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Synthesis, Characterisation and Biological Activity of Some New Sulpha/ Substituted Phenylazo Indoles

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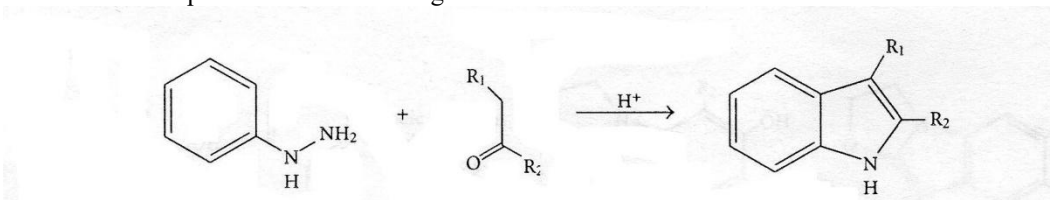
Abstract: ***A novel series of sulpha/ substituted phenyl azo indoles is synthesised by the condensation reaction of N.phenacyl sulpha/ substituted phenyl amine with diazonium salt of sulpha/substituted benzene. They were characterized by IR, [1]NMR and UV spectra and screened for their promising antituberculosis activity and antifertility activity.***

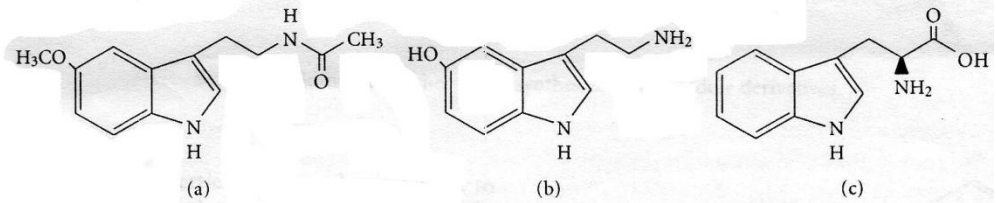
Keyword: indoles, sulpha/ substituted, drug, biological activity.

1. Introduction

Indole is an aromatic heterocyclic compound that has a bicyclic structure. It is an accepted constituent of fragrance and the precursor to many pharmaceuticals. One of the oldest and most reliable methods for synthesising substituted indoles is the Fischer Indole synthesis developed in 1883 (1).



SCHEME 1: Fischer indole synthesis.



SCHEME 2: Chemical formula of melatonin (a), serotonin (b), and tryptophan (c).

Indoles are present in many important biological compounds. Tryptophan is a significant indole derivative while serotonin and melatonin are biological active indole molecules. There are also many indole alkaloid derivatives found in nature.

Indoles derivatives represent many important classes of the therapeutical agents in medicinal chemistry such as anti cancer (2), anti oxidant (3), and anti HIV (4,5). Studies showed that some of 2- phenyl indole sulfmates are inhibitors of sulfamates with anti proliferative activity in breast cancer cells (6,7). Some of the sulphur containing2-phenyl indole derivatives show in vivo anti neoplastic and anti estrogenic activity (8,9).Melatonin and serotonin act as anti oxidant and play an important role in the immune system (10, 13) .

The biological and chemical significance of indole and its derivatives have been widely reported in literature. It has been great importance in clinical chemistry. In view of importance of indole, attempts have been made to synthesise a number of indole derivatives by various scientists. The derivatives of indole have been found in nervous system and claimed responsible for various physiological activity in human system.

The diversity of the structure encountered as well as their biological and pharmaceutical relevance, have motivated research aimed at the development of new economical, efficient and selective synthetic strategies, particularly for the synthesis of substituted indole rings (14, 15).

The main objective of the present work to synthesise novel active sulpha/substituted phenyl azo indoles displaying antituberculousis and antifertility activity. The new derivatives were tested for their capacity to inhibit antituberculousis and antfertility agents.

2. Experimental

Material

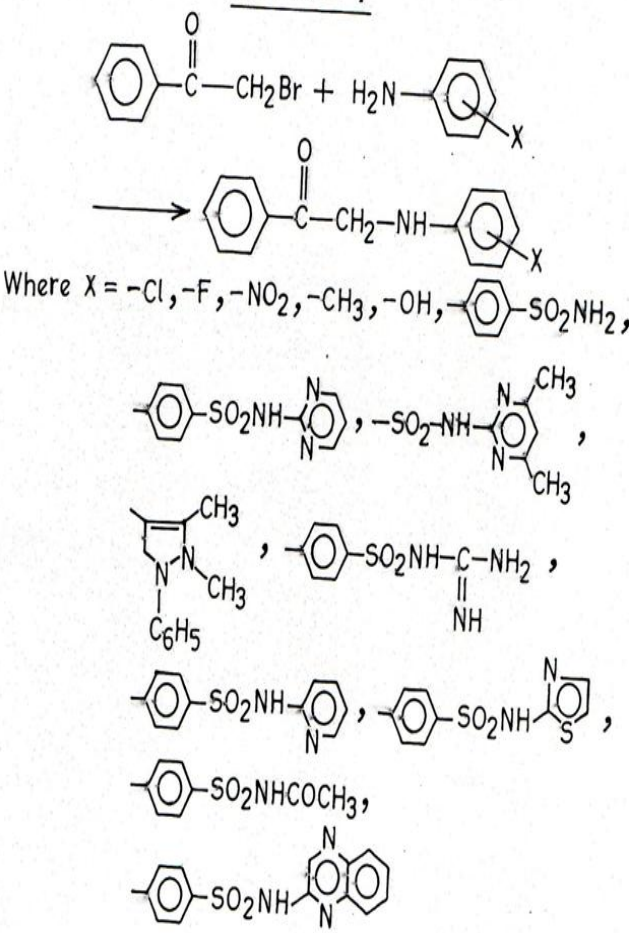
All the substituted phenyl amine, α- haloacyl benzene and reference compound were purchased from Aldrich chemical. Ethanol, glacial acetic acid and all other regents were purchased from S.D. Fine chem. Analytical TLC was performed on pre coated plastic sheet of selical gel. G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany).

General

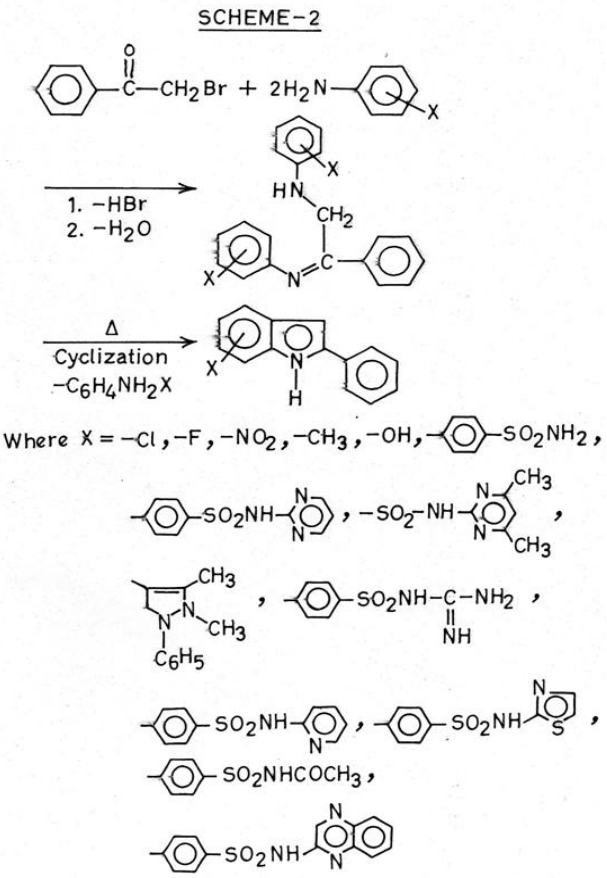
The melting point of the compounds was determined by using melting point apparatus MP-DSTID 2000V scientific and are uncorrected. The IR spectra of the synthesized compounds were recorded on Perkin-Elmer 1605 series using KBr pellets. ^{1}H NMR spectra were recorded at 300 MHz. on Bruker Ft. NMR spectrometer using TMS as internal standard.

EXPERIMENTAL METHOD ; Scheme of work

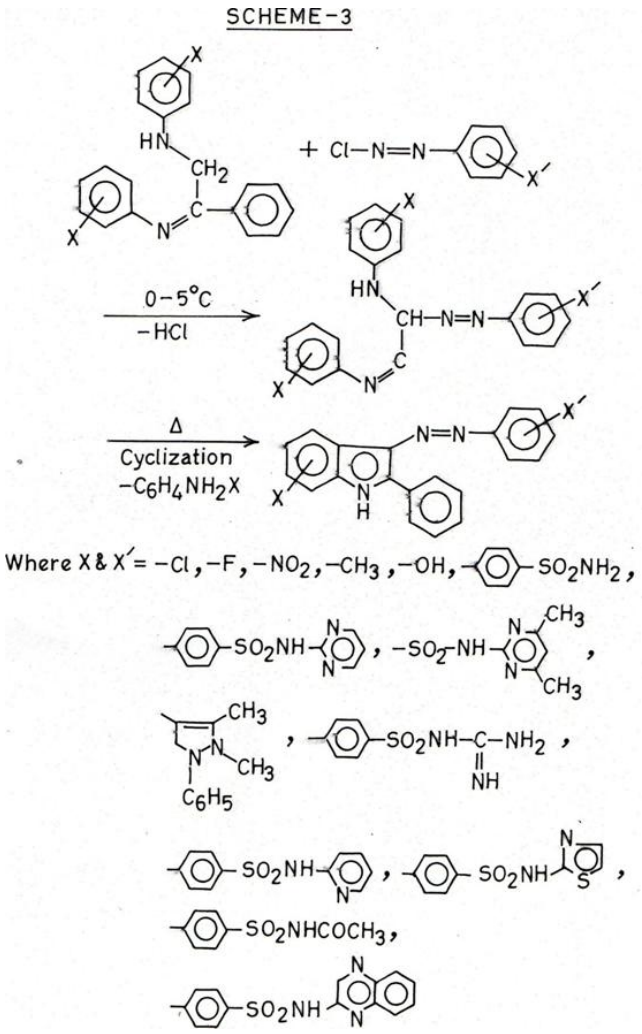
SCHEME-1



SCHEME-2



SCHEME-3



1- Synthesise of 2- phenyl-3 (sulphonoamidobenzene) azo 4-chloro indole.

A) Synthesis of 2- sulphonoamidobenzene azo substituted phenyl amino N- Phenacyl amine:

2- Sulphonoamidobenzene (5 gm) was dissolved in dil. HCl (4ml), water in sufficient amount and cooled to 0-5°C. Aqueous solution of sodium nitrite (4 gm) gradually added to sulphonoamidobenzenehydrochloride. The diazonium salt solution so obtained was filtered into a well cooled strirred mixture of sodium acetate (10gm) an N-phenacyl 4- chloro phenyl amine in ethanol (20ml) and shaken vigorously. A coloured precipipated, separated out, filtered dried and recrystallized from ethanol giving shining pale yellow needles.

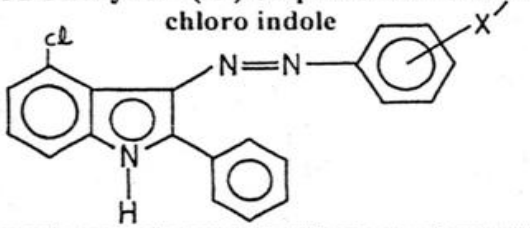
Yield=72%, M.P. = 183°
Molecular formula= $C_{32}H_{22}N_4Cl_2$ (Founded N= 10.21%, Cal. N=10.52%)
Rf Value= 0.4232
IR (KBr) = 1590 Cm^{-1} (N=N), 3140 Cm^{-1} (N-H Scratching of sulphonoamido group), 1350 Cm^{-1} (SO2 Vibration of sulphonoamide group)

B) Synthesis of 2- phenyl-3-(2- sulphonoamidobenzene) azo-4-chloro indole:

2 sulphonoamidobenzeneazo 4- Chloro phenyl N- phenacyl amine (3gm) was dissolved in sufficient amount of glacial acetic acid and refluxed on water bath for four hours .On cooling, a coloured crystalline solid compound separated out, filtered, recrystalised from ethanol.
Colour: SOF Yield=78% M.P. = 172° C
M.F. = $C_{26}H_{21}N_4O_2ClS$ (Found N = 11.13%, Calculated N = 11.47%)
IR (KBr) = 3260 Cm^{-1} (N-H stretching of sulphonamide and indole), 1580 Cm^{-1} (N-H bending), 1440 Cm^{-1} (N=N Stretching), 1370 Cm-1 and 1140 cm-1 (-SO2- Vibration of Sulphonamide)
NMR ($CDCl_3$) (in ppm) : 8.4 (s, 1H,-SO_2NH_2), 8.05 (s, 1H, indolyl NH), 7.5 (d, 4H, -N-C_6H_4- SO_2NH_2), 7.4 (d, 4H, -3, 5, 6, 7 -H of indole),7.1 -7.2 (m, 5H, aromatic protons)
By adopting above procedure 4- chloro, 4-Fluoro, 4-Hydroxyl,4-Nitro 2- sulphonoamido- benzene, N^1- 2-pyrimidyl. Sulphonoamidobenzene, N^1-2(3, 5 dimethyl pyramidyl sulphonoamidobenzene, 2,3 di methyl 1- phenyl pyrazolone, N^1-2 guanyl sulphonomido- benzene, N^1-2 pyridylsulphonoamidobenzene,N^1- 2 thiazolyl sulphonomidobenzene, N^1 -2 acetyl sulphonomidobenzene . N^1-2 Quinoxalyl sulphonoamidobenzene and. N^1-2 thiazolyl sulphonoamidobenzene derivatives were synthesised and the newly synthesized compound is recorded in table 1.

Table 1

Characteristics of 2-Phenyl-3 – (X') Sulpha/Substituted –Phenyl azo – 4 chloro indole



Substituted Group X'	M.P. °C	Yield %	Colour	Molecular Formula	Nitrogen found Found %	Cal. %	Rf value
4-Fluoro	117°C	70%	SP	$C_{20}H_{15}N_3ClF$	11.73	12.00	0.7652
4-Nitro	122°C	77%	OY	$C_{20}H_{15}N_4O_2Cl$	14.32	14.81	0.7731
4-Methyl	135°C	76%	GY	$C_{21}H_{18}N_3Cl$	11.87	12.10	0.6542
4-Hydroxy	137°C	72%	DYB	$C_{20}H_{16}N_3OCl$	11.72	12.03	0.7762
2-Sulphonoamido-benzene	172°C	78%	SOF	$C_{26}H_{21}N_4O_2ClS$	11.13	11.47	0.7853
N^1-2Pyrimidyl sulphonoamido benzene	168°C	80%	SP	$C_{30}H_{23}N_6O_2ClS$	14.56	14.84	0.6953
N^1-2(3,5 dimethyl) Pyrimidyl sulphono-amidobenzene	176°C	65%	GY	$C_{32}H_{27}N_6O_2ClS$	13.83	14.14	0.7762
2,3-Dimethyl-1 phenyl Pyrazolone	175°C	80%	DYB	$C_{37}H_{31}N_5Cl$	11.74	12.06	.0.7542
N^1-2Guanyl Sulphono-amidobenzene	177°C	85%	DY	$C_{27}H_{23}N_6O_2ClS$	15.52	15.84	0.6831
N^1-2Pyridyl Sulphono-amidobenzene	188°C	83%	DY	$C_{31}H_{23}N_6O_2ClS$	11.91	12.38	0.7955
N^1-2 thiazolyl Sulphonoamidobenzene	175°C	72%	SP	$C_{29}H_{22}N_5O_2Cl\,S_2$	12.64	12.93	0.7621
N^1-2 acetyl Sulphono – amidobenzene	167°C	80%	SON	$C_{28}H_{23}N_4O_3ClS$	10.27	10.56	0.6987
N^1-2 Quinoxalyl Sulphonoamidobenzene	165°C	90%	DY	$C_{34}H_{25}N_6O_2ClS$	13.35	13.63	0.8752

DY = Dull yellow, SPY = Shining Pale Yellow, GY = Golden Yellow, LY = Light Yellow, BY = Bright Yellow, RN = Red Needles, BON = Bright Orange Needles, OY = Orange Yellow, PY = Pale Yellow.

** The Rf value for all on silica gel – G plates (thickness 0.5 mm) with developer as benzene / ethanol (2:1)

2. Prepration of 2 – phenyl -5-sulpha/substituted- 3-phenyl substituted azo indoles

Sulpha/Substituted phenyl amine was dissolved in HCl, water is added in sufficient amount and
cooled to 0^o C. Aqueous solution of sodium nitrite was gradually added to sulpha/substituted phenyl amine hydrochloride. The diazonium salt solution so obtained was filtered into a well cooled stirred mixture of sodium acetate and sulpha/substituted phenyl amino N-phenacyl phenyl amine in ethanol and shaken vigourously, precipitate separated out , filtered, dried and recrystallizes from ethanol giving shining coloured needlesof sulpha/ substituted phenyl azo substituted phenyl amino N- phenacyl phenyl amine.
Sulpha/substituted phenyl azo phenyl amino N- phenacyl phenyl amine was dissolved in glacial acetic acid and refluxed on water bath for half an hour. On cooling a crystalline solid compound separated out , which is recrystallizes from ethanol.

(i) Synthesis of 2- phenyl- 5- sulphonoanifo benzene-3-phenyl fluoroazo indole

A light yellow crystalline yellow powder, M.P.= 172^0C, yield= 65%, molecular formula= $C_{26}H_{19}FN_4SO_2$, Analytical calculated = (C=66.37%,, H =4.07%, F=4.02%, N=11.87%, S=6.78%, O=6.78%,)
Found (C = 66.32%, H=4.04%, F=4.02%, N=11.57%, S=6.73% O=6.73%)
UV(λ_{max}) = 280, **IR (KBr) ν_{max} in cm^{-1}** 1325 (C-F), 760 (C-C), 1245 (C-N), 1560 (C=C or aromatic ring), 3040 (aromatic C-H), 3345 (N-H), 1445 (N=N), 1153 (SO_2), 3280 (NH_2), **^{1} NMR ($CDCl_3$) δ in ppm**: 5.9 (b, IH, NH), 7.75-6.40 (m, 16H, Ar-H), 11.5 (b, 2H, SO_2NH_2).

(ii) Synthesis of 2- phenyl -5- benzene sulphonamide- 3- phenyl chloroazoindole.

A light yellow crystalline powder, mp 170- 172^0C, Yield 69% molecular formula C_{26} $H_{19}ClN_4$ SO_2, (486.98), Anal Cal. C= 64.13%, H= 3.93%; Cl= 7.28%, N= 11.50%; S= 6.58%; O= 6.57% Found: C= 64.11%: H= 3.90%: Cl= 7.25%; N= 11.49%; S= 6.55%; O= 6.55%. **UV (λ_{max}) 277. IR (KBr) ν_{mas} cm^{-1}** 670 (C4-Cl), 760 (C –C), 1240 (C-N), 1565 (C=C or aromatic ring). 3045 (aromatic C-H), 3340 (N-H), 1445 (N=N), 1150 (SO_2), 3280 (NH_2), **^{1}NMR ($CDCl_3$) δ in ppm**: 5.9 (b. IH,NH), 7.65-6.75 (m. 16H, Ar-H), 11.5 (b, 2H, SO_2NH_2)

(iii) Synthesis of 2- phenyl -5- benzene sulphonamide – 3- phenylmethylazoindole

A light of yellow crystalline powder, mp 178-180^0C yield 73% molecular formula $C_{27}H_{22}N_4SO_2$, (466.56): Anal. Cal. C= 69.51%; H= 4.75%; N= 12.01%; S= 6.87%; O= 6.86% Found; C= 69.49%; H= 4.72%; N= 11.99%; S= 6.83%; O= 6.85%. **UV (λ_{max}) 273, IR (KBr) ν_{max} in cm^{-1}** 765 (C-C), 1245 (C-N), 1555 (C=C or aromatic ring), 3055 (aromatic C-H), 3340 (N –H) , 1445 (N=N) 1150 (SO_2), 3275 (NH_2), **^{1}NMR ($CDCl_3$) δ in ppm**: 2.25 (t, 3H, CH_3), 5.9 (b, 1H, NH) 7.65-6.75 (m, 16H, Ar-H), 10.5 (b, 2H, SO_2NH_2)

(iv) Synthsis of 2- phenyl -5- benzene sulphonamido-3 phenylhydoxyazoindole

A yellow crystalline powder, mp197-199^0C, yields 68%, molecular formula $C_{26}H_{20}N_4SO_3$, (468.53); Anal. Cal. C= 66.65%; H= 4.30%; N= 11.96%; S= 6.84%; O= 10.24%. Found; C= 66.63%; H= 4.29%; N= 11.93%; S= 6.81%; O= 10.21%. **UV(λ_{max}) 280, IR (KBr) ν_{max} in cm^{-1}** 1305 (C-OH), 760 (C-C), 1245 (C-N), 1560 (C=C or aromatic ring), 3040 (aromatic C-H), 3345 (N-H), 1445 (N=N), 1153 (SO_2), 3280 (NH_2), **^{1}NMR ($CDCl_3$) δ in ppm:** 5.9, (b, IH, NH) 4.3 (s, 1H, OH) 7.75-6.40 (m, 16H, Ar-H), 11.5 (b, 2H, SO_2NH_2).

3. Result and Discussion

Anti Tuberculosis Activity

Some of newly synthesized compound were tested for their antituberculosis activity against M. Tuber culosis H37 R_V by bactec 460 radiometric system at Southern Research Institute, Frederick Research Center, Frederick M D.

Primary screening of invitro tuberculosis activity was conducted at concentration of 12.5 µg/ml against mycobacterium tuberculosis H37 Rv in BACTEC12B medium using BACTEC 460 radiometric system. The anti tuberculoses activity of all newly synthesized compounds are compared with the standard Rifampin (Which has 96% inhibition at MIC of 0.031 µg/ml). Some of newly synthesized compound were screened for their anti tuberculosis activity. Some of them showed significant activity recorded in table 2.

Table : 2- ANTI TUBERCULOSIS ACTIVITY DATA OF SYNTHESIZED COMPOUNDS

S.No. Name of compound M.T.*

1. 2-phenyl-3-(N^1-2 thiazolyl sulphonamidobenzene azo) indole (+)
2. 2- phenyl-3 (4- chloro phenylazo)-4 chloro indole (+)
3. 2-phenyl-3-(2- sulphonamidobenzene azo) 4-methyl indole (+)
4. 2-phenyl-3-(N^1-2 acetyl sulphonamidobenzene azo) 4-(2-sulphonamido benzene) indole (+)

M.T*. = M.Tubercalosis H37Rv, (+) = positive

Anti fertility activity

The antifertility activity of newly synthesized compounds were studied in female albino rats mated coeval males of proven fertility by standard method (16). All were tested to prevent pregnancy at 20 mg./Kg dose on female albino rats. Some of them showed significant anti fertility activity (table 3).

(Table 3): Anti fertility activity data of newly synthesized compound

S.No Name of compound Anti fertility% inhibitation

1. 2 phenyl-3 (N^1-2 pyridyl sulphonoamidobenzene azo)-2-sulphonoamidobenzene indole 60
2. 2- phenyl-3 (4-chloro phenyl azo)-4-chloro indole 65
3. 2- phenyl-3 (4-Nitro phenyl azo)-4-chloro indole 68
4. 2- phenyl-3 (2-fluoro phenyl azo)-4- (2, 3 dimethyl 1-phenyl pyrazolone) indole 75

4. Acknowledgement

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