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Review Article

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A Review on Antioxidant Activities of Sydnone Derivatives

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ABSTRACT

Mesoionic compounds are dipolar five or six membered heterocyclic compounds containing both the delocalized negative and the positive charge, for which a totally covalent structure cannot be written and which cannot be represented satisfactorily by any one polar structure. The most important member of mesoionic category of compounds is the sydnone ring system. Sydnones are mesoionic compounds having the 1, 2, 3-oxadiazole skeleton and unique variation in electron density around the ring. These characteristics have encouraged extensive study of the chemical, physical, and biological properties of sydnones, as well as their potential application as antioxidants. This chapter covers synthesis and antioxidant activity of most potent molecules having sydnone ring. Most potent antioxidant molecules are 3-(2-carboxyphenyl) sydnone, 3-(2,4-dimethoxy-5-chlorophenyl) sydnone have IC50(µM) values are 0.11 and 0.16 respectively. Similarly compounds 4-[1-oxo-3-(4-chlorophenyl)-2-propenyl]-3-(4-fluorophenyl) sydnones, 4-[1-oxo-3-(4-N-dimethylphenyl)-2-propenyl]-3-(4-fluorophenylsydnones, 4-[1-oxo-3-(4-N-dimethylphenyl)-2-propenyl]-3-(4-chlorophenyl) sydnones, 4-[1-oxo-3-(4-chlorophenyl)-2-propenyl]-3-(4-chlorophenyl) sydnones are highly potent antioxidant activity with IC50 (µM), values are 4.18, 5.12, 4.15. and 4.26 respectively.

This delivers focus of future research in the development of potent antioxidant sydnone molecules. It will be used to design and development of structurally modified antioxidant sydnone derivatives to explore more potent antioxidant biodynamic molecules.

Keywords: Sydnone; Mesoionic compounds; 1,2,3-oxadiazolium-5-olates.Sydnone antioxidant; Free radical scavengers

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INTRODUCTION

Causes of Oxidation

Oxidants, commonly known as "free radicals," are also introduced through external sources such as exposure to the sun or pollution. Other mediums include stress, and intake of alcoholic beverages, unhealthy foods, and cigarette smoke. A poor diet also aids in the formation of free radicals [1-3].

Mechanism of Oxidants and Antioxidants

Oxidative stress occurs when the production of harmful molecules called free radicals is beyond the protective capability of the antioxidant defenses. Free radicals are chemically active atoms or molecular fragments that have a charge due to an excess or deficient number of electrons. Examples of free radicals are the superoxide anion, hydroxyl radical, and transition metals such as iron, copper and nitric acid [3].

Free radicals containing oxygen, known as Reactive Oxygen Species (ROS), are the most biologically significant free radicals. ROS include the radical's [3] superoxide and hydroxyl radical, plus derivatives of oxygen that do not contain unpaired electrons, such as hydrogen peroxide, singlet oxygen, and hypochlorous acid. Because they have one or more unpaired electrons, free radicals are highly unstable. They scavenge the body to grab or donate electrons, thereby damaging cells, proteins, and DNA (genetic material) [3]. The same oxidative process also causes oils to become rancid, peeled apples to turn brown, and iron to rust. It is impossible for us to avoid damage by free radicals. Antioxidants work by donating an electron to free radicals to convert them to harmless molecules. This protects cells from oxidative damage that leads to aging and various diseases [4]. Therefore, aim of this review based on sydnone molecules possessing free radical scavenging activities are being widely proposed as bases for the development of new approaches for pharmacological regulation of oxidative-antioxidative homeostatic imbalance (Figure 1).

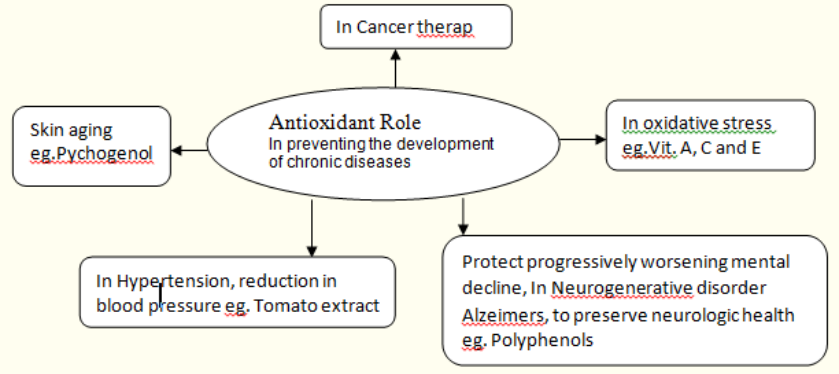
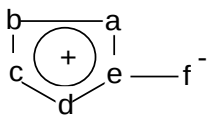


Figure 1. Mechanism of Oxidants and Antioxidants

Mesoionic Compounds

In 1955 Baker, Ollis and Poole described mesoionic compounds as*"a five-membered heterocycle which cannot be represented adequately by any one covalent or polar structure and have a sextet of electrons in union with the five atoms comprising the ring."* In accordance with above description, mesoionic molecules are represented by **i**, in which a, b, c, d, e and f atoms or groups from substituted carbon or heteroatoms.



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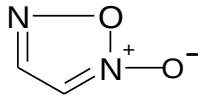

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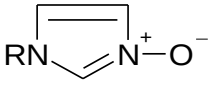

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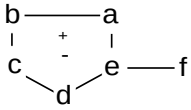

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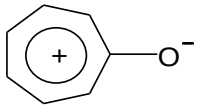

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Five-membered heterocyclic *N*-oxides and related *N*-imines and ylides (compound **ii** and **iii)** are not mesoionic compounds. Mesoionic compounds should be represented by structures of the type **iv**, but this explanation is no longer favored and the symbolism **i** is preferred. The large full circle and the positive sign in structure **i** represents delocalization of the π-electrons of the mesoionic ring in association with a partial positive charge; the exocyclic group f is associated with a corresponding partial negative charge. This polarization of the mesoionic compounds in which the ring tends towards a structure associated with a sextet of electrons led to their description as aromatic and analogy with the structure of troponev have been drawn. The original definition of mesoionic compounds comprised the possibility of six-membered mesoionic compounds but the modified definition is specifically restricted to five-membered heterocycles of type **i** [5].

Mesoionic compounds represent non-benzenoid aromatic heterocycle with various heteroatoms. It may be defined as "a five or six-membered heterocycle which cannot be represented satisfactorily by any one covalent or polar structure and has a sextet of electrons in association with the atoms comprising heterocyclic ring". These are included as subclass of betaines and can be signified by a general structure derived from carbon or hetero atoms. The heterocyclic atoms bear a fractional positive charge which is balanced by a corresponding partial negative charge located on exocyclic atom or group of atoms covalently attached to the ring through a carbon atom [5,6].

A Mesoionic compound represents heterocyclic betaines having well-known range of pharmacological activities and low toxicity [1,5]. Betaines are the five membered heterocycles with an exocyclic heteroatom covalently attached to the ring through a heteroatom and not through the carbon atom. These are neutral compounds and include *N*-oxides, *N*-imides etc.

Baker and Ollis in 1953, formalized some rules in order to consider a molecule as mesoionic as, it must

1) Possess a fully delocalized positive and negative charge.

2) Be planar and have a five-membered heterocyclic ring with an exocyclic atom or group which is capable of bearing negative charge density.

3) Possess substantial resonance energy.

The above characteristics clearly distinguish mesoionic systems from formally related dipolar species such as zwitter ions and ylides. Such species have some degree of charge fixation whereas the mesoionic systems contain delocalized charges. In the structure of sydnone ring, N (2) possesses positive character and C (4) is negative with both nucleophilic and acidic character [7].

Sydnones

Earl and Mackney in 1935, reported that "treatment of N-nitroso-N-phenylglycine (R=H) with acetic anhydride gave a neutral, anhydro derivative to which the bicyclic structure was assigned." It was found to have general utility and thus various analogues of the compound were synthesized as "sydnone".

In mesoionic systems, charge distribution is delocalized, not a single resonance form can be drawn accurately. Sydnones are a group of 1, 2, 3-oxadiazoles that are cyclic in nature (Figure 2) [5,6].

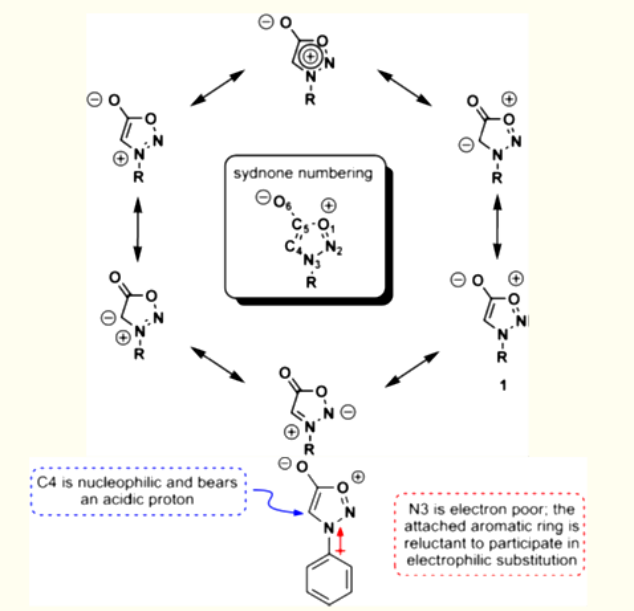
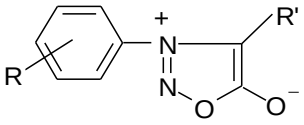


Figure 2. Mesoionic structure of sydnone

Physicochemical Properties and Electronic Structure

Sydnones are unique nitrogenous compounds and chemically 1, 2, 3-oxadiazolium-5-olates (**1**). These are nonbenzenoidheteroatomicmesoionic molecules and can be represented in dipolar canonical formulas [5,6].



Sydnones are pseudo-aromatic heterocyclic compounds, which are dipolar, bearing a unique variation of electron cloud around the ring. These compounds are stable with substantial polarity and are isolated as crystalline solids. Generally, aryl sydnones occur as solid crystals whereas alkyl sydnones appear to be either liquids or solids with low melting point. Sydnones are readily soluble in polar organic solvents but insoluble in water and are stable at room temperature. Wang and co-workers recommended that "Electrons of π bond of sydnones are unequally delocalized". Further study proved that N_2 and N_3 are neutral; C_4, O_1 and O_6 are negatively charged whereas C_5 was positively charged. They also stated that "There occurs little resonance interaction between sydnone ring and N_3 phenyl group" [7] (Figure 3).

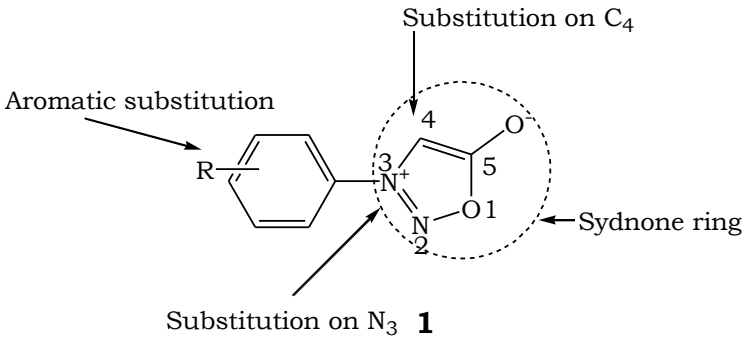


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Figure 3. General structure for sydnone molecule

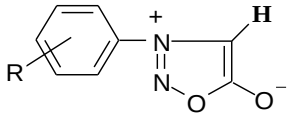
The Nuclear Magnetic Resonance (NMR) spectra showed that, the proton at carbon 4 of sydnone is strongly deshielded and usually shifted at 6.5-7.5 parts per million (ppm) depending on solvent. Infra-red (IR) spectrum shows strong absorption at ~ 1728-1758 cm^{-1} for carbonyl group and absorption near 3148 cm^{-1} for the C-H of C-4 proton.

Syndnoes are found to be an important class of mesoionic compounds with extensive range of biological activities which includes antibacterial, antifungal, anti-inflammatory, antitumour, antiarthritic, anti-pyretic, diuretic, antioxidant, analgesic, hypotensive, anticonvulsant, CNS depressant, anti-tubercular, hypoglycemic, antihemostatic and anthelmintic (ascaricidal) activities. Some sydnones are also commanding dopamine receptor inhibitors, respiratory stimulant, and CNS stimulant. The aim of this chapter is to focus on various syndnone derivatives with their structures and substituents having potent antioxidant activity. It will definitely assist the researchers working in this field to develop new sydnones as potent antioxidants [6].

Antioxidant activity of sydnone molecules

Mallur et al. [8] reported a series of phenyl substituted sydnones have strong DPPH free radicle scavenging activity. Sydnones scavenge DPPH radicle through donating H-atoms at 4^{th} position (Tables 1 and 2).

Table 1. Most potent antioxidant phenyl substituted sydnones with % DPPH scavenging activity



R	% DPPH scavenging activity
3-CH_3	34.93 ± 1.29
2-OCH_3	26.36 ± 0.52
3-OCH_3	28.05 ± 1.78
2-COOH	69.44 ± 1.85
2-NO_2	34.22 ± 1.78
4-NO_2	54.10 ± 3.94
4-Cl	35.90 ± 0.86
2,5-$(OCH_3)_2$	38.8 ± 4.23
2,4-$(OCH_3)_2$, 5-Cl	55.24 ± 0.24

Table 2. Antioxidant activity of phenyl substituted sydnones with % DPPH scavenging activity and $IC_{50\%}$.

R	% DPPH scavenging activity	$IC_{50\%}$ (µM)
2-COOH	69.44 ± 1.85	0.11
4-NO_2	54.10 ± 3.94	0.21
2,4-(-OCH_3), 5-Cl	55.24 ± 0.24	0.16
2,5-(-OCH_3)	38.8 ± 4.23	0.44

Concentrations of the potent compounds required to scavenge 50% DPPH radicle ($IC_{50\%}$) in reaction medium. Values were determined by linear analysis using at least five different concentrations in triplicate and represent mean of the data.

Asma et al. [9] reported series of 1-(3-arylsydnon-4-yl)-3-(5-aryloxy-3-methyl-1-phenyl-1H-pyrazol)-2-propen-1-one derivatives were synthesized by reacting different acetyl sydnone with various pyrazole aldehydes. The structures of the newly synthesized compounds were screened for their antioxidant property. Most potent Compound 1-(3-phenylsydnon-4-yl)-3-(5-phenyl-3-methyl-1-phenyl-1H-pyrazol)-2-propen-1-one having 40.1% radical scavenging activity (DPPH assay) (Figure 4).

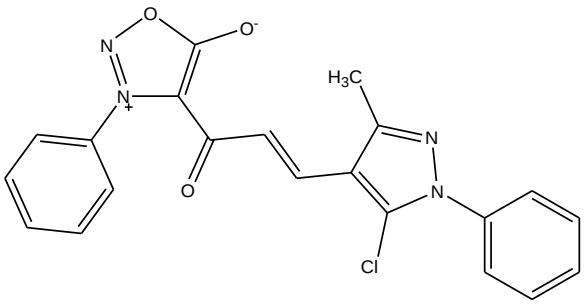


Figure 4. 1-(3-phenylsydnon-4-yl)-3-(5-phenyl-3-methyl-1-phenyl-1H-pyrazol)-2-propen-1-one

Anto et al. [10] reported sydnone substituted Chalcone: some of the substituted chalcones were found to inhibit lipid peroxidation and scavenge superoxides and hydroxyl radicals *in vitro*. Compounds also possess tumor reducing activity (Figure 5).

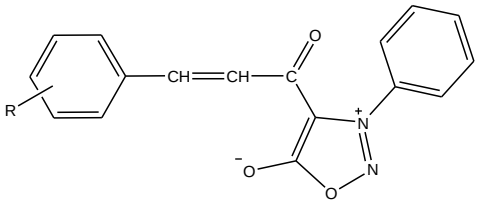


Figure 5. (R=H, 4-Cl, 4-OCH3, 4-NO2, 4-Br, 2,4-Cl, 4-N(CH3)2, 4-F, 4-CH3, 2,4-OCH3, 2-Cl, Furan ring)

Shih MH and Shih et al. [11,12] reported compounds, 4-methyl-2-[(3-arylsydnon-4-yl-methylene)hydrazono]-2,3-dihydro-thiazole-5-carboxylic acid ethyl esters and 4-phenyl-2-[(3-arylsydnon-4-yl-methylene)hydrazono]-2,3-dihydro-thiazoles exhibit the potent DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging activity, comparable to that of vitamin E (Figures 6 and 7).

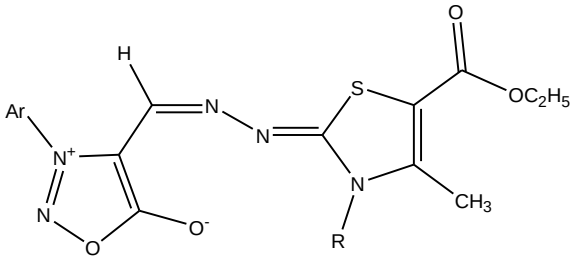


Figure 6. 4-methyl-2- [(3-aryl sydnon-4-yl- methylene) hydrazono]-2, 3-dihydro-thiazole-5-carboxylic acid ethyl esters where Ar= C_6H_5, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *p*-$C_2H_5OC_6H_4$, R=H

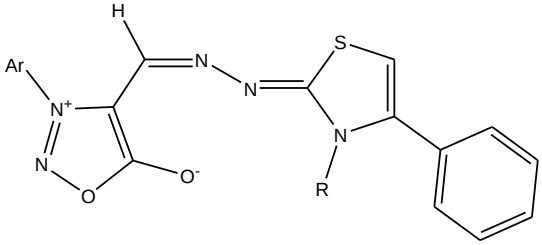
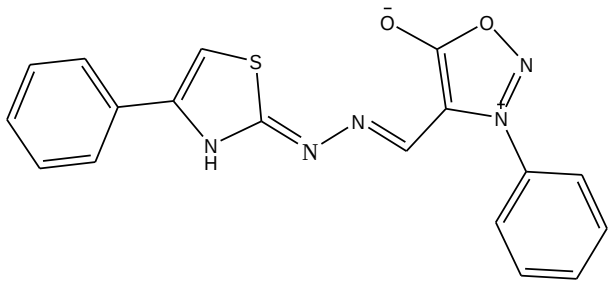


Figure 7. 4-phenyl-2- [(3-aryl sydnon-4-yl-methylene)hydrazono]-2, 3-dihydro-thiazoles where Ar= C_6H_5, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *p*-$C_2H_5OC_6H_4$, R=H

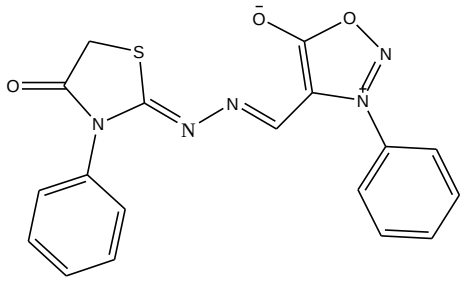
These compounds with 2,3-dihydrothiazole moiety scavenge DPPH radical very fast. Compounds exhibited very good radical scavenging activity 90-98% at a final concentration of 0.1 mM. The profiles of the scavenging effect of compounds on DPPH are comparable to that of vitamin E. Compounds exhibited strong activity, due to the presence of the functional group N-H in the 2,3-dihydrothiazole moiety, which can donate hydrogen atoms. After donating a hydrogen atom, compounds with 2,3-dihydrothiazole moiety exist in radical form, and the electron conjugation effect in the structure stabilizes the radical so that it does not become involved in a destructive biochemical reaction [11,12].

Sydnones substituted at C4 with thiazolidinone and thiazoline rings exhibited a moderate to potent DPPH free radical scavenging activity *in vitro.* Apparently, 2,3-dihydrothiazole ring linked to 3-phenylsydnone yielded powerful and rapid antioxidant compounds (LII) whose scavenging activities were comparable to that of *α-tocopherol*. On the other hand, sydnones bearing 4-oxo-thiazolidine (LIII) were less active. The absence of N-H group rendered the latter to be a weak scavenger [13] (Figures 8 and 9).

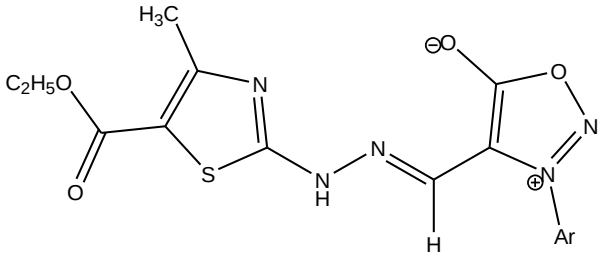


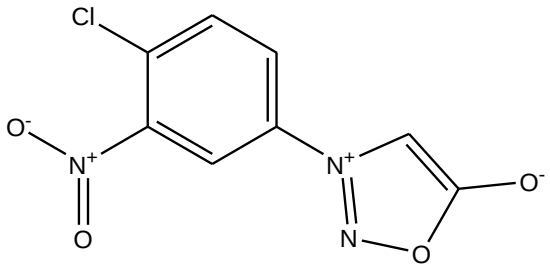
LII

Figure 8. Aromatic ring substituted hydrazinothiazole derivatives where Ar = p-CH3C6H4,p-CH3OC6H4, C6H5, p-ClC6H4, p-CNC6H4, 2-pyridyl, 2-furyl, 2-thiofuryl



LIII





3 -(4-chloro-3-nitrophenyl)sydnone

Figure 9. 3-(4-chloro-3-nitrophenyl)sydnone

Gozzi GJ et al. [14] reported, sydnone SYD-1 (3-[4-chloro-3-nitrophenyl]-1,2,3-oxadiazolium-5-olate] possesses important antitumor activity against Sarcoma 180 and Ehrlich tumors. NADPH oxidation was also inhibited by SYD-1 by approximately 48%. These results show that SYD-1 is able to prevent oxidative stress in isolated mitochondria and suggest that the antitumoral activity of SYD-1 is not mediated by the increasing generation of ROS.

Bhosale et al. [15] reported antioxidant activities of 4-[1-oxo-3-(substituted phenyl)-2-propenyl]-3-substituted phenyl sydnones (chalcones). Following compounds have shown potent antioxidant activity even at very low concentrations as compared to standard propyl gallate and 2-tert-butyl-4-hydroxyanisol (DPPH method) (Figures 10-12 and Tables 3-5).

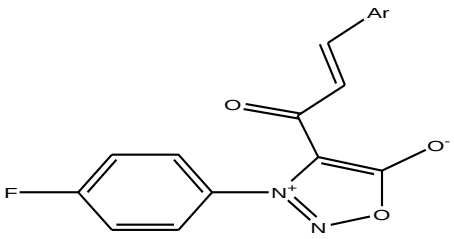


Figure 10. 4-[1-oxo-3-(substitutedphenyl)-2-propenyl]-3-(4-fluorophenyl)sydnones

Table 3. Antioxidant IC_{50} values

Ar	Antioxidant IC_{50} (µM) ± SEM
4-ClC_6H_4	4.18 ± 0.56
4-$N(CH_3)_2C_6H_3$	5.12 ± 1.12
2-Furyl	5.18 ± 0.27
C_6H_5	6.13 ± 0.01
2-OH, 3-quinolinyl	8.23 ± 2.43

$IC_{50,}$ value is the concentration of the sample required to inhibit 50% of radicals

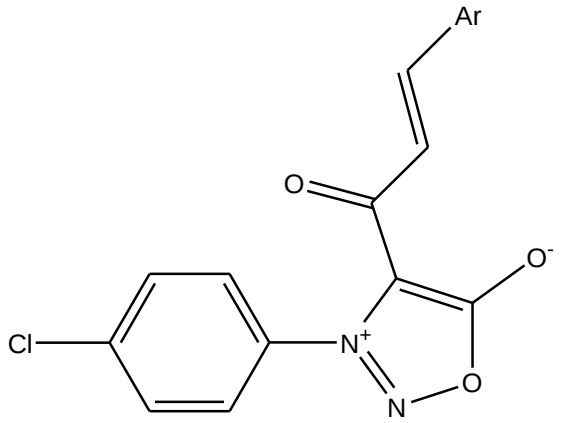


Figure 11. 4-[1-oxo-3-(substituted phenyl)-2-propenyl]-3-(4-chlorophenyl) sydnones

Table 4. Antioxidant IC_{50} values

Ar	Antioxidant IC_{50} (µM) ± SEM
4-$N(CH_3)_2C_6H_3$	04.15 ± 1.82
4-ClC_6H_4	04.26 ± 0.45
2-Furyl	6.18 ± 1.02
C_6H_5	7.43 ± 0.23

$IC_{50,}$ value is the concentration of the sample required to inhibit 50% of radicals

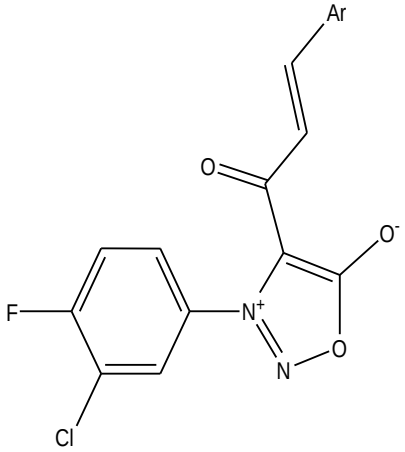


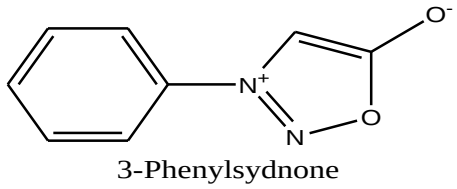
Figure 12. 4-[1-oxo-3-(substituted phenyl)-2-propenyl]-3-(3-chloro, 4-fluorophenyl) sydnones

Table 5. Antioxidant IC_{50} values

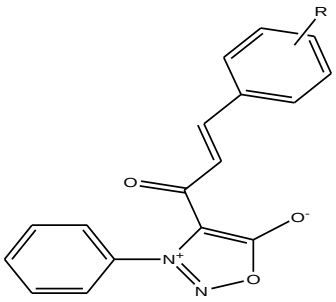
Ar	Antioxidant IC_{50} (µM) ± SEM
4-N(CH_3)C_6H_4	03.17 ± 0.42
4-ClC_6H_4	03.34 ± 0.56
2-Furyl	5.32 ± 0.27
C_6H_5	9.23 ± 1.78

$IC_{50,}$ value is the concentration of the sample required to inhibit 50% of radicals

Narla et al. [16] reported the antioxidant properties of 3-phenylsydnone in various models *in-vitro*. 3-Phenylsydnone scavenged the stable free radical, l, l-diphenyl-2-picrylhydrazyl, and inhibited the degradation of deoxyribose mediated by hydroxyl radicals, although, to a lesser extent than trolox, a water soluble analogue of vitamin E. Many antioxidants possess pro-oxidant properties due to their ability to reduce ferric ions; however, 3-phenylsydnone was free from pro-oxidant properties, and also inhibited the lipid peroxidation induced by iron, in rat brain homogenates (Figure 13a, 13b and Table 6).



3-Phenylsydnone



Figures 13: (a) and (b). Sydnonylchalcones

Table 6. Reduction of stable free radical, 1,1-diphenyl-2-picrylhydrazyl by 3-phenylsydnone

3-Phenylsydnone (µM)	Reduction (% ± s.d.)[a]
5	14.3 ± 0.3
25	39.5 ± 0.7
50	48.8 ± *0.5*
250	90.7 ± 0.9

[a]Reduction of l,l-dipheny1-2-picrylhydrazyl (100 µM) by 3-phenylsydnone was estimated in ethanolic solution at 517 nm. Percent reduction was calculated by comparing test with control and expressed as mean ± s.d. (n=3) (Table 7).

Table 7. Effects of 3-phenylsydnone and trolox on the degradation of deoxyribose mediated by hydroxyl radicals

Drug	Inhibition of TBARS % (±s.d)[a]			
	5 µM	10 µ	50 µM	100 µM
3-Phenylsydnone	0	24.2 ± 0.8	42.3 ± 1.0	64.9 ± 1.1
Trolox	25.4 ± 0.6	65.1 ± 1.0	71.3 ± 1.4	79.8 ± 1.7

TBARS: Thiobarbituric Acid-Reactive Substances. [a]Reaction mixture containing deoxyribose (2.8 mM), KH_2P04^- KOH buffer, pH 7.4 (20 mM), $FeCl_3$, (0.1 mM), EDTA (0.1 mM), H_20_2 (1 mM), ascorbate (0.1 mM) and test compound, in a final volume of 1 mL was incubated at 37°C for 1 hr. The degradation of deoxyribose was estimated as TBARS by measuring absorbance at 532 nm. Percent inhibition was calculated by comparing the amount of TBARS formed in test with control and expressed as mean ± s.d (n=3) (Table 8).

Table 8. Effect of 3-phenylsydnone and trolox on the lipid peroxidation induced by ferrous ions in rat brain homogenates[a]

Drug	**Inhibition of % (± s.d)[a]**		
	5 µM	10 µ	25 µM
3-Phenylsydnone	48.1 ± 1. 1	81.8 ± 0.8	87.5 ± 1.0
Trolox	51.3 ± 0.9	82.7 ± 0.8	84.9 ± 0.7

[a]The lipid peroxidation was stimulated by the addition of ferrous sulphate (100 µM) to a reaction mixture containing test compound, rat brain homogenate (0.5 mL, 10% w/v) and KCI (0.15 M**)** in a final volume of 1.5 mL. The reaction was stopped after 20 min. The amount of lipid peroxidation was measured as thiobarbituric acid reactive substances (TBARS). Percent inhibition was calculated by comparison with control experiments without test compounds and expressed as mean ± s.d (n=3) (Table 9).

Table 9. Effect of 3-phenylsydnone and trolox on the lipid peroxidation induced by ferrous ions in rat brain homogenate[a]

Drug	**Inhibition of % (± s.d)[a]**		
	5 µM	10 µ	25 µM
3-Phenylsydnone	28.4 ± 0.2	33.2 ± 0.4	92.6 ± 1.1
Trolox	22.6 ± 0.2	71.5 ± 0.7	87.8 ± 1.0

[a]The lipid peroxidation was stimulated by the addition of ferric chloride (100 µM). Inhibition was measured as in Table 7.

Thus, 3-phenylsydnone was considered non phenolic antioxidant and the antioxidant properties shown by the antitumour agents, sydnonyl chalcones, may also be due to the sydnone nucleus.

CONCLUSION

This paper discusses the synthesis of sydnones and the evaluation of their *in vitro* antioxidant activities and will be useful to research scholars for design and development of potent antioxidant molecules containing sydnone ring.

Based on phenyl substituted sydnones, molecules shows more potent antioxidant activity when *para* position of phenyl substituted with electron donating groups like $-CH_3$, $-OCH_3$, OC_2H_5, 2,4-(CH_3), 2,4-(OCH_3),5-Cl, -N-(CH_3). In same manner some electron withdrawing functional groups such as 4-NO_2, 4-Cl, 4-F, 4-COOH plays important role for enhancement of antioxidant activity.

Structure activity relationship study of sydnones for antoxidant molecules represents that, in case of chalcone, 3rd position of sydnone, aromatic phenyl ring along with substitution of halogens (-Cl, -F) at para position is more favorable while at 4th position effect of aromatic ring are as in following order (Figure 14).

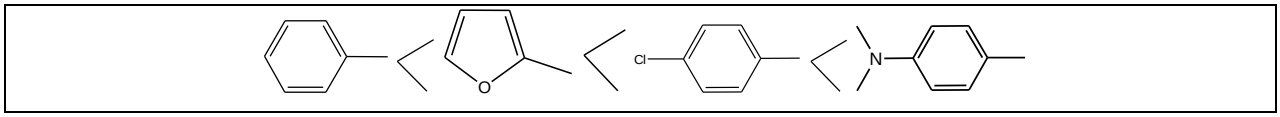


Figure 14. Aromatic phenyl ring along with substitution of halogens

In case of sydnonyl substituted thiazolidinone and thiazoline deriatives for potent antioxidant activity 3rd position of sydnone, *para* position hydrogen atom may be substituted with $-CH_3$, $-OCH_3$, OC_2H_5. Among series of thiazolidinone and thiazoline, 2,3-dihydrothiazole moieties are more stronger due to the presence of the functional group N-H in 2,3-dihydrothiazole ring.

Many sydnone compounds have exhibited better antioxidant activity. Mallur et al. [8] reported free radical scavenging mechanism- "sydnone scavenges DPPH radical through donating H-atom at 4th position and its strong radical activity arises from 1,2,3-oxadiazolium-5-olate ring." This report presents free radical scavenging activity of a series of sydnones, there structure activity relationship and possible mechanism for scavenging free radicals, which might be useful to designing and development of potent antioxidant molecule. Furthermore, different substituents attached to sydnone molecules may influence considerably free radical scavenging, therefore may provide new clues to design and modify sydnone to give better radical scavenging activity for future development as therapeutic agents for disease of oxidative stress origin.

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