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

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ABSTRACT

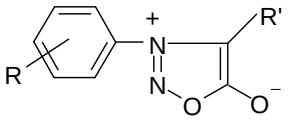
1, 2, 3-oxadiazolium-5-olate (Sydnone) is used as a versatile synthon in heterocyclic synthesis. A large number of sydnone derivatives have been synthesized with biological interest and reported to possess a wide spectrum of biological and pharmacological activities like antimicrobial, anti-inflammatory, analgesic, anti-pyretic, 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 (**1**), are unique, nonbenzenoid heteroatomic mesoionic compounds which can exclusively be represented by dipolar canonical formulas. [3]



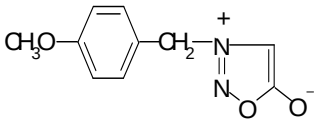
1

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]



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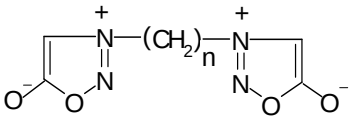

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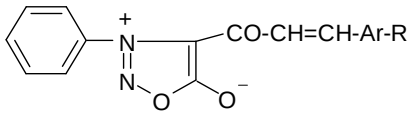
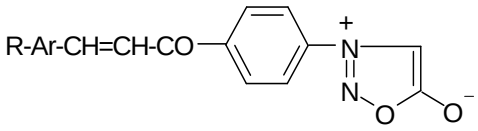


4

4a *Ar= Ph, R=4-CH_3*
4b *Ar= Ph, R=3-OCH_3, 4-OH,*
4c *Ar= Ph, R=4-CF_3*

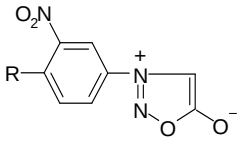
A number of polymethylene-bis-sydnones **3** have been synthesized and shown potent antitumor activity. [11] Satyanarayana *et al*., screened three derivatives (**4a, 4b, 4c**) for *in vitro* cytotoxicity in 56 cell lines representing cancers of non-small cell lung, colon, CNS, melanoma, ovarian, prostate, 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]



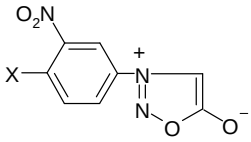
5

5a *Ar=Ph, R= H,* ***5b*** *Ar=Ph, R=4-CH_3,* ***5c*** *Ar=Ph, R=4-OCH_3,* ***5d*** *Ar=PH, R=2,4-$(OCH_3)_2$,* ***5g*** *Ar=Ph, R=3-Cl,* ***5h*** *Ar=Ph, R=2-Cl* ***5e*** *Ar=Ph, R=4-$NHCOCH_3$,* ***5f*** *Ar=Ph, R=4-Cl,* ***5g*** *Ar=Ph, R=3-Cl,* ***5h*** *Ar=Ph, R=2-Cl*

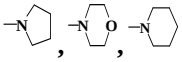
A series of N- (4'-substituted-3'-nitrophenyl) sydnone with potential antitumor activity was prepared based on active analogues. 4'-fluoro derivative (**6**, R=F) has an improved activity against all three cell lines MCF7 (Breast), NCI-H460 (Lung) and SF-268 (CNS). [14] The effects of new aryl-sydnones, 3-[4-X-3-nitrophenyl]-1,2,3-oxadiazolium-5-olates **(7a, 7b, 7c, 7d)** on the survival of mice bearing Sarcoma 180, Ehrlich carcinoma, B10MCII (Fibrous histiocytoma) and L1210 leukemia ascitic tumors, on proliferation of cultured tumor cells and on synthesis of DNA in L1210 leukemia were determined by Grynberg *et al* [15]. **7a** and **7b** *in-vivo* significantly enhanced the survival of S180, Ehrlich and B10MCII tumor-bearing mice. Furthermore, **7b** showed significant activity against L1210. **7c** and **7d** did not show antitumor activity. **7a** *in vitro* was the most cytotoxic and **7d** being the least active against all the above tumor cells. All screened derivatives inhibited thymidine uptake by L1210 cells. [15]



6 (R=F)

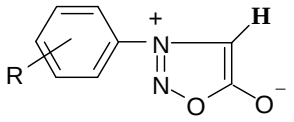


7a, 7b, 7c, 7d

X= Cl, 

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]

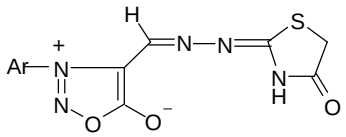


8a *R=2-CH_3,* ***8b*** *R=3-CH_3,* ***8c*** *R=4-CH_3,* ***8d*** *R=2-OCH_3,* ***8e*** *R=3-OCH_3,* ***8 f*** *R=4-OCH_3,* ***8g*** *R=4-Cl,* ***8h*** *R=4-NO_2,* ***8i*** *R=2-NO_2,* ***8j*** *R=2-COOH*

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) hydrazono]-2, 3-dihydro-thiazole-5-carboxylic acid ethyl ester **9a** and 4-phenyl-2- [(3-arylsydnon-4-yl-methylene) hydrazono]-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-(ethoxy carbonyl)-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]



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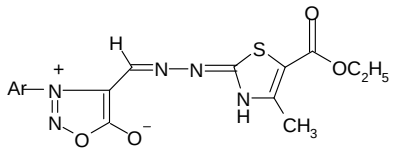
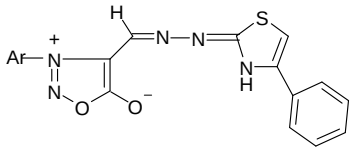
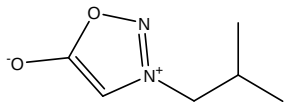


9a



9b



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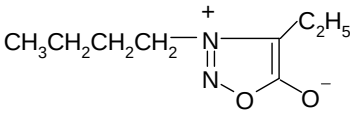
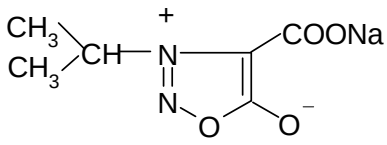
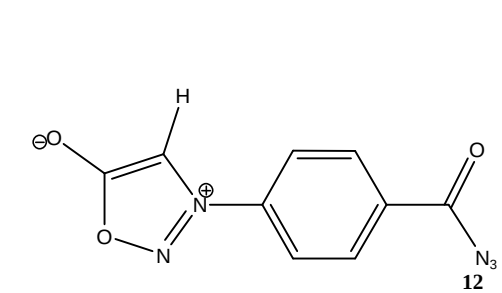


10a

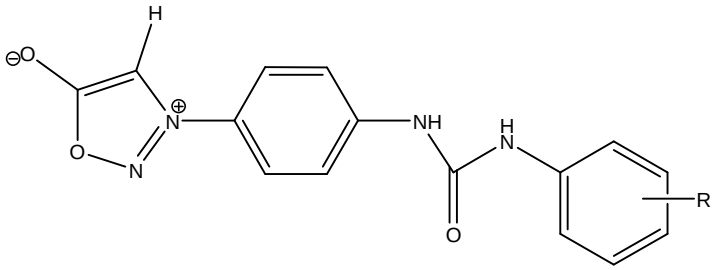


11

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]



12



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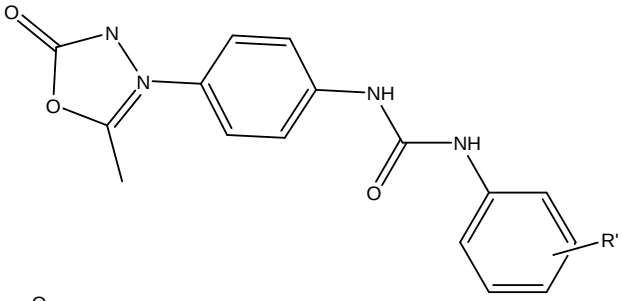
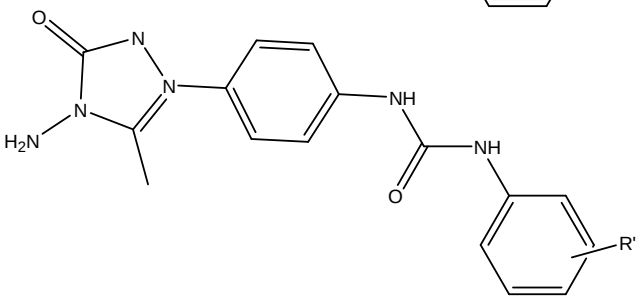
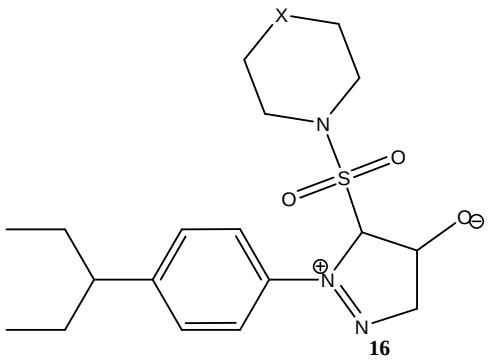


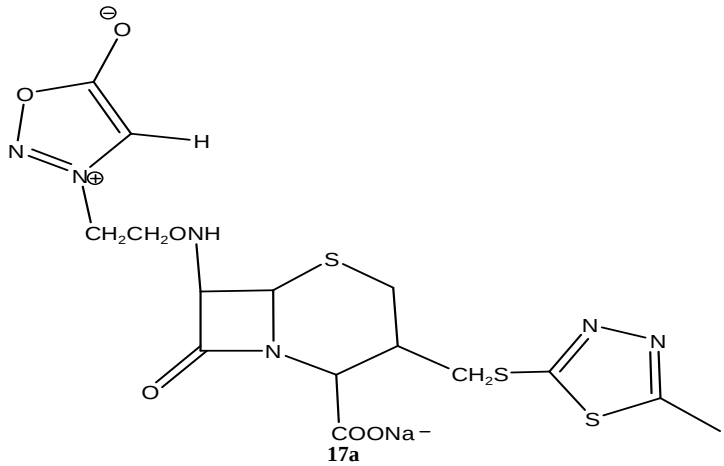


14

15



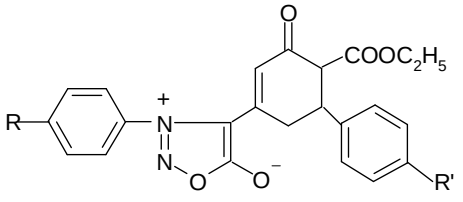
16



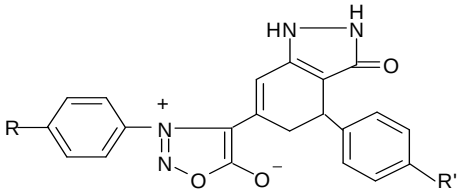
17a

16a *X=-O,* ***16b*** *X=-NH,* ***16c*** *X= -CH_2,* ***16d*** *X=-NCH_3* ***16e*** *X=-NCH_2CH_3* ***16f*** *X=-NC_6H_5* ***16g*** *X= -N-C_6H_4-4-OCH_3* ***16h X****= -N-C_6H_3-2, 3-Cl* ***16i X****=-N-C_6H_4-4-F* ***16j X****=-N-C_6H_3-2, 6-Cl*

Cephanone, 3-(5-methyl-1, 3, 4-thiadiazol-2-ylthio methyl)-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)] **18** and 4-(1',2',4',5'-tetrahydro-4'-arylindazolin -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]



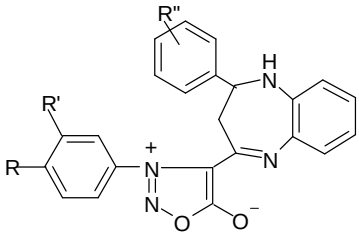
18



19

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*

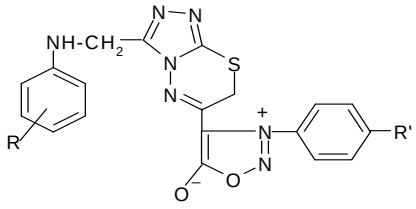
A number of 3-aryl-4-[2'-aryl-2', 4', 6', 7'-tetrahydro-(1'H)-1', 5'-benzodiazepine-4'-yl] sydnones **20** were synthesized and screened for antibacterial and antifungal activities by Kavali and Badami. Some of the compounds showed better antibacterial and antifungal activities than the reference drugs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



20

20a *R=H, R'=H, R''=H* ***20b*** *R=Br, R'=H, R''=H* ***20c****R=CH_3, R'=H, R''=H* ***20d****R=Cl, R'=H, R''=H* ***20e****R=CH_3, R'=H, R''=o-Cl* ***20f*** *R= OCH_3, R'=H, R''= H* ***20g*** *R=H, R'=H, R''=o-Cl* ***20h*** *R=H, R'=H, R''=p-Cl* ***20i*** *R=H, R'=H, R''=p-OCH_3* ***20j*** *R=H, R'=H, R''=p-NO_2* ***20k*** *R=CH_3 R'=H, R''=p-CH_3* ***20l*** *R= OCH_3, R'=H, R''=o-NO_2* ***20m*** *R=CH_3, R'=H, R''=p-Cl* ***20n*** *R=CH_3, R'=H, R''=o-NO_2* ***20o*** *R=Br, R'=H, R''=p-Cl* ***20p*** *R=Cl, R'=H, R''=p-CH_3* ***20q*** *R=Cl, R'=H, R''=o-Cl* ***20r*** *R=Cl, R'=H, R''=p-NO_2* ***20t*** *R=OCH_3, R'=H, R''=o-Cl*

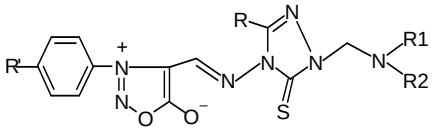
Kalluraya and Vishwanatha synthesized 3-substituted aryl-4-(3-arylaminomethyl-7H-S-triazolo [3, 4-b] [1, 3, 4] thiadiazin-6-yl)-sydnones **21**. Some of the compounds exhibited antifungal activity against *A. niger* and *C. albicans* and antibacterial activity against *S. typhi*, *Klebsiella*, *E. coli*,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



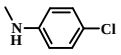
21

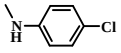
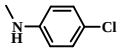
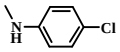
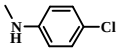
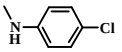
21a *R=H, R'=H* ***21b*** *R=4-Cl, R'=H* ***21c*** *R=2-Cl, R'=H* ***21d*** *R=4-CH_3, R'=H* ***21e*** *R= 4-OCH_3, R'=H* ***21f*** *R= H, R'=CH_3* ***21g*** *R=4-Cl, R'=CH_3* ***21h*** *R=2-Cl, R'=CH_3* ***21i*** *R=4-CH_3, R'=CH_3* ***21j*** *R=4-OCH_3, R'=CH_3* ***21k*** *R=H, R'=OCH_3* ***21l*** *R=2-Cl, R'=OCH_3* ***21m*** *R=4-CH_3, R'=OCH_3* ***21n****R=4-OCH_3,R'=OCH_3*

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]

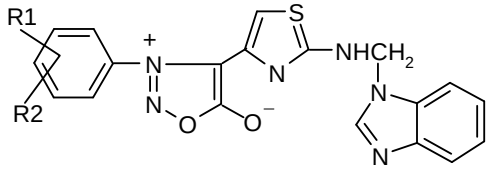


22

22a *R= H, R'=H, $R_{1=}$H, $R_{2=}$*  ***22b*** *R=H, R'=H, $R_{1=}$ H, $R_{2=}$*  ***22c*** *R=H, R'=H, $R_{1=}$ H, $R_{2=}$* 

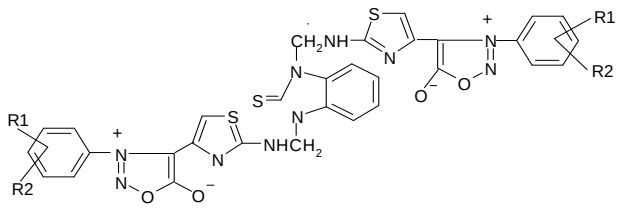
22d *R=H, R'=CH_3, $R_{1=}$H, $R_{2=}$*  ***22e*** *R=H, R'=CH_3, $R_{1=}$*  *, $R_{2=}$*  ***22f*** *R= H, R'=CH_3, $R_{1=}$H, $R_{2=}$*  ***22g*** *R= CH_3, R'= H, $R_{1=}$ H, R2=*  ***22h*** *R=CH_3, R'=H, $R_{1=}$H $R_{2=}$*  ***22i*** *R=CH_3, R'= H, $R_{1=}$H, $R_{2=}$*  ***22j*** *R=CH_3, R'=CH_3, $R_{1=}$ H, $R_{2=}$*  ***22k*** *R=CH_3, R'=CH_3, $R_{1=}$ H, $R_{2=}$*  ***22l*** *R=CH_3, R'=CH_3, $R_{1=}$ H, $R_{2=}$*  ***22m*** *R=C_3H_7, R'=H, $R_{1=}$ H, $R_{2=}$*  ***22n*** *R=C_3H_7, R'=H, $R_{1=}$ H, $R_{2=}$*  ***22o*** *R=C_3H_7, R'=H, $R_{1=}$ H, $R_{2=}$*  ***22p*** *R=C_3H_7, R'=CH_3, $R_{1=}$ H, $R_{2=}$*  ***22q*** *R=C_3H_7, R'=CH_3, $R_{1=}$ H, $R_{2=}$*  ***22r*** *R=C_3H_7 R'=$CH_3$$R_{1=}$ H, $NR_{2=}$* 

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]



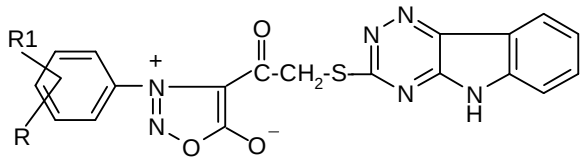
23

23a *R^1, R^2 =H* ***23b*** *R^1= 4-CH_3; R^2 =H* ***23c*** *R^1=2-CH_3; R^2 =H* ***23d*** *R^1=4-OCH_3; R^2 =H* ***23e*** *R^1=2-OCH_3; R^2 =H* ***23f*** *R^1=4-Cl; R^2 =H* ***23g*** *R^1= 3-Cl; R^2 =H* ***23h*** *R^1= 4-Br; R^2 =H* ***23i*** *R^1= 3-CH_3; R^2 =4-CH_3* ***23j*** *R^1= 3-Cl; R^2 =4-CH_3*



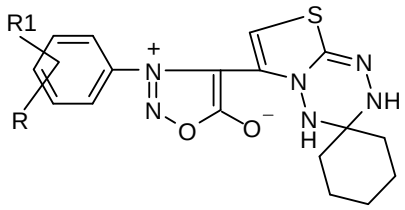
24

24a *R^1, R^2 =H* ***24b*** *R^1=4-CH_3; R^2 =H* ***24c*** *R^1=2-CH_3; R^2 =H* ***24d*** *R^1 =4-OCH_3; R^2=H* ***24e*** *R^1=2-OCH_3; R^2=H* ***24f*** *R^1=4-Cl; R^2 =H* ***24g*** *R^1=3-Cl; R^2 =H* ***24h*** *R^1= 4-Br; R^2 =H* ***24i*** *R^1= 3-CH_3; R^2 =4-CH_3* ***24j*** *R^1=3-Cl; R^2 =4-CH_3*



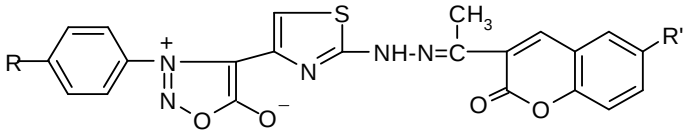
25

25a*R= H, R1=H* ***25b****R=H, R1=4-CH_3* ***25c*** *R=H, R1=2-CH_3* ***25d*** *R=H, R1=4-OCH_3* ***25e*** *R=H, R1=2-OCH_3* ***25f*** *R=H, R1= 4-Cl* ***25g*** *R=H, R1=3-Cl* ***25h*** *R=H, R1=4-Br* ***25i*** *R=3-CH_3, R1=4-CH_3* ***25j*** *R=2-CH_3, R1=5-CH_3* ***25k*** *R=4-CH_3, R1=3-Cl* ***25l*** *R=2-OCH_3, R1=4-Cl* ***25m*** *R=4-Cl, R1=3-F*



26

26a *R=H, R1=H* ***26b*** *R=H, R1=4-CH_3* ***26c*** *R=H, R1=2-CH_3* ***26d*** *R=H, R1=4-OCH_3* ***26e*** *R=H, R1=2-OCH_3* ***26f*** *R=H, R1=4-Cl* ***26g*** *R=H, R1=3-Cl* ***26h*** *R=H, R1=4-Br* ***26i*** *R=3-CH_3, R1=4-CH_3* ***26j*** *R=2-CH_3, R1=5-CH_3* ***26k*** *R=4-CH_3, R1=3-Cl* ***26l*** *R=2-OCH_3, R1=3-Cl* ***26m*** *R=4-Cl, R1=3-F*

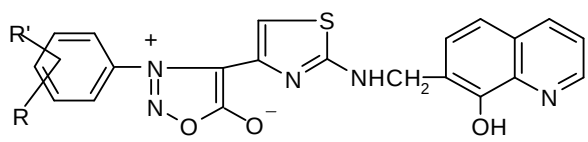


27

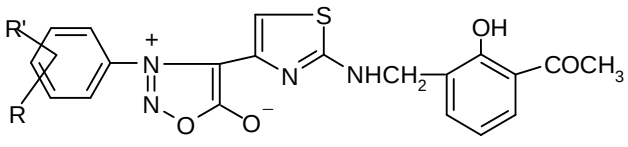
27a *R=H, R'=H* ***27b*** *R=CH_3, R'=H* ***27c*** *R=OCH_3, R'=H* ***27d*** *R=Cl, R'=H* ***27e*** *R=H, R'=Br* ***27f*** *R=CH_3, R'=Br* ***27g*** *R=OCH_3, R'=Br* ***27h*** *R=Cl, R'=Br* ***27i*** *R=H, R'=Cl* ***27j*** *R=CH_3, R'=Cl* ***27k*** *R=OCH_3, R'=Cl* ***27l*** *R=Cl, R'=Cl*

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. pyccyanous* 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. pyocyanous* and antifungal activity against *A. niger* and *R. bataticola*. A series of 3-aryl-4-[2-(3'-coumarylidene hydrazino)-4-thiazolyl] 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. pyocyanous* and *E. coli* and the antifungal activity against *A. niger* and *Rhizocona batiticola*; *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.



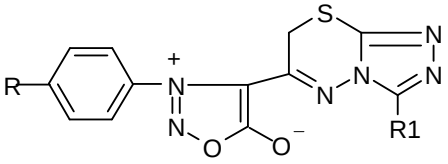
28



29

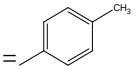
28a, 29a *R=H; R1= H* ***28b, 29b*** *R=H; R1=4-CH_3* ***28c, 29c*** *R=H; R1=2-CH_3* ***28d, 29d*** *R=H; R1=4-OCH_3* ***28e, 29e*** *R=H; R1=2-OCH_3* ***28f, 29f*** *R=H; R1=4-Cl* ***28g, 29g*** *R=H; R1=3-Cl* ***28h, 29h*** *R=H; R1=4-Br* ***28i, 29i*** *R=3-CH_3;*

R1=4-CH_3 ***28j, 29j*** *R=2-CH_3; R1=5-CH_3* ***28k, 29k*** *R=4-CH_3; R1=3-Cl* ***28l, 29l*** *R=2-OCH_3; R1=4-Cl* ***28m, 29m*** *R=4-Cl; R1=3-F*

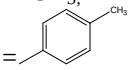


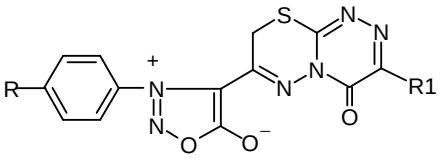
30

30a *R=H, R1= CH_3* ***30b*** *R=H, R1=C_6H_5* ***30c*** *R=CH_3 R1=CH_3* ***30d*** *R=CH_3, R1=C_6H_5* ***30e*** *R= CH_3, R1=*



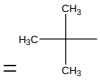
30f *R=OCH_3, R1=CH_3* ***30g*** *R= OCH_3, R1=C_6H_5* ***30h*** *R=OCH_3, R1=*



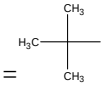


31

31a *R= H, R1= C_6H_5* ***31b*** *R=H, R1=*



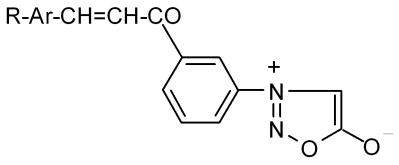
31c *R=H, R1= -CH_3* ***31d*** *R=CH_3, R1= C_6H_5* ***31e*** *R=CH_3, R1=*



31f *R=CH_3, R1=-CH_3* ***31g*** *R=OCH_3, R1= C_6H_5* ***31h*** *R=OCH_3, R1=*

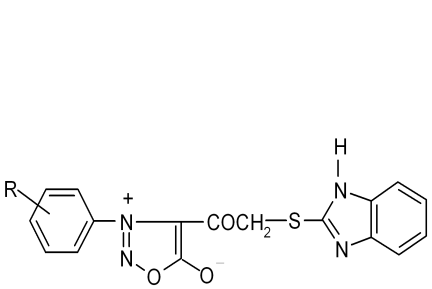
31i *R=OCH_3, R1=-CH_3*

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.

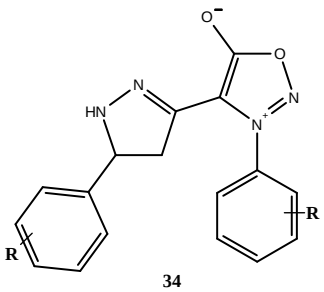


32

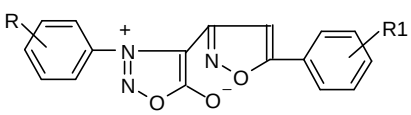
32a *Ar= Ph, R=H* ***32b*** *Ar=Ph, R=4-Cl* ***32c*** *Ar=Ph, R=4-CH_3* ***32d*** *Ar=Ph, R=4-OCH_3* ***32e*** *Ar=Ph, R=2-Cl* ***32f*** *Ar=Ph, R=2-CH_3* ***32g*** *AR=Ph, R=3- OCH_3*



33



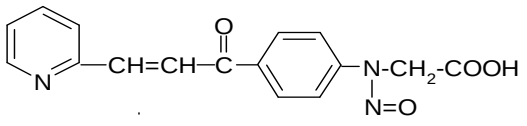
34



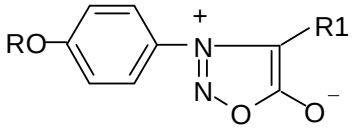
35

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]

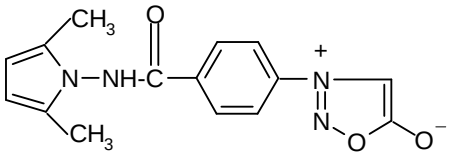
Compounds of series, 3-aryl-4-(5-aryl-2-pyrazolin-3-yl) sydnone (3**4**, R = H, OCH_3; R1 = H, OCH_3) and 3-aryl-4-(5-aryl-3-isoxazolyl) sydnone (**35**, R = H, OCH_3; R1 = H, OCH_3) were synthesized and screened for antibacterial, antifungal, anti-inflammatory, analgesic activities and some of the compounds 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=$PhCH_2$, 4-$ClC_6H_4CH_2$, 3-$MeC_6H_4CH_2$, 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-dimethylpyrrol-1-ylaminocarbonyl)]phenylsydnones**39**,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 pyocyanous*. 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]



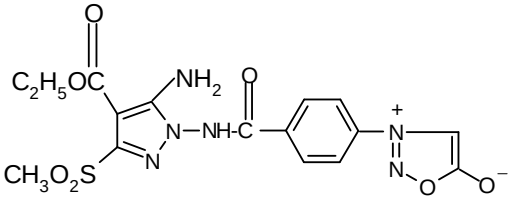
37



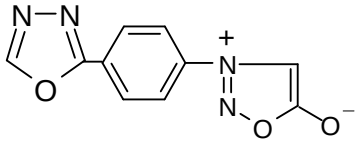
38



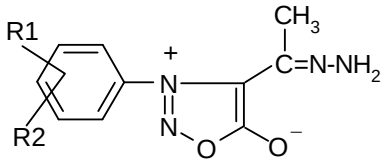
39



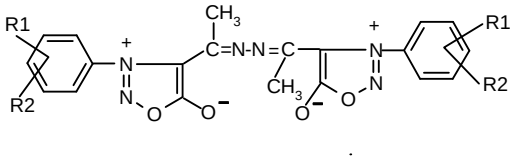
40



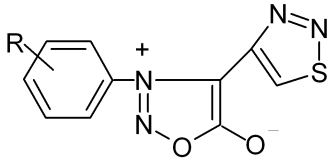
41



42



43

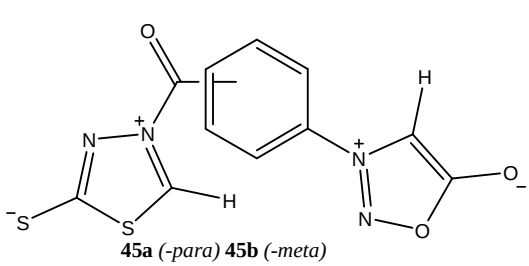


44

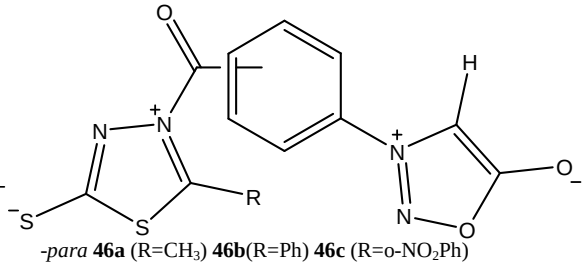
42a, ***43a*** *R1=H, R2=H****42b***, ***43b*** *R1=H, R2=4-*CH_3***42c***, ***43c*** *R1=H, R2=2-*CH_3***42d***, ***43d*** *R1=H, R2=4-*OCH_3 ***42e, 43e*** *R1=H, R2=2-*OCH_3***42f, 43f*** *R1=H, R2=4-Cl****42g, 43g*** *R1=H, R2=3-Cl* ***42h, 43h*** *R1=H, R2=4-Br* ***42i, 43i*** *R1=H, R2=4-*CO_2CH_3 ***42j, 43j*** *R1=H, R2=4-*$CO_2C_2H_5$ ***42k, 43k*** *R1=3-*CH_3, *R2=4-*CH_3 ***42l, 43l*** *R1=2-*CH_3, *R2=5-*CH_3 ***42m, 43m*** *R1=4-*CH_3, *R2=3-Cl* ***42n, 43n*** *R1=2-*OCH_3, *R2=4-Cl* ***42o, 43o*** *R1=4-Cl, R2=3-F*

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-(hydrazinocarbonyl)phenyl] sydnones. Among these only **45a** exhibited *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.



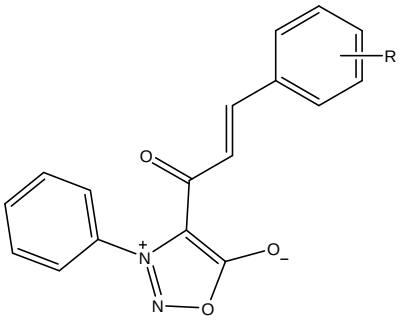
45a *(-para)* **45b** *(-meta)*



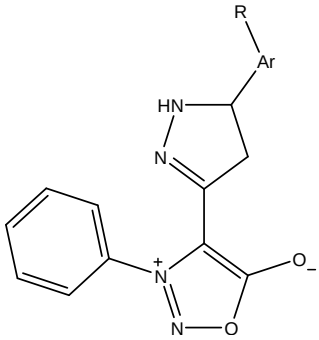
-para **46a** (R=CH_3) **46b**(R=Ph) **46c** (R=o-NO_2Ph)
-meta **46d** (R=CH_3) **46e**(R=Ph) **46f** (R=o-NO_2Ph)

Analgesic, anti-inflammatory and antiarthritic agents:

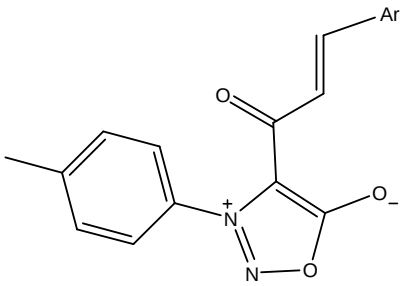
4-[1-oxo-(3-substituted aryl)-2-propenyl]-3-phenyl sydnones **47** and 4-[1-oxo-(3-substituted aryl)-2-propenyl]-3-(4-methoxyphenyl) sydnones **48** showed significant analgesic, antiarthritic and anti-inflammatory activities. [46] Some of the compounds also showed antiarthritic (adjuvant induced arthritis in rats) activities. 3-tertiary amino-4-tertiary amino methyl sydnone derivatives **49** and 3-hydrocarbon-4-tertiary amino methyl sydnones **50** showed analgesic activity. [47, 48] 3-arylthioalkyl-4-optionally substituted sydnones **51** showed anti-inflammatory and antibacterial activity. [49] 3, 4-disubstituted alkyl sydnones **52** also showed anti-inflammatory activity. [50]



47



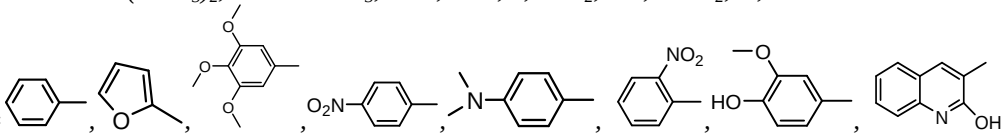
48 (i)

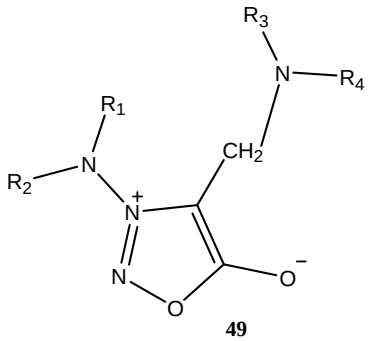


48(ii)

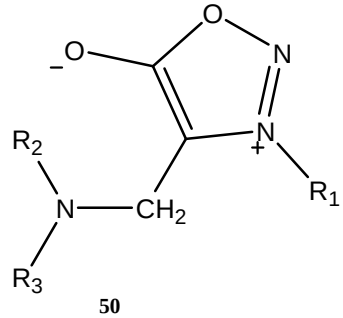
48(i) *Ar=Ph, Ph, Ph, Ph, Ph, Ph, Ph, Ph, Ph, Ph, Ph, 2-furyl, 2-thienyl R=H, 4-CH_3, 4-CH $(CH_3)_2$, 4-OCH_3, 2, 4-$(OCH_3)_2$, 4-$NHCOCH_3$, 4-Br, 4-Cl, 2, 4-Cl_2, 4-F, 4-NO_2, H, H*

48(ii) *Ar=*





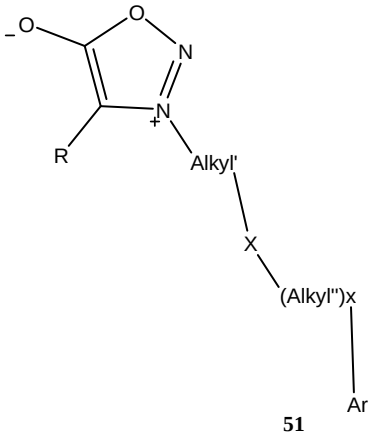
49



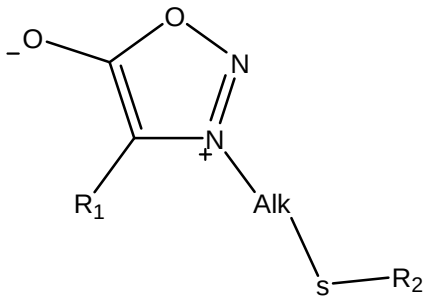
50

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_5), 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

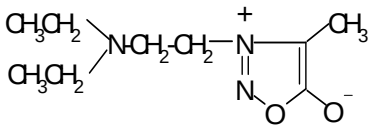


52

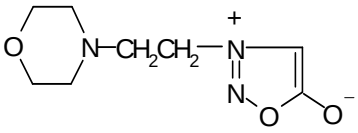
R= H, halogens, carboxyl, alkyl, benzyl, phenyl
Alkyl' and Alkl''= lower alkylene
X=Oxygen x=0, 1
Ar= phenyl, naphthyl, phenanthryl, pyridyl, furyl, thienyl

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

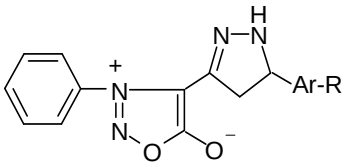
Analgesic effect was observed in a number of 3-aminoalkyl sydnones by Bruzzese *et al* [51], particularly with 3-diethylaminoethyl-4-methylsydnone **53** and 3-morpholinyl ethylsydnone **54**. They also noted hypoglycemic activity for several compounds in the series.



53

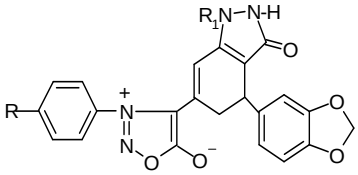


54

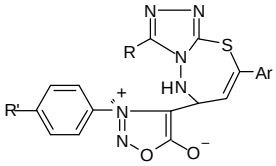


55

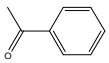
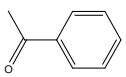
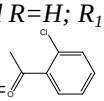
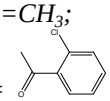
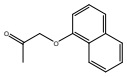
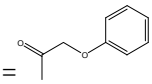
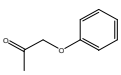
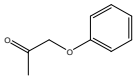
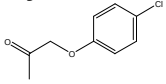
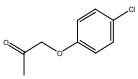
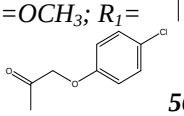
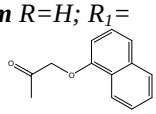
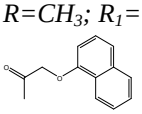
In an extensive study, Satyanarayana and Rao [52] synthesized 4-[5-(substituted aryl)-4, 5-dihydro-1H-pyrazol-3-yl]-3-phenyl sydnones **55** as analgesic, anti-inflammatory and antiarthritic agents. 3-aryl-4-[1'-substituted-2'-H-4',5'-dihydro-4'-(3,4-methylenedioxyphenyl)-3'-oxo-indazolin-6'-yl] sydnones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

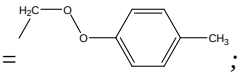


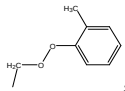
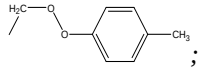
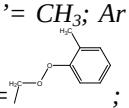
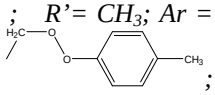
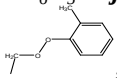
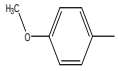
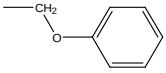
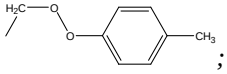
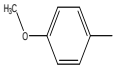
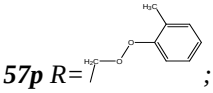
56

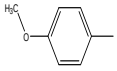
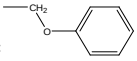
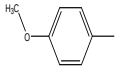
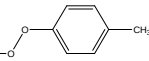
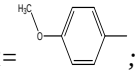
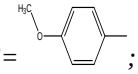
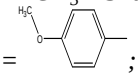
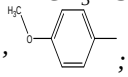
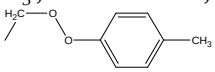
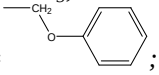
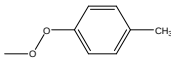
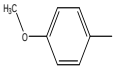


57

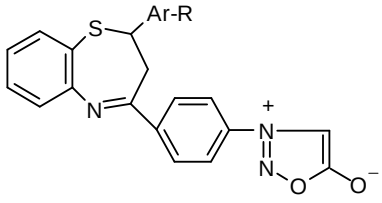
56a *R= H; R_1=H* ***56b*** *R=CH_3; R_1=H* ***56c*** *R= OCH_3; R_1=H* ***56d*** *R=H; R_1=*  ***56e*** *R=CH_3; R_1=*  ***56f*** *R= OCH_3; R_1=*  ***56g*** *R=H; R_1=*  ***56h*** *R=CH_3; R_1=*  ***56i*** *R=OCH_3; R_1=*  ***56r*** *R=OCH_3; R_1=*  ***56j*** *R=H; R_1=*  ***56k*** *R=CH_3; R_1=*  ***56l*** *R =OCH_3; R_1=*  ***56m*** *R=H; R_1=*  ***56n*** *R=CH_3; R_1=*  ***56o*** *R=OCH_3; R_1=*  ***56p*** *R=H; R_1=*  ***56q*** *R=CH_3; R_1=* 

57a *R= -CH_3; R'=H; Ar =-C_6H_5* ***57b*** *R=-C_6H_5; R'= H; Ar = -C_6H_5* ***57c*** *R =*  *;*

R'= H; Ar = -C_6H_5 ***57d*** *R=*  *; R'= H; Ar = -C_6H_5 57e R= -CH_3; R'= CH_3; Ar = -C_6H_5 57F R= -C_6H_5 R'= -CH_3; Ar = -C_6H_5* ***57g*** *R=*  *; R'= CH_3; Ar =-C_6H_5* ***57h*** *R=*  *; R'= CH_3; Ar = -C_6H_5* ***57i*** *R=-CH_3;R'=OCH_3;Ar=-C_6H_5* ***57j*** *R= -C_6H_5; R'= OCH_3; Ar = -C_6H_5* ***57k*** *R=*  *; R'= OCH_3; Ar = -C_6H_5* ***57l*** *R=*  *; R'= OCH_3; Ar = -C_6H_5* ***57m*** *R= -CH_3; R'= H; Ar =*  ***57n*** *R= -C_6H_5; R'= H; Ar=*  ***57o*** *R=*  *; R'= H; Ar=*  ***57p*** *R=*  *;*

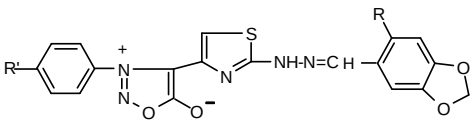
R'= H; Ar =  ***57q*** *R= -CH_3; R'=CH_3;Ar=*  ***57r*** *R= -C_6H_5; R'=CH_3; Ar =*  ***57s*** *R=*  *;R'=CH_3;Ar =CH_3* ***57t*** *R=*  *; R'=*  *; Ar = CH_3* ***57u*** *R=CH_3 ; R'=*  *; Ar =CH_3* ***57v*** *R=OCH_3; R'=*  *; Ar = -C_6H_5* ***57w*** *R=OCH_3; R'*  *; Ar =*  ***57x*** *R=OCH_3; R'=*  *; Ar =*  ***57y*** *R= -CH_3; R'=OCH_3; Ar =* 

3-substituted-6-(3-arylsydnonyl)-8-aryl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazepines **57** 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. [54] In the series 3-[4-[2,3-dihydro-2-(substituted aryl)-1,5-benzothiazepin-4-yl]sydnones **58**, only the phenyl substituted derivatives showed significant anti-inflammatory activity in carrageenan induced rat paw edema model. [55]



58

58a *Ar =Ph; R= H* ***58b*** *Ar=Ph; R=4-CH $_3$* ***58c*** *Ar=Ph; R=4-OCH_3* ***58d*** *Ar=Ph; R=2, 4-$(OCH_3)_2$* ***58e*** *Ar=Ph; R=4-$NHCOCH_3$*
58f *Ar=Ph; R=4-Cl* ***58g*** *Ar=Ph; R=3-Cl* ***58h*** *Ar= Ph; R=4-N $(CH_3)_2$* ***58i*** *Ar= Ph; R=2-Cl* ***58j*** *Ar=PH; R=2, 4-Cl_2*
58k *Ar=Ph; R=4-F* ***58l*** *Ar=2-furyl; R= H* ***58m*** *Ar=2-thienyl; R= H*

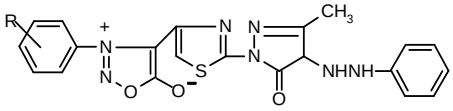


59

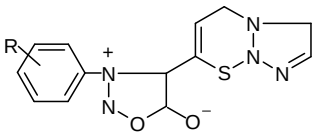
59a *R=H, R'=H* ***59b*** *R=NO_2, R'=H* ***59c*** *R=Br, R'=H* ***59d*** *R=H, R'=CH_3* ***59e*** *R=NO_2, R'=CH_3* ***59f*** *R=Br, R'=CH_3*
59g *R=H, R'=OCH_3* ***59h*** *R=NO_2, R'=OCH_3* ***59i*** *R=Br, R'=OCH_3*

Kalluraya *et al*., synthesized a series of 3-aryl-4-[substituted piperonylidenehydrazino-4-thiazolyl] sydnones **59** 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. [56]

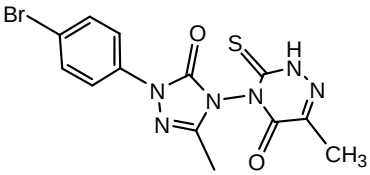
4-(arylsydnonyl)-2-(4-arylhydrazono-3-methyl-5-oxo-2-pyrazolin-1-yl) thiazoles 6**0** showed significant anti-inflammatory activity comparable with that of standard drug ibuprofen. Compounds containing chlorine and carboxylic substituents are more active. Few showed marked analgesic activity while most of the compounds showed promising CNS depressant activity comparable with that of standard drug pentobarbitone. [57] Triazolothiadiazines with aryl sydnone at sixth position **61** were synthesized by Kalluraya and Rahiman. Several compounds showed anti-inflammatory activity. [58]



60



61



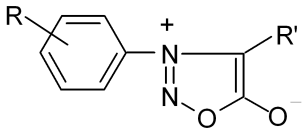
62

3-[4-(diethylamino)phenyl]-4-substituted-1-ylsulfonyl) sydnone and 4-acetyl-3-(4-chlorophenyl) sydnone showed promising antibacterial and anti-inflammatory activities. [59] Anti-inflammatory activity may be possibly through interference with synthesis of prostaglandins by blocking the enzyme *cyclooxygenase* (COX) and or *lipoxygenase enzymes* in the second phase of inflammation.

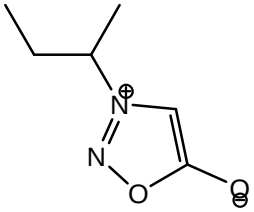
Miscellaneous activities:

Compound **62** synthesized with the integration of 1, 2, 4-triazole ring with 1, 2, 4-triazine-5-one, has been developed from 3-arylsydnones and proved antihaemostatic activity. [60] 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 **62a** may show related potential activities. [61] 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]



63



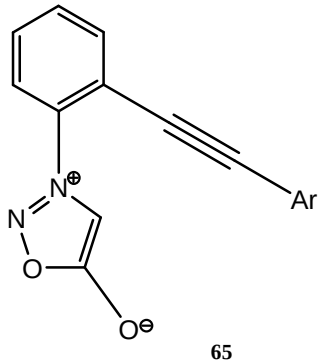
64

63a *R= H, R'=H* ***63b*** *R=2-Cl, R'=H* ***63c*** *R=3-Cl, R'=H* ***63d*** *R=4-Cl, R'=H* ***63e*** *R=2, 4-Cl_2, R'=H* ***63f*** *R=3, 4-Cl_2, R'=H*
63g *R=4-Br, R'=H* ***63h*** *R=4-NO_2, R'=H* ***63i*** *R=4-CH_3, R'=H* ***63j*** *R=4-OCH_3, R'=H* ***63k*** *R=2-C_2H_5, R'=H* ***63l*** *R=C_6H_5, R'=CH_3* ***63m*** *R=C_6H_5, R'=NO_2* ***63n*** *R=C_6H_5, R'=Cl* ***63o*** *R=C_6H_5, R'=Br* ***63p*** *R=CH_3, R'=H* ***63q*** *R=$C_6H_5CH_2$, R'=H*

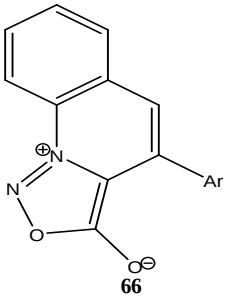
Some sydnone imines were found to be useful for the treatment and prophylaxis of cardiovascular diseases such as angina pectoris and hypertension.[63] A number of 3-alkyl sydnones were found to be potent CNS stimulants by Kier *et al.*[64] The 3-*sec*-butylsydnone **64** was found to be a powerful respiratory stimulant in a heavily barbitalised dog.

Recent medicinal uses of sydnone derivatives:

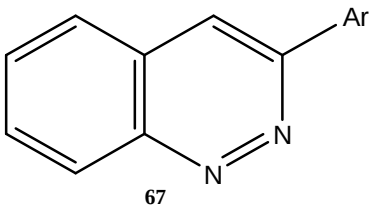
Reactions of *ortho*-alkynylphenyl sydnones **65** with various acids result in sydnoquinoline derivatives **66**. Treatment of *o*-alkynylphenylsydnones with trifluoroacetic acid provides novel 3-arylcinnolines **67**. [65]



65

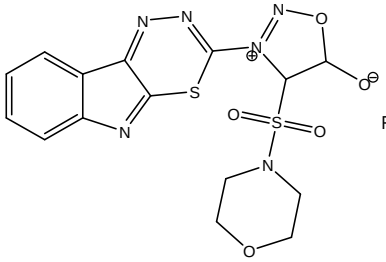


66

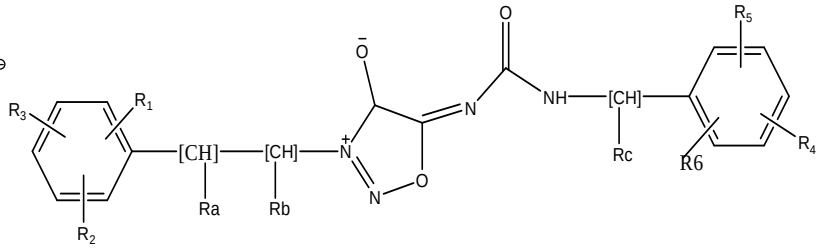


67

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]

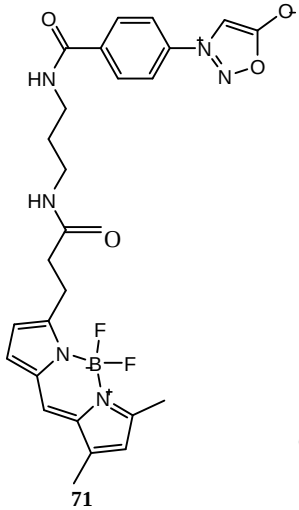


68

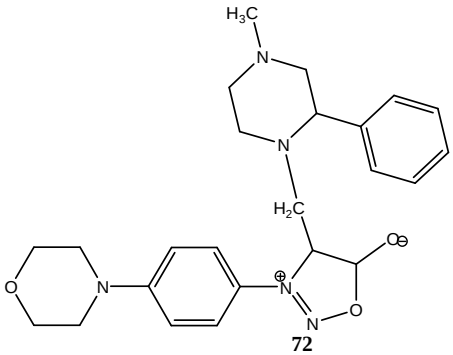


69

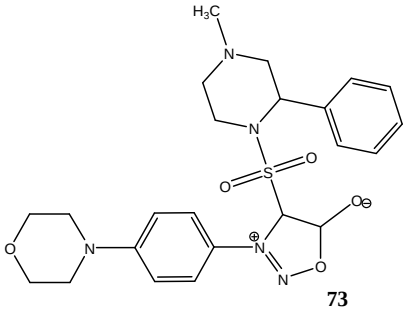
Wallace et al described the reaction of a phenyl sydnone 1, 3-dipole with a bicyclononyne dipolarophile. This strain-promoted reaction proceeds without transition metal catalysis in aqueous buffer, at physiological temperature and pressure with a rate comparable to that of other bioorthogonal reactions. 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]



71

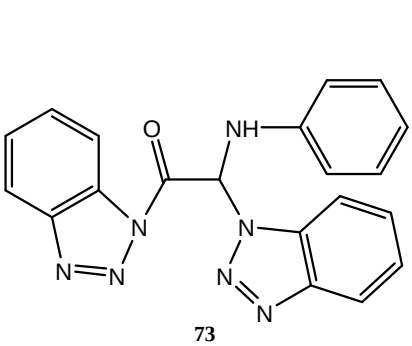


72

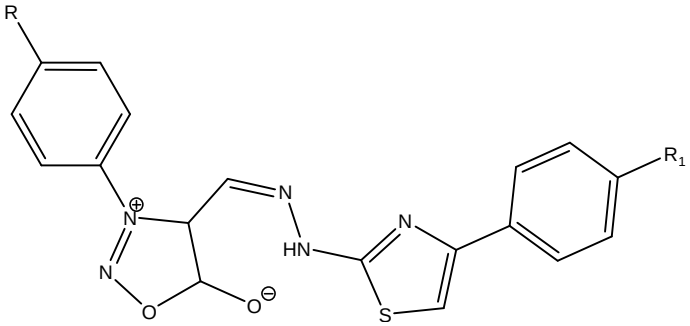


73

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]

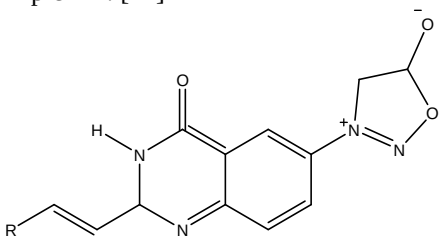


73

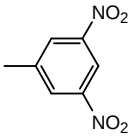


74 *R=H, CH_3 R1=H, CH_3, OCH_3, Cl, NO_2*

A series of 4-aryl-2-[3-arylsydnolydine-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]



75 R=



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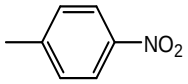
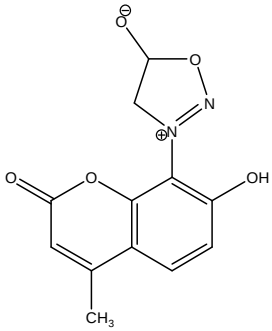
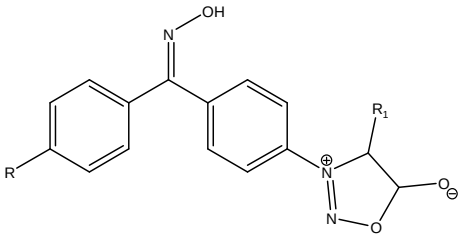
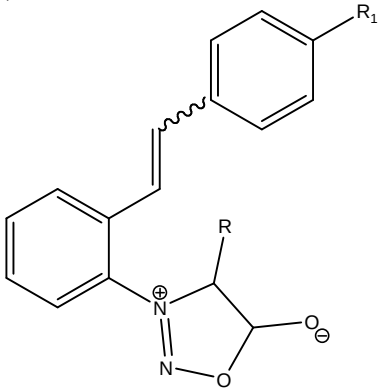




76

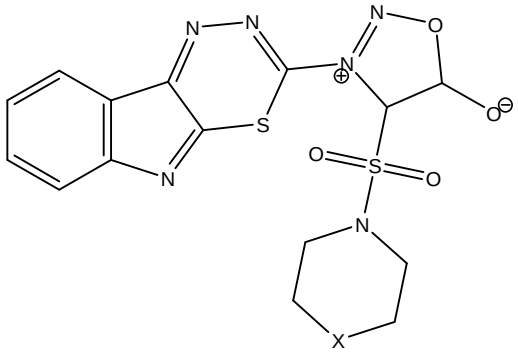


77 (R=-n-Bu, R1=Ph)



78 (R=CH_3 R'=CH_3) **79** (R=Ph, R'=Cl)

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.[72] A series of novel stilbene-sydnone derivatives were synthesized from methyl anthranilate *via* glycine- and nitrosoglycine derivatives the corresponding 3-(*o*-carbomethoxyphenyl)-4-H/Me/Ph-sydnones were prepared and transformed to stilbenylsydnone 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-[2-(4-methylphenyl) ethenyl] phenyl] sydnone **78** and *cis*-4-phenyl-3-[2-[2-(4-chlorophenyl) ethenyl]-phenyl] sydnone **79** showed the most pronounced activity.[73] Several 2-[{(4-Substituted-1-sulphonyl) Sydnon-3-yl}]-1, 3, 4-thiadiazino (6, 5-b) indoles **80** have shown antimicrobial and antihelmintic activity.[74]



80 X=O_2, NH_2, CH_2, NCH_3, N-C_6H_5, N-CH_2CH_3

CONCLUSION AND FUTURE OUTLOOK

This review shows that sydnones 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 sydnones are antitumour, antimicrobial, antioxidant, antiinflamatory-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 sydnones with multiple activities and same pattern can be applied for a series of different compoundswith 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 sydnones are fairly promising and deserve further investigation in the attempt of finding new therapeutic alternatives.

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