

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY
STUDY OF SULFONAMIDE DERIVATIVES OF DISUBSTITUTED
ANILINES



By:

TAHIR YOUNAS

ID: 13001140030

ADVISOR:

Dr. SOHAIL NADEEM

DEPARTMENT OF CHEMISTRY
SCHOOL OF SCIENCE
UNIVERSITY OF MANAGEMENT AND TECHNOLOGY, LAHORE,
PAKISTAN

2015

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL
ACTIVITY STUDY OF SULFONAMIDE DERIVATIVES OF
DISUBSTITUTED ANILINES

Submitted to University of Management and Technology Lahore

in partial fulfillment of the requirements

for the award of degree of

MASTER OF PHILOSOPHY

IN

CHEMISTRY

BY

TAHIR YOUNAS

ID:13001140030

SESSION: 2013-2015

DEPARTMENT OF CHEMISTRY

SCHOOL OF SCIENCE

UNIVERSITY OF MANAGEMENT AND TECHNOLOGY, LAHORE,
PAKISTAN

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

SYNTHESIS, CHARACTERIZATION AND
BIOLOGICAL ACTIVITY STUDY OF
SULFONAMIDE DERIVATIVES OF
DISUBSTITUTED ANILINES

By:

TAHIR YOUNAS

ID: 13001140030

A thesis submitted to the faculty of the Department of Chemistry, School of Science in partial fulfillment of the requirements for the degree of M.Phil. in Chemistry.

Thesis Committee:

1.

2.

3.

DEPARTMENT OF CHEMISTRY

SCHOOL OF SCIENCE

UNIVERSITY OF MANAGEMENT AND TECHNOLOGY, LAHORE, PAKISTAN 2015

DEDICATION

Dedicated to my beloved Father,

Muhammad Younas

May Allah bless his soul.

ACKNOWLEDGEMENT

In the name of **Allah**, the Most Gracious and the Most Merciful. All praises to Allah for the strengths and His blessings in completing my thesis.

May Allah's peace and blessing be upon our Beloved Prophet Muhammad (PBUH) who was a mercy on us from Almighty Allah, whose character and nobility has never seen before and after Him (PBUH).

Special appreciation goes to my supervisor, **Dr. Suhail Nadeem** for his supervision and constant kind support. His invaluable help, full of constructive comments and suggestions throughout the experimental and thesis works has contributed to the success of this research.

Not forgotten, my appreciation to **Dr. Aziz-ur-Rehman and Sir Shahid Rasool** from GC. Lahore for managing the technical supports especially IR, EIMS and NMR. His personal interest, support and knowledge regarding this topic are highly acknowledged.

I would like to express my appreciation to the Chairperson, Department of Chemistry Department, **Dr. Sammia Shahid** for her support and help towards my postgraduate affairs.

My acknowledgement also goes to all the teachers, technicians and office staffs of School of Science for their co-operations.

Sincere thanks to all my friends especially **Dr.Zain Gilani, Abrar ul Hassan** and **Fahadullah khan** and others for their kindness and moral support during my study. Thanks for the friendship and memories.

Last but not least, my deepest gratitude goes to my beloved parents, brothers and also to my sister for their endless love, prayers and encouragement.

Tahir Younas

TABLE OF CONTENTS

CH # 1	INTRODUCTION	1–5
1.1	Introduction	1
1.2	Spectrum of sulfonamides	1
1.3	Mechanism of action	2
1.4	Several factors influencing sulfonamide action	3
1.5	Allergic and Adverse reactions	3
1.6	Clinical uses	4
1.7	Sulfa drugs in the market	5

CH # 2	LITERATURE REVIEW	6–9
2.1	Shaabani A. <i>et. al.</i> (2007)	6
2.2	Gadad K. A. <i>et. al.</i> (2000)	6
2.3	Reddy N. S. <i>et. al.</i> (2004)	6
2.4	Kumar <i>et. al.</i> (2010)	6
2.5	Lehmler J. H. <i>et. al.</i> (2007)	7
2.6	Abdel-Monem W.R. (2004)	7
2.7	Joshi S. <i>et. al.</i> (2003)	7
2.8	Siddiqui N. <i>et. al.</i> (2007)	7
2.9	Radwan <i>et. al.</i> (1997)	7
2.10	Abele <i>et. al.</i> (2003)	7
2.11	Hanessian S. <i>et. al.</i> (2003)	8
2.12	Siddiqui <i>et al.</i> (2008)	8
2.13	Talaz <i>et. al.</i> (2009)	8
2.14	Mena <i>et. al.</i> (2010)	8
2.15	Moree J. W. <i>et. al.</i> (1996)	9
2.16	Sigman <i>et. al.</i> (2010)	9
2.17	Aziz-ur-Rehman <i>et. al.</i> (2011)	9
2.18	Begum <i>et. al.</i> (2012)	9
CH # 3	EXPERIMENTAL WORK	10-21
3.1	Synthesis of <i>N</i> -tetrahydrofurfuryl-4-Chlorobenzenesulfonamide (3)	10

3.2	General Synthesis of <i>N</i> -substituted derivatives of <i>N</i> -tetrahydrofurfuryl-4-chlorobenzene sulfonamide (5a-i)	11
3.3	Synthesis of <i>N</i> -Propyl- <i>N</i> -tetrahydrofurfuryl-4-chlorobenzenesulfonamide (5a)	12
3.4	Synthesis of <i>N</i> -(1-Methylethyl)- <i>N</i> -tetrahydrofurfuryl-4-chlorobenzenesulfonamide (5b)	13
3.5	Synthesis of <i>N</i> -Butyl- <i>N</i> -tetrahydrofurfuryl-4-chlorobenzenesulfonamide (5c)	14
3.6	Synthesis of <i>N</i> -Pentyl- <i>N</i> -tetrahydrofurfuryl-4-chlorobenzenesulfonamide (5d)	15
3.7	Synthesis of <i>N</i> -(1-Methylbutyl)- <i>N</i> -tetrahydrofurfuryl-4-chlorobenzenesulfonamide (5e)	16
3.8	Synthesis of <i>N</i> -(2-Chlorobenzyl)- <i>N</i> -tetrahydrofurfuryl-4-chlorobenzenesulfonamide (5f)	17
3.9	Synthesis of <i>N</i> -(4-Bromobenzyl)- <i>N</i> -tetrahydrofurfuryl-4-chlorobenzenesulfonamide (5g)	18
3.10	Synthesis of <i>N</i> -(2-phenylethyl)- <i>N</i> -tetrahydrofurfuryl-4-chlorobenzenesulfonamide (5h)	19
3.11	Synthesis of <i>N</i> -(3-phenylpropyl)- <i>N</i> -tetrahydrofurfuryl-4-chlorobenzenesulfonamide (5i)	20
3.12	Antibacterial activity	21

CH # 4	RESULTS AND DISCUSSION	22–38
4.1	<i>N</i> -tetrahydrofurfuryl-4-chlorobenzenesulfonamide (3)	22
4.2	<i>N</i> -Propyl- <i>N</i> -tetrahydrofurfuryl-4-chlorobenzenesulfonamide (5a)	24
4.3	<i>N</i> -(1-Methylethyl)- <i>N</i> -tetrahydrofurfuryl-4-chlorobenzenesulfonamide (5b)	26
4.4	<i>N</i> -Butyl- <i>N</i> -tetrahydrofurfuryl-4-chlorobenzenesulfonamide (5c)	28
4.5	<i>N</i> -Pentyl- <i>N</i> -tetrahydrofurfuryl-4-chlorobenzenesulfonamide (5d)	29
4.6	<i>N</i> -(1-Methylbutyl)- <i>N</i> -tetrahydrofurfuryl-4-chlorobenzenesulfonamide (5e)	30
4.7	<i>N</i> -(2-Chlorobenzyl)- <i>N</i> -tetrahydrofurfuryl-4-chlorobenzenesulfonamide (5f)	31
4.8	<i>N</i> -(4-Bromobenzyl)- <i>N</i> -tetrahydrofurfuryl-4-chlorobenzenesulfonamide (5g)	32
4.9	<i>N</i> -(2-phenylethyl)- <i>N</i> -tetrahydrofurfuryl-4-chlorobenzenesulfonamide (5h)	33
4.10	<i>N</i> -(3-phenylpropyl)- <i>N</i> -tetrahydrofurfuryl-4-chlorobenzenesulfonamide (5i)	34
4.11	Antibacterial activity (<i>In vitro</i>)	36
4.12	Table 1	37
		38
	Conclusion	
CH # 5	REFERENCES	39–41

ABSTRACT

Sulfonamides due to their medicinal importance are under consideration by the researchers. Chloro substituted sulfonamide, **3a-b**, has been synthesized with high yields by a single step nucleophilic substitution reaction of disubstituted anilines, **1a-b**, and 4-chlorobenzenesulfonyl chloride (**2**) in a weak basic aqueous medium. The synthesized sulfonamides, **3a-b**, were further subjected to electrophilic substitution reaction using ethyl iodide (**4**), benzyl chloride (**5**) and 4-chlorobenzyl chloride (**6**) in such a solvent which is polar aprotic to get *N*-substituted derivatives, **7a -b**, **8a-b** and **9a -b**, respectively. The suggested structures of all the prepared molecules were characterized using IR, ¹H-NMR and EIMS spectroscopic analysis. All these di-substituted sulfonamides were also evaluated for

their enzyme inhibition capacity, against lipoxygenase (LOX) and bacterial strains of Gram bacteria.

Overall Scheme:

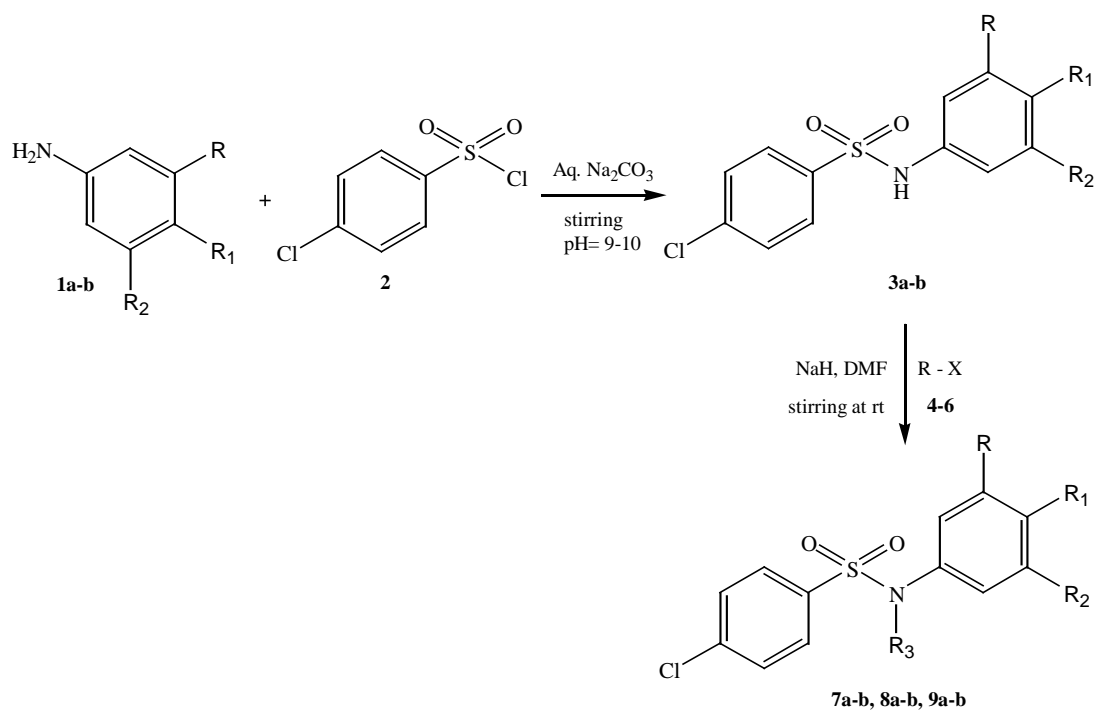


Table-A:

Compound	R	R ₁	R ₂	R ₃
7a	CH ₃	CH ₃	H	CH ₃ CH ₂
7b	CH ₃	-	CH ₃	CH ₃ CH ₂
8a	CH ₃	CH ₃	H	C ₆ H ₅ CH ₂
8b	CH ₃	-	CH ₃	C ₆ H ₅ CH ₂
9a	CH ₃	CH ₃	H	4-ClC ₆ H ₄ CH ₂
9b	CH ₃	-	CH ₃	4-ClC ₆ H ₄ CH ₂

TABLE OF CONTENTS

Serial No.	Chapter /Title	Page No.
1.0	INTRODUCTION	1-12
1.1	History of Azomethines	2
1.2	Chemistry of Azomethines	2
1.3	Stability of Azomethines	2

1.4	Classification of Azomethines	2
1.5	Synthesis of Azomethines	3
1.5.1	General Mechanism of Formation	3
1.5.2	Biological formation of Azomethines	4
1.6	Mechanism of Anti-Microbial Action of Azomethines	4
1.7	Applications of Schiff bases	5
1.7.1	Applications in Medicine and Pharmacy	5
1.7.2	Biological Activities	5
1.7.3	Antibacterial Activities	5
1.7.4	Antifungal Activities	6
1.7.5	Antiviral Activities	6
1.7.6	Antimalarial Activities	6
1.7.7	Anticancer and Cytotoxic Activities	6
1.7.8	Biocidal Activities	7
1.7.9	Pesticidal Activities	7
1.7.10	Anti-inflammable Activities	7
1.7.11	Applications in Modern Technology	7
1.7.12	Applications in Organic Synthesis	8
1.7.13	Plant Growth Regulator	8

1.7.14	Intermediates for Amino Acids	8
1.7.15	As Catalysts	8
1.7.16	As Flexidentate Lingand	9
1.7.17	Applications in Dyes	9
1.7.18	As Corrosion Inhibitor	9
1.7.19	Photochromism and Thermochromism	9
1.7.20	Reagents for Solvent Extraction	9
1.7.21	Applications in Polymerization	10
1.7.22	Applications in Organic Electronics	10
1.7.23	Sorbents in Solid Phase Extraction	10
1.7.24	Applications in HPLC	11
1.7.25	Nonlinear Optical Response	11
1.7.26	Miscellaneous Applications	11
1.8	Aims & Objective of Research	12
2.0	REVIEW OF LITERATURE	13-29
3.0	MATERIALS AND METHODS	30-37
3.1	General	30
3.2	Synthesis of ethyl 2-(2,4-dimethylphenoxy)acetate (2)	31
3.3	Synthesis of 2-(2,4-dimethylphenoxy)acetohydrazide (3)	31

3.4	Synthesis of <i>N'</i> -Substitutedbenzylidene-2-(2,4-dimethylphenoxy) acetohydrazide (5a-d)	32
3.4.1	Synthesis of <i>N'</i> -Benzylidene-2-(2,4-dimethylphenoxy)acetohydrazide (5a)	33
3.4.2	Synthesis of <i>N'</i> -(2,3-Dimethoxybenzylidene)-2-(2,4-dimethylphenoxy)acetohydrazide (5b)	34
3.4.3	Synthesis of <i>N'</i> -(2,5-Dimethoxybenzylidene)-2-(2,4-dimethylphenoxy)acetohydrazide (5c)	34
3.4.4	Synthesis of <i>N'</i> -(3,4-Dimethoxybenzylidene)-2-(2,4-dimethylphenoxy)acetohydrazide (5d)	35
3.5	Overall Scheme For Synthesis Of Azomethine Derivatives	36
3.6	Antibacterial Assays	36
3.7	Lipoxygenase Inhibition Activity	37
3.8	Statistical Analysis	37
4.0	RESULTS AND DISCUSSION	38-69
4.1	Interpretation of ethyl 2-(2,4-dimethylphenoxy)acetate (2)	39
4.2	Interpretation of 2-(2,4-dimethylphenoxy)acetohydrazide (3)	42
4.3	Interpretation of <i>N'</i> -Substitutedbenzylidene-2-(2,4-dimethylphenoxy) acetohydrazide (5a-d)	45
4.3.1	Interpretation of <i>N'</i> -Benzylidene-2-(2,4-dimethylphenoxy)acetohydrazide (5a)	45
4.3.2	Interpretation of <i>N'</i> -(2,3-Dimethoxybenzylidene)-2-(2,4-dimethylphenoxy)acetohydrazide (5b)	51

4.3.3	Interpretation of <i>N'</i> -(2,5-Dimethoxybenzylidene)-2-(2,4-dimethylphenoxy) acetohydrazide (5c)	57
4.3.4	Interpretation of <i>N'</i> -(3,4-Dimethoxybenzylidene)-2-(2,4-dimethylphenoxy) acetohydrazide (5d)	62
4.4	Antibacterial and anti-enzymatic activity (<i>in vitro</i>)	66
4.5	Conclusion	69
5.0	REFERENCES	70-77

LIST OF FIGURES

Serial No	Title	Page No.
1.1	Formation of Azomethine from primary amine and aldehyde/ketone through condensation	1
1.2	General structure an Azomethine	2
1.3	General mechanism of Azomethine formation	3

1.4	Mechanism of Azomethine formation in the Presence of Base	4
1.5	Formation of Azomethine in biological system	4
2.1	Complex Azomethine Derivative	16
2.2	Showing Schiff Base as Ligand	17
3.1	Melting Point Apparatus	30
3.2	NMR Spectrometer	30
3.3	IR Spectrometer	30
3.4	EMIS Spectrometer	30
3.5	TLC Chromatogram	30
3.6	Reflux through Condenser	31
3.7	Showing Condenser	32
3.8	Magnetic Stirrer	33
3.9	Showing Inhibition Zones	36
4.1	¹ H-NMR spectrum of 2	40-41
4.2	Mass fragmentation pattern of compound 2	41
4.3	¹ H-NMR spectrum of 3	43-44
4.4	Mass fragmentation pattern of compound 3	44
4.5	¹ H-NMR spectrum of 5a	46-47

4.6	¹³ C-NMR spectrum of 5a	47-50
4.7	Mass fragmentation pattern of compound 5a	50
4.8	¹ H-NMR spectrum of 5b	52-53
4.9	¹³ C-NMR spectrum of 5b	53-56
4.10	Mass fragmentation pattern of compound 5b	57
4.11	¹ H-NMR spectrum of 5c	59-60
4.12	Mass fragmentation pattern of compound 5c	60
4.13	EIMS spectrum of 5c	61
4.14	¹ H-NMR spectrum of 5d	63-64
4.15	Mass fragmentation pattern of compound 5d	65
4.16	EIMS spectrum of 5d	65-66

LIST OF TABLES

Serial No	Title	Page No.
4.1	%age inhibition of antibacterial activity	67
4.2	MIC values of antibacterial activity	68
4.3	Enzyme inhibition against LOX	68

NOMENCLATURE

Serial No	Abbreviations	Detail
1	NMR	Nuclear Magnetic resonance
2	FTIR	Fourier transform infrared
3	EIMS	Electron Impact Mass Spectrometry
4	MIC	Minimum inhibitory concentration
5	LOX	Lipoxygenase
6	IC ₅₀	