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Synthesis of new tetrahydropyridopyrazine derivatives via continuous flow chemistry approach and their spectroscopic characterizations

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Abstract

We report here the synthesis of different substituted tetrahydropyridopyrazine derivatives. This approach of synthesis has been designed in a way that in first simple chloro-amine coupling as an alternative of Buchwald coupling followed by heterogeneous hydrogenation of nitro to give amine and further cyclization of this amine with carboxylic acid was accomplished in a single process with the help of continuous flow hydrogenation reactor. This processing was a generation of hydrogen (in situ) by electrolysis of water molecule and using a prepacked cartridge of a palladium catalyst. In a further step, LAH was used to reduce lactam to a yielding product as tetrahydropyridopyrazine (TPP) scaffold. Final adducts were obtained using substituted benzoyl and sulfonyl derivatives.

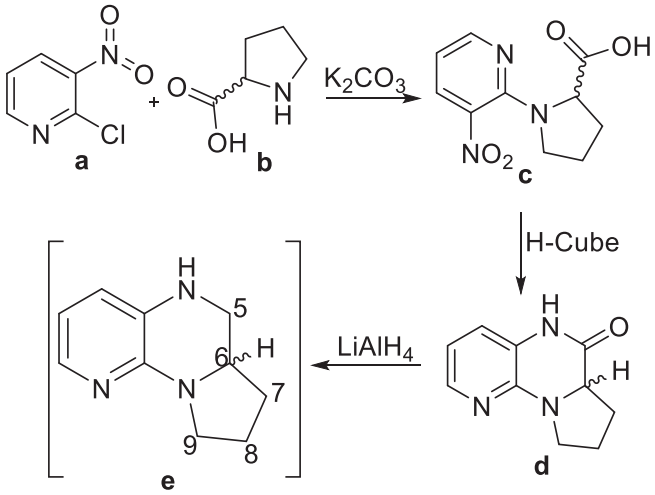
1 | INTRODUCTION

Preparation of nitrogen containing heterocyclic derivatives with a stereo center is a major challenge in stereo chemistry related synthesis. Out of which one of moiety is tetrahydropyridopyrazine (TPP) subunits. Nitrogen containing scaffolds were used as antitubercular (TB) [1], anaplastic lymphoma kinease (ALK) inhibitor [2], antidiabetic [3], anticancer [4], and PARP inhibitor. Various analogs of pyridopyrazines were part of various peptidomimetic scaffolds [5]. These analogs showed many biological activities like antimalarial precursor 2-alkoxycarbonylaminopyridine HIV-1 integrase inhibitors [6], ADP-Ribose polymerase inhibitors (PARP) [7], and inhibitors of *Mycobacterium tuberculosis* FtsZ (Filament temperature-sensitive protein Z) [8]. Some of the derivatives such as Pyrido [2, 3-d] pyrimidine acted as adenosine antagonists receptor [9].

In continuation to this, the effective method for new drug discoveries is the bioisosteric replacement of a functional group [10]. Due to their encouraging biological potential of TPP, some of the methods for the synthesis of TPP derivatives are found in the literature [11]. One of the most popular methods is the reduction of two ketonic groups [12]. Most of these methods invite a logical synthesis of one or two isomers of TPP bearing one stereogenic center [13]. Recently, we have synthesized a standard three-step synthetic approach for the stereo conflicting synthesis of TPP as a scaffold. This approach of synthesis has been designed with a coupling of both synthons DL-Proline and substituted pyridine [14]. Here, we have carried out this step with simple Chloro-amine coupling as an alternative of Buchwald coupling, followed by reduction and cyclization of the isolated intermediate in a single step via continuous flow hydrogenation reactor, using palladium as a catalyst to get an intermediate with one stereocenter. Then reduction of amidic ketone with a strong base [15] to yield TPP scaffold (Scheme 1).

The relative configuration of this intermediate at chiral atom (C6) remains constant after reaction with a suitable nucleophile and the product will become a stereospecific product. In this context to the synthesis of

compound **(d)**, continuous flow hydrogenation chemistry technology presents an interesting alternative to batch processing. Using H-Cube is promoted due to prepacked Pd-catalyst cartridge and in situ hydrogen generation that provide secure and authentic method to perform hydrogenation under bar pressure [16–18]. In this report, we explore the reduction and cyclization of compound **(c)** (Scheme 1) under a continuous flow chemistry approach and create a qualitative comparison with selectivity and reaction rate, which is newly reported for scale-up hydrogenation reactions performed by H-cube mini hydrogenation reactor.



SCHEME 1 Synthetic route for tetrahydropyridopyrazine scaffolds **(e)**

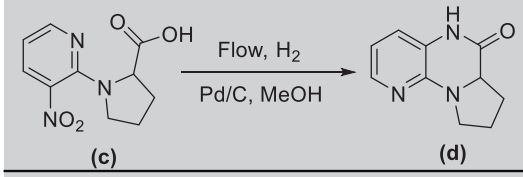
2 | RESULTS AND DISCUSSION

2.1 | Chemistry

Our principal focus was to reaction conditions optimization for catalytic heterogeneous hydrogenation using the H-cube mini hydrogenation reactor. The synthesis carried out via preparing 0.05 M stock solution of (3-nitropyridin-2-yl)proline (**c**) (Scheme 1) and TPP scaffolds (TPP) (**d**) in methanol. Started pumping this solution with ensuring that no air was introduced in vessel and clear solution was passed throughout the system using a standard Palladium catalyst (5% w/w and 10% w/w) in sealed cartridge with 1.0 and 2.0 mL/min flow rate, simultaneously at various temperature and hydrogen pressure.

The degree of conversion was monitored using TLC analysis. Approximately 10% conversion to d (Table 1, entry 1) was obtained on passing reaction mixture at a 1.0 mL/min flow rate over 5% Pd/C heated to 80°C and 25 bar (~350 PSI) pressure. Temperature and pressure will increase conversion growing up to 70% at 100°C and 40 bar pressure (Table 1, entry 3). However, an increase in catalyst concentration to 10% w/w Pd/C at 90°C and 40 bar pressure would give nearly 100% conversion (Table 1, entry 4). Due to this phenomenon, we have increased the temperature 90 to 95°C keeping the pressure same to get 100% conversion (Table 1, entry 5). The reaction was then performed by using different flow rates at different temperatures and pressures. Initially, there was no conversion at 2.0 mL/min flow rate over 5% Pd/C at 60°C and 25 bar pressure (Table 1, entry 6) but the

TABLE 1 Optimization of the reaction conditions



Entry	Catalyst	Flow rate (mL/min)	Temp (°C)	Pressure [bar]	Conversion [%]
1	Pd/C (5% w/w)	1.0	80	25	10
2	Pd/C (5% w/w)	1.0	90	30	30
3	Pd/C (5% w/w)	1.0	100	40	70
4	Pd/C (10%w/w)	1.0	90	40	95
5	**Pd/C (10%w/w)**	**1.0**	**95**	**40**	**100**
6	Pd/C (5% w/w)	2.0	60	25	-
7	Pd/C (5% w/w)	2.0	80	30	20
8	Pd/C (10% w/w)	2.0	80	30	60
9	**Pd/C (10%w/w)**	**2.0**	**100**	**35**	**100**

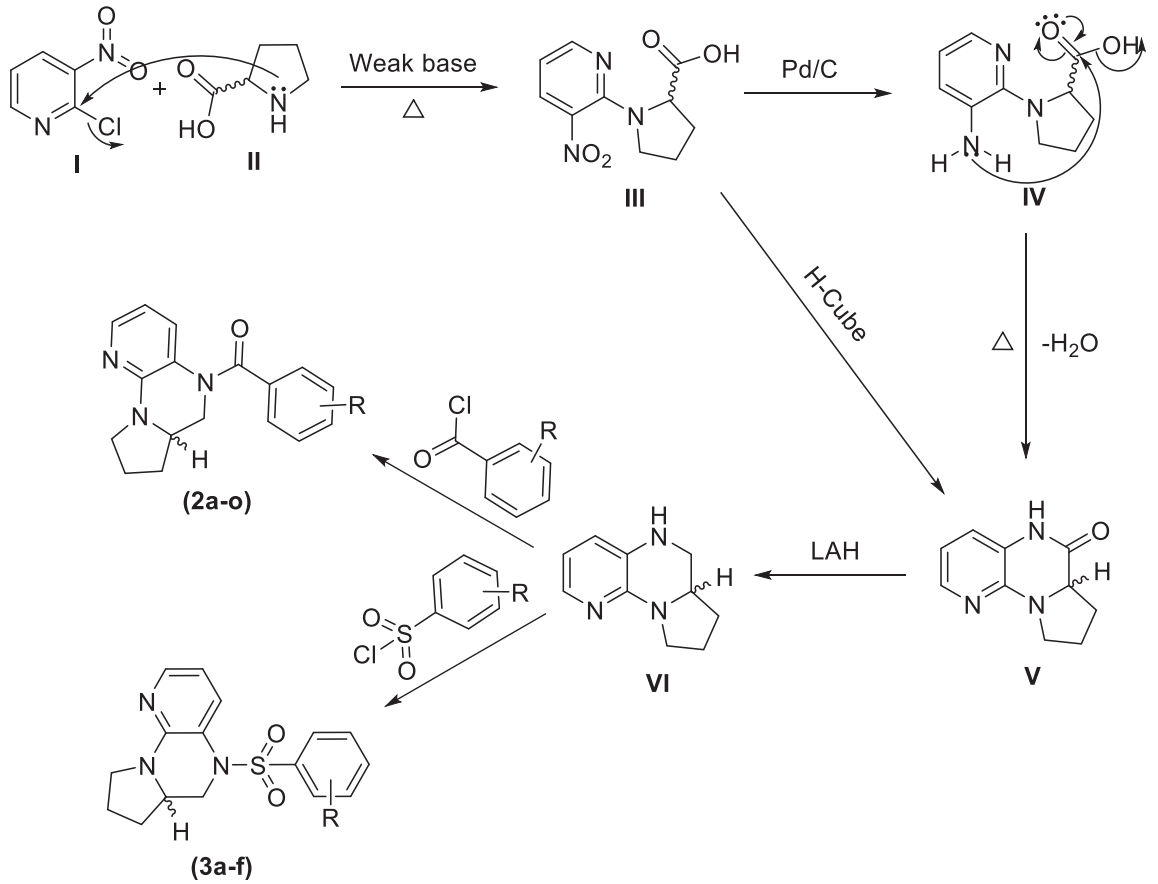
Note: Bold value indicates final optimal condition and all derivatives were synthesized according to entry 9.

slight increase in conversion shows the increase in temperature and pressure (Table 1, entry 7). An increase in catalyst concentration to 10% w/w Pd/C at same flow rate of 2.0 mL/min gave 60% of conversion and increase in temperature and pressure to 100°C and 35 bar gave conversion to 100% product (Table 1, entry 9). Therefore, the optimal conditions for the preparation of compound **(d)** are catalyst cartridge loading to 10% w/w at 100°C temperature and 35 bar pressure. There were no blockage issues found in the hydrogenation reaction. A plausible mechanism was proposed in accordance with previous literature reports [14–18] as shown in (Scheme 2).

We presume that the aromatic nucleophilic substitution reaction between compound **I** and compound **II** give intermediate **III**. This accelerates the intramolecular cyclization reaction by continuous flow synthesis approach subsequently reduction of a nitro group (intermediate **IV)** to form the intermediate **V**. It then treated with the strong reducing agent to reduce the amidic ketone to afford the desired scaffold **VI**. Then we demonstrate the possibility of reaction by synthesizing diverse substituted benzoyl derivatives **2a-o** using the chloroamine coupling reactions and various substituted sulfonyl derivatives **3a-f** (Scheme 2).

Further, we undertook the synthesis of (5-[substitutedphenyl]sulfonyl)-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazine, **3a-f** from the corresponding scaffold, TPP. The conversion was completed within 70 to 80 minutes to get brown color crude material as gummy liquid, which was purified by column chromatography using 230 to 400 mesh size silica gel using Ethyl acetate: *n*-Hexane (1:9, 3:7, and 4:6) as eluent to afford the desired product as off white to white solid with good yields in all cases. The nature of the substituent on the benzene sulfonyl chloride did not affect the reaction time.

A single crystal of (4-chlorophenyl)(6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-5[6*H*]-yl)methanone, **2a** (Figure 1) and (6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-5[6*H*]-yl)(p-tolyl)methanone, **2d** crystallized as a colorless block crystal, this species adopted a lattice type primitive triclinic crystal system containing P-1 space group. (Figure 2) [19–20]. A single crystal of (3-bromophenyl)(6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)methanone, **2h** crystallized as a



SCHEME 2 Synthetic route of (4-substituted phenyl)(6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-5(6H)-yl)methanone derivatives (**2a-o**) & 5-((substituted phenyl)sulfonyl)-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazine derivatives (**3a-f**)

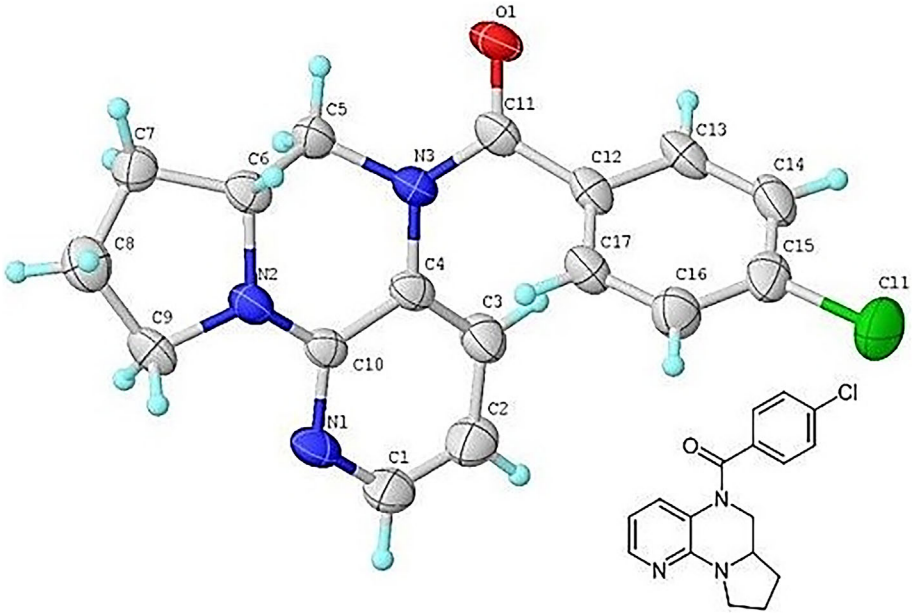


FIGURE 1 X-ray crystal structure compound 2a

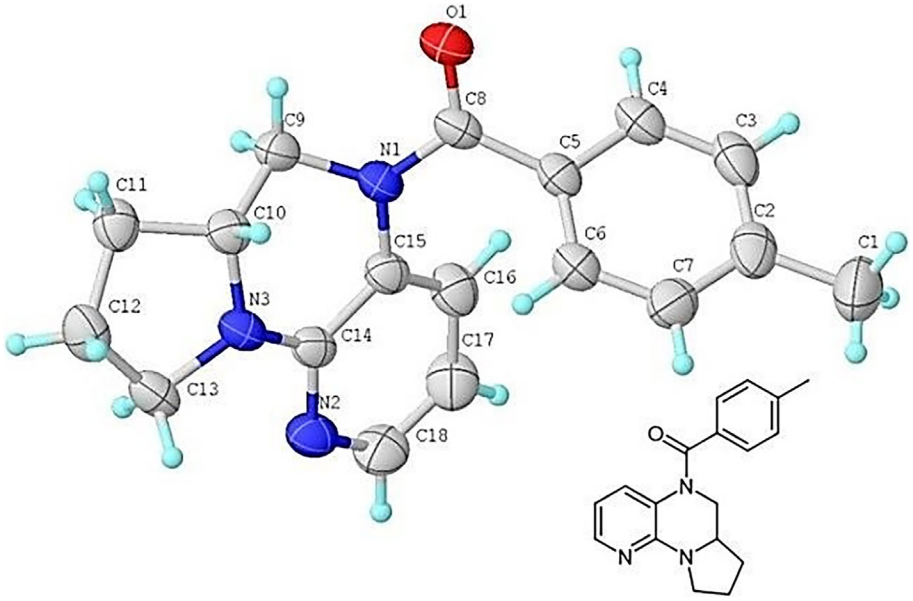


FIGURE 2 X-ray crystal structure compound 2d

yellow block crystal, this species adopted a primitive lattice type monoclinic crystal system space group P21/c, (Figure 3) [21].

3 | CONCLUSION

In conclusion, we developed two series of (4-substituted phenyl)(6a,7,8,9-tetrahydropyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazin-5(6*H*)-yl)methanone derivatives (**2a-o**) and 5-([substituted phenyl]sulfonyl)-5,6,6a,7,8,9-hexahydropyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazine derivatives (**3a-f**) by H-cube hydrogenator via continuous flow chemistry approach. Different benzoyl chloride containing an electron-donating group reacted slightly better than those containing an electron-withdrawing group. The simple benzoyl chloride provided a good yield of the corresponding products. All synthesized compounds were characterized by analytical techniques (FT-IR, ^{1}H NMR, ^{13}C NMR, Mass, and Elemental analysis). Compound **2a**, **2d,** and **2h** were also characterized by single crystal X-ray diffraction study.

4 | EXPERIMENTAL

4.1 | General

All chemicals were purchased from Merck, all purchased chemicals were used without further purification.

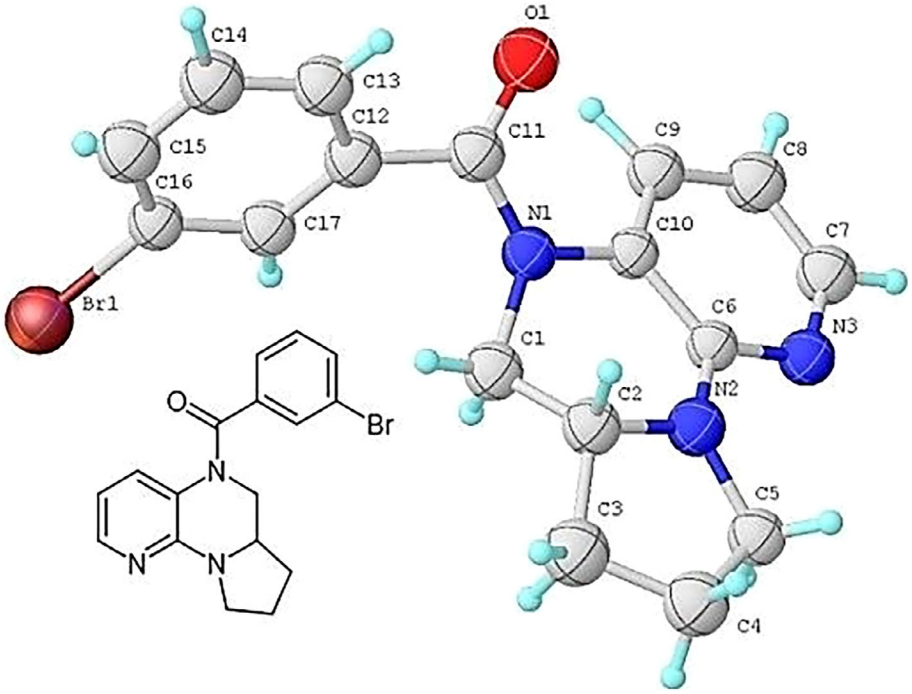


FIGURE 3 X-ray crystal structure of compound 2h

Reactions were monitored by thin layer chromatography (TLC) on silica gel-G plates (G60 F254 [Merck]) of 0.5 mm thickness, visualizing with ultraviolet light (254 and 365 nm), or with iodine vapor or aq. $KMnO_4$. Melting points were determined using a Buchi B-540 capillary apparatus. IR data were recorded on a Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method and are reported in cm^{-1} (KBr). NMR spectra were recorded on a Bruker Advance 400 MHz spectrometer (400 MHz for ^1H NMR and 101 MHz for ^{13}C NMR), respectively, in deuterated solvents like DMSO-d6 and $CDCl_3$. chemical shifts are referenced to the solvent residual signals with respect to tetramethylsilane. Elemental analysis was carried out on Euro EA 3000 elemental analyzer and the results are in agreement with the structures assigned. The control of reaction temperature was monitored by a ruby thermometer. Mass spectra were recorded on a Shimadzu GC-MS-QP-2010 mass spectrometer in EI (70 eV) model using direct inlet probe technique and m/z is reported in atomic units per elementary charge. Single crystal X-Ray was carried out using Rigaku-SCX Mini Single Crystal X-Ray diffractometer. Flow hydrogenation reaction was carried out on ThalesNano, Nanotechnology, H-Cube Mini Plus Hydrogenation Reactor.

4.1.1 | Synthesis of (3-nitropyridin-2-yl) proline (c)

To stir a solution of 2-chloro-3-nitropyridine, **a** (2.0 gm, 12.61 mmol), DL-Proline, **b** (1.44 gm, 12.61 mmol) in PhMe (30 mL) solvent after that addition of Potassium carbonate (5.23 gm, 37.84 mmol). The reaction mixture was stirred at 110°C for 6 hours. Progress of reaction was monitored by TLC. After completion of the reaction excess of solvent was evaporated under reduced pressure, then add 1 N HCl (40 mL), a yellow precipitate was observed, which was separated by filtration to give (3-nitropyridin-2-yl)proline **(c)** as a yellow solid: yield 2.8 gm (93%); mp 145°C to 146°C; ^1H NMR (400 MHz, DMSO-d_6): δ 12.547 (s, 1H, —COOH), 8.351 to 8.336 (q, 1H, $J = 1.6$, 4.4 Hz, ArH), 8.203 to 8.179 (q, 1H, $J = 1.6$, 8.0 Hz, ArH), 6.849 to 6.818 (q, 1H, $J = 4.4$, 8.0 Hz, ArH), 4.599 to 4.564 (t, 1H, $J = 14.0$ Hz, Chiral), 3.211 to 3.167 (qt, 1H, $J = 17.6$ Hz), 3.056 to 3.002 (m, 1H), 2.335 to 2.288 (m, 1H), 2.022 to 1.940 (m, 3H); Anal. calcd. for $C_{10}H_{11}N_3O_4$: C, 50.63; H, 4.67; N, 17.71. Found: C, 50.58; H, 4.68; N, 17.80.

4.1.2 | Synthesis of 6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo [1,2-a]pyrazin-6(5*H*)-one (d)

To stir a solution of (3-nitropyridin-2-yl)proline, **c** (2.8 gm, 11.8 mmol) in methanol (100 mL) in 250 mL conical flask. Stir it for 5 minutes at room temperature to get a clear yellow color solution. In the hydrogenator reactor (H-Cube mini plus) put the vessel containing inlet line into the clear solution and is passed through the system containing 35 bar pressure of H_2 gas and 90 °C temperature using a standard Palladium catalyst (10% w/w) cartridge at 2.0 mL/min flow rate. The degree of conversion

was established by monitoring on TLC plate. Collect the product continuously, excess solvent was evaporated under reduced pressure, to give 6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one **(d)** as light green solid; yield 1.8 gm (80%); mp 129°C to 130°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.473 (s, 1H, —NH), 7.712 to 7.702 (d, 1H, J = 4.0 Hz, ArH), 6.989 to 6.972 (d, 1H J = 6.8 Hz, ArH), 6.608 to 6.577 (qt, 1H, J = 7.2 Hz, ArH), 3.996 to 3975 (t, 1H, J = 8.4 Hz), 3.617 to 3.556 (m, 1H), 3.399 to 3.362 (m, 1H), 2.184 to 2.129 (m, 1H), 1.949 to 1.869 (m, 3H); Anal. calcd. for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.41; H, 5.82; N, 22.27.

4.1.3 | Synthesis of 5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazine (e)

To a stirred solution of 6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one, **d** (1.8 gm, 9.5 mmol) in THF (5 mL) and anhydrous diethyl ether (40 mL) in 50 mL dry RBF. Stir the reaction mixture to prepare a homogeneous solution, keep RBF in an ice bath at 0°C temperature followed by added Lithium aluminum hydride (1.08 gm, 28.5 mmol) quench wise over a time period of 15 minute. Stir the reaction mass at room temperature for 2 hr. During the progress of the reaction, the color of reaction mass gradually changes. After completion of reaction (checked on TLC plate, it shows fluorescent spot in the visible light region), the mixture becomes dark brown in color. The reaction mass quenched in saturated aqueous NH_4Cl solution (30 mL). (During the quenching of reaction mass, evolution of H_2 gas was observed) and product was extracted in ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and remove the solvent under *vacuum* to give desired 5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazine **(e)** as brown solid; yield 1.1 gm (66%); mp 112°C to 113°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.346 to 7.330 (d, 1H, J = 6.4 Hz, ArH), 6.609 to 6.587 (d, 1H, J = 8.8 Hz, ArH), 6.322 to 6.291 (t, 1H, J = 12.4 Hz, ArH), 5.642 to 5.636 (s, 1H, —NH), 3.511 to 3.465 (t, 1H, J = 18.4 Hz), 3.454 to 3.439 (t, 1H, J = 6.0 Hz), 3.425 to 3.345 (m, 2H), 2.632 to 2.570 (t, 1H, J = 24.8 Hz), 2.078 to 2.015 (m, 1H), 1.990 to 1.912 (m, 1H), 1.891 to 1.792 (m, 1H), 1.451 to 1.350 (m, 1H); Anal. calcd. for $C_{10}H_{13}N_3$: C, 68.54; H, 7.48; N, 23.98. Found: C, 68.51; H, 7.51; N, 24.07.

4.2 | General procedure-I for the synthesis of compounds (2a-o)

To a stirred solution of 5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazine, **e** (0.5 gm, 2.8 mmol) in dichloromethane (12 mL) in 50 mL dry RBF, after that keep into ice bath and dropwise additon of triethyl amine (1.19 mL, 8.5 mmol). Now, allow to stir the reaction mixture at O°C for 10 minutes and then add benzoylchloride substrate (3.4 mmol), further stir the reaction mass at room temperature for 2 hours. After completion of reaction (checked by TLC), the reaction mixture was poured in ice-cooled water (100 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and removed the solvent under *vacuum* to give crude material, which was purified by flash column chromatography using 230 to 400 mesh size silica gel using Ethyl acetate: *n*-Hexane (2:8, 4:6 and 5:5) as eluent to afford the pure product.

Substrate scope for the synthesis of benzoyl derivatives (2a-o) is shown in Supplementary Material file, Table S2.

4.2.1 | (4-chlorophenyl)(6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)methanone (2a)

Synthesized according to the general procedure-I and then isolated using 7:3 mixture of hexane and ethyl acetate for flash chromatography to get crystalline solid; yield 64%; mp 164°C to 165°C; IR (KBr, ν_{max}, cm^{-1}): 3267, 2968, 2883, 1645, 1595, 1450, 1410 (C—H bend), 1332, 1274, 1209, 1084, 844, 761; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.830 to 7.815 (dd, 1H, J = 1.2, 4.8 Hz), 7.487 to 7.423 (qt, 4H, J = 8.4, 17.2 Hz), 6.985 (br, 1H), 6.375 to 6.347 (t, 1H, J = 11.2 Hz), 4.624 (s, 1H), 3.728 to 3.678 (m, 1H), 3.619 to 3.573 (t, J = 9.6, 18.4 Hz), 3.485 to 3.415 (qt, 1H, J = 10.4, 18.0 Hz), 2.700 to 2.645 (m, 1H), 2.159 to 2.102 (m, 1H) 2.049 to 2.984 (m, 1H), 1.926 to 1.862 (m, 1H), 1.547 to 1.473 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.48, 148.67, 144.81, 135.36, 134.70, 130.65, 130.43, 128.91, 119.89, 110.81, 57.94, 47.31, 30.05, 23.74; MS: m/z [M^+] 313.00; Anal. calcd. for $C_{17}H_{16}ClN_3O$: C, 65.04; H, 5.14; N, 13.39. Found: C, 65.12; H, 5.10; N, 13.32

4.2.2 | (3-chlorophenyl)(6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)methanone (2b)

Synthesized according to the general procedure-I and then isolated using 7:3 mixture of hexane and ethyl acetate for flash chromatography to get isolated crystalline solid; yield 59%; mp 161°C to 162°C; IR (KBr, ν_{max}, cm^{-1}): 3277, 2966, 2875, 1647, 1597, 1498, 1402, 1330, 1261, 1207, 1082, 742, 688; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.838 to 7.828 (d, 1H, J = 4.0 Hz), 7.541 to 7.503 (t, 2H, J = 15.2 Hz), 7.450 to 7.412 (t, 1H, J = 15.2 Hz),

7.359 (s, 1H), 7.015 to 6.939 (br, 1H), 6.370 (s, 1H), 4.609 (br, 1H), 3.716 (s, 1H), 3.626 to 3.579 (t, 1H, $J = 18.8$ Hz), 3.473 to 3.402 (m, 1H), 2.674 (s, 1H), 2.137 to 2.110 (t, 1H, $J = 10.8$ Hz, 1H), 2.046 to 1.982 (m, 1H), 1.923 to 1.861 (qt, 1H, $J = 8.0, 17.2$ Hz), 1.513 to 1.468 (qt, 1H, $J = 7.6, 10.4$ Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.48, 148.18, 144.42, 137.54, 133.03, 130.26, 130.05, 129.96, 127.88, 126.66, 119.14, 110.26, 57.28, 46.81, 29.52, 23.23. MS: m/z [M^+] 313.00; Anal. calcd. for $C_{17}H_{16}ClN_3O$: C, 65.04; H, 5.14; N, 13.39. Found: C, 65.08; H, 5.19; N, 13.42.

4.2.3 | (4-nitrophenyl) (6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo [1,2-a]pyrazin-5(6*H*)-yl)methanone (2c)

Synthesized according to the general procedure-I and isolated using 8:2 mixture of hexane and ethyl acetate for flash chromatography to get crystalline solid; yield 61%; mp 152°C to 153°C; IR (KBr, ν_{max}, cm^{-1}): 3281, 2877, 1651, 1597, 1492, 1410, 1330, 1267, 1201, 1085, 826; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.262 to 8.243 (d, 2H, $J = 7.6$ Hz), 7.843 (s, 1H) 7.705 (s, 2H), 6.354 (s, 1H), 3.757 to 3.322 (m, 3H), 2.718 (s, 1H), 2.134 to 1.910 (m, 3H), 1.507 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 148.23, 147.98, 144.68, 141.74, 130.09, 129.50, 123.58, 110.30, 57.32, 46.80, 29.51, 23.24; MS: m/z [M^+] 324.00; Anal. calcd. for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27. Found: C, 63.01; H, 5.02; N, 17.32.

4.2.4 | (6a,7,8,9-tetrahydropyrido[3,2-e] pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)(p-tolyl) methanone (2d)

Synthesized according to the general procedure-I and isolated using 6:4 mixture of hexane and ethyl acetate for flash chromatography to get crystalline solid; yield 76%; mp 160°C to 161°C; IR (KBr, ν_{max}, cm^{-1}): 3267, 2968, 2887, 1649, 1595, 1454, 1408, 1334, 1276, 1209, 1107, 831; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.818 to 7.802 (dd, 1H, $J = 1.6, 4.8$ Hz), 7.318 to 7.298 (d, 2H, $J = 8.0$ Hz), 7.223 to 7.204 (d, 2H, $J = 7.6$ Hz), 6.973 (br, 1H), 6.366 to 6.336 (t, 1H, $J = 12.0$ Hz), 3.692 to 3.655 (m, 1H), 3.626 to 3.579 (t, 1H, $J = 18.8$ Hz), 3.482 to 3.412 (m, 1H), 2.688 to 2.633 (t, $J = 22.0$ Hz), 2.330 (s, 3H), 2.156 to 2.099 (m, 1H), 2.032 to 1.985 (q, 1H, $J = 5.6, 12.0$ Hz), 1.933 to 1.886 (m, 1H), 1.526 to 1.471 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.09, 148.15, 144.02, 140.06, 132.46, 129.77, 128.80, 128.25, 119.79, 110.34, 57.53, 46.84, 29.54, 23.23, 20.93. MS: m/z [M^+] 293.00; Anal. calcd. for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.73; H, 6.58; N, 14.26.

4.2.5 | (2,3-dichlorophenyl) (6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo [1,2-a]pyrazin-5(6*H*)-yl)methanone (2e)

Synthesized according to the general procedure-I and isolated using 8:2 mixture of hexane and ethyl acetate for flash chromatography to get crystalline solid; yield 54%; mp 158°C to 159°C; IR (KBr, ν_{max}, cm^{-1}): 3273, 2968, 2856, 1645, 1595, 1491, 1404, 1329, 1269, 1205, 1080, 796, 765, 684; MS: m/z [M^+] 347.00; Anal. calcd. for $C_{17}H_{15}Cl_2N_3O$: C, 58.64; H, 4.34; N, 12.07. Found: C, 58.60; H, 4.31; N, 12.13.

4.2.6 | (2,6-difluorophenyl) (6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo [1,2-a]pyrazin-5(6*H*)-yl)methanone (2f)

Synthesized according to the general procedure-I and isolated using 8:2 mixture of hexane and ethyl acetate for flash chromatography to get crystalline solid; yield 56%; mp 155 to 156°C; IR (KBr, ν_{max}, cm^{-1}): 3282, 2928, 2872, 1653, 1593, 1498, 1410, 1371, 1273, 1209, 1085, 1002, 756; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.790 to 7.308 (m, 8H), 6.540 (s, 1H), 6.184 (s, 1H), 5.001 (s, 1H), 3.595 to 3.574 (m, 2H) 3.447 to 3.363 (m, 2H), 1.994 (m, 4H); MS: m/z [M^+] 315.00; Anal. calcd. for $C_{17}H_{15}F_2N_3O$: C, 64.75; H, 4.80; N, 13.33. Found: C, 64.79; H, 4.86; N, 13.22.

4.2.7 | (2-fluorophenyl) (6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo [1,2-a]pyrazin-5(6*H*)-yl)methanone (2g)

Synthesized according to the general procedure-I and isolated using 9:1 mixture of hexane and ethyl acetate for flash chromatography to get crystalline solid; yield 63%; mp 157 to 158°C; IR (KBr, ν_{max}, cm^{-1}): 3277, 2970, 2872, 1651, 1595, 1496, 1408, 1327, 1255, 1203, 1084, 1037, 769; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.793 (s, 1H) 7.505 (s, 2H) 7.303 (s, 1H), 7.096 (s, 1H), 6.526 (s, 1H), 6.183 (s, 1H), 5.012 (s, 1H), 3.616 to 3.342 (m, 5H), 2.931 (s, 1H), 1.522 (br, 2H); Anal. calcd. for $C_{17}H_{16}FN_3O$: C, 68.67; H, 5.42; N, 14.13. Found: C, 68.62; H, 5.49; N, 14.21.

4.2.8 | (3-bromophenyl) (6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo [1,2-a]pyrazin-5(6*H*)-yl)methanone (2h)

Synthesized according to the general procedure-I and isolated using 7:3 mixture of hexane and ethyl acetate for flash chromatography to get crystalline solid; yield 73%; mp 169°C to 170°C; IR (KBr, ν_{max}, cm^{-1}): 3269, 2866,

1645, 1597, 1460, 1500, 1327, 1261, 1199, 1087, 759, 686; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.838 to 7.827 (d, 1H, J = 4.0 Hz), 7.672 to 7.623 (t, 2H, J = 19.6 Hz), 7.381 to 7.343 (t, 2H, J = 15.2 Hz), 6.976 (br, 1H), 6.372 (s, 1H), 4.596 (s, 1H), 3.717 (s, 1H), 3.626 to 3.579 (t, 1H, J = 18.8 Hz), 3.477 to 3.407 (m, 1H), 2.671 (s, 1H), 2.134 to 1.865 (m, 3H), 1.547 to 1.473 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 148.19, 144.43, 137.74, 132.95, 130.70, 130.49, 129.98, 127.05, 121.47, 110.26, 57.27, 46.81, 29.52, 23.22; MS: m/z [M^+] 357.00; Anal. calcd. for $C_{17}H_{16}BrN_3O$: C, 57.00; H, 4.50; N, 11.73. Found: C, 57.09; H, 4.57; N, 11.66.

4.3 | General procedure-II for the synthesis of compounds (3a-f)

To a stirred solution of 5,6,6a,7,8,9-hexahydropyrido [3,2-e]pyrrolo[1,2-a]pyrazine, **e** (0.5 g, 2.8 mmol) in dimethylformamide (15 mL) solvent after that addition of potassium carbonate (0.9 g, 7.1 mmol). Now, allow to stir the reaction mixture to prepare a homogeneous solution then add benzene sulfonyl chloride substrate (3.9 mmol). Further stir the reaction mixture at 90°C temperature for 1.5 hours. After completion of reaction (checked by TLC), the mixture becomes dark in color. Then cool the reaction mass to room temperature and pour into ice-cooled water (150 mL), and extract with ethyl acetate (3 × 20 mL). The combined organic layer is dried over anhydrous Na_2SO_4 and remove the solvent under *vacuum* to give crude material, which was purified by flash column chromatography using 230 to 400 mesh size silica gel using Ethyl acetate: *n*-Hexane (2:8, 4:6 and 5:5) as eluent to afford the pure product.

Substrate scope for the synthesis of sulfonyl derivatives (3a-f) is shown in Supplementary Material file, Table S3.

4.3.1 | 5-((4-chlorophenyl)sulfonyl)-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo [1,2-a]pyrazine (3a)

Synthesized according to the general procedure-II and isolated using 5:5 mixture of hexane and ethyl acetate for flash chromatography to get amorphous solid; yield 56%; mp 95°C to 96°C; IR (KBr, ν_{max}, cm^{-1}): 3084, 2875, 1591, 1491, 1354, 1282, 1203, 1165, 1080, 833, 759; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.937 to 7.927 (d, 1H, J = 4.0 Hz), 7.734 to 7.715 (d, 1H, J = 7.6 Hz), 7.654 (s, 4H), 6.628 to 6.597 (qt, 1H, J = 5.2, 7.6 Hz), 4.467 (dd, 1H, J = 3.2, 13.6 Hz), 3.436 to 3.284 (m, 4H), 2.996 to 2.961 (m, 1H), 2.767 to 2.706 (qt, 1H, J = 11.2, 13.6 Hz), 2.049 to 2.021 (m, 1H), 1.902 to 1.873 (m, 1H), 1.724 to 1.683 (m, 1H), 1.380 to 1.336 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 148.33, 145.37, 138.53, 137.39, 130.50, 129.80, 128.77, 116.39, 111.05, 54.52, 46.91, 46.26, 40, 29.76, 22.71; MS: m/z [M^+] 349.00; Anal. calcd. for $C_{16}H_{16}ClN_3O_2S$: C, 54.93; H, 4.61; N, 12.01; Found: C, 54.99; H, 4.55; N, 12.08.

4.3.2 | 5-((4-fluorophenyl)sulfonyl)-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo [1,2-a]pyrazine (3b)

Synthesized according to the general procedure-II and isolated using 5:5 mixture of hexane and ethyl acetate for flash chromatography to get amorphous solid; yield 58%; mp 99°C to 100°C; IR (KBr, νmax, cm^{-1}): 3097, 2974, 2856, 1591, 1492, 1338, 1284, 1203, 1168, 1080, 1055, 842; 1H NMR (400 MHz, CDCl3): δ 8.025 to 8.015 (d, 1H, J = 4.0 Hz), 7.898 to 7.880 (d, 1H, J = 7.2 Hz), 7.646 to 7.612 (qt, 2H, J = 5.2, 8.4 Hz), 7.139 to 7.097 (t, 2H, J = 16.8 Hz), 6.621 to 6.589 (qt, 1H, J = 5.2, 7.6 Hz), 4.508 to 4.464 (dd, 1H, J = 4.0, 14.0 Hz), 3.586 to 3.438 (m, 1H), 2.989 to 2.916 (m, 1H), 2.675 to 2.614 (qt, 1H, J = 10.8, 13.6 Hz), 2.083 to 1.975 (m, 2H), 1.859 to 1.764 (m, 1H), 1.406 to 1.267 (m, 1H); 13C NMR (100 MHz, CDCl3): δ 166.57, 164.02, 148.65, 145.66, 135.41, 135.38, 131.84, 129.87, 129.78, 129.61, 128.51, 117.06, 116.71, 116.49, 111.48, 54.58, 47.06, 46.85, 30.53, 23.22; MS: m/z [M+] 333.00; Anal. calcd. for C16H16FN3O2S: C, 57.64; H, 4.84; N, 12.60; Found: C, 57.58; H, 4.89; N, 12.68.

4.3.3 | 5-((4-bromophenyl)sulfonyl)-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo [1,2-a]pyrazine (3c)

Synthesized according to the general procedure-II and isolated using 5:5 mixture of hexane and ethyl acetate for flash chromatography to get amorphous solid; yield 49%; mp 100°C to 101°C; IR (KBr, νmax, cm-1): 3086, 2970, 2875, 1595, 1496, 1336, 1284, 1203, 1165, 1084, 840, 756; 1H NMR (400 MHz, CDCl3): δ 8.017 to 8.007 (d, 1H, J = 4.0 Hz), 7.889 to 7.869 (t, 1H, J = 8.0 Hz), 7.580 to 7.559 (d, 2H, J = 8.4 Hz), 7.475 to 7.454 (d, 2H, J = 8.4 Hz), 6.611 to 6.579 (qt, 1H, J = 5.2, 8.0 Hz), 4.503 to 4.459 (qt, 1H, J = 3.6, 13.6 Hz), 3.587 to 3.428 (m, 2H), 3.008 to 2.934 (m, 1H), 2.670 to 2.609 (qt, 1H, J = 10.8, 13.6 Hz), 2.083 to 1.970 (m, 2H), 1.871 to 1.777 (m, 3H), 1.403 to 1.299 (m, 1H); 13C NMR (100 MHz, CDCl3): δ 148.69, 145.88, 138.37, 132.58, 131.70, 128.58, 128.24, 116.92, 111.51, 54.61, 47.12, 46.84, 30.53, 23.21; MS: m/z [M+] 393.00; Anal. calcd. for C16H16BrN3O2S: C, 48.74; H, 4.09; N, 10.66; Found: C, 48.69; H, 4.18; N, 10.72.

4.3.4 | (mesitylsulfonyl)-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazine (3d)

Synthesized according to the general procedure and isolated using 5:5 mixture of hexane and ethyl acetate for flash chromatography to get amorphous solid; yield 63%; mp 98°C to 99°C; IR (KBr, νmax, cm^{-1}): 3290, 2958, 2874, 1591, 1487, 1342, 1284, 1205, 1161, 1076, 862, 746; 1H NMR (400 MHz, CDCl3): δ 7.972 to 7.957 (dd, 1H, J = 1.2, 4.8 Hz), 6.989 (s, 2H), 6.896 to 6.875 (dd, 1H, J = 0.8, 7.2 Hz), 6.396 to 6.364 (qt, 1H, J = 5.2, 7.6 Hz), 4.421 to 4.378 (dd, 1H, J = 3.6, 13.6 Hz), 3.774 to 3.531 (m, 3H), 2.580 to 2.520 (t, 8H, J = 24.0 Hz), 2.197 to 2.140 (m, 2H), 2.117 to 1.857 (m, 3H), 1.455 to 1.370 (m, 1H); 13C NMR (100 MHz, CDCl3): δ 149.42, 145.22, 143.28, 140.39, 133.33, 132.25, 130.66, 118.24, 110.83, 56.41, 46.88, 45.86, 30.61, 23.48, 22.90, 21.08; MS: m/z [M +] 357.00; Anal. calcd. for C19H23N3O2S: C, 63.84; H, 6.49; N, 11.76; Found: C, 63.91; H, 6.55; N, 11.71.

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CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

DATA AVAILABILITY STATEMENT

Data openly available in a public repository that issues datasets with DOIs The data that support the findings of this study are openly available in "figshare" at https://doi.org/10.6084/m9.figshare.14123582.

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[19] CCDC 1587326 contains the supplementary crystallographic data for compound 2a. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/getstructures.
[20] CCDC 1836511 contains the supplementary crystallographic data for compound 2d. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/getstructures.
[21] CCDC 1587328 contains the supplementary crystallographic data for compound 2h. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/getstructures.

SUPPORTING INFORMATION

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