

## Synthesis of novel imidazo[1,2-*a*]pyridines and evaluation of their antifungal activities

Füsun GÖKTAŞ<sup>1,\*</sup>, Nesrin CESUR<sup>1</sup>, Dilek ŞATANA<sup>2</sup>, Meltem UZUN<sup>2</sup>

<sup>1</sup>Department of Pharmaceutical Chemistry, Faculty of Pharmacy, İstanbul University, İstanbul, Turkey

<sup>2</sup>Department of Medical Microbiology, İstanbul Faculty of Medicine, İstanbul University, İstanbul, Turkey

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**Abstract:** New 2-(imidazo[1,2-*a*]pyridin-2-ylcarbonyl)-*N*-substituted hydrazinecarbothioamides (**4a–j**), *N*'-(3-substituted-4-oxo-1,3-thiazolidin-2-ylidene)imidazo[1,2-*a*]pyridine-2-carbohydrazides (**5a–f**), and *N*-(nonsubstituted/4-substituted phenyl)-5-(imidazo[1,2-*a*]pyridine-2-yl)-1,3,4-oxadiazole-2-amines (**6a–d**) were synthesized from imidazo[1,2-*a*]pyridine-2-carbohydrazide (**3**) and evaluated for antifungal activity against *Microsporum gypseum* NCPF 580, *M. canis*, *Trichophyton tonsurans* NCPF 245, *T. rubrum*, *Candida albicans* ATCC 10231, and *C. parapsilosis* ATCC 22019 using amphotericin B as the standard. The chemical structures of the compounds were confirmed by elemental analysis, IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, HMBC (<sup>13</sup>C, <sup>1</sup>H), and mass spectra. Most of the tested compounds showed moderate antifungal activity. Hydrazinecarbothioamide derivatives **4h** and **4f** exhibited the highest activity against *M. canis* (MIC: 2 µg mL<sup>-1</sup> and 4 µg mL<sup>-1</sup>, respectively).

**Key words:** Imidazo[1,2-*a*]pyridine, hydrazinecarbothioamide, 4-oxo-1,3-thiazolidine, 1,3,4-oxadiazole, antifungal activity

### 1. Introduction

Heterocycles are important molecular building blocks that are involved in the structural composition of crucial chemicals for humans, including pharmaceuticals, natural resources, veterinary and agricultural products, analytical reagents, and dyes. Imidazo[1,2-*a*]pyridine, a fused bicyclic 5-6-heterocycle with 1 ring junction nitrogen atom and 1 extra nitrogen atom in the 5-membered ring, is of interest because of the occurrence of its derivatives in biologically active compounds and the pharmacology of the system has also been extensively investigated.<sup>1</sup>

Human fungal infections have increased in the last 2 decades due to the increasing number of immunocompromised patients or those undergoing anticancer chemotherapy or transplantation.<sup>2</sup> On the other hand, the current antifungal therapy suffers from toxicity, nonoptimal pharmacokinetics, and some serious adverse drug interactions. New chemotherapeutic agents with higher efficiency, a broader spectrum, and lower toxicity are urgently needed for the treatment of fungal infections.<sup>3</sup>

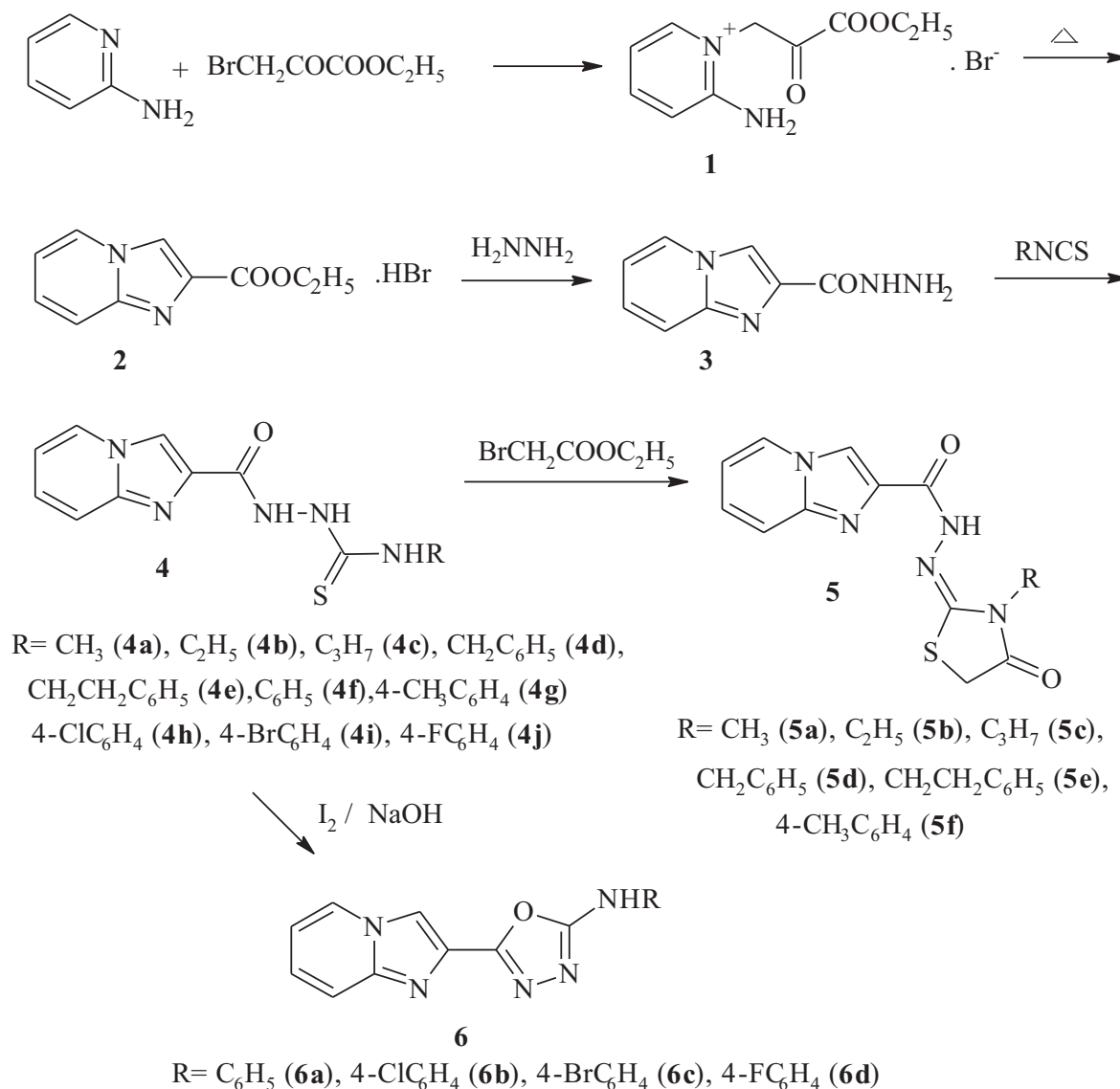
In previous papers, we reported the synthesis and biological activity of a series of imidazo[1,2-*a*]pyridines as antibacterials and antifungals.<sup>4–6</sup> The present work is an extension of our ongoing efforts toward the development and identification of new antifungal imidazo[1,2-*a*]pyridine derivatives bearing hydrazinecarbothioamide (**4a–j**), 1,3-thiazolidine (**5a–f**), or 1,3,4-oxadiazole (**6a–d**) moieties.

\*Correspondence: [fusung@istanbul.edu.tr](mailto:fusung@istanbul.edu.tr)

## 2. Results and discussion

### 2.1. Chemistry

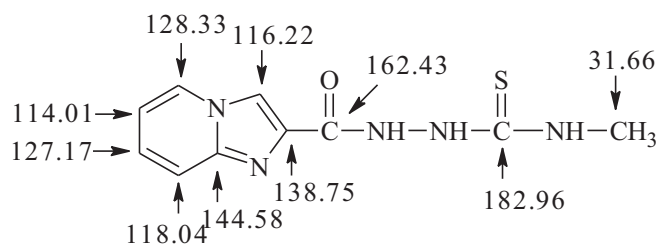
Ethyl imidazo[1,2-*a*]pyridine-2-carboxylate hydrobromide (**2**) was obtained from 2-aminopyridine and ethyl bromopyruvate by a 2-step procedure.<sup>7</sup> Heating **2** with hydrazine in ethanol gave imidazo[1,2-*a*]pyridine-2-carbohydrazide (**3**),<sup>8</sup> and **3** was reacted with alkyl or aryl isothiocyanates to achieve 2-(imidazo[1,2-*a*]pyridin-2-ylcarbonyl)-*N*-substituted hydrazinecarbothioamide (**4a-j**) (Scheme 1).



Scheme 1. Synthesis of compounds 4-6.

The structures of compounds **4a-j** were assigned by elemental analyses and spectral data; **4a-j** were confirmed by their IR spectra, which displayed absorption peaks at  $3395\text{--}3106\text{ cm}^{-1}$  for N-H,  $1682\text{--}1670\text{ cm}^{-1}$  for C=O, and  $1156\text{--}1144\text{ cm}^{-1}$  corresponding to C=S stretching vibrations.  $^1\text{H}$  NMR spectra showed  $\text{N}^2\text{-H}$ ,  $\text{N}^1\text{-H}$ , and N-H resonances in the 10.50–10.12 ppm, 9.87–9.19 ppm, and 9.77–7.89 ppm regions,

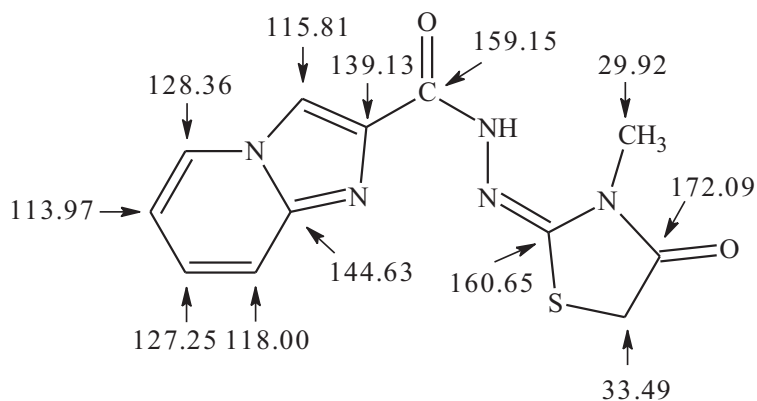
respectively.<sup>6,9–11</sup> The C<sub>5</sub>-, C<sub>3</sub>-, C<sub>8</sub>-, C<sub>7</sub>-, and C<sub>6</sub>-H resonances of the imidazo[1,2-*a*]pyridine system appeared in the 8.66–8.52 ppm, 8.53–8.39 ppm, 7.66–7.53 ppm, 7.43–7.29 ppm, and 7.07–6.91 ppm regions, respectively. HMBC (<sup>13</sup>C–<sup>1</sup>H) experiments were performed to establish the interfragment relationship and assign the proton and carbon signals of the prototype compounds **4a**, **g**, and **j**. The HMBC spectra of **4a**, **g**, and **j** exhibited resonances arising from C=S at 182.96–181.50 ppm and C=O at 162.43–160.93 ppm (Scheme 2)<sup>12</sup> and C<sub>8a</sub>, C<sub>2</sub>, C<sub>5</sub>, C<sub>7</sub>, C<sub>8</sub>, C<sub>3</sub>, and C<sub>6</sub> resonances of the imidazo[1,2-*a*]pyridine residue appeared in the 144.58–144.61, 138.71–138.75, 128.33–128.35, 127.17–127.21, 118.04–118.07, 116.22–116.25, and 114.01–114.03 ppm regions, respectively.<sup>13</sup> The mass spectra of **4a–j** also confirmed their molecular weights.



Scheme 2. <sup>13</sup>C NMR data of compound **4a**.

*N*'-(3-alkyl/aryl-4-oxo-1,3-thiazolidin-2-ylidene)imidazo[1,2-*a*]pyridine-2-carbohydrazide derivatives (**5a–f**) were prepared by reacting 2-(imidazo[1,2-*a*]pyridin-2-ylcarbonyl)-*N*-substituted hydrazinecarbothioamides (**4a–j**) with ethyl bromoacetate in the presence of sodium acetate. A new C=O band (1720–1697 cm<sup>-1</sup>) in the IR spectra of **5a–f** was particularly diagnostic for 4-oxo-1,3-thiazolidine formation.<sup>4–6,10,14,15</sup> Further support was obtained from the <sup>1</sup>H NMR spectra of **5a–f**, which showed signals due to the CH<sub>2</sub> protons at the 5 position of 4-oxo-1,3-thiazolidine ring at about 4.22–4.06 ppm.<sup>5,6,15,16</sup>

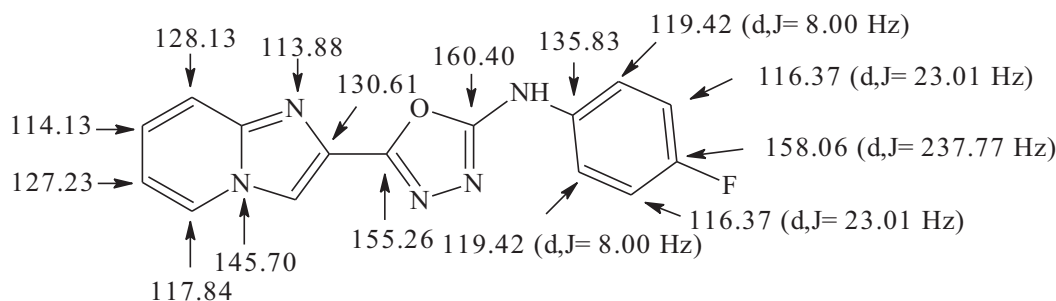
After cyclization, the absence of resonances assigned to the N<sup>1</sup>-H and N-H protons of the hydrazinecarbothioamides (**4a–f**) provided evidence of 4-oxo-1,3-thiazolidine formation. HMBC (<sup>13</sup>C–<sup>1</sup>H) experiments of **5a**, **b**, and **d**, chosen as prototypes, made it possible to differentiate the carbon atoms of 4-oxo-1,3-thiazolidine C=O and C<sub>2</sub> and also of amide C=O (Scheme 3). Abundant ions [M + H]<sup>+</sup> in the APCI+ or ESI+ mass spectra of **5a–f** confirmed their molecular weights.



Scheme 3. <sup>13</sup>C NMR data of compound **5a**.

On the other hand, 2-(imidazo[1,2-*a*]pyridin-2-ylcarbonyl)-*N*-substituted hydrazinecarbothioamides (**4f–j**) were oxidatively cyclized to 1,3,4-oxadiazole derivatives (**6a–d**), using iodine and potassium iodide in ethanolic

sodium hydroxide by the elimination of  $\text{H}_2\text{S}$ . The IR spectra of 1,3,4-oxadiazole derivatives showed N–H and C=N bands at about  $3244\text{--}3107\text{ cm}^{-1}$  and  $1669\text{--}1480\text{ cm}^{-1}$ , respectively. The absence of a C=O band in the IR spectra of **6a–d** supported the 1,3,4-oxadiazole structure. In the  $^1\text{H}$  NMR spectra, the disappearance of CONH and CSNH signals (**4f–j**) and the appearance of a new signal at about 10.91–10.64 ppm confirmed the formation of an oxadiazole ring.<sup>16,17</sup> HMBC ( $^{13}\text{C}\text{--}^1\text{H}$ ) experiments of representative **6d** also confirmed the structure of the oxadiazole ring (Scheme 4).<sup>17</sup> The APCI+ or ESI+ mass spectra of **6a–d** showed abundant ions  $[\text{M} + \text{H}]^+$  with different intensities.



Scheme 4.  $^{13}\text{C}$  NMR data of compound **6d**.

The purity of the synthesized compounds was established by elemental analysis.

## 2.2. Antifungal activity

The antifungal activities of compounds **4a–c**, **f–j**, **5a**, **b**, **f**, and **6a–d** were investigated against *Microsporum gypseum* NCPF 580, *M. canis*, *Trichophyton tonsurans* NCPF 245, *T. rubrum*, *Candida albicans* ATCC 10231, and *C. parapsilosis* ATCC 22019 by microdilution method. Antifungal activity data are given in the Table. All tested compounds exhibited varying degrees of antifungal activity; the highest activities were demonstrated by compounds **4h** and **4f** against *M. canis* at  $2\ \mu\text{g mL}^{-1}$  and  $4\ \mu\text{g mL}^{-1}$ , respectively.

Table. Antifungal activity data of compounds **4–6** (MIC  $\mu\text{g mL}^{-1}$ ).

Compound	<i>T. tonsurans</i> NCPF245	<i>T. rubrum</i>	<i>M. canis</i>	<i>M. gypseum</i> NCPF 580	<i>C. albicans</i> ATCC 10231	<i>C. parapsilosis</i> ATCC 22019
<b>4a</b>	32	32	32	32	64	64
<b>4b</b>	32	32	32	32	64	64
<b>4c</b>	32	16	16	32	32	64
<b>4f</b>	16	8	4	16	32	32
<b>4g</b>	8	16	16	16	64	64
<b>4h</b>	16	8	2	16	32	32
<b>4i</b>	8	8	8	16	64	64
<b>4j</b>	16	16	16	16	64	64
<b>5a</b>	32	32	32	32	64	64
<b>5b</b>	32	32	32	32	64	64
<b>5f</b>	16	32	16	32	32	32
<b>6a</b>	32	32	32	32	32	32
<b>6b</b>	32	16	32	32	32	32
<b>6c</b>	32	16	32	32	32	64
<b>6d</b>	32	16	32	32	32	64
Amphotericin B	0.25	2	0.5	0.5	0.5	0.5

### 3. Experimental

#### 3.1. Chemistry

Melting points were determined with a Buchi 530 apparatus in open capillary tubes and are uncorrected. IR spectra were recorded on KBr disks, using a PerkinElmer Model 1600 FT-IR spectrophotometer.  $^1\text{H}$  NMR spectra were obtained in  $\text{DMSO-d}_6$ , with Varian *UNITY INOVA* 400 (500 MHz), or Bruker (200 MHz) spectrophotometers using TMS as the internal standard.  $^{13}\text{C}$  NMR spectra were recorded at 150 and 75 MHz using the instruments mentioned above. EI and APCI mass spectra were determined with a Finnigan LCQ mass spectrometer. Elemental analyses were performed on a Thermo Finnigan Flash EA1112. Chemicals were purchased from Merck (Darmstadt, Germany), Fluka, and Sigma-Aldrich Chemical Co.

#### 2-Amino-1-(3-ethoxy-2,3-dioxopropyl)pyridinium bromide (**1**)<sup>7</sup>

To a suspension of 2-aminopyridine (0.09 mol) in dimethoxyethane (50 mL) was added ethylbromopyruvate (0.1 mol) and the reaction mixture was stirred for 2 h at room temperature. The precipitate was filtered, washed with  $\text{H}_2\text{O}$ , and used without further purification.

#### Ethyl imidazo[1,2-*a*]pyridine-2-carboxylate hydrobromide (**2**)<sup>7</sup>

Compound **1** (0.04 mol) in ethanol 96% (100 mL) was refluxed for 2 h. Ethanol was evaporated to 1/5 volume under reduced pressure, and then ether was added to give a solid residue. The crude product was filtered and used without further purification.

#### Imidazo[1,2-*a*]pyridine-2-carbohydrazide (**3**)<sup>8</sup>

A mixture of 0.03 mol **2** and 0.3 mol of hydrazine was heated for 2 h. After cooling, the precipitate was filtered, washed with cold water, and crystallized from ethanol 96%. Yield: 93%, mp 195–197 °C. IR ( $\text{cm}^{-1}$ ): 3429, 3317 (N–H), 1654 (C=O);  $^1\text{H}$  NMR  $\delta$  (ppm): 4.55 (2H, broad s,  $\text{NH}_2$ ); 6.96 (1H, t,  $J = 6.7$  Hz,  $\text{C}_6\text{-H}$ ); 7.32 (1H, t,  $J = 6.8$  Hz,  $\text{C}_7\text{-H}$ ); 7.58 (1H, d,  $J = 9.1$  Hz,  $\text{C}_8\text{-H}$ ); 8.36 (1H, s,  $\text{C}_3\text{-H}$ ); 8.58 (1H, d,  $J = 6.8$  Hz,  $\text{C}_5\text{-H}$ ); 9.48 (1H, s, CONH).

#### General procedure for the synthesis of 2-(imidazo[1,2-*a*]pyridin-2-ylcarbonyl)-*N*-substituted hydrazinecarbothioamide (**4a–j**)

First 0.075 mol of **3**, 0.075 mol of appropriate alkyl/aryl isothiocyanate, and 40 mL of absolute ethanol were refluxed 30 min. The solid formed was filtered and recrystallized from ethanol (96%).

**2-(Imidazo[1,2-*a*]pyridin-2-ylcarbonyl)-*N*-methylhydrazinecarbothioamide (**4a**)**. Yield: 60%, mp 265–266 °C. IR ( $\text{cm}^{-1}$ ): 3374, 3106 (N–H), 1670 (C=O), 1155 (C=S);  $^1\text{H}$  NMR  $\delta$  (ppm): 2.85 (3H, d,  $J = 4.4$  Hz,  $-\text{CH}_3$ ); 6.99 (1H, t,  $J_{6,7} = J_{6,5} = 6.8$  Hz,  $\text{C}_6\text{-H}$ ); 7.35 (1H, dd,  $J_{7,8} = 9.1$  Hz,  $J_{7,6} = 6.8$  Hz,  $\text{C}_7\text{-H}$ ); 7.60 (1H, d,  $J = 9.2$  Hz,  $\text{C}_8\text{-H}$ ); 7.89 (1H, broad s, N–H); 8.46 (1H, s,  $\text{C}_3\text{-H}$ ); 8.59 (1H, d,  $J_{5,6} = 6.8$  Hz,  $\text{C}_5\text{-H}$ ); 9.30 (1H, s,  $\text{N}^1\text{-H}$ ); 10.19 (1H, s,  $\text{N}^2\text{-H}$ );  $^{13}\text{C}$  NMR (HMBC)  $\delta$  (ppm): 182.96 (C=S); 162.43 (C=O); 144.58 (imidazo[1,2-*a*]pyridine  $\text{C}_{8a}$ ); 138.75 (imidazo[1,2-*a*]pyridine  $\text{C}_2$ ); 128.33 (imidazo[1,2-*a*]pyridine  $\text{C}_5$ ); 127.17 (imidazo[1,2-*a*]pyridine  $\text{C}_7$ ); 118.04 (imidazo[1,2-*a*]pyridine  $\text{C}_8$ ); 116.22 (imidazo[1,2-*a*]pyridine  $\text{C}_3$ ); 114.01 (imidazo[1,2-*a*]pyridine  $\text{C}_6$ ); 31.66 (imidazo[1,2-*a*]pyridine  $\text{CH}_3$ ); MS [APCI+] ( $m/z$ ): 250 ( $[\text{M} + \text{H}]^+$ , 8), 79 (100). Anal. calcd. for  $\text{C}_{10}\text{H}_{11}\text{N}_5\text{OS}$ : C: 48.18; H: 4.45; N: 28.09. Found: C: 47.82; H: 4.17; N: 27.65.

***N*-Ethyl-2-(imidazo[1,2-*a*]pyridin-2-ylcarbonyl)hydrazinecarbothioamide (4b).** Yield: 94%, mp 251–252 °C. IR (cm<sup>-1</sup>): 3262, 3140 (N–H), 1670 (C=O), 1149 (C=S); <sup>1</sup>H NMR δ (ppm): 1.05 (3H, t, *J* = 7.1 Hz, CH<sub>3</sub>); 3.42–3.48 (2H, m, –CH<sub>2</sub>–); 7.00 (1H, t, *J*<sub>6,7</sub> = *J*<sub>6,5</sub> = 6.7 Hz, C<sub>6</sub>–H); 7.36 (1H, dd, *J*<sub>7,8</sub> = 9.2 Hz, *J*<sub>7,6</sub> = 6.7 Hz, C<sub>7</sub>–H); 7.61 (1H, d, *J*<sub>8,7</sub> = 9.2 Hz, C<sub>8</sub>–H); 7.91 (1H, s, N–H); 8.47 (1H, s, C<sub>3</sub>–H); 8.60 (1H, d, *J*<sub>5,6</sub> = 6.7 Hz, C<sub>5</sub>–H); 9.24 (1H, s, N<sup>1</sup>–H); 10.16 (1H, s, N<sup>2</sup>–H). MS EI (m/z): 265 ([M + 2], 3), 264 (MH<sup>+</sup>, 10), 263 (M<sup>+</sup>, 36), 176 (100). Anal. calcd. for C<sub>11</sub>H<sub>13</sub>N<sub>5</sub>OS: C: 50.17; H: 4.98; N: 26.60. Found: C: 50.52; H: 4.81; N: 26.74.

**2-(Imidazo[1,2-*a*]pyridin-2-ylcarbonyl)-*N*-propylhydrazinecarbothioamide (4c).** Yield: 59%, mp 192–194 °C. IR (cm<sup>-1</sup>): 3265, 3140 (N–H), 1676 (C=O), 1144 (C=S); <sup>1</sup>H NMR δ (ppm): 0.73 (3H, t, *J* = 7.4 Hz, CH<sub>3</sub>); 1.41 (2H, m, –CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 3.25 (m, –CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and H<sub>2</sub>O); 6.91 (1H, t, *J*<sub>6,7</sub> = *J*<sub>6,5</sub> = 6.8 Hz, C<sub>6</sub>–H); 7.27 (1H, dd, *J*<sub>7,8</sub> = 9.1 Hz, *J*<sub>7,6</sub> = 6.8 Hz, C<sub>7</sub>–H); 7.53 (1H, d, *J*<sub>8,7</sub> = 9.1 Hz, C<sub>8</sub>–H); 7.84 (1H, broad s, N–H); 8.39 (1H, s, C<sub>3</sub>–H); 8.52 (1H, d, *J*<sub>5,6</sub> = 6.8 Hz, C<sub>5</sub>–H); 9.19 (1H, s, N<sup>1</sup>–H); 10.12 (1H, s, N<sup>2</sup>–H). MS [APCI+] (m/z): 278 ([M + H]<sup>+</sup>, 30), 177 (100). Anal. calcd. for C<sub>12</sub>H<sub>15</sub>N<sub>5</sub>OS: C: 51.97; H: 5.45; N: 25.25. Found: C: 51.44; H: 4.86; N: 24.99.

***N*-Benzyl-2-(imidazo[1,2-*a*]pyridin-2-ylcarbonyl)hydrazinecarbothioamide (4d).** Yield: 83%, mp 240–242 °C. IR (cm<sup>-1</sup>): 3374, 3152 (N–H), 1673 (C=O), 1145 (C=S); <sup>1</sup>H NMR δ (ppm): 4.72 (2H, d, *J* = 6.0 Hz, –CH<sub>2</sub>–); 7.00 (1H, t, *J*<sub>6,5</sub> = *J*<sub>6,7</sub> = 6.8 Hz, C<sub>6</sub>–H); 7.21–7.38 (6H, m, C<sub>7</sub>–H, phenyl); 7.61 (1H, d, *J*<sub>8,7</sub> = 9.2 Hz, C<sub>8</sub>–H); 8.50 (2H, s, C<sub>3</sub>–H, N–H); 8.60 (1H, d, *J*<sub>5,6</sub> = 6.8 Hz, C<sub>5</sub>–H); 9.46 (1H, s, N<sup>1</sup>–H); 10.35 (1H, s, N<sup>2</sup>–H). MS [ESI–] (m/z): 324 ([M–H]<sup>–</sup>, 67), 290 (100). Anal. calcd. for C<sub>16</sub>H<sub>15</sub>N<sub>5</sub>OS: C: 59.06; H: 4.65; N: 21.52. Found: C: 58.61; H: 4.72; N: 20.86.

**2-(Imidazo[1,2-*a*]pyridin-2-ylcarbonyl)-*N*-(2-phenylethyl)hydrazinecarbothioamide (4e).** Yield: 79%, mp 195–197 °C. IR (cm<sup>-1</sup>): 3395, 3135 (N–H), 1682 (C=O), 1148 (C=S); <sup>1</sup>H NMR δ (ppm): 2.81 (2H, t, *J* = 7.8 Hz, –CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>); 3.63 (2H, t, *J* = 7.8 Hz, –N–CH<sub>2</sub>–); 7.01 (1H, t, *J*<sub>6,7</sub> = *J*<sub>6,5</sub> = 6.8 Hz, C<sub>6</sub>–H); 7.17–7.29 (5H, m, phenyl); 7.38 (1H, t, *J*<sub>7,8</sub> = 9.1 Hz, C<sub>7</sub>–H); 7.62 (1H, d, *J*<sub>7,8</sub> = 9.1 Hz, C<sub>8</sub>–H); 8.01 (1H, broad s, N–H); 8.50 (1H, s, C<sub>3</sub>–H); 8.62 (1H, d, *J*<sub>5,6</sub> = 6.8 Hz, C<sub>5</sub>–H); 9.39 (1H, s, N<sup>1</sup>–H); 10.23 (1H, s, N<sup>2</sup>–H). MS [APCI+] (m/z): 340 ([M + H]<sup>+</sup>, 90), 219 (100). Anal. calcd. for C<sub>17</sub>H<sub>17</sub>N<sub>5</sub>OS: C: 60.16; H: 5.05; N: 20.63. Found: C: 59.85; H: 4.70; N: 20.50.

**2-(Imidazo[1,2-*a*]pyridin-2-ylcarbonyl)-*N*-phenylhydrazinecarbothioamide (4f).** Yield: 72%, mp 188–190 °C. IR (cm<sup>-1</sup>): 3260, 3107 (N–H), 1669 (C=O), 1156 (C=S). <sup>1</sup>H NMR δ (ppm): 7.01 (1H, t, *J*<sub>6,7</sub> = *J*<sub>6,5</sub> = 6.8 Hz, C<sub>6</sub>–H); 7.14 (1H, dd, *J* = 7.4, 9.0 Hz, phenyl 4–H); 7.30–7.40 (3H, m, C<sub>7</sub>–H, phenyl 2, 6–H); 7.51 (2H, dd, *J* = 6.8, 7.5 Hz, phenyl 3, 5–H); 7.64 (1H, d, *J*<sub>8,7</sub> = 9.1 Hz, C<sub>8</sub>–H); 8.51 (1H, s, C<sub>3</sub>–H); 8.62 (1H, d, *J*<sub>5,6</sub> = 6.8 Hz, C<sub>5</sub>–H); 9.73 (1H, broad s, N–H); 9.87 (1H, s, N<sup>1</sup>–H); 10.41 (1H, s, N<sup>2</sup>–H). MS [ESI–] (m/z): 310([M–H]<sup>–</sup>, 23), 276(100). Anal. calcd. for C<sub>15</sub>H<sub>13</sub>N<sub>5</sub>OS. 0.5 H<sub>2</sub>O: C: 56.23; H: 4.40; N: 21.86. Found: C: 56.91; H: 4.20; N: 21.69.

**2-(Imidazo[1,2-*a*]pyridin-2-ylcarbonyl)-*N*-(4-methylphenyl)hydrazinecarbothioamide (4g).** Yield: 59%, mp 198–200 °C. IR (cm<sup>-1</sup>): 3320, 3141 (N–H), 1671 (C=O), 1146 (C=S). <sup>1</sup>H NMR δ (ppm): 2.27 (3H, s, –CH<sub>3</sub>), 7.00 (1H, t, *J*<sub>6,7</sub> = *J*<sub>6,5</sub> = 6.8 Hz, C<sub>6</sub>–H); 7.12 (2H, d, *J* = 8.1 Hz, phenyl 3, 5–H); 7.34–7.39 (3H, m, C<sub>7</sub>–H, phenyl 2, 6–H); 7.64 (1H, d, *J*<sub>8,7</sub> = 9.2 Hz, C<sub>8</sub>–H); 8.50 (1H, s, C<sub>3</sub>–H); 8.62 (1H, d, *J*<sub>5,6</sub> = 6.8 Hz, C<sub>5</sub>–H); 9.43 (2H, broad s, N<sup>1</sup>–H, N–H); 10.50 (1H, s, N<sup>2</sup>–H). <sup>13</sup>C NMR (HMBC) δ (ppm): 181.50

(C=S); 162.00 (C=O); 144.61 (imidazo[1,2-*a*]pyridine C<sub>8a</sub>); 138.72 (imidazo[1,2-*a*]pyridin C<sub>2</sub>); 137.40 (phenyl C<sub>1</sub>); 134.57 (phenyl C<sub>4</sub>); 129.17 (phenyl C<sub>3</sub>, C<sub>5</sub>); 128.35 (imidazo[1,2-*a*]pyridine C<sub>5</sub>); 127.19 (imidazo[1,2-*a*]pyridine C<sub>7</sub>); 125.68 (phenyl C<sub>2</sub>, C<sub>6</sub>); 118.07 (imidazo[1,2-*a*]pyridine C<sub>8</sub>); 116.22 (imidazo[1,2-*a*]pyridine C<sub>3</sub>); 114.02 (imidazo[1,2-*a*]pyridine C<sub>6</sub>); 21.21 (imidazo[1,2-*a*]pyridine CH<sub>3</sub>). MS [APCI+] (m/z): 326 ([M + H]<sup>+</sup>, 14), 145 (100). Anal. calcd. for C<sub>16</sub>H<sub>15</sub>N<sub>5</sub>OS: C: 59.06; H: 4.65; N: 21.52. Found C: 58.27; H: 4.55; N: 21.70.

***N*-(4-Chlorophenyl)-2-(imidazo[1,2-*a*]pyridin-2-ylcarbonyl)hydrazinecarbothioamide (4h).**

Yield: 75%, mp 214–216 °C. IR (cm<sup>-1</sup>): 3260, 3142 (N–H), 1671 (C=O), 1149 (C=S). <sup>1</sup>H NMR δ (ppm): 6.92 (1H, t, *J*<sub>6,7</sub> = *J*<sub>6,5</sub> = 6.8 Hz, C<sub>6</sub>–H); 7.26–7.30 (3H, m, C<sub>7</sub>–H, phenyl 3,5-H); 7.43 (2H, s, phenyl 2,6-H); 7.55 (1H, d, *J*<sub>7,8</sub> = 9.1 Hz, C<sub>8</sub>–H); 8.41 (1H, s, C<sub>3</sub>–H); 8.52 (1H, d, *J*<sub>5,6</sub> = 6.8 Hz, C<sub>5</sub>–H); 9.68 (1H, broad s, N–H); 9.70 (1H, s, N<sup>1</sup>–H); 10.34 (1H, s, N<sup>2</sup>–H). MS [ESI<sup>-</sup>] (m/z): 344.0 ([M–H]<sup>-</sup>, 67); 310 (100). Anal. calcd. for C<sub>15</sub>H<sub>12</sub>ClN<sub>5</sub>OS: C: 52.10; H: 3.50; N: 20.25. Found C: 51.62; H: 3.52; N: 20.24.

***N*-(4-Bromophenyl)-2-(imidazo[1,2-*a*]pyridin-2-ylcarbonyl)hydrazinecarbothioamide (4i).**

Yield: 75%, mp 209–210 °C. IR (cm<sup>-1</sup>): 3260, 3147 (N–H), 1668 (C=O), 1154 (C=S); <sup>1</sup>H NMR δ (ppm): 7.07 (1H, dd, *J*<sub>6,7</sub> = 9.5 Hz, *J*<sub>6,5</sub> = 6.9 Hz, C<sub>6</sub>–H); 7.43 (1H, dd, *J*<sub>7,8</sub> = 8.5 Hz, *J*<sub>7,6</sub> = 7.3 Hz, C<sub>7</sub>–H); 7.46–7.54 (4H, m, phenyl); 7.66 (1H, d, *J*<sub>8,7</sub> = 8.5 Hz, C<sub>8</sub>–H); 8.53 (1H, s, C<sub>3</sub>–H); 8.66 (1H, d, *J*<sub>5,6</sub> = 6.9 Hz, C<sub>5</sub>–H); 9.77 (1H, broad s, N–H); 9.86 (1H, s, N<sup>1</sup>–H); 10.47 (1H, s, N<sup>2</sup>–H). MS [ESI<sup>-</sup>] (m/z): 390([M–H]<sup>-</sup>, 24), 356 (100). Anal. calcd. for C<sub>15</sub>H<sub>12</sub>BrN<sub>5</sub>OS. H<sub>2</sub>O: C: 44.12; H: 3.45; N: 17.15. Found: C: 43.74; H: 2.83; N: 17.46.

***N*-(4-Fluorophenyl)-2-(imidazo[1,2-*a*]pyridin-2-ylcarbonyl)hydrazinecarbothioamide (4j).**

Yield: 67%, mp 200–203 °C. IR (cm<sup>-1</sup>): 3330, 3147 (N–H), 1682 (C=O), 1184 (C=S). <sup>1</sup>H NMR δ (ppm): 7.00 (1H, t, *J*<sub>6,7</sub> = *J*<sub>6,5</sub> = 6.8 Hz, C<sub>6</sub>–H); 7.10–7.19 (2H, m, phenyl 3,5-H); 7.33–7.45 (3H, m, C<sub>7</sub>–H, phenyl 2,6-H); 7.64 (1H, d, *J*<sub>8,7</sub> = 9.2 Hz, C<sub>8</sub>–H); 8.51 (1H, s, C<sub>3</sub>–H); 8.62 (1H, d, *J*<sub>5,6</sub> = 6.8 Hz, C<sub>5</sub>–H); 9.74 (1H, s, N–H); 9.80 (1H, s, N<sup>1</sup>–H); 10.39 (1H, s, N<sup>2</sup>–H). <sup>13</sup>C NMR (HMBC) δ (ppm): 181.87 (C=S); 160.93 (C=O); 157.97 (d, *J* = 242.03 Hz, phenyl C<sub>4</sub>); 144.61 (imidazo[1,2-*a*]pyridine C<sub>8a</sub>); 138.71 (imidazo[1,2-*a*]pyridine C<sub>2</sub>); 136.31 (d, *J* = 2.4 Hz, phenyl C<sub>1</sub>); 128.35 (imidazo[1,2-*a*]pyridine C<sub>5</sub>); 128.09 (phenyl C<sub>2</sub>, C<sub>6</sub>); 127.21 (imidazo[1,2-*a*]pyridine C<sub>7</sub>); 118.05 (imidazo[1,2-*a*]pyridine C<sub>8</sub>); 116.25 (imidazo[1,2-*a*]pyridine C<sub>3</sub>); 115.29 (d, *J* = 23 Hz, phenyl C<sub>3</sub>, C<sub>5</sub>); 114.03 (imidazo[1,2-*a*]pyridine C<sub>6</sub>). MS [APCI<sup>-</sup>] (m/z): 328 ([M–H]<sup>-</sup>, 21), 294 (100). Anal. calcd. for C<sub>15</sub>H<sub>12</sub>FN<sub>5</sub>OS. 0.5 H<sub>2</sub>O: C: 53.24; H: 3.87; N: 20.70. Found C: 53.91; H: 3.51; N: 20.73.

**General procedure for the synthesis of *N*'-(3-substituted-4-oxo-1,3-thiazolidin-2-ylidene)imidazo[1,2-*a*]pyridine-2-carbohydrazide (5a–f)**

First 0.0035 mol of appropriate hydrazinecarbothioamide (4a–e, 4g) and 0.0055 mol of ethyl bromoacetate were refluxed in absolute ethanol (30 mL) in the presence of anhydrous CH<sub>3</sub>COONa (0.04 mol) for 3 h. The reaction mixture was cooled and the solid thus obtained was filtered, washed with water, and purified by crystallization from an ethanol–water mixture.

***N*'-(3-Methyl-4-oxo-1,3-thiazolidin-2-ylidene)imidazo[1,2-*a*]pyridine-2-carbohydrazide (5a).**

Yield: 86%, mp 281–283 °C. IR (cm<sup>-1</sup>): 3298, 3145 (N–H), 1697 (thia. C=O), 1670 (C=O). <sup>1</sup>H NMR δ (ppm): 3.13 (3H, s, –CH<sub>3</sub>); 4.08 (2H, s, thia. CH<sub>2</sub>); 7.00 (1H, t, *J*<sub>6,7</sub> = *J*<sub>6,5</sub> = 6.8 Hz, C<sub>6</sub>–H); 7.37 (1H, dd, *J*<sub>7,8</sub> = 9.2 Hz; *J*<sub>7,6</sub> = 6.8 Hz; C<sub>7</sub>–H) 7.64 (1H, d, *J*<sub>8,7</sub> = 9.2 Hz, C<sub>8</sub>–H); 8.46 (1H, s, C<sub>3</sub>–H); 8.60 (1H, d, *J*<sub>5,6</sub> = 6.8 Hz,

C<sub>5</sub>-H); 10.42 (1H, s, CONH). <sup>13</sup>C NMR δ (ppm): 172.09 (thia. C=O); 160.65 (thia. C<sub>2</sub>); 159.15 (CONH); 144.63 (imidazo[1,2-*a*]pyridine C<sub>8a</sub>); 139.13 (imidazo[1,2-*a*]pyridine C<sub>2</sub>); 128.36 (imidazo[1,2-*a*]pyridine C<sub>5</sub>); 127.25 (imidazo[1,2-*a*]pyridine C<sub>7</sub>); 118.00 (imidazo[1,2-*a*]pyridine C<sub>8</sub>); 115.81 (imidazo[1,2-*a*]pyridine C<sub>3</sub>); 113.97 (imidazo[1,2-*a*]pyridine C<sub>6</sub>); 33.49 (thia. C<sub>2</sub>); 29.92 (CH<sub>3</sub>). MS [APCI+] (m/z): 290 ([M + H]<sup>+</sup>, 100). Anal. calcd. for C<sub>12</sub>H<sub>11</sub>N<sub>5</sub>O<sub>2</sub>S: C: 49.82; H: 3.83; N: 24.21. Found C: 49.38; H: 3.94; N: 24.55.

***N'*-(3-Ethyl-4-oxo-1,3-thiazolidin-2-ylidene)imidazo[1,2-*a*]pyridine-2-carbohydrazide (5b).**

Yield: 92%, mp 223–224 °C. IR (cm<sup>-1</sup>): 3296, 3148 (N–H); 1707 (thia. C=O), 1680 (C=O). <sup>1</sup>H NMR δ (ppm): 1.58 (3H, t, *J* = 6.3 Hz, –CH<sub>2</sub>CH<sub>3</sub>); 3.75 (2H, q, *J* = 7.0 Hz, –CH<sub>2</sub>CH<sub>3</sub>); 4.08 (2H, s, thia. CH<sub>2</sub>); 7.00 (1H, t, *J*<sub>6,7</sub> = *J*<sub>6,5</sub> = 6.7 Hz, C<sub>6</sub>–H); 7.37 (1H, t, *J*<sub>7,8</sub> = 9.2 Hz; *J*<sub>7,6</sub> = 6.7 Hz; C<sub>7</sub>–H) 7.64 (1H, d, *J*<sub>8,7</sub> = 9.2 Hz, C<sub>8</sub>–H); 8.46 (1H, s, C<sub>3</sub>–H); 8.59 (1H, d, *J*<sub>5,6</sub> = 6.7 Hz, C<sub>5</sub>–H); 10.58 (1H, s, CONH). <sup>13</sup>C NMR (HMBC) δ (ppm): 171.86 (thia. C=O); 160.07 (thia. C<sub>2</sub>); 159.20 (CONH); 144.63 (imidazo[1,2-*a*]pyridine C<sub>8a</sub>); 139.17 (imidazo[1,2-*a*]pyridine C<sub>2</sub>); 128.35 (imidazo[1,2-*a*]pyridine C<sub>5</sub>); 127.22 (imidazo[1,2-*a*]pyridine C<sub>7</sub>); 118.00 (imidazo[1,2-*a*]pyridine C<sub>8</sub>); 115.77 (imidazo[1,2-*a*]pyridine C<sub>3</sub>); 113.95 (imidazo[1,2-*a*]pyridine C<sub>6</sub>); 38.29 (–CH<sub>2</sub>–CH<sub>3</sub>); 33.42 (thia. C<sub>5</sub>); 12.81 (–CH<sub>2</sub>–CH<sub>3</sub>). MS [APCI +] (m/z): 304 ([M + H]<sup>+</sup>, 100). Anal. calcd. for C<sub>13</sub>H<sub>13</sub>N<sub>5</sub>O<sub>2</sub>S: C: 51.47; H: 4.32; N: 23.09. Found C: 51.79; H: 4.19; N: 22.75.

***N'*-(4-Oxo-3-propyl-1,3-thiazolidin-2-ylidene)imidazo[1,2-*a*]pyridine-2-carbohydrazide (5c).**

Yield: 78%, mp 124–126 °C. IR (cm<sup>-1</sup>): 3295, 3137 (N–H); 1708 (thia. C=O); 1673 (C=O). <sup>1</sup>H NMR δ (ppm) 0.86 (3H, t, *J* = 7.5 Hz, –CH<sub>3</sub>); 1.61–1.67 (2H, m, –CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 3.65 (2H, t, *J* = 7.3 Hz, –CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 4.08 (2H, s, thia. CH<sub>2</sub>); 6.98 (1H, t, *J*<sub>6,7</sub> = *J*<sub>6,5</sub> = 6.8 Hz, C<sub>6</sub>–H); 7.36 (1H, dd, *J*<sub>7,8</sub> = 9.2 Hz; *J*<sub>7,6</sub> = 6.8 Hz; C<sub>7</sub>–H) 7.62 (1H, d, *J*<sub>8,7</sub> = 9.2 Hz, C<sub>8</sub>–H); 8.45 (1H, s, C<sub>3</sub>–H); 8.59 (1H, d, *J*<sub>5,6</sub> = 6.8 Hz, C<sub>5</sub>–H); 10.45 (1H, s, CONH). MS [ESI +] (m/z): 318 ([M + H]<sup>+</sup>, 100). Anal. calcd. for C<sub>14</sub>H<sub>15</sub>N<sub>5</sub>O<sub>2</sub>S. H<sub>2</sub>O: C: 50.13; H: 5.11; N: 20.88. Found C: 50.67; H: 4.93; N: 20.72.

***N'*-(3-Benzyl-4-oxo-1,3-thiazolidin-2-ylidene)imidazo[1,2-*a*]pyridine-2-carbohydrazide (5d).**

Yield: 79%, mp 242–244 °C. IR (cm<sup>-1</sup>): 3298, 3142 (N–H), 1700 (thia. C=O); 1685 (C=O). <sup>1</sup>H NMR δ (ppm) 4.16 (2H, s, thia. CH<sub>2</sub>); 4.91 (2H, s, N–CH<sub>2</sub>); 7.01 (1H, t, *J*<sub>6,7</sub> = *J*<sub>6,5</sub> = 6.8 Hz, C<sub>6</sub>–H); 7.27–7.39 (4H, m, phenyl 3,4,5-H, C<sub>7</sub>–H); 7.44 (2H, d, *J* = 7.0 Hz, phenyl 2,6-H); 7.64 (1H, d, *J* = 9.2 Hz, C<sub>8</sub>–H); 8.45 (1H, s, C<sub>3</sub>–H); 8.60 (1H, d, *J*<sub>5,6</sub> = 6.8 Hz, C<sub>5</sub>–H); 10.49 (1H, s, CONH). <sup>13</sup>C NMR (HMBC) δ (ppm) 172.14 (thia. C=O); 160.01 (thia. C<sub>2</sub>); 159.22 (CONH); 144.64 (imidazo[1,2-*a*]pyridine C<sub>8a</sub>); 139.13 (imidazo[1,2-*a*]pyridine C<sub>2</sub>); 136.58 (phenyl C<sub>1</sub>); 129.06 (phenyl C<sub>3</sub>/C<sub>5</sub>); 128.65 (phenyl C<sub>2</sub>/C<sub>6</sub>); 128.36 (imidazo[1,2-*a*]pyridine C<sub>5</sub>); 128.22 (phenyl C<sub>4</sub>); 127.22 (imidazo[1,2-*a*]pyridine C<sub>7</sub>); 118.02 (imidazo[1,2-*a*]pyridine C<sub>8</sub>); 115.79 (imidazo[1,2-*a*]pyridine C<sub>3</sub>); 113.96 (imidazo[1,2-*a*]pyridine C<sub>6</sub>); 46.27 (N–CH<sub>2</sub>); 33.38 (thia. C<sub>5</sub>). MS [APCI +] (m/z): 366 ([M + H]<sup>+</sup>, 100). Anal. calcd. for C<sub>18</sub>H<sub>15</sub>N<sub>5</sub>O<sub>2</sub>S. 0.5 C<sub>2</sub>H<sub>5</sub>OH: C: 58.75; H: 4.67; N: 18.03. Found C: 58.86; H: 5.14; N: 18.36.

***N'*-[4-Oxo-3-(2-phenylethyl)-1,3-thiazolidin-2-ylidene]imidazo[1,2-*a*]pyridine-2-carbohydrazide (5e).** Yield: 84%, mp 214–216 °C. IR (cm<sup>-1</sup>): 3278, 3160 (N–H); 1720 (thia. C=O); 1693 (C=O), <sup>1</sup>H NMR δ (ppm) 3.04 (2H, t, *J* = 7.8 Hz, CH<sub>2</sub>–C<sub>6</sub>H<sub>5</sub>); 3.98 (2H, t, *J* = 7.0 Hz, N–CH<sub>2</sub>); 4.06 (2H, s, thia. CH<sub>2</sub>); 7.07 (1H, t, *J*<sub>6,5</sub> = *J*<sub>6,7</sub> = 6.5 Hz, C<sub>6</sub>–H); 7.27–7.45 (5H, m, phenyl, C<sub>7</sub>–H); 7.70 (1H, d, *J*<sub>8,7</sub> = 9.3 Hz, C<sub>8</sub>–H); 8.52 (1H, s, C<sub>3</sub>–H); 8.67 (1H, d, *J*<sub>5,6</sub> = 6.5 Hz, C<sub>5</sub>–H); 10.58 (1H, s, CONH). MS [ESI +] (m/z): 380 ([M + H]<sup>+</sup>, 35), 362 (100). Anal. calcd. for C<sub>19</sub>H<sub>17</sub>N<sub>5</sub>O<sub>2</sub>S. H<sub>2</sub>O: C: 57.41; H: 4.81; N: 17.62. Found C: 57.79; H: 4.75; N: 17.63.



***N*'-[3-(4-Methylphenyl)-4-oxo-1,3-thiazolidin-2-ylidene]imidazo[1,2-*a*]pyridine-2-carbohydrazide (5f).** Yield: 66%, mp 254–255 °C. IR (cm<sup>-1</sup>): 3319, 3135 (N–H); 1712 (thia. C=O); 1693 (C=O). <sup>1</sup>H NMR δ (ppm): 2.37 (3H, s, –CH<sub>3</sub>); 4.22 (2H, s, thia. CH<sub>2</sub>); 7.00 (1H, t, *J*<sub>6,7</sub> = *J*<sub>6,5</sub> = 6.9 Hz, C<sub>6</sub>–H); 7.22–7.50 (5H, m, phenyl and C<sub>7</sub>–H); 7.64 (1H, d, *J*<sub>8,7</sub> = 9.1 Hz, C<sub>8</sub>–H); 8.44 (1H, s, C<sub>3</sub>–H); 8.58 (1H, d, *J*<sub>5,6</sub> = 6.9 Hz, C<sub>5</sub>–H); 10.38 (1H, s, CONH). MS [ESI +] (*m/z*): 366 ([M + H]<sup>+</sup>, 100). Anal. calcd. for C<sub>18</sub>H<sub>15</sub>N<sub>5</sub>O<sub>2</sub>S: C: 59.16; H: 4.14; N: 19.17. Found C: 59.03; H: 4.00; N: 19.17.

**General procedure for the synthesis of *N*-(nonsubstituted/4-substituted phenyl)-5-(imidazo[1,2-*a*]pyridine-2-yl)-1,3,4-oxadiazole-2-amine (6a–d).**

The appropriate hydrazinecarbothioamides (**4f–j**) (0.0035 mol) were suspended in ethanol 96% (30 mL), and aqueous sodium hydroxide (5 mL, 4 N) and iodine in potassium iodide solution (aqueous 5%) were added with shaking at room temperature until the color of iodine persisted. The solid separated was filtered, and purified by crystallization from ethanol 96%.

**5-(Imidazo[1,2-*a*]pyridin-2-yl)-*N*-phenyl-1,3,4-oxadiazol-2-amine (6a).** Yield: 86%, mp 236–238 °C. IR (cm<sup>-1</sup>): 3229, 3186 (N–H); 1662, 1546, 1480 (C=C, C=N). <sup>1</sup>H NMR δ (ppm) 6.93 (2H, t, *J* = 7.1 Hz, phenyl 4–H, C<sub>6</sub>–H); 7.28 (3H, t, *J* = 7.2 Hz, phenyl 2, 6–H, C<sub>7</sub>–H); 7.55 (3H, t, *J* = 8.3 Hz, phenyl 3,5–H, C<sub>8</sub>–H); 8.48 (1H, s, C<sub>3</sub>–H); 8.54 (1H, d, *J*<sub>5,6</sub> = 6.8 Hz, C<sub>5</sub>–H); 10.64 (1H, s, NH). MS [APCI +] (*m/z*): 278 ([M + H]<sup>+</sup>, 16); 161 (100). Anal. calcd. for C<sub>15</sub>H<sub>11</sub>N<sub>5</sub>S. 2 H<sub>2</sub>O: C: 57.50; H: 4.83; N: 22.35. Found C: 57.81; H: 4.78; N: 22.33.

***N*-(4-Chlorophenyl)-5-(imidazo[1,2-*a*]pyridin-2-yl)-1,3,4-oxadiazol-2-amine (6b).** Yield: 92%, mp 308–310 °C. IR (cm<sup>-1</sup>): 3220, 3107 (N–H); 1645, 1589, 1494 (C=C, C=N). <sup>1</sup>H NMR δ (ppm) 7.03 (1H, t, *J*<sub>6,7</sub> = *J*<sub>6,5</sub> = 6.9 Hz, C<sub>6</sub>–H); 7.38 (1H, dd, *J*<sub>7,6</sub> = 6.9 Hz, *J*<sub>7,8</sub> = 8.3 Hz, C<sub>7</sub>–H); 7.44 (2H, d, *J* = 8.8 Hz, phenyl 2,6–H); 7.65 (3H, d, *J* = 8.9 Hz, phenyl 3,5–H, C<sub>8</sub>–H); 8.58 (1H, s, C<sub>3</sub>–H); 8.63 (1H, d, *J*<sub>5,6</sub> = 6.9 Hz, C<sub>5</sub>–H); 10.91 (1H, s, NH). MS [ESI +] (*m/z*): 312 ([M + H]<sup>+</sup>, 36); 161 (100). Anal. calcd. for C<sub>15</sub>H<sub>10</sub>ClN<sub>5</sub>O. 0.5 H<sub>2</sub>O: C: 56.16; H: 3.45; N: 21.38. Found C: 56.79; H: 3.63; N: 21.73.

***N*-(4-Bromophenyl)-5-(imidazo[1,2-*a*]pyridin-2-yl)-1,3,4-oxadiazol-2-amine (6c).**

Yield: 96%, mp 284–286 °C. IR (cm<sup>-1</sup>): 3230, 3110 (N–H); 1669, 1580, 1484 (C=C, C=N). <sup>1</sup>H NMR δ (ppm): 7.04 (1H, dd, *J*<sub>6,7</sub> = 7.8 Hz, *J*<sub>6,5</sub> = 6.8 Hz, C<sub>6</sub>–H); 7.38 (1H, dd, *J*<sub>7,8</sub> = 9.1 Hz, *J*<sub>7,6</sub> = 7.8 Hz, C<sub>7</sub>–H); 7.54–7.62 (4H, m, phenyl); 7.66 (1H, d, *J*<sub>8,7</sub> = 9.1 Hz, C<sub>8</sub>–H); 8.58 (1H, s, C<sub>3</sub>–H); 8.63 (1H, d, *J*<sub>5,6</sub> = 6.8 Hz, C<sub>5</sub>–H); 10.91 (1H, s, NH). MS [APCI +] (*m/z*): 358 ([M + 2 + H]<sup>+</sup>, 100); 356 ([M + H]<sup>+</sup>, 94). Anal. calcd. for C<sub>15</sub>H<sub>10</sub>BrN<sub>5</sub>O. 0.5 H<sub>2</sub>O: C: 49.33; H: 3.04; N: 19.17. Found C: 49.01; H: 3.77; N: 18.88.

***N*-(4-Fluorophenyl)-5-(imidazo[1,2-*a*]pyridin-2-yl)-1,3,4-oxadiazol-2-amine (6d).** Yield: 94%, mp 226–228 °C. IR (cm<sup>-1</sup>): 3244, 3170 (N–H); 1628, 1593, 1457 (C=C, C=N). <sup>1</sup>H NMR δ (ppm): 7.02 (1H, t, *J*<sub>6,7</sub> = *J*<sub>6,5</sub> = 6.8 Hz, C<sub>6</sub>–H); 7.21 (2H, t, *J* = 8.78, 9.28 Hz, phenyl 2,6–H); 7.36, 7.38 (1H, dd, *J*<sub>7,8</sub> = 9.3 Hz, *J*<sub>7,6</sub> = 6.8 Hz, C<sub>7</sub>–H); 7.61–7.64 (3H, m, phenyl 3,5–H, C<sub>8</sub>–H); 8.55 (1H, s, C<sub>3</sub>–H); 8.62 (1H, d, *J*<sub>5,6</sub> = 6.8 Hz, C<sub>5</sub>–H); 10.71 (1H, s, NH). <sup>13</sup>C NMR (HMBC) δ (ppm): 160.40 (oxadia. C<sub>2</sub>); 158.06 (d, *J* = 237.77 Hz, phenyl C<sub>4</sub>); 155.26 (oxadia. C<sub>5</sub>); 145.70 (imidazo[1,2-*a*]pyridine, C<sub>8a</sub>); 135.83 (phenyl C<sub>1</sub>); 130.61 (imidazo[1,2-*a*]pyridine, C<sub>2</sub>); 128.13 (imidazo[1,2-*a*]pyridine, C<sub>5</sub>); 127.23 (imidazo[1,2-*a*]pyridine, C<sub>7</sub>); 119.42 (d, *J* = 8.43 Hz, phenyl C<sub>2</sub>/C<sub>6</sub>); 117.84 (imidazo[1,2-*a*]pyridine, C<sub>8</sub>); 116.37 (d, *J* = 23.01 Hz, phenyl C<sub>3</sub>/C<sub>5</sub>); 114.13 (imidazo[1,2-*a*]pyridine, C<sub>6</sub>); 113.88 (imidazo[1,2-*a*]pyridine, C<sub>3</sub>). MS [ESI +] (*m/z*): 296

([M + H]<sup>+</sup>, 40); 161 (100). Anal. calcd. for C<sub>15</sub>H<sub>10</sub>FN<sub>5</sub>O: C: 61.02; H: 3.41; N: 23.72. Found C: 60.60; H: 3.17; N: 23.66.

### 3.2. Antifungal activity

Microdilution was conducted according to a standard protocol by the National Committee for Clinical Laboratory Standards (NCCLS).<sup>18,19</sup> RPMI 1640 broth with L-glutamine without sodium bicarbonate was used and buffered with 3-(N-morfolino) propanesulfonic acid (MOPS). The medium was adjusted to pH 7.0 at 25 °C. Amphotericin B was provided by Sigma as the standard. All compounds were dissolved in 100% dimethylsulfoxide according to NCCLS methods.<sup>18,19</sup> The final concentrations were 64 to 0.03 µg/mL for all compounds.

Preparation of inoculum suspensions was based mainly on the NCCLS guidelines and described previously.<sup>19,20</sup> The isolates were subcultured onto potato dextrose agar (PDA) plates at 28 °C, over 7–14 days. The fungal colonies were covered with 1 mL of sterile 0.85% saline, and suspensions were made by gently probing the surface with the tip of a Pasteur pipette. The resulting mixture of conidia and hyphal fragments was withdrawn and transferred to a sterile tube. Heavy particles were allowed to settle for 15–20 min at room temperature; the upper suspension was mixed with a vortex for 15 s. The turbidity of supernatants was measured spectrophotometrically at 530 nm, and transmission was adjusted to 65% to 75%. These stock suspensions were diluted 1:50 in RPMI medium to obtain the final inoculum sizes, which ranged from  $0.4 \times 10^4$  to  $5 \times 10^4$  CFU/mL.

Preparation of inoculum suspensions of *C. albicans* and *C. parapsilosis* was based mainly on the NCCLS guidelines<sup>18</sup> and described previously.<sup>21</sup> Yeasts were grown on Sabouraud dextrose agar for 24 h at 35 °C and from the 24- to 48-h-old culture was suspended in 5 mL of sterile 0.85% saline.

The turbidity of mixed suspension was measured at 530 nm to obtain 75% to 77% transmission and adjusted to  $1 \times 10^6$  to  $5 \times 10^6$  CFU/mL by spectrophotometric method. These stock suspensions were diluted 1:50 in RPMI medium, and further diluted 1:20 with medium to obtain the 2-fold test inoculum ( $1 \times 10^3$  to  $5 \times 10^3$  CFU/mL). The (2-fold) inoculum was diluted 1:1 when wells were inoculated and the desired final inoculum size was achieved ( $0.5 \times 10^3$  to  $2.5 \times 10^3$  CFU/mL).

Microdilution plates (96 U-shaped) were prepared and frozen at -70 °C until needed. Rows 2 to 12 contained the series of compound dilutions in 100-µL volumes and the first row contained 100 µL of compound-free medium, which served as the growth control. Each well was inoculated on the day of the test with 100 µL of the corresponding inoculum. This step brought the compound dilutions and inoculum size to the final test concentrations given above. The microplates of dermatophytes were incubated at 28 °C for 7 days and the microplates of yeasts were incubated at 35 °C for 24 and 48 h. The microplates were read visually with the aid of an inverted reading mirror after 7 days for dermatophytes and after 24 and 48 h for yeasts. For all compounds, the MIC was defined as the lowest concentration showing 100% inhibition of growth.

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