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

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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 $-NO_2$ 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_NAr (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

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Derivatif kuinoksalinaerkenal 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 penonjolan 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-dichloroquinoxaline (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.

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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:

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Date: 14 December 2023

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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_f	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, pthalazine, cinnoline **(Figure 1.1)** (Mamedov *et al*., 2016).

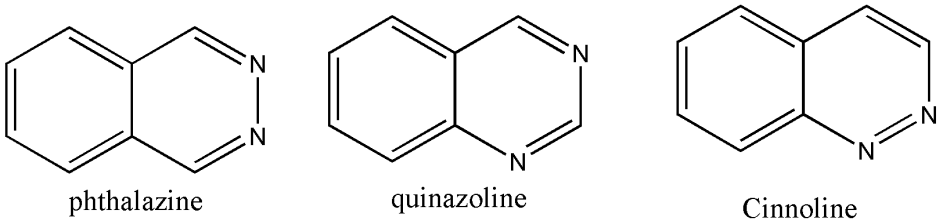


Figure 1.1 : Isomers of Quinoxalines

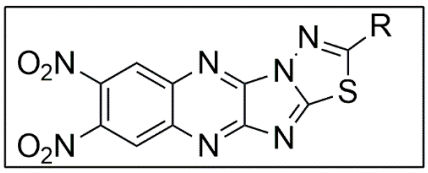
The biological and therapeutic features of quinoxaline and its derivatives have drawn attention in recent years. Natural quinoxalines are uncommon, but synthetic ones are used in gram-positive bacteria antibiotics such echinomycin, levomycin, and actinomycin (Pereira., 2015). Quinoxaline and its derivatives 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-ubstituted quinoxaline compounds may inhibit bacterial growth. The presence of 4-triflouromethylanilino, 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.).

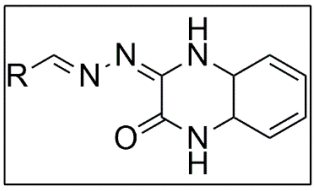
In the event of a pandemic, antibiotic resistance might increase, posing a problem for medical staff. It has been hypothesized that *Staphylococcus aureus* is a major contributor to bacterial infections during viral pandemics. However, there has not been sufficient research on the prevalence of *S. aureus* 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.



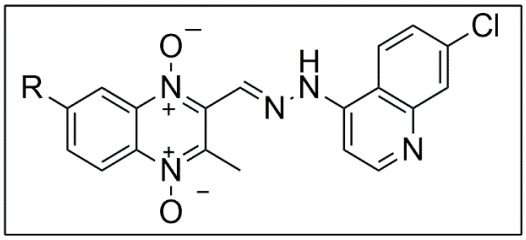
R= C_6H_5 or 4-NH_2 or -C_6H_4 or 2-OH-C_6H_4 Thiadiazolo[2',3':2,3]imidazo[4,5-b]quinoxaline.

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)



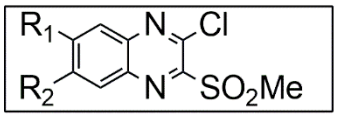
Quinoxaline containing sugar conjugates for eg. 3-(2-ßD-glucopyranosylidene hydrazinyl)quinoxalin-2(1H)-one, R= glucose. R can be also mannose or maltose or lactose or ribose and xylose.

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



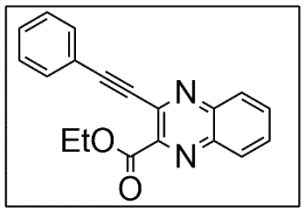
New hydrazine and hydrazide quinoxaline-1,4-di-N-oxide derivatives.
R= -OCH_3 or -Cl

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



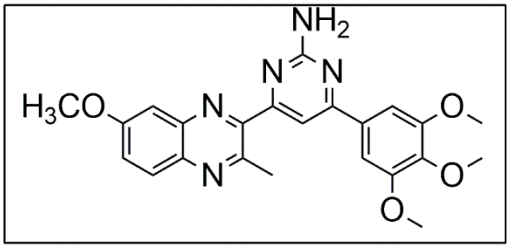
3-chloro-2-methylsulfonylquinoxalines

Anti-trypanosomal activity against *Trypnosoma 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 heter-oatoms 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,

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