BIOLOGICAL PROPERTIES
BIOLOGICAL ACTIVITY OF MESOIONIC COMPOUNDS

Mesoionic compounds in general, possess structural features which have been of considerable interest to medicinal chemists. A wide spectrum of biological activity has been claimed for a variety of type A mesoionic compounds. Their potential value as biological active substances can be explained by their dipolar structures.

The common structural feature found in these compounds is an oppositely charged four atom dipolar segment which is the hallmark of many pharmacologically active class of drugs\textsuperscript{10}.

\[ N-X-Y-\overline{O} \]

The presence of oppositely charged dipolar segment in mesoionic systems is of tremendous value to the medicinal chemists. It's significance perhaps lies in its ability to electrostatically interact with two complementary partially charged positions on receptor macromolecule, such as a protein helix. The comparatively small size of mesoionic ring, their planar aromatic character, their highly charged yet net neutral electrical character may be the important basis for expecting biological properties. Therefore, they are soluble to a much greater extent in non polar or lipoid solvents. Thus in vivo, the mesoions can cross lipid barrier even though they are internally appreciably ionic, permitting the relatively close approach of all ring atoms to a receptor surface.

Mesoionic compounds have been screened for various biological activities. Main claims for biological activity have been reviewed\textsuperscript{10,6}

Sydnones and sydnone imines have received much attention, in particular as antibacterial, analgesic, anti-inflammatory, anti-malarial and insecticidal agents.

Two sydnone imine derivatives, sydnofen (I) and sydnocarb (II) have undergone clinical trials as antidepressants\textsuperscript{6}.

\begin{align*}
\text{I} & \quad \text{II} \\
\text{C}_6\text{H}_5\text{CH}=\text{CH}-\text{N} & \quad \text{C}_6\text{H}_5\text{CH}=\text{CH}-\text{N} \\
\text{Cl} & \quad \text{NCONHC}_6\text{H}_5
\end{align*}
BIOLOGICAL ACTIVITY OF SYDNONE

Biological properties of sydnones were first studied by Brookes and Walker\textsuperscript{60} in 1957. Since then, a number of studies dealing with the search for physiologically active compounds in sydnone derivatives has much progressed. They screened 3-methyl-4-alkylsydnones as potential amino acid antagonists. Then on various substitutions and heterocyclic systems were introduced in the 3- and 4- positions of sydnone ring, in an effort to find a derivative good enough for clinical practice.

Though a wide range of biological activity is claimed for the sydnone derivatives, none of them have the properties good enough to be of practical use. Hence, the search for a suitable derivative still continues.

It is noteworthy, that products of acid or base hydrolysis of sydnones failed to give the biological activities seen for the intact sydnone, suggesting that it is the ring itself, rather than the in vivo degradation product, which is the active species.

The biological properties have been reviewed by Kier and Roche\textsuperscript{10}, Ollis and Ramsden\textsuperscript{6} and Newton and Ramsden\textsuperscript{61}.

An extensive pharmacological study of a large number of 3-arylsydnones has been carried out by Oehme et al\textsuperscript{17} and they have reported that the 3-aryl sydnones are less toxic than the 3-alkyl sydnones. The 3-alkyl sydnones in general exhibit CNS stimulation type of effect and the 3-aryl sydnones exert CNS depression effect.

The 3-(o-tolyl) and 3-(m-tolyl) sydnones (III) and (IV) were shown to have analgesic effect 1/30th of morphine.

\includegraphics{sydnone structures.png}

Fregly et al\textsuperscript{63} studied the diuretic and hypotensive properties of 3-sec.butylsydnone, 3-tolyl-4-ethylsydnone and 3-isopropylsydnone and found only the 3-butyl-4-ethylsydnone (V) to be most active.
Nyberg and Cheng\textsuperscript{64} tested N-piperonyl sydnone (VI) for antimalarial activity and found it to be active against *Plasmodium berghei* in mice at a dose of 10 mg/kg.

Later, Popoff and Singhal\textsuperscript{65} claimed antimalarial properties for a series of sulphonyl sydnones (VII) but the effect was mild as compared to the piperonylsydnone.

Daeniker and Druey\textsuperscript{66} have reported some antitumor activity for ethylene-bis-sydnone (VIII).

Hill et al.\textsuperscript{67,68} prepared a series of 3-(2-aryl thio) and 4-(methyl thio)sydnones (IX) and treated them for antiinflammatory activity. Several of these compounds were more potent than hydrocortisone and phenylbutazone versus adjuvant arthritis in mice.
A large number of cephalosporin (X) derivatives of sydnones also possess antistreptococcal and antistaphylococcal activity\textsuperscript{69} in vivo.

\[
\text{R'}
\begin{array}{c}
\text{N} \\
\text{\hspace{0.5cm} IN.} \\
\text{\hspace{4cm} CH}_2\text{CONH} \\
\text{\hspace{5.5cm} COONa} \\
\end{array}
\]

\[\text{X}\]

Davis \textit{et. al}\textsuperscript{70}, tested a number of 3-arylsydnones (XI) against leaf rust of wheat and bean, of fungus diseases. They noticed that chlorine at any position usually imparts biological activity to some extent.

\[
\text{Cl}
\begin{array}{c}
\text{N} \\
\text{\hspace{0.7cm} O} \\
\text{\hspace{2cm} N} \\
\text{\hspace{3.5cm} H} \\
\end{array}
\]

\[\text{XI}\]

4-Acetyl-3-phenylsydnone (XII) has shown modest hypotensive activity\textsuperscript{38}.

\[
\text{R}
\begin{array}{c}
\text{N} \\
\text{\hspace{0.5cm} O} \\
\text{\hspace{1cm} COCH}_3 \\
\end{array}
\]

\[\text{XII}\]

\textit{In view of these observation, successful attempts have been made in this laboratory, to prepare a large number of sydnone derivatives with the incorporation of biologically important heterocyclic moieties. The pharmacological activities exhibited by these compounds have been tabulated} (Table I)

Though many of these compounds showed promising activity at the preliminary testing, none of these exhibited sufficient activity for further evaluation.

Some of these sydnone derivatives were subjected to the Primary Herbicide Screening by Du Pont Agricultural Products, U. S. A. and antitubercular screening by TAACF, Birmingham, U. S. A.
### BIOLOGICAL PROPERTIES OF SYDNONES

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compound</th>
<th>Biological activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><img src="Image" alt="4-(4'-Thiazolyl)sydnones" /></td>
<td>Antiinflammatory</td>
<td>71</td>
</tr>
<tr>
<td>2.</td>
<td><img src="Image" alt="Phenylhydrazones of 3-(p-acetyl phenyl) sydnones" /></td>
<td>Antibacterial</td>
<td>72</td>
</tr>
<tr>
<td>3.</td>
<td><img src="Image" alt="Sydnone-4-sulfonamides" /></td>
<td>Antibacterial</td>
<td>73</td>
</tr>
<tr>
<td>4.</td>
<td><img src="Image" alt="4-[3-Methyl/aryl-7H-s-triazolo-(3,4-b)(1,4,4)thiadiazin-6-yl]-3-arylsydnones" /></td>
<td>Antibacterial and Antifungal</td>
<td>83</td>
</tr>
<tr>
<td>5.</td>
<td><img src="Image" alt="3-p-(Sulfonamido)phenylsydnones" /></td>
<td>Antibacterial and Antifungal</td>
<td>74</td>
</tr>
<tr>
<td>6.</td>
<td>![3-Aryl-4-<a href="Image">6-imidazo(2,1-b)thiazolysydnones</a></td>
<td>Antiinflammatory and antifungal</td>
<td>75</td>
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<tr>
<td>S. No.</td>
<td>Compound</td>
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<tr>
<td>7.</td>
<td><img src="image" alt="Chemical Structure" /> 3-[α/β(1-Pyrazolyl)phenyl]sydnones</td>
<td>CNS depression</td>
<td>76-77</td>
</tr>
<tr>
<td>8.</td>
<td><img src="image" alt="Chemical Structure" /> 3-[ρ-(5-Aryl-2-pyrazolin-3-yl)]phenylsydnones</td>
<td>Antibacterial and Antifungal</td>
<td>78</td>
</tr>
<tr>
<td>9.</td>
<td><img src="image" alt="Chemical Structure" /> 3-[4-(Alkoxycarbonyl)phenylsydnones</td>
<td>Antibacterial and Antifungal</td>
<td>79</td>
</tr>
<tr>
<td>10.</td>
<td><img src="image" alt="Chemical Structure" /> 4-[2-(Arylioureido)thiazolyl]-3-arylsydnones</td>
<td>Antiinflammatory</td>
<td>80</td>
</tr>
<tr>
<td>11.</td>
<td><img src="image" alt="Chemical Structure" /> 4-(2-Dialkyl/diaiylamino-4-phenyl-5-thiazolylcarbonyl)-3-arylsydnones</td>
<td>Analgesic, antiinflammatory and antibacterial</td>
<td>81</td>
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<tr>
<td>12.</td>
<td><img src="image" alt="Chemical Structure" /> ρ-(N-Substituted-N-phenyl-acetamido)-N-phenylsydnones</td>
<td>Antibacterial</td>
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<tr>
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<td>13.</td>
<td><img src="image1.png" alt="Compound 13" /></td>
<td>Antibacterial and antifungal</td>
<td>59</td>
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<td>14.</td>
<td><img src="image2.png" alt="Compound 14" /></td>
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<td>84</td>
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<td>15.</td>
<td><img src="image3.png" alt="Compound 15" /></td>
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<td>16.</td>
<td><img src="image4.png" alt="Compound 16" /></td>
<td>Antibacterial</td>
<td>86</td>
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<td>17.</td>
<td><img src="image5.png" alt="Compound 17" /></td>
<td>Antibacterial and antifungal</td>
<td>87</td>
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<table>
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<tr>
<td>18.</td>
<td><img src="image1" alt="Chemical Structure" /> 3-Aryl-4-[2-(3'-isatinylidenehydrazino)-4-thiazolyl] sydones</td>
<td>Antibacterial and antifungal</td>
<td>91</td>
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<td>19.</td>
<td><img src="image2" alt="Chemical Structure" /> 3-Aryl-4-[2'-(8''-hydroxy-7''-quinolyl methylamino) thiazol-4'-yl] sydones</td>
<td>Antibacterial and antifungal</td>
<td>92</td>
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<td>20.</td>
<td><img src="image3" alt="Chemical Structure" /> 3-Aryl-4-[2'-(substitutedcoumaryl-8''-methylamino) thiazol-4'-yl] sydones</td>
<td>Antifungal and antibacterial</td>
<td>92</td>
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<td>21.</td>
<td><img src="image4" alt="Chemical Structure" /> 3-Aryl-4-(2'-benzimidazolomercaptoacetyl) sydones</td>
<td>Antifungal and antibacterial</td>
<td>89</td>
</tr>
<tr>
<td>22.</td>
<td><img src="image5" alt="Chemical Structure" /> 3-Aryl-4-[3'-(1'·2'·4'-triazino[5',6'-b] indolo) mercapoacetyl] sydones</td>
<td>Antibacterial and antifungal</td>
<td>90</td>
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<td>Biological activity</td>
<td>Reference</td>
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<td>23.</td>
<td><img src="image1.png" alt="Compound" /></td>
<td>Antibacterial and antifungal</td>
<td>94</td>
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<tr>
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<td>3-Aryl-4-[6'-spiro(cyclohexane-1''',3'') (4H)[2H] thiazolo[3,2-b]-s-tetrazolo)] sydnone</td>
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<td>Azines of 4-acetyl-3-arylsydnones</td>
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<td></td>
<td>(p)-(Oxadiazolylsubstituted)phenyl sydnone</td>
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<tr>
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<td>3-[(p)-(5'-thione-4'-amino-1',2',4'-triazol-3-yl)] phenylsydnone</td>
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<td>27.</td>
<td><img src="image5.png" alt="Compound" /></td>
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<td>93</td>
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<td>3-[(p)-(5'-thione-1',3',4'-oxadiazol-2'-yl)] phenyl sydnone</td>
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<td>28.</td>
<td><img src="image6.png" alt="Compound" /></td>
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<td>Cu (II) complexes of 3-[(p)-(5-un/sub salicylidenehydrazinocarbonyl)]phenylsydnone</td>
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</table>
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