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ORIGINAL ARTICLE

Synthesis and Biological Evaluation of Some Novel Benzopyridazines Derivatives

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ABSTRACT

A series of benzopyridazines were prepared by reacting 4-Aryal-3-thiosemicarbazides with 2-carboxyl (Substituted benzophenone to give thiosemicarbazones. These on cyclodehydration gave the titled compounds. The synthesized compounds were characterized by means of IR, NMR and elemental analysis. These compounds were tested for their antifungal activities. All the synthesized compounds exhibited moderate to good antifungal activities when compared to the reference standards.

***Key words**: Synthesis Evaluation, Biological Evaluation, benzopyridazines*

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INTRODUCTION

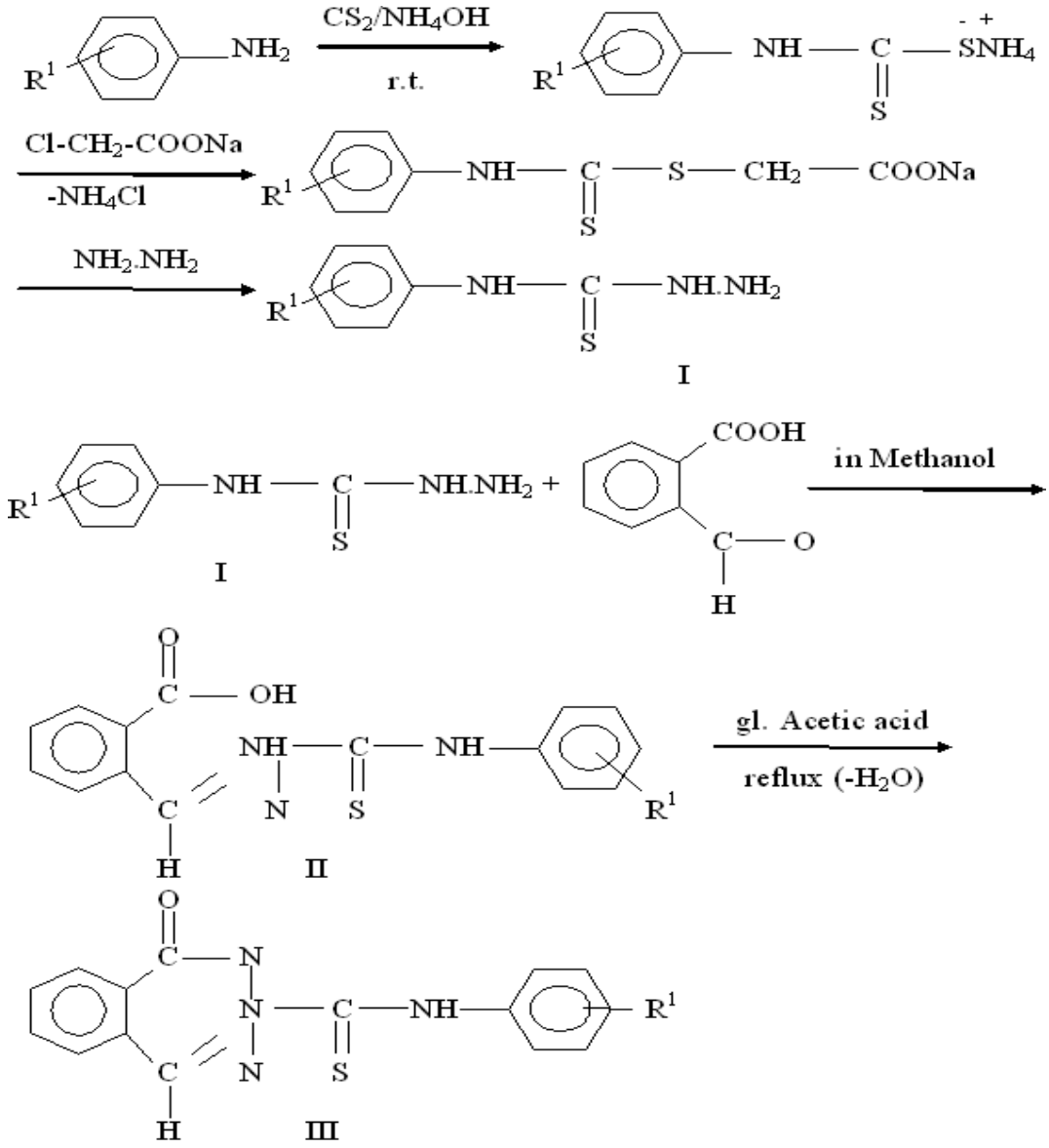
Pyridazines are associated with several biological activities like cardiovascular, hypotensive[2], antihypertensive[3], anti-thrombotic[4], antispasmodic[5], herbicidal[6] and fungicidal[7,8]. In the present communication we report the reaction of various thiosemicarbozides (I) with 2-carboxy (Substituted benzopheaone) to produce thiosemicarbazones (II). These on cyclodehydration gives the required pyridazines and these were screened for antifungal activities against Aspergillus niger and Aspergillus flavus.

EXPERIMENT

Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. The IR spectra were recorded in KBr on Perkin-Elmer model-157 spectrophotometer. The NMR spectra were recorded on Perkin-Elmer R- 32 spectrometer in DMSO– d_6 at 90 MH_2. The purity of the resulting compounds were checked by TLC using silicagel– G (Merck). Elemental analysis of all the compounds were satisfactory.
4-Aryl-3-thiosemicarbazides (I) required as starting material were synthesized form appropriate amines following the method of Kazakov et al[9].

4-Phynyl-1-(2-carboxybenzaldehyde) thiosemicarbazone IIa:

A mixture of 4-phenyl -3-thiosemicarbazide and 2-carboxy benzaldehyde, dissolved in methanol, was refluxed for 1 h. White crystals of the thiosemicarbazones were obtained on cooling. It was filtered, washed and recrystalized with ethanol. m.p. 197^{0}C, yield 72%. Anal. Calcd $C_{15}H_{13}N_3O_2S$: C 60.20; H 4.34; N 14.04; Found C 59.43; H 4.19; N 13.96%, IR (KBr) cm^{-1}; 3300 (-OH), 3140 (-NH), 1660 (C = O) of carboxylic acid, 1530 (C = N), 1055 (C = S), PMR (S) : 7.7 (m, 9H, Ar – H), 8.2 – 8.3 (bs, 1H, -N = CH), 8.9 (S, 1H, -NH) 9.9 (1H, S, -COOH). The other compounds prepared similarly are given in Table 1.



1-(4-thioanilido)-8-Keto-benzopyridazines (IIIa):

4-(chloro-phenyl)-(2-carboxybenzaldehyde)-thiosemicarbazone was cyclodehydrated by heating under reflux in glacial acetic acid for 2 hrs. The solid mass obtained was poured on crushed ice. filtered, washed with water and recrystalized from ethanol to get white crystalline solid. m.p. 223^{0}C, yield 85% Anal. Caled. $C_{15}H_{11}N_3O_6$: C 64.05; H 3.91; H 14.94; Found C 64.13; H 4.03; N 14.85; IR (KBr) cm^{-1}; 3300 (-NH), 1700 (C = O, Ketone), 1080 (C = S), 1540 (C = N), PMR (5) : 6.9 – 7.2 (M, 9H, ArH), 7.7 (S, 1H, N = CH). Other such compounds prepared are given in Table 2.

BIOLOGICAL EVALUATION

The newly synthesized compounds $III_{1\text{-}7}$ were screened for their antifungal activities against Aspergillus niger and Aspergillus flavus at three different concentrations of 1000, 100 and 10 ppm following Agar growth technique[10]. with three replications. All the tubes were incubated at 28^{0}C in B.O.D. incubator. The results were taken after 4 days and are recorded in Table 3.

All the compounds screened display moderate to good level of antifungal activity. Table 3 showed that all the compounds inhibited 50–60% of fungus growth at 1000 ppm compound 1 & 2 exhibited 60 – 70% of both fungus growth at 1000 ppm.

The most active compound of this investigation is $III_{(2)}$ which contains chlord atoms. The presence of H or methyl radicals effects the activity by about 10 – 20%. The compounds are more active on A. flavus than on A. niger.

Table 1: Physical data of thiosemicarbazones

Compound No.	R^1	m.p. ^0C	Yield (%)	Molecular formula
1.	H	197	72	$C_{15}H_{13}N_3O_2S$
2.	4-Cl	173	70	$C_{15}H_{12}N_3O_2SCl$
3.	2-CH_3	200	70	$C_{16}H_{15}N_3O_2S$
4.	3-CH_3	196	67	$C_{16}H_{15}N_2O_2S$
5.	4-CH_3	202	69	$C_{16}H_{15}N_3O_2S$
6.	2, 3-$(CH_3)_2$	209	65	$C_{17}H_{17}N_3O_2S$
7.	2, 6-$(CH_3)_2$	194	68	$C_{17}H_{17}N_3O_2S$

Table 2: Physical data of benzopyridazines

Compound No.	R^1	m.p. ^0C III	Yield (%)	Molecular formula
1.	H	223	85	$C_{15}H_{11}N_3OS$
2.	4-Cl	195	87	$C_{15}H_{10}N_3OSCl$
3.	2-CH_3	225	84	$C_{16}H_{13}N_3OS$
4.	3-CH_3	208	80	$C_{16}H_{13}N_3OS$
5.	4-CH_3	210	86	$C_{16}H_{13}N_3OS$
6.	2, 3-diCH_3	213	85	$C_{17}H_{15}N_3OS$
7.	2, 6-diCH_3	190	88	$C_{17}H_{15}N_3OS$

Table 3: Antifungal activity of Benzopyridazines

Sr.No.	Compound No.	A. niger			A. flavus		
		1000 ppm	100 ppm	10 ppm	1000 ppm	100 ppm	10 ppm
1.	1	60	40	30	63	44	35
2.	2	63	42	32	66	47	40
3.	3	55	32	21	58	36	23
4.	4	52	30	19	55	34	31
5.	5	58	34	20	63	38	32
6.	6	59	40	30	64	39	35
7.	7	57	38	29	62	38	34
8.	Carbendazim	94	90	86	97	92	88

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