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# Synthesis of oxadiazole, thiadiazole and tetrazole derivatives of *1H*- imidazo[*4,5-b*]pyridines

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**ABSTRACT**

*Oxadiazole, Tetrazole and Thiadiazole derivatives of 1H-Imidazo[4,5-b]pyridine are synthesized by using simple reagents like $I_2$/KI, NaOH, $H_2SO_4$ in an efficient manner. The structures of the synthesized compounds are analysed by IR, $^1$HNMR and Mass spectra.*

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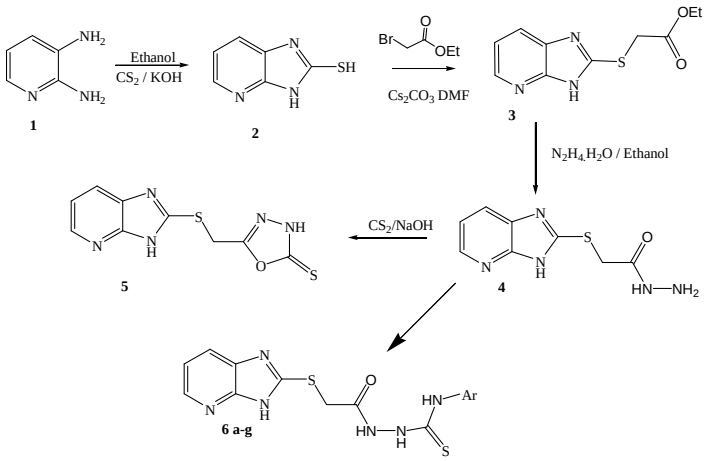
## INTRODUCTION

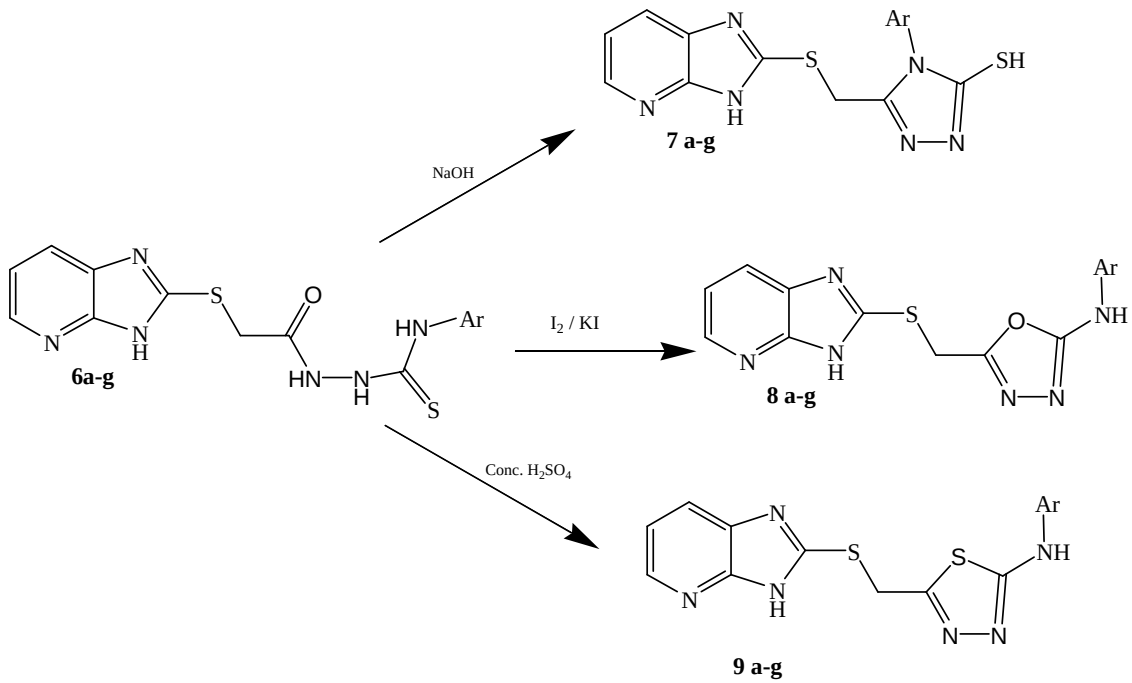
1,2,3-triazole nucleus is associated with diverse pharmacological activities such as analgesic, antiasthematic, diuretic antihypertensive and antiinflammatory properties which have made them important chemotherapeutic agents.[17-20] Derivatives of 1,3,4-oxadiazole are also known to have a broad spectrum of biological activities. Acyl hydrazides have been in general use as the starting materials in some 1,2,4-triazoles and 1,3,4-oxadiazole syntheses. Hence, we undertook the synthesis of oxadiazole, thiadiazole and tetrazole derivatives of 1*H*-imidazo[4,5-b]pyridines.

**Scheme 1**




*Ar = phenyl, 4-chlorophenyl, 2-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl*

**Scheme 2**




*Ar = phenyl, 4-chlorophenyl, 2-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl*

## MATERIALS AND METHODS

Chemicals and solvents were reagent grade and used without further purification. Melting points were determined on a capillary melting point apparatus and are uncorrected. The $^1$H NMR was recorded in the indicated solvent on a Varian 500 MHz spectrometer with TMS as internal standard. All chemical shifts (δ) were reported in ppm from internal TMS. Mass spectra were measured on a Jeol JMS D-300 spectrometer. Infrared spectra were recorded in KBr on Brucher-IFS-66 FTIR spectrophotometer. The homogeneity of the compounds was checked using precoated TLC plates (E.Merk Kieselgel 60 $F_{254}$).

**Ethyl 2-(3H-imidazo[4,5-b]pyridin-2-ylthio)acetate (3)**

3H-imidazo [4,5-b]pyridine-2-thiol **(2)** (0.01 mole) and bromoethylacetate (0.01 ml) in Ethanol (10 ml) were refluxed for 8 hrs in Ethanol. The reaction was monitored by TLC. After the completion of reaction it is neutralized with AcOH and poured on to crushed ice. The product was extracted and filtered to give the compound (**3**) with 87% yield.

M.P: 204$^0$C, IR: 3338 cm$^{-1}$(N-H), 3053 cm$^{-1}$(C-H aromatic), 1697 cm$^{-1}$(C=O), 1585 cm$^{-1}$(C=N).; $^1$H NMR (DMSO-$d_6$) : δ=1.23 (t, 3H), 4.12 (d, 2H), 4.73 (dd, 2H), 7.12 (d, 1H), 7.32 (d, 1H), 7.64 (d, 1H) 12.21 (brs ,1H).; Mass: m/z 237 (M+).

**2-(3H-Imidazo[4,5-b]pyridin-2-ylthio)acetohydrazide (4)**

Ethyl 2-(3H-imidazo[4,5-b]pyridin-2-ylthio)acetate **(3)** (0.03 mole) and hydrazinehydrate (0.03 ml) in DMF (10 ml) were refluxed for 8 hrs in Ethanol. The reaction was monitored by TLC. After the completion of reaction it is poured on to crushed ice and the product was extracted and filtered to give the compound (**4**) with 85% yield.

M.P: 217$^0$C, IR: 3582 cm$^{-1}$(N-H), 2953 cm$^{-1}$(C-H aromatic), 1651 cm$^{-1}$(C=O), 1587 cm$^{-1}$(C=N).; $^1$H NMR (DMSO-$d_6$) : δ=3.98 (brs, 1H) 4.35 (dd, 2H), 7.45 – 7.64 (m, 2H), 8.98 (brs, 1H), 12.72 (brs, 1H).; Mass: m/z 223 (M+).

**5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-1,3,4-oxadiazole-2(3H)-thione (5):**
The acid hydrazide **(4)** (1 g) and carbondisulphide (0.03 ml) in DMF (10 ml) were refluxed under constant stirring at 95-100$^{o}$C in the presence of KOH (1 ml). After 4 hrs $CS_2$ is distilled off. The solid obtained after the addition of AcOH (1 ml) and crushed ice, was washed with water and dried to give the compound (**5**) with 81% yield.

M.P: 232$^{0}$C, IR: 3300 cm$^{-1}$(N-H), 3196 cm$^{-1}$(C-H aromatic), 1661 cm$^{-1}$(C=O), 1567 cm$^{-1}$(C=N).; $^{1}$H NMR (DMSO-$d_6$) : δ=4.31 (s, 1H), 6.91(s, 1H), 7.62 -8.41 (m, 3H), 13.01 (brs, 1H).; Mass: m/z 266 (M+).

**1-(2-(3H-imidazo[4,5-b]pyridin-2-ylthio)acetyl)-4-arylthiosemicarbazides (6 a-g):**
The acid hydrazide **(4)** (0.01 mole) and aryl isothiocyanate (0.01 mole) were refluxed in ethanol (80 ml) for 4 hrs. The excess ethanol was removed under pressure, cooled and the separated solid, filtered and recrystalised.

*1-(2-(3H-imidazo[4,5-b]pyridin-2-ylthio)acetyl)-4-phenylthiosemicarbazide*
Yield: 90%, M.P:245$^{0}$C, IR: 3298 cm$^{-1}$(N-H), 3016 cm$^{-1}$(C-H aromatic), 1617 cm$^{-1}$(C=O), 1564 cm$^{-1}$(C=N). $^{1}$H NMR (DMSO-$d_6$) : δ=2.25 (s, 2H), 7.41-7.86 (m, 8H), 8.21 (d, 1H), 9.81 (brs, 1H), 10.55 (brs, 1H), 12.13 (brs, 1H); Mass: m/z 358 (M+).

*1-(2-(3H-imidazo[4,5-b]pyridin-2-ylthio)acetyl)-4-(4-chlorophenyl)thiosemicarbazide*
Yield: 89%, M.P: 238$^{0}$C, $^{1}$H NMR (DMSO-$d_6$) : δ=2.22 (s, 2H), 7.43-7.98 (m, 7H), 8.19 (d, 1H), 9.74 (brs, 1H), 10.25 (brs, 1H), 12.02 (brs, 1H); Mass: m/z 393 (M+).

*1-(2-(3H-imidazo[4,5-b]pyridin-2-ylthio)acetyl)-4-(2-chlorophenyl)thiosemicarbazide*
Yield: 75%, M.P: 221$^{0}$C, $^{1}$H NMR (DMSO-$d_6$) : δ=2.21 (s, 2H), 7.40-7.95 (m, 7H), 8.18 (d, 1H), 9.73 (brs, 1H), 10.24 (brs, 1H), 12.03 (brs, 1H); Mass: m/z 393 (M+).

*1-(2-(3H-imidazo[4,5-b]pyridin-2-ylthio)acetyl)-4-(4-fluorophenyl)thiosemicarbazide*
Yield: 78%, M.P: 235$^{0}$C, $^{1}$H NMR (DMSO-$d_6$) : δ=2.20 (s, 2H), 7.41-7.97 (m, 7H), 8.20 (d, 1H), 9.76 (brs, 1H), 10.23 (brs, 1H), 12.10 (brs, 1H); Mass: m/z 376 (M+).

*1-(2-(3H-imidazo[4,5-b]pyridin-2-ylthio)acetyl)-4-(4-methoxyphenyl)thiosemicarbazide*
Yield: 88%, M.P: 228$^{0}$C, $^{1}$H NMR (DMSO-$d_6$) : δ=2.23 (s, 2H), 7.42-7.98 (m, 7H), 8.22 (d, 1H), 9.78 (brs, 1H), 10.24 (brs, 1H), 12.12 (brs, 1H); Mass: m/z 388 (M+).

*1-(2-(3H-imidazo[4,5-b]pyridin-2-ylthio)acetyl)-4-(2-methoxyphenyl)thiosemicarbazide*
Yield: 84%, M.P: 243$^{0}$C, $^{1}$H NMR (DMSO-$d_6$) : δ=2.19 (s, 2H), 7.40-7.75 (m, 7H), 8.24 (d, 1H), 9.77 (brs, 1H), 10.25 (brs, 1H), 12.13 (brs, 1H); Mass: m/z 388 (M+).

*1-(2-(3H-imidazo[4,5-b]pyridin-2-ylthio)acetyl)-4-(3-methoxyphenyl)thiosemicarbazide*
Yield: 80%, M.P: 227$^{0}$C $^{1}$H NMR (DMSO-$d_6$) : δ=2.20 (s, 2H), 7.41-7.76 (m, 7H), 8.26 (d, 1H), 9.79 (brs, 1H), 10.22 (brs, 1H), 12.12 (brs, 1H); Mass: m/z 388 (M+).

**5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-4-phenyl-4H-1,2,4-triazole-3-thiols (7 a-g):**
To corresponding thiosemicarbazide **(6)** (0.014 mole), a solution of NaOH 2N (10 ml) was added. The reaction mixture was heated under reflux at 80-90 °C for four hours and then a solution of HCl 1N was added until it reached pH 4.5 when a solid product was formed. The rough product was separated and dried under vacuum at 55-60ºC and then it was recrystallized from ethanol.

*5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-4-phenyl-4H-1,2,4-triazole-3-thiol*
Yield: 89%, M.P: 252$^{0}$C, IR: 3334 cm$^{-1}$(N-H), 3055 cm$^{-1}$(C-H aromatic), 1697 cm$^{-1}$(C=O), 1597 cm$^{-1}$(C=N). $^{1}$H NMR (DMSO-$d_6$) : δ=3.98 (s, 2H), 6.91 – 7.95 (m, 9H) 10.01 (s,1H) , 13.12 (s,1H).; Mass: m/z 340 (M+).

*5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-4-(4-chlorophenyl)-4H-1,2,4-triazole-3-thiol*
Yield: 91%, M.P: 247$^{0}$C, $^{1}$H NMR (DMSO-$d_6$) : δ=3.95 (s, 2H), 6.90 – 7.94 (m, 8H) 10.11 (s,1H) , 13.11 (s,1H).; Mass: m/z 375 (M+).

*5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-4-(2-chlorophenyl)-4H-1,2,4-triazole-3-thiol*
Yield: 76%, M.P: 236$^0$C, $^1$H NMR (DMSO-$d_6$) : δ=3.96 (s, 2H), 6.91 – 7.93 (m, 8H) 10.10 (s,1H) , 13.10 (s,1H). Mass: m/z 375 (M+).

*5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-4-(4-fluorophenyl)-4H-1,2,4-triazole-3-thiol*
Yield: 78%, M.P: 227$^0$C, $^1$H NMR (DMSO-$d_6$) : δ=3.97 (s, 2H), 6.92 – 7.90 (m, 8H) 10.11 (s,1H) , 13.09 (s,1H). Mass: m/z 358 (M+).

*5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3-thiol*
Yield: 88%, M.P: 243$^0$C, $^1$H NMR (DMSO-$d_6$) : δ=3.99 (s, 2H), 6.91 – 7.89 (m, 8H) 10.10 (s,1H) , 13.10 (s,1H). Mass: m/z 370 (M+).

*5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-4-(2-methoxyphenyl)-4H-1,2,4-triazole-3-thiol*
Yield: 80%, M.P: 225$^0$C, $^1$H NMR (DMSO-$d_6$) : δ=3.94 (s, 2H), 6.89 – 7.89 (m, 8H) 10.06 (s,1H) , 13.12 (s,1H). Mass: m/z 370 (M+).

*5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-4-(3-methoxyphenyl)-4H-1,2,4-triazole-3-thiol*
Yield: 83%, M.P: 232$^0$C, $^1$H NMR (DMSO-$d_6$) : δ=3.92 (s, 2H), 6.87 – 7.89 (m, 8H) 10.11 (s,1H) , 13.10 (s,1H). Mass: m/z 370 (M+).

**5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-N-aryl-1,3,4-oxadiazol-2-amines (8a-g):**
To the corresponding thiosemicarbazide **(6)** (0.06 mole), $I_2$ / KI (5 ml) was added under stirring. The reaction mixture was stirred at room temperature for one hour and then was added drop wise in cold water and stirred again till a solid product was obtained that separated and dried under vacuum at 45-50 ºC. The rough product was purified by crystallization from ethanol.

*5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-N-phenyl-1,3,4-oxadiazol-2-amine*
Yield: 85%, M.P: 238$^0$C, IR: 3300 cm$^{-1}$(N-H), 3019 cm$^{-1}$(C-H aromatic), 1762 cm$^{-1}$(C=O), 1569 cm$^{-1}$(C=N). $^1$H NMR (DMSO-$d_6$) : δ=4.38 (d, 2H), 7.14 – 8.35 (m, 8H), 8.72 (s, 1H), 10.42 (brs, 1H), 12.31 (brs, 1H). Mass: m/z 324 (M+).

*5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-N-(4-chlorophenyl)-1,3,4-oxadiazol-2-amine*
Yield: 83%, M.P: 245$^0$C, $^1$H NMR (DMSO-$d_6$) : δ=4.37 (d, 2H), 7.13 – 8.34 (m, 7H), 8.71 (s, 1H), 10.41 (brs, 1H), 12.30 (brs, 1H). Mass: m/z 359 (M+).

*5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-N-(2-chlorophenyl)-1,3,4-oxadiazol-2-amine*
Yield: 86%, M.P: 228$^0$C, $^1$H NMR (DMSO-$d_6$) : δ=4.38 (d, 2H), 7.11 – 8.37 (m, 7H), 8.72 (s, 1H), 10.41 (brs, 1H), 12.30 (brs, 1H). Mass: m/z 359 (M+).

*5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-N-(4-fluorophenyl)-1,3,4-oxadiazol-2-amine*
Yield: 81%, M.P: 246$^0$C, $^1$H NMR (DMSO-$d_6$) : δ=4.36 (d, 2H), 7.11 – 8.36 (m, 7H), 8.71 (s, 1H), 10.42 (brs, 1H), 12.31 (brs, 1H). Mass: m/z 342 (M+).

*5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-N-(4-methoxyphenyl)-1,3,4-oxadiazol-2-amine*
Yield: 86%, M.P: 231$^0$C, $^1$H NMR (DMSO-$d_6$) : δ=4.37 (d, 2H), 7.11 – 8.35 (m, 7H), 8.70 (s, 1H), 10.41 (brs, 1H), 12.30 (brs, 1H). Mass: m/z 354 (M+).

*5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-N-(2-methoxyphenyl)-1,3,4-oxadiazol-2-amine*
Yield: 85%, M.P: 234$^0$C, $^1$H NMR (DMSO-$d_6$) : δ=4.36 (d, 2H), 7.10– 8.36 (m, 7H), 8.72 (s, 1H), 10.40 (brs, 1H), 12.31 (brs, 1H). Mass: m/z 354 (M+).

*5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-N-(3-methoxyphenyl)-1,3,4-oxadiazol-2-amine*
Yield: 82%, M.P: 241$^0$C, $^1$H NMR (DMSO-$d_6$) : δ=4.36 (d, 2H), 7.11 – 8.34 (m, 7H), 8.70 (s, 1H), 10.42 (brs, 1H), 12.30 (brs, 1H). Mass: m/z 354 (M+).

**5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-N-aryl-1,3,4-thiadiazol-2-amines (9a-g):**
To the corresponding thiosemicarbazide **(6)** (0.06 mole), conc.$H_2SO_4$ (5 ml) was added under stirring. At room temperature,the reaction micture was stirred for one hour and then stirred in cold water till a solid product was obtained. Then it is separated and dried under vacuum at 45-50ºC. The crude product was purified by crystallization from ethanol.

*5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-N-phenyl-1,3,4-thiadiazol-2-amine*
Yield: 85%, M.P: 225$^0$C, IR: 3291 cm$^{-1}$(N-H), 3056 cm$^{-1}$(C-H aromatic), 1660 cm$^{-1}$(C=O), 1586 cm$^{-1}$(C=N). $^1$H NMR (DMSO-$d_6$) : δ=4.12 (d, 2H), 6.65 – 8.13 (m, 8H), 10.25 (s, 1H) , 12.42 (s, 1H). Mass: m/z 341 (M+H).

*5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-N-(4-chlorophenyl)-1,3,4-thiadiazol-2-amine*
Yield: 90%, M.P: 231$^0$C, $^1$H NMR (DMSO-$d_6$) : δ=4.11 (d, 2H), 6.64 – 8.12 (m, 7H), 10.26 (s, 1H) , 12.43 (s, 1H). Mass: m/z 375 (M+).

*5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-N-(2-chlorophenyl)-1,3,4-thiadiazol-2-amine*
Yield: 86%, M.P: 243$^0$C, $^1$H NMR (DMSO-$d_6$) : δ=4.12 (d, 2H), 6.65 – 8.12 (m, 7H), 10.27 (s, 1H) , 12.41 (s, 1H). Mass: m/z 375 (M+).

*5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-N-(4-fluorophenyl)-1,3,4-thiadiazol-2-amine*
Yield: 80%, M.P: 209$^0$C, $^1$H NMR (DMSO-$d_6$) : δ=4.10 (d, 2H), 6.65 – 8.11 (m, 7H), 10.27 (s, 1H) , 12.40 (s, 1H). Mass: m/z 358 (M+).

*5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-N-(4-methoxyphenyl)-1,3,4-thiadiazol-2-amine*
Yield: 86%, M.P: 217$^0$C, $^1$H NMR (DMSO-$d_6$) : δ=4.12 (d, 2H), 6.64 – 8.13 (m, 7H), 10.24 (s, 1H) , 12.43 (s, 1H). Mass: m/z 370 (M+).

*5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-N-(2-methoxyphenyl)-1,3,4-thiadiazol-2-amine*
Yield: 86%, M.P: 227$^0$C, $^1$H NMR (DMSO-$d_6$) : δ=4.11 (d, 2H), 6.63 – 8.13 (m, 7H), 10.24 (s, 1H) , 12.42 (s, 1H). Mass: m/z 370 (M+).

*5-((3H-imidazo[4,5-b]pyridin-2-ylthio)methyl)-N-(3-methoxyphenyl)-1,3,4-thiadiazol-2-amine*
Yield: 80%, M.P: 232$^0$C, $^1$H NMR (DMSO-$d_6$) : δ=4.13 (d, 2H), 6.64 – 8.14 (m, 7H), 10.25 (s, 1H) , 12.41 (s, 1H). Mass: m/z 370 (M+).

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