Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry 15 (2007) 6782–6795
Bioorganic & Medicinal Chemistry

Synthesis and antidiabetic activity of 2,5-disubstituted-3-imidazol-2-yl-pyrrolo[2,3-*b*]pyridines and thieno[2,3-*b*]pyridines☆

Rajesh H. Bahekar,* Mukul R. Jain, Pradip A. Jadav, Vijay M. Prajapati, Dipam N. Patel, Arun A. Gupta, Ajay Sharma, Robby Tom, Debdutta Bandyopadhya, Honey Modi and Pankaj R. Patel

Zydus Research Centre, Cadila Healthcare Ltd, Sarkhej-Bavala N.H. 8A, Moraiya, Ahmedabad 382210, India

Received 5 June 2007; revised 31 July 2007; accepted 1 August 2007
Available online 10 August 2007

Abstract—In the present investigation, two series of 2,5-disubstituted-3-imidazol-2-yl-pyrrolo[2,3-*b*]pyridines (**2a**–**l**) and thieno[2,3-*b*]pyridines (**3a**–**l**) were designed as analogs of BL 11282 (**1**). The in vitro glucose dependent insulinotropic activity of all the test compounds was evaluated using RIN5F cell based assay and all the test compounds showed glucose and concentration dependent insulin secretion. The in vivo antidiabetic activities of most potent compounds from each series (**2c** and **3c**) were assessed in C57BL/6J mice. Compounds **2c** and **3c** showed dose dependent insulin secretion and significant glucose reduction in vivo. In general, compounds **2c** and **3c** were found to be equipotent at all the three different doses selected and with respect to BL 11282, both the test compounds were found to be more potent, at all the time points.

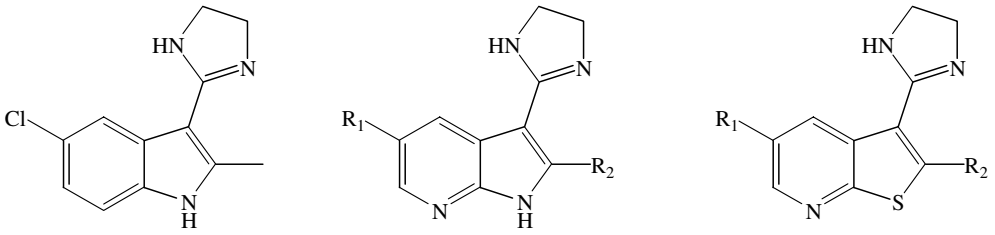
1. Introduction

The sulfonylurea class of antidiabetic drugs are known to block K_{ATP} channels in the β-cells and stimulate insulin secretion both at low and high glucose concentrations.[1] The strong insulinotropic effect of these compounds at low glucose concentrations is often associated with the hypoglycemic episodes in diabetic patients.[2] Therefore, agents that augment glucose-induced insulin secretion, without modulating the basal insulin secretion may be better therapeutic alternatives to sulfonylureas. In the last two decades, several arylimidazolines have been reported as potent stimulators of insulin secretion in the pancreatic β-cells.[3–5] However, most of the arylimidazolines possess both the K_{ATP} channel activity and a direct effect on exocytosis of insulin.[6–8] Arylimidazolines, which act via K_{ATP} channel are not therapeutically useful since they stimulate basal as well as glucose-induced insulin release. Therefore, such compounds are often associated with hypoglycemic episodes.[9]

The recent discovery of imidazoline compounds that do not stimulate basal insulin secretion, lack effect on K_{ATP} channel activity but markedly potentiate glucose-induced insulin secretion has attracted much attention as possible therapeutic agents for the treatment of type 2 diabetes.[10–12] One such novel imidazoline compound is BL 11282 (**1**; Fig. 1).[13,14] In pancreatic islets of diabetic db/db mice, BL 11282 was reported to restore the biphasic insulin secretion, by amplifying glucose-induced insulin secretion at a site distal to Ca^{2+}-influx.[15,16] Earlier, we reported synthesis and antidiabetic activity of hetero-aryl guanidine derivatives, which were designed as analog of BL 11282.[17] Knowing the in vitro glucose-dependent insulin secretion potential of BL 11282, in the present investigation, two series of arylimidazolines (2,5-disubstituted-3-imidazol-2-yl-pyrrolo[2,3-*b*]pyridine (**2a**–**l**) and 2,5-disubstituted-3-imidazol-2-yl-thieno[2,3-*b*]pyridine (**3a**–**l**)) were designed as analogs of BL 11282 (**1**). Compounds **2a**–**l** and **3a**–**l** were evaluated in vitro for their glucose-dependent insulinotropic activity using RIN5F (Rat Insulinoma) cell-based assay.[18,19] The in vivo antidiabetic activity of some of the selected arylimidazolines (compounds **2c** and **3c**) was assessed, using hyperglycemic C57BL/6J mice.[20,21]

Keywords: Arylimidazoline; Type 2 diabetes; Pyrrolo[2,3-*b*]pyridine; Thieno[2,3-*b*]pyridine; Insulinotropic; Antidiabetic.
☆ ZRC communication No. 227.
* Corresponding author. Tel.: +91 2717 250801; fax: +91 2717 250606; e-mail: rajeshbahekar@zyduscadila.com

0968-0896/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2007.08.005



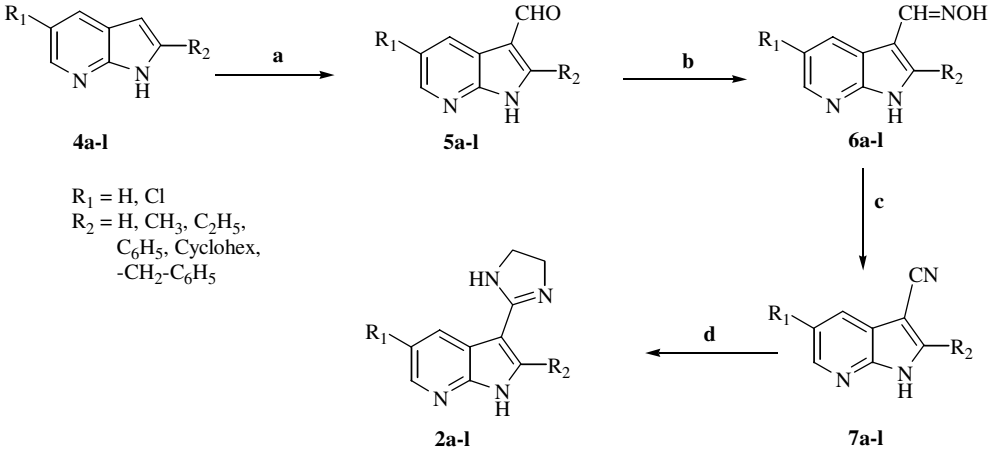
2a & 3a: R_1=H & R_2=H;
2b & 3b: R_1=Cl & R_2=H;
2c & 3c: R_1=Cl & R_2=CH_3;
2d & 3d: R_1=H & R_2=CH_3;
2e & 3e: R_1=H & R_2=C_6H_5;
2f & 3f: R_1=Cl & R_2=C_6H_5;
2g & 3g: R_1=H & R_2=Cyclohex;
2h & 3h: R_1=Cl & R_2=Cyclohex;
2i & 3i: R_1=H & R_2=C_2H_5;
2j & 3j: R_1=Cl & R_2=C_2H_5;
2k & 3k: R_1=H & R_2=CH_2-C_6H_5;
2l & 3l: R_1=Cl & R_2=CH_2-C_6H_5.

Figure 1. Structures of 2,5-disubstituted arylimidazoline derivatives.

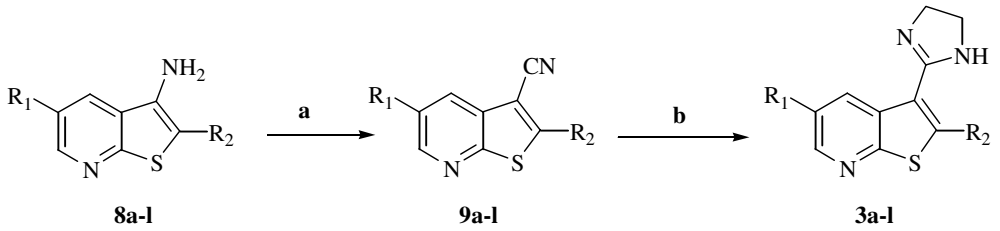
2. Chemistry

Several 2,5-disubstituted-3-(4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridines (**2a–l**) were synthesized using the synthetic route outlined in Scheme 1. 2,5-Disubstituted-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitriles (**7**) were condensed with ethylenediamine (EDA), using phosphorus pentasulfide (P_2S_5)[22] When the nucleophilic addition of EDA to compound **7**, in the presence of catalytic amounts of other sulfur reagents such as CS_2[23] or sulfur powder[24] was conducted, the formation of the imidazoline moiety did not take place. Attempts were also made to prepare the compounds **2a–l**, by either condensing the compound **7** with EDA using sodium methoxide[25] or condensing the corresponding esters of compound **7** with EDA, in the presence of the trimethylaluminum.[26] Both these reaction conditions lead to the formation of multiple by-products and poor yields (~5%). Compound **7**, in turn, was prepared from 2,5-disubstituted-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (**5**). In general, Compound **5** was first converted to 2,5-disubstituted-1*H*-Pyrrolo[2,3-*b*]pyridine-3-carbaldehyde oxime (**6**), mainly as a trans isomer, yields 66–71%. Dehydration of the corresponding oxime (**6**) with acetic anhydride followed by its hydrolysis leads to the formation of compound **7**, yields 66–70%.[27] Furthermore, compound **5** was prepared by Duff reaction, which involved formylation of 2,5-disubstituted-1*H*-pyrrolo[2,3-*b*]pyridine (**4**), at position-3, with hexamethylenetetramine (HMTA) in refluxing aqueous acetic acid.[28] The yields in this reaction were consistently good (69–78%) and the product was pure enough for the next step. When the formylation of 2,5-disubstituted-1*H*-pyrrolo[2,3-*b*]pyridine (**4**) was attempted under normal Vilsmeier reaction condition, using phosphorus oxychloride ($POCl_3$) and dimethylformamide (DMF), formation of 2,5-disubstituted-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (**5**) did not take place. This experiment confirms earlier observations about Vilsmeier reaction that the formylation of 7-azaindoles did not take place, when the '*NH*' of 7-azaindole is unsubstituted.[28] Furthermore, 2,5-disubstituted 7-azaindoles (**4**) were prepared starting from 5-substituted-3-methyl-pyridin-2-ylamine by either the directed ortho-lithiation reaction[29] or by the modified Madelung reaction, using sodium ethoxide as a catalyst.[30]

The synthesis of 2,5-disubstituted-3-(4,5-dihydro-1*H*-imidazol-2-yl)-thieno[2,3-*b*]pyridine (**3a–l**) was conducted, by the condensation of 2,5-disubstituted-thie-



Scheme 1. Reagents and conditions: (a) HMTA/acetic acid, 6 h, reflux; (b) NH_2OH/HCl, 60 °C; (c) Acetic anhydride, 4 h, reflux; (d) EDA/P_2S_5, 120 °C, 5 h.



Scheme 2. Reagents and conditions: (a) $HCl/NaNO_2/CuCN/NaCN$, reflux, 3 h; (b) EDA/P_2S_5, 120 °C, 5 h.

no[2,3-*b*]pyridine-3-carbonitrile (**9**), with EDA, using P_2S_5, Scheme 2.[22] Compound **9** (yields 66–72%) was prepared from 2,5-disubstituted-thieno[2,3-*b*]pyridin-3-ylamine (**8**) by Sandmeyer reaction, in which the diazonium salt was generated *in situ*, using a mixture of sodium nitrite ($NaNO_2$) and HCl, followed by the addition of a mixture of copper(I) cyanide, in an excess of sodium cyanide solution.[31] Compound **8** was prepared in turn starting from 2-mercapto-5-substituted-nicotinonitrile, via Thorpe–Ziegler isomerization.[32]

The overall percentage yield of compounds **2a–l** and **3a–l** was found to be in the range of 65–72%. The IR spectra (KBr; cm^{-1}) of compounds **5a–l** showed characteristic peaks for aldehyde group, in the region of 1690 (C=O stretching), compounds **6a–l** showed absorption peaks for oxime group, in the region of 1160 (–CH=N– stretching), compounds **7a–l** and **9a–l** showed peaks for nitrile group, in the range of 2260 (–CN–stretching). Final compounds **2a–l** and **3a–l** showed characteristic peaks in the region of ~3400 (N–H stretching), ~2885 (C–H stretching), 1610 (N–H bending), 1283 (C–N stretching), 1172 (C–N stretching) and 771 (C–H bending). ^{1}H NMR spectra of compounds **5a–l** showed characteristic chemical shift (δ ppm) at 9.89–9.98, due to 1*H* of aldehyde group, compounds **6a–l** showed chemical shift at 11.13-11.19, due to *OH* of oxime and compounds **2a–l** and **3a–l** showed chemical shift at 2.46–2.48 (s, 4H), due to 4 protons of imidazoline ring. The corresponding IR, ^{1}H NMR, ESI-MS, and CHN data are presented in Section 5.2. Synthesis of BL 11282 was conducted by literature procedure.[33]

3. Results and discussion

3.1. In vitro insulin secretion assay results

In vitro glucose-dependent or -independent insulin secretion properties of BL 11282 and test compounds (**2a–l** and **3a–l**; at 0.1, 1, and 10 μM concentrations) were determined using RIN5F cell assay. At 0-mM glucose load, incubation of test and standard compounds with RIN5F cells showed only basal insulin secretion. However, in presence of 16.7-mM glucose load, significant concentration dependent insulin secretions were observed, both for standard and test compounds. Further to validate the in vitro assay, RIN5F cells were incubated with Tolbutamide (sulfonylurea; at 0.1, 1, and 10 μM), both in presence or absence of glucose load. Tolbutamide showed significant insulin secretion both in presence or absence of glucose load (Table 1).

In pyrrolo[2,3-*b*]pyridine (**2a–l**) series, compounds **2c**, **2f**, and **2j** showed highest insulin secretion, compounds **2a–b** and **2g–i** showed minimal insulin secretion, while compounds **2d–e** and **2k–l** showed moderate insulin secretion, in presence of glucose load. In thieno[2,3-*b*]pyridine (**3a–l**), series, compounds **3c**, **3f**, and **3j** showed highest insulin secretion, compounds **3a–b** and **3g–i** showed minimal insulin secretion, while compounds **3d–e** and **3k–l** showed moderate insulin secretion, in presence of glucose load. In general, insulin secretion profile of compounds **2c**, **2f**, **2j**, **3c**, **3f**, and **3j** was found to be better than BL 11282. Furthermore, among these six compounds from two different series, compounds **2c** and **3c** were found to be most potent compounds.

Overall, in both the series, compounds with $R_1 = H$ showed less activity. Thus, compounds **2a**, **2g**, and **2i**, in pyrrolo[2,3-*b*]pyridine series and **3a**, **3g**, and **3i**, in thieno[2,3-*b*]pyridine series were found to be least active with respect to **2c**, **2f**, **2j**, **3c**, **3f**, and **3j**. Substitution of R_2 with hydrogen (compounds **2b** and **3b**) or cyclohex (compounds **2g**, **2h**, **3g**, and **3h**) significantly reduces activity. Compounds with chloro substitution at R_1 position and methyl, ethyl or phenyl substitution at R_2 were found to be most active compounds among both the series, indicating that the electron-withdrawing group (halogen) at R_1 position and hydrophobic substitutions (small alkyl and aryl groups) at R_2 position are favorable. Substitution of R_1 with hydrogen and R_2 with benzyl group (compounds **2k**, **2l**, **3k**, and **3l**) showed moderate insulin secretion. Overall, the glucose-dependent insulin secretion profile (in vitro results) of arylimidazolines (**2a–l** and **3a–l**) reported in this communication was found to be better than aryl-guanidines, reported earlier.[17]

3.2. The in vivo pharmacodynamic effects

In order to determine the in vivo antidiabetic activity (insulin secretion and glucose reduction) of the test and standard compounds, acute single dose 120-min time-course experiment was conducted, in male C57BL/6J mice (overnight fasted).[20,21] Compounds **2c** and **3c** were selected as representative compound from each series

Table 1. In vitro glucose-dependent insulin secretion activity of compounds **2a–l** and **3a–l**

Compound	R_1	R_2	Concd (μM)	Insulin secretion[a] (pg/μg/h)
Control 1 (0 mM glucose)				5.8 ± 0.66
Control 2 (16.7 mM glucose)				10.6 ± 0.62
Tolbutamide (0 mM glucose)			0.1/1/10	19.7 ± 0.61/20.7 ± 0.52/34.4 ± 0.16
Tolbutamide (16.7 mM glucose)			0.1/1/10	20.0 ± 0.56/21.4 ± 0.59/35.2 ± 0.36
BL 11282 (1)			0.1/1/10	16.3 ± 0.61/22.4 ± 0.52/36.5 ± 0.36
2a	H	H	0.1/1/10	12.1 ± 0.52/14.1 ± 0.16/28.0 ± 0.36
2b	Cl	H	0.1/1/10	12.4 ± 0.26/15.2 ± 0.33/29.6 ± 0.51
2c	Cl	CH_3	0.1/1/10	19.3 ± 0.16/27.7 ± 0.26/41.7 ± 0.22
2d	H	CH_3	0.1/1/10	14.9 ± 0.23/18.0 ± 0.34/32.4 ± 0.27
2e	H	C_6H_5	0.1/1/10	14.1 ± 0.15/18.1 ± 0.55/32.5 ± 0.44
2f	Cl	C_6H_5	0.1/1/10	18.2 ± 0.19/25.5 ± 0.46/39.2 ± 0.56
2g	H	Cyclohex	0.1/1/10	12.4 ± 0.31/14.3 ± 0.54/28.0 ± 0.26
2h	Cl	Cyclohex	0.1/1/10	12.6 ± 0.26/15.0 ± 0.46/28.9 ± 0.28
2i	H	C_2H_5	0.1/1/10	13.3 ± 0.25/16.4 ± 0.22/29.1 ± 0.28
2j	Cl	C_2H_5	0.1/1/10	18.9 ± 0.52/26.1 ± 0.51/39.9 ± 0.59
2k	H	CH_2–C_6H_5	0.1/1/10	14.8 ± 0.46/18.2 ± 0.26/32.6 ± 0.16
2l	Cl	CH_2–C_6H_5	0.1/1/10	14.4 ± 0.26/18.3 ± 0.46/31.9 ± 0.18
3a	H	H	0.1/1/10	12.2 ± 0.12/14.2 ± 0.19/28.2 ± 0.16
3b	Cl	H	0.1/1/10	12.6 ± 0.32/15.0 ± 0.23/29.0 ± 0.49
3c	Cl	CH_3	0.1/1/10	19.2 ± 0.19/27.5 ± 0.13/41.5 ± 0.29
3d	H	CH_3	0.1/1/10	14.5 ± 0.22/18.9 ± 0.27/31.8 ± 0.18
3e	H	C_6H_5	0.1/1/10	14.7 ± 0.14/18.0 ± 0.56/31.9 ± 0.12
3f	Cl	C_6H_5	0.1/1/10	18.0 ± 0.11/25.4 ± 0.19/39.0 ± 0.34
3g	H	Cyclohex	0.1/1/10	12.6 ± 0.16/14.7 ± 0.24/28.1 ± 0.36
3h	Cl	Cyclohex	0.1/1/10	12.9 ± 0.36/15.1 ± 0.25/28.7 ± 0.22
3i	H	C_2H_5	0.1/1/10	13.0 ± 0.19/15.5 ± 0.23/29.1 ± 0.11
3j	Cl	C_2H_5	0.1/1/10	18.5 ± 0.15/26.5 ± 0.14/39.8 ± 0.49
3k	H	CH_2–C_6H_5	0.1/1/10	14.4 ± 0.26/18.8 ± 0.17/31.6 ± 0.19
3l	Cl	CH_2–C_6H_5	0.1/1/10	13.9 ± 0.22/18.2 ± 0.31/31.9 ± 0.20

The total insulin content (pg) was divided with total protein (μg) to normalize difference in cell density between wells. $n = 3$, values represent mean ± SD.

[a] In vitro glucose-dependent (16.7-mM glucose load) insulin secretion with various concentrations of test and standard compounds was measured using Rat Insulinoma (RIN5F) cells.

along with the standard compound BL 11282. At 0 min time point (prior to the compounds' administration), animals were anesthetized using light ether anesthesia and blood (15–20 μL) was collected via retro-orbital route. Immediately after the 0 min blood collection, vehicle (normal saline solution)/test/standard compounds (suspended in saline solution) were injected to each group ($n = 6$), via intraperitoneal (ip) route of administration and the subsequent blood sampling was performed at 30, 60, and 120 min. Compounds **2c**, **3c**, and BL11282 were administered at 1, 10, and 100 μM/kg/10 mL doses. The blood samples, which were collected at different time points, were immediately subjected to glucose and insulin (only 30 min) estimations.

In the acute single dose 120-min time-course experiment, both the test compounds (**2c** and **3c**) and the standard compound showed dose dependent insulin secretion at

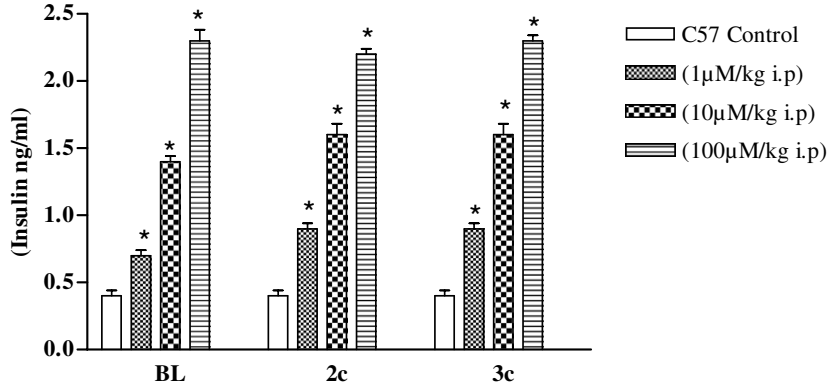


Figure 2. The serum insulin levels after single dose ip injection of vehicles/test compounds in C57BL/6J mice (in vivo). C57 mice were fasted overnight prior to vehicle/compounds administration (intraperitoneally; ip). For insulin estimation, blood samples were collected at 30 min and the insulin estimation were conducted using rat/mouse insulin ELISA kit. All values are mean ± SEM, $n = 6$, $^*p < 0.01$ versus control animals. BL = BL11282, **2c**, compound **2c**; **3c**, compound **3c**.

30 min, with respect to control (Fig. 2). Among compounds **2c**, **3c** and BL 11282, at lower dose (1 and 10 μM/kg/ip), both the test compounds showed slightly higher insulin secretion, with respect to same doses of BL 11282, while at higher concentration (100 μM/kg/ip), in vivo insulin secretion profile of BL 11282 and compounds **2c** and **3c** was found to be identical. Overall, these results correspond with our in vitro insulin secretion results (Table 1). In C57BL/6J mice, changes in blood glucose levels at various time points (30, 60, and 120 min), with compounds **2c**, **3c**, and BL 11282 are shown in Figure 3. In general, with respect to control, all the three compounds tested showed time and dose dependent glucose reduction. Compounds **2c** and **3c** were found to be equipotent in vivo at all the three different doses selected and with respect to BL 11282, both the test compounds were found to be more potent, at all the time points. BL 11282 showed glucose reduction only at 30 and 60-min. time points, while compounds **2c** and **3c** showed sustained glucose reduction upto 120 min, indicating that compounds **2c** and **3c** exhibit longer duration of action.

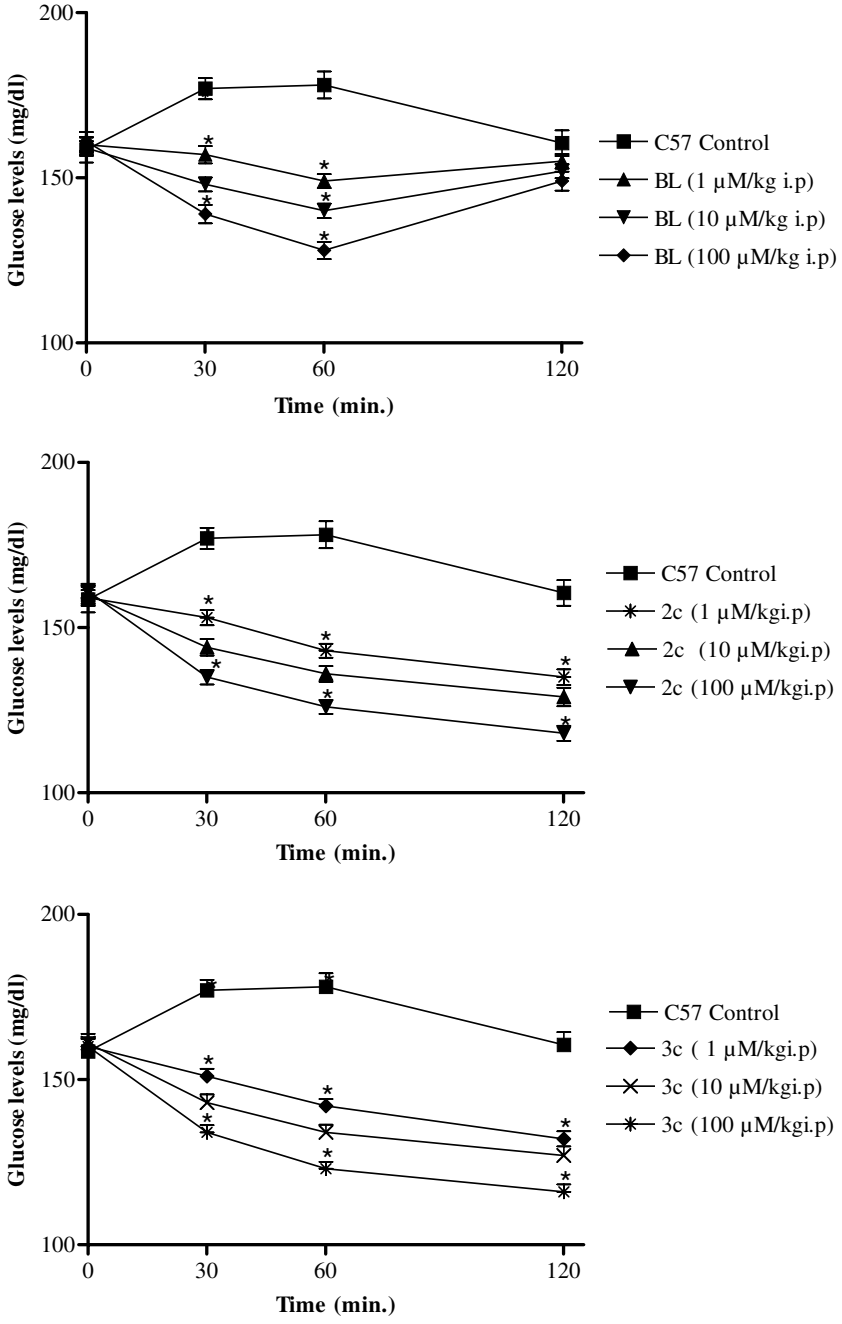


Figure 3. The serum glucose levels after single dose ip injection of vehicles/compounds in C57BL/6J mice (in vivo). C57BL/6J mice were fasted overnight prior to vehicle/compounds administration (intraperitoneally). For glucose estimation, blood samples were collected at 0, 30, 60, and 120 min and the glucose estimation was conducted with DPEC-GOD/POD method, using Spectramax-190, in 96-microwell plate reader. All values are mean ± SEM, $n = 6$, $^{*}p < 0.01$ versus control animals.

4. Conclusion

The glucose-dependent insulin secretion effect is one of the most desirable properties of novel insulin secretagogues. The new arylimidazolines (compounds **2a–l** and **3a–l**), which were designed as analogs of BL 11282 showed significant glucose-dependent insulin secretion (in vitro and in vivo) and reduction in the blood glucose level (in vivo). Among all the 24 new compounds tested in both the series, 5-Chloro-3-(4,5-dihydro-1*H*-imidazol-2-yl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (**2c**) and 5-Chloro-3-(4,5-dihydro-1*H*-imidazol-2-yl)-2-methyl-thieno[2,3-*b*]pyridine (**3c**) were found to be more potent than BL11282, indicating that the pyridine ring of pyrrolo-[2,3-*b*]pyridine (**2a–l**) and thiophene ring of thieno[2,3-*b*]pyridine (**3a–l**) act as bioisosteres of the benzene and indole ring systems of BL 11282 (**1**). Combined evaluation of our in vitro and in vivo results indicates that both the series of aryl imidazoline derivatives could be useful for the prevention and mitigation of type 2 diabetes.

5. Experimental

5.1. Chemistry

Melting points were determined in open glass capillaries, using a Scientific melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FT IR 8300 spectrophotometer (V_{max} in cm^{-1}, using KBr pellets). The ^1H NMR spectra were recorded on a Brucker Avance-300 spectrometer (300 MHz). Chemical shifts (δ) are reported in parts per million (ppm) relative to TMS, either in $CDCl_3$ or DMSO-d_6 solution. Signal multiplicities are represented by s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), br s (broad singlet), and m (multiplet). Mass spectra (ESI-MS) were obtained on a Shimadzu LC–MS 2010-A spectrometer. Elemental analyses were conducted, using a Perkin-Elmer 2400 CHN analyzer and values within limit of ±0.4% of the theoretical values were taken into consideration. Purity of synthesized compounds was checked by precoated TLC plates (E. Merck, Kieselgel 60 F_{254}) and the spots were visualized by iodine vapors. The chromatographic purification was conducted on silica gel (100–200-mesh size). All the chemicals used for the synthesis were purchased from Aldrich Company Limited, Dorset (UK).

5.2. Experimental details

5.2.1. General method for the synthesis of 2,5-disubstituted-3-(4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (2a–l; Scheme 1)

5.2.1.1. Synthesis of 1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (5a). A mixture of 1*H*-pyrrolo[2,3-*b*]pyridine **4** (15.25 mmol) and HMTA (22.85 mmol) in acetic acid (19 mL) was heated under reflux for 6 h. The reaction mixture was cooled to room temperature, diluted with water, and kept overnight. The solid obtained was filtered, washed with excess of ice cold water and dried. The crude compound obtained was recrystallized from hexane to get the pure product.[28] Using above procedure, total 12 derivatives of 2,5-disubstituted-1*H*-pyrrolo-[2,3-*b*]pyridine-3-carbaldehyde (**5a–l**) were prepared and their physicochemical properties and spectral data are listed below.

Yield: 77%; white solid; mp 194–196 °C (reported mp 216–217 °C, recrystallized from water[28]); IR (KBr): 3389, 2887, 1692, 1612 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.67 (br s, 1H, pyrrole ring *–NH*), 9.91 (s, 1H, *–CHO*), 8.46 (s, 1H, pyrrole ring *–CH*), 8.40–8.35 (m, 2H, pyridine ring), 7.29–7.27 (m, 1H, pyridine ring); MS (ESI) *m*/*z* 147 $[M+1]^+$; Anal. Calcd for $C_8H_6N_2O$: C, 65.68; H, 5.47; N 19.15. Found: C, 65.66; H, 5.43; N 19.11.

5.2.1.2. 5-Chloro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (5b). Yield: 78%; white solid; mp 199–202 °C; IR (KBr): 3391, 2885, 1691, 1610, 740 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.64 (br s, 1H, pyrrole ring *–NH*), 9.94 (s, 1H,*–CHO*), 8.79 (s, 1H, pyridine ring), 8.46 (s, 1H, pyrrole ring *–CH*), 7.99 (s, 1H, pyridine ring); MS (ESI) *m*/*z* 183 $[M+1]^+$, 184 $[M+2]^+$; Anal. Calcd for $C_8H_5ClN_2O$: C, 53.15; H, 2.76; N 15.50. Found: C, 53.11; H,2.73;N 15.48.

5.2.1.3. 5-Chloro-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (5c). Yield: 75%; white solid; mp 210–212 °C; IR (KBr): 3392, 2889, 1695, 1612, 1376, 738 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.61 (br s, 1H, pyrrole ring *–NH*), 9.89 (s, 1H, *–CHO*), 8.76 (s, 1H, pyridine ring), 7.95 (s, 1H, pyridine ring), 2.67 (s, 3H, *–CH_3*); MS (ESI) *m*/*z* 196 $[M+1]^+$, 197 $[M+2]^+$; Anal. Calcd for $C_9H_7ClN_2O$: C, 55.49; H, 3.59; N 14.38. Found: C, 55.46; H, 3.55; N 14.35.

5.2.1.4. 2-Methyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (5d). Yield: 76%; white solid; mp 226–228 °C; IR (KBr): 3390, 2891, 1695, 1611, 1372 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.68 (br s, 1H, pyrrole ring *–NH*), 9.93 (s, 1H, *–CHO*), 8.39–8.33 (m, 2H, pyridine ring), 7.28–7.26 (m, 1H, pyridine ring), 2.68 (s, 3H, *–CH_3*); MS (ESI) *m*/*z* 161 $[M+1]^+$; Anal. Calcd for $C_9H_8N_2O$: C, 67.42; H, 4.99; N 17.48. Found: C, 67.40; H, 4.96; N 17.44.

5.2.1.5. 2-Phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (5e). Yield: 70%; white solid; mp 232–235 °C; IR (KBr): 3401, 2884, 1691, 1611, 778 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.67 (br s, 1H, pyrrole ring *–NH*), 9.91 (s, 1H, *–CHO*), 8.39–8.34 (m, 2H, pyridine ring), 7.35–7.29 (m, 5H, benzene ring), 7.28–7.26 (m, 1H, pyridine ring); MS (ESI) *m*/*z* 223 $[M+1]^+$; Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.59; H, 4.49; N 12.59. Found: C, 75.55; H, 4.46; N 12.59.

5.2.1.6. 5-Chloro-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (5f). Yield: 69%; white solid; mp 190–192 °C; IR (KBr): 3398, 2887, 1702, 1612, 775, 734 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.69 (br s, 1H, pyrrole ring *–NH*), 9.93 (s, 1H, *–CHO*), 8.75 (s, 1H, pyridine ring), 7.96 (s, 1H, pyridine ring), 7.35–7.29 (m, 5H, benzene ring); MS (ESI) *m*/*z* 268 $[M+1]^+$,

269 $[M+2]^+$; Anal. Calcd for $C_{14}H_9ClN_2O$: C, 65.44; H, 3.50; N 10.90. Found: C, 65.41; H, 3.47; N 10.88.

5.2.1.7. 2-Cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (5g). Yield: 75%; white solid; mp 198–200 °C; IR (KBr): 3395, 2894, 1694, 1610, 1448 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.67 (br s, 1H, pyrrole ring –*NH*), 9.97 (s, 1H, –*CHO*), 8.37–8.33 (m, 2H, pyridine ring), 7.29–7.26 (m, 1H, pyridine ring), 2.13–2.11 (m, 1H, cyclohexyl ring), 1.27–1.24 (m, 10H, cyclohexyl ring); MS (ESI) *m*/*z* 229 $[M+1]^+$; Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.59; H, 7.00; N 12.26. Found: C, 73.56; H, 6.97; N 12.22.

5.2.1.8. 5-Chloro-2-cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (5h). Yield: 78%; white solid; mp 211–213 °C; IR (KBr): 3408, 2887, 1694, 1610, 1448, 742 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.69 (br s, 1H, pyrrole ring –*NH*), 9.93 (s, 1H, –*CHO*), 8.68 (s, 1H, pyridine ring), 7.94 (s, 1H, pyridine ring), 2.14–2.11 (m, 1H, cyclohexyl ring), 1.27–1.24 (m, 10H, cyclohexyl ring); MS (ESI) *m*/*z* 264 $[M+1]^+$, 265 $[M+2]^+$; Anal. Calcd for $C_{14}H_{15}ClN_2O$: C, 63.94; H, 5.70; N 10.65. Found: C, 63.91; H, 5.66; N 10.63.

5.2.1.9. 2-Ethyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (5i). Yield: 72%; white solid; mp 231–233 °C; IR (KBr): 3398, 2893, 1690, 1614, 1445, 1368 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.69 (br s, 1H, pyrrole ring –*NH*), 9.97 (s, 1H, –*CHO*), 8.39–8.32 (m, 2H, pyridine ring), 7.29–7.25 (m, 1H, pyridine ring), 2.18 (q, 2H, J = 7.1 Hz, $-CH_2CH_3$), 1.27 (t, 3H, J = 7.1 Hz, $-CH_2CH_3$); MS (ESI) *m*/*z* 175 $[M+1]^+$; Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.88; H, 5.74; N 16.07. Found: C, 68.84; H, 5.73; N 16.04.

5.2.1.10. 5-Chloro-2-ethyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (5j). Yield: 68%; white solid; mp 240–242 °C; IR (KBr): 3397, 2888, 1689, 1617, 1443, 1371, 736 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.67 (br s, 1H, pyrrole ring –*NH*), 9.98 (s, 1H, –*CHO*), 8.71 (s, 1H, pyridine ring), 7.94 (s, 1H, pyridine ring), 2.16 (q, 2H, J = 7.1Hz, $-CH_2CH_3$), 1.23 (t, 3H, J = 7.1Hz, $-CH_2CH_3$); MS (ESI) *m*/*z* 210 $[M+1]^+$, 211 $[M+2]^+$; Anal. Calcd for $C_{10}H_9ClN_2O$: C, 57.51; H, 4.31; N 13.42. Found: C, 57.47; H, 4.28; N 13.39.

5.2.1.11. 2-Benzyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (5k). Yield: 72%; white solid; mp 222–225 °C; IR (KBr): 3406, 2892, 1691, 1609, 1476, 778 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.72 (br s, 1H, pyrrole ring –*NH*), 9.93 (s, 1H, –*CHO*), 8.37–8.34 (m, 2H, pyridine ring), 7.37–7.26 (m, 6H, benzene ring and pyridine ring), 3.85 (s, 2H, benzyl $-CH_2$); MS (ESI) *m*/*z* 237 $[M+1]^+$; Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.18; H, 5.07; N 11.85. Found: C, 76.14; H, 5.04; N 11.83.

5.2.1.12. 5-Chloro-2-benzyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (5l). Yield: 77%; white solid; mp 236–238 °C; IR (KBr): 3401, 2887, 1689, 1613, 1468, 768 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.69 (br s, 1H, pyrrole ring –*NH*), 9.91 (s, 1H, –*CHO*), 8.74 (s, 1H, pyridine ring), 7.95 (s, 1H, pyridine ring), 7.31–7.26 (m, 5H, benzene ring), 3.87 (s, 2H, benzyl $-CH_2$); MS (ESI) *m*/*z* 272 $[M+1]^+$, 273 $[M+2]^+$; Anal. Calcd for $C_{15}H_{11}ClN_2O$: C, 66.49; H, 4.06; N 10.34. Found: C, 66.46; H, 4.02; N 10.31.

5.2.1.13. Synthesis of 1*H*-Pyrrolo[2,3-*b*]pyridine-3-carbaldehyde oxime (6a). A mixture of 1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde **5a** (8.22 mmol) and hydroxylamine hydrochloride (15.82 mmol) in water was heated at 60 °C for 30 min. To it, $NaHCO_3$ (19.64 mmol) was added and the reaction mixture was heated under reflux for 4 h at 100 °C. The reaction mixture was cooled to room temperature, the solid obtained was filtered, washed with the excess of ice-cold water, and dried. The crude product obtained was recrystallized from hexane to get the pure product.[27] Using above procedure, total 12 derivatives of 2,5-disubstituted-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde oxime (**6a**–**l**) were prepared and their physicochemical properties and spectral data are listed below.

Yield: 71%; white solid; mp 188–190 °C (reported mp 218–219 °C, recrystallized from ethanol–water (1:2)[27]); IR (KBr): 3392, 2895, 1611, 1168 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.09 (br s, 1H, pyrrole ring –*NH*), 11.17 (br s, 1H, –CH=N–*OH*), 8.21 (s, 1H, pyrrole ring –*CH*), 7.85 (d, 1H, J = 7.7 Hz, pyridine ring), 7.77 (s, 1H, –*CH*=N–OH), 7.41 (d, 1H, J = 7.7 Hz, pyridine ring), 7.13–7.06 (m, 1H, pyridine ring); MS (ESI) *m*/*z* 162 $[M+1]^+$; Anal. Calcd for $C_8H_7N_3O$: C, 59.57; H, 4.34; N 26.06. Found: C, 59.54; H, 4.31; N 26.02.

5.2.1.14. 5-Chloro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde oxime (6b). Yield: 69%; white solid; mp 196–198 °C; IR (KBr): 3407, 2889, 1614, 1162, 741 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.92 (br s, 1H, pyrrole ring –*NH*), 11.13 (br s, 1H, –CH=N–*OH*), 8.79 (s, 1H, pyridine ring), 8.21 (s, 1H, pyrrole ring –*CH*), 7.89 (s, 1H, pyridine ring), 7.74 (s, 1H, –*CH*=N–OH); MS (ESI) *m*/*z* 197 $[M+1]^+$, 198 $[M+2]^+$; Anal. Calcd for $C_8H_6ClN_3O$: C, 49.07; H, 3.06; N 21.47. Found: C, 49.04; H, 3.02; N 21.44.

5.2.1.15. 5-Chloro-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde oxime (6c). Yield: 68%; white solid; mp 173–175 °C; (68% yield); IR (KBr): 3396, 2893, 1610, 1369, 1169, 738 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.94 (br s, 1H, pyrrole ring –*NH*), 11.17 (br s, 1H, –CH=N–*OH*), 8.76 (s, 1H, pyridine ring), 7.94 (s, 1H, pyridine ring), 7.71 (s, 1H, –*CH*=N–OH), 2.69 (s, 3H, $-CH_3$); MS (ESI) *m*/*z* 211 $[M+1]^+$, 212 $[M+2]^+$; Anal. Calcd for $C_9H_8ClN_3O$: C, 51.52; H, 3.82; N 20.03. Found: C, 51.49; H, 3.79; N 20.00.

5.2.1.16. 2-Methyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde oxime (6d). Yield: 69%; white solid; mp 179–181 °C; IR (KBr): 3412, 2904, 1613, 1371, 1159 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.02 (br s, 1H, pyrrole ring –*NH*), 11.19 (br s, 1H, –CH=N–*OH*), 7.87 (d, 1H, J = 7.7 Hz, pyridine ring), 7.75 (s, 1H, –*CH*=N–OH), 7.48 (d, 1H, J = 7.8 Hz, pyridine ring), 7.14–7.08 (m, 1H, pyridine ring), 2.63 (s, 3H, $-CH_3$); MS (ESI)

m/*z* 176 $[M+1]^+$; Anal. Calcd for $C_9H_9N_3O$: C, 61.64; H, 5.13; N 23.97. Found: C, 61.61; H, 5.10; N 23.94.

5.2.1.17. 2-Phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde oxime (6e). Yield: 66%; white solid; mp 193–195 °C; IR (KBr): 3398, 2897, 1609, 1162, 778 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.07 (br s, 1H, pyrrole ring –*NH*), 11.17 (br s, 1H, –CH=N–*OH*), 7.89 (d, 1H, J = 7.7 Hz, pyridine ring), 7.77 (s, 1H, –*CH*=N–OH), 7.41 (d, 1H, J = 7.7 Hz, pyridine ring), 7.32–7.26 (m, 5H, benzene ring), 7.15–7.11 (m, 1H, pyridine ring); MS (ESI) *m*/*z* 238 $[M+1]^+$; Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.81; H, 4.64; N 17.70. Found: C, 70.78; H, 4.63; N 17.67.

5.2.1.18. 5-Chloro-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde oxime (6f). yield: 69%; white solid; mp 172–174 °C; IR (KBr): 3401, 2889, 1610, 1164, 775, 734 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.87 (br s, 1H, pyrrole ring –*NH*), 11.18 (br s, 1H, –CH=N–*OH*), 8.72 (s, 1H, pyridine ring), 7.98 (s, 1H, pyridine ring), 7.74 (s, 1H, –*CH*=N–OH), 7.34–7.27 (m, 5H, benzene ring); MS (ESI) *m*/*z* 273 $[M+1]^+$, 274 $[M+2]^+$; Anal. Calcd for $C_{14}H_{10}ClN_3O$: C, 61.83; H, 3.68; N 15.46. Found: C, 61.80; H, 3.63; N 15.42.

5.2.1.19. 2-Cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde oxime (6g). Yield: 71%; white solid; mp 184–186 °C; IR (KBr): 3398, 2892, 1613, 1451, 1167 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.89 (br s, 1H, pyrrole ring –*NH*), 11.13 (br s, 1H, –CH=N–*OH*), 7.88 (d, 1H, J = 7.7 Hz, pyridine ring), 7.71 (s, 1H, –*CH*=N–OH), 7.44 (d, 1H, J = 7.7 Hz, pyridine ring), 7.14–7.09 (m, 1H, pyridine ring), 2.16–2.13 (m, 1H, cyclohexyl ring), 1.27–1.21 (m, 10H, cyclohexyl ring); MS (ESI) *m*/*z* 244 $[M+1]^+$; Anal. Calcd for $C_{14}H_{17}N_3O$: C, 69.05; H, 6.98; N 17.26. Found: C, 69.02; H, 6.95; N 17.22.

5.2.1.20. 5-Chloro-2-cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde oxime (6h). Yield: 70%, white solid; mp 188–190 °C; IR (KBr): 3404, 2892, 1613, 1439, 1161, 742 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.92 (br s, 1H, pyrrole ring –*NH*), 11.13 (br s, 1H, –CH=N–*OH*), 8.78 (s, 1H, pyridine ring), 7.94 (s, 1H, pyridine ring), 7.72 (s, 1H, –*CH*=N–OH), 2.14–2.11 (m, 1H, cyclohexyl ring), 1.27–1.22 (m, 10H, cyclohexyl ring); MS (ESI) *m*/*z* 279 $[M+1]^+$, 280 $[M+2]^+$; Anal. Calcd for $C_{14}H_{16}ClN_3O$: C, 60.48; H, 5.76; N 15.12. Found: C, 60.45; H, 5.72; N 15.10.

5.2.1.21. 2-Ethyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde oxime (6i). Yield: 66%; white solid; mp 168–170 °C; IR (KBr): 3403, 2892, 1609, 1443, 1372, 1164 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.93 (br s, 1H, pyrrole ring –*NH*), 11.15 (br s, 1H, –CH=N–*OH*), 7.84 (d, 1H, J = 7.6 Hz, pyridine ring), 7.75 (s, 1H, –*CH*=N–OH), 7.46 (d, 1H, J = 7.6 Hz, pyridine ring), 7.14–7.09 (m, 1H, pyridine ring), 2.19 (q, 2H, J = 7.1Hz, –CH_2CH_3), 1.26 (t, 3H, J = 7.1Hz, –CH_2CH_3); MS (ESI) *m*/*z* 190 $[M+1]^+$; Anal. Calcd for $C_{10}H_{11}N_3O$: C, 63.42; H, 5.81; N 22.19. Found: C, 63.39; H, 5.79; N 22.16.

5.2.1.22. 5-Chloro-2-ethyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde oxime (6j). Yield: 68%; white solid; mp 171–173 °C; IR (KBr): 3399, 2893, 1612, 1446, 1375, 1169, 736 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.79 (br s, 1H, pyrrole ring –*NH*), 11.13 (br s, 1H, –CH=N–*OH*), 8.74 (s, 1H, pyridine ring), 7.97 (s, 1H, pyridine ring), 7.73 (s, 1H, –*CH*=N–OH), 2.18 (q, 2H, J = 7.1 Hz, –CH_2CH_3), 1.26 (t, 3H, J = 7.1Hz, –CH_2CH_3); MS (ESI) *m*/*z* 225 $[M+1]^+$, 226 $[M+2]^+$; Anal. Calcd for $C_{10}H_{10}ClN_3O$: C, 53.65; H, 4.47; N 18.78. Found: C, 53.61; H, 4.43; N 18.74.

5.2.1.23. 2-Benzyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde oxime (6k). Yield: 70%; white solid; mp 182–184 °C; IR (KBr): 3404, 2889, 1611, 1469, 1161, 773 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.03 (br s, 1H, pyrrole ring –*NH*), 11.14 (br s, 1H, –CH=N–*OH*), 7.86 (d, 1H, J = 7.7 Hz, pyridine ring), 7.74 (s, 1H, –*CH*=N–OH), 7.44 (d, 1H, J = 7.8 Hz, pyridine ring), 7.27–7.18 (m, 5H, benzene ring), 7.15–7.11 (m, 1H, pyridine ring), 3.87 (s, 2H, benzyl –CH_2); MS (ESI) *m*/*z* 252 $[M+1]^+$; Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.63; H, 5.17; N 16.71. Found: C, 71.61; H, 5.13; N 16.69.

5.2.1.24. 5-Chloro-2-benzyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde oxime (6l). Yield: 68%; white solid; mp 188–190 °C; IR (KBr): 3406, 2897, 1608, 1471, 1169, 769 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.97 (br s, 1H, pyrrole ring –*NH*), 11.13 (br s, 1H, –CH=N–*OH*), 8.78 (s, 1H, pyridine ring), 7.97 (s, 1H, pyridine ring), 7.74 (s, 1H, –*CH*=N–OH), 7.29–7.18 (m, 5H, benzene ring), 3.85 (s, 2H, benzyl –CH_2); MS (ESI) *m*/*z* 287 $[M+1]^+$, 288 $[M+2]^+$; Anal. Calcd for $C_{15}H_{12}ClN_3O$: C, 62.99; H, 4.20; N 14.69. Found: C, 62.96; H, 4.17; N 14.66.

5.2.1.25. Synthesis of 1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (7a). A mixture of 1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde oxime **6a** (6.21 mmol) and acetic anhydride (53 mmol) was heated under reflux for 4 h. The reaction mixture was cooled to room temperature and poured into ice-cold water. The solid obtained was filtered and washed with excess of ice-cold water. The white solid was suspended in water (20 mL) and the aqueous suspension was heated under reflux for 3 h. The reaction mixture was cooled to room temperature and poured into ice-cold water. The solid obtained was filtered, washed with excess of ice-cold water and the crude product obtained was recrystallized from a mixture of ethyl acetate hexane (1:9), to get the pure product.[27] Using above procedure, total 12 derivatives of 2,5-disubstituted-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (**7a–l**) were prepared and their physicochemical properties and spectral data are listed below.

Yield: 68%; white solid; mp 226–228 °C (reported mp 262–265°C, recrystallized from aqueous ethanol[27]); IR (KBr): 3396, 2893, 2237, 1610 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.09 (br s, 1H, pyrrole ring –*NH*), 8.41 (s, 1H, pyrrole ring –*CH*), 8.38–8.35 (m, 2H, pyridine ring), 7.29–7.27 (m, 1H, pyridine ring); MS (ESI) *m*/*z* 144 $[M+1]^+$; Anal. Calcd for $C_8H_5N_3$:

C, 67.06; H, 3.49; N 29.33. Found: C, 67.02; H, 3.46; N 29.30.

5.2.1.26. 5-Chloro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (7b). Yield: 67%; white solid; mp 232–234 °C; IR (KBr): 3401, 2887, 2232, 1612, 743 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.04 (br s, 1H, pyrrole ring *–NH*), 8.77 (s, 1H, pyridine ring), 8.45 (s, 1H, pyrrole ring *–CH*), 7.97 (s, 1H, pyridine ring); MS (ESI) *m/z* 179 $[M+1]^+$, 180 $[M+2]^+$; Anal. Calcd for $C_8H_4ClN_3$: C, 54.05; H, 2.25; N 23.65. Found: C, 54.01; H, 2.22; N 23.61.

5.2.1.27. 5-Chloro-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (7c). Yield: 69%; white solid; mp 218–220 °C; IR (KBr): 3398, 2896, 2239, 1609, 1367, 739 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.98 (br s, 1H, pyrrole ring *–NH*), 8.78 (s, 1H, pyridine ring), 7.98 (s, 1H, pyridine ring), 2.58 (s, 3H, *–CH*$_3$); MS (ESI) *m/z* 193 $[M+1]^+$, 194 $[M+2]^+$; Anal. Calcd for $C_9H_6ClN_3$: C, 56.36; H, 3.13; N 21.92. Found: C, 56.32; H, 3.10; N 21.89.

5.2.1.28. 2-Methyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (7d). Yield: 66%; white solid; mp 225–227 °C; IR (KBr): 3392, 2896, 2235, 1617, 1364 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.02 (br s, 1H, pyrrole ring *–NH*), 8.37–8.33 (m, 2H, pyridine ring), 7.29–7.26 (m, 1H, pyridine ring), 2.56 (s, 3H, *–CH*$_3$); MS (ESI) *m/z* 158 $[M+1]^+$; Anal. Calcd for $C_9H_7N_3$: C, 68.71; H, 4.45; N 26.72. Found: C, 68.69; H, 4.42; N 26.69.

5.2.1.29. 2-Phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (7e). Yield: 68%; white solid; mp 238–240 °C; IR (KBr): 3397, 2895, 2228, 1613, 769 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.04 (br s, 1H, pyrrole ring *–NH*), 8.39–8.35 (m, 2H, pyridine ring), 7.35–7.29 (m, 5H, benzene ring), 7.28–7.25 (m, 1H, pyridine ring); MS (ESI) *m/z* 220 $[M+1]^+$; Anal. Calcd for $C_{14}H_9N_3$: C, 76.62; H, 4.10; N 19.15. Found: C, 76.59; H, 4.07; N 19.11.

5.2.1.30. 5-Chloro-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (7f). Yield: 70%; white solid; mp 217–219 °C; IR (KBr): 3403, 2897, 2234, 1610, 773, 736 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.99 (br s, 1H, pyrrole ring *–NH*), 8.79 (s, 1H, pyridine ring), 7.99 (s, 1H, pyridine ring), 7.35–7.29 (m, 5H, benzene ring); MS (ESI) *m/z* 256 $[M+1]^+$, 257 $[M+2]^+$; Anal. Calcd for $C_{14}H_8ClN_3$: C, 66.22; H, 3.15; N 16.55. Found: C, 66.20; H, 3.12; N 16.51.

5.2.1.31. 2-Cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (7g). Yield: 69%; white solid; mp 216–218 °C; IR (KBr): 3399, 2889, 2237, 1609, 1446 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.67 (br s, 1H, pyrrole ring *–NH*), 8.37–8.33 (m, 2H, pyridine ring), 7.29–7.25 (m, 1H, pyridine ring), 2.13–2.10 (m, 1H, cyclohexyl ring), 1.27–1.24 (m, 10H, cyclohexyl ring); MS (ESI) *m/z* 226 $[M+1]^+$; Anal. Calcd for $C_{14}H_{15}N_3$: C, 74.57; H, 6.65; N 18.64. Found: C, 74.54; H, 6.62; N 18.61.

5.2.1.32. 5-Chloro-2-cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (7h). Yield: 66%; white solid; mp 222–224 °C; IR (KBr): 3402, 2893, 2239, 1615, 1443, 740 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.69 (br s, 1H, pyrrole ring *–NH*), 8.69 (s, 1H, pyridine ring), 7.97 (s, 1H, pyridine ring), 2.15–2.11 (m, 1H, cyclohexyl ring), 1.27–1.24 (m, 10H, cyclohexyl ring); MS (ESI) *m/z* 261 $[M+1]^+$, 262 $[M+2]^+$; Anal. Calcd for $C_{14}H_{14}ClN_3$: C, 64.68; H, 5.39; N 16.17. Found: C, 64.64; H, 5.36; N 16.14.

5.2.1.33. 2-Ethyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (7i). Yield: 68%; white solid; mp 233–235 °C; IR (KBr): 3394, 2889, 2232, 1611, 1446, 1371 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.93 (br s, 1H, pyrrole ring *–NH*), 8.35–8.32 (m, 2H, pyridine ring), 7.29–7.24 (m, 1H, pyridine ring), 2.37 (q, 2H, J = 7.1Hz, *–CH*$_2$CH$_3$), 1.24 (t, 3H, J = 7.1Hz, –CH$_2$*CH*$_3$); MS (ESI) *m/z* 172 $[M+1]^+$; Anal. Calcd for $C_{10}H_9N_3$: C, 70.09; H, 5.25; N 24.53. Found: C, 70.06; H, 5.21; N 24.50.

5.2.1.34. 5-Chloro-2-ethyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (7j). Yield: 67%; white solid; mp 230–232 °C; IR (KBr): 3409, 2893, 2236, 1613, 1447, 1370, 734 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.97 (br s, 1H, pyrrole ring *–NH*), 8.70 (s, 1H, pyridine ring), 7.97 (s, 1H, pyridine ring), 2.36 (q, 2H, J = 7.2 Hz, *–CH*$_2$CH$_3$), 1.24 (t, 3H, J = 7.2 Hz, –CH$_2$*CH*$_3$); MS (ESI) *m/z* 209 $[M+1]^+$, 210 $[M+2]^+$; Anal. Calcd for $C_{10}H_8ClN_3$: C, 58.11; H, 3.87; N 20.34. Found: C, 58.08; H, 3.84; N 20.31.

5.2.1.35. 2-Benzyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (7k). Yield: 66%; white solid; mp 234–236 °C; IR (KBr): 3402, 2889, 2229, 1611, 1472, 773 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.93 (br s, 1H, pyrrole ring *–NH*), 8.41–8.39 (m, 2H, pyridine ring), 7.31–7.26 (m, 6H, benzene ring and pyridine ring), 3.82 (s, 2H, benzyl *–CH*$_2$); MS (ESI) *m/z* 234 $[M+1]^+$; Anal. Calcd for $C_{15}H_{11}N_3$: C, 77.16; H, 4.72; N 18.00. Found: C, 77.13; H, 4.69; N 17.98.

5.2.1.36. 5-Chloro-2-benzyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (7l). Yield: 69%; white solid; mp 231–233 °C; IR (KBr): 3405, 2896, 2234, 1612, 1464, 767 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.01 (br s, 1H, pyrrole ring *–NH*), 8.76 (s, 1H, pyridine ring), 7.98 (s, 1H, pyridine ring), 7.31–7.26 (m, 5H, benzene ring), 3.84 (s, 2H, benzyl *–CH*$_2$); MS (ESI) *m/z* 269 $[M+1]^+$, 270 $[M+2]^+$; Anal. Calcd for $C_{15}H_{10}ClN_3$: C, 6.72; H, 3.73; N 15.69. Found: C, 6.69; H, 3.70; N 15.66.

5.2.1.37. Synthesis of 3-(4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (2a). A mixture of 1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile **7a** (2.10 mmol), P_2S_5 (53 mmol), and EDA (6 mL) was heated under reflux for 5 h. The reaction mixture was cooled to room temperature and poured into ice-cold water. The solid obtained was filtered, washed with excess of ice cold water and dried under vacuum. The crude compound obtained was recrystallized from methanol to get the pure product.[22] Using above procedure, total 12 derivatives of 2,5-disubstituted-3-(4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (**2a**–**l**) were prepared and their physicochemical properties and spectral data are listed below.

Yield: 69%; white solid; mp 267–269 °C; IR (KBr): 3393, 2888, 1612 1284, 1175, 769 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.03 (br s, 1H, pyrrole ring *–NH*), 8.46–8.43 (m, 1H, pyridine ring), 8.24–8.21 (m, 1H, pyridine ring), 7.89 (s, 1H, pyrrole ring *–CH*), 7.13–7.09 (m, 1H, pyridine ring), 6.67 (br s, 1H, imidazoline ring *–NH*), 3.55–3.52 (m, 4H, imidazoline ring); MS (ESI) *m/z* 187 $[M+1]^+$; Anal. Calcd for $C_{10}H_{10}N_4$: C, 64.44; H, 5.37; N 30.07. Found: C, 64.41; H, 5.34; N 30.04.

5.2.1.38. 5-Chloro-3-(4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (2b). Yield: 68%; white solid; mp 262–265 °C; IR (KBr): 3398, 2889, 1610, 1285, 1174, 774 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.09 (br s, 1H, pyrrole ring *–NH*), 8.78 (s, 1H, pyridine ring), 7.98 (s, 1H, pyridine ring), 7.89 (s, 1H, pyrrole ring *–CH*), 6.67 (br s, 1H, imidazoline ring *–NH*), 3.55–3.51 (m, 4H, imidazoline ring); MS (ESI) *m/z* 222 $[M+1]^+$, 223 $[M+2]^+$; Anal. Calcd for $C_{10}H_9ClN_4$: C, 54.38; H, 4.08; N 25.38. Found: C, 54.35; H, 4.05; N 25.35.

5.2.1.39. 5-Chloro-3-(4,5-dihydro-1*H*-imidazol-2-yl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (2c). Yield: 67%; white solid; mp 256–257 °C; IR (KBr): 3395, 2887, 1611, 1376, 1283, 1168, 736 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.98 (br s, 1H, pyrrole ring *–NH*), 8.79 (s, 1H, pyridine ring), 7.94 (s, 1H, pyridine ring), 6.67 (br s, 1H, imidazoline ring *–NH*), 3.56–3.54 (m, 4H, imidazoline ring), 2.53 (s, 3H, *–CH_3*); MS (ESI) *m/z* 236 $[M+1]^+$, 237 $[M+2]^+$; Anal. Calcd for $C_{11}H_{11}ClN_4$: C, 56.24; H, 4.68; N 23.86. Found: C, 56.21; H, 4.65; N 23.84.

5.2.1.40. 3-(4,5-Dihydro-1*H*-imidazol-2-yl)-2-Methyl-1*H*-pyrrolo[2,3-*b*]pyridine (2d). Yield: 71%; white solid; mp 260–262 °C; IR (KBr): 3396, 2893, 1611, 1372, 1279, 1173, 774 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.07 (br s, 1H, pyrrole ring *–NH*), 8.45–8.42 (m, 1H, pyridine ring), 8.22–8.20 (m, 1H, pyridine ring), 7.13-7.09 (m, 1H, pyridine ring), 6.65 (br s, 1H, imidazoline ring *–NH*), 3.57–3.54 (m, 4H, imidazoline ring), 2.54 (s, 3H, *–CH_3*); MS (ESI) *m/z* 201 $[M+1]^+$; Anal. Calcd for $C_{11}H_{12}N_4$: C, 65.92; H, 5.99; N 2.79. Found: C, 65.89; H, 5.96; N 2.77.

5.2.1.41. 3-(4,5-Dihydro-1*H*-imidazol-2-yl)-2-Phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (2e). Yield: 66%; white solid; mp 252–253 °C; IR (KBr): 3404, 2889, 1609, 1289, 1176, 776 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.11 (br s, 1H, pyrrole ring *–NH*), 8.47–8.45 (m, 1H, pyridine ring), 8.28–8.25 (m, 1H, pyridine ring), 7.29–7.17 (m, 5H, benzene ring), 7.14–7.10 (m, 1H, pyridine ring), 6.63 (br s, 1H, imidazoline ring *–NH*), 3.56–3.53 (m, 4H, imidazoline ring); MS (ESI) *m/z* 263 $[M+1]^+$; Anal. Calcd for $C_{16}H_{14}N_4$: C, 73.19; H, 5.34; N 21.35. Found: C, 73.16; H, 5.31; N 21.31.

5.2.1.42. 5-Chloro-3-(4,5-dihydro-1*H*-imidazol-2-yl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (2f). Yield: 72%; white solid; mp 242–245 °C; IR (KBr): 3402, 2889, 1612, 1286, 1176, 773, 734 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.09 (br s, 1H, pyrrole ring *–NH*), 8.81 (s, 1H, pyridine ring), 7.99 (s, 1H, pyridine ring), 7.26–7.17 (m, 5H, benzene ring), 6.65 (br s, 1H, imidazoline ring *–NH*), 3.55–3.53 (m, 4H, imidazoline ring); MS (ESI) *m/z* 298 $[M+1]^+$, 299 $[M+2]^+$; Anal. Calcd for $C_{16}H_{13}ClN_4$: C, 64.70; H, 4.38; N 18.87. Found: C, 64.67; H, 4.34; N 18.85.

5.2.1.43. 2-Cyclohexyl-3-(4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (2g). Yield: 69%; white solid; mp 271–273 °C; IR (KBr): 3398, 2892, 1610, 1446, 1283, 1171, 775 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.97 (br s, 1H, pyrrole ring *–NH*), 8.47–8.44 (m, 1H, pyridine ring), 8.25–8.22 (m, 1H, pyridine ring), 7.13–7.08 (m, 1H, pyridine ring), 6.67 (br s, 1H, imidazoline ring *–NH*), 3.57–3.54 (m, 4H, imidazoline ring), 2.17–2.13 (m, 1H, cyclohexyl ring), 1.27–1.22 (m, 10H, cyclohexyl ring); MS (ESI) *m/z* 269 $[M+1]^+$; Anal. Calcd for $C_{16}H_{20}N_4$: C, 71.54; H, 7.45; N 20.86. Found: C, 71.52; H, 7.41; N 20.84.

5.2.1.44. 5-Chloro-3-(4,5-dihydro-1*H*-imidazol-2-yl)-2-cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridine (2h). Yield: 66%; white solid; mp 279–281 °C; IR (KBr): 3402, 2896, 1610, 1442, 1286, 1173, 742 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.98 (br s, 1H, pyrrole ring *–NH*), 8.79 (s, 1H, pyridine ring), 7.99 (s, 1H, pyridine ring), 6.65 (br s, 1H, imidazoline ring *–NH*), 3.57–3.55 (m, 4H, imidazoline ring), 2.17–2.14 (m, 1H, cyclohexyl ring), 1.24–1.20 (m, 10H, cyclohexyl ring); MS (ESI) *m/z* 304 $[M+1]^+$, 305 $[M+2]^+$; Anal. Calcd for $C_{16}H_{19}ClN_4$: C, 63.40; H, 6.27; N 18.49. Found: C, 63.37; H, 6.23; N 18.46.

5.2.1.45. 3-(4,5-Dihydro-1*H*-imidazol-2-yl)-2-Ethyl-1*H*-pyrrolo[2,3-*b*]pyridine (2i). Yield: 68%; white solid; mp 236–238 °C; IR (KBr): 3396, 2896, 1612, 1447, 1371, 1287, 1174 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.09 (br s, 1H, pyrrole ring *–NH*), 8.46–8.42 (m, 1H, pyridine ring), 8.24–8.21 (m, 1H, pyridine ring), 7.13–7.09 (m, 1H, pyridine ring), 6.67 (br s, 1H, imidazoline ring *–NH*), 3.57–3.54 (m, 4H, imidazoline ring), 2.19 (q, 2H, $J = 7.2$ Hz, *–CH_2*CH_3), 1.27 (t, 3H, $J = 7.2$ Hz, –CH_2*CH_3*); MS (ESI) *m/z* 215 $[M+1]^+$; Anal. Calcd for $C_{12}H_{14}N_4$: C, 67.20; H, 6.53; N 26.13. Found: C, 67.16; H, 6.50; N 26.10.

5.2.1.46. 5-Chloro-3-(4,5-dihydro-1*H*-imidazol-2-yl)-2-ethyl-1*H*-pyrrolo[2,3-*b*]pyridine (2j). Yield: 69%; white solid; mp 230–232 °C; IR (KBr): 3397, 2898, 1612, 1442, 1371, 1284, 1176, 736 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.96 (br s, 1H, pyrrole ring *–NH*), 8.77 (s, 1H, pyridine ring), 7.96 (s, 1H, pyridine ring), 6.66 (br s, 1H, imidazoline ring *–NH*), 3.56–3.54 (m, 4H, imidazoline ring), 2.18 (q, 2H, $J = 7.2$ Hz, *–CH_2*CH_3), 1.27 (t, 3H, $J = 7.2$ Hz, –CH_2*CH_3*); MS (ESI) *m/z* 250 $[M+1]^+$, 251 $[M+2]^+$; Anal. Calcd for $C_{12}H_{13}ClN_4$: C, 57.89; H, 5.23; N 22.52. Found: C, 57.86; H, 5.20; N 22.49.

5.2.1.47. 2-Benzyl-3-(4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (2k). Yield: 71%; white solid; mp 263–265 °C; IR (KBr): 3404, 2897, 1612, 1469, 1282, 1175, 776 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 12.08 (br s, 1H, pyrrole ring *–NH*), 8.46–8.44 (m,

1H, pyridine ring), 8.28–8.26 (m, 1H, pyridine ring), 7.29–7.17 (m, 5H, benzene ring), 7.16–7.10 (m, 1H, pyridine ring), 6.65 (br s, 1H, imidazoline ring –*NH*), 3.56–3.54 (m, 4H, imidazoline ring), 3.87 (s, 2H, benzyl –*CH*$_2$); MS (ESI) *m*/*z* 277 [M+1]$^+$; Anal. Calcd for $C_{17}H_{16}N_4$: C, 73.82; H, 5.79; N 20.26. Found: C, 73.80; H, 5.76; N 20.23.

5.2.1.48. 5-Chloro-3-(4,5-dihydro-1*H*-imidazol-2-yl)-2-benzyl-1*H*-pyrrolo[2,3-*b*]pyridine (2l). Yield: 70%; white solid; mp 281–283 °C; IR (KBr): 3404, 2892, 1612, 1468, 1284, 1172, 764 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.03 (br s, 1H, pyrrole ring –*NH*), 8.79 (s, 1H, pyridine ring), 7.97 (s, 1H, pyridine ring), 7.26–7.17 (m, 5H, benzene ring), 6.65 (br s, 1H, imidazoline ring –*NH*), 3.55–3.53 (m, 4H, imidazoline ring), 3.86 (s, 2H, benzyl –*CH*$_2$); MS (ESI) *m*/*z* 312 [M+1]$^+$, 313 [M+2]$^+$; Anal. Calcd for $C_{17}H_{15}ClN_4$: C, 65.64; H, 4.83; N 18.02. Found: C, 65.61; H, 4.80; N 18.00.

5.2.2. General method for the synthesis of 2,5-disubstituted-3-(4,5-dihydro-1*H*-imidazol-2-yl)-thieno[2,3-*b*]pyridine (3a–l)

5.2.2.1. Synthesis of Thieno[2,3-*b*]pyridin-3-carbonitrile (9a). A mixture of thieno[2,3-*b*]pyridin-3-ylamine **8** (2.21 mmol), $NaNO_2$ (2.43 mmol), and concentrated HCl (1 mL) was stirred at 5 °C for 2 h. The pH of the reaction mixture was adjusted with $NaHCO_3$ to 7 and to it, a mixture of CuCN (2.65 mmol) and NaCN (2.65 mmol), dissolved in water (5 mL), was added. The reaction mixture was heated under reflux for 3 h, cooled to room temperature, diluted with the ice-cold water, and the solid obtained was filtered, washed with water, and dried to get the pure compound.[31] Using above procedure, total 12 derivatives of 2,5-disubstituted-thieno[2,3-*b*]pyridin-3-carbonitrile (**9a**–**l**) were prepared and their physicochemical properties and spectral data are listed below.

Yield: 68%; white solid; mp 96–98 °C; IR (KBr): 3125, 2886, 2237, 838 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.41 (s, 1H, thiophene ring –*CH*), 8.25–8.24(m, 1H, pyridine ring), 7.97–7.94 (m, 1H, pyridine ring), 7.27–7.19 (m, 1H, pyridine ring); MS (ESI) *m*/*z* 161 [M+1]$^+$; Anal. Calcd for $C_8H_4N_2S$: C, 59.98; H, 2.52; N 17.49. Found: C, 59.95; H, 2.50; N 17.46.

5.2.2.2. 5-Chloro-thieno[2,3-*b*]pyridin-3-carbonitrile (9b). Yield: 70%; white solid; mp 92–94 °C; IR (KBr): 3129, 2887, 2232, 872, 743 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.41 (s, 1H, thiophene ring –*CH*), 8.79–8.76 (m, 1H, pyridine ring), 7.96–7.94 (m, 1H, pyridine ring); MS (ESI) *m*/*z* 195 [M+1]$^+$, 196 [M+2]$^+$; Anal. Calcd for $C_8H_3ClN_2S$: C, 49.37; H, 1.55; N 14.39. Found: C, 49.34; H, 1.51; N 14.36.

5.2.2.3. 5-Chloro-2-methyl-thieno[2,3-*b*]pyridin-3-carbonitrile (9c). Yield: white solid; mp 99–101 °C; IR (KBr): 3128, 2896, 2234, 1367, 869, 739 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.81–8.77 (m, 1H, pyridine ring), 7.97–7.95 (m, 1H, pyridine ring), 2.48 (s, 3H, –*CH*$_3$); MS (ESI) *m*/*z* 209 [M+1]$^+$, 210 [M+2]$^+$; Anal. Calcd for $C_9H_5ClN_2S$: C, 51.80; H, 2.42; N 13.42. Found: C, 51.77; H, 2.40; N 13.40.

5.2.2.4. 2-Methyl-thieno[2,3-*b*]pyridin-3-carbonitrile (9d). Yield: 70%; white solid; mp 111–113 °C; IR (KBr): 3132, 2891, 2232, 1364, 873 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.26–8.24 (m, 1H, pyridine ring), 7.97–7.93 (m, 1H, pyridine ring), 7.29–7.26 (m, 1H, pyridine ring), 2.51 (s, 3H, –*CH*$_3$); MS (ESI) *m*/*z* 175 [M+1]$^+$; Anal. Calcd for $C_9H_6N_2S$: C, 62.04; H, 3.47; N 16.08. Found: C, 62.02; H, 3.43; N 16.04.

5.2.2.5. 2-Phenyl-thieno[2,3-*b*]pyridin-3-carbonitrile (9e). Yield: 71%; white solid; mp 106–108 °C; IR (KBr): 3129, 2886, 2228, 874, 769 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.29–8.27 (m, 1H, pyridine ring), 7.98–7.95 (m, 1H, pyridine ring), 7.34–7.29 (m, 5H, benzene ring), 7.28–7.26 (m, 1H, pyridine ring); MS (ESI) *m*/*z* 237 [M+1]$^+$; Anal. Calcd for $C_{14}H_8N_2S$: C, 71.16; H, 3.14; N 11.86. Found: C, 71.13; H, 3.11; N 11.83.

5.2.2.6. 5-Chloro-2-phenyl-thieno[2,3-*b*]pyridin-3-carbonitrile (9f). Yield: 69%; white solid; mp 93-95 °C; IR (KBr): 3130, 2889, 2231, 869, 771, 736 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.79–8.76 (m, 1H, pyridine ring), 7.98–7.97 (m, 1H, pyridine ring), 7.33-7.29 (m, 5H, benzene ring); MS (ESI) *m*/*z* 271 [M+1]$^+$, 272 [M+2]$^+$; Anal. Calcd for $C_{14}H_7ClN_2S$: C, 62.11; H, 2.61; N 10.35. Found: C, 62.08; H, 2.58; N 10.31.

5.2.2.7. 2-Cyclohexyl-thieno[2,3-*b*]pyridin-3-carbonitrile (9g). Yield: 66%; white solid; mp 90–92 °C; IR (KBr): 3127, 2889, 2234, 1446, 881 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.27–8.24 (m, 1H, pyridine ring), 7.97–7.95 (m, 1H, pyridine ring), 7.29–7.27 (m, 1H, pyridine ring), 2.19–2.17 (m, 1H, cyclohexyl ring), 1.27–1.21 (m, 10H, cyclohexyl ring); MS (ESI) *m*/*z* 243 [M+1]$^+$; Anal. Calcd for $C_{14}H_{14}N_2S$: C, 69.39; H, 5.82; N 11.56. Found: C, 69.35; H, 5.80; N 11.53.

5.2.2.8. 5-Chloro-2-cyclohexyl-thieno[2,3-*b*]pyridin-3-carbonitrile (9h). Yield: 68%; white solid; mp 109–111 °C; IR (KBr): 3127, 2891, 2232, 1443, 874, 743 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.80–8.78 (m, 1H, pyridine ring), 7.96–7.93 (m, 1H, pyridine ring), 2.18–2.17 (m, 1H, cyclohexyl ring), 1.27–1.23 (m, 10H, cyclohexyl ring); MS (ESI) *m*/*z* 277 [M+1]$^+$, 278 [M+2]$^+$; Anal. Calcd for $C_{14}H_{13}ClN_2S$: C, 60.75; H, 4.73; N 10.12. Found: C, 60.71; H, 4.70; N 10.10.

5.2.2.9. 2-Ethyl-thieno[2,3-*b*]pyridin-3-carbonitrile (9i). Yield: 69%; white solid; mp 106–108 °C; IR (KBr): 3132, 2889, 2232, 1446, 1371, 870 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.29–8.27 (m, 1H, pyridine ring), 7.97–7.93 (m, 1H, pyridine ring), 7.29–7.27 (m, 1H, pyridine ring), 2.19 (q, 2H, J = 7.1Hz, –*CH*$_2$CH$_3$), 1.26 (t, 3H, J = 7.1Hz, –CH$_2$*CH*$_3$); MS (ESI) *m*/*z* 189 [M+1]$^+$; Anal. Calcd for $C_{10}H_8N_2S$: C, 63.80; H, 4.28; N 14.88. Found: C, 63.77; H, 4.24; N 14.84.

5.2.2.10. 5-Chloro-2-ethyl-thieno[2,3-*b*]pyridin-3-carbonitrile (9j). Yield: 66%; white solid; mp 99–101 °C; IR (KBr): 3129, 2890, 2232, 1447, 1370, 873,

734 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 8.79–8.76 (m, 1H, pyridine ring), 7.98–7.95 (m, 1H, pyridine ring), 2.17 (q, 2H, $J = 7.1$ Hz, $-CH_2CH_3$), 1.24 (t, 3H, $J = 7.1$Hz, $-CH_2CH_3$); MS (ESI) *m/z* 223 $[M+1]^+$, 224 $[M+2]^+$; Anal. Calcd for $C_{10}H_7ClN_2S$: C, 53.93; H, 3.17; N 12.58. Found: C, 53.90; H, 3.13; N 12.54.

5.2.2.11. 2-Benzyl-thieno[2,3-*b*]pyridin-3-carbonitrile (9k). Yield: 70%; white solid; mp 88–90 °C; IR (KBr): 3128, 2889, 2237, 1471, 869, 773 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 8.27–8.23 (m, 1H, pyridine ring), 7.94–7.92 (m, 1H, pyridine ring), 7.33–7.28 (m, 5H, benzene ring), 7.27–7.26 (m, 1H, pyridine ring), 3.81 (s, 2H, benzyl $-CH_2$); MS (ESI) *m/z* 251 $[M+1]^+$; Anal. Calcd for $C_{15}H_{10}N_2S$: C, 71.97; H, 4.03; N 11.19. Found: C, 71.94; H, 4.00; N 11.16.

5.2.2.12. 5-Chloro-2-benzyl-thieno[2,3-*b*]pyridin-3-carbonitrile (9l). Yield: 72%; white solid; mp 112–114 °C; IR (KBr): 3129, 2896, 2234, 1462, 874, 767 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 8.79–8.77 (m, 1H, pyridine ring), 7.98–7.95 (m, 1H, pyridine ring), 7.34–7.28 (m, 5H, benzene ring), 3.79 (s, 2H, benzyl $-CH_2$); MS (ESI) *m/z* 285 $[M+1]^+$, 286 $[M+2]^+$; Anal. Calcd for $C_{15}H_9ClN_2S$: C, 63.27; H, 3.19; N 9.84. Found: C, 63.24; H, 3.15; N 9.81.

5.2.2.13. Synthesis of 3-(4,5-dihydro-1*H*-imidazol-2-yl)-thieno[2,3-*b*]pyridine (3a). A mixture of Thieno[2,3-*b*]pyridine-3-carbonitrile **9a** (0.63 mmol), EDA (2 mL), and P_2S_5 (0.23 mmol) was refluxed at 120 °C for 5 h. The reaction mixture was poured into ice and extracted with DCM. The DCM layer was washed with water and brine. Finally, the organic layer was dried over anhydrous Na_2SO_4 and evaporated to get greenish solid. The pure product was obtained by recrystallization from a mixture of ethyl acetate hexane (1:9).[22] Using above procedure, total 12 derivatives of 2,5-disubstituted-3-(4,5-dihydro-1*H*-imidazol-2-yl)-thieno[2,3-*b*]pyridine (**3a**–**l**) were prepared and their physicochemical properties and spectral data are listed below.

Yield: 65%; white solid; mp 142–144 °C; IR (KBr): 3132, 2893, 2234, 1289, 1178, 838, 776 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 8.41 (s, 1H, thiophene ring $-CH$), 8.25–8.24 (m, 1H, pyridine ring), 7.97–7.94 (m, 1H, pyridine ring), 7.27–7.19 (m, 1H, pyridine ring), 6.15 (br s, 1H, imidazoline ring $-NH$), 3.54–3.52 (m, 4H, imidazoline ring); MS (ESI) *m/z* 204 $[M+1]^+$; Anal. Calcd for $C_{10}H_9N_3S$: C, 59.09; H, 4.46; N 20.67. Found: C, 59.06; H, 4.42; N 20.64.

5.2.2.14. 5-Chloro-3-(4,5-dihydro-1*H*-imidazol-2-yl)-thieno[2,3-*b*]pyridine (3b). Yield: 67%; white solid; mp 149–151 °C; IR (KBr): 3134, 2897, 2235, 1289, 1173, 872, 747 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 8.43 (s, 1H, thiophene ring $-CH$), 8.79–8.77 (m, 1H, pyridine ring), 7.99–7.96 (m, 1H, pyridine ring), 6.21 (br s, 1H, imidazoline ring $-NH$), 3.55-3.52 (m, 4H, imidazoline ring); MS (ESI) *m/z* 238 $[M+1]^+$, 239 $[M+2]^+$; Anal. Calcd for $C_{10}H_8ClN_3S$: C, 50.53; H, 3.39; N 17.68. Found: C, 50.50; H, 3.36; N 17.64.

5.2.2.15. 5-Chloro-3-(4,5-dihydro-1*H*-imidazol-2-yl)-2-methyl-thieno[2,3-*b*]pyridine (3c). Yield: 66%; white solid; mp 161–163 °C; IR (KBr): 3136, 2896, 2232, 1367, 1285, 1175, 873, 741 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 8.83-8.79 (m, 1H, pyridine ring), 7.99–7.97 (m, 1H, pyridine ring), 6.19 (br s, 1H, imidazoline ring $-NH$), 3.54–3.52 (m, 4H, imidazoline ring), 2.46 (s, 3H, $-CH_3$); MS (ESI) *m/z* 253 $[M+1]^+$, 254 $[M+2]^+$; Anal. Calcd for $C_{11}H_{10}ClN_3S$: C, 52.48; H, 4.00; N 16.69. Found: C, 52.44; H, 3.98; N 16.66.

5.2.2.16. 3-(4,5-Dihydro-1*H*-imidazol-2-yl)-2-methyl-thieno[2,3-*b*]pyridine (3d). Yield: 70%; white solid; mp 166–168 °C; IR (KBr): 3129, 2893, 2234, 1364, 1279, 1179, 873, 768 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 8.27–8.25 (m, 1H, pyridine ring), 7.97–7.95 (m, 1H, pyridine ring), 7.27–7.21 (m, 1H, pyridine ring), 6.17 (br s, 1H, imidazoline ring $-NH$), 3.55–3.52 (m, 4H, imidazoline ring), 2.48 (s, 3H, $-CH_3$); MS (ESI) *m/z* 218 $[M+1]^+$; Anal. Calcd for $C_{11}H_{11}N_3S$: C, 60.80; H, 5.10; N 19.34. Found: C, 60.77; H, 5.07; N 19.30.

5.2.2.17. 3-(4,5-Dihydro-1*H*-imidazol-2-yl)-2-phenyl-thieno[2,3-*b*]pyridine (3e). Yield: 66%; white solid; mp 181–183 °C; IR (KBr): 3126, 2891, 2234, 1281, 1176, 874, 773 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 8.27–8.25 (m, 1H, pyridine ring), 7.97–7.95 (m, 1H, pyridine ring), 7.34–7.29 (m, 5H, benzene ring), 7.24–7.21 (m, 1H, pyridine ring), 6.13 (br s, 1H, imidazoline ring $-NH$), 3.55–3.52 (m, 4H, imidazoline ring); MS (ESI) *m/z* 291 $[M+1]^+$; Anal. Calcd for $C_{16}H_{13}N_3S$: C, 68.79; H, 4.69; N 15.04. Found: C, 68.76; H, 4.67; N 15.00.

5.2.2.18. 5-Chloro-3-(4,5-dihydro-1*H*-imidazol-2-yl)-2-phenyl-thieno[2,3-*b*]pyridine (3f). Yield: 70%; white solid; mp 188–190 °C; IR (KBr): 3133, 2892, 2231, 1283, 1172, 869, 772, 739 cm^{-1}.^1H NMR (300 MHz, DMSO-d_6) δ 8.81–8.79 (m, 1H, pyridine ring), 7.98–7.97 (m, 1H, pyridine ring), 7.32–7.26 (m, 5H, benzene ring), 6.17 (br s, 1H, imidazoline ring $-NH$), 3.56–3.52 (m, 4H, imidazoline ring); MS (ESI) *m/z* 315 $[M+1]^+$, 316 $[M+2]^+$; Anal. Calcd for $C_{16}H_{12}ClN_3S$: C, 61.24; H, 3.85; N 13.39. Found: C, 61.21; H, 3.83; N 13.36.

5.2.2.19. 2-Cyclohexyl-3-(4,5-dihydro-1*H*-imidazol-2-yl)-thieno[2,3-*b*]pyridine (3g). Yield: 68%; white solid; mp 176–178 °C; IR (KBr): 3127, 2891, 2234, 1443, 1283, 1173, 881, 773 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 8.29–8.27 (m, 1H, pyridine ring), 7.99–7.97 (m, 1H, pyridine ring), 7.25–7.21 (m, 1H, pyridine ring), 6.19 (br s, 1H, imidazoline ring $-NH$), 3.55–3.53 (m, 4H, imidazoline ring), 2.18–2.15 (m, 1H, cyclohexyl ring), 1.27–1.23 (m, 10H, cyclohexyl ring); MS (ESI) *m/z* 286 $[M+1]^+$; Anal. Calcd for $C_{16}H_{19}N_3S$: C, 67.33; H, 6.71; N 14.72. Found: C, 67.30; H, 6.69; N 14.70.

5.2.2.20. 5-Chloro-3-(4,5-dihydro-1*H*-imidazol-2-yl)-2-cyclohexyl-thieno[2,3-*b*]pyridine (3h). Yield: 69%; white solid; mp 171–173 °C; IR (KBr): 3129, 2895, 2232, 1447, 1289, 1171, 874, 776, 743 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 8.81–8.79 (m, 1H, pyridine ring), 7.98–7.97 (m, 1H, pyridine ring), 6.19 (br s, 1H, imidazoline ring $-NH$), 3.54–3.52 (m, 4H, imidazoline

ring), 2.19–2.15 (m, 1H, cyclohexyl ring), 1.28–1.25 (m, 10H, cyclohexyl ring); MS (ESI) *m/z* 321 $[M+1]^+$, 322 $[M+2]^+$; Anal. Calcd for $C_{16}H_{18}ClN_3S$: C, 60.08; H, 5.67; N 13.14. Found: C, 60.04; H, 5.63; N 13.11.

5.2.2.21. 3-(4,5-Dihydro-1*H*-imidazol-2-yl)-2-ethyl-thieno[2,3-*b*]pyridine (3i). Yield: 67%; white solid; mp 147–149 °C; IR (KBr): 3134, 2893, 2232, 1446, 1371, 1282, 1170, 873, 774 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 8.27–8.25 (m, 1H, pyridine ring), 7.98–7.95 (m, 1H, pyridine ring), 7.27–7.24 (m, 1H, pyridine ring), 6.17 (br s, 1H, imidazoline ring –*NH*), 3.55–3.52 (m, 4H, imidazoline ring), 2.19 (q, 2H, $J = 7.1$Hz, $-CH_2CH_3$), 1.24 (t, 3H, $J = 7.1$Hz, $-CH_2CH_3$); MS (ESI) *m/z* 232 $[M+1]^+$; Anal. Calcd for $C_{12}H_{13}N_3S$: C, 62.31; H, 5.66; N 18.17. Found: C, 62.29; H, 5.63; N 18.14.

5.2.2.22. 5-Chloro-3-(4,5-dihydro-1*H*-imidazol-2-yl)-2-ethyl-thieno[2,3-*b*]pyridine (3j). Yield: 66%; white solid; mp 152–154 °C; IR (KBr): 3123, 2889, 2229, 1443, 1372, 1286, 1172, 873, 778, 739 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 8.79–8.76 (m, 1H, pyridine ring), 7.99–7.97 (m, 1H, pyridine ring), 6.19 (br s, 1H, imidazoline ring –*NH*), 3.54–3.52 (m, 4H, imidazoline ring), 2.17 (q, 2H, $J = 7.1$Hz, $-CH_2CH_3$), 1.22 (t, 3H, $J = 7.1$Hz, $-CH_2CH_3$); MS (ESI) *m/z* 267 $[M+1]^+$, 268 $[M+2]^+$; Anal. Calcd for $C_{12}H_{12}ClN_3S$: C, 54.23; H, 4.55; N 15.81. Found: C, 54.20; H, 4.51; N 15.79.

5.2.2.23. 2-Benzyl-3-(4,5-dihydro-1*H*-imidazol-2-yl)-thieno[2,3-*b*]pyridine (3k). Yield: 70%; white solid; mp 162-164 °C; IR (KBr): 3125, 2887, 2234, 1467, 1279, 1172, 869, 773 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 8.25–8.23 (m, 1H, pyridine ring), 7.97–7.95 (m, 1H, pyridine ring), 7.32–7.29 (m, 5H, benzene ring), 7.24–7.22 (m, 1H, pyridine ring), 6.13 (br s, 1H, imidazoline ring –*NH*), 3.55–3.52 (m, 4H, imidazoline ring), 3.81 (s, 2H, benzyl $-CH_2$); MS (ESI) *m/z* 294 $[M+1]^+$; Anal. Calcd for $C_{17}H_{15}N_3S$: C, 69.59; H, 5.15; N 14.32. Found: C, 69.56; H, 5.11; N 14.29.

5.2.2.24. 5-Chloro-3-(4,5-dihydro-1*H*-imidazol-2-yl)-2-benzyl-thieno[2,3-*b*]pyridine (3l). Yield: 68%; white solid; mp 167–169 °C; IR (KBr): 3122, 2893, 2237, 1451, 1283, 1172, 874, 767 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 8.81–8.78 (m, 1H, pyridine ring), 7.98–7.96 (m, 1H, pyridine ring), 7.32–7.26 (m, 5H, benzene ring), 6.17 (br s, 1H, imidazoline ring –*NH*), 3.56–3.52 (m, 4H, imidazoline ring), 3.83 (s, 2H, benzyl $-CH_2$); MS (ESI) *m/z* 328 $[M+1]^+$, 329 $[M+2]^+$; Anal. Calcd for $C_{17}H_{14}ClN_3S$: C, 62.28; H, 4.30; N 12.82. Found: C, 62.24; H, 4.26; N 12.80.

5.3. In vitro glucose-dependent insulin secretion (RIN5F cell assay screening protocol)

Rat Insulinoma (RIN5F) cells were cultured in RPMI 1640 medium supplemented with sodium pyruvate (1 mM) Hepes and Glucose (4.5 g/L) in a humidified incubator (5% CO_2), at 37 °C. After trypsinization, RIN5F cells were seeded at a concentration of 0.2×10^6 cells per well, in 12-well plates. The cells were grown overnight to 80% confluence and insulin secretion experiments were performed as follows.[18,19] Cells were washed once with PBS solution followed by 40 min. incubation in fresh Krebs-Ringer Balanced Buffer containing NaCl (115 mmol/L), KCl (4.7 mmol/L), $CaCl_2$ (1.28 mmol/L), $MgSO_4.7H_2O$ (1.2 mmol/L), KH_2PO_4 (1.2 mmol/L), $NaHCO_3$ (10 mmol/L), and Hepes (25 mmol/L), containing glucose (1.1 mM) and B.S.A (0.5%), pH 7.4. The buffer was replaced after 40 min and the cells were incubated (37 °C) with the test and the standard compounds, at different concentrations, for 30 min both in the presence (16.7 mM) and absence (0 mM) of glucose load. The supernatant was collected and the insulin amount was measured by ultrasensitive Rat insulin ELISA kit (Crystal Chem, IL). The protein was estimated in the supernatant using Bicinchoninic Acid kit, according to the manufacturer's protocol (Sigma–Aldrich, MO). The total insulin content obtained in picogram (pg) was divided with the total protein (μg) in order to normalize for differences in cell density between wells.

5.4. Demonstration of in vivo efficacy of test compounds in C57BL/6J mice

5.4.1. Animals. Acute single dose 120-min time-course experiments were conducted in male C57BL/6J mice, age 8–12 weeks, mean body weight 25–30 g, bred in-house. Animals were housed in groups of 6 animals per cage, for a week, in order to habituate them to vivarium conditions (25 ± 4 °C, 60–65% relative humidity, 12:12 h light:dark cycle, with lights on at 6.00 a.m.). All the animal experiments were conducted according to the internationally valid guidelines following approval by the 'Zydus Research Center Animal Ethical Committee'.

5.4.2. Procedure. The in vivo glucose lowering properties of some of the representative test compounds **2c** and **3c** and standard compound BL 11282 were evaluated in C57BL/6J animal models as described below. Two days prior to the study, the animals were randomized and divided into 5 groups ($n = 6$), based upon their fed glucose levels. On the day of experiment, food was withdrawn from all the cages, water was given ad libitum and animals were kept for overnight fasting. Vehicle (normal saline)/test/standard compounds were administered intraperitoneally on a body weight basis soon after the 0 min. blood collection from each animal and the subsequent blood collections were done at 30, 60 and 120 min, via retro-orbital route, under light ether anesthesia.[20,21]

Blood samples were centrifuged and the separated serum was immediately subjected to glucose estimation. Serum for insulin estimation was stored at −70 °C until used for the insulin estimation. The glucose estimation was conducted with DPEC-GOD/POD method (Ranbaxy Fine Chemicals Limited, Diagnostic Division, India), using Spectramax-190, in 96-microwell plate reader (Molecular Devices Corporation, Sunnyvale, California). Mean values of duplicate samples were calculated using Microsoft excel and the GraphPad Prism software (Ver 4.0) was used to plot a 0 min base line corrected line graph, area under the curve (0–120 min AUC),

and baseline corrected area under the curve (0 min BCAUC). The AUC and BCAUC obtained from graphs were analyzed for one-way ANOVA, followed by Dunnett's post test, using GraphPad prism software. Furthermore, the insulin estimation was conducted using rat/mouse insulin ELISA kit (Linco Research, Missouri, USA). Changes in the blood insulin and glucose levels with compounds **2c**, **3c**, and BL11282 are shown in Figures 2 and 3, respectively.

Acknowledgments

We are grateful to the management of Zydus Group for encouragement. We thank the analytical department for giving analytical support.

References and notes

1. Ashcroft, F. M. *Horm. Metab. Res.* **1996**, *28*, 456.
2. Pfeiffer, E. F.; Thum, C.; Raptis, S.; Beischer, W.; Ziegler, R. *Horm. Metab. Res.* **1976**, 112.
3. Schulz, A.; Hasselblatt, A. *Naunyn Schmiedeberg's Arch. Pharmacol* **1989**, *340*, 321.
4. Le Brigand, L.; Virsolvy, A.; Manechez, D.; Godfroid, J. J.; Guardiola-Lemaitre, B.; Gribble, F. M.; Ashcroft, F. M.; Bataille, D. *Br. J. Pharmacol.* **1999**, *128*, 1021.
5. Eglen, R. M.; Hudson, A. L.; Kendall, D. A.; Nutt, D. J.; Morgan, N. G.; Wilson, V. G.; Dilon, M. P. *Trends Pharmacol. Sci.* **1998**, *19*, 381.
6. Plant, T. D.; Henquin, J. C. *Br. J. Pharmacol.* **1990**, *101*, 115.
7. Proks, P.; Ashcroft, F. M. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 11716.
8. Zaitsev, S. V.; Efanov, A. M.; Efanova, J. B.; Larsson, O.; Ostenson, C. G.; Gold, G.; Berggren, P. O.; Efendic, S. *Diabetes* **1996**, *45*, 1610.
9. Cerasi, E.; Efendic, S.; Luft, R. *Lancet* **1969**, *2*, 301.
10. Morgan, N. G. *Exp. Opin. Invest. Drugs* **1999**, *8*, 575.
11. Jakobsen, P.; Madsen, P.; Andersen, H. *Eur. J. Med. Chem.* **2003**, *38*, 357.
12. Morgan, N. G.; Chan, S. L. F.; Mourtada, M.; Monks, L. K.; Ramsden, C. *Ann. N. Y. Acad. Sci.* **1999**, *381*, 217.
13. Mest, H. J.; Raap, A.; Schloss, J.; Treinies, I.; Paal, M.; Giese, U.; Koivisto, V. *Naunyn Schmiedeberg's Arch. Pharmacol.* **2001**, *364*, 47.
14. Efendic, S.; Efanov, A. M.; Berggen, P.; Zaitsev, S. V. *Diabetes* **2002**, *51*, S448.
15. Brenner, M. B.; Gromada, J.; Efanov, A. M.; Bokvist, K.; Mest, H. J. *Ann. N. Y. Acad. Sci.* **2003**, *1009*, 332.
16. Efanov, A. M.; Zaitse, S. V.; Mest, H. J.; Raap, A.; Appelskog, I. B.; Larsson, O.; Berggren, P. O.; Efendic, S. *Diabetes* **2001**, *50*, 797.
17. Bahekar, R. H.; Jain, M. R.; Goel, A.; Patel, D. N.; Prajapati, V. M.; Gupta, A. A.; Jadav, P. A.; Patel, P. R. *Bioorg. Med. Chem.* **2007**, *15*, 3248.
18. Montrose-Rafizadeh, C.; Wang, Y.; Janczewski, T. E.; Henderson, T. E.; Egan, J. M. *Mol. Cell. Endocrinol.* **1997**, *130*, 109.
19. Wang, X.; Zhou, J.; Doyle, M. E.; Egan, J. M. *Endocrinology* **2001**, *5*, 1820.
20. Chen, D.; Wang, M. *Diabetes Obesity Metabolism* **2005**, *7*, 307.
21. Kim, J. G.; Baggio, L. L.; Bridon, D. P.; Castaigne, J. P.; Robitaille, M. F.; Jette, L.; Benquet, C.; Drucker, D. J. *Diabetes* **2003**, *52*, 751.
22. Anastassiadou, M.; Danoun, S.; Crane, L.; Mouysset, G. B.; Payard, M.; Caignard, D. H.; Rettori, M. C.; Renard, P. *Bioorg. Med. Chem.* **2001**, *9*, 585.
23. Corbel, J. C.; Uriac, P.; Huet, J.; Martin, C. A. E.; Advenier, C. *Eur. J. Med. Chem.* **1995**, *30*, 3.
24. Doyle, T. J.; Haseltine, J. *J. Heterocycl. Chem.* **1994**, *31*, 1417.
25. Chapleo, C. B.; Myers, P. L.; Butler, R. C. M.; Davis, J. A.; Doxey, J. C.; Higgins, S. D.; Mayers, M.; Roach, A. G.; Smith, C. F. C.; Stillings, M. R.; Welbourn, A. P. *J. Med. Chem.* **1984**, *27*, 570.
26. Neef, G.; Eder, U.; Sauer, G. *J. Org. Chem.* **1981**, *46*, 2824.
27. Robison, M. M.; Robison, B. L. *J. Am. Chem. Soc.* **1956**, *78*, 1247.
28. Verbiscar, A. J. *J. Med. Chem.* **1972**, *15*, 149.
29. Hands, D.; Bishop, B.; Cameron, M.; Edwards, J. S.; Cottrll, I. F.; Wright, S. H. B. A. *Synthesis* **1996**, 877.
30. Herbert, R.; Wibberley, D. G. *J. Chem. Soc.* **1969**, 1505.
31. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; ELBS: England, 1989, pp 938.
32. Kaigorodova, Y. A.; Vasilin, V. K.; Konyushkin, L. D.; Usova, Y. B.; Krapivin, G. D. *Molecules* **2000**, *5*, 1085.
33. Hary, U.; Roettig, U.; Paal, M. *Tetrahedron Lett.* **2001**, *42*, 5187.