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, ¹H 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).

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 sulfamates 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 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 antituberculous and antifertility activity. The new derivatives were tested for their capacity to inhibit antituberculous and antifertility 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. 1H NMR spectra were recorded at 300 MHz. on Bruker Ft. NMR spectrometer using TMS as internal standard.

**EXPERIMENTAL METHOD ; Scheme of work**

**SCHEME - 1**

Where \( X = -\text{Cl}, -\text{F}, -\text{NO}_2, -\text{CH}_3, -\text{OH}, -\text{SO}_2\text{NH}_2, \)

\[ \text{SCHEME - 2} \]

1. \(-\text{HBr}\)
2. \(-\text{H}_2\text{O}\)

\[ \Delta \]

Cyclization

\(-\text{C}_6\text{H}_4\text{NH}_2X\)

Where \( X = -\text{Cl}, -\text{F}, -\text{NO}_2, -\text{CH}_3, -\text{OH}, -\text{SO}_2\text{NH}_2, \)

\[ \text{SCHEME - 3} \]

\(+\text{Cl-N=N-C}-\text{NH}_2\)

\[ 0\text{—5°C} \]

\(-\text{HCl}\)

\[ \Delta \]

Cyclization

\(-\text{C}_6\text{H}_4\text{NH}_2X\)

Where \( X & X' = -\text{Cl}, -\text{F}, -\text{NO}_2, -\text{CH}_3, -\text{OH}, -\text{SO}_2\text{NH}_2, \)
1- Synthesis of 2- phenyl-3 (sulphonoamidobenzene) azo 4-chloro indole.

A) Synthesis of 2- sulphonoamidobenzeneazo 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 sulphonamidobenzenehydrochloride. The diazonium salt solution so obtained was filtered into a well cooled stirred mixture of sodium acetate (10gm) an N-phenacyl 4- chloro phenyl amine in ethanol (20ml) and shaken vigorously. A coloured precipitate separated out, filtered and recrystallized from ethanol giving shining pale yellow needles.

Yield=72%, M.P. = 183°
Molecular formula= C$_{32}$H$_{22}$N$_4$Cl$_2$ (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$^{-1}$ (SO$_2$ Vibration of sulphonamide 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°
M.F. = C$_{26}$H$_{21}$N$_4$O$_2$ClS (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 (-SO$_2$- Vibration of Sulphonamide)

NMR (CDCl$_3$) (in ppm): 8.4 (s, 1H, -SO$_2$NH$_2$), 8.05 (s, 1H, indolyl NH), 7.5 (d, 4H, -N-C$_6$H$_4$- SO$_2$NH$_2$), 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- sulphonamido- benzene, N$_1$- 2-pyrimidyl. Sulphonamidobenzene, N$_1$-2(3, 5 dimethyl pyridimyl sulphonamido benzene, 2,3 di methyl 1- phenyl pyrazolone, N$_1$-2 guanyl sulphonamido benzene, N$_1$-2 pyridylsulphonamidd benzene,N$_1$-2 thiazoly1 sulphonamidobenzene, N$_1$ -2 acetyl sulphonamidobenzene . N$_1$-2 Quinoxalyl sulphonamidobenzene and. N$_1$-2 thiazolyl sulphonamidobenzene derivatives were synthesised and the newly synthesized compound is recorded in table 1.

### Table 1

<table>
<thead>
<tr>
<th>Substituted Group X'</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Color</th>
<th>Molecular Formula</th>
<th>Nitrogen found %</th>
<th>Found</th>
<th>Cal. %</th>
<th>RF Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Fluoro</td>
<td>117°C</td>
<td>70%</td>
<td>SP</td>
<td>C$<em>{28}$H$</em>{21}$N$_4$ClF</td>
<td>11.73</td>
<td>12.00</td>
<td>0.7652</td>
<td></td>
</tr>
<tr>
<td>2-Nitro</td>
<td>122°C</td>
<td>70%</td>
<td>OY</td>
<td>C$<em>{28}$H$</em>{21}$N$_4$ClO</td>
<td>14.32</td>
<td>14.81</td>
<td>0.7731</td>
<td></td>
</tr>
<tr>
<td>2-Methyl</td>
<td>135°C</td>
<td>65%</td>
<td>GY</td>
<td>C$<em>{28}$H$</em>{21}$N$_4$ClN</td>
<td>11.87</td>
<td>12.10</td>
<td>0.6542</td>
<td></td>
</tr>
<tr>
<td>2-Hydroxyl</td>
<td>137°C</td>
<td>72%</td>
<td>DYB</td>
<td>C$<em>{28}$H$</em>{21}$N$_4$OCl</td>
<td>11.72</td>
<td>12.03</td>
<td>0.7762</td>
<td></td>
</tr>
<tr>
<td>2-Sulphonamido-benzene</td>
<td>172°C</td>
<td>78%</td>
<td>SOF</td>
<td>C$<em>{28}$H$</em>{21}$N$_4$O$_2$ClS</td>
<td>11.13</td>
<td>11.47</td>
<td>0.7853</td>
<td></td>
</tr>
<tr>
<td>N$_1$-2Pyrimidyl sulphonamido benzene</td>
<td>168°C</td>
<td>80%</td>
<td>SP</td>
<td>C$<em>{28}$H$</em>{21}$N$_4$O$_2$ClS</td>
<td>14.56</td>
<td>14.84</td>
<td>0.6953</td>
<td></td>
</tr>
<tr>
<td>N$_1$-2(3,5 dimethyl) Pyrimidyl sulphonamido benzene</td>
<td>176°C</td>
<td>70%</td>
<td>65%</td>
<td>C$<em>{28}$H$</em>{21}$N$_4$O$_2$ClS</td>
<td>13.83</td>
<td>14.14</td>
<td>0.7762</td>
<td></td>
</tr>
<tr>
<td>2,3-Dimethyl-1 phenyl Pyrazolone</td>
<td>175°C</td>
<td>80%</td>
<td>DYB</td>
<td>C$<em>{28}$H$</em>{21}$N$_4$Cl</td>
<td>11.74</td>
<td>12.06</td>
<td>0.7542</td>
<td></td>
</tr>
<tr>
<td>N$_1$-2 Guanyl Sulphonamido benzene</td>
<td>177°C</td>
<td>85%</td>
<td>DY</td>
<td>C$<em>{28}$H$</em>{21}$N$_4$ClO</td>
<td>15.52</td>
<td>15.84</td>
<td>0.6831</td>
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</tr>
<tr>
<td>N$_1$-2 Pyridyl Sulphonamido benzene</td>
<td>188°C</td>
<td>83%</td>
<td>DY</td>
<td>C$<em>{28}$H$</em>{21}$N$_4$OCl</td>
<td>11.91</td>
<td>12.38</td>
<td>0.7955</td>
<td></td>
</tr>
<tr>
<td>N$_1$-2 Thiadiazol Sulphonamido benzene</td>
<td>175°C</td>
<td>72%</td>
<td>SP</td>
<td>C$<em>{28}$H$</em>{21}$N$_4$O$_2$Cl S$_2$</td>
<td>12.64</td>
<td>12.93</td>
<td>0.7621</td>
<td></td>
</tr>
<tr>
<td>N$_1$-2 Acetyl Sulphonamido benzene</td>
<td>167°C</td>
<td>80%</td>
<td>SON</td>
<td>C$<em>{28}$H$</em>{21}$N$_4$O$_2$Cl</td>
<td>10.27</td>
<td>10.56</td>
<td>0.6987</td>
<td></td>
</tr>
<tr>
<td>N$_1$-2 Quinoxalyl Sulphonamido benzene</td>
<td>165°C</td>
<td>90%</td>
<td>DY</td>
<td>C$<em>{28}$H$</em>{21}$N$_4$O$_2$Cl</td>
<td>13.35</td>
<td>13.63</td>
<td>0.8752</td>
<td></td>
</tr>
</tbody>
</table>

** The RF value for all on silica gel – G plates (thickness 0.5 mm) with developer as benzene / ethanol (3:1).**

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2. Preparation 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° 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 vigorously, precipitate separated out, filtered, dried and recrystallizes from ethanol giving shining coloured needes of 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- sulphonyanilino benzene-3-phenyl fluorooazo indole

A light yellow crystalline yellow powder, M.P. 172°C, yield 65%, molecular formula C_{26}H_{36}FN_{4}SO_{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 (ν_{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 (C-H), 3300 (N-H), 1445 (N=N), 1150 (SO), 3280 (NH), 1 NMR (CDCl3) δ in ppm: 5.9 (b, NH, NH), 7.75-6.40 (m, 16H, Ar-H), 11.5 (b, 2H, SO_{2}NH2).

(ii) Synthesis of 2- phenyl -5- benzene sulphonamido- 3- phenyl chloroaizooindole.

A light yellow crystalline powder, mp 170-172°C. Yields 69% molecular formula C_{26}H_{36}ClN_{4}SO_{2}, (468.96). 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 (ν_{max}) 277. IR (KBr) ν_{max} cm^{-1} 670 (C=4-CI), 4 (2, 3 dimethyl 1-pyridyl sulphonoamidobenzene azo)-4-(2-sulphonamido benzene) indole (+). M.T.*, M. Tuberculosis H37 Rv, (+) positive.

Anti fertility activity

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

Anti Tuberculosis Activity

Table : 2- ANTI TUBERCULOSIS ACTIVITY DATA OF SYNTHESIZED COMPOUNDS

<table>
<thead>
<tr>
<th>S.No</th>
<th>Name of compound M.T.*</th>
<th>Anti fertility % inhibition</th>
<th>Anti Tuberculosis Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-phenyl-3-(N'-2 thiazolyl sulphonamidobenzeno azo) indole (+)</td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td>2</td>
<td>2- phenyl-3- (4- chloro phenylazo)-4chloro indole (+)</td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td>3</td>
<td>2-phenyl-3-(2- sulphonamidobenzene azo) 4-methyl indole (+)</td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td>4</td>
<td>2-phenyl-3-(N'-2 acetyl sulphonamidobenzene azo) 4-(2- sulphonamido benzene) indole (+)</td>
<td>96%</td>
<td>96%</td>
</tr>
</tbody>
</table>

Anti Tuberculosis Activity

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

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References