New Insights Into the Promising Antibacterial Activity of Thiophene or Chromene Moiety Containing Aryl Sulfonamide

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Abstract

Background: Aryl sulfonamides bearing thiophene and chromene moieties have been reviewed for their antibacterial activity and their synthetic methods. Heterocyclic moiety containing aryl sulfonamide compounds are dispersed in nature and are crucial for life. Diverse investigational strategies towards a structural relationship that cognizance upon the exploration of optimized candidates have grown to be extremely crucial.

Method: Literature research tells that for a series of thiophene or chromene moiety containing aryl sulfonamide compoundsare vital in medicinal and industrial chemistry.Aryl sulfonamidescontainingheterocyclic moieties display pharmacological activities against pathogenic microbes.

Result:Recent various disciplinary reported articles had been cited in this review article to define the potentialantibacterial properties of thiophene-arylsulfonamide and chromene-arylsulfonamide.

Conclusion: The finding of this review confirms the importance of aryl sulfonamidescontaining thiophene or chromene moiety as potential antibacterial agents. These final resultswill give ideasto the synthesis and developmentof reactions leading to the potential derivativesfor betterpharmacological applications.

Introduction

The millions of people are affected by infectious diseases caused by bacteria which lead to the death of many people worldwide.[1] In developing countries, bacterial infections caused by pathogenic micro-organism lead to life-threatening diseases.[2] Presently, antibacterial agents which are commonly in use are Fidaxomicin, Cethromycin, Daptomycin, Torezolid and Solithromycin.[3] Antibacterial agents/Antibiotics are used to kill or control the growth of pathogenic bacteria but the long term usage of antibacterial agents there are chances that bacteria develop resistance against antibacterial/antibiotics.[4-5] In the current situation, multidrug-resistant microbial pathogens have emerged which affect the treatment of infectious diseases.[6] Some of the antibacterial agents like tetracycline are persistent in nature, owing to which they kill beneficial bacteria and cause gastrointestinal distress, yellowing of teeth[7], increased intestinal peristalsis related to erythromycin therapy[8],cause discolouration of skin[9], condrotoxicity[10], ototoxicity[11], retinopathy[12], lactic acidosis and serotonin syndrome[13], aplastic anemia[14], hepatitis[15], neuromuscular blockade[16] and neoplasia.[17] Numerous pathogenic bacteria occur in nature but the available antibacterial agents or antibiotics have limited inhibitory or killing action on bacteria. Few antibiotics have been found to exhibit activity against Gram-negative and Gram-positive bacteria.[18-19]

Organic chemistry has a significant impact on our lives, as organic compounds are extensively distributed and play a vital role in various biological fields. This approach has emerged and come to the centre stage in the form of Green Chemistry. The class of sulfonamide is an emerging group of research

and most of the organic chemists are engaged in the synthesis of novel sulfonamide.[20-23]Sulfonamide derivatives are usually prepared by the reaction of ammonia or primary or secondary amines with a sulfonyl chloride.[24] Sulfonamide derivatives have been obtained by the reactivity of sulfinic acid salt with highly electrophilic nitrogen from various organic sources.[25-26] Intermolecular free radical reactions of pentafluorophenylvinyl sulfonate with subsequent aminolysis reaction are a very convenient route to synthesize sulfonamides.[27] Among the broad variety of medicinal compounds, the functional groups of sulfonamide pharmacophore play a unique role in drug design.[28]Sulfonamidesdisplay a broad range of biological activities,including activity against microbial infection.[29-30] Derivatives of sulfonamides used for the treatments of infectious diseases caused by pathogenic microorganisms due to their growth-inhibiting tendency.[31] Compounds carrying sulfonamide core moieties, which construct them significantly in drug development, have demonstrated significant biological activities.[32]

Sulfonamides an antibiotic drug are linked with medicinal activities. Sulfonamides have lately exposed them to be distinctly competent synthons within the practice of diverse treasured biologically active compounds.[33] The derivatives of 9-sulfonylamino scaffold were enhanced antibacterial property against an array of minocycline and tetracycline-resistant pathogens as an example, staphylococcus aureus developed resistant from methicillin, carbapenems, penicillin, quinolone, cephems etc[34-36], while sulfonamides and their combination healing procedures are gaining more attention by means of the day in antimicrobial drug research.[37] As a result, it is viable to expand a sequence of sulfonamides with alkyl amide side chain amendment on carboxyl for enhanced antibacterial efficiency. Sulfonamides have medicinal applications and many of them are broadly utilized in therapeutic as antimicrobial[38], antitumor[39-40], anticancer[41], antiviral[42], anti-HIV[43], antidiabetic[44], antimalarial[45], antitubercular[46], analgesic[47], antioxidant[48], antihypertensive[49], antileishmanial[50], anti-inflammatory[51], anticonvulsant[52], diuretic[53], anti-carbonic anhydrase[54] and antiplatelet.[55]

Aryl sulfonamides

Aryl sulfonamides possess promising antibacterial properties. Singular sequences of effective thioether benzenesulfonamides are found to be inhibitors of carbonic anhydrases.[56]As an integral part of their structure, the majority of pharmacologically active compounds described in the literature contain a heterocyclic ring. Most of the biologically active compounds contain heterocyclic rings, such as thiophene, chromene, pyrrole, indole, triazole, tetrazole, imidazole, pyrrolidine, quinoline, isoquinoline, benzoxazole, benzimidazole, benzothiazole.[57-58]p-Toluene sulfonamide[59]containing heterocyclic components are extensively used, predominantly in pharmaceuticals. Aryl sulfonamides containing heterocyclic moieties[60]particularly chromene and thiophene constitute a crucial class of drugs and exhibit biological properties including antibacterial, antifungal, anticancer, antitumor, anti-HIV, anti-viral, anti-inflammatory, enzyme inhibitory, and many others. Aryl sulfonamide derivatives containing thiophene and chromene moieties have diverse biological properties.[61-62]

Sulfonamide core systems are found in nature.[63] Natural and synthetic sulfonamide molecules are attentive and influencing functional group of research due to their broad-spectrum biological and medicinal properties.[64] p-Toluene sulfonamides, the important class of sulfonamides, have been reported to exhibit numerous biological properties[65] mainly its applications found in these fields such as pharmaceutical, material science and agriculture. Generally, there are several reported synthesis processes for sulfonamide core-centric biologically active scaffold.[66-67]

Method Of Preparation

Synthesis of aryl sulfonamides

The reaction of aminobenzaldehyde and dicholorotosyl chloride in presence of chloroform at ambient temperature to form impure sulfonamide compounds. Impure compounds washed with acetone and finally, crude compounds were recrystallized in acetonitrile with the good yield to form the pure product of arylaldehyde aryl sulfonamide**(1)**.[68]N-arylacid aryl sulfonamide**(2)** was prepared by the reaction of amino benzoic acid and p-toluenesulfonyl chloride in water medium without organic solvent. The pH of the reaction was maintained due to the addition of Na_2CO_3 and concentrated HCl.[69].Ates *et al*. (2012)[70]reported the preparation of pyrrole-p-toluene sulfonamide **(3)** by the reaction of heterocyclic pyrrole and p-toluenesulfonyl chloride in presence of tetra hydro furan and n-butyl lithium at temperature −78 °C under mild condition. A direct procedure for the synthesis of aryl sulfonamide derivatives**(4)** was reported by Kamal *et al*. (2008).[71] The process involves the reaction of substituted arylamine and p-toluene sulphonyl chloride in presence of green solvent water at ambient temperature. The crude product of sulfonamide derivatives was purified by column chromatography on silica gel. An efficient method was developed for the synthesis of sulfonamide derivatives **(5)** involves two-component reaction of substituted acyl benzyl amine and tosyl-chloride using triethylamine (TEA) as catalyst and dichloromethane (DCM) as solvent at 0^oC.[72]N-substituted -3H-benzo[d]imidazol-5-yl) benzenesulfonamide**(6)**compounds have been synthesized by the reaction of substituted benzo[d]imidazol-5-amine and benzene sulphonyl chloride in pyridine and acetone at room temperature.[73]Zarchi and Aslani,(2012)[74]investigated a new catalytic process for the synthesis of aryl-p-toluene sulfonamide**(7)**. In this reaction, acetonitrile reacts with methoxyaniline in presence of catalyst poly (4-vinyl pyridine) [P_4-VP] at ambient temperature. The reaction of ethyl 5-amino-3-methylbenzofuran-2-carboxylate and fluoro tosyl-chloride in dichloromethane (DCM) in presence of pyridine as a basic catalyst at ambient temperature afforded ethyl 5-(4-fluorophenylsulfonamido)-3-methylbenzofuran-2-carboxylate **(8)** in good yield.[75]

Synthesis of N, N-substituted benzenesulfonohydrazide **(09)** was carried out by the reaction of aryl triazenes, hydrazine and sulfur dioxide in presence of catalyst $BF_3.OEt_2$ and methylcynide at 60^oC under mild conditions.[76]Wang *et al*. (2017)[77]developed method for the preparation of alkyl aryl sulfonamide derivatives**(10)**. Aryl hydrazine, hydrazines and potassium metabisulfite ($K_2S_2O_5$) react together in

methylcynide under an air atmosphere at 40^{o}C. In this process, aryl hydrazine was oxidized by air into aryl radicals and potassium metabisulfite was used to generate sulfur dioxide to the formation of sulfonamide derivatives.

Some sulfonamide moieties containing compounds are available for commercial importance and widely used in the clinic. Sulfonamides antibiotics are clinically approved drugs were used to prevent many infectious diseases including pathogenic bacteria known as sulfa drugs Antibacterial drugsulfisoxazole (**1**) were reported in the modified form such as synthesized metal (II)-sulfonamide are [Ni (sulfisoxazole)$_2$(H_2O)$_4$].2H_2O and [Cu (sulfisoxazole)$_2$(H_2O)$_4$].2H_2O were reported as efficient antibacterial agents.[78-79] Some new derivatives of sulfisoxazole containing 4-thiazolidinone and 2,3-dihydrothiazoles were evaluated against micro-organisms. Synthesized derivatives of sulfisoxazole possessed promising antimicrobial activity against various bacteria and fungus.[80] Sulfamethoxazole **(2)** is clinical used well known antibacterial drug. Synthesized complexes of lanthanide metal (La, Pr, Nd, Sm, Gd, Tb, Dy and Y) with sulfamethoxazole shows antibacterial activity.[81] The potential *in-vitro* release sulfamethoxazole drug is due to the water-soluble nature and shows an effective antibacterial property.[82]Majewsky *et al*., (2014)[83]reported the synthesizedderivatives of sulfamethoxazole and substituted sulfamethoxazole are potent antimicrobial agents. Silver complex with sulfamethoxazole[84]and Pt(II) and Pd(II) sulfamethoxazole complex[85] were synthesized and evaluated against bacterial strains. The antibacterial drug sulfathiazole **(3)** and modified form reported in the literature with antibacterial activity such as Ni (II) complex with cephalosporin and sulfathiazole[86], silver complex with sulfathiazole[84], Cu (II) complex with nimesulide and sulfathiazole as ligand[87],sulfathiazole-amantadine is a promising antibacterial agent.[88] Sulfamethizole **(4)** drug used for the treatment of various diseases but it's also used as an antibacterial agent. The combination of sulfamethizole with amdinocilin was reported by efficient inhibition of *Escherichia coli* strain of infected mouse.[89] Antibiotic sulfadiazine **(5)** were reported in modified form such as silver sulfadiazine as an antibacterial agent[90], Synthesized antibacterial metal ligand [ML(H_2O)$_3$] complex, these transition metal are [M(II)=Co, Mn, Zn and Ni] with cephalothin and sulfadiazine as ligands.[91]Sulfamethazine **(6)** used as antibacterial drug and some modified and combined structure enhanced antibacterial activities such as p-aminobenzoic acid and sulfamethazine.[92] Sulfamehazineand tiamulin mixture possessed synergistic antibacterial properties against pathogenic bacteria were isolated from pigs.[93]The chlorothiazide and hydro chlorothiazide are the class of sulphones series were evaluated as antibacterial and antifungal.[94]

Sulfonamide core moiety scaffolds have been found to exhibit diverse significant biological properties also found in some natural compounds. Generally, sulfonamide moiety compounds were isolated from marine actinomycetes. Cytotoxic monoterpene-alkaloid (-)-altemicidin were isolated from active fractions of *Streptomyces sioyaensis*.[95](-)-Altemicidin showed inhibitory activity against bacterial strains (Muralidharan andDeecaraman, 2017)[96]were reported mild growth inhibition against *Xanthomonas species*. The bromotyrosine-cysteine derivatives, psammaplin A and C were extracted from the sponge *Psammaplysilla purpurea* are efficient antibacterial agents.[97] Nucleocidin are fluorinated sugar structure

used as an antibiotic and it were obtained from soil microbe *Streptomyces calvus*[98] and *Streptomyces alboflavus.*[99] In addition, potent antibacterial activity against both Gram (positive and negative) pathogenic bacteria strains.

1.2 Thiophene moiety containing sulfonamide derivatives

For the preparation of thiophene moiety containing sulfonamide derivatives via Suzuki cross-coupling reaction, a convenient approach was published in the literature.[100] Thiophene moiety containing compounds are excellent bioactive agents. They have been found to exhibit various biological activities such as antimicrobial[101-102], anti-HIV[103], anti-inflammatory[104], anticancer.[105] Cytochrome inhibition has been observed in some thiophene derivatives.[106]

Thiophene-2-sulfonamides derivatives are also regarded as inhibitors of carbonic anhydrase, and the literature indicates that diuretic activity is also seen in many of its simple derivatives.[107]

1.2.1 Method of preparation

Synthesis of thiophene moiety containing sulfonamide derivatives

An efficient process was developed for the synthesis of thiophene sulfonamide derivatives **(1)**. It was two-component reactions of thiophene sulfonylcholoride and aminoacid in presence of triethylamine (Et_3N) as a catalyst in solvent water and dioxane.[108] These compounds were used as metalloproteinase inhibitors. The reaction of bromothiophene-2-sulfonylchloride and tert-butyl 2-aminoethylcarbamate in DCM gives tert-butyl 2-(3-bromothiophene-2-sulfonamide)ethylcarbamate which on reaction with 2-substituted oxyphenylboronic acid catalyzed by $Pd(OAc)_2$ gives N-(2-aminoethyl)-3-(2-methoxyphenyl)thiophene-2-sulfonamides **(2)**.[109] (R)-N-(2-(4-(4-(5-((1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-2oxoethyl)thiophene-2-sulfonamide **(3)** synthesized by the reaction of (R)-5-((1H-1,2,3-triazol-1-yl)methyl)-3-(4-(4-(2-aminoacetyl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one with 2-thiophenesulfonyl chloride in triethanolamine (TEA) and CH_3CN exhibits significant antibacterial activity.[110]

The reaction of benzenesulfonamide and (benzothiophen-3-yl)-3-chloropropan-1-one using THF as solvent and K_2CO_3 as catalyst affords substituted benzothiophene (N-aryl) sulfonamide **(4)** in good yield.[111] The synthesized thiophene aryl sulfonamide **(5)** was evaluated *in-vitro* antibacterial activity against pathogenic bacteria such as *B.subtilis, E.coli, B. megaterium and P.flourescens*.[112] Thiophene moiety containing N-substituted aryl sulfonamides **(6)** have been synthesized from the reaction of 3-(thiophene-2-ylmethylamino)propanenitrile with p-toluenesulfonyl chloride using Et_3N as catalyst and DCM as a solvent.[113] (E)-3-(dimethylamino)-1-(thiophene-2yl) prop-2-en-1-one reacts with 4-amino-N-substituted benzenesulfonamide in absolute ethanol and glacial acetic acid to afford (E)-4-(3-oxo-3-(thiophene-2-yl)prop-1-enylamino)benzenesulfonamide **(7)**.[114] Nasr *et al*. (2014)[115] reported the synthesis of N-substituted thiophene aryl sulfonamide **(8)** by the condensation reaction of N-substituted isoxazole

aryl sulfonamide and pyrazol-3-oxo-propanenitile in dioxane to form intermediate product under reflux condition then further reaction with isothiocyanatomethane and chloropropan-2-one in presence of NaOEt gives isoxazole-thiophene aryl sulfonamide. The compound has been found to exhibit inhibitory activity against microbes.

Some compounds of thiophene containing aryl sulfonamide possessed co-ordinate bond with various metal and act as a multi-dentate ligand. The (E)-N-(4-methoxy-1,2,5-thiadiazole-3-yl)-4-(thiophene-2-ylmethyleneamino)benzene sulfonamide**(9)** were used as ligand to formed metal complexes with a transition metal such metals are Fe(II), Fe(III), Co(II), Cu(II), Cd(II), NI(II) and Zn(II) were assayed antibacterial activities.[116]Zemede *et al.* (2015)[117] reported the synthesis of metal complex **(10)**, thiophene aryl sulfonamide used as ligand and attached with the transition metal. Co-ordination complex of the metal with ligands having two moles of thiophene aryl sulfonamide occurs. Such ligand and metal complexes possessed efficient antibacterial properties.

Some compounds widely used as antibacterial agents such as (oxalylamino-methylene)-thiophene sulfonamide (OMTS)**(1)** compound was evaluated for the selective inhibition of bacterial protein. The pathogenic bacteria, *Mycobacterium tuberculosis* inhibited by OMTS were reported by Grundner *et al*. (2007).[118]Naidu *et al*. (2015)[119]reported for the evaluation of 6-(4-(5-bromothiophen-2-ylsulfonyl)piperazin-1-yl)phenanthridine**(2)** antibacterial activity against pathogenic *Mycobacterium tuberculosis* bacteria.Substituted benzyl thiophene sulfonamide**(3)** compounds showed potent antimicrobial activity against pathogenic bacteria *Campylobacter jejuni* and *Campylobacter coli* in humans and chickens.[120] The synthesized hydroxyl-thiophene containing sulfonamides**(4)** compound used for dyeing polyester fabrics and fabrics possessed antibacterial properties against most of the bacterial strain positive as well as negative.[121]

Thiophene-sulfonamide compound does not exist in a natural source. Thiophene exists in natural sources with promising biological applications but the compounds of thiophene moiety sulfonamide scaffold only available in synthesized form.

1.3 Chromene moiety containing sulfonamide derivatives

The core entity of several biologically vigorous natural products, as well as synthetic therapeutic agents, consists of unsaturated 1-benzopyran derivatives, widely known as chromenes.[122]The chromene nucleus is, thus, widely known in medicinal chemistry as a privileged scaffold.[123]4H-chromene and 2H-chromene are an isomeric form of each other, which depending on their substitution pattern, can be differentiated by the site of unsaturation and show a range of pharmacological properties. Chromene moieties play a significant role with structural aryl sulfonamide scaffold which can be easily transformed into functionalized diverse biologically active molecules.[124] Naturally occurring[125] and synthetic chromene compounds possess antibacterial properties.[126]A number of pathways are available for their synthesis, but there is a significant need for approaches that include chromenes from precursors that are readily available.[127]

Some synthesized sulfonamide derived chromenes were investigated for antibacterial, antifungal and cytotoxic.[128] Chromone is known as a single molecule that can be paired with various receptors groups.[129] Due to its useful activities and low toxicity, chromone is regarded as a desirable source for the synthesis of new drugs.[130]

1.3.1 Method of preparation

Synthesis of chromene moiety containing sulfonamide derivatives

Ghorab *et al*., (2016)[131]developed method for the synthesis of sulfonamides containing chromene moiety. 3-(3-Dimethylamino)propnoyl)-2H-chromen-2-one reacts with 4-amino-N-substituted benzenesulfonamide in absolute ethanol and glacial acetic acid to form (E)-4-(3-oxo-3-(2-oxo-2H-chromen-3-yl)prop-1-enylamino) benzenesulfonamide **(1)**. Significant *in-vitro* antibacterial activity against pathogenic bacterial strains were reported for 4-(((2,4-dioxo-2H-chrome-3(4H)-ylidene)methyl)amino)-N-substituted benzenesulfonamide **(2)** compounds synthesized by the reaction of 4-hydroxycoumarin, substituted sulfonamide and ethylorthoformate in 2-butanol.[132]Amin *et al*. (2018)[133]developed two-step synthesis for the preparation of furo[3,2-g] chromene aryl sulfonamide **(3)** by the reaction of furo[3,2-g] chromene and sulfurochloridic acid to form furo[3,2-g] chromene sulfonylcholride under ambient condition. While the next step of the reaction further proceeds by the addition of amine arylsulfonamide in presence of pyridine to form main product derivatives under reflux condition with high yields.Substituted 2-oxo-N-(4-(N-(pyrimidine-2-yl)sulfamoyl) phenyl)2H-chromene-3-carboxamide **(4)** were synthesized by the reaction of 2-cyano-N-(4-(pyrimidine-2-yl)sulfamoyl)phenyl)acetamide with substituted salicylaldehydes in presence of fused sodium acetate in acetic acid. The compounds exhibited excellent antibacterial activity.[134]

Reddy *et al*., (2005)[135]reported a process in which coumarin 3-(N-aryl) sulfonamides **(5)** were synthesized by the reaction of 3-anilino-3-oxopropionate with substituted salicylaldehydes using piperidine as catalyst and ethanol as solvent under reflux condition.A mild new method for the synthesis of benzochromene-p-toluene sulfonamide **(6)** was reported by Soussi *et al*. (2011)[136]using benzochromenone and aryl sulfonamide in presence of lead acetate, cesium carbonate and xantphos as catalyst and dioxane as solvent at 100^{o}C.Okasha *et al*. (2019)[137] reported the synthesis of substituted (Z)-4-((2-amino-3-cyano-4-phenyl-4H-chromen-6-yl) benzenesulfonamide **(7)** derivatives by the reaction of benzaldehyde, malanonitrile to form 2-benzylidenemalononitrile. 2-benzylidenemalononitrile further react with (E)-4-((2, 4-dihydroxyphenyl)diazenyl)benzenesulfonamide. Whole reaction completed at reflux temperature in the presence of piperidine as a catalyst in ethanol. Synthesized derivatives were evaluated against microbes (bacteria and fungi) and possessed effective antimicrobial properties. Sabt *et al*., (2018)[138]reported a process in which2H-chromen-2-one reacts with sulfurochloridic acid at 100^{o}C to form 2-oxo-2H-chromene-6-sulfonyl chloride. Chromene sulfonyl chloride further reacts with 1-(4-aminophenyl)ethanone in pyridine to afford N-(4-acetylphenyl)-2-oxo-2H-chromene-6-sulfonamide **(8)**.The reaction of cyanoacetamide aryl sulfonamide and salicylaldehyde in the presence of piperidine catalyst and dioxane

solvent to afford 2-iminochromene aryl sulfonamide**(9)** was evaluated on microbes. 2-iminochromene aryl sulfonamide processed both antibacterial and antifungal activities.[139]

Chromene-sulfonamide compound does not exist in a natural source. Chromene and its derivatives exist in various natural sources with promising biological applications but the compounds of chromene moiety sulfonamide scaffold only available in synthesized form.

Conclusion

Aryl sulfonamides bearing thiophene or chromene moieties have been reviewed for their antibacterial activity and their synthetic methods.The review will provide insight to readers,to tap the potential of these classes of compounds. More compounds of these classes need to be synthesized with wide structural variation in order to establish structure-activity relationship and find out new compounds having promising antibacterial properties.

Declarations

Conflict of Interest

There is no conflict of interest between coauthor.

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Figures

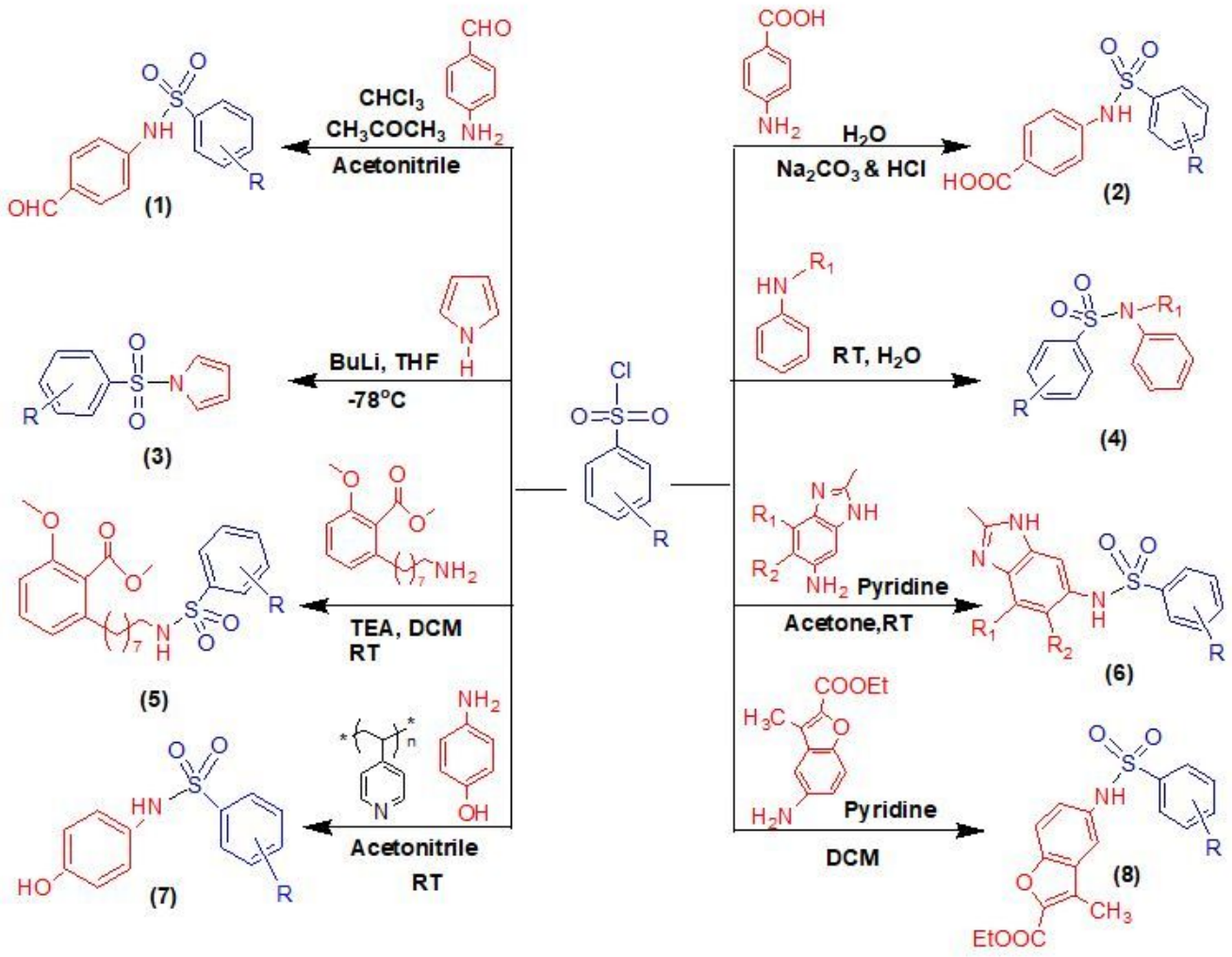

Figure 1

1Preparation methods of aryl sulfonamides

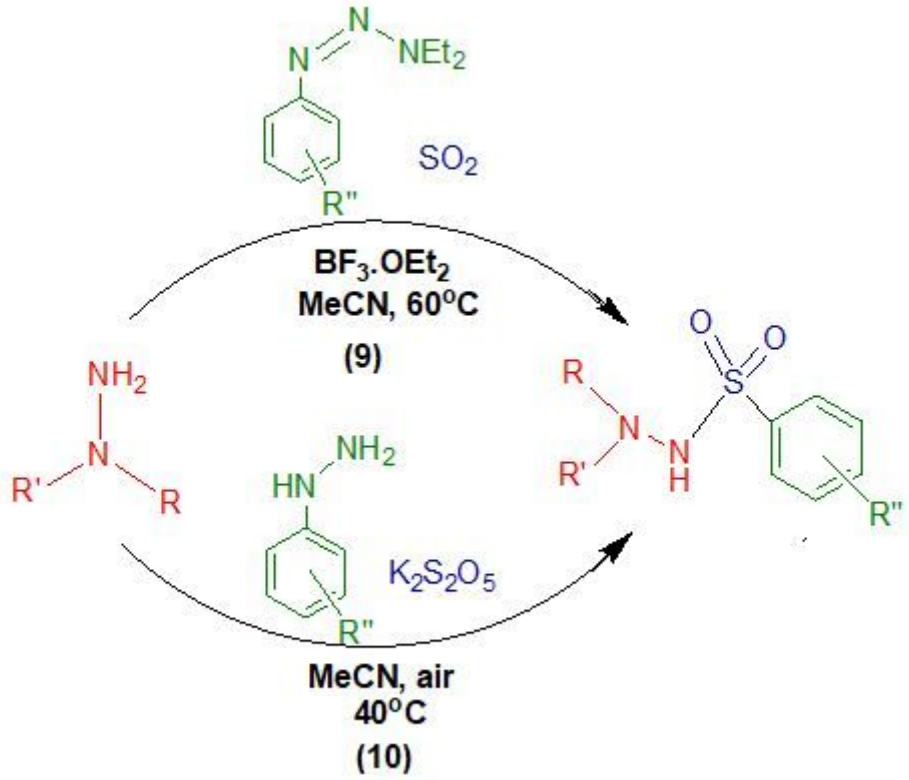

Figure 2

Advance method for the preparation of aryl sulfonamides.

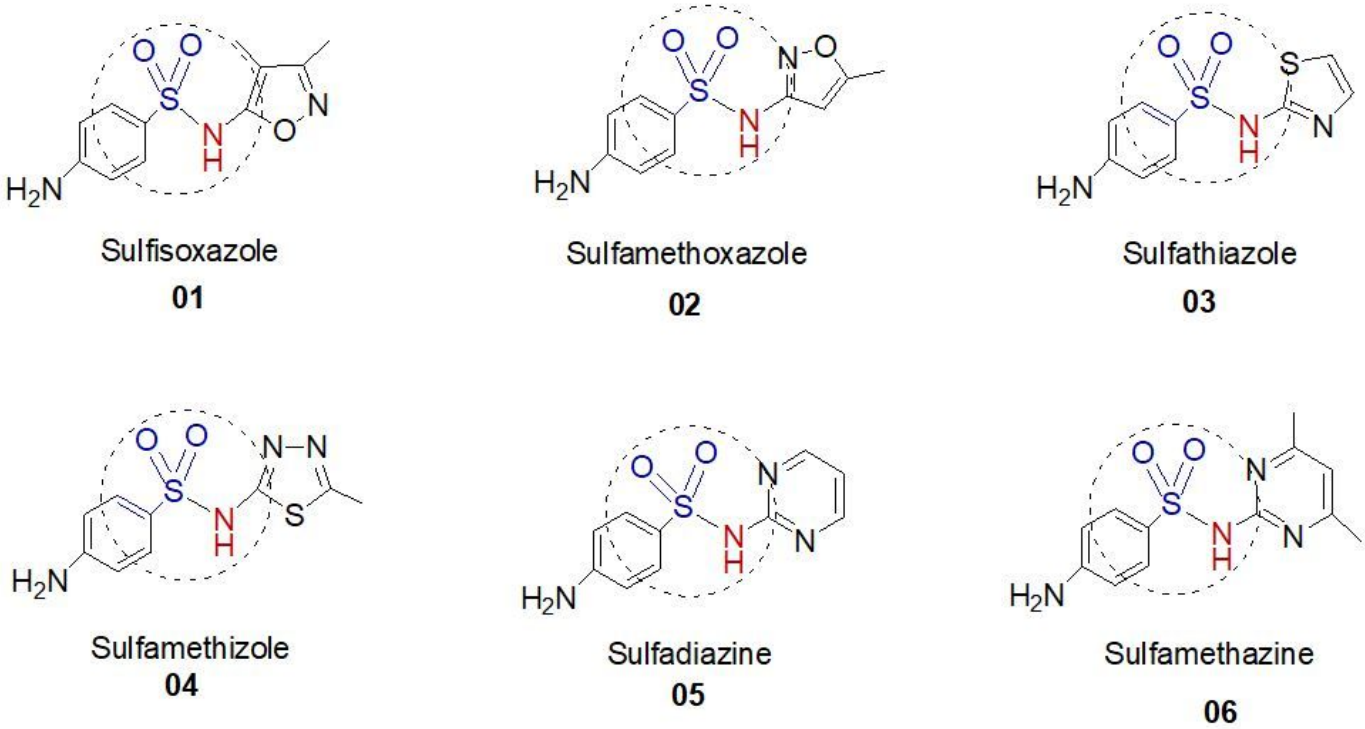

Figure 3

Bioactive heterocyclic containing aryl sulfonamide agents

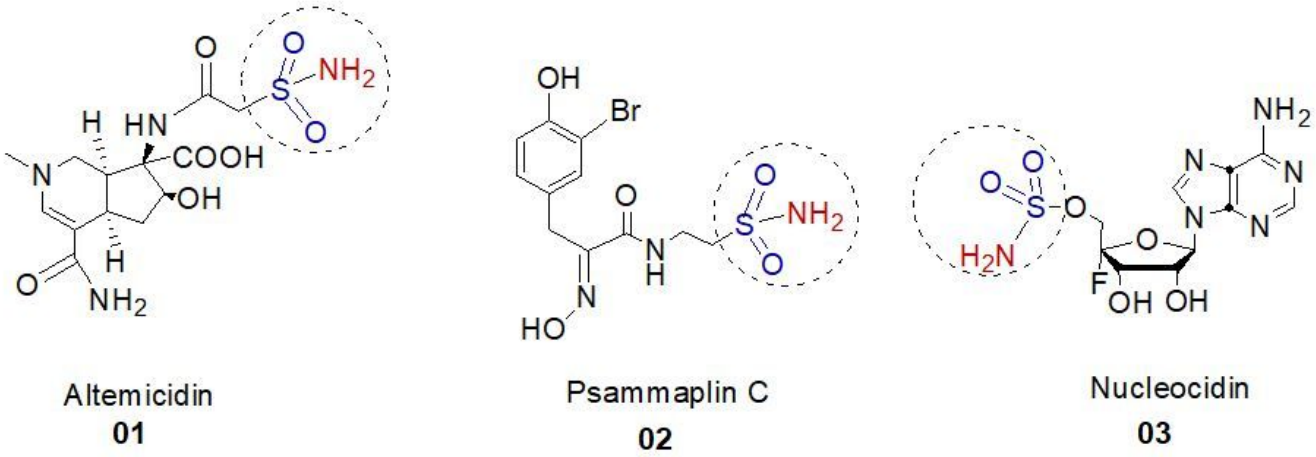

Figure 4

Natural bioactive sulfonamide compounds

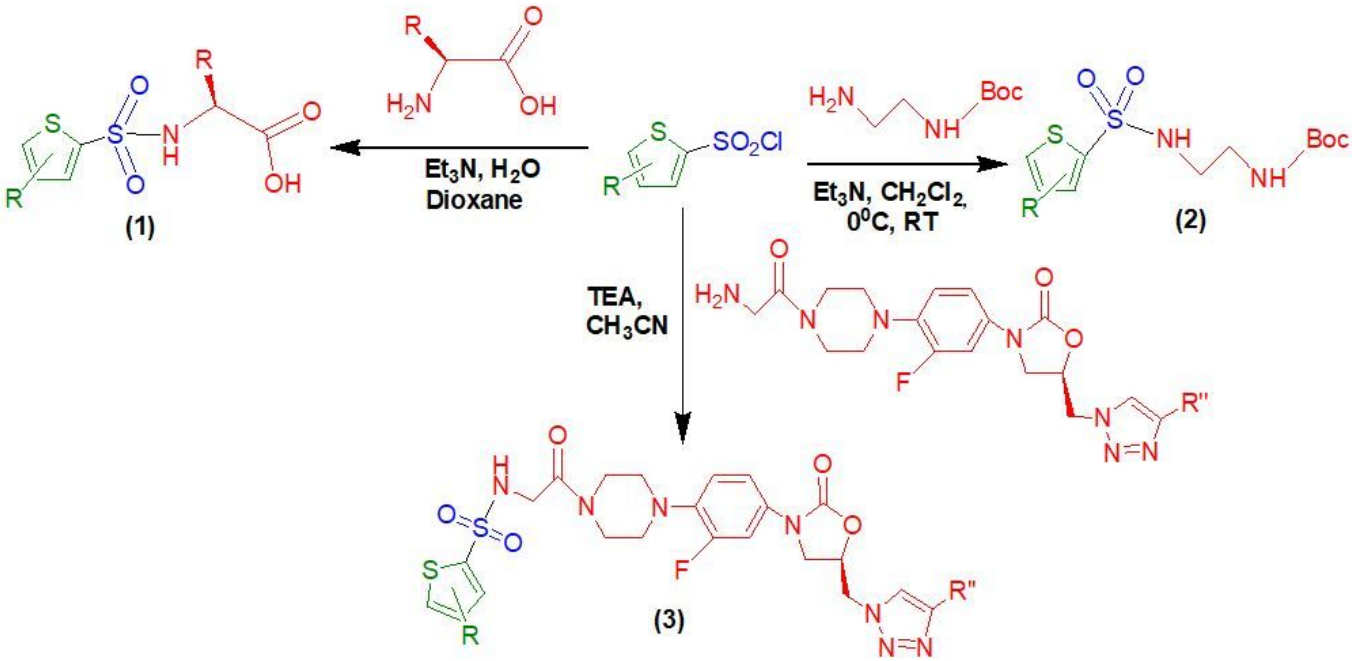

Figure 5

Preparation methods of thiophene-aryl sulfonamides

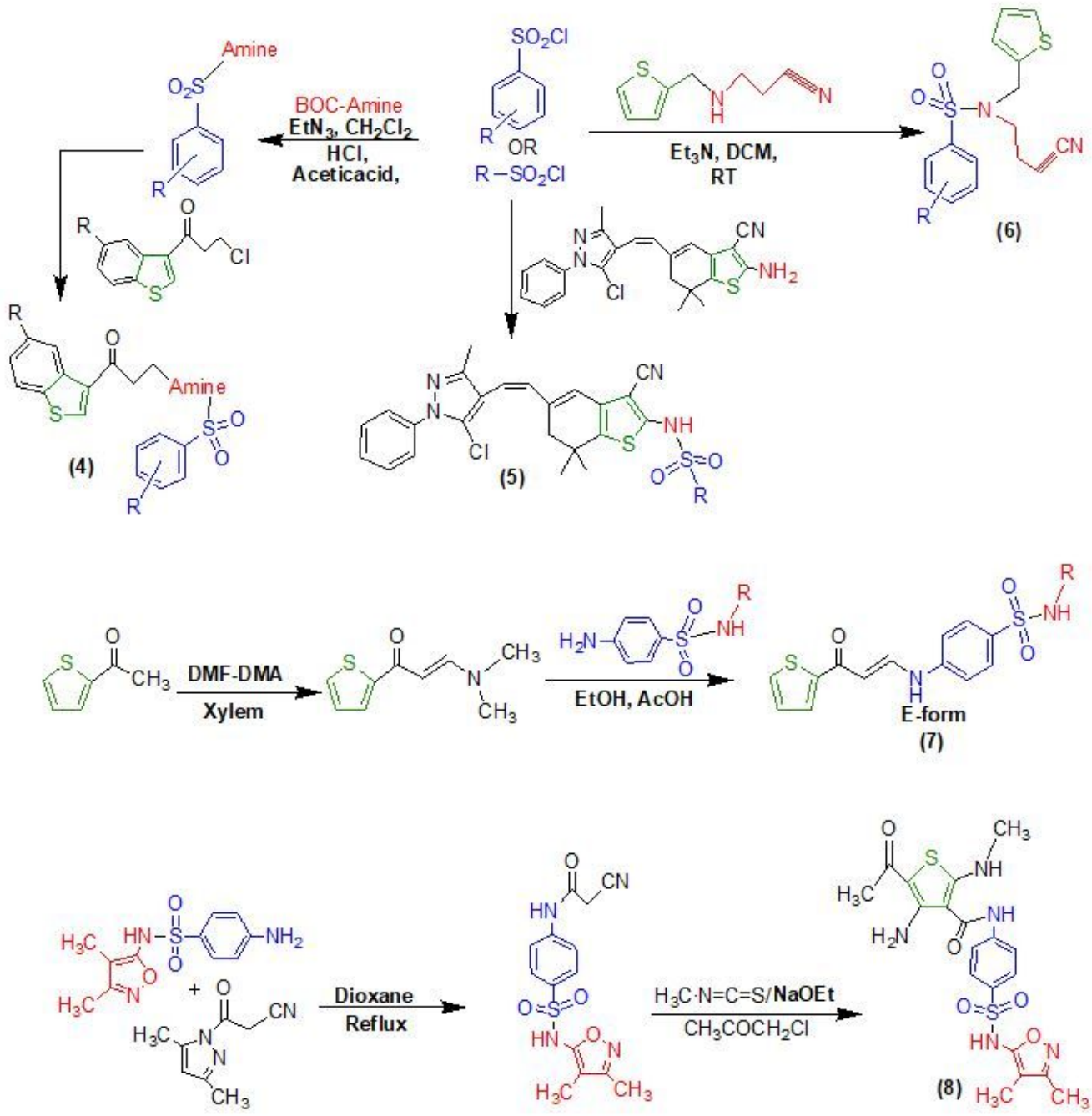

Figure 6

Preparation methods of myriad thiophene containing aryl sulfonamides

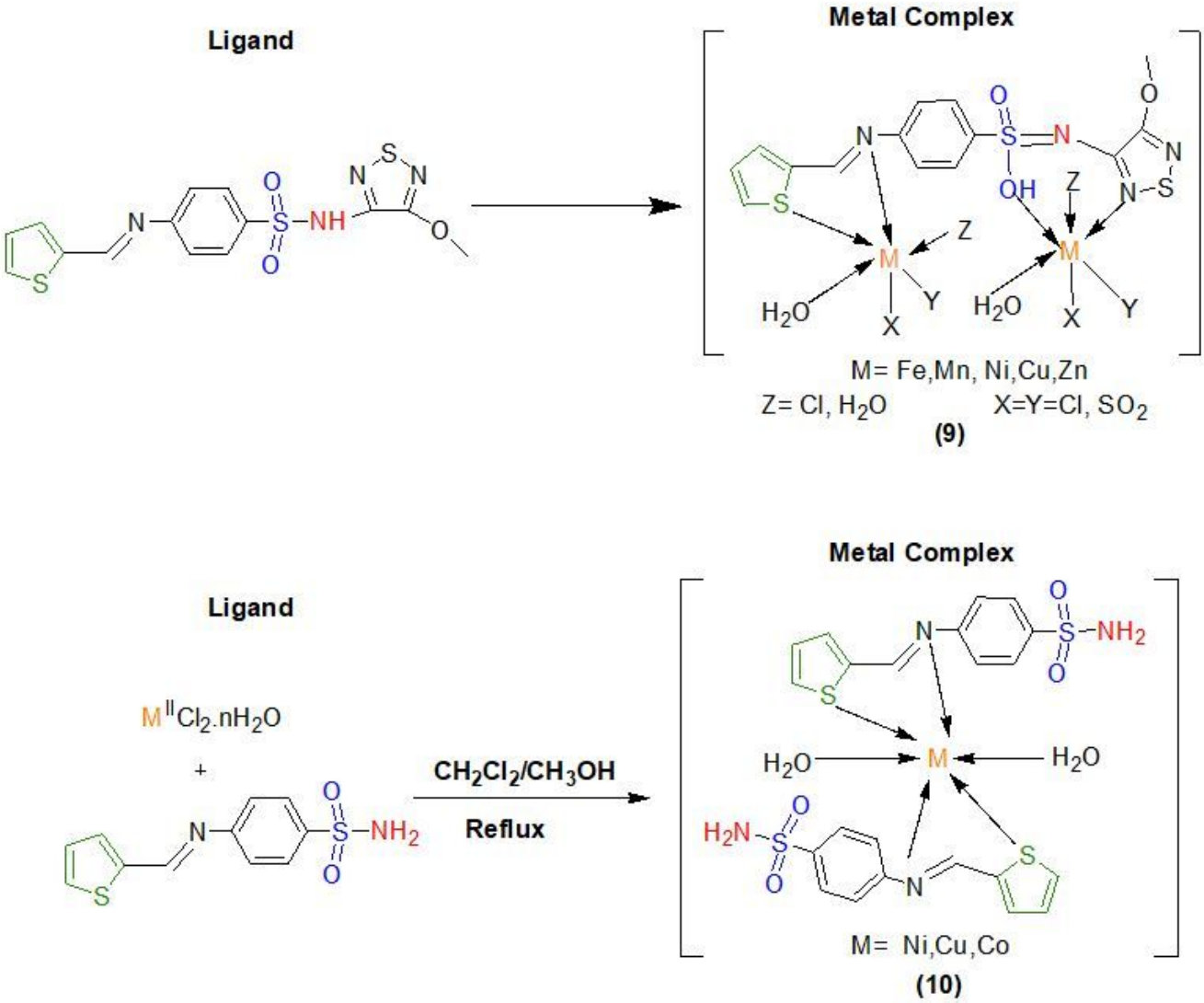

Figure 7

Preparation methods of organometallic complexes of thiophene-aryl sulfonamides

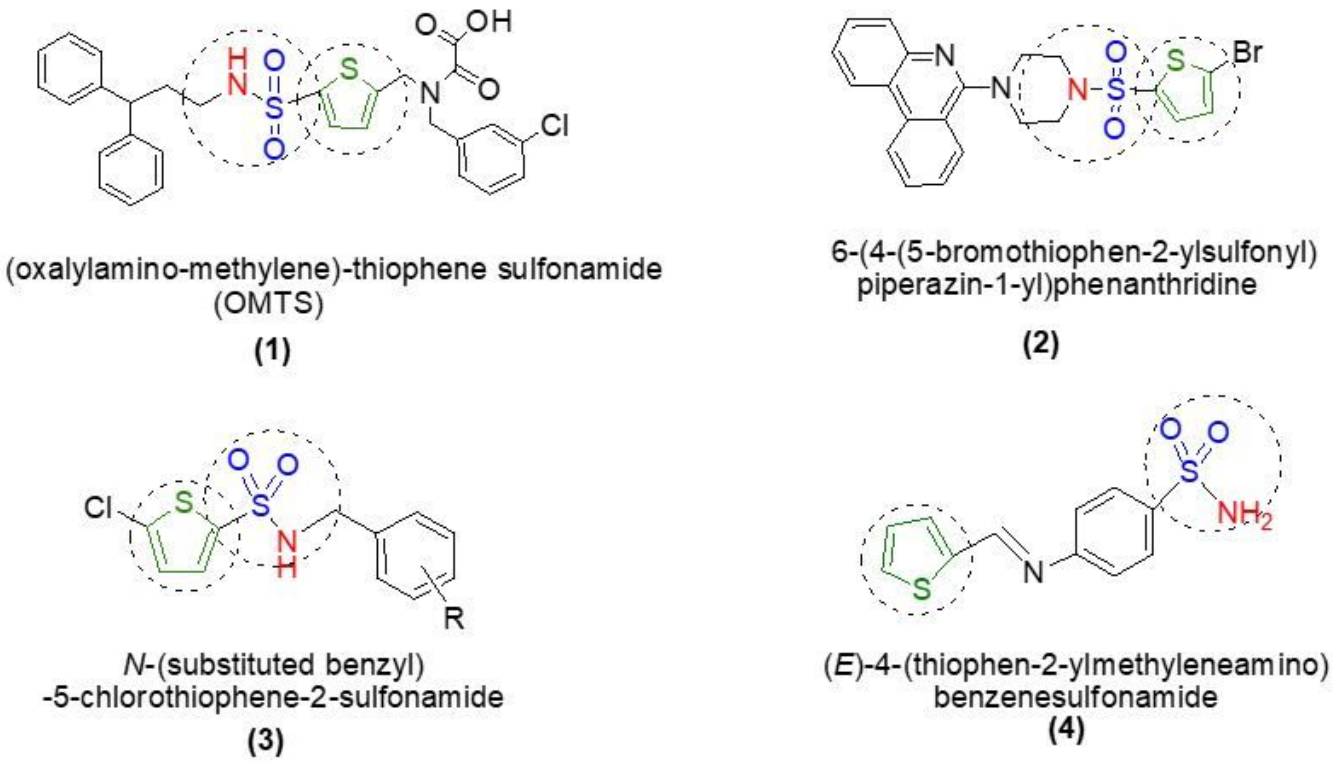

Figure 8

Bioactivethiophene-sulfonamides agents

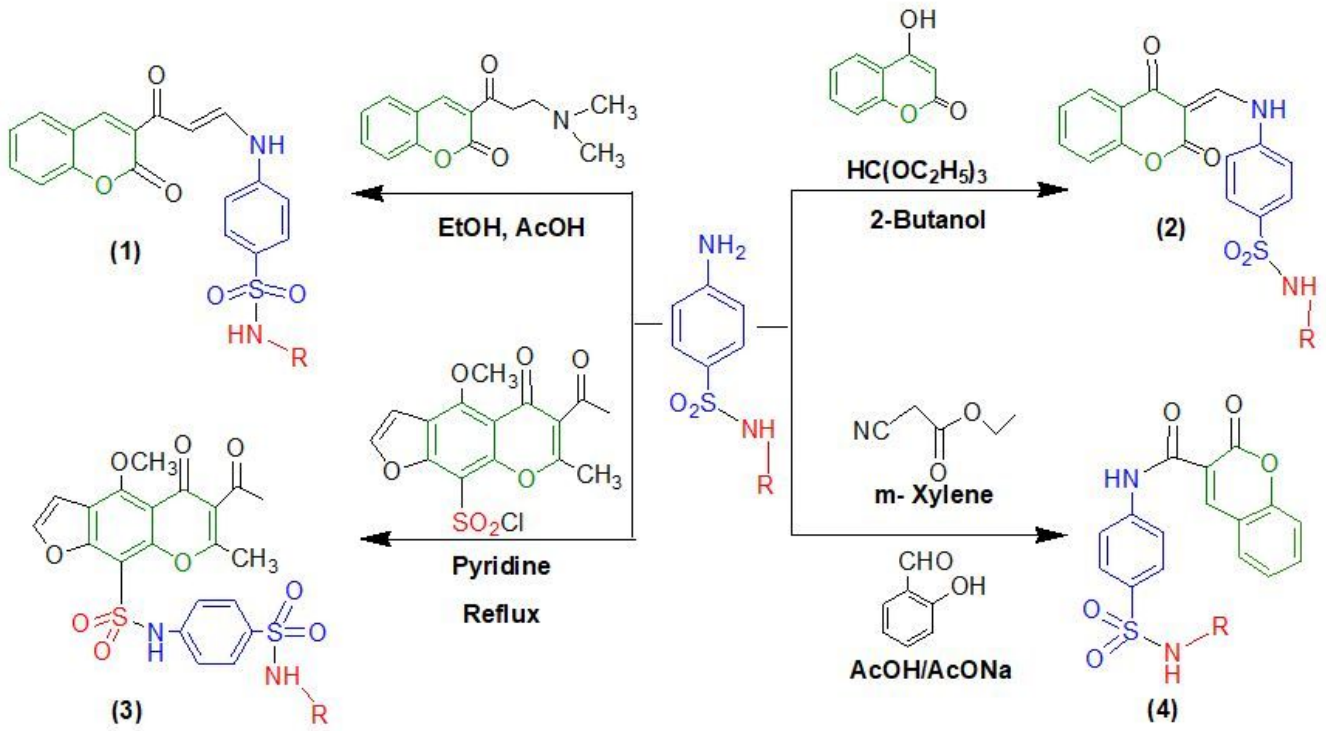

Figure 9

Preparation methods of chromene containing aryl sulfonamides

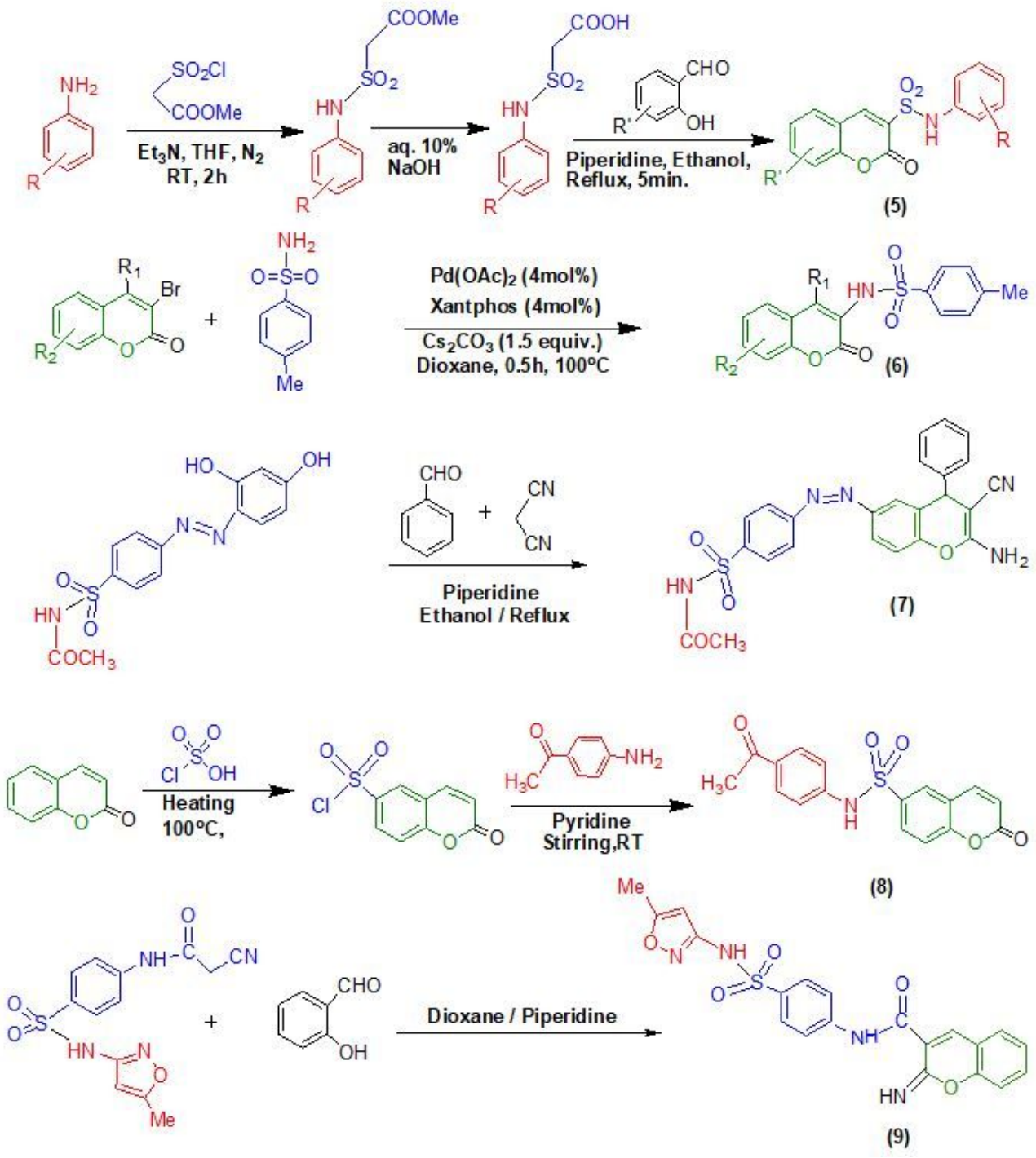

Figure 10

Preparation methods of myriad chromene containing aryl sulfonamides

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