جـــامعة الفـــيوم
Fayoum University
Faculty of Science
Chemistry Department

Synthesis And Reaction Of Some Heterocyclic Derivatives Containing Phthalazine Nucleus, With Expected Biological Activity.

By

Samar Ahmed Mohamed Mohamed

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SYNTHESIS AND REACTION OF SOME HETEROCYCLIC DERIVATIVES CONTAINING PHTHALAZINE NUCLEUS, WITH EXPECTED BIOLOGICAL ACTIVITY.

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Samar Ahmed Mohamed Mohamed

B.Sc. in Chemistry (Special Chemistry),

Fayoum University (2013)

Prof. Dr. Ahmed Yousef El-Kady,

Prof. of Organic Chemistry, Chemistry Department,

Faculty of Science, Fayoum University

Signature:

Prof. Dr. Abdelmoneim Abdelsalam Makhlouf,

Prof. of Organic Chemistry, Chemistry Department

Faculty of Science, Fayoum University.

Signature:

Vice dean for graduate studies and research

Prof. Dr/ Mohammed Saied Abu El-Ghar

Approval Sheet

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Faculty of Science, Fayoum University.

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SYNTHESIS AND REACTION OF SOME HETEROCYCLIC WITH DERIVATIVES CONTAINING PHTHALAZINE NUCLEUS, EXPECTED BIOLOGICAL ACTIVITY

Phthalazine and phthalazinone derivatives are of utmost importance owing to their significant biological activities and pharmacological properties. Herein, benzoic acid derivative **2**, benzoxazin-1-one derivative **3**, and oxophthalazin-2(1*H*)-yl)acetohydrazide **13** were utilized as precursors to construct a novel series of phthalazinones bearing various valuable function groups in excellent yields *via* several simple and promising approaches. Finally, the antimicrobial activity of newly-synthesized phthalazines was screened against different microbial strains; namely, Gram-negative and Gram-positive bacteria utilizing Amoxicillin as a standard drug.

The thesis consists of the following parts:

1) **Summary**

2) **Introduction:**

In this section brief literature review of different preparation methods and reactions of phthalazine derivatives were discussed.

3) **Results and Discussion**

It deals with the discussion of the experimental methods adopted for the synthesis of the designed compounds as well as the different analytical methods applied for the characterization of the new compounds.

In this part the author synthesized 2-(4-isopropylbenzoyl)benzoic acid **(2)** by the reaction of cumene with phthalic anhydride under Friedel Craft's condition. Condensation of benzoic acid derivative **2** with hydrazine hydrate in boiling ethanol afforded the target compound 4-(4-isopropyl phenyl)phthalazin-1(2*H*)-one **(4)**.

Behavior of 2-(4-isopropylbenzoyl)benzoic acid (2) toward nitrogen nucleophiles: (Scheme 1)

(1) Reaction with hydroxylamine hydrochloride:

Reaction of 2-(4-isopropylbenzoyl)benzoic acid **2** with hydroxylamine hydrochloride in pyridine produced 4-(4-isopropylphenyl)-1*H* benzo[*d*][1,2]oxazin-1-one **(3)**.

(2) Reaction with hydrazine hydrate:

Reaction of 2-(4-isopropylbenzoyl)benzoic acid with hydrazine hydrate in ethanol yielded 4-(4-isopropyl phenyl)phthalazin-1(2*H*)-one **(4).**

(3) Reaction with thiosemicarbazide:

Reaction of 2-(4-isopropylbenzoyl)benzoic acid (**2)** with thiosemicarbazide under reflux for 10 hours in pyridine afforded 4-(4-isopropylphenyl)-1-oxophthalazine-2(1*H*)-carbothioamide **(5).**

(4) Reaction with thiocarbonohydrizde:

Attempts were effort to cyclize compound **2** in refluxing pyridine and thiocarbonohydrizde afforded 4-(4-isopropylphenyl)-1-oxophthalazine-2(1*H*)-carbothiohydrazide **(6)** which was formed *via* elimination of two water molecules.

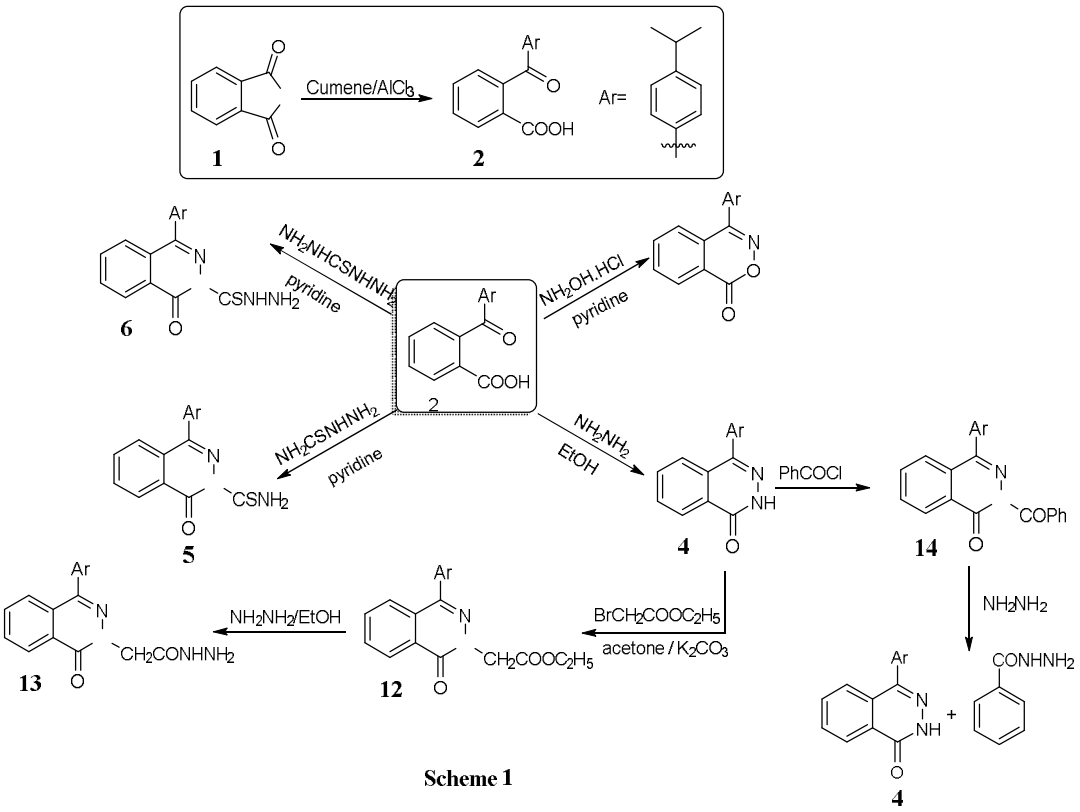
Behavior of 4-(4-Isopropyl phenyl)phthalazin-1(2*H*)-one (4) toward carbon electrophiles: (Scheme 1)

(a) Reaction with ethyl bromoacetate:

Phthalazinone **4** was treated with ethyl bromoacetate to afford the corresponding phthalazine acetic acid ethyl ester **12**. On other hand, the structure of the esters **12** was established chemically *via* the interaction with hydrazine hydrate to afford 2-(4-(4-isopropylphenyl)-1-oxophthalazin-2(1*H*)-yl)acetohydrazide **(13).**

(b) Reaction with benzoyl chloride:

When phthalazinone **4** and benzoyl chloride were refluxed on steam bath the product obtained was identified as 2-benzoyl-4-(4-isopropylphenyl)phthalazin-1(2*H*)-one **(14)**. Hydrazinolysis of compound **14** with hydrazine hydrate in ethanol gave a mixture of benzoyl hydrazine and phthalazinone **4**.



Scheme 1

(I)Behavior of 4-(4-Isopropylphenyl)-1*H*-benzo[*d*][1,2]oxazin-1-one (3) toward nitrogen nucleophiles: (Scheme 2)

(a) Reaction with ammonium acetate:

Amonolysis of benzoxazinone **3** was carried out through its fusion with ammonium acetate at 150 ^{o}C to afford phthalazinone **4**.

(b) Reaction with benzylamine:

The preparation of 2-benzyl-4-(4-isopropylphenyl)phthalazin-1(2*H*)-one **(7)** was achieved through the reaction of benzoxazinone **3** with benzyl amine in ethanol.

(c) Reaction with thiosemicarbazide:

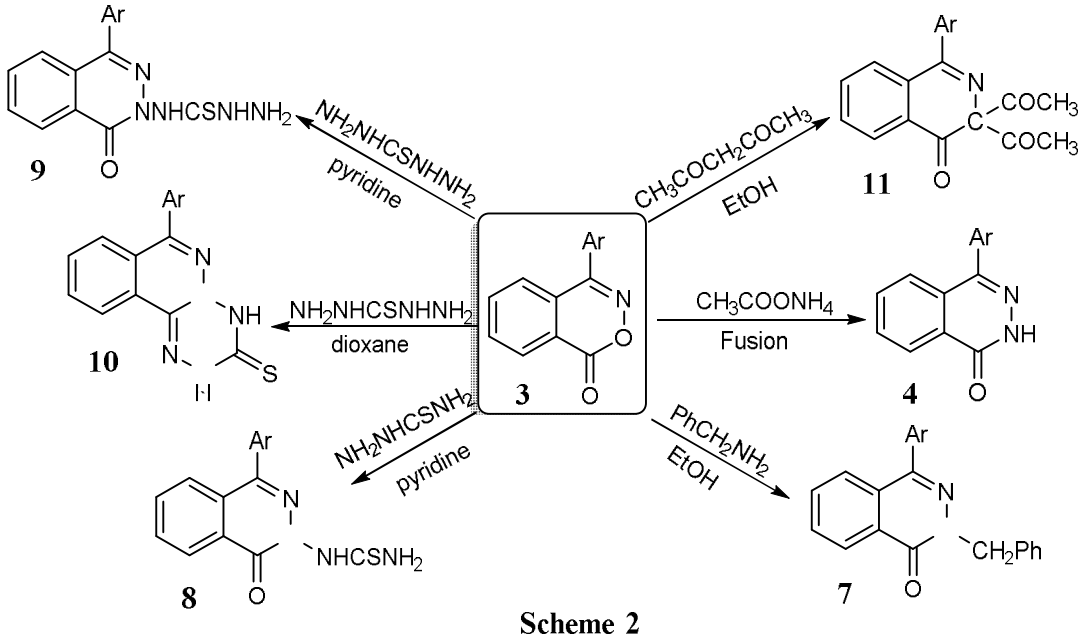
The reaction of benzoxazinone **3** with thiosemicarbazide under reflux for 10 h in boiling pyridine afforded 1-(4-(4-isopropylphenyl)-1-oxophthalazin-2(1*H*)-yl)thiourea **(8)**.

(d)Reaction with thiocarbonohydrizde:

Benzoxazinone **3** reacted with thiocarbonohydrizde in pyridine to produce *N*-(4-(4-isopropylphenyl)-1-oxophthalazin-2(1*H*)-yl)hydrazinecarbothioamide **(9)**. A new fused tricyclic system containing the tetrazino moiety **10** was obtained through the effect of thiocarbonohydrizde on benzoxazinone **3** under reflux in dioxane to give 7-(4-isopropylphenyl)-2*H*-[1,2,4,5]tetrazino[6,1-a]phthalazin-3(4*H*)-thione **(10)**.

(ii) Reaction with carbon nucleophile:

The behaviour of benzoxazinone **(3)** toward carbon nucleophiles exemplified acetylacetone in basic medium gave 1,1'-(1-(4-isopropylphenyl)-4-oxo-3,4-dihydroisoquinoline-3,3-diyl)bis(ethan-1-one) **(11)**.



Scheme 2

Behavior of 2-(4-(4-Isopropylphenyl)-1-oxophthalazin-2(1*H*)-yl)acetohydrazide (13) toward carbon electrophiles: (Scheme 3and 4)

(a) Reaction with aromatic aldehydes:

To get a new series of expected biologically active Schiff bases it was interest to condense hydrazide **13** with different aromatic aldehydes; namely, benzaldehyde, *p*-chlorobenzaldehyde, or *p*- nitro benzaldehyde in ethanol to give the corresponding Schiff bases **15a-c**, respectively.

Cyclization of aryl methylidene hydrazide derivatives **15a–c** by boiling with acetic anhydride afforded the oxadiazole derivative **16a -c**.

(b) Reaction with carbon disulphide:

Cyclization of **13** using carbon disulphide in alcoholic potassium hydroxide gave the corresponding oxadiazolo-2-thione derivative **17**.

(c) Reaction with triethylorthoformate:

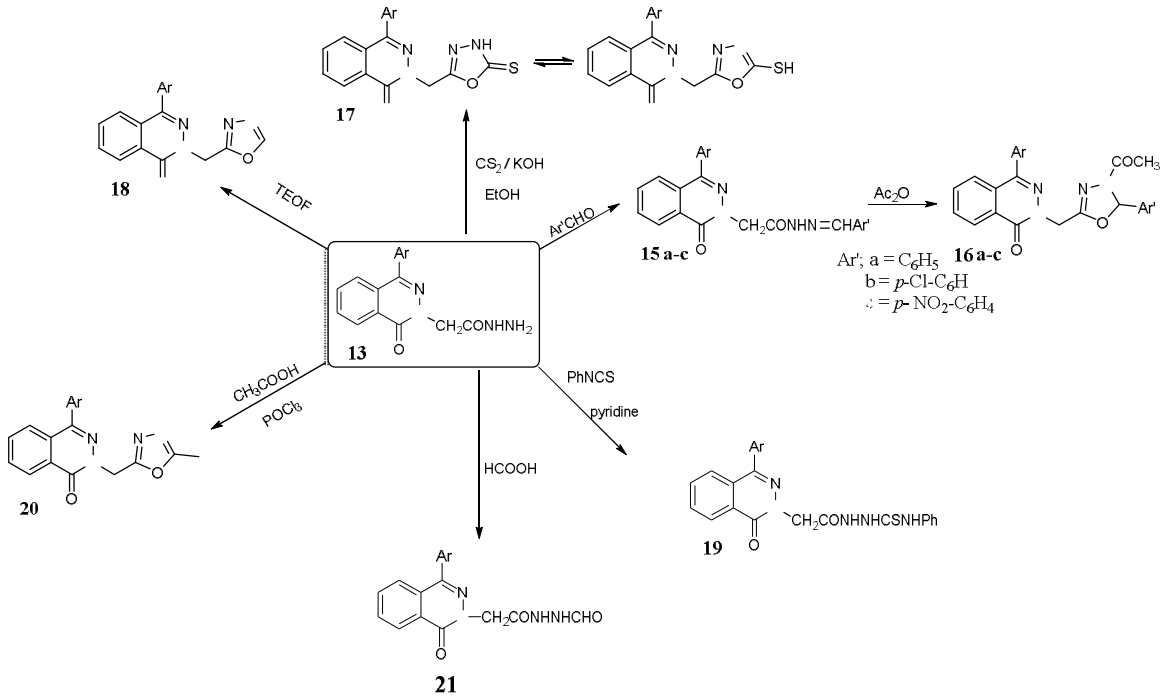
The hydrazide derivative **13** reacted with triethylorthoformate to afford the corresponding oxadiazole derivative **18**.

(d)Reaction with phenyl isocyanate:

The hydrazide derivative **13** reacted with phenyl isothiocyanate to give the corresponding thiocarbamate derivative **19.**

(e) Reaction with carboxylic acid derivatives:

The interaction of hydrazide **13** with acetic acid in presence of phosphorus oxychloride afforded oxadiazolophthalazine derivative **20**. On the other hand interaction of hydrazide **13** with formic acid afforded *N*′-formyl-2-(4-(4-isopropylphenyl)-1-oxophthalazin-2(1*H*)-yl)acetohydrazide**(21)**.



Scheme 3

(f) Reaction with acetyl acetone, diethylmalonate and malononitrile:

Interaction of hydrazide **13** with acetyl acetone, diethylmalonate and malononitrile afforded the corresponding pyrazole derivatives **22-24**.

(g) Reaction with phthalic anhydride:

Compound **13** reacted with phthalic anhydride as the dicarbonyl compound in cyclic structure to afford *N*-(1,3-dioxoisoindolin-2-yl)-2-(4-(4-isopropylphenyl)-1-oxophthalazin-2(1*H*)-yl)acetamide **(25)**.

(h) Reaction with Acrylonitrile:

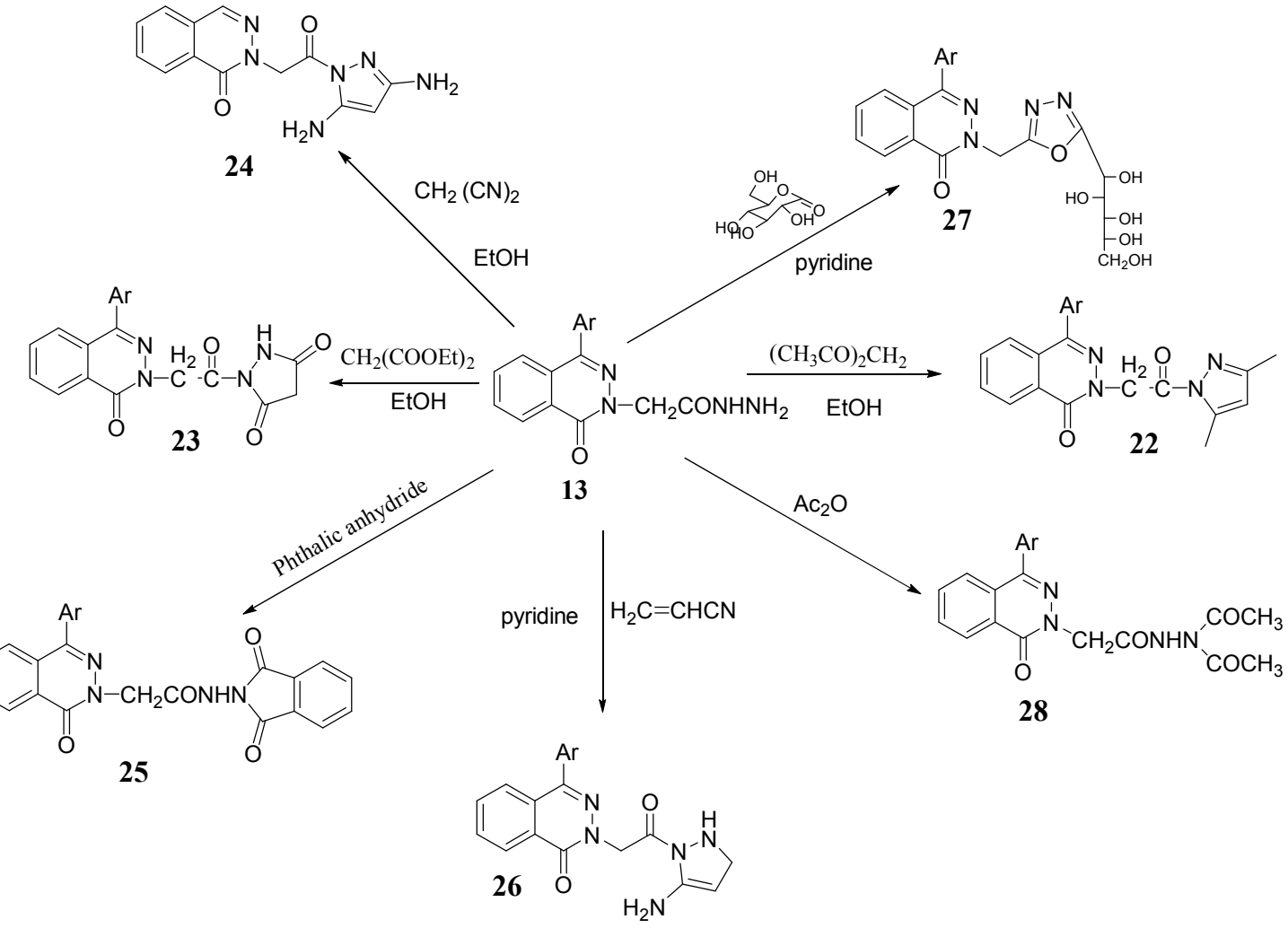
The hydrazide derivative **13** reacted with acrylonitrile to yield 2-(2-(5-amino-2,3-dihydro-1*H*-pyrazol-1-yl)-2-oxoethyl)-4-(4-isopropylphenyl)phthalazin-1(2*H*)-one **(26).**

i)Reaction with D-glucono-1,5-lactone:(

When the hydrazide **13** was allowed to react with D-glucono-1,5-lactone in pyridine it gave rise *C*-Nucleoside **27**.

(j) Reaction with Acetic anhydride:

Acetylation of hydrazide **13** with acetic anhydride gave *N′*,*N′*-diacetyl-2-(4-(4-isopropylphenyl)-1-oxophthalazin-2(1*H*)-yl)acetohydrazide (**28**).



Scheme 4

Finally, the antimicrobial activity of newly-synthesized phthalazines was screened against different microbial strains; namely, Gram-negative and Gram-positive bacteria utilizing Amoxicillin as a standard drug.