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Synthesis and some reactions of 2-acetylimidazo[4,5-*b*]pyridine. Antituberculotic activity of the obtained compounds

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2-Acetylimidazo[4,5-*b*]pyridine was prepared and its reactions with some aromatic amines and sulfur (Willgerodt-Kindler reaction), some aromatic aldehydes, some carboxylic acid hydrazides as well as thiourea were investigated. New imidazo[4,5-*b*]pyridine derivatives with different substituents in 2-position (*N*-arylthioamides, imines, α, β-unsaturated ketones, hydrazido-hydrazones and aminothiazole) were obtained. Most of the synthesized compounds were tested *in vitro* for their antituberculotic activity.

1. Introduction

As a continuation of our search for new compounds with antituberculotic activity in a group of imidazo[4,5-*b*]-pyridines [1, 2] we synthesized and tested a series of novel derivatives of this heterocyclic system.

2. Investigations, results and discussion

2.1. Chemistry

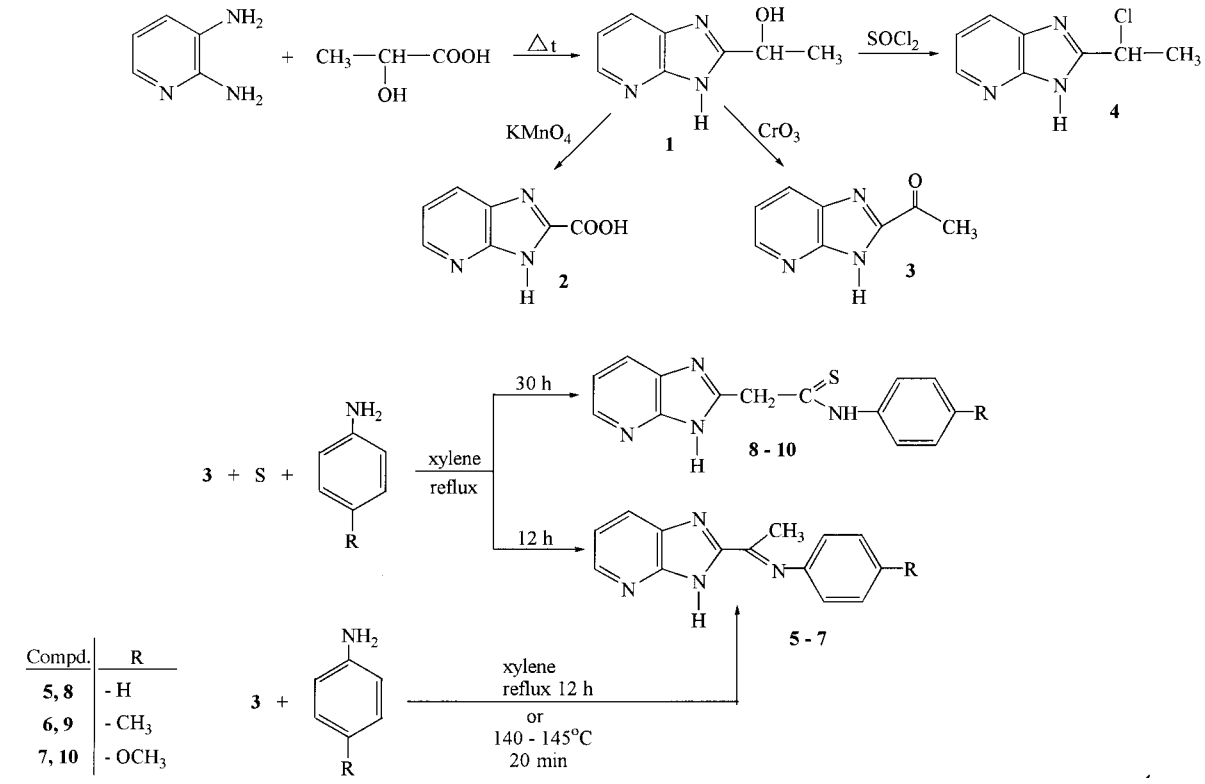
The starting compound for the synthesis of 2-acetylimidazo-[4,5-*b*]pyridine (**3**) was 2-(1-hydroxyethyl)-1 H-imidazo[4,5-*b*]pyridine (**1**). It was obtained on reaction of 2,3-diaminopyridine with lactic acid.

Oxidation of **1** with potassium permanganate led to the earlier described 2-imidazo[4,5-*b*]pyridinecarboxylic acid (**2**) [3] whereas its oxidation with chromic acid in acetic acid gave the expected **3**. By reaction of **1** with thionyl chloride 2-(1-chloroethyl)-1 *H*-imidazo[4,5-*b*]pyridine (**4**) was prepared (Scheme 1).

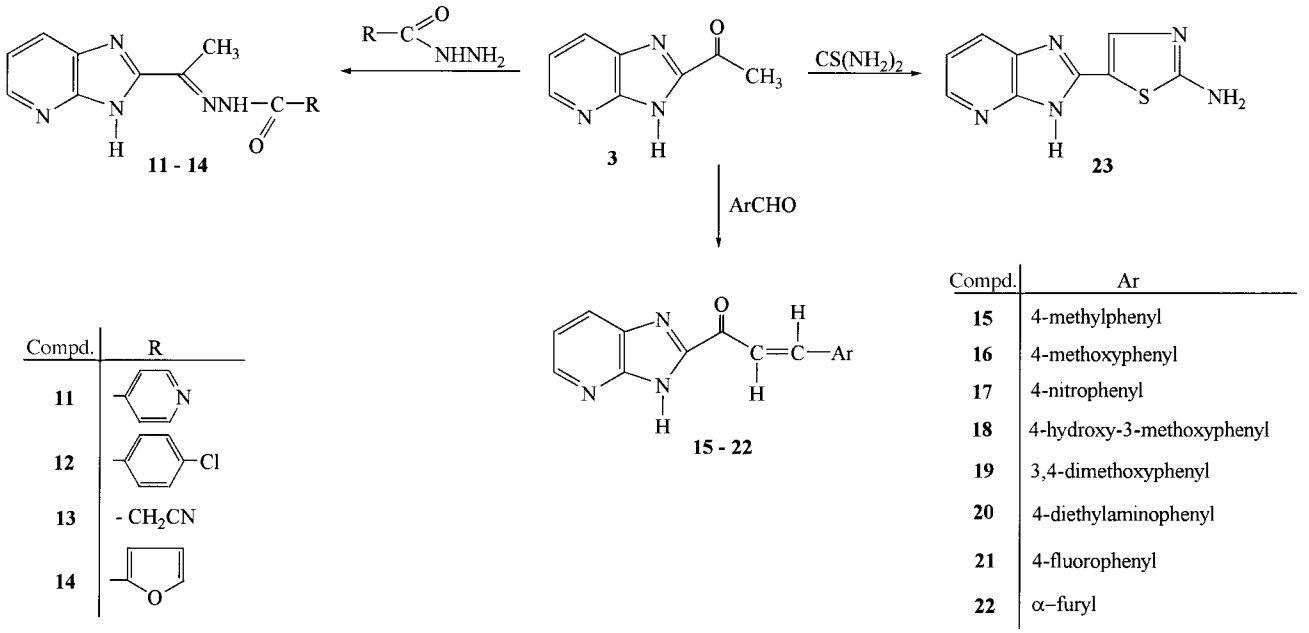
2-Acetylimidazo[4,5-*b*]pyridine (**3**) was then used for further reactions with some aromatic amines and sulfur (Willgerodt-Kindler reaction), some aromatic aldehydes, some carboxylic acid hydrazides and thiourea.

Willgerodt-Kindler reactions were carried out in boiling xylene, the molar ratio of substrates (**3**/amine/sulfur) was 1 : 2 : 3. The course of this reaction (confirmed by many experiments) is given in Scheme 1. After 12 h of reflux, the imines **5**–**7** were obtained whereas 30 h of reflux gave the *N*-arylthioamides **8**–**10**. The same imines **5**–**7** were also obtained as a result of reflux of **3** and an appropriate amine in xylene (in the absence of sulfur) or by heating of these substrates at 140–145 °C (in the absence of solvent and sulfur). The proposed structures of compounds **5**–**10** were confirmed by their IR, ^{1}H NMR and MS spectral data.

Scheme 1



Scheme 2



The formation of the imines **5**–**7** in the Willgerodt-Kindler reaction suggests that they are the intermediate compounds in the conversion of **3** into the *N*-arylthioamides **8**–**10**. Attempts to obtain **8** from **5**, however, were unsuccessful. Compound **5** even when refluxed with sulfur in xylene for 30 h remained unchanged.

Furthermore, in reaction of **3** with some aromatic aldehydes the appropriate, α,β-unsaturated ketones **15**–**22** were obtained. The reacton of **3** with some carboxylic acid hydrazides yielded the corresponding hydrazido-hydrazones **11**–**14** whereas the reaction with thiourea led to the aminothiazolyl derivative **23** (Scheme 2).

Table: Physicochemical data and antituberculotic activity of compounds 1–23

Compd.	M.p. (°C) solvent	Molecular formula Yield %	Antituberculotic activity MIC (μg/ml) *Mycobacterium*			Compd.	M.p. (°C) solvent	Molecular formula Yield %	Antituberculotic activity MIC (μg/ml) *Mycobacterium*		
			$H_{37}Rv$	192*	210**				$H_{37}Rv$	192*	210**
1	177–178 A	$C_8H_9N_3O$ (46)				**12**	318–320 DMF/H_2O	$C_{15}H_{12}ClN_5O$ (76)	100	100	50
2	148–150 H_2O	$C_7H_5N_3O$ (57)				**13**	268–270 DMF/H_2O	$C_{11}H_{10}N_6O$ (42)	50	50	50
3	250–251 DMF/H_2O	$C_8H_7N_3O$ (61)				**14**	295–297 DMF/H_2O	$C_{13}H_{11}N_5O_2$ (64)	50	50	50
4	155–157 B	$C_8H_8ClN_3$ (63)				**15**	270–272 DMF	$C_{16}H_{13}N_3O$ (61)	25	50	50
5	240–242 B	$C_{14}H_{12}N_4$ (59)	50	100	50	**16**	271–273 DMF	$C_{16}H_{13}N_3O_2$ (57)	25	50	50
6	238–240 B	$C_{15}H_{14}N_4$ (74)	50	50	50	**17**	278–280 DMF	$C_{15}H_{10}N_4O_3$ (55)	12.5	25	6.2
7	208–211 B	$C_{15}H_{14}N_4O$ (72)	50	50	50	**18**	270–272 DMF/H_2O	$C_{16}H_{13}N_3O_3$ (57)	12.5	50	50
8	294–296 DMF/H_2O	$C_{14}H_{12}N_4S$ (23)	16	16	62	**19**	273–276 DMF	$C_{17}H_{15}N_3O_3$ (75)	50	12.5	12.5
9	292–293 DMF/H_2O	$C_{15}H_{14}N_4S$ (37)	125	62	62	**20**	248–250 DMF	$C_{19}H_{20}N_4O$ (70)	25	50	50
10	266–268 DMF/H_2O	$C_{15}H_{14}N_4OS$ (42)	12.5	12.5	25	**21**	303–305 DMF	$C_{15}H_{10}FN_3O$ (60)	50	50	50
11	292–294 DMF/H_2O	$C_{14}H_{12}N_6O$ (48)	3.1	3.1	3.1	**22**	270–272 DMF/H_2O	$C_{13}H_9N_3O_2$ (60)	>100	>100	>100
						23	342–344 H_2O	$C_9H_7N_5S$ (51)	50	100	50

A – acetone, B – benzene
MIC – minimal inhibitory concentration; $H_{37}Rv$ – Mycobacterium tuberculosis (standard strain)

* Bacterial strain isolated from patiens succeptible towards isonicotinhydrazide, ethambutol and rifampicine
** Bacterial strain isolated from patiens resistant against isonicotinhydrazide, ethambutol and rifampicine

According to spectroscopic data all compounds **15**–**22** exist in the E-configuration. Their IR spectra show the out-of-plane C−H bending vibrations band at 980 cm^{-1} (the characteristic band of trans alkenes) [4]. Besides, the coupling constants of the olefinic proton signals in the ^{1}H NMR spectra (recorded for representative compounds **15**, **16**) were of 16 Hz. The physical characteristics and yields of the compounds synthesized are summarized in the Table.

2.2. Pharmacological data

Compounds **5**–**23** were tested *in vitro* for their antituberculotic activity. The following three bacterial strains were used: *Mycobacterium tuberculosis* $H_{37}Rv$; the strain isolated from patients and resistant against isonicotinhydrazide, ethambutol and rifampicine, as well as the bacterial strain isolated from patients and susceptible towards isonicotinhydrazide, ethambutol and rifampicine.
Antibacterial activity of the compounds was determined in liquid Youmans medium containing 10% bovine serum according to the method previously described [1]. The results obtained are listed in the Table.

3. Experimental

The m.p.'s are uncorrected. IR spectra: Specord 75 spectrophotometer (pellets in KBr). ^{1}H NMR: 80 MHz Tesla 478 or Varian Unity 500 Plus spectrometers with TMS as internal standard; chemical shifts in δ ppm. MS spectra: LKS 9000 S apparatus with direct inlet, ionization energy 70 eV. Elementary analyses were carried out in the Department of Physical Chemistry Medical University of Gdańsk. Analytical results were within ±0.4% of the theoretical values.

3.1. 2-(1-Hydroxyethyl)imidazo[4,5-b]pyridine (1)

2,3-Diaminopyridine (10.9 g, 0.1 mol) and 90% lactic acid (30 ml, 0.3 mol) were heated at 140–145 °C with stirring for 4 h. The reaction mixture was then cooled to about 50 °C, treated with 30 ml of acetone and allowed to stand in the refrigerator overnight. The precipitated solid was filtered off and recrystallized.
IR (cm^{-1}): 3500–2700, 1110. ^{1}H NMR (DMSO-d_6): 1.64 (d, J = 7 Hz, 3 H, CH_3), 5.00–5.27 (q, J = 7 Hz, 1 H, $CHCH_3$), 6.05 (s, 1 H, OH), 7.25–7.41 (d, d, J_1 = 5 Hz, J_2 = 6 Hz, 1 H, C-6), 8.07 (d, J = 8 Hz, 1 H, C-7), 8.46 (d, J = 5 Hz, 1 H, C-5). MS, m/z (%): 163 (65) M^+, 148 (47), 146 (19), 121 (12), 120 (100), 119 (12), 93 (14), 92 (21), 28 (23).

3.2. 2-Imidazo[4,5-b]pyridinecarboxylic acid (2)

To a boiling solution of $KMnO_4$ (0.01 mol) in 30 ml H_2O a boiling solution of compound **1** (0.006 mol) and Na_2CO_3 (0.006 mol) in 30 ml H_2O was added portionwise with stirring. Then the combined solutions were heated on a boiling water bath for 2 h with occasional shaking. The hot reaction mixture was filtered off and the filtrate after cooling was acidified to pH 2–3 with conc. HCl. The resulting precipitate was filtered off and recrystallized. Acid **2** is identical with the one reported in our previous work [3].

3.3. 2-Acetylimidazo[4,5-b]pyridine (3)

A solution of chromium trioxide (3 g, 0.03 mol) in H_2O (10 ml) was added dropwise to a solution of **1** (4.9 g, 0.03 mol) in glacial acetic acid (30 ml) at 90 °C with stirring. The reaction mixture was then heated at 100–110 °C for 5–10 min and poured into H_2O (ca 400 ml). A flocculent precipitate was filtered off and recrystallized.
IR (cm^{-1}): 3060, 2980, 1690. ^{1}H NMR (DMSO-d_6): 2.81 (s, 3 H, CH_3), 7.41–7.61 (d, d, J_1 = 5 Hz, J_2 = 6 Hz, 1 H, C-6), 8.29 (d, J = 9 Hz, 1 H, C-7), 8.66 (d, J = 4 Hz, 1 H, C-5). MS, m/z (%): 161 (100) M^+, 146 (13), 133 (51), 119 (55), 118 (12), 92 (38), 91 (13), 65 (12), 64 (22), 43 (95), 29 (12), 28 (14), 15 (15).

3.4. 2-(1-Chloroethyl)imidazo[4,5-b]pyridine (4)

To a suspension of dry compound **1** (0.5 g, 0.003 mol) in $CHCl_3$ (10 ml), 2 ml of $SOCl_2$ was added and the mixture was refluxed for 3 h. The solvent and the excess of $SOCl_2$ were then completely removed under reduced pressure, the dry residue was treated while cooling with $NaHCO_3$ and the precipitate formed was filtered off and recrystallized.
^{1}H NMR (DMSO-d_6): 1.98 (d, J = 8 Hz, 3 H, CH_3), 5.50 (q, J = 8 Hz, 1 H, CH), 7.25 (d, d, J_1 = 6 Hz, J_2 = 4 Hz, 1 H, C-6), 8.00 (d, J = 7 Hz, 1 H, C-7), 8.37 (d, J = 4 Hz, 1 H, C-5). MS, m/z (%): 183 (18), 182 (5), 181 (79) M^+, 166 (4), 149 (4), 147 (29), 146 (100), 145 (9), 144 (16), 120 (8), 119 (11), 118 (4), 103 (8), 93 (21), 92 (8), 91 (5), 78 (8), 73 (6), 66 (13), 65 (9), 64 (13), 63 (4), 54 (7), 53 (4), 52 (8), 45 (5), 44 (52), 43 (6), 41 (6), 40 (6), 39 (19), 38 (14), 35 (5).

3.5. 2-(Imidazo[4,5-b]pyridine)-N-arylethanethioamides 8–10

A mixture of **3** (0.004 mol), finely powdered sulfur (0.012 mol) and an appropriate amine (aniline, *p*-toluidine or *p*-anisidine) (0.008 mol) in dry xylene (20 ml) was refluxed for 30 h. After cooling the solid obtained was collected, boiled with benzene, filtered off and recrystallized. After 12 h of reflux only compounds **5**–**7** were obtained.
8: IR (cm^{-1}): 3420, 3040, 2920, 1620, 1590, 1480, 1290. MS, m/z (%): 270 (5), 269 (17), 268 (100) M^+, 267 (34), 266 (12), 236 (48), 235 (74), 234 (19), 165 (28), 164 (23), 163 (42), 159 (14), 132 (18), 120 (19), 119 (17), 93 (16), 92 (10), 77 (41), 64 (73), 32 (15).
9: IR (cm^{-1}): 3420, 3060, 2920, 1610, 1580, 1480, 1290, 800. MS, m/z (%): 284 (2), 283 (8), 282 (42) M^+, 281(18), 250 (60), 249 (55), 248 (9), 165 (12), 164 (9), 163 (17), 132 (11), 120 (11), 106 (8), 93 (8), 91 (21), 66 (8), 65 (15), 64 (100), 39 (9), 32 (16), 28 (16).
10: IR (cm^{-1}): 3500, 3060, 2920, 1620, 1590, 1520, 1310, 1260, 1040, 830. MS, m/z (%): 300 (1,5), 299 (4), 298 (21) M^+, 267 (15), 266 (100), 265 (66), 256 (12), 252 (8), 251 (52), 250 (9), 224 (12), 210 (9), 192 (31), 165 (8), 163 (12), 160 (38), 133 (16), 132 (10), 128 (21), 123 (12), 120 (10), 119 (10), 108 (17), 106 (9), 96 (22), 93 (10), 92 (18), 91 (21), 78 (9), 77 (17), 66 (8), 65 (8), 64 (8), 63 (8), 44 (8), 39 (11), 32 (12), 28 (10), 18 (35).

3.6. 2-(1-Aryliminoethyl)imidazo[4,5-b]pyridines 5–7

Compound **3** (0.002 mol) and an appropriate amine (aniline, *p*-toluidine or *p*-anisidine) (0.003 mol) were heated at 155–165 °C with stirring for 20 min. After cooling the solid obtained was washed with ether and recrystallized.
5: IR (cm^{-1}): 3420, 3060, 2950, 1620. ^{1}H NMR ($CDCl_3$): 2.63 (s, 3 H, CH_3), 7.00–7.52 (m, 6 H), 8.18 (d, J = 6 Hz, 1 H), 8.56 (d, J = 5 Hz, 1 H). MS, m/z (%): 236 (40) M^+, 235 (100), 221 (20), 195 (12), 194 (12), 145 (3), 118 (14), 78 (6), 77 (55), 51 (20).
6: IR (cm^{-1}): 2430, 3040, 2960, 1620, 830. ^{1}H NMR ($CDCl_3$): 2.63 (s, 3 H, CH_3), 2.86 (s, 3 H, CH_3), 6.80 (d, J = 10 Hz, 4 H, Ar-H), 7.05–7.40 (m, 1 H, C-6), 8.06 (d, J = 8 Hz, 1 H, C-7), 8.57 (d, J = 5 Hz, 1 H, C-5). MS, m/z (%): 250 (51) M^+, 249 (100), 235 (33), 209 (15), 208 (13), 182 (6), 91 (30), 65 (21), 39 (7).
7: IR (cm^{-1}): 3450, 3060, 2950, 1630, 1440, 1270, 1060, 800. ^{1}H NMR ($CDCl_3$): 2.53 (s, 3 H, CH_3), 3.87 (s, 3 H, OCH_3), 6.97 (s. 4 H, Ar-H), 7.12–7.37 (m, 1 H, C-6), 8.17 (d, J = 8 Hz, 1 H, C-7), 8.57 (d, J = 5 Hz, 1 H, C-5). MS, m/z (%): 266 (93) M^+, 265 (100), 251 (41), 250 (7), 225 (11), 224 (7), 222 (7), 210 (15), 161 (34), 146 (7), 133 (25), 120 (8), 119 (29), 103 (9), 92 (39), 91 (7), 78 (49), 77 (31), 64 (19), 63 (9), 52 (15), 51 (12), 50 (9), 43 (24), 39 (16), 38 (8), 18 (18).

3.7. Hydrazide-hydrazones 11–14

A mixture of **3** (0.002 mol) and appropriate carboxylic acid hydrazide (0.0025 mol) in anh. ethanol (10 ml) was treated with piperidine (0.2 ml) and refluxed for 2–2.5 h. Then the solution was concentrated under reduced pressure and separated solid was filtered off and recrystallized.
11: IR (cm^{-1}): 3430, 1690, 1660, 1560, 1280. MS, m/z (%): 280 (5) M^+, 175 (6), 174 (82), 147 (6), 146 (100), 144 (7), 120 (4), 106 (15), 93 (18), 92 (5), 79 (6), 78 (40), 66 (12), 65 (5), 52 (5), 51 (26), 50 (5), 39 (11).
12: IR (cm^{-1}): 3260, 1660, 1540, 1270, 850. MS, m/z (%): 313 (4.3) M^+, 175 (9), 174 (95), 147 (9), 146 (100), 144 (11), 141 (22), 140 (5), 139 (75), 119 (5), 113 (14), 111 (48), 93 (15), 92 (6), 76 (9), 75 (22), 74 (5), 66 (15), 65 (7), 64 (6), 52 (6), 51 (6), 50 (9), 39 (13), 38 (7).
13: IR (cm^{-1}): 3300, 2220, 1690, 1660, 1530, 1400. MS, m/z (%): 242 (11) M^+, 202 (27), 174 (22), 147 (8), 146 (100), 145 (7), 144 (12), 120 (7), 93 (25), 92 (10), 91 (5), 78 (8), 68 (9), 66 (19), 65 (8), 64 (8), 54 (6), 52 (7), 44 (5), 42 (7), 41 (6), 40 (15), 39 (18), 38 (11).
14: IR (cm^{-1}): 3600–2400, 1700, 1680, 1620, 1570, 1300. MS, m/z (%): 269 (8.8) M^+, 175 (6), 174 (90), 147 (8), 146 (100), 144 (6), 120 (4), 119 (4), 95 (78), 93 (14), 92 (4), 78 (4), 67 (4), 66 (10), 65 (4), 64 (4), 44 (6), 39 (32), 38 (7).

3.8. 1-(Imidazo[4,5-b]pyridine-2-yl)-3-aryl-2-propen-1-ones 15–22

To a suspension of **3** (0.002 mol) and an appropriate aldehyde (0.003 mol) in anh. ethanol (10 ml) 0.2 ml of piperidine was added and the mixture was refluxed for 1 h. After cooling the precipitated solid was filtered off and recrystallized.
15: IR (cm^{-1}): 3350–2400 (NH), 1690 (C=O), 1625 (C=C), 980 (trans C=C), 795 (1,4-disubst. arom). ^{1}H NMR (DMSO-d_6): 2.36 (s, 3 H, CH_3), 7.31 (d, J = 8 Hz, 2 H, Ar-H), 7.40 (d, d, J_1 = 4 Hz, J_2 = 5 Hz, 1 H, C-6),

7.78 (d, J = 8 Hz, 2 H, Ar-H), 7.97 (d, J = 16 Hz, 1 H, H-vinyl), 8.06 (d, J = 16 Hz, 1 H, H-vinyl), 8.17 (br s, 1 H, C-7), 8.56 (d, J = 4 Hz, 1 H, C-5). MS, m/z (%): 263 (28) M^+, 235 (16), 234 (100), 119 (17), 117 (10), 116 (12), 115 (29), 92 (7), 91 (24), 65 (12), 64 (8), 63 (6), 39 (11).

16: IR (cm^{-1}): 3600–2400 (NH), 1680 (C=O), 1610 (C=C), 1280 (ArO-), 1100 (CH_3O), 980 (trans C=C), 840 (1,4-disubst. arom). ^1H NMR (DMSO-d_6): 3.84 (s, 3 H, OCH_3), 7.06 (d, J = 9 Hz, 2 H, Ar-H), 7.38 (d, d, J_1 = 4 H, J_2 = 5 Hz, 1 H, C-6), 7.85 (d, J = 9 Hz, 2 H, Ar-H), 7.97 (d, d, $J_1 = J_2$ = 16 Hz, 2 H, H-vinyl), 8.15 (d, J = 7 Hz, 1 H, C-7), 8.54 (d, J = 6 Hz, 1 H, C-5). MS, m/z (%): 279 (36) M^+, 251 (21), 250 (100), 236 (14), 235 (6), 208 (13), 207 (17), 161 (16), 133 (29), 132 (16), 119 (40), 118 (23), 117 (9), 103 (10), 92 (28), 91 (21), 90 (24), 89 (30), 77 (18), 76 (7), 73 (8), 65 (16), 64 (38), 63 (23), 51 (11), 44 (17), 43 (23), 42 (11), 40 (12), 39 (20), 38 (13).

17: IR (cm^{-1}): 3460–2400 (NH), 1680 (C=O), 1630 (C=C), 1520, 1360 (NO_2), 980 (trans C=C), 860 (1,4-disubst. arom.). MS, m/z (%): 294 (72) M^+, 285 (10), 266 (22), 265 (94), 243 (9), 220 (17), 219 (52), 130 (11), 120 (9), 119 (10), 118 (13), 102 (41), 101 (9), 92 (22), 91 (13), 90 (15), 76 (22), 75 (12), 64 (15), 63 (9), 52 (9), 51 (15), 50 (10), 39 (12).

18: IR (cm^{-1}): 3600–2400 (NH, OH), 1650 (C=O), 1620 (C=C), 1430, 1260, 1060 (OH, C–O), 980 (trans C=C), 890, 805 (1,2,4-trisubst. arom.). MS, m/z (%): 295 (82) M^+, 267 (16), 266 (100), 252 (9), 251 (14), 224 (9), 148 (7), 146 (10), 133 (8), 120 (15), 119 (36), 118 (7), 117 (7), 105 (11), 92 (10), 91 (10), 89 (16), 78 (13), 77 (11), 65 (7), 64 (12), 63 (8), 52 (7), 51 (12), 39 (11).

19: IR (cm^{-1}): 3440 (NH), 1670 (C=O), 1630 (C=C), 1280 (ArO-), 1090 (CH_3O-), 980 (trans C=C), 870, 800 (1,2,4-trisubst. arom.). MS, m/z (%): 309 (66) M^+, 281 (23), 280 (100), 266 (10), 264 (8), 162 (9), 147 (7), 120 (7), 119 (31), 118 (9), 92 (8), 91 (13), 89 (7), 77 (10), 76 (7), 64 (7), 51 (10).

20: IR (cm^{-1}): 3600–2400 (NH), 1660 (C=O), 1580 (C=C), 980 (trans C=C), 820 (1,4-disubst. arom.). MS, m/z (%): 320 (83) M^+, 306 (18), 305 (100), 290 (16), 277 (11), 247 (9), 158 (16), 146 (22), 130 (14), 120 (8), 119 (8), 102 (7), 103 (6), 77 (5).

21: IR (cm^{-1}): 3400–2400 (NH), 1680 (C=O), 1610 (C=C), 980 (trans C=C), 810 (1,4-disubst. arom.). MS, m/z (%): 267 (35) M^+, 239 (17), 238 (100), 149 (6), 121 (13), 120 (9), 119 (29), 101 (22), 95 (4), 92 (6), 75 (7), 64 (3), 44 (7), 43 (3), 41 (3), 39 (4).

22: IR (cm^{-1}): 3300–2400 (NH), 1660 (C=O), 1600 (C=C), 1270 (C–O–C), 980 (trans C=C). MS, m/z (%): 239 (89) M^+, 211 (23), 210 (100), 185 (55), 183 (16), 182 (13), 170 (10), 157 (34), 146 (8), 121 (20), 120 (7), 119 (28), 118 (4), 93 (8), 92 (25), 91 (9), 79 (4), 66 (7), 65 (74), 64 (17), 63 (15), 39 (52), 38 (10).

3.9. 2-(2-Aminothiazol-5-yl)imidazo[4,5-b]pyridine (**23**)

A mixture of **3** (0.002 mol) thiourea (0.003 mol) and I_2 (0.003 mol) in anh. ethanol (10 ml) was refluxed for 4 h with stirring. After cooling the resultant precipitate was filtered off and recrystallized.

IR (cm^{-1}): 3600–2400, 1620, 1580, 1510, 970. ^1H NMR (DMSO-d_6): 7.55–7.72 (m, 1 H, C-6), 7.90 (s, 1 H, C-4 thiazol), 8.35 (d, J = 7 Hz, 1 H, C-7), 8.62 (d, J = 6 Hz, 1 H, C-5). MS, m/z (%): 219 (4), 218 (10), 217 (100) M^+, 176 (10), 175 (74), 145 (13), 128 (54), 127 (25), 119 (9), 111 (9), 97 (15), 95 (10), 93 (12), 85 (12), 83 (15), 81 (10), 71 (18), 69 (17), 57 (33), 55 (18), 41 (11).

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