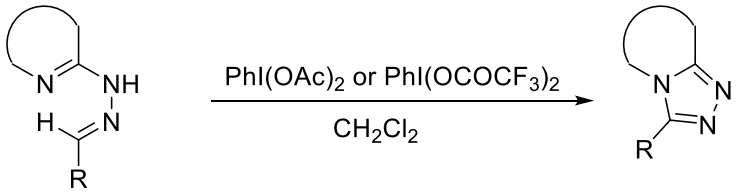
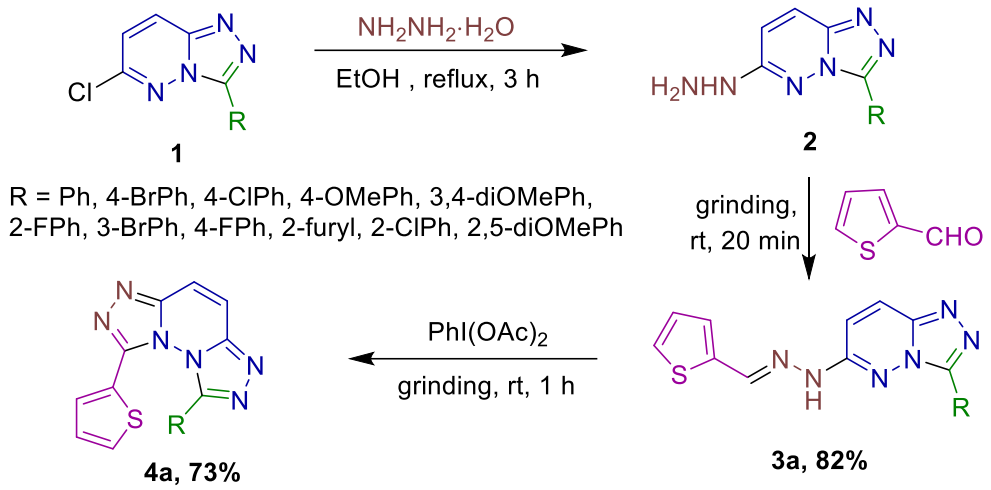


Figure 2. Cyclization of hydrazones to 1,2,4-triazoles using hypervalent iodine reagents.

The precursors, 3-aryl-6-hydrazino-1,2,4-triazolo[4,3-*b*]pyridazines (**2**), were prepared from 3-aryl-6-chloro-1,2,4-triazolo[4,3-*b*]pyridazines (**1**) as previously reported by us.[47] Initially, 6-hydrazino-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine (**2**) was ground with thiophene-2-carbaldehyde in a pestle and mortar at room temperature. TLC monitoring of the reaction mixture displayed the appearance of a new spot and complete consumption of the reactants within 20 minutes. Workup of reaction afforded the key intermediate, 3-phenyl-6-(thiophen-2-ylmethylene)hydrazino-1,2,4-triazolo[4,3-*b*]pyridazine (**3a**), which was confirmed by its spectral data viz., IR, ^{1}H NMR, ^{13}C NMR and HRMS. Next, the oxidative cyclization of hydrazone **3a** was carried out using 1.1 equivalents of IBD as the oxidant under grinding conditions for 1 hour at room temperature, affording unsymmetrical bis-1,2,4-triazolo[4,3-*b*][3',4'-*f*]pyridazine derivative **4a** in 73% yields (Scheme 1).

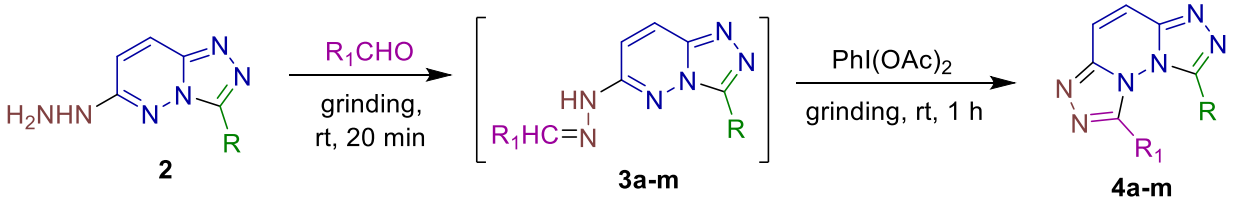


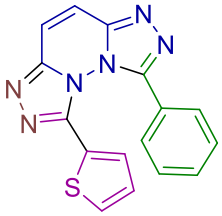
Scheme 1. IBD-mediated synthesis of unsymmetrical bis-1,2,4-triazolo-[4,3-*b*][3',4'-*f*]pyridazine (**4a**).

Under the optimized conditions, the substrate scope was explored by grinding 3-aryl-6-hydrazino-1,2,4-triazolo[4,3-*b*]pyridazines (**2**) bearing electron-withdrawing (-Cl, -Br, and -F) or electron-donating substituents (-CH_3 and –OCH_3, -diOCH_3) on the aryl ring with appropriately substituted aromatic and heteroaromatic aldehydes, followed by the addition of IBD, which resulted in the formation of unsymmetrical bis-1,2,4-triazolo[4,3-*b*][3',4'-*f*]pyridazine derivatives (**4a-m**) in high yields (67-87%) as shown in Table 1. This operationally simple approach to the desired bis-1,2,4-triazolopyridazines (**4**), involving solvent-free grinding of crude hydrazones (**3**) with IBD without prior purification, exhibited a broad substrate scope under mild reaction conditions and provided a valuable alternative to hazardous metal-based reagents. Aromatic aldehydes bearing either electron-donating substituents such as methyl or electron-withdrawing substituents such as halogens had no significant effect on the reaction yield (Table 1; **4b**, 86% vs. **4k**, 86%), suggesting that electronic factors do not substantially influence the cyclization efficiency. Notably, pre-isolation of hydrazones was not required, and the transformation proceeded efficiently in the presence of various substituents (R group) on 3-aryl-6-hydrazino-1,2,4-triazolo[4,3-*b*]pyridazines (**2**), regardless of steric and electronic variation. The reaction was also compatible with heteroaryl substituents such as thienyl and furyl ring (**4a** and **4j**, respectively). These results highlight the synthetic utility and generality of IBD-mediated oxidative cyclization under a solvent-free grinding protocol.

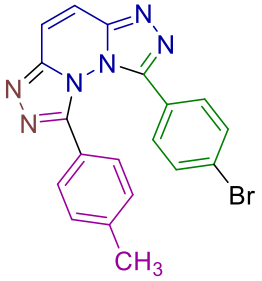
Compared to traditional in-solvent synthetic methods, this environmentally benign approach using IBD as a green oxidant offers improved efficiency, shorter reaction times, and eliminates the need for organic solvents and the labor-intensive work-up steps typically required for hydrazone isolation. These advantages align well with the principles of green chemistry and make the protocol highly attractive for the scalable synthesis of bioactive triazolopyridazine frameworks.

Table 1. Substrate scope and isolated yield of unsymmetrical bis-1,2,4-triazolo-[4,3-*b*][3',4'-*f*]pyridazines[a].

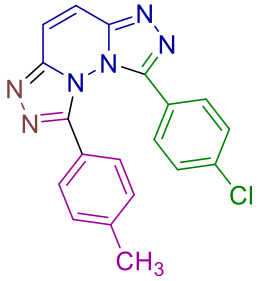




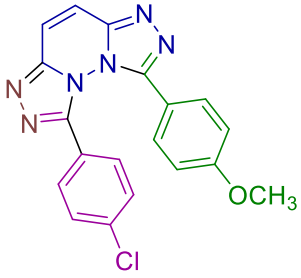
4a, 75%



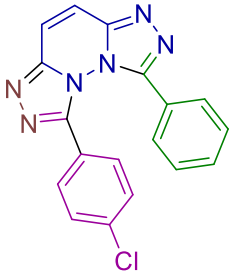
4b, 86%



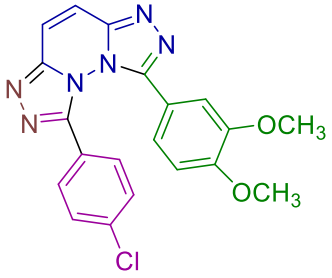
4c, 77%



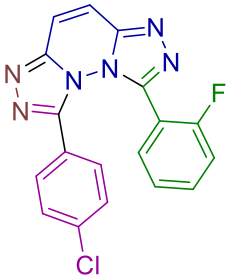
4d, 72%



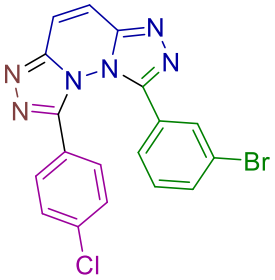
4e, 70%



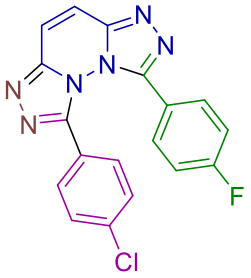
4f, 87%



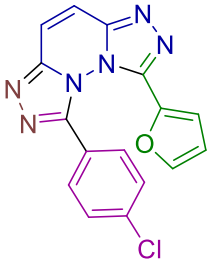
4g, 83%



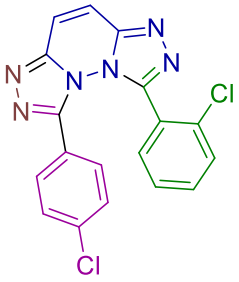
4h, 81%



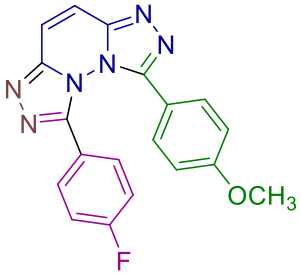
4i, 67%



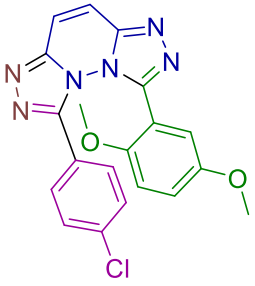
4j, 68%



4k, 86%



4l, 71%



4m, 72%

[a]General condition: **2** (2.0 mmol) and aldehyde (2.0 mmol) ground at room temperature for 20 min., followed by grinding with IBD (2.2 mmol) for 1 h.

Hydrazone intermediate **3a** was isolated only in case of thiophene-2-carbaldehyde. Other hydrazones were not isolated. The IR spectrum of **3a** showed characteristic absorption peaks at 3194 and 1641 cm^{-1},

corresponding to −NH and CN group stretching. ^{1}H NMR spectrum of compound **3a** exhibited a sharp singlet at δ 8.30 ppm for aldehydic proton and a broad singlet at δ 11.63 ppm for NH. Moreover, compound **3** exhibited a pair of doublets of one proton intensity at δ 7.48-7.52 ppm and 8.19-8.21 ppm corresponding to pyridazine protons H-5 and H-4, respectively having the coupling constant ^{3}J = ∼10 Hz. The downfield shift in signal proton at position-4 of pyridazine ring may be attributed to the lone pair effect of the nitrogen of the triazole ring on the H-4. The structure of bis-1,2,4-triazolo-[4,3-*b*][3',4'-*f*]pyridazines (**4**) was established using IR, ^{1}H NMR, ^{13}C NMR, and microanalysis. IR spectra of compounds **4a-m** displayed the characteristic stretching vibrations in the region 1602-1638 cm^{-1} which are ascribed to the C=N group and there is no absorption in the region of NH stretch and bend, manifesting the oxidation of hydrazones **3** to title compounds **4** and this result is in agreement with the previous research.[47] ^{1}H NMR spectra of **4a-m** showed the absence of singlet signals for aldehydic proton and for NH proton, thus suggesting the cyclization of hydrazones **3** into bis-triazoles **4**. Further ^{1}H NMR spectra of **4** exhibited a pair of doublets for H-5 and H-4 of pyridazine ring at δ 7.61-7.86 and 7.66-7.89 ppm, respectively having the coupling constant ^{3}J= ∼10.2 Hz.

***In vitro* cytotoxic evaluation**

Ten synthesized compounds (**4a-h**, **k**, and **m**) were evaluated for their *in vitro* cytotoxic activity against human lung cancer (A-459) and leukemia (MOLT-4) cell lines by using the MTT [3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide] cell proliferation assay (Table 2). Doxorubicin was used as the standard drug. When the synthesized compounds were initially screened at 10 µM concentration against these two cancer cell lines, two compounds (**4b** and **4c**) bearing C-1 *p*-bromophenyl and *p*-chlorophenyl groups showed moderate anti-cancer activity (Table 2).

Table 2. *In vitro* cytotoxic activities of compounds **4** against two cancer cell lines.

Tested Compd.	R	R_1	% Cell Survival ± S.D.[a]	
			A549	**MOLT-4**
Buffer			100.00 ± 5.83	100 ±12.12
4a	-C_6H_5	-2'-thienyl	102.06 ± 16.20	116.96 ± 17.47
4b	-*p*-BrC_6H_4	-*p*-$CH_3C_6H_4$	70.52 ± 8.40	88.04 ± 22.18
4c	-*p*-ClC_6H_4	-*p*-$CH_3C_6H_4$	70.72 ± 10.70	69.94 ± 22.56
4d	-*p*-ClC_6H_4	-*p*-$OCH_3C_6H_4$	97.89 ± 17.38	101.13 ± 21.62
4e	-*p*-ClC_6H_4	-C_6H_5	96.34 ± 12.39	100.58 ± 25.51
4f	-*p*-ClC_6H_4	3,4-di$OCH_3C_6H_3$	93.76 ± 11.35	104.50 ± 33.75
4g	-*p*-ClC_6H_4	-*o*-FC_6H_4	106.79 ± 13.99	104.34 ± 26.75
4h	-*p*-ClC_6H_4	-*m*-BrC_6H_4	85.08 ± 8.34	113.54 ± 26.95
4k	-*p*-ClC_6H_4	-*o*-ClC_6H_4	96.00 ± 12.02	106.62 ± 27.54
4m	-*p*-ClC_6H_4	2,5-di$OCH_3C_6H_3$	92.27 ± 13.27	106.45 ± 23.36
Doxorubicin			53.07 ± 3.99	13.32 ± 1.65

[a] The activity data represents mean values ± SD of experiments conducted in triplicates at three independent times.

Conclusions

In summary, an efficient, convenient and environmentally benign approach for the synthesis of unsymmetrical bis-1,2,4-triazolo-[4,3-*b*][3',4'-*f*]pyridazines *via* oxidative cyclization of 6-arylidenehydrazino-3-aryl-1,2,4-

triazolo[4,3-*b*]pyridazines using iodobenzene diacetate as a green and selective oxidant was developed. Compared to other conventional methods, the present metal-free protocol is remarkably superior in terms of ease of handling, readily available starting materials, solvent-free synthesis, faster reaction rates, mild conditions, better yields, broad substrate scope and operational simplicity. The resulting unsymmetrical bis-triazolopyridazines represent a valuable class of nitrogen-rich heterocycles with potential applications in medicinal chemistry and materials science.

Experimental Section

General. Melting points are taken in open glass capillaries in an electrical apparatus and are uncorrected. IR spectra were recorded on a Buck Scientific IR M-500 spectrophotometer in KBr pellets (ν_{max} in cm^{-1}). Analytical TLC was performed using Merck Kieselgel 60 F254 silica gel plates. Visualization was performed by UV light (254 nm).^{1}H (400 MHz and 500 MHz) and ^{13}C NMR (100 MHz) spectra for analytical purpose were recorded on a Bruker instrument using $CDCl_3$ or DMSO-d_6 as a solvent at IIT Mandi, Himachal Pradesh, India and chemical shifts are expressed in δ units (parts per million) downfield from TMS as an internal reference. The coupling constants (*J*) are given in Hz. High-resolution mass spectra (HRMS) were measured in the ESI$^+$ mode at CIL, GJU, Hisar. Elemental analyses were also performed at Sophisticated Analytical Instrument Facility (SAIF), Panjab University, Chandigarh, India.

Synthesis of 3-phenyl-6-(2-(thiophen-2''-ylmethylene)hydrazinyl)-[1,2,4]triazolo[4,3-*b*]pyridazine (3a). An equimolar mixture of 6-hydrazino-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine (**2**) (0.452 g, 2.0 mmol) and thiophene-2-carbaldehyde (0.224 g, 2.0 mmol) was ground in a pestle and mortar. The TLC of the reaction mixture evinced the completion of the reaction within 20 min, as there were no spots corresponding to the reactants on TLC. On completion of the reaction, ethanol (3 mL) was added to the reaction mixture. A solid separated which was filtered and crystallized using ethanol to afford **3a**. Yield 82%; m.p. 248-250 °C; IR (KBr, cm^{-1}): 3194 (–NH str.), 1641 (C=N str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.07-7.09 (t, 1H, $J_{4'', 5''}$ =4.8 Hz, $J_{3'', 4''}$ =3.8 Hz, $J_{3'', 5''}$ = 1.0 Hz, thiophene-4''-H), 7.35-7.39 (m, 2H, thiophene-3'',5''-H), 7.48-7.52 (d, 1H, *J*=10.68 Hz, pyridazine-5H), 7.55-7.57 (m, 3H, Ph-3', 4', 5'-H), 8.19-8.21 (d, 1H, *J*=9.96 Hz, pyridazine-4H), 8.30 (s, 1H, -CH), 8.41-8.43 (d, 2H, *J*=7.2 Hz, Ph-2', 6'-H), 11.63 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 114.27, 125.81, 126.87, 127.51, 127.55, 128.45, 128.50, 129.23, 130.03, 130.44, 138.68, 139.92, 146.49, 153.63. HRMS (ESI): *m/z* 321.0848 [M + H]$^+$. Anal. Calcd. for $C_{16}H_{12}N_6S$: C, 59.98; H, 3.78; N, 26.23. Found: C, 59.74; H, 3.42, N, 26.56.

Synthesis of 1-Phenyl-8-(thiophen-2''-yl)bis([1,2,4]triazolo)[4,3-*b*:3',4'-*f*]pyridazine (4a). A mixture of 3-phenyl-6-(2-(thiophen-2-ylmethylene)hydrazinyl)-[1,2,4]triazolo[4,3-*b*]pyridazine (**3a**) (0.32 g, 1.0 mmol) and iodobenzene diacetate (0.35 g, 1.1 mmol, 1.1 equiv) was ground thoroughly in a porcelain mortar with a pestle at room temperature. The progress of the reaction was monitored by TLC, which indicated completion within 1 h. The crude residue was triturated with petroleum ether to remove iodobenzene and then recrystallized from ethanol to afford compound **4a**. Yield 75%; m.p. 232-234 °C; IR (KBr, cm^{-1}): transparent in the region of –NH str., 1638 (C=N str.); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.55-6.57 (t, 1H, $J_{4'', 5''}$ =4.7 Hz, $J_{3'', 4''}$ =4.13 Hz, $J_{3'', 5''}$ = 1.25 Hz, thiophene-4''-H), 6.83-6.84 (dd, 1H, $J_{3'', 4''}$ =3.5 Hz, $J_{3'', 5''}$ = 1.15 Hz, thiophene-3''-H), 7.14-7.16 (m, 1H, Ph-4'-H), 7.18-7.19 (d, 1H, $J_{4'', 5''}$ =4.55 Hz, thiophene-5''-H), 7.21-7.24 (m, 2H, Ph-3', 5'-H), 7.38-7.39 (m, 2H, Ph-2', 6'-H), 7.65 (s, 2H, pyridazine-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 118.18, 118.36, 125.56, 126.97, 128.13, 128.23,

128.89, 130.00, 130.67, 131.80, 143.47, 146.79, 146.85, 148.25. HRMS (ESI): *m/z* 319.0694 $[M + H]^+$. Anal. Calcd. for $C_{16}H_{10}N_6S$: C, 60.36; H, 3.17; N, 26.40. Found: C, 60.69; H, 3.42, N, 26.69.

General procedure for one-pot synthesis of unsymmetrical bis-1,2,4-triazolo-[4,3-*b*][3',4'-*f*]pyridazine (4a-m). An equimolar mixture of 6-hydrazino-3-aryl/heteroaryl-1,2,4-triazolo[4,3-*b*]pyridazine (**2**) (2.0 mmol) and the appropriate aldehyde (2.0 mmol) was ground in a mortar and pestle for 15–20 minutes at room temperature, resulting in the formation of the corresponding 6-arylidenehydrazino-3-aryl-1,2,4-triazolo[4,3-*b*]pyridazine (**3**). Upon completion of the reaction, as indicated by TLC, IBD (2.2 mmol, 1.1 equiv) was added, and the mixture was ground thoroughly for an additional 1 h. The solid that precipitated after trituration with petroleum ether was filtered and recrystallized from ethanol to afford the corresponding unsymmetrical bis-1,2,4-triazolo[4,3-b][3',4'-f]pyridazine derivatives (**4a–m**).

1-(4'-Bromophenyl)-8-(4''-methylphenyl)bis([1,2,4]triazolo)[4,3-*b*:3',4'-*f*]pyridazine (4b). Yield 86%; m.p. 256-258 °C; IR (KBr, cm^{-1}): transparent in the region of –NH str., 1603 (C=N str.); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.32 (s, 3H, CH_3), 6.93-6.95 (d, 2H, J_o=7.7 Hz, Ph-3'', 5''-H), 7.15-7.17 (d, 2H, J_o=8.35 Hz, Ph-3', 5'-H), 7.18-7.22 (m, 4H, Ph-2', 6', 2'', 6''-H), 7.67-7.69 (d, 1H, *J*=10.15 Hz, pyridazine-H), 7.70-7.72 (d, 1H, *J*=10.0 Hz, pyridazine-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.53, 118.47, 118.84, 124.34, 124.51, 129.33, 129.61, 131.41, 131.60, 136.69, 140.59, 147.71, 149.48, 166.80. Anal. Calcd. for $C_{19}H_{13}BrN_6$: C, 56.31; H, 3.23; N, 20.74. Found: C, 56.69; H, 3.57, N, 20.39.

1-(4'-Chlorophenyl)-8-(4''-methylphenyl)bis([1,2,4]triazolo)[4,3-*b*:3',4'-*f*]pyridazine (4c). Yield 77%; m.p. 247-248 °C; IR (KBr, cm^{-1}): transparent in the region of –NH str., 1623 (C=N str.); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.29 (s, 3H, CH_3), 6.91-6.93 (m, 2H, Ph-3'', 5''-H), 7.01-7.04 (m, 2H, Ph-3', 5'-H), 7.16-7.18 (m, 2H, Ph-2', 6'-H), 7.22-7.24 (m, 2H, Ph-2'', 6''-H), 7.69 (s, 2H, pyridazine-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.45, 117.96, 118.45, 123.23, 124.98, 128.85, 128.95, 129.55, 130.15, 137.02, 141.82, 146.66, 148.21. Anal. Calcd. for $C_{19}H_{13}ClN_6$: C, 63.25; H, 3.63; N, 23.29. Found: C, 63.57; H, 3.90, N, 23.63.

1-(4'-Chlorophenyl)-8-(4''-methoxyphenyl)bis([1,2,4]triazolo)[4,3-*b*:3',4'-*f*]pyridazine (4d). Yield 72%; m.p. 240-242 °C; IR (KBr, cm^{-1}): transparent in the region of –NH str., 1613 (C=N str.); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.80 (s, 3H, OCH_3), 6.60-6.62 (d, 2H, J_o=8.75 Hz, Ph-3'', 5''-H), 7.04-7.06 (d, 2H, J_o=8.5 Hz, Ph-3', 5'-H), 7.19-7.22 (d, 2H, J_o=8.7 Hz, Ph-2'', 6''-H), 7.23-7.25 (d, 2H, J_o=8.45 Hz, Ph-2', 6'-H), 7.64-7.66 (d, 1H, *J*=10.15 Hz, pyridazine-H), 7.67-7.69 (d, 1H, *J*=10.15 Hz, pyridazine-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.54, 114.38, 117.79, 118.18, 118.48, 124.96, 128.88, 130.23, 130.67, 136.88, 147.17, 148.07, 161.62. Anal. Calcd. for $C_{19}H_{13}ClN_6O$: C, 60.56; H, 3.48, N, 22.30. Found: C, 60.92; H, 3.21, N, 22.66.

1-(4'-Chlorophenyl)-8-phenyl-bis([1,2,4]triazolo)[4,3-*b*:3',4'-*f*]pyridazine (4e). Yield 70%; m.p. 256-258 °C; IR (KBr, cm^{-1}): transparent in the region of –NH str., 1629 (C=N str.); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.02-7.04 (d, 2H, J_o=8.3 Hz, Ph-3', 5'-H), 7.13-7.16 (t, 2H, J_o=7.8 Hz, Ph-3'', 5''-H), 7.22-7.24 (d, 2H, J_o=8.55 Hz, Ph-2', 6'-H), 7.28-7.31 (m, 3H, Ph-2'', 4'', 6''-H), 7.70-7.72 (d, 1H, *J*=10.45 Hz, pyridazine-H), 7.72-7.74 (d, 1H, *J*=10.4 Hz, pyridazine-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 118.63, 118.81, 126.16, 127.48, 128.71, 128.88, 129.49, 130.30, 131.16, 135.45, 146.83, 147.51, 147.61, 147.64. Anal. Calcd. for $C_{18}H_{11}ClN_6$: C, 62.34; H, 3.20, N, 24.24. Found: C, 62.66; H, 3.42, N, 24.59.

1-(4'-Chlorophenyl)-8-(3'',4''-dimethoxyphenyl)bis([1,2,4]triazolo)[4,3-*b*:3',4'-*f*]pyridazine (4f). Yield 87%; m.p. 150-152 °C; IR (KBr, cm^{-1}): transparent in the region of –NH str., 1631 (C=N str.); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.74 (s, 3H, Ph-4''-OCH_3), 3.86 (s, 3H, Ph-3''-OCH_3), 6.57-6.59 (d, 1H, J_o=8.3 Hz, Ph-5''-H), 6.66-6.67 (d, 1H, J_m=1.9 Hz, Ph-2''-H), 6.89-6.91 (dd, 1H, J_o=8.3 Hz, J_m=2.0 Hz, Ph-6''-H), 7.05-7.07 (d, 2H, J_o=8.4 Hz, Ph-3', 5'-H), 7.21-7.23 (d, 2H, J_o=8.45 Hz, Ph-2', 6'-H), 7.63-7.65 (d, 1H, *J*=10.2 Hz, pyridazine-H), 7.66-7.68 (d, 1H, *J*=10.15 Hz, pyridazine-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.02, 56.12, 111.15, 111.56, 117.86, 118.12, 118.48,

122.89, 125.01, 128.78, 129.74, 136.73, 146.51, 146.95, 147.19, 148.03, 148.63, 151.27. Anal. Calcd. for $C_{20}H_{15}ClN_6O_2$: C, 59.05; H, 3.72, N, 20.66. Found: C, 59.39; H, 3.33, N, 20.98.

1-(4'-Chlorophenyl)-8-(2''-fluorophenyl)bis([1,2,4]triazolo)[4,3-*b*:3',4'-*f*]pyridazine (4g). Yield 83%; m.p. 188-190 °C; IR (KBr, cm^{-1}): transparent in the region of –NH str., 1610 (C=N str.); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.56-6.60 (t, 1H, J_o=9.20 Hz, J= 0.85 Hz, Ph-5''-H), 7.03-7.09 (m, 2H, Ph-3', 5'-H), 7.13-7.16 (t, 1H, J_o=7.5 Hz, Ph-3''-H), 7.27-7.31 (m, 3H, Ph-2', 4'', 6'-H), 7.61-7.65 (t, 1H, J_o=7.4 Hz, J= 1.65 Hz, Ph-6''-H), 7.68-7.70 (d, 1H, J=10.3 Hz, pyridazine-H), 7.70-7.72 (d, 1H, J=10.3 Hz, pyridazine-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 115.99, 116.14-116.30 (d, $^2J_{C\text{-}F}$=16 Hz, Ph-3'', 5''-C), 118.03, 118.54, 123.94, 124.87, 128.96, 130.56, 130.98, 133.39-133.46 (d, $^3J_{C\text{-}F}$=9 Hz, Ph-2'', 6''-C), 137.51, 143.50, 146.63, 146.98, 147.25, 158.28-160.27 (d, $^1J_{C\text{-}F}$=199 Hz, Ph-4''-C). Anal. Calcd. for $C_{18}H_{10}ClFN_6$: C, 59.27; H, 2.76, N, 23.04. Found: C, 59.63; H, 2.89, N, 23.33.

1-(3'-Bromophenyl)-8-(4''-chlorophenyl)bis([1,2,4]triazolo)[4,3-*b*:3',4'-*f*]pyridazine (4h). Yield 81%; m.p. 190-192 °C; IR (KBr, cm^{-1}): transparent in the region of –NH str., 1612 (C=N str.); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.07-7.10 (t, 1H, J=8.8 Hz, Ph-5'-H), 7.11-7.13 (d, 2H, J=7.95 Hz, Ph-3'', 5''-H), 7.29-7.30 (m, 3H, Ph-H), 7.38-7.41 (t, 2H, J=8.8 Hz, Ph-H), 7.70-7.72 (d, 1H, J=10.25 Hz, pyridazine-H), 7.73-7.75 (d, 1H, J=10.3 Hz, pyridazine-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 118.71, 118.88, 122.28, 126.04, 128.38, 128.74, 129.02, 129.40, 129.59, 130.84, 130.95, 132.35, 133.10, 135.67, 146.15, 146.61, 147.61. Anal. Calcd. for $C_{18}H_{10}BrClN_6$: C, 50.79; H, 2.37, N, 19.74. Found: C, 50.42; H, 2.69; N, 19.51.

1-(4'-Chlorophenyl)-8-(4''-fluorophenyl)bis([1,2,4]triazolo)[4,3-*b*:3',4'-*f*]pyridazine (4i). Yield 67%; m.p. 254-256 °C; IR (KBr, cm^{-1}): transparent in the region of –NH str., 1617 (C=N str.); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.84-6.86 (m, 2H, Ph-3'', 5''-H), 7.10-7.12 (d, 2H, J_o=6.15 Hz, Ph-3', 5'-H), 7.25-7.30 (m, 4H, Ph-2'' , 6'', 2', 6'-H), 7.72 (s, 2H, pyridazine-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 115.75-115.98 (d, $^2J_{C\text{-}F}$ = 23 Hz, Ph-3'' , 5''-C), 118.64, 118.81, 123.95-123.99 (d, J = 4 Hz), 126.21, 126.23, 128.89, 131.36, 132.19-132.28 (d, $^3J_{C\text{-}F}$ = 9 Hz, Ph-2'' , 6''-C), 135.58, 146.66, 146.79, 147.52, 147.64, 162.17-164.65 (d, $^1J_{C\text{-}F}$ = 248 Hz, Ph-4''-C). Anal. Calcd. for $C_{18}H_{10}ClFN_6$: C, 59.27; H, 2.76, N, 23.04. Found: C, 59.59; H, 2.96, N, 23.42.

1-(4'-Chlorophenyl)-8-(furan-2''-yl)bis([1,2,4]triazolo)[4,3-*b*:3',4'-*f*]pyridazine (4j). Yield 68%; m.p. 160-162 °C; IR (KBr, cm^{-1}): transparent in the region of –NH str., 1606 (C=N str.); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.20-6.21 (dd, 1H, $J_{3'',\ 4''}$ =3.4 Hz, $J_{4'',\ 5''}$ =1.85 Hz, furan-4''-H), 6.83-6.84 (d, 1H, $J_{3'',\ 4''}$ =3.5 Hz, furan-3''-H), 7.01 (d, 1H, $J_{4'',\ 5''}$=1.45 Hz, furan-5''-H), 7.19-7.21 (d, 2H, J_o=8.35 Hz, Ph-3', 5'-H), 7.43-7.45 (d, 2H, J_o=8.5 Hz, Ph-2', 6'-H), 7.66-7.68 (d, 1H, J=10.45 Hz, pyridazine-H), 7.68-7.70 (d, 1H, J=10.4 Hz, pyridazine-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 112.37, 114.93, 117.79, 118.34, 124.44, 128.95, 129.12, 136.94, 138.56, 140.22, 145.34, 146.38, 146.62, 147.54. Anal. Calcd. for $C_{16}H_9ClN_6O$: C, 57.07; H, 2.69, N, 24.96. Found: C, 57.45; H, 3.01, N, 24.69.

1-(2'-Chlorophenyl)-8-(4''-chlorophenyl)bis([1,2,4]triazolo)[4,3-*b*:3',4'-*f*]pyridazine (4k). Yield 86%; m.p. 140-141 °C; IR (KBr, cm^{-1}): transparent in the region of –NH str., 1611 (C=N str.); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.95-6.98 (m, 1H, Ph-H), 7.03-7.10 (m, 3H, Ph-H), 7.22-7.27 (m, 3H, Ph-H), 7.48-7.50 (m, 1H, Ph-H), 7.71 (s, 2H, pyridazine-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 118.12, 118.41, 123.82, 126.76, 127.32, 128.95, 130.06, 130.64, 132.36, 132.66, 134.06, 137.45, 145.54, 146.39, 146.70, 147.11. Anal. Calcd. for $C_{18}H_{10}Cl_2N_6$: C, 56.71; H, 2.64; N, 22.05. Found: C, 56.49; H, 2.89, N, 22.41.

1-(4'-Fluorophenyl)-8-(4''-methoxyphenyl)bis([1,2,4]triazolo)[4,3-*b*:3',4'-*f*]pyridazine (4l). Yield 71%; m.p. 212-214 °C; IR (KBr, cm^{-1}): transparent in the region of –NH str., 1610 (C=N str.); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.80 (s, 3H, OCH_3), 6.62-6.64 (d, 2H, J_o=8.68 Hz, Ph-3'', 5''-H), 6.78-6.82 (t, 2H, J_o=8.56 Hz, Ph-3', 5'-H), 7.23-7.25 (d, 2H, J_o=8.68 Hz, Ph-2'', 6''H), 7.32-7.36 (dd, 2H, J_o=8.76 Hz, $J_{(m)HF}$=5.32 Hz, Ph-2', 6'-H), 7.67-7.69 (d, 1H, J=10.36 Hz, pyridazine-H), 7.70-7.72 (d, 1H, J=10.36 Hz, pyridazine-H). Anal. Calcd. for $C_{19}H_{13}FN_6O$: C, 63.33; H, 3.64; N, 23.32. Found: C, 63.71; H, 3.43, N, 23.69.

1-(4'-Chlorophenyl)-8-(2'',5''-dimethoxyphenyl)bis([1,2,4]triazolo)[4,3-*b*:3',4'-*f*]pyridazine (4m). Yield 72%; m.p. 210-212 °C; IR (KBr, cm^{-1}): transparent in the region of –NH str., 1610 (C=N str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.35 (s, 3H, Ph-5''-OCH_3), 3.71 (s, 3H, Ph-2''-OCH_3), 6.43-6.45 (d, 1H, J_o=9.12 Hz, Ph-3''-H), 6.76-6.79 (dd, 1H, J_o=9.12 Hz, J_m=3.16 Hz, Ph-4''-H), 6.92-6.93 (d, 1H, J_m=3.08 Hz, Ph-6''-H), 7.13 (s, 2H, Ph-3', 5'-H), 7.42 (s, 2H, Ph-2', 6'-H), 7.84-7.86 (d, 1H, *J*=10.2 Hz, pyridazine-H), 7.87-7.89 (d, 1H, *J*=10.16 Hz, pyridazine-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.67, 56.22, 112.40, 116.52, 116.88, 117.93, 118.42, 118.83, 125.24, 128.68, 135.66, 145.32, 146.90, 147.11, 147.40, 150.88, 153.40. Anal. Calcd. for $C_{20}H_{15}ClN_6O_2$: C, 59.05; H, 3.72; N, 20.66. Found: C, 59.32; H, 3.49, N, 20.96.

Cytotoxicity viability assay

Cells were seeded at a density of 50,000 per mL into a 96-well plate and treated with various compounds at a final concentration of 10 µM. The cells were then incubated for 48 h. An MTT cell proliferation kit from ATCC (#30-1010K) was used to assess cell viability. At the end of incubation, 10 µL of MTT reagent was added to each well, and the cells were placed back in the incubator for 4 h. Subsequently, 100 µL of detergent (from the kit) was added, and absorbance at 570 nm wavelength was recorded using a BioTek Synergy 2 spectrophotometer. Data was calculated as the percentage of cell survival using the following formula:

% Cell survival = $(100/A_t * A_s)$

Where A_t and A_s are the absorbance of wells treated with test compounds and solvent control, respectively.

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Supplementary Material

^{1}H NMR, ^{13}C NMR and biological assay arefacilitiesd in the Supplementary Information file.

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