



**SYNTHESIS OF QUINOXALINE DERIVATIVES AND THEIR  
ANTIBACTERIAL ACTIVITY AGAINST PATHOGENIC BACTERIA**

By

**HENA KHATOON**

**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia,  
in Fulfilment of the Requirements for the Degree of Doctor of Philosophy**

**May 2023**

**FS 2023 2**

All material contained within the thesis, including without limitation text, logos, icons, photographs, and all other artwork, is copyright material of Universiti Putra Malaysia unless otherwise stated. Use may be made of any material contained within the thesis for non-commercial purposes from the copyright holder. Commercial use of material may only be made with the express, prior, written permission of Universiti Putra Malaysia.

Copyright © Universiti Putra Malaysia



Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

## SYNTHESIS OF QUINOXALINE DERIVATIVES AND THEIR ANTIBACTERIAL ACTIVITY AGAINST PATHOGENIC BACTERIA

By

HENA KHATOON

May 2023

**Chairman : Associate Professor Emilia Abdul Malek, PhD**  
**Faculty : Science**

Quinoxaline derivatives, in which nitrogen substitutes for one or more carbon atoms in the naphthalene ring, are a significant class of hetero-cyclic compounds, and are well known in the pharmaceutical industry, and have been shown to possess a broad spectrum of biological activities. These formulations make use of straightforward techniques to create quinoxaline derivatives from aryl-thiols (mercaptan) compounds. Inspired by the biological prominence of quinoxaline derivatives and trying to solve bacterial resistance problems, in this study, 24 quinoxaline derivatives were synthesized. These series were synthesized from the reaction of 2,3-dichloroquinoxaline (2,3-DCQ), 2-chloroquinoxaline (2-CQ), 2-chloro-3-methyl quinoxaline (3-MCQ) with two different aromatic aryl-thiols (mercaptan) and phenols in a single step to investigate the activities aromatic derivatives. The compounds were synthesized using different solvent systems, dimethylformamide (DMF)/ potassium triphosphate ( $K_3PO_4$ ), methanol (MeOH)/ triethylamine ( $Et_3N$ ), acetone/ 0.1N sodium hydroxide (NaOH), and dimethylformamide/potassium carbonate (DMF/  $K_2CO_3$ ), depending on the nucleophilicity of the mercaptan compounds. A comparative study was used to compare the efficiency of these solvent systems to synthesize the same target compounds regarding the reaction time, percentage yield, purity of the compounds, and benignity towards the environment. The structures of twenty-four compounds were confirmed by applying spectroscopic analysis (1D and 2D nuclear magnetic resonance (NMR), Fourier transform infrared (FTIR), and gas chromatography mass spectrometry (GCMS)). In addition, four different bacteria were used to evaluate the antibacterial efficacy of the compounds (1-15): three Gram-negative (*Escherichia coli* (*E. coli*), *Salmonella Typhimurium*, *Enterobacter aerogenes*), and Gram-positive (*Bacillus Pumilus*). To assess a drug's efficacy against a particular bacterial species, the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) assays are frequently performed. The synthesized molecules displayed a better role as antibacterial agents than their analogs. Compounds 8 and 14 have the strongest antibacterial activity for *Bacillus pumilus*, with an inhibition zone of 10 and 9 mm (MIC ranging at about 5 and 2.5 mg/mL, followed by MBC at 2.5 mg/mL). A similar pattern of antibacterial

properties was observed against *E. coli*. Compounds **1** and **3** have an inhibition zone (IZ) of 7 and 6 mm and MIC of 1.25 and 5 mg/mL, respectively. Similarly, di-substituted derivatives **8**, **13**, and **14** have the best IZ of 11, 12, and 12 (mm) (MIC of 2.5, 5 and 5 mg/mL, followed by MBC of 2.5, 5 and 2.5 mg/mL). Due to impressive antibacterial properties, the compounds were also studied for their physio-chemical and drug-likeness properties *via* Swiss ADME software. It was found that molecules **9** and **11** displayed remarkable drug-likeness properties without violating the rules and a bio-availability score of 0.55. Like-wise molecular docking studies provided good interactions between protein and ligands (synthesized compounds). The molecular docking studies were performed on compounds **8**, **12**, **13**, **14**, **19** and **21**. Compound **12** had the best docking score of -8.60 kcal/mol followed by compound **13** (-8.01 kcal/mol) for DNA gyrase protein. Compounds **12** and **13** are classified as di-substituted quinoxaline derivatives having electron-withdrawing -NO<sub>2</sub> and -COOH, which enhanced the formation of H-bonding with amino acids. Compounds **12**, **13** and **8** had a similar effect with PBP1a protein (-8.01 kcal/mol for compound **8**, -8.16 kcal/mol for compound **12** and -7.97 kcal/mol for compound **13**). The reaction conditions for the synthesized compounds were straightforward and produced using S<sub>N</sub>Ar (aromatic nucleophilic substitution reaction) mechanism. Antibacterial assays and docking investigations revealed that the sulfur bridge made the molecule into a powerful antibacterial agent. Two symmetrical sulfur bridges were shown to have increased antibacterial activity, making them a prime option for medication development.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

## SINTESIS DERIVATIF QUINOKSALIN DAN AKTIVITI ANTIBAKTERIA MEREKA TERHADAP BAKTERIA PATOGENIK

Oleh

HENA KHATOON

Mei 2023

**Pengerusi** : **Profesor Madya Emilia binti Abd Malek, PhD**  
**Fakulti** : **Sains**

Derivatif kuinoksalina dikenal dalam industri farmaseutikal dan telah terbukti mempunyai spektrum aktiviti biologi yang luas, termasuk sifat antiviral dan antibakteria. Dalam tesis ini, kami telah merancang untuk memperkenalkan beberapa sebatian heterosiklik kuinoksalina baharu ke dalam literatur sebagai sumbangan kami. Dalam penyediaan ini, kami telah menggunakan kaedah mudah untuk menyediakan derivatif kuinoksalina menggunakan sebatian mercapto. Diilhamkan oleh penjonolan biologi derivatif kuinoksalina dan cuba menyelesaikan masalah rintangan bakteria, dalam kajian ini, 24 derivatif kuinoksalina telah disintesis. Siri ini disintesis daripada tindak balas 2,3-dichloroquinoline (2,3-DCQ), 2-klorokuinoksalina (2-CQ), 2-kloro-3-methylkuinoksalina (3-MCQ) dengan dua merkaptan aromatik yang berbeza dan fenol dalam satu langkah untuk menyiasat aktiviti derivatif aromatik.

Sebatian telah disintesis menggunakan sistem pelarut yang berbeza, DMF/  $K_3PO_4$ , MeOH/  $Et_3N$ , aseton/ 0.1N NaOH, dan DMF/  $K_2CO_3$ , bergantung kepada kenukleofilikan sebatian merkaptan. Kajian perbandingan telah digunakan untuk membandingkan kecekapan sistem pelarut ini untuk mensintesis sebatian sasaran yang sama mengenai masa tindak balas, peratusan hasil, ketulenan sebatian, dan benigna terhadap alam sekitar. Tambahan pula, struktur dua puluh empat sebatian telah disahkan dengan menggunakan analisis TLC dan spektrometri (1D dan 2D NMR, FTIR, dan GCMS). Selain itu, empat bakteria yang berbeza digunakan untuk menilai keberkesanan antibakteria senyawa (1-15): tiga gram negatif (*Escherichia coli* (*E. coli*), *Salmonella Typhimurium*, *Enterobacter aerogenes*), dan gram positif (*Bacillus pumilus*). Kajian MIC dan MBC meningkatkan lagi pemahaman yang lebih baik tentang molekul sebagai antibakteria. Molekul yang disintesis dengan 2,3-diklorokuinoksalina menunjukkan peranan yang lebih baik sebagai agen antibakteria berbanding analognya. Sebagai contoh, sebatian 5 dan 6 mempamerkan zon perencatan 15 mm untuk *Bacillus pumilus*, hampir setanding dengan antibiotik standard chlorohexidine (20 mm). Disebabkan sifat antibakteria yang mengagumkan, sebatian itu juga dikaji untuk sifat fisiokimia dan

keserupaan dadah melalui perisian Swiss ADME. Didapati bahawa molekul **9** dan **11** mempamerkan sifat serupa dadah yang luar biasa tanpa melanggar peraturan dan skor bioavailibiliti 0.55. Kajian dok molekul yang sama juga menyediakan interaksi yang baik antara protein dan ligan (sebatian tersintesis). Kajian dok molekul dilakukan pada sebatian **8, 12, 13, 14, 19** dan **21**. Sebatian **12** mempunyai skor dok terbaik sebanyak -8.60 kcal/mol diikuti oleh sebatian **13** (-8.01 kcal/mol) untuk protein girase DNA. Sebatian **12** dan **13** dikelaskan sebagai derivatif kuinoksalina tersubstitusi yang mempunyai penarikan elektron  $-NO_2$  dan  $-COOH$ , yang meningkatkan pembentukan ikatan H dengan asid amino. Begitu juga sebatian **12, 13** dan **8** mempunyai kesan yang sama dengan protein PBP1a (-8.16 kcal/mol untuk sebatian **12** dan -7.97 kcal/mol untuk sebatian **13**). Kesimpulannya, keadaan reaksi untuk bahan kimia yang disintesis adalah mudah dan dihasilkan dengan cara yang bertanggungjawab terhadap alam sekitar. Ujian antibakteria dan penyelidikan penyertaan mendedahkan bahawa jambatan sulfur menjadikan molekul itu menjadi agen antibakteri yang kuat. Dua jambatan sulfur simetrik telah ditunjukkan untuk meningkatkan aktiviti antibakteria, menjadikannya pilihan utama untuk pembangunan ubat.

## ACKNOWLEDGEMENTS

In the name of Allah, the most gracious, the most merciful; peace and blessing for Prophet Mohammed (SAW).

First and foremost, I would like to thank my supervisor, Dr. Emilia binti Abd Malek, for her support and tremendous patience with me over the past three years. Without her understanding, encouragement, and guidance, it would be difficult to complete this research. Her understanding and research experience helped me overcome all my hurdles. Apart from research, her prompt reply to messages and emails helped me speed up my thesis evaluation. This work could not be brought to light without you, Dr. Emilia.

My heartfelt thanks and appreciation go to Dr. Siti Munirah and Dr. Yaya Rukayadi for their co-supervision, in-person meetings, and invaluable advice.

Thank you very much to Safwan Pekam (Institute of Bio Science, UPM) for his invaluable assistance in anti-bacterial evaluation. His guidance, along with that of Dr. Yaya Rukayadi, helped me evaluate the biological significance of my synthesized compounds.

I am especially grateful to the Department of Chemistry's technical staff for their assistance in analyzing my samples: En. Salahuddin (Institute of Bioscience) for NMR analysis, Puan Nurul Syazwani for GCMS, and Puan Noor Hanaliza for FTIR.

Continuous prayer and unconditional love from my family, especially my father and husband, were the main sources of power that directed and assisted me in spite of all the personal hardships that I faced during my journey.

I also thank my dad for helping me financially to continue my studies in Malaysia. His financial and spiritual support has been invaluable to me over the last three years.

Many thanks to my daughter Yusra Khan for bearing with me while waiting outside my lab. I cannot forget all the time that you spent sitting alone, waiting for your mom to take you home. Your sweet smile and hugs make me forget about my lab work fatigue.

Thanks to my husband, Ifthikar Ahmed Khan, for financially supporting me every month and waiting patiently for me to complete my lab work.

I'd also like to thank all of my Malaysian friends, especially Bushra Khan, for assisting me in overcoming my depression as a result of the Coronavirus lockdown. Without your help, it would have been difficult to cope with the adverse conditions due to lockdown.





This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

**Emilia binti Abdul Malek, PhD**

Associate Professor ChM.  
Faculty of Science  
Universiti Putra Malaysia  
(Chairman)

**Siti Munirah binti Mohd Faudzi, PhD**

Senior Lecturer  
Faculty of Science  
Universiti Putra Malaysia  
(Member)

**Yaya Rukayadi, PhD**

Associate Professor  
Faculty of Food Science and Technology  
Universiti Putra Malaysia  
(Member)

---

**ZALILAH MOHD SHARIFF, PhD**

Professor and Dean  
School of Graduate Studies  
Universiti Putra Malaysia

Date: 14 December 2023

## TABLE OF CONTENTS

	Page
<b>ABSTRACT</b>	i
<b>ABSTRAK</b>	iii
<b>ACKNOWLEDGEMENTS</b>	v
<b>APPROVAL</b>	vii
<b>DECLARATION</b>	ix
<b>LIST OF TABLES</b>	xv
<b>LIST OF FIGURES</b>	xvii
<b>LIST OF SCHEMES</b>	xxi
<b>LIST OF ABBREVIATIONS</b>	xxiv
<b>CHAPTER</b>	
<b>1 INTRODUCTION</b>	1
1.1 Problem statement	4
1.2 Objectives	5
<b>2 LITERATURE REVIEW</b>	6
2.1 Synthesis of quinoxaline derivatives	6
2.1.1 Using K-10 bentonite clay	6
2.1.2 Utilizing a heterogeneous phosphate-based catalyst (triple super phosphate (TSP), and diammonium phosphate (DAP), mono-ammonium phosphate (MAP))	7
2.1.3 Using the lanthanide reagent (CAN)	8
2.1.4 Employing Iron as a Catalyst	8
2.1.5 Fluorinated alcohols in synthesis (HFIP)	9
2.1.6 Pyridine as a catalyst in the synthesis of quinoxalines	10
2.1.7 Synthesis with a solid acid catalyst	10
2.1.8 Quinoxaline synthesis utilizing catalytic amounts of acetic acids	11
2.1.9 Synthesis of quinoxalines using secondary amines in boiling benzene	11
2.1.10 Diketone- and 6-chloro-7-fluoro-1,2-diaminobenzene-based quinoxaline synthesis	12
2.1.11 Synthesis of novel 2,3-diaminoquinoxaline derivatives	13
2.1.12 Synthesis of methyl-2-[3-(3-phenylquinoxalin-2-ylsulfanyl) propanamidoalkanoates and <i>N</i> -Alkyl-3-((3-phenylquinoxalin-2-ylsulfanyl) propanamides	14
2.1.13 Synthesis of chloroquinoxaline derivatives	15
2.1.14 Synthesis of <i>N</i> -((4-(2-methylquinoxaline-3-yloxy)phenyl) methylene)-4-substituted	

	benzenamine and 4-(2-methyl quinoxaline-3-yloxy) benzaldehyde	16
2.1.15	Synthesis of 2-(5-Arylthiazolo[2,3-c][1,2,4]triazol-3-yl)quinoxaline derivatives	17
2.1.16	Synthesis of Spiro [thiazolidine-quinoxaline] derivatives	18
2.1.17	Synthesis of bistetrazoloquinoxalines	18
2.1.18	Synthesis of substituted quinoxaline piperazinyl phenyl thiazoles	19
2.1.19	Synthesis of derivatives of quinoxaline-2,3(1 <i>H</i> ,4 <i>H</i> )-dithione	20
2.1.20	Synthesis of [1,2,4]triazolo[4,3-a]quinoxaline and bis([1,2,4]triazolo) [4,3-a:30,40-c]quinoxaline	22
2.1.21	Synthesis of thiadiazino and thiazolo quinoxaline derivatives	22
2.1.22	Synthesis of quinoxaline-2-carboxylate-1,4-dioxide	24
2.1.23	Synthesis of [1,2,4]triazolo[4,3-a]quinoxalines derivatives	25
2.1.24	Synthesis of 2,3-bis(aryl-thio)quinoxaline	26
2.1.25	Chemo selective arylation of thiols	26
2.2	Prevalence of Anti-Microbial Resistance (AMR) in <i>E. coli</i> , <i>B. pumilus</i> , <i>E. aerogenes</i> and <i>Salmonella typhimurium</i>	27
2.3	Antibacterial activity of quinoxaline derivatives	29
2.4	Antibacterial Activity of quinoxaline derivatives against methicillin-resistant <i>Staphylococcus aureus</i>	32
2.5	Anti-HIV activity of quinoxaline derivatives	33
2.6	Anticancer activity of quinoxaline derivatives	34
2.7	Pharmacokinetics, drug-likeness and medicinal chemistry	36
	2.7.1 Structure and bioavailability radar	36
	2.7.2 Physico-chemical properties	36
	2.7.3 Lipophilicity	37
	2.7.4 Drug-likeness	37
	2.7.5 Medicinal Chemistry	38
2.8	ADMET analysis of newly synthesized quinoxaline derivatives	38
2.9	Molecular docking via Swiss dock software	39
	2.9.1 Docking results for Pyrrolo[2,3-b]quinoxalines	40
<b>3</b>	<b>MATERIALS AND METHODS</b>	42
3.1	Materials	42
3.2	General Analytical and Spectroscopic Technique	42
	3.2.1 Thin Layer Chromatography (TLC)	42
	3.2.2 Melting point	42
	3.2.3 Nuclear Magnetic Resonance (NMR) Spectroscopy	42
	3.2.4 Fourier Transform Infrared (FTIR) Spectroscopy	43
	3.2.5 Mass Spectroscopic Analysis (DIMS)	43
	3.2.6 Yield Calculations	43

3.2.7	Recrystallization method	43
3.3	General procedure for preparation of 2-chloro-3-(arylthiol) quinoxaline (1-5)	44
3.3.1	Synthesis of 4-((3-chloroquinoxalin-2-yl)sulfanyl) aniline 1	45
3.3.2	Synthesis of 2-chloro-3-(3,5-dimethylphenylthio) quinoxaline (2)	46
3.3.3	Synthesis of 2-chloro-3-(4-methoxyphenylthio)quinoxaline (3)	47
3.3.4	Synthesis of 2-chloro-3-(naphthalen-2-ylthio)quinoxaline (4)	48
3.3.5	Synthesis of 2-(4-tert-butylbenzylthio)-3-chloroquinoxaline (5)	49
3.4	General procedure for the synthesis of 2-chloro-3-(arylphenoxy) quinoxaline (6 and 7)	49
3.4.1	Synthesis of 2-chloro-3-(3-nitrophenoxy) quinoxaline (6)	50
3.4.2	Synthesis of 2-chloro-3-(4-nitrophenoxy) quinoxaline (7)	51
3.5	General procedure for synthesis of 2,3-bis(arylthiol)quinoxaline	52
3.5.1	Synthesis of 2,3-bis(4-methoxyphenylthio) quinoxaline (8)	54
3.5.2	Synthesis of 2,3-di (thio-4-tert butyl benzyl) quinoxaline (9)	55
3.5.3	Synthesis of 2,3-bis(3,5-dimethylphenylthio) quinoxaline (10)	56
3.5.4	Synthesis of 2,3-bis(naphthalen-2-ylthio) quinoxaline (11)	57
3.5.5	Synthesis of 2,3-bis(4-nitrophenylthio) quinoxaline (12)	58
3.5.6	Synthesis of 3,3'-(quinoxaline-2,3-diyl)disulfanediy) dibenzoic acid (13)	59
3.5.7	Synthesis of 4,4'-(quinoxaline-2,3-diyl)di(sulfanediy)) dianiline (14)	60
3.5.8	Synthesis of 2,3-bis(2-pyrimidinylsulfanyl)quinoxaline (15)	61
3.6	Synthesis of 2,3-bis (3-nitrophenoxy) quinoxaline (16)	62
3.7	Synthesis of 4-chloro-12 <i>H</i> -quinoxalino[2,3- <i>b</i> ]1,4-benzotiazine (17)	63
3.8	Synthesis of 5-nitro-1 <i>H</i> -benzo[d]imidazole-2-thiol (18)	64
3.9	General procedure for the synthesis of derivatives of 2-(arylthiol) quinoxaline	65
3.9.1	Synthesis of 3-(quinoxalin-2-ylthio) benzoic acid (19)	65
3.9.2	Synthesis of 2-(4-(quinoxaline-2-ylthio) phenylthiol) quinoxaline (20)	66
3.9.3	Synthesis of 2-(naphthalen-2-ylthio)quinoxaline (20)	67

3.10	General Procedure for the synthesis of derivatives of 3-methyl-2-(aryl-thiol) quinoxaline	68
3.10.1	Synthesis of 3-(3-methylquinoxalin-2-ylthio) benzoic acid (23)	69
3.10.2	Synthesis of 2-(3-methylquinoxalin-2-ylthio) benzoic acid (24)	70
3.10.3	Synthesis of 3-methyl- (naphthalen-2-ylthio) quinoxaline (25)	71
3.11	ADMET (absorption, distribution, metabolism, excretion, toxicity) properties of synthesized quinoxaline derivatives	72
3.12	Antimicrobial Assay	73
3.12.1	MIC and MBC determination	73
3.13	Molecular docking study of synthesized quinoxaline derivatives	74
<b>4</b>	<b>RESULTS AND DISCUSSION</b>	<b>76</b>
4.1	Synthesis and characterization of 2-chloro-3-(aryl-thiol)quinoxaline (1-5)	76
4.2	Synthesis of 2-chloro-3-(aryl phenoxy) quinoxaline (6 and 7) and 2,3-bis (3-nitrophenoxy) quinoxaline (16)	82
4.3	Synthesis of 2,3-bis (aryl-thiol) quinoxaline (8 – 15)	91
4.4	Synthesis of 4-chloro-12 <i>H</i> -quinoxalino[2,3- <i>b</i> ]1,4-benzotiazine (17)	107
4.5	Synthesis of 5-Nitro-1 <i>H</i> -benzo[d]imidazole2-thiol (18)	110
4.6	Synthesis of 3-(quinoxalin-2-ylthio) benzoic acid (19)	115
4.7	<i>In vitro</i> antibacterial screening of synthesized compounds	121
4.8	Physio-chemical and drug-likeness of quinoxaline derivatives	126
4.8.1	Structure and bio-availability radar	126
4.8.2	Graphical Output	128
4.9	Molecular docking study	129
<b>5</b>	<b>CONCLUSION</b>	<b>135</b>
5.1	Conclusion	135
5.2	Recommendations	136
	<b>REFERENCES</b>	<b>137</b>
	<b>APPENDICES</b>	<b>149</b>
	<b>BIODATA OF STUDENT</b>	<b>213</b>
	<b>LIST OF PUBLICATIONS</b>	<b>214</b>

## LIST OF TABLES

Table		Page
2.1	Comparison of vancomycin and quinoxaline derivative compounds MIC results for MRSA isolates	33
4.1	Important protons of compounds 1-5 (all chemical shifts (*) in ppm)	78
4.2	Important carbon chemical shift for compounds 1-5 (all chemical shifts in ppm)	79
4.3	The experimental and calculated values of compounds 1-5	82
4.4	Important protons of compounds 6 and 7 (all chemical shifts (*) in ppm)	84
4.5	Important carbon chemical shift for compounds 6 and 7 (all chemical shifts in ppm)	85
4.6	<sup>1</sup> H- <sup>1</sup> H COSY, HSQC correlations for 2-chloro-3-(3-nitrophenoxy) quinoxaline (compound 6)	88
4.7	The experimental and calculated values of compounds 6, 7 and 16	89
4.8	Physical properties of compounds 1-7 and 16	91
4.9	The solvent/base systems used for synthesizing compounds 8 to 15	91
4.10	Important <sup>1</sup> H NMR peaks for compounds 8-15. (d-doublet, dd-doublet of doublet, m-multiplet, s-singlet for all chemical shifts in ppm (*))	95
4.11	Important <sup>13</sup> C NMR peaks related to compounds 8-15 (all chemical shifts in ppm)	96
4.12	<sup>1</sup> H- <sup>1</sup> H COSY, HSQC correlations for 2,3-bis(naphthalen-2-ylthio) quinoxaline (compound 11)	101
4.13	Physical properties of compounds 1-15	105
4.14	FTIR frequencies of the major functional groups in compounds 8 to 15	106
4.15	<sup>1</sup> H- <sup>1</sup> H-COSY and HSQC of compound 21	120
4.16	Antibacterial activity of quinoxaline derivatives against <i>Bacillus pumilus</i> (Gram-positive bacteria)	123
4.17	Antibacterial activity of quinoxaline derivatives against <i>Escherichia coli</i> ( <i>E.coli</i> ) (Gram-negative bacteria)	124

4.18	Antibacterial activity of quinoxaline derivatives against <i>Enterobacter Aerogenes</i> (Gram-negative bacteria)	125
4.19	Physio-chemical properties of compounds 1 to 16	128
4.20	The effects of hydrogen-bond interactions between synthetic compounds and DNA gyrase sub-unit B (DNAG)	131
4.21	The results of produced compounds' hydrogen bond interactions with penicillin-binding protein 1a (PBP1a)	132



## LIST OF FIGURES

Figure	Page
1.1 Isomers of Quinoxalines	1
1.2 Examples of the biologically active quinoxaline derivatives	4
2.1 Images of <i>E.coli</i> and the ways it can spread	28
2.2 Example of quinoxaline antibiotic 'Echinomycin' (Katagiri <i>et al.</i> , 1975)	30
2.3 8-Chloro-1,4-substituted[1,2,4]triazolo[4,3-a] quinoxaline derivatives core	30
2.4 Thiadiazolo[2',3':2,3]imidazo[4,5-b]quinoxaline derivatives	31
2.5 Quinoxaline <i>N, N</i> -dioxide derivatives	31
2.6 6-chloro-7-fluoro quinoxaline derivatives	34
2.7 3-[(7-Fluoro-2-methyl-3-oxo-3,4-dihydroquinoxalin-1(2 <i>H</i> )-yl)sulfonyl] thiophene2-carboxylate	34
2.8 Ethyl 3-(arylethynyl)quinoxaline-2-carboxylates	35
2.9 11-{[3-(Dimethylamino)propoxy]imino}- <i>N</i> -[3-(dimethylamino)propyl]-11 <i>H</i> -indeno[1,2-b]quinoxaline-6-carboxamide	35
2.10 Quinoxaline derivatives (88-91)	39
2.11 Structures of 2-substituted pyrrolo[2,3- b]quinoxalines	41
3.1 Swiss ADME submission page	72
3.2 Set up for MIC and MBC assays (Emery Pharma)	73
3.3 Interpretation of MIC results	74
3.4 Flowchart of protein-ligand docking simulations using UCSF Chimera and SwissDock	75
4.1 <sup>1</sup> H NMR spectra of 4-((3-chloroquinoxalin-2-yl) sulfanyl) aniline (1)	80
4.2 <sup>13</sup> C NMR spectra of 4-((3-chloroquinoxalin-2-yl) sulfanyl) aniline (1)	80
4.3 Fragmentation pattern of 4-((3-chloroquinoxalin-2-yl)sulfanyl)aniline (1)	81
4.4 Mass spectrum of 4-((3-chloroquinoxalin-2-yl) sulfanyl) aniline (1)	82



4.5	Structures of compounds 6, 7 and 16	84
4.6	<sup>1</sup> H NMR spectra of 2-chloro-3-(3-nitrophenoxy) quinoxaline (6)	85
4.7	<sup>13</sup> C NMR spectra of 2-chloro-3-(3-nitrophenoxy) quinoxaline (6)	86
4.8	Important <sup>1</sup> H NMR and <sup>13</sup> C NMR signals for compounds 1-7	86
4.9	Major correlations in the COSY spectrum of 2-chloro-3-(3-nitrophenoxy) quinoxaline (6)	87
4.10	An expanded section for the aromatic protons in <sup>1</sup> H- <sup>1</sup> H COSY NMR spectrum of compound 6	87
4.11	An expanded section for aromatic protons and carbons in the HSQC NMR spectrum of compound 6	88
4.12	Fragmentation pattern of 2-chloro-3-(3-nitrophenoxy) quinoxaline (6)	89
4.13	Mass spectrum of 2-chloro-3-(3-nitrophenoxy) quinoxaline (6)	90
4.14	FTIR spectrum of 2-chloro-3-(3-nitrophenoxy) quinoxaline (6)	90
4.15	<sup>1</sup> H NMR spectra of 2,3-bis(4-methoxyphenylthio) quinoxaline (8)	95
4.16	<sup>13</sup> C NMR spectra for 2,3-bis(4-methoxyphenylthio)quinoxaline (compound 8)	97
4.17	<sup>1</sup> H NMR spectra of 2,3-bis(naphthalen-2-ylthio) quinoxaline (11)	98
4.18	Major correlations in the COSY spectrum of 2,3-bis(naphthalen-2-ylthio) quinoxaline (compound 11)	98
4.19	An expanded section of aromatic protons in COSY NMR spectrum of 2,3-bis(naphthalen-2-ylthio) quinoxaline (compound 11)	99
4.20	An expanded section for aromatic protons and carbons in the HSQC NMR spectrum of compound 11	100
4.21	<sup>13</sup> C NMR spectra for 2,3-bis(naphthalen-2-ylthio) quinoxaline (compound 11)	100
4.22	Fragmentation pattern of 2,3-bis(4-methoxyphenylthio) quinoxaline (8)	102
4.23	Mass fragmentation spectrum of 2,3-bis(4-methoxyphenylthio) quinoxaline (8)	103
4.24	Mass fragmentation spectrum of 2,3-bis(naphthalen-2-ylthio) quinoxaline (compound 11)	104

4.25	Mass fragmentation spectrum of 2,3-bis(naphthalen-2-ylthio) quinoxaline (compound 11)	104
4.26	FTIR spectrum of 2,3-bis(4-methoxyphenylthio) quinoxaline (8)	106
4.27	<sup>1</sup> H NMR spectra for compound (17)	107
4.28	<sup>13</sup> C NMR spectrum of compound 17	108
4.29	Fragmentation pattern of compound 17	109
4.30	Mass spectrum of compound (17)	109
4.31	FTIR spectrum of compound 17	110
4.32	Regio isomers of compound 18	111
4.33	<sup>1</sup> H NMR spectra for compound (18)	111
4.34	<sup>13</sup> C NMR spectrum of compound 18	112
4.35	Fragmentation of compound 18	113
4.36	Mass spectrum of compound (18 a and 18 b)	114
4.37	FTIR spectrum of compound 18 a and 18 b	114
4.38	<sup>1</sup> H NMR spectrum for 3-(quinoxalin-2-ylthio) benzoic acid (19)	115
4.39	<sup>13</sup> C NMR spectrum for 3-(quinoxalin-2-ylthio) benzoic acid (19)	116
4.40	Fragmentation pattern of 3-(quinoxalin-2-ylthio) benzoic acid	117
4.41	Mass spectrum of 3-(quinoxalin-2-ylthio) benzoic acid	117
4.42	FTIR spectrum of 3-(quinoxalin-2-ylthio) benzoic acid	118
4.43	<sup>1</sup> H NMR spectrum for 2-(naphthalen-2-ylthio)quinoxaline	118
4.44	Proton correlations in COSY for compound 21	119
4.45	An expanded section for the aromatic protons in the COSY NMR spectrum of compound 21	119
4.46	<sup>13</sup> C NMR spectrum for 2-(naphthalen-2-ylthio)quinoxaline (21)	120
4.47	An expanded section for aromatic protons and carbons in the HSQC NMR spectrum of compound 21	121
4.48	Petri dishes of <i>Bacillus pumilus</i> activity	123
4.49	Petri dishes for <i>Escherichia coli</i>	124

4.50	Petri dishes for <i>Enterobacter aerogenes</i>	125
4.51	Petri dishes for <i>Salmonella Typhimurium</i>	126
4.52	Bio-availability radar, the first glimpse of the molecule to be drug-like	127
4.53	The BOILED-Egg allows for spontaneous evaluation of passive gastrointestinal absorption (HIA) and brain penetration (BBB) for the position of the molecules in the WLOGP-versus-TPSA referential	129
4.54	3D interactions and Hydrogen bonding with the tested compounds (13 and 14) with PBP1a protein	133
4.55	3D interactions and Hydrogen bonding with the tested compounds (13 and 14) with DNAG protein	134

## LIST OF SCHEMES

Scheme	Page
2.1 Reagents and conditions for the synthesis of 2,3-diphenylquinoxaline (a) K-10 bentonite clay, EtOH, RT, and 20 minutes	7
2.2 Synthetic pathway to prepare 2,3-diphenylquinoxaline using phosphate catalyst (MAP, DAP, or TSP)	7
2.3 Synthetic route to prepare quinoxaline derivatives with CAN as a catalyst	8
2.4 Reagents and conditions for the synthesis of pyrrolo[1,2-a]quinoxaline derivatives (a,b) FeCl <sub>3</sub> (20 mol%), 70% TBHP (3 equiv), CF <sub>3</sub> SO <sub>3</sub> H (10 mol%), tert-butanol (0.5 mL), RT, 10 hours, and Ar	9
2.5 Synthetic route to produce 2,3-disubstituted quinoxalines using HFIP	9
2.6 Synthetic process to prepare 2-phenylquinoxaline derivative with pyridine as catalyst	10
2.7 Synthesis of quinoxaline derivatives using catalyst TiO <sub>2</sub> -Pr-SO <sub>3</sub> H	10
2.8 Synthesis of pyrrolo[1,2-a]quinoxalines	11
2.9 Synthetic pathway to prepare indoloquinoxalines	12
2.10 Synthesis of derivatives of 6-chloro-7-fluoroquinoxaline derivative; reagents and conditions (a) HOAc/Ac <sub>2</sub> O, (b) 70% HNO <sub>3</sub> /conc. H <sub>2</sub> SO <sub>4</sub> , (c) conc. H <sub>2</sub> SO <sub>4</sub> , and (d) zinc/hydrazinium monoformate (e) ethanol, CH <sub>3</sub> OH, HOAc:CH <sub>3</sub> OH (3:2)/NaOAc, and HOAc/NaOAc	13
2.11 Synthetic pathway to prepare 2,3-diaminoquinoxaline derivatives	13
2.12 Synthetic pathway to prepare S-alkylation of phenyl quinoxaline-2(1H)-thione with reagents and conditions: (a) triethylamine/ ethanol/ reflux/ 78°C/ CH <sub>2</sub> =CHCOOC <sub>2</sub> H <sub>5</sub>	14
2.13 Reagents and conditions for the synthesis of <i>N</i> -Alkyl-3-((phenylquinoxalin-2-ylsulfanyl)propanamides (36) and methyl-2-[3-(3-phenylquinoxalin-2-ylsulfanyl)propanamidoalkanoates (35) a) NH <sub>2</sub> NH <sub>2</sub> / C <sub>2</sub> H <sub>5</sub> OH/ 78°C/ reflux/ 4 hours b) NaNO <sub>2</sub> / HCl/ H <sub>2</sub> O/ reflux/ 15 minutes c) NH <sub>2</sub> (CH <sub>2</sub> ) <sub>n</sub> CHRCOOCH <sub>3</sub> .HCl/ triethylamine d) NHR <sub>1</sub> R <sub>2</sub> / ethyl acetate/ 25°C/ 24 hours	14
2.14 Synthetic procedure for quinoxaline derivative (39); Reagents and conditions (a) <i>meta</i> -aminobenzoic acid in butanol/ conc HCl/ reflux for 5 hours (b) thionyl chloride in dry benzene/ reflux for 5 hours (c) Ar-NH <sub>2</sub> and TEA in dry DCM/ reflux for 5 hours	15

2.15	Reagents and conditions for the synthesis of thiourea quinoxaline derivatives 41 and 42 are (a) <i>para</i> phenylenediamine/ <i>n</i> -BuOH, (b) benzene sulphonyl chlorides in dry pyridine/ reflux for 2 hours (c) isothiocyanates or phenyl isocyanates in dry toluene/ reflux for 5 hours	16
2.16	Synthesis of quinoxaline schiff bases 44 and 45; reagents and conditions (a) 4-hydroxybenzaldehyde/ K <sub>2</sub> CO <sub>3</sub> / CH <sub>3</sub> CN/ reflux (b) amines/ ethanol/ reflux (c) <i>p</i> -aminophenol/ K <sub>2</sub> CO <sub>3</sub> / CH <sub>3</sub> CN/ reflux (d) benzaldehyde/ EtOH/ reflux	17
2.17	Synthesis of (2-(5-Arylthiazolo[2,3- <i>c</i> ][1,2,4]triazol-3-yl)quinoxaline (46)	17
2.18	Synthetic pathway to prepare spiro[thiazolidine-quinoxaline] (51)	18
2.19	Synthetic pathway to prepare bistetrazoquinoxalines	19
2.20	Synthetic pathway to prepare piperazinyl quinoxalines (54, 56)	19
2.21	Synthesis to prepare 4-{4-[2-(4-(2-substitutedquinoxalin-3-yl)piperazin-1-yl)}phenylthiazoles (59)	20
2.22	Synthesis of quinoxaline thiols (61)	21
2.23	Reagents and conditions for the synthesis of quinoxaline-2,3-dithiones (a) alkynonitriles (b) 3-phenyl-2-propynonitrile (c) acetylene (d) dioxane and heated at 20–25°C for 1 hour	21
2.24	Reaction conditions to prepare (69, 70, 71); reagents and conditions (a) NH <sub>2</sub> NH <sub>2</sub> .H <sub>2</sub> O/ EtOH at room temperature, (b) triethyl orthoformate reflux for 4 hours, (c) NH <sub>2</sub> NH <sub>2</sub> .H <sub>2</sub> O/ ethanol reflux for 4 hours, (d) amines/TEA/ reflux for 4 hours, (e) alcohols/TEA/ reflux for 4 hours	22
2.25	Synthesis of 73, 74, 75, and 76; reagents and conditions a) POCl <sub>3</sub> b) (i) acetonitrile reflux for 8 hours c) (ii) acetonitrile reflux 8 hours (iii) acetonitrile containing DMF reflux for 5 hours	23
2.26	Synthesis of quinoxaline-2-carboxylate-1,4-dioxide (78, 79, 80, and 81)	24
2.27	Synthesis of derivatives of [1,2,4]triazolo[4,3- <i>a</i> ]quinoxalines derivatives (88)	25
2.28	Synthesis of 2,3-bis(aryl-thiol)quinoxaline (86)	26
2.29	Synthesis of quinoxaline sulfanyl derivatives (87)	27
4.1	Plausible mechanism for quinoxaline derivatives formation	77
4.2	Synthesis of 6 and 16	83

4.3	Synthesis of 2-chloro-3-(4-nitrophenoxy) quinoxaline (7)	83
4.4	The reaction and purification pathway for compound 12	93
4.5	The reaction pathway for compound 13	94
4.6	Synthesis of (17)	107



## LIST OF ABBREVIATIONS

Å	Angstrom
δ	Chemical shift
DIMS	Direct Insertion Mass Spectroscopy
DMF	Dimethylformamide
DMSO	Dimethyl Sulfoxide
Ev	Electron Volt
FTIR	Fourier Transform Infrared
GCMS	Gas Chromatography Mass Spectroscopy
GHz	Giga Hertz
Hz	Hertz
IC50	Half Inhibitory Concentration
J	NMR Coupling Constant
M	Molar concentration
MHz	Mega Hertz
MIC	Minimum Inhibitory Concentration
MBC	Minimum Bactericidal Concentration
Mp	Melting Point
MS	Mass Spectroscopy
MW	Microwave
m/z	Mass to Charge ratio
Da	Dalton
R <sub>f</sub>	Retention factor
RSD	Relative Standard Deviation
THF	Tetrahydrofuran
TLC	Thin layer Chromatography

NMR	Nuclear Magnetic Resonance
2,3-DCQ	2,3-dichloroquinoxaline
2-CQ	2-chloroquinoxaline
3-MCQ	2-chloro-3-methylquinoxaline
CADD	Computer aided drug design
Mercaptan	aryl-thiols

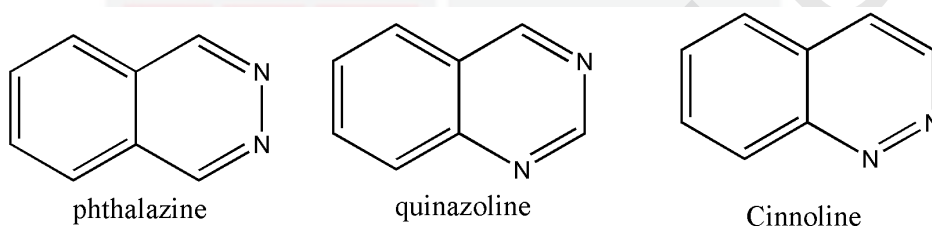




## CHAPTER 1

### INTRODUCTION

Hetero-cycles are vital compounds of organic chemistry studied under heterocyclic chemistry, with an array of physiological and biological processes certifying them a crucial role in medicinal chemistry. Quinoxalines are nitrogen-containing hetero-cycles, formed by the fusion of benzene and pyrazine ring, hence the name benzo[a]pyrazine. They also have other less familiar names, like benzopyrazine, 1,4-benzodiazine, phenopiazine, phenpiazine, quinazine, chinoxalin. Quinoxalines are isomeric to quinazoline, phthalazine, cinnoline (**Figure 1.1**) (Mamedov *et al.*, 2016).



**Figure 1.1 : Isomers of Quinoxalines**

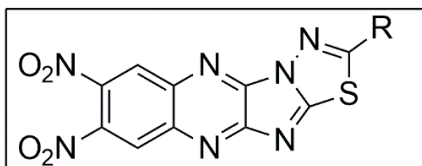
The biological and therapeutic features of quinoxaline and its derivatives have drawn attention in recent years. Natural quinoxalines are uncommon, but synthetic ones are used in gram-positive bacteria antibiotics such echinomycin, levomycin, and actinomycin (Pereira., 2015). Quinoxaline and its derivatives are explored for their biological activity (**Figure 1.2**) against infectious disorders, including anti-fungal (Teja *et al.*, 2016), anti-bacterial (Teja *et al.*, 2016), antiviral, antimicrobial, anti-inflammation (Tariq *et al.*, 2018), anti-malarial (Quiliano *et al.*, 2017), and malignant cells (Peraman *et al.*, 2016). Quinoxalines contain several biological features and are essential to schizophrenia medicines.

Organosulfur compounds are defined as organic molecules that include one or more carbon-sulfur linkages. There is a great variation in the chemical structures and bio-active properties of organosulfur compounds (El-Atawy., 2019) that have been found to be effective against a wide spectrum of bacteria, fungi, and viruses. In addition, numerous medicines used to treat fungal, bacterial, and other pathogen-causing disorders are typically more effective when sulphur and nitrogen are present together as one moiety (Li *et al.*, 2015). Recent research (Abbas *et al.*, 2017) indicates that dis-substituted quinoxaline compounds may inhibit bacterial growth. The presence of 4-trifluoromethylanilino, 4-hydroxyanilino, or phenylthio groups at positions 2 and/or 3 on the quinoxaline ring has been associated as good to moderate antibacterial activity. In order to achieve the desired antibacterial effects, the current study in this thesis focussed on substitution of the quinoxaline ring at positions 2 and 3 with aromatic thiol groups.

In light of the rise of antimicrobial resistance (AMR), research on the antibacterial activity of quinoxaline derivatives is highly sought after. Antibiotic resistance occurs when bacteria stop responding to a drug that was formerly effective against them. For e.g., Benzyl penicillin is no longer effective against several common bacteria and fungi, including *Staphylococcus aureus* ('golden staph' or MRSA) and *Neisseria gonorrhoeae* (the cause of gonorrhoea). Penicillin used to be the go-to treatment for these illnesses. Antibiotic resistance is a major problem since certain bacteria have developed resistance to almost all of the drugs now in use to treat bacterial infections. Similarly, *Enterobacteriaceae* are a large family of Gram-negative bacteria that includes a number of pathogens such as *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Escherichia.coli*, *Shigella*, *Proteus*, *Serratia* and other species. These pathogens are present in the human intestinal tract and are a normal part of the gut flora. *Enterobacteriaceae*, like all bacteria, can develop resistance to antibiotics, including the carbapenem group of antibiotics, which are sometimes referred to as the last line of antibiotic treatment against resistant organisms (*Antibiotic Resistant Bacteria*, n.d.).

In the event of a pandemic, antibiotic resistance might increase, posing a problem for medical staff. It has been hypothesized that *Staphylococcus aureus* is a major contributor to bacterial infections during viral pandemics. However, there has not been sufficient research on the prevalence of *S. aureus* co-infection leading to bacteremia in patients with viral infections. (Espinosa Perez *et al.*, 2022).

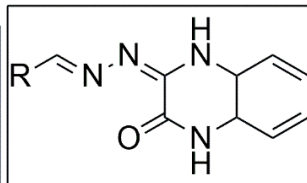
In order to combat the rising problem of bacteria developing resistance to antibiotics, a number of new compounds of quinoxaline derivatives bearing a sulphur bridge were synthesized as antibacterial agents after careful consideration of the literature on the topic.



R= C<sub>6</sub>H<sub>5</sub> or 4-NH<sub>2</sub> or -C<sub>6</sub>H<sub>4</sub> or 2-OH-C<sub>6</sub>H<sub>4</sub>  
 Thiadiazolo[2',3':2,3]imidazo[4,5-b]quinoxaline.

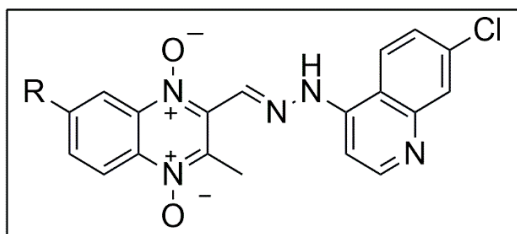
Antibacterial against gram-positive (*S.aureus* and *Bacillus cereus*) and gram-negative bacteria (*E.coli*, *P.aeruginosa*).

Antifungal activity against *A.niger* and *A.fumigatus* (Teja et al., 2016)



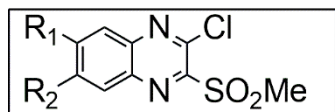
Quinoxaline containing sugar conjugates for eg. 3-(2-βD-glucopyranosylidene hydrazinyl)quinoxalin-2(1H)-one, R= glucose. R can be also mannose or maltose or lactose or ribose and xylose.

Antitubercular activity against *mycobacterium tuberculosis* H 37 Rv (Peraman et al., 2016)



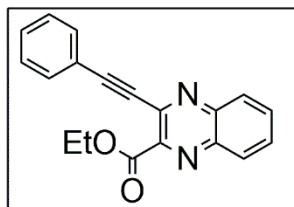
New hydrazine and hydrazide quinoxaline-1,4-di-N-oxide derivatives.  
 R= -OCH<sub>3</sub> or -Cl

Antimalarial activity in vitro against chloroquine sensitive (3D7) and drug resistant Dd2 strains of *Plasmodium falciparum* (Quiliano et al., 2017)



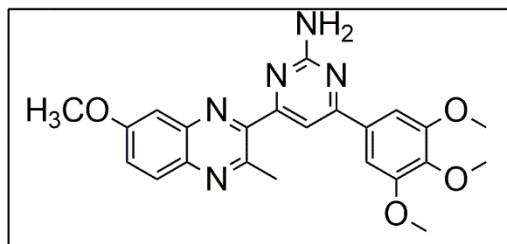
3-chloro-2-methylsulfonylquinoxalines

Anti-trypanosomal activity against *Trypanosoma cruzi* and *Leishmania amazonensis* (Cogo et al., 2015).



Ethyl-3-(arylethynyl)quinoxaline-2-carboxylates

Anti-cancer activity against human non-small cell lung carcinoma (A549) and glioblastoma (U87-MG) cell lines (Hajri et al., 2016).



4-(7-methoxy-3-methylquinoxalin-2-yl)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-amine

Anti-inflammatory activity against Carrageenan-induced paw edema (41%) similar to that of indomethacin (47%) used as a reference drug (Tariq et al., 2018)

Figure 1.2 : Examples of the biologically active quinoxaline derivatives

## 1.1 Problem statement

The antimicrobial resistance is a serious peril to global health, because of careless and overuse of antibiotics. Hence, there is a continuous demand for antimicrobial agents effective against resistant pathogenic microorganisms. Moreover, a pandemic situation can also arise when an unknown type of bacteria or virus is perceived in human beings and is highly contagious. The mutations of pathogens are well-known making them difficult to control (Salazar *et al.*, 2022). The patients admitted to hospitals with viral infection symptoms receive antibiotic treatment to lessen their risk of developing secondary bacterial infections. This has led to an increase in the prevalence of resistant bacteria (Wilson *et al.*, 2021). Antimicrobial resistance has increased, raising worries that bacterial resistance to antibiotics will impede our capacity to handle another large epidemic. Several emerging biological illnesses may be untreatable by our current drugs.

The organosulfur compounds have a proven record of antibacterial activity and their properties get enhanced by the presence of sulfur and nitrogen as one moiety (El-Atawy., 2019). Hence, the synthesized quinoxaline sulfanyl derivatives bearing nitrogen and sulfur as heteroatoms play a pivotal role as an antibacterial agent. The synthesis of new

quinoxaline sulfanyl derivatives helps in closing the gap for preparation of new antibiotics. For example, synthesis of 2,3-bis (arylthiol)quinoxaline like 2,3-dithiophenylquinoxaline, 2,3-di(thio-4-fluorophenyl) quinoxaline are active in case of *S.aureus*, *B.subtilis*, and *E.coli*. (El-Atawy., 2019). Therefore, novel quinoxaline compounds were synthesised and tested for their antibacterial efficacy in light of the aforementioned feature of thio quinoxaline derivatives. Many strains of bacteria that have become resistant to antibiotics can be eliminated by the manufacture of novel quinoxaline sulfanyl derivatives.

## 1.2 Objectives

This research aimed to synthesize a new set of quinoxaline derivatives (**1** to **24**) with useful antibacterial activity that can be used as an essential moiety in medicinal drugs. The specific objectives were set as the following:

1. To synthesize 2-chloroquinoxalines, 3-methyl-2-chloroquinoxalines and 2,3-dichloroquinoxalines derivatives using conventional methods.
2. To evaluate the antibacterial activities of the synthesized compounds
3. To determine the physio-chemical and drug-likeness properties of the synthesized quinoxaline derivatives *in silico*.
4. To evaluate the binding affinity of the synthesized compounds towards DNA Gyrase sub-unit b centre (DNAG) and penicillin-binding protein (PBP1a) *via in silico* approach,

## REFERENCES

- Aarthy, M., & Singh, S. K. (2018). Discovery of potent inhibitors for the inhibition of dengue envelope protein: an in-silico approach. *Current Topics in Medicinal Chemistry*, 18(18), 1585-1602.
- Abbas, H. A. S., Al-Marhabi, A. R., & Ammar, Y. A. (2017). Design, synthesis and biological evaluation of 2, 3-disubstituted and fused quinoxalines as potential anticancer and antimicrobial agents. *Acta Pol. Pharm*, 74(2), 445-458.
- Abu-Hashem, A.A.; Gouda, M.A.; Badria, F.A. synthesis of some new pyrimido [2', 1': 2, 3] thiazolo [4, 5-b] quinoxaline derivatives as anti-inflammatory and analgesic agents. *Eur. J. Med. Chem.* **2010**, 45, 1976–1981.
- Ahmed, E. A., Mohamed, M. F., & Omran, O. A. (2022). Novel quinoxaline derivatives as dual EGFR and COX-2 inhibitors: synthesis, molecular docking and biological evaluation as potential anticancer and anti-inflammatory agents. *RSC advances*, 12(39), 25204-25216.
- Ajaikumar, S.; Pandurangan, A. Efficient synthesis of quinoxaline derivatives over ZrO<sub>2</sub>/M<sub>x</sub>O<sub>y</sub> (M=Al, Ga, In and La) mixed metal oxides supported on MCM-41 mesoporous molecular sieves. *Appl. Catal. A Gen.* **2009**, 357, 184–192.
- Allan, P.N.; Ostrowska, M.I.; Patel, B. Acetic acid catalyzed one-pot synthesis of pyrrolo[1, 2-a]quinoxaline derivatives. *Synlett* **2019**, 3019, 2148–2152.
- Ammar, Y.A.; Farag, A.A.; Ali, A.M.; Hessein, S.A.; Askar, A.A.; Fayed, E.A.; Elsis, D.M.; Ragab, A. Antimicrobial evaluation of thiadiazino and thiazolo quinoxaline hybrids as potential DNA gyrase inhibitors; design, synthesis, characterization and morphological studies. *Bioorg. Chem.* **2020**, 99, 103841.
- An, Z.; Wu, M.; Ni, J.; Qi, Z.; Yu, G.; Yan, R.; Zhao, L.-B. FeCl<sub>3</sub> -Catalyzed synthesis of pyrrolo[1,2-a]quinoxaline derivatives from 1-(2-aminophenyl)pyrroles through annulation and cleavage of cyclic ethers. *Chem. Commun.* **2017**, 53, 11572–11575.
- Anastas, P.; Warner, J. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, UK, 1998; Volume 30.
- Anju, V. T., Siddhardha, B., & Dyavaiah, M. (2020). Enterobacter Infections and Antimicrobial Drug Resistance. *Model Organisms for Microbial Pathogenesis, Biofilm Formation and Antimicrobial Drug Discovery*, 175–194.
- Antibiotic resistant bacteria.* (n.d.). Better Health Channel. <https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/antibiotic-resistant-bacteria>
- Arnott, J. A., & Planey, S. L. (2012). The influence of lipophilicity in drug discovery and design. *Expert opinion on drug discovery*, 7(10), 863-875.

- Atghia, S.V.; Beigbaghlou, S.S. Nanocrystalline titania-based sulfonic acid (TiO<sub>2</sub>-Pr-SO<sub>3</sub>H) as a new, highly efficient, and recyclable solid acid catalyst for the preparation of quinoxaline derivatives. *J. Nanostructure Chem.* **2013**, *3*, 38.
- Baashen, M. Quinoxaline-2,3(1H,4H)-dithione: Synthesis and reactions. *Phosphorus Sulfur Silicon Relat. Elem.* **2018**, *193*, 350–357.
- Baell, J. B., & Holloway, G. A. (2010). New substructure filters for removal of pan assay interference compounds (PAINS) from screening libraries and for their exclusion in bioassays. *Journal of medicinal chemistry*, *53*(7), 2719-2740.
- Balouiri, M., Sadiki, M., & Ibsouda, S. K. (2016). Methods for in vitro evaluating antimicrobial activity: A review. *Journal of pharmaceutical analysis*, *6*(2), 71-79.
- Barea, C.; Pabón, A.; Galiano, S.; Pérez-Silanes, S.; González, G.; Deysard, C.; Monge, A.; Deharo, E.; Aldana, I. Antiplasmodial and leishmanicidal activities of 2-cyano-3-(4-phenylpiperazine-1-carboxamido) quinoxaline 1,4-dioxide derivatives. *Molecules* **2012**, *17*, 9451–9461.
- Beitia, J. (2010, December 14). Tripotassium Phosphate: From Buffers to Organic Synthesis. *Synlett*, *2011*(01), 139–140.
- Bini, E.J.; Weinshel, E.H. Severe exacerbation of asthma: A new side effect of interferon- $\alpha$  in patients with asthma and chronic hepatitis C. *Mayo Clin. Proc.* **1999**, *74*, 367–370.
- Blair, J. M., Webber, M. A., Baylay, A. J., Ogbolu, D. O., & Piddock, L. J. (2015). Molecular mechanisms of antibiotic resistance. *Nature reviews microbiology*, *13*(1), 42-51.
- Brenk, R., Schipani, A., James, D., Krasowski, A., Gilbert, I. H., Frearson, J., & Wyatt, P. G. (2008). Lessons learnt from assembling screening libraries for drug discovery for neglected diseases. *ChemMedChem: Chemistry Enabling Drug Discovery*, *3*(3), 435-444.
- Bronckaers, A.; Gago, F.; Balzarini, J.; Liekens, S. The dual role of thymidine phosphorylase in cancer development and chemotherapy. *Med. Res. Rev.* **2009**, *29*, 903–953.
- Cai, J.-J.; Zou, J.; Pan, X.-Q.; Zhang, W. Gallium (III) triflate-catalyzed synthesis of quinoxaline derivatives. *Tetrahedron Lett.* **2008**, *49*, 7386–7390.
- Carta, A.; Paglietti, G.; Nikookar, M.E.R.; Sanna, P.; Sechi, L.; Zanetti, S. Novel substituted quinoxaline 1,4-dioxides with in vitro antimycobacterial and anticandida activity. *Eur. J. Med. Chem.* **2002**, *37*, 355–366.
- Carta, A.; Paglietti, G.; Nikookar, M.E.R.; Sanna, P.; Sechi, L.; Zanetti, S. Novel substituted quinoxaline 1,4-dioxides with in vitro antimycobacterial and anticandida activity. *Eur. J. Med. Chem.* **2002**, *37*, 355–366.



- Charpentier, C.; Karmochkine, M.; Laureillard, D.; Tisserand, P.; Bélec, L.; Weiss, L.; Piketty, C.; Si-Mohamed, A. Drug resistance profiles for the HIV integrase gene in patients failing raltegravir salvage therapy\*. *HIV Med.* **2008**, *9*, 765–770.
- Chemboli, R., Kapavarapu, R., Deepti, K., Prasad, K. R. S., Reddy, A. G., Kumar, A. N., ... & Pal, M. (2021). Pyrrolo [2, 3-b] quinoxalines in attenuating cytokine storm in COVID-19: their sonochemical synthesis and in silico/in vitro assessment. *Journal of Molecular Structure*, *1230*, 129868.
- Cheng, Tiejun, Yuan Zhao, Xun Li, Fu Lin, Yong Xu, Xinglong Zhang, Yan Li, Renxiao Wang, and Luhua Lai. "Computation of octanol– water partition coefficients by guiding an additive model with knowledge." *Journal of chemical information and modelling* *47*, no. 6 (2007): 2140-2148.
- Chudobova, D., Dostalova, S., Blazkova, I., Michalek, P., Ruttkay-Nedecky, B., Sklenar, M., Nejdil, L., Kudr, J., Gumulec, J., Tmejova, K., Konecna, M., Vaculovicova, M., Hynek, D., Masarik, M., Kynicky, J., Kizek, R., & Adam, V. (2014, March 19). Effect of Ampicillin, Streptomycin, Penicillin and Tetracycline on Metal Resistant and Non-Resistant Staphylococcus aureus. *International Journal of Environmental Research and Public Health*, *11*(3), 3233–3255.
- Cogo, J., Kaplum, V., Sangi, D. P., Ueda-Nakamura, T., Correa, A. G., & Nakamura, C. V. (2015). Synthesis and biological evaluation of novel 2, 3-disubstituted quinoxaline derivatives as antileishmanial and antitrypanosomal agents. *European Journal of Medicinal Chemistry*, *90*, 107-123.
- Coltart, C.E.M.; Lindsey, B.; Ghinai, I.; Johnson, A.M.; Heymann, D.L. The Ebola outbreak, 2013–2016: Old lessons for new epidemics. *Philos. Trans. R. Soc. B Biol. Sci.* **2017**, *372*, 20160297.
- Contreras-Martel, C., Job, V., Di Guilmi, A. M., Vernet, T., Dideberg, O., & Dessen, A. (2006). Crystal structure of penicillin-binding protein 1a (PBP1a) reveals a mutational hotspot implicated in  $\beta$ -lactam resistance in *Streptococcus pneumoniae*. *Journal of molecular biology*, *355*(4), 684-696.
- Dai, Y.; Hartandi, K.; Ji, Z.; Ahmed, A.A.; Albert, D.H.; Bauch, J.L.; Bouska, J.J.; Bousquet, P.F.; Cunha, G.A.; Glaser, K.B.; et al. Discovery of N-(4-(3-Amino-1H-indazol-4-yl)phenyl)-N'-(2-fluoro-5-methylphenyl)urea (ABT-869), a 3-aminoindazole-based orally active multitargeted receptor tyrosine kinase inhibitor. *J. Med. Chem.* **2007**, *50*, 1584–1597.
- Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific reports*, *7*(1), 1-13.
- Danilova, I. V., Toymontseva, A. A., Baranova, D. S., & Sharipova, M. R. (2016, October 6). The Genetic Mechanism of Resistance to Antibiotics in *Bacillus pumilus* 3-19 Strain. *BioNanoScience*, *7*(1), 88–91.



- De Clercq, E. (Ed.) *Advances in Antiviral Drug Design*; Elsevier: Amsterdam, The Netherlands, 1996.
- Di, L., Artursson, P., Avdeef, A., Ecker, G. F., Faller, B., Fischer, H., ... & Sugano, K. (2012). Evidence-based approach to assess passive diffusion and carrier-mediated drug transport. *Drug discovery today*, 17(15-16), 905-912.
- Egan, W. J., Merz, K. M., & Baldwin, J. J. (2000). Prediction of drug absorption using multivariate statistics. *Journal of medicinal chemistry*, 43(21), 3867-3877.
- El Newahie, A.M.S.; Nissan, Y.M.; Ismail, N.S.M.; El Ella, D.A.A.; Khojah, S.M.; Abouzid, K.A.; El Ella, D.A. Design and synthesis of new quinoxaline derivatives as anticancer agents and apoptotic inducers. *Molecules* **2019**, 24, 1175.
- El Rayes, S.M.; Aboelmagd, A.; Gomaa, M.S.; Ali, I.A.I.; Fathalla, W.; Pottoo, F.H.; Alam Khan, F. Convenient synthesis and anticancer activity of methyl 2-[3-(3-Phenyl-quinoxalin-2-ylsulfanyl)propanamido]alkanoates and N-Alkyl 3-((3-Phenyl-quinoxalin-2-yl)sulfanyl)propanamides. *ACS Omega* **2019**, 4, 18555–18566.
- El-Atawy, M. A., Hamed, E. A., Alhadi, M., & Omar, A. Z. (2019). Synthesis and antimicrobial activity of some new substituted quinoxalines. *Molecules*, 24(22), 4198.
- Elfadil, A., Alzahrani, A. M., Abdullah, H., Alsamhan, H., Abujamel, T. S., Ahmed, H. E., & Jiman-Fatani, A. (2023, April). Evaluation of the Antibacterial Activity of Quinoxaline Derivative Compound Against Methicillin-Resistant *Staphylococcus aureus*. *Infection and Drug Resistance, Volume 16*, 2291–2296.
- Espinosa Perez, M., García Fenoll, R., Mormeneo Bayo, S., Martínez Álvarez, R. M., Frutos Millán, V., Villuendas Usón, M. C., Palacián Ruiz, M. P., Arbonés Mainar, J. M., Martínez Jiménez, M. C., & Ramos Paesa, C. (2022, July 22). Impact of *Staphylococcus aureus* bacteremia in COVID-19 patients. *Revista Española De Quimioterapia*, 35(5), 468–474.
- Essassi, E.M.; Ahoya, C.A.; Bouhfid, R.; Daouda, B.; Hançali, A.; Zouihri, H.; Zerzouf, A.; El Aouad, R. Synthesis and antibacterial activity of new spiro[thiadiazoline-quinoxaline] derivatives. *Arkivoc* **2011**, 2011, 217–226.
- Esteban-Gamboa, A.; Balzarini, J.; Esnouf, R.; De Clercq, E.; Camarasa, M.J.; Pérez-Pérez, M.J. Design, synthesis, and enzymatic evaluation of multisubstrate analogue inhibitors of *Escherichia coli* thymidine phosphorylase. *J. Med. Chem.* **2000**, 43, 971–983.
- Finks, J., Wells, E., Dyke, T. L., Husain, N., Plizga, L., Heddurshetti, R., ... & Miller, C. (2009). Vancomycin-resistant *Staphylococcus aureus*, Michigan, USA, 2007. *Emerging infectious diseases*, 15(6), 943.
- Gao, J., Zhu, J., Chen, L., Shao, Y., Zhu, J., Huang, Y., ... & Lv, X. (2014). Synthesis of benzimidazo [2, 1-b] benzothiazole derivatives through sequential Cu-

catalyzed domino coupling and Pd-catalyzed Suzuki reaction. *Tetrahedron Letters*, 55(22), 3367-3373.

- Garcia-Ramon, D. C., Molina, C. A., Osuna, A., & Vilchez, S. (2016, January 19). An in-depth characterization of the entomopathogenic strain *Bacillus pumilus* 15.1 reveals that it produces inclusion bodies similar to the parasporal crystals of *Bacillus thuringiensis*. *Applied Microbiology and Biotechnology*, 100(8), 3637–3654.
- Gatica, J., & Cytryn, E. (2013, February 2). Impact of treated wastewater irrigation on antibiotic resistance in the soil microbiome. *Environmental Science and Pollution Research*, 20(6), 3529–3538.
- Ghose, A. K., Viswanadhan, V. N., & Wendoloski, J. J. (1999). A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases. *Journal of combinatorial chemistry*, 1(1), 55-68.
- Gris, J.; Glisoni, R.; Fabian, L.; Fernández, C.G.-C.; Moglioni, A.G. Synthesis of potential chemotherapeutic quinoxalinone derivatives by biocatalysis or microwave-assisted Hinsberg reaction. *Tetrahedron Lett.* **2008**, 49, 1053–1056.
- Grosdidier A, Zoete V, Michielin O (2011) Fast docking using the CHARMM force field with EADock DSS. *J Comput Chem* 32:2149–2159.
- Guthridge, I., Smith, S., Law, M., Binotto, E., & Hanson, J. (2021). Efficacy and Safety of Intravenous Lincosamide Therapy in Methicillin-Resistant *Staphylococcus aureus* Bacteremia. *Antimicrobial Agents and Chemotherapy*, 65(9), e00343-21.
- Hajri, M., Esteve, M. A., Khoumeri, O., Abderrahim, R., Terme, T., Montana, M., & Vanelle, P. (2016). Synthesis and evaluation of in vitro antiproliferative activity of new ethyl 3-(arylethynyl) quinoxaline-2-carboxylate and pyrido [4, 3-b] quinoxalin-1 (2H)-one derivatives. *European journal of medicinal chemistry*, 124, 959-966.
- Hann, M. M., & Keserü, G. M. (2012). Finding the sweet spot: the role of nature and nurture in medicinal chemistry. *Nature reviews Drug discovery*, 11(5), 355-365.
- Hasaninejad, A.; Zare, A.; Shekouhy, M.; Moosavi-Zare, A.R. Bentonite clay K-10 as an efficient reagent for the synthesis of quinoxaline derivatives at room temperature. *E-J. Chem.* **2009**, 6, S247–S253
- Heberle' G, de Azevedo WF Jr (2011) Bio-inspired algorithms applied to molecular docking simulations. *Curr Med Chem* 18:1339–1352.
- Henen, M.A.; El Bialy, S.A.A.; Goda, F.E.; Nasr, M.N.A.; Eisa, H.M. [1,2,4]Triazol[4,3-a]quinoxaline: Synthesis, antiviral, and antimicrobial activities. *Med. Chem. Res.* **2012**, 21, 2368–2378.

- Heravi, M.M.; Bakhtiari, K.; Bamoharram, F.F.; Tehrani, M.H. Wells-dawson type heteropolyacid catalyzed synthesis of quinoxaline derivatives at room temperature. *Mon. Für Chem. Chem. Mon.* **2007**, *138*, 465–467.
- Huang, T.-K.; Wang, R.; Shi, L.; Lu, X.-X. Montmorillonite K-10: An efficient and reusable catalyst for the synthesis of quinoxaline derivatives in water. *Catal. Commun.* **2008**, *9*, 1143–1147.
- Husain, A.; Madhesia, D. Recent advances in pharmacological activities of quinoxaline derivatives. *J. Pharm. Res.* **2011**, *4*, 924–929.
- Ibrahim, M.; Taghour, M.; Metwaly, A.; Belal, A.; Mehany, A.; Elhendawy, M.; Radwan, M.; Yassin, A.; El-Deeb, N.; Hafez, E.; et al. Design, synthesis, molecular modeling and anti-proliferative evaluation of novel quinoxaline derivatives as potential DNA intercalators and topoisomerase II inhibitors. *Eur. J. Med. Chem.* **2018**, *155*, 117–134.
- Irfan, A.; Sabeeh, I.; Umer, M.; Naqvi, A.Z.; Fatima, H.; Yousaf, S.; Fatima, Z. A review on the therapeutic potential of quinoxaline derivatives. *World J. Pharm. Res.* **2017**, *6*, 47–68.
- Jafarpour, M.; Rezaeifard, A.; Danehchin, M. Easy access to quinoxaline derivatives using alumina as an effective and reusable catalyst under solvent-free conditions. *Appl. Catal. A Gen.* **2011**, *394*, 48–51.
- Jaso, A.; Zarranz, B.; Aldana, I.; Monge, A. Synthesis of new quinoxaline-2-carboxylate 1, 4-dioxide derivatives as anti-mycobacterium tuberculosis agents. *J. Med. Chem.* **2005**, *48*, 2019–2025.
- Kakuta, H.; Zheng, X.; Oda, H.; Harada, S.; Sugimoto, Y.; Sasaki, K.; Tai, A. Cyclooxygenase-1-selective inhibitors are attractive candidates for analgesics that do not cause gastric damage. Design and in vitro/in vivo evaluation of a benzamide-type cyclooxygenase-1 selective inhibitor. *J. Med. Chem.* **2008**, *51*, 2400–2411.
- Katagiri, K., Yoshida, T., & Sato, K. (1975). Quinoxaline Antibiotics. *Mechanism of Action of Antimicrobial and Antitumor Agents*, 234–251.
- Khaksar, S.; Rostamzad, F. A novel one-pot synthesis of quinoxaline derivatives in fluorinated alcohols. *Bull. Korean Chem. Soc.* **2012**, *33*, 2581–2584.
- Khan, M. A., Saeed, M., Badshah, A., Muhammad, N., Khan, J., Khan, F. A., ... & ur Rahman, S. (2011). Design, formulation, optimization and evaluation of sustained release tablets of domperidone. *African Journal of Pharmacy and Pharmacology*, *5*(16), 1882-1887.
- Khurana, J. M., & Sahoo, P. K. (1992). Chemoselective alkylation of thiols: a detailed investigation of reactions of thiols with halides. *Synthetic communications*, *22*(12), 1691-1702.
- Kim J, Yang G, Ha J (2017) Targeting of AMP-activated protein kinase: prospects for computer-aided drug design. *Expert Opin Drug Discov* *12*:47–59.

- Kim, Y.B.; Kim, Y.H.; Park, J.Y.; Kim, S.K. Synthesis and biological activity of new quinoxaline antibiotics of echinomycin analogues. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 541–544.
- Krishnakumar, B.; Swaminathan, M. Solvent free synthesis of quinoxalines, dipyrrophenazines and chalcones under microwave irradiation with sulfated Degussa titania as a novel solid acid catalyst. *J. Mol. Catal. A Chem.* **2011**, *350*, 16–25.
- Lewine, R.R.; Fogg, L.; Meltzer, H.Y. Assessment of negative and positive symptoms in schizophrenia. *Schizophr. Bull.* **1983**, *9*, 368–376.
- Li, J.-L.; Zhao, W.; Zhou, C.; Zhang, Y.-X.; Li, H.-M.; Tang, Y.-L.; Liang, X.-H.; Chen, T.; Tang, Y.-J. Comparison of carbon-sulfur and carbon-amine bond in therapeutic drug: 4 $\beta$ -S-aromatic heterocyclic podophyllum derivatives display antitumor activity. *Sci. Rep.* **2015**, *5*, 14814–14830.
- Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (2001). CAS: 528: DC% 2BD3MXitVOhs7o% 3D: Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. vol. 46, issue 1-3. *Adv Drug Deliv Rev*, 3-26.
- Liu, W. T., Chen, E. Z., Yang, L., Peng, C., Wang, Q., Xu, Z., & Chen, D. Q. (2021). Emerging resistance mechanisms for 4 types of common anti-MRSA antibiotics in *Staphylococcus aureus*: A comprehensive review. *Microbial pathogenesis*, *156*, 104915.
- Ma, C., Taghour, M. S., Belal, A., Mehany, A. B., Mostafa, N., Nabeeh, A., ... & Al-Karmalawy, A. A. (2021). Design and synthesis of new quinoxaline derivatives as potential histone deacetylase inhibitors targeting hepatocellular carcinoma: in silico, in vitro, and SAR studies. *Frontiers in chemistry*, *9*, 725135.
- Macalino SJ, Gosu V, Hong S, Choi S (2015) Role of computer-aided drug design in modern drug discovery. *Arch Pharm Res* 38:1686–1701.
- Mahanthesh, M., Ranjith, D., Yaligar, R., Jyothi, R., Narappa, G., & Ravi, M. (2020). Swiss ADME prediction of phytochemicals present in *Butea monosperma* (Lam.) Taub. *Journal of Pharmacognosy and Phytochemistry*, *9*(3), 1799-1809.
- Malek, B.; Bahammou, I.; Zimou, O.; El Hallaoui, A.; Ghailane, R.; Boukhris, S.; Souzi, A. Eco-friendly synthesis of quinoxaline derivatives using mineral fertilizers as heterogeneous catalysts. *J. Turk. Chem. Soc. Sect. A Chem.* **2020**, *7*, 427–440.
- Mamedov, V. A., & Quinoxalines, A. (2016). Synthesis, Reactions, Mechanisms and Structure.
- Martin, Y. C. (2005). A bioavailability score. *Journal of medicinal chemistry*, *48*(9), 3164-3170.
- Meltzer, H.Y. What's atypical about atypical antipsychotic drugs? *Curr. Opin. Pharmacol.* **2004**, *4*, 53–57.

- Mishra, A.; Kumar, M.; Mishra, A.; Kumar, A.; Kant, R.; RS, T. Synthesis and antibacterial studies of some new amides of 5-sulphosalicylic acid. *Neoplasma* **1990**, *41*, 291–296.
- Mohd, H.A.; Al-Tawfiq, J.A.; Memish, Z.A. Middle East respiratory syndrome coronavirus (MERS-CoV) origin and animal reservoir. *Viol. J.* **2016**, *13*, 1–7.
- Montana, M., Montero, V., Khoumeri, O., & Vanelle, P. (2020). Quinoxaline derivatives as antiviral agents: a systematic review. *Molecules*, *25*(12), 2784.
- More, S.V.; Sastry, M.N.V.; Yao, C.-F. Cerium (iv) ammonium nitrate (CAN) as a catalyst in tap water: A simple, proficient and green approach for the synthesis of quinoxalines. *Green Chem.* **2006**, *8*, 91–95.
- Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS et al (2009) AutoDock4 and AutoDockTools4: automated docking with selective receptor flexibility. *J Comput Chem* *30*:2785–2791.
- Muegge, I., Heald, S. L., & Brittelli, D. (2001). Simple selection criteria for drug-like chemical matter. *Journal of medicinal chemistry*, *44*(12), 1841-1846.
- Myneedu, V. P., Singhal, R., Khayyam, K. U., Sharma, P. P., Bhalla, M., Behera, D., & Sarin, R. (2015). First and second line drug resistance among treatment naïve pulmonary tuberculosis patients in a district under Revised National Tuberculosis Control Programme (RNTCP) in New Delhi. *Journal of epidemiology and global health*, *5*(4), 365-373.
- Nageswar, Y.V.D.; Reddy, K.H.V.; Ramesh, K.; Murthy, S.N. Recent developments in the synthesis of quinoxaline derivatives by green synthetic approaches. *Org. Prep. Proced. Int.* **2013**, *45*, 1–27.
- Park, K.L.; Ko, N.Y.; Lee, J.H.; Kim, D.K.; Kim, H.S.; Kim, A.-R.; Her, E.; Kim, B.; Kim, H.S.; Moon, E.-Y.; et al. 4-Chlorotetrazolo[1,5-a]quinoxaline inhibits activation of Syk kinase to suppress mast cells in vitro and mast cell-mediated passive cutaneous anaphylaxis in mice. *Toxicol. Appl. Pharmacol.* **2011**, *257*, 235–241.
- Patel, S.B.; Patel, B.D.; Pannecouque, C.; Bhatt, H.G. Design, synthesis and anti-HIV activity of novel quinoxaline derivatives. *Eur. J. Med. Chem.* **2016**, *117*, 230–240.
- Peraman, R., Kuppusamy, R., Killi, S. K., & Reddy, Y. P. (2016). New conjugates of quinoxaline as potent antitubercular and antibacterial agents. *International Journal of Medicinal Chemistry*, 2016.
- Pereira, F., & Aires-de-Sousa, J. (2018). Computational methodologies in the exploration of marine natural product leads. *Marine drugs*, *16*(7), 236.
- Pereira, J. A., Pessoa, A. M., Cordeiro, M. N. D., Fernandes, R., Prudêncio, C., Noronha, J. P., & Vieira, M. (2015). Quinoxaline, its derivatives and applications: A State-of-the-Art review. *European Journal of Medicinal Chemistry*, *97*, 664-672.

- Pereira, M.D.F.; Thiéry, V. One-pot synthesis of pyrrolo[1,2-a]quinoxaline derivatives via iron-promoted aryl nitro reduction and aerobic oxidation of alcohols. *Org. Lett.* **2012**, *14*, 4754–4757.
- Perlman, S. (2020). Another decade, another coronavirus. *New England Journal of Medicine*, *382*(8), 760-762.
- Peters, L., Olson, L., Khu, D. T., Linnros, S., Le, N. K., Hanberger, H., Najoc, T.B., Tran, M., & Larsson, M. (2019). Multiple antibiotic resistance as a risk factor for mortality and prolonged hospital stay: a cohort study among neonatal intensive care patients with hospital-acquired infections caused by gram-negative bacteria in Vietnam. *PloS one*, *14*(5), e0215666.
- Phillips, M.A. CCCXVII.—The formation of 2-substituted benzimidazoles. *J. Chem. Soc.* **1928**, 2393–2399.
- Pirelahi, H., Abdoh, Y., & Tavassoli, M. (1977). The effect of electron withdrawing groups on the stability of thiabenzenes. *Journal of Heterocyclic Chemistry*, *14*(2), 199-201.
- Podsiadły, R.; Sokołowska, J. Synthesis of novel oxidizable polymerization sensitizers based on the dithiinoquinoxaline skeleton. *Dye. Pigment.* **2012**, *92*, 1300–1307.
- Poirel, L., Madec, J. Y., Lupo, A., Schink, A. K., Kieffer, N., Nordmann, P., & Schwarz, S. (2018, July 27). Antimicrobial Resistance in *Escherichia coli*. *Microbiology Spectrum*, *6*(4). <https://doi.org/10.1128/microbiolspec.arba-0026-2017>.
- Poradowska, H., & Kaniewska, A. (1981). The mass spectra of halogeno derivatives of quinoxaline. *Organic Mass Spectrometry*, *16*(1), 5-11.
- Quiliano, M., Pabón, A., Ramirez-Calderon, G., Barea, C., Deharo, E., Galiano, S., & Aldana, I. (2017). New hydrazine and hydrazide quinoxaline 1, 4-di-N-oxide derivatives: In silico ADMET, antiplasmodial and antileishmanial activity. *Bioorganic & medicinal chemistry letters*, *27*(8), 1820-1825.
- Saha, S.; Chant, D.; Welham, J.; McGrath, J. A systematic review of the prevalence of schizophrenia. *PLoS Med.* **2005**, *2*, e141.
- Salazar, C. B., Spencer, P., Mohamad, K., Jabeen, A., Al Abdulmonem, W., & Fernández, N. (2022). Future pandemics might be caused by bacteria and not viruses: Recent advances in medical preventive practice. *International Journal of Health Sciences*, *16*(3), 1.
- Sarges, R.; Howard, H.R.; Browne, R.G.; Lebel, L.A.; Seymour, P.A.; Koe, B.K. 4-Amino[1,2,4]triazolo[4,3-a]quinoxalines. A novel class of potent adenosine receptor antagonists and potential rapid-onset antidepressants. *J. Med. Chem.* **1990**, *33*, 2240–2254.
- Sekhar, K.V.G.C.; Rao, V.S.; Deuther-Conrad, W.; Sridhar, D.; Nagesh, H.N.; Kumar, V.S.; Kumar, M.M.K. Design, synthesis, and preliminary in vitro and in vivo pharmacological evaluation of 4-{4-[2-(4-(2-substitutedquinoxalin-3-yl)



- piperazin-1-yl) ethyl] phenyl} thiazoles as atypical antipsychotic agents. *Med. Chem. Res.* **2013**, *22*, 1660–1673.
- Sepkowitz, K.A. AIDS—The first 20 years. *N. Engl. J. Med.* **2001**, *344*, 1764–1772.
- Shaabani, A.; Rezayan, A.H.; Behnam, M.; Heidary, M. Green chemistry approaches for the synthesis of quinoxaline derivatives: Comparison of ethanol and water in the presence of the reusable catalyst cellulose sulfuric acid. *Comptes Rendus Chim.* **2009**, *12*, 1249–1252.
- Sharma, R.; Sharma, C. Zirconium(IV)-modified silica gel: Preparation, characterization and catalytic activity in the synthesis of some biologically important molecules. *Catal. Commun.* **2011**, *12*, 327–331.
- Shibinskaya, M.O.; Lyakhov, S.A.; Mazepa, A.V.; Andronati, S.A.; Turov, A.V.; Zholobak, N.M.; Spivak, N.Y. Synthesis, cytotoxicity, antiviral activity and interferon inducing ability of 6-(2-aminoethyl)-6H-indolo [2, 3-b] quinoxalines. *Eur. J. Med. Chem.* **2010**, *45*, 1237–1243.
- Singh, D.P.; Deivedi, S.K.; Hashim, S.R.; Singhal, R.G. Synthesis and antimicrobial activity of some new quinoxaline derivatives. *Pharmaceuticals* **2010**, *3*, 2416–2425.
- Srinivas, B.; Prasanna, B.; Ravinder, M. One pot synthesis of substituted bistetrazolo-[1, 5-a: 5', 1'-c]-quinoxalines. *Chem. Sci. Trans.* **2013**, *2*, 1074–1077.
- Sun, Q.; Liu, L.; Yang, Y.; Zha, Z.; Wang, Z. Unexpected activated carbon-catalyzed pyrrolo[1,2-a]quinoxalines synthesis in water. *Chin. Chem. Lett.* **2019**, *30*, 1379–1382.
- Sun, Y., Duan, X., Wang, L., & Wu, J. (2016, January). Enhanced maltose production through mutagenesis of acceptor binding subsite +2 in *Bacillus stearothermophilus* maltogenic amylase. *Journal of Biotechnology*, *217*, 53–61. <https://doi.org/10.1016/j.jbiotec.2015.11.007>
- Suthar, S. K., Chundawat, N. S., Pal Singh, G., M. Padrón, J., Payghan, P. V., & Jhala, Y. K. (2022). Evaluation of anti-bacterial activity of novel 2, 3-diaminoquinoxaline derivatives: design, synthesis, biological screening, and molecular modeling studies. *Egyptian Journal of Basic and Applied Sciences*, *9*(1), 162-179.
- Taeger, E.; El-Hewehi, Z. Synthese von in 5-Stellung mono-und disubstituierten 2-Mercapto-4-phenyl- $\Delta$ 2-1, 3, 4-thiadiazolinen und 2, 3-Dimercaptochinoxalin. *J. Für Prakt. Chem.* **1962**, *18*, 255–261.
- Tang, X.-Y.; Gong, Y.; Huo, H.-R. Metal-free synthesis of pyrrolo[1,2-a]quinoxalines mediated by TEMPO oxoammonium salts. *Synthesis* **2018**, *50*, 2727–2740.
- Tariq, S., Somakala, K., & Amir, M. (2018). Quinoxaline: An insight into the recent pharmacological advances. *European Journal of Medicinal Chemistry*, *143*, 542-557.

- Teague, S. J., Davis, A. M., Leeson, P. D., & Oprea, T. (1999). The design of leadlike combinatorial libraries. *Angewandte Chemie International Edition*, 38(24), 3743-3748.
- Teja, R., Kapu, S., Kadiyala, S., Dhanapal, V., & Raman, A. N. (2016). Heterocyclic systems containing bridgehead nitrogen atom: Synthesis and antimicrobial activity of thiadiazolo [2', 3': 2, 3] imidazo [4, 5-B] quinoxaline. *Journal of Saudi Chemical Society*, 20, S387-S392.
- Trott O, Olson AJ (2010) AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *J Computer Chem* 31:455-461.
- Tseng, C. H., Chen, Y. R., Tzeng, C. C., Liu, W., Chou, C. K., Chiu, C. C., & Chen, Y. L. (2016, January). Discovery of indeno[1,2- b ]quinoxaline derivatives as potential anticancer agents. *European Journal of Medicinal Chemistry*, 108, 258-27.
- Veber, D. F., Johnson, S. R., Cheng, H. Y., Smith, B. R., Ward, K. W., & Kopple, K. D. (2002). Molecular properties that influence the oral bioavailability of drug candidates. *Journal of medicinal chemistry*, 45(12), 2615-2623.
- Vieira, M.; Pinheiro, C.; Fernandes, R.; Noronha, J.; Prudêncio, C. Antimicrobial activity of quinoxaline 1,4-dioxide with 2- and 3-substituted derivatives. *Microbiol. Res.* **2014**, 169, 287-293.
- Wadavrao, S.B.; Ghogare, R.; Narsaiah, A.V. A simple and efficient protocol for the synthesis of quinoxalines catalyzed by pyridine. *Org. Commun.* **2013**, 6, 23.
- Wang, D., Wu, W., Wang, T., Pan, Y., Tang, K., She, X., Ding, W., & Wang, H. (2015, May). Salmonella L-forms: formation in human bile in vitro and isolation culture from patients' gallbladder samples by a non-high osmotic isolation technique. *Clinical Microbiology and Infection*, 21(5), 470.e9-470.e16.
- Wang, S.; Yan, J.; Wang, X.; Yang, Z.; Lin, F.; Zhang, T. Synthesis and evaluation of the  $\alpha$ -glucosidase inhibitory activity of 3-[4-(phenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one derivatives. *Eur. J. Med. Chem.* **2010**, 45, 1250-1255.
- Wills, R.J.; Dennis, S.; Spiegel, H.E.; Gibson, D.M.; Nadler, P.I. Interferon kinetics and adverse reactions after IV infusion, IM and SQ routes of administration. *Clin. Pharmacol. Ther.* **1984**, 35, 722-727.
- Wilson, E.A.; Demmig-Adams, B. Antioxidant, anti-inflammatory, and antimicrobial properties of garlic and onions. *Nutr. Food Sci.* **2007**, 37, 178-183.
- Wilson, L. A., Van Katwyk, S. R., Weldon, I., & Hoffman, S. J. (2021). A global pandemic treaty must address antimicrobial resistance. *Journal of Law, Medicine & Ethics*, 49(4), 688-691.
- Wright, G. (2003, October). Mechanisms of resistance to antibiotics. *Current Opinion in Chemical Biology*, 7(5), 563-569.



- Wu, Q., Sabokroo, N., Wang, Y., Hashemian, M., Karamollahi, S., & Kouhsari, E. (2021). Systematic review and meta-analysis of the epidemiology of vancomycin-resistance *Staphylococcus aureus* isolates. *Antimicrobial Resistance & Infection Control*, *10*, 1-13.
- Xia, R.; Guo, T.; Chen, M.; Su, S.; He, J.; Tang, X.; Jiang, S.; Xue, W. Synthesis, antiviral and antibacterial activities and action mechanism of penta-1,4-dien-3-one oxime ether derivatives containing a quinoxaline moiety. *N. J. Chem.* **2019**, *43*, 16461–16467.
- Xu, B., Sun, Y., Guo, Y., Cao, Y., & Yu, T. (2009, April). Synthesis and biological evaluation of N4-(hetero)arylsulfonylquinoxalinones as HIV-1 reverse transcriptase inhibitors. *Bioorganic & Medicinal Chemistry*, *17*(7), 2767–2774.
- Xu, H., & Chen, Y. (2007, April 30). C(aryl)-O Bond Formation from Aryl Methanesulfonates via Consecutive Deprotection and S<sub>N</sub>Ar Reactions with Aryl Halides in an Ionic Liquid. *Molecules*, *12*(4), 861–867.
- Yang, C., Li, H., Zhang, T., Chu, Y., Zuo, J., & Chen, D. (2020, February 20). Study on antibiotic susceptibility of *Salmonella typhimurium* L forms to the third and fourth generation cephalosporins. *Scientific Reports*, *10*(1).
- Yu, L.; Gan, X.; Zhou, D.; Meneghetti, F.; Zeng, S.; Hu, D. Synthesis and antiviral activity of novel 1,4-pentadien-3-one derivatives containing a 1,3,4-thiadiazole moiety. *Molecules* **2017**, *22*, 658.
- Zhang, X.Z.; Wang, J.X.; Sun, Y.J.; Zhan, H.W. Synthesis of quinoxaline derivatives catalyzed by PEG-400. *Chin. Chem. Lett.* **2010**, *21*.