REVIEW ARTICLE

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Biological Activities of Sulfonamides

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Sulfonamides exhibit broad range of biological activities. Several sulfonamides are used in therapy such as celecoxib, nimesulide, delavirdine, acetazolamide, methazolamide, furosemide, ethoxzolamide, dichlorphenamide, dorzolamide, brinzolamide, sulpiride, sotalol, tolbutamide, chlorpropamide, tolazamide, acetohexamide, glipizide, gliburide, glymidine, zonisamide, thiothixene and famotidine. So far, modifications of the sulfonamides have proven highly effective and modifications that have been made so far do not exhaust the possible changes that can be made to improve potency and efficacy of these sulfonamides. The present review highlights the recently synthesized sulfonamides possessing important potential biological activities. It would be interesting to see whether new sulphonamide derivatives can be utilized as potent therapeutic agents in future.

In 1932, Domagk studied a bright red dye, later to be named prontosil (1) and found that it caused remarkable cures of streptococcal infections in mice[1]. However, prontosil was inactive on bacterial cultures. Domagk's studies on Prontosil continued, and in 1933, the first of many human cures of severe staphylococcal septicemia was reported[2]. Prontosil's inactivity *in vitro*, but excellent activity *in vivo*, attracted much attention. In 1935, Trefouel and coworkers reported their conclusions from structure activity study of sulfonamide azo dyes, that the azo linkage was metabolically broken to release the active ingredient, sulfanilamide (2). Their reported finding was confirmed in 1937 when Fuller[3] isolated sulfanilamide from the blood and urine of patients being treated with prontosil.

Following prontosil's dramatic success, a cascade of sulfonamide derivatives began to be synthesized. Today, sulfonamide–trimethoprim combinations are used extensively for opportunistic infections in patients with AIDS[4] (*Pneumocystis carinii* pneumonia treatment and prophylaxis, cerebral toxoplasmosis treatment and prophylaxis), urinary tract infections and in burn therapy. They are also the drugs of choice or alternates for a few other types of infections, but their overall use is otherwise quite limited in modern therapy, having been largely replaced by antibiotics. Inspite of these replacements a lot of research is going on to develop more promising sulfonamide derivatives as antimicrobial. The strongly electron withdrawing character of the aromatic SO_2 group makes the nitrogen atom to which it is directly attached partially electropositive. This, in turn increases the acidity of hydrogen atoms attached to the nitrogen so that this functional group is slightly acidic pKa 10.4. Replacement of one of the NH_2 hydrogens by an electron withdrawing heteroaromatic ring was not only consistent with antimicrobial activity but also greatly acidified the remaining hydrogen and dramatically enhanced potency. Sulfathiazole, a widely used drug has a pKa value of about 5 and substitution on the N of the sulfonamide generally increases the acidity .The acidity of this group is also responsible for the diuretic activity of sulfonamides like acetazolamide.

The term Sulfonamide is commonly used to refer to antibacterials that are (i) aniline substituted sulfonamides, the sulfanilamides, (ii) prodrugs that produce sulfanilamide

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(sulfasalazine) and (iii) nonaniline sulfonamides (mafenide). However, several other widely used classes of drugs are also sulfonamides or sulfanilamides. The sulfonamide derivatives showed two main side effects, hypoglycemia and carbonic anhydrase inhibition. These side effects were studied for the development of drugs with maximal action of these kinds. These studies led to discovery of many useful therapeutically active drugs namely furosemide (high ceiling diuretic), thiazide derivatives (diuretic agents), sulfonylureas (antidiabetic agents), celecoxib (antiinflammatory agent), sulpiride (antipsychotic agent), sotalol (β - blocker) and delavirdine (antiHIV agent). In addition to these activities, sulfonamides are documented in literature to possess other significant biological activities also such as anticancer activity, 5-HT_6 receptor antagonists, analgesic, anticonvulsant, in the treatment of alopecia and certain memory disorders. The present review highlights the recently synthesized sulfonamide derivatives possessing potential biological activities.

Antimicrobial activity:

The antibacterial action of sulfonamides is by way of interference with bacterial biochemical reaction lacking in man and represents the first Magic Bullet. The discovery of antimetabolite mechanism of action led to the synthesis of analogues of metabolite p-aminobenzoic acid (PABA)[5] and other sulfonamide derivatives. But efforts for synthesis of analogues PABA were not successful in synthesizing useful compounds. Bharmal *et al.*[6] synthesized some new N-aryl-sulfonamido-2-chloro-8-methylquinolin-3-yl-azomethines (3) and tested them for antimicrobial activity against gram positive, gram negative bacterial strains and antifungal activity towards *Aspergillus niger*. The compounds were moderately active against different strains of bacteria and fungus. Significant activity was observed in compounds having R=4-acetamidophenyl, 3-carboxy-4-chlorophenyl, 3-carboxy-6-methylphenyl and 2,4-dichlorophenyl. Shah *et al.*[7] synthesized some new sulfonamide arylamides and thiourea derivatives having 2-amino-4-(6'-methoxy-β-naphthyl)-thiazole moiety. The compounds were screened for antimicrobial activity against *B. megaterium, B. subtilis, E. coli, P. fluorescence* and *A. awamori*. Most of the compounds showed mild to moderate antimicrobial activity. Patel *et al.*[8] reported the synthesis and antimicrobial activity of sulfonamide derivatives (4). The compounds containing R=4-methylphenyl showed moderate to good activity, R=phenyl exhibited good antimicrobial activity that was comparable with standard drug ampicillin against *B. subtilis*, R=3-carboxy-4-methylphenyl showed comparable activity with standard drug norfloxacin against *E. coli*. Joshi *et al.*[9] carried out synthesis and comparative study on antibacterial activity of sulfonamides and Mannich bases derived from them. The compounds were screened for their antibacterial activity against various gram positive and gram negative bacteria and were analyzed statistically. The results have shown that the compounds are quite active against pathogen under study and were nontoxic.

Gadad *et al.*[10] prepared some 5-guanylhydrazone/thicyanato-6-arylimidazo-[2,1-b]-1,3,4-thiadiazole-2-sulfonamide derivatives (5). All the compounds were screened for antibacterial activity against *E. coli, S. aureus, S. typhi, P. aeruginosa* and Pneumococci. The compounds were more active when R=p-chlorophenyl, p-bromophenyl, p-nitrophenyl against both *E. coli* and *S. aureus*. They also concluded that presence of 5-guanylhydrazone and 5-thiocyanato group result in increased antibacterial activity. Similarly, synthesis and antimicrobial activity of sulfonamide has been reported by Briganti *et al.*[11], Vigorita *et al.*[12], Bhatt *et al.*[13] and Zeljka *et al.*[14].

Carbonic anhydrase inhibitors:

Carbonic anhydrases are wide spread enzymes present in animals in at least 14 different isoforms. Some of these isozymes are cytosolic (CA I, CAII, CA III, CAVII, CAXIII), others are membrane bound (CAIV, CAIX, CAXII, CAXIV). CAVI is secreted in saliva and milk. Three cytosolic catalytic forms are also known (CARP VIII, CARPX and CARPXI). The catalytically active isoform, which plays important physiological and patho-physiological functions is strongly inhibited by aromatic and heterocyclic sulphonamides. It has been demonstrated recently that molecules that act as CA activators bind at the entrance of the enzyme active site, participating in facilitated proton transfer process between the active site and the reaction medium. In addition to CA II activator adducts, X-ray crystallographic studies have also been reported for ternary complexes of this enzyme with activators and anion (azide) inhibitors. The use of CA isozyme activators as potential memory enhancing drugs has been reported.

Shortly after the treatment of bacterial infections with sulfanilamide, it was observed to produce a mild diuresis characterized by the presence of urinary sodium and a substantial amount of bicarbonate[15]. It was subsequently shown that it induced this effect through inhibition of carbonic anhydrase[16]. Because of its relatively weak carbonic anhy-

drase inhibitory activity, sulfonyl containing compounds were synthesized and screened for their ability to inhibit carbonic anhydrase *in vitro*. This yielded prototype acetazolamide[17-20] (21) and methazolamide. Today also sulfonamide derivatives are being investigated for their carbonic anhydrase inhibitory activity because inhibition (but also activation) of this enzyme may be exploited clinically in the treatment or prevention of a variety of disorders[21]. Two more clinically used carbonic anhydrase inhibitor sulfonamides, ethoxzolamide and dichlorphenamide, have been used for more than 40 years as diuretics whereas additional two drugs dorzolamide (clinically launched in 1995) and the structurally related brinzolamide (used since 1999) are topically acting antiglaucoma CAIs. Kakeya *et al.*[22] applied Hansch–Fujitas equation to an analysis of natriuretic activity of sulphonamide carbonic anhydrase Δ inhibitor using π, π c as hydrophobic parameters and σ, Δ pka, Δ ppm and Δ fr as electronic parameters. Sixteen benzenesulphonamide derivatives were satisfactorily applied to the SA analysis of heterocyclic sulfonamides. They concluded that a strong natriuretic activity was observed for sulphonamides which have an optimal hydrophobicity and low electronegativity at the sulfamoyl group or a strong inhibitory activity against carbonic anhydrase. Garaj *et al.*[23] reported the synthesis and inhibition of cytosolic/tumor-associated carbonic anhydrase isozyme I, II and IX with sulphonamides incorporating 1,2,4–triazine moieties. Cecchi A *et al.*[24] prepared a series of sulphonamides incorporating 4-thioureido benzolamide moieties from aminobenzolamide and thiophosgene followed by the reaction of the thiocyanato intermediate with aliphatic/aromatic amines or hydrazine and investigated as inhibitors of the zinc enzyme carbonic anhydrase. Hassan *et al.*[25] synthesized schiffs bases from aromatic/heterocyclic sulphonamides and aminosulphonamide derivatives, such as sulphanilamide, homosulphanilamide. Metal complexes of some of these schiffs bases were also prepared and tested as inhibitors of carbonic anhydrase. Chazalette *et al.*[26] synthesized a series of aromatic sulphonamides incorporating indane moieties starting from 1- and 2-indanamine and their activity as inhibitors of two carbonic anhydrase isozymes h CAI and II was studied. They reported that the new sulphonamides incorporating acetamido, 4-choloro-benzoyl, valproyl, tetra and pentafluorobenzoyl moieties acted as very potent inhibitors of isozyme h CAI. Supuran *et al.*[27] reported that sulphonamide COX-2 selective inhibitors except rofecoxib (containing methylsulfone) act as nanomolar inhibitors of several isozymes of carbonic anhydrase.

Cyclooxygenase-2 inhibitors:

Non-steroidal antiinflammatory drugs have been found to prevent the production of prostaglandins (PGs) by inhibiting the conversion of arachidonic acid to PGs by the constitutive cyclooxygenase enzyme. In the 90s, a previously unknown enzyme in the human arachidonic acid/prostaglandin pathway was discovered[28-30], and designated cyclooxygenase II (COX-2) or prostaglandin G/H synthase II. COX-2 plays a major role in prostaglandin biosynthesis in inflammatory cells and in central nervous system. These observations suggest that COX-1 and COX-2 serve different physiological and pathological functions. The differential tissue distribution of COX-1 and COX-2 provide a rationale for the development of selective COX-2 inhibitors as antiinflammatory and analgesic agents that lack gastrointestinal and hematological liabilities exhibited by currently marketed NSAIDs. This hypothesis has been validated and has led to the marketing of diaryl heterocyclics such as celecoxib (6), parecoxib (27), valdecoxib (28), etoricoxib, lumiracoxib and rofecoxib (26) as COX-2 inhibitors. The development of Celecoxib as COX-2 inhibitors has potentiated the research involving sulfonamides as COX-2 inhibitors.

Li *et al.*[31] have identified an extensive series of 1,2-diarylcyclopentenes that act as potent and selective COX-2 inhibitors. Replacement of methyl sulfone moiety with a sulfonamide group on the second phenyl group was found to provide a substantial enhancement of *in vivo* potency, especially, in the rat adjuvant-induced arthritis model, albeit with some decrease in COX-2 selectivity. It is also reported that *in vitro* COX-1/COX-2 selectivity in sulfonamide series can be increased in many cases by simply incorporating a halogen atom at the 3-position of one of the phenyl ring. The selective COX-2 inhibitor sulfonamide (7) has been shown to be a remarkably orally active antiinflammatory agent with no indication of gastrointestinal toxicity. Huang *et al.*[32] have reported a novel series of 5,6-diaryl spiro (2,4)-hept-5-enes as highly potent and selective COX-2 inhibitors. Methylsulfone and sulfonamide (8) were shown to have superior *in vivo* pharmacological profile, low GI toxicity, good oral bioavailability and better duration of action. They have also reported[33] some more sulfonamides as potent and selective COX-2 inhibitors.

A series of sulfonamides containing 1,5-diarylpyrazole derivatives[34] were prepared and evaluated for their ability to block COX-2 *in vitro* and *in vivo*. Extensive structure activity relationship was carried out within this series and many

potent and selective inhibitors of COX-2 were identified. Since an early structural lead SC-236 (9) exhibited unacceptably long plasma half life, several pyrazole analogs containing potential metabolic sites were evaluated further *in vivo* in an effort to identify compounds with acceptable pharmacokinetic profiles. This work led to identification of SC-58635, Celecoxib (6) which is currently in use as a drug. Puig *et al.*[35] have prepared a series of 3,4-diaryloxazolone and evaluated for their ability to inhibit COX-2. Extensive structure activity relationship identified several potent and selective COX-2 inhibitors. The replacement of methyl sulfone group on the 4 -phenyl ring by a sulfonamide moiety resulted in compounds with superior *in vivo* antiinflammatory properties such as (10-13). COX-2 inhibitory activity of sulfonamides has also been reported by Hu *et al.*[36-37], Padakanti *et al.*[38] and Rao *et al.*[39].

AntiHIV activity:

The acquired immunodeficiency syndrome (AIDS) is due to a retrovirus, the human immunodeficiency virus (HIV). The world became aware of this disease in the summer of 1981, and it has exploded in successive waves in various regions of the world and today, India has the second largest population of HIV infected individuals. For the treatments of AIDS, two major classes of drugs are used namely nucleoside reverse transcriptase inhibitors and non nucleoside reverse transcriptase inhibitors (NNRTIs). The NNRTIs are a class of chemically distinct synthetic compounds that block reverse transcriptase activity. They are active against only HIV-1 and not HIV-2. Three NNRTIs are FDA approved namely nevirapine, efavirenz and delavirdine (14). Among these delavirdine was discovered after investigating a large number of sulfonamide derivatives and still these are being investigated for their anti HIV activity.

Boyer *et al.*[40] synthesized a series of compounds which possessed various sulfonyl moieties substituted at the 4 - position of C_3-phenyl ring substituents of the dihydropyran-2-one ring system. The sulfonyl substituents added were reported to fill the additional S (3)' pocket producing potent inhibitors of target enzyme. All analogs were reported to display decent binding to HIV protease and several compounds were shown to possess very good antiviral efficacy and safety margin. Vazquez *et al.*[41] synthesized various α and β-amino acid hydroxyethylamino sulfonamides and subjected them for anti HIV activity. The compounds were reported as retroviral protease inhibitors. Compound (15) (cbz = benzyloxycarbonyl) showed good activity. Thaisrivongs *et al.*[42] reported sulfonamides containing 4-Hydroxycoumarin and 4-hydroxy-2-pyrones as anti HIV agent. They used previously known compound, phenprocoumon, as lead template to discover non-peptidic HIV protease inhibitors. They replaced carboxamide moiety by sulfonamide functionality that led to a series of non amino acid containing promising HIV protease inhibitors. The most active diastereomer of sulfonamide containing pyrone moiety (16) showed improved antiviral activity. Compounds (16) and (17) were found to be mixture of stereoisomers. The components were studied for their enzyme inhibitory and *in vitro* antiviral activities. For compound (17) two individual enantiomers were shown to be very close in activity. For compound (16) two diastereoisomers were found to be slightly more active than remaining two diastereoisomers. Harvey *et al.*[43] synthesized sulfonamide substituted cyclooctylpyranones as non-peptidic HIV protease inhibitors. In this series p-cyanophenyl sulfonamide derivative (18) emerged as promising inhibitor and it was selected for further development and entered phase-II clinical trials. Sulfonamide derivatives as potential anti HIV agents are also studied by Aristoff *et al.*[44] and Pomarnacka *et al.*[45].

Anticancer activity:

Until recently, the only approach for the treatment of cancer was surgery, for localized and accessible tumors, and radiotherapy. The era of chemotherapy of malignant diseases was born in 1941 when Higgins demonstrated that the administration of estrogen produced regression of metastatic prostate cancer. This was followed by the discovery of many alkylating agents, antimetabolites, anticancer antibiotics, platinum containing compounds and some natural products as anticancer agents. In recent years, a great variety of sulfonamide compounds have been investigated in experimental animals, and a few have proven useful in the treatment of human neoplasm, at acceptable level of toxicity, to deserve the designation of chemotherapeutic agents. Gotteland *et al.*[46] reported preparation of methionine containing aniline derived sulfonamides as inhibitors of protein farnesyl transferase (PFTase) and geranylgeranyl transferase (GGTase). In their study compound (19) inhibited PFTase with IC_{50}=20 nM. A focused compound library of novel N-(7-indolyl) benzenesulfonamides (20) for the discovery of potent cell cycle inhibitors is reported by Takashi *et al.*[47]. For this type of compounds, cell cycle analysis with P388 murine leukemia cells revealed that there were two different classes of potent cell cycle inhibitors; one disrupted mitosis and the other caused G1 accumulation. They also described the structure activity relationship of the substituent pattern on this pharmacophore.

Scozzafava *et al.*[48] reported arylsulfonyl-N, N-diethyldithiocarbamates as novel antitumour agents. The reactivity of these new derivatives against cysteine and glutathione has been investigated in order to identify derivatives that might label a critical cysteine residue of tubulin (Cys 239 of human β2 tubulin chain). Some of the most reactive compounds showed moderate to powerful tumor growth inhibitory properties against several leukemia, non-small cell lung, ovarian melanomas, colon, CNS, renal, prostate and breast cancer cell lines *in vitro*. Synthesis, *in vitro* anticancer and anti HIV evaluation of new 2-mercaptobenzenesufonamides is reported by Pomarnacka *et al.*[45]. CA IX and CA XII (isoenzymes) are predominantly found in cancer cells[49]. Ilies *et al*[50] reported two series of halogenated sulfonamides. The first consists of mono/dihalogenated sulfanilamides (22), whereas the second one consists of the mono/dihalogenated aminobenzolamides (23), incorporating equal or different halogens. These sulfonamide derivatives were investigated as inhibitors of transmembrane, tumor associated isozyme CA IX. This first detailed CA IX inhibition study revealed many interesting leads suggesting the possibility to design even more potent and eventually CA IX selective inhibitors, with putative application as antitumour agents. A novel class of N-hydroxysulfonamides as intraocular pressure lowering agents has been reported by Francesco *et al* [51]. In this study, inhibition of three CA isozymes, hCA I, hCA II and bCA IV (h=human, b=bovine) with the prepared compound has been investigated. Susceptibility to inhibition was generally: hCA II > bCA IV > hCA I. Some of the new inhibitors showed very good antiglaucoma action when administered directly into the eye in experimental animals, acting as more efficient intraocular pressure lowering agents as compared to standard drug dorzolamide. Supuran *et al* [52] also reported synthesis of substituted ureido and thioureido derivatives of aromatic/heterocyclic sulfonamides with increased affinity for isozyme I.

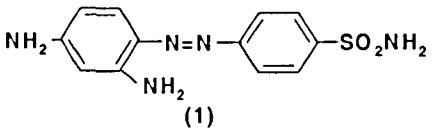
Hypoglycemic activity:

In 1942, p-aminobenzenesulfonamidoisopropylthiadiazole (an antibacterial sulfonamide) was found to produce hypoglycemia. These results stimulated research for the development of synthetic hypoglycemic agents, several of which are in use today. Sulfonylureas, sulfonamide derivatives, became widely available in 1955 for the treatment of non-insulin dependent diabetes mellitus (NIDDM) and are still in use. Currently used sulfonylurea hypoglycemic agents are tolbutamide, chlorpropamide, tolazamide, acetohexamide, glipizide and gliburide. Because of these developments, a large number of sulfonamides are being investigated for their hypoglycemic activity. Preparation of N-substituted sulfonamide derivatives for treatment and prevention of diabetes has been reported by Toshisada *et al.*[53]. The title compound (24) [R_2 is hydrogen or halogen; A' is halogen, halogenated lower alkyl, halogenated lower alkoxy, or the like; X_2 is O or SO_2; N is an integer of 2 to 5; m is an integer of 3 to 5; X_3 is a single bond, lower alkylene, or lower alkenylene; and B' is optionally substituted phenyl ring] were prepared. They demonstrated good hypoglycemic activity of 3 compounds of this invention.

Hiroshi *et al.*[54] reported preparation of heterocyclic moiety containing sulfonamide compounds as hypoglycemic. These compounds also have cGMP-PDE inhibitory, bronchodilating, vasodilating, smooth muscle cell inhibitory and antiallergenic effects. The compound 3-(2,4-dichlorobenzyl)-2-methyl-5-(1-pentanesulfonylcarbamoyl) benzo[b]furan at 10mg/kg gave 71% decrease of blood sugar in mice. Preparation of substituted sulfonamides as 5-HT_6 receptor modulators for the treatment of CNS disorders, obesity and type II diabetes is reported by Katarina *et al*[55]. The compound (25) is reported to be potentially useful for the prophylaxis and treatment of medical conditions relating to obesity, type II diabetes and/or disorders of the CNS. Novel antidiabetic arylsulfonamidothiazoles that exert action through selective inhibition of the 11β-hydroxysteroid dehydrogenase type I (11β-HSD I) enzyme, thereby attenuating hepatic gluconeogenesis has been reported by Barf *et al.*[56]. The diethylamide derivative was shown to be a potent inhibitor of human 11β-HSD I (IC_{50}=52 nM), whereas the N-methylpiperazinamide analogue only inhibited murine 11β-HSD I (IC_{50}=96 nM). Both compounds showed >200 selectivity over human and murine 11β-HSD 2, substantiating the 11β-HSD I enzyme as a target for treatment of type 2 diabetes mellitus.

Miscellaneous activities:

In addition to the above mentioned biological activities, sulfonamides are also reported to possess some other important activities such as inhibitor of glycoprotein IIb/IIIa receptors, a platelet receptor that plays a key role in platelet aggregation and adhesion. An α-sulfonamide isoxazoline analog, DMP-802, a novel oral antiplatelet agent with high affinity, relatively slow dissociation rate and specificity for human GP IIb/IIIa receptors has been reported by Mousa *et al.*[57-58]. Synthesis of novel 3-(octahydropyrido-[1,2-a]pyrazin-2-yl)-phenyl analog and 3-(hexahydropyrrolo-[1,2-a]pyrazin-2-yl)-phenyl-2-benzo[b]thiophene sul-



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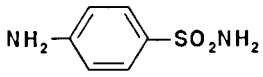

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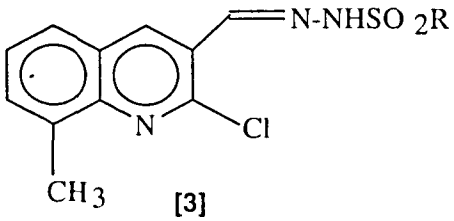

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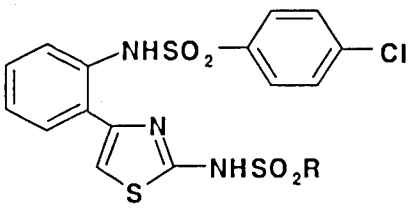

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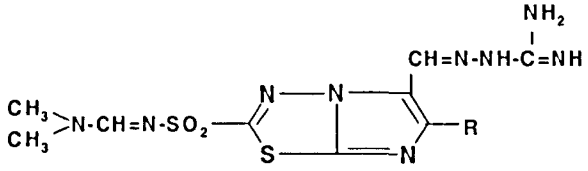

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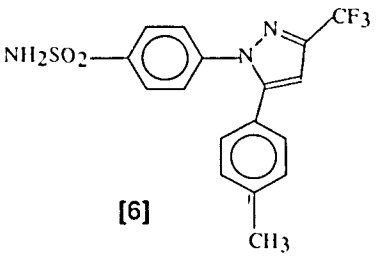

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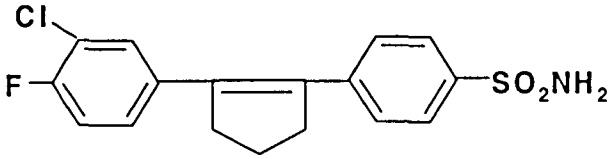

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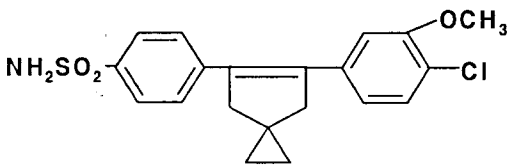

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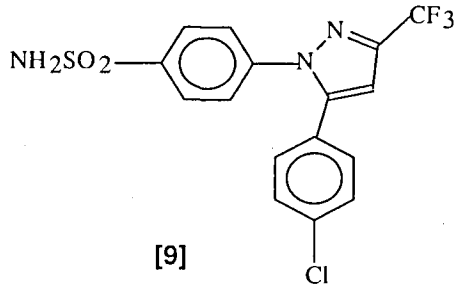

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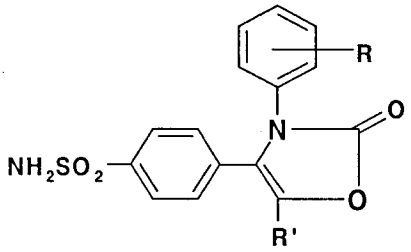
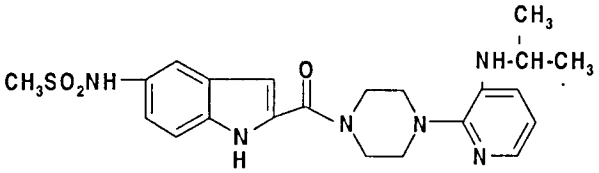


(10) R=H, R'=CH_3
(11) R=H, R'=H
(12) R=2F, R'=H
(13) R=3F, R'=H



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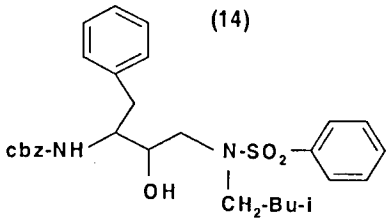

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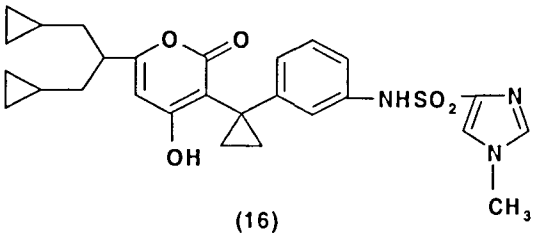

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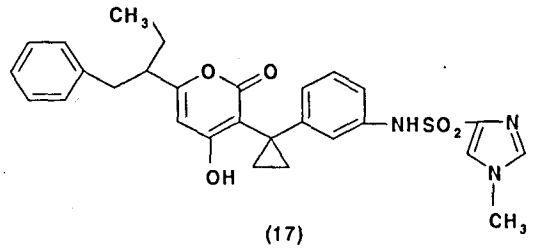

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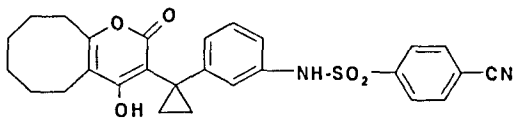

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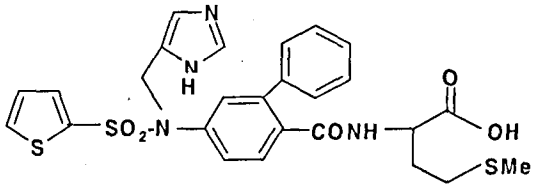

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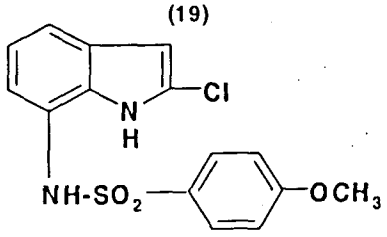
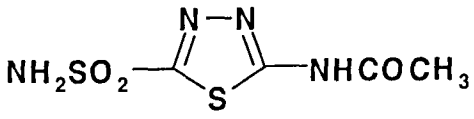
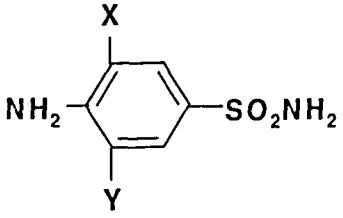


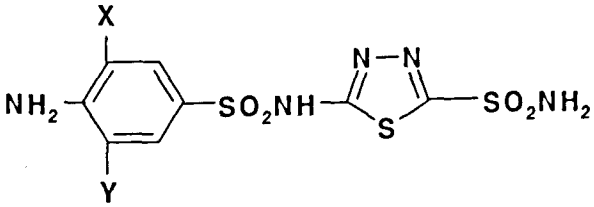
(20)



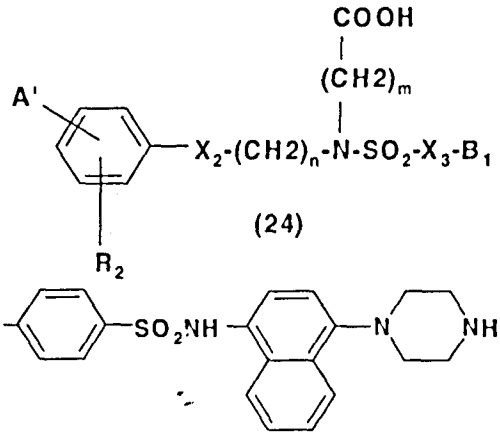
(21)



(22) X and Y= F, Cl, Br, I

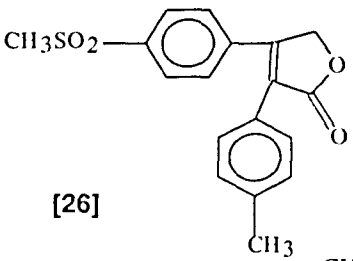


(23) X and Y= F, Cl, Br, I

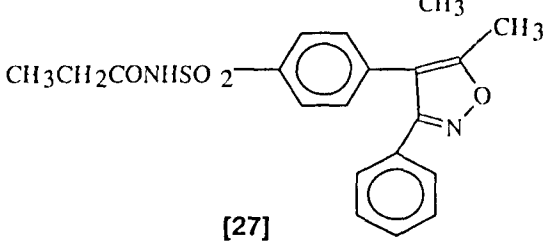


(24)

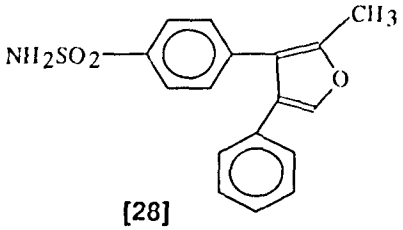
(25)



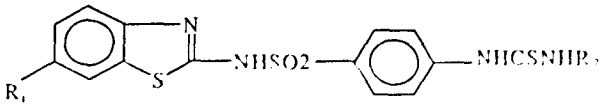
[26]



[27]



[28]



(29) $R_1 = F, R_2 = CH_3$
(30) $R_1 = F, R_2 = C_2H_5$
(31) $R_1 = Cl, R_2 = CH_3$
(32) $R_1 = Cl, R_2 = C_2H_5$
(33) $R_1 = Br, R_2 = CH_3$
(34) $R_1 = Br, R_2 = C_2H_5$
(35) $R_1 = OCH_3, R_2 = C_2H_5$

fonamide derivative is described by Bromidge *et al.*[59] as potent and selective 5-HT_6 receptor antagonists. The compounds showed high affinity for the 5-HT_6 receptor, excellent selectivity against a range of other receptors and good brain penetration. Slawinski[60] reported the synthesis and cardiovascular effects of some S-substituted 4-chloro-2-mercapto-5-methyl-N-(4-alkyl-4H-1,2,4-triazol-3-yl) benzenesulfonamides. The antiarrythmic effect of few compounds was comparable to the reference procainamide. N-linked sulfonamides of heterocyclic thioesters for treating vision disorders, improving vision, treating memory impairment, or enhancing memory performance in animals has been reported by Ross *et al.*[61]. Use of these types of compounds in the treatment of alopecia and promoting hair growth is also reported by Steiner *et al.*[62]. The carbonic anhydrase inhibitors acetazolamide, ethoxzolamide, sulthiame and disamide have anticonvulsant properties. Acetazolamide and disamide are primarily effective against petitmal, ethoxzolamide against grandmal, and sulthiame against psychomotor seizures. Zonisamide is a broad spectrum antiepileptic agent, effective in the treatment of refractory seizures. Anticonvulsant activity of analogs of acetazolamide is also reported by Chufan *et al.*[63]. Siddiqui *et al*[64] synthesized some 2-[{4-(alkylthioureido) phenyl} sulphonamido]-6-substituted benzothiazole by condensation of 2-(4-aminophenyl sulphonamido)-6-substituted benzothiazoles with alkyl isothiocyanates .The compound (35) with methoxy substitution showed maximum analgesic activity in the series. Highly significant results were also observed with compounds (30), (34), whereas other compounds of this series showed a decrease in analgesic activity.

So far, modifications of sulfonamides have proven highly effective and modifications that have been made so far do not exhaust the possible changes that can be made to improve potency and efficacy of these sulfonamides. It would be interesting to see whether these derivatives can be utilized as potent therapeutic agents in future.

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