ISSN: 2249 –4820

Chemistry & Biology Interface, 2011, 1, 2, 251-262

Chemistry & Biology Interface

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Research Article

An efficient synthesis of highly functionalized imidazoles and thiazoles under microwave irradiation

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Received 21 September 2011; Accepted 9 October 2011

Keywords: Imidazoles and Thiazoles, *N*-Boc protection, *N*-Boc deprotection, Microwave irradiation, Silica.

Abstract: A novel and efficient synthesis of highly substituted imidazoles and thiazoles has been described using microwave irradiation. The synthesis involve protection and deprotection of *N*-Boc group using silica under microwave irradiation to regenerate the parent 4-(2-(4-fluorophenyl)*H*-imidazo[1,2-a]pyridin-3-yl)pyridin-2-amine derivatives in high yields. The present procedure has the significance of short reaction time, easy work up process, reusability of silica and excellent yields of products with high chemical purity. All the synthesized molecules were characterized by spectroscopic analysis and chemical purity was checked by UPLC.

Introduction

The key roles imidazole[1,2-a]pyridine participate in cellular processes have made them expensive leads for drug discovery. The major and potential biological activities of heterocycles containing a fused imidazoles and thiazoles e.g. ligands for detecting β-amyloid plaques in the brain, p38 MAP kinase inhibitors, benzodiazepine receptor ligands (Zolpidem), corticotrophin releasing factor receptor ligands,[1] reactivity of the pyridine moiety of the inadequately studied. Several inhibitors of p38 MAP kinase have been confirmed to efficiently reduce cytokine levels in functional assays as well as in animal test.[2,3] Numbers of compounds were derived from the prototypical pyridine-4-yl imidazole and the structural requirements for p38 inhibition have been extensively discussed. Considering the potential utility of imidazoles and thiazoles.[4-6] We have synthesized highly substituted imidazole and thiazole derivatives via novel method of *N*-BOC deprotection of amino group using microwave irradiation.

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Among these, imidazoles and thiazoles bearing pyridine moieties demonstrated to have significant pharmacological properties. For example, zolpidem (**1**) and alpidem (**2**) are prescribed for the treatment of hypnotic (Figure-1). Moreover, pyridine-4-yl imidazole derivatives (**3**) and acetylaminopyridines (**4**) found potent inhibitors of p38MAPK (Figure-1).

These tremendous biological potential of the pyridine bearing imidazole and thiazole scaffolds have attracted many chemist to synthesize these classes of molecules. The classical methods for synthesis of imidazoles and thiazoles involves conventional heating. The existing methods has major drawback of long reaction time, lengthy workup procedure and lower yields. Thus, the synthesis of structurally diverse imidazole and thiazole based small molecules is of great implications in medicinal chemistry.

BOC (tert-butoxycarbonyl) protective group has found very wide use in organic synthesis.[7] The *N*-tert-butyloxycarbonyl protection (Boc) is specifically used in peptide and nucleoside syntheses as well as in heterocyclic chemistry. *N*-Boc deprotection is generally achieved under mild acidic conditions.[8] such as trifluoroacetic acid (TFA), H_2SO_4, pTSA, methanesulfonic acid, aqueous phosphoric acid (H_3PO_4) [9] or with Lewis acids such as $TiCl_4$, $BF_3{\cdot}OEt_2$, TMSI, $SnCl_4$, TMSOTf, $AlCl_3$, $Sn(OTf)_2$, and $ZnBr_2$.[8-10] It can also be carried out with montmorillonite K-10 clay,[11] ceric ammonium nitrate (CAN),[12] $CeCl_3 7H_2O$–NaI system,[13] tetrabutylammonium fluoride (TBAF),[14] and by thermolytic conditions.[15] Recently, ion exchange chromatography was used to expedite purification of libraries of amines or amine derivatives.[16] However, the existing methods suffers from such drawbacks like, lower yield, high reaction temperature, tedious workup process etc. Therefore, a new selective method for its removal is importance. Stafford et al have recently reported a method for the selective removal of one BOC group from *t*-butylimidodicarbonates, and *N*-BOC substituted amides, employing magnesium perchlorate as a Lewis acid.[17] We observed that *N*-BOC protected indoles and hetero condensed pyrroles could be deprotected simply by adsorbing the substrate onto silica gel, followed by gentle heating under reduced pressure.[18] Moreover, the deprotection carried out using TFA and HCl was afforded trifluroacetic acid and hydrochloride salt, respectively. However, in these methods to get free amine, the compound was basified then extract with suitable solvent and evaporated.[19]

To our knowledge, this is the first method for the cleavage of *N*-Boc group from imidazoles and thiazoles using silica under microwave irradiation and without pressure. Thus, we wish to report an efficient and rapid process for the synthesis of novel imidazoles and thiazoles using microwave irradiation for biological interest. The reaction was heterogeneous in nature and afforded pure products without basification.

Materials and Methods

All Melting points of the synthesized compounds were recorded by open capillary method and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV. All the reaction was carried out in Q-pro-M microwave synthesizer. The IR spectra were recorded on a Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on

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Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. ^{1}H NMR was determined in $CDCl_3$/DMSO solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds were carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

Experimental Section

The synthesis of tert-butyl 4-methylpyridin-2-ylcarbamate (**6**) and tert-butyl 4-(1-bromo-2-(4-fluorophenyl)-2-oxoethyl) pyridin-2-ylcarbamate (**8**) was carried out using reported method.[20-21]

Preparation of 1-(4-fluorophenyl)-2-(2-(*N*-Boc amino)pyridin-4-yl)ethanone (7)

A mixture of tert-butyl 4-methylpyridin-2-ylcarbamate (0.1mole) was dissolve in dry THF in to 250ml round bottom flask. *N*-Butyl lithium (0.3mole) was added drop wise to the above flask at -78 °C. Resulting reaction mixture was stirred at room temperature for 35 min. Now the (4-fluorophenyl)(morpholino)methanone (0.1mole) was added drop wise in to the reaction mixture at -78 °C. The reaction mixture was stirred for 2 h at room temperature. After completion of reaction, it was poured in to the ice and extracted with ethyl acetate. The organic layer was separated out and dried with sodium sulphate then organic layer evaporated under vacuum to give yellow oily compound. The compound was purified by Colum chromatography by silica gel 230-400 mash. TLC (EtoAc: Hexane: 2:8). Yield: 61%, IR (KBr) cm^{-1}: 3313 (-NH. str), 1278 (C-N, str), 1148 (C-F), 3150 (Ar, C-H, str), 1515 (Ar, C=C, str), 3107 (-CH_3, str), 1718 (C=O), 1354 (-CH_3, ban). ^{1}H NMR 400 MHz: (DMSO-d6, δ ppm): 1053 (s, 9H, -CH_3), 4.26 (s, 2H, - CH_2), 6.85-8.28 (m, 7H, Ar-H), 9.46 (S, 1H, -NH). ^{13}C NMR 400 MHz: (DMSO-d6, δ ppm):28.3, 45.0, 80.9, 113.4, 115.8, 116.0, 119.2, 131.13, 131.2, 132.6, 132.7, 145.9, 147.4, 152.8, 153.0, 164.6, 167.2, 194.3 Mass: [m/e (%)], M. Wt.: 330 C, H, N analysis, Calculated: C, 65.44; H, 5.80; N, 8.48; Found: C, 65.36; H, 5.89; N, 8.42.

Preparation of tert-butyl-4-(2-(4-fluorophenyl)*H*-imidazo[1,2-a]pyridin-3-yl) pyridin-2-ylcarbamate derivatives (9a-o)

Tert-butyl 4-(1-bromo-2-(4-fluorophenyl)-2-oxoethyl) pyridin-2-ylcarbamate (0.1 mole) were treated with substituted 2-amino pyridine/thiazole (0.1 mole) under microwave irradiation at 200W (100 °C) in DMF. The reaction mixture was poured into ice to give solid compound. TLC (EtoAc: Hexane: 4:6).

Preparation of 4-(2-(4-fluorophenyl)*H*-imidazo[1,2-a]pyridin-3-yl)pyridin-2-amine derivatives (10a-o)

The typical procedure, *N*-BOC-4-(3-(3-fluorophenyl)*H*-imidazo[1,2-a]pyridin-2-yl) pyridin-2-ylcarbamate derivatives (0.1 mole) were treated with acidic silica (0.2 mole) under microwave irradiation 300W (70 °C) in methanol. All the BOC-amine was deprotected in 2.5-5.0 min (Table 2). The reaction was readily monitored by TLC. After completion of reaction, the silica was removed by simple filtration and the solvent was evaporated to dryness to give desired product. The pure 4-(3-(3-fluorophenyl)*H*-imidazo[1,2-a]pyridin-2-yl)pyridin-2-amine derivatives were isolated between 80-90% yield in one step. No additional purification steps were required. The resulting compound was chromatographed with 4:6 Ethyl

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acetate/Hexane containing 1% acetic acid as eluents. The final compounds furthermore conformed by ^{1}H NMR spectra, here *N*-Boc protected amide proton was observed at 8.0-9.0 δ ppm where *N*-Boc deprotected free amine proton was demonstrated at 5.5-6.5 δ ppm.

Results and Discussion

Initially, we have synthesized tert-butyl 4-methylpyridin-2-ylcarbamate **6** through *N*-BOC protection of 4-methylpyridin-2-amine **5** using reported method.[20] Further, the reaction of compound **6** with 4-fluorophenly morpholino methanone in the presence of n-butyllithium and dry THF at -76 °C afforded 1-(4-fluorophenyl)-2-(2-(*N*-Boc amino)pyridin-4-yl)ethanone **7** which on bromination[21] using *N*-bromoscuccinamide gave tert-butyl 4-(1-bromo-2-(4-fluorophenyl)-2-oxoethyl) pyridin-2-ylcarbamate **8**. The reactions were simple, clean and furnish compounds **7** and **8** in high yields.

Indeed, the condensation reaction of compound **8** with 2-amino pyridine and thiourea was observed using methanol as solvent under microwave irradiation. We observed that it requires 15 and 12.5 minutes to complete the reaction and gives the products **9a** and **9k** with 56% and 62% (Table 1, Entries 1 & 2), respectively. When isopropyl alcohol and THF were used as solvent it provides the products with lower yields and required long reaction time (Table 1, Entries 3, 4, 7 & 8). We found that when DMF was used as solvent it gives excellent yields of products **9a** and **9k** with short reaction time 3.0 and 3.5 minutes, respectively (Table 1, Entries 5 & 6). Under this optimized condition all the compounds have been synthesized and results are cited in table 2.

We have been planned to deprotection of amine group using various solvents under microwave irradiation. We observed, when the reaction was carried out in methanol using acidic silica it afforded the compound **10a** in higher yield. With this optimized condition, all the reactions were proceed smoothly and yielded desired products **10a-o** without any trace of starting material after 3.0 to 3.5 min.

Conclusion

We have explored a novel, rapid and efficient methodology for the synthesis of highly functionalized imidazoles and thiazoles using microwave irradiation. This process involves protection and deprotection of amine functionality by BOC. The deprotection of amine group has been carried out using SiO_2 under microwave irradiation with short reaction time and afforded products with high chemical purity. The main advantage of this process is silica gel, which is inexpensive and non-toxic material and reusable after reaction. The process delivers very high yields of the products for biological interest. All the synthesized molecules have more than 95% chemical purity.

Spectral Data

4-(3-(3-fluorophenyl)*H*-imidazo[1,2-a]pyridin-2-yl)pyridin-2-amine (**10a**)

Purity: 95.63, IR (KBr) cm^{-1}: 3355 (-NH, str), 1285 (C-N, str), 1580 (-NH, ban) 1028 (C-F), 3052 (Ar, C-H, str), 1523 (Ar, C=C, str). ^{1}H NMR 400 MHz: (DMSO-d6, δ ppm): 6.12 (s, 2H, -NH_2), 6.63-7.67 (m, 9H, Ar-H), 8.05 (d, 1H, Ar-H), 8.19 (d, 1H, Ar-H). ^{13}C NMR 400 MHz: (DMSO-d6, δ ppm): 109.6, 112.6, 113.0, 114.7, 115.0, 117.0, 123.1, 125.3, 129.4, 129.6, 129.7, 142.5, 144.8, 145.0, 158.3, 114.9; Mass: [m/e (%)], M. Wt.: 304. C, H, N analysis,

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Calculated: C, 71.04; H, 4.31; N, 18.41Found: C, 70.87; H, 4.29; N, 18.10.

4-(2-(3-fluorophenyl)-8-methyl*H*-imidazo[1,2-a]pyridin-3-yl)pyridin-2-amine (10b)

Purity: 95.09, IR (KBr) cm^{-1}: 3331 (-NH. str), 1290 (C-N, str), 1153 (C-F), 3171 (Ar, C-H, str), 1510 (Ar, C=C, str), 3103 (-CH_3, str), 1348 (-CH_3, ban). ^{1}H NMR 400 MHz: (DMSO-d6, δ ppm): 1.72 (s, 3H, -CH_3), 4.61 (s, 2H, -NH_2), 6.7-7.6 (m, 8H, Ar-H), 8.01 (d, 1H, Ar-H, *J*=6.4Hz), 8.27 (d, 1H, Ar-H, *J*=3.2Hz). ^{13}C NMR 400 MHz: (DMSO-d6, δ ppm):20.2 105.4, 107.5, 110.2, 115.9, 123.4, 123.0, 124.2, 128.5, 128.2, 132.4, 132.5, 134.2, 140.1, 143.5, 145.2, 146.0, 159.5, 162.5. Mass: [m/e (%)], M.W.: 318. C, H, N analysis, Calculated: C, 71.68; H, 4.75; N, 17.60Found: C, 70.90; H, 4.62; N, 17.23.

4-(2-(3-fluorophenyl)-7-methyl*H*-imidazo[1,2-a]pyridin-3-yl)pyridin-2-amine (10c)

Purity: 96.84, IR (KBr) cm^{-1}: 3330 (-NH. str), 1296 (C-N, str), 1082 (C-F), 3070 (Ar, C-H, str), 1552 (Ar, C=C, str), 2860 (-CH_3, str), 1378 (-CH_3, ban). ^{1}H NMR 400 MHz: (DMSO-d6, δ ppm): 1.75 (s, 3H, -CH_3), 4.71 (s, 2H, -NH_2), 6.62 (s, 1H, Ar-H) 6.79-7.62 (m, 9H, Ar-H). ^{13}C NMR 400 MHz: (DMSO-d6, δ ppm): 21.5, 105.0, 105.2, 111.3, 117.9, 123.5, 124.7, 124.8, 126.2, 129.3, 131.4, 133.7, 137.3, 141.3, 142.4, 143.5, 146.6, 159.2, 166.5; Mass: [m/e (%)], M. Wt.: 318. C, H, N analysis, Calculated: C, 71.68; H, 4.75; N, 17.60 Found: C, 70.93; H, 4.70; N, 17.20.

4-(2-(3-fluorophenyl)-6-methyl*H*-imidazo[1,2-a]pyridin-3-yl)pyridin-2-amine (10d)

Purity: 97.45, IR (KBr) cm^{-1}: 3312 (-NH. str), 1254 (C-N, str), 1042 (C-F), 3052 (Ar, C-H, str), 1523 (Ar, C=C, str), 2972 (-CH_3, str), 1344 (-CH_3, ban).^{1}H NMR 400 MHz: (DMSO-d6, δ ppm): 1.65 (s, 3H, -CH_3), 4.53 (s, 2H, -NH_2), 6.65 (s, 1H, Ar-H) 6.79-7.62 (m, 9H, Ar-H). ^{13}C NMR 400 MHz: (DMSO-d6, δ ppm): 20.9, 104.7, 106.3, 114.6, 119.4, 123.8, 124.3, 124.7, 125.7, 128.2, 137.6, 137.7, 138.1, 141.5, 143.4, 144.7, 148.5, 159.9, 163.6; Mass: [m/e (%)], M. Wt.: 318. C, H, N analysis, Calculated: C, 71.68; H, 4.75; N, 17.60 Found: C, 71.50; H, 4.66; N, 17.52.

4-(2-(3-fluorophenyl)-5-methyl*H*-imidazo[1,2-a]pyridin-3-yl)pyridin-2-amine (10e)

Purity: 96.14, IR (KBr) cm^{-1}: 3386 (-NH. str), 1296 (C-N, str), 1128 (C-F), 3042 (Ar, C-H, str), 1563 (Ar, C=C, str), 2828 (-CH_3, str), 1372 (-CH_3, ban). ^{1}H NMR 400 MHz: (DMSO-d6, δ ppm): 1.61 (s, 3H, -CH_3), 4.65 (s, 2H, -NH_2), 6.78 (s, 1H, Ar-H) 6.73-7.52 (m, 9H, Ar-H). ^{13}C NMR 400 MHz: (DMSO-d6, δ ppm): 21.5, 107.3, 108.3, 114.3, 117.9, 123.4, 123.7, 126.1, 127.2, 128.8, 132.7, 134.6, 137.9, 141.7, 142.5, 142.9, 145.5, 156.1, 168.3; Mass: [m/e (%)], M. Wt.: 318. C, H, N analysis, Calculated: C, 71.68; H, 4.75; N, 17.60 Found: C, 71.50; H, 4.66; N, 17.52.

4-(7-bromo-2-(3-fluorophenyl)*H*-imidazo[1,2-a]pyridin-3-yl)pyridin-2-amine (10f)

Purity: 99.52, IR (KBr) cm^{-1}: 3392 (-NH. str), 1268 (C-N, str), 1025 (C-F), 3056 (Ar, C-H, str), 1572 (Ar, C=C, str), 534 (C-Br). ^{1}H NMR 400 MHz: (DMSO-d6, δ ppm): 4.62 (s, 2H, -NH_2), 6.53 (s, 1H, Ar-H), 6.6-7.67 (m, 9H, Ar-H), ^{13}C NMR 400 MHz: (DMSO-d6, δ ppm): 104.8, 112.8, 107.5, 112.3, 122.5, 125.4, 126.2, 127.6, 127.9, 129.8, 132.1, 132.5, 134.8, 144.4, 146.7, 148.7, 158.6, 163.8. Mass: [m/e (%)], M. Wt.: 382. C, H, N analysis, Calculated: C, 56.42; H, 3.16; N, 14.62 Found: C, 56.50; H, 3.25; N, 14.51.

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4-(7-chloro-2-(3-fluorophenyl)*H*-imidazo[1,2-a]pyridin-3-yl)pyridin-2-amine (10g)

Purity: 96.38, IR (KBr) cm-1: 3362 (-NH. str), 1242 (C-N, str), 1058 (C-F), 3072 (Ar, C-H, str), 1549 (Ar, C=C, str), 725 (C-Cl). ^{1}H NMR 400 MHz: (DMSO-d6, δ ppm): 4.51 (s, 2H, -NH_2), 6.58 (s, 1H, Ar-H), 6.63-7.71 (m, 9H, Ar-H), ^{13}C NMR 400 MHz: (DMSO-d6, δ ppm): 101.3, 105.8, 115.3, 117.4, 124.2, 124.3, 125.8, 125.8, 126.5, 127.8, 134.6, 136.5, 137.4, 141.4, 142.7, 142.4, 158.3, 162.6. Mass: [m/e (%)], M. Wt.: 338. C, H, N analysis, Calculated: C, 63.82; H, 3.57; N, 16.54Found: C, 63.55; H, 3.51; N, 16.48.

4-(2-(3-fluorophenyl)-7-iodo*H*-imidazo[1,2-a]pyridin-3-yl)pyridin-2-amine (10h)

Purity: 95.77, IR (KBr) cm^{-1}: 3382 (-NH str), 1241 (C-N, str), 1032 (C-F), 3079 (Ar, C-H, str), 1585 (Ar, C=C, str), 492 (C-I). ^{1}H NMR 400 MHz: (DMSO-d6, δ ppm): 4.62 (s, 2H, -NH_2), 6.61 (s, 1H, Ar-H), 6.65-7.69 (m, 9H, Ar-H), ^{13}C NMR 400 MHz: (DMSO-d6, δ ppm): 102.6, 106.7, 107.6, 112.5,116.2, 123.1, 123.0, 124.8, 125.5, 132.5, 135.2, 135.7, 136.9, 147.3, 149.1, 149.7, 162.7, 168.3. Mass: [m/e (%)], M. Wt.: 430. C, H, N analysis, Calculated: C, 50.25; H, 2.81; N, 13.02 Found: C, 50.05; H, 2.62; N, 13.35.

4-(6,8-dichloro-2-(3-fluorophenyl)*H*-imidazo[1,2-a]pyridin-3-yl)pyridin-2-amine (10i)

Purity: 97.55, IR (KBr) cm^{-1}: 3346 (-NH str), 1275 (C-N, str), 1015 (C-F), 3053 (Ar, C-H, str), 1575 (Ar, C=C, str), 742 (C-Cl). ^{1}H NMR 400 MHz: (DMSO-d6, δ ppm): 4.62 (s, 2H, -NH_2), 6.62-7.71 (m, 7H, Ar-H), 7.53 (s, 1H, Ar-H), 8.21 (s, 1H, Ar-H). ^{13}C NMR 400 MHz: (DMSO-d6, δ ppm): 101.8, 107.6, 110.3, 114.2, 123.4, 124.9, 125.6, 126.5, 127.3, 129.8, 132.5, 133.9, 135.2, 138.6, 146.0, 148.9, 162.3, 168.7; Mass: [m/e (%)], M. Wt.: 349. C, H, N analysis, Calculated: C, 57.93; H, 2.97;N, 15.01 Found: C, 58.25; H, 2.29; N, 15.43.

4-(2-(3-fluorophenyl)-6-nitro*H*-imidazo[1,2-a]pyridin-3-yl)pyridin-2-amine (10j)

Purity: 97.61, IR (KBr) cm^{-1}: 3382 (-NH str), 1262 (C-N, str), 1046 (C-F), 3041 (Ar, C-H, str), 1568 (Ar, C=C, str), 1545 (-NO_2). ^{1}H NMR 400 MHz: (DMSO-d6, δ ppm): 4.60 (s, 2H, -NH_2), 6.65-7.75 (m, 7H, Ar-H), 7.72 (s, 1H, Ar-H), 8.96 (s, 1H, Ar-H), ^{13}C NMR 400 MHz: (DMSO-d6, δ ppm): 104.6, 105.6, 114.5, 115.7, 115.7, 121.5, 121.6, 129.4, 130.4, 130.7, 135.8, 143.2, 145.6, 146.7, 147.8, 152.9, 159.7, 162.4. Mass: [m/e (%)], M. Wt.: 349. C, H, N analysis, Calculated: C, 63.82; H, 3.57; N, 16.54Found: C, 63.78; H, 3.29; N, 16.32.

4-(2-amino-4-(3-fluorophenyl)thiazol-5-yl)pyridin-2-amine (10k)

Purity: 96.13, IR (KBr) cm^{-1}: 3356 (-NH. str), 1243 (C-N, str), 1043 (C-F), 3092 (Ar, C-H, str), 1575 (Ar, C=C, str). ^{1}H NMR 400 MHz: (DMSO-d6, δ ppm): 5.9 (s, 2H, -NH2), 7.8 (s, 2H, -NH2), 6.18 (d, 1H, Ar-H, *J*=4.8Hz), 6.2 (s, 1H, Ar-H), 7.1 (t, 2H, Ar-H), 7.4 (t, 2H, Ar-H), 7.3 (d, 1H, Ar-H, *J*=5.2Hz). ^{13}C NMR 400 MHz: (DMSO-d6, δ ppm): 103.4, 104.1, 107.2, 112.3, 114.2, 124.6, 131.9, 137.5, 142.3, 145.6, 151.0, 158.7, 163.2, 172.9; Mass: [m/e (%)], M. Wt.: 286. C, H, N analysis, Calculated: C, 58.73; H, 3.87; N, 19.57; S, 11.20Found: C, 58.63; H, 3.52; N, 19.21; S, 11.10.

4-(4-(3-fluorophenyl)-2-(methylamino)thiazol-5-yl)pyridin-2-amine (10l)

Purity: 96.44, IR (KBr) cm^{-1}: 3330 (-NH. str), 1295 (C-N, str), 1082 (C-F), 3070 (Ar, C-H, str), 1552 (Ar, C=C, str), 2868 (-CH_3,

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str), 1356 (-CH_3, ban). ^{1}H NMR 400 MHz: (DMSO-d6, δ ppm): 2.53 (s, 3H, -CH_3), 5.93 (s, 2H, -NH_2), 6.82 (s, 1H, -NH_2), 6.65-7.23 (m, 6H, Ar-H), 7.92 (s, 1H, Ar-H). ^{13}C NMR 400 MHz: (DMSO-d6, δ ppm): 29.5, 103.0, 104.2, 108.2, 115.2, 115.4, 124.8, 130.8, 134.5, 154.3, 142.5, 146.2, 152.9, 167.2, 168.5, Mass: [m/e (%)], M. Wt.: 300. C, H, N analysis, Calculated: C, 59.98; H, 4.36; N, 18.65; S, 10.68Found: C, 59.88; H, 4.26; N, 18.23; S, 10.47.

4-(2-(diphenylamino)-4-(3-fluorophenyl)thiazol-5-yl)pyridin-2-amine (10m)

Purity: 98.22, IR (KBr) cm^{-1}: 3346 (-NH. str), 1272 (C-N, str), 1016 (C-F), 3076 (Ar, C-H, str), 1582 (Ar, C=C, str). ^{1}H NMR 400 MHz: (DMSO-d6, δ ppm): 4.52 (s, 2H, -NH_2), 6.62-7.68 (m, 16H, Ar-H), 8.01 (s, 1H, Ar-H). ^{13}C NMR 400 MHz: (DMSO-d6, δ ppm): 103.7, 104.2, 107.8, 114.1, 115.2, 117.5, 117.8, 118.5, 119.7, 121.0, 124.5, 126.4, 129.7, 130.7, 134.2, 135.2, 140.2, 141.9, 142.9, 146.9, 148.6, 148.9, 151.4, 158.6, 162.5, 173.0, Mass: [m/e (%)], M. Wt.: 438. C, H, N analysis, Calculated: C, 71.21; H, 4.37; N, 12.78; S, 7.31Found: C, 71.18; H, 4.25; N, 12.92; S, 7.45.

***N*-(5-(2-aminopyridin-4-yl)-4-(3-fluorophenyl)thiazol-2-yl)acetamide (10n)**

Purity: 96.33, IR (KBr) cm^{-1}: 3302 (-NH), 1224 (C-N, str), 1687 (-CONH), 2866 (-CH_3, str), 1361 (-CH_3, ban). ^{1}H NMR 400 MHz: (DMSO-d6, δ ppm): 2.13 (s, 3H, -CH_3), 4.65 (s, 2H, -NH_2), 7.36 (s, 1H, -NH), 6.66-7.26 (m, 6H, Ar-H), 7.96 (s, 1H, Ar-H). ^{13}C NMR 400 MHz: (DMSO-d6, δ ppm): 23.8, 103.0, 105.0, 108.6, 114.2, 115.4, 124.7, 130.8, 135.6, 149.8, 150.7, 152.3, 158.4, 164.5, 167.2, 167.4; Mass: [m/e (%)], M. Wt.: 328. C, H, N analysis, Calculated: C, 58.52; H, 3.99; N, 17.06; O, 4.87; S, 9.77Found: C, 58.31; H, 4.21; N, 17.25; O, 4.95; S, 10.01.

4-(2-hydrazine-4-(3-fluorophenyl)thiazol-5-yl)pyridin-2-amine (10o)

Purity: 97.22, IR (KBr) cm^{-1}: 3375 (-NH. str), 1265 (C-N, str), 1056 (C-F), 3059 (Ar, C-H, str), 1547 (Ar, C=C, str). ^{1}H NMR 400 MHz: (DMSO-d6, δ ppm): 4.60 (s, 2H, -NH_2), 3.50 (s, 2H, -NH_2), 4.02 (s, 1H, -NH), 6.63-7.22 (m, 6H, Ar-H), 7.82 (s, 1H, Ar-H). ^{13}C NMR 400 MHz: (DMSO-d6, δ ppm): 104.6, 107.5, 107.7, 114.2, 116.8, 127.5, 130.5, 132.8, 146.0, 147.6, 153.6, 159.2, 162.4, 173.4; Mass: [m/e (%)], M. Wt.: 301. C, H, N analysis, Calculated: C, 55.80; H, 4.01; N, 23.24; S, 10.64 Found: C, 55.42; H, 3.87; N, 23.95; S, 10.54.

Acknowledgements

The authors are thankful to FIST-DST and SAP-UGC for their generous financial and instrumentation support. Special thanks are due to “National Facility for Drug Discovery through New Chemical Entities (NCE's) Development & Instrumentation Support to Small Manufacturing Pharma Enterprises” Programme under Drug & Pharma Research Support (DPRS) jointly funded by Department of Science & Technology, New Delhi, Government of Gujarat Industries Commissionerate & Saurashtra University, Rajkot.

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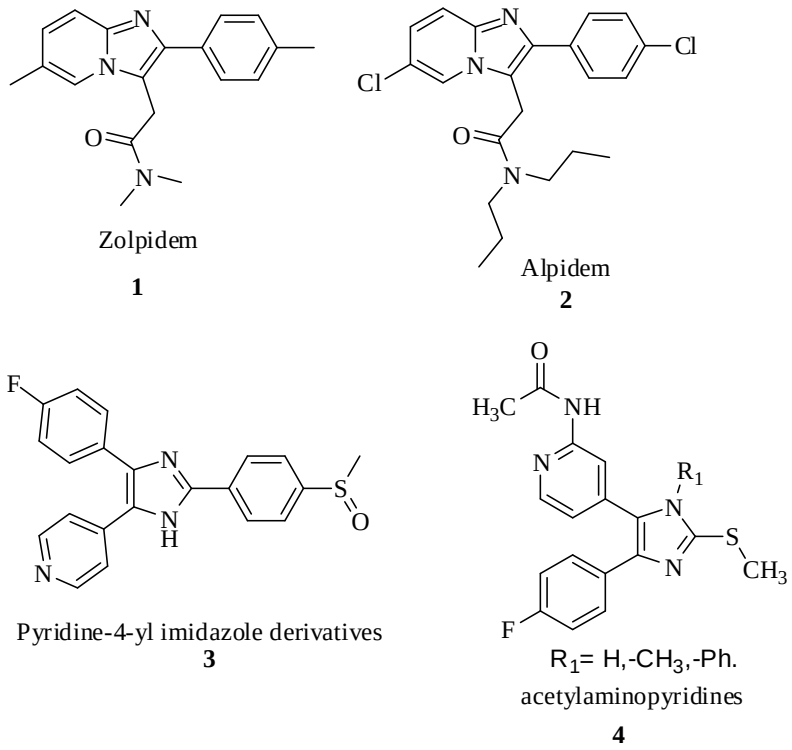

Figure-1 Biologically active imidazoles and thiazoles containing pyridine group (**1-4**).

Table 1. Optimization of the reaction condition for the synthesis of **9a** and **9k**.

Entry	Products	Solvent	Time[a] min	Yields[b] %
1	**9a**	MeOH	15.0	56
2	**9k**	MeOH	12.5	62
3	**9a**	iPA	10.5	67
4	**9k**	iPA	11.0	65
5	**9a**	DMF	3.0	87
6	**9k**	DMF	3.5	81
7	**9a**	THF	6.5	70
8	**9k**	THF	8.0	69

[a]All reactions were conducted at 200W and 100°C temp of the solvent used.
[b]Isolated yields after purification

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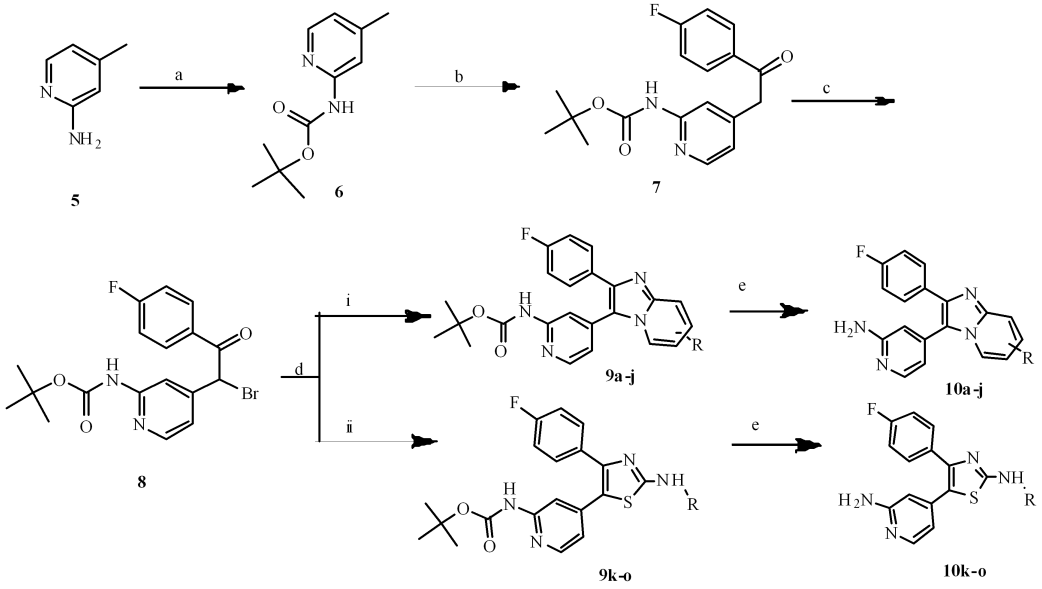
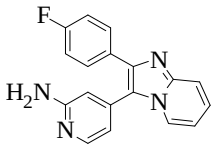
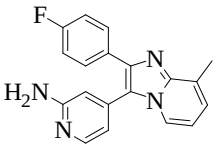
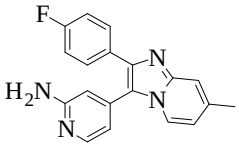
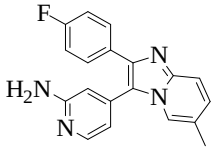


Sechem-1 Synthesis of 4-(2-(4-fluorophenyl)*H*-imidazo[1,2-a]pyridin-3-yl)pyridin-2-amine derivatives. (a) $(Boc)_2O$, t-BuOH, 28 °C, 24 h (b) *N*-butyllithium, dry THF, (4-fluorophenyl) (morpholino)methanone, -76 °C (c) *N*-bromo succinamide, 27 °C, 1 h (d) (i) 2-amino pyridine derivatives, 200 W, 100 °C (ii) thiourea derivatives, DMF, 200 W, 100 °C (e) acidic silica, 300 W, 70 °C.

Table 2. Synthesis of highly substituted novel imidazoles and thiazoles.

Entry	Products	M.F.	M.W.	mp °C	R_f value	Yield%
10a		$C_{18}H_{13}FN_4$	304.11	184-186	0.36	87
10b		$C_{19}H_{15}FN_4$	318.13	156-157	0.39	85
10c		$C_{19}H_{15}FN_4$	318.13	196-198	0.51	85
10d		$C_{19}H_{15}FN_4$	318.13	210-212	0.42	87

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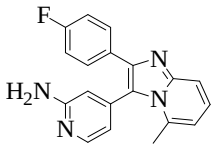
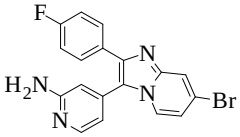
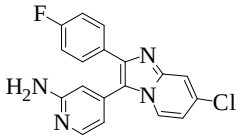
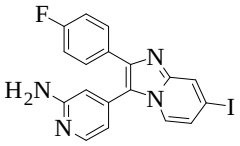
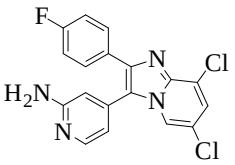
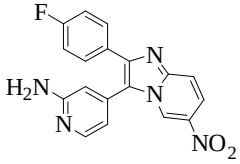
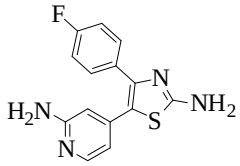
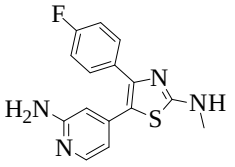
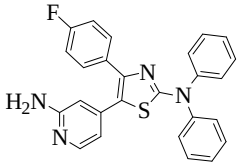
10e		$C_{19}H_{15}FN_4$	318.13	246-248	0.48	76
10f		$C_{18}H_{12}BrFN_4$	382.02	188-190	0.37	88
10g		$C_{18}H_{12}ClFN_4$	338.7	176-178	0.46	88
10h		$C_{18}H_{12}BrFN_4$	349.2	212-214	0.33	85
10i		$C_{18}H_{11}Cl_2FN_4$	373.2	276-278	0.53	87
10j		$C_{18}H_{12}FN_5O_2$	349.32	222-224	0.38	72
10k		$C_{14}H_{11}FN_4S$	286.07	189-191	0.41	87
10l		$C_{15}H_{13}FN_4S$	300.08	256-258	0.50	85
10m		$C_{26}H_{19}FN_4S$	438.5	156-158	0.48	84

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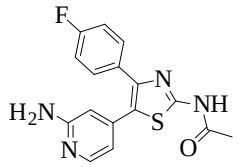
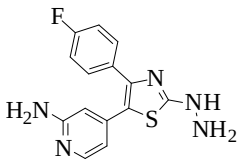
10n		$C_{16}H_{13}FN_4OS$	328.08	179-181	0.36	87
10o		$C_{14}H_{12}FN_5S$	301.08	245-247	0.44	74

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