Ph. D Thesis

Entitled

Synthesis of new azole, azine and their fused derivatives with pharmaceutical uses

Presented
By

AMR SALAH AHMED IBRAHIM ABOU-ZIED


For Fulfillment of Ph. D Degree

Chemistry Department

Faculty of Science

Cairo University

Giza, Egypt

2011-2012
Title of Ph. D Thesis

Synthesis of new azole, azine and their fused derivatives with pharmaceutical uses

Name of candidate: Amr Salah Ahmed Ibrahim Abou-zied

This thesis has been approved for submission by the

Supervisors:

1- Prof. Dr. Sherif Mourad Sherif

Signature

2- Prof. Dr. Wagnat Wahba Wardakhan

Signature

Prof. Dr. Mohamed Ahmed Badawy

Chairman of Chemistry Department
Faculty of Science, Cairo University
ABSTRACT

**Name:** Amr Salah Ahmed Ibrahim Abouzied

**Title of Thesis:** Synthesis of new azole, azine and their fused derivatives with pharmaceutical uses

**Degree Ph. D**  Unpublished Doctor of Philosophy Thesis, Faculty of Science, Cairo University, 2011-2012

**Part I**, synthesis of hydrazide-hydrazone derivatives and their uses for the synthesis of heterocyclic and fused heterocyclic compounds.

**Part II**, synthesis of new thiophene derivatives together with their uses to synthesis new azole and azine derivatives.

The synthesized products were evaluated through three cancer cell lines namely breast adenocarcinoma, non-small cell lung cancer and CNS cancer.

**Key words:** Hydrazide-hydrazone, Thiophene, Pyridone, Thiazole

**Supervisors:**

1- Prof. Dr. Sherif Mourad Sherif

2- Prof. Dr. Wagnat Wahba Wardakhan

Prof. Dr. Mohamed Ahmed Badawy

Chairman of Chemistry Department
Faculty of Science, Cairo University
ACKNOWLEDGEMENT

I wish to express my sincere gratitude to Prof. Dr. Sherif Mourad Sherif, Professor of Organic Chemistry, Department of Chemistry, Faculty of Science, Cairo University, for his kind supervision the practical work in its various steps. I have drawn on his knowledge and enriched my ideas through continuous and valuable discussion and final representation of this work.

Also, I wish to express my deep gratitude to Prof. Dr. Wagnat Wahba Wardakhan, Professor of Organic Chemistry and head of the general Department of Pharmaceutical Organic Chemistry, National Organization for Drug Control and Research, for her great effort, suggest the research plan of the Ph. D work, careful guidance, helpful discussion and advice during implementation of the schemes of the entire work, I owe her the success I achieve in this work.
DEDICATION

I dedicate this dissertation to my Parents, my dearest wife, my daughters (Kenzy, Gody), my son (Moaz) and my best friend (Akim).
CONTENTS

ENGLISH SUMMARY............................................................... i

GENERAL PART

I. Synthetic strategies and applications of thiophene, azole and
    azine derivatives.............................................................. 1

   I.1. Synthesis of thiophenes and their fused derivatives via
        Gewald reaction.......................................................... 1

   I.2. Synthesis of thiophenes ring system and their
        substituted derivatives............................................... 14

   I.3. Synthesis of thiophenes and their azole and azine
        derivatives from nitrites............................................. 26

   I.4. Synthesis of fused thiophenes and their azole and azine
        derivatives starting from thiophenes and other
        heterocyclic systems................................................... 37

II. Biological activity of thiophenes and their fused derivatives.. 62

Part I: The reaction of 2-cyanoacetohydrazide with furan-2-
        aldehyde: novel synthesis of thiophene, azole, azine and
        coumarin derivatives and their antitumor evaluation.............. 78

   I.1. Introduction............................................................ 78

   I.2. Results and Discussion............................................. 79

   I.3. Experimental......................................................... 91

   I.4. Antitumor activity.................................................. 108

Part II: New approaches for the uses of thiophene derivatives 112
to synthesis of azoles and azines with antitumor activity

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>II.1. Introduction</td>
<td>112</td>
</tr>
<tr>
<td>II.2. Results and Discussion</td>
<td>113</td>
</tr>
<tr>
<td>II.3. Experimental</td>
<td>122</td>
</tr>
<tr>
<td>II.4. Biological Activity</td>
<td>143</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>147</td>
</tr>
<tr>
<td>ARABIC SUMMARY</td>
<td></td>
</tr>
</tbody>
</table>
Part I

The reaction of 2-cyanoacetohydrazide with furan-2-aldehyde: novel synthesis of thiophene, azole, azine and coumarin derivatives and their antitumor evaluation

2-cyanoacetohydrazide (1) reacted with furan-2-aldehyde (2) to give the hydrazide-hydrazo compound 3. The condensation of 3 with benzaldehyde (4) in ethanolic/piperidene solution gave the benzylidene derivative 5. The reaction of compound 5 with either hydrazine hydrate (6a) or phenylhydrazine (6b) gave the pyrazole derivatives 7 and 8 respectively. On the other hand the reaction of 5 with either malononitrile (9a) or ethyl cyanoacetate (9b) gave the pyridine derivatives 10 and 11 respectively. Further confirmation of the reaction products 10 and 11 was achieved through an alternative synthetic route involving treatment of the starting compound 3 with benzylidene carbonitrile reagents 12a,b to afford the same pyridone derivatives 10 and 11 respectively. On the other hand compound 3 reacted with salicylaldehyde (13) to give the coumarin derivative 14. The reaction of 3 with either acetylacetone (15a) or ethyl acetoacetate (15b) gave the pyridine derivatives 16a and 16b, respectively. The reaction of 3 with either malononitrile (9a) or ethyl cyanoacetate (9b) gave the 2-pyridone derivatives 17a and 17b, respectively (cf. Scheme 1).
The reaction of 3 with either acetophenone (18) or 4-methoxyacetophenone (19) in ammonium acetate gave the Knoevenagel condensated products 20 and 21 respectively. The reaction of compound 3 with aryl diazonium chlorides 22a-d gave the phenylhydrazone
derivatives \textit{23a-d}. Compound \textit{23a} reacted with ethyl cyanoacetate (9b) to give the pyridazine derivative \textit{24}. On the other hand, the reaction of \textit{23a} with phenyl isothiocyanate (25) gave the triazine derivative \textit{26}. The reaction of compound \textit{3} with phenyl isothiocyanate (25) in DMF solution containing KOH gave the intermediate potassium sulphide salt \textit{27}. The latter intermediate underwent heterocyclization upon reaction with \(\alpha\)-halocarbonyl compounds \textit{28a-c} to give the thiazole derivatives \textit{29a-c}. Compound \textit{3} reacted with acetoacetanilide (30) to afford the pyridine derivative \textit{31}. Compound \textit{3} reacted with either malononitrile (9a) or ethyl cyanoacetate (9b) and elemental sulfur to form the thiophene derivatives \textit{32a} and \textit{32b} respectively. Moreover, compound \textit{3} reacted with cyclohexanone (33) and elemental sulfur to form the tetrahydrobenzo[b]thiophene derivative \textit{34}. Carrying the same reaction but using cyclopentanone (35) instead of cyclohexanone gave the cyclopenta[b]thiophene derivative \textit{36} (cf. Scheme 2). All tested compounds were subjected to antitumor evaluation and most of them showed potent activity.
Part II

New approaches for the uses of thiophene derivatives to synthesis of azoles and azines with antitumor activity

Acetoacitanilide derivatives \(1a-c\) reacted with either malononitrile \((2a)\) or ethyl cyanoacetate \((2b)\) and elemental sulfur in refluxing ethanol containing triethylamine to give the thiophene derivatives \(3a-f\) respectively. (cf. Scheme 3)

\[
\begin{align*}
1a, \ R &= H \\
b, \ R &= CH_3 \\
c, \ R &= Cl \\
2a, \ X &= CN \\
b, \ X &= COOEt \\
3a-f \\
\end{align*}
\]

\[
\begin{array}{|c|c|c|}
\hline
 3 & X & R \\
\hline
 a & CN & H \\
b & COOEt & H \\
c & CN & CH_3 \\
d & COOEt & CH_3 \\
e & CN & Cl \\
f & COOEt & Cl \\
\hline
\end{array}
\]

Scheme (3)

Compound \(3a\) condensed with benzaldehyde \((4)\) to give the benzaldehyde derivative \(5\). Moreover, it reacted with acetic anhydride \((6)\) in the presence of acetic acid to give the \(N\)-acetyl derivative \(7\). On the other hand, compound \(3a\) reacted with either malononitrile \((2a)\) or ethyl cyanoacetate \((2b)\) to give the thieno[2,3-b]pyridine derivatives \(8a\) and \(8b\) respectively. Carrying the last reaction but in dry conditions in an oil bath at 120 °C in the presence of ammonium acetate gave the Knoevenagel condensation products \(9a\) and \(9b\) respectively. The reaction of compound \(3a\) with phenyl isothiocyanate \((10)\) in the presence of triethylamine gave the thieno[2,3-d]pyrimidine derivative \(11\). The reaction of a cold solution
(AcOH/HCl) of 3a with sodium nitrite solution gave the non-isolable diazonium salt. The latter coupled with acetylacetone (12) to give the hydrazone derivative 13. The reaction of compound 3a with ethyl cyanoacetate (2b) in the presence of dimethylformamide gave the amide derivative 14 (cf. Scheme 4).

Thus, compound 14 reacts with benzaldehyde (4) to give the benzal derivative 15. Moreover, the reaction of 14 with salicylaldehyde (16) gave the coumarin derivative 17. On the other hand the reaction of compound 14 with malononitrile (2a) and elemental sulfur gave the thiophen-2-yl derivative 18. Compound 14 reacted with phenyl isothiocyanate (10) in DMF/KOH solution followed by reaction with α-haloketones 19a-c gave the thiophene derivatives 20a-c respectively. Moreover, the reaction of compound 14 with benzenediazonium chloride in ethanol/sodium hydroxide solution gave the phenylhydrazone.
derivative 21. The reaction of 14 with malononitrile (2a) in the presence of 1,4-dioxane containing triethylamine gave the pyridine derivative 22. Carrying the last reaction but in dry conditions in an oil bath at 120°C in the presence of ammonium acetate gave the Knoevenagel condensation product 23. Compound 14 cyclized in the presence of 1,4-dioxane and triethylamine to give the thienopyridine derivative 24 (cf. Scheme 5).

The reaction of acetoacetanilide derivatives 1a-c with phenyl isothiocyanate (10) in DMF/KOH solution gave the non-isolable potassium sulphide salts 25a-c, the reaction of 25a-c with α-halocarbonyl compounds 19a-c gave the thiophene derivatives 26a-i respectively (cf. Scheme 6). The intermediate potassium sulphide salts 25a-c reacted with hydrochloric acid followed by reaction with hydrazine hydrate to give pyrazole derivatives 27a-c respectively (cf. Scheme 6).
ENGLISH SUMMARY

\[
\begin{align*}
&\text{27a, } R = H \\
&\text{b, } R = CH_3 \\
&\text{c, } R = Cl
\end{align*}
\]

\[
\begin{align*}
&\text{i) HCl} \\
&\text{ii) NH}_2\text{NH}_2 \\
&\text{iii) -H}_2\text{O}
\end{align*}
\]

\[
\begin{align*}
&\text{1a, } R = H \\
&\text{b, } R = CH_3 \\
&\text{c, } R = Cl
\end{align*}
\]

\[
\begin{align*}
&\text{19a, } X = Cl, Y = CH_3 \\
&\text{b, } X = Br, Y = Ph \\
&\text{c, } X = Cl, Y = OEt
\end{align*}
\]

\[
\begin{align*}
&\text{26a-i}
\end{align*}
\]

\[
\begin{array}{|c|c|c|}
\hline
R & Y & \\
\hline
\text{a} & H & CH_3 \\
\hline
\text{b} & H & Ph \\
\hline
\text{c} & H & OEt \\
\hline
\text{d} & CH_3 & CH_3 \\
\hline
\text{e} & CH_3 & Ph \\
\hline
\text{f} & CH_3 & OEt \\
\hline
\text{g} & Cl & CH_3 \\
\hline
\text{h} & Cl & Ph \\
\hline
\text{i} & Cl & OEt \\
\hline
\end{array}
\]

\text{Scheme (6)}
I. Synthetic strategies and applications of thiophene, azole and azine derivatives

Thiophenes and their substituted derivatives are of interest to the organic community over the past decades because of their aromatic character contributes to their reactivity, stability, chemical, physical, biological and electronics activity such as organic light emitting diodes (OLEDs), organic thin-film transistors (OTFTs), organic photovoltaics (OPVs), dye sensitized solar cells (DSSCs), and nonlinear optical (NLO) chromophores. Benzothiophenes are also luminescent components used in organic materials; in addition they are regarded as important units in liquid crystal research. Though, thiophene derivatives have been prepared by various methods, elaboration of the existing thiophene skeleton with multiple substituents at the desired positions is still a challenging task. The most efficient protocol for carrying out the synthesis of such thiophene derivatives is the Gewald method.

I.1. Synthesis of thiophenes and their fused derivatives via Gewald reaction

The most convenient method for preparing thiophenes with a high degree of functionality is the Gewald method in which elemental sulfur is reacted with an activated carbonitrile and an aldehyde, ketone or 1,3-dicarbonyl compound in the presence of a base. Gewald's synthesis was undertaken to form thiophene derivative 2 by reacting of 2-amino-4-phenylpenta-1,3-dien-1,1,3-tricarbonitrile (1) with elemental sulfur in the presence of triethylamine.
A mixture of enaminonitrile 3, methylenenitrile 4 and elemental sulfur in refluxing 1,4-dioxane in the presence of a catalytic amount of piperidine enabled the synthesis of 4-(5-amino-thiophene-3-yl)pyridine derivatives 5.

Al-said et al. reported the synthesis of thiophene and its fused derivatives via Gewald's synthesis by reacting 2-cyanoacetohydrazide (7) with 1-[4-(piperidin-1-ylsulfonyl)phenyl]ethanone (6) to give hydrazide-hydrazone derivative 8 which reacted with either malononitrile or ethyl cyanoacetate and elemental sulfur in the presence of triethylamine to give the corresponding thiophene derivatives 9 and 10 respectively.
Özbek et al.\textsuperscript{23} reported simple access to new 5-aminothiophene carboxylic acid \textbf{13} which is regarded as dipeptideisosteres startind by modified Gewald reaction by employing siloxycyclopropane \textbf{11}. 

\begin{align*}
\text{Me}_3\text{SiO} & \quad + \quad \text{CO}_2\text{R}^2 \quad + \quad S_8 \quad \rightarrow \\
\textbf{11} & \quad \text{CN} \quad \text{CN} \quad \text{CN} \\
\text{MeO}_2\text{C} & \quad \text{H}_2\text{N} \quad \text{NH}_2 \\
\textbf{12} & \quad \text{X} \quad \text{X} \\
\textbf{13} & \quad \text{CO}_2\text{R}^1 \\
R^1 & = H \\
R^2 & = \text{tBu, Me}
\end{align*}

\textbf{Amr et al.}\textsuperscript{24} reported the synthesis of 2-amino-\textit{N}-(3-methoxyphenyl)-4,5,6,7-tetrahydrobenzo[\textit{b}]thiophene-3-carboxamide (\textbf{17}) according to Gewald procedures.
Pinto et al\textsuperscript{25} described the synthesis of 5-alkoxythiophenes 20 by an extension of the Gewald thiophene synthesis and a four component condensation reaction by which 5-aminothiophenes 19 are formed; has also been disclosed which could have potential in combinational chemistry for the preparation of diverse libraries. The authors surmised that the presence of a heteroatom would render the methylene group in the alkoxy methyl ketones more acidic than the group and would therefore direct the condensation reaction predominantly towards the 5-regioisomer.

Reaction of phenoxyacetone with ethyl cyanoacetate (4b) and sulfur in the presence of morpholine resulted not in 5-phenoxythiophene but in 5-morpholinothiophene (26). The morpholine displaced the phenoxy group. The reaction constituted a four component condensation reaction.
Baraldi et al\textsuperscript{26} discussed the synthesis of 2-amino-3-heteroaroylthiophenes 31-35 as potential allosteric enhancers at the human A\textsubscript{1} receptor. The synthetic procedure depended on Gewald method. The appropriate β-ketonitriles 27-30 were reacted with the appropriate ketones (butanone, cyclopentanone, cyclohexanone and 4-benzylpiperidone) in the presence of a base (morpholine) to give the Knoevenagel intermediate. This intermediate, in turn, was reacted with elemental sulfur to provide the desired thiophene ring formation (compounds 31-35).