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Synthesis of 1,3-dihydro-5-substituted-3-[[4-[1-(*p*-sulphamylphenylimino) ethyl] phenyl] imino]-2H-indol-2-ones and Their *in vitro* Antibacterial Screening

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A number of title compounds **(4–15)** have been synthesised by treating 3-[(4-acetylphenyl) imino]-1,3-dihydro-5-substituted-2H-indol-2-one **(1–3)** with various sulphonamide bases. The *in vitro* antibacterial properties of these compounds against *S. aureus* and *B. subtilis* were evaluated and some of these were found to exhibit marked activity.

Key Words: 1,3-dihydro-5-substituted-3-[[4-[1-(*p*-sulphamyl-phenylimino)ethyl] phenyl] imino]-2H-indol-2-ones, Antibacterial screening.

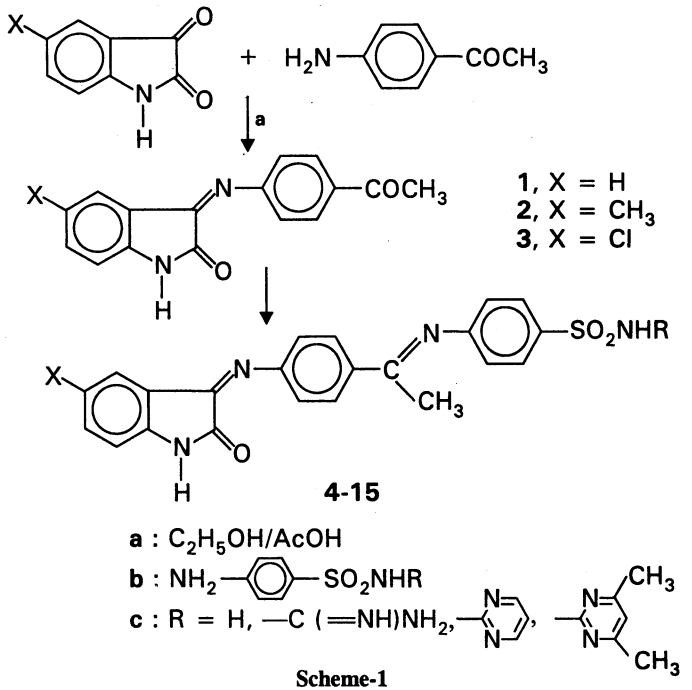
INTRODUCTION

In view of the encouraging results obtained during the course of our earlier work[1–3] on the synthesis and screening of analogs of substituted indol-2-ones, no report having been published on the antibacterial screening of these sulphonamidophenyl derivatives, it was thought of interest to synthesize new indol-2-one derivatives having sulphonamide residue attached through an imino linkage.

The present paper describes the synthesis and *in vitro* antibacterial screening of 1,3-dihydro-5-substituted-3-[[4-[1-(*p*-sulphamylphenylimino) ethyl] phenyl] imino]-2H-indol-2-ones **(4–15)**.

These were prepared by treating 3-[(4-acetylphenyl)imino]-1,3-dihydro-5-substituted-2H-indol-2-ones **(1–3)**, obtained by the reaction of 5-substituted indol-2,3-diones with *p*-aminoacetophenone with various sulphonamide bases. The homogeneity and purity of these compounds were tested by TLC and the structure confirmed by elemental analysis and IR spectral data.

The IR spectra of different 3-[(4-acetylphenyl)imino]-1,3-dihydro-5-substituted-2H-indol-2-one **(1–3)** show a peak around 3330 cm^{-1}, a doublet in the region 1730–1690 cm^{-1} which could be assigned to NH stertching frequencies of CO of indolinone and ketonic CO and (C=N) bonding, respectively, whereas in the IR spectra of **(4–15)** disappearence of band in the region around 1690 cm^{-1} confirms the Schiff condensation. Further, the appearence of band in the vicinity of 1250 and 1090 cm^{-1} in these IR spectra represents the respective asymmetric and symmetric stretching modes of vibration of (S=O) from sulphonamido group[4].



Scheme-1

EXPERIMENTAL

Different indol-2,3-diones for this work have been synthesised in the manner reported earlier[5].

Synthesis of 3-[(4-acetylphenyl) imino]-1,3-dihydro-5-substituted-2H-indol-2-ones (1–3)

Appropriate indol-2,3-dione (0.01 mol) was added to a solution of *p*-aminoacetophenone (0.01 mol) in 20 mL ethyl alcohol containing few drops of glacial acetic acid and the mixture was heated under cooling. The solid mass thus separated was recrystallised from ethanol and are reported in Table-1.

TABLE-1
3-[(4-ACETYLPHENYL) IMINO]-1,3-DIHYDRO-5-SUBSTITUTED 2H-INDOL-2-ONES

Compd No.	X	m.p. (°C)	Yield (%)	m.f.	Analysis (%), found (calcd.)		
					C	H	N
1.	H	247	80	$C_{16}H_{12}N_2O_2$	72.31 (72.72)	4.62 (4.54)	10.22 (10.60)
2.	Cl	232	77	$C_{16}H_{11}ClN_2O_2$	64.12 (64.32)	3.60 (3.60)	9.50 (9.38)
3.	CH_3	254	70	$C_{17}H_{14}N_2O_2$	73.71 (73.38)	5.23 (5.03)	9.43 (10.07)

Synthesis of 1,3-dihydro-5-substituted-3-[[4-[1-(*p*-sulphamylphenylimino) ethyl] phenyl] imino]-2H-indol-2-ones (4–15)

In a typical reaction to a solution of 0.01 mol of respective **(1–3)** in 30 mL ethanol containing sodium acetate (0.01 mol) was added an ethanolic suspension of respective sulphonamide base (0.01 mol). The resulting mixture was refluxed after adding few drops of glacial acetic acid for about 4 h. The solid product which separated out in pouring into ice-cold water was filtered, washed in cold ethanol and recrystallized from the same solvent (Table-2). Analytical samples were purified by preperative TLC over silica gel.

TABLE-2
PHYSICO-CHEMICAL DATA OF 1,3-DIHYDRO-5-SUBSTITUTED-3-[[4-1-(*p*-SULPHAMYLPHENYLIMINO-ETHYL] PHENYL] IMINO)-2H-INDOL-2-ONES

Compd. No.	X	R	m.p. (°C)	Yield (%)	m.f.	Analysis, found (calcd.)		
						C	H	N
4.	H	H	229	65	$C_{22}H_{18}N_4O_3S$	63.75 (63.15)	4.45 (4.30)	13.00 (13.39)
5.	H	—C(=NH)NH_2	275	60	$C_{23}H_{20}N_6O_3S$	60.20 (60.00)	4.54 (4.35)	17.95 (18.26)
6.	H	Diazino	175	70	$C_{26}H_{20}N_6O_3S$	63.23 (62.90)	4.59 (4.03)	16.04 (16.93)
7.	H	Dimidino	140	50	$C_{28}H_{24}N_6O_3S$	64.00 (64.12)	4.75 (4.58)	15.50 (16.03)
8.	Cl	H	231	70	$C_{22}H_{17}ClN_4O_3S$	59.06 (58.34)	3.80 (3.76)	12.00 (12.37)
9.	Cl	—C(=NH)NH_2	219	62	$C_{23}H_{19}ClN_6O_3S$	56.00 (55.81)	3.92 (3.84)	16.20 (16.98)
10.	Cl	Diazino	201	66	$C_{26}H_{19}ClN_6O_3S$	59.22 (58.81)	3.75 (3.50)	15.49 (15.83)
11.	Cl	Dimidino	135	55	$C_{28}H_{23}ClN_6O_3S$	60.34 (60.16)	4.50 (4.12)	15.32 (15.04)
12.	CH_3	H	188	60	$C_{23}H_{20}N_4O_3S$	64.00 (63.88)	4.59 (4.62)	13.00 (12.96)
13.	CH_3	—C(=NH)NH_2	253	60	$C_{24}H_{22}N_6O_3S$	60.50 (60.75)	4.55 (4.64)	17.32 (17.72)
14.	CH_3	Diazino	213	60	$C_{27}H_{22}N_6O_3S$	64.00 (63.52)	4.25 (4.31)	16.22 (16.47)
15.	CH_3	Dimidino	165	50	$C_{29}H_{26}N_6O_3S$	65.22 (64.68)	5.50 (5.39)	15.00 (15.61)

Antibacterial activity

Agar plate diffusion technique[6] was employed for the determination of antibacterial spectrum. Filter paper (Whatman No. 41) discs (5 mm diameter) saturated with the solution of the test compounds (10 mg/mL in ethanol) were placed on nutrient agar [1.5% (w/v) agar-agar, 5% (w/v) NaCl, 0.5% (w/v) glucose and 3.5% (w/v) peptone; pH 6.8–7.0] plates after drying up the solvent. Each disc contained approximately 150 μg of the substance. The plates were incubated at the optimum growth temperature of 37°C and the zones of inhibition around the discs were measured after 24 h. All the experiments were carried out in triplicate and the results of the antibacterial screening cited in Table-3 indicate a mean value.

TABLE-3
ANTIBACTERIAL ACTIVITY OF THE COMPOUNDS

Compd. No.	Mean area of inhibition (*S. aureus*)	After 24 h (*B. subtilis*)
Indol-2, 3-dione	–	–
1.	–	–
2.	–	+
3.	–	–
4.	+	+
5.	+	+
6.	++	+++++
7.	+	+
8.	++	++
9.	++	+++
10.	++	+++
11.	++	++
12.	+	+
13.	+	+
14.	++	+
15.	+	+
16.	+++++	+++++

where – = no inhibition
+ = zone size of 5–8 mm
++ = zone size of 8–10 mm
+++ = zone size of 10–12 mm
++++ = zone size of 12–15 mm
+++++ = zone size of 15 mm.

RESULTS AND DISCUSSION

All the compounds possess activity against both the organisms tested. Comparatively, compound nos. **6, 8, 9, 10,** and **11** possess high antibacterial activity; the activity of 6 against *Bacillus subtilis* is noteworthy.

It is interesting to note that the parent indol-2,3-dione and 3-[(4-acetylphenyl) imino]-1,3-dihydro-5-substituted-2H-indol-2-ones **(1–3)** have apparently no bacterial interaction as compared to the final compounds **(4–15)**. When these results were compared with those reported earlier[1], it revealed that the introduction of sulphonamide residue alone is responsible for enhancing the activity.

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