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Synthesis and antimicrobial activity of 5-substituted-1H-indole-2, 3-dione-3-N-(4'-substitutedphenyl) thiosemicarbazone

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ABSTRACT

A number of new 5-substituted-1H-indole-2,3-dione-3-N-(4'-substitutedphenyl) thiosemicarbazone (4a-o) have been synthesized from istain (Indole-2,3-dione) and screened for antibacterial activity.

Keywords: Istain, thiosemicarbazone, synthesis, antibacterial activity.

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INTRODUCTION

Compound having istain (Indole-2,3-dione) moiety possess various biological activities *viz*. anticonvulsant [1-2], antimicrobial [3], anticancer [4-5], anti-HIV [6-7] etc. In this study a series of 5-substituted-1H-indole-2,3-dione-3-N-(4′-substitutedphenyl)-thiosemicarbazone (4a-o) have been prepared by refluxing equimolar quantities of 5-substituted-3-hydrazono-1,3-dihydro-2H-indole-2-one (2a-c) and p-substituted phenylisothiocyanate (3a-e). 5-substituted-3-hydrazono-1,3-dihydro-2H-indole-2-one (2a-c) have been synthesized by refluxing of 5-substituited-1H-indole-2,3-dione (1a-c) with hydrazine hydrate in the presence of alcohol. 4- Substituted phenylisothiocyanate (3a-e) were prepared by reaction of 4-substituted aromatic amines with carbon disulfide in presence of ammonia [8]. 5-Substituted-1H-indole-2,3-dione-3-N-(4′-substitutedphenyl)-thiosemicarbazone (4a-o) yielded according to Scheme 1.

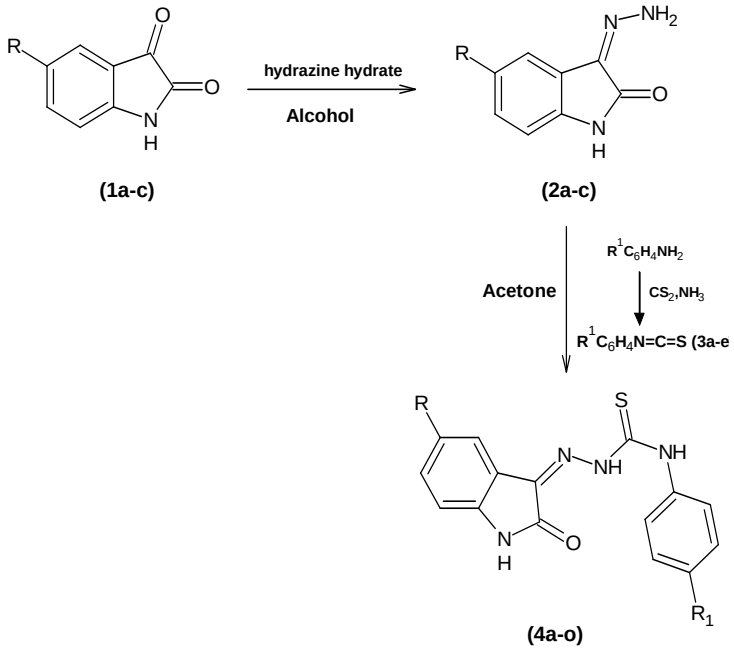
MATERIAL AND METHODS

All chemicals were obtained from Center Drug House (CDH), New Delhi. All chemicals and solvents used were of analytical grade.

Experimental

All melting points were determined in open capillary and are uncorrected. The purity of the compounds was checked by thin layer chromatography on silica gel G plates using benzene: ethanol (9 : 1) solvent system as mobile phase and iodine vapour as visualizing agent. IR spectra (KBr) were recorded on a Thermo IR 200 spectrophotometer and 1H-NMR (DMSO-d6) on Bruker Avance II 400 MHz spectrometer using TMS as internal standard. Mass spectra recorded on a Joel mass spectrophotometer at 70eV.

Scheme 1



4a-e : R = NO_2 ; R^1 = CH_3, OCH_3, Cl, F, Br
4f-j : R = H ; R^1 = CH_3, OCH_3, Cl, F, Br
4k-o : R = Br ; R^1 = CH_3, OCH_3, Cl, F, Br

5-Nitro-1H-indole-2 3-dione (1a) [10]:

In a round bottomed flask 9.0g (0.05 mol) of chloral hydrate in 85 ml of water was placed. To this mixture 7.0g of sodium sulfate and a solution of 4.1g (0.03 mol) p-nitro aniline in 20 ml of water containing 4.1g conc. sulphuric acid (sp. gr., 1.84) was added to dissolve the amine and finally a solution of 7.0g (0.1 mol) of hydroxylamine hydrochloride in 17 ml of water were added in the flask. It was then added at a rate such that vigorous boiling begins in about 40-45 min. After two min of vigorous boiling the reaction was complete. During the heating period some of the isonitrosoacetanilide separated out. On cooling the solution in running water the remainder was crystallized. It was filtered with suction, dried in air. Concentrated sulphuric acid (20.0g) was heated to 50°C and then 5.4g (0.03 mol) of dry isonitrosoacetanilide was added in such a rate as to keep the temperature between 60-70°C external cooling was applied at this stage so that the reaction could be carried out more rapidly. After the addition of all isonitrosoacetanilide, the solution was heated to 80°C and was kept at this temperature for about 10 min to complete the reaction. Then the reaction mixture was cooled to room temperature and poured upon ten to twelve times its volume of crushed ice. After standing for about 90 min the product was filtered with suction and washed with cold water to remove the sulphuric acid. The crude product was then dried in air, yield : 56% ; m.p. 178 °C ; υ_{max} 3290 (2^0 NH), 1565 (symmetric N=O), 1347 (asymmetric N=O), 1710 (C=O), 1440 (C=C), 730 (Ar-H) ; δ (DMSO-d_6) 5.8 (s, 2H, NH_2), 9.5 (s, 1H, NH of indole), 6.1-6.7 (m, 3H, Ar-H) The other compounds of the series were prepared by similar procedure (yield : 50-57 %) : 1b, m.p. 174°C; c, 176 °C.

3-Hydrazono-5-nitro-1,3-dihydro-2H-indole-2-one (2a)

A equimolar (0.05) quantities of 5-nitro-1H-indole-2,3-dione (1a) and hydrazine hydrate were dissolved in warm ethanol (50ml) was refluxed for 1hr. After 1hr., precipitation occurred. The precipitate of 2a resulted was collected and crystallized using methanol, yield : 65% ; m.p. 162 °C ; υ_{max} 3425 (1^0 NH), 3290 (2^0 NH), 1620 (C=N), 1565 (symmetric N=O), 1347 (asymmetric N=O), 1710 (C=O), 1440 (C=C), 730 (Ar-H) ; δ (DMSO-d_6) 5.8 (s, 2H, NH_2), 9.5 (s, 1H, NH of indole), 6.1-6.7 (m, 3H, Ar-H). The other compounds of the series were prepared by similar procedure (yield : 50-57 %) : 2b, m.p. 161°C ; c, 166 °C.

5-Nitro-1H-indole-2, 3dione-3-N-(4′-methylphenyl)thiosemicarbazones (4a)

A equimolar (0.01) quantities of 3-hydrazono-5-nitro-1,3-dihydro-2H-indole-2-one (2a) and p-methyl phenylisothiocyanate (3a) were refluxed for 3hr in acetone, then cooled at room temperature. The product was obtained by filtration, dried and crystallized from ethanol, yield : 71% ; m.p. 116°C ; υ_{max} 3330 (2^0 NH), 1565 (symmetric N=O), 1347 (asymmetric N=O), 1730 (C=O), 1620 (C=N), 1100 (C=S), 1440 (C=C), 1310 (C-H), 780 (Ar-H) ; δ (DMSO-d_6): 2.26-2.53 (s, 3H, 4′-CH_3), 6.53-6.89 (m, 7H, 4, 6, 7, 2′, 3′, 5′, 6′ Ar-H), 10.1 (s, 2H, 2×NH), 9.5 (s, 1H, NH of indole) ; m/z 355 (M^+). (Found : C, 71.93 ; H, 6.54 ; N, 20.21, Calcd. ; C, 72.01 ; H, 6.91 ; N, 20.74%). The other compounds of the series were prepared by similar procedure (yield : 65-85 %) : 4b, 122°C ; c, 115°C ; d, 118°C ; e, 123°C ; f, 114°C ; g, 121°C ; h, 118°C ; i, 120°C ; j, 125°C ; k, 112°C ; l, 120°C ; m, 125°C ; n, 124°C ; o, 123°C.

RESULT AND DISCUSSION

A series of 5-substituted-1H-indole-2,3-dione-3-N-(4'-substitutedphenyl) thiosemicarbazone (4a-o) was synthesized and their structure was elucidated by elemental analysis, IR, ^{1}H-NMR and Mass spectra. Yields, melting points, calculated Log P in Table 1. The compounds were screened for antibacterial activity against *E. coli* (Gram negative) and *S. aureus* (Gram positive) by Cup – plate method[9]. All the observations are given in Table 2.

Table 1: Physical data of the compounds 4a-o

Compounds	R	R^1	M. pt (^{0}C)	Yield (%)	*R_f	Calculated Log P# value
4a	NO_2	CH_3	116	71	0.41	3.18 ± 0.93
4b	NO_2	OCH_3	122	73	0.46	2.67 ± 0.94
4c	NO_2	Cl	115	75	0.42	3.71 ± 0.94
4d	NO_2	F	118	67	0.48	3.89 ± 0.97
4e	NO_2	Br	123	60	0.43	3.89 ± 0.97
4f	H	CH_3	114	84	0.40	5.60 ± 0.66
4g	H	OCH_3	121	73	0.44	5.78 ± 0.68
4h	H	Cl	118	81	0.47	3.98 ± 0.67
4i	H	F	120	73	0.46	3.44 ± 0.69
4j	H	Br	125	77	0.45	4.16 ± 0.69
4k	Br	CH_3	112	77	0.40	4.22 ± 0.69
4l	Br	OCH_3	120	67	0.45	3.71 ± 0.69
4m	Br	Cl	125	72	0.43	4.75 ± 0.69
4n	Br	F	124	73	0.49	4.21 ± 0.73
4o	Br	Br	123	69	0.44	4.93 ± 0.73

* Benzene (9): Ethanol (1), # Caluated by ACD/ChemSketch

Table 2 Antibacterial Screening results of compounds 4a-o

S.No	Compounds	Antibacterial Activity			
		E. coli		*S. aureus*	
		50 ug/ml	100ug/ml	50ug/ml	100ug/ml
1	4a	++	+++	++	+++
2	4b	++	+++	++	+++
3	4c	++	+++	++	+++
4	4d	+	++	++	+++
5	4e	+	++	+	++
6	4f	++	+++	+	++
7	4g	++	++	++	+++
8	4h	+	++	++	+++
9	4i	+	++	+	++
10	4j	++	++	++	+++
11	4k	++	+++	++	++
12	4l	+	++	++	+++
13	4m	++	+++	+	++
14	4n	++	+++	++	+++
15	4o	+	++	++	++
Standard	Sterptomycin	+++	++++	+++	++++

(5-10 mm) = + Active, (10-15 mm) = ++ mildly active, (15-20 mm) = +++ moderately active, (21 mm, up) = ++++ highly active.

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