A Convenient and Facile Hantzsch Synthesis of Aryl Imidazo [1,2-*b*]Isoxazolyl-*N*-aryl Thiazol Amines

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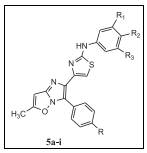

The Hantzsch synthesis of novel aryl imidazo[1,2-*b*]isoxazolyl-*N*-aryl thiazol amines **5** analogues were described. Reaction of 3-aminoisoxazole **1** with substituted phenacyl bromides **2** in dry ethanol afforded the corresponding 6-methyl-3-arylimidazo[1,2-*b*]isoxazoles **3** in good yields. Compounds **3** on reaction with chloroacetyl chloride in 1,4-dioxane furnished the corresponding 2-chloro-1-(6-methyl-3-arylimidazo[1,2-*b*] isoxazol-2-yl)ethanones **4**. Compounds **4** on heating with *N*-aryl thioureas in an oil bath underwent cyclization to afford the title compounds *viz*., imidazo[1,2-*b*]isoxazolyl-*N*-aryl thiazol amines **5** in moderate to good yields by Hantzsch synthesis.

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INTRODUCTION

Fused heterocycles are reported to show a wide variety of applications in medicinal chemistry [1,2]. Despite several reports on the synthesis of fused heterocycles, there is a continuing demand for development of new methods for the synthesis of novel fused heterocycles because of their plethora of medicinal applications [3]. Five-membered heterocycles are important building blocks of an extensive number of biologically active compounds [4]. Imidazoles in biological systems attracted great interest because of their chemical and biochemical characteristics. Even today, research in imidazole chemistry continues to be unabated. Compounds with an imidazole ring system have numerous pharmacological properties and play important role in biochemical processes [5,6]. Medicinal properties of imidazole include anticancer, β-lactamase inhibitor, carboxypeptidase inhibitor, hemeoxygenase inhibitor, antiaging, anticoagulant, anti-inflammatory, antibacterial, antifungal, antiviral, antitubercular, antidiabetic, and antimalarial activity [7–17].Thus, high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents.

The synthesis of thiazole derivatives is important because of their wide range of pharmaceutical and biological properties. One classical and widely used method for the synthesis of thiazole nucleus is the Hantzsch reaction [18–20]. Thiazoles are important class of natural and synthetic compounds and display a wide range of biological activities such as cardiotonic [21], fungicidal [22], sedative [23], anaesthetic [24], bactericidal [25], and anti-inflammatory activity [26].

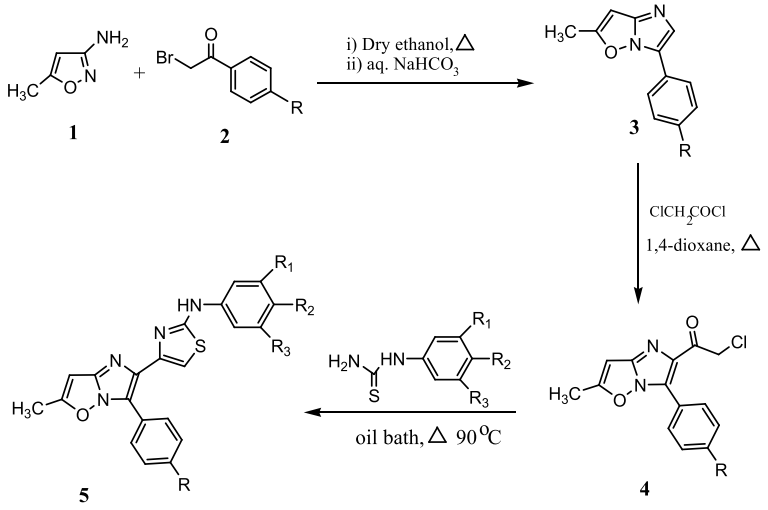
Biological activity of substituted isoxazoles has made them a focus of medicinal chemistry over the years. Isoxazoles are potent analgesic, anti-inflammatory [27], antimicrobial [28], COX-2 inhibitory [29], antitubercular [30], anticonvulsant [31], and anticancer agents [32]. In view of the high degree of bioactivity shown by these heterocyclic systems, and our search for biologically active heterocyclic compounds [33], it was envisaged to construct a system, which possess these moieties in a single molecular frame and to explore the additive effects towards their biological activities. Hence, we are reporting herein the synthesis of imidazo[1,2-*b*]isoxazolyl-*N*-aryl thiazol amines.

RESULTS AND DISCUSSION

The synthesis of 6-methyl-3-arylimidazo[1,2-*b*]isoxazoles **3** was achieved by the reaction of 3-amino-5-methylisoxazole **1** with substituted phenacyl bromides**2** in dry ethanol followed by treatment with aqueous $NaHCO_3$. Compounds **3** on reaction with chloroacetyl chloride in 1,4-dioxane furnished the corresponding 2-chloro-1-(6-methyl-3-arylimidazo[1,2-*b*]isoxazol-2-yl)ethanones **4**. Compounds **4** on heating with *N*-aryl thioureas in an oil bath at 90°C in methanol underwent cyclization to furnish the title compounds *viz*., imidazo[1,2-*b*]isoxazolyl-*N*-aryl thiazol amines **5** in moderate to good yields by Hantzsch synthesis (**Scheme** 1).The structures of the products were established on the basis of elemental analyses and by spectral (IR, ^{1}H NMR, ^{13}C NMR, and MS) data.

Optimum conditions for carrying out the Hantzsch synthesis were ascertained by carrying out a series of reactions of 2-chloro-1-(6-methyl-3-arylimidazo[1,2-b]isoxazol-2-yl) ethanones **4** with *N*-aryl thioureas. The results, which are summarized in Table 1 showed that, maximum yield

Scheme 1 [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



3& 4	R
a	H
b	Cl
c	CH_3
d	OCH_3
e	Br
f	CN

5	R	R_1	R_2	R_3
a	H	H	H	H
b	Cl	H	H	H
c	CH_3	H	H	H
d	OCH_3	H	H	H
e	Br	H	H	H
f	CN	H	H	H
g	H	Cl	H	H
h	H	H	Cl	H
i	H	H	OCH_3	H
j	Cl	Cl	H	H
k	Br	H	Cl	H
l	CH_3	Cl	H	Cl
m	OCH_3	Cl	H	Cl

Table 1

Screening of solvents, reaction time, and temperature for the synthesis of **5a**.

Solvent	Temperature (°C)	Time (h)	Yield* (%)
No solvent	90	8	Trace
Methanol	60	8	55
Methanol	90	6	60
Methanol	90	8	68
Methanol	120	8	68
Ethanol	90	8	58
CH_3CN	90	8	32
DMF	90	8	45
THF	90	8	25
Toulene	90	8	27
Water	90	8	Trace
DMSO	90	8	35
Et_2O	90	8	20

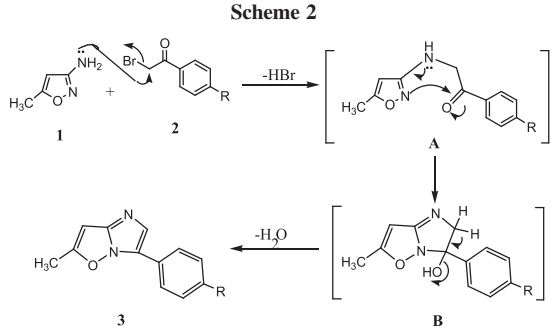
*Isolated and optimized yields

of **5a** (68%) was obtained by heating at 90°C for 8 h in methanol. The presence of electron withdrawing groups Cl, Br, and CN on benzene ring decreased yield of products, whereas electron releasing groups CH_3 and OCH_3 enhanced the yields, but the difference is not remarkable.

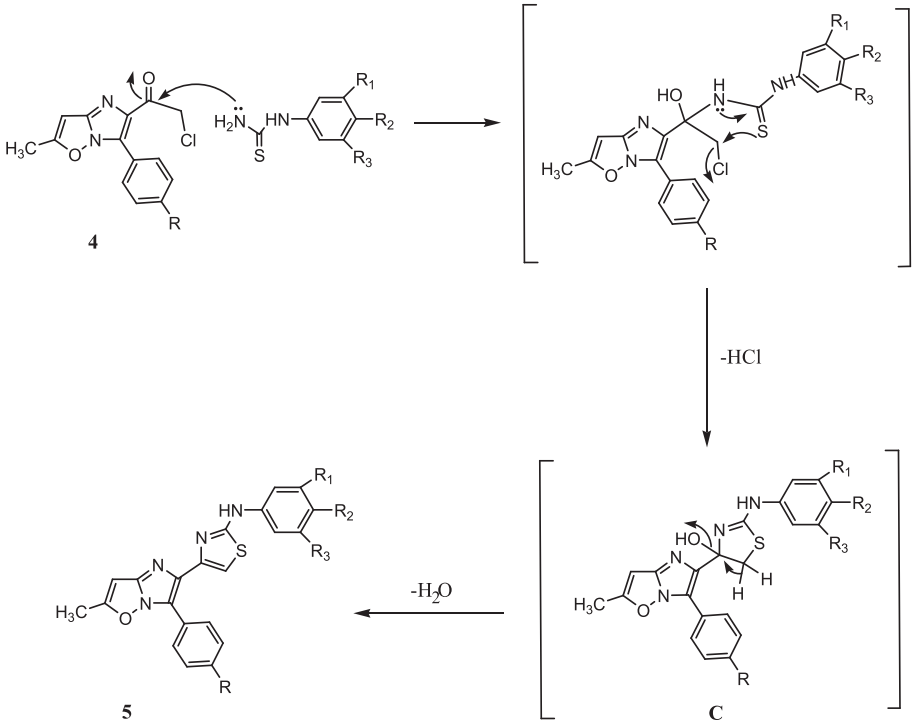
The plausible mechanism for the formation of 6-methyl-3-aryl imidazolo[1,2-*b*]isoxazoles **3** is depicted in the **Scheme** 2. The amino group of isoxazole makes a nucleophilic attack on bromine bearing carbon there by displaces HBr to give intermediate **A**. The C=N group of isoxazole activated by NH group attacks carbonyl group and undergoes intramolecular cyclization to give compound **B**, which then undergoes spontaneous dehydration by the action of $NaHCO_3$ to afford the compounds **3**.

A mechanistic rationalization for the formation of thiazole ring could be explained as follows: the amino group

Scheme 2



Scheme 3



of aryl thiourea attacks the carbonyl group initially, followed by the attack of C=S group, being activated by NH group, on halogen bearing carbon which eliminates HCl to give cyclized product **C**.**C** undergoes dehydration to afford the thiazole ring (**Scheme** 3).

CONCLUSION

In conclusion, we have successfully developed an easy practical access to a novel series of imidazo[1,2-*b*] isoxazolyl-*N*-aryl thiazol amines derivatives. Thus, the mild reaction conditions, easy work up procedure, good yields, and readily available starting materials make this reaction an attractive method for the preparation of title compounds. This synthesis benefits from a simple method of purification, which does not require chromatography. This ease of purification compliments this synthetic technology practical, easy to perform, and facile.

EXPERIMENTAL

All the melting points were determined on a Cintex melting point apparatus and are uncorrected. Analytical TLC was performed on Merck precoated 60 F_{254} silica gel plates. Visualization was done by exposing to iodine vapour. IR spectra (KBr pellet) were recorded on a Perkin-Elmer BX series FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini 300-MHz spectrometer. ^{13}C NMR spectra were recorded on a Bruker 75-MHz spectrometer. Chemical shift values are given in ppm (δ) with tetramethyl silane as internal standard. Mass spectral measurements were carried out by EI method on a Jeol JMC-300 spectrometer at **7**0 ev. Elemental analyses were performed on a Carlo Erba 106 and Perkin-Elmer model 240 analysers.

General procedure for the synthesis of 6-methyl-3-aryl imidazo[1,2-*b*]isoxazoles (3a–f). A solution of 3-amino-5-methylisoxazole **1** (0.01 mol), and ω-bromo acetophenone **2** (0.01 mol) in dry ethanol (20 mL) was refluxed for 8 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured on to 25 mL of saturated $NaHCO_3$ solution with stirring. This mixture was extracted with chloroform (3 × 20 mL), and the combined organic layers were distilled under reduced pressure. The resulting solid was purified by recrystallization from ethyl acetate.

6-Methyl-3-phenylimidazo[1,2-b]isoxazole(3a). Pale yellow; yield 75%, m.p. 126–128°C; IR (KBr) cm^{-1}: 1635 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.20 (s, 3H, CH_3), 6.10 (s, 1H, isoxazole–H), 7.00 (s, 1H, imidazole–H), 7.10–7.65(m, 5H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):12.38, 100.52, 120.01, 122.03, 127.45, 127.50, 128.62, 129.31, 129.48, 133.10, 136.07, 169.63. EI-MS [M + H]$^+$ *m/z* 199. *Anal.* Calcd. for $C_{12}H_{10}N_2O$: C, 72.72; H, 5.05; N, 14.14. Found. C, 72.75; H, 5.03; N, 14.12%.

3-(4-Chlorophenyl)-6-methylimidazo[1,2-b]isoxazole(3b). Pale yellow; yield 72%, m.p. 150–152°C; IR (KBr) cm^{-1}: 1630 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.25 (s, 3H,

CH_3), 6.10 (s, 1H, isoxazole–H), 6.95(s, 1H, imidazole–H), 7.20 (d, 2H, ArH), 7.60 (d, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.57, 100.42, 120.14, 122.17, 127.38, 127.63, 128.51, 129.57, 129.98, 133.02, 136.45, 169.63. EI-MS $[M+H]^+$ *m/z* 233. *Anal*. Calcd. for $C_{12}H_9N_2OCl$: C, 62.06; H, 3.87; N, 12.06. Found. C, 62.04; H, 3.88; N, 12.04%.

6-Methyl-3-(4-methylphenyl)imidazo[1,2-b]isoxazole(3c). Pale yellow; yield 75%, m.p. 130–132°C; IR (KBr) cm^{-1}: 1620 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.22 (s, 3H, isoxazole–CH_3), 2.52 (s, 3H, ArCH_3), 6.10 (s, 1H, isoxazole–H), 6.95 (s, 1H, imidazole–H), 7.10 (d, 2H, ArH), 7.65 (d, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.20, 28.54, 100.55, 120.34, 122.76, 127.57, 127.84, 128.34, 129.26, 129.83, 133.12, 136.67, 169.45. EI-MS $[M+H]^+$ *m/z* 213. *Anal*. Calcd. for $C_{13}H_{12}N_2O$: C, 73.58; H, 5.66; N, 13.20. Found.C,73.60;H,5.68;N,13.18%.

3-(4-Methoxyphenyl)-6-methylimidazo[1,2-b]isoxazole(3d). Pale yellow; yield 78%, m.p. 141–143°C; IR (KBr) cm^{-1}: 1625 (C=N), 1215 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.25 (s, 3H, isoxazole–CH_3), 3.60 (s, 3H, OCH_3), 6.10 (s, 1H, isoxazole–H), 7.00 (s, 1H, imidazole–H), 7.20 (d, 2H, ArH), 7.55 (d, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.11, 56.23, 100.14, 120.28, 122.59, 127.36, 127.66, 128.22, 129.17, 129.43, 133.10, 136.42, 169.39. EI-MS $[M+H]^+$ *m/z* 229. *Anal*. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.42; H, 5.26; N, 12.28. Found. C, 68.44; H, 5.22; N, 12.26%.

3-(4-Bromophenyl)-6-methylimidazo[1,2-b]isoxazole (3e). Pale yellow; yield 71%, m.p. 162–164°C; IR (KBr) cm^{-1}: 1630 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.21 (s, 3H, CH_3), 6.10 (s, 1H, isoxazole–H), 6.92 (s, 1H, imidazole–H), 7.21 (d, 2H, ArH), 7.66 (d, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):12.31, 100.43, 120.21, 122.16, 127.24, 127.63, 128.56, 129.20, 129.39, 133.05, 136.17, 169.55. EI-MS $[M+H]^+$ *m/z* 277. *Anal*. Calcd. for $C_{12}H_9N_2OBr$: C, 52.17; H, 3.26; N, 10.14. Found. C, 52.19; H, 3.25; N, 10.12%.

4-(6-Methylimidazo[1,2-b]isoxazol-3-yl)benzonitrile (3f) Pale yellow; yield 71%, m.p. 156–158°C; IR (KBr) cm^{-1}: 1627 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.20 (s, 3H, CH_3), 6.13 (s, 1H, isoxazole–H), 6.89(s, 1H, imidazole–H), 7.22 (d, 2H, ArH), 7.65 (d, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.22, 100.55, 110.13, 120.28, 122.17, 127.33, 127.68, 128.47, 129.29, 129.41, 133.12, 136.23, 169.63. EI-MS $[M+H]^+$ *m/z*224. *Anal*. Calcd. for $C_{13}H_9N_3O$: C, 69.64; H, 4.01; N, 18.75. Found. C, 69.60; H, 3.98; N, 18.76%.

General procedure for the synthesis of 2-chloro-1-(6-methyl-3-arylimidazo[1,2-*b*]isoxazol-2-yl)ethanones (4a–f). Chloroacetyl chloride (0.01 mol) was added to a well stirred solution of imidazo[1,2-*b*]isoxazoles **3** (0.01 mol) in 1,4-dioxane (20 mL) by stirring at 70°C. After stirring for 30 min the reaction mixture was refluxed at 105°C for 5 h. After completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool to room temperature. The solid thus obtained was filtered and recrystallized from ethanol.

2-Chloro-1-(6-methyl-3-phenylimidazo[1,2-b]isoxazol-2-yl)ethanone (4a). Pale yellow; yield 80%, m.p. 156–158°C; IR (KBr) cm^{-1}: 1630 (C=N), 1710 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.25 (s, 3H, isoxazole–CH_3), 4.22 (s, 2H, CH_2), 6.00 (s, 1H, isoxazole–H), 7.20–7.68 (m, 5H, Ar—H).^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):12.82, 43.82, 100.21, 127.31, 127.58, 128.52, 129.19, 129.39, 132.01, 133.16, 136.07, 143.01, 169.62, 192.41. EI-MS $[M+H]^+$ *m/z* 275. *Anal*. Calcd. for $C_{14}H_{11}N_2O_2Cl$: C, 61.31; H, 4.01; N, 10.21. Found. C, 61.33; H, 4.04; N, 10.24%.

2-Chloro-1-(3-(4-chlorophenyl)-6-methylimidazo[1,2-b]isoxazol-2-yl)ethanone (4b). Pale yellow; yield 78%, m.p. 190–192°C; IR (KBr) cm^{-1}: 1620 (C=N), 1705 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.20 (s, 3H, isoxazole–CH_3), 4.25 (s, 2H, CH_2), 6.05 (s, 1H, isoxazole–H), 7.00 (d, 2H, Ar—H), 7.40 (d, 2H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):12.61, 43.72, 100.37, 127.28, 127.54, 128.61, 129.17, 129.42, 132.00, 133.13, 136.19, 143.21, 169.53, 192.39. EI-MS $[M+H]^+$ *m/z* 309. *Anal*. Calcd. for $C_{14}H_{10}N_2O_2Cl_2$: C, 54.54; H, 3.24; N, 9.09. Found. C, 54.53; H, 3.26; N 9.05%.

2-Chloro-1-(6-methyl-3-p-tolylimidazo[1,2-b]isoxazol-2-yl)ethanone (4c). Pale yellow; yield 82%, m.p. 148–150°C; IR (KBr) cm^{-1}: 1630 (C=N), 1705 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.25 (s, 3H, isoxazole–CH_3), 2.50 (s, 3H, Ar—CH_3), 4.25 (s, 2H, CH_2), 6.10 (s, 1H, isoxazole–H), 7.05 (d, 2H, Ar—H), 7.55 (d, 2H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):12.62, 26.32, 43.53, 100.11, 127.27, 127.66, 128.41, 129.10, 129.42, 132.11, 133.21, 136.32, 143.13, 169.52, 192.58. EI-MS $[M+H]^+$ *m/z* 289. *Anal*. Calcd. for $C_{15}H_{13}N_2O_2Cl$: C, 62.50; H, 4.51; N, 9.72. Found. C, 62.52; H, 4.48; N, 9.75%.

2-Chloro-1-(3-(4-methoxyphenyl)-6-methylimidazo[1,2-b]isoxazol-2-yl)ethanone (4d). Pale yellow; yield 80%, m.p. 152–154°C; IR (KBr) cm^{-1}: 1622 (C=N), 1705 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.28 (s, 3H, isoxazole–CH_3), 3.65 (s, 3H, OCH_3), 4.30 (s, 2H, CH_2), 6.05 (s, 1H, isoxazole–H), 7.20 (d, 2H, Ar—H), 7.42 (d, 2H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):12.51, 43.75, 59.20 100.36, 127.41, 127.65, 128.38, 129.14, 129.40, 132.09, 133.20, 136.13, 143.22, 169.48, 192.37. EI-MS $[M+H]^+$ *m/z* 305. *Anal*. Calcd. for $C_{15}H_{13}N_2O_3Cl$: C, 59.21; H, 4.27; N, 9.21. Found. C, 59.25; H, 4.29; N, 9.24%.

2-Chloro-1-(3-(4-bromophenyl)-6-methylimidazo[1,2-b]isoxazol-2-yl)ethanone (4e). Pale yellow; yield 75%, m.p. 200–202°C; IR (KBr) cm^{-1}: 1621 (C=N), 1710 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.24 (s, 3H, isoxazole–CH_3), 4.26 (s, 2H, CH_2), 6.05 (s, 1H, isoxazole–H), 7.22 (d, 2H, Ar—H), 7.61 (d, 2H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):12.40, 43.77, 100.16, 127.28, 127.46, 128.45, 129.10, 129.40, 132.21, 133.07, 136.18, 143.11, 169.53, 192.56. EI-MS $[M+H]^+$ *m/z* 353. *Anal*. Calcd. for $C_{14}H_{10}N_2O_2ClBr$: C, 47.72; H, 2.84; N, 7.95. Found. C, 47.70; H, 2.85; N, 7.93%.

4-(2-(2-Chloroacetyl)-6-methylimidazo[1,2-b]isoxazol-2-yl) benzonitrile (4f). Pale yellow; yield 71%, m.p. 197–199°C; IR (KBr) cm^{-1}: 1621 (C=N), 1710 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.24 (s, 3H, isoxazole–CH_3), 4.26 (s, 2H, CH_2), 6.05 (s, 1H, isoxazole–H), 7.22 (d, 2H, Ar—H), 7.61 (d, 2H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):12.40, 43.77, 100.16, 112.46, 127.28, 127.46, 128.45, 129.10, 129.40, 132.21, 133.07, 136.18, 143.11, 169.53, 192.56. EI-MS $[M+H]^+$ *m/z* 300. *Anal*. Calcd. for $C_{15}H_{10}N_3O_2Cl$: C, 60.00; H, 3.33; N, 14.00. Found. C, 60.03; H, 3.36; N, 14.03%.

General procedure for the synthesis of 4-(6-methyl-3-arylimidazo[1,2-*b*]isoxazol-2-yl)-*N*-aryl-thiazol-2-amines (5a–m). 2-Chloro-1-(6-methyl-3-arylimidazo[1,2-*b*]isoxazol-2-yl)ethanones **4** (0.01 mol) and substituted phenyl thiourea (0.01 mol) were taken in a round bottomed flask, and methanol (10 mL) was added to this mixture and was refluxed in an oil bath at 90°C for 8 h. Termination of the reaction was monitored by TLC. The solid mass obtained after cooling was filtered and washed with cold methanol (15 mL). The filtrate was discarded. The crude product was purified by recrystallization form ethylacetate.

4-(6-Methyl-3-phenylimidazo[1,2-b]isoxazol-2-yl)-N-phenylthiazol-2-amine (5a). Pale yellow; yield 68%, m.p. 168–170°C; IR (KBr) cm^{-1}: 1630 (C=N), 3210 (NH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.25 (s, 3H, isoxazole–CH_3), 6.10 (s, 1H, isoxazole–H), 7.10 (s, 1H, thiazole–H), 7.21–7.72 (m, 10H, Ar—H), 10.50 (bs, 1H, NH, D_2O exchangeable).^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):12.62, 100.42, 104.51, 122.08, 126.41, 126.63, 127.42, 127.64, 128.41, 128.73, 129.24, 129.56, 129.68, 129.87, 133.10, 136.11, 139.27, 143.17, 149.55, 159.01, 169.63. EI-MS $[M+H]^+$ *m/z* 373. *Anal*. Calcd. for $C_{21}H_{16}N_4OS$: C, 67.74; H, 4.30; N, 15.05. Found. C, 67.72; H, 4.33; N, 15.02%.

4-(3-(4-Chlorophenyl)-6-methylimidazo[1,2-b]isoxazol-2-yl)-N-phenylthiazol-2-amine (5b). Pale yellow; yield 61%, m. p. 212–214°C; IR (KBr) cm^{-1}: 1625 (C=N), 3215 (NH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.22 (s, 3H, isoxazole–CH_3), 6.05 (s, 1H, isoxazole–H), 7.00 (s, 1H, thiazole–H), 7.15–7.66 (m, 9H, Ar—H), 10.05 (bs, 1H, NH, D_2O exchangeable). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):12.51, 100.27, 104.43, 122.16, 126.37, 126.60, 127.39, 127.59, 128.38, 128.75, 129.28, 129.41, 129.58, 129.89, 133.04, 136.10, 139.23, 143.21, 149.50, 159.16, 169.53. EI-MS $[M+H]^+$ *m/z* 407. *Anal*. Calcd. for $C_{21}H_{15}ClN_4OS$: C, 62.06; H, 3.69; N, 13.79. Found. C, 62.03; H, 3.65; N, 13.81%.

4-(6-Methyl-3-p-tolylimidazo[1,2-b]isoxazol-2-yl)-N-phenylthiazol-2-amine (5c). Pale yellow; yield 72%, m.p. 182–184 C; IR (KBr) cm^{-1}: 1621 (C=N), 3212(NH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.20 (s, 3H, isoxazole–CH_3), 2.48 (s, 3H, Ar—CH_3), 6.10 (s, 1H, isoxazole–H), 7.14 (s, 1H, thiazole–H), 7.25–7.68 (m, 9H, Ar—H), 10.21 (bs, 1H, NH, D_2O exchangeable). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.43, 27.22, 100.36, 104.57, 122.17, 126.33, 126.47, 127.41, 127.60, 128.38, 128.70, 129.22, 129.66, 129.74, 129.80, 133.16, 136.18, 139.18, 143.08, 149.46, 159.11, 169.59. EI-MS $[M+H]^+$ *m/z* 387. *Anal*. Calcd. for $C_{22}H_{18}N_4OS$: C, 68.39; H, 4.66; N, 14.50. Found. C, 68.37; H, 4.69; N, 14.53%.

4-(3-(4-Methoxyphenyl)-6-methylimidazo[1,2-b]isoxazol-2-yl)-N-phenylthiazol-2-amine (5d). Pale yellow; yield 73%, m.p. 175–177°C; IR (KBr) cm^{-1}: 1615 (C=N), 3235 (NH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.20 (s, 3H, isoxazole–CH_3),3.62 (s, 3H, OCH_3), 6.10 (s, 1H, isoxazole–H), 7.10 (s, 1H, thiazole–H), 7.10–7.54 (m, 9H, Ar—H), 9.96 (bs, 1H, NH, D_2O exchangeable). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.61, 55.37, 100.44, 104.60, 122.21, 126.38, 126.65, 127.55, 127.61, 128.33, 128.64, 129.12, 129.46, 129.60, 129.84, 133.18, 136.22, 139.25, 143.16, 149.50, 159.15, 169.60. EI-MS $[M+H]^+$ *m/z* 403. *Anal*. Calcd. for $C_{22}H_{18}N_4O_2S$: C, 65.67; H, 4.47; N, 13.93. Found. C, 65.69; H, 4.45; N, 13.96%.

4-(3-(4-Bromophenyl)-6-methylimidazo[1,2-b]isoxazol-2-yl)-N-phenylthiazol-2-amine (5e). Pale yellow; yield 66%, m. p. 232–234°C; IR (KBr) cm^{-1}: 1625 (C=N), 3205 (NH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.00 (s, 3H, isoxazole–CH_3), 6.10 (s, 1H, isoxazole–H), 7.06 (s, 1H, thiazole–H), 7.10–7.45 (m, 9H, Ar—H), 10.20 (bs, 1H, NH, D_2O exchangeable).^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.51, 100.39, 104.48, 122.11, 126.52, 126.68, 127.39, 127.55, 128.36, 128.69, 129.18, 129.46, 129.59, 129.77, 133.14, 136.09, 139.22, 143.25, 149.45, 159.17, 169.58. EI-MS $[M+H]^+$ *m/z* 451. *Anal*. Calcd. for $C_{21}H_{15}BrN_4OS$: C, 56.00; H, 3.33; N, 12.44. Found. C, 56.02; H, 3.35; N, 12.47%.

4-(6-Methyl-2(2-phenylamino)thiazol-4-yl)imidazo[1,2-b]isoxazol-2-yl)benzonitrile (5f). Pale yellow; yield 61%, m.p. 170–172°C; IR (KBr) cm^{-1}: 1623 (C=N), 3218(NH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.20 (s, 3H, isoxazole–CH_3), 6.10 (s, 1H, isoxazole–H), 7.00 (s, 1H, thiazole–H), 7.17–7.57 (m, 9H, Ar—H), 10.18 (bs, 1H, NH, D_2O exchangeable). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.25, 100.26, 104.51, 111.21, 122.10, 126.27, 126.50, 127.41, 127.74, 128.36, 128.66, 129.18, 129.45, 129.56, 129.80, 133.23, 136.19, 139.17, 143.12, 149.92, 159.34, 169.59. EI-MS $[M+H]^+$ *m/z* 398. *Anal*. Calcd. for $C_{22}H_{15}N_5OS$: C, 66.33; H, 3.76; N, 17.58. Found. C, 66.30; H, 3.72; N, 17.60%.

N-(3-Chlorophenyl)-4-(6-methyl-3-phenylimidazo[1,2-b]isoxazol-2-yl)thiazol-2-amine (5g). Pale yellow; yield 62%, m.p. 214–216°C; IR (KBr) cm^{-1}: 1625 (C=N), 3220 (NH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.25 (s, 3H, isoxazole–CH_3), 6.08 (s, 1H, isoxazole–H), 7.02 (s, 1H, thiazole–H), 7.10–7.65 (m, 9H, Ar—H), 10.25 (bs, 1H, NH, D_2O exchangeable). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.52, 100.36, 104.55, 122.00, 126.28, 126.56, 127.45, 127.72, 128.39, 128.75, 129.28, 129.60, 129.71, 129.83, 133.20, 136.18, 139.24, 143.10, 149.42, 159.11, 169.53. EI-MS $[M+H]^+$ *m/z* 407. *Anal*. Calcd. for $C_{21}H_{15}ClN_4OS$: C, 62.06; H, 3.69; N, 13.79. Found. C, 62.08; H, 3.67; N, 13.80%.

N-(4-Chlorophenyl)-4-(6-methyl-3-phenylimidazo[1,2-b]isoxazol-2-yl)thiazol-2-amine (5h). Pale yellow; yield 64%, m.p. 226–228°C; IR (KBr) cm^{-1}: 1622 (C=N), 3228 (NH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.20 (s, 3H, isoxazole–CH_3), 6.10 (s, 1H, isoxazole–H), 7.02 (s, 1H, thiazole–H), 7.20–7.45 (m, 9H, Ar—H), 10.00 (bs, 1H, NH, D_2O exchangeable).^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.42, 100.27, 104.57, 122.01, 126.44, 126.57, 127.40, 127.59, 128.38, 128.75, 129.19, 129.55, 129.60, 129.84, 133.14, 136.07, 139.25, 143.09, 149.43, 159.21, 169.61. EI-MS $[M+H]^+$ *m/z* 407. *Anal*. Calcd. for $C_{21}H_{15}ClN_4OS$: C, 62.06; H, 3.69; N, 13.79. Found. C, 62.04; H, 3.65; N, 13.83%.

N-(4-Methoxyphenyl)-4-(6-methyl-3-phenylimidazo[1,2-b]isoxazol-2-yl)thiazol-2-amine (5i). Pale yellow; yield 68%, m.p. 160–162°C; IR (KBr) cm^{-1}: 1620 (C=N), 3230(NH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.20 (s, 3H, isoxazole–CH_3), 3.57 (s, 3H, OCH_3), 6.00 (s, 1H, isoxazole–H), 7.05 (s, 1H, thiazole–H), 7.15–7.80 (m, 9H, Ar—H), 10.15 (bs, 1H, NH, D_2O exchangeable). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.55, 56.32, 100.21, 104.46, 122.17, 126.38, 126.52, 127.36, 127.58, 128.37, 128.74, 129.32, 129.58, 129.52, 129.77, 133.21, 136.09, 139.24, 143.17, 149.42, 159.06, 169.60. EI-MS $[M+H]^+$ *m/z* 403. *Anal*. Calcd. for $C_{22}H_{18}N_4O_2S$: C, 65.67; H, 4.47; N, 13.93. Found. C, 65.64; H, 4.43; N, 13.90%.

N-(3-Chlorophenyl)-4-(3-(4-chlorophenyl)-6-methylimidazo[1,2-b]isoxazol-2-yl)thiazol-2-amine (5j). Pale yellow; yield 60%, m.p. 240–242°C; IR (KBr) cm^{-1}: 1620 (C=N), 3210 (NH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.20 (s, 3H, isoxazole–CH_3), 6.00 (s, 1H, isoxazole–H), 7.12 (s, 1H, thiazole–H), 7.22–7.75 (m, 9H, Ar—H), 10.15 (bs, 1H, NH, D_2O exchangeable). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.47, 100.38, 104.55, 122.03, 126.38, 126.60, 127.33, 127.54, 128.40, 128.68, 129.24, 129.52, 129.67, 129.90, 133.15, 136.19, 139.25, 143.17, 149.42, 159.17, 169.59. EI-MS $[M+H]^+$ *m/z* 441. *Anal*. Calcd. for $C_{21}H_{14}Cl_2N_4OS$: C, 57.27; H, 3.18; N, 12.72. Found. C, 57.29; H, 3.17; N, 12.70%.

4-(3-(4-Bromophenyl)-6-methylimidazo[1,2-b]isoxazol-2-yl)-N-(4-chlorophenyl)thiazol-2-amine (5k). Pale yellow; yield 77%, m.p. 185–187 C; IR (KBr) cm^{-1}: 1632 (C=N), 3216 (NH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.21 (s, 3H, isoxazole–CH_3), 6.11 (s, 1H, isoxazole–H), 7.13 (s, 1H, thiazole–H), 7.01–7.71 (m, 8H, Ar—H), 10.16 (bs, 1H, NH, D_2O exchangeable).^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.54, 100.33, 104.45, 122.11, 126.51, 126.68, 127.32, 127.52, 128.40, 128.71, 129.14, 129.52, 129.9, 129.70, 133.12, 136.18, 139.31, 143.20, 149.45, 159.11, 169.53. EI-MS $[M+H]^+$ *m/z* 485. *Anal*. Calcd. for $C_{21}H_{14}N_4OSBrCl$: C, 52.06; H, 2.89; N, 11.57. Found. C, 52.01; H, 2.90; N, 11.55%.

N-(3,5-Dichlorophenyl)-4-methyl-3-p-tolylimidazo[1,2-b]isoxazol-2-yl)thiazol-2-amine (5l). Pale yellow; yield 63%, m.p. 202–204 C; IR (KBr) cm^{-1}: 1626 (C=N), 3212 (NH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.20 (s, 3H, isoxazole–CH_3), 2.42 (s, 3H, Ar—CH_3), 6.02 (s, 1H, isoxazole–H), 7.16 (s, 1H, thiazole–H), 7.08–7.64 (m, 8H, Ar—H), 10.50 (bs, 1H, NH, D_2O exchangeable).^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.48, 26.42, 100.40, 104.44, 122.18, 126.38, 126.45, 127.36, 127.55, 128.32, 128.64, 129.15, 129.45, 129.69, 129.77, 133.15, 136.10, 139.31, 143.20, 149.50, 159.12, 169.59. EI-MS $[M+H]^+$ *m/z* 452. *Anal*. Calcd. for $C_{22}H_{13}N_4OSCl_2$: C, 58.14; H, 2.86; N, 12.33. Found. C, 58.11; H, 2.81; N, 12.37%.

N-(3,5-Dichlorophenyl)-4-(3-(4-methoxyphenyl)-6-methylimidazo[1,2-b]isoxazol-2-yl)thiazol-2-amine (5m). Pale yellow; yield 62%, m.p. 218–220°C; IR (KBr) cm^{-1}: 1628 (C=N), 3211 (NH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.22 (s, 3H, isoxazole–CH_3), 3.28 (s, 3H, Ar—OCH_3), 6.11 (s, 1H, isoxazole–H), 7.18 (s, 1H, thiazole–H), 7.11–7.68 (m, 8H, Ar—H), 10.22 (bs, 1H, NH, D_2O exchangeable).^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.56, 52.36, 100.36, 104.41, 122.03, 126.36, 126.55, 127.41, 127.69, 128.33, 128.54, 129.19, 129.60, 129.77, 129.92, 133.18, 136.12, 139.25, 143.10, 149.45, 159.09, 169.55. EI-MS $[M+H]^+$ *m/z* 468. *Anal*. Calcd. for $C_{22}H_{13}N_4O_2SCl_2$: C, 56.17; H, 2.76; N, 11.91. Found. C, 56.14; H, 2.80; N, 11.95%.

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