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Regioselective synthesis of dipyrrolopyrazine (DPP) derivatives *via* metal free and metal catalyzed amination and investigation of their optical and thermal properties†

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Pyrazine is an important molecular scaffold employed in organic optoelectronic materials. Here we report efficient methods for the synthesis of dipyrrolopyrazine, and pyrrolothieno-pyrazine derivatives that involve regio-selective amination reactions of dihalo-pyrrolopyrazines. The developed protocol readily affords either 2-amino- or 3-amino-pyrrolopyrazines from the corresponding 2-bromo-3-chloro-5*H*-pyrrolo[2,3-*b*]pyrazines. When the amination reactions are carried under metal free under microwave irradiation, 3-amino-pyrrolopyrazines are obtained exclusively. In contrast, Buchwald cross coupling of the 2-bromo-3-chloro-5*H*-pyrrolo[2,3-*b*]pyrazines affords only 2-amino-pyrrolopyrazine. The pyrrolopyrazine scaffolds were converted to the respective 1,7- and 1,5-dihydrodipyrrolo[2,3-*b*]pyrazines derivatives using Sonogashira reactions. A comprehensive study of the optical properties, thermal properties, and molecular packing of the synthesized compounds was carried out. The results indicate that the 1,7-derivatives may be promising organic materials for optoelectronic applications.

1. Introduction

Fused heterocyclic compounds are important and valuable substances, especially in the field of optoelectronics.[1] In particular, multicyclic pyrazine fused aromatic compounds are attracting great interest as promising electronic materials that are used to construct field effect transistors,[2,3] light-emitting diodes,[4,5] and photovoltaic cells.[6,7] During the past decade, substances containing the interesting pyrrolo[2,3-*b*]pyrazine molecular scaffold have been prepared, albeit in poor yields. The first efficient synthesis of pyrrolo[2,3-*b*]pyrazine starting from a halo-pyrazine derivative was described by Corey and co-workers. The key step route involved palladium catalysed Sonogashira cross-coupling followed by base induce C–N cyclization to produce pyrrolo[2,3-*b*]pyrazine.[8,9] Interestingly, Simpson *et al.* described a one-pot protocol for the preparation of pyrrolo[2,3-*b*]pyrazine starting with a halo-pyrazine derivative.[10,11] More recently, a strategy relying on a crucial C–N nucleophilic aromatic substitution reaction under microwave (MW) irradiation conditions was developed to prepare this substance.[12–15] It is well known that (metal catalysed) reactions, like the one employed in this sequence, carried out under MW conditions proceed with enhanced regio- and stereoselectivities.[16]

Benzodithiophene (BDT) is another intriguing heterocyclic scaffold that has been used as the foundation for highly efficient optoelectronic devices.[17–22] Although it has been shown that materials containing 2,6-diphenyl BDT analogues are good organic field effect transistors, these substances in polymers undergo rapid degradation caused by to photo-oxidation in air.[12] Substitution of the benzene ring in BDT by a pyrazine moiety suppresses the photo-oxidation process. As a result, pyrazine fused dithiophenes serve as the basis for the development of new n-type transistors. Like BDT, dithienopyrazine (DTP) is planar and it undergoes molecular π–π stacking in the solid state.[23,24] In an effort to prepare new pyrazine fused polycyclic aromatic compounds and explore their potential use as optoelectronics materials, we have conducted an investigation exploring the synthesis of substituted dipyrrolopyrazine derivatives (DPP). At the outset, we hypothesized that the DPP derivatives would be less prone to photo-oxidation than their BDT analogues. Furthermore, it was expected that DPPs would be planar molecule in which the pyrrole ring participates in electron delocalization leading to potentially beneficial electronic properties.

In the studies described below, we developed efficient routes for the synthesis of new 2- and 3-amine functionalised pyrrolopyrazine which serve as advanced precursors to variety of new DPP derivatives. The routes for this purpose utilize key, regioselective 2- and 3-C–N functionalization reactions of 2-bromo-3-

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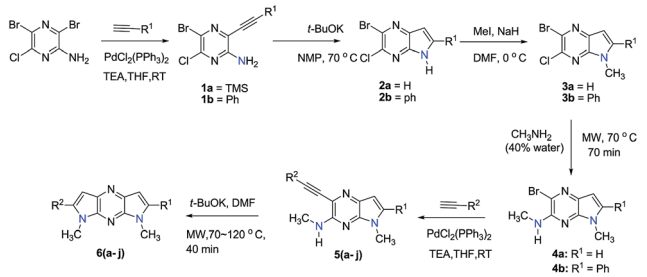
chloro-5*H*-pyrrolo[2,3-*b*]pyrazines **2a,b** using MW irradiation (metal free conditions) and metal catalysed conditions, respectively. The products of these processes were employed to prepare 1,7- and 1,5-dihydrodipyrrolo[3,2-*b*:3′,2′-*e*]pyrazine derivatives (DPP), whose optical, thermal and morphological properties were evaluated. Finally, to assess the applicability of the DPP derivatives to optoelectronics, a systematic investigation of the photo physical and thermal properties of these substances were performed.

2. Results and discussion

2.1 Synthesis and characterization

The 2-bromo-3-chloro-5*H*-pyrrolo[2,3-*b*]pyrazines **2a,b**, key intermediates in the routes for synthesis of the 1,7- and 1,5-dihydrodipyrrolo[3,2-*b*:3′,2′-*e*]pyrazines, were prepared in two steps starting with commercially available 3,5-dibromo-6-chloropyrazin-2-amine. The sequences commenced with Sonogashira cross-coupling of a dibromo-chloropyrazine using appropriate alkynes (Scheme 1). *t*-BuOK promoted intramolecular cyclization then produces **2a,b** in good yields. In addition to the 5-NH substrates **3c,d**, pyrrolopyrazines containing the electron donating 5-NMe (**3a,b**) and electron withdrawing 5-NTs (**3e**) substituents were prepared from **2a,b** to explore the challenging C–N coupling process.

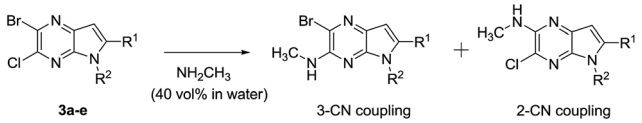


Scheme 1 Synthesis of 1,7-dihydrodipyrrolo[2,3;3′2′-*e*]pyrazine derivatives.

Under normal conditions (40 vol% in water, 60 °C), the pyrrolopyrazine derivatives **3a–e** did not react with methylamine to produce the corresponding amination products. Exploratory studies showed that the use of MW conditions with THF as the solvent facilitate the C–N bond forming substitution reactions of these pyrrolopyrazine derivatives and methylamine, although little selectivity was observed to occur between C–N bond formation at the 2-bromo and 3-chlorosubstituted centers. Specifically, reactions of the free amines **3c,d** and *N*-tosyl derivative **3e** react under these conditions form mixtures of 2- and 3-*N*-methylamine coupling products (Table 1). Interestingly, under solvent free conditions, the *N*-Me derivatives **3a,b** react to produce exclusively the 3-*N*-methylamine products **4a,b** in 69% and 39% yield, respectively. The 5-*N*-methylamine derivatives **4a,b**, formed in the manner described above were then used to prepare the 1,7-dihydrodipyrrolo[2,3-*b*;3′2′-*e*]pyrazines **6a–j**. To this end, $Pd(PPh_3)_2Cl_2$ catalysed Sonogashira reaction of **4a,b** with a series of terminal alkynes were carried out to generate the respective 2-ethynyl-*N*,5-dimethyl-5*H*-pyrrolo[2,3-*b*]pyrazin-3-amines **5a–j** (59–74%, Table 2). Finally, *t*-BuOK mediated intramolecular cyclization of **5a–j** form the corresponding target 1,7-dihydrodipyrrolo[2,3-*b*:3′,2′-*e*]pyrazines **6a–j** in good to excellent yields (63–96%).

Our attention was next focussed at the synthesis of the 1,5-dihydrodipyrrolo[3,2-*b*:3′,2′-*e*]pyrazine derivatives. For this purpose, **3a,b** were subjected to reactions using the standard Buchwald coupling conditions. $Pd(OAc)_2$ with xantphos as the ligand was selected as the catalyst together with *t*-butyl carbamate as the coupling partner in the process.[25] As expected, these reactions takes place exclusively at the 2-bromo positions in **3a,b** to give the respective 2-*N*-Boc protected derivatives **7a,b** in good yields. Subsequent *N*-methylation of **7a,b** followed by Boc removal using TFA produces the corresponding 2-*N*-methylamine derivatives **9a,b**. Sonogashira cross coupling reactions of **9a,b** with a variety of different terminal alkynes were investigated. In accordance with the earlier observations, under non-MW conditions the starting materials remained unreactive. Fortunately, under MW (Scheme 2), the desired products **10a–k**

Table 1 The influence of 5-*N*-substituents on C–N coupling reactions of pyrrolopyrazines[a]



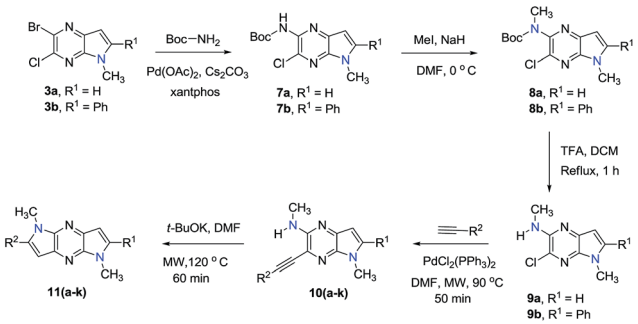
Compound	R^1/R^2	Solvent	Temp. (°C)	Time (min)	3-CN : 2-CN[b]
3a	H/Me	Neat	60	70	100 : 0 (69%)[c]
3b	Ph/Me	Neat	60	70	100 : 0 (39%)[c]
3a	H/Me	THF	60	60	Complex mixture
3c	Ph/H	Neat	65	70	Mixture
3d	H/H	Neat	65	70	50 : 50
3e	H/Ts	Neat	60	50	20 : 30[d]

[a] All reactions were carried out under microwave (MW) conditions. [b] LC/MS analysis. [c] Isolated yields. [d] About 50% starting material was detected by LC/MS analysis, in addition to the product of its detosylation.

Table 2 Substrate scope for preparation 1,7-dihydrodipyrrolo[3,2-*b*:3′,2′-*e*]pyrazine derivatives

No	R^1	R^2	Yield (%)	No	R^1	R^2	Yield (%)
5a	H	TMS	66	**6a**	H	H	78[b]
5b	H		68	**6b**	H		96
5c	H		65	**6c**	H		90
5d	H		69	**6d**	H		88
5e	H		70	**6e**	H		92
5f	H		71	**6f**	H		89
5g	H		74	**6g**	H		91
5h	H		59[a]	**6h**	H		76
5i			67	**6i**			63
5j			64[a]	**6j**			74

[a] Trace amounts of cyclization product was observed. [b] The TMS group was displaced during the reaction due to high basicity of the *t*-BuOK.



Scheme 2 Synthesis of 1,5-dihydrodipyrrolo[2,3-*b*;3′2′-*e*]pyrazine derivative.

were detected and could be isolated in average to good yields were detected and could be isolated in average to good yields (41–82%) from **9a,b**. Attempts at preparation of the target 1,5-dihydrodipyrrolo[3,2-*b*:3′,2′-*e*]pyrazine derivatives from **10a–k** by using intramolecular cyclization under non-MW conditions proved to be futile. However, under optimized condition developed above (MW irradiation for 50 min at 120 °C), the corresponding 1,5-DPP **11a–k** are obtained in excellent yields (Table 3).

The structures of the 1,7- and 1,5-dihydrodipyrrolo[3,2-*b*:3′,2′-*e*]pyrazines, synthesized using the sequences described above, were confirmed by using NMR spectroscopy, LCMS and HRMS analysis (see ESI†). It is noteworthy that the NMR spectra of **6a–j** and **11a–f** exhibit similar features.

Finally, the pyrrolo[3,2-*e*]thieno[2,3-*b*]pyrazines **13a,b** were prepared by using the methodology developed in the effort

Table 3 Substrate scope for preparation of 1,5-dihydrodipyrrolo[3,2-*b*:3′,2′-*e*]pyrazine derivatives

No	R^1	R^2	Yield (%)	No	R^1	R^2	Yield (%)
10a	H	TMS	53[a]	**11a**	H	H	87[b]
10b	H		62[a]	**11b**	H		91
10c	H		41	**11c**	H		84
10d	H		52[a]	**11d**	H		78
10e	H		61[a]	**11e**	H		82
10f			68	**11f**			92
10g			74	**11g**			90
10h			78	**11h**			90
10i			66	**11i**			83
10j			69	**11j**			85
10k			82	**11k**			91

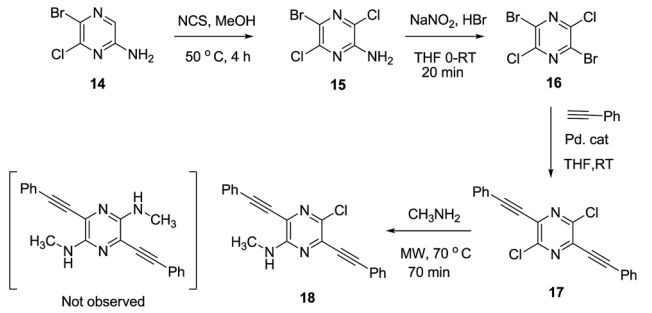
[a] Trace amount of cyclization product was also observed. [b] TMS group was displaced during reaction due to high basicity of the reagent.

described above. Accordingly, palladium catalysed reactions of **3a,b** and phenyl acetylene followed by intramolecular cyclization[26] gives **13a,b** in moderate yields (Scheme 3).

In an attempt to develop a more efficient routes for synthesis of the highly interesting symmetric 1,5-dipyrrolopyrazines, the double cyclization strategy was depicted in Scheme 4 was explored. For this purpose, symmetric 2,5-dibromo-3,6-dichloro pyrazine (**16**) was prepared using literature procedures and subjected to a double Sonogashira coupling process. The bis-acetylene derivative **17** was produced in only low yield along with unreacted starting material in this reaction. Next, displacement of both chlorides in **17** with methyl amine groups was examined. However, only the mono-aminated product **18** is produced. Therefore this route was abandoned in favour of the aforementioned protocol.

The solubility and stabilities of the dipyrrolopyrazine derivatives in diverse organic solvents is an important criteria for their applications in optoelectronic devices. Therefore, the solubilities of these crystalline substances were assessed. All of the tested dipyrrolopyrazine proved to be highly soluble in

Scheme 3 Annulation sequence for synthesis of pyrrolo[3,2-*e*]thieno[2,3-*b*]pyrazine.



Scheme 4 Double cyclization approach to prepare 1,5-dihydrodipyrrolo[3,2-*b*:3′,2′-*e*]pyrazine.

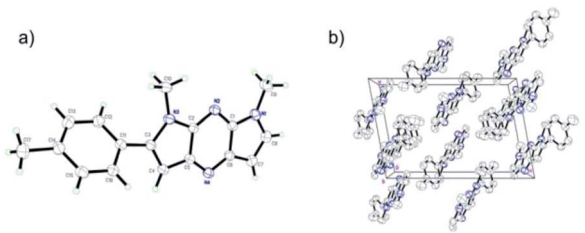


Fig. 1 (a) Crystal structure of **6f**. (b) Packing diagram of **6f** viewed along *b* axis in a bulk single crystal.

CH_2Cl_2, MeOH, THF and $CHCl_3$. Additionally, all of the crystalline in nature. Pyrrolopyrazines have long shelf lives, ranging up to one year at room temperature. Next, a comparative study of the optical and thermal properties of the three different pyrazine cores was undertaken.

2.2 Crystallographic analysis

A single crystal of pyrrolopyrazine **6f** was grown by slow evaporation of a mixture of ether and dichloromethane. X-ray crystallographic analysis revealed that **6f** forms monoclinic crystal system with space group *P*2(1)/*n* and is planar with the exception of slight twist of the phenyl substituent. Furthermore, possibly as a consequence of its planar backbone, pyrrolopyrazine derivative **6f** adopt a near perfect orthogonal orientation in the crystalline state[27] (Fig. 1).

3. Photophysical properties

3.1 Thermal properties

The thermal properties of one member of each of the three types of pyrazine derivative prepared above (**6i**, **11f**, and **13b**) were subjected to thermogravimetric analysis and differential scanning calorimetry (Fig. 2). The phase transitions of the selected compounds were analysed using DSC under a nitrogen atmosphere with a heating rate of 10 °C min^{-1}. The results of both the TGA and DSC analyses reveal that all of these substances possess high thermal stabilities. A sharp endothermic melting peak was observed in each case, which confirms the highly crystalline nature of the compounds (Table 5). Furthermore, the

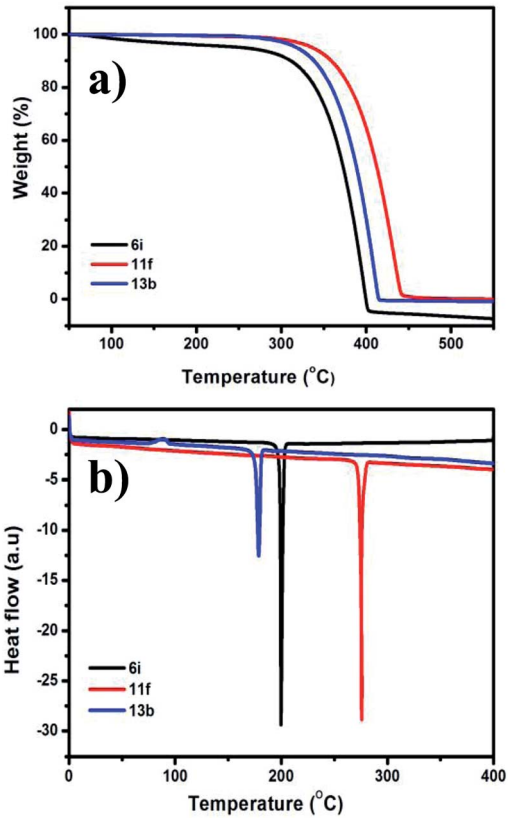


Fig. 2 (a) TGA and (b) DSC thermograms of the **6i**, **11f**, and **13b** recorded with a heating rate of 10 °C min^{-1} under nitrogen atmosphere.

high T_d and T_m of **6i**, **11f**, and **13b** indicate that they have remarkable thermal stabilities.

3.2 Optical properties

The optical properties of the prepared pyrazine derivatives in dichloromethane were evaluated by using absorption and emission spectroscopy (Fig. 3). The results show that the presence of the phenyl substituent (*i.e.*, in **6i,j**) and acetylene (**5a–j**) groups on the pyrrolopyrazine core result in a significant bathochromic shift with respect to those of unsubstituted pyrrolopyrazine derivatives. The extended conjugation in the substituted compounds is the likely reasons for the observed bathochromic shift. The absorption maxima (λ_{max}) occur between 386–410 nm for the acyclic compounds **5a–j** and at 358–380 nm for the cyclic analogues **6a–j**, respectively. A similar trend is observed for the 1,5-dihydrodipyrrolo[3,2-*b*:3′,2′-*e*]pyrazine derivatives **11a–k** (Table 4). Substitution at positions 2 and 6 of the DPP core (*i.e.*, **11i,g**) leads to a longer conjugation length, thereby resulting in red shift of the absorption maximum. The absorption spectrum of **6h** is especially remarkable in that it displays an unusually large bathochromic shift, presumably as a result of intramolecular charge transfer excitation (ICT), in addition to a localised π–π* transition as observed in Fig. 3(b). Comparisons of the results of the

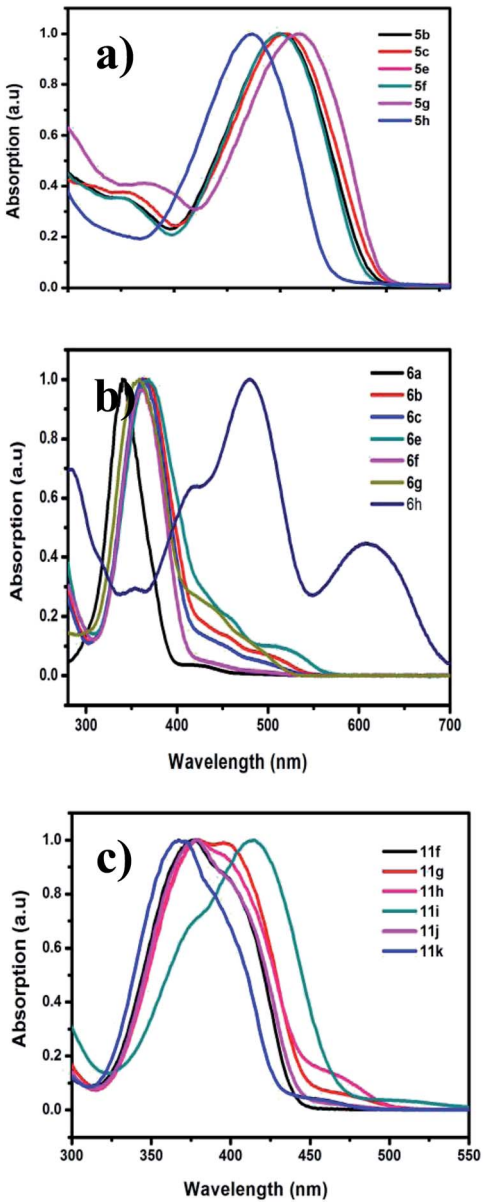


Fig. 3 UV-vis absorption spectra of DPP derivatives in DCM. (a) Acyclic compounds **5**, (b) cyclic compounds **6**, (c) cyclic 2,6-substituted DPP series **11**.

Table 4 UV-visible spectroscopic data of DPP derivatives

Molecules	$\lambda_{max}{}^{a}$ (nm)	$E_g^{opt b}$ (eV)	Molecules	$\lambda_{max}{}^{a}$ (nm)	$E_g^{opt b}$ (eV)
5b	400	2.76	**6f**	366	2.81
5c	402	2.73	**6g**	479, 613	1.75
5e	400	2.76	**6h**	358	2.65
5f	400	2.76	**11f**	378	2.76
5g	410	2.72	**11g**	385	2.66
5h	386	2.88	**11h**	381	2.61
6b	360	2.81	**11i**	413	2.66
6c	360	2.96	**11j**	380	2.78
6e	367	2.66	**11k**	367	2.81

[a] Absorption spectra measured in DCM solvent. [b] Optical band gap calculated from the UV-vis absorption onset in solution.

Table 5 Optical and thermal properties of selected scaffolds

Molecules	$\lambda_{max}{}^{a}$ (nm)	$\lambda_{max}{}^{b}$ (nm)	$E_g^{opt c}$ (eV)	$T_d{}^{d}$ (°C)	$T_m{}^{e}$ (°C)
6i	378	443	2.70	298	200
11f	377	450	2.78	342	280
13b	384	446	2.94	340	184

[a] Absorption spectra. [b] Emission spectra both measured in DCM solvent. [c] Optical band gap calculated from the UV-vis absorption onset in solution. [d] Degradation temperature observed from TGA corresponding to 5% weight loss at 10 °C min^{-1} under a nitrogen atmosphere. [e] Melting temperature observed from DSC at 10 °C min^{-1} under nitrogen atmosphere.

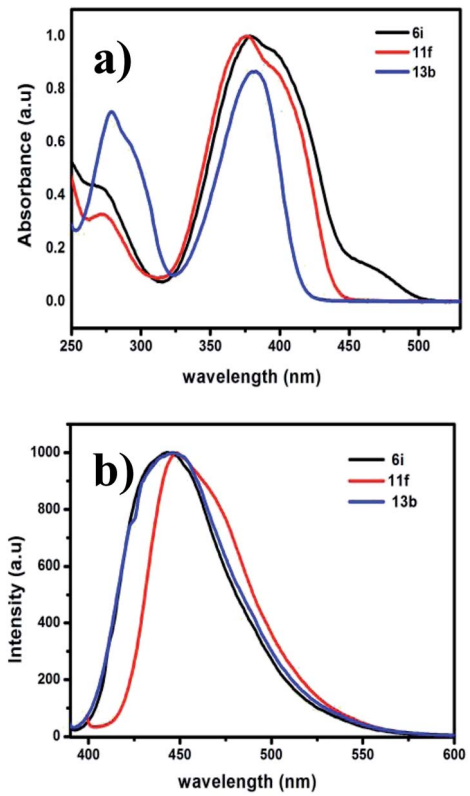


Fig. 4 (a) UV-vis absorption spectra of **6i**, **11f**, and **13b** in DCM. (b) Emission spectra of **6i**, **11f**, and **13b** in DCM when excited at 375 nm.

spectroscopy studies reveal that **6i** and **13b** have similar absorption and emission properties (Table 5). Interestingly, **11f** shows a significant red shift in its absorption spectrum (Fig. 4). The optical band gap energies (E_g) for **6i**, **11f**, and **13b** approximated using the onset of their absorption bands, are 2.7, 2.78, and 2.94 eV, respectively.

3.3 Structural and morphological characteristics

The structural and morphological properties of **6i**, **11f**, and **13b** were evaluated by using X-ray diffraction analysis. Each molecule displays a series of sharply resolved diffraction peaks, indicating that all the compounds possess a high degree of ordering in the solid state (Fig. 5).

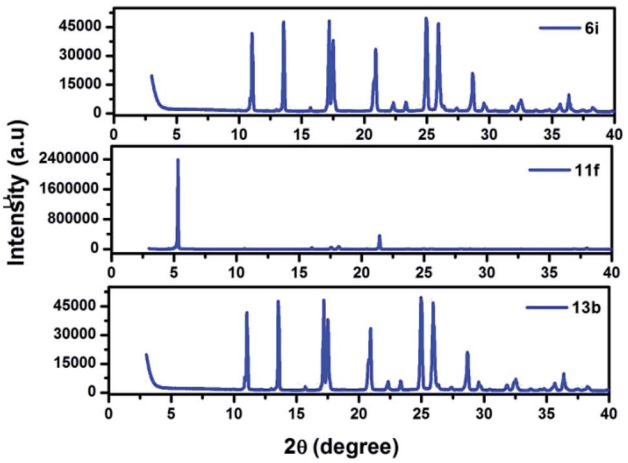


Fig. 5 Powder X-ray diffraction patterns of **6i**, **11f**, and **13b** at room temperature.

4. Experimental section

4.1 General method and materials

All chemicals and solvents are of reagent grade unless otherwise indicated. Reactions with air sensitive materials were carried out under a nitrogen atmosphere. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker 500 MHz NMR spectrometer and are given in ppm (δ) units relative to protons and carbons in the deuterated solvent. Mass spectra were recorded using 6400 Triple Quadrupole LC/MS (Agilent). High-resolution mass spectrometry was performed using a 6550 iFunnel Q-TOF LC/MS system (Agilent). UV-vis spectra were recorded using Varian cary-50 spectrophotometer. TGA and DSC were performed with TGA 3 plus and DSC 2 STAR system, respectively. X-ray diffraction and single crystal XRD analysis was performed using a Smartlab and Bruker D8 Discover X-ray Diffractometer with GADDS, respectively.

5-Bromo-6-chloro-3-((trimethylsilyl)ethynyl)pyrazin-2-amine (1a). To a stirred solution of 3,5-dibromo-6-chloro-pyrazin-2-ylamine (2.0 g, 7.04 mmol) in anhydrous THF (20 mL) at 0 °C, TEA (2.1 g, 21 mmol) and CuI (0.13 g, 0.7 mmol) were added subsequently. The mixture was purged thoroughly with nitrogen for 20 min followed by the addition of $Pd(PPh_3)_2Cl_2$ (0.49 g, 0.7 mmol). Next, TMS–acetylene (1.0 mL, 7.04 mmol) was added drop wise and the mixture was allowed to slowly warm to 15 °C over a period of 3 h. Then the mixture was diluted with water and extracted with EtOAc (3×). The combined organic extracts were concentrated in vacuum and the residue was subjected to silica gel column chromatography to give title compound as a yellow solid. Yield: 81%. The NMR data was found to be identical to that reported in literature. Yield: 81%, LC-MS (ESI): m/z = 306.10 $[M + 2]^+$.

5-Bromo-6-chloro-3-(phenylethynyl)pyrazin-2-amine (1b). The above procedure was followed and the reaction mixture is stirred at room temperature for 2 h. Yield: 83%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63–7.55 (m, 2H), 7.50–7.38 (m, 3H), 5.27 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.3, 145.9, 132.0, 129.9, 128.6, 123.9, 122.4, 120.9, 98.0, 82.4. LC-MS (ESI): m/z = 310.1 $[M + 2]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{12}H_7BrClN_3$, 307.9585; found 307.9606.

2-Bromo-3-chloro-5*H*-pyrrolo[2,3-*b*]pyrazine (2a). To a solution of 5-bromo-6-chloro-3-((trimethylsilanyl)ethynyl)pyrazin-2-amine (1.0 g, 3.2 mmol) in anhydrous NMP (20 mL) a solution of *t*-BuOK in NMP (0.7 g, 6.5 mmol) was added slowly under a nitrogen atmosphere. The mixture was refluxed at 80 °C for 1 h, cooled to ambient temperature, and diluted with EtOAc and water. The organic layer was separated, dried over $MgSO_4$, concentrated to give a light brown solid. This material was used directly without further purification. Yield: 72%, ^{1}H NMR (500 MHz, DMSO) δ 12.52 (s, 1H), 8.1 (d, J = 1.8 Hz, 1H), 6.70 (d, J = 1.8 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 139.1, 139.1, 138.5, 134.4, 129.9, 100.7. LC-MS (ESI): m/z = 234.0 $[M + 2]^+$.

2-Bromo-3-chloro-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazine (2b). Yield: 78%, ^{1}H NMR (500 MHz, DMSO) δ 12.97 (s, 1H), 8.02 (d, J = 7.7 Hz, 2H), 7.55 (t, J = 7.5 Hz, 2H), 7.48 (t, J = 7.2 Hz, 1H), 7.24 (s, 1H). ^{13}C NMR (126 MHz, DMSO) δ 145.8, 140.8, 139.6, 139.0, 130.5, 130.3, 130.3, 129.6, 126.5, 97.6. LC-MS (ESI): m/z = 310.0 $[M + 2]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{12}H_7BrClN_3$, 307.9585; found 307.9604.

2-Bromo-3-chloro-5-methyl-5*H*-pyrrolo[2,3-*b*]pyrazine (3a). To a solution of 2-bromo-3-chloro-5*H*-pyrrolo[2,3-*b*]pyrazine (3.0 g, 12.9 mmol) in DMF (40 mL) at 0 °C, NaH (60% dispersion in mineral oil, 0.36 g, 12.9 mmol) was added carefully under nitrogen atmosphere. After stirring for 30 min, MeI (0.8 mL, 12.9 mmol) was added and the mixture was warmed slowly to room temperature. After 3 h, the mixture is poured into ice-coldwater and the precipitate was collected by vacuum filtration. The crude solid is dissolved in EtOAc and subjected to silica gel chromatography to give title compound. (20% EA : hexane). Yield: 90%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 3.6 Hz, 1H), 6.65 (d, J = 3.5 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.6, 138.6, 138.0, 134.7, 131.0, 100.6, 31.8. LC-MS (ESI): m/z = 248.0 $[M + 2]^+$. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_7H_5BrClN_3$, 245.9428; found 245.9436.

2-Bromo-3-chloro-5-methyl-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazine (3b). Yield: 88%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, J = 8.3, 4.4 Hz, 5H), 6.70 (s, 1H), 3.86 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.9, 140.2, 140.0, 138.2, 131.2, 130.6, 129.6, 129.1, 128.9, 100.1, 30.2. LC-MS (ESI): m/z = 324.0 $[M + 2]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{13}H_9BrClN_3$, 321.9741; found 321.9762.

2-Bromo-*N*,5-dimethyl-5*H*-pyrrolo[2,3-*b*]pyrazin-3-amine (4a). To 2-bromo-3-chloro-5-methyl-5*H*-pyrrolo[2,3-*b*]pyrazine (0.1 g, 0.4 mmol) is added methylamine (2 mL, 40% solution in water). The mixture was stirred at reflux for 40 min in a microwave vial. After cooling, the mixture was extracted with EtOAc. The organic layer was washed with water and dried over $MgSO_4$, and concentrated in vacuum giving a residue that was subjected to silica gel chromatography to give desired product. Yield: 69%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (d, J = 3.6 Hz, 1H), 6.43 (d, J = 3.6 Hz, 1H), 5.13 (s, 1H), 3.75 (s, 3H), 3.07 (d, J = 5.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.6, 139.3, 129.5, 127.0, 121.4, 100.1, 31.1, 28.7. LC-MS (ESI): m/z = 241.1 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_8H_9BrN_4$, 241.0083; found 241.0090.

2-Bromo-*N*,5-dimethyl-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazin-3-amine (4b). Yield: 41%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 7.6 Hz, 2H), 7.49 (t, J = 7.3 Hz, 2H), 7.42 (t, J = 7.1 Hz, 1H), 6.54 (s, 1H), 5.19 (s, 1H), 3.79 (s, 3H), 3.13 (d, J = 4.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.6, 141.1, 140.2, 132.2, 129.8, 128.8, 128.6, 128.1, 121.6, 100.0, 29.7, 28.7. LC-MS (ESI): m/z = 317.0 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{14}H_{13}BrN_4$, 317.0396; found 317.0406.

4.2 General procedure for Sonogashira reactions

To a stirred solution of 2-bromo-*N*,5-dimethyl-5*H*-pyrrolo[2,3-*b*]pyrazin-3-amine (0.2 g, 0.8 mmol) in THF (15 mL) was added TEA (0.25 mL, 24 mmol), $Pd(PPh_3)_2Cl_2$ (0.058 g, 0.08 mmol), CuI (0.015 g, 0.08 mmol) under a nitrogen atmosphere. After 10 min, TMS–acetylene (0.11 g, 0.8 mmol) was added dropwise. The mixture was stirred at room temperature for 1.5 h and concentrated to give a residue that was diluted with water and extracted with EtOAc. The organic layer was washed with water and dried over $MgSO_4$, and concentrated in vacuum to give a residue that was subjected to silica gel chromatography to afford the desired compound.

***N*,5-Dimethyl-2-((trimethylsilyl)ethynyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-3-amine (5a).** Mp: 126–128 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.45 (s, 1H), 5.30 (s, 1H), 3.76 (d, J = 8.2 Hz, 3H), 3.11 (d, J = 4.7 Hz, 3H), 0.32 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6, 139.6, 130.1, 128.0, 119.4, 101.1, 101.0, 100.1, 30.8, 28.2, 0.3. LC-MS (ESI): m/z = 259.2 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_{18}N_4Si$, 259.1373; found 259.1378.

***N*,5-Dimethyl-2-(phenylethynyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-3-amine (5b).** Mp: 136–138 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, J = 6.5, 2.9 Hz, 2H), 7.43–7.29 (m, 3H), 7.03 (d, J = 3.6 Hz, 1H), 6.47 (d, J = 3.6 Hz, 1H), 5.35 (d, J = 3.8 Hz, 1H), 3.76 (s, 3H), 3.12 (d, J = 5.0 Hz, 3H). ^{13}C NMR (126 $CDCl_3$) δ 152.4, 139.6, 131.7, 130.3, 128.7, 128.4, 127.9, 122.5, 119.6, 100.9, 94.3, 85.7, 30.9, 28.2. LC-MS (ESI): m/z = 263.1 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{14}N_4$, 263.1291; found 263.124.

2-((3-Fluorophenyl)ethynyl)-*N*,5-dimethyl-5*H*-pyrrolo[2,3-*b*]pyrazin-3-amine (5c). Mp: 110–112 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (ddd, J = 21.2, 15.5, 7.8 Hz, 3H), 7.09 (d, J = 8.3 Hz, 1H), 7.05 (d, J = 3.5 Hz, 1H), 6.48 (d, J = 3.5 Hz, 1H), 5.33 (d, J = 3.3 Hz, 1H), 3.76 (s, 3H), 3.13 (d, J = 4.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.3 (d, J = 246.8 Hz), 161.3, 152.5, 139.7, 130.2, 130.0 (d, J = 8.7 Hz), 128.3, 127.6 (d, J = 3.0 Hz), 124.3 (d, J = 9.5 Hz), 119.0, 118.4, 118.3, 116.1, 115.9, 100.9, 92.9 (d, J = 3.4 Hz), 86.6, 30.9, 28.2. LC-MS (ESI): m/z = 281.2 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{13}FN_4$, 281.1197; found 281.1202.

2-((4-Fluorophenyl)ethynyl)-*N*,5-dimethyl-5*H*-pyrrolo[2,3-*b*]pyrazin-3-amine (5d). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, J = 7.6, 5.9 Hz, 2H), 7.32–7.27 (m, 1H), 7.08 (t, J = 8.4 Hz, 2H), 6.42 (d, J = 3.0 Hz, 1H), 5.21 (s, 1H), 3.82 (s, 3H), 3.12 (d, J = 4.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9 (d, J = 251.0 Hz), 154.1, 136.6, 135.3, 133.8 (d, J = 8.5 Hz), 132.9, 118.4, 118.4, 115.8 (d, J = 22.2 Hz), 98.9, 94.4, 85.5, 31.6, 28.7. LC-MS (ESI): m/z = 281.2 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{13}FN_4$, 281.1197; found 281.1202.

2-((4-Methoxyphenyl)ethynyl)-*N*,5-dimethyl-5*H*-pyrrolo[2,3-*b*]pyrazin-3-amine (5e). Mp: 148–150 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 8.3 Hz, 2H), 7.03 (d, J = 3.0 Hz, 1H), 6.90 (d, J = 8.3 Hz, 2H), 6.47 (d, J = 2.9 Hz, 1H), 5.37 (d, J = 4.0 Hz, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 3.13 (d, J = 4.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0, 152.2, 139.4, 133.2, 130.1, 127.7, 120.1, 114.5, 114.1, 100.8, 94.4, 84.4, 55.3, 30.9, 28.2. LC-MS (ESI): m/z = 293.2 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{17}H_{16}N_4O$, 293.1397; found 293.1403.

***N*,5-Dimethyl-2-(*p*-tolylethynyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-3-amine (5f).** Mp: 132–134 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 6.8 Hz, 2H), 7.19 (d, J = 7.0 Hz, 2H), 7.04 (s, 1H), 6.48 (s, 1H), 5.38 (s, 1H), 3.77 (s, 3H), 3.14 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.3, 139.5, 139.0, 131.6, 130.2, 129.2, 127.8, 119.9, 119.4, 100.9, 94.6, 85.1, 30.9, 28.2, 21.5. LC-MS (ESI): m/z = 277.2 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{17}H_{16}N_4$, 277.1448; found 277.1452.

2-(Cyclopropylethynyl)-*N*,5-dimethyl-5*H*-pyrrolo[2,3-*b*]pyrazin-3-amine (5g). Mp: 122–124 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (d, J = 3.1 Hz, 1H), 6.42 (d, J = 3.1 Hz, 1H), 5.30 (s, 1H), 3.74 (s, 3H), 3.09 (d, J = 4.9 Hz, 3H), 1.62–1.43 (m, 1H), 0.94 (d, J = 8.4 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.4, 139.1, 129.6, 127.3, 120.5, 100.7, 98.9, 72.2, 30.8, 28.2, 9.0, 0.3. LC-MS (ESI): m/z = 227.2 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{13}H_{14}N_4$, 227.1291; found 227.126.

2-((4-(Dimethylamino)phenyl)ethynyl)-*N*,5-dimethyl-5*H*-pyrrolo[2,3-*b*]pyrazin-3-amine (5h). Mp: 180–182 °C. LC-MS (ESI): m/z = 306.3 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{18}H_{19}N_5$, 306.1713; found 306.1717.

***N*,5-Dimethyl-6-phenyl-2-(phenylethynyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-3-amine (5i).** Mp: 199–200 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 3.4 Hz, 2H), 7.57 (d, J = 6.9 Hz, 2H), 7.50 (t, J = 6.9 Hz, 2H), 7.45–7.38 (m, 4H), 6.58 (s, 1H), 5.41 (s, 1H), 3.81 (s, 3H), 3.18 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.4, 141.4, 141.1, 132.2, 131.7, 130.6, 128.8, 128.7, 128.6, 128.4, 128.1, 122.5, 119.8, 100.7, 94.5, 85.8, 29.5, 28.3. LC-MS (ESI): m/z = 339.2 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{22}H_{18}N_4$, 339.1604; found 339.1607.

2-((4-(Dimethylamino)phenyl)ethynyl)-*N*,5-dimethyl-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazin-3-amine (5j). Mp: 129–131 °C. LC-MS (ESI): m/z = 382.3 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{24}H_{23}N_5$, 382.2026; found 382.2026.

4.3 General procedure for cyclization of DPP derivatives

A solution of *N*,5-dimethyl-2-((trimethylsilyl)ethynyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-3-amine (0.09 g, 0.34 mmol) in NMP (5 mL) containing *t*-BuOK (0.078 g, 0.7 mmol) was stirred at reflux for 2 h. The mixture was quenched with water and extracted with EtOAc. The combined organic layers were concentrated in vacuum to give a residue that was subjected to silica gel chromatography eluting with 20% EtOAc to afford the titled compound as a pale yellow solid.

1,7-Dimethyl-1,7-dihydrodipyrrolo[2,3-*b*:3′,2′-*e*]pyrazine (6a). Mp: 168–170 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 3.5 Hz, 1H), 6.69 (d, J = 3.6 Hz, 1H), 3.90 (s, 3H). ^{13}CNMR (126 MHz, $CDCl_3$) δ 138.4, 136.2, 130.8, 99.7, 31.3. LC-MS (ESI): m/z = 187.1

$[M + H]^+$. HRMS (ESI) *m/z*: $[M + H]^+$ calculated for $C_{10}H_{10}N_4$, 187.0978; found 187.0988.

1,7-Dimethyl-2-phenyl-1,7-dihydrodipyrrolo[2,3-*b*:3′,2′-*e*]pyrazine (6b). Mp: 165–166 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 7.3 Hz, 2H), 7.51 (t, J = 7.5 Hz, 2H), 7.44 (d, J = 7.4 Hz, 1H), 7.35 (d, J = 3.6 Hz, 1H), 6.77 (s, 1H), 6.69 (d, J = 3.6 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.8, 140.3, 138.3, 136.6, 136.4, 132.3, 130.6, 129.1, 128.6, 128.4, 99.9, 99.8, 31.4, 29.8. LC-MS (ESI): *m/z* = 263.2 $[M + H]^+$. HRMS (ESI) *m/z*: $[M + H]^+$ calculated for $C_{16}H_{14}N_4$, 263.1291; found 263.1303.

2-(3-Fluorophenyl)-1,7-dimethyl-1,7-dihydrodipyrrolo[2,3-*b*:3′,2′-*e*]pyrazine (6c). Mp: 187–188 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, J = 14.2, 7.7 Hz, 1H), 7.43–7.36 (m, 2H), 7.32 (d, J = 8.7 Hz, 1H), 7.14 (t, J = 7.2 Hz, 1H), 6.81 (d, J = 4.6 Hz, 1H), 6.71 (t, J = 5.0 Hz, 1H), 3.93 (dd, J = 9.7, 4.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.7 (d, J = 246.8 Hz), 142.2, 140.3, 138.5, 136.9, 136.0, 134.3 (d, J = 8.1 Hz), 131.0, 130.2 (d, J = 8.5 Hz), 124.7, 115.9 (d, J = 22.4 Hz), 115.2 (d, J = 21.0 Hz), 100.5, 99.8, 31.3, 29.9. LC-MS (ESI): *m/z* = 281.1 $[M + H]^+$. HRMS (ESI) *m/z*: $[M + H]^+$ calculated for $C_{16}H_{13}FN_4$, 281.1197; found 281.1206.

2-(4-Fluorophenyl)-1,7-dimethyl-1,7-dihydrodipyrrolo[2,3-*b*:3′,2′-*e*]pyrazine (6d). Mp: 158–159 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60–7.51 (m, 2H), 7.35 (d, J = 3.6 Hz, 1H), 7.23–7.12 (m, 2H), 6.73 (s, 1H), 6.69 (d, J = 3.7 Hz, 1H), 3.92 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.8, 161.8, 142.6, 140.1, 138.3, 136.7, 136.3, 130.8 (d, J = 8.2 Hz), 130.7, 128.4 (d, J = 3.3 Hz), 115.7 (d, J = 21.7 Hz), 99.8 (d, J = 15.8 Hz), 31.3, 29.7. LC-MS (ESI): *m/z* = 281.1 $[M + H]^+$. HRMS (ESI) *m/z*: $[M + H]^+$ calculated for $C_{16}H_{13}FN_4$, 281.1197; found 281.1209.

2-(4-Methoxyphenyl)-1,7-dimethyl-1,7-dihydrodipyrrolo[2,3-*b*:3′, 2′-*e*]pyrazine (6e). Mp: 155–156 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 3.6 Hz, 1H), 7.00 (d, J = 8.7 Hz, 2H), 6.70 (s, 1H), 6.67 (d, J = 3.6 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 143.8, 140.1, 138.1, 136.5, 136.4, 130.4, 130.3, 124.6, 114.1, 99.6, 99.0, 55.3, 31.3, 29.7. LC-MS (ESI): *m/z* = 293.2 $[M + H]^+$. HRMS (ESI) *m/z*: $[M + H]^+$ calculated for $C_{17}H_{16}N_4O$, 293.1397; found 293.1406.

1,7-Dimethyl-2-*p*-tolyl-1,7-dihydrodipyrrolo[2,3-*b*:3′,2′-*e*]pyrazine (6f). Mp: 174–176 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 3.6 Hz, 1H), 7.33 (d, J = 7.9 Hz, 2H), 6.76 (s, 1H), 6.71 (d, J = 3.6 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.0, 140.2, 138.4, 138.2, 136.6, 136.5, 130.51, 129.4, 129.4, 129.0, 99.7, 99.5, 31.3, 29.8, 21.3. LC-MS (ESI): *m/z* = 277.3 $[M + H]^+$. HRMS (ESI) *m/z*: $[M + H]^+$ calculated for $C_{17}H_{16}N_4$, 277.1448; found 277.1455.

2-Cyclopropyl-1,7-dimethyl-1,7-dihydrodipyrrolo[2,3-*b*:3′,2′-*e*]pyrazine (6g). Mp: 163–165 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (d, J = 3.1 Hz, 1H), 6.26 (s, 1H), 3.93 (d, J = 4.5 Hz, 3H), 3.91 (d, J = 4.5 Hz, 3H), 1.99 (d, J = 5.1 Hz, 1H), 1.07 (d, J = 6.5 Hz, 2H), 0.85 (d, J = 3.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.5, 139.3, 137.8, 136.5, 135.7, 129.6, 99.6, 95.2, 31.3, 28.0, 8.1, 6.9. LC-MS (ESI): *m/z* = 227.2 $[M + H]^+$. HRMS (ESI) *m/z*: $[M + H]^+$ calculated for $C_{13}H_{14}N_4$, 227.1291; found 227.1304.

4-(1,7-Dimethyl-1,7-dihydrodipyrrolo[2,3-*b*:3′,2′-*e*]pyrazin-2-yl)-*N*,*N*-dimethylaniline (6h). Mp: 188–190 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 3.6 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 6.66 (d, J = 3.6 Hz, 1H), 6.65 (s, 1H), 3.94 (d, J = 3.7 Hz, 6H), 3.04 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 146.1, 141.5, 139.8, 135.7, 133.8, 130.82, 130.0, 119.7, 112.0, 98.9, 97.5, 40.3, 31.7, 30.0. LC-MS (ESI): *m/z* = 306.2 $[M + H]^+$. HRMS (ESI) *m/z*: $[M + H]^+$ calculated for $C_{18}H_{19}N_5$, 306.1713; found 306.1717.

1,7-Dimethyl-2,6-diphenyl-1,7-dihydrodipyrrolo[2,3-*b*:3′,2′-*e*]pyrazine (6i). Mp: 197–199 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 7.2 Hz, 2H), 7.55 (t, J = 7.5 Hz, 2H), 7.48 (d, J = 7.4 Hz, 1H), 6.81 (s, 1H), 3.97 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.7, 141.8, 134.9, 132.2, 129.1, 128.7, 128.5, 99.3, 30.1. LC-MS (ESI): *m/z* = 339.2 $[M + H]^+$. HRMS (ESI) *m/z*: $[M + H]^+$ calculated for $C_{22}H_{18}N_4$, 339.1604; found 339.1607.

4-(1,7-Dimethyl-6-phenyl-1,7-dihydrodipyrrolo[2,3-*b*:3′,2′-*e*]pyrazin-2-yl)-*N*,*N*-dimethylaniline (6j). Mp: 231–233 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (s, 2H), 7.51 (s, 4H), 7.44 (d, J = 6.2 Hz, 1H), 6.84 (d, J = 6.9 Hz, 2H), 6.77 (s, 1H), 6.67 (s, 1H), 3.93 (s, 6H), 3.05 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.3, 144.8, 142.9, 140.2, 139.8, 137.4, 136.3, 132.5, 129.9, 129.0, 128.6, 128.2, 119.9, 112.1, 99.9, 98.2, 40.3, 29.9. LC-MS (ESI): *m/z* = 382.2 $[M + H]^+$. HRMS (ESI) *m/z*: $[M + H]^+$ calculated for $C_{24}H_{23}N_5$, 382.2026; found 382.2037.

4.4 General method for Buchwald reaction

***tert*-Butyl 3-chloro-5-methyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-ylcarbamate (7a).** An air-dried RB flask was charged sequentially with 1,4-dioxane (50 mL), *t*-amyl alcohol (10 mL), 2-bromo-3-chloro-5-methyl-5*H*-pyrrolo[2,3-*b*]pyrazine (2.2 g, 8.9 mmol), $Pd(OAc)_2$ (0.2 g, 0.89 mmol), xantphos (0.51 g, 0.89 mmol), Cs_2CO_3 (5.82 g, 17 mmol) and *t*-butyl carbamate (1.04 g, 8.9 mmol). The resultant suspension was stirred at reflux at 90 °C for 3 h. Once the reaction was determined to be complete by using TLC, the mixture was cooled to room temperature, diluted with EtOAc and filtered through a pad of Celite. The filtrate was concentrated in vacuum. The residue was subjected to silica gel column chromatography to afford desired product as a crystalline solid. Yield: 78%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.13 (s, 1H), 6.64 (s, 1H), 3.87 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.4, 138.7, 136.9, 136.0, 133.6, 132.2, 100.8, 81.5, 31.7, 28.2. LC-MS (ESI): *m/z* = 305.2 $[M + Na]^+$. HRMS (ESI) *m/z*: $[M + H]^+$ calculated for $C_{12}H_{15}ClN_4O_2$, 283.0956; found 283.0961.

***tert*-Butyl3-chloro-5-methyl-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-ylcarbamate (7b).** Yield: 76%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (m, J = 15.4, 7.1 Hz, 5H), 7.22 (s, 1H), 6.74 (s, 1H), 3.83 (s, 3H), 1.57 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.5, 146.6, 139.0, 138.5, 136.2, 131.6, 131.1, 129.1, 129.1, 128.8, 100.6, 81.4, 30.1, 28.3. LC-MS (ESI): *m/z* = 381.2 $[M + Na]^+$. HRMS (ESI) *m/z*: $[M + H]^+$ calculated for $C_{18}H_{19}ClN_4O_2$, 359.1269; found 359.1290.

***tert*-Butyl3-chloro-5-methyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl-(methyl) carbamate (8a).** To a solution of 2-bromo-3-chloro-5*H*-pyrrolo[2,3-*b*]pyrazine (2.76 g, 9.7 mmol) in DMF (35 mL) under nitrogen atmosphere at 0 °C was added NaH (60% dispersion in mineral oil, 0.44 g, 10 mmol) carefully. After 30 min, MeI

(0.6 mL, 9.7 mmol) was added and the mixture is warmed slowly to ambient temperature. After 3 h, the mixture was poured into ice-cold water and the precipitate is collected by vacuum filtration. The crude solid was subjected to silica gel chromatography. Yield: 92%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (s, 1H), 6.65 (s, 1H), 3.90 (s, 3H), 3.29 (d, J = 0.8 Hz, 3H), 1.37 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 143.1, 139.6, 138.5, 136.5, 134.2, 100.8, 80.9, 35.1, 31.8, 28.1. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{13}H_{17}ClN_4O_2$, 297.1113; found 297.1118.

***tert*-Butyl 3-chloro-5-methyl-6-phenyl-5*H*-pyrrolo[2,3-*b*] pyrazin-2-yl(methyl)carbamate (8b).** Yield: 95%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dt, J = 10.7, 7.0 Hz, 5H), 6.73 (s, 1H), 3.89 (s, 3H), 3.32 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 147.3, 143.5, 140.1, 139.0, 136.7, 130.9, 129.4, 129.1, 128.9, 100.4, 80.9, 30.9, 30.2, 28.2. LC-MS (ESI): m/z = 317.1 [M − butyl]$^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{19}H_{21}ClN_4O_2$, 373.1426; found 373.1445.

3-Chloro-*N*,5-dimethyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-amine (9a). A solution of *tert*-butyl 3-chloro-5-methyl-5*H*-pyrrolo[2,3-*b*] pyrazin-2-yl(methyl)carbamate (2.6 g, 8.7 mmol) in DCM (50 mL) containing TFA (5.0 mL, 43 mmol) was stirred at room temperature for 10 min then refluxed for 50 min. The mixture was made basic by addition of 1 M NaOH solution and extracted with DCM. The organic layer was dried over $MgSO_4$, and concentrated in vacuum to get the desired product. Yield: 96%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, J = 3.3 Hz, 1H), 6.44 (d, J = 5.0 Hz, 1H), 4.98 (s, 1H), 3.80 (d, J = 1.8 Hz, 3H), 3.11 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.9, 135.2, 133.5, 130.7, 128.0, 98.7, 31.6, 29.0. LC-MS (ESI): m/z = 197.0 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_8H_9ClN_4$, 197.0589; found 197.0595.

3-Chloro-*N*,5-dimethyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-amine (9b). Yield: 98%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 7.2 Hz, 2H), 7.51 (t, J = 7.4 Hz, 2H), 7.45 (t, J = 7.2 Hz, 1H), 6.55 (s, 1H), 5.00 (s, 1H), 3.81 (s, 3H), 3.13 (d, J = 4.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.0, 143.6, 135.5, 135.2, 131.9, 129, 128.7, 128.5, 128.0, 99.0, 30.0, 28.9; LC-MS (ESI): m/z = 273.2 [M + H]$^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{14}H_{13}ClN_4$, 273.0902; found 273.0919.

4.5 General procedure for Sonogashira reaction

To a stirred solution of 3-chloro-*N*,5-dimethyl-5*H*-pyrrolo[2,3-*b*] pyrazin-2-amine (0.2 g, 1.0 mmol) in DMF (2 mL) was added TEA (0.3 mL, 3.0 mmol), CuI (0.019 g, 0.1 mmol), $Pd(PPh_3)_2Cl_2$ (0.07 g, 0.1 mmol) and TMS–acetylene (0.1 mL, 1.0 mmol). The mixture subjected to microwave irradiation for 50 min at 90 °C. Then the reaction mixture was cooled to ambient temperature and diluted with water and extracted with EtOAc twice. The combined organic layer was concentrated in vacuum to give a residue that was subjected to silica column chromatography to give desired compound as a brown solid.

3-((4-Fluorophenyl)ethynyl)-*N*,5-dimethyl-5*H*-pyrrolo[2,3-*b*] pyrazin-2-amine (10c). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, J = 14.2, 7.7 Hz, 1H), 7.43–7.36 (m, 2H), 7.32 (d, J = 8.7 Hz, 1H), 7.14 (t, J = 7.2 Hz, 1H), 6.81 (d, J = 4.6 Hz, 1H), 6.71 (t, J = 5.0 Hz, 1H), 3.93 (dd, J = 9.7, 4.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9 (d, J = 251.0 Hz), 152.8, 136.6, 135.6, 133.8 (d, J = 8.5 Hz), 132.9, 119.0, 118.1, 115.8 (d, J = 22.2 Hz), 98.9, 95.3, 86.3, 33.1, 29.88. LC-MS (ESI): m/z = 281.1 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{13}FN_4$, 281.1197; found 281.1201.

***N*,5-Dimethyl-6-phenyl-3-(phenylethynyl)-5*H*-pyrrolo[2,3-*b*] pyrazin-2-amine (10f).** Mp: 171–173 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66–7.63 (m, 2H), 7.59–7.56 (m, 2H), 7.52 (d, J = 7.2 Hz, 2H), 7.47–7.44 (m, 1H), 7.40 (dd, J = 4.2, 2.3 Hz, 3H), 6.56 (s, 1H), 5.31 (d, J = 5.5 Hz, 1H), 3.85 (s, 3H), 3.17 (d, J = 5.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2, 145.7, 137.1, 136.8, 131.9, 131.8, 129.0, 128.9, 128.7, 128.6, 128.4, 122.3, 117.8, 99.4, 95.7, 86.1, 30.0, 29.7, 28.8; LC-MS (ESI): m/z = 339.3 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{22}H_{18}N_4$, 339.1604; found 339.1624.

3-((4-Methoxyphenyl)ethynyl)-*N*,5-dimethyl-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-amine (10g). LC-MS (ESI): m/z = 369.2 [M + H]$^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{23}H_{20}N_4O$, 369.1710; found 369.1715.

***N*,5-Dimethyl-3-(*p*-tolylethynyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-amine (10h).** Mp: 144–146 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J = 7.2 Hz, 2H), 7.56–7.50 (m, 4H), 7.46 (t, J = 7.3 Hz, 1H), 7.22 (d, J = 7.9 Hz, 2H), 6.56 (s, 1H), 5.31 (d, J = 4.8 Hz, 1H), 3.85 (s, 3H), 3.17 (d, J = 5.0 Hz, 3H), 2.41 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2, 145.5, 139.2, 137.0, 136.6, 131.9, 131.7, 129.2, 129.0, 128.7, 128.6, 119.2, 118.0, 99.4, 96.1, 85.4, 30.0, 28.8, 21.6. LC-MS (ESI): m/z = 353.2 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{23}H_{20}N_4$, 353.1761; found 353.1766.

3-((4-(Dimethylamino)phenyl)ethynyl)-*N*,5-dimethyl-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-amine (10i). LC-MS (ESI): m/z = 382.3 $[M + H]^+$.

3-((3-Fluorophenyl)ethynyl)-*N*,5-dimethyl-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-amine (10j). Mp: 158–160 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J = 7.2 Hz, 2H), 7.53 (t, J = 7.5 Hz, 2H), 7.47 (t, J = 7.3 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.40–7.33 (m, 2H), 7.14–7.08 (m, 1H), 6.56 (s, 1H), 5.25 (d, J = 4.7 Hz, 1H), 3.85 (s, 3H), 3.17 (d, J = 5.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.3 (d, J = 247.0 Hz), 153.3, 146.1, 137.1 (d, J = 4.0 Hz), 131.8, 130.0 (d, J = 8.6 Hz), 129.2, 129.0, 128.7, 127.7 (d, J = 3.1 Hz), 124.2, 124.1, 118.54 (d, J = 23.0 Hz), 117.1, 116.26 (d, J = 21.2 Hz), 99.4, 94.3 (d, J = 3.4 Hz), 86.9, 30.0, 28.8. LC-MS (ESI): m/z = 357.2 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{22}H_{17}FN_4$, 357.1510; found 357.1515.

3-(Cyclopropylethynyl)-*N*,5-dimethyl-6-phenyl-5*H*-pyrrolo [2,3-*b*]pyrazin-2-amine (10k). LC-MS (ESI): m/z = 303.2 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{19}H_{18}N_4$, 303.1604; found 303.1610.

4.6 General procedure for cyclization

A suspension containing *N*,5-dimethyl-3-((trimethylsilyl) ethynyl)-5*H*-pyrrolo[2,3-*b*]pyrazin-2-amine (0.125 g, 0.48 mmol) in DMF (2 mL) and *t*-BuOK (0.1 g, 9.6 mmol) was stirred at 120 °C for 1 h under microwave. The reaction mixture was cooled to room temperature, diluted with EtOAc and water. The organic layer was separated, washed with water and dried over $MgSO_4$, and concentrated in vacuum to give a pale yellow crystal which was subjected to silica gel column chromatography to give desired compound.

1,5-Dimethyl-1,5-dihyrodipyrrolo[3,2-*b*:3′,2′-*e*]pyrazine (11a). Mp: 192–193 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 3.6 Hz, 2H), 6.66 (d, J = 3.6 Hz, 2H), 3.94 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.6, 134.9, 132.0, 98.7, 31.6. LC-MS (ESI): m/z = 187.1 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{10}H_{10}N_4$, 187.0978; found 187.0988.

1,5-Dimethyl-2-phenyl-1,5-dihyrodipyrrolo[3,2-*b*:3′,2′-*e*]pyrazine (11b). Mp: 156–157 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 7.4 Hz, 2H), 7.51 (t, J = 7.0 Hz, 2H), 7.47–7.43 (m, 1H), 7.41 (s, 1H), 6.75 (s, 1H), 6.68 (s, 1H), 3.95 (s, 3H), 3.94 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.9, 141.4, 140.0, 135.1, 134.6, 132.2, 131.7, 129.1, 128.6, 128.5, 99.1, 98.9, 31.7, 30.0. LC-MS (ESI): m/z = 263.1 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{14}N_4$, 263.1291; found 263.1309.

2-(4-Fluorophenyl)-1,5-dimethyl-1,5-dihydrodipyrrolo[3,2-*b*:3′,2′-*e*]pyrazine (11c). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60–7.51 (m, 2H), 7.35 (d, J = 3.6 Hz, 1H), 7.23–7.12 (m, 2H), 6.73 (s, 1H), 6.69 (d, J = 3.7 Hz, 1H), 3.92 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.8 (d, J = 248.8 Hz), 142.6, 140.1, 138.3, 136.7, 136.3, 130.9, 130.8, 130.7, 128.4 (d, J = 3.3 Hz), 115.7 (d, J = 21.7 Hz), 99.8 (d, J = 15.8 Hz), 31.3, 29.7. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{13}FN_4$, 281.1197; found 284.1212.

4-(1,5-Dimethyl-1,5-dihydrodipyrrolo[3,2-*b*:3′,2′-*e*]pyrazin-2-yl)-*N*,*N*-dimethylaniline (11d). Mp: 154–155 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 3.6 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 6.66 (d, J = 3.6 Hz, 1H), 6.65 (s, 1H), 3.94 (d, J = 3.7 Hz, 6H), 3.04 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 146.1, 141.5, 139.8, 135.7, 133.8, 130.8, 130.0, 119.7, 112.0, 98.9, 97.5, 40.3, 31.7, 30.0. LC-MS (ESI): m/z = 306.2 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{18}H_{19}N_5$, 306.1713; found 306.1722.

4-(1,5-Dimethyl-1,5-dihydrodipyrrolo[3,2-*b*:3′,2′-*e*]pyrazin-2-yl)benzonitrile (11e). Mp: 268–269 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 7.9 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 3.2 Hz, 1H), 6.84 (s, 1H), 6.69 (d, J = 3.3 Hz, 1H), 3.97 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.1, 141.8, 140.3, 136.6, 135.6, 134.4, 132.9, 132.4, 129.4, 118.5, 111.9, 100.9, 99.0, 31.7, 30.3. LC-MS (ESI): m/z = 288 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{17}H_{13}N_5$, 288.1244; found 288.1257.

1,5-Dimethyl-2,6-diphenyl-1,5-dihyrodipyrrolo[3,2-*b*:3′,2′-*e*]pyrazine (11f). Mp: 258–260 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.63 (m, 2H), 7.55 (t, J = 7.5 Hz, 2H), 7.48 (t, J = 7.4 Hz, 1H), 6.80 (s, 1H), 3.99 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.7, 141.8, 134.9, 132.2, 129.1, 128.7, 128.5, 99.3, 30.1; LC-MS (ESI): m/z = 339.2 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{22}H_{18}N_4$, 339.1604; found 339.1610.

2-(4-Methoxyphenyl)-1,5-dimethyl-6-phenyl-1,5-dihydrodipyrrolo[3,2-*b*:3′,2′-*e*]pyrazine (11g). Mp: 228–230 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 7.2 Hz, 2H), 7.60–7.52 (m, 4H), 7.47 (t, J = 7.4 Hz, 1H), 7.07 (d, J = 8.6 Hz, 2H), 6.79 (s, 1H), 6.73 (s, 1H), 3.98 (s, 3H), 3.96 (s, 3H), 3.91 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9, 144.7, 144.3, 141.7, 135.1, 134.5, 132.3, 130.4, 129.1, 128.7, 128.4, 124.6, 114.7, 114.2, 99.3, 98.6, 55.4, 30.1, 30.0. LC-MS (ESI): m/z = 369.2 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{23}H_{20}N_5O$, 369.1710; found 369.1717.

1,5-Dimethyl-2-phenyl-6-*p*-tolyl-1,5-dihydrodipyrrolo[3,2-*b*:3′,2′-*e*]pyrazine (11h). Mp: 204–206 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.64 (m, 2H), 7.56–7.53 (m, 4H), 7.48 (d, J = 7.4 Hz, 1H), 7.36 (d, J = 7.9 Hz, 2H), 6.79 (s, 1H), 6.76 (s, 1H), 3.99 (s, 3H), 3.98 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.9, 144.4, 141.8, 141.8, 138.6, 135.0, 134.7, 132.3, 129.4, 129.3, 129.1, 129.0, 128.7, 128.5, 99.3, 98.9, 30.15, 30.1, 21.3. LC-MS (ESI): m/z = 353.3 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{23}H_{20}N_4$, 353.1761; found 353.1774.

4-(1,5-Dimethyl-6-phenyl-1,5-dihydrodipyrrolo[3,2-*b*:3′,2′-*e*]pyrazin-2-yl)-*N*,*N*-dimethylaniline (11i). Mp: 219–220 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 7.2 Hz, 2H), 7.54 (dd, J = 8.2, 4.9 Hz, 4H), 7.47 (d, J = 7.4 Hz, 1H), 6.87 (d, J = 8.7 Hz, 2H), 6.79 (s, 1H), 6.70 (s, 1H), 3.98 (s, 6H), 3.08 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 145.9, 143.7, 141.9, 141.7, 135.5, 134.1, 132.4, 130.0, 129.1, 128.7, 128.3, 119.7, 112.1, 99.3, 97.7, 40.3, 30.1, 30.1. LC-MS (ESI): m/z = 382.3 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{24}H_{23}N_5$, 382.2026; found 382.2035.

2-(3-Fluorophenyl)-1,5-dimethyl-6-phenyl-1,5-dihydrodipyrrolo[3,2-*b*:3′,2′-*e*]pyrazine (11j). Mp: 234–236 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.64 (m, 2H), 7.55 (t, J = 7.5 Hz, 2H), 7.53–7.47 (m, 2H), 7.44 (d, J = 7.7 Hz, 1H), 7.36 (dd, J = 9.4, 1.9 Hz, 1H), 7.18 (d, J = 1.7 Hz, 1H), 6.81 (s, 1H), 6.80 (s, 1H), 4.00 (s, 3H), 3.99 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.7 (d, J = 246.8 Hz), 145.1, 143.0 (d, J = 2.4 Hz), 141.9 (d, J = 10.2 Hz), 135.3, 134.5, 134.3 (d, J = 8.2 Hz), 132.1, 130.3, 130.3, 129.1, 128.7, 128.6, 124.8 (d, J = 2.9 Hz), 115.9 (d, J = 22.4 Hz), 115.4 (d, J = 21.1 Hz), 99.9, 99.3, 30.2, 30.1. LC-MS (ESI): m/z = 357.3 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{22}H_{17}FN_4$, 357.1510; found 357.1527.

2-Cyclopropyl-1,5-dimethyl-6-phenyl-1,5-dihydrodipyrrolo[3,2-*b*:3′,2′-*e*]pyrazine (11k). Mp: 120–121 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62–7.58 (m, 2H), 7.49 (dd, J = 10.7, 4.2 Hz, 2H), 7.42 (td, J = 7.1, 1.1 Hz, 1H), 6.74 (s, 1H), 6.26 (s, 1H), 3.97 (d, J = 1.3 Hz, 3H), 3.93 (d, J = 0.8 Hz, 3H), 2.03–1.96 (m, 1H), 1.09 (d, J = 8.2 Hz, 2H), 0.86 (d, J = 5.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.6, 143.5, 141.4, 140.9, 135.0, 133.8, 132.4, 129.1, 128.6, 128.2, 99.2, 94.6, 30.0, 28.2, 8.2, 7.1. LC-MS (ESI): m/z = 303.3 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{19}H_{18}N_4$, 303.1604; found 303.1620.

3-Chloro-5-methyl-2-(phenylethynyl)-5*H*-pyrrolo[2,3-*b*]pyrazine (12b). The procedure described above for **5a** was used. The titled compound was obtained as pale yellow solid with 72% yield. LC-MS (ESI): m/z = 344.1 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{21}H_{14}ClN_4$, 344.0949; found 344.0954.

4.7 General procedure for preparing pyrrolothienopyrazine

To a solution of 3-chloro-5-methyl-2-(phenylethynyl)-5*H*-pyrrolo[2,3-*b*]pyrazine (0.12 g 0.4 mmol) in DMF (4 mL) was added $Na_2S \cdot 5H_2O$ (0.14 g, 1.2 mmol). The mixture was refluxed for 1 h, cooled to ambient temperature then diluted with EtOAc and water. The organic layer was separated, dried over $MgSO_4$, and concentrated in vacuum to give a residue that was subjected to silica gel column chromatography to give a desired compound.

7-Methyl-2-phenyl-7*H*-pyrrolo[3,2-*e*]thieno[2,3-*b*]pyrazine (13a). Yield: 74%, light brown solid. Mp: 196–197 °C, ^{1}H NMR (500 MHz,

$CDCl_3$) δ 7.82–7.78 (m, 2H), 7.75 (s, 1H), 7.52 (d, J = 3.6 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.42 (d, J = 7.3 Hz, 1H), 6.74 (d, J = 3.6 Hz, 1H), 3.97 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.9, 146.3, 144.1, 139.4, 138.9, 134.1, 133.9, 129.1, 128.9, 126.3, 117.8, 100.3, 31.6. LC-MS (ESI): m/z = 266.1 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{15}H_{11}N_4S$, 266.0746; found 266.0751.

7-Methyl-2,6-phenyl-7*H*-pyrrolo[3,2-*e*]thieno[2,3-*b*]pyrazine (13b). Yield: 69%, light brown solid. Mp: 194–196 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 7.5 Hz, 2H), 7.74 (s, 1H), 7.63–7.60 (m, 2H), 7.54 (t, J = 7.3 Hz, 2H), 7.50–7.45 (m, 3H), 7.39 (t, J = 7.4 Hz, 1H), 6.78 (s, 1H), 3.93 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.5, 146.9, 146.7, 143.9, 141.2, 139.1, 134.1, 131.4, 129.1, 129.1, 129.0, 128.8, 128.8, 126.2, 117.8, 100.1, 30.0. LC-MS (ESI): m/z = 342.2 $[M + H]^+$. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{21}H_{16}N_4S$, 342.1059; found 342.1068.

5-Bromo-3,6-dichloropyrazine-2-amine (15). Yield: 90%, pale yellow solid. Mp: 129–130 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.7, 145.5, 129.4, 121.5. LC-MS (ESI): m/z = 339.9 $[M - 1]^-$.

2,5-Dibromo-3,6-dichloropyrazine (16). To a solution of 5-bromo-3,6-dichloropyrazin-2-amine (0.1 g, 0.4 mmol) in THF (1 mL), HBr (2 mL) at 0 °C was added $NaNO_2$ (0.07 g, 1.0 mmol) slowly. The mixture was stirred at 0 °C for 20 min and then made basic by using 1 M NaOH and extracted with EtOAc (3×). The combined organic layers were dried over $MgSO_4$, and concentrated to give a residue that was subjected to silica gel column chromatography to give desired compound as pale a yellow solid. Yield: 77%, mp: 93–94 °C, ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6, 136.3.

2,5-Dichloro-3,6-bis(phenylethynyl)pyrazine (17). To a stirred solution of 2,5-dibromo-3,6-dichloropyrazine (0.6 g, 1.97 mmol) in THF (10 mL), then TEA (1.3 mL, 13 mmol), $Pd(PPh_3)_2Cl_2$ (0.27 g, 0.34 mmol) and CuI (75 mg, 0.34 mmol) were added subsequently under nitrogen atmosphere. After 10 min, phenyl acetylene (0.42 g, 4 mmol) was added drop wise and the mixture was stirred at room temperature for 1.5 h. The mixture was concentrated in a vacuum to give a residue that was diluted with water and extracted with EtOAc (2×). The combined organic layer was washed with water and dried over $MgSO_4$, and concentrated in vacuum to give a residue that was subjected to silica gel column chromatography to yield the desired compound as pale yellow solid. Yield 38%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 7.0 Hz, 4H), 7.43 (dt, J = 14.5, 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.5, 135.8, 132.4, 130.4, 128.6, 120.9, 100.3, 84.3. LC-MS (ESI): m/z = 349.0 $[M + H]^+$.

5. Conclusions

In the study described above, we developed a convenient method for the synthesis of 1,5- and 1,7-dihydrodipyrrolo[2,3-*b*;3′2′-*e*]pyrazine derivatives. Protocols were devised to generate either 2-amino- or 3-amino-pyrrolopyrazines from the corresponding 2-bromo-3-chloro-5*H*-pyrrolo[2,3-*b*]pyrazines. Specifically, amination reactions of the dihalo substrates carried under metal free conditions in the presence of methylamine under MW irradiation produce 3-amino-pyrrolopyrazine exclusively. In contrast, Buchwald cross coupling affords 2-amino-pyrrolopyrazine. The pyrrolo pyrazine scaffolds were converted to the respective 1,7- and 1,5-DPP derivatives using the Sonogashira coupling reactions. All the synthesized compounds were found to be highly crystalline and readily soluble in organic solvents. Furthermore, the prepared pyrazine derivatives have high thermal stabilities, suggesting that they have high potential for use in organic electronic devices. Ongoing research in our laboratory is aimed at exploring interesting features of the 1,5-dihydrodipyrrolo[3,2-*b*:3′,2′-*e*]pyrazine molecular scaffold.

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References

1 J. Zhang, J. Wang, X. Xu, S. Chen, Q. Zhang, C. Yao, X. Zhuang, A. Pan and L. Li, *J. Mater. Chem. C*, 2015, **3**, 5933–5939.
2 Z. Liang, Q. Tang, R. Mao, D. Liu, J. Xu and Q. Miao, *Adv. Mater.*, 2011, **23**, 5514–5518.
3 K. Liu, C.-L. Song, Y.-C. Zhou, X.-Y. Zhou, X.-J. Pan, L.-Y. Cao, C. Zhang, Y. Liu, X. Gong and H.-L. Zhang, *J. Mater. Chem. C*, 2015, **3**, 4188–4196.
4 Y.-I. Park, J.-H. Son, J.-S. Kang, S.-K. Kim, J.-H. Lee and J.-W. Park, *Chem. Commun.*, 2008, 2143–2145, DOI: 10.1039/b718873k.
5 L. Yan, D. Zhao, J. Lan, Y. Cheng, Q. Guo, X. Li, N. Wu and J. You, *Org. Biomol. Chem.*, 2013, **11**, 7966–7977.
6 P. Henriksson, C. Lindqvist, B. Abdisa, E. Wang, Z. George, R. Kroon, C. Müller, T. Yohannes, O. Inganäs and M. R. Andersson, *Sol. Energy Mater. Sol. Cells*, 2014, **130**, 138–143.
7 X. Lu, G. Zhou, H. Wang, Q. Feng and Z.-S. Wang, *Phys. Chem. Chem. Phys.*, 2012, **14**, 4802–4809.
8 C. R. Hopkins and N. Collar, *Tetrahedron Lett.*, 2004, **45**, 8087–8090.
9 C. R. Hopkins and N. Collar, *Tetrahedron Lett.*, 2004, **45**, 8631–8633.
10 I. Simpson, S. A. St-Gallay, S. Stokes, D. T. E. Whittaker and R. Wiewiora, *Tetrahedron Lett.*, 2015, **56**, 1492–1495.
11 A. Keivanloo, M. Bakherad, H. Nasr-Isfahani and S. Esmaily, *Tetrahedron Lett.*, 2012, **53**, 3126–3130.
12 G. Bashiardes, I. Safir, A. S. Mohamed, F. Barbot and J. Laduranty, *Org. Lett.*, 2003, **5**, 4915–4918.
13 G. Xu and Y.-G. Wang, *Org. Lett.*, 2004, **6**, 985–987.
14 D. R. Sauer, D. Kalvin and K. M. Phelan, *Org. Lett.*, 2003, **5**, 4721–4724.
15 L. Shi, M. Wang, C.-A. Fan, F.-M. Zhang and Y.-Q. Tu, *Org. Lett.*, 2003, **5**, 3515–3517.
16 F. Y. Kwong and S. L. Buchwald, *Org. Lett.*, 2003, **5**, 793–796.

17 C. Bathula, C. E. Song, S. Badgujar, S.-J. Hong, I.-N. Kang, S.-J. Moon, J. Lee, S. Cho, H.-K. Shim and S. K. Lee, *J. Mater. Chem.*, 2012, **22**, 22224–22232.
18 E. Zhu, G. Ge, J. Shu, M. Yi, L. Bian, J. Hai, J. Yu, Y. Liu, J. Zhou and W. Tang, *J. Mater. Chem. A*, 2014, **2**, 13580–13586.
19 Q. Meng, L. Jiang, Z. Wei, C. Wang, H. Zhao, H. Li, W. Xu and W. Hu, *J. Mater. Chem.*, 2010, **20**, 10931–10935.
20 H. Wang, Y. Xu, X. Yu, R. Xing, J. Liu and Y. Han, *Polymers*, 2013, **5**, 1272.
21 H. Dong, C. Wang and W. Hu, *Chem. Commun.*, 2010, **46**, 5211–5222.
22 C. Bathula, M. Kim, C. E. Song, W. S. Shin, D.-H. Hwang, J.-C. Lee, I.-N. Kang, S. K. Lee and T. Park, *Macromolecules*, 2015, **48**, 3509–3515.
23 Y. Geng, J. Wang, S. Wu, H. Li, F. Yu, G. Yang, H. Gao and Z. Su, *J. Mater. Chem.*, 2011, **21**, 134–143.
24 Z. Liang, Q. Tang, J. Liu, J. Li, F. Yan and Q. Miao, *Chem. Mater.*, 2010, **22**, 6438–6443.
25 S. Van Epps, B. Fiamengo, J. Edmunds, A. Ericsson, K. Frank, M. Friedman, D. George, J. George, E. Goedken, B. Kotecki, G. Martinez, P. Merta, M. Morytko, S. Shekhar, B. Skinner, K. Stewart, J. Voss, G. Wallace, L. Wang, L. Wang and N. Wishart, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 693–698.
26 S. K. Kolli, A. Nakhi, R. Medishetti, S. Yellanki, P. Kulkarni, R. Ramesh Raju and M. Pal, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 4460–4465.
27 CCDC deposit number 1536706.