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Note

Synthesis and pharmacological study of thiazolidinones and mannich bases of 4-amino-3-mercapto-5-pyridin-3′-yl-[1,2,4]-triazole

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4-Amino-5-(3-pyridyl)-4*H*-1,2,4-triazole-3-thiol **1** is prepared from methyl nicotinate through a multi-step reaction sequence[1]. Compound **1** react with various aromatic aldehydes in the presence of gl. acetic acid to give 4-substituted-benzal-amino-3-mercapto-5-pyridin-3′yl-[1,2,4]-triazoles **2a-i**, which on further cyclo-condensation with thioacetic acid afforded 3-(3′-mercapto-5′-pyridin-3′′-yl-[1, 2, 4]-triazole-4′-yl)-2-aryl-1, 3-thiazolidin-4-ones **3a-i**. Compounds **2a-i** on reaction with formaldehyde and with different aromatic amines in dioxane yielded 2-[bis-aryl-amino-methyl]-5-pyridin-3′-yl-4-substituted-banzal-amino-2,3-dihydro-[1,2,4]-triazlole-3-thiones **4a-i**. The pharmacological evaluations have been performed for their antimicrobial and antitubercular activities.

Keywords: Methyl nicotinate, [1,2,4]-triazole, thiazolidinones, Mannich base, antimicrobial activity, antitubercular activity

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Various substituted 4-thiazolidinone derivatives are associated with diverse pharmacological activities such as antitumor[1,2], antidiabetic[3], antiparkinsons[4], antiviral[5], anthelminitic[6] and analgesic[7] effects. Of late, much interest has been generated on the synthesis of Mannich bases due to their wide variety of biological activities. They are found to exhibit antineoplastic, analgesic and antibiotic activity. Several therapeutic important molecules prepared through mannich reactions have received more attention in recent years[8-10].

Prompted by these observations and in continuation of our work on the synthesis of biologically active nitrogen and sulfur containing heterocycles, we report herein the reaction of aromatic aldehydes with 4-amino-5-(3-pyridyl)-4*H*-1,2,4-triazole-3-thiol in the presence of gl. acetic acid to give 4-substituted-benzal-amino-3-mercapto-5-pyridin-3′yl-[1,2,4]-triazoles **2a-i**. Compounds **2a-i** on further cyclo-condensation with thioacetic acid afforded 3-(3′-mercapto-5′-pyridin-3′′-yl-[1,2,4]-triazol-4′yl)-2-aryl-1,3-thiazolidin-4-ones **3a-i**, while in the presence of primary/secondary amine and formaldehyde furnished the 2-[bis-aryl-amino-methyl]-5-pyridin-3′-yl-4-substituted-banzal-amino-2, 3-dihydro-[1, 2, 4]-triazlole-3-thiones **4a-i**. (**Scheme I**).

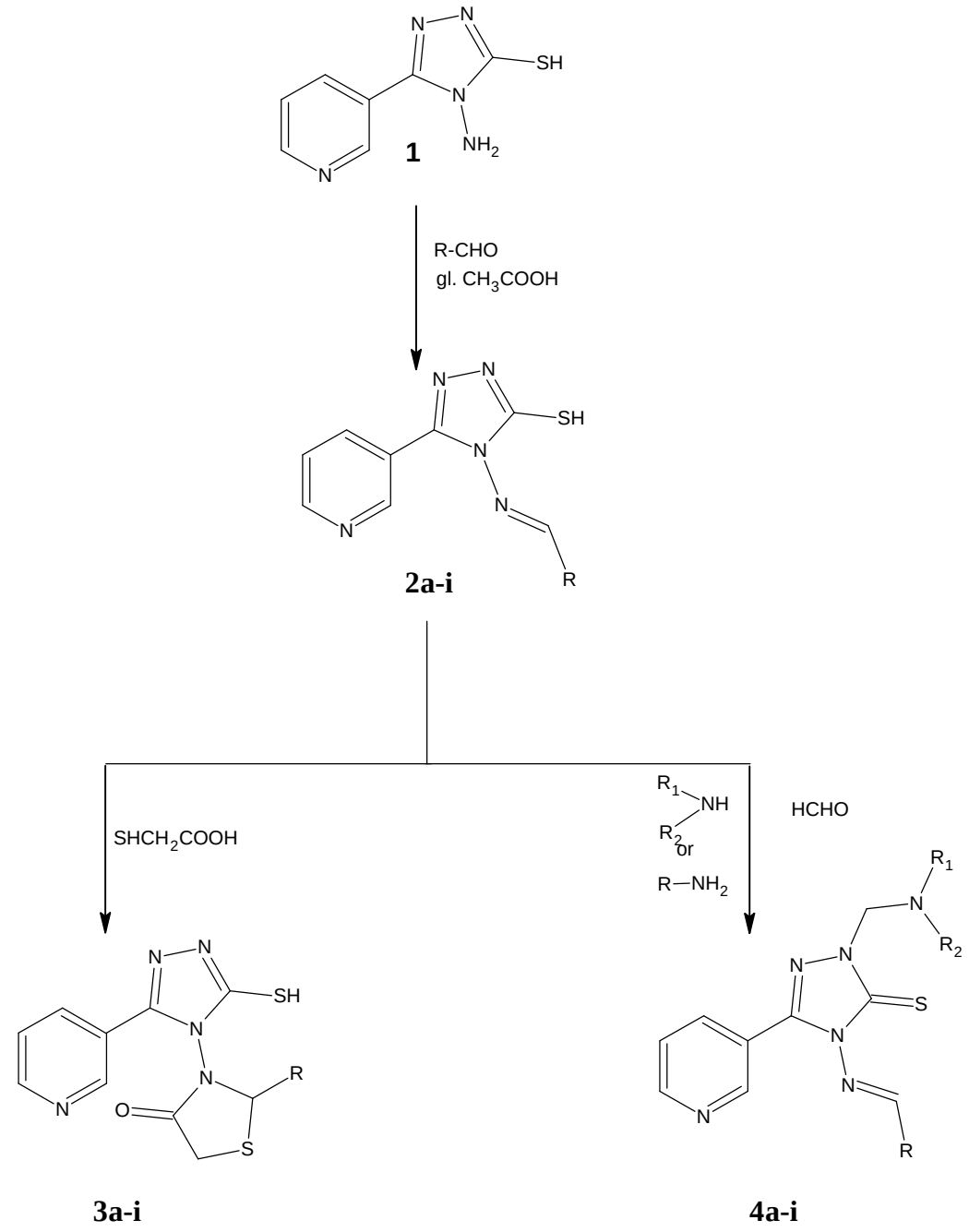
The structures of the synthesized compounds **2-4a-i** have been confirmed by elemental analysis and IR, ^{1}H NMR, and mass spectral data **(Table I)**. The bioassay indicated most of the synthesized compounds possess significant inhibitory effects on various microbes under identical conditions, the standard antibiotics showed zones of inhibition like ampicillin 20-24 mm, amoxicillin 21-25, norfloxacin 18-25, benzyl penicillin 15-20 mm, against bacterial strains and griseofulvin 18-24 mm showed zones of inhibition against *Aspergillus niger*. None of the tested compounds showed significant *in vitro* antituberculosis activity at 6.25 μg/mL (MIC rifampin 0.25 μg/mL).

Antitubercular activity

Primary screening of the compounds for antitubercular activity have been conducted at 6.25 μg /mL towards *Mycobacterium tuberculosis* $H_{37}Rv$ in BACTEC 12B medium using the BACTEC 460 radiometric system. The compounds demonstrating at least >90% inhibitions in the primary screen have been compared with standard drug rifampicin at 0.25 μg/mL concentrations and showed 98% inhibition. The data % inhibitions are recorded in (**Table II**).

Antimicrobial activity

The antimicrobial activity was assayed by using the cup-plate agar diffusion method[11] by measuring the zone of inhibition in mm. All the compounds were screened *in vitro* for their antimicrobial activity against variety of bacterial strains such as *Bacillus megaterium*, *Staphylococcus substillis*, *Escherichia coli*, *Proteus vulgaris*, and fungi *Aspergillus niger* at 40 μg/mL concentration. Standard drugs like ampicillin, amoxicillin, norfloxacin, benzyl penicillin and griseofulvin were used for the comparison purpose **(Table II)**.



Scheme I

Experimental Section

TLC was used to access the reactions and purity of the compounds synthesized. The melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8400 instrument in KBr disc. ^{1}H NMR spectra were recorded on a Bruker AC-300 MHz FT NMR using TMS as internal standard, chemical shifts are in δ, ppm. Mass spectra were recorded on a Jeol D-300 spectrometer. All the synthesized compounds gave satisfactory elemental analysis.

Synthesis of 4-{[(*E*/*Z*)-1-(4-methoxyphenyl)-methylidene]amino}-5-(3-pyridiyl)-4*H*-1,2,4-triazol-3-yl-hydrosulfide 2d. To a solution of 4-amino-5-(3-pyridyl)-4*H*-1,2,4-triazole-3-thiol (1.93 g, 0.01 mole) in 10 mL of dimethyl formamide, 4-methoxy benzaldehyde (1.36 g, 0.01mole) and 1 mL gl. acetic acid as a catalyst was added. The reaction mixture

Table I—Characterization data of compounds **2a-i**, **3a-i** and **4a-I**

Compd	R	m.p. °C	Yield (%)	1H NMR (δ, ppm) X	1H NMR (δ, ppm) Ar-H
2a	4-Cl-C_6H_4-	173	58	-	6.96-14.04 (m,10H)
2b	2-Cl-C_6H_4-	168	60	-	6.96-14.02 (m,10H)
2c	2-OH-C_6H_4-	140	54	-	6.92-14.03 (m,11H)
2d	4-OCH_3-C_6H_4-	198	45	3.92 (s, 3H)	6.98-14.04 (m,10H)
2e	2-OCH_3-C_6H_4-	213	40	3.96 (s, 3H)	6.95-14.09 (m,10H)
2f	3,4-$(OCH_3)_2$-C_6H_3-	198	68	3.89 (s, 6H)	6.94-14.08 (m,9H)
2g	3-C_6H_5-O-C_6H_4-	205	60	-	6.96-14.01 (m,15H)
2h	3-Br-C_6H_4-	167	48	-	6.95-14.11 (m,10H)
2i	3-NO_2-C_6H_4-	170	59	-	6.88-14.05 (m,10H)
3a	4-Cl-C_6H_4-	122	48	-	4.17-7.62 (m,12H)
3b	2-Cl-C_6H_4-	108	54	-	4.12-7.65 (m,12H)
3c	2-OH-C_6H_4-	112	52	-	4.14-7.62 (m,13H)
3d	4-OCH_3-C_6H_4-	180	52	3.90 (s, 3H)	4.17-7.62 (m,12H)
3e	2-OCH_3-C_6H_3-	70	48	3.92 (s, 3H)	4.19-7.60 (m,12H)
3f	4-CH_3-C_6H_3-	90	60	2.4 (s,2H)	4.10-7.32 (m,12H)
3g	3-C_6H_5-O-C_6H_4-	104	64	-	4.13-7.52 (m,12H)
3h	3-Br-C_6H_4-	140	44	-	4.15-7.62 (m,12H)
3i	3-NO_2-C_6H_4-	120	47	-	4.23-7.69 (m,12H)
4a	3-NO_2-C_6H_4-	240	58	-	5.81-9.81 (m,19H)
4b	3,4-$(OCH_3)_2$-C_6H_3-	225	55	3.96 (s,3H) 3.94 (s,3H)	5.75-9.78 (m,18H)
4c	2,4-$(Cl)_2$-C_6H_3-	260	61	-	5.48-9.59 (m,18H)
4d	3-(2-Cl-6-OCH_3-C_9HN)C_9HN) C_6H_3- C_9H_4N)	210	60	3.9 (s,2H)	5.74-9.84 (m,21H)
4e	2-OCH_3-C_6H_3-	190	55	3.96 (s,3H)	5.86-9.83 (m,16H)
4f	4-OCH_3-C_6H_3-	220	58	3.96 (s,2H)	5.81-9.81 (m,17H)
4g	2-C_4H_3 S	165	64	5.8 (s,2H)	5.85-9.79 (m,19H)
4h	4-CH_3-S-C_6H_4-	215	52	2.6 (s,3H)	5.80-9.78 (m,22H)
4i	2-Cl-C_6H_4-	204	48	-	5.82-9.76 (m,22H)

Where, X = CH_3 or OCH_3

was refluxed for 5-6 hr The contents were cooled and poured onto crushed ice and thus the separated solid was isolated and crystallized from ethanol to give **2d**. Yield: 45%, m.p. 198°C. Found: C, 57.84; H, 4.19; N, 22.46. $C_{15}H_{13}N_5OS$ required: C, 57.86; H, 4.21; N, 22.49 %. IR (KBr, cm^{-1}) spectra of the compounds showed bands at 2962 (CH-CH str.), 2360 (S-H str.), 1640 (C=N, str.), 1267 (C-O-C str.), 700 (C-S str.). ^{1}H NMR (300 MHz $CDCl_3$+DMSO-d_6),: δ 14.04 (s,1H, -SH), 6.98-9.96 (m, 9H, Ar-H), 3.86 (s, 3H, Ar-OCH_3). Mass spectra of compound exhibited molecular ion peak at *m/z* 311(M^+), other important fragment was observed at 154 (M^+).

Similarly, compounds **2a-i** were prepared by the condensation of 4-amino-5-(3-pyridyl)-4*H*-1,2,4-triazole-3-thiol **1** with other aromatic aldehydes and their characterization data are recorded in **(Table I)**.

Synthesis of 2-(4-methoxyphenyl)-3-(3-pyridinyl)-5-sulfanyl-4*H*-[1,2,4-triazol-4-yl]1,3-thiazolan-4-one 3d. A mixture of 4-(*p*-methoxy-benzal-amino)-3-mercapto-5-pyridin-3′-yl-[1, 2, 4]-triazole (3.11 g, 0.01 mole) and mercapto acetic acid (0.92 g, 0.01 mole) in dry dioxane was refluxed for 12 hr at 120°C. The reaction mixture was cooled and neutralized with 10% sodium bicarbonate solution. The solid product thus separated was filtered and washed with water and crystallized from ethanol to give **3d.** Yield 52%, m.p. 180°C. Found: C, 52.95; H, 3.89; N, 18.16%.$C_{17}H_{15}N_5O_2S_2$ required C, 52.97; H, 3.92; N, 18.17%. IR (KBr, cm^{-1}) spectra of the compounds showed bands at 3398 (N-H str.), 2950 (CH-CH str.), 2358 (S-H str.), 1710 (C=O, carbonyl), 688 (C-S str.). ^{1}H NMR (300 MHz $CDCl_3$+DMSO-d_6), δ: 6.91-7.62 (m, 9H, Ar-H), 4.61 (s, 1H, -CH),

Table II—Antitubercular and Antimicrobial screening results of compounds **2a-i, 3a-i** and **4a-I**

Compd	% Inhibition Antitubercular activity	Zones of inhibition in mm				
		Antibacterial activity				Antifungal activity
		B. mega	*S. substilis*	*E. coli*	*P. vulgaris*	*A. niger*
2a	0	24	20	16	18	21
2b	0	20	14	20	20	18
2c	-	19	18	12	14	20
2d	0	18	16	18	14	24
2e	-	16	18	19	13	22
2f	-	16	13	23	17	16
2g	-	20	19	13	12	24
2h	-	21	20	12	15	16
2i	-	23	22	15	18	18
3a	-	22	17	20	14	19
3b	-	18	20	16	19	16
3c	-	20	14	19	20	21
3d	-	16	19	14	21	18
3e	-	15	17	16	15	14
3f	-	17	16	14	17	23
3g	-	23	18	21	16	20
3h	-	19	22	18	12	15
3i	-	23	21	17	13	19
4a	-	16	18	21	17	20
4b	-	21	17	15	20	19
4c	-	20	22	20	16	22
4d	-	18	21	19	18	17
4e	-	15	16	18	14	19
4f	-	24	23	22	21	23
4g	-	20	14	17	20	22
4h	-	17	19	20	13	14
4i	-	21	21	13	18	18
Ampicillin	-	20	24	22	20	00
Amoxicillin	-	21	24	25	18	00
Norfloxacin	-	18	17	18	18	00
Benzyl penicillin	-	10	18	15	15	00
Griseofulvin	-	00	00	00	00	24
Rifampicin	98	00	00	00	00	24

4.17 (s, 2H, -CH_2), 3.90 (s, 3H, Ar-OCH_3). Mass spectra of compound exhibited molecular ion peak at m/z 385 (M^+).

Similarly, compounds **3a-i** were prepared by the condensation of 4-substituted-benzal-amino-3-mercapto-5-pyridin-3′yl-[1,2,4]-triazoles **2a-i** with mercapto acetic acid **(Table I)**.

Synthesis of 1-[(4-chloroanilino)-methlyl-4-{[(*E/Z*)-1-phenylmethylidene]amino}-3-(3-pyridiyl)-4,5-dihydro-1*H*-1,2,4-triazole-5-thione 4f. A mixture of 4-(*p*-methoxy-benzal-amino)-3-mercapto-5-pyridin-3′yl-[1,2,4]-triazole (3.11 g, 0.01 mole), formaldehyde (0.3g, 0.01 mole) and *p*-chloroaniline (1.28 g, 0.01 mole) in dioxane (50 mL) was stirred for 24 hr and left overnight at 0°C. The product was isolated, and crystallized from dioxane to give **4f.** Yield: 58%, m.p. 220°C. Found: C, 58.56; H, 4.22; N, 18.61%. $C_{22}H_{19}ClN_6OS$ required: C, 58.60; H, 4.25; N, 18.64%. IR (KBr, cm^{-1}) spectra of the compounds showed bands at 2950 (CH-CH str.), 1602 (C=N, str.), 1225 (C-O-C

str.), 696 (C-S str.). ^{1}H NMR (300 MHz $CDCl_3$+DMSO-d_6), δ: 9.81 (s, 1H, =CH), 9.73 (s, 1H, -NH), 7.10-8.86 (m, 12H, Ar-H), 5.81 (s, 2H, N-CH_2-N), 3.96 (s, 3H, Ar-OCH_3). Mass spectra of compound exhibited molecular ion peak at m/z 451 (M^+), other important fragment was observed at 154 (M^+).

Similarly, compounds **4a-i** were prepared by the condensation of 4-substituted-benzal-amino-3-mercapto-5-pyridin-3′yl-[1,2,4]-triazoles **2a-i** with primary/secondary amine and formaldehyde **(Table I)**.

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