Research Article

Synthesis of Sulphonamide Bridged Indole Derivatives

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ABSTRACT

Esters (**9a-c**) on reaction with hydrazine hydrate in ethanol yielded substituted indole-2-carboxyhydrazides (**10a-c**). 1,3,6-trihydro-2-thio-4-one-5,6-dione pyrimidine-5-sulphoxyl chloride (**7**) was prepared by chlorosulphonation of 2-thiouracil.Compound **(7)** on reaction with 5-substituted-3-amino-2-phenyl indoles (**5a-c**) in pyridine and absolute ethanol under reflux temperature yielded 1,2,3,4-tetrahydro-2-thio-4-one/5,6-dione-pyrimidine-5-(5-substituted-2-phenylindole-3'-yl)-5-sulphonamide (**8a-c**). The compound **(7)** on reaction with 5-substituted-3-phenyl indole 2-carbohydrazide (**10a-c**) in absolute ethanol yielded (**11a-c**) in presence of catalytic amount of pyridine the 1,3,6-trihydro pyrimidine-5-(5-substituted-3-phenylindole-2-carboxyl) sulphonyl hydrozino-2-thio-4-one or 5-6, dione (**11a-c**).

Keywords: indole-2-carboxyhydrazides, chlorosulphonation, 2-thiouracil, sulphonamide bridge.

INTRODUCTION

Several 5-substituted pyrimidine and its derivatives form a component in a number of useful drugs and are associated with many biological activities. Therefore, pyrimidine and indole derivatives are important synthons to the synthetic organic chemists as is evident from the literature reports[1-4].

The pyrimidine analogues are found to be important part of the biologically active molecules known as drugs. These molecules possess a property of inhibiting the biosynthesis of pyrimidine nucleotides. This is because they mimic the natural metabolites. The inhibition of biosynthesis of pyrimidine nucleotides leads to the interference in cellular functions, such as synthesis of nucleic acid etc. The molecules containing pyrimidine moiety, known for their inhibition properties are, deoxycytidine, thymidine are inhibitors of DNA synthesis and 5-flourouracil is a effective inhibitor of RNA functions and synthesis of thymidylate. These inhibitors of pyrimidine derivatives are in use for the treatment of variety of infections such as neoplastic diseases, psoriasis and infections due to fungi etc.

Emergency of drug resistance strains is one of the principle constraints of therapy. Resistance can develop as a result of one or more factors such as over production of PABA, altered permeability of organism to sulphonamides. Different sulphonamides have shown cross-resistance[11-15]. Resistance strains can be developed by random mutation and selection. In plasmodia, resistance can also develop by a bypass mechanism, i.e., ability of the organism to use performed folic acid[16-19].

EXPERIMENTAL

Ethyl 3,5-disubstituted indole-2-carboxylates (9a-c): These were prepared according to the literature procedure[20]**.**

3,5-Disubstituted indole-2-carboxyhydrazides (10a-c): These were prepared according to the literature procedure[21].

Substituted 3-amino-2-phenyl indole (5a-c): These were prepared according to the literature procedure[22].

1,3,6-trihydro-2-thio-4-one 5,6-dione pyrimidine-5-sulphonyl chloride[7]

This was achieved by the chlorosulphonation of 2-thiouracil using excess of chlorosulphonic acid and keeping the mixture at 120^0C for 8 hrs.

1,3,6-trihydro pyrimidine-5-(5-substituted-3-phenylindole-2-carboxyl) sulphonyl hydrazino-2-thio-4-one or 5,6-dione (8a-c).

A mixture of **7** (0.01 mole) and 5-subsituted-3-amino-2-phenylindole **(8a-c)** (0.016 mol) and pyridine in (50 mL) absolute ethanol was heated under reflux for 8-12 hrs. then cooled, the product was filtered off and crystallized from the proper solvent.

1,3,6-trihydro-2-thio-4-one-5,6-dione-pyrimidine-5-(5-substituted-2-phenylindole-3'-yl)-5-sulphonamide (11a-c).

A mixture of 7 (0.01 mole) and 5-substituted-3-phenylindole-2-carboxyhydrazide **(11a-c)** (0.016 mol) and pyridine in (50 mL) absolute ethanol was heated under reflux for 8-12 hrs. then cooled, the product was filtered off and crystallized from the proper solvent.

RESULTS AND DISCUSSIONS

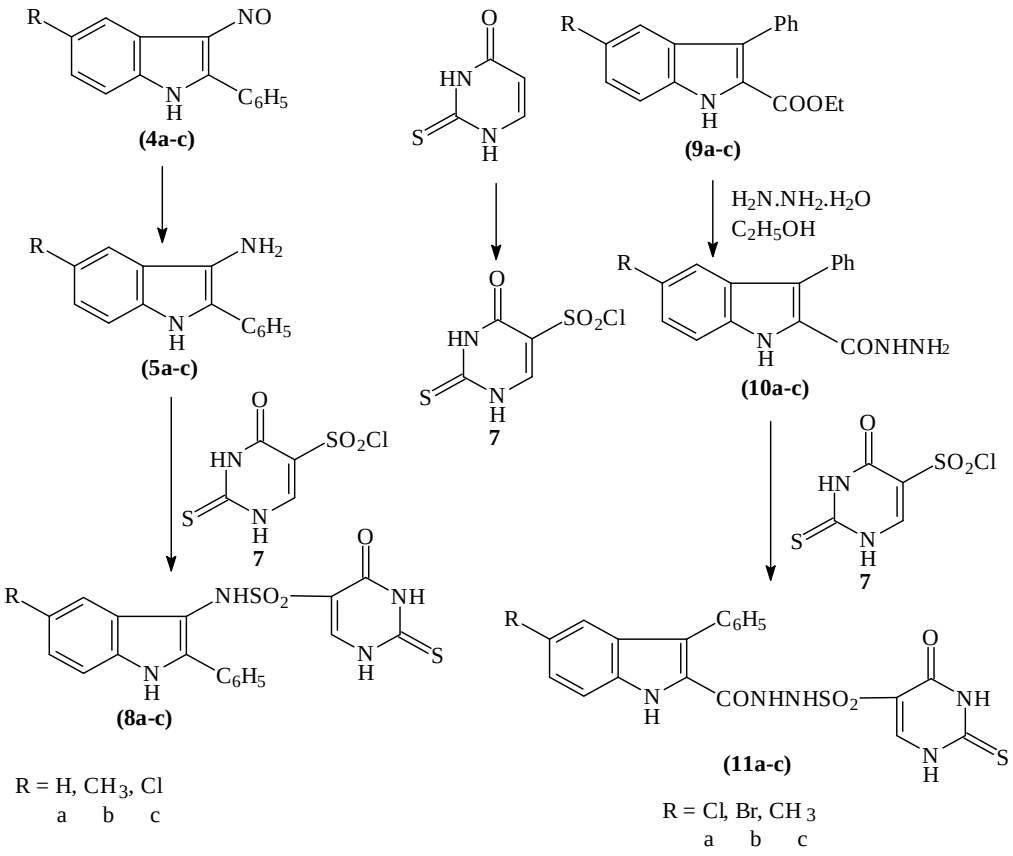
2-phenyl indoles on nitrosation with $NaNO_2$/Acid yields nitroso indoles **(4a-c)**. These **(4a-c)** on reduction with sodium dithionate, to yielded substituted 3-aminoindoles (**5a-c**).Various ethyl indole-2-carboxylates (**9a-c**) were prepared according to the Fisher method. These esters (**9a-c**) on reaction with hydrazine hydrate in ethanol yielded substituted indole-2-carboxyhydrazides (**10a-c**). 1,3,6-trihydro-2-thio-4-one-5,6-dione pyrimidine-5-sulphoxyl chloride[7] was prepared by chlorosulphonation of 2-thiouracil.

Compound **7** on reaction with 5-substituted-3-amino-2-phenyl indoles (**5a-c**) in pyridine and absolute ethanol under reflux temperature yielded 1,2,3,4-tetrahydro-2-thio-4-one/5,6-dione-pyrimidine-5-(5-substituted-2-phenylindole-3'-yl)-5-sulphonamide (**8a-c**). The IR spectrum of **8b** exhibited an absorption peak at 3268 cm^{-1} due to the NH function of indole. The peak at 1700 cm^{-1} can be assigned for cyclic C=O of pyrimidine systems. The broad peak at 1393 cm^{-1} for $–N-SO_2-$ function and 1288 cm^{-1} is for $–SO_2$ group. The ^1H NMR of **8b** displayed sharp singlet at 11.3 δ is due to NH of cyclic uracil and another singlet at 11.1 δ, is also due to the cyclic uracil NH. The singlet at 8.9 is due to $NHSO_2$ group, peak of indole NH is merged in DMSO solvent peak, a sharp singlet at 2.2 δ is due to Ar-CH_3 group. The peaks from 7.3-7.9 δ is for aromatic protons.

Mass spectrum of **8b** did not exhibit the molecular ion peak. It losses $-C_4H_3N_2OS$ and gives the peak at m/z 344, further it undergone fragmentation to gave peak at 297 by loosing –OSH group, nitronium cation disappears from the molecule and gave the peak at 270, further it looses –Br to exhibit the peak at 190. It supports the structure of **8b.**

The compound **7** on reaction with 5-substituted-3-phenyl indole 2-carbohydrazide (**10a-c**) in absolute ethanol yielded (**11a-c**) in presence of catalytic amount of pyridine the 1,3,6-trihydro pyrimidine-5-(5-substituted-3-phenylindole-2-carboxyl) sulphonyl hydrozino-2-thio-4-one or 5-6, dione (**11a-c**). **11a** exhibited characteristic absorption peaks in their IR spectrum. The peak 3450 cm^{-1} for indole NH, 1350-1320 cm^{-1} ($-N-SO_2$) 1200 cm^{-1} ($-SO_2$). ^1H NMR spectrum of **11a** displayed two singlets at 11.15 and 11.3 δ is due to the NH protons of cyclic uracil ring, NHNH peak is at 12.1 δ, indole NH peak is merged in aromatic proton peaks, 3 protons of methyl group were exhibited singlet at 1.2 δ and there is a moisture peak at 2.5 δ, peaks from 7.3-7.6 δ is for aromatic protons.

Mass spectrum of **11a** displayed a peak at 265, it undergoes fragmentation at NH-NH & gave the peak at 250, further it looses –NH to gave the peak at 234. -CH_3 disappeared from the compound & shows the peak at 219, by loosing –CHO group the compound exhibits the peak at 190. This proves the structural evidence for **11a**.



Scheme

Table 1: Characterization data of 1,3,6-trihydro-2-thio-4-one-5,6-dione-pyrimidine-5(5-substituted-2-phenylindole-3'-yl)-5-sulphonamide and 1,3,6-trihydropyrimidine-5-(5-substituted)-3-phenylindole-2-carboxyl) sulphonyl hydrazino-2-thio-4-one or 5,6-dione

Compd.	M.P. (^{0}C)	Yield (%)	Molecular formula	Found (calc.)			IR (cm^{-1})	NMR (ppm)
				C	H	N		
8a	280-282	50	$C_{19}H_{14}N_5O_4S_2Cl$	48.00 (48.12)	2.94 (2.90)	13.50 (13.52)	3420-3410 (NH), 1700 (C=O), 1200 (-SO_2)	12.8 (indole NH), 12.6 (CONH), 7.8-8.3 (Ar-H)
8b	230-232	58	$C_{19}H_{14}N_5O_4S_2Br$	44.70 (44.72)	2.74 (2.73)	13.72 (13.70)	3410-3218 (NH), 1690 (C=O), 1230 (-SO_2)	12.2 (indole NH), 11.5 (CONH), 7.3-7.8 (Ar-H)
8c	260-262	52	$C_{20}H_{17}N_5O_4S_2$	52.00 (52.74)	3.70 (3.73)	15.30 (15.38)	3390 (indo NH), 1750 (C=O), 1190 (-SO_2)	11.7 (indole NH), 11.6 (CONH), 7.2-7.7 (Ar-H)
11a	198-200	55	$C_{18}H_{14}N_4O_3S_2$	54.27 (54.24)	3.51 (3.50)	14.07 (14.01)	3275 (indole NH), 1703 (C=O), 1212 (-SO_2)	11.9 (indole NH), 8.4 (Uracil NH), 7.2-7.6 (Ar-H)
11b	270-272	70	$C_{19}H_{13}N_4O_3S_2$	55.74 (55.67)	3.17 (3.12)	13.69 (13.59)	3400-3200 NH, 1700 (C=O), 1340-1320 (N-SO_2), 1200 (-SO_2)	12.1 (indole NH), 8.3 (Uracil NH), 7.3-7.8 (Ar-H)
11c	260-262	62	$C_{18}H_{13}N_4O_3S_2$	59.17 (59.10)	3.56 (3.52)	15.24 (15.02)	3304 (indole NH), 1682 (C=O), 1255 (-SO_2)	12.5 (indole NH), 8.8 (Uracil NH), 7.3-8.2 (Ar-H)

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