Experimental Procedure for Synthesis and Biologically of Antimalarial Heterocyclic Compounds

***Jagtap Anant Kishanrao, **Dr. Kailas Narayn Sonune**
**Research Scholar, **Research Supervisor,*
Department of Chemistry,
Himalayan University,
Itanagar, Arunachal Pradesh

ABSTRACT

Introduction: *In 1933, Gerhand Domagk discovered "Prontosil Red," the chemical responsible for the medicine's antibacterial effect, lending credence to the current notion of drug discovery.*

Aim of the study: *the main aim of the study is experimental procedure for synthesis and biologically of Quinoline-pyrazolicchalcone*

Material and method: *To verify the choice of the quinoline ring made after conducting a literature review, docking simulations were carried out.*

Conclusion: *Quinoline-pyrazolicchalcone hybrids were synthesised and biologically screened as part of the current study, which aimed to create novel antimalarial heterocyclic compounds.*

INTRODUCTION

Overview

In 1933, Gerhand Domagk discovered "Prontosil Red," the chemical responsible for the medicine's antibacterial effect, lending credence to the current notion of drug discovery. The development of sulfonamides highlights how distinct compounds have contrasting effects on bacterial and human cells. This crucial consideration spurred Florey and Chain to look into penicillin 10 years after its discovery by Alexander Fleming in 1939.

Penicillin's remarkable chemotherapeutic qualities and the rapid speed with which it was created for wound therapy have made it a widely used, low-cost medicine.

We have created heterocycles with a quinoline moiety in light of the usefulness of heterocyclic compounds. These nuclei have been developed to accommodate a wide range of substituents, and synthetic products have been prepared to test their pharmacological profile against various bacterial strains. When Rungo separated quinoline from coaltar in 1834, it was a major scientific breakthrough. It is also found in oil from the state of California. Similar to pyridine, quinoline may be easily manufactured in a lab. In most cases, this is influenced by a response that was found by Skraup in Australia in 1881. This process involves heating a combination of aniline, nitrobenzene, glycerol, and strong sulphuric acid. Pseudomonas aeruginosa strains also frequently cause these infections. Both in the general population and in hospitals, infectious diseases caused by the bacteria Escherichia coli and Staphylococcus aureus are fairly frequent. Urinary tract infections (also known as UTIs) and necrotizing enterocolitis are two conditions that are often caused by E. coli in hospitalised patients. In addition to being a significant etiological agent of infection, S. aureus is also one of the leading causes of morbidity and mortality.

LITERATURE REVIEW

Mazur, Marcelina (2022) As novel resistance mechanisms emerge and propagate internationally, microbial resistance is reaching alarmingly high levels throughout the globe. Considering the annual volume of medications entering the global market, the development of novel compounds having antibacterial action is falling short. Research aimed at discovering novel antimicrobial compounds that may ultimately be used as first line defence against the worst infections is, thus, warranting of special emphasis. The purpose of this Special Issue, entitled "Design and Synthesis of New Antimicrobial Agents," is to include articles that report on the most recent findings from studies conducted on the creation, synthesis, characterisation, and development of antibiotics and other antimicrobial agents. Compound structural characterisation and activity assessment should be included in the publication.

Abdelgawad, Mohamed & Alsanea (2022) Element and spectrum analyses were used to completely characterise all the newly synthesised compounds. In addition, compounds IIIf-h were shown to have a similar impact to celecoxib but a lower ulcerogenic liability than indomethacin in a stomach ulcerogenic potential experiment.

Satheeshkumar, Rajendran & Sivalingam (2022) Novel heterocyclic compounds with a variety of pharmacological characteristics may be synthesised using quinoline, which is why new synthetic techniques and their use in drug development have been extensively investigated in the present state of medicinal chemistry. Many additional procedures have been utilized to synthesize these heterocycles using quinoline scaffolds, including Friedländer quinoline synthesis. An aminobenzaldehyde-keto condensation is used in the Friedländer process. Quinoline nuclei were obtained using the Friedländer reaction and have since been used to produce quinoline derivatives with an array of new biological properties, including anticancer, antimalarial, antibacterial, antifungal, antibiotic and leishmanial activity. It has never been done in the world of medicinal chemistry previously that the Friedländer reaction may be employed to synthesize various bioactive heterocyclic quinine compounds. Most of this study focuses on Friedländer's quinoline synthesis and discoveries from 2010 to the present in order to focus on biological and pharmacological action.

Satheeshkumar, Rajendran & Sivalingam (2022) Novel heterocyclic compounds with a variety of pharmacological characteristics may be synthesised using quinoline, which is why new synthetic techniques and their use in drug development have been extensively investigated in the present state of medicinal chemistry. Many additional procedures have been utilized to synthesize these heterocycles using quinoline scaffolds, including Friedländer quinoline synthesis. An aminobenzaldehyde-keto condensation is used in the Friedländer process. Quinoline nuclei were obtained using the Friedländer reaction and have since been used to produce quinoline derivatives with an array of new biological properties, including anticancer, antimalarial, antibacterial, antifungal, antibiotic and leishmanial activity. It has never been done in the world of medicinal chemistry previously that the Friedländer reaction may be employed to synthesize various bioactive heterocyclic quinine compounds. Most of this study focuses on Friedländer's quinoline synthesis and discoveries from 2010 to the present in order to focus on biological and pharmacological action.

Qadir, Tanzeela & Amin, Andleeb & Sharma (2022) Because of their synthetic value and the results of considerable synthetic research, the number of heterocyclic molecules is rapidly growing. They have several applications in the realm of medical chemistry. Other common uses include dyestuff, disinfectants, corrosion inhibitors, antioxidants, and copolymer production. An effective method for synthesising newly discovered heterocyclic compounds and their moieties will always exhibit certain defining features. Past studies have shown that a comprehensive understanding of the biological system is necessary for the development of almost 90% of medications utilising heterocyclic chemicals.

METHODOLOGY

To verify the choice of the quinoline ring made after conducting a literature review, docking simulations were carried out. The crystal structure of Plasmodium falciparum lactate dehydrogenase, 1U4S, accommodated all 20

ligands. Table 4.1 lists the dimensions of a grid box with a 0.375 grid spacing along the x, y, and z axes. Table 4.2 displays the outcome of the docking simulations. According to the research, quinine had the best dock score of - 7.7 kCal/mol and was shown to be bound in the active region of the receptor protein, as shown in Figure 4.1. The choice of the quinoline ring as an antimalarial was thus positively supported by the docking, and the synthesis of hybrids containing quinoline will now be described.

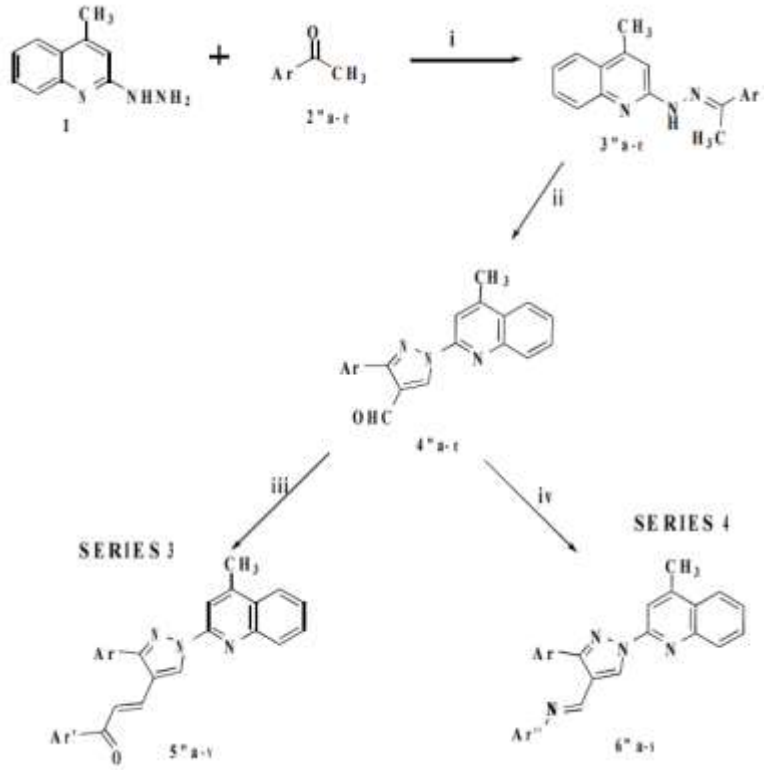
Table 3.1: x, y, z coordinates of grid box (PDB ID: 1U4S)

center_x	25.7
center_y	27.108
center_z	9.283
size_x	40
size_y	40
size_z	40

RESULTS

Series 3

List of chemicals produced in Table 4.8 is shown in Scheme 4.3, which outlines the whole synthetic process of series 3.



Scheme 4.1 Synthesis of Chalcone (5''a-v) schiff's base (6''a-s) . Reagents and Conditions: i) 1 - 2 drops Glacial acetic acid, Ethanol, Stir, 60°C, 6 hr. ii) DMF, POCl3, Stir, 55 - 60°C, 5 hr. iii) Acetic acid, Sodium acetate, re flux, 4 hr. iv) Glacial acetic acid, Ethanol, reflux, 8 hr.

Table 4.1 List of synthesized derivatives of series 3(3 - (1- (4- methylquinolin -2 - yl) - 3 - aryl- 1H -pyrazol -4 - yl)- 1 - arylprop- 2 -en - 1 - one s)

S.No.	Comp	Ar	Ar'
1.	5"a	C_6H_5	C_6H_5
2.	5"b	C_6H_5	p-$CH_3C_6H_4$
3.	5"c	C_6H_5	p-$OCH_3C_6H_4$
4.	5"d	C_6H_5	p-ClC_6H_4
5.	5"e	p-ClC_6H_4	C_6H_5
6.	5"f	p-ClC_6H_4	p-ClC_6H_4
7.	5"g	p-ClC_6H_4	p-$CH_3C_6H_4$
8.	5"h	p-ClC_6H_4	p-$OCH_3C_6H_4$
9.	5"i	p-ClC_6H_4	2-thienyl
10.	5"j	p-ClC_6H_4	C_6H_5
11.	5"k	p-$OCH_3C_6H_4$	p-$OCH_3C_6H_4$
12	5"l	p-$OCH_3C_6H_4$	p-$CH_3C_6H_4$
13	5"m	p-$OCH_3C_6H_4$	p-ClC_6H_4
14	5"n	p-$OCH_3C_6H_4$	2-thienyl
15	5"o	2-thienyl	C_6H_5
16	5"p	2-thienyl	p-$OCH_3C_6H_4$
17	5"q	2-thienyl	p-$CH_3C_6H_4$
18	5"r	2-thienyl	p-ClC_6H_4
19	5"s	$C_6H_4CH_3$	C_6H_5
20	5"t	$C_6H_4CH_3$	p-$OCH_3C_6H_4$
21	5"u	$C_6H_4CH_3$	p-$CH_3C_6H_4$

22	5"v	$C_6H_4CH_3$	p-CIC_6H_4

- **General experimental procedure for synthesis of 1 - (4- methylquinolin - 2 - yl)- 2 - (1-arylethylidene)hydrazines (3''a- e) :**

Various ketones were added to a combination of 2-hydrazino-4-methylquinoline and compound (1) 2.07 g (0.012mol) in EtOH (20 ml) (0.012 mol). For six hours at 60°C, the mixture was mixed with one drop of glacial acetic acid. Filtration and ethanol washing were used to generate the final solution.

Table 4.2 List of Acetophenones used

S.No.	Name	Quantity(g)
1	Acetophenone (1"a)	1.44
2	p-chloroacetophenone (1"b)	1.86
3	p-methoxyacetophenone (1"c)	1.8
4	2-acetylthiophene (1"d)	1.5
5	p-methylacetophenone (1"e)	1.62

- **General experimental procedure for synthesis of 1 - (4- methylquinolin - 2 - yl)- 3 - aryl - 1H - pyrazole- 4 -carbaldehydes (4''a- e)**

To the Vilsmeier-Haack reagent, Hydrazone (0.006mol) was added, and the reaction mixture was agitated at 55-60 °C for 5 hours with the addition of DMF, 10ml, and POCl3 (2.2 eq). A cold water rinse and neutralisation with sodium hydroxide were then performed on the solution. After the solid was filtered, washed, and re-crystallized from ethanol, it was ready to be dissolved.

Table 4.3 List of 1 - (4- methylquinolin- 2 -yl)- 2 - (1 -ar ylethylidene)hydrazines used

Sr. No.	IUPAC Name	Quantity (g)
1	1-(4-methylquinolin-2yl)-2-(1-phenylethylidene)hydrazine(3"a)	1.64
2	1-(1-(4-chlorophenyl)ethylidene)-2-(4-methylquinolin-2-yl)hydrazine (3"b)	1.84
3	1-(1-(4-methoxyphenyl)ethylidene)-2-(4-methylquinolin-2-yl) hydrazine (3"c)	1.8
4	1-(4- methylquinolin-2-yl)-2-(1-(thiophen-2-yl)ethyli dene)-hydrazine (3"d)	1.68
5	1-(4- methylquinolin-2-yl)-2-(1-p-tolylethylidene)hydrazine (3"e)	1.72

- **General experimental procedure for synthesis of 3 - (1- (4- methylquinolin - 2- yl)- 3 - aryl - 1H - pyrazol-4 - yl)- 1 - aryl prop- 2 - en - 1 -one s (5 a - v) 75 3 - aryl - 1H - pyrazol-4 - yl)- 1 - aryl prop- 2 - en - 1 -one s (5a - v)**

Sodium acetate (4 mmol) and formyl pyrazole, 4"(3 mmol) were used to buffer a solution of different aromatic ketones (2 mmol) in 17.5 ml acetic acid. After 4 hours of refluxing, the reaction mixture was dumped into a bowl of ice cold water. Filtrated, rinsed with water, and then recrystallized with acetic acid-DMF (2:1) to get the desired chemicals.

Table 4.4 List of 1 -(4 -methylquinolin - 2- yl) -3 - aryl- 1H- pyrazole - 4 -Used

Sr. No.	IUPAC Name	Quantity (g)
1	1-(4-methylquinolin-2yl)-3-phenyl-1H-pyrazole-4-carbaldehyde (4”a)	0.94
2	3-(4-chlorophenyl)-1-(4-methylquinolin-2-yl)-1H-pyrazole-4-carbaldehyde (4”b)	1.04
3	3-(4-methoxyphenyl)-1-(4-methylquinolin-2-yl)-1H-pyrazole-4-carbaldehyde (4”c)	1.03
4	1-(4- methylquinolin-2-yl)-3-(thiophen-2-yl)-1H-pyrazole-4-carbaldehyde (4”d)	0.96
5	1-(4- methylquinolin-2-yl)-3-p-tolyl-1H-pyrazole-4-carbaldehyde (4”e)	0.98

- **Data interpretation of 3 - (1- (4- methylquinolin - 2 - yl)-3 - aryl - 1H - pyrazol- 4 - yl)- 1 - aryl prop- 2 - en - 1- ones (Series 3)**

After the Vilsmeier - Haack reaction, the chalcone analogues (4"a-e) were transformed into their chalcone analogues (5"a-v) by ClaisenSchimdt condensation. The IR, 1 H NMR, mass spectrometry, and elemental analyses validated the structure of all synthesised target series. IR. There were two C-H stretch peaks that corresponded to the aldehyde group around 2735 and 2869 cm-1 that vanished following the synthesis of chalcone, as shown by IR analysis.

The synthesis of hydrazone was validated by the appearance of a wide singlet of NH at 8.3 in 1HNMR spectra. the next synthesis yielded two features that peaked at around 9.4 and 10.14 (the protons at C5 and C6), respectively. Chalcone's, unsaturation was also proven by a proton almost at 7.6 that was deshielded, confirming the doublet. The J value between ethylenic protons was found to be roughly 15.5 Hz, which suggested the creation of the trans-isomer, according to this study. Analysis of elements and mass spectra helped prove the structure's existence.

CONCLUSION

Quinoline-pyrazolicchalcone hybrids were synthesised and biologically screened as part of the current study, which aimed to create novel antimalarial heterocyclic compounds. According to the results of the antimalarial

assessment, compound 5'u had the greatest activity among the synthetic series in both in vitro and animal studies, and this was confirmed by in silico analysis. Due to the impressive findings, more research is needed to investigate the antimalarial potential of produced series aimed targeting the cysteine protease falcipain-2.

REFERENCES

1. Shreeve, Jean'ne & Gao, Haixiang & Zhang, Qinghua. (2020). Fused Heterocycle-Based Energetic Materials (2012-2019). Journal of Materials Chemistry A. 8. 10.1039/C9TA12704F.
2. Siham Lahsasni.(2018). Synthesis, Characterization, and Antibacterial and Anti-Inflammatory Activities of New Pyrimidine and Thiophene Derivatives. Volume 2018 |Article ID 8536063 | https://doi.org/10.1155/2018/8536063
3. Sumit Tahlan.(2019). Pharmacological significance of heterocyclic 1*H*-benzimidazole scaffolds: a review.
4. Suvarna Arunkumar S (2015) – "A Review on Synthetic Heterocyclic Compounds in Agricultural and other Applications", International Journal of PharmTech Research CODEN (USA): IJPRIF, ISSN: 0974-4304 Vol.8, No.8, pp 170-179, 2015
5. Syed, Sabir & Alhazza, Mansour & Ibrahim, Ahmed. (2016). A review on heterocyclic moieties and their applications. Catalysis for Sustainable Energy. 2. 10.1515/cse-2015-0009.
6. Tahlan, Sumit & Kumar, Sanjiv & Narasimhan, Balasubramanian. (2019). Pharmacological significance of heterocyclic 1H-benzimidazole scaffolds: a review. BMC Chemistry. 13. 10.1186/s13065-019-0625-4.
7. Taylor, Alexandria & Robinson, Ralph & Fobian, Yvette & Blakemore, David & Jones, Lyn & Fadeyi, Olugbeminiyi. (2016). Modern Advances in Heterocyclic Chemistry in Drug Discovery. Organic & biomolecular chemistry. 14. 10.1039/c6ob00936k.
8. Theivendren Panneer Selvam, et al (2012) – "A mini review of pyrimidine and fused pyrimidine marketed drugs", Research in Pharmacy, VOL 2, ISSUE 4, 2012 /
9. Theivendren, Panneerselvam. (2014). Biological activities of Fused Imidazole Derivatives – A Review. 10.13140/2.1.1612.3202.
10. Toma, Alexandra & Mogosan, Cristina & Vlase, Laurian & Denisa, Leonte & Zaharia, Valentin. (2017). Heterocycles 39. Synthesis, characterization and evaluation of the anti-inflammatory activity of thiazolo[3,2-b][1,2,4]triazole derivatives bearing pyridin-3/4-yl moiety. Medicinal Chemistry Research. 26. 10.1007/s00044-017-1959-x.