

## Dedication:

Dedicated to:

***The spirit of my father.....***

## Acknowledgements

I would like to express my deep thanks to Dr. Ahmed Elsadig Mohammed Saeed, my supervisor for suggesting the idea of this work and for his helpful advice and guidance during the course of this work.

I am greatly indebted to my Co-supervisor Dr.Izzaldin Elfateh Barakat for help and notable assistance in this work.  
I would also like to thank the following:

The staff of Chemistry Department in Sudan University of Science and Technology and offer my special thanks to Ustaz Abd Elkariem Mohamed for his help.

The staff of Instrument Laboratories in the Faculty of Science, Sudan University for assisting me in UV and IR spectroscopy analysis.

Ustaz Elsadig Hassan (Amipharma labs) and L. Gareeballa (Sudan Custom labs) for their help in IR spectroscopy analysis.

## Abstract

Twenty eight sulphonylureas derivatives together with their corresponding intermediates were prepared in this work. The synthetic designing of these compounds was based upon suitable retrosynthetic analysis of the target molecule through the use of the disconnection approach. Accordingly the target sulphonylureas were prepared in a three step reaction. Aryl sulphonylchloride were allowed to react with ammonia or hydrazine to form sulphonamides which were allowed to react with ethyl chloroformate to form the corresponding carbamate.

The final step involved the nucleophilic acyl substitution of some selected amines and the intermediate carbamate to form the required aryl sulphonylureas. The synthetic pathway and the mechanisms of the different reactions were given and discussed in chapter three of this work. Spectral data of the intermediate and final compounds were discussed and compared with each other in order to elucidate the structure of the prepared compounds.

## الخلاصة

تم تحضير ثمان وعشرين مركب في هذه الدراسة هي عبارة عن مركبات نهائية ووسطية لمركب السلفونايل بوريا وقد استهدفت الدراسة التغيير في المجموعات المستبدلة التي ترتبط بحلقة البنزين (مجموعة السلفونايل) ومن جهة أخرى المجموعة المرتبطة بذرة النتروجين في البوريا (أي الأمين المتفاعل مع المركب الوسيط (الكارباميت)).

يتم تحضير هذه المركبات بثلاث خطوات الأولى تفاعل الأمونيا مع كلوريد السلفونايل الذي يعطي السلفوناميد حيث يتفاعل مع ايثايل كلوروفورميت في وسط قاعدي وتسخين ليعطي الكارباميت الذي يتفاعل مع الأمين ليعطي السلفونايل بوريا.

من جانب آخر قد أجريت عدة محاولات لمعالجة الهيدرزاين بدلاً من الأمونيا ولكن بعد عدة محاولات كانت أغليها لا تعطي النتائج المتوقعة تحصلنا على طريقة مثلى لاعطاء مركبات ذات نتائج جيدة وقد تم تتبع النتائج بواسطة كروماتوغرافية الطبقة الرقيقة وتم تحديد المركبات النهائية والوسيلة بواسطة التحليل بالأشعة فوق البنفسجية، الأشعة تحت الحمراء، طيف الرنين النووي المغناطيسي وطيف الكتلة.

عملية التخلق الصديدي التحليلية وميكانيكيات التفاعل تم مناقشتها بالتفصيل في الفصل الثالث وكذلك البيانات الطيفية تم مناقشتها في ذات الفصل.

## List of content

Dedication.....	i
Acknowledgement.....	ii

Abstract.....	iii
.....	iv

## الخلاص

List of content.....	v	
List of schemes.....	viii	
List of tables.....	ix	
<b>1</b>		
<b>1.1</b>	Sulphonylureas .....	2
<b>1.1.1</b>	General chemistry and synthesis.....	4
<b>1.1.2</b>	Structure –activity relationship of sulphonylureas.....	6
<b>1.2</b>	Chemistry of related functional groups .....	9
<b>1.2.1</b>	Sulphonation of aromatic ring.....	9
<b>1.2.1.1</b>	Substitution reactions of benzene derivatives.....	9
<b>1.2.1.2</b>	Sulphonic acid derivatives.....	10
<b>1.2.1.2.1</b>	Sulphonyl chlorides.....	11
<b>1.2.1.2.2</b>	Sulphonate esters.....	11
<b>1.2.1.2.3</b>	Sulphonamides.....	12
<b>1.2.1.2.3.1</b>	Synthesis of Sulponamides.....	13
<b>1.2.1.2.4</b>	Aryl sulphonyl hydrazide ( $\text{SO}_2\text{NHNH}_2$ ).....	14
<b>1.2.2</b>	Amide formation.....	15
<b>1.2.2.1</b>	Derivatives of amides.....	15
<b>1.2.2.2</b>	Synthesis of amides.....	16
<b>1.2.2.2.1</b>	Reaction of amine with acid chloride.....	16
<b>1.2.2.2.2</b>	Acylation of amines by esters.....	16
<b>1.2.2.2.3</b>	Reaction of acids with ammonia.....	17
<b>1.2.2.2.4</b>	Reaction of acid anhydrides with amine.....	18
<b>1.2.2.2.5</b>	Reaction of ammonia and carbon dioxide.....	18
<b>1.2.2.2.6</b>	Rearrangement of oximes .....	18
<b>1.2.2.3</b>	Physical properties of amides.....	19
<b>1.2.2.4</b>	Chemical properties of amides.....	20
<b>1.2.2.4.1</b>	Hydrolysis of amides.....	20
<b>1.2.2.4.2</b>	Conversion into imides .....	20
<b>1.2.2.4.3</b>	Hofmann degradation.....	21
<b>1.2.2.4.4</b>	Acidity of N–H groups.....	21
<b>1.2.3</b>	Carbamates.....	22
<b>1.2.4</b>	Sulphonyl carbazates.....	23
<b>1.3</b>	Aim of the project.....	24
<b>2.</b>	<b>Chapter two: Materials and Methods.....</b>	26
<b>2.1</b>	Materials.....	27
<b>2.1.1</b>	Common reagents.....	27
<b>2.1.2</b>	Chemicals.....	27
<b>2.1.3</b>	Solvents.....	27

2.1.4	Thin Layer Chromatography (TLC).....	28
2.1.5	Instruments.....	28
2.1.5.1	Infra Red Spectroscopy (IR).....	28
2.1.5.2	Ultra Violet Spectroscopy (UV) .....	28
2.1.5.3	Proton Nuclear Magnetic Resonance ( <sup>1</sup> H NMR).....	28
2.1.5.4	Mass Spectroscopy (MS) .....	28
2.1.5.5	General instruments.....	28
2.2	Methods.....	29
2.2.1	Preparation of <i>p</i> -acetamido benzene sulphonyl chloride (Id).....	29
2.2.2.	General procedure for the preparation of aryl sulphonamide (I, II, III, IV).....	29
2.2.3	General procedure for preparation of the N-aryl sulphonyl carbamates (V,VI,VII, VIII) .....	29
2.2.4	General procedure for the preparation of N-aryl sulphonyl –N- alkyl urea's (IX, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII, XIX, XX).....	30
2.2.5	General procedure for the preparation of sulphonyl hydrazide (XXI,XXII,XXIII) .....	30
2.2.6	General procedure for the preparation of sulphonyl carbazate (XXIV, XXV,XXVI).....	31
2.2.7	General procedure for the preparation of N- phenyl sulphonamide -N-alkyl and N-(substituted phenyl) urea(XXVII, XXVIII).....	31
2.2.8	Attempted procedure for the preparation of sulphonylhydrazide (XXI,XXII,XXIII).....	31
2.2.9	Attempted procedure for the preparation of sulphonyl carbazate (XXIV,XXV, XXVI) .....	32
3.	<b>Chapter three: Discussion.....</b>	71
	<b>Conclusion and Recommendations.....</b>	83
4.	<b>References.....</b>	84
	<b>Appendix.....</b>	92

## List of Schemes

<b>Scheme 1-1</b>	Sulphonylureas used as oral antidiabetic drugs.....	8
<b>Scheme 2-1</b>	Chemical Structure of the prepared sulphonamide.....	33
<b>Scheme 2-2</b>	Chemical Structure of the prepared carbamate.....	34
<b>Scheme 2-3</b>	Chemical structure of prepared Benzene sulphonyl ureas.....	35
<b>Scheme 2-4</b>	Chemical structure of prepared <i>p</i> -Bromobenzene sulphonylureas.....	36
<b>Scheme 2-5</b>	Chemical structure of prepared Toluene sulphonylureas.....	37
<b>Scheme 2-6</b>	Chemical structure of prepared <i>p</i> -Acetamidobenzene sulphonylureas.....	37
<b>Scheme 2-7</b>	Chemical structure of prepared sulphonylhydrazide.....	38
<b>Scheme 2-8</b>	Chemical structure of prepared sulphonyl carbazole.....	38
<b>Scheme 2-9</b>	Chemical structure of prepared .....	38
<b>Scheme 3-1</b>	General retrosynthetic approach in sulphonylureas...	72

## LIST OF TABLES

<b>Table 2-1a</b>	Chemical names of sulphonyl chlorides.....	39
<b>Table 2-1b</b>	Chemical names of sulphonamides and sulphonyl	
	hydrazide (intermediates).....	40
<b>Table 2-1c</b>	Chemical names of carbamate and sulphonyl carbazole (Intermediates).....	41
<b>Table 2-1d</b>	Chemical names of prepared sulphonylureas.....	42
<b>Table 2-2a</b>	Reaction condition for the preparation sulphonamide and sulphonyl hydrazide (intermediate).....	43
<b>Table 2-2b</b>	Reaction condition for the preparation of carbamates (intermediates).....	44
<b>Table 2-2c</b>	Reaction condition for the preparation of sulphonyl carbazates (intermediate).....	45
<b>Table 2-2d</b>	Reaction condition for the preparation of N-(aryl Sulphonyl) N-alkyl or aryl ureas (sulphonylureas).....	46
<b>Table 2-2e</b>	Reaction condition for the preparation of N-alkyl and N-(substituted phenyl) urea .....	48
<b>Table 2-3a</b>	Molecular weight and molecular formula of the prepared sulphonamides and sulphonyl hydrazide (intermediate).....	49
<b>Table 2-3b</b>	Molecular weight and molecular formula of the prepared sulphonyl carbamates (intermediate).....	50
<b>Table 2-3c</b>	Molecular weight and molecular formula of the prepared sulphonyl carbazates (intermediate).....	50
<b>Table 2-3d</b>	Molecular weight and molecular formula of the prepared sulphonylureas.....	51
<b>Table 2-4a</b>	IR data of the prepared sulphonamides and sulphonyl hydrazid (intermediate).....	52
<b>Table 2-4b</b>	IR data of the prepared sulphonyl carbamates (intermediate).....	53
<b>Table 2-4c</b>	IR data of the prepared sulphonyl carbazates (intermediate).....	54

<b>Table 2-4d</b>	IR data of the prepared sulphonylureas.....	55
<b>Table 2-4e</b>	IR data of the prepared N-phenyl sulphonamide N-alkyl and N-(substituted phenyl) urea. (Sulphonamideureas) .....	57
<b>Table 2-5a</b>	<sup>1</sup> H-NMR data of the prepared sulphonyl urea.....	58
<b>Table 2-5b</b>	<sup>1</sup> H-NMR data of the compound sulphonamideurea..... <sup>1</sup> H-NMR data of the compound <i>p</i> -Bromo	59
<b>Table 2-5c</b>	sulphonamide & <i>p</i> -Bromo sulphonylcarbamates (intermediate).....	59
<b>Table 2-6a</b>	Mass spectroscopy data of the prepared intermediate (sulphonamids and sulphonyl carbamate).....	60
<b>Table 2-6b</b>	Mass Spectroscopy data of the some prepared sulphonylureas .....	61
<b>Table 2-6c</b>	Mass spectroscopy data of the prepared sulphonylureas.....	62
<b>Table 2-7a</b>	UV data of the some prepared sulphonamides and sulphonyl hydrazide(intermediate) .....	63
<b>Table 2-7b</b>	UV data of the prepared sulphonyl carbamates (intermediate)..... UV data of the prepared sulphonyl carbazates	64
<b>Table 2-7c</b>	(intermediate).....	64
<b>Table 2-7d</b>	UV data of the prepared sulphonylureas.....	65
<b>Table 2-8a</b>	Rf. values of sulphonamides and sulphonyl hydrazide (intermediate).....	67
<b>Table 2-8b</b>	Rf. Values of sulphonyl carbamates (intermediate)...	68
<b>Table 2-8c</b>	Rf. Values of sulphonyl carbazates(intermediate).....	68
<b>Table 2-8d</b>	Rf. Values of sulphonylureas.....	69
<b>Table 2-8e</b>	Rf. Values of sulphonamideureas.....	70