SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME NITROGEN - CONTAINING HETEROCYCLIC DERIVATIVES

By

Mahmoud Mohamed Abdelati Abdelgawwad

A thesis submitted in partial fulfillment

Of

The requirement for the degree of

Master of Science

In

Organic Chemistry

Department of chemistry

Faculty of Science, Fayoum

FAYOUM UNIVERSITY

2023

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME NITROGEN - CONTAINING HETEROCYCLIC DERIVATIVES

By

Mahmoud Mohamed Abdelati Abdelgawwad

(Bachelor's degree of science 2018)

Prof. Dr / Abdelmoneim Abdelsalam Makhlouf

Professor of Organic Chemistry - Faculty of Science - Fayoum University

Signature /

Prof. Dr / Ayman Mohamed Salah Youssef

Professor of Organic Chemistry - Faculty of Science - Fayoum University

Signature /

Ass. Dr / Zeinab Ramadan Farag

Ass. Prof. of Organic Chemistry - Faculty of Science - Fayoum University

Signature /

Approval Sheet

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME NITROGEN - CONTAINING HETEROCYCLIC DERIVATIVES

By

Mahmoud Mohamed Abdelati Abdelgawwad

(Bachelor's degree of science 2018)

This thesis for M.Sc. degree has been

Approved by:

Prof. Dr / Abdelmoneim Abdelsalam Makhlouf

Professor of Organic Chemistry - Faculty of Science - Fayoum University

Signature /

Prof. Dr / Ayman Mohamed Salah Youssef

Professor of Organic Chemistry - Faculty of Science - Fayoum University

Signature /

Ass. Dr / Zeinab Ramadan Farag

Ass. Prof. of Organic Chemistry - Faculty of Science - Fayoum University

Signature /

Date of Examination: / / 2023

SUMMARY

Synthesis of new pyrans, pyridines, pyrazoles, and pyrimidines, together with some of their fused derivatives was undertaken, starting from acetone dicarboxylic dianilide. Microanalytical and spectral studies collectively confirmed the structure. The synthesized compounds were screened for their biological activity against human pathogenic bacterial strains *Escherichia coli, Staphylococcus aureus, Bacillus subtilis*, and *Pseudomonas aeruginosa*. The majority of the tested compounds were proved to exhibit moderate to high antibacterial activity. Molecular docking of some synthesized compounds was studied against the bacterial protein receptors obtained from the Protein Data Bank. The results are in good accordance with the experimental results.

Synthesis of new heterocyclic derivatives based on 3-oxo-N^1,N^5-diaryl pentanediamide (1a,b) (Scheme 1)

I) Synthesis of 3-oxo-N^1,N^5-diaryl (bis 2-chlorophenyl) pentanediamide (1a,b)

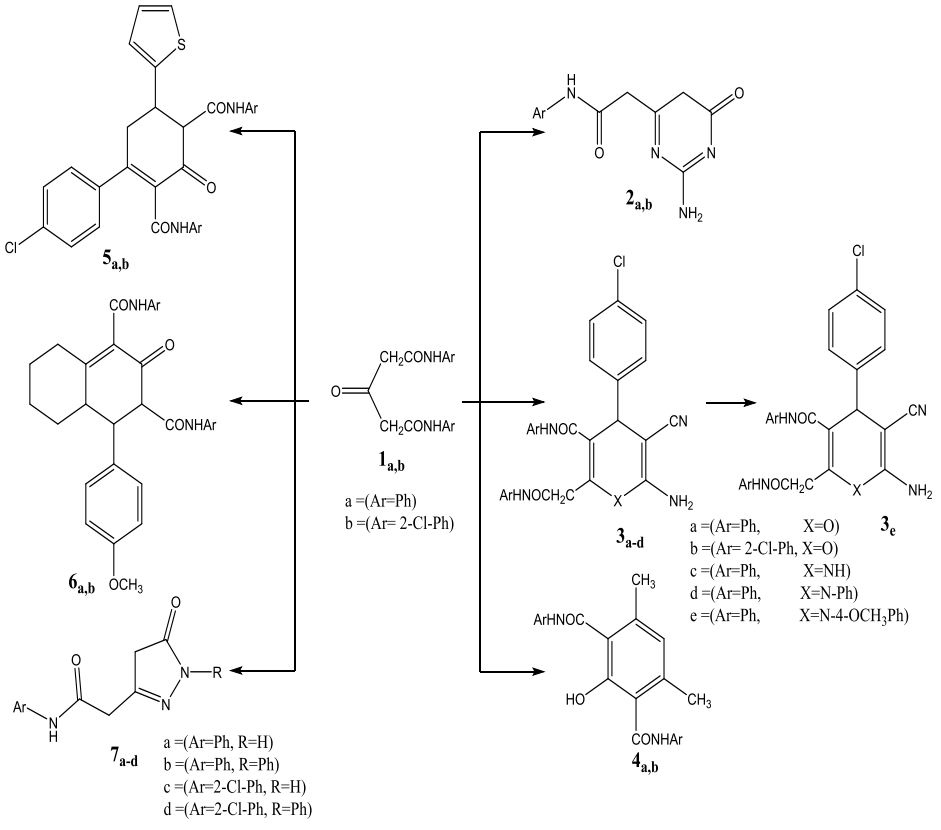
diethyl 3-oxopentanedioate was reacted with aniline and/or 2-chloroaniline afforded 3-oxo-N^1,N^5-diarylpentanediamide **(1a,b)**[1].

II) Synthesis of 2-(2-amino-6-oxo-5,6-dihydropyrimidin-4-yl)-*N*-arylacetamide (2a,b)

Compounds **1a,b** were refluxed with guanidinium hydrochloride forming **2a,b**.

III) Synthesis of 6-amino-4-(4-chlorophenyl)-5-cyano-2-(2-oxo-2-(phenylamino)ethyl)- *N*-aryl-4*H*-pyran-3-carboxamide (3a,b)

One-pot reaction of compounds **1a,b** with 2-(4-chlorobenzylidene) malononitrile and piperidine was used to yield **3a,b**.



***Scheme 1*: reactions of acetonedicarboxanilide**

IV) Synthesis of 6-amino-4-(4-chlorophenyl)-5-cyano-2-(2-oxo-2-(phenylamino) ethyl)-*N*-phenyl-1,4-dihydropyridine-3-carboxamide (3c,d)

Compound **1a** was treated with 2-(4-chlorobenzylidene) malononitrile in the presence of ammonium acetate or aniline in absolute ethanol to produce **3c,d**.

V) Synthesis of 6-amino-4-(4-chlorophenyl)-5- cyano-1-(4-methoxyphenyl)-2-(2-oxo-2-(phenylamino)ethyl)-*N*-phenyl-1,4-dihydropyridine-3-carboxamide (3e)

Compound **3a** was reacted with p-anisidine in DMF afforded **3e**.

VI) Synthesis of 2-hydroxy-4,6-dimethyl-N^1,N^3-diarylisophthalamide (4a,b)

Compounds **1a,b** were reacted with acetylacetone in the presence of sodium methoxide afforded **4a,b**.

VII) Synthesis of 4'-chloro-3-oxo-N^2,N^4-diaryl-5-(thiophen-2-yl) -3,4,5,6-tetrahydro- [1,1'-biphenyl]-2,4 dicarboxamide (5a,b)

Compounds **1a,b** were refluxed with 1-(4-chlorophenyl)-3--(thiophen-2-yl)prop-2-en-1-one in the presence of sodium hydroxide in ethanol giving **5a,b**.

VIII) Synthesis of 4-(4-methoxyphenyl)-2-oxo-N^1,N^3-diaryl-2,3,4,4a,5,6,7,8-octahydro naphthalene-1,3-dicarboxamide (6a,b)

Compounds **1a,b** were refluxed with 2-(4-methoxybenzylidene) cyclohexan-1-one in the presence of sodium hydroxide in ethanol to yield **6a,b**.

IX) Synthesis of pyrazole derivatives 7a-d

Treatment of Compounds **1a,b** with hydrazine in ethanol yielded 2-(5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)-*N*-arylacetamide **(7a,c)**.

Furthermore, the treatment with phenylhydrazine in acetic acid produced 2-(5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-*N*-arylacetamide **(7b,d)**.

Reactions of pyrazolone 7a-d (Scheme 2)

IX.1) Reaction with diazonium salt of aniline derivatives

An equivalent amount of Compounds **7a,b** were reacted with diazonium salt of p-anisidine affording 2-(4-(2-(4-methoxyphenyl) hydrazineylidene) -5-oxo- 4,5-dihydro -1*H*-pyrazol-3-yl) -*N*-phenyl acetamide **8a,b**.

IX.2) Formation of 5-(4-methoxyphenyl)-6- (phenylamino)-2,5-dihydro-3H-pyrazolo [4,3-c]pyridazin-3-one (9a,b)

Compounds **8a,b** were refluxed with thionyl chloride in the presence of DMF producing **9a,b**.

IX.3) Reaction with triethyl orthoformate

A mixture of compounds **7a,b,** and triethyl orthoformate was refluxed in acetic anhydride to yield 2-(4-(ethoxymethylene)-5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)-*N*-phenylacetamide **(10a,b)**.

IX.4) Formation of compounds 11a-d

Compounds **10a,b** were reacted with hydrazine hydrate in absolute ethanol to afford 5-amino-6-(phenylamino)-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]pyridin-3-one **(11a,b)**.

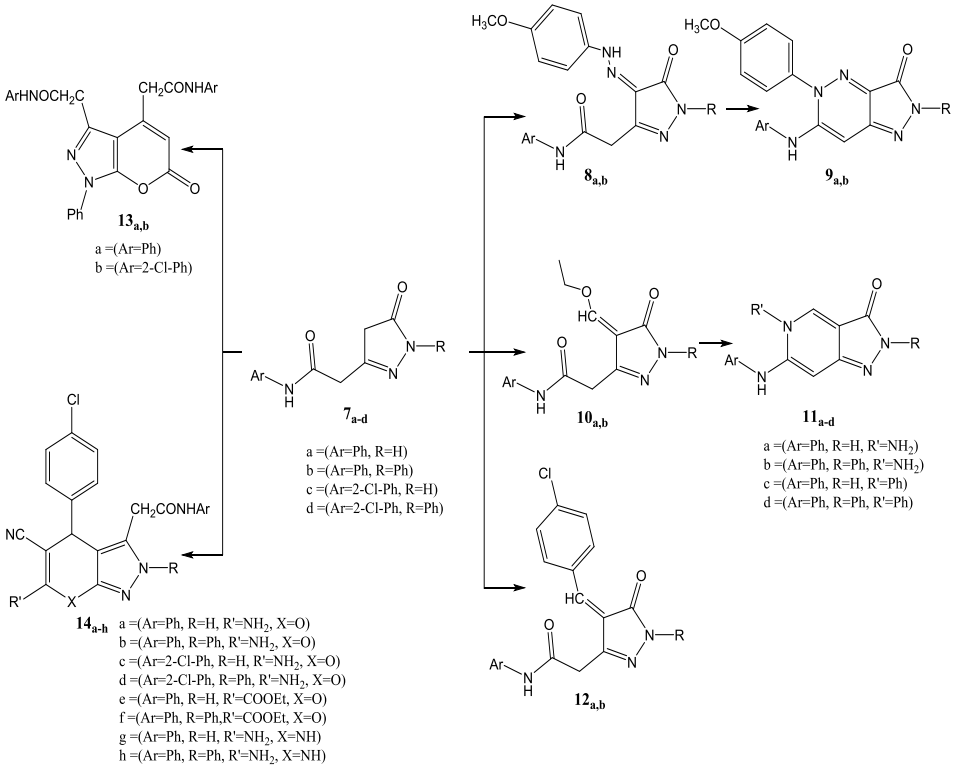
In the same way the treatment with aniline instead of hydrazine hydrate gave 5-phenyl-6-(phenylamino)-2,5-dihydro-3H-pyrazolo[4,3-c]pyridin-3-one **(11c,d)**.

IX.5) Formation of compounds 12a,b

P-chlorobenzaldehyde was added to a solution of compounds **7a,b** in the presence of piperidine, produced 2-(4-(4-chlorobenzylidene)-5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)-*N*-phenylacetamide **(12a,b)**.

IX.6) Formation of 2,2'-(6-oxo-1-phenyl-1,6-dihydropyrano [2,3-*c*]pyrazole-3,4-diyl)bis(*N*-arylacetamide) (13a,b)

Compound **7b** was reacted with 3-oxo-N^1,N^5-diarylpentanediamide **(1a,b)** to yield **13a,b**.



***Scheme 2:* reaction of pyrazolone**

IX.7) Formation of pyranopyrazole 14a-d

One-pot reaction of compounds **7a-d**, malononitrile, and p-chlorobenzaldehyde was used to give 2-(6-amino-4-(4-chlorophenyl) -5-cyano- 2,4-dihydropyrano[2,3-*c*] pyrazol-3-yl)-*N*-arylacetamide **(14a-d)**. On the other hand, the replacement of malononitrile by ethyl cyanoacetate yielded ethyl 4-(4-chlorophenyl) -5-cyano-3-(2-oxo-2- (phenylamino) ethyl) -(2-phenyl) 2,4-dihydropyrano [2,3-c]pyrazole-6-carboxylate **(14e,f)** successfully.

IX.8) Formation of 2-(6-amino-4-(4-chlorophenyl)-5-cyano-4,7-dihydro-2*H*-pyrazolo [3,4-b]pyridin-3-yl) -*N*-phenylacetamide (14g,h)

Compounds **7a,b** were refluxed with 2-(4-chlorobenzylidene) malononitrile and ammonium acetate in ethanol to form **14g,h**.

Reactions of pyranopyrazole 14a,b (Scheme 3)

IX.7.1) Formation of 2-(6-amino-4-(4-chlorophenyl)-5-cyano-7-(4-methoxyphenyl) -2-phenyl-4,7- dihydro-2*H*-pyrazolo[3,4-*b*] pyridin-3-yl)-*N*-phenylacetamide (14i)

Treatment of compound **14b** with p-anisidine in DMF exhibited **14i**.

IX.7.2) Formation of 2-(5-amino-4-(4-chlorophenyl)-6-cyano-7-oxo-(2-phenyl) 2,4,7,8-tetrahydropyrazolo[4',3':5,6] pyrano[2,3-b] pyridin-3-yl)-N-phenylacetamide (15a,b)

Compound **14a,b** was reacted with ethyl cyanoacetate to afford **15a,b**.

IX.7.3) Reaction with triethyl orthoformate

Compounds **14a,b** were refluxed with triethyl orthoformate to produce ethyl *N*-(4-(4-chlorophenyl)-5- cyano-3-(2-oxo-2-(phenylamino) ethyl)-2,4- dihydropyrano[2,3-*c*] pyrazol-6-yl) formimidate **(16a,b)**.

IX.7.4) Formation of 2-(6-amino-4-(4-chlorophenyl)-5-imino-2,4,5,6-tetrahydropyrazolo[4',3':5,6]pyrano [2,3-d]pyrimidin-3-yl)-*N*-phenylacetamide (17a-d)

Compounds **16a,b** were treated with hydrazine hydrate and/or aniline in ethanol to give **17a-d**.

IX.7.5) Reaction with formic acid

Compounds **14a,b** were reacted with formic acid to produce 2-(4-(4-chlorophenyl)-5- oxo-2,4,5,8-tetrahydro pyrazolo[4',3':5,6] pyrano [2,3-*d*]pyrimidin-3-yl)-*N*-phenylacetamide **18a,b**.

IX.7.6) Acylation Reaction

Compounds **14a,b** were refluxed in a mixture of glacial acetic acid and acetic anhydride to give 2-(4-(4-chlorophenyl)-7-methyl-5-oxo-2,4,5,6-tetrahydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidin-3-yl)-*N*-phenylacetamide **(19a,b)**.

IX.7.7) Reaction with formamide

Refluxing Compounds **14a,b** with a solution of formamide to afford 2-(5-amino-4-(4-chlorophenyl)-2,4-dihydropyrazolo[4',3':5,6] pyrano[2,3-d]pyrimidin-3-yl)-*N*-phenylacetamide **(20a,b)**.

IX.7.8) Reaction with malononitrile

Compounds **14a,b** were refluxed with malononitrile in DMF or ethanol in the presence of piperidine to afford 2-(5,7-diamino-4-(4-chlorophenyl)-6-cyano-2,4 dihydropyrazolo [4',3':5,6]pyrano [2,3-*b*]pyridin-3-yl)-*N*-phenylacetamide **(21a,b)**.

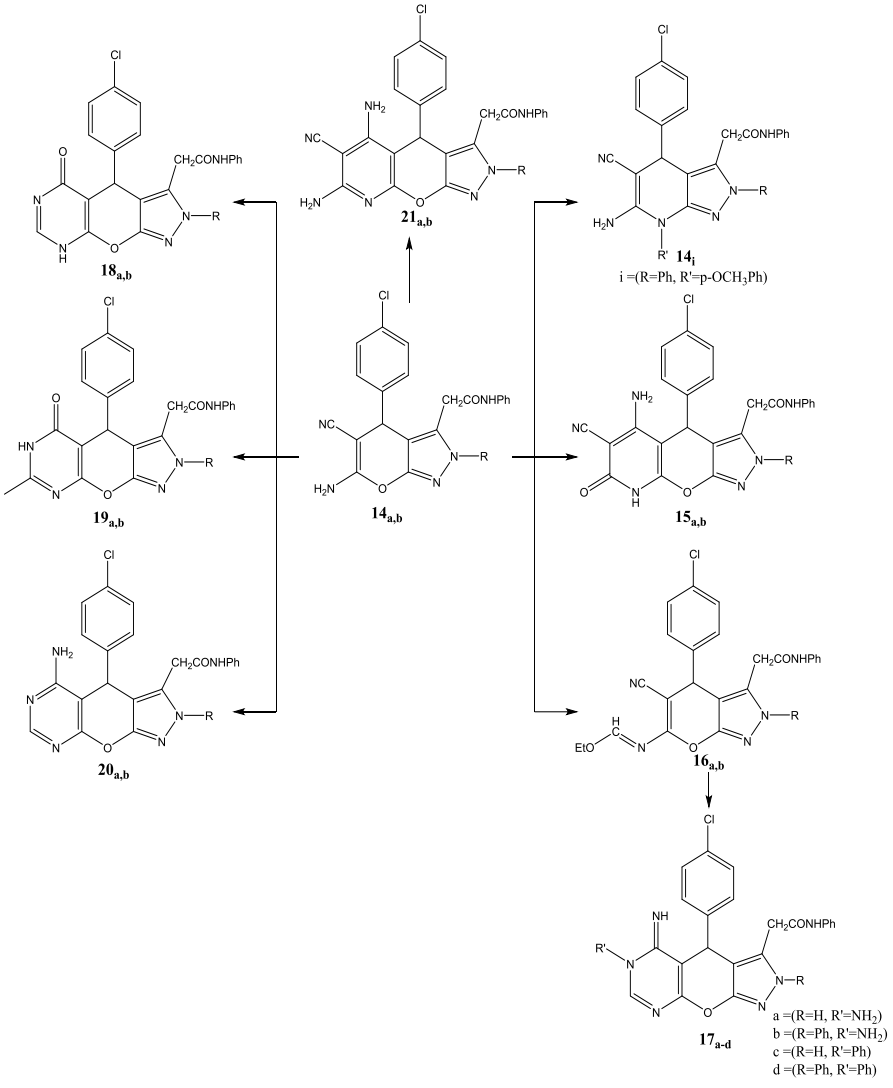
Application

I) Antimicrobial activity

All synthesized compounds were evaluated for their *in vitro* antibacterial activity against gram-positive and gram-negative bacteria.

II) Molecular docking

Molecular docking studies were performed against *S. aureus* tyrosyl-tRNA synthetase for the synthesized compounds.



***Scheme 3*: reactions of pyranopyrazole**

III) *In silico* ADMET study

ADMET studies were conducted using Molinspiration, ProTox-II and pkCSM prediction.

IV) Quantum calculations and (MEP) maps

Molecular orbital (MO) calculations and molecular electrostatic potential (MEP) maps were conducted for the most active derivatives