Review Article

Biological activities of 1, 2, 3-oxadiazolium-5-olate derivatives

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ABSTRACT

1, 2, 3-oxadiazolium-5-olate (Sydnone) is used as a versatile synthon in heterocyclic synthesis. A large number of sydnone derivatives have been synthesized with biological interest and reported to possess a wide spectrum of biological and pharmacological activities like antimicrobial, anti-inflammatory, analgesic, antipyretic, antitumour, antiarthritic and antioxidant properties. Among all the mesoionic compounds, sydnone ring is the most widely studied because of ease of its synthesis from primary amines and it is the only mesoionic ring which undergoes a wide variety of chemical reactions of synthetic utility. Sydnones form a subclass of mesoionic compounds which again form a subclass of mesomeric betaines. These characteristics of five membered heterocyclic mesoionic compounds have encouraged concentration on the study of chemical, physical and biological properties of sydnones, as well as their potential applications. Thus there is wide scope to explore more novel sydnones as a potent biodynamic molecules.

INTRODUCTION

Mesoionic compounds are distinct type of heterocycles (five and six membered) which belong to the class of nonbenzenoid aromatics. Mesoionics are compounds having both delocalized negative and positive charges, for which a totally covalent structure cannot be drawn and which can exclusively be represented by dipolar canonical formulas. Mesoionic heterocycles contain two or more heteroatoms with an exocyclic heteroatom (oxygen, nitrogen, and sulphur). The formal positive charge is associated with the ring atoms and the formal negative charge is associated with ring atoms or an exocyclic heteroatom (oxygen, nitrogen, and sulphur). The most important member of the mesoionic category of compounds is the sydnone ring system. These characteristics of five membered heterocyclic mesoionic compounds have encouraged highlighting their potential biological activities. Sydnones are mesoionic compounds having the 1,2,3-oxadiazole skeleton bearing an oxygen atom attached to the fifth position.[1, 23] Sydnoneimines are compounds of sydnone having an imino group in place of the exocyclic oxygen atom. [2]

Sydnones of pharmacological interest:

Sydnones, are chemically 1, 2, 3-oxadiazolium-5-olates (I), are unique, nonbenzenoid heteroatomic mesoionic compounds which can exclusively be represented by dipolar canonical formulas. [3]
The most striking potential applications of sydnone are their antioxidant, antimicrobial, anti-inflammatory, analgesic and anti-tumor activities. A large number of sydnone derivatives have been synthesized and reported to possess a wide spectrum of biological and pharmacological activities like antimicrobial, anti-inflammatory, analgesic, anti-pyretic, antitumour, antiarthritic and antioxidant properties. [4, 5, 6, 7, 8, 9, 12, 66]

Anticancer activities

Greco et al., have screened a series of sydnones for anticancer activity and it was found that, 3-(p-methoxybenzyl)sydnone 2 was effective against carcinoma-755 in mice. The same compound was found inactive against sarcoma-180 and leukemia-1210. [10]

A number of polymethylene-bis-sydrones 3 have been synthesized and shown potent antitumor activity. [11] Satyanarayana et al., screened three derivatives (4a, 4b, 4c) for in vitro cytotoxicity in 56 cell lines representing cancers of non-small cell lung, colon, CNS, melanoma, ovarian, prostate, breast and leukemia and all these compounds exhibited promising activity. Average growth inhibition of 50% was in the range of 1.7-3.5 µM. 4a was highly selective against SNB-75 tumor cell line of CNS. [13]

Antioxidant activity

Compounds of the series 3-(substituted phenyl)-1,2,3-oxadiazolium-5-olate have shown potential DPPH radical scavenging activity. Methyl substitution at ortho and meta position of the phenyl ring of sydnone (8a, 8b) improved the radical scavenging activity. Surprisingly, it was observed that methyl substitution at para position (8c) could not improve radical scavenging activity of 3-phenyl sydnone. Similar observations were made for methoxy substitution. Chloro and nitro substitution at para position (8g, 8h) and carboxyl and nitro at ortho position (8i, 8j) showed potent DPPH radical scavenging activity. [9]
N N O

O

H

R

8a R=2-CH 3, 8b R=3-CH 3, 8c R=4-CH 3, 8d R=2-OCH 3, 8 e R=3-OCH 3, 8 f R=4-OCH 3, 8 g R=4-Cl, 8 h R=4-NO 2, 8 i R=2-NO 2, 8 j R=2-COOH

Some compounds of the series 4-[1-oxo- (3-substituted aryl)-2-propenyl]-3-phenylsydnones 4 and 3-[4-[3-(substituted aryl)-1-oxo-2- propenyl] phenyl] sydnones 5, were found to inhibit lipid peroxidation and scavenged superoxides and hydroxyl radicals in vitro. The heterocyclic substituted sydnone derivatives that possess 4-oxo-thiazolidine 9 and thiazoline 9a, 9b groups were prepared by Shih and Ying. [16] Among these compounds, 4-methyl-2- [(3-arylsydnon-4-yl- methylene) hydrazone]-2, 3-dihydro-thiazole-5-carboxylic acid ethyl ester 9a and 4-phenyl-2- [(3-arylsydnon-4-yl-methylene) hydrazone]-2, 3-dihydro-thiazoles 9b exhibited the potent DPPH (1, 1-diphenyl-2-picrylhydrazyl) radical scavenging activity, comparable to that of vitamin E. The antioxidant activity of sydnones may have been attributed to various mechanisms, among which are prevention of chain initiation, binding of transition metal ion catalyst, decomposition of peroxides, prevention of continued hydrogen abstraction, reductive capacity and radical scavenging.

**Antihypertensive and antianginal activity:** Sydnone imine compounds showed antihypertensive and antianginal activity. [17] 3-aminosydnoneimine compounds showed reduction in pulmonary systemic blood pressure. [18] Some azodyestuffs containing a sydnone ring were prepared by the diazonium coupling of 3-(para/meta-aminophenyl)sydnones with phenol or 1-naphthol/2-naphthol possesses a significant response of coronary dilation and inhibition of collagen induced platelet aggregation. [19] Molsidomine, N-(ethoxycarbonyl)-3-(4-morpholinyl)-sydnone imine is mesoionic sydnone imine an orally active, long acting vasodilator drug. [20]

**Diuretic and hypotensive properties:** Diuretic and hypotensive properties of 3-sec-butylsydnone 10, 3-butyl-4-ethylsydnone 10a and 3-iso-propyl-4-sodium carboxylate sydnone 11 were studied by Fregly et al. With comparable doses, 10a was the most active with respect to urinary output. [21, 22]

Antimicrobial activity:
3-[4-(azidocarbonyl)] phenylsydnone 12 obtained from 3-(4-hydrazinocarbonyl) phenylsydnone on Curtius rearrangement with alcohols, water and amines afforded the corresponding carbamates, 4,4’-(sydnone-3-yl) diphenyl urea and N-aryl-N’- [4-(sydnon-3-yl)phenyl] ureas (13). Compounds on one-pot ring conversion yielded the 1, 3, 4-oxadiazolin-2-one derivatives 14, which on reaction with N 2H 4 gave the 4-amino-1, 2, 4-triazolin-3-ones 15. All these compounds exhibited moderate antimicrobial activity against *Escherichia coli* (gram-negative), *Micrococcus luteus* (gram-positive) and two fungal strains, *Asperigillus niger* and *Penicillium notatum*. [23-24] Compounds of series 3-[4-(diethylamino) phenyl]-4-(substituted-1-ylsulfonyl) sydnone 16 exhibited moderate activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa*. [25]
Cephanone, 3-(5-methyl-1, 3, 4-thiadiazol-2-ylthiom ethyl)-7-[2-(3-sydnone) acetamido]-3-cephem--4-carboxylic acid sodium salt 17 is a semisynthetic cephalosporin derivative with a broad spectrum antibacterial similar to that of cephalothin. The compound was active in vitro against a variety of gram-positive and gram-negative bacteria. All tested strains of Staphylococcus aureus tested were inhibited by concentrations of 6.2 µg or less of cephanone per ml. [26] In a study undertaken by Hosamani and Badami, 3-[4-(6'-carbethoxy-5'-arylcyclohex-2'-en-1'-one-3'-yl)]

\[
\begin{align*}
16a & \quad X=-O, \\
16b & \quad X=-NH, \\
16c & \quad X=-CH_2, \\
16d & \quad X=-NCH_2CH_3, \\
16e & \quad X=-NC_6H_5, \\
16f & \quad X=-N-C_6H_4-4-OCH_3, \\
16g & \quad X=-N-C_6H_4-2, \\
16h & \quad X=-N-C_6H_4-2, 3-Cl, \\
16i & \quad X=-N-C_6H_4-4-F, \\
16j & \quad X=-N-C_6H_4-2, 6-Cl.
\end{align*}
\]

18a, 19a R=H, R’=H
18b, 19b R=H, R’=CH_3
18c, 19c R=H, R’=OCH_3
18d, 19d R=H, R’=Cl
18e, 19e R=OCH_3, R’=H
18f, 19f R=OCH_3, R’=CH_3
18g, 19g R=OCH_3, R’=OCH_3
18h, 19h R=OCH_3, R’=Cl
18i, 19i R=CH_3, R’=H
18j, 19j R=CH_3, R’=CH_3
18k, 19k R=CH_3, R’=OCH_3
18l, 19l R=CH_3, R’=Cl
18m, 19m R=Cl, R’=H
18n, 19n R=Cl, R’=CH_3
18o, 19o R=Cl, R’=OCH_3
18p, 19p R=Cl, R’=Cl

18 and 4-(1’,2’,4’,5’-tetrahydro-4’-aryldiazolidin-3’-one-6’-yl) arylsydnones 19 were synthesized and tested for
antimicrobial activity. The \( p \)-chloro and \( p \)-methyl derivative in 18 series showed moderate activity against *Bacillus* and *E. coli*. None of the compounds showed antifungal activity against tested organisms. [27]

A number of 3-aryl-4-(\[2\]-aryl-2', 4', 6', 7'-tetrahydro-(1'H)-1', 5'-benzodiazepine-4'-yl) sydnones 20 were synthesized and screened for antibacterial and antifungal activities by Kavali and Badami. Some of the compounds showed better antibacterial and antifungal activities than the reference drugs used in the study. [28]

\[
\begin{align*}
20a & \quad R=H, R'=H, R''=H \\
20b & \quad R=Br, R'=H, R''=H \\
20c & \quad R=Br, R'=H, R''=H \\
20d & \quad R=Cl, R'=H, R''=H \\
20e & \quad R=Br, R'=H, R''=Cl \\
20f & \quad R=OCH\_3, R'=H, R''=H \\
20g & \quad R=H, R'=H, R''=Cl \\
20h & \quad R=H, R'=H, R''=Cl \\
20i & \quad R=H, R'=H, R''=p-Cl \\
20j & \quad R=H, R'=H, R''=p-Cl \\
20k & \quad R=H, R'=H, R''=OCH\_3 \\
20l & \quad R=H, R'=H, R''=OCH\_3 \\
20m & \quad R=H, R'=H, R''=OCH\_3 \\
20n & \quad R=H, R'=H, R''=OCH\_3 \\
20o & \quad R=H, R'=H, R''=OCH\_3 \\
20p & \quad R=H, R'=H, R''=OCH\_3 \\
20q & \quad R=H, R'=H, R''=H \\
20r & \quad R=H, R'=H, R''=Cl \\
20s & \quad R=H, R'=H, R''=Cl \\
20t & \quad R=H, R'=H, R''=Cl \\
20u & \quad R=H, R'=H, R''=Cl \\
20v & \quad R=H, R'=H, R''=Cl \\
20w & \quad R=H, R'=H, R''=Cl \\
20x & \quad R=H, R'=H, R''=Cl \\
20y & \quad R=H, R'=H, R''=Cl \\
20z & \quad R=H, R'=H, R''=Cl \\
\end{align*}
\]

Kalluraya and Vishwanatha synthesized 3-substituted aryl-4-(3-arylaminomethyl-7H-S-triazolo \[3, 4-b\] \[1, 3, 4\] thiadiazin-6-yl)-sydnones 21. Some of the compounds exhibited antifungal activity against *A. niger* and *C. albicans* and antibacterial activity against *S. typhi*, *Klebsiella*, *E. coli*, *S. aureus* and *B. subtilis*. [29]

\[
\begin{align*}
21a & \quad R=H, R'=H \\
21b & \quad R=4-Cl, R'=H \\
21c & \quad R=2-Cl, R'=H \\
21d & \quad R=4-CH\_3, R'=H \\
21e & \quad R=4-OCH\_3, R'=H \\
21f & \quad R=H, R'=CH\_3 \\
21g & \quad R=4-Cl, R'=CH\_3 \\
21h & \quad R=2-Cl, R'=CH\_3 \\
21i & \quad R=4-CH\_3, R'=CH\_3 \\
21j & \quad R=4-OCH\_3, R'=CH\_3 \\
21k & \quad R=H, R'=OCH\_3 \\
21l & \quad R=2-Cl, R'=OCH\_3 \\
21m & \quad R=4-Cl, R'=OCH\_3 \\
21n & \quad R=4-CH\_3, R'=OCH\_3 \\
\end{align*}
\]

A number of sydnone Mannich bases, 1-aminoethyl-3-(substituted)-4-(3-aryl-4-sydnonyldiene)amino-1, 2, 4-triazole-5-thiones 22 were synthesized by Rahiman *et al.*, and some compounds have shown antimicrobial, anti-inflammatory, analgesic and CNS depressant activities. [30]
Mannich base of sydnones, 3-aryl-4-[2'-(1''-methylaminobenzimidazole)-thiazol-4'-yl]sydnones 23 and 1''-3''-bis-{3-aryl-4-[2'-aminomethyl]thiazol-4'-yl]sydnonyl}benzimidazol-2''-thiones 24, have shown antifungal activity against *R. bataticola* and *C. albicans* and methyl substituted compounds showed enhanced antifungal activity. [31]
A number of 3-aryl-4-[3-(1', 2', 4'-triazino-5', 6'-b] indolo) mercaptoacetyl] sydnones 25 were synthesized and tested for antibacterial and antifungal activity by cup plate method against E. coli, P. pyocyanaus and A. niger, R. bataticola respectively by Mallur and Badami. [32] The halogen substituted derivatives of these compounds showed both the activities substantially. In an investigation by Mallur and Badami, [33] 3-aryl-4- [6'-spiro (cyclohexane-1'', 3''-(4'-H)-[2H] thiazolo [3, 2-b]-S-tetrazino] sydnones 26 were synthesized and tested for antibacterial / antifungal activities. Only the halogenated compounds showed antibacterial activity against E. coli and P. pyocyanaus and antifungal activity against A. niger and R. bataticola. A series of 3-aryl-4-[2-(3'-'coumarylidene hydrazino)-4-thiazoly] sydnones 27 reported moderate antibacterial activity at 20 mg concentration against E. coli and inactive against S. aureus for all the synthesized compounds. The methyl and halogen substituted derivatives showed equal activity to that of standard drug against A. niger and C. albicans. [34]

Novel 3-aryl-4-[2-(8''-hydroxy-7''-quinolinylmethylamino)-thiazol- 4'-yl] sydnones 28 and 3-aryl-4-[2-(3''-acetyl-2''-hydroxybenzylamino)-thiazol-4'-yl] sydnones 29 were synthesized as possible antimicrobial agents by Mallur and Badami. [35] The antibacterial testing was carried out by cup-plate method at 20 µg concentration against P. pyocyanaus and E. coli and the antifungal activity against A. niger and Rhizocona bataticola; p-chloro and m-chloro derivatives in both the series showed potent antimicrobial activity. Only p-chloro derivative in the quinolinyl series showed 99% inhibition against Mycobacterium avium at 12.5 µg/ml concentration.
A series of 4-[3-methyl/aryl-7H-S-triazol [3, 4-b] [1, 3, 4] thiadiazin-6-yl]-3-arylsydnones 30 were synthesized and evaluated for antibacterial and antifungal activities by Yelamaggad et al. [36] Some of the compounds showed the antibacterial activity against *S. aureus* and *E. coli* equivalent to standard drug, while no compound showed inhibition against fungi *C. albicans* and *A. niger*. Synthesis of a series of 3-substituted-7- (3-aryl-4-sydnonyl-8H-1, 2, 4-triazin-5-one [3, 4-a] [1, 3, 4] thiadiazines 31 is reported by Kalluraya et al. Some derivatives showed good activity against *S. aureus* and moderate activity against *E. coli*. Sydnone derivatives of chalcone moiety 32 were prepared by Moustafa and Eisa [37] from 3-(3-acetylphenyl) sydnones. These compounds showed moderate antimicrobial activity.

\[
32a \quad Ar= Ph, R=H \\
32b \quad Ar=Ph, R=4-Cl \\
32c \quad Ar=Ph, R=4-CH \\
32d \quad Ar=Ph, R=4-OCH \\
32e \quad Ar=Ph, R=2-Cl \\
32f \quad Ar=Ph, R=2-CH \\
32g \quad AR=Ph, R=3- OCH
\]

Mallur and Badami synthesized a series of 3-aryl-4- (2'-benzimidazolmercaptoacetyl) sydnone (33, R =H, 4-CH\(_3\), 4-Cl, 3-Cl, 2-CH\(_3\)); the halogen substituted derivatives showed potent antibacterial and antifungal activity. [38] Compounds of series, 3-aryl-4-(5-aryl-2-pyrazolin-3-yl) sydnone (34, R = H, OCH\(_3\); R1 = H, OCH\(_3\)) and 3-aryl-4-(5-aryl-3-isoxazolyl) sydnone (35, R = H, OCH\(_3\); R1 = H, OCH\(_3\)) were synthesized and screened for antibacterial, antifungal, anti-inflammatory, analgesic activities and some of the compounds have shown potent activity. [39] Several sydnone derivatives, 4-[[3-aryl) propenyl] phenylsydnones 36 were synthesized and screened for antibacterial, fungicidal and antibacterial activities along with their chalcone intermediates by Pilli et al. [40] All compounds are much more potent against *Gram-negative* bacteria than *Gram-positive* bacteria. The intermediate N-nitroso-N-[4-[3-(2-pyridyl) propenyl-1-oxo] phenyl] glycine 37 was active against *C. albicans*. Several 3-[4'-alkoxyphenyl] (38a, R=Pr, Bu, R\(_1\)=H) and 3-[4'-arylalkoxyphenyl] (38b, R=PhCH\(_3\), 4-ClC\(_6\)H\(_4\)CH\(_2\), 3-MeC\(_6\)H\(_4\)CH\(_2\), R\(_1\)=H) sydnone and their 4-acetyl and 4-bromo derivatives 38c, d R1 = COCH\(_3\), Br) have been synthesized by Dhruv *et al.* and shown moderate antimicrobial activity. [41] The different heteroaromatic rings were developed at the 4-position of the phenyl nucleus of 3-phenylsydnone to give 3-[4-(2, 5-dimethyl[pyrrol-1-ylaminocarbonyl])phenylsydnones39, 3-[4-(5-amino-4-ethoxycarbonyl-3-methylsulfonylpyrazol)-1-ylcarbonyl]-phenylsydnones, 40 and 3-[4-(1, 3, 4-oxadiazol-2-yl)]-phenylsydnones 41 showed moderate antimicrobial activity. [42] Hydrazones 42 and symmetrical azines 43 of 4-acetyl-3-phenylsydnones were prepared and screened for antibacterial and antifungal activities by Shinge *et al.* [43]. In both the series, compounds with halogen substitution on phenyl ring exhibited potent antibacterial activity against *E. coli* and *Pseudomonas pyocyaneous*. Only the methyl substituted analogs in hydrazone series showed potent activity against *A. Niger* and *R. bataticola*. The m-chloro derivative in azine series showed moderate activity against *R. bataticola*. Some 4-(1, 2, 3-thiadiazol-4-yl)-3-arylsydnones (44, R= H, 2-CH\(_3\), 4-Cl) have been synthesized by Patil *et al.* [44] and have shown moderate antibacterial and antihemostatic activity. [44]
Antitubercular activity:
Bismesoionic compounds, 3-[4/3-(2-Sulphido-5H-1,3,4-thiadiazolium-4-carbonyl)phenyl]sydnones \((45a, 45b)\) and 3-[4/3-(5-Methyl-2-sulphido-1,3,4-thiadiazolium-4-carbonyl)phenyl]sydnones \((46a, 46d)\), 3-[4/3-(5-Phenyl-2-sulphido-1,3,4-thiadiazolium-4-carbonyl)phenyl]sydnones \((46b, 46e)\), 3-[4/3-(5-o-Nitrophenyl-2-sulphido-1,3,4-thiadiazolium-4-carbonyl)phenyl]sydnones \((46c, 46f)\) have been synthesized from 3-[4/3-(hydrazinecarbonyl)phenyl] sydnones. Among these only \(45a\) exhibited \textit{in vitro} antitubercular activity and all compounds \(45, 46\) showed potent antimicrobial activity. \[45\] Antitubercular activity possibly due to its lipophilicity and the ability to penetrate into the cell membrane.

Analgesic, anti-inflammatory and antiarthritic agents:
4-[1-oxo-(3-substituted aryl)-2-propenyl]-3-phenyl sydnones \(47\) and 4-[1-oxo-(3-substituted aryl)-2-propenyl]-3-(4-methoxyphenyl) sydnones \(48\) showed significant analgesic, antiarthritic and anti-inflammatory activities. \[46\] Some of the compounds also showed antiarthritic (adjuvant induced arthritis in rats) activities, 3-tertiary amino-4-tertiary amino methyl sydnone derivatives \(49\) and 3-hydrocarbon-4-tertiary amino methyl sydnone \(50\) showed analgesic activity. \[47, 48\] 3-arylthioalkyl-4-optionally substituted sydnones \(51\) showed anti-inflammatory and antibacterial activity. \[49\] 3, 4-disubstituted alkyl sydrones \(52\) also showed anti-inflammatory activity. \[50\]
**48(i) Ar=Ph, Ph, Ph, Ph, Ph, Ph, Ph, Ph, Ph, Ph, 2-furyl, 2-thienyl R=H, 4-CH_3, 4-CH(CH_3)_2, 4-OCH_3, 2, 4-(OCH_3)_2, 4-NHCOCH_3, 4-Br, 4-Cl, 2, 4-Cl_2, 4-F, 4-NO_2, H, H**

**48(ii) Ar=**

**49** R_1 and R_2 = methyl, allyl or pyrrolidino, R_1+R_2= morpholino or piperidino, R_3 and R_2= alkyl (C_1-C_9), allyl or benzyl, R_3 , , R_2= morpholino, piperidino, 4-benzylpiperazino hexamethylenimino, 4-formylpiperazino, hexamethylenipiperolino or pyrrolidino

**50** R_1=Hydrocarbon C_1-C_6 atoms, R_2 and R_3=C_1-C_5 alkyl, C_2-C_5 alkenyl, C_7-C_9=aralkyl, -NR_2R_3= 5-7 membered heterocyclic ring are analgesics of low toxicity in mammals

**51**

R= H, halogens, carboxyl, alkyl, benzyl, phenyl
Alkyl’ and Alk’= lower alkylene
X=Oxygen x=0, 1
Ar= phenyl, naphthyl, phenanthryl, pyridyl, furyl, thiényl

**52**

R1=H, Halogens, lower alkyl or cycloalkyl
R2= Lower alkyl, cycloalkyl or adamantyl
Alk=lower alkylene

Analgesic effect was observed in a number of 3-aminoalkyl sydnones by Bruzzese et al [51], particularly with 3-diethylaminoethyl-4-methylsydnone 53 and 3-morpholinyl ethylsydnone 54. They also noted hypoglycemic
activity for several compounds in the series.

In an extensive study, Satyanarayana and Rao [52] synthesized 4-[5-(substituted aryl)-4, 5-dihydro-1H-pyrazol-3-yl]-3-phenyl sydnones 55 as analgesic, anti-inflammatory and antiarthritic agents. 3-aryl-4-[1’-substituted-2’-H-4’,5’-dihydro-4’-(3,4-methylenedioxyphenyl)-3’-oxo-indazolin-6’-yl] sydnones 56 were synthesized by Kalluraya and Rahman [53] and the compounds with o-chlorobenzoyl moiety showed significant anti-inflammatory and analgesic activity.

56a R= H; R1=H 56b R=CH3; R2=H 56c R = OCH3; R1=H 56d R=H; R3= 56e R=CH3

R=OCH3; R1= 56f R=OCH3; R1= 56g R=H; R1= 56h R=CH3; R1= 56i R=OCH3;

R1= 56j R=H; R1= 56k R=CH3; R1= 56l R = OCH3; R1= 56m R = H; R3= 56n R = CH3; R1= 56o R = OCH3;

R1= 56p R = H; R1= 56q R = CH3; R1= 56r R = OCH3; R1= 56s R = CH3; R1=

57a R= -CH3; R’= H; Ar = C6H5; 57b R = -CH3; R’= H; Ar = -C6H5; 57c R =

R’= H; Ar = -C6H5; 57d R = ; R’= H; Ar = -C6H5; 57e R = -CH3; R’= H; Ar = -C6H5; 57f R= -C6H5

R’= -CH3; Ar = -C6H5; 57g R= ; R’= CH3; Ar = -C6H5; 57h R= ; R’= CH3; Ar = -C6H5; 57i

R= -CH3; R’= OCH3; Ar = -C6H5; 57j R= -CH3; R’= OCH3; Ar = -C6H5; 57k R =

R’= -CH3; Ar = -C6H5; 57l R = ; R’= OCH3; Ar = -C6H5; 57m R = -CH3; R’= H; Ar =

57n R = -C6H5; R’= H; Ar= 57o R = ; R’= H; Ar= 57p R =

R’= H; Ar= 57q R = -CH3; R’= CH3; Ar= 57r R = -CH3; R’= CH3; Ar= 57s R=

=CH3; 57t R = ; R’= CH3; Ar = 57u R = CH3; R’= ; Ar =

=CH3; 57v R = OCH3; R’= ; Ar = -C6H5; 57w R = OCH3; R’= ; Ar =

57x R = OCH3; R’= ; Ar = 57y R = -CH3; R’= OCH3; Ar =
3-substituted-6-(3-arylsydnonyl)-8-aryl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazepines were synthesized and evaluated for analgesic, anti-inflammatory and anthelmintic activities by Kalluraya et al. Some compounds have shown good analgesic and anti-inflammatory activities but excellent anthelmintic activity comparable to standard drug. In the series 3-[4-[(2,3-dihydro-2-(substituted aryl)-1,5-benzothiazepin-4-yl)sydnone, only the phenyl substituted derivatives showed significant anti-inflammatory activity in carrageenan induced rat paw edema model.

Kalluraya et al., synthesized a series of 3-aryl-4-[substituted piperonylidenehydrazino-4-thiazolyl] sydrones and evaluated for biological activities. Most of the compounds showed potent anti-inflammatory activity, but in acetic acid induced test none of the compounds showed significant analgesic activity. In anthelmintic screening against earthworms, the compound bearing nitro and methoxy substituents showed potent activity.

4-(arylsydnonyl)-2-(4-arylhydrazono-3-methyl-5-oxo-2-pyrazolin-1-yl) thiazoles showed significant anti-inflammatory activity comparable with that of standard drug ibuprofen. Compounds containing chlorine and carboxylic substituents are more active. Few showed marked analgesic activity while most of the compounds showed promising CNS depressant activity comparable with that of standard drug pentobarbitone.

Triazolothiadiazines with aryl sydnone at sixth position were synthesized by Kalluraya and Rahiman. Several compounds showed anti-inflammatory activity.

Miscellaneous activities

Compound synthesized with the integration of 1, 2, 4-triazole ring with 1, 2, 4-triazine-5-one, has been developed from 3-arylsydrones and proved antihaemostatic activity. Coumarins (2H-1-benzopyrans) possess a variety of biological activities such as antibacterial, antifungal, antimicrobial, anticancer, antiulcer and antifeedant. It was also found that coumarins display a very strong anti-invasive activity

in vitro against human mammary carcinoma cells. Further biological screening of synthesized compound 3-[(7-Acetoxy-4-methylcoumarin-8-yl)-methyl] sydnone may show related potential activities. Mesocarb is a mesoionic sydnone imine, shown to act as dopamine reuptake inhibitor which is slow in action but longer lasting and less neurotoxic than dextroamphetamine. Mesocarb is still used for a variety of applications; which include
counteracting the sedative effects of benzodiazepine drugs, increasing workload capacity and cardiovascular function, treatment of hyperactivity in children as a nootropic, and as a drug to enhance resistance to extremely cold temperature. It is also listed as having antidepressant and anticovulsant properties. A number of 3-substituted sydnones 63, viz, 3-aryl compounds showed ascaricidal activity. [62]

\[
\begin{align*}
63a & \quad R = H, R' = H \\
63b & \quad R = 2-Cl, R' = H \\
63c & \quad R = 3-Cl, R' = H \\
63d & \quad R = 4-Cl, R' = H \\
63e & \quad R = 2, 4-Cl_2, R' = H \\
63f & \quad R = 3, 4-Cl_2, R' = H \\
63g & \quad R = 4-Br, R' = H \\
63h & \quad R = 4-NO_2, R' = H \\
63i & \quad R = 4-CH_3, R' = H \\
63j & \quad R = 4-OCH_3, R' = H \\
63k & \quad R = 2-C_6H_5, R' = H \\
63l & \quad R = 2, 4-C_6H_5, R' = H \\
63m & \quad R = 2-C_6H_5, R' = CH_3 \\
63n & \quad R = 2-C_6H_5, R' = NO_2 \\
63o & \quad R = 2-C_6H_5, R' = Cl \\
63p & \quad R = 2-C_6H_5, R' = Br \\
63q & \quad R = 2-C_6H_5, R' = H \\
63r & \quad R = 2-C_6H_5, R' = CH_3 \\
63s & \quad R = 2-C_6H_5, R' = NO_2 \\
63t & \quad R = 2-C_6H_5, R' = Cl \\
63u & \quad R = 2-C_6H_5, R' = Br \\
63v & \quad R = 2-C_6H_5, R' = H \\
63w & \quad R = 2-C_6H_5, R' = CH_3 \\
63x & \quad R = 2-C_6H_5, R' = NO_2 \\
63y & \quad R = 2-C_6H_5, R' = Cl \\
63z & \quad R = 2-C_6H_5, R' = Br \\
63aa & \quad R = 2-C_6H_5, R' = H \\
63ab & \quad R = 2-C_6H_5, R' = CH_3 \\
63ac & \quad R = 2-C_6H_5, R' = NO_2 \\
63ad & \quad R = 2-C_6H_5, R' = Cl \\
63ae & \quad R = 2-C_6H_5, R' = Br \\
63af & \quad R = 2-C_6H_5, R' = H \\
63ag & \quad R = 2-C_6H_5, R' = CH_3 \\
63ah & \quad R = 2-C_6H_5, R' = NO_2 \\
63ai & \quad R = 2-C_6H_5, R' = Cl \\
63aj & \quad R = 2-C_6H_5, R' = Br \\
63ak & \quad R = 2-C_6H_5, R' = H \\
63al & \quad R = 2-C_6H_5, R' = CH_3 \\
63am & \quad R = 2-C_6H_5, R' = NO_2 \\
63an & \quad R = 2-C_6H_5, R' = Cl \\
63ao & \quad R = 2-C_6H_5, R' = Br \\
63ap & \quad R = 2-C_6H_5, R' = H \\
63aq & \quad R = 2-C_6H_5, R' = CH_3 \\
63ar & \quad R = 2-C_6H_5, R' = NO_2 \\
63as & \quad R = 2-C_6H_5, R' = Cl \\
63at & \quad R = 2-C_6H_5, R' = Br \\
63au & \quad R = 2-C_6H_5, R' = H \\
63av & \quad R = 2-C_6H_5, R' = CH_3 \\
63aw & \quad R = 2-C_6H_5, R' = NO_2 \\
63ax & \quad R = 2-C_6H_5, R' = Cl \\
63ay & \quad R = 2-C_6H_5, R' = Br \\
63az & \quad R = 2-C_6H_5, R' = H \\
63aa & \quad R = 2-C_6H_5, R' = CH_3 \\
63ab & \quad R = 2-C_6H_5, R' = NO_2 \\
63ac & \quad R = 2-C_6H_5, R' = Cl \\
63ad & \quad R = 2-C_6H_5, R' = Br \\
63ae & \quad R = 2-C_6H_5, R' = H \\
63af & \quad R = 2-C_6H_5, R' = CH_3 \\
63ag & \quad R = 2-C_6H_5, R' = NO_2 \\
63ah & \quad R = 2-C_6H_5, R' = Cl \\
63ai & \quad R = 2-C_6H_5, R' = Br \\
63aj & \quad R = 2-C_6H_5, R' = H \\
63ak & \quad R = 2-C_6H_5, R' = CH_3 \\
63al & \quad R = 2-C_6H_5, R' = NO_2 \\
63am & \quad R = 2-C_6H_5, R' = Cl \\
63an & \quad R = 2-C_6H_5, R' = Br \\
63ao & \quad R = 2-C_6H_5, R' = H \\
63ap & \quad R = 2-C_6H_5, R' = CH_3 \\
63aq & \quad R = 2-C_6H_5, R' = NO_2 \\
63ar & \quad R = 2-C_6H_5, R' = Cl \\
63as & \quad R = 2-C_6H_5, R' = Br \\
63at & \quad R = 2-C_6H_5, R' = H \\
63au & \quad R = 2-C_6H_5, R' = CH_3 \\
63av & \quad R = 2-C_6H_5, R' = NO_2 \\
63aw & \quad R = 2-C_6H_5, R' = Cl \\
63ax & \quad R = 2-C_6H_5, R' = Br \\
63ay & \quad R = 2-C_6H_5, R' = H \\
63az & \quad R = 2-C_6H_5, R' = CH_3 \\
63aa & \quad R = 2-C_6H_5, R' = NO_2 \\
63ab & \quad R = 2-C_6H_5, R' = Cl \\
63ac & \quad R = 2-C_6H_5, R' = Br \\
63ad & \quad R = 2-C_6H_5, R' = H \\
63ae & \quad R = 2-C_6H_5, R' = CH_3 \\
63af & \quad R = 2-C_6H_5, R' = NO_2 \\
63ag & \quad R = 2-C_6H_5, R' = Cl \\
63ah & \quad R = 2-C_6H_5, R' = Br \\
63ai & \quad R = 2-C_6H_5, R' = H \\
63aj & \quad R = 2-C_6H_5, R' = CH_3 \\
63ak & \quad R = 2-C_6H_5, R' = NO_2 \\
63al & \quad R = 2-C_6H_5, R' = Cl \\
63am & \quad R = 2-C_6H_5, R' = Br \\
63an & \quad R = 2-C_6H_5, R' = H \\n
Some sydnone imines were found to be useful for the treatment and prophylaxis of cardiovascular diseases such as angina pectoris and hypertension.[63] A number of 3-alkyl sydnones were found to be potent CNS stimulants by Kier et al.[64] The 3-sec-butylsydnone 64 was found to be a powerful respiratory stimulant in a heavily barbitalised dog.

**Recent medicinal uses of sydnone derivatives**

Reactions of ortho-alkynylphenyl sydnones 65 with various acids result in sydnoquinoline derivatives 66. Treatment of o-alkynylphenylsydnones with trifluoroacetic acid provides novel 3-arylcinnolines 67. [65]

Indole derivatives were reported for antimicrobial, insecticidal and anthelmintic activities. Compound 68 displayed significant biological spectrum. Derivatives of structure 69 may be used as dopamine receptor inhibitors. [66]
Wallace et al described the reaction of a phenyl sydnone 1, 3-dipole with a bicyclononyne dipolarophile. This strain-promoted reaction proceeds without transition metal catalysis in aqueous buffer, at physiological temperature and pressure with a rate comparable to that of other bioorthogonal reactions. They also demonstrate the quantitative and specific labelling of a genetically encoded bicyclononyne with a sydnone fluorophore conjugate 70, demonstrating the utility of this approach for bioorthogonal protein labelling.[67] Compound 71 and 72 showed highest activity against S. aureus, B. subtilis, P. aeruginosa and E. coli. Both compounds have phenyl group at 2nd position and methyl group at 4th position. [68]

Amide benzotriazole derivatives synthesized from sydnone fragment were reported to display good antitubercular activities. Amino benzotriazole 73 was manifested to be a potent antitubercular agent with better inhibition (MIC=4.5 µg/mL) against M. tuberculosis than standard drugs streptomycin (MIC=7.5 µg/mL) and pyrazinamide (MIC=10 µg/mL). [69]

A series of 4-aryl-2-[3-arylsydnone-4-hydrazono-] thiazoles 74 compounds were screened for their antibacterial and antifungal studies. Compounds containing chloro and nitro groups showed promising activity. Quinazoline derivatives condensed with sydnone have been synthesized and evaluated for their antimicrobial activity. Compound 75 possessing nitro group at 4th position of phenyl ring at vinyl linkage are found to posses the highest activity against S. aureus, B. subtilis, E. coli and P. aeruginosa. [70] Compounds 76 containing coumarinyl sydnone derivatives from 4-methyl-7-hydroxy-8-nitro coumarin were synthesized. The antimicrobial evaluation of the compounds showed that some of them revealed promising broad spectrum antimicrobial activity with respect to standard drug Ampicillin. [71]
A series of benzophenone oximes appended with sydnone bearing different substituents on aroyl moiety were synthesized to evaluate in vivo and in vitro for their inhibitory activity against purified phospholipase A2 (PLA2) enzymes from snake venom and human inflammatory pleural and ascites fluid. In vivo and in vitro inhibition studies were carried out against PLA2. The substituent at the aroyl ring was responsible for enhancing the inhibition towards PLA2 enzymes. The most active interacting compound 77 from in vitro inhibition of PLA2 activity showed similar potency in the in vivo neutralization of PLA2 induced mouse paw edema and hemolytic activity. Thus, the in vitro inhibition correlated well with the in vivo inhibition and hence the reported derivatives are therapeutically important anti-inflammatory drugs. A series of novel stilbene-sydnone derivatives were synthesized from methyl anthranilate via glycine- and nitrosoglycine derivatives the corresponding 3-(o-carbomethoxy phenyl)-4-H/Me/Ph-sydnone were prepared and transformed to stilbenysydnone derivatives (by Witting reaction with various phosphonium salts) and evaluated for their cytotoxic properties on five cancer cell lines, whereby the cis-4-methyl-3-[2-(4-methylphenyl) ethenyl] phenyl] sydnone 78 and cis-4-phenyl-3-[2-(4-chlorophenyl) ethenyl]-phenyl] sydnone 79 showed the most pronounced activity. Several 2-[(4-Substituted-1-sulphonyl) Sydnon-3-yl]-1, 3, 4-thiadiazino (6, 5-b) indoles have shown antimicrobial and antihelmintic activity.

CONCLUSION

This review shows that sydnone are highly versatile and robust members of the mesoionic class of hetero aromatic compounds. They possess an array of remarkable chemical and physicochemical properties, as well as a variety of biological activities. Due to the large variety of structures that have been tested so far it is difficult to establish SAR. Maximum structural modification takes at N-3 and C-4. The most explored properties of sydnone are antitumour, antimicrobial, antioxidant, antiinflammatory-analgesic activities. In this area, the presence of substituents (aromatic/alliphatic/heterocyclic) especially at N-3 and C-4 has proven to adopt an essential role on the molecules efficiency. Different substituents and their positions on phenyl ring differently influence DPPH activity and therefore, may provide clues to design and develop better free radical scavenging sydnone with multiple activities and same pattern can be applied for a series of different compounds with different biological activities. With respect to their functionalisation, modern techniques such as metal catalysed cross-coupling and direct arylation processes have been found to be directly applicable to these unusual compounds like they are to the more common heteroaromatic substrates. The cycloaddition of alkene and alkynes with sydnones consistently gives pyrazole products. To conclude, some of the ascertained properties of sydnone are fairly promising and deserve further investigation in the attempt of finding new therapeutic alternatives.

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