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Synthesis and characterization of new thiazole involving isatin for studying their antimicrobial activity

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1-(Substituted-1-ylmethyl)indoline-2,3-dione **1a-c** have been synthesized from different types of secondary amine with isatin and formaldehyde in alcohol. The compound **1** have then been converted to the respective compound **2a-g** (Z)3-(4-subsitutedphenylimino)-1-(substituted-1-ylmethyl)indolin-2-one by treatment with different types of primary amines. Interaction of compound **2** with thioglycolic acid and chloro acetyl chloride results in cyclization to give compound spiro isatin derivatives compounds **3a-g**. The anti-microbial activity screening of novel spiro isatin substituted compounds have also been carried out.

Keywords: Isatin, thiazole, Schiff base, Mannich base, formaldehyde, secondary amine, primary amine

Designing and synthesis of some novel heretocyclic Spiro-thiazole compounds showing good pharmacological and antimicrobial activity are reported here. The presence of Schiff base and isatin moiety in this series of compounds enhances the microbial activity further. Schiff bases have been extensively used as the substrates in the preparation of a number of industrial and biologically active compounds. On the other hand, isatin and its derivatives are versatile lead molecules as the potential bioactive agent because they exhibit broad spectrum of activity like anti-fungal[1, 2], antiviral[3], anti-mycobacterial[4], anti-inflamatory[5], anti-convulsant[6], anti-cancer[7, 8], anti-tubercular[9, 10], anti-HIV[11, 12], etc. The five membered heterocyclic ring containing nitrogen and sulfur has always been a subject of mystery for researchers because of wide range of heterocycles explored as the privileged candidates in drug discovery. Thiazoles have been identified to play a necessary role in medicinal chemistry[13]. Its derivatives display a wide range of biological activities such as cardiotonic, fungicidal, sedative, anesthetic, bactericidal and anti-inflammatory[14, 15]. As per the extensive literature review, it can be found a lot of reports about the spiro compounds related to Schiff bases. In addition, spiro compounds are also reported from Schiff base with isatin moiety and most of the compounds having biological importance. Thus it was thought to study spiro compounds based on isatin moiety[16]. The biological data drive us to synthesize new spiro derivatives bearing thiazole ring. The newly synthesized compounds were thoroughly characterized by elemental analysis, FTIR, ^{1}H and ^{13}C-NMR.

Experimental Section

Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. TLC using silica gel was used to check the purity of the compounds.The structure of the synthesized compounds was elucidated using FTIR 8400 spectrophotometer in KBr disc and 1HNMR spectra was taken on a Bruker AMX (400MHz) FT-NMR.

Synthesis of 1-(substituted-1-ylmethyl)indoline-2,3-dione

A mixture of 2º amine (0.001M) and formaldehyde (0.01M) by cooling in ice bath. Then warm on water bath for 1hr at 70ºC and then add isatine (0.005M) and continue heating on water bath up to 2-3 hours at 80ºC. Then by doing confirm the reaction. Allow it for cooling so that crystals are formed. Which are filtered, washed with ethanol, dried and the melting point is recorded. The compounds of this category are presented in Table I along with their characterization data.

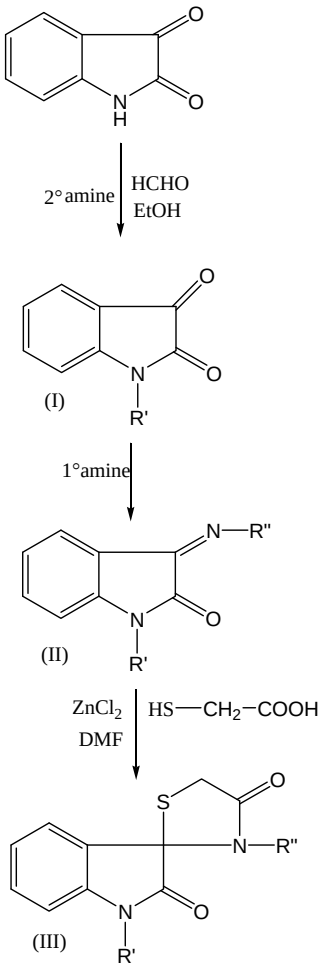
Synthesis of (Z)3-(4-subsitutedphenylimino)-1-(substituted-1-ylmethyl)indolin-2-one

A mixture of **1** (0.02M) and 1º amine (0.02M) in anhydrous pyridine (30 ml) was heated under reflux

on a sand-bath for 6 hours. Subsequently, the reaction mixture was poured into ice-cold water (100 ml) containing conc. HCl (10 ml). A solid started to separate out which was allowed to settle down for 1 hour. It was filtered off and washed successively with water. After drying in a vacuum desiccator, it was recrystallized from ethanol. The compounds of this category are presented in Table II along with their characterization data.

Synthesis of 3-(4-subsitutedphenylimino) thiazol-20-yl)-1-(substituted-1-ylmethyl)indolin-2-one

The target compounds were synthesized in the following manner. A mixture of different type of methyl indolin-2-one substituted group (0.01mole) and thioglycollic acid (0.01mole) containing in trace $ZnCl_2$ (0.1 gm) in dimethylformamide (DMF) was heated under reflux for 4 hours. It was poured into crushed ice and stirred vigorously. Solidification occurred after fifteen minutes. It was filtered off and washed with cold water. Recrystallization from ethanol gave analytically pure sample (Scheme I). The compounds of this category are presented in Table III along with their characterization data.



Scheme I

Table I — Characterization data for compounds **1a-c**

R’	Compd	Mol. Formula	Mol. Wt.	m.p. (°C)	Yield (%)
Morpholine	**1a**	$C_{13}H_{14}N_2O_3$	246	179	71
Piperidine	**1b**	$C_{14}H_{16}N_2O_2$	244	182	76
Diphenyl amine	**1c**	$C_{21}H_{16}N_2O_2$	328	118	69

Table II — Characterization data for compounds **2a-g**

R’	R”	Compd	Mol. Formula	Mol. Wt.	m.p. (°C)	Yield (%)
Morpholine	*p*-chloro aniline	**2a**	$C_{19}H_{18}ClN_3O_2$	355	320	75
	p-bromo aniline	**2b**	$C_{19}H_{18}BrN_3O_2$	400	120	78
	p-amino phenol	**2c**	$C_{19}H_{19}N_3O_3$	337	60	82
Piperidine	*p*-chloro aniline	**2d**	$C_{20}H_{20}ClN_3O$	353	110	84
	p-bromo aniline	**2e**	$C_{20}H_{20}BrN_3O$	397	118	74
Diphenyl amine	*p*-chloro aniline	**2f**	$C_{27}H_{20}ClN_3O$	437	90	72
	p-bromo aniline	**2g**	$C_{27}H_{20}BrN_3O$	482	78	81

Table III — Characterization data for compounds **3a-g**

R’	R”	Compd	Mol. Formula	Mol. Wt.	m.p. (°C)	Yield (%)
Morpholine	*p*-chloro aniline	**3a**	$C_{21}H_{20}ClN_3O_3S$	429	310	84
	p-bromo aniline	**3b**	$C_{21}H_{20}BrN_3O_3S$	474	290	75
	p-amino phenol	**3c**	$C_{21}H_{21}N_3O_4S$	411	59	81
Piperidine	*p*-chloro aniline	**3d**	$C_{22}H_{22}ClN_3O_2S$	427	260	74
	p-bromo aniline	**3e**	$C_{22}H_{22}BrN_3O_2S$	472	230	76
Diphenyl amine	*p*-chloro aniline	**3f**	$C_{29}H_{22}ClN_3O_2S$	512	58	89
	p-bromo aniline	**3g**	$C_{29}H_{22}BrN_3O_2S$	556	62	71

Results and Discussion

Thiazol is one of the important heterocyclic structures with special significance for the synthesis of organic compounds. The spectral data reveals that the structures of all the synthesised compounds are in good agreement with the proposed ones. N-Mannich bases of isatin Schiff bases are formed with the supports of secondary amines and Isatin. All the synthesized compounds were tested for in vitro antibacterial activity. It has been observed that all the compounds tested showed mild to moderate activity against tested bacteria.

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