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THE SYNTHESIS AND MICROBIOLOGICAL ACTIVITY OF NEW 4-CHLOROPYRIDIN-2-YL DERIVATIVES

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Abstract – Synthesis of 4-chloropicolinamidrazone derivatives starting from 4-chloropicolinamide is described. The desired compounds were formed by reactions of methyl 4-chloropicolinohydrazonamide or 4-chloro-*N'*-methylpicolinohydrazonamide with suitable counter partners (carbon disulfide, alkyl halides, aldehydes, ketones, carbohydrazonamides or isothiocyanates) or *via* 4-chloropicolinimidate, obtained by a convenient method from nitrile with catalytic amount of DBU. Selected products were screened for bacteriostatic and tuberculostatic activity.

INTRODUCTION

Development of mycobacterial resistance to conventional drugs is one of the major difficulties in the treatment of tuberculosis, and a major factor in increasing demand for new antituberculosis agents. Looking Looking for new structures with potential tuberculostatic activity, we pay attention to a recent report suggesting that tuberculostatic activity of pyridin-2-yl-formamide thiosemicarbazones (**A**) is related to their co-planarity[1]. The hypothesis prompted us to synthesis of new 2-substituted pyridine derivatives. To increase probability that the prepared compounds will bear the desired activity, the pyridine ring was connected with structural fragments witch have already been present in tuberculostatic compounds namely: namely: amidrazones (**B**),[2] thiosemicarbazones (**C**), and thioureas (**D**)[3] (Figure 1). Moreover some of them them fulfill the requirement of co-planarity with the pyridine moiety.

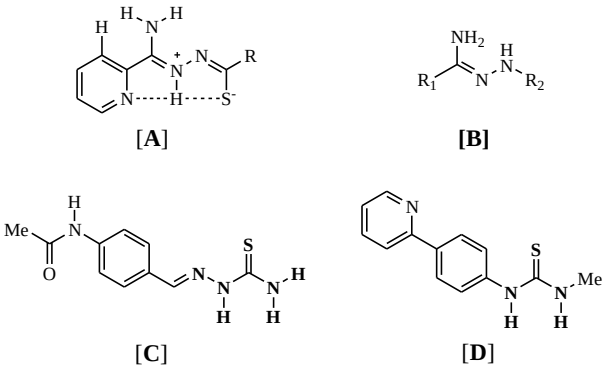
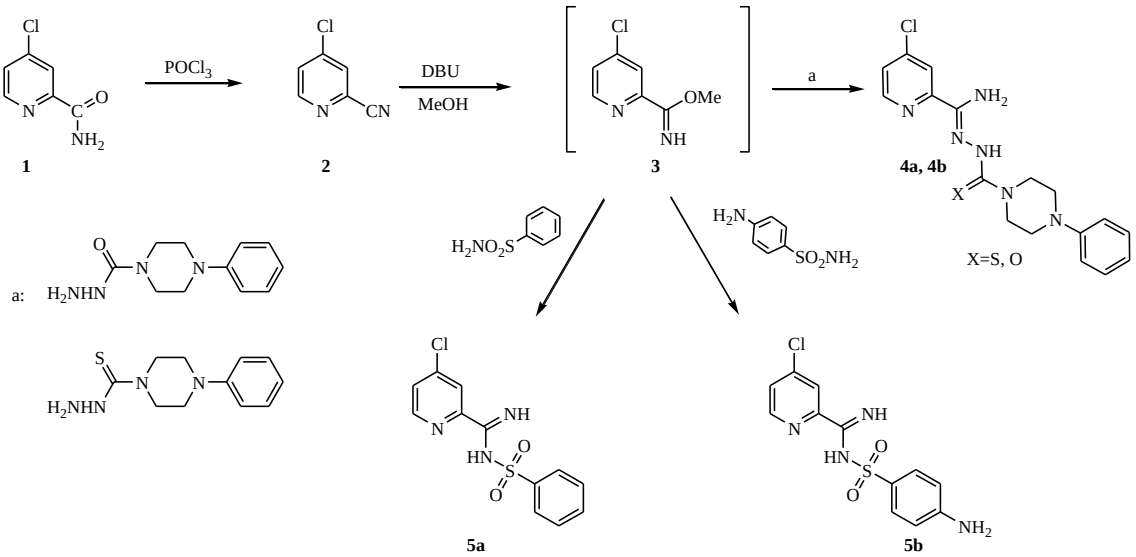


Figure 1

CHEMISTRY

A first set of compounds possessing the desired, outlined above structural characteristic, was prepared from imidate **3**, as the key intermediate. Starting 4-chloropicolinonitrile (**2**)[4] was prepared, with one of general metods, from amide **1**[4] using a dehydrating agent (Scheme 1). Treatment of methanolic solution of the nitrile (**2**) with catalytic amount of DBU resulted in formation of methyl 4-chloropicolinimidate (**3**). The DBU catalyzed formation of imidates was the best for our compound, and seems to be a viable alternative to the catalysis with alkali metal methanolate.[5, 6] When sodium methanolate was used, chlorine atom was converted to methoxy group. Reaction of the formed *in situ* imidate **3** with 4-phenylpiperazine-1-carbothiohydrazide and 4-phenylpiperazine-1-carbohydrazide gave amidrazones **4a** – **4b,** respectively. ^{1}H NMR spectra of the products demonstrated NH protons, as two-protons singlet at 6.28 (for **4a**) and 6.58 (for **4b**) and one-proton singlets at 8.58 (for **4a**) and 8.60 (for **4b**), which confirms structures shown at Scheme 1. Analogous reaction of imidate **3** with benzenesulfonamide and aminobenzenosulfonamide gave amidines **5a** – **5b,** respectively. ^{1}H NMR spectra of the products demonstrated NH protons, as two broad singlets at 8.29 and 8.92 (for **5a**) and two broad singlets at 8.12 and 8.88 (for **5b**), which confirms structures shown at Scheme 1.

Next group of compounds originated from amidrazone **6** as the key intermediate. The starting material 4-chloropicolinohydrazonamide (**6**) was prepared by reaction of nitrile **2** with hydrazine monohydrate. Subsequently, it was reacted under various reaction conditions, with carbon disulfide. As expected, reaction of **6** with carbon disulfide in plane methanol gave 5-(4-chloropyridin-2-yl)-1,3,4-thiadiazole-2(3*H*)-thione (**7**). Two tautomers (**7a** and **7b**) seem to be possible for the compound, and the δ value 14.96 for the exchangeable proton suggested that it is connected with nitrogen (**7a**).

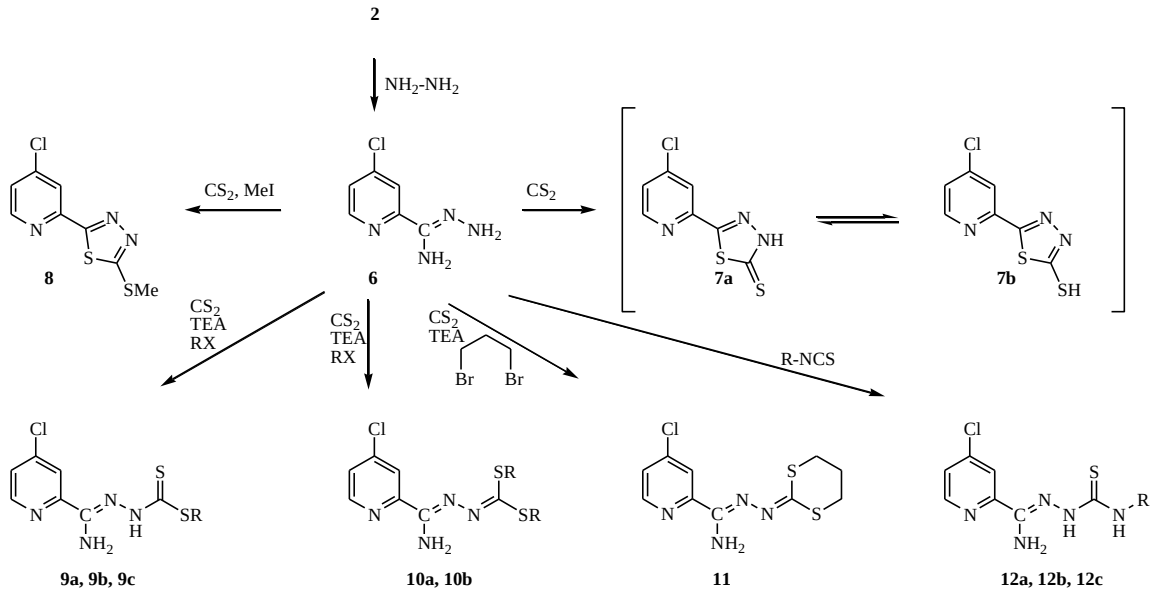


Scheme 1. Products formed *via* imidate **3**.

The conclusion was supported by IR (KBr), which demonstrated a strong absorption at 1235 cm^{-1}, which could correspond to C=S group. Thus, the reaction proceeded analogously as reported earlier[7] for similar compounds. The same reagent **6** but with addition of methyl iodide gave corresponding *S*-methylthiadiazole derivative **8**. Surprisingly, analogous condensation – alkylation reactions run in the presence of equimolar amount of triethylamine (TEA), resulted in formation of linear dithiocarbazoic acid monoesters **9a** - **c** as the main products, while in the presence of excess of TEA, dithiocarbazoic acid diesters **10a**, **b** were obtained. Replacement of methyl iodide by 1,3-dibromopropane gave 1,3-dithiolane derivative **11**. Further, compound **6** was reacted with appropriate isothiocyanates to give *N*-methyl, allyl and *p*-chlorophenyl thiosemicarbazides **12a** - **c** (Scheme 2).

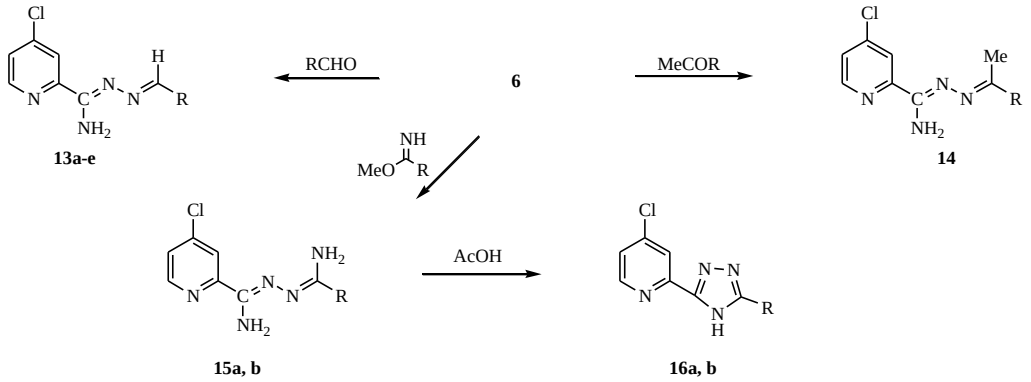
In the next step of the work, compounds with differently modified side chain in position 2 of the pyridine moiety were obtained, by reactions of compound **6** with aldehydes, ketones and iminoesters (Scheme 3). Reaction of 4-chloropicolinohydrazonamide (**6**) with 4-chlorobenzaldehyde, 5-nitrofuran-2-carbaldehyde, 5-nitrothiophene-2-carbaldehyde, 4-hydroxy-3-methoxybenzaldehyde or 4-(dimethylamino)benzaldehyde gave corresponding condensation products **13a** - **e**. Similarly, reaction with 1-(thiophen-2-yl)ethanone gave 4-chloro-*N*′-[1-(thiophen-2-yl)ethylidene]picolinohydrazonamide (**14**). Reaction of amidrazone **6** with iminoesters lead initially, at room temperature, to corresponding carbimidates **15a**, **b**, while heating of the products in AcOH caused intramolecular cyclization to 1,2,4-triazole derivatives **16a**, **b**.

Still another group of the required compounds originated from amidrazone **17**, which itself was prepared by reaction of nitrile **2** with methylhydrazine (Scheme 4). The compounds were prepared to check, by comparison with products derived from **6**, how methylation of the nitrogen atom will influence their



No	9a	9b	9c	10a	10b	12a	12b	12c
R	Me	Bu	Bn	Me	Bn	Me	$CH_2CH=CH_2$	*p*-Cl-Ph

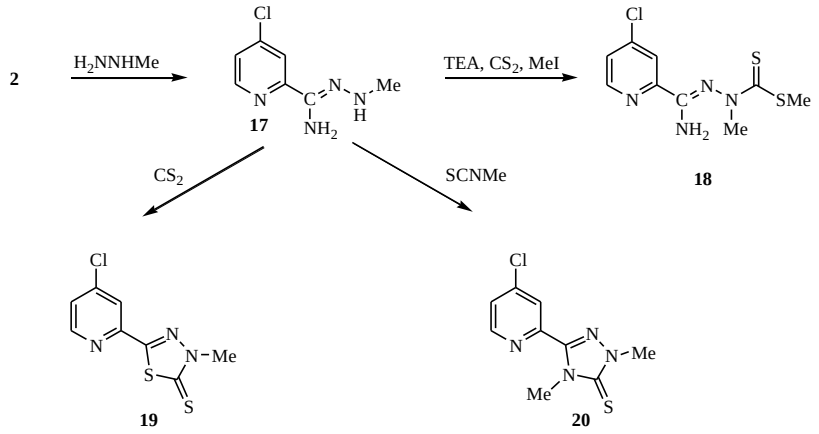
Scheme 2. Products formed *via* amidrazone **6**.



No	13a	13b	13c	13d	13e	14	15a, 16a	15b, 16b
R								

Scheme 3. Products formed *via* amidrazone **6**.

tuberculostatic activity. Essentially, the obtained results were similar to those for demethylated derivative **6** (Scheme 2) except the reaction with isothiocyanatomethane, which gave in the same conditions 1,2,4-triazole **20** (Scheme 4).



Scheme 4. Products formed *via* 4-chloro-*N'*-methylpicolinohydrazonamide **17**.

MICROBIOLOGICAL ACTIVITY

Antimicrobial activities of compounds were tested using the plate dilution technique in Brucella agar supplemented with 5 % lamb blood,[8] against 26 strains of anaerobic bacteria and agar dilution technique with Miller-Hinton agar against 25 strains of aerobic bacteria (Table 1), isolated from the oral cavity, respiratory system and abdominal cavity. The antibacterial activity of the tested compounds was also performed against the following standard bacterial strains: *Bacteroides fragilis* ATCC 25285, *Fusobacterium nucleatum* ATCC 25586, *Peptostreptococcus anaerobius* ATCC 27337, *Peptostreptococcus magnus* ATCC 29328, *Propionibacterium acnes* ATCC 11827. *Staphylococcus aureus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212, *Klebsiella pneumonia* ATCC 13883, *Acinetobacter baumannii* ATCC 19606, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853. The minimal inhibitory concentration (MIC) was defined as the lowest concentration of derivative that inhibited growth of bacteria. Metronidazole and amikacin were used as the reference substances. The investigation of susceptibility of aerobic and anaerobic bacteria to the compounds **2**, **6**, **9a**, **9a**, **13a – e, 14** are summarized in Table 1. The tested derivatives exhibited diversified activity against aerobic and anaerobic bacteria. Compounds **9a** (100 % of susceptible strains) and **13b** (72 % of susceptible susceptible strains) were found to be more active then the other compounds at concentrations in the range from ≤ 6.2 to 100 μg/mL against the aerobes. The anaerobes were the most susceptible at concentrations in the range from ≤ 6.2 to 100 μg/mL to derivatives **9a** (50 %) and **2** (35 %). Compounds **13c** – **e** and **14** did not exhibit any activity against aerobic and anaerobic bacteria.

Selected compounds **2** – **10b**, **12a** – **20** were tested for their tuberculostatic activity towards the standard Mycobacterium tuberculosis $H_{37}Rv$ strain and two wild strains isolated from the tuberculotic patients: one (Spec. 210) resistant to *p*-aminosalicylic acid (PAS), isonicotinic acid hydrazide (INH), etambutol (ETB) and rifampicine (REP) and the other (Spec. 192) fully susceptible to the drugs administered. The

tuberculostatic activity was determined *in vitro* by classical test tube method with Youman's liquid medium containing 10 % of bovine serum. In comparison with some of tuberculosis drugs: isonicotinic acid hydrazide (MIC 0.5 μg/mL), viomycin (MIC 6.2 μg/mL), cycloserine (MIC 5 μg/mL) and pyrazinamid (MIC 25 μg/mL), it was concluded that tested compounds showed no significant tuberculostatic activity (MIC 25 – 100 μg/mL).

Table 1. Antibacterial Activity of tested compounds **2**, **6**, **9a**, **13a – e**, **14**

	MIC (μg/ mL)						
Anaerobic bacteria	**Compound no**	**2**	**6**	**9a**	**13a**	**13b**	**13c – e, 14**
Gram positive:	Metronidazole*						
Finegoldia magna (2)	≤ 0.4	≤ 6.2	50	100	25	≥ 200	≥ 200
Micromonas micros (3)	≤ 0.4	50	50	≤ 6.2	25	≥ 200	≥ 200
Actinomyces israelii (2)	3.1	≥ 200	≥ 200	50	≥ 200	≥ 200	≥ 200
Propionibacterium acnes(2)	≥ 100	≥ 200	≥ 200	100	≥ 200	≥ 200	≥ 200
Gram-negative:							
Prevotella bivia (1)	≤ 0.4	100	≥ 200	≥ 200	≥ 200	≥ 200	≥ 200
Prevotella buccalis (2)	≤ 0.4	≥ 200	≥ 200	≥ 200	≥ 200	≥ 200	≥ 200
Prevotella intermedia (2)	≤ 0.4	≥ 200	≥ 200	≥ 200	≥ 200	≥ 200	≥ 200
Prevotella loescheii (1)	≤ 0.4	≥ 200	≥ 200	≥ 200	≥ 200	≥ 200	≥ 200
Porphyromonas saccharolytica (2)	≤ 0.4	100	≥ 200	100	≥ 200	≥ 200	≥ 200
Fusobacterium nucleatum (1)	≤ 0.4	100	≥ 200	100	≥ 200	≥ 200	≥ 200
Fusobacterium necrophorum (2)	1.6	≥ 200	≥ 200	100	≥ 200	≥ 200	≥ 200
Bacteroides fragilis (3)	≤ 0.4	50	≥ 200	≥ 200	≥ 200	≥ 200	≥ 200
Bacteroides ureolyticus (3)	6.2	≥ 200	≥ 200	≤ 6.2	≥ 200	≥ 200	≥ 200
Aerobic bacteria	Amikacin**						
Gram positive:							
Staphylococcus aureus (4)	≤ 6.2	≥ 200	≥ 200	≤ 6.2	≥ 200	25	≥ 200
Corynebacterium spp (2)	25	≥ 200	≥ 200	25	≥ 200	25	≥ 200
Gram-negative:							
Klebsiella pneumoniae (3)	≤ 6.2	≥ 200	≥ 200	50	≥ 200	50	≥ 200
Acinetobacter baumannii (2)	≤ 6.2	≥ 200	≥ 200	≤ 6.2	≥ 200	50	≥ 200
Escherichia coli (6)	≤ 6.2	≥ 200	≥ 200	25	≥ 200	50	≥ 200
Pseudomonas aeruginosa (6)	≤ 6.2	≥ 200	≥ 200	50	≥ 200	100	≥ 200
Pseudomonas stutzeri (2)	12.5	≥ 200	≥ 200	50	≥ 200	100	≥ 200

*Metronidazole (Sigma)

**Amikacin sulfate salt (Sigma)

EXPERIMENTAL

Melting points were obtained with Boetius apparatus and are uncorrected. Elemental analyses for C, H, N and S were performed on Carlo-Erba 1108 instrument. The IR spectra were taken using Mattson Satellite spectrophotometer, and the ^{1}H NMR spectra were obtained on Varian Gemini 200 MHz apparatus.

4-Chloropicolinonitrile (2)

4-Chloropicolinamide (**1**) (5.0 g, 32 mmol) was susspended in dry dioxane (30 mL) and $POCl_3$ (5 mL, 53.6 mmol) was added. The mixture was refluxed for 1.5 h and then the solution was evaporated. Ice (20 g) was added to the residue, and the precipitated solid was collected by filtration and crystallized from H_2O to give 4-chloropicolinonitrile (**2**) (2.21 g, 50 %) as colorless solid, mp 80 – 82 °C (83 – 84 °C).[5] ^{1}H NMR ($CDCl_3$) δ 7.56 (1H, dd, J_1 = 1.9 Hz, J_2 = 5.4 Hz), 7.73 (1H, d, J = 1.9 Hz), 8.64 (1H, d, J = 5.4 Hz); IR (KBr) ν 3086, 2240, 1570, 1547, 1461, 1381, 847, 465 cm^{-1}.

4-Chloro-*N*′-(4-phenylpiperazine-1-carbonothioyl)picolinohydrazonamide (4a)

4-Chloropicolinonitrile (**2**) (0.511 g, 4 mmol) was dissolved in anhydrous MeOH (10 mL) containing DBU (0.2 mL), as a catalyst. The mixture was refluxed for 10 min. Next 4-phenylpiperazine-1-carbothiohydrazide (0.944 g, 4 mmol) was added, and reflux was continued for 1 min and the mixture was left at rt for 5 h. The reaction mixture was acidified with acetic acid (0.3 mL), the product was filtered off and crystallized from dioxane to give 4-chloro-*N*'-(4-phenylpiperazine-1-carbonothioyl)picolinohydrazonamide (**4a**) (0.78 g, 52 %) as a yellow crystals, mp 160 – 163 °C. ^{1}H NMR ($CDCl_3$) δ 3.28 (4H, m), 4.18 (4H, m), 6.86 (2H, s), 6.95 (5H, m), 7.41 (1H, dd, J_1 = 2.0 Hz, J_2 = 5.3 Hz), 7.98 (1H, d, J = 2.0 Hz), 8. 54 (1H, d, J = 5.3 Hz), 8.58 (1H, s); IR (KBr) ν 3388, 3269, 2923, 1599, 1340, 1227, 1017, 758 cm^{-1}; Anal. Calcd for $C_{17}H_{19}ClN_6S$: C, 54.46; H, 5.11; N, 22.42; S, 8.55. Found: C, 54.32; H, 5.09; N, 22.39; S, 8.53.

4-Chloro-*N*′-(4-phenylpiperazine-1-carbonyl)picolinohydrazonamide (4b)

4-Chloropicolinonitrile (**2**) (0.249 g, 1.8 mmol) was dissolved in anhydrous MeOH (5 mL) containing DBU (0.1 mL), as a catalyst. The mixture was refluxed for 10 min and then cooled. 4-Phenylpiperazine-1-carbohydrazide (0.396 g, 1.8 mmol) was added and the mixture was stirred at rt for 2 h. The reaction mixture was acidified with acetic acid, the obtained solid was filtered off, and crystallized from MeOH to give 4-chloro-*N*'-(4-phenylpiperazine-1-carbonyl)picolinohydrazonamide (**4b**) (0.312 g, 50 %) as a yellow crystals, mp 296 – 298 °C. ^{1}H NMR (DMSO–d_6) δ 3.17 (4H, d, J = 5.1 Hz), 3.57 (4H, d, J = 5.1 Hz), 6.58 (2H, s), 6.80 – 7.27 (5H, m), 7.56 (1H, dd, J_1 = 2.1 Hz, J_2 = 5.3 Hz), 8.02 (1H, d, J = 2.1 Hz), 8.53 (1H, d, J = 5.3 Hz), 8.60 (1H, s); IR (KBr) ν 3430, 3333, 3232, 2814, 1631, 1539, 1425, 1229, 1156, 999, 761 cm^{-1}. Anal. Calcd for $C_{17}H_{19}ClN_6O$: C, 56.90; H, 5.34; N, 23.42. Found: C, 56.79; H, 5.32; N, 23.40.

4-Chloro-*N*′-(phenylsulfonyl)picolinimidamide (5a)

4-Chloropicolinonitrile (**2**) (0.277 g, 2 mmol) was dissolved in anhydrous MeOH (5 mL) containing DBU (0.2 mL), as a catalyst. The mixture was refluxed for 10 min, then the benzenosulfonamide (0.309 g, 1.8 mmol) was added, and the mixture was refluxed for 10 h. The reaction was cooled to rt, and the precipitated

solid was filtered off and washed with water. The product was crystallized from MeOH to give 4-chloro-*N'*-(phenylsulfonyl)picolinimidamide (**5a**) (0.235 g, 40 %) as colorless crystals, mp 119 – 121 °C. ^{1}H NMR ($CDCl_3$) δ 7.58 – 7.67 (3H, m), 7.85 (1H, dd, J_1 = 1.9 Hz, J_2 = 5.3 Hz), 8.00 (2H, d, J = 7.3 Hz), 8.10 (1H, d, J = 1.9 Hz), 8.29 (1H, bs), 8.68 (1H, d, J = 5.3 Hz), 8.92 (1H, bs); IR (KBr) ν 3418, 3311, 1618, 1574, 1285, 1142, 1084, 791, 590 cm^{-1}. Anal. Calcd for $C_{12}H_{10}ClN_3O_2S$: C, 48.73; H, 3.41; N, 14.21; S, 10.84. Found: C, 48.61; H, 3.40; 14.19; S, 10.81.

***N'*-(4-aminophenylsulfonyl)-4-chloropicolinimidamide (5b)**

4-Chloropicolinonitrile (**2**) (0.257 g, 1.85 mmol) was dissolved in anhydrous MeOH (5 mL) containing DBU (0.1 mL), as a catalyst. The mixture was refluxed for 10 min. Then 4-aminobenzenosulfonamide (0.287 g, 1.67 mmol) was added and the mixture was refluxed for 1.5 h. After cooling down the precipitated solid was filtered off and crystallized from EtOH to give *N'*-(4-aminophenylsulfonyl)-4-chloropicolinimidamide (**5b**) (0.197 g, 34 %) as a bright solid, mp 206 - 209 °C. ^{1}H NMR (DMSO-d_6) δ 5.96 (2H, s), 6.58 (2H, d, J = 8.7 Hz), 7.59 (2H, d, J = 8.7 Hz), 7.81 (1H, dd, J_1 = 1.9 Hz, J_2 = 5.3 Hz), 8.04 (1H, d, J = 1.9 Hz), 8.12 (1H, bs), 8.65 (1H, d, J = 5.3 Hz), 8.88 (1H, bs); IR (KBr) ν 3447, 3423, 3336, 1613, 1589, 1503, 1429, 1265, 1140,1084, 791, 572 cm^{-1}. Anal. Calcd for $C_{12}H_{11}ClN_4O_2S$: C, 46.38; H, 3.57; N, 18.03; S, 10.32. Found: C, 46.30; H, 3.56; N, 17.99; S, 10.29.

4-Chloropicolinohydrazonamide (6)

A mixture of 4-chloropicolinonitrile (**2**) (1.385 g, 10 mmol) and hydrazine monohydrate (5 mL, 103 mmol) in MeOH (20 mL) was heated under reflux for 30 min and the solvent was evaporated. The residue was diluted with benzene (10 mL) and evaporated again. Ice (10 g) was added to the residue, the formed solid was filtered off and crystallized from MeOH to give 4-chloropicolinohydrazonamide (**6**) (1.15 g, 67 %) as a yellow solid, mp 107 – 109 °C. ^{1}H NMR ($CDCl_3$) δ 4.67 (2H, bs), 5.22 (2H, s), 7.29 (1H, s), 8.06 (1H,s), 8.41 (1H, d, J = 5.4 Hz); IR (KBr) ν 3439, 3330, 3203,1655, 1625,1550, 1577, 1345, 882, 724 cm^{-1}. Anal. Calcd for $C_6H_7ClN_4$: C, 42.24; H, 4.14; N, 32.84. Found: C, 42.18; H, 4.12; N, 32.79.

5-(4-Chloropyridin-2-yl)-1,3,4-thiadiazole-2(3*H*)-thione (7)

4-Chloropicolinohydrazonamide (**6**) (0.511 g, 3 mmol) was dissolved in MeOH (5 mL) and on cooling CS_2 (1 mL, 16.5 mmol) was added. The mixture was left at rt for 24 h. Ice (20 g) was added to the reaction mixture and the precipitated solid was filtered off and crystallized from MeOH to give 5-(4-chloropyridin-2-yl)-1,3,4-thiadiazole-2-thiol (**7**) (0.24 g, 35 %) as a yellow solid, mp 175 – 177 °C. ^{1}H NMR (DMSO–d_6) δ 7.66 (1H, dd, J_1 = 2.0 Hz, J_2 = 5.7 Hz), 8.08 (1H, d, J = 2.0 Hz), 8.62 (1H, d, J = 5.7 Hz), 14.96 (1H, s); IR (KBr) ν 3088, 2994, 2890, 1574, 1471, 1401, 1294, 1235, 1073, 782, 728 cm^{-1}. Anal. Calcd for $C_7H_4ClN_3S_2$: C, 36.60; H, 1.76; N, 18.29; S, 27.92. Found: C, 36.54; 1.75; N, 18.25; S, 27.88.

2-(4-Chloropyridin-2-yl)-5-(methylthio)-1,3,4-thiadiazole (8)

4-Chloropicolinohydrazonamide (**6**) (0.511 g, 3 mmol) was dissolved in anhydrous MeOH (10 mL). On cooling, CS_2 (1 ml, 16.5 mmol) and MeI (0.24 mL, 3.9 mmol) were added, and the mixture was stirred at rt for 1 h. The precipitated solid was filtered off and crystallized from MeOH:H_2O (1:1) to give 2-(4-chloropyridin-2-yl)-5-(methylthio)-1,3,4-thiadiazole (**8**) (0.42 g, 57 %) as colorless crystals, mp 122 – 123 °C. ^{1}H NMR ($CDCl_3$) δ 2.85 (3H, s), 7.36 (1H, dd, J_1 = 2.0 Hz, J_2 = 5,4 Hz), 8.32 (1H, d, J = 2.0 Hz), 8.53 (1H, d, J = 5.4 Hz); IR (KBr) ν 1577, 1554, 1396, 1360, 1082, 834, 739 cm^{-1}. Anal. Calcd for $C_8H_6ClN_3S_2$: C, 39.42; H, 2.48; N, 17.24; S, 26.31. Found: C, 39.37; H, 2.47; N, 17.20; S, 26.27.

General method for synthesis of compounds 9a-c

A solution of 4-chloropicolinohydrazonamide (**6**) (0.852 g, 5 mmol) in MeOH (15 mL) containing 0.83 mL of triethylamine (6 mmol) was cooled to 0 ºC and then CS_2 (0.36 mL, 6 mmol) was added, and the mixture was stirred at rt for 1 h. Next, iodomethane (5 mmol) (for compound **9a**), buthyl iodid (5 mmol) (for **9b**), (chloromethyl)benzene (5 mmol) (for **9c**) was added, and the mixture was stirred at rt for 2 h. The precipitated solid was filtered off and crystallized.

Methyl 2-[amino(4-chloropyridin-2-yl)methylene]hydrazinecarbodithioate (9a)

The crude product was crystallized from MeOH to give yellow solid (89 %), mp 159 – 160 °C. ^{1}H NMR (Acetone) δ 2.56 (3H, s), 6.99 (2H, s), 7.59 (1H, dd, J_1 = 2.1 Hz, J_2 = 5.1 Hz), 8.22 (1H, d, J = 2.1 Hz), 8.57 (1H, d, J = 5.1 Hz), 10.93 (1H, s); IR (KBr) ν 3384, 3280, 2911, 1665, 1577, 1365, 1317, 1002, 958, 741 cm^{-1}. Anal. Calcd for $C_8H_9ClN_4S_2$: C, 36.85; H, 3.48; N, 21.49; S, 24.59. Found: C, 36.79; H, 3.46; N, 21.44; S, 24.54.

Butyl 2-[amino(4-chloropyridin-2-yl)methylene]hydrazinecarbodithioate (9b)

The crude product was crystallized from EtOH to give yellow solid (32 %), mp 121 – 122 °C. ^{1}H NMR (Acetone) δ 0.95 (3H, s), 1.45 (2H, m), 1.67 (2H, m), 3.25 (2H, t, J = 7.2 Hz), 6.99 (2H, s), 7.58 (1H, dd, J_1 = 2.0 Hz, J_2 = 5.5 Hz), 8.22 (1H, d, J = 2.0 Hz), 8.57 (1H, d, J = 5.5 Hz), 10.83 (1H, s); IR (KBr) ν 3404, 3311, 2957, 1661, 1508, 1366, 1318, 994, 737 cm^{-1}. Anal. Calcd for $C_{11}H_{15}ClN_4S_2$: C, 43.63; H, 4.99; N, 18.50; S, 21.18. Found: C, 43.56; H, 4.97; N, 18.45; S, 21.14.

Benzyl 2-[amino(4-chloropyridin-2-yl)methylene]hydrazinecarbodithioate (9c)

The crude product was crystallized from MeOH to give yellow solid (38 %), mp 218 – 221 °C. ^{1}H NMR ($CDCl_3$) δ 4.34 (2H, s), 7.06 - 7.98 (9H, m), 8.45 (1H, d, J = 4.9 Hz), 9.74 (1H, s); IR (KBr) ν 3434, 3323, 2923, 1660, 1574, 1469, 1361, 1312, 1241, 1068, 1000, 831, 735, 693, 473 cm^{-1}. Anal. Calcd for $C_{14}H_{13}ClN_4S_2$: C, 49.92; H, 3.89; N, 16.63; S, 19.04. Found: C, 49.79; H, 3.87; N, 16.59; S, 18.98.

Dimethyl amino(4-chloropyridin-2-yl)methylenecarbonohydrazonodithioate (10a)

A solution of 4-chloropicolinohydrazonamide (**6**) (0.852 g, 5 mmol) and triethylamine (1.66 mL, 11.5 mmol) in MeOH (10 mL) was cooled to 0 ºC and then CS_2 (0.3 mL, 5 mmol) was added, and the mixture

was stirred at rt for 0.5 h. Iodomethane (0.62 mL, 10 mmol) was added, and the mixture was stirred at rt for 2 h. The solvent was evaporated and diethyl eter (30 mL) was added to the residue. The precipitated solid was filtered off and crystallized from EtOH to give dimethyl amino(4-chloropyridin-2-yl)methylenecarbonohydrazonodithioate (**10a**) (1.09 g, 79 %) as a yellow solid, mp 101 – 103 °C. ^{1}H NMR ($CDCl_3$) δ 2.55 (3H, s), 2.59 (3H, s), 6.15 (2H, s), 7.34 (1H, dd, J_1 = 1.9 Hz, J_2 = 5.3Hz), 8.35 (1H, s), 8.46 (1H, d, J = 5.3Hz); IR (KBr) ν 3469, 3359, 1613, 1548, 1460, 1345, 1035, 944, 745 cm^{-1}. Anal. Calcd for $C_9H_{11}ClN_4S_2$: C, 39.34; H, 4.03; N, 20.39; S, 23.34. Found: C, 39.29; H, 4,02; N, 20.35; S, 23.30.

Dibenzyl amino(4-chloropyridin-2-yl)methylenecarbonohydrazonodithioate (10b)

A solution of 4-chloropicolinohydrazonamide (**6)** (0.341 g, 2 mmol) and triethylamine (0.84 mL, 6 mmol) in MeOH (10 mL) was cooled to 0 ºC and then CS_2 (0.18 mL, 3 mmol) was added. The mixture was stirred at rt for 1 h. Next, benzyl chloride (0.46 mL, 4 mmol) was added and the mixture was stirred at rt for 24 h. The formed precipitate was filtered off and crystallized from MeOH:H_2O (1:1) to give dibenzyl amino(4-chloropyridin-2-yl)methylenecarbonohydrazonodithioate (**10b**) (0.28 g, 33 %) as a yellow solid, mp 83 – 84 °C. ^{1}H NMR ($CDCl_3$) δ 4.31 (2H, s), 4.42 (2H, s), 5.95 (2H, s), 7.31 – 7.45 (10H, m), 7.47 (1H, d, J = 2.1 Hz), 8.26 (1H, d, J = 2.1 Hz), 8.44 (1H, d, J = 5.4 Hz);); IR (KBr) ν 3456, 3365, 1616, 1548, 1461, 1416, 1348, 1239, 1011, 742, 696 cm^{-1}. Anal. Calcd for $C_{21}H_{19}ClN_4S_2$: C, 59.07; H, 4.49; N, 13.12; S, 15.02, Found: C, 58.94; H, 4.47; N, 13.08; S, 14.99.

4-Chloro-*N′*-(1,3-dithian-2-ylidene)picolinohydrazonamide (11)

A solution of 4-chloropicolinohydrazonamide (**6)** (0.511 g ,3 mmol) and triethylamine (1.05 mL, 7.5 mmol) in MeOH (10 mL) was cooled to 0 ºC and then CS_2 (0.27 mL, 4.5 mmol) was added. The mixture was stirred at rt for 1 h. Next, 1,3-dibromopropane (0.36 mL, 3.6 mmol) was added, and the mixture was stirred at rt for 3 h. The mixture was neutralized with diluted acetic acid and extracted with dichloromethane (3 x 30 mL). The organic layer was dried over anhydrous $MgSO_4$ (2 g) for 12 h and evaporated give 4-chloro-*N′*-(1,3-dithian-2-ylidene)picolinohydrazonamide (**11**) (0.27 g, 31 %) as a yellow solid, mp 166 – 169 °C. ^{1}H NMR ($CDCl_3$) δ 2.48 (2H, m), 3.23 (2H, m), 3.74 (2H, t, J = 5.2 Hz), 6.31 (2H, s), 7.41 (1H, dd, J_1 = 3.3 Hz, J_2 = 5.1 Hz), 8.36 (1H, s), 8.47 (1H, d, J = 5.1 Hz); IR (KBr) ν 3437, 3307, 2937, 2677, 2491, 1627, 1574, 1433, 1170, 1036, 952 cm^{-1}. Anal. Calcd for $C_{10}H_{11}ClN_4S_2$: C, 41.88; H, 3.87; N, 19.53; S, 22.36. Found: C, 41.81; H, 3.86; N, 19.49; S, 22.32.

General method for compounds 12a-c

A solution of 4-chloropicolinohydrazonamide (**6)** (0.511 g, 3 mmol) in dry dioxane (5 mL) was treated with isothiocyanatomethane (0.22 g, 3 mmol) (for **12a**), allyl isothiocyanate (0.291 mL, 3 mmol) (for **12b**) and

1-chloro-4-isothiocyanatobenzene (0.508 g, 3 mmol) (for **12c**) and heated under reflux for 15 min. The reaction mixture was then cooled and poured into petroleum ether (30 mL). The product was filtered off and crystallized from MeOH:H_2O (2:1) or dioxane (**12c**).

2-[Amino(4-chloropyridin-2-yl)methylene]-*N*-methylhydrazinecarbothioamide (12a)

Reaction with isothiocyanatomethane. Product **12a** was isolated as a yellow solid (0.31g, 42 %), mp 175 – 177 °C. ^{1}H NMR (DMSO–d_6) δ 3.02 (3H, d, J = 4.6 Hz), 6.92 (2H, s), 7.56 (1H, dd, J_1 = 2.1 Hz, J_2 = 5.4 Hz), 8.42 (1H, d, J = 4.6 Hz), 8.53 (1H, d, J = 5.4 Hz), 8.62 (1H, d, J = 2.1 Hz), 10.07 (1H, s); IR (KBr) ν 3440, 3405, 3351, 3279, 3175, 1656, 1550, 1430, 1259, 1070, 711 cm^{-1}. Anal. Calcd for $C_8H_{10}ClN_5S$: C, 39.43; H, 4.14; N, 28.74; S, 13.16. Found: C, 39.38; H, 4.13; N, 28.69; S, 13.13.

***N*-Allyl-2-[amino(4-chloropyridin-2-yl)methylene]hydrazinecarbothioamide (12b)**

Reaction with allyl isothiocyanate. Product **12b** was isolated as a yellow solid (0.66 g, 82 %), mp 158 – 160 °C. ^{1}H NMR ($CDCl_3$) δ 4.43 (2H, s), 5.24 (1H, s), 5.32 (1H, d, J = 15.6 Hz), 6.00 (1H, s), 6.44 (2H, s), 7.35 (1H, s), 7.59 (1H, s), 8.06 (1H, s), 8.45 (1H, s), 9.81 (1H, s); IR (KBr) ν 3423, 3365, 3269, 1655, 1575, 1541, 1431, 1295, 1222, 828, 714 cm^{-1}. Anal. Calcd for $C_{10}H_{12}ClN_5S$: C, 44.52; H, 4.48; N, 25.96; S, 11.89. Found: C, 44.46; H, 4.46; N, 25.90; S, 11.85.

2-[Amino(4-chloropyridin-2-yl)methylene]-*N*-(4-chlorophenyl)hydrazinecarbothioamide (12c)

Reaction with 1-chloro-4-isothiocyanatobenzene. Product **12c** was isolated as a white solid (0.20 g, 20 %), mp 164 – 166 °C. ^{1}H NMR (DMSO–d_6) δ 7.14 (2H, s), 7.42 (2H, d, J = 8.3 Hz), 7.57 (2H, d, J = 8.3 Hz), 7.59 (1H, d, J = 5.3 Hz), 8.54 (1H, d, J = 5.3 Hz), 8.77 (1H, s), 10.03 (1H, s), 10.50 (1H, s); IR (KBr) ν 3401, 3281, 3229, 2968, 1665, 1577, 1533, 1467, 1334, 1200, 1090, 828, 721 cm^{-1}. Anal. Calcd for $C_{13}H_{11}Cl_2N_5S$: C, 45.89; H, 3.26; N, 20.58; S, 9.42. Found: C, 45.79; H, 3.25; N, 20.52; S, 9.39.

General procedure for compound 13a-e

A solution of 4-chloropicolinohydrazonamide (**6)** (0.341 g, 2 mmol) in MeOH (5 mL) was treated with 4-chlorobenzaldehyde (0.281 g, 2 mmol) (for **13a**), 5-nitrofuran-2-carbaldehyde (0.282 g, 2 mmol) (for **13b**), 5-nitrothiophene-2-carbaldehyde (0.314 g, 2 mmol) (for **13c**), 4-hydroxy-3-methoxybenzaldehyde (0.304 g, 2 mmol) (for **13d**) or 4-(dimethylamino)benzaldehyde (0.298 g, 2 mmol) (for **13e**) and stirred at rt for 1h. The product was filtered off and crystallized from MeOH to give compounds **13a-e**, respectively.

4-Chloro-*N′*-(4-chlorobenzylidene)picolinohydrazonamide (13a)

Reaction with 4-chlorobenzaldehyde. Product **13a** was isolated as a yellow solid (0.304 g, 52 %), mp 132 – 134 ºC. ^{1}H NMR (DMSO–d_6) δ 7.17 (1H, s), 7.32 (1H, s), 7.51 (2H, d, J = 7.8 Hz), 7.71 (1H, d, J = 4.8 Hz), 7.98 (2H, d, J = 7.8 Hz), 8.23 (1H, s), 8.50 (1H, s), 8.65 (1H, d, J = 4.8 Hz); IR (KBr) ν 3491,

3375,1623,1548, 1464, 1327, 1087, 1011, 836, 732 cm^{-1}. Anal. Calcd for $C_{13}H_{10}Cl_2N_4$: C, 53.26; H, 3.44; N, 19.11. Found: C, 53.13; H, 3.43; N, 19.08.

4-Chloro-*N′*-[(5-nitrofuran-2-yl)methylene]picolinohydrazonamide (13b)

Reaction with 5-nitrofuran-2-carbaldehyde. Produkt **13b** was isolated as a red solid (0.4 g, 68 %), mp 174 – 177 ºC. ^{1}H NMR (DMSO–d_6) δ 7.43 (1H, d, J = 3.9 Hz), 7.59 (2H, bs), 7.74 (1H, dd, J_1 = 1.9 Hz, J_2 = 5.4 Hz), 7.84 (1H, d, J = 3.9 Hz), 8.24 (1H, d, J = 1.9 Hz), 8.41 (1H, s), 8.67 (1H, d, J = 5.4 Hz); IR (KBr) ν 3474, 3348, 1624, 1551, 1467, 1347, 1252, 1179, 1008, 735 cm^{-1}. Anal. Calcd for $C_{11}H_8ClN_5O_3$: C, 44.99; H, 2.75; N, 23.85. Fund: C, 44.87; H, 2.74; N, 23.79.

4-Chloro-*N′*-[(5-nitrothiophen-2-yl)methylene]picolinohydrazonamide (13c)

Reaction with 5-nitrothiophene-2-carbaldehyde. Product **13c** was isolated as a yellow solid (0.276 g, 45 %), mp 218 – 220 ^{o}C. ^{1}H NMR ($CDCl_3$) δ 7.03 (1H, s), 7.04 (1H, s), 7.29 (1H, d, J = 3.6 Hz), 7.47 (1H, dd, J_1 = 5.1 Hz, J_2 = 1.9 Hz), 7.94 (1H, d, J = 1.9 Hz); 8.08 (1H, s); 8.54 (1H, d, J = 3.6 Hz); 8.56 (1H, d, J = 1.9 Hz); IR (KBr) ν 3454, 3356, 1614, 1551, 1486, 1337, 1205, 1060, 814, 733, 708 cm^{-1}. Anal. Calcd for $C_{11}H_8ClN_5O_2S$: C, 42.66, H, 2.60; N, 22.61; S, 10.35. Found: C, 42.59; H, 2.59; N, 22.56; S, 10.32.

4-Chloro-*N′*-(4-hydroxy-3-methoxybenzylidene)picolinohydrazonamide (13d)

Reaction with 4-hydroxy-3-methoxybenzaldehyde. Product **13d** was isolated as a yellow solid (0.438 g, 74 %), mp 130 – 131 ^{o}C. ^{1}H NMR (DMSO–d_6) δ 3.85 (3H, s); 6.79 (1H, d, J = 7.8 Hz); 7.05 (2H, s); 7.17 (1H, d, J = 7.8 Hz); 7.62 (1H, s); 7.66 (1H, d, J = 5.1 Hz); 8.20 (1H, s); 8.36 (1H, s); 8.61 (1H, d, J = 5.1 Hz); 9.49 (1H, s); IR (KBr) ν 3476, 3362, 1621, 1521, 1465, 1285, 1117, 1032, 854, 728, 501 cm^{-1}. Anal. Calcd for $C_{14}H_{13}ClN_4O_2$: C, 55.18; H, 4.30; N, 18.39. Found: C, 55.04; H, 4.28; N, 18.35.

4-Chloro-*N′*-[4-(dimethylamino)benzylidene]picolinohydrazonamide (13e)

Reaction with 4-(dimethylamino)benzaldehyde. Product **13e** was isolated as a yellow solid (0.168 g, 28 %), mp 149 – 151 ^{o}C. ^{1}H NMR (DMSO–d_6) δ 2.97 (6H, s); 6.71 (2H, d, J = 8.5 Hz); 6.88 (2H, s); 7.64 (1H, d, J = 3.3 Hz); 7.69 (2H, d, J = 8.5 Hz); 8.20 (1H, s); 8.36 (1H, s); 8.61 (1H, d, J = 5.4 Hz); IR (KBr) ν 3494, 3376, 1604, 1546, 1369, 1175, 812, 728, 587 cm^{-1}. Anal. Calcd for $C_{15}H_{16}ClN_5$: C, 59.70; H, 5.34; N, 23.21. Found: C, 59.64; H, 5.32; N, 23.17.

4-Chloro-*N′*-[1-(thiophen-2-yl)ethylidene]picolinohydrazonamide (14)

A solution of 4-chloropicolinohydrazonamide (**6)** (0.341 g, 2 mmol) in MeOH (10 mL) containing 1 mL of acetic acid, as a catalyst, was treated with 1-(thiophen-2-yl)ethanone (0.252 g, 2 mmol). The mixture was left at rt for 1 h. The formed precipitate was filtered off, and crystallized from MeOH to give 4-chloro-*N′*-[1-(thiophen-2-yl)ethylidene]picolinohydrazonamide (**14**) as a yellow solid (0.456 g, 82 %), mp 167 – 169 ^{o}C. ^{1}H NMR (DMSO–d_6) δ 2.52 (3H, s); 7.04 (2H, bs); 7.15 (1H, t, J = 4.8 Hz); 7.63 (1H, d, J = 3.4 Hz); 7.71 (1H, dd, J_1 = 5.3 Hz, J_2 = 1.4 Hz); 7.85 (1H, d, J = 4.8 Hz); 8.45 (1H, d, J = 1.4 Hz); 8.66

(1H, d, *J* = 5.3 Hz); IR (KBr) ν 3438, 3311, 1613, 1548, 1466, 1417, 1294, 1018, 832, 717 cm^{-1}. Anal. Calcd for $C_{12}H_{11}ClN_4S$: C, 51.70; H, 3.98; N, 20.10; S, 11.50. Found: C, 51.61; H, 3.96; N, 20.05; S, 11.47.

***N′*-[Amino(4-chloropyridin-2-yl)methylene]pyrimidine-2-carbohydrazonamide (15a)**

A solution of pyrimidine-2-carbonitrile (0.525 g, 5 mmol) and triethylamine (0.5 mL) in MeOH (10 mL), was refluxed for 2 h. Next, the solvent was evaporated, and MeOH (5 mL) followed by 4-chloropicolinohydrazonamide (**6**) (0.852 g, 5 mmol) and acetic acid (0.2 mL) were added to the residue. The mixture was stirred for 5 min, and the formed precipitate was filtered off and crystallized from MeOH/H_2O (1:1) to give *N′*-[amino(4-chloropyridin-2-yl)methylene]pyrimidine-2-carbohydrazonamide (**15a**) (0.497 g, 35 %) as a yellow crystals, mp 188 – 190 °C. ^{1}H NMR (DMSO–d_6) δ 6.39 (2H, s); 6.52 (2H, s); 7.31 (2H, m); 8.39 (1H, d, *J* = 1.9 Hz); 8.46 (1H, d, *J* = 5.4 Hz); 8.84 (2H, d, *J* = 4.8 Hz); IR (KBr) ν 3296, 1611, 1547, 1443, 1349, 1038, 817, 639 cm^{-1}. Anal. Calcd for $C_{11}H_{10}ClN_7$: C, 47.92; H, 3.66; N, 35.56. Found: C, 47.82; H, 3.65; N, 35.49.

***N′*-[Amino(4-chloropyridin-2-yl)methylene]pyrazine-2-carbohydrazonamide (15b)**

Methyl pyrazine-2-carbimidate (0.274 g, 2 mmol) was added to a solution of 4-chloropicolinohydrazonamide (**6**) (0.341 g, 2 mmol) and acetic acid (o.1 mL) in MeOH (10 mL) and the mixture was stirred at rt for 5 min. The formed solid was filtered off and crystallized from EtOH to give *N′*-[amino(4-chloropyridin-2-yl)methylene]pyrazine-2-carbohydrazonamide (**15b**) (0.418 g, 76 %) as a yellow crystals, mp 255 – 257 °C. ^{1}H NMR (DMSO–d_6) δ 7.45 (2H, s), 8.54 - 8.70 (6H, m), 9.65 (2H, s); IR (KBr) ν 3400, 3293, 1605, 1548, 1464, 1425, 1020, 714 cm^{-1}. Anal. Calcd for $C_{11}H_{10}ClN_7$: C, 47.92; H, 3.66; N, 35.56. Found: C, 47.81; H, 3.65; N, 35.48.

General method for compounds 16a and 16b.

A solution of 1 mmol of *N′*-[amino(4-chloropyridin-2-yl)methylene]pyrimidine-2-carbohydrazonamide **(15a)** or *N′*-[amino(4-chloropyridin-2-yl)methylene]pyrazine-2-carbohydrazonamide **(15b)** in glacial acetic acid (3 mL) was refluxed for 1 h. The reaction mixture was then cooled and poured into cold water. The formed solid product was filtered off, and crystallized from MeOH/H_2O (2:1) to give compounds **16a** and **16b**, respectively.

2-[5-(4-Chloropyridin-2-yl)-4*H*-1,2,4-triazol-3-yl]pyrimidine (16a)

Reaction with methyl pyrimidine-2-carbimidate. Product **16a** was isolated as colorless solid (0.219 g, 85 %), mp 204 – 205 °C. ^{1}H NMR (DMSO–d_6) δ 7.62 (2H, m), 8.20 (1H, s), 8.71 (1H, d, *J* = 5.4 Hz), 9.01 (2H, d, *J* = 4.8 Hz), 11.25 (1H, s); IR (KBr) ν 3444, 1565, 1452, 1396, 1210, 1152, 789, 754 cm^{-1}. Anal. Calcd for $C_{11}H_7ClN_6$: C, 51.08; H, 2.73; N, 32.49. Found: C, 50.96; H, 2.72; N, 32.41.

2-[5-(4-chloropyridin-2-yl)-4*H*-1,2,4-triazol-3-yl]pyrazine (16b)

Reaction with methyl pyrazine-2-carbimidate. Product **16b** was isolated as colorless solid (0.229 g, 89 %), mp 217 – 219 °C. ^{1}H NMR (DMSO–d_6) δ 6.92 (1H, m), 7.61 (1H, s), 8.41 (1H, d, J = 5.2 Hz), 8.74 (2H, m), 9.32 (1H, m), 11.15 (1H, s); IR (KBr) ν 3435, 1633, 1556, 1380, 1160, 1019, 788, 763 cm^{-1}. Anal. Calcd for $C_{11}H_7ClN_6$: C, 51.08; H, 2.73; N, 32.49. Found: C, 51.01; H, 2.72; N, 32.43.

4-Chloro-*N′*-methylpicolinohydrazonamide (17)

A mixture of 4-chloropicolinonitrile (0.415 g, 3 mmol) and methyl hydrazine (0.32 mL, 6 mmol) in MeOH (3 mL) was refluxed for 30 min and the solvent was evaporated. The residue was diluted with benzene (10 mL), and evaporated again. Ice (10 g) was added to the residue, the product was filtered off and crystallized from benzene: petroleum ether (1:10) to give 4-chloro-*N′*-methylpicolinohydrazonamide (**17**) (0.26 g, 47 %) as a yellow crystals, mp 102 – 104 °C. ^{1}H NMR ($CDCl_3$) δ 3.01 (3H, s), 5.15 (2H, s), 7.25 (1H, dd, J_1 = 1.9 Hz, J_2 = 5.3 Hz), 7.28 (1H, s), 8.12 (1H, d, J = 1.9 Hz), 8.39 (1H, d, J = 5.3 Hz); IR (KBr) ν 3326, 3206, 1648, 1574, 1548, 1475, 1346, 1071, 829, 735 cm^{-1}. Anal. Calcd for $C_7H_9ClN_4$: C, 45.54; H, 4.91; N, 30.35. Found: C, 45.46; H, 4.89; N, 30.29.

Methyl 2-[amino(4-chloropyridin-2-yl)methylene]-1-methylhydrazinecarbodithioate (18)

A solution of 4-chloro-*N′*-methylpicolinohydrazonamide (**17)** (0.554 g, 3 mmol) and triethylamine (0.5 mL, 3.6 mmol) in MeOH (15 mL) was cooled to 0 ºC and then CS_2 (0.22 mL, 3.6 mmol) was added. The reaction mixture was stirred at rt for 1.5 h. Next, iodomethane (0.19 mL, 3 mmol) was added and the mixture was stirred at rt for next 1 h. The solvent was evaporated and petroleum ether (20 mL) was added to the residue. The precipitated solid was filtered off and crystallized from MeOH:H_2O (3:2) to give methyl 2-[amino(4-chloropyridin-2-yl)methylene]-1-methylhydrazinecarbodithioate (**18**) (0.230 g, 28 %) as a yellow solid, mp 175 – 177 °C. ^{1}H NMR ($CDCl_3$) δ 2.55 (3H, s), 3.73 (3H, s), 6.15 (2H, s), 7.47 (1H, dd, J_1 = 2.1 Hz, J_2 = 5.2 Hz), 8.37 (1H, d, J = 2.1 Hz), 8.53 (1H, d, J = 5.2 Hz); IR (KBr) ν 3409, 3294, 2917, 1629, 1575, 1368, 1100, 987, 740 cm^{-1}. Anal. Calcd for $C_9H_{11}ClN_4S_2$: C, 39.34; H, 4.03; N, 20.39; S, 23.34. Found: C, 39.28; H, 4.01; N, 20.34; S, 23.28.

5-(4-Chloropyridin-2-yl)-3-methyl-1,3,4-thiadiazole-2(3*H*)-thione (19)

A solution of 4-chloro-*N′*-methylpicolinohydrazonamide **(17)** (0.554 g, 3 mmol) in MeOH (5 mL) was cooled to 0 ºC and then CS_2 (1 mL, 16.5 mmol) was added. The reaction mixture was left at rt for 12 h. The solid product was filtered off and crystallized from EtOH:H_2O (4:1) to give 5-(4-chloropyridin-2-yl)-3-methyl-1,3, 4-thiadiazole-2(3*H*)-thione (**19**) (0.432 g, 59 %) as a yellow crystals, mp 181 – 183 °C. ^{1}H NMR ($CDCl_3$) δ 3.97 (3H, s), 7.38 (1H, dd, J_1 = 2.0 Hz, J_2 = 5.4 Hz), 8.01 (1H, d, J = 2.0 Hz), 8.51 (1H, d, J = 5.4 Hz); IR (KBr) ν 3056, 1572, 1404, 1295, 1135, 1101, 757 cm^{-1}. Anal. Calcd for $C_8H_6ClN_3S_2$: C, 39.42; H, 2.48; N, 17.24; S, 26.31. Found: C, 39.33; H, 2.47; N, 17.20; S, 26.26.

3-(4-Chloropyridin-2-yl)-1,4-dimethyl-1*H*-1,2,4-triazole-5(4*H*)-thione (20)

Method A:

A solution of 4-chloro-*N'*-methylpicolinohydrazonamide **(17)** (0.369 g, 2 mmol) in dry dioxane (5 mL) was treated with isothiocyanatomethane (0.15 g, 2 mmol) and refluxed for 15 min. The reaction mixture was then cooled and poured into petroleum ether (30 mL). The product was filtered off and crystallized from H_2O to give 3-(4-chloropyridin-2-yl)-1,4-dimethyl-1*H*-1,2,4-triazole-5(4*H*)-thione (**20**) (0.147 g, 31 %) as a yellow solid, mp 169 – 170 °C.

Method B:

Isothiocyanatomethane (0.15 g, 2 mmol) was added to a solution of 4-chloro-*N'*-methylpicolinohydrazonamide **(17)** (0.369 g, 2 mmol) in MeOH (5 mL), and the mixture was stirred at rt for 1 h. Next, the solvent was evaporated and ice (20 g) was added to the residue. The precipitate was filtered off and crystallized from MeOH:H_2O (1:1) to give 3-(4-chloropyridin-2-yl)-1,4-dimethyl-1*H*-1,2,4-triazole-5(4*H*)-thione (**20**) (0.25 g, 52 %) as a yellow solid, mp 169 – 170 °C. ^{1}H NMR ($CDCl_3$) δ 3.91 (3H, s), 4.06 (3H, s), 7.41 (1H, dd, J_1 = 2.0 Hz, J_2 = 5.4 Hz), 8.05 (1H, d, J = 2.0 Hz), 8.57 (1H, d, J = 5.4 Hz); IR (KBr) ν 3054, 1576, 1480, 1364, 1162, 1343, 767 cm^{-1}. Anal. Calcd for $C_9H_9ClN_4S$: C, 44.91; H, 3.77; N, 23.28; S, 13.32. Found: C, 44.82; H, 3.76; N, 23.22; S, 13.29.

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