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SYNTHESIS AND BIOLOGICAL ACTIVITY OF A NOVEL SERIES OF 2- PHENYL SULPHA/SUBSTITUTED INDOLES

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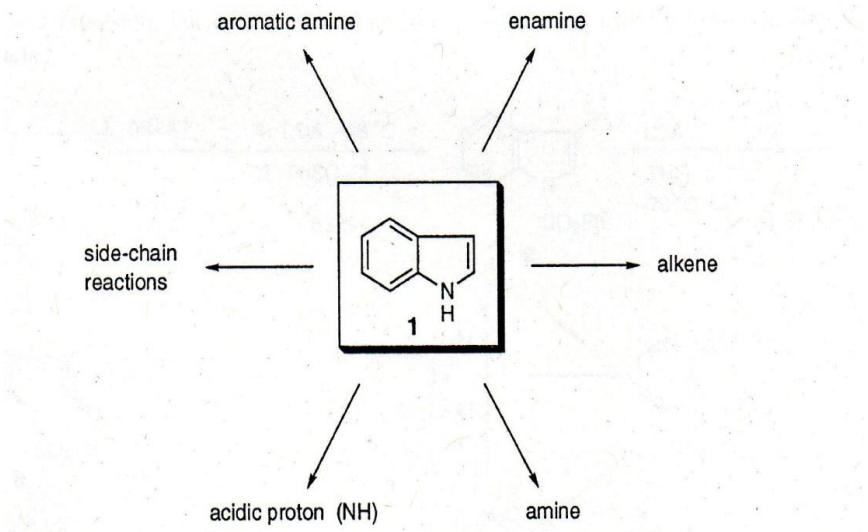
ABSTRACT
A Novel series of 2-phenyl sulpha/substituted Indoles were synthesised by refluxing the mixture of phenacyl bromide and sulpha/ substituted phenyl amine in presence of glacial acetic acid, forming cyclisation of resulting product. They were characterised by IR, ^{1}HNMR and UVspectra. They were also screened for their promising antituberculosis and anti-inflammatory activity.

KEYWORDS: Indoles, sulpha/substituted, antituberculosis activity, anti-inflammatory activity.

INTRODUCTION

Hetereocyclic compounds are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics etc. A practical method for the synthesis of such compounds in of great interest in synthetic organic chemistry.[1] Nitrogen containing heterocyclic compounds play an important role in medicinal chemistry and also contribute to the society by helping in different processes.

Simple nitrogen containing heterocycles attached to sulphonamido moieties have received a large amount of attention in literature, as a consequence of their exciting biological properties and their role as pharmacophores of considerable historical importance. Heterocyclic sulphonamides are used as carbonic anhydrase inhibitiors[2 – 4], anti bacterial agents[5], anticancer, anti-inflammatory and analgesic agents[6], β- 3- adrenergic receptor agonistists.[7] Although the chemistry of Indole[8] has been investigated for more than 100 years as summarised in scheme[1], recent times have been development of new indole chemistry, such as lithiated Indoles and indole radicals for use in synthesis.[9, 10]



Indoles are one of the most important nitrogen containing heterocyclic compounds. The Indole nucleus is important moiety found in a large number of natural or synthetic alkaloids.[9,11] One of the naturally occurring indoles, tryptophan, has a high sensitivity of tryptophyl residue in proteins and oxidation of tryptophan has been implicated in the photo degradation and photo yellowing of wool.[12]

In addition to this, molecules containing an Indole scaffolod are partial agonists and antagonists of neurotensine[13], agonists of somatostatin receptor[14] and also thrombin receptor anta-agonists[15] and selective factor inhibitors.[16] Many other indole alkaloids with biological activity also exist, including those that cause cell cycle arrest at C_{12}/M- transition.[17] Nakazawa et. al.[18] have prepared several indole derivatives and tested for their antithrombotics and allergy inhibitor activitity.

Based on above mentioned research results, the aim of the present work was to synthesise a novel series of 2-phenyl sulpha/substituted indoles by refluxing the mixture of phenacylbromide and sulpha/substituted phenylamine in presence of glacial acetic acid and cyclisation of resulting product. The synthesis of compounds was illustrated in scheme (1 and 2).

Experimental Section

Material

All the substituted phenylamine, α- haloacyl benzene and reference compound were purchased from Aldrich Chemical. Ethanol, Glacial acetic acid and all other reagents were purchased from S.D. Fine Chem. Analytical TLC was performed on precoated plastic sheet of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany).

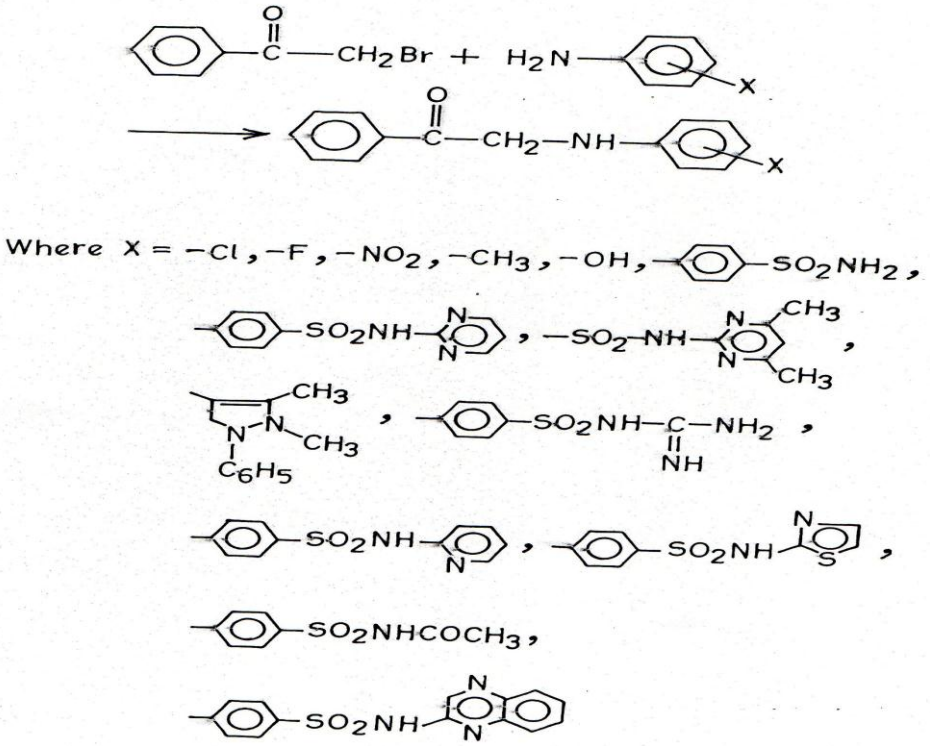
General

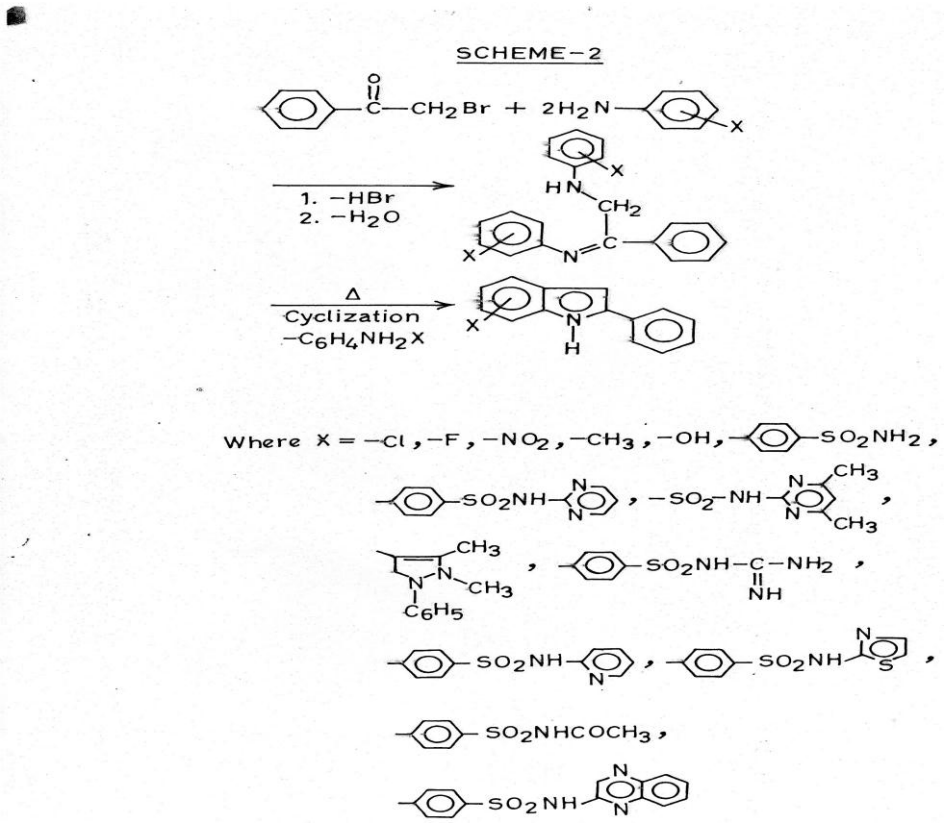
The melting point of the newly synthesised compounds were determined by using melting point apparatus (MP-DSTID 2000V scientific) and were uncorrected. The IR spectra of the synthesised compounds were recorded on IR spectrophotometer (perkin Elmer 1605 series) using KBr pellets. ^{1}HNMR spectra were recorded at 300 MHz on Bruker Ft. NMR spectrometer using $CDCl_3$ and the chemical shift (δ) reported are in ppm, using TMS as internal reference.

Experimental Method

EXPERIMENTAL METHOD: Scheme Of Work

SCHEME – 1





1- Synthesis of 2- phenyl 4- methyl indole

Phenacyl bromide and 4- methyl aniline (1: 2) ratio was dissolved in 20 ml Ethanol. The reaction mixture was heated on water bath for 1 hour and then cooled. on cooling a crystalling solid mass seprated out, filtered and recystallised from Ethanol. The crystalline solid mass was dissolved in 30 ml acetic acid and refluxed for 3 hours on water bath. On cooling, the yellow colour solid mass separated out, filtered washed and recrystallized from ethanol and pyridine/acetic acid (1:1).

RESULT

Yield = 63% Colour = DY, M.P. = 167^0C, mol. for. = $C_{15}H_{14}N$ (Found N = 6.55% Cal. N = 6.73%)
Rfvalue = 0.8324.
IR(KBr) (v_{max} in cm^{-1}) = 3140 (-NH stretch for indole), 660 (- CH_3)
NMR($CDCl_3$) (δ in ppm): 2 4 [s, 3H, CH_3]
6.85-7.50 [m, 5H. ArH] 7.45 [d, 4H, 3,5,6,7 H of indole ring]

2- Synthesis of 2-Phenyl-4 [N^1-2-Pyrimidyl sulphonoamido benzene] indole.

Above procedure were adopted for the synthesis of this compound.

RESULT

Yield = 90%, Colour = Shining green yellow, M.P. = 168^0c
Molecular formula = $C_{24}H_{19}N_4O_2S$
(Found N = 12.87%, cal. N = 13.88%) Rf value = 0.9497
IR (KBr) (v_{max} in cm-1): 3250 (-NH stretch for indole)
1360 and 1140 (-SO_2-vibration of – SO_2NH_2group)
NMR (CDCl3) (δ in ppm): 9. 1 [s, 1H, SO_2NH_2],
7.8 [s, 3H, 4,5 and 6H pf pyrimidyl group],
7.5[d, 4H, -C_6H_4-SO_2NH_2],
7.35 d, 4H, 3, 5, 6 and 7H pf indole ring],
7.1 – 7.2 [m, 5H, C_6H_5 at position of indole ring]

3- Synthesis of 2-phenyl-4 [N^1 -2 - (3,5 di methyl) pyrimidyl sulphonoamidobenzene] indole.

same procedure were adopted.

RESULT

yield: 92% Colour = Light Brown M.P. 170^0C
Mol. For. = $C_{26}H_{23}N_4O_2S$ (Found N=11.92%, .Cal.N = 12.30%) Rf value = 0.9053
IR (KBr) (v_{max} in cm^{-1}): 3215 (-NH stretch for indole)
665 & 670 (-CH_3 for pyrimidyl group),
1360 and 1145 (-SO_2 – Vibration of – SO_2NH_2 group).
NMR (CDCl3) (δ in ppm): 9.3[s, 1H, -SO_2NH_2],
7.9 [s, 4 and 6H of pyrimidyl group]
2.4 [s, 6H, CH_3]
7.30 [d, 4H, 3, 5, 6 and 7H of indole ring]
7.1-7.2 [m, 5H, C_6H_5 at position of indole ring]

4- Synthesis of 2-phenyl-4-(N^1 -2 pyridyl sulphonoamidobenzene) indole

Same procedure were adopted.

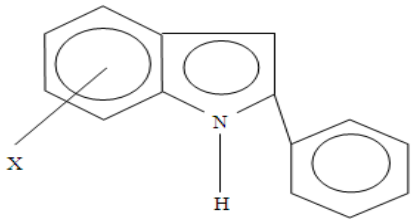
RESULT

Yield = 67% Colour = Colourless flakes., M.P. = 156^0C
Mol. For. = $C_{25}H_{20}O_2N_3S$, (Found N = 9.57% Cal. N. = 9.85%)

Rf value = 0.7832
IR (KBr) (v_{max} in cm-1): 3250 (-NH stretch for indole)
1355 and 1130 (-SO_2 – Vibration of – SO_2NH_2 group).
NMR (CDCl3) (δ in ppm): 9.3 [s, 1H,-SO_2 NH_2]
7.8 [s,3H,4 and 5H of pyridyl group]
7.3 [d, 4H, -C_6H_4 – SO_2NH_2]
7.35[d, 4H, 3,5,6 and 7H of indole ring]
7.12 (dd, N,-C_5H_4N)
7.1 – 7.2 [m, 5H, C_6H_5 at position of indole ring]

By adopting same procedure 4- chloro, 4 –Fluroro, 4-Nitro, 4-Hydroxy,2-Sulphonoamidobenzene,N^1-2Guanyl sulphonoamidobenzene, -2, 3di methyl -1 Phenyl Pyrazolone, N^1 – 2 Thiazolyl sulphonoamidobenzene, N^1–2acetyl Sulphonoamidobenzene N^1 – 2 Quinoxalyl sulphonoamidobenzene were synthesiised The newly Synthesised Compounds are characterised in the given table 1.

Table 1: Characteristics of 2- Phenyl Sulpha/Substituted Indole



S.No.	Subsituted Group 'X'	M.P. 'C'	Yield %	Colour	Molecular Formula	Nitrogen found		Rf value
1-	4-Cholo	172^{0}C	65%	SYBN	$C_{14}H_{11}NCI$	5.92	6.14	0.8765
2-	4- Fluoro	165^{0}C	72%	SYN	$C_{14}H11NF$	6.48	6.63	0.8162
3-	4- Nitro	157^{0}C	63%	SON	$C_{14}H11N_2O_2$	11.51	11.71	0.8542
4-	4- Methyl[1]	167^{0}C	63%	SYF	$C_{15}H_{14}N$	6.53	6.73	0.8892
5-	4- Hydroxy	169^{0}C	77%	CPr	$C_{14}H_{12}NO$	6.41	6.66	0.8165
6-	2- Sulphonoamido benzene	171^{0}C	88%	LPYN	$C_{20}H_{17}N_2O_2S$	7.81	8.02	0.8362
7-	N^1-2Pyrimidyl-sulphonoamido benzene	168^{0}C	90%	SGY Pr	$C_{24}H_{19}N_4O_2S$	12.87	13.88	0.8362
8-	N^1-2(3,5 dimethyl) Pyrimidyl sulphono-amidobenzene	170^{0}C	92%	SLB	$C_{26}H_{23}N_4O_2S$	11.92	12.30	0.8554
9-	2,3- Dimethyl-1 phenyl Prrazolone	172.5^{0}C	85%	PY Na	$C_{31}H_{27}N_3$	9.22	9.52	0.8633
10-	N^1 – 2 Guanyl Sulphono-amidobenzene	153^{0}C	75%	SLYF	$C_{21}H_{19}O_2N_4S$	14.06	- 14.32	0.8752
11-	N^1 – 2 Pyridyl Sulphono-amidobenzene	156^{0}C	67%	SCF	$C_{25}H_{20}O_2N_3S$	9.57	9.85	0.8440
12-	N^1 -2 Thiazolyl sulphono- amidobenzene	166^{0}C	72%	SBGF	$C_{23}H_{17}N_3O_2S_2$	9.54	9.72	0.8292
13-	N^1-2 acetyl Sulphono-amidobenzene	168^{0}C	78%	YF	$C_{22}H_{19}N_2O_3S$	6.88	7.16	0.8594
14-	N^1- 2 Quinoxalyl Sulphonoamido-benzene	149^{0}C	69%	DBF	$C_{28}H_{21}N_4O_2S$	11.33	11.74	0.8346

DY = Dull Yellow, SPY= Shining Pale Yellow, GY = Golden Yellow, LY = Light Yellow, BY = Bright Yellow, RN = Red Neddles, BON = Bright Orange Neddles, 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).

RESULT AND DISCUSSION

Antituberculosis activity

All the newly synthesised compound were tested for their antituberculosis activity against M. Tuberculosis H37 Rv by bactec 460 radiometric system at Southern Research Institute, Frederick Research Centre, Frederick, M D.

Primary Screening of invitro tuberculosis activity was conducted at concentration of 12.5 µg/ml against mycobacterium tuberculosis H37 Rv in BACTEC 12B medium using BACTEC 460 radiometric system. The antituberculosis activity of all newly synthesised compounds are compared with the standard Rifampin (which has 96% inhibition at MIC of 0.31 µg/ml. Some of newly synthesised compounds were screened for their

antituberculosis activity. Some of them showed significant activity recorded in table (2).

Table – 2 – Antituberculosis activity Data of newly Synthesised compounds.

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

1- 2-phenyl 4-Hydroxy Indole (+)
2- 2 phenyl -4 – (N^1 -2thiazolyl sulphonoamido benzene) Indole (+)
3- 2- phenyl – 4 – methyl Indole 0
4- 2 – phenyl- 4 – Fluoro Indole 0
5- 2- phenyl – 4 – (N^1 -2-Guanyl sulphonoamido benzene) indole. (+)

***M.T**. = M. Tuberculosis H37Rv
(+) = Positive

Anti inflammatory activity

All newly synthesised compounds were screened for their anti inflammatory activity with the help of following method as compared to standard Indomethacin at 200 µg/ml.

Mice of either sex weighing between 15 and 25 gm were divided into groups of 5 each.

carrageenin solution (1.0%, 0.025ml) in normal saline was injected in the left planter aponeurosis, after one hour, the oral feeding of drug. one group acted as control and received only the vehicle and another group received, a standard anti-inflammatory compound (Indomethacin). Both the hind limbs of all the groups were cut 4 hours after the carrageenin injection at level of the ankle Joint. Difference between the weight of the left and right limbs gave the amount of edma developed. Difference in the amount of edema developed in each group from the control group in used to calculate the percentage inhabitation.

Some of newly synthesised compound show signigicant anti-inflammatory activity recorded in table 3.

Table 3 ALD_{50} and Antiinflammatory activity data.

S.No.	Name of Compound	Approximate ALD_{50} Dose(mg/kg Mice P.O.		Antiinflammatory Activity of inhibition
1-	2-phenyl-4(2,3 di methyl -1phenyl pyrazolone indole	>1000	200	74
2-	2- phenyl -4 (N^1-2phenyl sulphonamidophenyl Indole	681	200	79
3-	2- phenyl-4 (N^1-2acetyl sulphonamido benzene) Indole	825	168	77
4-	2 phenyl – 4 -nitro Indole	681	198	79
5-	2-phenyl-4-Fluoro Indole	825	173	62

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