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# Synthesis and antitumor activity of novel *N*-(8-(3-ureidophenyl)imidazo [1,2-*a*]pyridin-6-yl)acetamide derivatives

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A series of *N*-(8-(3-ureidophenyl)imidazo[1,2-*a*]pyridin-6-yl)acetamide derivatives have been synthesized and evaluated for antitumor activity against SMMC7721 cells and HCT116 cells *in vitro* in order to initially screen out their biological properties and to reveal the role of 8-substituted urea phenyl imidazo[1,2-a]pyridine fragment in the ability of compounds to antitumor activity. The antitumor activity test has shown that most compounds exhibit excellent anticancer activity against SMMC7721 cells and HCT116 cells. The experimental results have proved that *N*-(8-(3-ureidophenyl)imidazo[1,2-*a*]pyridin-6-yl)acetamide derivatives containing imidazo[1,2-*a*]pyridine and urea are promising for further in-depth study of antitumor properties.

**Keywords**: Imidazo[1,2-a]pyridine, Urea, Antitumor activity

Fused imidazo[1,2-*a*]pyridine attracted chemists due to their potential biological and pharmacological activity. Therefore, imidazo[1,2-*a*]pyridine is recognized as a "drug prejudice" scaffold in drug design[1]. According to relevant literature reports in recent years, imidazo[1,2-*a*]pyridine derivatives have become one of the hotspots in the current chemical industry due to their remarkable biological activity, which include anti-inammatory[2,3], antiviral[4-6], antiulcer[7,8], antifungal[9], anticancer[10], and anxiolytic[11] properties. Drugs containing imidazo[1,2-a]pyridine skeleton (Fig. 1) such as Soraprazan[12], Zolimidine[13], Olprinone[14], Alpidem[15], Zolpidem[16], Saripidem[17], demonstrate the wide treatment areas in this type of drug skeletons. Various imidazo[1,2-*a*]pyridine derivatives have been used as lead drug molecules which are currently in human clinical trials. Therefore, synthesis of compounds containing imidazo[1,2-*a*]pyridine is of great value to the development of medicine.

Urea and its derivatives (Fig. 2) play a significant role in pharmaceuticals and drug design due to the capability of the urea functionality to form multiple stable hydrogen bonds with protein and receptor targets[18]. It is the significant biological activity of a large number of urea derivatives that have been used in a wide range of medical applications, such as anti-HIV, anticancer, antidiabetic agents, anticonvulsive, antibacterial, anti-tuberculosis, and other medicinal compounds[19-25]. For example, Sorafenib (Fig. 2) as urea derivatives is a multikinase inhibitor[26] which has become an anti-tumor drug. Lisuride[27] has considerable value in the treatment of Parkinson's disease, It is known that Ritonavir[28] is an antiviral protein inhibitor, and is one of the key components of current antiretroviral therapies[29]. Cariprazine as a dopamine receptor partial agonist is a schizophrenia drug[30]. In addition, arylurea derivatives have been found to inhibit expression of enzymes like β-secretase[31], Acyclooxygenase COX-2[32], and cyclophilin A[33] which make them interesting molecules with bioactive activity for drug designing. In recent years, due to their growing application in the syntheses of medicinal agents, we designed and synthesized a series of 8-substituted urea derivatives showing good anticancer activity against SMMC7721 cells and HCT116 cells.

## Experimental Details

All the chemicals and reagents were used from commercial supplies. Using TMS as an internal standard, $^1$H NMR (400 MHz) spectra were recorded in DMSO-$d_6$ solvent on a JEOL-ECX NMR spectrometer. Mass spectral studies were conducted on an Agilent 1100 organic mass spectrometer. The

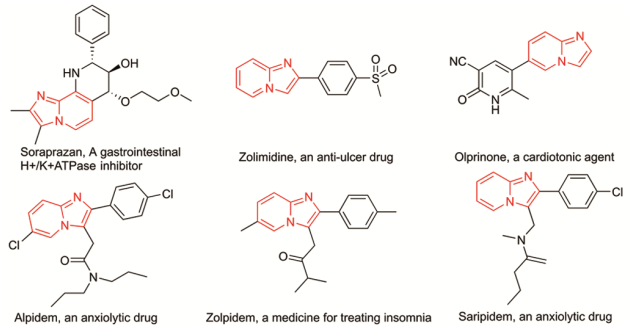



Fig. 1 — Structure of active imidazo[1,2-*a*]pyridine

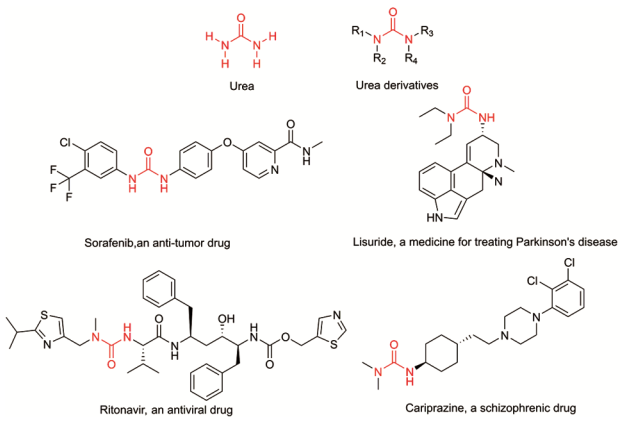



Fig. 2 — Structures of urea and selected urea derivatives

reactions mentioned here were monitored by TLC. The crude products obtained by synthesis were purified by recrystallization and column chromatography. Thin-layer chromatography was performed on silica gel GF254.

**Synthesis of intermediate 6-nitroimidazo[1,2-*a*]pyridine (2)**

Bromoacetaldehyde diethyl acetal **(1)** (108.09 mL, 702.06 mmol), concentrated HCl (10 mL) and water (150 mL) were added to a 500 mL flaskd and stirred vigorously at 80°C for 2 h. After this, the mixture was allowed to cool to room temperature and alkalinized with $Na_2CO_3$ in ice bath. Subsequently, 5-nitropyridin-2-amine (50 g, 359.43 mmol) was added to the resulting mixture and stirred vigorously at 65°C for 2 h. After this time, the mixture was allowed to cool to room temperature and alkalized with 10% NaOH solution, a large amount of yellow solid was precipitated, filtered, and the filter cake was dried to obtain purified compound **2** (56.7 g, yield 96.71%).

**Synthesis of intermediate 8-iodo-6-nitroimidazo [1,2-*a*]pyridine (3)**

Morpholine (48 mL) was slowly added dropwise to a solution of intermediate **2** (30.00 g, 183.90 mmol) and $I_2$ (116.7 g, 459.79 mmol) in MeOH (200 mL) at 0°C, After stirring for 0.5 h at room temperature, the reaction solution was filtered, and the filter cake was slurried with EtOH to obtain purified compound **3** (48 g, yield 90.31%).

**Synthesis of intermediate 8-iodoimidazo[1,2-*a*]pyridin-6-amine (4)**

In a 500 mL flask, compound **3** (30 g, 103.79 mmol) was added in mixed solution of EtOH (91 mL) and water (9.0 mL). Concentrated HCl (0.6 mL) was added followed by Fe powder (28.9 g, 517.50 mmol). The mixture was stirred under reflux for 3 h, which was filtered with diatomite. The filtrate is alkalinized with ammonia and then extracted with EtOH. The extraction fluid was concentrated to obtain brown solid compound **4** (23 g, yield 85.53%).

**Synthesis of intermediate *N*-(8-iodoimidazo[1,2-*a*]pyridin-6-yl)acetamide (5)**

In a 250 mL flask, compound **4** (20 g, 77.21 mmol) was added in acetic anhydride (100 mL). After stirring for 2 h at 130°C, quenching with water, the reaction solution was extracted with EtOH (100 mL×3) and the organic phase was washed with saturated sodium bicarbonate solution. The extraction fluid was concentrated to obtain brown solid compound **5** (20 g, yield 86.02%).

**General synthetic procedure for intermediates 7a-7k**

Taking **7a** as an example, a mixture of $CO(OCCl_3)_2$ (4.74 g, 15.98 mmol) and 100 mL $CH_2Cl_2$ was stirred for ten minutes at room temperature to become transparent. Then compound **6** (10.0 g, 45.64 mmol) was added into the flask, which was stirred about 1 h and after it was concentrated under reduced pressure. Then $CH_2Cl_2$ (100 mL) was added to the concentrated solution. Subsequently, triethylamine (12.7 mL) and cyclohexylamine (10.44 mL) were added slowly to the flask in an ice-water bath, after stirring for 2 h at 130°C, the reaction solution was concentrated under reduced pressure. A large amount of white solid was precipitated in this concentrated liquid by adding dilute 1 mol/L HCl (100 mL). After it is filtered, the filter cake was washed with saturated $NaHCO_3$ and dried to obtain the crude product, which was recrystallized with EtOH (100 mL) to obtain the white solid **7a**.

**General procedure for synthesis of *N*-(8-(3-ureidophenyl)imidazo[1,2-*a*]pyridin-6-yl)acetamide derivatives 8a-8k**

The intermediate **5** (1.37 g, 4.75 mmol) and intermediates **7a-7k** (1 g, 2.90 mmol) were to a

solution of saturated $Na_2CO_3$ (6 mL), 1,4-dioxane (30 mL) and Pd(dppf)$Cl_2$ (0.04 g, 0.05 mmol). The reaction mixture was stirred under reflux. After it was concentrated under reduced pressure to obtain the yellow solid, which was slurried with MeOH. The seriflux was filtered, the filtrate was concentrated and purified on silica gel chromatography to obtain a pale yellow solid **8a-8k**.

***N*-(8-(3-(3-cyclohexylureido)phenyl)imidazo[1,2-*a*]pyridin-6-yl)acetamide (8a):** Pale yellow solid; yield: 26.30%; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.09 (s, 1H), 9.16 (s, 1H), 8.43 (s, 1H), 8.12 (s, 1H), 8.05 (s, 1H), 7.58-7.51 (m, 2H), 7.43 (d, $J$ = 7.9 Hz, 1H), 7.31 (d, $J$ = 7.3 Hz, 2H), 6.06 (d, $J$ = 7.5 Hz, 1H), 3.44 (s, 1H), 2.06 (s, 3H), 1.78 (d, $J$ = 8.5 Hz, 2H), 1.62 (d, $J$ = 12.5 Hz, 2H), 1.50 (d, $J$ = 12.2 Hz, 1H), 1.26-1.14 (m, 5H), 0.81 (s, 1H). MS (ESI) *m/z*: 392.21 $[M+H]^+$.

***N*-(8-(3-(3-(tert-butyl)ureido)phenyl)imidazo [1,2-*a*]pyridin-6-yl)acetamide (8b):** Yellow solid; yield: 26.30%; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.18 (s, 1H), 9.24 (s, 1H), 8.44 (s, 1H), 8.15 (d, $J$ = 13.3 Hz, 2H), 7.61 (d, $J$ = 7.5 Hz, 2H), 7.46 (d, $J$ = 7.9 Hz, 1H), 7.38 (d, $J$ = 6.9 Hz, 2H), 6.06 (s, 1H), 2.14 (s, 3H), 1.33 (s, 9H). MS (ESI) *m/z*: 366.19 $[M+H]^+$.

***N*-(8-(3-(3-cyclopentylureido)phenyl)imidazo [1,2-*a*]pyridin-6-yl)acetamide (8c):** Yellow solid; yield: 17.50%; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.10 (s, 1H), 9.16 (s, 1H), 8.39 (s, 1H), 8.12 (s, 1H), 8.06 (s, 1H), 7.59-7.47 (m, 2H), 7.43 (d, $J$ = 10.5 Hz, 1H), 7.31 (d, $J$ = 7.2 Hz, 2H), 6.14 (d, $J$ = 7.5 Hz, 1H), 3.93 (s, 1H), 2.06 (s, 3H), 1.81 (d, $J$ = 10.8 Hz, 3H), 1.55 (d, $J$ = 31.8 Hz, 4H), 1.36 (s, 2H). MS (ESI) *m/z*: 378.19 $[M+H]^+$.

***N*-(8-(3-(3-(furan-2-ylmethyl)ureido)phenyl)-imidazo[1,2-*a*]pyridin-6-yl)acetamide (8d):** Yellow solid; yield: 30.76%; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.56 (s, 1H), 9.47 (s, 1H), 8.96 (s, 1H), 8.42 (s, 1H), 7.93 (d, $J$ = 35.4 Hz, 2H), 7.63 (s, 1H), 7.55 (dd, $J$ = 1.8, 0.9 Hz, 1H), 7.46 (s, 1H), 7.41 (t, $J$ = 7.8 Hz, 1H), 7.27 (d, $J$ = 8.4 Hz, 1H), 6.75 (t, $J$ = 5.8 Hz, 1H), 6.36 (dd, $J$ = 3.2, 1.9 Hz, 1H), 6.22 (d, $J$ = 3.9 Hz, 1H), 4.28-4.25 (m, 2H), 2.11 (s, 3H). MS (ESI) *m/z*: 390.16$[M+H]^+$.

**(*R*)-*N*-(8-(3-(3-(1-phenylethyl)ureido)phenyl) imidazo[1,2-*a*]pyridin-6-yl)acetamide (8e):** Yellow solid; yield: 53.15%; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.71 (s, 1H), 9.59 (s, 1H), 9.04 (s, 1H), 8.56 (s, 1H), 8.11 (s, 1H), 7.90 (s, 1H), 7.75 (s, 1H), 7.49 (d, J = 6.1 Hz, 2H), 7.41-7.35 (m, 4H), 7.31-7.23 (m, 2H), 7.04 (d, $J$ = 7.9 Hz, 1H), 4.86 (q, $J$ = 7.4 Hz, 1H), 2.18 (s, 3H), 1.42 (d, $J$ = 6.9 Hz, 3H). MS (ESI) *m/z*: 414.19$[M+H]^+$.

**(*R*)-*N*-(8-(3-(3-(1-phenylethyl)ureido)phenyl)-imidazo[1,2-*a*]pyridin-6-yl)acetamide (8f):** Brown solid; yield: 44.29%; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.30 (s, 1H), 9.35 (s, 1H), 8.63 (s, 1H), 8.26 (s, 1H), 8.11 (s, 1H), 7.77 (s, 1H), 7.51 (s, 1H), 7.47 (d, $J$ = 6.3 Hz, 2H), 7.41 (d, $J$ = 7.7 Hz, 1H), 7.37 (d, $J$ = 4.3 Hz, 4H), 7.30-7.23 (m, 1H), 6.72 (d, $J$ = 7.7 Hz, 1H), 4.95-4.74 (m, 1H), 2.14 (s, 3H), 1.42 (d, $J$ = 7.0 Hz, 3H). MS (ESI) *m/z*: 414.19$[M+H]^+$.

***N*-(8-(3-(3-isopropylureido)phenyl)imidazo[1,2-*a*]pyridin-6-yl)acetamide (8g):** Yellow solid; yield: 25.97%; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.62 (s, 1H), 9.60 (s, 1H), 8.61 (d, $J$ = 33.3 Hz, 2H), 8.14 (s, 1H), 7.90 (s, 1H), 7.74 (s, 1H), 7.48 (s, 2H), 7.25 (s, 1H), 6.30-6.10 (m, 1H), 3.87-3.72 (m, 1H), 2.19 (s, 3H), 1.20-1.05 (m, 6H). MS (ESI) *m/z*: 352.18$[M+H]^+$.

***N*-(8-(3-(3-(o-tolyl)ureido)phenyl)imidazo[1,2-*a*]pyridin-6-yl)acetamide (8h):** Yellowish brown solid; yield: 35.27%; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.16 (s, 1H), 9.24 (d, $J$ = 12.0 Hz, 2H), 8.29 (s, 1H), 8.13 (s, 1H), 7.98 (s, 1H), 7.90 (d, $J$ = 8.0 Hz, 1H), 7.65 (d, $J$ = 8.5 Hz, 2H), 7.59 (s, 1H), 7.44 (d, $J$ = 7.9 Hz, 1H), 7.40 (d, $J$ = 1.7 Hz, 1H), 7.21-7.14 (m, 2H), 6.95 (t, $J$ = 7.8 Hz, 1H), 2.27 (s, 3H), 2.12 (s, 3H). MS (ESI)*m/z*: 400.18$[M+H]^+$.

***N*-(8-(3-(3-(thiazol-2-yl)ureido)phenyl)imidazo [1,2-*a*]pyridin-6-yl)acetamide (8i):** Yellow solid; yield: 17.59%; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.19 (s, 1H), 9.24 (s, 1H), 9.18 (s, 1H), 8.27 (s, 1H), 8.13 (s, 1H), 7.73 (d, J = 9.1 Hz, 1H), 7.58 (d, $J$ = 13.0 Hz, 2H), 7.47 (s, 1H), 7.39 (s, 2H), 7.29 (d, $J$ = 8.9 Hz, 1H), 7.13 (d, $J$ = 7.3 Hz, 1H), 2.12 (s, 3H). MS (ESI)*m/z*: 391.10$[M-H]^+$.

***N*-(8-(3-(3-propylureido)phenyl)imidazo[1,2-*a*]-pyridin-6-yl)acetamide (8j):** Gray solid; yield: 17.59%; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.16 (s, 1H), 9.20 (s, 1H), 8.52 (s, 1H), 8.11 (d, $J$ = 9.8 Hz, 2H), 7.72 (s, 1H), 7.56 (s, 1H), 7.51 (d, $J$ = 7.7 Hz, 1H), 7.33 (d, $J$ = 13.0 Hz, 2H), 2.11 (s, 3H), 1.99 (s, 1H), 1.16 (d, $J$ = 12.6 Hz, 8H). MS (ESI)*m/z*: 392.21$[M+H]^+$.

***N*-(3-(6-acetamidoimidazo[1,2-*a*]pyridin-8-yl)-phenyl)-2-methylpiperidine-1-carboxamide (8k):** Yellow solid; yield: 43.28%; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.60 (s, 1H), 9.59 (s, 1H),

8.77 (s, 1H), 8.56 (s, 1H), 8.13 (s, 1H), 7.91 (s, 1H), 7.73 (s, 1H), 7.50 (d, $J$ = 5.5 Hz, 2H), 7.25 (d, $J$ = 5.7 Hz, 1H), 6.34 (s, 1H), 3.08 (d, $J$ = 5.5 Hz, 2H), 2.19 (s, 3H), 1.48 (q, $J$ = 7.2 Hz, 2H), 0.98-0.85 (m, 3H). MS (ESI)*m/z*: 350.16$[M-H]^+$.

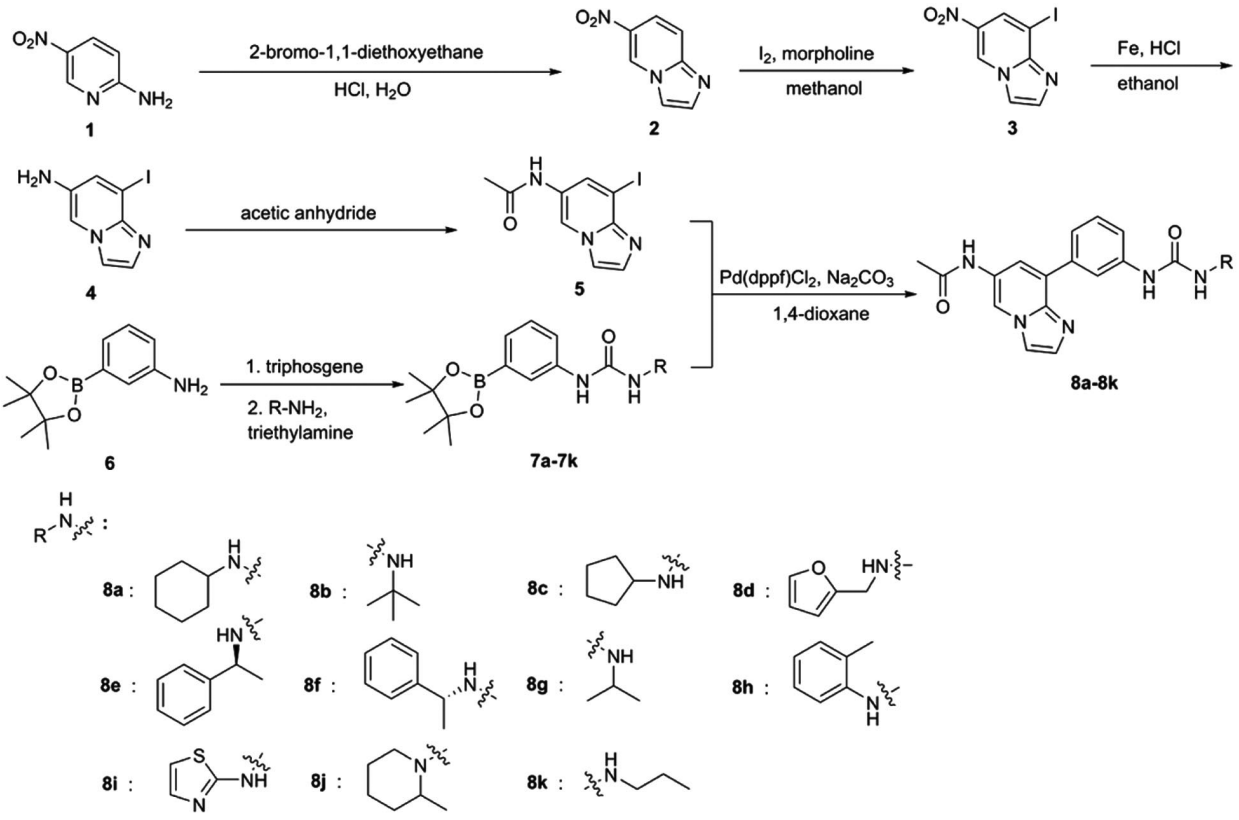
The spectral details of selected compounds are given in the Supplementary Information.

**MTT assay in vitro**

The antiproliferative activity of the compounds **8a-8k** was evaluated against SMMC7721 cells and HCT116 cells using the standard MTT assay in vitro. The cancer cell line was cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10 % fetal bovine serum (FBS). Approximate $4 \times 10^3$ cells, suspended in DMEM medium, were plated onto each well of a 96-well plate and incubated in 5% $CO_2$ at 37°C for 24 h. The tested compounds at the final concentration of 5 μM was added to the culture medium and the cell cultures were continued for 72 h. Fresh MTT was added to each well at a terminal concentration of 5 mg/mL, and incubated with cells at 37°C for 4 h. The formazan crystals were dissolved in 150 mL DMSO for each well, and the absorbance at 490 nm (for absorbance of MTT formazan) and 630 nm (for the reference wavelength) were measured with an ELISA reader. The compound was tested three times.

**Results and Discussion**

Prompted by the aforementioned biological activities of imidazo[1,2-*a*]pyridine and urea derivatives, we sought to combine these structural scaffolds to design and synthesize new derivatives of *N*-(8-(3-ureidophenyl)imidazo[1,2-*a*]pyridin-6-yl)acetamide. The detailed synthetic route for the preparation of *N*-(8-(3-ureidophenyl)imidazo[1,2-*a*]pyridin-6-yl) acetamide derivatives are summarized in Scheme 1. 6-Nitroimidazo[1,2-*a*]pyridine **(2)** was prepared by 5-nitropyridin-2-amine **(1)** on reaction with 2-bromo-1,1-diethoxyethane in the presence of sodium bicarbonate in the water, which was then subjected to substitution reaction with $I_2$ and morpholine to generate 8-iodo-6-nitroimidazo[1,2-*a*]pyridine **(3)**. 8-Iodoimidazo[1,2-*a*]pyridin-6-amine **(4)** was obtained from the nitro reduction of 8-iodo-6-nitroimidazo[1,2-*a*]pyridine **(3)**. Subsequently, compound **4** was converted into the corresponding key intermediate **5** through reaction with acetic anhydride under saturated $NaHCO_3$ system.




Scheme 1 — Synthetic route to compounds **8a-8k**

Table 1 — Antitumor activity of the synthesized compounds against SMMC7721 and HCT116 cells *in vitro*

| Compound | Inhibition rate (%) | |
|---|---|---|
| | SMMC7721 (100 μmol/L) | HCT116 (100 μmol/L) |
| **8a** | 23.33 | - |
| **8b** | 12.95 | - |
| **8c** | 6.82 | - |
| **8d** | 3.00 | - |
| **8e** | 6.62 | - |
| **8f** | 1.78 | - |
| **8g** | - | 2.11 |
| **8h** | - | 8.23 |
| **8i** | 18.84 | 5.39 |
| **8j** | - | 26.47 |
| **8k** | - | 1.42 |
| **Sonidegib** | 16.08 | 17.28 |

The arylurea intermediates **(7a-7k)** were obtained with 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) aniline **(6)** as starting materials, which were reacted with triphosgene in $CH_2Cl_2$. After reaction was completed, it was concentrated under reduced pressure in order to remove volatile component, then react with various amine compounds. The compounds **8a–8k** were obtained by coupling compound **5** and arylurea intermediates **7a-7k** through Suzuki reaction.

Here in, the synthesized novel compounds **8a-8k** were evaluated for anticancer activity against SMMC7721 cells and HCT116 cells in vitro by the MTT array, and the commercial antitumor agents Sonidegib were used as the positive control drugs. The results of the compounds **8a-8k** screening presented in Table 1 show that **8a**, **8b**, **8c**, **8d**, **8e**, **8i** possessed excellent antitumor activity against SMMC7721 cells, with inhibition rates of 23.33%, 12.95%, 6.82%, 3.00%, 18.84% at 100 μmol/L, respectively, especially, compounds **8a** and **8i** exhibited similar or even better activity (23.33%, 18.84%) in the inhibitory activity than Sonidegib (16.08%). Meanwhile, Table 1 showed that **8j** demonstrated the best inhibitory effect against HCT 116 cells in vitro, with inhibition rates of 26.47% at 100 μmol/L, which was better than that of commercial Sonidegib (17.28%).

## Conclusion

To conclude, a series of *N*-(8-(3-ureidophenyl) imidazo[1,2-*a*]pyridin-6-yl)acetamide derivatives containing imidazo[1,2-*a*]pyridine and urea were synthesized and a preliminary study of their antitumor activity against SMMC7721 cells and HCT116 cells by the MTT assay in vitro. The bioassays result demonstrated that some of the synthesized compounds exhibited excellent antitumor activity against SMMC7721 cells and HCT116 cells. This work demonstrated that the compounds **8a** and **8j** containing 8-substituted urea phenyl imidazo[1,2-*a*]pyridine fragment are promising for further in-depth study of antitumor properties.

## Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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