

## Synthesis and biological evaluation of some new amide derivatives of sulphonamide

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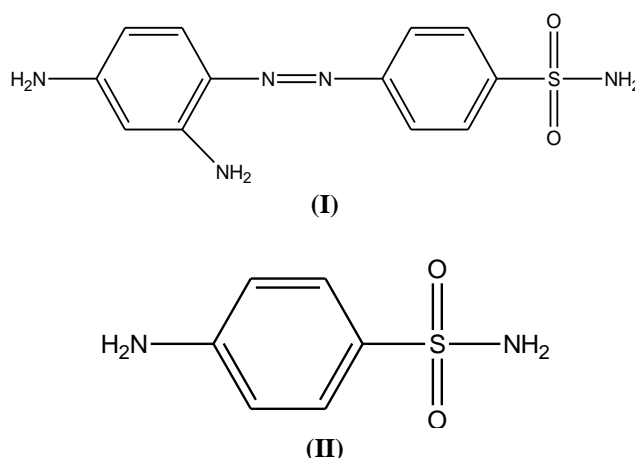
### Abstract

A series of substituted amide derivatives of Sulphonamides were synthesized, and their anticonvulsant activity and antimicrobial activity were evaluated which include the MES model and by Cup-plate method. However, further studies need to be carried out to ascertain the precise mechanism of action of anticonvulsant activity of these molecules. The compounds.N-(4-Acetylsulfamoyl-phenyl)-4-(4-chloro-3-methyl-phenyl)-4-oxo-butamide (HP-1) showed significant anticonvulsant activity. Some compounds show the good antibacterial activity against *Escherichia coli*. The Compound 4-(4-chloro-3-methyl-phenyl)-4-oxo-N-(4-sulfamoyl-phenyl)-butamide (HP-2) and 4-(4-Methoxy-phenyl)-4-oxo-N-(4-Sulfomoyl-Phenyl)-butamide(HP-3) showed significant inhibitory characteristics with stronger antimicrobial activity against MTCC-521 gram negative bacteria.

**Keywords:** Sulphonamide derivatives, Anticonvulsant activity and antibacterial activity.

### 1. Introduction

A sulfonamide grouping is derived from a sulfonic acid group by replacing its hydroxyl group with an amino group. Sulfonamides, also known as sulfa drugs, have a history that dates back to almost 70-80 years. A sulfonyl group plays a very important role as a key constituent of number of biologically active molecules.[1,2] Sulfonamides occupy a unique position in the drug industry and exhibit a wide spectrum of biological activities.[3,4] The first clinically used sulfonamide was named prontosil I that showed protective action against streptococci in mice. Prontosil was active in vivo, but ineffective in vitro, which led to the conclusion that prontosil itself was not the active drug. When metabolized in the body, prontosil produces sulfanilamide II, which is the real active agent. It acts by interfering with p-aminobenzoic acid utilization by the infecting bacteria.[5]

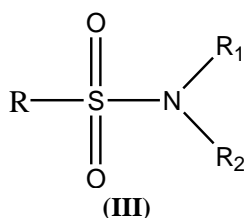


**Figure 1: Prontosil and sulphonamide**

This discovery started great efforts in the investigation and production of new sulfonamides. Several drugs containing sulfonamide functionality are in clinical use which include antibacterial and antifungal drugs,[6,7] carbonic anhydrase inhibitors,[8-10] anti-inflammatory agents,[11] anticonvulsant agents,[12] antimigraine agents,[13] hypoglycemic, protease inhibitors[14] and agents acting against diabetic mellitus.[15] They are also found to have extensive applications in cancer chemotherapy.[16] Viagra, a sulfa drug is one of the recent block buster molecules used for erectile dysfunction.[17] Some sulfonamides have proved to be useful as herbicides[18] and fungicides.[19] Aryl sulfonyl substituted derivatives have been used as protecting groups for oxygen and nitrogen functionality. Sulfonamide derivatives of azo dyes have been reported to improve stability and lubrication.[20]

### 1.2 Structure

Sulfonamides are compounds, which have a general structure represented by **III**. In this structure, R may be alkyl, aryl or hetero aryl etc. R<sub>1</sub>, R<sub>2</sub> may be hydrogen, alkyl, aryl or hetero aryl groups.



**Figure 2: General Structure**

### 1.3 History of Sulfonamides

In 1932, the German dye manufacturing company prepared a red azo dye, named prontosil for its dye properties.[21] Remarkably, it was discovered that prontosil showed antibacterial action when it was used to dye wool. In 1935, Gerhard Domagk published the results of his research work indicating that prontosil was capable of curing staphylococcal infections in mice and rabbits.[22] In 1939, Domagk earned nobel prize in medicine for this important discovery but an order from Hitler prevented Domagk from accepting the honour.[23] After sulfanilamide discovery, thousands of chemical variations were studied and the best therapeutic results were obtained from the compounds in which one hydrogen of the SO<sub>2</sub>NH<sub>2</sub> group was replaced by heterocyclic ring. To date more than twenty thousand sulfanilamide derivatives, analogs and related compounds have been synthesized. These synthesis have resulted in the discovery of new compounds with varying pharmacological properties.[24]

## 2. Experimental protocols

### 2.1 Chemistry

All the chemicals and solvents, purchased from Merck (India), Spectrochem (India), Sigma-Aldrich (India), CDH (India) and S.D. Fine were used without further purification. Thin layer chromatographic analysis of compounds was performed on silica gel G coated glass plates. The adsorbent silica gel G was coated to a thickness of about 0.25 mm on previously cleaned TLC plates of 20x5 cm using conventional spreader. The plates were placed in hot air oven at 105<sup>o</sup>C for 30 min. The solutions of compounds were applied as a spot on the activated plate about 2 cm above from the lower edge. The mobile phases were selected according to the polarity of compounds. Melting points were determined by using open capillary melting point apparatus and are reported uncorrected. Compounds were placed in one end of the sealed capillary and placed in the caves made for the capillary. Thermometer was placed in the cave. The temperature at which compound starts melting and the temperature at which it completely melts was recorded as a melting point range. FT-IR spectra (KBr) were recorded on a Perkin-Elmer Spectrometer BX-II spectrophotometer. The <sup>1</sup>H-NMR and spectra were recorded on Bruker 400 MHz High Resolution NMR spectrometer using TMS as an internal standard. Chemical shifts were reported in ppm (δ) and signals were described as singlet (s), doublet (d), triplet (t) and multiplet (m).

### 2.2 General method for the synthesis of 4-oxo-4-(substitutedphenyl) butanoic acid (1)

Succinic anhydride (0.1 mole) was reacted with Anisole/2-Chlorotoluene (50 mL) in the presence of anhydrous aluminium chloride (0.1125 mole). The reaction mixture was refluxed for 2-4 h and after completion of the reaction an excess solvent was removed by steam distillation. The residue was purified by dissolving in sodium hydroxide solution, filtering, followed by addition of hydrochloric acid. The solid mass so obtained was filtered, washed with cold water, dried and crystallized from ethanol to give the desired 4-oxo-4-(substituted phenyl)butanoic acids (**1**), which gave effervescence with sodium bicarbonate solution.

### 2.3 General procedure for the synthesis of amides (2)

Amides derivatives were synthesized by dissolving 4-oxo-4-(substituted phenyl) butanoic acid (**1**) (0.001 mol) and sulfanilamide / sulfacetamide (0.001 mol) in a minimum quantity of dry pyridine, separately. The two solutions were then mixed together and stirred magnetically followed by the addition of phosphorous oxychloride (0.9 mL) dropwise, while maintaining the temperature below 5<sup>o</sup>C. The mixtures were stirred for another 0.5 h and left overnight. The reaction mixture was then poured into ice

cold water and a solid mass, which separated out, was filtered, washed, dried and crystallized from ethanol.

### 2.3.1 Scheme-1

#### Step-1: Synthesis of 4-(4-Chloro-3-methyl-phenyl)-4-oxo-butyric acid (1)

Succinic anhydride (0.1 mole) was reacted with 2-Chlorotoluene (50 mL) in the presence of anhydrous aluminium chloride (0.1125 mole). The reaction mixture was refluxed for 2-4 h and after completion of the reaction an excess solvent was removed by steam distillation. The residue was purified by dissolving in sodium hydroxide solution, filtering, followed by addition of hydrochloric acid. The solid mass so obtained was filtered, washed with cold water, dried and crystallized from ethanol to give the desired 4-(4-Chloro-3-methyl-phenyl)-4-oxo-butyric acid (1), which gave effervescence with sodium bicarbonate solution. The physico-chemical data was calculated: Rf value 0.48, % yield 65.61, melting point 95-97<sup>o</sup>C, Cream color solid.

#### Step-2: synthesis of N-(4-Acetylsulfamoyl-phenyl)-4-(4-Chloro-3-methyl-phenyl)-4-oxo-butyramide (HP-1)

N-(4-Acetylsulfamoyl-phenyl)-4-(4-Chloro-3-methyl-phenyl)-4-oxo-butyramide (2) were synthesized by dissolving 4-(4-Chloro-3-methyl-phenyl)-4-oxo-butyric acid (1) (0.001 mol) and sulfacetamide (0.001 mol) in a minimum quantity of dry pyridine, separately. The two solutions were then mixed together and stirred magnetically followed by the addition of phosphorous oxychloride (0.9 mL) drop wise, while maintaining the temperature below 5<sup>o</sup>C. The mixtures were stirred for another 0.5 h and left overnight. The reaction mixture was then poured into ice cold water and a solid mass, which separated out, was filtered, washed, dried and crystallized from ethanol. The physico-chemical data was calculated: Rf value 0.64, % yield 60, melting point 172-174<sup>o</sup>C, Brown color solid.

### 2.3.2 Scheme-2:

#### Step-1: Synthesis of 4-(4-Chloro-3-methyl-phenyl)-4-oxo-butyric acid (1)

Succinic anhydride (0.1 mole) was reacted with 2-Chlorotoluene (50 mL) in the presence of anhydrous aluminium chloride (0.1125 mole). The reaction mixture was refluxed for 2-4 h and after completion of the reaction an excess solvent was removed by steam distillation. The residue was purified by dissolving in sodium hydroxide solution, filtering, followed by addition of hydrochloric acid. The solid mass so obtained was filtered, washed with cold water, dried and crystallized from methanol to give the desired 4-(4-Chloro-3-methyl-phenyl)-4-oxo-butyric acid (1), which gave effervescence with sodium bicarbonate solution. The physico-chemical data was calculated: Rf value 0.48, % yield 65.61, melting point 95-97<sup>o</sup>C, Cream color solid.

#### Step-2: Synthesis of 4-(4-Chloro-3-methyl-phenyl)-4-oxo-N-(4-sulfamoyl-phenyl) butyramide (HP-2)

4-(4-Chloro-3-methyl-phenyl)-4-oxo-N-(4-sulfamoyl-phenyl) butyramide (2) were synthesized by dissolving 4-(4-Chloro-3-methyl-phenyl)-4-oxo-butyric acid (1) (0.001 mol) and sulfanilamide (0.001 mol) in a minimum quantity of dry pyridine, separately. The two solutions were then mixed together and stirred magnetically followed by the addition of phosphorous oxychloride (0.9 mL) dropwise, while maintaining the temperature below 5<sup>o</sup>C. The mixtures were stirred for another 0.5 h and left overnight. The reaction mixture was then poured into ice cold water and a solid mass, which separated out, was filtered, washed, dried and crystallized from ethanol. The physico-chemical data was calculated: Rf value 0.42, % yield 58, melting point 192-194<sup>o</sup>C, Brown color solid.

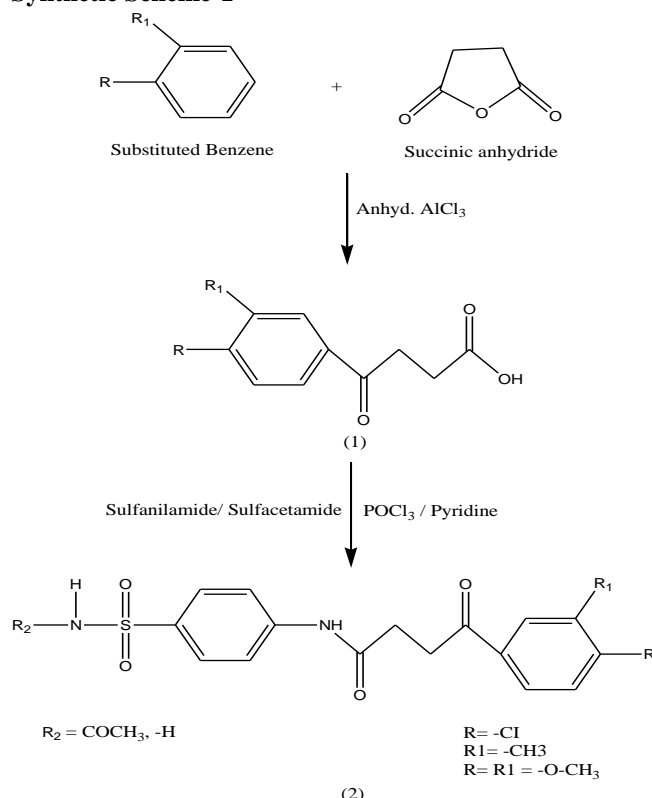
### 2.3.3 Scheme-3:

#### Step-1: Synthesis of 4-(4-Methoxy-phenyl)4-oxo-butyric acid (1)

Succinic anhydride (0.1 mole) was reacted with Anisole (50 mL) in the presence of anhydrous aluminium chloride (0.1125 mole). The reaction mixture was refluxed for 2-4 h and after completion of the reaction an excess solvent was removed by steam distillation. The residue was purified by dissolving in sodium hydroxide solution, filtering, followed by addition of hydrochloric acid. The solid mass so obtained was filtered, washed with cold water, dried and crystallized from methanol to give the desired 4-(4-Methoxy-phenyl)4-oxo-butyric acid (1), which gave effervescence with sodium bicarbonate solution. The physico-chemical data was calculated: Rf value 0.48, % yield 65.61, melting point 95-97<sup>o</sup>C, Cream color solid.

#### Step-2: Synthesis of 4-(4-Methoxy-phenyl)-4-oxo-N-(4-Sulfomoyl-Phenyl-) butyramide (HP-3)

4-(4-Methoxy-phenyl)-4-oxo-N-(4-Sulfomoyl-Phenyl-) butyramide (2) were synthesized by dissolving 4-(4-Methoxy-phenyl)4-oxo-butyric acid (1) (0.001 mol) and sulfanilamide (0.001 mol) in a minimum quantity of dry pyridine, separately. The two solutions were then mixed together and stirred magnetically followed by the addition of phosphorous oxychloride (0.9 mL) dropwise, while maintaining the temperature below 5<sup>o</sup>C. The mixtures were stirred for another 0.5 h and left overnight. The reaction mixture was then poured into ice cold water and a solid mass, which separated out, was filtered, washed, dried and crystallized from ethanol. The physico-chemical data was calculated: Rf value 0.54, % yield 62, melting point 180-182<sup>o</sup>C, Brown color solid.

**Synthetic Scheme-1****Synthesize compound is- HP-1, HP-2 and HP-3****Characterization of the synthesized compounds****N-(4-Acetylsulfamoyl-phenyl)-4-(4-Chloro-3-methyl-phenyl)-4-oxo-butylamide (HP-1)**

Brown colored flakes, M.F. C<sub>19</sub>H<sub>19</sub>ClN<sub>2</sub>O<sub>5</sub>S, M.P. 172-174 °C, Rf 0.64, % yield 60, IR (KBr, cm<sup>-1</sup>, ν): 3359.69(-NH<sub>2</sub>-); 3182.61(-NH-); 1674.59(-C=O); 1334.35(-SO<sub>2</sub>-); 711.39(-C-Cl). <sup>1</sup>H NMR (500 MHz, DMSO-*d*), δ 10.23 (s, 1H, -NH), 7.27-7.71 (m, 7H, Ar-H), 2.52-3.32 (t, 4H, CH<sub>2</sub>-CH<sub>2</sub>), 1.92 -3.38 (s, 6H, -CH<sub>3</sub>, -O-CH<sub>3</sub>), MS (m/z+) [M+1] 422.05.

**4-(4-Chloro-3-methyl-phenyl)-4-oxo-N-(4-sulfamoyl-phenyl)-butylamide (HP-2)**

Brown colored flakes, M.F. C<sub>17</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>4</sub>S, M.P. 192-194 °C, Rf 0.42, % yield 58, IR (KBr, cm<sup>-1</sup>, ν): 3415.56(-NH<sub>2</sub>-);

3237.61(-NH-); 1690.12(-C=O); 1409.65(-SO<sub>2</sub>-); 709.08(-C-Cl). <sup>1</sup>H NMR (500 MHz, DMSO-*d*), δ 10.21 (s, 1H, -NH), 6.91 (s, 2H, -NH<sub>2</sub>), 7.27-7.81 (m, 7H, Ar-H), 2.21-3.22 (t, 4H, CH<sub>2</sub>-CH<sub>2</sub>), 1.98 (s, 3H, -CH<sub>3</sub>), MS (m/z+) [M+1] 380.06.

**4-(4-Methoxy-phenyl)-4-oxo-N-(4-Sulfomoyl-Phenyl)-butylamide (2) (HP-3)**

Brown colored flakes, M.F. C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>S, M.P. 168-170 °C, Rf 0.58, % yield 54, IR (KBr, cm<sup>-1</sup>, ν): 3340.53(-NH<sub>2</sub>-); 3250.94(-NH-); 1659.10(-C=O); 1397.80(-SO<sub>2</sub>-). <sup>1</sup>H NMR (500 MHz, DMSO-*d*), δ 10.23 (s, 1H, -NH), 6.94 (s, 2H, -NH<sub>2</sub>), 7.27 -7.76 (m, 8H, Ar-H), 2.88-3.32 (t, 4H, CH<sub>2</sub>-CH<sub>2</sub>), 3.76 (s, 3H, -O-CH<sub>3</sub>) MS (m/z+) [M+1] 404.09.

**2.4 Pharmacological evaluation****2.4.1 Anticonvulsant Activity**

The compounds were primarily subjected for evaluating their anticonvulsant activity and then screened compounds were subjected to study various phases of MES. The results are shown in Table 1. The compounds N-(4-Acetylsulfamoyl-phenyl)-4-(4-chloro-3-methyl-phenyl)-4-oxo-butylamide (HP-1) showed significant anticonvulsant activity i.e. 66.33% protection. 4-(4-chloro-3-methyl-phenyl)-4-oxo-N-(4-sulfamoyl-phenyl)-butylamide (HP-2) and 4-(4-Methoxy-phenyl)-4-oxo-N-(4-Sulfomoyl-Phenyl)-butylamide (HP-3) showed mild anticonvulsant activity i.e. 50.33% protection.

**2.4.2 Antibacterial activity**

A series were compound 4-(4-chloro-3-methyl-phenyl)-4-oxo-N-(4-sulfamoyl-phenyl)-butylamide (HP-2) and 4-(4-Methoxy-phenyl)-4-oxo-N-(4-Sulfomoyl-Phenyl)-butylamide (HP-3) showed stronger antimicrobial activity against MTCC-521 gram (-)ve bacteria were evaluated after Cup-plate method. The results are shown in Table 2. The studied products are still under investigation. Their antibiotic properties have promising applications in the control of infections.

**3. Result and discussion****Table 1: Anticonvulsant activity of compounds**

Treatment	Dose (mg/kg)	Various phase of convulsions (time in sec)				
		Flexion	Extension	Stupor	Recovery	%Protection
Control	Tween 80	4.416±0.43	14.88±0.31	80.68±0.19	122.1±0.91	33.33
Std.	25	0.592±0.12**	1.22±0.13**	29.01±0.92**	61.47±0.46**	100
HP-1	50	2.823±0.29*	7.92±0.42**	64.84±0.22*	81.88±0.20**	66.33
HP-2	50	2.120±0.30*	11.23±0.48	55.32±0.38**	102.3±0.43*	50.33
HP-3	50	3.045±0.25	9.15±0.30*	58.13±0.25**	94.45±0.12*	50.33

Values represent the mean ± SD of six animals each group (n=6), HP-1, HP-2 and HP-3 test compounds.

\*indicates p<0.05, \*\*indicates p<0.01 and when compared to the control group. (The mean difference was considered significant at 0.01 level).

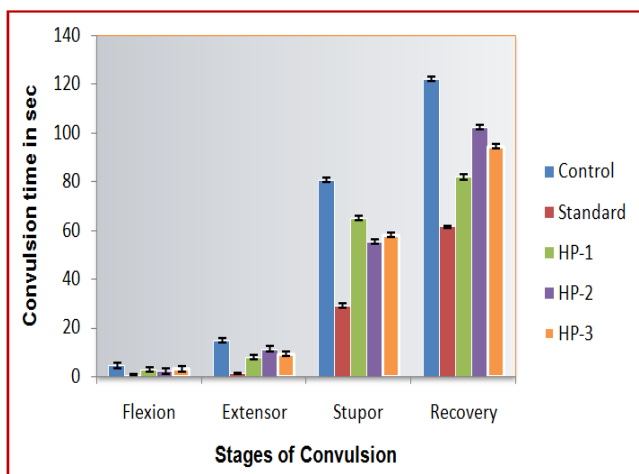


Figure 3: Anticonvulsant activity of compounds

Table 2: Antibacterial activity of compounds

Compound code	Zone of inhibition in mm		
	<i>E. coli</i> (MTCC-521)		
	10 µg/ml	30 µg/ml	50 µg/ml
HP-1	3	3	5
HP-2	2	4	7
HP-3	4	4	6
Ampicillin	5	9	13
Control	-	-	-

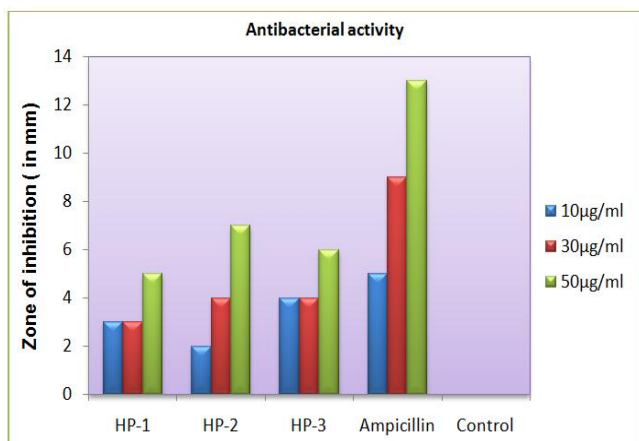


Figure 4: Antibacterial Activity

#### 4. Conclusion

The compounds N-(4-Acetylsulfamoyl-phenyl)-4-(4-chloro-3-methyl-phenyl)-4-oxo-butylamide (HP-1) showed significant anticonvulsant activity. Some compounds show the good antibacterial activity against *Escherichia coli*. The Compound 4-(4-chloro-3-methyl-phenyl)-4-oxo-N-(4-sulfamoyl-phenyl)-butylamide (HP-2) and 4-(4-Methoxy-phenyl)-4-oxo-N-(4-Sulfomoyl-Phenyl)-butylamide (HP-3) showed significant inhibitory characteristics with stronger antimicrobial activity against MTCC-521 gram negative bacteria.

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