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Design, synthesis, and biological evaluation of substituted-*N*-(thieno[2,3-*b*]pyridin-3-yl)-guanidines, *N*-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidines, and *N*-(1*H*-indol-3-yl)-guanidines☆

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Abstract—Sulfonylureas stimulate insulin secretion independent of the blood glucose concentration and therefore cause hypoglycemia in type 2 diabetic patients. Over the last years, a number of aryl-imidazoline derivatives have been identified that stimulate insulin secretion in a glucose-dependent manner. In the present study, we have developed three series of substituted *N*-(thieno[2,3-*b*]pyridin-3-yl)-guanidine (**2a–l**), *N*-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (**3a–l**), and *N*-(1*H*-indol-3-yl)-guanidine (**4a–l**) as new class of antidiabetic agents. In vitro glucose-dependent insulinotropic activity of test compounds **2a–l**, **3a–l**, and **4a–l** was evaluated using RIN5F (Rat Insulinoma cell) based assay. All the test compounds showed concentration-dependent insulin secretion, only in presence of glucose load (16.7 mmol). Some of the test compounds (**2c**, **3c**, and **4c**) from each series were found to be equipotent to BL 11282 (standard aryl-imidazoline), which indicated that the guanidine group acts as a bioisostere of imidazoline ring system.

1. Introduction

The incidence of type 2 diabetes is increasing worldwide due to changing lifestyle and prevalence of obesity and the metabolic syndrome.[1] Clinically type 2 diabetes is characterized by elevated blood glucose level, caused by decreased insulin secretion from the pancreas, insulin resistance or both.[2] In diabetic patients it is important to control the elevated blood glucose level, both for the prevention and mitigation of diabetic complications.[3,4] Today many therapeutic options are available to treat hyperglycemia.[5] However, most of the insulin secretagogues which are commonly in practice exhibit serious side-effects such as hypoglycemia.[6] Therefore, agents that do not stimulate basal insulin secretion but augment glucose-induced insulin secretion hold a better therapeutic option for the safe and effective treatment of the type 2 diabetes.

In this regard, endogenous incretin hormone such as glucagon-like peptide (GLP-1) and its synthetic analog Exendin-4 appears to be very promising for the treatment and management of type 2 diabetes.[7] However, the GLP-1 agonists, which are available in the market or under clinical development, are peptide-based drugs and therefore mainly administered by the parenteral route of administration. Thus, the patient incompliance is going to be the major problem with such GLP-1 mimetics, until an oral drug or a non-invasive delivery system is made available.

In the last two decades, several aryl-imidazolines are reported to be potent stimulators of insulin secretion.[8,9] Aryl-imidazolines are known to bind with a putative I_3 receptor (a 3rd imidazoline binding site distinct from two imidazoline receptors I_1 and I_2) in pancreatic β-cells and thereby regulate insulin secretion.[10–12] Such aryl-imidazolines do not bind to α-adrenoceptors or K_{ATP} channels and exhibit only glucose-dependent insulin

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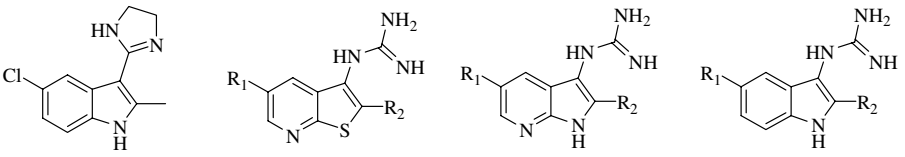


BL11282 (1) 2a-l 3a-l 4a-l

2,3&4a: R_1=H & R_2=H; **2,3&4b**: R_1=Cl & R_2=H;
2,3&4c: R_1=Cl & R_2=CH_3; **2,3&4d**: R_1=H & R_2=CH_3;
2,3&4e: R_1=H & R_2=C_6H_5; **2,3&4f**: R_1=Cl & R_2=C_6H_5;
2,3&4g: R_1=H & R_2=Cyclohex; **2,3&4h**: R_1=Cl & R_2=Cyclohex;
2,3&4i: R_1=H & R_2=C_2H_5; **2,3&4j**: R_1=Cl & R_2=C_2H_5;
2,3&4k: R_1=H & R_2=CH_2-C_6H_5; **2,3&4l**: R_1=Cl & R_2=CH_2-C_6H_5;

Figure 1. General structures of arylimidazoline (BL 11282) and hetero-aryl guanidine derivatives.

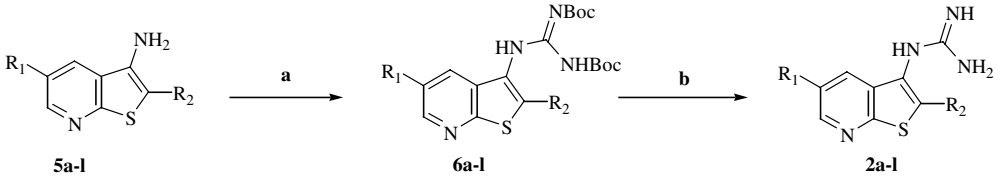
secretion.[13] Thus, aryl-imidazolines have developed substantial interest and have potential to become therapeutic agents for the treatment of type 2 diabetes.[14,15]

One such novel imidazoline compound is BL 11282 (**1**; Fig. 1).[16] Interestingly, BL 11282 does not block K_{ATP} channel and has shown glucose-dependent insulin secretion (in vitro), a pharmacological profile similar to GLP-1 agonist.[17,18] Knowing the in vitro glucose-dependent insulin secretion potential of BL 11282, in the present investigation, three series of hetero-aryl guanidine derivatives, mainly substituted *N*-(thieno[2,3-*b*]pyridin-3-yl)-guanidines (**2a**–**l**), *N*-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidines (**3a**–**l**), and *N*-(1*H*-indol-3-yl)-guanidines (**4a**–**l**), were designed as analog of BL 11282 and their in vitro glucose-dependent insulinotropic activity was evaluated using RIN5F (Rat insulinoma) cell-based assay.

2. Chemistry

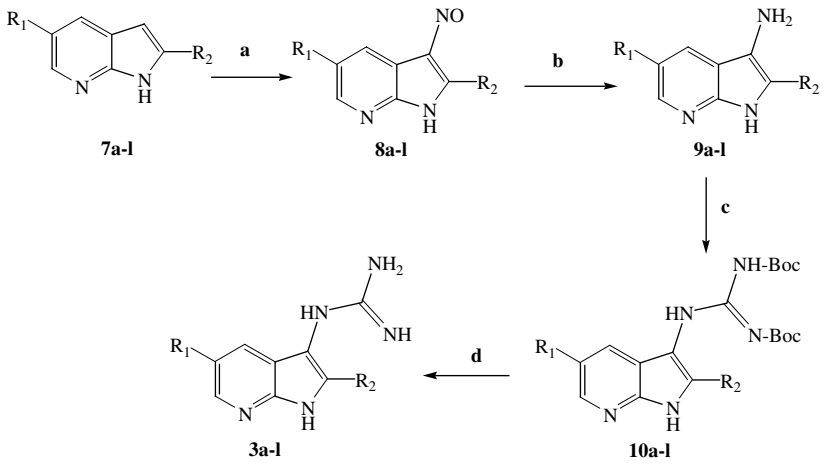
Synthesis of hetero-aryl guanidines (**2**–**4**) was carried out, using appropriate synthetic routes (Schemes 1–3). Initially, attempts were made to prepare hetero-aryl guanidines using commercially available guanylating reagents such as cyanamide,[19] *O*-methylisourea hydrogen sulfate,[20] 2-ethyl-2-thiopseudo hydrobromide,[21] 3,5-dimethylpyrazole-1-carboxamidine nitrate,[22] and 1*H*-pyrazole-1-carboxamidine hydrochloride.[23,24] However, none of the guanylating agents showed sufficient reactivity toward heteroaryl amines (compounds **5**, **9**, and **13**). Therefore, synthesis of compounds **2**–**4** was carried out by condensation of respective heteroaryl amines with bis-Boc-thiourea, using mercuric chloride ($HgCl_2$).[25–29] In this reaction, metal salt $HgCl_2$ was used to increase the reactivity of bis-Boc-thiourea, via its complex formation with the sulfur atom. When the same reaction was attempted without using a metal salt, instead of guanylated product, it led to the formation of unsymmetrical thiourea, indicating that the addition of metal salt is crucial for the facile reaction.[30] The bis-Boc-thiourea was used as a guanylating agent because the strong electron-withdrawing Boc-groups, present on bis-Boc-thiourea, increase the reactivity of thiourea and thereby facilitate the guanylation reaction, under the mild reaction condition.[31] The bis-Boc-thiourea was prepared from thiourea and di-*tert*-butyl-dicarbonate, in tetrahydrofuran (THF), using the literature procedure.[31] Finally, the bis-Boc-protected hetero-aryl guanidines (**6**, **10**, and **14**) upon deprotection with trifluoroacetic acid (TFA) cleavage mixture lead to the formation of title compounds **2**–**4**.

The starting material 2,5-disubstituted-thieno[2,3-*b*]pyridin-3-ylamine (**5**) was prepared from 2-mercapto-5-substituted-nicotinonitrile and different alkyl halides.[32] Intermediate compound 2,5-disubstituted-3-amino-7-azaindole (**9**) was prepared starting from 2,5-disubstituted-7-azaindole (**7**). In this reaction, nitrosation of the compound **7** was carried out by treatment with sodium nitrite ($NaNO_2$) and 2,5-disubstituted-3-nitroso-7-azaindole **(8)** was obtained, which was subsequently reduced to compound **9**, by treatment with sodium dithionite ($Na_2S_2O_4$) in sodium hydroxide (NaOH) and ethanol.[33] Furthermore, compound **7** was prepared starting from 5-substituted-3-methyl-pyridin-2-ylamine, by the directed ortho-lithiation reaction.[34] The 2,5-disubstituted-3-amino-indole (**13**) was prepared starting from 2,5-disubstituted-indole (**11**). In this reaction, nitration

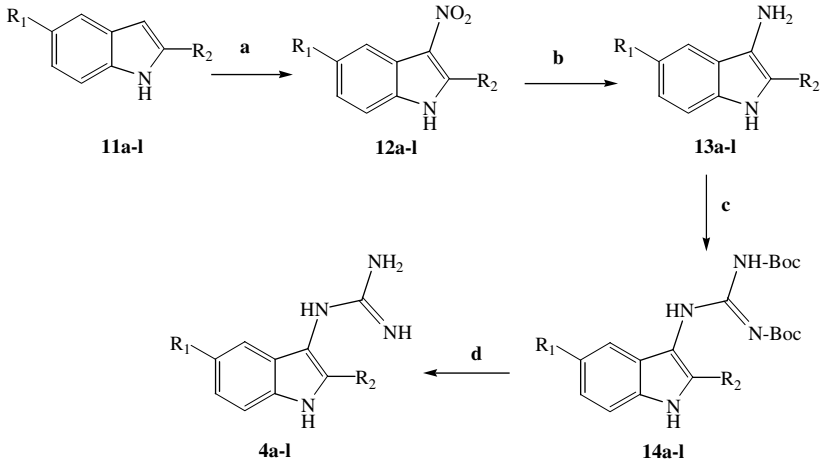


5a-l 6a-l 2a-l

Scheme 1. Reagents and conditions: (a) bis-Boc-thiourea, DMF, $HgCl_2$, TEA, 48 h stirring; (b) TFA:DCM (1:1, v/v), 1 h stirring at rt.



Scheme 2. Reagents and conditions: (a) $NaNO_2$, acetic acid, 30 min stirring at rt; (b) $Na_2S_2O_4$, NaOH, ethanol, 30 min reflux; (c) bis-Boc-thiourea, $HgCl_2$, TEA, DMF, 3 days stirring; (d) DCM:TFA (1:1, v/v), 1 h stirring at rt.



Scheme 3. Reagents and conditions: (a) $AgNO_3$, benzoyl chloride, ACN, 0 °C stirring for 45 min; (b) Pd/C (10%), H_2 (g); 50 psi, ethanol, 3 h; (c) bis-Boc-thiourea, $HgCl_2$, TEA, DMF, 3 day stirring; (d) DCM:TFA (1:1, v/v), 1 h stirring at rt.

of the compound **11** was carried out by treatment with benzoyl nitrate and 2,5-disubstituted-3-nitro-indole (**12**) was obtained, which was subsequently reduced to compound **13**, by treatment with Palladium charcoal.[35] The starting material 2,5-disubstituted-indoles (**11**) was prepared from aniline or *p*-chloro aniline, according to the Fischer indole synthesis.[36–38]

In general, compounds **2a**–**l**, **3a**–**l**, and **4a**–**l** were prepared in good yield, under the mild reaction condition, and the overall percentage yield was found to be in the range of 60–70%. The Infrared (IR) spectra of compounds **2**–**4** showed peaks in the region of ~3400 (N–H stretching) and 1600 (C–N bending), due to free NH_2 groups of guanidine. Compounds **6**, **10**, and **14** showed absorption peaks in the region of ~2850 (C–H stretching, aromatic), 1710 (C═O stretching), 1375 (C—H stretching, CH_3), and 1050 (C—O stretching), mainly due to bis-Boc groups. Compounds **5**, **9**, and **13** showed peaks in the region of ~3400 (N—H stretching) and 1610 (N—H bending), due to free amino group, and compounds **8** and **12** showed peak in the region of ~1540 (N═O stretching), due to nitroso group.

The ^{1}H NMR spectra of compounds **6**, **10**, and **14** showed chemical shift (δ ppm) in the range of ~1.3 (s, 9H) and 1.54 (s, 9H), due to bis-Boc groups. Compounds **2**–**4** showed disappearance of signals due to bis-Boc group and appearance of additional signals in the range of ~6.6 (br s, 2H) and 6.9 (s, 1H), due to –NH_2 and NH groups of free guanidine. Compounds **5**, **9**, and **13** showed chemical shift in the range of ~8.78 (br s, 2H), due to free amino group. The corresponding IR, ^{1}H NMR, ESI-MS, and CHN data are presented in Section 5.2. Synthesis of BL 11282 was carried out by literature procedure[37]. The Exendin-4 used in the in vitro assay was prepared in-house by Fmoc-based solid-phase peptide synthesis approach (peptide content 94%).

3. Results and discussion

3.1. In vitro insulin secretion assay results

In vitro glucose-dependent or -independent insulin secretion properties of test compounds **2a**–**l**, **3a**–**l**, and

4a–l were determined using a RIN5F cell assay.[39,40] Insulin secretion, both in presence and absence of 16.7 mM glucose was measured for Exendin-4, at 0.1, 1, and 10 nM and compounds **1**, **2a–l**, **3a–l**, and **4a–l**, at 0.1, 1, and 10 μM concentrations. 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), both in presence or absence of glucose load (0 and 16.7 mM), at 0.1 and 1 μM concentrations. Tolbutamide showed significant insulin secretion both in presence or absence of glucose load (Tables 1–3).

In thieno[2,3-*b*]pyridin-3-yl-guanidine series (**2a–l**), compounds **2c**, **2f**, and **2j** showed highest insulin secretion, compounds **2a**, **2b**, **2g–i**, **2k** and **2l** showed minimal insulin secretion, while compounds **2d** and **2e** showed moderate insulin secretion (Table 1). Among compounds **2c**, **2f**, and **2j**, compound **2c** showed highest insulin secretion. In 1*H*-pyrrolo[2,3-*b*]pyridin-3-yl-guanidine series (**3a–l**), compounds **3c**, **3f**, and **3j** showed highest insulin secretion, compounds **3a**, **3b**, **3g**, **3i**, **3k**, and **3l** showed minimal insulin secretion, while compounds **3d** and **3e** showed moderate insulin secretion (Table 2). In 1*H*-indol-3-yl-guanidine series (**4a–l**), compounds **4c**, **4f**, and **4j** showed highest insulin secretion, compound **4a**, **4b**, **4g**, **4i**, **4k**, and **4l** showed minimal insulin secretion, while compounds **4d** and **4e** showed moderate insulin secretion (Table 3). Among the compounds **4c**, **4f**, and **4j**, compound **4c** showed highest insulin secretion. In general, insulin secretion profile of compounds **2c**, **2f**, **2j**, **3c**, **3f**, and **3j** was found to be comparable with that of BL 11282, while compounds **4c**, **4f**, and **4j** showed BL 11282 like insulin secretion, in vitro. Furthermore, among these nine compounds from three different series, compounds **2c**, **3c**, and **4c** were found to be most potent compounds and among these three most potent compounds, compound *N*-(2-methyl, 5-chloro-1*H*-indol-3-yl)-guanidine (**4c**) was found to be equipotent to BL 11282.

Overall, substitution of R_1 with hydrogen atom drastically reduces potency of the test compound, in all the three series and as a result, compounds **2a**, **2g**, **2i**, **2k**, **3a**, **3g**, **3i**, **3k**, **4a**, **4g**, **4i**, and **4k** were found to be least potent compounds, among the representative compounds from each series. Substitution of R_2 with hydrogen (**2b**, **3b**, and **4b**), cyclohexyl (**2h**, **3h**, and **4h**) or benzyl group (**2l**, **3l**, and **4l**) significantly reduces activity. Among all the three series, compounds **2a**, **2b**, **2g–i**, **2k**, **2l**, **3a**, **3b**, **3g–i**, **3k**, **3l**, **4a**, **4b**, **4g–i**, **4k**, and **4l** were found to be the least potent compounds. Compounds with chloro-substitution at R_1 position and CH_3 group at R_2 position were found to be the most potent compounds among all the three series, indicating that small hydrophobic (alkyl group) substitution at R_2 position is favorable. Substitution of R_1 with H and R_2 with methyl or phenyl groups (**2d**, **2e**, **3d**, **3e**, **4d**, and **4e**) showed moderate insulin secretion.

4. Conclusions

Most of the clinically available sulfonylurea class of insulin secretagogues showed hypoglycemia because they cause glucose-independent insulin secretion. Therefore, for a safe and effective treatment of type 2 diabetes, it is essential to develop insulin-secreting agents, which show glucose-dependent insulin secretion only. In the recent years, many essential features of the aryl-imidazolines have been reviewed and as a result, imidazolines have emerged as promising therapeutic agent for the treatment of type 2 diabetes.[41,42] Aryl-imidazoline derivative, BL 11282 (**1**), showed

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

Compound	R_1	R_2	Concn (μM)	Insulin secretion (pg/μg/h)[a]
Control 1 (0 mM glucose)				6 ± 0.66
Control 2 (16.7 mM glucose)				10 ± 0.62
Tolbutamide (0 mM glucose)			0.1/1	19.6 ± 0.61 / 26.0 ± 0.52
Tolbutamide (16.7 mM glucose)			0.1/1	19.9 ± 0.56 / 27.1 ± 0.59
BL 11282 (**1**)			0.1/1/10	16.4 ± 0.61 / 20.6 ± 0.52 / 36.4 ± 0.36
EX-4 peptide (nM)			0.1/1/10	19.2 ± 0.56 / 22.5 ± 0.59 / 40.5 ± 0.61
2a	H	H	0.1/1/10	10.1 ± 0.52 / 12.1 ± 0.16 / 14.1 ± 0.36
2b	Cl	H	0.1/1/10	10.2 ± 0.26 / 12.2 ± 0.33 / 14.2 ± 0.51
2c	Cl	CH_3	0.1/1/10	15.1 ± 0.16 / 18.1 ± 0.26 / 32.1 ± 0.22
2d	H	CH_3	0.1/1/10	11.1 ± 0.23 / 15.1 ± 0.34 / 29.1 ± 0.27
2e	H	C_6H_5	0.1/1/10	11.1 ± 0.15 / 15.1 ± 0.55 / 27.9 ± 0.44
2f	Cl	C_6H_5	0.1/1/10	14.9 ± 0.19 / 17.8 ± 0.46 / 31.6 ± 0.56
2g	H	Cyclohex	0.1/1/10	10.1 ± 0.31 / 12.1 ± 0.54 / 14.1 ± 0.26
2h	Cl	Cyclohex	0.1/1/10	10.5 ± 0.26 / 12.5 ± 0.46 / 14.5 ± 0.28
2i	H	C_2H_5	0.1/1/10	10.6 ± 0.25 / 12.6 ± 0.22 / 14.6 ± 0.28
2j	Cl	C_2H_5	0.1/1/10	14.8 ± 0.52 / 17.8 ± 0.51 / 31.5 ± 0.59
2k	H	CH_2–C_6H_5	0.1/1/10	10.5 ± 0.46 / 12.5 ± 0.26 / 14.5 ± 0.16
2l	Cl	CH_2–C_6H_5	0.1/1/10	10.6 ± 0.26 / 12.6 ± 0.46 / 14.5 ± 0.18

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

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

Compound	R_1	R_2	Concn (μM)	Insulin secretion (pg/μg/h)[a]
Control 1 (0 mM glucose)				6 ± 0.66
Control 2 (16.7 mM glucose)				10 ± 0.62
Tolbutamide (0 mM glucose)			0.1/1	19.6 ± 0.61 / 26.0 ± 0.52
Tolbutamide (16.7 mM glucose)			0.1/1	19.9 ± 0.56 / 27.1 ± 0.59
BL 11282 (**1**)			0.1/1/10	16.4 ± 0.61 / 20.6 ± 0.52 / 36.4 ± 0.36
EX-4 peptide (nM)			0.1/1/10	19.2 ± 0.56 / 22.5 ± 0.59 / 40.5 ± 0.61
3a	H	H	0.1/1/10	10.5 ± 0.16 / 12.5 ± 0.26 / 14.5 ± 0.22
3b	Cl	H	0.1/1/10	10.5 ± 0.42 / 12.5 ± 0.39 / 14.6 ± 0.60
3c	Cl	CH_3	0.1/1/10	15.5 ± 0.15 / 19.1 ± 0.19 / 35.1 ± 0.20
3d	H	CH_3	0.1/1/10	11.5 ± 0.42 / 15.5 ± 0.39 / 29.5 ± 0.60
3e	H	C_6H_5	0.1/1/10	11.5 ± 0.31 / 15.5 ± 0.36 / 28.5 ± 0.22
3f	Cl	C_6H_5	0.1/1/10	15.2 ± 0.61 / 18.1 ± 0.33 / 33.1 ± 0.12
3g	H	Cyclohex	0.1/1/10	10.2 ± 0.17 / 12.5 ± 0.45 / 14.5 ± 0.19
3h	Cl	Cyclohex	0.1/1/10	10.8 ± 0.60 / 13.1 ± 0.41 / 15.1 ± 0.19
3i	H	C_2H_5	0.1/1/10	10.8 ± 0.61 / 13.0 ± 0.16 / 15.0 ± 0.32
3j	Cl	C_2H_5	0.1/1/10	15.1 ± 0.60 / 18.1 ± 0.36 / 33.1 ± 0.39
3k	H	CH_2–C_6H_5	0.1/1/10	10.9 ± 0.66 / 12.6 ± 0.36 / 14.9 ± 0.14
3l	Cl	CH_2–C_6H_5	0.1/1/10	10.9 ± 0.16 / 12.9 ± 0.26 / 15.0 ± 0.46

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

Table 3. In vitro glucose-dependent insulin secretion activity of compounds **4a–l**

Compound	R_1	R_2	Concn (μM)	Insulin secretion (pg/μg/h)[a]
Control 1 (0 mM glucose)				6 ± 0.66
Control 2 (16.7 mM glucose)				10 ± 0.62
Tolbutamide (0 mM glucose)			0.1/1	19.6 ± 0.61 / 26.0 ± 0.52
Tolbutamide (16.7 mM glucose)			0.1/1	19.9 ± 0.56 / 27.1 ± 0.59
BL 11282 (**1**)			0.1/1/10	16.4 ± 0.61 / 20.6 ± 0.52 / 36.4 ± 0.36
EX-4 peptide (nM)			0.1/1/10	19.2 ± 0.56 / 22.5 ± 0.59 / 40.5 ± 0.61
4a	H	H	0.1/1/10	10.9 ± 0.36 / 13.0 ± 0.39 / 15.0 ± 0.30
4b	Cl	H	0.1/1/10	11.1 ± 0.26 / 13.2 ± 0.22 / 15.5 ± 0.29
4c	Cl	CH_3	0.1/1/10	16.1 ± 0.43 / 20.1 ± 0.45 / 36.0 ± 0.31
4d	H	CH_3	0.1/1/10	12.1 ± 0.36 / 16.1 ± 0.35 / 30.1 ± 0.46
4e	H	C_6H_5	0.1/1/10	12.1 ± 0.26 / 16.1 ± 0.22 / 29.1 ± 0.21
4f	Cl	C_6H_5	0.1/1/10	15.9 ± 0.19 / 19.5 ± 0.44 / 35.5 ± 0.45
4g	H	Cyclohex	0.1/1/10	10.9 ± 0.27 / 13.1 ± 0.38 / 15.1 ± 0.43
4h	Cl	Cyclohex	0.1/1/10	11.2 ± 0.33 / 13.2 ± 0.31 / 15.9 ± 0.34
4i	H	C_2H_5	0.1/1/10	11.1 ± 0.44 / 13.4 ± 0.49 / 16.1 ± 0.56
4j	Cl	C_2H_5	0.1/1/10	15.8 ± 0.36 / 19.5 ± 0.26 / 35.2 ± 0.46
4k	H	CH_2–C_6H_5	0.1/1/10	11.1 ± 0.38 / 13.1 ± 0.22 / 15.1 ± 0.29
4l	Cl	CH_2–C_6H_5	0.1/1/10	11.2 ± 0.16 / 13.2 ± 0.19 / 15.4 ± 0.55

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

glucose-dependent insulin secretion from the pancreatic β-cells, without modulating the K_{ATP} channels.[16] Results of the present study indicated that all the three series of hetero-aryl guanidines, which were designed as analog of BL 11282, showed glucose- and concentration-dependent insulin secretion. Among all the 36 new compounds tested, compound *N*-(2-methyl, 5-chloro-1*H*-indol-3-yl)-guanidine (**4c**; $R_1 = Cl$ and $R_2 = CH_3$) was found to be equipotent to BL11282. Overall, the in vitro profile of the test compounds appears like the BL11282, indicated that guanidine group acts as a bioisostere of imidazoline ring system. Combined evaluation of our in vitro results suggests that this new class of compounds could be useful for the prevention and mitigation of type2 diabetes. The in vivo pharmacological and detailed mechanistic studies to investigate the exact mode of action of our test compounds are in progress and will be published elsewhere.

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 IR8300 spectrophotometer (V_{max} in cm^{-1}, using KBr pellets). The ^1H NMR spectra were recorded on a Brucker Avanc-300 spectrometer (300 MHz). The 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), t (triplet), q (quartet), br s (broad singlet), and m (multiplet). Mass spectra (ESI MS) were obtained on Shimadzu LCMS 2010-A spectrometer. Elemental analyses were carried out, 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 carried out 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 *N*-(2,5-disubstituted-thieno[2,3-*b*]pyridin-3-yl)-guanidine (2a–l; Scheme 1).

5.2.1.1. Synthesis of bis-Boc-*N*-(thieno[2,3-*b*]pyridin-3-yl)-guanidine (6a). A mixture of thieno[2,3-*b*]pyridin-3-ylamine (**5a**; 0.1 g, 0.666 mmol), bis-Boc-thiourea (0.184 g, 0.666 mmol), $HgCl_2$ (0.179 g, 0.666 mmol) and triethylamine (TEA; 0.25 mL, 1.8 mmol), in dry dimethylformamide (DMF; 6 mL) was stirred for 48 h, under nitrogen atmosphere. The reaction mixture was poured onto crushed ice and solid product was filtered. The crude product was purified by column chromatography, using a mixture of petroleum ether and ether (8:2) as an eluent system, fractions were evaporated, and white solid product was isolated. Yield: 61%; white solid; mp 125–127 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N═), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 6.10 (s, 1H, thiophene ring), 7.21–7.22 (d, 1H, pyridine ring), 7.31–7.32 (dd, 1H, pyridine ring), 8.51–8.52 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 393.2 $[M+1]^+$; analysis for $C_{18}H_{24}N_4O_4S$ (392), calcd: C, 55.08; H, 6.16; N 14.28. Found: C, 55.05; H, 6.13; N 14.25.

5.2.1.2. Bis-Boc-*N*-(5-chloro-thieno[2,3-*b*]pyridin-3-yl)-guanidine (6b). Yield: 60%; white solid; mp 129–131 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N═), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 7.21–7.22 (d, 1H, pyridine ring), 8.51–8.52 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 427.2 $[M+1]^+$, 428.2 $[M+2]^+$; analysis for $C_{18}H_{23}ClN_4O_4S$ (426), calcd: C, 50.64; H, 5.43; N 13.12. Found: C, 50.63; H, 5.41; N, 13.10.

5.2.1.3. Bis-Boc-*N*-(5-chloro-2-methyl-thieno[2,3-*b*]pyridin-3-yl)-guanidine (6c). Yield: 65%; white solid; mp 135–137 °C; IR (KBr): 3400, 2850, 1710, 1610, 1375 1050, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N═), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 2.41 (s, 3H, –CH_3), 7.2 (d, 1H, pyridine ring), 8.51–8.52 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 441 $[M+1]^+$, 442 $[M+2]^+$; analysis for $C_{19}H_{25}ClN_4O_4S$ (440), calcd: C, 51.75; H, 5.71; N 12.71. Found: C, 51.73; H, 5.70; N, 12.68.

5.2.1.4. Bis-Boc-*N*-(2-methyl-thieno[2,3-*b*]pyridin-3-yl)-guanidine (6d). Yield: 63%; white solid; mp 147–149 °C; IR (KBr): 3400, 2850, 1710, 1610, 1375 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N═), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 2.41 (s, 3H, –CH_3), 7.21–7.22 (d, 1H, pyridine ring), 7.31–7.32 (dd, 1H, pyridine ring), 8.51–8.52 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 407 [M+1]+; analysis for $C_{19}H_{26}N_4O_4S$ (406), calcd: C, 56.14; H, 6.45; N, 11.96. Found: C, 56.11; H, 6.43; N 11.93.

5.2.1.5. Bis-Boc-*N*-(2-phenyl-thieno[2,3-*b*]pyridin-3-yl)-guanidine (6e). Yield: 63%; white solid; mp 143–145 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N═), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 7.21–7.22 (d, 1H, pyridine ring), 7.30–7.31 (dd, 1H, pyridine ring), 7.33–7.42 (m, 5H, benzene ring), 8.51–8.52 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 187.2 $[M+1]^+$; analysis for $C_{24}H_{28}N_4O_4S$ (186), calcd: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.50; H, 6.00; N, 11.98.

5.2.1.6. Bis-Boc-*N*-(5-chloro-2-phenyl-thieno[2,3-*b*]pyridin-3-yl)-guanidine (6f). Yield: 64%; white solid; mp 127–129 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N═), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 7.21–7.22 (d, 1H, pyridine ring), 7.31– 7.41 (m, 5H, benzene ring), 8.51–8.52 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 469 $[M+1]^+$, 470 $[M+2]^+$; analysis for $C_{24}H_{27}ClN_4O_4S$ (468), calcd: C, 57.31; H, 5.41; N, 11.14. Found: C, 57.29; H, 5.39; N, 11.12.

5.2.1.7. Bis-Boc-*N*-(2-cyclohexyl-thieno[2,3-*b*]pyridin-3-yl)-guanidine (6g). Yield: 66%; white solid; mp 107–105 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.29–1.30 (m, 6H, –cyclohex), 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N═), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 1.58–1.59 (m, 4H, –cyclohex), 2.76–2.77 (m, 1H, –cyclohex), 7.21–7.22 (d, 1H, pyridine ring), 7.31–7.32 (dd, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 475.2 [M+1]+; analysis for $C_{24}H_{34}N_4O_4S$ (474), calcd: C, 60.73; H, 7.22; N, 11.80. Found: C, 60.70; H, 7.20; N, 11.77.

5.2.1.8. Bis-Boc-*N*-(5-chloro-2-cyclohexyl-thieno[2,3-*b*]pyridin-3-yl)-guanidine (6h). Yield: 61%; white solid; mp 114–116 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050, 775, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.29-1.30 (m, 6H, –cyclohex), 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N═), 1.56 (s, 9H, $(CH_3)_3C$—O— CO—NH—), 1.58–1.59 (m, 4H, –cyclohex), 2.76–2.77 (m, 1H, –cyclohex), 7.21–7.22 (d, 1H, Pyridine ring), 8.52–8.53 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 510.2 $[M+1]^+$, 511.2 $[M+2]^+$; analysis for $C_{24}H_{33}ClN_4O_4S$ (509), calcd: C, 56.63; H, 6.53; N, 11.01. Found: C, 56.60; H, 6.50; N, 11.00.

5.2.1.9. Bis-Boc-*N*-(2-ethyl-thieno[2,3-*b*]pyridin-3-yl)-guanidine (6i). Yield: 63%; white solid; mp 119–121 °C; mp 121 °C; IR (KBr): 3400, 2850, 1710, 1610, 1375 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, 3H, –CH_2CH_3), 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N=), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 2.59–2.60 (m, 2H, –CH_2CH_3), 7.20–7.21 (d, 1H, pyridine ring), 7.31–7.32 (dd, 1H, pyridine ring), 8.53–8.54 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 421 $[M+1]^+$; analysis for $C_{20}H_{28}N_4O_4S$ (420.1), calcd: C, 57.12; H, 6.71; N, 13.32. Found: C, 57.09 H, 6.69; N, 13.29.

5.2.1.10. Bis-Boc-*N*-(5-chloro-2-ethyl-thieno[2,3-*b*]pyridin-3-yl)-guanidine (6j). Yield: 66%; white solid; mp 113–115 °C; IR (KBr): 3400, 2850, 1710, 1610, 1375 1050, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24–1.25 (t, 3H, –CH_2CH_3), 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N=), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 2.59–2.60 (m, 2H, –CH_2CH_3), 7.21–7.22 (d, 1H, pyridine ring), 8.51–8.53 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 455 $[M+1]^+$, 456 $[M+2]^+$; analysis for $C_{20}H_{27}ClN_4O_4S$ (454.2), calcd: C, 52.80; H, 5.98; N, 12.31. Found: C, 52.78; H, 5.96; N, 12.29.

5.2.1.11. Bis-Boc-*N*-(2-benzyl-thieno[2,3-*b*]pyridin-3-yl)-guanidine (6k). Yield: 67%; white solid; mp 113–115 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N=), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 3.81 (s, 2H, –CH_2–Ph), 7.21–7.23 (dd, 1H, pyridine ring), 7.30–7.31 (d, 1H, pyridine ring), 7.33–7.40 (m, 5H, benzene ring), 8.51–8.52 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 483.2 $[M+1]^+$; analysis for $C_{25}H_{30}N_4O_4S$ (482.2), calcd: C, 62.22; H, 6.27; N, 11.61. Found: C, 62.20; H, 6.24; N, 11.58.

5.2.1.12. Bis-Boc-*N*-(2-benzyl-5-chloro-thieno[2,3-*b*]pyridin-3-yl)-guanidine (6l). Yield: 67%; white solid; mp 134–136 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$):δ 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N=), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 3.81 (s, 2H, –CH_2–Ph), 7.21–7.22 (d, 1H, pyridine ring), 7.32–7.44 (m, 5H, benzene ring), 8.53–8.54 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 518.2 $[M+1]^+$, 519.2 $[M+2]^+$; analysis for $C_{25}H_{29}ClN_4O_4S$ (517), calcd: C, 58.07; H, 5.65; N, 10.84. Found: C, 58.03; H, 5.61; N, 10.82.

5.2.1.13. Synthesis of *N*-(thieno[2,3-*b*]pyridin-3-yl)-guanidine (2a). A cleavage mixture of TFA: DCM (1: 1 v/v; 10 mL) was added to Bis-Boc-*N*-(thieno[2,3-*b*]pyridin-3-yl)-guanidine (**6a**; 0.1 g, 0.255 mmol) and stirred for 1 h at room temperature. The reaction mixture was evaporated to dryness and traces of TFA were removed by azeotroping with ether. The residue obtained was dissolved in water, basified with $NaHCO_3$, upto pH 8. The aqueous layer was extracted with DCM and the organic layer was washed with water and brine solution. The DCM layer was dried over Na_2SO_4 and evaporated to obtain the solid residue. The residue was dissolved in methanol, precipitated with diisopropylether, and the solid product was filtered and dried. Yield: 60%; white solid; mp 137–139 °C; IR (KBr): 3430, 2854, 1610 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.10 (s, 1H, thiophene ring), 7.22–7.23 (d, 1H, pyridine ring), 7.33–7.34 (dd, 1H, pyridine ring), 8.55–8.56 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 193.2 $[M+1]^+$; analysis for $C_8H_8N_4S$ (192.2), calcd: C, 58.07; H, 5.65; N, 10.84. Found: C, 58.03; H, 5.61; N, 10.82.

5.2.1.14. *N*-(5-Chloro-thieno[2,3-*b*]pyridin-3-yl)-guanidine (2b). Yield: 63%; white solid; mp 140–142 °C; IR (KBr): 3430, 2854, 1610, 774 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.20–7.21 (d, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 227.4 $[M+1]^+$, 228.4 $[M+2]^+$; analysis for $C_8H_7ClN_4S$ (226.2), calcd: C, 42.39; H, 3.11; N, 24.72. Found: C, 42.36; H, 3.08; N, 24.69.

5.2.1.15. *N*-(5-Chloro-2-methyl-thieno[2,3-*b*]pyridin-3-yl)-guanidine (2c). Yield: 60%; white solid; mp 150–151 °C; IR (KBr): 3400, 2854, 1610, 1375, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H, –CH_3), 7.23–7.24 (d, 1H, pyridine ring), 8.54–8.55 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 241.2 $[M+1]^+$, 242.2 $[M+2]^+$; analysis for $C_9H_9ClN_4S$ (240.1), calcd: C, 44.91; H, 3.77; N, 23.28. Found: C, 44.88; H, 3.74; N, 23.25.

5.2.1.16. *N*-(2-Methyl-thieno[2,3-*b*]pyridin-3-yl)-guanidine (2d). Yield: 61%; white solid; mp 126–127 °C; IR (KBr): 3400, 2854, 1610, 1375 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H, –CH_3), 7.21–7.22 (d, 1H, pyridine ring), 7.31–7.32 (dd, 1H, pyridine ring), 8.51–8.52 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 207.5 $[M+1]^+$; analysis for $C_9H_{10}N_4S$ (206.2), calcd: C, 52.41; H, 4.89; N, 27.16. Found: C, 52.38; H, 4.86; N, 27.13.

5.2.1.17. *N*-(2-Phenyl-thieno[2,3-*b*]pyridin-3-yl)-guanidine (2e). Yield: 63%; white solid; mp 158–159 °C; IR (KBr): 3430, 2854,1610 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.21–7.22 (d, 1H, pyridine ring), 7.29–7.30 (dd, 1H, pyridine ring), 7.31–7.41 (m, 5H, benzene ring), 8.51–8.52 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 269.3 $[M+1]^+$; analysis for $C_{14}H_{12}N_4S$ (268.1), calcd: C, 62.66; H, 4.51; N, 20.88. Found: C, 62.63; H, 4.48; N, 20.84.

5.2.1.18. *N*-(5-Chloro-2-phenyl-thieno[2,3-*b*]pyridin-3-yl)-guanidine (2f). Yield: 66%; white solid; mp 125–126 °C; IR (KBr): 3400, 2854, 1610, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.31–7.42 (m, 5H, benzene ring), 7.21–7.22 (d, 1H, pyridine ring), 8.51–8.52 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 303.2 $[M+1]^+$, 304.2 $[M+2]^+$; analysis for $C_{14}H_{11}ClN_4S$ (302), calcd: C, 55.53; H, 3.66; N, 18.50. Found: C, 55.50; H, 3.63; N, 18.47.

5.2.1.19. *N*-(2-Cyclohexyl-thieno[2,3-*b*]pyridin-3-yl)-guanidine (2g). Yield: 67%; white solid; mp 128–131 °C; IR (KBr): 3400, 2854, 1610, 1410.,720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.29–1.31 (m, 6H, –cyclohex),

1.58–1.59 (m, 4H, –cyclohex), 2.76–2.77 (m, 1H, –cyclohex), 7.21–7.22 (d, 1H, pyridine ring), 7.30–7.31 (dd, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 275.2 $[M+1]^+$; analysis for $C_{14}H_{18}N_4S$ (274), calcd: C, 61.28; H, 6.61; N, 20.42. Found: C, 61.25; H, 6.58; N, 20.39.

5.2.1.20. *N*-(5-Chloro-2-cyclohexyl-thieno[2,3-*b*]pyridin-3-yl)-guanidine (2h). Yield: 71%; white solid; mp 133–135 °C; IR (KBr): 3400, 2854, 1610, 1410, 775, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.29–1.31 (m, 6H, –cyclohex), 1.58–159 (m, 4H, –cyclohex), 2.76–2.77 (m, 1H, –cyclohex), 7.22–7.23 (d, 1H, pyridine ring), 8.51–8.50 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 309.2 $[M+1]^+$, 310.2 $[M+2]^+$; analysis for $C_{14}H_{17}ClN_4S$ (308.1), calcd: C, 54.45; H, 5.55; N, 18.14. Found: C, 54.42; H, 5.51; N, 18.11.

5.2.1.21. *N*-(2-Ethyl-thieno[2,3-*b*]pyridin-3-yl)-guanidine (2i). Yield: 63%; white solid; mp 127–129 °C; IR (KBr): 3400, 2854, 1610, 1400, 1375 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24–1.26 (t, 3H, –CH_2CH_3), 2.59–2.60 (m, 2H, –CH_2CH_3), 7.21–7.22 (d, 1H, pyridine ring), 7.33–7.34 (dd, 1H, pyridine ring), 8.54–8.55 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 221.3 $[M+1]^+$; analysis for $C_{10}H_{12}N_4S$ (220.1), calcd: C, 54.52; H, 5.49; N, 25.43. Found: C, 54.49; H, 5.45; N, 25.40.

5.2.1.22. *N*-(5-Chloro-2-ethyl-thieno[2,3-*b*]pyridin-3-yl)-guanidine (2j). Yield: 65%; white solid; mp 134–136 °C; IR (KBr): 3400, 2854, 1610, 1400, 1375, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24–1.25 (t, 3H, –CH_2CH_3), 2.59–2.60 (m, 2H, –CH_2CH_3), 7.21–7.22 (d, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 255.5 $[M+1]^+$, 256.5 $[M+2]^+$; analysis for $C_{10}H_{11}ClN_4S$ (254), calcd: C, 47.15; H, 4.35; N, 21.99. Found: C, 47.11; H, 4.31; N, 21.96.

5.2.1.23. *N*-(2-Benzyl-thieno[2,3-*b*]pyridin-3-yl)-guanidine (2k). Yield: 63%; white solid; mp 117–119 °C; IR (KBr): 3400, 2854, 1610, 1400 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 2H, –CH_2–Ph), 7.30–7.40 (m, 5H, benzene ring), 7.30–7.31 (d, 1H, pyridine ring), 7.21–7.22 (dd, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 283.6 $[M+1]^+$; analysis for $C_{15}H_{14}N_4S$ (282.1), calcd: C, 63.80; H, 5.00; N, 19.84. Found: C, 63.76; H, 4.98; N, 19.81.

5.2.1.24. *N*-(2-Benzyl-5-chloro-thieno[2,3-*b*]pyridin-3-yl)-guanidine (2l). Yield: 66%; white solid; mp 130–131 °C; IR (KBr): 3400, 2854, 1610, 1400, 775, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 2H, –CH_2–Ph), 7.31–7.39 (m, 5H, benzene ring), 7.19–7.20 (d, 1H, pyridine ring), 8.49–8.50 (d, 1H, pyridine ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 317.3 $[M+1]^+$, 318.3 $[M+2]^+$; analysis for $C_{15}H_{13}ClN_4S$ (316), calcd: C, 56.87; H, 4.14; N, 17.68. Found: C, 56.84; H, 4.11; N, 17.65.

5.2.2. General method for the synthesis of *N*-(2,5-disubstituted-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (3a–l; Scheme 2).

5.2.2.1. Synthesis of 3-nitroso-1*H*-pyrrolo[2,3-*b*]pyridine (8a). To a solution of pyrrolo[2,3-*b*]pyridine (**7a**, 0.2 g, 1.69 mmol), dissolved in acetic acid (5 mL), a solution of $NaNO_2$ (0.1 g) in water (5 mL) was added and the reaction mixture was stirred at room temperature for 30 min. The mixture was diluted with water, the solid obtained was filtered, dried, and recrystallized from chloroform. Yield: 66%; yellow solid; mp 216–218 °C; IR (KBr): 3400, 2845, 1610, 1540 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.61 (s, 1H, pyrrole ring), 7.38–7.39 (m, 1H, pyridine ring), 7.65–7.66 (d, 1H, pyridine ring), 8.51–8.52 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m*/*z* 147.8 $[M+1]^+$; analysis for $C_7H_5N_3O$ (147.2), calcd: C, 57.14; H, 3.43; N, 28.56; Found: C, 57.12; H, 3.45; N, 28.52.

5.2.2.2. 5-Chloro-3-nitroso-1*H*-pyrrolo[2,3-*b*]pyridine (8b). Yield: 60%; yellow solid; mp 224–226 °C; IR (KBr): 3400, 2845, 1610, 1545, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.60 (s, 1H, pyrrole ring), 7.65–7.66 (d, 1H, pyridine ring), 8.48–8.49 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m*/*z* 181.9 $[M+1]^+$, 182.9 $[M+2]^+$; analysis for $C_7H_4ClN_3O$ (181.5), calcd: C, 46.30; H, 2.22; N, 23.14. Found: C, 46.26; H, 2.24; N, 23.12.

5.2.2.3. 5-Chloro-2-methyl-3-nitroso-1*H*-pyrrolo[2,3-*b*]pyridine (8c). Yield: 63%; yellow solid; mp 230–232 °C; IR (KBr): 3400, 2845, 1610, 1545, 1375 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 3H, Methyl), 7.65–7.66 (d, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 11.7 (s, 1H, –NH). MS (ESI) *m*/*z* 196.3 $[M+1]^+$, 197.3 $[M+2]^+$; analysis for $C_8H_6ClN_3O$ (195.6), calcd: C, 49.12; H, 3.09; N, 21.48; Found: C, 49.15; H, 3.12; N, 21.43.

5.2.2.4. 2-Methyl-3-nitroso-1*H*-pyrrolo[2,3-*b*]pyridine (8d). Yield: 67%; yellow solid; mp 206–208 °C; IR (KBr): 3400, 2845, 1610, 1545, 1375 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 3H, Methyl), 7.32–7.33 (m, 1H, pyridine ring), 7.65–7.66 (d, 1H, pyridine ring), 8.51–8.52 (d, 1H, pyridine ring), 11.7 (s, 1H, –NH). MS (ESI) *m*/*z* 162.8 $[M+1]^+$; analysis for $C_8H_7N_3O$ (161.2), calcd: C, 59.62; H, 4.38; N, 26.07; Found: C, 59.58; H, 4.35; N, 26.11.

5.2.2.5. 3-Nitroso-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (8e). Yield: 68%; yellow solid; mp 234–236 °C; IR (KBr): 3400, 2845, 1610, 1545 1435 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.40 (m, 5H, benzene ring), 7.21–7.22 (m, 1H, pyridine ring), 7.60–7.61 (d, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m*/*z* 223.8 $[M+1]^+$; analysis for $C_{13}H_9N_3O$ (223.2), calcd: C, 69.95; H, 4.06; N, 18.82; Found: C, 69.93; H, 4.10; N, 18.80.

5.2.2.6. 5-Chloro-3-nitroso-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (8f). Yield: 63%; yellow solid; mp 256–258 °C; IR (KBr): 3400, 2845, 1610, 1545 1435, 770 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.18–7.19

(d, 1H, pyridine ring), 7.29–7.38 (m, 5H, benzene ring), 8.48–8.49 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m/z* 258 $[M+1]^+$, 259 $[M+2]^+$; analysis for $C_{13}H_8ClN_3O$ (257.2), calcd: C, 60.60; H, 3.13; N, 16.31. Found: C, 60.56; H, 3.12; N, 16.28.

5.2.2.7. 2-Cyclohexyl-3-nitroso-1*H*-pyrrolo[2,3-*b*]pyridine (8g). Yield: 66%; yellow solid; mp 222–224 °C; IR (KBr): 3400, 2845, 1610, 1545 1440, 1375, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.29–1.30 (m, 6H, –cyclohex), 1.58–1.59 (m, 4H, –cyclohex), 7.21–7.22 (m, 1H, pyridine ring), 7.60–7.61 (d, 1H, pyridine ring), 2.76–2.77 (m, 1H, –cyclohex), 8.51–8.52 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m/z* 229.7 $[M+1]^+$; analysis for $C_{13}H_{15}N_3O$ (229.2), calcd: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.13; H, 6.62; N, 18.31.

5.2.2.8. 5-Chloro-2-cyclohexyl-3-nitroso-1*H*-pyrrolo-[2,3-*b*]pyridine (8h). Yield: 69%; yellow solid; mp 228–230 °C; IR (KBr): 3400, 2845, 1610, 1545 1440, 1375, 775, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.28–1.29 (m, 6H, –cyclohex), 1.57–1.58 (m, 4H, –cyclohex), 7.59–2.60 (d, 1H, pyridine ring), 2.77–2.78 (m, 1H, –cyclohex), 8.49–8.50 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m/z* 264.7 $[M+1]^+$, 265.7 $[M+2]^+$; analysis for $C_{13}H_{14}ClN_3O$ (263.7), calcd: C, 59.21; H, 5.35; N, 15.93. Found: C, 59.17; H, 5.30; N, 15.90.

5.2.2.9. 2-Ethyl-3-nitroso-1*H*-pyrrolo[2,3-*b*]pyridine (8i). Yield: 62%; yellow solid; mp 213–215 °C; IR (KBr): 3400, 2845, 1610, 1545 1440, 1375 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.24–1.25 (t, 3H, $-CH_2CH_3$), 2.59–2.60 (m, 2H, $-CH_2CH_3$), 7.00–7.13 (m, 1H, pyridine ring), 7.53–7.54 (d, 1H, pyridine ring), 8.52–8.53 (d, 1H, Pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m/z* 175.9 $[M+1]^+$; analysis for $C_9H_9N_3O$ (175.2), calcd: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.68; H, 5.21; N, 23.97.

5.2.2.10. 5-Chloro-2-ethyl-3-nitroso-1*H*-pyrrolo[2,3-*b*]pyridine (8j). Yield: 65%; yellow solid; mp 218–220 °C; IR (KBr): 3400, 2845, 1610, 1545 1440, 1375, 745 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.22–1.23 (t, 3H, $-CH_2CH_3$), 2.59–2.60 (m, 2H, $-CH_2CH_3$), 7.48–7.49 (d, 1H, pyridine ring), 8.51–8.52 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m/z* 210.3 $[M+1]^+$, 211.3 $[M+2]^+$; analysis for $C_9H_8ClN_3O$ (209.6), calcd: C, 51.56; H, 3.85; N, 20.04. Found: C, 51.52; H, 3.82; N, 20.06.

5.2.2.11. 2-Benzyl-3-nitroso-1*H*-pyrrolo[2,3-*b*]pyridine (8k). Yield: 64%; yellow solid; mp 230–232 °C; IR (KBr): 3400, 2845, 1610, 1545 1440 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 2H, $-CH_2$–Ph), 7.28–7.29 (m, 1H, pyridine ring), 7.31–7.40 (m, 5H, benzene ring), 7.70–7.71 (d, 1H, pyridine ring), 8.48–8.49 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m/z* 237.8 $[M+1]^+$; analysis for $C_{14}H_{11}N_3O$ (237.2.6), calcd: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.84; H, 4.65; N, 17.74.

5.2.2.12. 2-Benzyl-5-chloro-3-nitroso-1*H*-pyrrolo[2,3-*b*]pyridine (8l). Yield: 66%; yellow solid; mp 236–238 °C; IR (KBr): 3400, 2845, 1610, 1545 1440, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 2H, $-CH_2$–Ph), 7.22–7.23 (m, 5H, benzene ring), 7.77–7.78 (d, 1H, pyridine ring), 8.54–8.55 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m/z* 272.5 $[M+1]^+$, 273.5 $[M+2]^+$; analysis for $C_{14}H_{10}ClN_3O$ (271.6), calcd: C, 61.89; H, 3.71; N, 15.47. Found: C, 61.85; H, 3.73; N, 15.43.

5.2.2.13. Synthesis of 3-amino-1*H*-pyrrolo[2,3-*b*]pyridine (9a). A mixture of 3-nitroso-1*H*-pyrrolo[2,3-*b*]pyridine (**8a**; 0.1 g, 0.680 mmol), $Na_2S_2O_4$ (0.34 g, 1.97 mmol), and NaOH (1.1 mL; 2 N) in ethanol (10 mL) was heated under reflux for 30 min. The yellow solid obtained was filtered, washed with water, and dried to get the pure compound **9a**.Yield: 74%; yellow solid; mp 194–196 °C; IR (KBr): 3400, 2845, 1610 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.61 (s, 1H, pyrrole ring), 7.38–7.39 (m, 1H, pyridine ring), 7.65–7.66 (d, 1H, pyridine ring), 8.51–8.52 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m/z* 133.8 $[M+1]^+$; analysis for $C_7H_7N_3$ (133.2), calcd: C, 63.14; H, 5.30; N, 31.56. Found: C, 63.16; H, 5.32; N, 31.53.

5.2.2.14. 5-Chloro-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylamine (9b). Yield: 62%; yellow solid; mp 202–204 °C; IR (KBr): 3400, 2845, 1610, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.69 (s, 1H, pyrrole ring), 7.66–7.67 (d, 1H, pyridine ring), 8.52–8.53 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m/z* 168.3 $[M+1]^+$, 169.3 $[M+2]^+$; analysis for $C_7H_6ClN_3$ (167.5), calcd: C, 15.17; H, 3.61; N, 21.15. Found: C, 15.15; H, 3.63; N, 21.12.

5.2.2.15. 5-Chloro-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylamine (9c). Yield: 67%; yellow solid; mp 197–199 °C; IR (KBr): 3400, 2845, 1610, 1375, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 3H, methyl), 7.65–7.66 (d, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 11.70 (s, 1H, –NH). MS (ESI) *m/z* 182.3 $[M+1]^+$, 183.3 $[M+2]^+$; analysis for $C_8H_8ClN_3$ (181.6), calcd: C, 52.90; H, 4.44; N, 23.14. Found: C, 52.92; H, 4.47; N, 23.10.

5.2.2.16. 2-Methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylamine (9d). Yield: 62%; yellow solid; mp 200–202 °C; IR (KBr): 3400, 2845, 1600, 1375 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 3H, methyl), 7.32–7.33 (m, 1H, pyridine ring), 7.65–7.66 (d, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 11.70 (s, 1H, –NH). MS (ESI) *m/z* 148 $[M+1]^+$; analysis for $C_8H_9N_3$ (147.2), calcd: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.26; H, 6.18; N, 28.58.

5.2.2.17. 2-Phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylamine (9e). Yield: 68%; yellow solid; mp 207–209 °C; IR (KBr): 3400, 2845, 1600, 1375 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.20–7.21 (m, 1H, pyridine ring), 7.30 –7.40 (m, 5H, benzene ring), 7.60–7.61 (d, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m/z* 209.8 $[M+1]^+$; analysis for $C_{13}H_{11}N_3$ (209.2), calcd: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.60; H, 5.33; N, 20.11.

5.2.2.18. 5-Chloro-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylamine (9f). Yield: 67%; yellow solid; mp 213–215 °C; IR (KBr): 3400, 2845, 1600, 776 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.40 (m, 5H, benzene ring), 7.20–7.21 (m, 1H, pyridine ring), 7.60–7.61 (d, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m*/*z* 244.3 $[M+1]^+$, 245.3 $[M+2]^+$; analysis for $C_{13}H_{10}ClN_3$ (243.6), calcd: C, 64.07; H, 4.14; N, 17.24. Found: C, 64.09; H, 4.11; N, 17.20.

5.2.2.19. 2-Cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylamine (9g). Yield: 66%; yellow solid; mp 215–217 °C; IR (KBr): 3400, 2845, 1600, 1400, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.29–1.30 (m, 6H, –cyclohex), 1.58–1.59 (m, 4H, –cyclohex), 2.76–2.77 (m, 1H, –cyclohex), 7.20–7.21 (m, 1H, pyridine ring), 7.60–7.61 (d, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m*/*z* 215.8 $[M+1]^+$; analysis for $C_{13}H_{17}N_3$ (215.2), calcd: C, 72.52; H, 7.96; N, 19.52. Found: C, 72.55; H, 7.99; N, 19.50.

5.2.2.20. 5-Chloro-2-cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylamine (9h). Yield: 60%; yellow solid; mp 209–211 °C; IR (KBr): 3400, 2845, 1600, 1400, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.29–1.30 (m, 6H, –cyclohex), 1.57–1.58 (m, 4H, –cyclohex), 2.76–2.77 (m, 1H, –cyclohex), 7.50–7.51 (d, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m*/*z* 250.8 $[M+1]^+$, 251.8 $[M+2]^+$; analysis for $C_{13}H_{16}ClN_3$ (250), calcd C, 62.52; H, 6.46; N, 16.83. Found: C, 62.48; H, 6.43; N, 16.79.

5.2.2.21. 2-Ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylamine (9i). Yield: 72%; yellow solid; mp 202–204 °C; IR (KBr): 3400, 2845, 1600, 1400, 1375 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.24–1.25 (t, 3H, $-CH_2CH_3$), 2.59–2.60 (m, 2H, $-CH_2CH_3$), 7.20–7.21 (m, 1H, pyridine ring), 7.50–7.51 (d, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m*/*z* 161.9 $[M+1]^+$; analysis for $C_9H_{11}N_3$ (161.2), calcd: C, 67.06; H, 6.88; N, 26.07. Found: C, 67.01; H, 6.80; N, 26.00.

5.2.2.22. 5-Chloro-2-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylamine (9j). Yield: 71%; yellow solid; mp 212–214 °C; IR (KBr): 3400, 2845, 1600, 1400, 1375, 770 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.24–1.25 (t, 3H, $-CH_2CH_3$), 2.59–2.60 (m, 2H, $-CH_2CH_3$), 7.48–7.49 (d, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m*/*z* 196 $[M+1]^+$, 197 $[M+2]^+$; analysis for $C_9H_{10}ClN_3$ (195.5), calcd: C, 55.25; H, 5.15; N, 21.48. Found: C, 55.23; H, 5.12; N, 21.51.

5.2.2.23. 2-Benzyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylamine (9k). Yield: 67%; yellow solid; mp 218–220 °C; IR (KBr): 3400, 2845, 1600, 1400 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 2H, $-CH_2-$Ph), 7.30 – 7.40 (m, 5H, benzene ring), 7.30–7.31 (m, 1H, pyridine ring), 7.71–7.72 (d, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS(ESI) *m*/*z* 223.8 $[M+1]^+$; analysis for $C_{14}H_{13}N_3$ (223.2), calcd: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.28; H, 5.89; N, 18.85.

5.2.2.24. 2-Benzyl-5-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylamine (9l). Yield: 63%; yellow solid; mp 222–224 °C; IR (KBr): 3400, 2845, 1600, 1400, 776 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 2H, $-CH_2-$Ph), 7.29–7.31 (m, 5H, benzene ring), 7.70–7.71 (d, 1H, pyridine ring), 8.49–8.50 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m*/*z* 223.8 $[M+1]^+$, 224.8 $[M+2]^+$; analysis for $C_{14}H_{13}N_3$ (223.2), calcd: C, 65.25; H, 4.69; N, 16.30. Found: C, 65.22; H, 4.66; N, 16.27.

5.2.2.25. Synthesis of bis-Boc-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (10a). Synthesis of compound **10a** was carried out starting from 3-amino-1*H*-pyrrolo[2,3-*b*]pyridine (**9a**), using a general procedure described for the synthesis of compound **6a**. Yield: 72%; white solid; mp 292–294 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H, $(CH_3)_3C-O-CO-N=$), 1.56 (s, 9H, $(CH_3)_3C-O-CO-NH-$), 6.60 (s, 1H, Pyrrole ring), 7.20–7.21 (d, 1H, pyridine ring), 7.68–7.69 (dd, 1H, Pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m*/*z* 375.8 $[M+1]^+$; analysis for $C_{18}H_{25}N_5O_4$ (375.3), calcd: C, 57.59; H, 6.71; N, 18.65. Found: C, 57.56; H, 6.75; N, 18.68.

5.2.2.26. Bis-Boc-*N*-(5-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (10b). Yield: 61%; white solid; mp 297–299 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H, $(CH_3)_3C-O-CO-N=$), 1.56 (s, 9H, $(CH_3)_3C-O-CO-NH-$), 6.60 (s, 1H, pyrrole ring), 7.68–7.69 (dd, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m*/*z* 410.2 $[M+1]^+$, 411.2 $[M+2]^+$; analysis for $C_{18}H_{24}ClN_5O_4$ (409.5), calcd: C, 52.75; H, 5.90; N, 17.09. Found: C, 52.72; H, 5.93; N, 17.05.

5.2.2.27. Bis-Boc-*N*-(5-chloro-2-methyl-1*H*-pyrrolo-[2,3-*b*]pyridin-3-yl)-guanidine (10c). Yield: 64%; white solid; mp 296–298 °C; IR (KBr): 3400, 2850, 1710, 1610, 1375, 1050, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H, $(CH_3)_3C-O-CO-N=$), 1.56 (s, 9H, $(CH_3)_3C-O-CO-NH-$), 2.10 (s, 1H, $-CH_3$ proton), 7.68–7.69 (dd, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m*/*z* 424 $[M+1]^+$, 425 $[M+2]^+$; analysis for $C_{19}H_{26}ClN_5O_4$ (423.5), calcd: C, 53.84; H, 6.18; N, 16.52. Found: C, 53.82; H, 6.19; N, 16.55.

5.2.2.28. Bis-Boc-*N*-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (10d). Yield: 72%; white solid; mp 286–288 °C; IR (KBr): 3400, 2850, 1710, 1610, 1375, 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H, $(CH_3)_3C-O-CO-N=$), 1.56 (s, 9H, $(CH_3)_3C-O-CO-NH-$), 2.10 (s, 1H, $-CH_3$ proton), 7.20–7.21 (d, 1H, pyridine ring), 7.68–7.69 (dd, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m*/*z* 389.8 $[M+1]^+$; analysis for $C_{19}H_{27}N_5O_4$ (389.2), calcd: C, 58.60; H, 6.99; N, 17.98. Found: C, 58.58; H, 6.96; N, 17.97.

5.2.2.29. Bis-Boc-*N*-(2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (10e). Yield: 68%; white solid; mp

>300 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N=), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 7.30–7.40 (m, 5H, benzene ring), 7.20–7.21 (m, 1H, pyridine ring), 7.61–7.62 (d, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m/z* 452.1 $[M+1]^+$; analysis for $C_{24}H_{29}N_5O_4$ (451), calcd: C, 63.84; H, 6.47; N, 15.51. Found: C, 63.82; H, 6.49; N, 15.47.

5.2.2.30. Bis-Boc-*N*-(5-chloro-2-Phenyl-1*H*-pyrrolo-[2,3-*b*]pyridin-3-yl)-guanidine (10f). Yield: 63%; white solid; mp >300 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N=), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 7.31–7.41 (m, 5H, benzene ring), 7.61–7.62 (d, 1H, pyridine ring), 8.48–8.49 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m/z* 485.8 $[M+1]^+$, 486.8 $[M+2]^+$; analysis for $C_{24}H_{28}ClN_5O_4$ (485), calcd: C, 59.32; H, 5.81; N, 14.41. Found: C, 59.29; H, 5.78; N, 14.45.

5.2.2.31. Bis-Boc-*N*–(2-cyclohexyl-1*H*-pyrrolo[2,3-*b*]-pyridin-3-yl)-guanidine (10g). Yield: 64%; white solid; mp 295–297 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.29–1.30 (m, 6H, –cyclohex), 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N=), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 1.57–1.58 (m, 4H, –cyclohex), 2.76–2.77 (m, 1H, –cyclohex), 7.21–7.22 (m, 1H, pyridine ring), 7.61–7.62 (d, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m/z* 457.8 $[M+1]^+$; analysis for $C_{24}H_{35}N_5O_4$ (457.2), calcd: C, 63.00; H, 7.71; N, 15.31. Found: C, 63.03; H, 7.75; N, 15.28.

5.2.2.32. Bis-Boc-*N*-(5-chloro-2-cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (10h). Yield: 62%; white solid; mp >300 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050, 775, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.29–1.30 (m, 6H, –cyclohex), 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N=), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 1.58–1.59 (m, 4H, –cyclohex), 2.76–2.77 (m, 1H,–cyclohex), 7.59–7.60 (d, 1H, pyridine ring), 8.52–8.53 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m/z* 492.6 $[M+1]^+$, 493.6 $[M+2]^+$; analysis for $C_{24}H_{34}ClN_5O_4$ (492), calcd: C, 58.59; H, 6.97; N, 14.23. Found: C, 58.56; H, 6.94; N, 14.26.

5.2.2.33. Bis-Boc-*N*-(2-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (10i). Yield: 60%; white solid; mp 286–288 °C; IR (KBr): 3400, 2850, 1710, 1610, 1375 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.24–1.25 (t, 3H, $-CH_2CH_3$), 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N=), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 2.59–2.60 (m, 2H, $-CH_2CH_3$), 7.20–7.21 (d, 1H, pyridine ring), 7.67–7.68 (dd, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS(ESI) *m/z* 404.3 $[M+1]^+$; analysis for $C_{20}H_{29}N_5O_4$ (403.5), calcd: C, 59.54; H, 7.24; N, 17.36. Found: C, 59.52; H, 7.23; N, 17.39.

5.2.2.34. Bis-Boc-*N*-(5-chloro-2-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (10j). Yield: 71%; white solid; mp 294–296 °C; IR (KBr): 3400, 2850, 1710, 1610, 1375 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.22–1.23 (t, 3H, $-CH_2CH_3$), 1.40 (s, 9H, $(CH_3)_3C$—O—CO—N=), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 2.59–2.60 (m, 2H, $-CH_2CH_3$), 7.67–7.68 (dd, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m/z* 437.8 $[M+1]^+$, 438.8 $[M+2]^+$; analysis for $C_{20}H_{28}ClN_5O_4$ (437), calcd: C, 54.85; H, 6.44; N, 15.99. Found: C, 54.82; H, 6.47; N, 15.96.

5.2.2.35. Bis-Boc-*N*-(2-benzyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (10k). Yield: 68%; white solid; mp >300 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N=), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 3.81 (s, 2H, $-CH_2$–Ph), 7.28–7.29 (m, 1H, pyridine ring), 7.30–7.40 (m, 5H, benzene ring), 7.66–7.67 (dd, 1H, pyridine ring), 8.47–8.48 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m/z* 467 $[M+1]^+$; analysis for $C_{25}H_{31}N_5O_4$ (465.5), calcd: C, 64.50; H, 6.71; N, 15.04. Found: C, 64.47; H, 6.74; N, 15.07.

5.2.2.36. Bis-Boc-*N*-(2-benzyl-5-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (10l). Yield: 66%; white solid; mp >300 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N=), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 3.81 (s, 2H, $-CH_2$–Ph), 7.33 – 7.43 (m, 5H, benzene ring), 7.56–7.57 (dd, 1H, pyridine ring), 8.51–8.52 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH. MS (ESI) *m/z* 500.2 $[M+1]^+$, 501.2 $[M+2]^+$; analysis for $C_{25}H_{30}ClN_5O_4$ (499.5), calcd: C, 60.05; H, 6.05; N, 14.01. Found: C, 60.09; H, 6.08; N, 14.03.

5.2.2.37. Synthesis of *N*-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (3a). Synthesis of compound **3a** was carried out starting from bis-Boc-*N*-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (**10a**), using a general procedure described for the synthesis of compound **2a**. Yield: 58%; white solid; mp 218–220 °C; IR (KBr): 3430, 2854, 1610 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.70 (s, 1H, Pyrrole ring), 7.10–7.11 (m, 1H, pyridine ring), 7.67–7.68 (d, 1H, pyridine ring), 8.20–8.21 (d, 1H, pyridine ring), 11.77 (s, 1H, –NH). MS (ESI) *m/z* 175.8 $[M+1]^+$; analysis for $C_8H_9N_5$ (175.2), calcd: C, 54.85; H, 5.18; N, 39.98. Found: C, 54.82; H, 5.19; N, 39.95.

5.2.2.38. *N*-(5-Chloro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (3b). Yield: 63%; white solid; mp 224–226 °C; IR (KBr): 3430, 2854,, 1610, 774 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.69 (s, 1H, pyrrole ring), 7.64–7.65 (d, 1H, pyridine ring), 8.22–8.23 (d, 1H, pyridine ring), 11.77 (s, 1H, –NH). MS (ESI) *m/z* 210 $[M+1]^+$, 211 $[M+2]^+$; analysis for $C_8H_8ClN_5$ (209.5), calcd: C, 45.83; H, 3.85; N, 33.41. Found: C, 45.80; H, 3.88; N, 33.44.

5.2.2.39. *N*-(5-Chloro-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (3c). Yield: 69%; white solid; mp 227–229 °C; IR (KBr): 3400, 2854, 1610, 1375, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 3H, Methyl), 7.80 (s, 1H, pyridine ring), 8.48 (s, 1H, pyridine ring), 11.70 (s, 1H, –NH). MS (ESI) *m/z* 224.2 $[M+1]^+$,

225.2 $[M+2]^+$; analysis for $C_9H_{10}ClN_5$ (223.5), calcd: C, 48.33; H, 4.51; N, 31.31. Found: C, 48.30; H, 4.55; N, 31.28.

5.2.2.40. *N*-(2-Methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (3d). Yield: 65%; white solid; mp 214–216 °C; IR (KBr): 3400, 2854, 1610, 1375 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 3H, methyl), 7.10–7.11 (m, 1H, pyridine ring), 7.67 (s, 1H, pyridine ring), 8.50 (s, 1H, pyridine ring), 11.70 (s, 1H, –NH). MS (ESI) *m*/*z* 189.8 $[M+1]^+$; analysis for $C_9H_{11}N_5$ (189.2), calcd: C, 57.13; H, 5.86; N, 37.01. Found: C, 57.10; H, 5.89; N, 37.05.

5.2.2.41. *N*-(2-Phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (3e). Yield: 68%; white solid; mp 236–238 °C; IR (KBr): 3430, 2854, 1610 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.03–7.04 (m, 1H, benzene ring), 7.12–7.13 (m, 1H, pyridine ring), 7.39–7.48 (m, 2H, benzene ring), 7.67–7.68 (d, 1H, pyridine ring), 7.97–7.98 (d, 2H, benzene ring), 8.20–8.21 (d, 1H, pyridine ring), 11.77 (s, 1H, –NH). MS (ESI) *m*/*z* 251.8 $[M+1]^+$; analysis for $C_{14}H_{13}N_5$ (251.2), calcd: C, 66.92; H, 5.21; N, 27.87. Found: C, 66.89; H, 5.22; N, 27.85.

5.2.2.42. *N*-(5-Chloro-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (3f). Yield: 63%; white solid; mp 243–245 °C; IR (KBr): 3400, 2854, 1610, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.10–7.11 (m, 1H, benzene ring), 7.39–7.48 (m, 2H, benzene ring), 7.80 (s, 1H, pyridine ring), 7.96–7.97 (d, 2H, benzene ring), 8.48 (s, 1H, pyridine ring), 11.71 (s, 1H, –NH). MS (ESI) *m*/*z* 285.8 $[M+1]^+$, 286.8 $[M+2]^+$; analysis for $C_{14}H_{12}ClN_5$ (285), calcd: C, 58.85; H, 4.23; N, 24.51. Found: C, 58.82; H, 4.26; N, 24.48.

5.2.2.43. *N*-(2-Cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (3g). Yield: 65%; white solid; mp 228–230 °C; IR (KBr): 3400, 2854, 1610, 1410, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.29–1.30 (m, 6H, –cyclohex), 1.58–1.59 (m, 4H, –cyclohex), 2.76–2.77 (m, 1H, –cyclohex), 7.20–7.21 (m, 1H, pyridine ring), 7.65–7.66 (d, 1H, pyridine ring), 8.51–8.52 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m*/*z* 257.8 $[M+1]^+$; analysis for $C_{14}H_9N_5$ (257), calcd: C, 65.34; H, 7.44; N, 27.22. Found: C, 65.32; H, 7.47; N, 27.18.

5.2.2.44. *N*-(5-Chloro-2-cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (3h). Yield: 61%; white solid; mp 234–236 °C; IR (KBr): 3400, 2854, 1610, 1410, 775, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.29–1.30 (m, 6H, –cyclohex), 1.58–1.59 (m, 4H, –cyclohex), 2.76–2.77 (m, 1H, –cyclohex), 7.66–7.67 (d, 1H, pyridine ring), 8.50–8.51 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m*/*z* 292.3 $[M+1]^+$, 293.3 $[M+2]^+$; analysis for $C_{14}H_{18}ClN_5$ (291.5), calcd: C, 57.63; H, 6.22; N, 24.00. Found: C, 57.60; H, 6.18; N, 24.04.

5.2.2.45. *N*-(2-Ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (3i). Yield: 63%; white solid; mp 218–220 °C; IR (KBr): 3400, 2854, 1610, 1400, 1375 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.24–1.25 (t, 3H, $-CH_2CH_3$), 2.59–2.60 (m, 2H, $-CH_2CH_3$), 7.22–7.23 (m, 1H, pyridine ring), 7.74–7.75 (d, 1H, pyridine ring), 8.49–8.50 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m*/*z* 203.7 $[M+1]^+$; analysis for $C_{10}H_{13}N_5$ (203.2), calcd: C, 59.10; H, 6.45; N, 34.46. Found: C, 59.13; H, 6.48; N, 34.42.

5.2.2.46. *N*-(5-Chloro-2-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (3j). Yield: 67%; white solid; mp 224–226 °C; IR (KBr): 3400, 2854, 1610, 1400, 1375, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.22–1.23 (t, 3H, $-CH_2CH_3$), 2.58–2.59 (m, 2H, $-CH_2CH_3$), 7.44–7.45 (d, 1H, pyridine ring), 8.48–8.49 (d, 1H, pyridine ring), 11.65 (s, 1H, –NH). MS (ESI) *m*/*z* 238.4 $[M+1]^+$, 239.4 $[M+2]^+$; analysis for $C_{10}H_{12}ClN_5$ (237.6), calcd: C, 50.53; H, 5.09; N, 29.46. Found: C, 50.50; H, 5.11; N, 29.49.

5.2.2.47. *N*-(2-Benzyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (3k). Yield: 66%; white solid; mp 232–234 °C; IR (KBr): 3400, 2854, 1610, 1400 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 2H, $-CH_2-$Ph), 7.12–7.13 (m, 1H, pyridine ring), 7.28–7.29 (d, 1H, pyridine ring), 7.30 – 7.41 (m, 5H, benzene ring), 8.55–8.56 (d, 1H, pyridine ring). MS (ESI) *m*/*z* 265.7 $[M+1]^+$; analysis for $C_{15}H_{15}N_5$ (265.1), calcd: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.88; H, 5.73; N, 26.44.

5.2.2.48. *N*-(2-Benzyl-5-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-guanidine (3l). Yield: 68%; white solid; mp 240–242 °C; IR (KBr): 3400, 2854, 1610, 1400, 775, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 2H, $-CH_2-$Ph), 7.23–7.24 (m, 5H, benzene ring), 7.31–7.32 (d, 1H, pyridine ring), 8.52–8.53 (d, 1H, pyridine ring). MS (ESI) *m*/*z* 300.3 $[M+1]^+$, 301.3 $[M+2]^+$; analysis for $C_{15}H_{14}ClN_5$ (299.6.1), calcd: C, 60.10; H, 4.71; N, 23.36. Found: C, 60.13; H, 4.75; N, 23.38.

5.2.3. General method for the synthesis of *N*-(2,5-disubstituted-1*H*-indol-3-yl)-guanidine (4a–l; Scheme 3).

5.2.3.1. Synthesis of 3-nitro-1*H*-indole (12a). To a mixture of indole (**11a**; 1 g, 8.55 mmol) and silver nitrate ($AgNO_3$; 1.55 g, 9.1 mmol), dissolved in acetonitrile (8 mL), a solution of benzoyl chloride (1.25 g, 9.1 mmol) was added dropwise, at 0 °C. The reaction mixture was stirred at 0 °C for 45 min. The mixture was diluted with water (200 mL), extracted with benzene (3 × 30 mL), and the extract was washed with Na_2CO_3 solution (2 N). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to obtain the amorphous material. Residue obtained was acidified with HCl (2 N) solution. The white precipitate obtained was filtered, dried and recrystallized from Benzene to get the pure compound **12a**. Yield: 61%; yellow solid; mp 212–213 °C; IR (KBr): 3400, 2845, 1610, 1540 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.60 (s, 1H, pyrrole ring), 7.38–7.39 (m, 1H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 7.65–7.66 (d, 1H, benzene ring), 8.55–8.56 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 163.2 $[M+1]^+$; analysis for $C_8H_6N_2O_2$ (162), calcd: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.22; H, 3.70; N, 17.25.

5.2.3.2. 5-Chloro-3-nitro-1*H*-indole (12b). Yield: 60%; yellow solid; mp 218–220 °C; IR (KBr): 3400, 2845,

1610, 1545, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.61 (s, 1H, pyrrole ring), 7.55–7.56 (d, 1H, benzene ring), 7.65–7.66 (d, 1H, benzene ring), 8.44–8.45 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 197.3 $[M+1]^+$, 198.3 $[M+2]^+$; analysis for $C_8H_5ClN_2O_2$ (196), calcd: C, 48.88; H, 2.56; N, 14.25. Found: C, 48.84; H, 2.52; N, 14.21.

5.2.3.3. 5-Chloro-2-methyl-3-nitro-1*H*-indole (12c). Yield: 63%; yellow solid; mp 203–205 °C; IR (KBr): 3400, 2845, 1610, 1545, 1375 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.14 (s, 3H, Methyl), 7.55–7.56 (d, 1H, benzene ring), 7.65–7.66 (d, 1H, benzene ring), 8.55–8.56 (d, 1H, benzene ring), 11.70 (s, 1H, –N*H*). MS (ESI) *m*/*z* 211.3 $[M+1]^+$, 212.3 $[M+2]^+$; analysis for $C_9H_7ClN_2O_2$ (210), calcd: C, 51.32; H, 3.35; N, 13.30. Found: C, 51.30; H, 3.31; N, 13.27.

5.2.3.4. 2-Methyl-3-nitro-1*H*-indole (12d). Yield: 67%; yellow solid; mp 246–248 °C; IR (KBr): 3400, 2845, 1610, 1545, 1375 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.14 (s, 3H, methyl), 7.32–7.33 (m, 1H, benzene ring), 7.54–7.55 (d, 1H, benzene ring), 7.65–7.66 (d, 1H, benzene ring), 8.50–8.51 (d, 1H, benzene ring), 11.69 (s, 1H, –NH). MS (ESI) m/z 177.2 $[M+1]^+$; analysis for $C_9H_8N_2O_2$ (176), calcd: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.32; H, 4.55; N, 15.86.

5.2.3.5. 3-Nitro-2-phenyl-1*H*-indole (12e). Yield: 68%; yellow solid; mp 237–239 °C; IR (KBr): 3400, 2845, 1610, 1545 1435 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.40 (m, 5H, benzene ring), 7.21–7.22 (m, 1H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 7.66–7.67 (d, 1H, benzene ring), 8.52–8.53 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 239.5 $[M+1]^+$; analysis for $C_{14}H_{10}N_2O_2$ (238.2), calcd: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.55; H, 4.22; N, 11.73.

5.2.3.6. 5-Chloro-3-nitro-2-phenyl-1*H*-indole (12f). Yield: 63%; yellow solid; mp 223–225 °C; IR (KBr): 3400, 2845, 1610, 1545 1435, 770 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 –7.39 (m, 5H, benzene ring), 7.41–7.42 (d, 1H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 8.50–8.51 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 273.3 $[M+1]^+$, 274.3 $[M+2]^+$; analysis for $C_{14}H_9ClN_2O_2$ (272), calcd: C, 61.66; H, 3.33; N, 10.27. Found: C, 61.63; H, 3.30; N, 10.24.

5.2.3.7. 2-Cyclohexyl-3-nitro-1*H*-indole (12g). Yield: 66%; yellow solid; mp 207–209 °C; IR (KBr): 3400, 2845, 1610, 1545 1440, 1375, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.29–1.30 (m, 6H, –cyclohex), 1.58–1.59 (m, 4H, –cyclohex), 2.76–2.77 (m, 1H, –cyclohex), 7.21–7.22 (m, 1H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 7.66–7.67 (d, 1H, benzene ring), 8.52–8.53 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 245.3 $[M+1]^+$; analysis for $C_{14}H_{16}N_2O_2$ (244), calcd: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.80; H, 6.56; N, 11.43.

5.2.3.8. 5-Chloro-2-cyclohexyl-3-nitro-1*H*-indole (12h). Yield: 69%; yellow solid; mp 224–225 °C; IR (KBr): 3400, 2845, 1610, 1545 1440, 1375, 775, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.29–1.30 (m, 6H, –cyclohex), 1.58–1.59 (m, 4H, –cyclohex), 2.75–2.76 (m, 1H, –cyclohex), 7.53–7.54 (d, 1H, benzene ring), 7.68–7.69 (d, 1H, benzene ring), 8.48–8.49 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 279.5 $[M+1]^+$, 280.5 $[M+2]^+$; analysis for $C_{14}H_{15}ClN_2O_2$ (278.1), calcd: C, 58.99; H, 4.95; N 10.58. Found: C, 58.96; H, 4.91; N, 10.54.

5.2.3.9. 2-Ethyl-3-nitro-1*H*-indole (12i). Yield: 62%; yellow solid; mp 213–215 °C; IR (KBr): 3400, 2845, 1610, 1545 1440, 1375 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.23–1.24 (t, 3H, $-CH_2CH_3$), 2.59–2.60 (m, 2H, $-CH_2CH_3$), 7.22–7.23 (m, 1H, benzene ring), 7.54–7.55 (d, 1H, benzene ring), 7.57–7.58 (d, 1H, benzene ring), 8.53–8.54 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 191.2 $[M+1]^+$; analysis for $C_{10}H_{10}N_2O_2$ (190), calcd: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.11; H, 5.27; N, 14.70.

5.2.3.10. 5-Chloro-2-ethyl-3-nitro-1*H*-indole (12j). Yield: 65%; yellow solid; mp 223–224 °C; IR (KBr): 3400, 2845, 1610, 1545 1440, 1375, 745 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.26–1.27 (t, 3H, $-CH_2CH_3$), 2.61–2.62 (m, 2H, $-CH_2CH_3$), 7.48–7.49 (d, 1H, Benzene ring), 7.55–7.56 (d, 1H, benzene ring), 8.51–8.52 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 225.3 $[M+1]^+$, 226.3 $[M+2]^+$; analysis for $C_{10}H_9ClN_2O_2$ (224.1), calcd: C, 54.47; H, 4.04; N, 12.47. Found: C, 54.43; H, 4.00; N, 12.43.

5.2.3.11. 2-Benzyl-3-nitro-1*H*-indole (12k). Yield: 64%; yellow solid; mp 237–239 °C; IR (KBr): 3400, 2845, 1610, 1545 1440 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 2H, $-CH_2$–Ph), 7.30–7.40 (m, 5H, benzene ring), 7.43–7.44 (m, 1H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 7.77–7.78 (d, 1H, benzene ring), 8.53–8.54 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 253.2 $[M+1]^+$; analysis for $C_{15}H_{12}N_2O_2$ (252), calcd: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.40; H, 4.76; N, 11.07.

5.2.3.12. 2-Benzyl-5-chloro-3-nitro-1*H*–indole (12l). Yield: 66%; yellow solid; mp 225–226 °C; IR (KBr): 3400, 2845, 1610, 1545 1440, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 2H, $-CH_2$–Ph), 7.29–7.30 (m, 5H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 7.71–7.72 (d, 1H, benzene ring), 8.56–8.57 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 287.2 $[M+1]^+$, 288.2 $[M+2]^+$; analysis for $C_{15}H_{11}ClN_2O_2$ (286), calcd: C, 62.84; H, 3.87; N, 9.77. Found: C, 62.80; H, 3.83; N, 9.75.

5.2.3.13. Synthesis of 3-amino-1*H*-indole (13a). A mixture of 3-nitro-1*H*-indole (**12a**; 0.2 g, 1.234 mmol) and Pd/C (10%; 100 mg), dissolved in ethanol (10 mL), was hydrogenated for 3 h, at 50 psi. The reaction mixture was filtered and the excess of ethanol was evaporated under reduced pressure. Solid product was recrystallized from petroleum ether to obtain the pure compound **13a**. Yield: 61%; yellow solid; mp 115–117 °C; IR (KBr): 3400, 2845, 1610 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.60 (s, 1H, pyrrole ring), 7.38–7.39 (m, 1H, benzene

ring), 7.55–7.56 (d, 1H, benzene ring), 7.65–7.66 (d, 1H, benzene ring), 8.52–8.53 (d, 1H, benzene ring), 11.65 (s, 2H, –NH_2). MS (ESI) *m*/*z* 133.3 $[M+1]^+$; analysis for $C_8H_8N_2$ (132), calcd: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.68; H, 6.07; N, 21.17.

5.2.3.14. 5-Chloro-1*H*-indol-3-ylamine (13b). Yield: 64%; yellow solid; mp 104–105 °C; IR (KBr): 3400, 2845, 1610, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.59 (s, 1H, pyrrole ring), 7.45–7.46 (d, 1H, benzene ring), 7.61–7.62 (d, 1H, benzene ring), 8.48–8.49 (d, 1H, benzene ring), 11.65 (s, 2H, –NH_2). MS (ESI) *m*/*z* 168.3 $[M+1]^+$, 169.3 $[M+2]^+$; analysis for $C_8H_7ClN_2$ (167), calcd: C, 57.67; H, 4.23; N, 16.81. Found: C, 57.64; H, 4.20; N, 16.79.

5.2.3.15. 5-Chloro-2-methyl-1*H*-indol-3-ylamine (13c). Yield: 67%; yellow solid; mp 137–139 °C; IR (KBr): 3400, 2845, 1610, 1375, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.14 (s, 3H, methyl), 7.55–7.56 (d, 1H, benzene ring), 7.69–7.70 (d, 1H, benzene ring), 8.55–8.56 (d, 1H, benzene ring), 11.70 (s, 2H, –NH_2). MS (ESI) *m*/*z* 181.1 $[M+1]^+$, 182.1 $[M+2]^+$; analysis for $C_9H_9ClN_2$ (180), calcd: C, 59.84; H, 5.02; N, 15.51. Found: C, 59.81; H, 5.00; N, 15.49.

5.2.3.16. 2-Methyl-1*H*-indol-3-ylamine (13d). Yield: 62%; yellow solid; mp 115–116 °C; IR (KBr): 3400, 2845, 1600, 1375 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.14 (s, 3H, methyl), 7.32–7.33 (m, 1H, benzene ring), 7.51–7.52 (d, 1H, benzene ring), 7.58–7.59 (d, 1H, benzene ring), 8.49–8.50 (d, 1H, benzene ring), 11.66 (s, 2H, –NH_2). MS (ESI) *m*/*z* 148.2 $[M+1]^+$; analysis for $C_9H_{10}N_2$ (147), calcd: C, 73.94; H, 6.89; N, 19.16. Found: C, 73.91; H, 6.87; N, 19.13.

5.2.3.17. 2-Phenyl-1*H*-indol-3-ylamine (13e). Yield: 68%; yellow solid; mp 108–110 °C; IR (KBr): 3400, 2845, 1600, 1375 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.13–7.18 (m, 5H, benzene ring), 7.20–7.21 (m, 1H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 7.63–7.64 (d, 1H, benzene ring), 8.52–8.53 (d, 1H, benzene ring), 11.65 (s, 2H, –NH_2). MS (ESI) *m*/*z* 210.2 $[M+1]^+$; analysis for $C_{14}H_{12}N_2$ (209), calcd: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.72; H, 5.79; N, 13.42.

5.2.3.18. 5-Chloro-2-phenyl-1*H*-indol-3-ylamine (13f). Yield: 66%; yellow solid; mp 125–127 °C; IR (KBr): 3400, 2845, 1600, 776 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 – 7.40 (m, 5H, benzene ring), 7.42–7.43 (d, 1H, benzene ring), 7.45–7.46 (d, 1H, benzene ring), 8.51–8.52 (d, 1H, benzene ring), 11.65 (s, 2H, –NH_2). MS (ESI) *m*/*z* 243.2 $[M+1]^+$, 244.2 $[M+2]^+$; analysis for $C_{14}H_{11}ClN_2$ (242), calcd: C, 69.28; H, 4.57; N 11.54. Found: C, 69.25; H, 4.54; N 11.51.

5.2.3.19. 2-Cyclohexyl-1*H*-indol-3-ylamine (13g). Yield: 69%; yellow solid; mp 109–111 °C; IR (KBr): 3400, 2845, 1600, 1400, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.29–1.30 (m, 6H, –cyclohex), 1.58–1.59 (m, 4H, –cyclohex), 2.76–2.77 (m, 1H, –cyclohex), 7.21–7.22 (m, 1H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 7.61–7.62 (d, 1H, benzene ring), 8.50–7.51 (d, 1H, benzene ring), 11.65 (s, 2H, –NH_2). MS (ESI) *m*/*z* 216.2 $[M+1]^+$; analysis for $C_{14}H_{18}N_2$ (215), calcd: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.42; H, 8.43; N, 13.05.

5.2.3.20. 5-Chloro-2-cyclohexyl-1*H*-indol-3-ylamine (13h). Yield: 71%; yellow solid; mp 127–129 °C; IR (KBr): 3400, 2845, 1600, 1400, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.29–1.30 (m, 6H, –cyclohex), 1.58–1.59 (m, 4H, –cyclohex), 2.75–2.76 (m, 1H, –cyclohex), 7.54–2.55 (d, 1H, benzene ring), 7.61–7.62 (d, 1H, benzene ring), 8.49–8.50 (d, 1H, benzene ring), 11.65 (s, 2H, –NH_2). MS (ESI) *m*/*z* 250.2 $[M+1]^+$, 251.2 $[M+2]^+$; analysis for $C_{14}H_{17}ClN_2$ (249), calcd: C, 67.60; H, 6.89; N, 11.26. Found: C, 67.57; H, 6.86; N, 11.23.

5.2.3.21. 2-Ethyl-1*H*-indol-3-ylamine (13i). Yield: 67%; yellow solid; mp 129–131 °C; IR (KBr): 3400, 2845, 1600, 1400, 1375 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.22–1.23 (t, 3H, –CH_2CH_3), 2.59–2.60 (m, 2H, –CH_2CH_3), 7.55–7.56 (d, 1H, benzene ring), 7.61–7.62 (m, 1H, benzene ring), 7.65–7.66 (d, 1H, benzene ring), 8.45–8.46 (d, 1H, benzene ring), 11.65 (s, 2H, –NH_2). MS (ESI) *m*/*z* 161.2 $[M+1]^+$; analysis for $C_{10}H_{12}N_2$ (160), calcd: C, 74.97; H, 7.55; N, 17.48. Found: C, 74.94; H, 7.52; N, 17.44.

5.2.3.22. 5-Chloro-2-ethyl-1*H*-indol-3-ylamine (13j). Yield: 67%; yellow solid; mp 124–136 °C; IR (KBr): 3400, 2845, 1600, 1400, 1375, 770 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24–1.25 (t, 3H, –CH_2CH_3), 2.59–2.60 (m, 2H, –CH_2CH_3), 7.48–7.49 (d, 1H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 8.51–8.52 (d, 1H, benzene ring), 11.65 (s, 2H, –NH_2). MS (ESI) *m*/*z* 195.2 $[M+1]^+$, 196.2 $[M+2]^+$; analysis for $C_{10}H_{11}ClN_2$ (194), calcd: C, 61.70; H, 5.70; N, 14.39. Found: C, 61.67; H, 5.67; N, 14.36.

5.2.3.23. 2-Benzyl-1*H*-indol-3-ylamine (13k). Yield: 62%; yellow solid; mp 143–145 °C; IR (KBr): 3400, 2845, 1600, 1400 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 2H, –CH_2–Ph), 7.29 – 7.39 (m, 5H, benzene ring), 7.42–7.43 (m, 1H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 7.76–7.77 (d, 1H, benzene ring), 8.51–8.52 (d, 1H, benzene ring), 11.65 (s, 2H, –NH_2). MS (ESI) *m*/*z* 224.3 $[M+1]^+$; analysis for $C_{15}H_{14}N_2$ (223), calcd: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.03; H, 6.31; N, 12.56.

5.2.3.24. 2-Benzyl-5-chloro-1*H*-indol-3-ylamine (13l). Yield: 61%; yellow solid; mp 124–126 °C; IR (KBr): 3400, 2845, 1600, 1400, 776 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 2H, –CH_2–Ph), 7.34–7.42 (m, 5H, benzene ring), 7.70–7.71 (d, 1H, benzene ring), 8.55–8.56 (d, 1H, benzene ring), 11.65 (s, 2H, –NH_2). MS (ESI) *m*/*z* 257.4 $[M+1]^+$, 258.4 $[M+2]^+$; analysis for $C_{15}H_{13}ClN_2$ (256), calcd: C, 70.18; H, 5.10; N, 10.91. Found: C, 70.14; H, 5.06; N, 10.87.

5.2.3.25. Synthesis of bis-Boc-N-(1*H*-indol-3-yl)-guanidine (14a). Synthesis of compound **14a** was carried out starting from 3-amino-1*H*-indole (**13a**), using a general procedure described for the synthesis of compound **6a**.

Yield: 62%; white solid; mp 188–189 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N═), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 6.60 (s, 1H, pyrrole ring), 7.20–7.21 (d, 1H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 7.68–7.69 (dd, 1H, benzene ring), 8.49–8.50 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 375.3 $[M+1]^+$; analysis for $C_{19}H_{26}N_4O_4$ (374), calcd: C, 60.95; H, 7.00; N, 14.96. Found: C, 60.91; H, 6.98; N, 14.93.

5.2.3.26. Bis-Boc-*N*-(5-chloro-1*H*-indol-3-yl)-guanidine (14b). Yield: 63%; white solid; mp 168–169 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N═), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 6.60 (s, 1H, pyrrole ring), 7.55–7.56 (d, 1H, benzene ring), 7.68–7.69 (dd, 1H, benzene ring), 8.50–8.51 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 409.3 $[M+1]^+$, 410.3 $[M+2]^+$; analysis for $C_{19}H_{25}ClN_4O_4$ (408), calcd: C, 55.81; H, 6.16; N, 13.70. Found: C, 55.78; H, 6.14; N, 13.68.

5.2.3.27. Bis-Boc-*N*-(5-chloro-2-methyl-1*H*-indol-3-yl)-guanidine (14c). Yield: 58%; white solid; mp 168–169 °C; IR (KBr): 3400, 2850, 1710, 1610, 1375, 1050, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N═), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 2.16 (s, 3H, methyl), 7.80 (s, 1H, benzene ring), 8.48 (s, 1H, benzene ring), 11.70 (s, 1H, –N*H*). MS (ESI) *m*/*z* 423.2 $[M+1]^+$, 424.2 $[M+2]^+$; analysis for $C_{20}H_{27}ClN_4O_4$ (422), calcd: C, 56.80; H, 6.44; N, 13.25. Found: C, 56.77; H, 6.42; N, 13.23.

5.2.3.28. Bis-Boc-*N*-(2-methyl-1*H*-indol-3-yl)-guanidine (14d). Yield: 70%; white solid; mp 155–157 °C; IR (KBr): 3400, 2850, 1710, 1610, 1375, 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N═), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 2.16(s, 3H, methyl), 7.11–7.12 (m, 1H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 7.67 (s, 1H, benzene ring), 8.53 (s, 1H, benzene ring), 11.72 (s, 1H, –N*H*). MS (ESI) *m*/*z* 389.2 $[M+1]^+$; analysis for $C_{20}H_{28}N_4O_4$ (388), calcd: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.81; H, 7.25; N, 14.40.

5.2.3.29. Bis-Boc-*N*-(2-phenyl-1*H*-indol-3-yl)-guanidine (14e). Yield: 65%; white solid; mp 152–153 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N═), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 7.44–7.45 (m, 5H, benzene ring), 7.23–7.24 (m, 1H, benzene ring), 7.56–7.57 (d, 1H, benzene ring), 7.67–7.68 (d, 1H, benzene ring), 8.58–8.59 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 451.1 $[M+1]^+$ $C_{25}H_{30}N_4O_4$ (450), calcd: C, 66.65; H, 6.71; N, 12.44. Found: C, 66.63; H, 6.68; N, 12.41.

5.2.3.30. Bis-Boc-*N*-(5-chloro-2-Methyl-1*H*-indol-3-yl)-guanidine (14f). Yield: 67%; white solid; mp 172–174 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N═), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 7.30 –7.40 (m, 5H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 7.60–7.61 (d, 1H, benzene ring), 8.50–8.51 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 485.3 $[M+1]^+$, 486.3 $[M+2]^+$; analysis for $C_{25}H_{29}ClN_4O_4$ (484), calcd: C, 61.91; H, 6.03; N, 11.55. Found: C, 61.88; H, 6.00; N, 11.53.

5.2.3.31. Bis-Boc-*N*-(2-cyclohexyl-1*H*-indol-3-yl)-guanidine (14g). Yield: 68%; white solid; mp 142–143 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.27–1.28 (m, 6H, –cyclohexyl), 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N═), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 1.58–1.59 (m, 4H, –cyclohexyl), 2.76–2.77 (m, 1H, –cyclohexyl), 7.20–2.21 (m, 1H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 7.60–7.61 (d, 1H, benzene ring), 8.50–8.51 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 457.3 $[M+1]^+$; analysis for $C_{25}H_{36}N_4O_4$ (456), calcd: C, 65.76; H, 7.95; N, 12.27. Found: C, 65.73; H, 7.93; N, 12.24.

5.2.3.32. Bis-Boc-*N*-(5-chloro-2-cyclohexyl-1*H*-indol-3-yl)-guanidine (14h). Yield: 61%; white solid; mp 158–159 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050, 775, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.29–1.30 (m, 6H, –cyclohex), 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N═), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—N), 1.58–1.59 (m, 4H, –cyclohex), 2.76–2.77 (m, 1H, –cyclohex), 7.55–7.56 (d, 1H, benzene ring), 7.60–7.61 (d, 1H, benzene ring), 8.49–8.50 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 491.2 $[M+1]^+$, 492.2 $[M+2]^+$; analysis for $C_{25}H_{35}ClN_4O_4$ (490), calcd: C, 61.15; H, 7.18; N, 11.41. Found: C, 61.11; H, 7.15; N, 11.38.

5.2.3.33. Bis-Boc-*N*-(2-ethyl-1*H*-indol-3-yl)-guanidine (14i). Yield: 63%; white solid; mp 168–169 °C; IR (KBr): 3400, 2850, 1710, 1610, 1375 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.23–1.24 (t, 3H, –CH_2CH_3), 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N═), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—N—), 2.58–2.59 (m, 2H, –CH_2CH_3), 7.23–7.24 (d, 1H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 7.67–7.68 (dd, 1H, benzene ring), 8.54–8.55 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 403.2 $[M+1]^+$; analysis for $C_{21}H_{30}N_4O_4$ (402), calcd: C, 62.67; H, 7.51; N, 13.92. Found: C, 62.64; H, 7.49; N, 13.88.

5.2.3.34. Bis-Boc-*N*-(5-chloro-2-ethyl-1*H*-indol-3-yl)-guanidine (14j). Yield: 66%; white solid; mp 170–171 °C; IR (KBr): 3400, 2850, 1710, 1610, 1375 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24–1.25 (t, 3H, –CH_2CH_3), 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N═), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 2.59–2.60 (m, 2H, –CH_2CH_3), 7.55–7.56 (d, 1H, benzene ring), 7.67–7.68 (dd, 1H, benzene ring), 8.50–8.51 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 437.2 $[M+1]^+$, 438.2 $[M+2]^+$; analysis for $C_{21}H_{29}ClN_4O_4$ 9436), calcd: C, 57.73; H, 6.69; N, 12.82. Found: C, 57.70; H, 6.66; N, 12.80.

5.2.3.35. Bis-Boc-*N*-(2-benzyl-1*H*-indol-3-yl)-guanidine (14k). Yield: 69%; white solid; mp 185–186 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050 cm^{-1}. ^1H NMR

(300 MHz, $CDCl_3$): δ 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N═), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 3.81 (s, 2H, –CH_2–Ph), 7.30–7.40 (m, 5H, benzene ring), 7.42–7.43 (m, 1H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 7.61–7.62 (dd, 1H, benzene ring), 8.50–8.51 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 465.3 $[M+1]^+$; analysis for $C_{26}H_{32}N_4O_4$ (464), calcd: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.19; H, 6.91; N, 12.03.

5.2.3.36. Bis-Boc-*N*-(5-chloro-2-benzyl-1*H*-indol-3-yl)-guanidine (14l). Yield: 60%; white solid; mp 153–154 °C; IR (KBr): 3400, 2850, 1710, 1610, 1050, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H, $(CH_3)_3C$—O—CO—N═), 1.56 (s, 9H, $(CH_3)_3C$—O—CO—NH—), 3.81 (s, 2H, –CH_2–Ph), 7.22–7.23 (m, 5H, benzene; 7.55–7.56 (d, 1H, benzene ring), 7.66–7.67 (dd, 1H, benzene ring), 8.52–8.53 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 499.2 $[M+1]^+$, 500.2 $[M+2]^+$; Anal. Calcd for $C_{26}H_{31}ClN_4O_4$ (498), calcd: C, 62.58; H, 6.26; N, 11.23. Found: C, 62.55; H, 6.22; N, 11.20.

5.2.3.37. Synthesis of *N*-(1*H*-Indol-3-yl)-guanidine (4a). Synthesis of compound **4a** was carried out starting from bis-Boc-*N*-(1*H*-indol-3-yl)-guanidine (**14a**), using a general procedure described for the synthesis of compound **2a**. Yield: 61%; white solid; mp 122–123 °C; IR (KBr): 3430, 2854, 1610 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.70 (s, 1H, pyrrole ring), 7.13–7.14 (m, 1H, benzene ring), 7.56–7.57 (d, 1H, benzene ring), 7.68–7.69 (d, 1H, benzene ring), 8.22–8.23 (d, 1H, benzene ring), 11.77 (s, 1H, –N*H*). MS (ESI) *m*/*z* 175 $[M+1]^+$; analysis for $C_9H_{10}N_4$ (174), calcd: C, 62.05; H, 5.79; N, 32.16. Found: C, 62.01; H, 5.75; N, 32.13.

5.2.3.38. *N*-(5-Chloro-1*H*-indol-3-yl)-guanidine (4b). Yield: 66%; white solid; mp 99–101 °C; IR (KBr): 3430, 2854, 1610, 774 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.70 (s, 1H, pyrrole ring), 7.55–7.56 (d, 1H, benzene ring), 7.67–7.68 (d, 1H, benzene ring), 8.20–8.21 (d, 1H, benzene ring), 11.77 (s, 1H, –NH); MS (ESI) m/z 209.3 $[M+1]^+$, 210.3 $[M+2]^+$; analysis for $C_9H_9ClN_4$ (208), calcd: C, 51.81; H, 4.35; N, 26.85. Found: C, 51.78; H, 4.31; N, 26.82.

5.2.3.39. *N*-(5-Chloro-2-methyl-1*H*-indol-3-yl)-guanidine (4c). Yield: 60%; white solid; mp 138–139 °C; IR (KBr): 3400, 2854, 1610, 1375, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.16 (s, 3H, methyl), 7.80 (s, 1H, benzene ring), 8.48 (s, 1H, benzene ring), 11.70 (s, 1H, –N*H*). MS (ESI) *m*/*z* 223.1 $[M+1]^+$, 224.1 $[M+2]^+$; analysis for $C_{10}H_{11}ClN_4$ (222), calcd: C, 53.94; H, 4.98; N, 25.16. Found: C, 53.92; H, 4.95; N, 25.12.

5.2.3.40. *N*-(2-Methyl-1*H*-indol-3-yl)-guanidine (4d). Yield: 66%; white solid; mp 125–126 °C; IR (KBr): 3400, 2854,1610, 1375 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.16 (s, 3H, methyl), 7.13–7.14 (m, 1H, benzene ring), 7.54–7.55 (d, 1H, benzene ring), 7.67 (s, 1H, Benzene ring), 8.5 (s, 1H, benzene ring), 11.7 (s, 1H, –N*H*). MS (ESI) *m*/*z* 189.2 $[M+1]^+$; analysis for $C_{10}H_{12}N_4$ (188), calcd: C, 63.81; H, 6.43; N, 29.77. Found: C, 63.77; H, 6.40; N, 29.73.

5.2.3.41. *N*-(2-Phenyl-1*H*-indol-3-yl)-guanidine (4e). Yield: 63%; white solid; mp 118–119 °C; IR (KBr): 3430, 2854, 1610 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.03–7.04 (m, 1H, benzene ring), 7.12–7.13 (m, 1H, benzene ring), 7.39–7.48 (m, 2H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 7.67–7.68 (d, 1H, benzene ring), 7.96–7.97 (d, 2H, benzene ring), 8.20–8.21 (d, 1H, benzene ring), 11.77 (s, 1H, –N*H*). MS (ESI) *m*/*z* 251.2 $[M+1]^+$; analysis for $C_{15}H_{14}N_4$ (250), calcd: C, 71.98; H, 5.64; N, 22.38. Found: C, 71.95; H, 5.60; N, 22.34.

5.2.3.42. *N*-(5-Chloro-2-phenyl-1*H*-indol-3-yl)-guanidine (4f). Yield: 67%; white solid; mp 145–147 °C; IR (KBr) 3400, 2854, 1610, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.11–7.12 (m, 1H, benzene ring), 7.39–7.48(m, 2H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 7.8 (s, 1H, benzene ring), 7.97–7.98 (d, 2H, benzene ring), 8.48 (s, 1H, benzene ring), 11.7 (s, 1H, –N*H*). MS (ESI) *m*/*z* 285.2 $[M+1]^+$, 286.2 $[M+2]^+$; analysis for $C_{15}H_{13}ClN_4$ (284), calcd: C, 63.27; H, 4.60; N, 19.68. Found: C, 63.23; H, 4.56; N, 19.64.

5.2.3.43. *N*-(2-Cyclohexyl-1*H*-indol-3-yl)-guanidine (4g). Yield: 61%; white solid; mp 115–116 °C; IR (KBr): 3400, 2854, 1610, 1410, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.29–1.30 (m, 6H, –cyclohex), 1.58–1.59 (m, 4H, –cyclohex), 2.76–2.77 (m, 1H, –cyclohex), 7.20–7.21 (m, 1H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 7.62–7.63 (d, 1H, benzene ring), 8.52–8.53 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 257.2 $[M+1]^+$; analysis for $C_{15}H_{20}N_4$ (256), calcd: C, 70.28; H, 7.86; N, 21.86. Found: C, 70.25; H, 7.82; N, 21.83.

5.2.3.44. *N*-(5-Chloro-2-cyclohexyl-1*H*-indoyl-3-yl)-guanidine (4h). Yield: 65%; white solid; mp 138–139 °C; IR (KBr): 3400, 2854, 1610, 1410, 775, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.29–1.31 (m, 6H, –cyclohex), 1.58–1.59 (m, 4H, –cyclohex), 2.76–2.77 (m, 1H, –cyclohex), 7.55–7.56 (d, 1H, benzene ring), 7.66–7.77 (d, 1H, benzene ring), 8.50–8.51 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 292.2 $[M+1]^+$, 293.2 $[M+2]^+$; analysis for $C_{15}H_{19}ClN_4$ (291), calcd: C, 61.96; H, 6.59; N, 19.27. Found: C, 61.92; H, 6.56; N, 19.24.

5.2.3.45. *N*-(2-Ethyl-1*H*-indol-3-yl)-guanidine (4i). Yield: 67%; white solid; mp 133–134 °C; IR (KBr): 3400, 2854, 1610, 1400, 1375.cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.22–1.23 (t, 3H, –CH_2CH_3), 2.59–2.60 (m, 2H, –CH_2CH_3), 7.22–7.23 (m, 1H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 7.70–7.71 (d, 1H, benzene ring), 8.53–8.54 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 203.2 $[M+1]^+$; analysis for $C_{11}H_{14}N_4$ (202), calcd: C, 65.32; H, 6.98; N, 27.70. Found: C, 65.28; H, 6.96; N, 27.66.

5.2.3.46. *N*-(5-Chloro-2-ethyl-1*H*-indol-3-yl)-guanidine (4j). Yield: 60%; white solid; mp 148–149 °C; IR (KBr): 3400, 2854, 1610, 1400, 1375, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24–1.25 (t, 3H, –CH_2CH_3), 2.59–2.60 (m, 2H, –CH_2CH_3), 7.55–7.56 (d, 1H, benzene ring), 7.70–7.71 (d, 1H, benzene ring), 8.53–8.54 (d, 1H, benzene ring), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 237.2 $[M+1]^+$, 238.2 $[M+2]^+$; analysis

for $C_{11}H_{13}ClN_4$ (236), calcd: C, 55.82; H, 5.54; N, 23.67. Found: C, 55.79; H, 5.51; N, 23.64.

5.2.3.47. *N*-(2-Benzyl-1*H*-indol-3-yl)-guanidine (4k). Yield: 63%; white solid; mp 103–105 °C; IR (KBr): 3400, 2854, 1610, 1400 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 2H, –C*H*$_2$–Ph), 7.21–7.29 (m, 1H, benzene ring), 7.32 – 7.43 (m, 5H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 7.63–7.64 (dd, 1H, benzene ring), 8.53–8.54 (d, 1H, benzene ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 265.2 $[M+1]^+$; analysis for $C_{16}H_{16}N_4$ (264), calcd: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.68; H, 6.06; N, 21.17.

5.2.3.48. *N*-(2-Benzyl-5-chloro-1*H*-indol-3-yl)-guanidine (4l). Yield: 69%; white solid; mp 124–126 °C; IR (KBr): 3400, 2854, 1610, 1400, 775, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 2H, –C*H*$_2$–Ph), 7.31 – 7.40 (m, 5H, benzene ring), 7.55–7.56 (d, 1H, benzene ring), 7.63–7.64 (dd, 1H, benzene ring), 8.55–8.56 (d, 1H, benzene ring), 9.97 (s, 1H, –N*H*), 11.65 (s, 1H, –N*H*). MS (ESI) *m*/*z* 299.2 $[M+1]^+$, 300.2 $[M+2]^+$; analysis for $C_{16}H_{15}ClN_4$ (298), calcd: C, 64.32; H, 5.06; N, 18.75. Found: C, 64.28; H, 5.02; N, 18.73.

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

RIN5F (rat insulinoma) 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.[39,40]

Cells were washed once with phosphate-buffered saline (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), $MgSO_4 \cdot 7H_2O$ (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 BSA (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 ultra sensitive 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.

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References and notes

1. Wagman, A. S.; Nuss, J. M. *Curr. Pharm. Des.* **2001**, *7*, 417.
2. Cavaghan, M. K.; Ehrmann, D. A.; Polonsky, K. S. *J. Clin. Invest.* **2000**, *106*, 329.
3. Chen, K. W.; Boyko, E. J.; Bergstrom, R. W.; Leonetti, D. L.; Morris, L. N.; Wahl, P. W.; Fujimoto, F. W. *Diabetes Care* **1995**, *18*, 747.
4. Haffner, S. M.; Miettinin, H.; Gaskill, S. P.; Stern, M. *Diabetes Care* **1995**, *18*, 1201.
5. Chehade, J. M.; Mooradian, A. D. *Drugs* **2000**, *60*, 95.
6. Burge, M. R.; Sood, V.; Sobhy, T. A.; Rassam, A. G.; Schade, D. S. *Diabetes Obes. Metab.* **1999**, *1*, 199.
7. Perry, T. A.; Greig, N. H. *Trends Pharmacol. Sci.* **2003**, *24*, 377.
8. Schulz, A.; Hasselblatt, A. *Naunyn Schmiedeberg's Arch. Pharmacol.* **1989**, *340*, 321.
9. Le Brigand, L.; Virsolvy, A.; Manechez, D.; Godfroid, J. J.; Guardiola-Lemaitre, B.; Gribble, M.; Ashcroft, F. M.; Bataille, D. *Br. J. Pharmacol.* **1999**, *128*, 1021.
10. 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.
11. Brown, C. A.; Loweth, A. C.; Smith, S. A.; Morgan, N. G. *Br. J. Pharmacol.* **1993**, *108*, 312.
12. Chan, S. F.; Brown, C. A.; Scarpello, K. E.; Morgan, N. G. *Br. J. Pharmacol.* **1994**, *112*, 1065.
13. Hoy, M.; Olsen, H. L.; Andersen, H. S.; Okvist, K.; Buschard, K.; Hansen, J.; Jacobsen, P.; Petersen, J. S.; Rorsman, P.; Gromada, J. *Eur. J. Pharmacol.* **2003**, *466*, 213.
14. Mest, H. J.; Raap, A.; Schloss, J.; Treinies, I.; Paal, M.; Giese, U.; Koivisto, V. *Naunyn Schmiedeberg's Arch. Pharmacol.* **2001**, *364*, 47.
15. Morgan, N. G.; Chan, S. L. F.; Mourtada, M.; Monks, L. K.; Ramsden, C. A. *Ann. N.Y. Acad. Sci.* **1999**, *381*, 217.
16. Efendic, S.; Efanov, A. M.; Berggen, P.; Zaitsev, S. V. *Diabetes* **2002**, *51*, S448.
17. Brenner, M. B.; Gromada, J.; Efanov, A. M.; Bokvist, K.; Mest, H. J. *Ann. N.Y. Acad. Sci.* **2003**, *1009*, 332.
18. 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.
19. Davis, T. L. *Org. Synth.* **1927**, *7*, 46.
20. Cosand, W. L.; Merrifield, R. B. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 2771.
21. Braun, C. E. *J. Am. Chem. Soc.* **1933**, *55*, 1280.
22. Bannard, R. A. B.; Casselman, A. A.; Cockburn, W. F.; Brown, G. M. *Can. J. Chem.* **1958**, *36*, 1541.
23. Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *Tetrahedron Lett.* **1993**, *34*, 3389.
24. Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *J. Org. Chem.* **1992**, *57*, 2497.
25. Cunha, S.; Costa, M. B.; Napolitano, H. B.; Lariucci, C.; Vencato, I. *Tetrahedron* **2001**, *57*, 1671.
26. Levallet, C.; Lerpiniere, J.; Ko, S. Y. *Tetrahedron* **1997**, *53*, 5291.
27. Jeong, J. H.; Murray, B. W.; Takayama, S.; Wong, C. H. *J. Am. Chem. Soc.* **1996**, *118*, 4227.
28. Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677.
29. Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, *5*, 737.
30. Poss, M. A.; Iwanowicz, E.; Reid, J. A.; Lin, J.; Gu, Z. *Tetrahedron Lett.* **1992**, *33*, 5933.
31. Iwanowicz, E.; Poss, M. A.; Lin, J. *Syn. Comm.* **1993**, *23*, 1443.
32. Kaigorodova, Y. A.; Vasilin, V. K.; Konyushkin, L. D.; Usova, Y. B.; Krapivin, G. D. *Molecules* **2000**, *5*, 1085.
33. Herbert, R.; Wibberley, D. G. *J. Chem. Soc.* **1969**, 1505.

34. Hands, D.; Bishop, B.; Cameron, M.; Edwards, J. S.; Cottrll, I. F.; Wright, S. H. B. *Synthesis* **1996**, 877.
35. Berti, G.; Settimo, A. D.; Nannipieri, E. *J. Chem. Soc. (C)* **1968**, 2145.
36. Fischer, E.; Schmitt, T. *Chem. Ber* **1888**, *21*, 1071.
37. Homel, P.; Zajac, N.; Atkinson, J. G.; Girord, Y. *J. Org. Chem.* **1994**, *59*, 6372.
38. Hary, U.; Roettig, U.; Paal, M. *Tetrahedron Lett.* **2001**, *42*, 5187.
39. Montrose-Rafizadeh, C.; Wang, Y.; Janczewski, T. E.; Henderson, T. E.; Egan, J. M. *Mol. Cell. Endocrinol.* **1997**, *130*, 109.
40. Wang, X.; Zhou, J.; Doyle, M. E.; Egan, J. M. *Endocrinology* **2001**, *5*, 1820.
41. Morgan, N. G.; Chan, S. L. F. *Curr. Pharm. Des.* **2001**, *7*, 1413.
42. Proks, P.; Treinies, I.; Mest, H. J.; Trapp, S. *Eur. J. Pharmacol.* **2002**, *452*, 11.