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NOTE

Synthesis and Antifungal Screening of Some Novel Sulfur Containing Heterocyclic Compounds

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To a mixture of ketone (N-methyl piperidone), ethylcyano-acetate and sulfur in alcohol was added morpholine dropwise and continue the stirring until sulfur dissolves. After keeping it overnight in refrigerator, 2-amino-3-carbethoxy-6-N-methyl-4,5,6,7 tetrahydropyrido(b)thiophene (**I**) resulted out. The compound **I** was then reacted with carbon disulphide, NaOH, dimethyl sulphate in dimethyl sulphoxide under cold condition to form compound **II**. This was refluxed with hydrazine hydrate in isopropanol as a solvent to get the cyclized compound **III**. Finally, the compound **III** was reacted with substituted aryl aldehydes to yield a total of nine new Schiff bases. Of the nine Schiff bases screened for antifungal activity the compounds **JSB 7** and **JSB 8** was found to exhibit good antifungal activity.

Key Words: Synthesis, Pyrimidin-4(3H)-ones, Antifungal screening.

Thienopyrimidinones have been shown to possess a variety of pharmacological activities including antimicrobial[1], antiinflammatory[2] and gastric antiscretory[3]. Considering the importance of such compounds, in the present paper, the synthesis and characterization of some new 3-amino-2-mercapto-7-N-methyl-5,6,7,8-tetrahydropyrido(b)thieno [2,3-d]pyrimidin-4(3H)-ones[4-13] and their antifungal screening are reported.

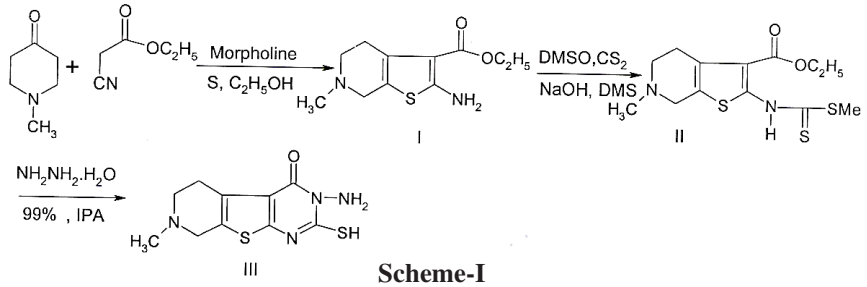
Melting points were determined in open capillaries and are uncorrected. The IR spectrum were run on Perkin Elmer FT-IR spectrophotometer (model no.-RX I) in KBr pellets. ^{1}H NMR was obtained using Jeol max 400 MHz in DMSO-d_6 solvent using TMS as internal reference. Mass spectra were recorded from MALDI mass spectrometer.

All the solvents and chemicals were of analytical grade. Reagents and solvents were used without further purification.

Synthesis of 2-amino-3-carbethoxy-6-N-methyl-4,5,6,7-tetrahydropyrido(b)thiophene (I): In a mixture of ketone (N-methyl piperidone) (0.04 mol), ethylcyanoacetate (0.04 mol) and sulfur (0.04 mol) in 20 mL alcohol was added 5 mL of morpholine dropwise and continue the stirring until sulfur dissolves. Then keeping it overnight in refrigerator forms 2-amino-3-carbethoxy-6-N-methyl-4,5,6,7-tetrahydropyrido(b)thiophene (**I**). IR (KBr, cm^{-1}): 3480 and 3310 $\nu(NH_2)$ 1080 ν(-C-O-ester), 1690 ν(C = O ester), 1499 ν(Ar-C = C) (**Scheme-I**).

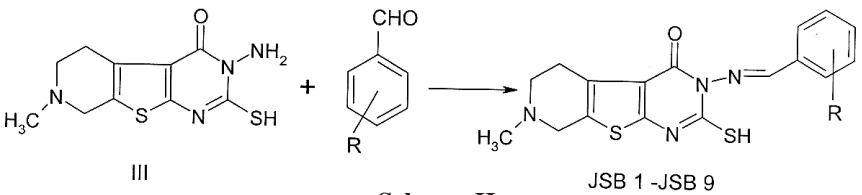
Synthesis of methyl-N-[3-carbethoxy-6-N-methyl-4,5,6,7-tetrahydropyrido(b)thienyl]dithiocarbamate (II): The compound **I** was then reacted with carbon disulphide, NaOH, dimethyl sulphate in dimethyl sulphoxide under cold condition to form methyl-N-[3-carbethoxy-6-N-methyl-4,5,6,7-tetrahydropyrido(b) thienyl]dithiocarbamate. IR (KBr, cm^{-1}): 3428 ν(NH), 1640 ν(C = O), 2935 ν(C-H aliphatic), 1457 ν(Ar-C = C) (**Scheme-I**).

Synthesis of 3-amino-2-mercapto-7-N-methyl-5,6,7,8-tetrahydropyrido(b)thieno[2,3-d]pyrimidin-4(3H)-one (III): The intermediate compound **II** was refluxed with hydrazine hydrate in isopropanol to get the cyclized product i.e. 3-amino-2-mercapto-7-N-methyl-5,6,7,8-tetrahydropyrido (b)thieno[2,3-d]pyrimidin-4(3H)one. M^+ 268. IR (KBr, cm^{-1}): 3310, 3462 ν(NH_2), 1680 ν(C = O), 2570 ν(SH), 1540 ν(Ar-C = C). NMR (in DMSO): δppm = 4.5 (s, 2H, NH_2), 3.43 (s,1H, SH), 2.63 (t, 2H, CH_2), 2.83 (t, 2H, CH_2), 2.35 (s,3H,N-CH_3), 3.1 (s, 2H, CH_2) (**Scheme-I**).



Scheme-I

Synthesis of 3-(2'-nitro phenylazomethine)-2-mercapto-7-N-methyl-5,6,7,8-tetra hydropyrido(b)thieno[2,3-d] pyrimidin-4(3H)-one (JSB 3): A mixture of the compound **III** (0.005 mol) and ortho nitrobenzaldehyde (0.005 mol) in methanol (40 mL) containing few drops of glacial acetic acid as catalyst was refluxed for two hours. The reaction mixture was cooled, and the solid obtained was filtered and washed with ethanol, dried and recrystallized from dimethylformamide and water mixture to yield totally nine pure compounds. The other compounds of the series were prepared in the same manner. IR (KBr, cm^{-1}): 3310 ν(NH), 1660 - ν(C = O), 1540 - ν(N = CH), 1580 - ν(Ar-C = C), 1520 - ν(NO_2). NMR δ ppm (in DMSO) = 3.43 (s, 1H, SH), 8.23 (d, 1H, CH at 2'), 7.92 (t, 1H, CH at 5'), 7.74 (t, 1H, CH at 4'), 8.1 (d, 1H, CH at 3'), 6.67 (s, 1H, CH at –C-H), 2.67 (t, 2H, CH_2 at 5), 2.85 (t, 2H, CH_2 at 6), 2.34 (s, 3H, CH_3 at N-CH_3), 3.12 (s, 2H, CH_2 at 8) **(Scheme-II)**.



Scheme-II

TABLE-1
PHYSICAL DATA AND ANTIFUNGAL SCREENING RESULTS

Comp. No.	R/X	m.p. (ºC)	R_f	m.w.	Yield (%)	*Aspergillus niger*	*Candida albicans*
I	--	105	0.41	40	70	--	--
II	--	132	0.71	316	81	--	--
III	--	242	0.31	268	58	--	--
JSB 1	2-Hydroxy	256	0.65	372	68	8	2
JSB 2	4-Hydroxy	275	0.76	372	65	9	2
JSB 3	2-Nitro	270	0.71	401	72	12	8
JSB 4	4-Nitro	270	0.60	401	74	NA	NA
JSB 5	4-Methoxy	259	0.67	386	76	11	6
JSB 6	2-Chloro	251	0.79	355	70	6	NA
JSB 7	4- Dimethyl amino	265	0.68	399	69	12	6
JSB 8	3,4,5-Trimethoxy	266	0.67	444	80	8	13
JSB 9	3-Methoxy-4-hydroxy	263	0.78	402	76	8	8
Miconazole	--	--	--	--	--	20	15

All the compounds were coloured and crystalline, having high melting point and are insoluble in water and common organic solvents, but are soluble in DMF and DMSO. All the compounds were screened for antifungal activity. In present study, the antifungal activity was carried out by the agar diffusion method. Here response of organisms to the synthesized compounds were measured and compared with the response of the standard reference drug. The standard reference drug used in the present work was Miconazole. Activities of these compounds have been executed on MH agar plates. Compound JSB 7 with (4-dimethyl amino group at R) showed maximum activity against *A. niger* and JSB 8 (3,4,5-trimethoxy group) at R showed modrate activity against *C. albicans*.

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