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ARTICLE

Synthesis, characterization, and antidiabetic activity of 6-methoxyimidazo[1,2-*b*]pyridazine derivatives

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The present article describes the synthesis, characterization, and antidiabetic activity of 6-methoxyimidazo[1,2-*b*]pyridazine derivatives **7a-l**. The synthetic sequence for the preparation of these derivatives involves the following prominent reactions: (a) *Step 1*: involves the high-pressure amination reaction; (b) *Step 2*: involves the Zinc oxide nanoparticle-catalyzed cyclization reaction; (c) *Step 3*: involves the methoxylation; (d) *Step 4*: involves the bromination reaction; (e) *Step 5*: involves the Suzuki coupling reaction; (f) *Step 6*: involves the reduction of the $-NO_2$ group; (g) *Step 7*: involves Boc protection of the 1^o amino group (h) *Step 8*: involves diazotization of the amine group and finally the last of the synthesis (i) *Step 9*: involves the saponification of the ethyl ester group. Furthermore, the structures of the newly synthesized 6-methoxyimidazo[1,2-*b*]pyridazine derivatives **7a–l** were determined using ^{1}H NMR, ^{13}C NMR, and Mass and IR spectroscopic analyses. These derivatives were evaluated for their antidiabetic property and the results revealed that most of the compounds exhibited significant potency. It is worth mentioning that compounds **7b** (69.87%), **7f** (69.0%), **7h** (68.79%), and **7l** (68.61%) with substitution R = *para*-NH_2, *para*-COOH, *meta*-NH_2, and *meta*-COOH, respectively, showed significant (good) hypoglycemic activity when compared to the standard drug insulin (50 mg/kg b.w) in reducing the blood glucose level.

KEYWORDS

6-methoxyimidazo[1,2-*b*]pyridazine, antidiabetic, Suzuki reaction, zinc oxide nanoparticles

1 | INTRODUCTION

The chemistry of pyridazines and their fused heterocyclic derivatives has attracted significant attention due to their synthetic and operative biological importance. Numerous derivatives of pyridazine including 1,2,4-triazole, imidazole, isoxazole, and triazine rings have been revealed to show potential for an extensive range of applications in biological and therapeutic areas.[1,2] Some of the examples of imidazole and pyridazine rings that are fused together to form unique heterocyclic ring systems are imidazo[1,2-*b*]pyridazine[3] and imidazo[4,5-*d*] pyridazine.[4]

Presently, imidazopyridazines are importantly considered by researchers because of their varied biological activities viz., anticancer[5] and activity against human immunodeficiency virus.[6]

Several imidazo[1,2-*b*]pyridazines have demonstrated biological activity including inhibition of the central nervous system, antipyretic and hypothermal activities, anticonvulsant activity, analgesic, and antispasmotic activities. In addition to the above activities, imidazo[1,2-*b*]pyridazine has been shown to exhibit the following biological activities such as antitumor,[5] antileukemic,[7] antiviral,[8] and inhibition of protein kinase,[9] mTOR,[10] IKKβ,[11] VEGFR2,[12] and Syk.[13]

The combination of two moieties upsurges the biological activity of both and thus it was worth synthesizing some new heterocyclic derivatives having two moieties in the

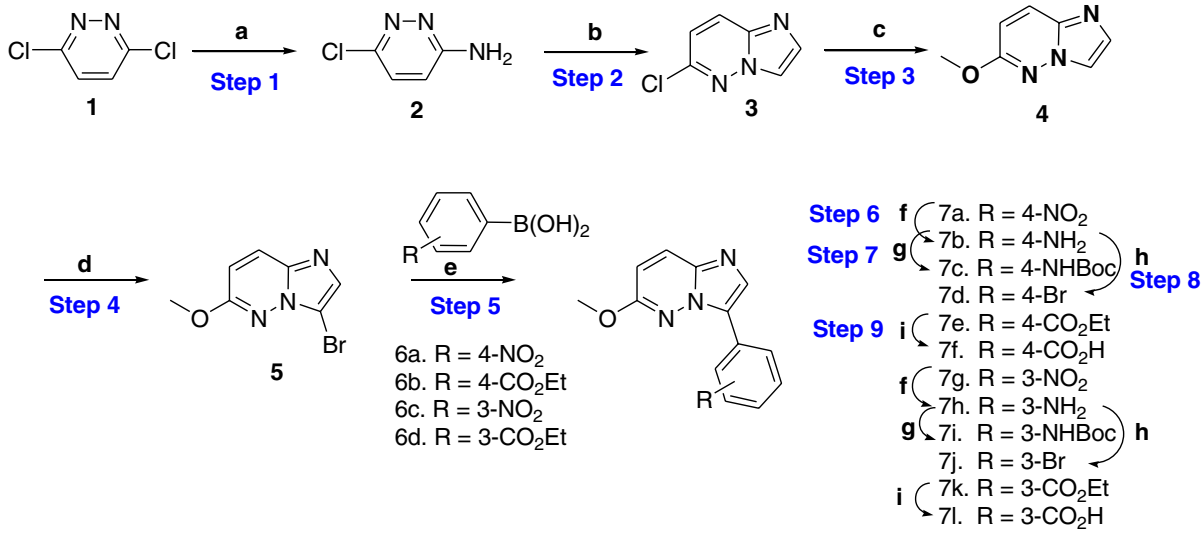
same molecules. Therefore encouraged at the importance of these heterocyclic nuclei, it is of interest to synthesize new imidazo[1,2-*b*]pyridazine derivatives. The present article describes the synthesis, characterization, and antidiabetic activity of 6-methoxyimidazo[1,2-*b*]pyridazine derivatives. To the best of our knowledge, so far, the synthesis and antidiabetic properties of these derivatives have not been reported in the literature.

2 | RESULTS AND DISCUSSION

The synthesis of 6-methoxyimidazo[1,2-b]pyridazine derivatives **7a–l** is presented in Scheme 1**.** Amination of 3,6-dichloropyridazine **1** in the presence of aq.ammonia in a pressure bomb vessel at 125°C for 24 hr produced 6-Chloropyridazin-3-ylamine **2**. ZnO NP-catalyzed[14] cyclization of amine **2** in the presence of 40% aq. chloroacetaldehyde in *n*-butanol at 100°C for 3 hr produced 6-chloro-imidazo[1,2-*b*] pyridazine **3.** Methoxylation of chloro compound **3** in the presence of sodium methoxide in 2-methyl-tetrahydrofuran (2-Me THF) at reflux for 2 hr produced 6-methoxy-imidazo [1,2-*b*]pyridazine **4**. Bromination of 6-methoxy-imidazo [1,2-*b*]pyridazine **4** in the presence of 1,3-dibromo-5,5-dimethylhydantoin in dichloromethane at room temperature for 2 hr produced 3-Bromo-6-methoxy-imidazo[1,2-*b*] pyridazine **5**. The Suzuki reaction of bromide **5** with aryl boronic acid **6a–6d** in the presence of $Pd(PPh_3)_4$, K_2CO_3 in 2-Me-THF, and water at reflux for 10 hr resulted in the corresponding heteroaryl-aryl-coupled products **7a, 7e, 7g,** and **7k,** respectively. Reduction of nitro compounds **7a** and **7g** in the presence of stannous chloride, conc. HCl in ethanol at room temperature for 4.5 hr gave the corresponding amine compounds **7b** and **7h**. Bocylation of **7b** and **7h** in the presence of Boc anhydride, aq.10% acetic acid in 1,4-dioxane at room temperature for 12 hr gave the corresponding bocylated compounds **7c** and **7i.** Diazotization of amine compounds **7b** and **7h** in the presence of *para*-toluenesulfonic acid, sodium nitrite, and potassium bromide in acetonitrile at 20°C, 4 hr produced the respective bromide compounds **7d** and **7j**. Hydrolysis of **7e** and **7k** in the presence of lithium hydroxide monohydrate in the mixture of THF:MeOH:water at room temperature for 16 hr resulted in the corresponding carboxylic acids **7f** and **7l**.

The structural characterization of all the synthesized 6-methoxyimidazo[1,2-b]pyridazine derivatives **7a–l** and their associated intermediates was carried out using ^{1}H NMR, ^{13}C NMR, IR, and Mass spectroscopy techniques. As a representative example, the structural elucidation of 4-(6-methoxy-imidazo[1,2-*b*]pyridazin-3-yl)-benzoic acid ethyl ester **7e** is described here. *^{1}H NMR interpretation*: The proton signals resonating at 8.30 ppm as singlets with one proton integration are assigned to the imidazole ring, while the proton signals resonating at 8.14 and 7.03 ppm as doublets (J = 9.7 Hz) with one proton integration are assigned to the pyridazine ring. The proton signals resonating at 8.39 and 8.09 ppm as doublets (J = 8.6 Hz) with two proton integration correspond to a new *para*-substituted ethyl benzoate (aromatic) ring. The ethyl group protons flanked to the aromatic ring resonated at 4.34 ppm (quartet, 2H) and 1.34 ppm (triplet, 3H), respectively, and the characteristic methoxy group protons resonated at 4.05 ppm as singlets.

Mass interpretation: *m/z*, 298.1 with $[M + H]^+$ corresponds to the molecular weight of the desired compound **7e**.



SCHEME 1 Synthesis of 6-methoxyimidazo[1,2-b]pyridazine derivatives **7a–l**. *Reaction conditions*: (a) Aq. Ammonia, pressure bomb vessel, 125°C, 24 hr; (b) 40% aq. Chloroacetaldehyde, ZnO NP's, *n*-butanol, 100°C, 3 hr; (c) sodium methoxide, 2-me THF, reflux, 2 hr; (d) 1,3-Dibromo-5,5-dimethylhydantoin, dichloromethane, room temperature, 2 hr; (e) arylboronic acid **6a**–**6d**, potassium carbonate, $Pd(PPh_3)_4$, 2-me-THF, water, reflux, 10 hr; (f) stannous chloride dehydrate, conc. HCl, ethanol, room temperature, 4.5 hr; (g) Boc anhydride, aq. 10% acetic acid, 1,4-dioxane, room temperature, 12 hr; (h) *para*-toluenesulfonic acid, sodium nitrite, potassium bromide, acetonitrile, 20°C, 4 hr; and (i) Lithium hydroxide monohydrate, THF: MeOH: Water, room temperature, 16 hr

IR interpretation: The stretching frequencies in the region 2,981, 1,726, 1,454, 1,260, and 1,099 cm^{-1} correspond to –C–H, –C=O, –C=C, –C–N, and C–O groups, respectively. The above analytical interpretation thus confirms the structures of the compound **7e**. ***^{13}C NMR interpretation***: The spectra revealed that the compound contains 16 carbon atoms. A peak at 56.06 is assigned to "methoxy" carbon and the carbon signal at 168.32 is the characteristic carbonyl signal (carboxylic group).The peaks at 165.66, 121.92, and 123.84 are assigned to the pyridazine ring, while the peaks in the region 139.06, 132.34, and 117.48 are assigned to the imidazole ring. The carbon signals in the region 125.78–130.42 and 143.12 are assigned to the benzene ring. Similarly, the structure of the remaining compounds in the series was characterized as described above.

2.1 | Antidiabetic activity

The results of the antidiabetic activity of the synthesized 6-methoxyimidazo[1,2-b]pyridazine derivatives **7a–l** are tabulated in Table 1. Insulin was used as a standard drug for the purpose of the study and showed 70.28% blood glucose-lowering activity at the dose of 50 mg/kg.p.o. All these derivatives exhibited significant hypoglycemic properties, but with a certain degree of variation, and showed a significant reduction in blood glucose as compared to control diabetic rats at 50 mg/kg body weight for 3rd and 7th days.

From Table 1, it is observed that compounds **7b** (69.87%), **7f** (69.0%), **7h** (68.79%), and **7l** (68.61%) with substitution R = *para*-NH_2, *para*-COOH, *meta*-NH_2, and *meta*-COOH, respectively, showed significant (good) hypoglycemic activity when compared to the standard drug insulin (50 mg/kg b.w) in reducing the blood glucose level, while the compounds **7c** (67.08%), **7e** (66.34%), **7i** (65.15%), and **7k** (64.54%) with substitution R = *para*-NHBoc, *para*-CO_2Et, *meta*-NHBoc, and *meta*-CO_2Et showed moderate hypoglycemic activity. The remaining compounds in the series viz., compounds **7a** (58.55%), **7d** (54.91%), **7g** (51.21%), and **7j** (53.23%) with substitution R = *para*-nitro, *para*-Bromo, *meta*-Nitro *para*-bromo, *meta*-nitro, and *meta*-bromo displayed weak hypoglycemic activity. Furthermore, it is observed that *para* substituted "R" group in the main scaffold exhibited more potency compared to the *meta* substituted 'R' group especially the following groups such as *para*-NH_2 and *para*-COOH.

Further exploration of the above-established results toward the synthesis, toxicity studies, and mode of action of hypoglycemic activity may lead to the development of an efficient drug candidate for diabetes mellitus.

3 | EXPERIMENTAL

3.1 | Materials and methods

All the chemicals were commercially procured from Alfa Aesar. Melting points were determined in open glass capillaries on a Stuart SMP30 apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Shimadzu FTIR 8400S spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker DPX 400 spectrophotometer using tetramethylsilane (TMS) as internal standard, $CDCl_3$ and DMSO-d_6 as solvents and the signals are reported as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet), and coupling constants in Hz. HRMS spectra were recorded on a XevoQ-Tof mass spectrometer. Elemental analysis was performed

TABLE 1 Results of hypoglycemic effects of hydrazone derivatives **7a–l**

	Blood glucose level[a] (mg/dL)			
Treatment (mg/kg b.Wp.o)	**Day 0**	**Day 3**	**Day 7**	**Hyperglycemic activity (%)**
Control (0.5% CMC)	342.0 ± 1.44	368.4 ± 2.84**	387.2 ± 3.18**	
Insulin	350.00 ± 2.26	146.30 ± 2.74**	104.10 ± 1.56**	70.28
7a	358.33 ± 3.84	272.65 ± 4.68**	148.50 ± 4.25**	58.55
7b	355.20 ± 3.16	277.44 ± 5.18**	107.00 ± 4.36**	69.87
7c	346.44 ± 1.86	245.22 ± 3.16**	115.50 ± 5.65**	67.08
7d	351.88 ± 3.22	288.20 ± 4.40**	158.64 ± 1.92**	54.91
7e	341.46 ± 4.40	251.28 ± 4.46**	114.92 ± 2.82**	66.34
7f	359.46 ± 2.85	281.84 ± 2.88**	111.40 ± 3.74**	69.00
7g	339.54 ± 2.22	294.46 ± 2.92	165.64 ± 5.01	51.21
7h	356.64 ± 3.36	276.00 ± 4.32**	111.30 ± 2.88**	68.79
7i	337.38 ± 1.54	234.42 ± 2.46**	117.55 ± 3.60**	65.15
7j	353.72 ± 4.22	291.84 ± 1.65	165.40 ± 3.68	53.23
7k	339.78 ± 3.85	240.66 ± 2.13**	120.48 ± 1.96**	64.54
7l	348.88 ± 2.58	294.32 ± 5.28**	108.50 ± 3.82**	68.61

[a] Values are represented as mean ± *SEM*. Data were analyzed using analysis of variance and group means were compared with the Tukey–Kramer Post ANOVA test. The values were considered when $p < 0.01$. **$p < 0.001$; Tabulated data are expressed as mean ± *SEM*; ($n = 6$).

on a perkin CHNS elemental analyzer. Silica gel 60F24 of Merck precoated plates was employed for their thin layer chromatography (TLC) analysis to check the purity of the compounds, the spot being located under UV light and iodine vapors.

3.1.1 | 6-Chloro-pyridazin-3-ylamine (2)

A mixture of 3,6-dichloropyridazine **1** (5 g, 33.56 mmol) and aq. ammonia (125 mL) was taken in a steel pressure bomb vessel and heated at 125°C for 24 hr. The reaction mixture was cooled to room temperature for 24 hr and the precipitated solid was filtered and washed with water followed by pet-ether and dried to obtain compound **2**. Brown solid; *Yield*: 3.0 g, 70%; M.p.: 226–228°C; IR (KBr): υ_{max} 3,473 (–N–H str), 3,136 (–C–H str), 1,634 (–C=N str), 1,551 (–C=C– str), 1,051 –C–N str), and 753 (C–Cl) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.37(d, J = 9.5 Hz, 1H), 6.85(d, J = 9.5 Hz, 1H), and 6.62 (brs, 2H);^{13}C NMR (100 MHz, DMSO-d_6): δ 121.32, 130.51, 145.02, and 160.63; ESI MS: *m/z*, 130 $[M + H]^+$; Elemental analysis $C_4H_4ClN_3$ calcd. (found) %: C 37.09 (36.99), H 3.11 (3.10), and N 32.44 (32.40).

3.1.2 | 6-Chloro-imidazo[1,2-*b*]pyridazine (3)[14]

To a suspension of compound **2** (2.5 g, 19.38 mmol), 40% aq. chloroacetaldehyde (4.54 g, 58.14 mmol) in *n*-butanol (30 mL), ZnO nanoparticles[14] (15 mol%) were added and heated to 100°C for 3 hr. The reaction mixture was filtered while hot and the catalyst was recovered back. The filtrate was cooled to 0°C and the precipitated solid was collected by filtration and washed with *n*-Hexane to obtain compound **3**. Light Brown solid; *Yield*: 2.6 g, 93%; M.p.: 120–122°C; IR (KBr): υ_{max} 3,081 (–C–H str), 1,607 (–C=N str), 1,513 (–C=C– str), 1,123 (–C–N str), and 791 (C–Cl) cm^{-1}; ^{1}H NMR (400 MHz,DMSO-d_6) δ: 8.5 (brs, 1H), 8.32 (brs, 1H), 7.95 (brs, 1H), and 7.54 (brs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.69, 139.67, 130.64, 128.56, 126.64, and 115.68; ESI MS: *m/z*, 154.1 $[M + H]^+$; Elemental analysis, $C_6H_4ClN_3$, calcd. (found) %: C 46.93 (46.90), H 2.63 (2.59), and N 27.36 (27.31); Note: the ZnO NP catalyst was recovered from the reaction by centrifugation. After washing with EtOAc and drying at 300°C, the recovered ZnO NP was reused three consecutive times.

3.1.3 | 6-Methoxy-imidazo[1,2-*b*]pyridazine (4)

To a solution of compound **3** (5 g, 32.55 mmol) in 2-MeTHF (30 mL), sodium methoxide (3.5 g, 65.1 mmol) was added and heated to reflux for 2 hr. The reaction mixture was cooled to rt and poured into ice cold water (200 mL), further extracted with 2-Me-THF (4 × 25 mL), and the combined organics were washed with water (2 × 50 mL), brine (3 × 20 mL), dried over Na_2SO_4, concentrated to obtain compound **4.** Pale yellow solid; *Yield*:3.4 g, 75%; M.p.: 129–130°C; IR (KBr): υ_{max} 3,007 (–C–H str), 1,460 (–C=N str), 1,410 (–C=C– str), and 1,105 (–C–N str) cm^{-1}; ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.79 (d, J = 9.5, 1H), 7.74 (s, 1H), 7.6 (s, 1H), 6.68 (d, J = 9.6 Hz, 1H), and 4.0 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 1.65.7, 135.1, 127.8, 125.5, 119.3, 115.4, and 55.9; ESI MS: *m/z*, 150.1 $[M + H]^+$; Elemental analysis, $C_7H_7N_3O$, calcd. (found) %: C 56.37 (56.28), H 4.73 (4.69), and N 28.17 (28.15).

3.1.4 | 3-Bromo-6-methoxy-imidazo[1,2-*b*]pyridazine (5)

To a solution of compound **4** (5 g, 33.52 mmol) in dichloromethane (100 mL), 1,3-Dibromo-5,5-dimethylhydantoin (5.36 g, 18.77 mmol) was added. The reaction mixture was stirred at room temperature for 2 hr. After completion of the reaction (checked by TLC), it was diluted with water (50 mL) and stirred for 15 min. The organic layer was separated and washed with water followed by brine solution, and dried over Na_2SO_4, filtered, and evaporated under reduced pressure to obtain compound **5**. Pale yellow solid; *Yield*: 4.4 g, 58%; M.p.: 201–202°C; IR (KBr): υ_{max} 3,007 (–C–H str), 1,460 (–C=N str), 1,410 (–C=C– str), 1,105 (–C–N str), and 811 (C–Br str) cm^{-1}; ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.79 (d, J = 9.7 Hz, 1H), 7.6 (s, 1H), 6.75 (d, J = 9.7 Hz, 1H), and 4.1 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.22, 138.14, 138.04, 130.01, 126.23, 120.06, and 56.13; ESIMS: *m/z*, 230 $[M + 2]^+$; Elemental analysis, $C_7H_6BrN_3O$, calcd. (found) %: C 36.87 (36.81), H 2.65 (2.63), and N 18.43 (18.40).

3.2 | General experimental procedure for the preparation of compounds 7a, 7e, 7g, and 7k (Suzuki reaction)

To a stirred solution of **5** (1 g, 4.38 mmol) and aryl boronic acids **6a–6d** (4.38 mmol) in 2-methyl tetrahydrofuran (2-Me-THF) (25 mL) and H_2O (10 mL), K_2CO_3 (0.72 g, 5.25 mmol) was added. The reaction mixture was degassed and then under the flow of nitrogen, Pd $(PPh_3)_4$ (0.1 g, 0.088 mmol) was added and heated to reflux for 10 hr. After the completion of the reaction, checked by TLC, the reaction mixture was cooled to room temperature and diluted with water (20 mL). The organic layer was washed with water, followed by brine solution, dried over Na_2SO_4, filtered, and evaporated under reduced pressure to obtain the crude compounds **7a**, **7e**, **7g,** and **7k**. The crude products were purified using column chromatography (silica gel, 100–200 mesh, eluted with 35% isopropylacetate-*n*-Hexane) to afford the respective purified compounds **7a**, **7e**, **7g,** and **7k**.

3.2.1 | 6-methoxy-3-(4-nitrophenyl)imidazo[1,2-*b*] pyridazine 7a

Yellow solid; M.p.: 125–126°C; *Yield*: (1 g, 72%); IR (KBr): υ_{max} 3,064 (–C–H str), 1,595 (–C=N str), 1,526 (C–NO_2 str) 1,450 (–C=C– str), 1,142 (–C–N str), and 1,016 (C–O–C) cm^{-1}; ^{1}H NMR (400 MHz, DMSO–d_6) δ 8.58 (d,

J = 8.4 Hz 2H), 8.48 (s, 1H), 8.32 (d, J = 9.5 Hz, 1H), 8.20 (d, J = 8.6 Hz, 2H), 7.15 (d, J = 9.7 Hz, 1H), and 3.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.46, 148.33, 140.11, 135.62, 128.32, 125.18, 122.82, 119.05, 115.92, and 111.26; ESI MS: *m/z,* 271.3 $[M + H]^+$; Elemental analysis, $C_{13}H_{10}N_4O_3$, calcd. (found) %: C 57.78 (57.73), H 3.73 (3.69), and N 20.73 (20.65).

3.2.2 | 4-(6-Methoxy-imidazo[1,2-*b*]pyridazin-3-yl)-benzoic acid ethyl ester (7e)

Yellow solid; M.p.: 88–89°C; *Yield*: (1 g, 67%); IR (KBr): υ_{max} 2,981 (–C–H str), 1,726 (–C=O str), 1,454 (–C=C– str), 1,099 (–C–N str), and 1,260 (C–O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (d, J = 8.6 Hz 2H), 8.30 (s, 1H), 8.14 (d, J = 9.5 Hz, 1H), 8.09 (d, J = 8.6 Hz, 2H), 7.03 (d, J = 9.7 Hz, 1H), 4.34 (q, J = 7.22 Hz, 2H), 4.05 (s, 3H), and 1.34 (t, J = 7.22 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.32, 165.66, 143.12, 139.06, 132.34, 130.42, 128.22, 125.78, 123.84, 121.92, 117.48, 69.33, 56.06, and 15.26; ESI MS: *m/z,* 298.1 $[M + H]^+$; Elemental analysis: $C_{16}H_{15}N_3O_3$, calcd. (found) %: C 64.64 (64.61), H 5.09 (5.04), and N 14.13 (14.08).

3.2.3 | 6-methoxy-3-(3-nitrophenyl)imidazo[1,2-*b*] pyridazine 7g

Light brown solid; M.p.:134–135°C; *Yield*: 663 mg, 56%; IR (KBr): υ_{max} 3,064 (–C–H str), 1,595 (–C=N str), 1,526 (C–NO_2 str) 1,450 (–C=C– str), 1,142 (–C–N str), and 1,016 (C–O–C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.22 (s, 1H), 8.10 (d, J = 9.5 Hz, 1H), 7.92 (d, J = 7.4 Hz, 1H), 7.76 (t, J = 8 Hz, 1H), 7.50 (d, J = 1.56 Hz, 1H), 6.90 (d, J = 9.5 Hz, 1H), and 4.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.72, 148.93, 135.12, 134.06, 133.66, 130.26, 125.52, 122.13, 121.15, 120.06, 119.34, 122.08, and 55.92; ESI MS:*m/z,* 271.1 $[M + H]^+$; Elemental analysis: $C_{13}H_{10}N_4O_3$, calcd. (found) %: C 57.78 (57.71), H 3.73 (3.66), and N 20.73 (20.70).

3.2.4 | Ethyl3-(6-methoxyimidazo[1,2-*b*]pyridazin-3-yl) benzoate 7k

Light brown solid; M.p.: 92–94°C; *Yield*: 663 mg, 56%; IR (KBr): υ_{max} 2,972 (–C–H str), 1,719 (–C=O str), 1,437 (–C=N str), 1,240 (–C–O str), and 1,119 (C–N) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.30 (s, 1H), 8.26 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 9.5 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H),7.55 (d, J = 2.2 Hz, 1H), 6.88 (d, J = 9.7 Hz, 1H), 3.99 (s, 3H); 4.30 (q, J = 7.20 Hz, 2H), and 1.30 (t, J = 7.22 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.04, 165.74, 135.12, 133.06, 131.84, 130.76, 130.31, 129.95, 129.23, 125.52, 122.04, 120.08, 119.35, 60.92, 55.96, and 14.14; ESI MS: *m/z,* 298.3 $[M + H]^+$; Elemental analysis: $C_{16}H_{15}N_3O_3$, calcd. (found) %: C 64.64 (64.60), H 5.09 (5.04), and N 14.13 (14.10).

3.3 | Experimental procedure for the preparation of compounds 7b and 7h: (reduction of NO_2 to NH_2)

To a stirred solution of ethanol (20 mL) containing compound **7a** (1 g, 3.7 mmol), stannous chloride dihydrate ($SnCl_2.2H_2O$, 2.7 g, 11.84 mmol) and concentrated HCl (0.5 mL) were added. The reaction mixture was stirred at room temperature for 4.5 hr. After completion of the reaction, (checked by TLC), the reaction mixture was diluted with isopropyl acetate (150 mL) and water (150 mL). The pH of the reaction contents was adjusted to 12–13 with 20% aq sodium hydroxide solution (30 mL). The inorganic precipitate was filtered through the celite bed and the organic layer was washed with water (3 × 25 mL), brine solution (2 × 25 mL), and dried over anhydrous sodium sulfate and evaporated to afford compound **7b,** and was utilized in the next step without any further purification. Yellow viscous liquid; *Yield*: 0.72 g, 82%; Similarly, compound **7h** was prepared from the corresponding 3-nitro compound **7g** as per the above procedure.

*4-(6-methoxyimidazo[1,2-b]pyridazin-3-yl)benzenamine (**7b**)*: The crude compound was utilized as such in the next step.

*3-(6-Methoxy-imidazo[1,2-b]pyridazin-3-yl)phenylamine (**7h**)*: Light brown syrupy liquid; *Yield*: Quantitative yield; IR (KBr): υ_{max} 3,484 (–N–H str), 2,980 (–C–H str), 1,605 (–C=N str), 1,468 (–C=C– str), 1,213 (–C–O str), and 1,060 (C–N str) cm^{-1}; ^{1}HNMR (400 MHz, DMSO-d_6, D_2O exchangeable) δ 8.27 (s, 1H), 8.23 (d, J = 9.6 Hz, 1H), 7.92 (brs, 1H), 7.78 (brs, 1H), 7.48 (m, 1H), 7.20–7.10 (m, 2H), and 4.07 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.74, 148.76, 135.16, 133.92, 130.13, 125.53, 122.02, 120.02, 119.33, 117.52, 116.31, 114.28, and 55.92; ESI MS*: m/z*, 241 $[M + H]^+$; Elemental analysis: $C_{13}H_{12}N_4O$, calcd. (found) %: C 64.99 (64.93), H 5.03 (4.99), and N 23.32 (23.28).

3.4 | Experimental procedure for the preparation of compounds 7c and 7i: (Boc protection of NH_2 to NHBoc)

To a solution of compound **7h** (0.5 g, 2.08 mmol) in 10% aqAcOH (20 mL), a solution of Boc-anhydride (Boc_2O) (0.48 g, 2.18 mmol) in 1,4-dioxane (20 mL) was added. The reaction mixture was stirred at room temperature for 12 hr. After the completion of the reaction (checked by TLC), water (30 mL) was added and the mixture was extracted with cyclopentyl methyl ether (2 × 25 mL). The aqueous phase was basified to pH 14 using 1N NaOH and extracted with cyclopentyl methyl ether (2 × 25 mL). The combined organic layer was washed with water (2 × 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to obtain compound **7i**. Pale yellow syrupy liquid; *Yield*: 600 mg, 85%; Similarly, compound **7c** was prepared from the corresponding amino compound **7b** as per the above procedure.

3.4.1 | [4-(6-Methoxy-imidazo[1,2-*b*]pyridazin-3-yl)-phenyl] carbamic acid tert-butyl ester (7c)

Compound **7c:** Off-white solid; M.p.: 78–79°C; *Yield*:1 g, 67%; IR (KBr): υ_{max} 3,310 (–N–H str), 2,932 (–C–H str), 1,648 (–C=O str), 1,502 (–C=N str), 1,427 (–C=C– str), 1,152 (–C–N str), and 1,247 (C–O str) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 6.8 Hz, 2H), 7.89–7.80 (m, 2H), 7.50 (d, J = 8.5 Hz, 2H), 6.73 (d, J = 9.7 Hz, 1H), 6.59 (br s, 1H), 4.05 (s, 3H), and 1.75 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.48, 154.02, 138.22, 135.66, 130.34, 126.20, 123.32, 121.88, 117.78, 115.66, 80.05, 56.02, and 26.82; ESI MS: *m/z,* 341 $[M + H]^+$.Elemental analysis: $C_{18}H_{20}N_4O_3$, calcd. (found) %: C 63.52 (63.50), H 5.92 (5.86), and N 16.46 (16.42).

3.4.2 | [3-(6-Methoxy-imidazo[1,2-*b*]pyridazin-3-yl)-phenyl] carbamic acid tert-butyl ester (7i)

Compound **7i**: Pale yellow syrupy liquid; *Yield*: 600 mg, 85%; IR (KBr): υ_{max} 3,313 (–N–H str), 2,934 (–C–H str), 1,685 (–C=O str), 1,543 (–C=N str), 1,482 (–C=C– str), 1,174 (C–O str), and 1,107 (–C–N str) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, D_2O exchange) δ 8.46 (s, 1H), 7.92 (s, 1H), 7.85(d, J = 9.5 Hz, 1H), 7.70 (d, J = 7.4 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.20 (d, J = 1.56 Hz, 1H), 6.74 (d, J = 9.5 Hz, 1H), 4.10 (s, 3H), and 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.72, 153.95, 136.42, 135.16, 133.32, 129.58, 125.53, 123.14, 122.08, 121.62, 119.50, 119.32, 79.51, 55.93, and 28.5 (3C); ESI MS: *m/z,* 341.0 $[M + H]^+$. Elemental analysis: $C_{18}H_{20}N_4O_3$, calcd. (found) %: C 63.52 (63.47), H 5.92 (5.88), and N 16.46 (16.41).

3.5 | Experimental procedure for the preparation of compounds 7d and 7j: (diazotization reaction)

To a solution of compound **7b** (1 g, 4.16 mmol) in acetonitrile (15 mL), para-toulenesulfonic acid (2.15 g, 12.48 mmol) was added. The resulting suspension of amine salt (**7b**) was cooled to 10–15°C and to this was added, gradually, a solution of sodium nitrite (0.57 g, 8.26 mmol) and potassium bromide (1.24 g, 10.42 mmol) in water (5 mL). The reaction mixture was stirred for 15 min then allowed to come to 20°C and stirred for 4 hr. To the reaction mixture was then added water (30 mL), 1M aqueous sodium bicarbonate solution (adjusted to pH = 9–10), and sodium thiosulfate(2M, 12 mL). The precipitated was filtered, washed with pet-ether, and dried to obtain compound **7d**. Pale yellow solid; *Yield*: 0.73 g, 58%; similarly, compound **7j** was prepared from the corresponding amino compound **7h** as per the above procedure.

3.5.1 | 3-(4-bromophenyl)-6-methoxyimidazo[1,2-*b*] pyridazine (7d)

White solid; M.p.: 133–134°C; *Yield*: (1 g, 82%); IR (KBr): υ_{max} 2,988 (–C–H str), 1,454 (–C=N str), 1,408 (–C=C– str), 1,110(–C–N str), and 806 (C–Br str) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.52 (d, J = 8.2 Hz 2H), 8.42 (s, 1H), 8.28 (d, J = 9.5 Hz, 1H), 8.10 (d, J = 8.6 Hz, 2H), 7.10 (d, J = 9.7 Hz, 1H), and 3.98 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.76, 135.14, 132.26 (2C), 132.10, 129.72 (2C), 125.54, 123.18, 122.06, 120.08, 119.33, and 55.92; ESI MS: *m/z,*305.1 $[M + H]^+$; Elemental analysis: $C_{13}H_{10}BrN_3O$, calcd. (found) %: C 51.34 (51.30), H 3.31 (3.29), and N 13.82 (13.77).

3.5.2 | 3-(3-bromophenyl)-6-methoxyimidazo[1,2-*b*] pyridazine (7j)

White solid;M.p.: 141–142°C; *Yield*: 1 g, 85%; IR (KBr): υ_{max} 2,992 (–C–H str), 1,450 (–C=N str), 1,412 (–C=C– str), 1,104(–C–N str), and 810 (C–Br str) cm^{-11}; H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.92 (s, 1H,), 7.85 (d, J = 9.5 Hz, 1H), 7.70 (d, J = 7.4 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.20 (d, J = 1.56 Hz, 1H), 6.74 (d, J = 9.5 Hz, 1H), 4.10 (s, 3H), and 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.73, 135.36, 135.18, 133.13, 131.56, 131.74, 126.52, 125.55, 123.64, 122.10, 120.08, 119.38, and 55.94; ESI MS: *m/z*, 341.0$[M + H]^+$; Elemental analysis: $C_{13}H_{10}BrN_3O$, calcd. (found) %: C 51.34 (51.30), H 3.31 (3.29), and N 13.84 (13.81).

3.6 | Experimental procedure for the preparation of 7f and 7l: (hydrolysis of ethyl ester)

To a solution of compound **7e** (1 g, 3.39 mmol) in a mixture of THF (30 mL), MeOH (6 mL), and H_2O (6 mL), LiOH. H_2O (0.42 g, 10.17 mmol) was added at room temperature and stirred for 16 hr. The reaction mixture was concentrated in vacuo and the residue was dissolved in water (30 mL), washed with EtOAc (30 mL), the aqueous layer was acidified (pH 2) with 6N HCl, and the precipitated solid was collected by filtration, washed with water, and dried to obtain **7f**.

3.6.1 | 4-(6-Methoxy-imidazo[1,2-*b*]pyridazin-3-yl)-benzoic acid (7f)

Pale brown solid; M.p.:150–152°C; *Yield*: 0.80 g, 88%; IR (KBr): υ_{max} 3,437 (–O–H str), 2,970 (–C–H str), 1,697 (–C=O str), 1,550 (–C=N str), 1,431 (–C=C– str), 1,213 (C–O), and 1,117 (–C–N str) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.42 (brs, 1H), 8.33 (d, J = 8.0 Hz, 2H), 8.23 (brs, 1H), 8.09 (d, J = 8 Hz, 2H), 7.20 (brs, 1H), and 4.05 (s, 3H);^{13}C NMR (100 MHz, DMSO-d_6): δ 169.40, 165.76, 138.34, 135.16, 130.83 (2C), 130.33, 127.48 (2C), 125.54, 122.06, 120.0, 119.36, and 55.92; ESI MS: *m/z*, 270.0 $[M + H]^+$; Elemental analysis: $C_{14}H_{11}N_3O_3$, calcd. (found) %: C 62.45 (62.40), H 4.12 (4.09), and N 15.61 (15.56).

3.6.2 | 3-(6-methoxyimidazo[1,2-b]pyridazin-3-yl)benzoic acid 7l

White solid; M.p.: 138–139°C; *Yield*: 720 mg, 80%; IR (KBr): υ_{max} 3,428 (–O–H str), 2,966 (–C–H str), 1,692

(–C=O str), 1,544 (–C=N str), 1,434 (–C=C– str), 1,201 (C–O), and 1,117 (–C–N str) cm^{-1}; ^1H NMR ($CDCl_3$, D_2O exchangeable) δ 8.52 (s, 1H), 8.38 (s, 1H), 8.20 (d, J = 9.5 Hz, 1H), 7.90 (d, J = 7.4 Hz, 1H), 7.44 (t, J = 8 Hz, 1H), 7.35 (d, J = 1.56 Hz, 1H), 6.86 (d, J = 9.5 Hz, 1H), and 3.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.46, 165.77, 135.18, 132.76, 133.08, 130.82, 130.74, 130.34, 129.28, 125.56, 122.06, 120.11, and 55.92; ESI MS: *m/z*, 270.1 $[M + H]^+$; Elemental analysis: $C_{14}H_{11}N_3O_3$, calcd. (found) %: C 62.45 (62.41), H, 4.12 (4.10), and N 15.61 (15.59).

3.6.3 | Experimental procedure for antidiabetic studies[15–18]

(a) Acute toxicity: These studies were carried out as per the standard experimental procedures. The LD_{50} cut-off value of the test compounds was fixed as 50 mg/kg, as screening dose for evaluation of antidiabetic activity. All the animal experiments were conducted by the approval of Institutional Animal Ethics Committee, Anurag Group of Institutions (formerly Lalitha college of Pharmacy), Hyderabad, India. During the study period, guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Institutional Animals Ethics Committee (IAEC) were followed for the maintenance of animals. *(b) Alloxan induction of experimental diabetes*: Overnight-fasted swiss albino mice are injected with alloxan (50 mg/kg) in saline buffer intraperitoneally and hyperglycemia was confirmed in animals after 72 hr. Blood glucose levels were determined and mice having blood glucose levels <145 mg/dL were excluded from experiment and rest were divided into 10 groups. *(c) Experimental design*: Animals were divided into 14 groups of 6 animals (n = 6): Group 1 diabetic animals (vehicle) received 0.5% CMC (1 mL); Group 2 diabetic animals received insulin 50 mg/kg. Group (3–14) diabetic animals received compounds **7a–l** in a single dose of 50 mg/kg body weight orally, respectively, for 7 days continuously. *(d) Blood glucose measurement*: Blood was withdrawn from the tail vain each time. Blood glucose was measured at an interval of 0, 3, and 7 days. At the end of 0, 3, and 7 days, blood samples were withdrawn from a tail vein by snipping the tip of the tail and the blood glucose level was measured using an Accu Sure Blood Glucose Monitoring System (Dr. Gene Health & Wellness)

4 | CONCLUSIONS

In summary, the present article describes the synthesis and characterization of certain 6-methoxyimidazo[1,2-*b*]pyridazine derivatives **7a–l**. The structure of these derivatives was confirmed using ^1H NMR, ^{13}C NMR, Mass, and IR spectroscopic analyses. These derivatives were further evaluated for their antidiabetic properties and the results revealed that most of the compounds exhibited significant potency. Compounds **7b** (69.87%), **7f** (69.0%), **7h** (68.79%), and **7l** (68.61%) with substitution R = *para*-NH_2, *para*-COOH, *meta*-NH_2, and *meta*-COOH, respectively, showed significant (good) hypoglycemic activity when compared to the standard drug insulin (50 mg/kg b.w) in reducing the blood glucose level, while the compounds **7c** (67.08%), **7e** (66.34%), **7i** (65.15%), and **7k** (64.54%) with substitution R = *para*-NHBoc, *para*-CO_2Et, *meta*-NHBoc, and *meta*-CO_2Et showed moderate hypoglycemic activity. The remaining compounds in the series viz., compounds **7a** (58.55%), **7d** (54.91%), **7g** (51.21%), and **7j** (53.23%) with substitution R = *para*-Nitro, *para*-Bromo, *meta*-Nitro, and *meta*-Bromo displayed weak hypoglycemic activity.

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SUPPORTING INFORMATION

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