Synthesis of sulfa drug complexes and study as topical agents

INTRODUCTION

The Sulfonamides are Synthetic antimicrobial agents with wide spectrum encompassing most gram-positive and many gram-negative organisms (1,2).The first sulfonamide, trade-named Prontosil see (fig.1), was a prodrug.Experiments with Prontosil began in 1932 in the laboratories of Bayer AG, at that time a component of the huge German chemical trust IG Farben. The Bayer team believed that coal-tar dyes which are able to bind preferentially to bacteria and parasites might be used to attack harmful organisms in the body. After years of fruitless trial-and-error work on hundreds of dyes, a team led by physician/researcher Gerhard Domagk(3) (working under the general direction of Farben executive Heinrich Hörlein) finally found one that worked: a red dye synthesized by Bayer chemist Josef Klarer that had remarkable effects on stopping some bacterial infections in mice(4) .Prontosil, as Bayer named the new drug, was the first medicine ever discovered that could effectively treat a range of bacterial infections inside the body.

It had a strong protective action against infections caused by

streptococci, including blood infections, childbed fever, and erysipelas, and a lesser effect on infections caused by other cocci. However, it had no effect at all in the test tube, exerting its antibacterial action only in live animals. Later, it was discovered by Bovet,(5).

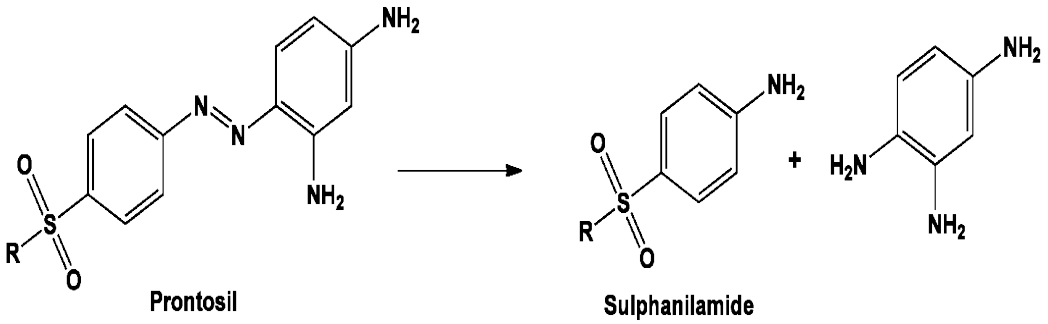


Fig.1. Synthesis of sulphanamide from prontosil

The condensation product of sulfa drugs with aldehydes , ketones or their derivative are biologically very active(6). Beside having good complexing ability and the activity increase on complexation(7).

Many chemotherapeutically important sulfa drugs like sulfapyridine , sulfadiazine ,etc. posses SO_2NH moiety which is an important toxophoric function(8) in addition the hetrocyclic moiety which contain sulfur , oxygen or nitrogen atoms cause an enhanced the bioactivites of sulfa drugs.Sulfonamide or sulphonamide is the basis of several groups of drugs. The original antibacterial

sulfonamides (sometimes called sulfa drugs or sulpha drugs) are synthetic antimicrobial agents that contain the sulfonamide group. Some sulfonamides are also devoid of antibacterial activity, e.g., the anticonvulsant sultiame. The sulfonylureas and thiazide diuretics are newer drug groups based on the antibacterial sulfonamides(.9,10).

Sulfonamide drugs were the first antibiotics to be used systemically, and paved the way for the antibiotic revolution in medicine. The sulfa drugs, derived from so-called azo-dyes, should better be understood as being part and parcel of a system of invention that had developed in the German pharmaceutical industry from the late nineteenth century. In the specific case of prontosil, Bayer (later part of IG Farben) had pursued a research and development strategy on anti-infective therapy from pre-First World War days. Eventually, the medicine turned out to be effective against such conditions as pneumonia, gonorrhoea and others. Lesch carefully reconstructs the reception in major national drug markets like France, Germany, Great Britain and the US in the late 1930s.Lesch singles out the example of sulfapyridine, popularly known as M&B 693, developed by the British company May & Baker, and follows in some detail the trajectory of this drug. That the sulfas sparked the therapeutic revolution is not only connected to the fact that they

were actually the first of a series of “miracle drugs” that came to be invented between the 1930s and the 1960s, but also that other typical features of that historical phenomenon such as standardization of medical practice and a close link between medical and industrial technologies are shown to be present in their history.(11)

Sulfonamides from sulfonic acid Sulfonyl chloride occurs as intermediate starting from sulfonic acid. As an easy and handy, this synthesis is performed under microwave irradiation, and has shown a good functional group tolerance, and is high yielding (fig .2).(12)

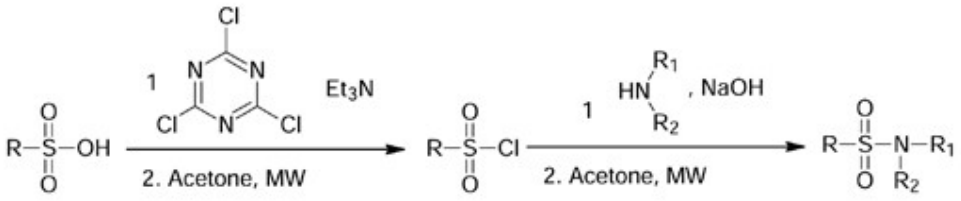


Fig. 2. Synthesis of sulfonamides with using microwave irradiation.

This reaction was also performed in classical heating delivered corresponding sulfonamide in good to excellent yields.

Sulfonamides from sulfonamides; another innovative example of sulfonamides synthesis was illustrated in the synthesis of 2-amino-9H-purin-6-sulfonamide. Mild and selective oxidants have been used by Revankar et al. .They reported the oxidation of

2-amino-9H-purin-6-sulfenamide using one equivalent of m-CPBA in 48% yield (Fig. 3). More amounts of m-CPBA (4eq) delivered target compound with slightly better 53% yield.(13)

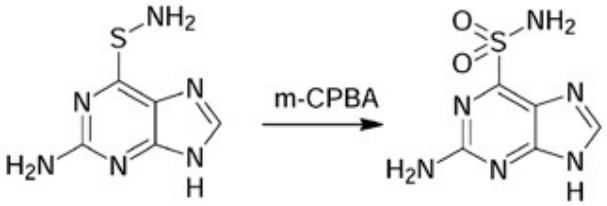


Fig.3. Oxidation of sulfenamides with using m-CPBA

Sulfonamides via using transition metal catalyst;The first one is Pd. For example a biaryl phosphine ligand, t-BuXPhos and K3PO4 in tert-amyl alcohol was found to be the optimal base-solvent combination for a Pdcatalyzed sulfonamidation of aryl nonafluorobutanesulfonates. The reaction conditions were tolerant of various functional groups. The only identified limitation of this methodology is the inability of 2,6-disubstituted aryl nonaflates to efficiently participate in the reaction.fig(4) .(14)

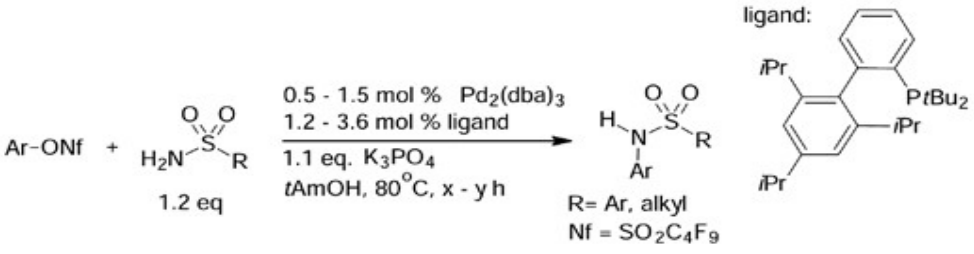


Fig. 4. Pd-catalyzed sulfonamidation

The second metal, used more often, is Cu. It is more likely to be used for large scale synthesis. An effective method for N-arylation

on sulfonamide using 0.1 equivalent of copper(II) acetate in air and arylboronic acid to get N-arylsulfonamide near-quantitative yield .fig.(5) .(15)

Fig.5. Pd-catalyzed cross-coupling

Experimental part:

Materials and instruments:

1. The entire chemicals were supplied by Fluca or Merk .
2. Melting points were determined by open tube capillary method by (melting point |SMP3|, DENVER Instrument) .
3. FTIR spectra of all compounds were recorded by FTIR using KBr disc .
4. A model:UV-1100 spectrophotometer provided with 1cm matched quartz cell was used for all absorbance measurments .

Procedure for complexe formulation :

Silver nitrate($AgNo_3$),Copper sulfate ($CuSO_4.5H_2O$) in 0.192gm 0.249 gm, respectively and Aluminium nitrate ($Al(No_3)_3.9H_2O$) 0.288 gm was dissolved in ethanol to get solution (1mmol). Ethanolic solution of sulfonamide was prepered with (1mmol) concentration .Both of solutions were mixed at 80 c° and stirred at 800 rpm for 2hrs .Cooled the reaction mixture untill change in coloration occure indicating pricipitation of metal -complexes .Complexe formed were recovered by vaccum filtration from reaction mixture. Washed and recrystallized with ehtanol solvent .

Results and Discussion:

Some physical and chemical proprties of the sulfonamide and metal complexes are listed in Table (1) .All the complexes are coloured crystalline solid ,stable at room temperature.

Table(1) physical and chemical properties of sulfonamide metal complexes

Compound number	Metal (M)	Molecular formula	Molecular wieght	Melting point	%yield (%w/w)	color
1	Ag	$C_6H_6N_2O_2SAg$	279.87	236-238	68.99	brown
2	Cu	$C_{12}H_{16}N_4O_4S_2Cu$	407.5	>300 decomposed	86.00	Green
3	Al	$C_{18}H_{24}N_6O_6S_3Al$	543.0	244-246	75.06	brown

Electronic absorption spectra :

The electronic absorption spectra of the complexes in ethanol were recorded on shimadzu UV-1100 Spectrophotometer in the range of 200 to 500 *nm.*

The electronic absorption spectra of all the reactents (1×10^{-3})of sulfonamide and (1×10^{-3}) of metal ions($AgNo_3$, $CuSO_4.5H_2O$, $Al(No_3)_3.9H_2O$) ,along with those of the prepared complexes are

shown in fig.(1),(2),(3).these spectra revealed the presence of the absorption bands that correspond to the complexe intractions. These bands are absorved at 270*nm*,275*nm*, and 290*nm* for Ag-sulfa ,Cu-sulfa, and Al-sulfa complexes respectively. These absorption bands well know to be characteristic of the formulation of complexes. Figures 1,2, and 3 shown the absorption of the sulfonamide ,metal ions and complexe formation .

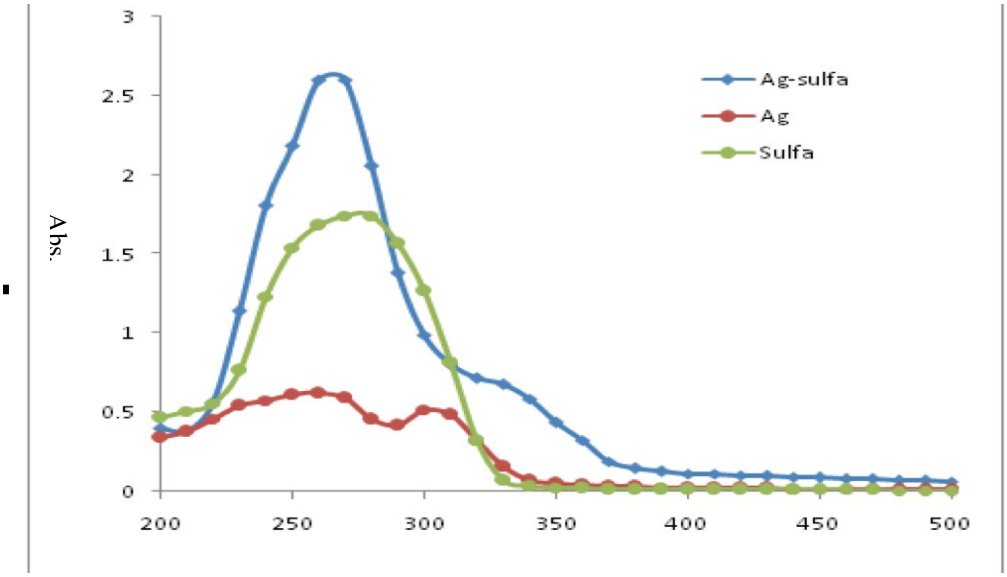


Fig.(1): Electron absorption spectra of Ag-sulfa complexe.

:indicate the formation of Ag-sulfa complexe .

: indicate the the spectra of Ag metal alon .

: indicate the spectra of sulfonamid alon .

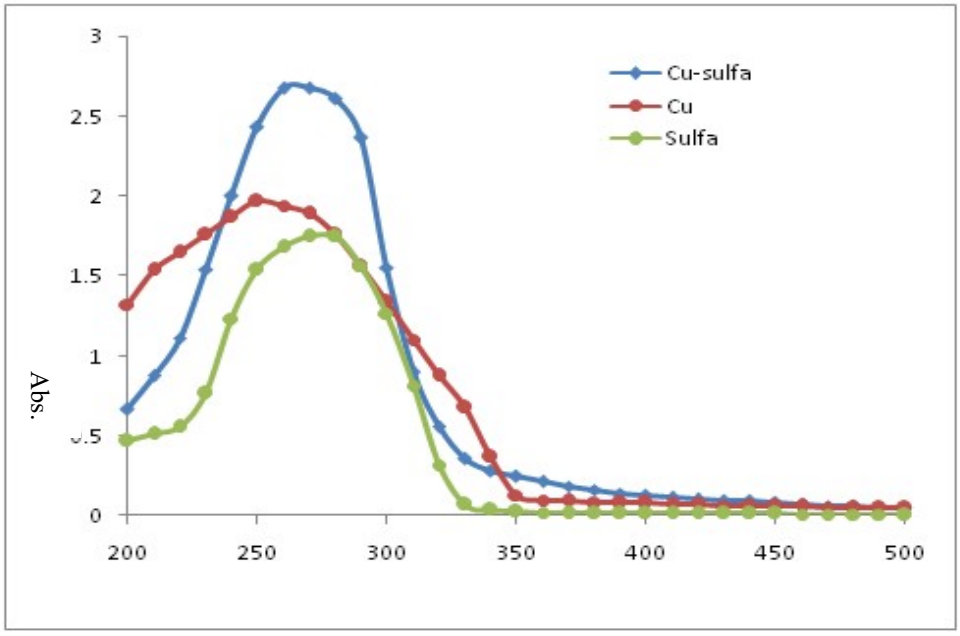
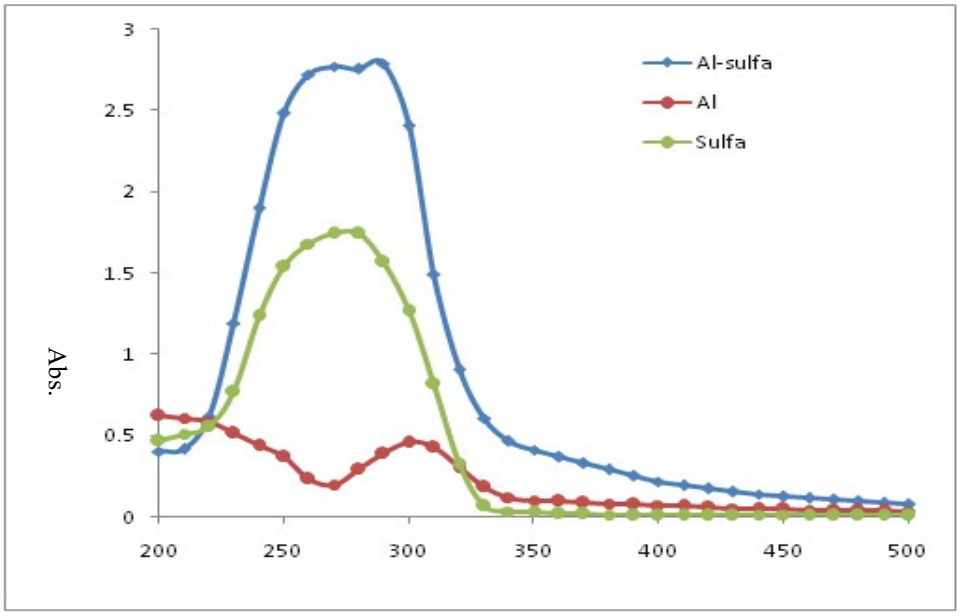


Fig.(2): Electron absorption spectra of Cu-sulfa complexe.

——— :indicate the formation of Cu-sulfa complexe .

——— : indicate the the spectra of Cu metal alon .

——— : indicate the spectra of sulfonamid alon .



Wave length

Fig.(3): Electron absorption spectra of Al-sulfa complexe.

——— :indicate the formation of Ag-sulfa complexe .

——— : indicate the the spectra of Ag metal alon .

——— : indicate the spectra of sulfonamid alon .

Infrared spectra

The infrared spectra of sulfonamide and metal complexes were recorded in KBr phase between 400-4000 cm^{-1} with the Shimadzm IR-470 spectrophotometer.The selected absorption band are showed in table (2) .

IR .spectra show absorption bands for sulfonamide (ligand) at 1095057(-SO band), 1149.57 (-SONH), 3479.58(-N-H band) and 563.21 (C-C band).

The IR spectra shows absorption bands at 1095.75 (-S=O), 1153.43 (-SONH band) and 3383.14(-NH-str.) and 439.77 (-MO bend) . These bands are for copper sulfanilamide complex.

Silver sulfanilamide complex, IR. spectra show absorption band at 1091.71 (-S=O band) ,1153.43 (-SONH band) , 3383.14 (-NH str.) and 466.77 (M-O band) .

Aluminum sulfanilamide complex , IR. Spectra show absorption band at 1095.57 (-S=O band), 1157.29 (-SONH bend) , 3360.00 (-NH str.) and 462.92 (-M-O band) .Fig.(4) show the infrared spectra of sulfonamide and it's metal complexes

Table 2 major IR. Bands (in cm^{-1}) of the sulfon amide and it's complexes .

	Stretching vibration			
Assignments	***sulfonalamide***	***Complex Ag-sulfonalamide***	***Complex Cu-sulfonalamid***	***Complex Al-sulfonalamid***
S=O (bending)	***1095.57***	***1091.71***	***1095.57***	***1095.57***
-SONH (bending)	***1149.57***	***1153,43***	***1153.43***	***1157.29***
-N-H (Streching)	***3479.58***	***3383.14***	***3383.14***	***3360.00***
C-C (bending)	***563.21***	***540.00***	***543.93***	***547.78***
vM-O	_____	***466.77***	***439.77***	***462.92***

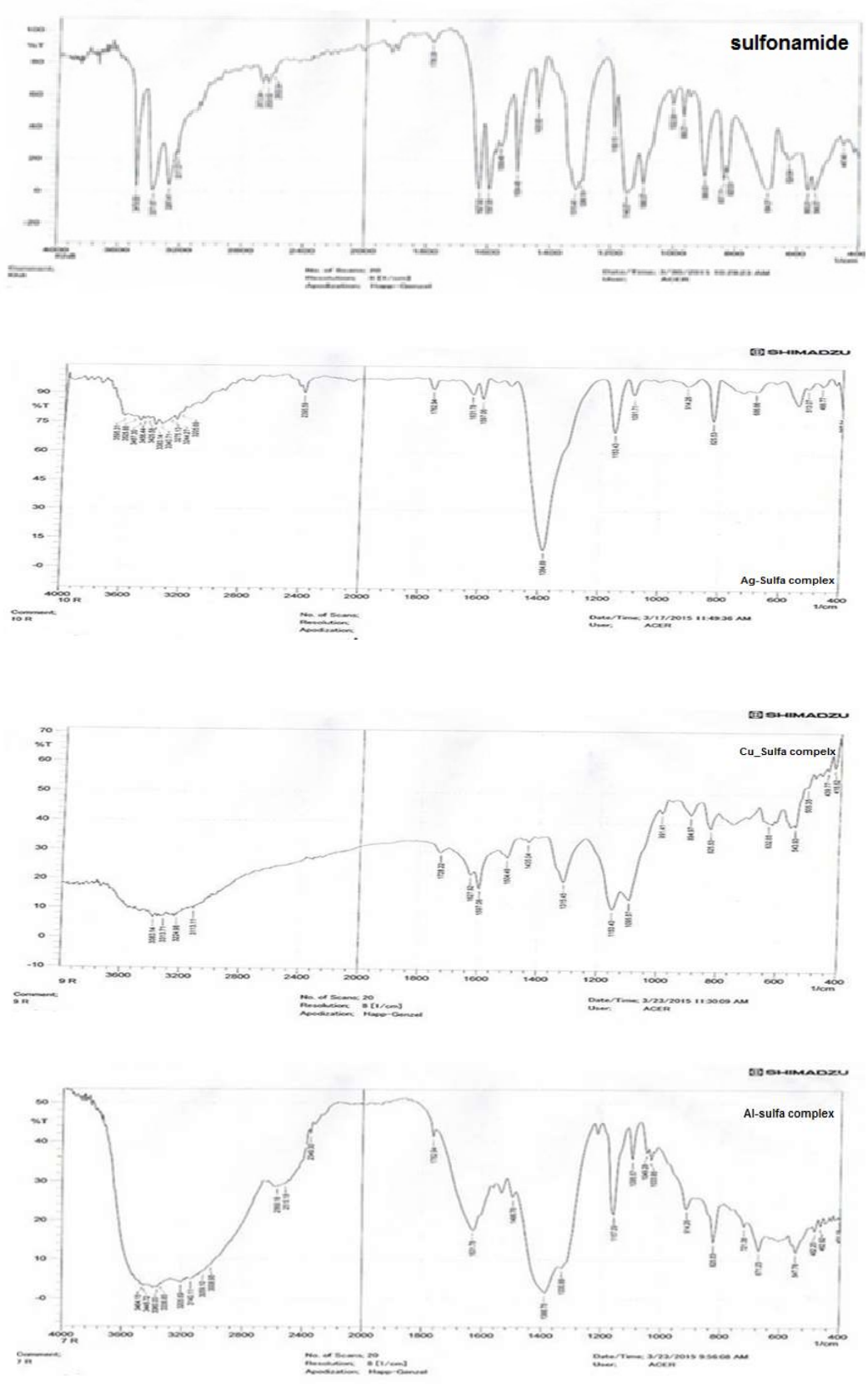
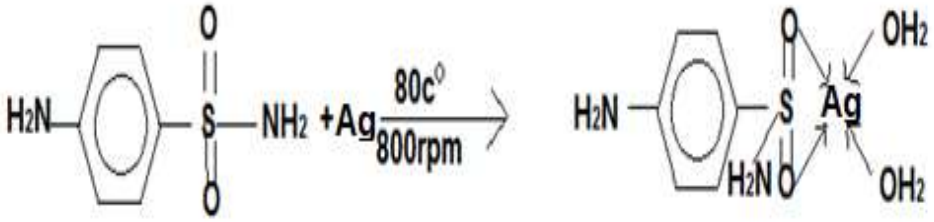
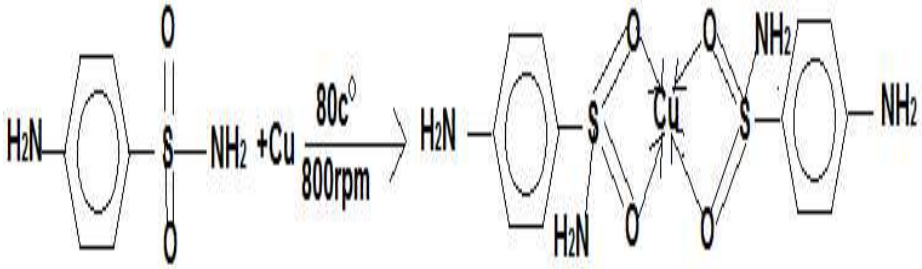
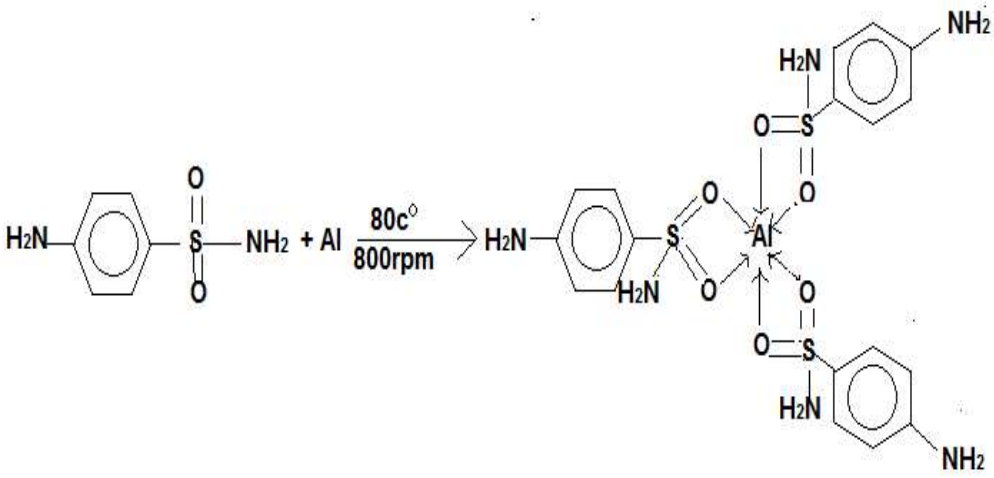


Fig.(4):FTIR spectra ror sulfonamide and it's metal complexes







Scheme of synthesis of metal complexes derived from sulfonamide with Ag ion ,Cu ion and with Al ion

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