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Synthesis of Some Heterocyclic Compounds with Mixed System and Relevant Compounds

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Approval Sheet

Synthesis of Some Heterocyclic Compounds with Mixed System and Relevant Compounds

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CONTENTS

List of Abbreviations

Abbreviations	Name
DCM	Dichloro methane
THF	Tetrahydro furane
m- CPBA	m-Chloroper benzoic acid
DCC	N,N-Dichlorohexyl carbodiimid
TSCl	Tosyl chloride
NMM	N-Methyl morphline

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Synthesis and anticancer activity of novel quinazolinone and benzamide derivatives

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Abstract

In trying to develop new anticancer agents, a series of quinazolinone and benzamide derivatives were synthesized via reaction of 6-iodo-2-phenyl-4*H*-benzoxazin-4-one with nitrogen nucleophiles, namely, formamide, ammonium acetate,hydrazine hydrate, hydroxylamine hydrochloride, substituted aromatic amines, benzyl
amine, and/or thiocarbonohydrazide. All compounds were fully characterized bymeans of IR, MS, and 1H-NMR spectra. Some of the synthesized compounds wereevaluated in vitro for their anti-proliferative activity against HePG-2 and MCF-7 celllines. 2-(Benzoylamino)-*N*-(4-hydroxyphenyl)-5-iodobenzamide and tetrazino[1,6-
c]quinazoline-3(4*H*)-thione derivative were the most potent against the two cancer cells comparable to that of doxorubicin. Most of the synthesized compounds also exhibited good cytotoxic activity.

Keywords Anticancer activity · Quinazolin-4(3*H*)-one · Benzoxazinone · Hepatocellular carcinoma · Michigan Cancer Foundation-7

Introduction

Pharmacologically, quinazolin-4-ones are among the most important classes of heterocyclic compounds. The stability of the quinazolinone nucleus has inspired medicinal chemists to introduce many bioactive moieties to this nucleus to synthesize new potential medicinal agents. The quinazolinone skeleton is a frequently

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Abstract

6-Iodo-2-phenyl-4H-3, 1 benzoxazin-4-one was utilized to construct a variety of new quinazoline-4(3H)-one derivatives *via* reaction with some nitrogen nucleophiles namely, formamide, ammonium acetate, hydrazine hydrate, hydroxylamine hydrochloride, substituted aromatic amines, benzyl amine, and / or thiocarbonohydrazide. Some of quinazolin -4(3H)-one derivatives utilize to syntheses new acetohydrazide derivative, which react with different electrophilic reagent to give different heterocyclic compounds. All the compounds were fully characterized by means of IR, MS, and ^{1}H-NMR spectra. In trying to develop new anticancer agents, a series of quinazolinone derivatives were evaluated in *vitro* for their anti-proliferative activity against HePG-2 and MCF-7 cell lines. Tetrazino[1,6-c]quinazoline-3(4H)-thione **5**, 2-(benzoylamino)-N-(4-hydroxyphenyl)-5-iodobenzamide **10**, and triazolothiadiazin-2-phenylquinazolinone derivative **41** were the most potent against the two cancer cells comparable to that of doxorubicin. Most of the synthesized compounds also exhibited good cytotoxic activity.

SUMMARY

The work can be divided into three main parts:-

i- Chemical behaviour of benzooxazinone towards different nucleophiles.

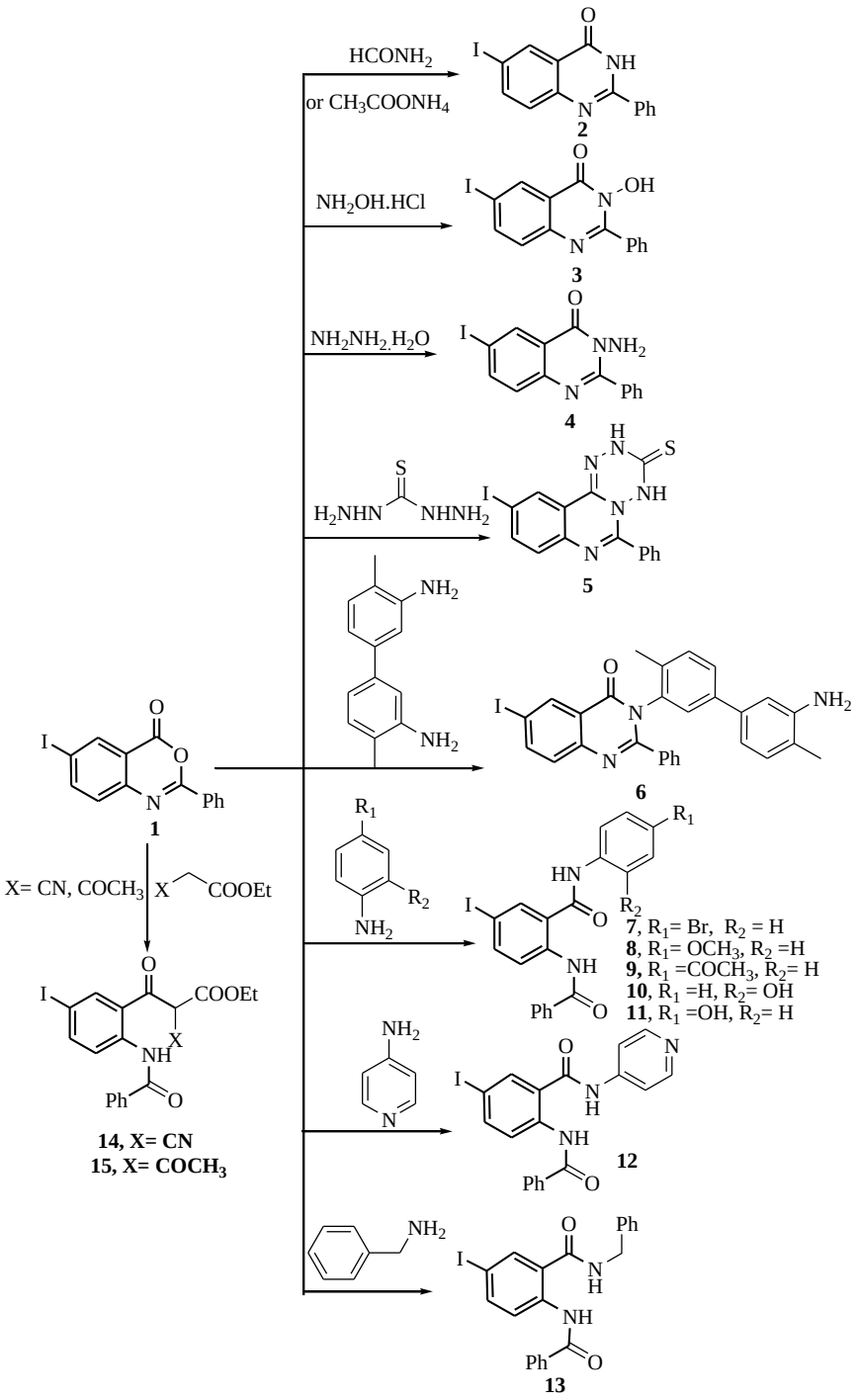
ii- Reactivity of quinazolinone towards electrophilic reagents

iii- Reactivity of acetohydrazide derivative

First part: Chemical behaviour of benzooxazinone towards different nucleophiles

6-Iodo-2-phenyl-4H-benzoxazin-4-one **1** was prepared from stirring 5-iodoanthranilic acid with benzoyl chloride in dry pyridine at room temperature. Aminolysis of benzoxazinone **1** was conducted through its reaction with formamide and / or fusion with ammonium acetate at 150 °C to afford quinazolinone **2**. When benzoxazinone **1** reacted with hydroxylamine hydrochloride in pyridine and / or hydrazine hydrate, quniazolinone derivatives **3** and **4** was obtained, respectively. A new fused tricyclic system containing the tetrazino moiety **5** was obtained through the effect of thiocarbonohydrazide on benzoxazinone **1**.

On the other hand, treatment of benzoxazinone **1** with some nitrogen nucleophiles namely, 3'-amino-4,4'-dimethyl-1,1'-biphenyl-3-ylamine, p-bromoaniline, p-anisidine, p-aminoacetophenone, p-aminophenol, o-aminophenol, p-aminopyridine and /or benzylamine in ethanol under reflux afforded quinazolinone derivative **6** and / or 5-iodobenzamide derivatives **7-13**. The behaviour of benzoxazinone **1** towards carbon nucleophiles exemplified by ethyl cyanoacetate and / or ethyl acetoacetate in dry pyridine get compounds **14** and **15** respectively [cf. scheme I].

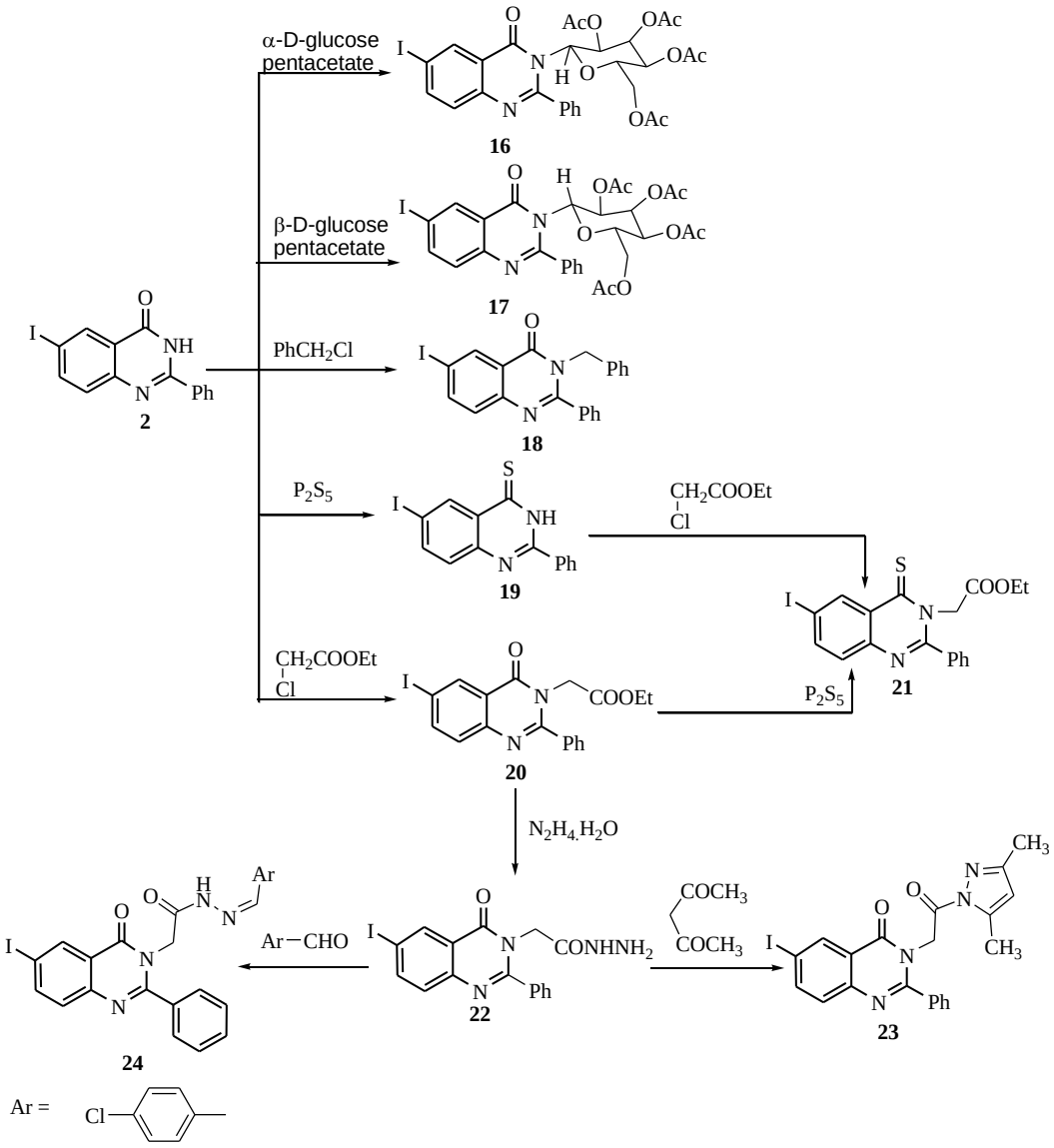


Scheme I

<u>Second part</u>: Reactivity of quinazolinone towards electrophilic reagents

Glycosylation of quinazolinone **2** with α-D-glucose pentaacetate and / or β-D-glucose pentaacetate in ethanol gave glycosides **16** and **17**, respectively. Also, when quinazolinone **2** was submitted to react with benzyl chloride in ethanol under refluxing temperature, 3-benzyl-4(3*H*)-quinazolinone **18** was isolated.

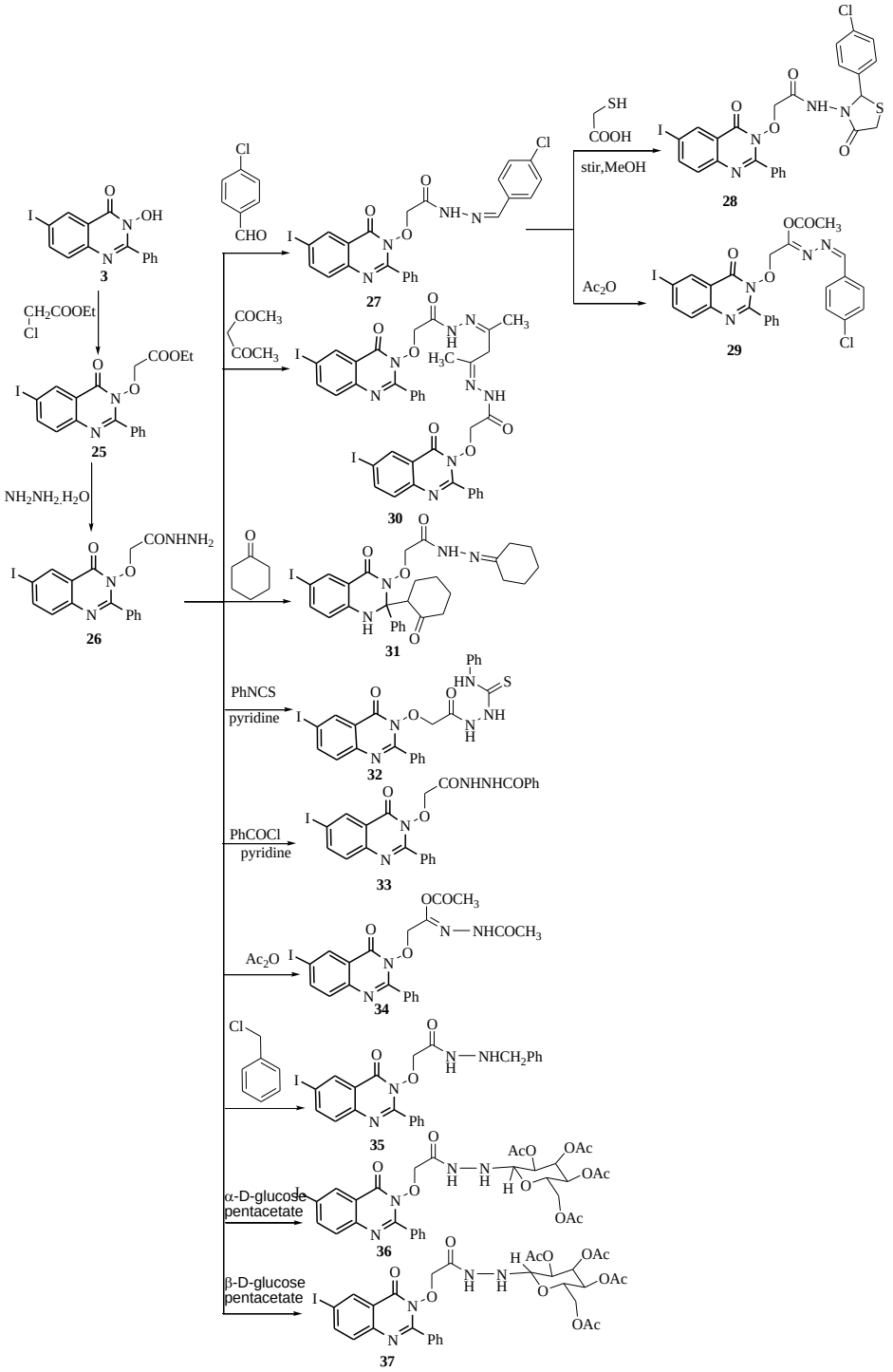
Thiation of quinazolinone **2** with phosphorus pentasulfide in dry toluene gave quinazolinthione **19**, Reaction of the latter compound and / or quinazolinone **2** towards carbon electrophile namely ethyl chloroacetate in the presence of anhydrous K_2CO_3 in dry acetone afforded the corresponding N-alkyl derivatives **20** and **21** respectively. It was found that the thiation proceeded *via* reaction of N-alkyl derivative **20** with phosphorus pentasulfide in dry toluene to afford the corresponding thiated compound **21**. Hydrazinolysis of N-alkyl derivative **20** with hydrazine hydrate in ethanol gave acetohydrazide **22**. The latter compound has been allowed to react with acetyl acetone and / or p-chlorobenzaldehyde to afford pyrazole derivative **23** and the hydrazone derivative **24**, respectively [cf. scheme II].



Scheme II

<u>Third part</u>: Reactivity of acetohydrazide derivative

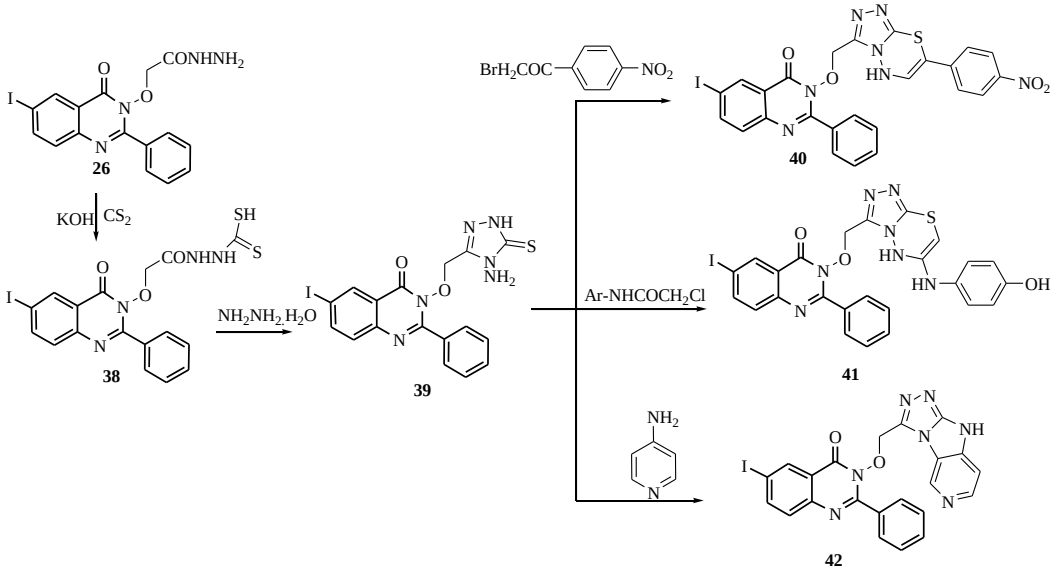
The behavior of quinazolinone **3** towards carbon electrophile namely ethyl chloroacetate in the presence of anhydrous K_2CO_3 in dry acetone has been investigated to afford the corresponding O-alkyl derivative **25**. Hydrazinolysis of O-alkyl derivative **25** with hydrazine hydrate in ethanol gave acetohydrazide **26**. Condensation of acetohydrazide **26** with p-chlorobenzaldehyde in ethanol yielded the hydrazone derivative **27**. Cyclization of the latter compound with thioglycolic acid in methanol with stirring at room temperature afforded 4-oxothiazolidinquinazolinone **28**. Acetylation of hydrazone derivative **27** with acetic anhydride gave compound **29**. Reaction of acetohydrazide derivative **26** with acetyl acetone, cyclohexanone, phenyl isothiocyanate, benzoyl chloride, acetic anhydride, benzyl chloride under reflux gave bis compound **30**, compounds **31-35**, respectively. Glycosylation of acetohydrazide **3** with α-D-glucose pentaacetate and / or β-D-glucose pentaacetate in ethanol gave glycosides **36** and **37** respectively [cf. scheme III].



Scheme III

The reaction of acetohydrazide derivative **26** with carbon disulphide in ethanol gave quinazolinone derivative **38.** Hydrazinolysis of latter compound with hydrazine hydrate in ethanol gave triazolquinazolinone derivative **39**. Reaction of triazolquinazolinone derivative **39** and ω-bromo-p-nitro-acetophenone, 2-chloro-N-(4-hydroxyphenyl)acetamide and / or 4-amino pyridine in ethanol to give

compound **40** triazolothiadiazinquinazolinone derivative **41** and / or triazoloimidazopyridinquinazolinone **42**, respectively [cf. scheme IV].



Scheme IV

Biological Activity

In support of our commitment to discover and construct biologically active heterocycles we have screened the antitumor activity of synthesized compounds was evaluated, a series of quinazolinone derivatives were evaluated in *vitro* for their anti-proliferative activity against HePG-2 and MCF-7 cell lines. Tetrazino[1,6-c]quinazoline-3(4H)-thione **5**, 2-(benzoylamino)-N-(4-hydroxyphenyl)-5-iodobenzamide **10**, and triazolothiadiazin-2-phenylquinazolinone derivative **41** were the most potent against the two cancer cells comparable to that of doxorubicin. Most of the synthesized compounds also exhibited good cytotoxic activity.

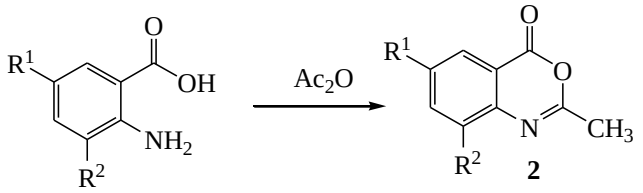
INTRODUCTION

Synthesis of benzoxazine-4-one derivatives:

1. From anthranilic acid derivatives with

1.1. Acetic anhydride

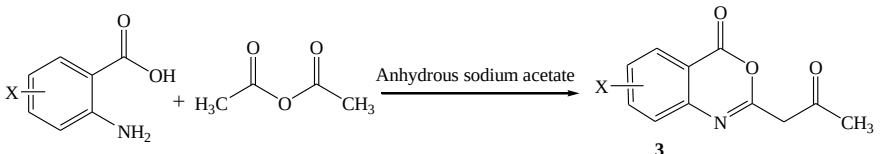
The disubstituted anthranilic acid **1** were allowed to react with acetic anhydride to produce 6,8-disubstitued 2-methyl-4H-benzoxazine-4-one derivatives (**2a-e**) **[Girija, Dr. K. etal, 2010; Mohammed, F.K. etal, 2009; El-Hashash, M.A. etal, 2011; Taylor, E.C.etal, 1960; Bain, D. I. etal, 1968; Finer, J. T. etal, 2001].**



1 **2**

a , R^1 , R^2 = H
b, R^1 , R^2 =Br
C, R^1 ,R^2 =OMe
d, R^1,R^2 = COOH
e , R^1, R^2 = NO_2

The synthesis of 2-acetonyl benzoxazinone (**3**) was obtained by heating of anthranilic acid **1** with excess acetic anhydride in the presence of anhydrous sodium acetate **[Hassan, H. M. 1992; Ubich, H. etal, 1967].**



1 **3**

X = H, Me, Cl, OMe, CF_3, NMe, NO_2

1.2. Acid chlorides

To a solution of anthranilic acid **1** dissolved in pyridine, with benzoyl chloride at room temperature to afford 2-phenyl-4H-benzo[d][1,3]oxazin-4-one (**4**) and also synthesis of 2-substituted 4H-