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Sydnones: A Brief Review

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Abstract: Sydnones are mesoionic heterocyclic aromatic compounds. They have been widely studied for some important biological activities like antiviral, antitumor, antimicrobial, anti-inflammatory, anticancer, analgesic, anthelmintic and antihypertensive activities. The aim of the present article is to review the available information on sydnones and the derivatives of sydnones and also a look at the future perspectives.

Keywords: Sydnone, mesoionic, oxadiazolium.

INTRODUCTION

Sydnones are unique, dipolar heteroaromatic members of the general class of mesoionic compounds. Chemically they are 1, 2, 3-oxadiazolium-5-olates [1]. A large number of sydnone derivatives have been synthesized with biological interest [2-4] and reported to possess a wide spectrum of biological activities such as antiviral [5], antimicrobial [6], antiinflammatory [6], analgesic [6], anthelmintic [6], antitumor [7], free radical scavenging [8] and nitric oxide donor [9] activity. The potential value of sydnones as biologically active substances is found in their planar aromatic character, their relatively small size and variation in electron density around the ring. It is believed that the ionic resonance structures of sydnones promote significant interactions with biological molecules. The stimulant drugs feprosidine and mesocarb are substructures of sydnones imine in which the keto group of sydnones (=O) is replaced by imino group (=NH).

PHYSICAL PROPERTIES

With a few exceptions, sydnones are stable compounds that exhibit considerable polarity. Arylsydnones are generally crystalline solids. Alkylsydnones are often liquids or low-melting solids that can be distilled *in vacuo* without appreciable decomposition. Concentrated acids cause degradation of sydnones yielding hydrazine derivatives [10]. Sydnones are soluble in a variety of organic solvents with the main exceptions being nonpolar solvents such as petroleum ether and hexanes. Additionally, sydnones are generally not water-soluble unless a polar functional group is present.

CHEMISTRY

Synthesis

Since their original preparation [11] in 1935 by Earl and Mackney, the only general route to sydnones (2) is still *via* the cyclodehydration of *N*-substituted *N*-nitroso-α-amino acids as shown in (Scheme **1**). While the substituent R can be alkyl, aryl, or hydrogen, the R^1 must be alkyl or aryl. If R' is a hydrogen, prototropy occurs to afford a neutral species. The preparation of the *N*-nitroso amino acid generally involves the nitrosation of an *N*-substituted glycine with nitrous acid. Since this nitrosation step requires the use of strongly acidic reaction conditions, sydnones containing acid-sensitive functional groups have been unattainable by this methodology. However, a variation upon this standard method has been developed in which nitrosation is effected under neutral conditions using isoamyl nitrite and dimethoxyethane [12]. Thus, some otherwise unattainable sydnones can now be successfully generated in good to excellent yield.

Earl and Mackney originally employed acetic anhydride at room temperature for six days for cyclodehydration[11]. Since then, several modifications have been made that include heating in acetic anhydride or thionyl chloride, treatment with phosphorus pentoxide, or the use of trifluoroacetic anhydride (TFAA). The reaction with TFAA has become the method of choice since it usually occurs rapidly (<15 minutes) at low temperature (-5°C to 0°C) and in high yields (>90% for *N*-phenylsydnone). The only foreseeable drawback to its use is the far greater cost of this reagent compared to others.

Newer synthetic strategies for accomplishing the aforementioned cyclization have also been put forth. Amongst these are the uses of acetic anhydride at room temperature facilitated by ultrasonification [13], halo iminiumsalts [14], *N,N*-dimethylchlorosulfitemethaniniumchloride [15] and 2-chloro-1,3-dimethylimidazolinium chloride [16]. Although these new methods are interesting, it is unlikely that they will replace the fast, efficient, and reliable TFAA cyclization.

Azarifar *et al.,* have reported several one-pot syntheses of sydnones [17]. One approach employs dibromo-dimethylhydantoin [18]. This one-pot procedure avoids isolation of the toxic nitrosamine intermediate and makes use of cheap commercially available materials. Moreover, this approach gives good yields for the preparation of a range of sydnones among all methods. Synthesis of sydnones from

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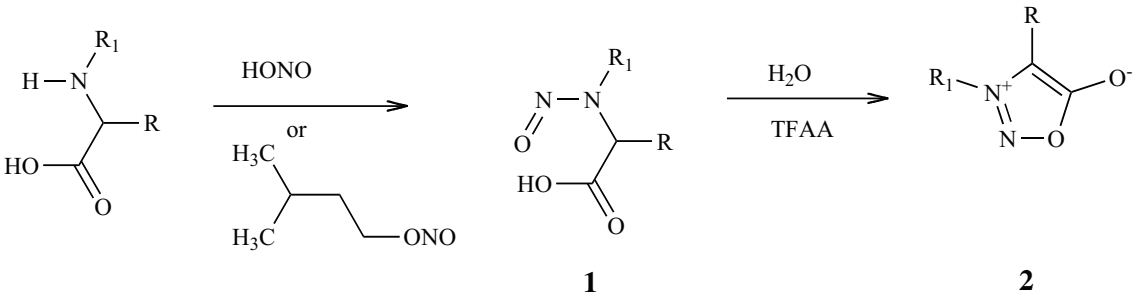


Scheme (**1**).

readily available anilines have also been carried out to obtain fused ring sydnones [19].

SPECTRAL STUDIES

In their NMR spectra, the proton (when present) at the C-4 position of the sydnone ring is greatly deshielded in comparison to saturated congeners, usually appearing between 6.5-7.5 ppm. This, then, suggests a polar nature and the presence of an aromatic ring current. Additionally, the infrared spectra of sydnones include two very prominent features, namely a strong carbonyl stretch at ~ 1730-1760 cm^{-1} and a stretch of medium intensity at ~ 3150 cm^{-1} for the C-H absorption of the C-4 ring proton (when present) [20]. Moreover, the latter is different from what would be expected for either an alkyl or aryl substituent or from an epoxide with comparable ring strain, which absorb at around 2900-3050 cm^{-1}, and therefore is particularly useful in determining if the C-4 position in sydnones are substituted or not.

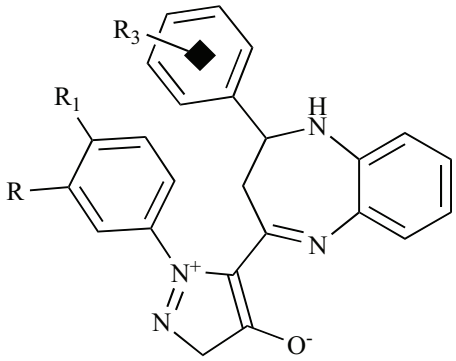
With regard to the carbonyl stretch, a single, strong band is usually observed. However, due to Fermi resonance splitting, in some cases multiple bands have been observed [21]. Further, as stated above, the sydnone carbonyl typically appears at ~1730-1760 cm^{-1} but, when compared to congeneric carbonyl containing species, such as a γ-lactone [which absorbs at 1770 cm^{-1}] and tropone [which absorbs at 1638 cm^{-1}], one might conclude that the exocyclic C=O bond at the sydnone C-5 position is closer in length to that of a double bond than a single bond. This contention is further supported by the results of X-ray crystallographic analysis of various 3-substituted and 3,4-disubstituted sydnones which show that the exocyclic C=O bond is closer in length to that of a double bond. However, integrated absorption measurements suggest that a high degree of carbonyl bond polarization, rather than bond strength, is responsible for the relatively high energy of absorption. Additionally, molecular orbital calculations and vibrational force constants obtained from vibrational spectra indicate a lower π-bond order for the sydnone carbonyl than those of alicyclic esters [22], thus supporting the argument that contributions from other vibrational modes cause the sydnone carbonyl group to absorb at a higher frequency than anticipated.

It has been demonstrated, by both theoretical and spectroscopic studies, that protonation of a sydnone moiety occurs at the exocyclic oxygen [23]. This complements earlier investigations where bond orders and charge densities of various sydnones were correlated to the calculated and observed dipole moments and the observed UV maxima [24]. These studies thus support the contention that substantial charge density resides on the exocyclic oxygen.

PHARMACOLOGICAL USES

Antimicrobial

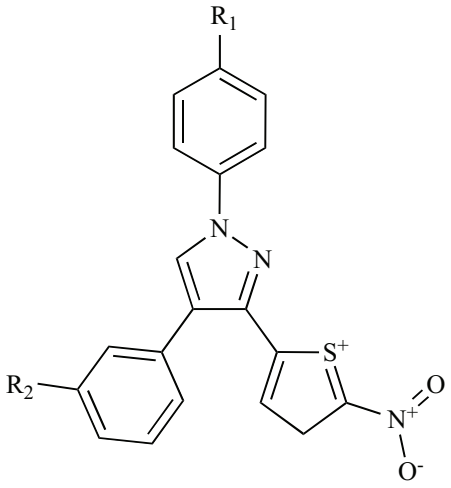
Prashanth Shinge *et al.,* have synthesized a series of benzodiazepine derivatives of sydnones (3) and screened them for their *in vitro* antimicrobial activity against two bacteria, namely *E. coli* and *C. bacillus* and two fungal cultures, *A. candida* and *R. bataticola* [25,26] using reference drugs Norfloxacin and Griseofulvin, respectively. The same investigators have carried out a one-pot synthesis of 4-(4-chlorophenylazo)-5-methyl-2-aryl-1, 2-dihydro-pyrazol-3-ones from 3-arylsydnones and studied them for their antimicrobial activity. All the synthesized compounds exhibited more antimicrobial activity than the standard drugs. The results of the antibacterial screening show that compounds substituted with halogen, methyl and nitro exhibit growth inhibitory activity that are more relevant than that of the reference compounds and this activity varies with the substitutions at the phenyl rings.



3

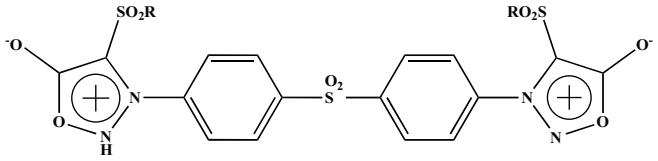
Satheesha Rai *et al.,* have synthesized 1,3,4-trisubstituted pyrazoles(4) via 1,3-dipolar cycloaddition of sydnones and studied their antibacterial activity against four bacterial strains, namely E.coli (ATCC-25922), Staphylococcus aureus (ATCC-25923), Pseudomonas aeruginosa (ATCC-27853) and Bacillus subtilis (recultured) [27]. The antifungal activity was studied against the fungi Candida albicans (NCIM No. 3100), by the serial dilution method. The tested compounds showed good inhibition at a concentration of

0.125 mg/mL concentration. They also studied the antimicrobial activity of sydnones sulphonamide compounds and found them to be effective antimicrobial agents. The studies revealed that the presence of cholrine atom in the aryl moiety increased the potency of the pyrazoles against the tested bacterial strains.



4

Sharukh Asundaria *et al.,* have studied the antimicrobial activity of a set of bis-sydnones (5) against gram positive bacteria, namely *S.pneumoniae* and *S.aureus* and gram negative bacteria *E.coli* and *P.aeruginosa* [28,29]. The reference drugs used were Streptomycin and Penicillin-G, respectively. The compounds synthesized exhibited moderate activity when compared to the standard.

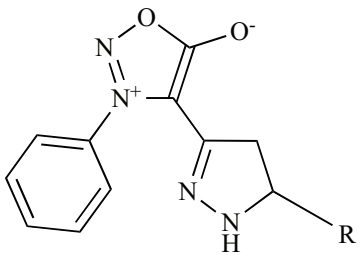


5

Antiinflammatory

Satyanarayana *et al.,* have synthesized 4-[5-(substituted aryl)-4,5-dihydro-1H-pyrazol-3-yl]-3-phenylsydnones (6) by condensing 4-[1-oxo-3-(substituted aryl)-2-propenyl]-3-phenylsydnones with hydrazine to yield fourteen compounds [30]. The compounds were tested for their antiinflammatory activity with phenylbutazone and ibuprofen as standards. The halogenated derivatives were found to exhibit more activity compared to other synthesized compounds. These when further tested for their antiarthritic activity showed activity equal to or less than the standard.

Shreenivas Deshpande *et al.,* have studied the antiinflammatory activity of 4-[1-oxo-3- (substituted aryl)-2-propenyl]-3-(4-chlorophenyl) sydnones (7) using carageenan induced rat paw edema method [31]. The synthesized compounds were found to have significant antiinflammatory activity comparable to the standard, namely Ibuprofen.



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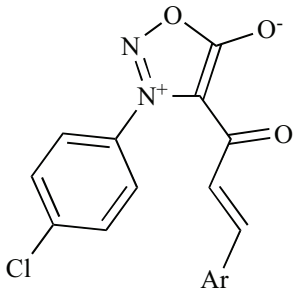
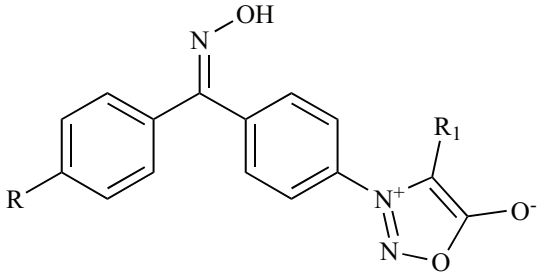


7

Ravindra Kamble *et al.,* synthesized and studied benzophenone oxime derivatives of sydnones (8a-h) for their antiinflammatory activity [32]. The synthesized compounds were also evaluated for their inhibitory activity against purified phospholipase A_2 enzymes from snake venom and human inflammatory pleural and ascites fluid. The compounds exhibited activity similar to that of the standard Luffariellin B when a hydrophobic group is present in the aroyl moiety and the 4th position of the sydnones ring was substituted by a phenyl ring. It was also observed that a hydrophobic alkyl group reduced the activity whereas the absence of either group resulted in very weak activity.



8a-h

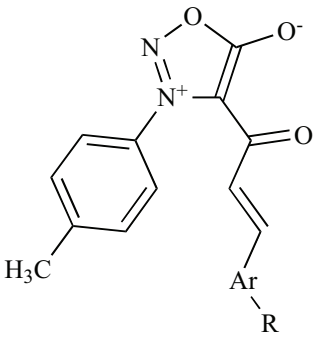
a; R = H,R_1 = H, b; R = CH_3,R_1 = H, c; R = n-propyl,R_1 = H, d; R = n-butyl,R_1 = H,

e; R = H,R_1 = Ph, f; R = CH_3,R_1 = Ph, g; R = n-propyl,R_1 = Ph, h; R = n-butyl,R_1 = Ph.

Analgesic

Satyanarayana *et al.,* have synthesized and evaluated 4-[5-(substituted aryl)-4,5-dihydro-1*H*-pyrazol-3-yl]-3-phenylsydnones and their derivatives for analgesic activity at 100mg/kg in acetic acid induced assay in mice [30]. Among the six compounds that exhibited significant activity, 4-fluoro compound exhibited the highest activity in the series. The standard used was aspirin. These same authors have

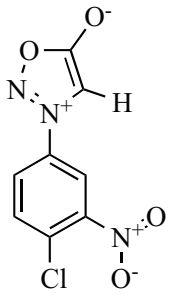
synthesized and evaluated some 4-[1-Oxo-3- (substituted aryl)-2-propenyl]-3-(4-methylphenyl) sydnones (9) [33]. The compounds having electron-withdrawing substituents like chloro and nitro at *para* position exhibited more antibacterial activity. The furyl and *para* chloro phenyl analogs showed good analgesic activity. Thus 3-(substituted phenyl)sydnone derivatives possessing substituted styrylketone moieties appear to be another interesting source of antibacterial and analgesic compounds.



9

Anticancer

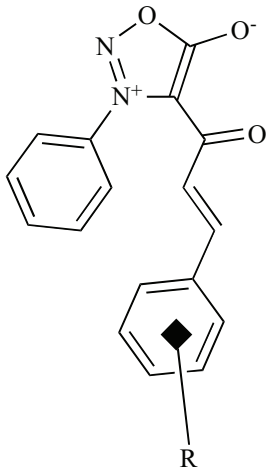
Gerusa Clazer Halila *et al.,* have studied the antitumor activity of SYD-1(3-[4-chloro-3-nitrophenyl]-1,2,3-oxadiazolium-5-olate)(10) [34]. They showed that the effect of this compound on mitochondrial metabolism is due to its inhibitory effect of electron transport through the respiratory chain.



10

Satyanarayana *et al.,* have synthesized a novel structural feature containing 4-[1-oxo-(substituted aryl)-2-propenyl]-3-phenylsydnones (11) and screened them for their anticancer activity [35]. These compounds contained two pharmacophores, an unsaturated ketone moiety and a sydnone ring. All the three compounds synthesized exhibited promising *in vitro* cytotoxicity in 56 cell lines representing cancers of non-small cell lung, colon, CNS, melanoma, ovarian, prostrate, breast and leukemia. The average growth inhibition of 50% was in the range of 1.7-3.5. The methyl derivative was highly selective against SNB-75 tumor cell line of CNS. It was active at less than one nano mole. However, it showed moderate *in vivo* activity in hollow fiber assay model.

Grynberg *et al.,* have studied the effect of some aryl sydnones on murine tumors [36]. The compounds, 3-[4-X-3-nitrophenyl]-1,2,3-oxadiazolium-5-olates (12), where X = Cl, pyrrolidino, piperidino and morpholino, were synthesized and studied for the survival of mice bearing Sarcoma 180, Ehrlich carcinoma, B10MCII (Fibrous histiocytoma) and L1210 leukemia ascitic tumours proliferation of cultured tumour cells and on the synthesis of DNA in L1210 leukemia. The chloro and pyrrolidino derivatives significantly enhanced the survival of S180, Ehrilich and B10MCII tumour-bearing mice in *in vivo* studies. Further the pyrrolidino derivative showed significant activity against L1210. Piperidino and morpholino derivatives did not show any antitumour activity. The chloro derivative was the most cytotoxic against all the above tumour cells. All the compounds tested inhibited thymidine uptake by L1210 cells, the morpholino derivative being the least active.



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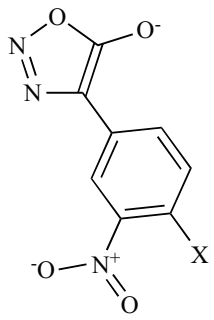
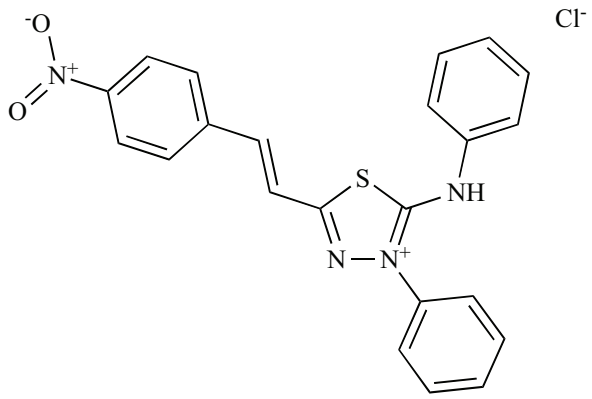


12

Senff Ribeirol *et al.,* have studied the effect of 4-Phenyl-5-(4-nitro-cinnamoyl)-1,3,4-thiadiazolium-2-phenylamine chloride (13) on human melanoma cells(MEL-85, SK-MEL, A2058 and MEWO) [37]. The compound was found to decrease the viability and proliferation of MEL-85, SK-MEL, A2058 and MEWO cell lines *in vitro*, showing considerable cytotoxic activity on these human cells. Besides its cytotoxic properties, the compound was also found to interfere in cell features involved in tumour development such as adhesion to ECM components. This study proved the compound to be a potent drug against B16-F10 murine melanoma both *in vitro* and *in vivo*.



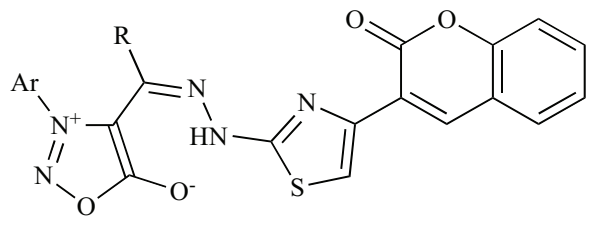
13

Free Radical Scavenging

Stelia Carolina Mendez-Sanchez *et al.,* have studied the effect of 4-phenyl-5-(4-nitro-cinnamoyl)-1,3,4-thiadiazolium-2-phenylamine chloride(13) on lipoperoxidation and its ability to scavenge free radicals[38]. It was observed that the compound promoted a strong inhibition of the lipoperoxidation induced by Fe^{3+}–ADP/2-oxoglutarate in isolated mitochondria (95% ± 0.27 at the highest concentration of 80 nmol mg^{-1} protein) in a dose-dependent manner. However, at the same concentration its effect was less intense (22% ± 3.46) when the lipoperoxidation was initiated by peroxyl radicals generated from the azocompound, AAPH. Lipid peroxidation in both coupled and uncoupled submitochondrial particles initiated with Fe^{2+}/NADH was also inhibited by the compound. The inhibition was about four times greater in coupled particles (34% at 80 nmol mg^{-1} protein) in relation to uncoupled particles. The mesoionic compound showed ability of scavenging superoxide radical (7, 11 and 31% for 25, 38 and 80 μM, respectively).

Antidiabetic

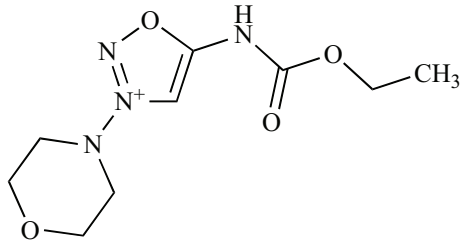
Gireesh Tegginamath *et al.,* have reported a novel one-pot synthesis of sydnones appended to coumarines (14) via thiazole in the presence of silica sulphuric acid as a heterogeneous catalyst [39]. The compounds were screened for α-amylase inhibition (antidiabetic) as well as DNA cleavage activity. The preliminary *in vitro* antidiabetic activity of these novel series of thiazole derivatives have shown that some of the chlorine substituted (electron withdrawing group) compounds exhibit good α-amylase inhibition and good DNA cleavage activity.



14

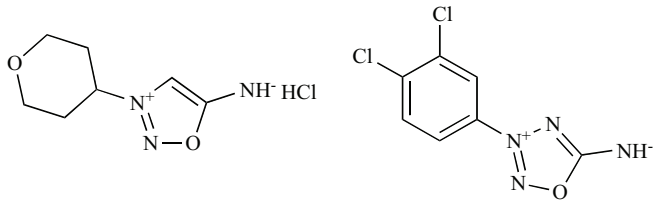
Nitric Oxide Donor

Molsydomine (15) is an effective antihypertensive. This activity has been connected recently to its ability to release nitrogen monoxide *in vivo* [40]. This ability to act as a NO donor arises from hydrolysis of the side chain of molsydomine accompanied by decarboxylation and opening of the sydnonimine ring under these conditions to give *N*-nitroso derivative. It is known that *N*-nitroso compounds are readily oxidized in the organism, the final result of which is liberation of nitrogen monoxide.



15

Kankaanranta *et al.,* have studied the NO releasing capacity of two 3-aryl substituted oxatriazole-5-imine derivatives (16) and these were compared to a known NO donor, 4-Phenyl-5-(4-nitro-cinnamoyl)-1,3,4-thiadiazolium-2-phenylamine chloride [41]. It was found that both these derivatives induced an increase in cyclic GMP production in human platelets and neutrophils. The IC_{50} values were not found to be very different for both the derivatives. The authors have tried to establish a relationship between their biological activities and their ability to release nitric oxide.

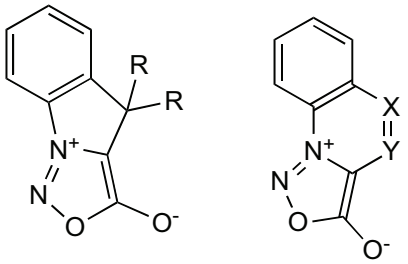


16

FUTURE PERSPECTIVES

Sydnones and sydnonimines have been widely studies due to the array of biological activities exhibited by their nucleus. Studies have been carried out on sydnones with various substituents at the 4th position of the ring by subjecting them to a range of reactions like lithiation, bromination, modification of C4 halogenated sydnones. The cycloaddition of sydnones with various alkenes and alkynes have also gained significant interest in the recent years. Sydnones have been known to be novel precursors of pyrazoles (via cycloaddition). Some vasodialators like molsidomine and Darsidomine are known for their nitric oxide donor capacity.

Though 4-subtituted sydnones have been fairly studied, fused ring sydnones have gained a lot of interest in recent years because ring fusion is a route which may lead to molecules with interesting biological activity. Mainly two types fused ring sydnones have been of interest (17).



17

Very few reports are available on the synthesis and biological evaluation of these fused ring sydnones and their applications. Future work should, therefore, give importance to fused ring sydnones and their derivatives.

CONCLUSION

In conclusion sydnones are highly versatile and robust members of the class of mesoionic compounds. They are known for their wide array of synthetic applications and biological activity. The literature reveals that sydnones have diverse biological potential. The easy synthetic routes to sydnones have attracted the attention of chemists, pharmacologists and researchers. Sydnones seem to have a great potential and remain largely unexplored.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Stewert, F. H. C. The chemistry of the sydnones**.** *Chem Rev.,* **1964**, *64*, 129.

[2] Ollis, W.D.; Ramsden, C. A. Mesoionic compounds. *Adv Heterocycl Chem.,* **1976**, *19*, 1.

[3] Kier,L.B.; Roche, E. B. Medicinal chemistry of the mesoionic compounds. *J Pharm Sci.,* **1967**, *56*, 149.

[4] Ackermann, E. On the pharmacology of sydnone and sydnonimine: A survey. *Pharmazie,* **1967**, *22*, 537.

[5] Pandey, V. K; Mukesh; Tandon, M. Synthesis and antiviral activity of quinazolinyl syndnones. *Indian J Heterocycl Chem.,* **2006**, *15*, 399.

[6] Kalluraya, B.; Rahiman, M.A.; Banji, D. Sydnone derivatives: part V -synthesis and pharmacological properties of some novel triazolothiadiazepin. *Indian J Chem.,* **2002**, *41B*, 1712.

[7] Dunkley, C. S.; Thoman, C. J. Synthesis and biological evaluation of a novel phenyl substituted sydnone series as potential antitumor agents. *Bioorg Med Chem Lett.,* **2003**, *13*, 2899.

[8] Mallur, S. G.; Tiwari, A. K.; Chinna Raju, B.; Suresh Babu, K.; Zehra Ali, A.; Sastry, B. S.; Madhusudana Rao, J. Synthesis and evaluation of phenyl substituted sydnones as potential DPPH scavengers. *Indian J Chem.,* **2007**, *46B,* 1686.

[9] Satyanarayana, K.; Deshpande, S. R.; Subbarao, B.; Rao, M .N. A. Synthesis and nitric oxide donor activity of phenylsydnones. *Indian Drugs,* **2002**, *39*, 578.

[10] Aziz, S.; Tillett, J. G. The hydrolysis of some 3-alkylsydnones. *Tetrahedron Lett.* **1969**, *33*, 2855.

[11] Earl, J. C. and Mackney, A. W., The action of acetic anhydride on *N*-nitrosophenylglycine and some of its derivatives. *J. Chem. Soc*., ***1935***, 899.

[12] *Applegate,J.; Turnbull, K.* The Efficient *Synthesis* of 3-Arylsydnones under Neutral Conditions, *Synthesis*, **1988**, 1011-1012.

[13] Chem. Abstr., 122, 265312x , **1995**.

[14] T. Isobe, *Jpn. Kokai Tokkyo Koho*, JP 08 12, 658 [96, 12,658]. Chem. Abstr., **1996**, *124*, 317175t.

[15] B. Sain and J. S. Sandho, *Chem. Ind.* (London), **1990**, *21*, 709. Chem. Abstr., **1991**, 114, 81717h.

[16] Isobe, T. *The construction of heterocycles through dehydration reactions. J. Org. Chem*., **1999**, *64*, 6989.

[17] Azarifar, D.; Ghasemnejad-Borsa, H.; Tajbaksh, M.; Habibzadeh, S. DABCO-Cl2 mediated synthesis. *Heterocycles*, **2007**, *71*, 1815.

[18] Azarifar,D.; GhasemnijadBorsa, H. Dibromomethylhydantoin mediated synthesis. *Synthesis*, **2006**, 1123.

[19] Roshini Chandrasekhar, Nanjan, M.J.; Gopalan,B. Synthesis and characterization of of 3-Hydroxy-4, 5-dihydro[1,2,3] Oxadiazolo [3,4-A]Quinolin-10-ium and its Fluoro derivative. *International Journal of Chemtech Research*, 3(3), **2011**, 1125.

[20] Tien, J. M.; Hunsberger, I.M. Sydnones. III. Preparation and Interconversion of Mercurated Derivatives of N-(3-Pyridyl)-sydnone. *J. Am. Chem. Soc.,* **1961**, *83*, 178.

[21] Chem. Abstr., **1962**, *57*, 6763.

[22] Ivanova, T. M.; Yashunski, V. G. Vibrational spectra, force fields and electronic structures of sydnones .*Theochem*., **1982**, *4*, 327.

[23] Tanka, S.; Yokai, M. *Bull. Chem. Soc. Jpn*., **1983**, *56*, 2198.

[24] L. B. Kier and E. B. Roche. Molecular orbital calculations of the electronic structure of sydnones. *J. Pharm. Sci*., **1966**, *55*, 807;

[25] Jyothi Kavali,R.; Bharthi Badami, V. 1,5-Benzodiazepine derivatives of 3-arylsydnones: synthesis and antimicrobial activity of 3-aryl-4-[2'-aryl-2',4',6',7'-tetrahydro-(1'H)-1',5'-benzodiazepine-4'-yl]sydnones,*Il Farmaco*, **2000**, *55*, 406-409.

[26] Prashant Shinge, S.; Prashant Latthe, R.; Bharati Badami, V. Sydnones as Masked Hydrazines for the Synthesis of 4-Arylazo-1,2-dihydro-pyrazol-3-one Derivatives. *An International Journal for Rapid Communication of Synthetic Organic Chemistry*, **2005**, *36*, 2169-2176.

[27] Satheesha Rai, N.; Balakrishna Kalluraya ; Lingappa , B.; Shaliny Shenoy ;Vedavati Puranic, G. Convenient access to 1,3,4-trisubstituted pyrazoles carrying 5-nitrothiophene moiety via 1,3-dipolar cycloaddition of sydnones with acetylenic ketones and their antimicrobial evaluation. *European Journal of Medicinal Chemistry*, **2008**, *43*, 1715-1720.

[28] Shahrukh Asundaria, T.; Keshav Patel, C. Synthesis and characterization of somesulphonamide based bis–sydnones and their *in vitro* antimicrobial activity. *Indian Journal of chemistry,* **2010**, *49B*, 960-964.

[29] Shahrukh Asundaria, T.; Nikul Patel, S.; Keshav Patel, C. Novel 3–[4–(diethylamino)phenyl]–4–substituted–1–ylsulfonyl)sydnones: Synthesis, Characterization and antimicrobial studies. *Org. Commun.* **2010**, *3*, 30-38.

[30] Satyanarayana, K.; Rao, M. N. A. Synthesis of 4-[5-(substituted aryl)- 4,5-dihydro-1*H*-pyrazol-3-yl]-3-phenyl-sydnones as antiinflammatory,antiarthritic and analgesic agents. *European Journal of Chemistry,* **1995**, *30*, 641-645.

[31] Shreenivas. Deshpande, R.; Vasantakumar Pai, K. Synthesis and biological activities of certain mesoionic sydnone compounds containing chalcone moiety. *J. Basic Clin. Pharm.,* **2010**, 147-152.

[32] Ravindra Kamble, R.; Sudha Belgur, S.; Ravindranath; Aladkatti; Imthiyaz Ahmed Khazi. Synthesis and evaluation of benzophenone oxime derivatized with sydnones as inhibitors of secretory phospholipase A_2 with anti-inflammatory activity. *Chem. Pharm. Bull.,* **2009**, *57,*16.

[33] Shreenivas Deshpande, R.; Vasantakumar Pai, K. Synthesis, Antibacterial and Analgesic Activities of 4-[1-Oxo-3-(substituted aryl)-2-propenyl]-3-(4-methylphenyl) sydnones. *E. J. Chem.,* **2010**, *7*, 59-64.

[34] Gerusa Clazer Halila, Maria Benigna Martinelli de Oliveira, Aurea Echevarria, Alice Carneiro Belém, Maria Eliane Merlin Rocha, Eva Gunilla Skare Carnieri, Glaucia Regina Martinez, Guilhermina Rodrigues Noleto and Silvia Maria Suter Correia Cadena. Effect of sydnone SYD-1, a mesoionic compound, on energy-linked functions of rat liver mitochondria. *Chem. Biol. Interac.,* **2007**, *169*, 160-170.

[35] Satyanarayana, K.; Deshpande, S. R.; Subba Rao, B.; Rao, M.N.A. Anticancer activity of 4-[1-Oxo-(Substituted Aryl)-2-Propenyl]-3-Phenylsydnones. *Ind. J. Pharm. Sci.,* **2004**, *66*, 679-683.

[36] Grynberg, N.; Gomes, R.; Shinzato, T.; Echevarria, A.; Miller, J. Synthesis and *in vivo* antitumor activity of new heterocyclic derivatives of the 1,3,4-thiadiazolium-2-aminide class. *Anticancer Res.,* **1992**, *12*, 1025-1028.

[37] Senff-Ribeiro1, A.; Echevarria, A.; Silva, E.F.; Franco, C. R. C.; Veiga, S. S.; Oliveira, M.B.M. Cytotoxic effect of a new 1,3,4-

thiadiazolium Mesoionic compound (MI-D) on cell lines of human melanoma. *Br. J. Cancer,* **2004**, *91*, 297-304.

[38] Stelia Carolina Mendez-Sanchez, Glaucia Regina Martinez, Silvia Romão, Aurea Echevarria, Edson Fernandes Silva, Maria Eliane Merlin Rocha, Guilhermina Rodrigues Noleto, Eva Gunilla Skare Carnieri, Silvia Maria Suter Correia Cadena and Maria Benigna Martinelli de Oliveira. *Chemico-Biological Interactions,* **2009**, *179,* 125-130**.**

[39] Gireesh Tegginamath, Ravindra Kamble, R.; Pramod Kattimani, P.; Sheetal Margankop, B. Synthesis of 3-aryl-4-({2-[4-(6-substituted-coumarin-3-yl)-1,3-thiazol-2-yl]hydrazinylidene}methyl/ethyl)-sydnones using silica sulfuric acid and their antidiabetic, DNA cleavage activity. *Arab. J. Chem.,* **2011**.

[40] Levina, V.; Grigor'ev, N.V.; Granik, V. G. Psychotropic Preparations Sydnophen and Sydnocarb as Donors of Nitrogen Monoxide. Chem. Of heterocyclic compounds, **2004**, *40*, 507.

[41] Kankaanranta, H.; Rydell, E.; Petersson, A.S.; Holm, P.; Moilanen, E.; Corell, T.; Karup, G.; Vuorinen, P.; Pedersen, S.B.; Wennmalm, A.; Metsi-Ketela, T. Nitric oxide-donating properties of mesoionic 3-aryl substituted oxatriazole-5-imine derivatives. *Br. J. Pharm.,* **1996**, *117*, 401-406.

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