# بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / سلوي محمود عقل

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

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| ملاحظات: لا يوجد |

**Ain Shams University**
**Faculty of Science**
**Chemistry Department**

# New innovative study, reactions and anticipated biological evaluation of some heterocyclic compounds

A Thesis Submitted for the degree of Ph. D. of Science

(Chemistry)

**By**

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M.Sc. in Chemistry, Faculty of Science
Cairo University, 2019

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**2022**

## Approval Sheet

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(M. Sc. 2019)

**For Ph. D. Degree in Organic Chemistry**

| **Thesis Advisors** | **Thesis Approved** |
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# Acknowledgment

Firstly, I would like to thank God for what I achieved,

I would be happy to express my deep gratitude to **Prof. Dr. Sameh Ahmed Rizk,** for his valuable and constructive suggestion during the planning and development of this research work.

I would like to express my great appreciation to **Prof. Dr. Abdelgawad Ali Fahmi,** for his advice and assistance to keep up my progress.

I`m eager to express my great appreciation to **Dr. Sayed Karam Ramadan** for his patient guidance, enthusiastic encouragement, and useful critiques of this research work.

My grateful thanks for Dr**. Mostafa Kamel** for his support.

Finally, Thanks for my beloved friends and family`s support.

# *Contents*

**The original work of this thesis is presented in two parts:**

## Part I: New innovative study, reactions and anticipated biological evaluation of some heterocyclic compounds

The key material, 3-(3-(1,3-diphenyl-1*H*-pyrazol-4-yl)acryloyl)-2*H*-chromen-2-one was synthesized and its behavior towards malononitrile, hydrazine-hydrate , thiourea, thiosemicarbazide, 2-aminoaniline, and 6-aminothiouracil was investigated aiming to synthesize a new series of pyrazole-based heterocycles *viz*. pyranochromene, diazepine, pyrimidochromene, triazepine, benzodiazepine, pyrimidine, and pyrimidopyrimidine derivatives. Density functional theory based on quantum chemical computation outline the structure optimization of the intermediate that reacted to afford the desired product. The antiproliferative screening against HepG2 and MCF7 cancer cell lines disclosed that the most potent compounds against two cell lines were compounds **9** and **17** as compared to doxorubicin which may be due to their presence in more tautomeric structures. Also, the minimized energy, dipole moment, ionization potential, transferred electrons, and charge density distribution revealed that the greater value of 0.126 and 0.8 for pyrazole derivatives **9** and **17**, respectively indicates the maximum transfer of electron and hence, greater tendency of scavenging radicals and rapidly reduce oxygen to superoxide

## Part II:Synthesis of 2-cyano-*N*-((2-oxo-1,2-dihydroquinolin-3-yl)methylene)acetohydrazide

2cyano-*N*'-((2-oxo-1,2-dihydroquinolin-3-yl)methylene) ethanohydrazide was synthesized in 87% yield *via* condensation of 3-formyl-2-oxoquinoline with 2-cyanoethanohydrazide. The titled compound was then treated with some electrophilic reagents to construct some novel quinoline-based heterocyclic systems, for example pyrazole, thiazoline, pyridine, pyrimidine, chromene, and thiophene derivatives. The behavior of the titled compound towards hydrazine and phenylhydrazine was examined. Seven substances were screened for their *in vitro* antiviral activity against infectious bursal disease virus (IBDV) in specific pathogen-free (SPF) chicken embryos and evaluation of immune-boosting properties of these substances in SPF chicks. The antiviral results disclosed that compounds **22a** and **3 4**exhibited the most potency as compared to the reference drug, ribavirin. Therefore, they are considered as promising antiviral additives in vaccine production of IBVD vaccine to increase the immune stimulant. Not worthy, six compounds were screened for their hemorrhoidal effect which serves as rodenticidal product.

**Keywords**: Chromene; Pyrazole; Pyrimidopyrimidine; Pyrimidochromen; IBD Virus; Quinoline; Pyrimidine; Rodenticidal, Anticoagulant.

Among heterocyclic compounds, Pyrazoles and quinolines occupy important roles in the heterocyclic synthesis and various applications in a lot of fields.

**The work of this thesis consists of two parts:**

## Part I: New innovative study, reactions and anticipated biological evaluation of some heterocyclic compounds

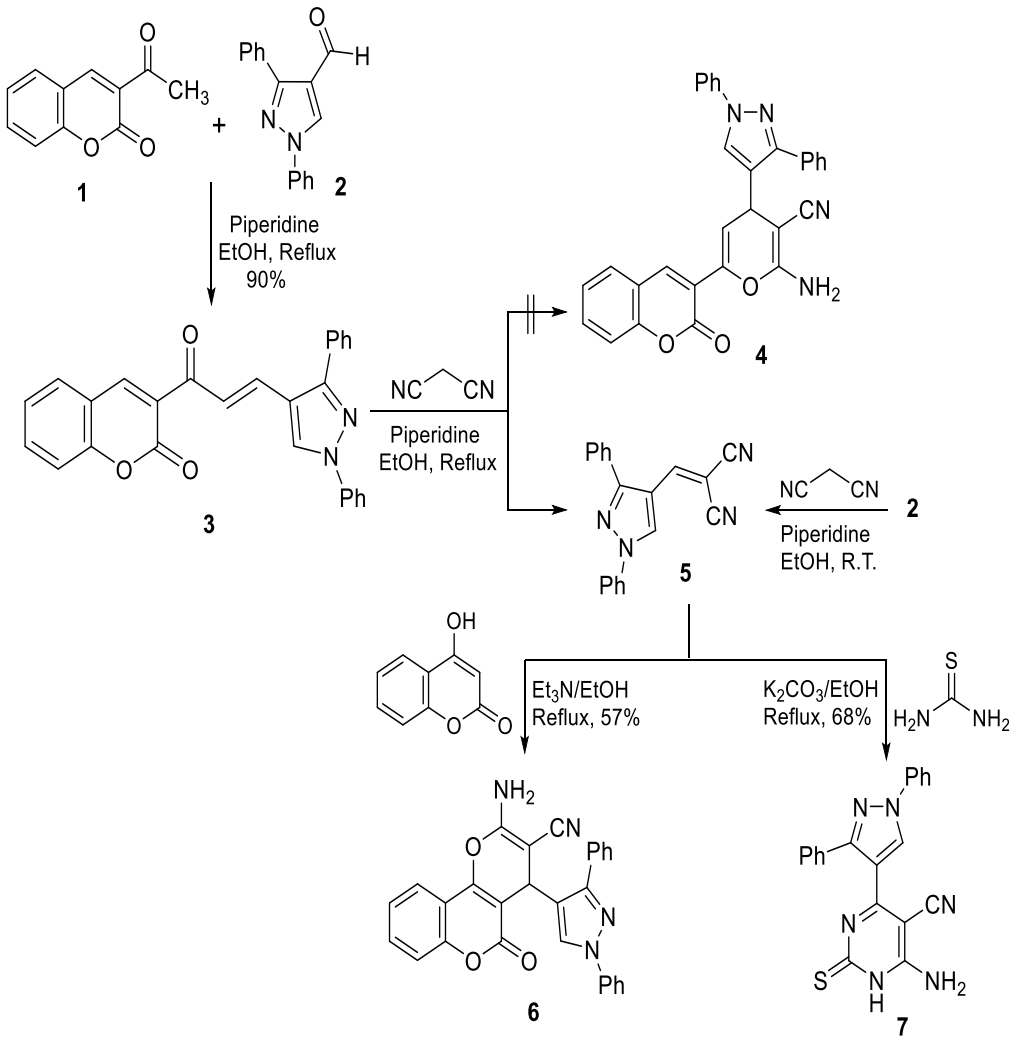
A novel series of fused and pyrazole-based heterocyclic systems like chromenopyran, chromenodiazepine, diazepine, chromenopyrimidine, triazepinethione, benzodiazepine, and pyrimidopyrimidine derivatives, was prepared from the chalcone derivative namely, 3-(3-(1,3-diphenyl-1*H*-pyrazol-4-yl)acryloyl)-2*H*-chromen-2-one **(**cf. **Schemes 1-4)**.

Treating the chalcone **3** with malononitrile in boiling ethanol and piperidine failed to produce 2-amino-3-cyanopyran derivative **4** and afforded the arylidene malononitrile **5** as a sole product which was identical in all respects with an authentic sample prepared from condensation of pyrazole aldehyde **2** with malononitrile at an ambient temperature. In turn, the pyranochromene derivative **6** was obtained upon cyclocondensation of compound **5** with 4-hydroxycoumarin in boiling ethanol and triethylamine. It was worthy that, cyclocondensation reaction of compound **5** with thiourea in boiling ethanol including anhydrous potassium carbonate led to the formation of 6-aminopyrimidin-5-carbonitrile derivative **7** (**Scheme 1**).

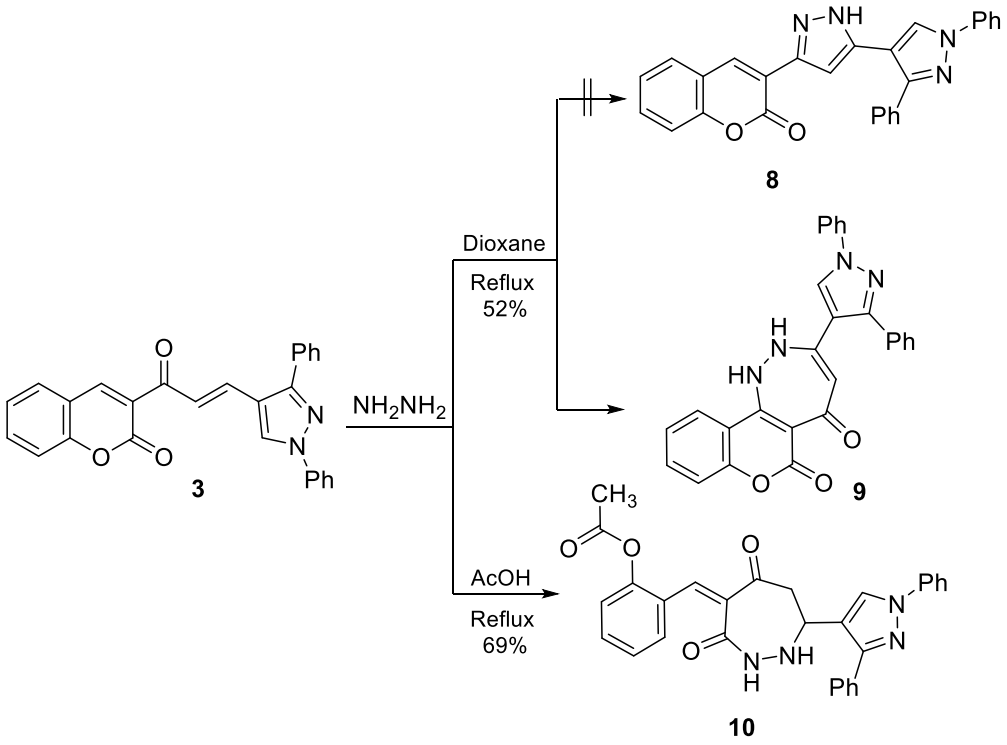
When chalcone **3** was treated with hydrazine in boiling dioxane, chromenodiazepine derivative **9** was obtained instead of 3-coumarinyl-5-pyrazolylpyrazole derivative **8** ,Derivative **10** was

obtained when chalcone **3** refluxed with hydrazine hydrate in glacial acetic acid (**Scheme 2**). The reaction of chalcone **3** with thiourea was not successful in boiling dioxane while in boiling sodium ethoxide acquired the chromenopyrimidine derivative **12** instead of pyrimidinethione derivative **11** (**Scheme 3**).

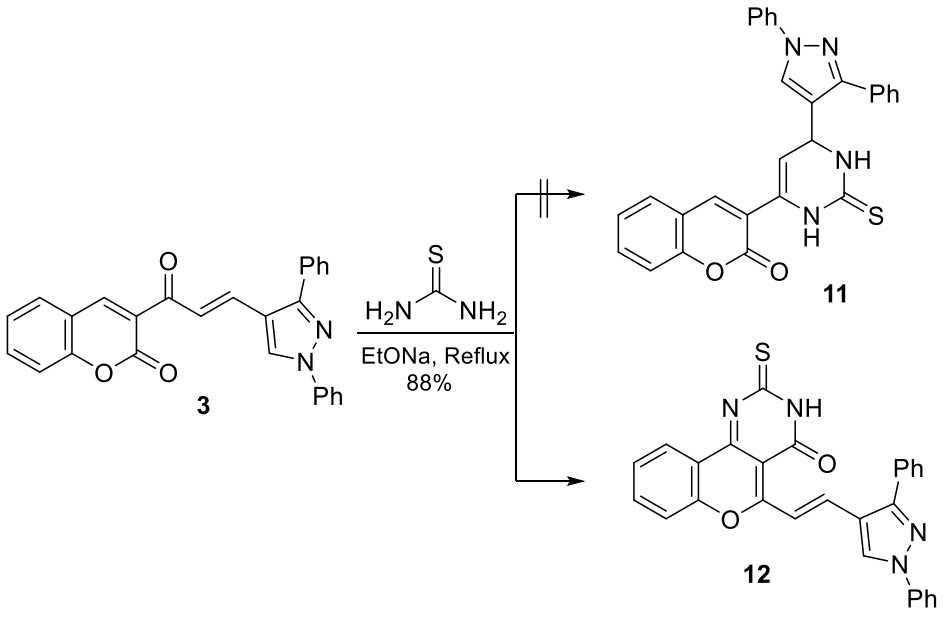
Interaction of chalcone **3** with thiosemicarbazide in boiling dioxane failed to furnish the pyrazole derivative **13** and afforded the triazepinethione derivative **14**. In a similar manner, 2-aminoaniline reacted with chalcone **3** in boiling dioxane to provide benzodiazepine derivative **15.** In contrast, pyridopyrimidine derivative **17** was obtained instead of pyridopyrimidine derivative **16** upon treating chalcone **3** with 6-aminothiouracil in boiling dioxane including piperidine (**Scheme 4**). All synthesized compounds were characterized by using IR, $^{1}$H NMR, and the mass spectra. DFT study was investigated for the synthesized compounds.


Piperidine
EtOH, Reflux
90%
Piperidine
EtOH, Reflux
Piperidine
EtOH, R.T.
Et3N/EtOH
Reflux, 57%
K2CO3/EtOH
Reflux, 68%

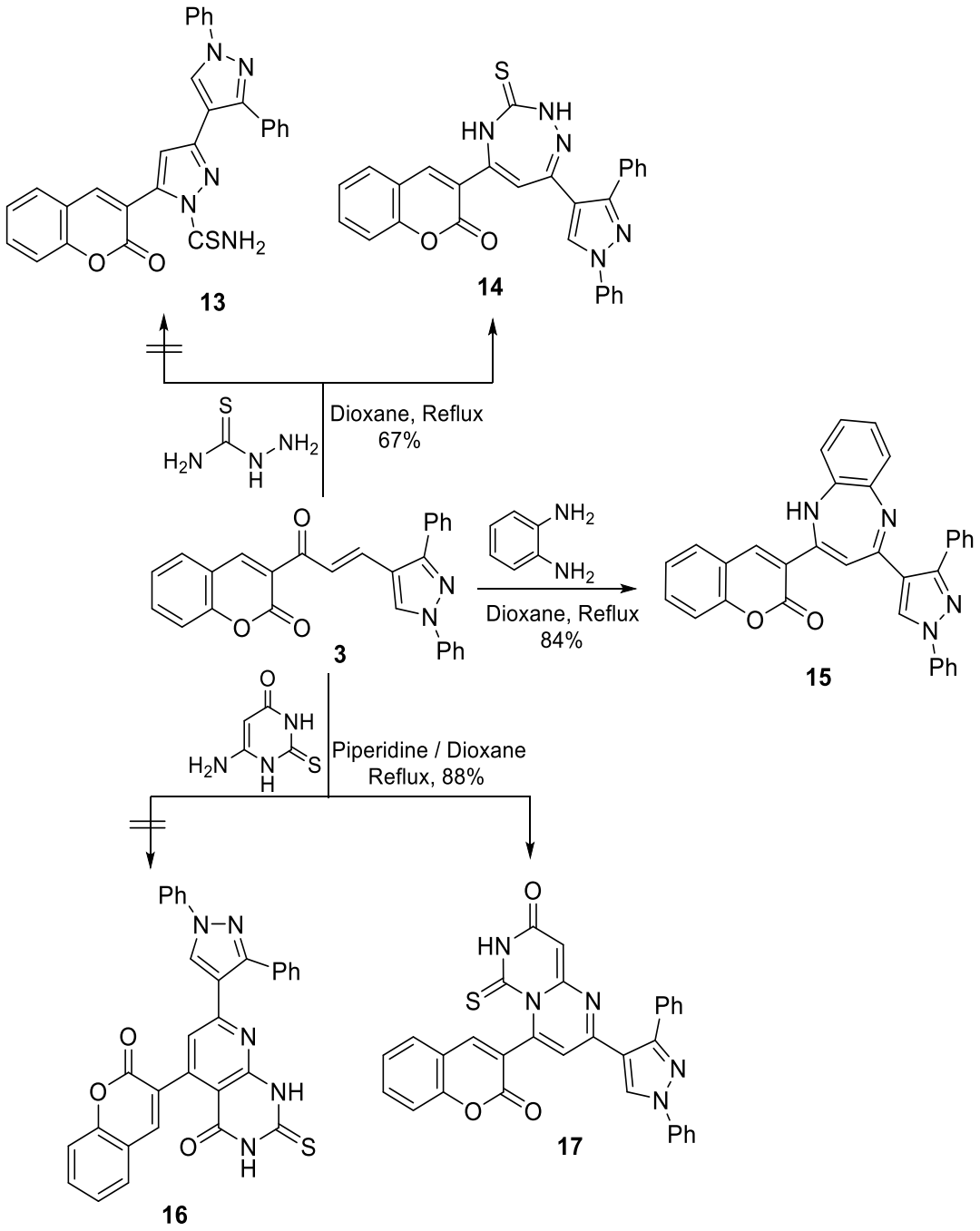
**Scheme 1**




**Scheme 2**




**Scheme 3**




**Scheme 4**

The antiproliferative screening of the synthesized compounds was measured against two tumor cell lines (Hepatocellular carcinoma (HepG2) and Mammary gland breast cancer (MCF7)

using MTT assay. The results showed that the most potent compounds against two cell lines were compounds **9** and **17** as compared to doxorubicin. The compounds **6**, **12**, and **15** were moderately potent against HepG2 cell line. Moderate activity was shown against MCF7 cell line by the compounds **12**, **14**, and **15**. The rest of compounds displayed weak activity.

## Part II:Synthesis of 2-cyano-*N*-((2-oxo-1,2-dihydroquinolin-3-yl)methylene)acetohydrazide

In this part, a novel series of quinoline-based heterocycles was synthesized using the cyanoaceto-hydrazone building block **(**cf. **Schemes 5)**. The cyanoaceto-hydrazone derivative **20** was synthesized by condensation of 2-oxo-3-formylquinoline (**18)** with cyanoaceto-hydrazide (**141)** in refluxing dioxane (**Scheme 5**). The quinoline-cyanoacetohydrazone **20** was isolated a mixture of anti/syn isomers, which was heated under reflux in acetic acid glacial to give the pyrazole derivative **21**.

Condensation of cyanoaceto-hydrazone derivative **20** and 4-methoxybenzaldehyde or 1,3-diphenylpyrazole-4-carbaldehyde in dioxane including piperidine at room temperature afforded compounds **22a**,**b**, respectively. The pyridine derivative **23** was obtained by heating a solution of derivative **22a** and malononitrile in dioxane containing triethylamine, while the reaction of derivative **22a** and hydrazine hydrate in boiling dioxane furnished the aminopyrazole derivative **24**. Stirring a mixture of **20** and 2-

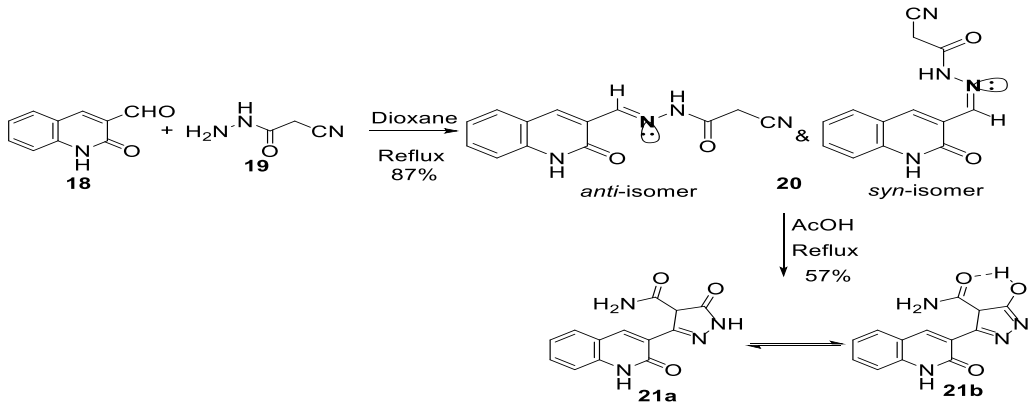
hydroxybenzaldehyde in dioxane and piperidine at room temperature gave the iminochromene derivative **26**. The reaction of compound **20** with arylidene malononitrile **5** in dioxane including triethylamine achieved the pyridine derivative **28**. In turn, interaction of compound **20** with ethyl 2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)acrylate **(29)** in dimethylformamide including triethylamine provided the hydroxypyridone derivative **31** (cf. **Scheme 6**).

Noteworthy, treating a solution of compound **20** with ethyl acetoacetate in dimethylformamide including piperidine led to the formation of pyridinedione derivative **33**. The reaction of **20** and malononitrile in dimethylformamide containing triethylamine acquired the triazolopyridone derivative **35**. On the other hand, cyclocondensation of compound **20** with malononitrile and elemental sulfur in dimethylformamide including triethylamine led to the construction of thiophene derivative **36**. Heating a solution of compound **20** and phenyl isothiocyanate in dimethylformamide containing triethylamine furnished the pyrimidine derivative **37**.

Interestingly the phenylcarbamodithioate derivative **39** (instead of thiazoline derivative **38**) was obtained *via* interaction of compound **20**, elemental sulfur and phenyl isothiocyanate in dimethylformamide containing triethylamine (cf. **Scheme 7)**.

Treating compound **20** with hydrazine-hydrate in dimethylformamide gave the triazolopyrazoloquinoline derivative **41** instead of aminopyrazole derivative **40**. Condensation of

compound **41** with 4-methoxybenzaldehyde in dioxane and triethylamine afforded the oxirane derivative **42**. Hydrazinolysis of compound **20** or quinoline aldehyde **18** and hydrazine in dioxane furnished the azine derivative **43**. Finally, reaction of compound **20** with phenylhydrazine reflux in dioxane failed to construct aminopyrazole derivative **44**, and afforded the phenylhydrazone derivative **45**, which was confirmed with an authentic sample prepared from reflux of **18** with phenylhydrazine in dioxane **(**cf. **Scheme 8)**.




**Scheme 5**