بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
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MONA MAGHRABY

Faculty of Science
Ain Shams University
Chemistry Department

Synthesis Of Nitrogen Heterocyclic Compounds With Expected Pharmaceutical Activity

Thesis Submitted by

Mustafa Ahmed Elsayed Gouda

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Thesis Advisors

Prof. Dr. Mounir Abdu Ibrahiem Salem

Professor of Organic Chemistry, Faculty of Science, Ain Shams University

Prof.Dr. Eman Abdel-Fattah Abdel-Hafez El-Bordany

Professor of Organic Chemistry, Faculty of Science, Ain Shams University

Dr. Naglaa Fawzy Hassan Mahmoud

Associate Professor of Organic Chemistry, Faculty of Science, Ain Shams University

To
Department of chemistry
Faculty of Science
Ain Shams University
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Faculty of Science
Ain Shams University
Chemistry Department

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Faculty of Science, Ain Shams University

Thesis Advisors **Thesis Approval**

Prof. Dr. Mounir Abdu Ibrahiem Salem **…….**

Professor of Organic Chemistry,

Faculty of Science, Ain Shams University

Prof. Dr. Eman Abdel-Fattah Abdel-Hafez El-Bordany **…….**

Professor of Organic Chemistry,

Faculty of Science, Ain Shams University

Dr. Naglaa Fawzy Hassan Mahmoud **…….**

Associate Professor of Organic Chemistry,

Faculty of Science, Ain Shams University

Head of Chemistry department

Prof. Dr. Ayman Ayoub Abdel-Shafi

بِسْمِ اللّهِ الرَّحْمنِ الرَّحِيمِ

قَالُواْ سُبْحَانَكَ لاَ عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ
الْعَلِيمُ الْحَكِيمُ

صدق اللَّهُ العظيم

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Aim of the work

The research aims to achievement of the following goals.

1. Create new methods to synthesis a number of pyrido[2,3-*d*]pyrimidine-4(*1H*) dione derivatives and imidazoles carrying pyrazole moiety by different routes.
2. using the 7-amino-pyridopyrimidine-6-carbonitrile derivative, 2-amino-pyrimidine-3-carbonitrile, 3-phenyl-2-thioxoimidazolidin-4-one and 5-phenyl-2,4-dihydro-*3H*-pyrazol-3-one as a key starting material for synthesis of new heterocyclic compounds.
3. Elucidation of the structural features of the synthesized compounds *via* elemental analysis and spectrometric methods such as IR., MS., ^{1}H-NMR and ^{13}C-NMR Spectra.
4. Evaluation the pharmaceutical activity for new synthesized compounds.

Synthesis Of Nitrogen Heterocyclic Compounds With Expected Pharmaceutical Activity

By

Mustafa Ahmed Elsayed Gouda

Abstract:

Part I : We aiming to synthesize polyfunctional substituted heterocyclic compounds of potential biological activity, the synthesis of poly-functionalized 7-amino-5-(4-methoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido [2,3-*d*]pyrimidine-6-carbonitrile and 2-amino-4-(4-methoxyphenyl)-5-oxo-5*H*-dipyrido[1,2-a:3',2'-*e*]pyrimidine-3-carbonitrile was achieved *via* one-pot multicomponent reactions of the barbituric acid and/or 3*H*-pyrido [1,2-*a*]pyrimidine-2,4-dione, anisaldehyde, ammonium acetate and malononitrile or three-component reactions of barbituric acid and/or 3*H*-pyrido[1,2-*a*]pyrimidine-2,4-dione, arylidine of malononitrile and ammonium acetate and study the biological activities of the synthesized compounds as antioxidant, anticancer and DNA damage**.** Most of the synthesized compounds were tested for their *in vitro.*

Part II: synthesis some new substituted imidazoles carrying pyrazole moiety to be nucleus for the future work.

Keywords: pyridopyrimidine carbonitrile, oxazolopyridopyrimidine, di, trioxo pyridothiazolo-pyrimidine, thioxoimidazolidin-4-one, pyrazol-3-one, molecular docking and anticancer.

Summary

The original work of this thesis can be classified into two parts:

Part (I):

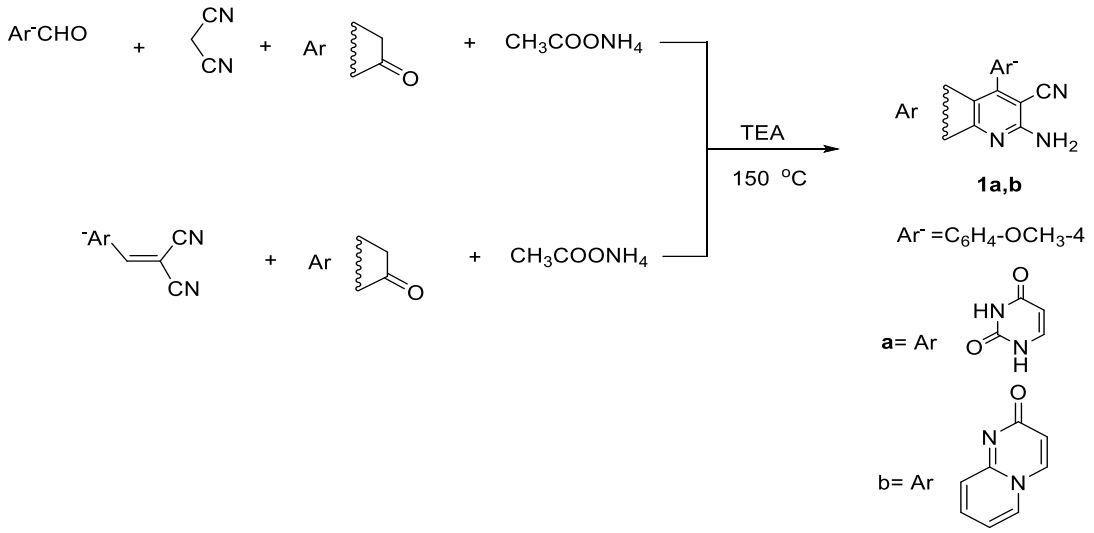
Multicomponent reactions, solvent-free synthesis of pyrido[2,3-*d*]pyrimidine-4(1*H*) dione derivatives and evaluation the pharmaceutical activity for new synthesized compounds.

Part (II):

Synthesis of some new substituted imidazoles carrying pyrazole moiety.

Part (I)

In resumption of our work aiming to synthesize polyfunctional substituted heterocyclic compounds of potential biological activity, the synthesis of poly-functionalized 7-amino-5-(4-methoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido [2,3-*d*]pyrimidine-6-carbonitrile (**1a)** and 2-amino-4-(4-methoxyphenyl)-5-oxo-5*H*-dipyrido[1,2-*a:*3',2'-*e*]pyrimidine-3-carbonitrile (**1b)** was achieved *via* one-pot multicomponent reactions of the barbituric acid and/or 3*H*-pyrido [1,2-*a*]pyrimidine-2,4-dione, anisaldehyde, ammonium acetate and malononitrile or three-component reactions of barbituric acid and/or 3*H*-pyrido[1,2-*a*]pyrimidine-2,4-dione, arylidine of malononitrile and ammonium acetate in presencse of drops of triethylamine (TEA), under fusion at 150 ^{o}C **(Scheme 1)**.



Scheme 1, synthesis of **1a, b**

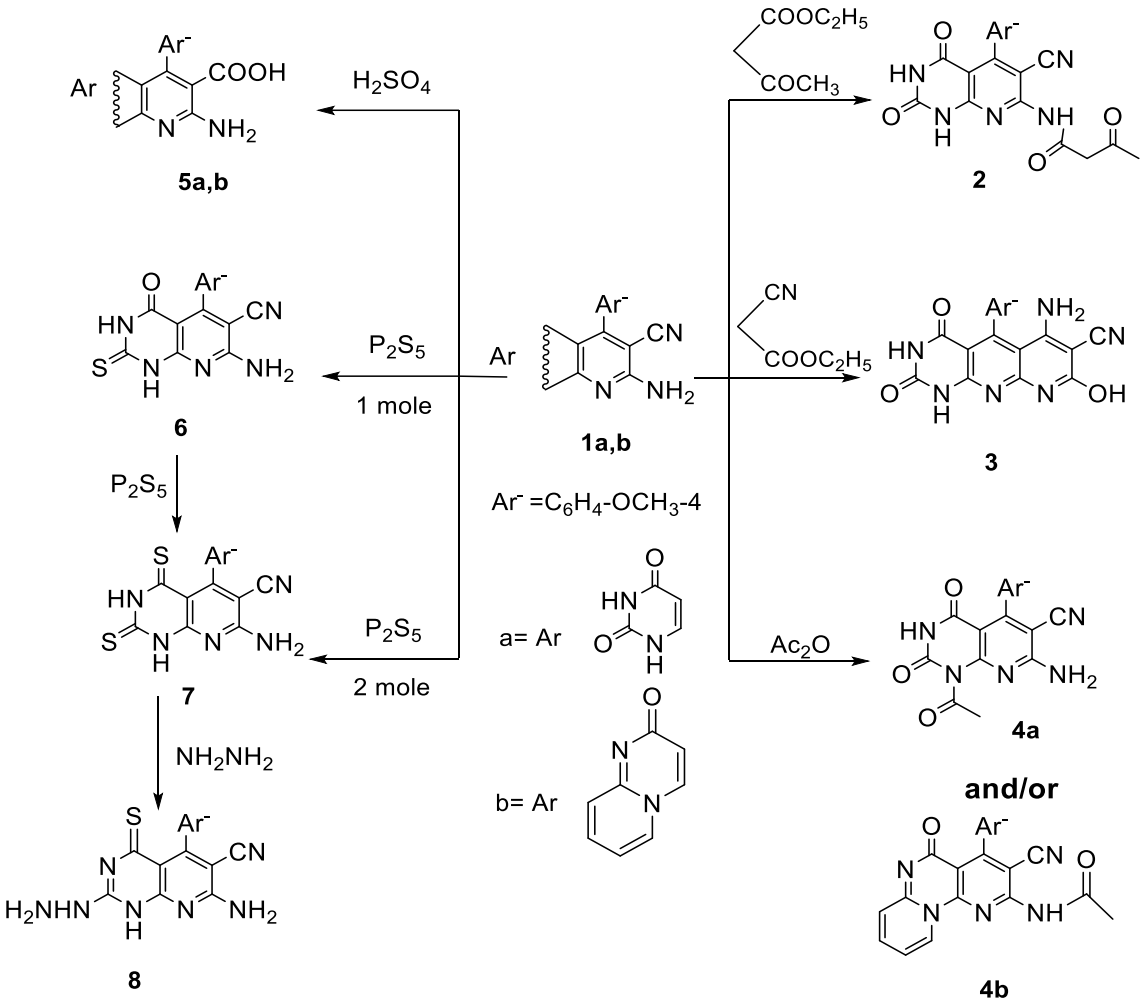
Presence of cyano group in *ortho* location relative to an amino group is considered as a flexible site for the synthesis of different polycyclic structures. Condensation of 7-amino-pyridopyrimidine-6-carbonitrile derivative **1a** with ethyl acetoacetate and/or ethyl cyanoacetate in ethanol afforded *N*-(6-cyano-5-(4-methoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidin-7-yl)-3-oxo-butanamide **2** and 6-amino-8-hydroxy-5-(4-methoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimido-[4,5-*b*][1,8]naphthayridine-7-carbonitrile **3**.

On the other hand the pyridopyrimidine derivatives **1a** and **1b** were acetylated by using acetic anhydride to give the monoacetyl derivatives 1-Acetyl-7-amino-5-(4-methoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile **4a,** *N*-(3-cyano-4-(4-methoxyphenyl)-5-oxo-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrimidin-2-yl) acetamide **4b**. acetylation of **1a** occurred on NH group of pyrimidine but acetylation of **1b** occurred on NH_2 group which was revealed from elemental analysis and spectral data.

However acid hydrolysis of 7-amino-pyridopyrimidine-6-carbonitrile derivatives **1a,b** with sulfuric acid (70%) gave the pyrido[2,3-*d*]pyrimidine-6-carboxylic acids

7-Amino-5-(4-methoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine -6-carboxylic acid **5a,** 2-Amino-4-(4-methoxyphenyl)-5-oxo-5*H*-dipyrido[1,2-*a*:3', 2'-*e*]pyrimidine-3-carboxylic acid **5b.**

Sulfurization of derivative **1a** by using one mole of phosphorous pentasulfide gave 7-amino-5-(4-methoxyphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbo nitrile **6** while using two mole of phosphorous pentasulfide gave 7-amino-5-(4-methoxyphenyl)-2,4-dithioxo-1,2,3,4-tetrahydropyrido[2,3-*d*] pyrimidine-6-carbonitrile **7**. Upon refluxing an alcoholic solution of derivative **7** with hydrazine hydrate (75%), **7-**amino-4-hydrazinyl-5-(4-methoxyphenyl)-2-thioxo-1,2-dihydro pyrido[2,3-*d*] pyrimidine-6-carbonitrile **8** was afforded. **(Scheme 2)**.



(Scheme 2) reactions of compound **1a** with ethyl acetoacetate, ethyl cyanoacetate, phosphorous pentasulfide and reactions of **1a, b** with acetic anhydride and sulfuric acid (70%).

Additionally, Reaction of pyridopyrimidine derivative **1a** with phenyl isothiocyanate and/or carbon disulphide gave 1-(6-Cyano-5-(4-methoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidin-7-yl)-3-phenylthiourea **9** and 5-(4-Methoxyphenyl)-6,8-dithioxo-6,7,8,9-tetrahydropyrido[2,3-*d*:6,5-*d'*]dipyrimidine -2,4(1*H*,3*H*)-dione **10**, respectively.

In the same context, Cyclocondensation of pyridopyrimidine derivatives **1a, b** with formamide afforded 6-Amino-5-(4-methoxyphenyl)pyrido[2,3-*d*:6,5-*d'*]