CODEN (USA): IAJPBB **ISSN: 2349-7750**

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com ***Review Article***

SULPHUR CONTAINING DRUGS AND THEIR SYNTHESIS - A REVIEW

Mukhtar Ahmad Wani

Department of Chemistry, Degree College Boys Anantnag Jammu & Kashmir (India)

Abstract:

Sulfur-derived functional groups can be found in a broad range of pharmaceuticals and natural products. For centuries, sulfur continues to maintain its status as the dominating heteroatom integrated into a set of 362 sulfur-containing FDA approved drugs (besides oxygen or nitrogen) through the present. Sulfonamides, thioethers, sulfones and Penicillin are the most common scaffolds in sulfur containing drugs, which are well studied both on synthesis and application during the past decades

Keywords: pharmaceuticals, sulfur-containing FDA, Penicillin, scaffolds

Corresponding author:
Mukhtar Ahmad Wani,

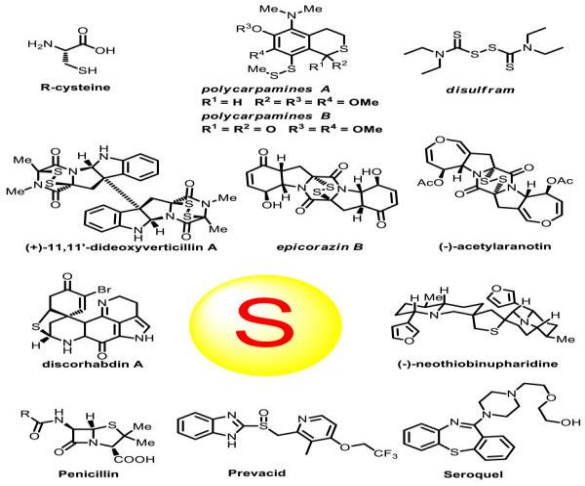
Department of Chemistry,
Degree College, Anantnag,
Jammu & Kashmir (India).

QR code

*Please cite this article in press as Mukhtar Ahmad Wani, **Sulphur Containing Drugs and Their Synthesis- A Review**, Indo Am. J. Pharm. Sci, 2014; 1(6):529-533.*

INTRODUCTION:

Sulfur containing compounds often show different biological activities and serve important functions in applications in the pharmaceutical industry [1-3]. Variety of sulfur containing scaffolds widely exists in natural products and drugs (Fig. 1). For instance, epidithiodiketopiperazine (ETP), characterized by sulfur atoms and a diketopiperazine structure, comprises a large number of metabolites, which display a range of biological activities including antiviral, antibacterial, antiallergic, antimalarial and cytotoxic properties [4-5]. Prevacid is a proton-pump inhibitor (PPI) which inhibits the stomach's production of gastric acids [6]. Seroquel is an atypical antipsychotic approved for the treatment of schizophrenia, bipolar disorder, and in the XR version along with a selective serotonin reuptake inhibitor (SSRI) to treat major depressive disorder [7].



Suphoamide Containg Drugs

From a historical perspective, sulfonamides have been a leading constituent in new drugs since the first appearance in the 1930s [8], occupying six decades over the past 100 years.

Sulfonamide drugs were the first antibiotics to be used systemically, and paved the way for the new antibiotic revolution in medicine. Nevertheless, antibiotics are not the only function of sulfonamides. Table 1 showed a list of sulfonamide containing scaffolds in pharmaceutical molecules with different indications. For example, cyclothiazide is a diuretic and antihypertensive that was originally introduced in the United States in 1963 by Eli Lilly [9].

Methods for Synthesis

One of the most conventional routes to sulfonamide involves the direct N-S bond formation *via* an addition-elimination process (Fig. 2). Sulfonyl chloride is a common substrate in this type of reactions, which reacts with aryl or alkyl amines to afford the corresponding sulfonamide in large scale [10-12].

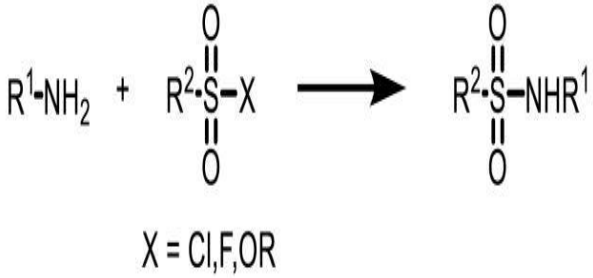


Fig 2: sulfonamide involves the direct N-S bond formation *via* an addition-elimination process

To date, such an approach is a general method for the preparation of sulfonamide in pharmaceutical industry which still needs further improvement. In 2006, a facile sulfonamide synthesis in water under pH control was reported by Deng and co-workers [13]. The desired sulfonamide was afforded in up to 98% yield and with greater than 95% purity by simply acidifying the solution with concentrated HCl to pH=2.0 and collecting precipitated product after the reaction. Furthermore, the reaction was easily scalable to 100 grams. This method is also suitable for various amino compounds and arylsulfonyl chlorides (Fig. 3).

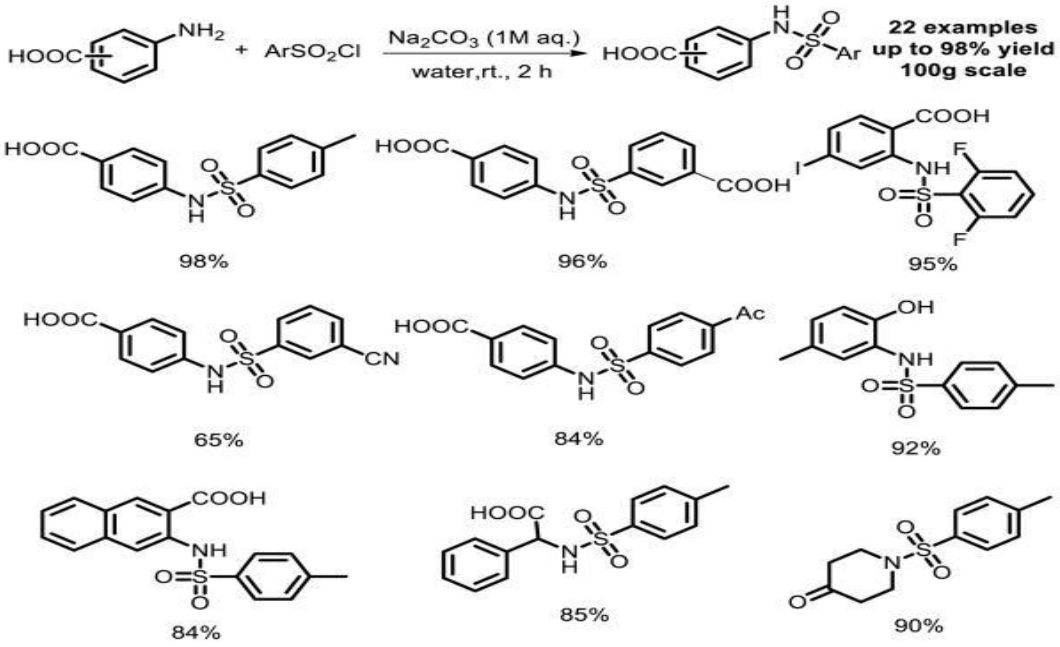
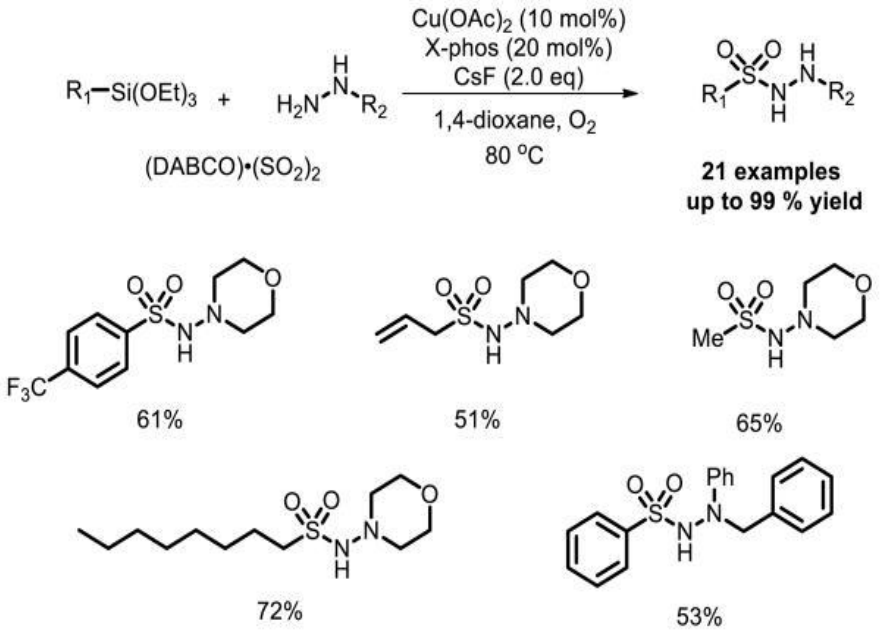


Fig 3:Aryl-, alkenyl- and alkyl groups can be incorporated into the final products

A three-component reaction of triethoxysilanes, DABSO, and hydrazines catalyzed by copper(II) acetate was reported by Wang *et al.* [14], leading to *N*-aminosulfonamides in good yields. This is the first example of using a copper catalyzed aminosulfonylation process through the insertion of sulfur dioxide. Aryl-, alkenyl- and alkyl groups can be incorporated into the final products (Fig. 3).



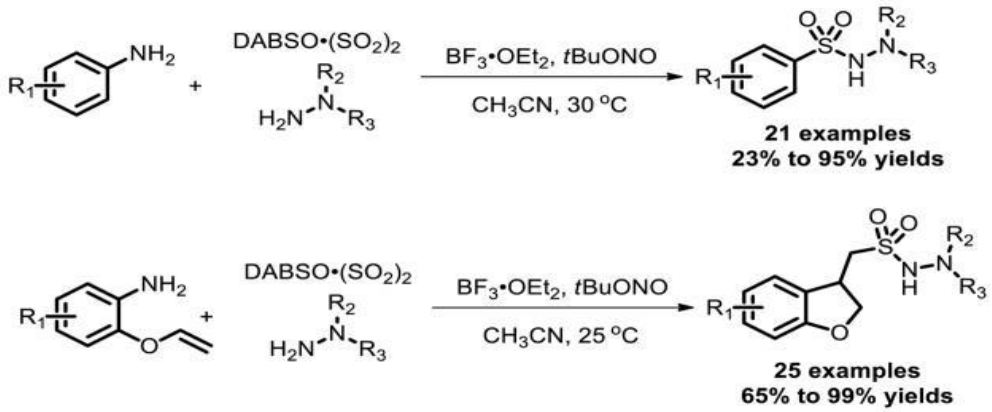


Fig 4: intramolecular 5-*exo*-cyclization and insertion of SO_2 reaction was a radical process

A metal free coupling of aromatic and heteroaromatic amines with DABSO and hydrazines, leading to aryl *N*-aminosulfonamides in good to excellent yields, was reported by Wu *et al.* in 2014 [15]. Different functional groups including ester, hydroxyl, chloro and trifluoromethyl groups are compatible under these conditions. Subsequently, they disclosed that when 2-(allyloxy)anilines were used instead of amines, a cascade reaction was triggered to give the 1-(2,3-dihydrobenzofuran-3-yl)-methanesulfonohydrazides in good yields [16-17]. This cascade intramolecular 5-*exo*-cyclization and insertion of SO_2 reaction was a radical process (Fig. 4).

While these examples represent an important achievement in sulfonylation chemistry, amine nucleophiles remain incompatible with these types of couplings. To address this limitation, a new protocol was developed by Buchwald and co-workers [18]. They demonstrated that phenyl chlorosulfate represents an excellent $[SO_2Cl]^+$ synthon in the context of Pd catalyzed Suzuki Miyaura cross-coupling, which provided different kinds of sulfonamides in good to excellent yields.

CONCLUSION:

In summary, the most common sulfur containing drugs and recent advances in the synthesis of the core scaffolds, including sulfonamides, thioethers, sulfones and penicillins are presented. Other sulfur containing moieties such as thiophenes and thiazoles can be found in pharmaceutical molecules as well. Although many novel protocols have been developed, some challenges still remain.

REFERENCES:

1. **a)** Bernardi F, Csizmadia IG, Mangini A. In: Organic Sulfur Chemistry. Theoretical and Experimental Advances. Bernardi F, Csizmadia IG, Mangini A, editors. Elsevier; Amsterdam, The Netherlands: 1985. **b)** Block E. Reactions of Organosulfur Compounds. Academic Press; New York: 1978. **c)** Patai S, Rappoport Z. The Chemistry of Organic Selenium and Tellurium Compounds. John Wiley & Sons; New York: 1986–1987. **d)** McReynolds MD, Dougherty JM, Hanson PR. Synthesis of phosphorus and sulfur heterocycles via ring-closing olefin metathesis. Chem Rev. 2004;104:2239–2258. **e)** Ager DJ. Silicon-containing carbonyl equivalents. Chem Soc Rev. 1982;11:493.

2. **a)** Guo H, Sun B, Gao H, Chen X, Liu S, Yao X, Liu X, Che Y. Diketopiperazines from the *cordyceps*-colonizing fungus *Epicoccum nigrum*. J Nat Prod. 2009;72:2115–2119. **b)** Wang J-M, Ding G-Z, Fang L, Dai J-G, Yu S-S, Wang Y-H, Chen X-G, Ma S-G, Qu J, Xu S, Du D. Thiodiketopiperazines produced by the endophytic fungus Epicoccum nigrum. J Nat Prod. 2010;73:1240–1249.

3. Piscitelli SC, Goss TF, Wilton JH, D'Andrea DT, Goldstein H, Schentag JJ. Effects of ranitidine and sucralfate on ketoconazolebioavailability. Antimicrob Agents Chemother. 1991;35:1765–1771.

4. Thase ME, MacFadden W, Weisler RH, Chang W, Paulsson BR, Khan A, Calabrese JR, Bolder G. Efficacy of quetiapine monotherapy in bipolar I and II depression: A double-blind, placebo-controlled study (The BOLDER II Study) Journal of Clinical Psychopharmacology. 2006;26:600–609.

5. Lesch JE. The First Miracle Drugs: How the Sulfa Drugs Transformed Medicine. Oxford University Press; 2007.
6. Sittig M. Pharmaceutical Manufacturing Encyclopedia. Park Ridge, Noyes Publications; N.J., U.S.A: 1988. p. 1756.
7. For a list of top drugs by year, see: [Accessed on April 24, 2015];.
8. Ilardi EA, Vitaku E, Njardarson JT. Data-mining for sulfur and fluorine: an evaluation of pharmaceuticals to reveal opportunities for drug design and discovery. J Med Chem. 2014;57:2832–2842.
9. Anderson KK. In: Sulfonic Acids and Their Derivatives in Comprehensive Organic Chemistry. Barton DHR, Ollis WD, Jones DN, editors. Vol. 3. Pergamon Press; Oxford: 1979. pp. 331–350.
10. Deng X, Mani NS. A facile, environmentally benign sulfonamide synthesis in water. Green Chem. 2006;8:835–838.
11. Gioiello A, Rosatelli E, Teofrasti M, Filipponi P, Pellicciari R. Building a sulfonamide library by eco-friendly flow synthesis. ACS Comb Sci. 2013;15:235–239.
12. Tang X, Huang L, Qi C, Wu X, Wu W, Jiang H. Copper-catalyzed sulfonamides formation from sodium sulfinates and amines. Chem Commun. 2013;49:6102–6104.
13. Wei W, Liu C, Yang D, Wen J, You j, Wang H. Metal-free direct construction of sulfonamides via iodine-mediated coupling reaction of sodium sulfinates and amines at room temperature. Adv Synth Catal. 2015;357:987–992.
14. Zhang W, Xie J, Rao B, Luo M. Iron-catalyzed *N* arylsulfonamide formation through directly using nitroarenes as nitrogen sources. J Org Chem. 2015;80:3504–3511.
15. Liu G, Fan C, Wu J. Fixation of sulfur dioxide into small molecules. Org Biomol Chem. 2015;13:1592–1599.
16. Pandya R, Murashima T, Tedeschi L, Barrett AGM. Facile one-pot synthesis of aromatic and heteroaromatic sulfonamides. J Org Chem. 2003;68:8274–8276.
17. Bouchez LC, Dubbaka SR, Turks M, Vogel P. Sulfur dioxide mediated one-pot, three- and four-component syntheses of polyfunctional sulfonamides and sulfonic esters: study of the stereoselectivity of the ene reaction of sulfur dioxide. J Org Chem. 2004;69:6413–6418.
18. Woolven H, Gonzalez-Rodriguez C, Marco I, Thompson AL, Willis MC. DABCO-bis(sulfur dioxide), DABSO, as a convenient source of sulfur dioxide for organic synthesis: utility in sulfonamide and sulfamide preparation. Org Lett. 2011;13:4876–4878.