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Design, Synthesis, Anti-Cancer Activity, and *in silico* Studies of Novel Imidazo[1,2-*a*]pyridine Derivatives

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Abstract—A novel series of imidazo [1,2-*a*]pyridine derivatives has been designed, synthesized and tested for the anti-proliferative activity against three different human cancer cell lines. Most of the synthesized compounds exhibit anti-proliferative activity with IC_{50} values ranging from 5.35–59.8 μM. Six compounds demonstrate efficient inhibition of growth of all cell lines with IC_{50} values close to that of standard drug, and the compound **16h** is more potent than the standard drug cisplatin for the HeLa cell line.

Keywords: synthesis, imidazo[1,2-*a*]pyridine, anticancer activity, molecular docking

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INTRODUCTION

Imidazopyridine derivatives possess a vast variety of biological activities [1] including antifungal, anti-inflammatory, antitumor, and many more [2–5]. Various drugs containing imidazo[1,2-*a*]pyridine scaffold are currently available on the market [6–9].

Urea derivatives have attracted close attention as building blocks in the molecules of anticancer agents due to their significant inhibitory activity against protein tyrosine kinases (PTKs), DNA topoisomerase, Raf kinase, and NADH oxidase, that play a vital role in the cell proliferation [10]. Sorafenib, a diaryl urea derivative has been reported to inhibit several kinases, such as VEGFR (vascular endotheliael growth factor receptor), Raf and platelet derived growth factor receptor [11].

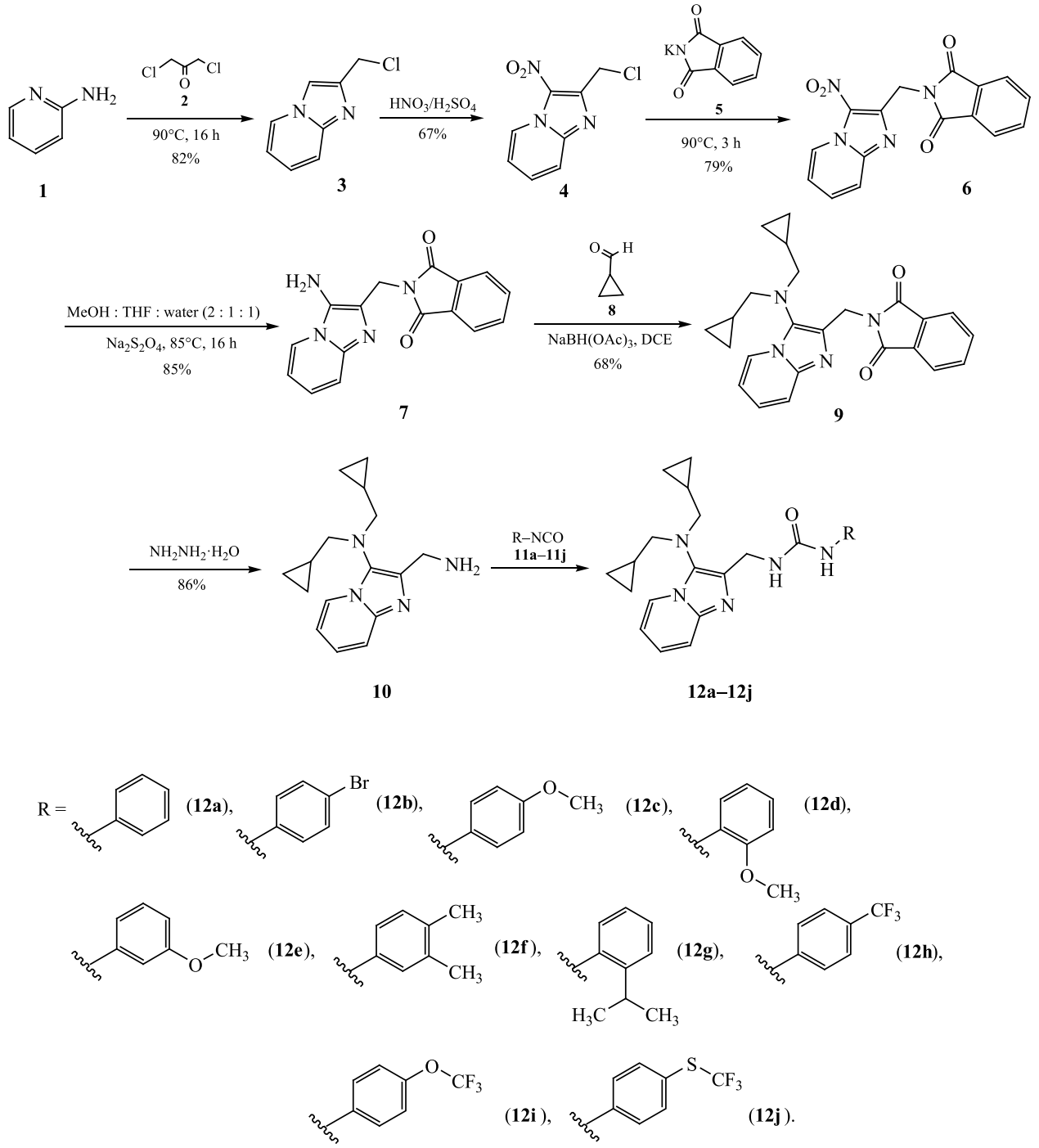
Shuch important chemotherapeutic activities of both pharmacophores (imidazo[1,2-*a*]pyridine and urea moieties) gave an impulse to our design and synthesys of anticancer agents with enhanced potency and/or reduced toxicity.

RESULTS AND DISCUSSION

Synthesis of target molecules was achieved in seven steps, starting with treatment of 2-amino pyridine (**1**) by 1,3-dichloroacetone (**2**) and formation of 2-(chloromethyl)imidazo[1,2-*a*]pyridine (**3**), which upon nitration followed by coupling with potasium pthalimide (**5**) gave 2-[(3-nitroimidazo[1,2-*a*]pyridin-2-yl)methyl]-isoindoline-1,3-dione (**6**). Reduction of the intermediate **6** in presence of $Na_2S_2O_4$ led to the crucial intermediate **7** which was used in reductive amination with compounds **8** and **13** followed by pathalimide deprotection with hydrazine hydrate which gave intermediates **9** and **15,** respectively. Finally, the latter compounds **9** and **15** reacted with aryl isocyanates **11a**–**11j** in presence of TEA with formation of the corresponding target compounds **12a**–**12j** (Scheme 1) and **16a**–**16j** (Scheme 2).

Anticancer activity. *In vitro* anti-proliferative activity of all synthesized compounds **12a**–**12j** and **16a**–**16j** was assessed by the MTT colorimetric assay [12, 13] against MCF-7 (human breast adenocarcinoma) cell line, HeLa (human cervix) cell line and HT-29 (human colorectal adenocarcinoma) cell lines (Table 1) using the anticancer drug cisplatin as a reference. Among the tested compounds, the product **16h** containing 4-CF_3-phenyl ring exhibited potent inhibitory activity against HeLa, MCF-7, and HT-29 cell lines with IC_{50} values of 11.26, 5.35, and 9.30 μM, respectively. Replacement of 4-CF_3-phenyl ring with 4-OCF_3-phenyl ring in **16i** led to decreased anticancer activity, but the activity was still essentially retained. Replacement of 4-OCF_3-phenyl ring with 4-OCH_3-phenyl in **16c** led to further decrease in anticancer activity. Compounds with 4-OCH_3, 2-OCH_3, and 4-OCF_3 substituents (**12c**, **12d** and, **12i**) displayed moderate antiproliferative activity against all three tested cancer cell lines. It is important to note that compound **16h** was more potent than the standard drug cisplatin

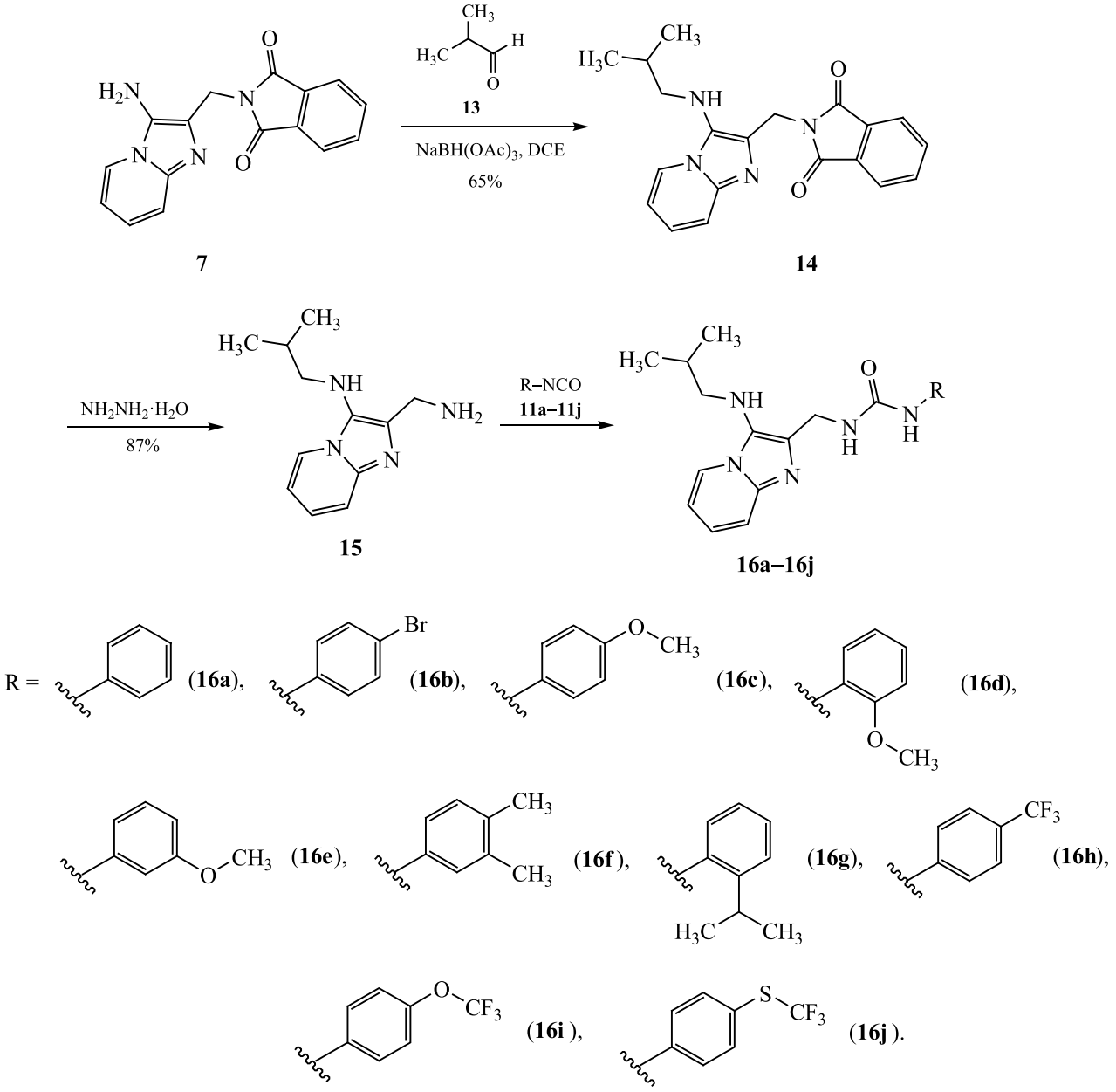
Scheme 1. Synthesis of the title compounds **12a–12j**.



for the HeLa cell line with IC_{50} value of 11.26 μM. The accumulated data, would be a basis of the following SAR studies.

Molecular docking. The possible binding mode of designed compounds in the $PI3K_{\alpha}$ active site was approached by molecular docking studies. Imidazo [1,2-*a*]pyridine derivatives selected from chemexper studies were docked on the active site of $PI3K_{\alpha}$. This provided guidance for selection of derivatives to be synthesized for better $PI3K_{\alpha}$ inhibitors. The selective protein retrieved from the data bank (PDB: 4EPW) was used for this purpose. All docking procedures were carried out by MOE (Molecular Operating Environment) software 2008.10. All synthesized compounds were fit into the

Scheme 2. Synthesis of the title compounds **16a**–**16j**.



active site of PI3K$_\alpha$ enzyme and demonstrated good *in vitro* PI3K$_\alpha$ inhibitory activity, suggesting high potency of the synthesized compounds. The sample docking results are presented in Fig. 1.

EXPERIMENTAL

All chemicals were purchased from Sigma–Aldrich and Combi-blocks and used without further purification. Melting points were uncorrected and determined in one end open capillary tubes using a Guna Digital Melting Point apparatus. Elemental analyses were carried out on a Perkin-Elmer 240 CHN elemental analyzer. ^{1}H and ^{13}C NMR spectra were measured on a Bruker AMX 300 spectrometer operating at 400/300 MHz for ^{1}H and 100 MHz for ^{13}C NMR using TMS as an internal standard. Mass spectra were measured on an Agilent technologies Mass spectrometer.

2-(Chloromethyl)imidazo[1,2-*a*]pyridine (3). A mixture of compounds **1** (30.0 g, 0.319 mol) and **2** (40.19 g, 0.319 mol) in ethanol (160 mL) was refluxed for 16 h, then cooled down to room temperature and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (100–

Table 1. *In vitro* anti-proliferative activity of the synthesized compounds **12a–12j** and **16a–16j**

Compound	IC_{50}, μg/mL			Compound	IC_{50}, μg/mL		
	HeLa	MCF-7	HT-29		HeLa	MCF-7	HT-29
12a	36.25	42.28	59.83	**16a**	32.89	36.56	42.36
12b	25.82	38.26	42.25	**16b**	20.89	25.63	29.25
12c	13.58	7.28	11.57	**16c**	13.68	7.56	11.85
12d	15.23	9.57	14.25	**16d**	14.25	10.89	13.58
12e	16.35	11.69	16.51	**16e**	19.23	15.36	19.34
12f	18.29	22.39	26.85	**16f**	22.52	25.38	29.51
12g	21.68	23.58	18.25	**16g**	25.36	28.36	31.67
12h	18.21	11.34	13.86	**16h**	11.26	5.35	9.30
12i	14.56	10.05	12.25	**16i**	12.82	6.25	13.23
12j	15.22	10.31	12.23	**16j**	29.19	30.26	32.66
				Cisplatin	11.56	4.05	8.07

200 mesh), eluted by EtOAc : hexanes (1 : 1) to afford 2-(chloromethyl)imidazo[1,2-*a*]pyridine (**3**) as a alight brown solid, yield 82%. ^{1}H NMR ($CDCl_3$) spectrum, δ, ppm: 4.77 s (2H, CH_2Cl), 6.79 t (1H, J = 6.6 Hz, H_{Ar}), 7.18 t (1H, J = 7.8 Hz, H_{Ar}), 7.57 d (1H, J = 9.0 Hz, H_{Ar}), 7.61 s (1H, H_{Ar}), 8.07 d (1H, J = 6.9 Hz, H_{Ar}). Found, %: C 57.61; H 4.15; Cl 21.22, N 16.79. $C_8H_7ClN_2$. Calculated, %: C 57.67; H 4.23; Cl 21.28, N 16.81. MS (*m/z*): 167.1 $[M + H]^+$.

2-(Chloromethyl)-3-nitroimidazo[1,2-*a*]pyridine (4). To a solution of compound **3** (40.0 g, 0.240 mol) in H_2SO_4 (100 mL) cooled to 0°C was added fuming HNO_3 (98%) (30.0 mL, 0.72 mol) dropwise over a period of 60 min. The resulting reaction mixture was warmed up to ambient temperature and stirred for another 2 h then poured onto crushed ice (600 mL). The aqueous layer was extracted with dichloromethane (500×2 mL), the combined organic layers were washed with saturated $NaHCO_3$ solution (300 mL), brine (300 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was triturated in MeOH (150 mL), filtered off and dried under vaccum to afford pure product **4** as a yellow solid, yield 67%. ^{1}H NMR ($CDCl_3$) spectrum, δ, ppm: 5.13 s (2H, CH_2Cl), 7.33 t (1H, J = 7.2 Hz, H_{Ar}), 7.69 t

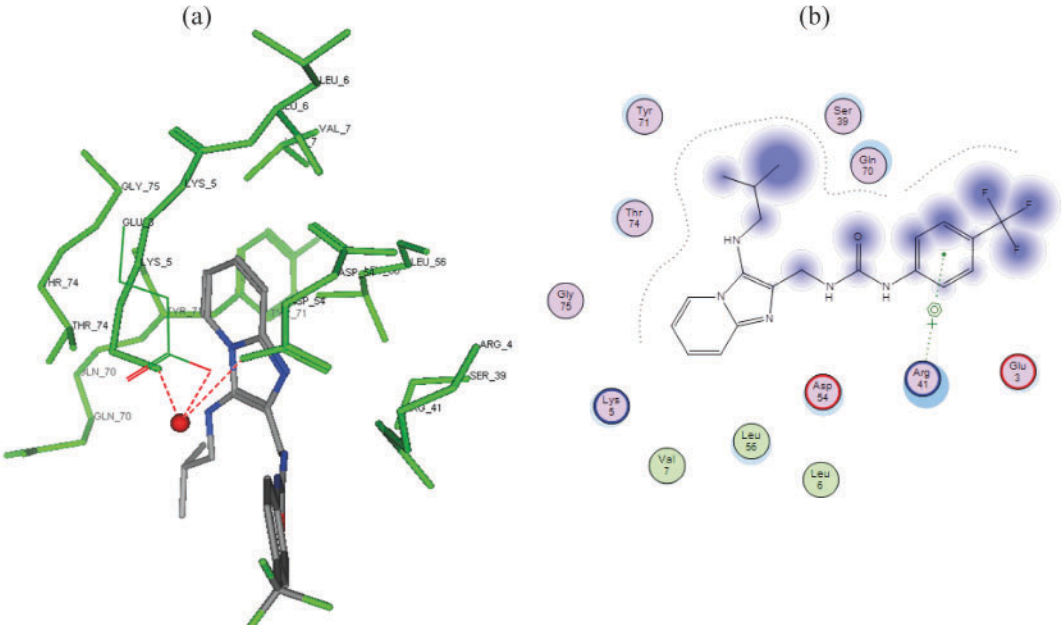


Fig. 1. (a) Three-dimensional representation of the interacting mode of **16h** on PI3K enzyme and (b) two-dimensional representation of the interacting mode of **16h** on PI3K enzyme.

(1H, J = 7.2 Hz, H_{Ar}), 7.87 d (1H, J = 8.7 Hz, H_{Ar}), 9.45 d (1H, J = 7.2 Hz, H_{Ar}). Found, %: C 45.39; H 2.89; Cl 16.79, N 19.79; O 15.06. $C_8H_6ClN_3O_2$. Calculated, %: C 45.41; H 2.86; Cl 16.75, N 19.86; O 15.12. MS (*m/z*): 212.1 $[M + H]^+$.

2-[(3-Nitroimidazo[1,2-*a*]pyridin-2-yl)methyl]-isoindoline-1,3-dione (6). A mixture of compound **4** (19.0 g, 0.09 mol) with potassium 1,3-dioxoisoindolin-2-ide (**5**) (18.3 g, 0.10 mol) in DMF(100 mL) was heated at 90°C for 3 h. The reaction mixture was cooled down to room temperature and diluted with water (800 mL), the resulted solids were filtered off, washed with water (500 mL) and dried under vaccum to afford pure compound **6** as a brown solid, yield 79%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 5.30 s (2H, CH_2N), 7.48 t (1H, J = 6.9 Hz, H_{Ar}), 7.76–7.88 m (2H, H_{Ar}), 7.90–7.99 m (4H, H_{Ar}), 9.39 d (1H, J = 6.9 Hz, H_{Ar}). Found, %: C 59.58; H 3.11; N 17.32; O 19.88. $C_{16}H_{10}N_4O_4$. Calculated, %: C 59.63; H 3.13; N 17.38; O 19.86. MS (*m/z*): 323.1 $[M + H]^+$.

2-[(3-Aminoimidazo[1,2-*a*]pyridin-2-yl)methyl]-isoindoline-1,3-dione (7). A suspension of compound **6** (20.0 g, 0.062 mol) in a mixture of MeOH (200 mL) with THF (100 mL) was charged with a solution of $Na_2S_2O_4$ in water (100 mL) at room temperature and heated to 85°C for 16 h. The reaction mixture was cooled down to room temperature and concentrated under reduced pressure until MeOH and THF were evaporated. The residue was diluted with an excess of water (600 mL), the resulted solids were filtered off, washed with an excess of water and dried under vaccuum to afford pure compound **7** as a brown solid, yield 85%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.88 s (2H, CH_2N), 4.92 s (2H, NH_2), 6.79 t (1H, J = 6.6 Hz, H_{Ar}), 6.97 t (1H, J = 7.2 Hz, H_{Ar}), 7.26 d (1H, J = 9.0 Hz, H_{Ar}), 7.83–7.90 m (4H, H_{Ar}), 8.04 d (1H, J = 6.9 Hz, H_{Ar}). Found, %: C 65.71; H 4.08; N 19.11; O 10.89. $C_{16}H_{12}N_4O_2$. Calculated, %: C 65.75; H 4.14; N 19.17; O 10.95. MS (*m/z*): 293.1 $[M + H]^+$.

2-({3-[Bis(cyclopropylmethyl)amino]imidazo[1,2-*a*]pyridin-2-yl}methyl)isoindoline-1,3-dione (9). A suspension of compounds **7** (5.00 g, 0.0171 mol) and **8** (3.63 g, 0.0376 mol) in DCE (100 mL) was charged with AcOH (1.95 mL, 0.0342 mol) at room temperature and stirred for 1 h. The reaction mixture was cooled to 0°C and $Na(OAc)_3BH$ (10.87 g, 0.0513 mol) was added portion wise. Upon completion of the addition reaction the mixture was warmed up to ambient temperature and stirred for 16 h, then cooled down to 0°C and diluted with saturated $NaHCO_3$ solution (60.0 mL). The aqueous layer was extracted with dichloromethane (300×2 mL), the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography by silica gel (100–200 mesh, MeOH : DCM = 2 : 98) to afford the pure product **9** as yellow solid, yield 68%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.00 br. s (4H, $2CH_2$), 0.27 br. s (4H, $2CH_2$) 0.85 m (2H, 2CH), 3.08 d (4H, J = 6.9 Hz, $2CH_2N$), 4.89 s (2H, CH_2N), 6.85 t (1H, J = 6.9 Hz, H_{Ar}), 7.13 t (1H, J = 6.9 Hz, H_{Ar}), 7.32 d (1H, J = 8.7 Hz, H_{Ar}), 7.85–7.90 m (4H, H_{Ar}), 8.31 d (1H, J = 6.6 Hz, H_{Ar}). Found, %: C 71.91; H 5.96; N 13.05; O 7.88. $C_{24}H_{24}N_4O_2$. Calculated, %: C 71.98; H 6.04; N 13.99; O 7.99. MS (*m/z*): 401.1 $[M + H]^+$.

2-(Aminomethyl)-*N*,*N*-bis(cyclopropylmethyl) imidazo[1,2-*a*]pyridin-3-amine (10). A suspension of compound **9** (4.50 g, 0.012 mol) in ethanol (90 mL) was mixed with hydrazine hydrate (98%) (5.8 mL, 0.12 mol) at room temperature and heated at 90°C for 1 h, then cooled down to room temperature. The solids formed were filtered off, the filtered cake was washed with DCM (50 mL), the combined filtrate was concentrated under reduced pressure to give compound **10** as yellow gel, yield 86%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: –0.10 br. s (4H, $2CH_2$), 0.24 br. s (4H, $2CH_2$), 0.73–0.80 m (2H, 2HC), 2.97 d (4H, J = 6.8 Hz, $2CH_2N$), 3.77 s (2H, CH_2N), 6.82–6.86 m (1H, H_{Ar}), 7.12–7.16 m (1H, H_{Ar}), 7.39 d (1H, J = 9.2 Hz, H_{Ar}), 8.28 d (1H, J = 6.8 Hz, H_{Ar}). Found, %: C 71.11; H 8.26; N 20.59. $C_{16}H_{22}N_4$. Calculated, %: C 71.08; H 8.20; N 20.72. MS (*m/z*): 271.1 $[M + H]^+$.

2-{[3-(Isobutylamino)imidazo[1,2-*a*]pyridin-2-yl]-methyl}isoindoline-1,3-dione (14). A suspension of compound **7** (5.00 g, 0.0171 mol,) with isobutyraldehyde **13** (1.35 g, 0.0188 mol) in DCE (100 mL) was mixed with AcOH (1.95 mL, 0.0342 mol) at room temperature and stirred for 1 h. The reaction mixture was cooled down to 0°C and $Na(OAc)_3BH$ (10.87 g, 0.0513 mol) was added portions wise. Upon completion of addition the reaction mixture was warmed up to ambient temperature and stirred for 16 h, then cooled down to 0°C and diluted with saturated $NaHCO_3$ solution (60.0 mL). The aqueous layer was extracted with dichloromethane (300×2 mL), the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 100–200 mesh, MeOH : DCM = 2 : 98) to afford pure compound **14** as a yellow solid, yield 65%. ^{1}H NMR ($CDCl_3$) spectrum, δ, ppm: 1.11 d (6H, J = 6.6 Hz, $2CH_3$), 1.88–1.97 m (1H, HC), 2.84 t (2H,

J = 6.6 Hz, CH_2NH), 4.20 t (1H, J = 6.6 Hz, NH), 4.99 s (2H, CH_2N), 6.74 t (1H, J = 6.6 Hz, H_{Ar}), 7.06 t (1H, J = 6.9 Hz, H_{Ar}), 7.48 d (1H, J = 10.5 Hz, H_{Ar}), 7.67 q (2H, J = 3.3 Hz, H_{Ar}), 7.82 t (2H, J = 4.8 Hz, H_{Ar}), 7.98 d (d, J = 6.3 Hz, H_{Ar}). Found, %: C 68.91; H 5.68; N 16.11; O 9.11. $C_{20}H_{20}N_4O_2$. Calculated, %: C 68.95; H 5.79; N 16.08; O 9.18. MS (*m/z*): 349.1 $[M + H]^+$.

2-(Aminomethyl)-*N*-isobutylimidazo[1,2-*a*]-pyridin-3-amine (15). A suspension of compound **14** (3.50 g, 0.010 mol) in ethanol (90 mL) was mixed with hydrazine hydrate (98%) (4.8 mL, 0.10 mol) at room temperature and heated at 90°C for 1 h. The reaction mixture was cooled down to room temperature, the precipitated solids were filtered off, the filter cake was washed with DCM (50 mL), the combined filtrate was concentrated under reduced pressure to afford compound **15** as a yellow gel, yield 87%. ^{1}H NMR ($CDCl_3$) spectrum, δ, ppm: 1.10 d (6H, J = 6.6 Hz, $2CH_3$), 1.88–1.97 m (1H, CH), 2.84 t (J = 7.2 Hz, CH_2NH), 3.90 s (2H, CH_2N), 4.20 t (1H, J = 6.6 Hz, NH), 6.82–6.85 m (1H, H_{Ar}), 7.12–7.16 m (1H, H_{Ar}), 7.39 d (1H, J = 6.9 Hz, H_{Ar}), 8.28 d (1H, J = 5.1 Hz, H_{Ar}). Found, %: C 66.11; H 8.52; N 25.11. $C_{12}H_{18}N_4$. Calculated, %: C 66.02; H 8.31; N 25.67. MS (*m/z*): 219.1 $[M + H]^+$.

Synthesis of title compounds 12a–12j and 16a–16j. To an ice cold solution of an appropriate amine (1.00 mmol) in dichloromethane (10 mL) were added TEA (3.00 mmol) and a solution of an aryl isocyanate (1.10 mmol) in dichloromethane (4.0 mL), and the mixture was stirred at room temperature for 2 h, then diluted with water (20 mL) and extracted with dichloromethane (3×20 mL). The organic layer was washed with H_2O (20 mL), brine solution (10 mL), dried over Na_2SO_4, and concentrated. The obtained crude product was purified by flash column chromatography (MeOH : DCM = 2 : 98) to afford the corresponding pure title compounds as off white solids.

1-({3-[Bis(cyclopropylmethyl)amino]imidazo-[1,2-*a*]pyridin-2-yl}methyl)-3-phenylurea (12a). Yield 87%, mp 160–162°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: –0.05 br. s (4H, $2CH_2$), 0.23 br. s (4H, $2CH_2$), 0.75–0.79 m (2H, 2CH), 3.01 d (4H, J = 4.8 Hz, $2CH_2N$), 4.40 d (2H, J = 4.8 Hz, $ArCH_2$), 6.48 br. s (1H, NH), 6.86–6.90 m (2H, H_{Ar}), 7.17–7.24 m (3H, H_{Ar}), 7.36–7.45 m (3H, H_{Ar}), 8.32 d (1H, J = 6.9 Hz, H_{Ar}), 8.69 br. s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 3.0, 10.1, 36.6, 58.6, 111.3, 116.3, 117.4, 120.9,123.5, 123.8, 127.7, 128.6, 137.0, 140.5, 140.6, 155.0. Found, %: C 70.86; H 6.88; N 17.11; O 4.08. $C_{23}H_{27}N_5O$. Calculated, %: C 70.92; H 6.99; N 17.98; O 4.11. MS (*m/z*): 390.2 $[M + H]^+$.

1-({3-[Bis(cyclopropylmethyl)amino]imidazo-[1,2-*a*]pyridin-2-yl}methyl)-3-(4-bromophenyl)urea (12b). Yield 76%, mp 170-172°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: –0.00 br. s (4H, $2CH_2$), 0.28 br. s (4H, $2CH_2$), 0.81–0.83 m (2H, 2CH), 3.07 d (4H, J = 4.8 Hz, $2CH_2N$), 4.46 d (2H, J = 4.8 Hz, $ArCH_2$), 6.59 br. s (1H, NH), 6.94 t (1H, J = 6.6 Hz, H_{Ar}), 7.26 t (1H, J = 7.2 Hz, H_{Ar}), 7.43–7.50 m (5H, H_{Ar}), 8.38 d (1H, J = 6.9 Hz, H_{Ar}), 8.90 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 3.0, 10.1, 36.6, 58.5, 111.3, 112.2, 116.3, 119.3, 123.5, 123.8, 127.7, 131.3, 136.8, 139.9, 140.6, 154. Found, %: C 59.11; H 5.56; Br, 17.01; N 14.88; O 3.39. $C_{23}H_{26}BrN_5O$. Calculated, %: C 58.98; H 5.60; Br, 17.06; N 14.95; O 3.42. MS (*m/z*): 468.1 $[M + 2H]^+$.

1-({3-[Bis(cyclopropylmethyl)amino]imidazo-[1,2-*a*]pyridin-2-yl}methyl)-3-(4-methoxyphenyl)urea (12c). Yield 78%, mp 150–152°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: –0.00 br. s (4H, $2CH_2$), 0.28 br. s (4H, $2CH_2$), 0.77–0.83 m (2H, 2CH), 3.06 d (4H, J = 6.3 Hz, $2CH_2N$), 3.74 s (3H, OCH_3), 4.44 d (2H, J = 4.8 Hz, $ArCH_2$), 6.41 br. s (1H, NH), 6.86 d (2H, J = 8.7 Hz, H_{Ar}), 6.93 t (1H, J = 6.6 Hz, H_{Ar}), 7.25 t (1H, J = 7.2 Hz, H_{Ar}), 7.33 d (2H, J = 8.7 Hz, H_{Ar}), 7.48 d (1H, J = 4.5 Hz, H_{Ar}), 8.37 d (1H, J = 6.9 Hz, H_{Ar}), 8.54 s (1H, NH). ^{13}C NMR ($CDCl_3$) spectrum, δ_C, ppm: 3.4, 10.3, 14.1, 22.7, 29.3, 29.7, 31.9, 37.5, 55.5, 59.6, 111.6, 114.1, 116.4, 121.7, 123.3, 124.5, 129.0, 132.7, 136.9, 141.5, 155.3. Found, %: C 68.79; H 6.93; N 16.58; O 7.58. $C_{24}H_{29}N_5O_2$. Calculated, %: C 68.71; H 6.97; N 16.69; O 7.63. MS (*m/z*): 420.2 $[M + H]^+$.

1-({3-[Bis(cyclopropylmethyl)amino]imidazo-[1,2-*a*]pyridin-2-yl}methyl)-3-(2-methoxyphenyl)urea (12d). Yield 72%, mp 120–122°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: –0.05 br. s (4H, $2CH_2$), 0.22 br. s (4H, $2CH_2$), 0.76–0.79 m (2H, 2CH), 3.01 d (4H, J = 6.4 Hz, $2CH_2N$), 3.81 s (3H, OCH_3), 4.39 d (2H, J = 5.2 Hz, $ArCH_2$), 6.80–6.89 m (3H, H_{Ar}), 6.94 d. d (1H, J_1 = 8.0 Hz, J_2 = 2.4 Hz, H_{Ar}), 7.17–7.21 m (1H, H_{Ar}), 7.25 t (1H, J = 4.8 Hz, NH), 7.42 d (1H, J = 9.2 Hz, H_{Ar}), 8.08 d. d (1H, J_1 = 7.2 Hz, J_2 = 2.0 Hz, H_{Ar}), 8.16 s (1H, NH), 8.33 d (1H, J = 7.2 Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$) spectrum, δ_C, ppm: 3.4, 10.3, 29.7, 37.4, 55.2, 59.7, 109.8, 111.4, 116.6, 118.9, 120.9, 121.3, 123.2, 124.0, 128.9, 129.5, 136.8, 141.5, 147.7, 156.0. Found, %: C 68.76; H 6.91; N 16.56; O 7.56. $C_{24}H_{29}N_5O_2$. Calculated, %: C 68.71; H 6.97; N 16.69; O 7.63. MS (*m/z*): 420.2 $[M + H]^+$.

1-({3-[Bis(cyclopropylmethyl)amino]imidazo-[1,2-*a*]pyridin-2-yl}methyl)-3-(3-methoxyphenyl)urea (12e). Yield 77%, mp 130–132°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: –0.03 br. s (4H, $2CH_2$), 0.24 br. s (4H, $2CH_2$), 0.78–0.82 m (2H, 2CH), 3.03 d (4H, J = 6.4 Hz, $2CH_2N$), 3.82 s (3H, OCH_3), 4.42 d (2H, J = 4.8 Hz, $ArCH_2$), 6.84–6.91 m (3H, H_{Ar}), 6.91–6.97 m (1H, H_{Ar}), 7.19–7.21 m (1H, H_{Ar}), 7.23 t (1H, J = 14.8 Hz, NH), 7.44 d (1H, J = 8.8 Hz, H_{Ar}), 8.10 d. d (1H, J_1 = 7.2 Hz, J_2 = 2.0 Hz, H_{Ar}), 8.18 s (1H, NH), 8.34 d. d (1H, J_1 = 6.8 Hz, J_2 = 1.2 Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$) spectrum, δ_C, ppm: 3.8, 10.7, 37.8, 55.6, 60.1, 110.2, 111.8, 117.0, 119.2, 121.3, 121.6, 123.5, 124.4, 129.3, 129.9,137.1, 141.9, 148.1, 156.4. Found, %: C 68.67; H 6.90; N 16.55; O 7.59. $C_{24}H_{29}N_5O_2$. Calculated, %: C 68.71; H 6.97; N 16.69; O 7.63. MS (*m/z*): 420.2 $[M + H]^+$.

1-({3-[Bis(cyclopropylmethyl)amino]imidazo-[1,2-*a*]pyridin-2-yl}methyl)-3-(3,4-dimethylphenyl)-urea (12f). Yield 79%, mp125–127°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: –0.05 br. s (4H, $2CH_2$), 0.22 br. s (4H, $2CH_2$), 0.75–0.79 m (2H, 2CH), 2.12 s (3H, $ArCH_3$), 2.15 s (3H, $ArCH_3$), 3.01 d (4H, J = 5.6 Hz, $2CH_2N$), 4.39 d (2H, J = 4.8 Hz, $ArCH_2$), 6.41 t (1H, J = 4.8 Hz, NH), 6.88 d. t (1H, J_2 = 6.8 Hz, J_2 = 1.2 Hz, H_{Ar}), 6.96 d (1H, J = 8.0 Hz, H_{Ar}), 7.09–7.13 m (2H, H_{Ar}), 7.18–7.22 m (1H, H_{Ar}), 7.43 d (1H, J = 9.2 Hz, H_{Ar}), 8.32 d (1H, J = 6.8 Hz, H_{Ar}), 8.48 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 3.5, 10.6, 19.0,20.1, 37.1, 59.1, 111.8, 115.6, 116.8, 119.4, 124.0,124.3, 128.2, 128.9, 130.0, 136.5, 137.6, 138.7, 141.1, 155.5. Found, %: C 71.83; H 7.42, N 16.68; O 3.81. $C_{25}H_{31}N_5O$. Calculated, %: C 71.91; H 7.48; N 16.77; O 3.83. MS (*m/z*): 418.3 $[M + H]^+$.

1-({3-[Bis(cyclopropylmethyl)amino]imidazo-[1,2-*a*]pyridin-2-yl}methyl)-3-(2-isopropylphenyl)-urea (12g). Yield 72%, mp 90–92°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: –0.06 br. s (4H, $2CH_2$), 0.21 br. s (4H, $2CH_2$), 0.75–0.78 m (2H, 2CH), 1.13 d (6H, J = 6.8 Hz, $2CH_3$), 3.00 br. s (4H, $2CH_2N$), 3.07–3.13 m (1H, ArCH), 4.41 d (2H, J = 4.8 Hz, $ArCH_2$), 6.86–6.90 m (2H, H_{Ar}), 6.96 t (1H, J = 7.6 Hz, NH), 7.07 t (1H, J = 7.2 Hz, H_{Ar}), 7.18–7.22 m (2H, H_{Ar}), 7.43 d (1H, J = 8.8 Hz, H_{Ar}), 7.67 d (1H, J = 8.0 Hz, H_{Ar}), 7.88 s (1H, NH), 8.33 d (1H, J = 6.8 Hz, H_{Ar}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 3.0, 10.1, 23.1, 26.5, 36.8, 58.7, 111.3, 116.3, 122.6, 122.8, 123.5, 123.8, 124.9, 125.5, 127.8, 136.4, 137.1, 138.2, 140.6, 155.5. Found, %: C 72.28; H 7.76; N 15.63; O 3.68. $C_{26}H_{33}N_5O$. Calculated, %: C 72.36; H 7.71; N 16.23; O 3.71. MS (*m/z*): 432.3 $[M + H]^+$.

1-({3-[Bis(cyclopropylmethyl)amino]imidazo-[1,2-*a*]pyridin-2-yl}methyl)-3-[4-(trifluoromethyl)-phenyl]urea (12h). Yield 78%, mp 160–162°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: –0.01 br. s (4H, $2CH_2$), 0.27 br. s (4H, $2CH_2$), 0.81–0.84 m (2H, 2CH), 3.05 d (4H, J = 6.0 Hz, $2CH_2N$), 4.46 d (2H, J = 4.5 Hz, $ArCH_2$), 6.70 br. s (1H, NH), 6.93 t (1H, J = 6.6 Hz, H_{Ar}), 7.25 t (1H, J = 6.9 Hz, H_{Ar}), 7.48 d (1H, J = 9.0 Hz, H_{Ar}), 7.59 br. s (4H, H_{Ar}), 8.36 d (1H, J = 6.6 Hz, H_{Ar}), 9.15 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 3.8, 10.9, 37.4, 59.3, 112.1,113.6, 117.1, 118.9, 124.3, 124.7, 128.5, 128.9, 131.9, 137.5, 138.2, 141.4, 144.5, 155.4. Found, %: C 62.98; H 5.69; F 12.40; N 15.29; O 3.48. $C_{24}H_{26}F_3N_5O$. Calculated, %: C 63.01; H 5.73; F 12.46; N 15.31; O 3.5. MS (*m/z*): 458.2 $[M + H]^+$.

1-({3-[Bis(cyclopropylmethyl)amino]imidazo-[1,2-*a*]pyridin-2-yl}methyl)-3-[4-(trifluoromethoxy)-phenyl]urea (12i). Yield 82%, mp 140–142°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: –0.05 br. s (4H, $2CH_2$), 0.22 br. s (4H, $2CH_2$), 0.75–0.79 m (2H, 2CH), 3.01 d (4H, J = 5.6 Hz, $2CH_2N$), 4.41 d (2H, J = 4.8 Hz, $ArCH_2$), 6.55 t (1H, J = 4.8 Hz, NH), 6.87–6.91 m (1H, H_{Ar}), 7.18–7.23 m (3H, H_{Ar}), 7.43–7.50 m (3H, H_{Ar}), 8.33 d (J = 6.8 Hz, H_{Ar}), 8.92 s (1H, NH). ^{13}C NMR ($CDCl_3$) spectrum, δ_C, ppm: 3.3, 10.3, 37.1, 59.5, 111.9, 116.0, 116.7, 119.2, 121.4, 121.8, 123.4, 124.3, 124.9, 129.1, 137.1, 138.8, 141.6, 143.4, 156.4. Found, %: C 60.82; H 5.48; F 12.09; N 14.82; O 6.73. $C_{24}H_{26}F_3N_5O_2$. Calculated, %: C 60.88; H 5.53; F 12.04; N 14.79; O 6.76. MS (*m/z*): 474.2 $[M + H]^+$.

1-({3-[Bis(cyclopropylmethyl)amino]imidazo-[1,2-*a*]pyridin-2-yl}methyl)-3-{4-[(trifluoromethyl)-thio]phenyl}urea (12j). Yield 80%, mp 120–122°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: –0.23 br. s (4H, $2CH_2$), 0.00 br. s (4H, $2CH_2$), 0.53–0.57 m (2H, 2CH), 2.78 d (4H, J = 5.6 Hz, $2CH_2N$), 4.21 d (2H, J = 4.8 Hz, $ArCH_2$), 6.46 t (1H, J = 4.8 Hz, NH), 6.66 d. t (1H, J_1 = 6.8 Hz, J_2 = 0.8 Hz, H_{Ar}), 6.98 d. t (1H, J_1 = 6.4 Hz, J_2 = 0.8 Hz, H_{Ar}), 7.22 d (1H, J = 9.2 Hz, H_{Ar}), 7.35 d (4H, J = 8.8 Hz, H_{Ar}), 8.10 d (1H, J = 6.8 Hz, H_{Ar}), 8.91 s (NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 3.0, 10.1, 36.6, 58.5, 111.3, 112.8, 116.3, 118.1, 123.5, 123.9, 127.7, 128.1, 131.15, 136.7, 137.4, 140.6, 143.7, 154.8. Found, %: C 58.76; H 5.31; F 11.61; N 14.34; O 3.25; S 6.47. $C_{24}H_{26}F_3N_5OS$. Calculated, %: C 58.88; H 5.35; F 11.64; N 14.31; O 3.27; S 6.55. MS (*m/z*): 490.2 $[M + H]^+$.

1-{[3-(Isobutylamino)imidazo[1,2-*a*]pyridin-2-yl]methyl}-3-phenylurea (16a). Yield 82%, mp 160–162°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.97 d (6H, J = 6.8 Hz, $2CH_3$), 1.68–1.78 m (1H, CH), 2.75 t (2H, J = 6.8 Hz, CH_2N), 4.38 d (2H, J = 5.2 Hz, $ArCH_2$),), 4.77 t (1H, J = 6.8 Hz, NH), 6.54 t (1H, J = 4.8 Hz, NH), 6.86–6.90 m (2H, H_{Ar}), 7.12–7.14 m (1H, Ar), 7.16–7.22 m (2H, H_{Ar}), 7.24–7.42 m (3H, H_{Ar}), 8.13 d (1H, J = 6.8 Hz, H_{Ar}), 8.65 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ C ppm: 20.3, 28.7, 36.3, 55.8, 111.3, 116.5, 117.5, 121.0, 122.7, 122.9, 127.5, 128.6, 133.0, 139.8, 140.4, 155.3. Found, %: C 67.54; H 6.77; N 20.71; O 4.66. $C_{19}H_{23}N_5O$. Calculated, %: C 67.63; H 6.87; N 20.76; O 4.74. MS (*m/z*): 338.2 $[M + H]^+$.

1-(4-Bromophenyl)-3-{[3-(isobutylamino)imidazo-[1,2-*a*]pyridin-2-yl]methyl}urea (16b). Yield 74%, mp 155–157°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.94 d (6H, J = 6.4 Hz, $2CH_3$), 1.65–1.75 m (1H, CH), 2.72 t (2H, J = 6.8 Hz, CH_2N), 4.32 d (2H, J = 5.2 Hz, $ArCH_2$), 4.74 t (1H, J = 6.8 Hz, NH), 6.38 t (1H, J = 5.2 Hz, NH), 6.77–6.86 m (3H, H_{Ar}), 7.08–7.12 m (1H, H_{Ar}), 7.24 t (2H, J = 8.8 Hz, H_{Ar}), 7.37 d (1H, J = 9.2 Hz, H_{Ar}), 8.09 d (1H, J = 6.8 Hz, H_{Ar}), 8.41 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.7, 30.2, 37.8, 57.2, 112.7, 115.3, 118.0, 120.7, 124.2, 124.3, 128.9, 134.7, 135.0, 141.2, 155.3, 157.0. Found, %: C 54.78; H 5.25; Br 19.11; N 16.85; O 3.79. $C_{19}H_{22}BrN_5O$. Calculated, %: C 54.82; H 5.33; Br 19.19; N 16.82; O 3.84.

1-{[3-(Isobutylamino)imidazo[1,2-*a*]pyridin-2-yl]-methyl}-3-(4-methoxyphenyl)urea (16c). Yield 75%, mp 115–117°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.97 d (6H, J = 6.8 Hz, $2CH_3$), 1.70–1.77 m (1H, CH), 2.75 t (2H, J = 6.8 Hz, CH_2N), 3.70 s (3H, $ArCH_3$), 4.37 d (2H, J = 5.2 Hz, $ArCH_2$), 4.79 t (1H, J = 6.8 Hz, NH), 6.44 t (1H, J = 5.2 Hz, NH), 6.46–6.89 m (3H, H_{Ar}), 7.11–7.16 m (1H, H_{Ar}), 7.29 d (2H, J = 9.2 Hz, H_{Ar}), 7.41 d (1H, J = 8.8 Hz, H_{Ar}), 8.12 d (1H, J = 6.8 Hz, H_{Ar}), 8.47 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 20.3, 28.7, 36.3, 55.1, 55.8, 111.3, 113.8, 116.5, 119.2, 122.7, 122.8, 127.5, 133.2, 133.5, 139.8, 153.9, 155.5. Found, %: C 65.31; H 6.83; N 19.15; O 8.64. $C_{20}H_{25}N_5O_2$. Calculated, %: C 65.37; H 6.86; N 19.06; O 8.71. MS (*m/z*): 368.2 $[M + H]^+$.

1-{[3-(Isobutylamino)imidazo[1,2-*a*]pyridin-2-yl]-methyl}-3-(2-methoxyphenyl)urea (16d). Yield 69%, mp 180–182°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.97 d (6H, J = 6.6 Hz, $2CH_3$), 1.67–1.80 m (1H, CH), 2.75 t (2H, J = 6.6 Hz, CH_2N), 3.79 s (3H, $ArCH_3$), 4.35 d (2H, J = 5.1 Hz, $ArCH_2$), 4.74 t (1H, J = 6.6 Hz, NH), 6.83–6.95 m (4H, H_{Ar}), 7.13 t (1H, J = 6.6 Hz, NH), 7.27 t (1H, J = 5.1 Hz, H_{Ar}), 7.40 d (1H, J = 9.0 Hz, H_{Ar}), 8.06–8.12 m (3H, H_{Ar}). ^{13}C NMR spectrum (DMSO-d_6), δ_C ppm: 20.3, 28.7, 36.2, 55.6, 55.8, 110.5, 111.2, 116.5, 118.1, 120.4, 120.9, 122.7, 122.8, 127.6, 129.4, 133.2, 139.8, 147.3, 155.3. Found, %: C 65.33; H 6.82; N 19.03; O 8.62. $C_{20}H_{25}N_5O_2$. Calculated, %: C 65.37; H 6.86; N 19.06; O 8.71. MS (*m/z*): 368.2 $[M + H]^+$.

1-{[3-(Isobutylamino)imidazo[1,2-*a*]pyridin-2-yl]-methyl}-3-(3-methoxyphenyl)urea (16e). Yield 72%, mp 150–152°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.97 d (6H, J = 6.8 Hz, $2CH_3$), 1.68–1.77 m (1H, CH), 2.75 t (2H, J = 6.6 Hz, CH_2N), 3.70 s (3H, $ArCH_3$), 4.37 d (2H, J = 4.8 Hz, $ArCH_2$), 4.77 t (1H, J = 6.4 Hz, NH), 6.46–6.53 m (2H, H_{Ar}), 6.84–6.89 m (2H, Ar), 7.09–7.15 m (3H, H_{Ar}), 7.41 d (1H, J = 8.8 Hz, H_{Ar}), 8.13 d (1H, J = 6.8 Hz, H_{Ar}), 8.67 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 20.3, 28.7, 36.3, 54.8, 55.8, 103.4, 106.3, 109.9, 111.3, 116.5, 122.7, 122.9, 127.4, 129.3, 133.0, 139.8, 141.6, 155.2, 159.6. Found, %: C 65.31; H 6.80; N 19.11; O 8.58. $C_{20}H_{25}N_5O_2$. Calculated, %: C 65.37; H 6.86; N 19.06; O 8.71. MS (*m/z*): 368.2 $[M + H]^+$.

1-(3,4-Dimethylphenyl)-3-{[3-(isobutylamino)-imidazo[1,2-*a*]pyridin-2-yl]methyl}urea (16f). Yield 76%, mp 155–157°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.97 d (6H, J = 6.8 Hz, $2CH_3$), 1.67–1.77 m (1H, CH), 2.12 s (3H, $ArCH_3$), 2.15 s (3H, $ArCH_3$), 2.75 t (2H, J = 6.8 Hz, CH_2N), 4.35 d (2H, J = 5.2 Hz, $ArCH_2$), 4.76 t (1H, J = 6.8 Hz, NH), 6.45 t (1H, J = 5.2 Hz, NH), 6.87 d. t (1H, J_1 = 6.4 Hz, J_2 = 0.8 Hz, H_{Ar}), 6.96 d (1H, J = 7.6 Hz, H_{Ar}), 7.10–7.16 m (3H, H_{Ar}), 7.41 d (1H, J = 8.8 Hz, H_{Ar}), 8.12 d (1H, J = 6.8 Hz, H_{Ar}), 8.43 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 18.6, 19.6, 20.3, 28.7, 36.3, 55.8, 111.3, 115.1, 116.5, 118.9, 122.7, 122.9, 127.4, 128.5, 129.5, 133.1, 136.0, 138.1, 139.7, 155.3. Found, %: C 69.10; H 7.41; N 19.22; O 4.35. $C_{21}H_{27}N_5O$. Calculated, %: C 69.01; H 7.45; N 19.16; O 4.38. MS (*m/z*): 366.1 $[M + H]^+$.

1-{[3-(Isobutylamino)imidazo[1,2-*a*]pyridin-2-yl]-methyl}-3-(2-isopropylphenyl)urea (16g). Yield 74%, mp 125–127°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.97 d (6H, J = 6.8 Hz, $2CH_3$), 1.13 d (6H, J = 6.8 Hz, $2CH_3$), 1.67–1.77 m (1H, CH), 2.75 t (2H, J = 6.4 Hz, CH_2N), 3.06–3.13 m (1H, ArCH), 4.37 d (2H, J = 4.8 Hz, $ArCH_2$), 4.79 t (1H, J = 6.4 Hz, NH), 6.87–7.00 m (3H, H_{Ar}), 7.06–7.22 m (3H, H_{Ar}), 7.41 d (1H, J = 8.8 Hz, H_{Ar}), 7.86 s (1H, NH), 8.14 d (1H, J = 6.8 Hz, H_{Ar}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 20.3, 23.0, 26.5,

55.8, 28.7, 36.4, 111.3, 122.6, 122.8, 122.9, 125.0, 125.5, 127.5, 133.0, 136.3, 138.3, 139.8, 155.8. Found, %: C 69.58; H 7.66; N 18.52; O 4.25. $C_{22}H_{29}N_5O$. Calculated, %: C 69.63; H 7.70; N 18.45; O 4.22. MS (*m/z*): 380.2 $[M + H]^+$.

1-{[3-(Isobutylamino)imidazo[1,2-*a*]pyridin-2-yl]methyl}-3-[4-(trifluoromethyl)phenyl]urea (16h). Yield 78%, mp 190–192°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.98 d (6H, J = 6.8 Hz, $2CH_3$), 1.68–1.77 m (1H, CH), 2.76 t (2H, J = 6.4 Hz, CH_2N), 4.42 d (2H, J = 5.2 Hz, $ArCH_2$), 4.77 t (1H, J = 6.8 Hz, NH), 6.72 t (1H, J = 5.2 Hz, NH), 6.89 d. t (1H, J_1 = 6.8 Hz, J_2 = 0.8 Hz, H_{Ar}), 7.13–7.17 m (1H, H_{Ar}), 7.43 d (1H, J = 8.8 Hz, H_{Ar}), 7.59 q (4H, J = 9.2 Hz, H_{Ar}), 8.14 d (1H, J = 6.8 Hz, H_{Ar}), 9.12 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 20.3, 28.7, 36.3, 55.8, 111.3, 117.1, 122.7, 122.9, 126.0, 127.4, 132.7, 139.8, 144.1, 154.8. Found, %: C 59.33; H 5.42; F 14.01; N 17.19; O 3.90. $C_{20}H_{22}F_3N_5O$. Calculated, %: C 59.25; H 5.47; F 14.06; N 17.27; O 3.95. MS (*m/z*): 406.2 $[M + H]^+$.

1-{[3-(Isobutylamino)imidazo[1,2-*a*]pyridin-2-yl]methyl}-3-[4-(trifluoromethoxy)phenyl]urea (16i). Yield 82%, mp 110–112°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.97 d (6H, J = 6.6 Hz, $2CH_3$), 1.66–1.79 m (1H, CH), 2.75 t, (2H, J = 6.6 Hz, CH_2N), 4.38 d (2H, J = 4.8 Hz, $ArCH_2$), 4.75 t (1H, J = 6.3 Hz, NH), 6.58 t (1H, J = 5.1 Hz, NH), 6.88 t (1H, J = 6.6 Hz, H_{Ar}), 7.14 t (1H, J = 6.6 Hz, H_{Ar}), 7.22 d (2H, J = 8.4 Hz, H_{Ar}), 7.41 d (1H, J = 9.0 Hz, H_{Ar}), 7.48 d (2H, J = 9.0 Hz, H_{Ar}), 8.12 d (1H, J = 6.6 Hz, H_{Ar}), 8.87 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 20.3, 28.7, 36.3, 55.8, 111.3, 116.5, 118.5, 118.9, 121.4, 121.6, 122.7, 122.9, 127.4, 132.8, 139.7, 139.8, 141.9, 155.1. Found, %: C 57.21; H 5.21; F 13.48; N 16.66; O 7.51. $C_{20}H_{22}F_3N_5O_2$. Calculated, %: C 57.00; H 5.26; F 13.52; N 16.62; O 7.59. MS (*m/z*): 422.1 $[M + H]^+$.

1-{[3-(Isobutylamino)imidazo[1,2-*a*]pyridin-2-yl]-methyl}-3-{4-[(trifluoromethyl)thio]phenyl}urea (16j). Yield 80%, mp 155–157°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.97 d (6H, J = 6.6 Hz, $2CH_3$), 1.68–1.77 m (1H, CH), 2.75 t (2H, J = 6.6 Hz, CH_2N), 4.39 d (2H, J = 4.8 Hz, $ArCH_2$), 4.75 t (1H, J = 6.3 Hz, NH), 6.69 t (1H, J = 4.8 Hz, NH), 6.89 t (1H, J = 6.9 Hz, NH), 7.16 t (1H, J = 6.9 Hz, H_{Ar}), 7.42 d (1H, J = 9.0 Hz, H_{Ar}), 7.55 t (4H, J = 9.3 Hz, H_{Ar}), 8.14 d (1H, J = 6.6 Hz, H_{Ar}), 9.08 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 20.3, 28.7, 36.3, 55.7, 111.4, 112.9, 116.4, 118.2, 122.8, 123.1, 127.5, 128.0, 131.1, 132.6, 137.4, 139.8, 143.6, 154.8. Found, %: C 54.82; H 5.01; F 13.13; N 16.06; O 3.69; S 7.28. $C_{20}H_{22}F_3N_5OS$. Calculated, %: C 54.91; H 5.07; F 13.03; N 16.01; O 3.66; S 7.33. MS (*m/z*): 438.1 $[M + H]^+$.

In vitro evaluation of anticancer activity. The MCF-**7** (human breast adenocarcinoma) cell line, HeLa (human cervix) cell line and HT-29 (human colorectal adenocarcinoma) cell lines were purchased from NCCS, Pune. The procedure was carried out according to the well documented method [12, 13]. The percentage growth inhibition was calculated and concentration of test drugs needed to inhibit cell growth by 50% was generated from the dose-response curves for each cell line using with origin software.

Molecular docking. Docking was performed on Windows 2002 using MOE 2008.10 version. Phosphoinositide 3-kinasewas retrieved from the protein data bank (PDB code: 4EPW) and the enzyme was visualized using sequence option and further co-factors were deleted. The partial charge of protein was adjusted with the help of force field method AMBER 99. Later, the protein was subjected to 3D protonation at cut off 12.0, and further hydrogen was added according to standard geometry and the receptor energy was minimized using force field MMFF94x at 0.01 kJ/mol gradients. The ligand structures were generated according to the routine procedure. Docking was performed using the option simulation followed by docking on selected active site amino acids using sequence option, and eventually docked using setting options such as receptor and solvent, alpha triangle, selected residues, affinity dG, force field refinement, and best 30 poses. The resulting best pose score values in the series were used for analysis of docking and interactions.

CONCLUSIONS

We report the synthesis of novel imidazo[1,2-*a*]-pyridine derivatives starting from commercially available 2-aminopyridine and 1,3-dichloroacetone. All the newly synthesized compounds have been characterized by ^{1}H and ^{13}C NMR and MS spectra and evaluated for in vitro anticancer activity against three human cancer cell lines HeLa, MCF-7, and HT29. The compounds **12c**, **12d, 12i**, **16c**, **16h**, and **16i** demonstrate moderate to high anti-proliferative activity against all tested cell lines. The compound **16h** is determined to be more potent than the standard drug cisplatin for the HeLa cell line.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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