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Faculty of Science
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Synthesis and Reactions of Some Heterocyclic compounds of Expected Biological Activity

A thesis

**Submitted in partial fulfillment
of the requirements of master degree in chemistry**

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

﴿وَأَنْزَلَ اللَّهُ عَلَيْكَ الْكِتَابَ وَالْحِكْمَةَ وَعَلَّمَكَ مَا لَمْ تَكُنْ تَعْلَمُ وَكَانَ فَضْلُ اللَّهِ

عَلَيْكَ عَظِيمًا﴾

صدق الله العظيم

سورة النساء آية (١١٣)

DEDICATION

To

My Husband



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Dear: Esraa A. Abdel-Wahab

Your article Studies on 4 H-3,1 benzoxazin ones.
A convenient synthesis of novel heterocycles
with antimicrobial activity.

2

By

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2

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Sincerely yours

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Prof. A.A. Salem

ABSTRACT

N-(2-(4-chlorophenyl)-1-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)vinyl)-2-(1,3-dioxoisindolin-2-yl)acetamide **2** was synthesized by treatment of anthranilic acid with (Z)-2-((4-(4-chlorobenzylidene)-5-oxo-4,5-dihydrooxazol-2-yl)methyl)isoindoline-1,3-dione **1** in boiling butanol. The reactions of **2** with nitrogen and carbon nucleophiles and with carbon electrophiles was investigated.

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TABLE OF CONTENTS

1. SUMMARY	i
2. AIM OF THE WORK.....	iii
3. INTRODUCTION	1
1. Importance of 4H-3,1-benzoxazin-4-ones.....	1
1.1 Pharmaceutical applications of 4H-3,1-benzoxazin-4-ones	1
1.2 Industrial applications	3
2. Synthesis of 4H-3,1-benzoxazin-4-ones	3
2.1 From anthranilic acids	3
2.1.1 Via the action of acid chlorides on anthranilic acid	3
2.1.2 Via the action of acid anhydrides on anthranilic acid	8
2.1.3 Via reaction of anthranilic acid with aromatic carboxylic acid	11
2.1.4 Reaction of substituted anthranilic acid with Boc-protected amino acids	12
2.1.5 Reaction of substituted anthranilic acid with 2,2-dihydro fluoroalkanoic acid	13
2.1.6 Synthesis of Bis(411)-3,1-benzoxazin-4-one derivatives :-	13
2.1.7 From interaction of anthranilic acid with heterocyclic compounds	14
2.1.7.1 From 4-arylidene-2-aryl-oxazolin-5-one	14
2.1.7.2 From iminodithiazole	14
2.1.7.3 From (4H)-3,2-benzoxazin-4-one	15
2.1.7.4 From 3- methyl-2-(ethoxycarbonylmethoxy) quinoxaline	15
2.1.7.5 From 2-ethoxycarbonyl-4(3H)-quinazolin-4-one	15
2.1.7.6 From substituted coumarin.....	16
2.1.7.7 From hetero-ring opening of furanone derivatives	17
2.1.7.8 From hetero-ring opening of 1,3-dioxin-4-one derivatives	17
2.2 From N-acylanthranilic acid.....	17
2.2.1 Acetic anhydride as cyclizing agent.....	17
2.2.2 Thionyl chloride as cyclizing agent	18
2.2.3 Vilsmeier reagents as cyclizing agent.....	18
2.2.4 Cyanuric chloride as cyclizing agent.....	19
2.2.5 Dicyclohexylcarbodiimide as cyclizing agent.....	19
2.3 From 2-methyl-4H-3,1-benzoxazin-4-one	20
2.4 From isatoic anhydrides	21
2.4.1 Reaction of isatoic anhydride with acid anhydrides.....	21

2.4.2 Reaction of isatoic anhydride with acid chlorides.....	22
2.4.3 Reaction of isatoic anhydride with phosphoryl- stabilized anions.....	23
2.5 Oxidation of indoles	23
2.6 Miscellaneous.....	24
2.6.1 From β -(Triphenylphosphoranylidene)amino esters	24
2.6.2 From iminophosphorane.....	25
2.6.3 From N-benzenesulphonylanthranilic acid	25
2.6.4 From thioamide derivatives	25
2.6.5 From electrochemical trichloroacetylanilides.....	25
2.6.6 CO ₂ Incorporation reaction using arynes	26
2.6.7 From 2-(1H-1,2,3-benzotrizol-1-yl)phenylethanone	26
2.6.8 From heating of acetylanthranilic acid by microwave	27
2.6.9 Thermolysis of 2-(3-benzoylthioureido)-4,5-dimethoxy benzoic acid	28
2.6.10 Thermally induced cyclization of ketenimines	28
2.6.11 From o-iodoaniline	28
3. Reactions of 4H-3,1-benzoxazin-4-ones.....	30
3.1 Reactions with Hydrogen nucleophiles.....	30
3.2 Reactions with Oxygen nucleophiles.....	30
3.3 Reactions with nitrogen nucleophiles.....	31
3.3.1 Ammonolysis	32
3.3.2 Hydrazinolysis.....	33
3.3.2.1 Reactions with hydrazine hydrate.....	33
3.3.2.2 Reaction with hvdrazine hydrate in presence of carbondisulphide	37
3.3.2.3 Reaction with subsituted hydrazines	38
3.3.2.4 Reactions with hydroxylamine hydrochloride	40
3.3.2.5 Reactions with thiosemicarbazide and aminoguanidines.....	40
3.3.3 Aminolysis	41
3.3.3.1 Reactions with primary nonaromatic amines	41
3.3.3.2 Reactions with secondary amines.....	43
3.3.3.3 Reactions with alkylamines	44
3.3.3.3.1 Reactions with benzylamine	44
3.3.3.3.2 Reactions with phenylethylamine	45
3.3.3.4 Reactions with anilines.....	48
3.3.3.4.1 Reactions with p-bromoanilines	49
3.3.3.4.2 Reactions with p-aminodiphenylamine	49

3.3.3.4.3 Reactions with o-toluidine	49
3.3.3.4.4 Reactions with 2-substituted and/or 2,6-disubstituted anilines	50
3.3.3.4.5 Reactions with anilines containing reactive function groups	51
3.3.3.4.5.1 Reaction with 2-cyanoanilines	51
3.3.3.4.5.2 Reactions with p-aminoacetophenone	52
3.3.3.4.5.3 Reactions with 4-hydroxyanilines	53
3.3.3.4.5.4 Reactions with sulphanilamide	53
3.3.3.5 Reactions with amino heterocyclic compounds	54
3.3.3.6 Reactions with diamines	56
3.3.3.6.1 Reactions with o-phenylenediamine	56
3.3.3.6.2 Reactions with ethylenediamine	58
3.3.3.6.3 Reactions with p-phenylenediamine	58
3.3.3.7 Reactions with aminoacids	59
3.3.3.8 Reactions with aminoalcohols	60
3.3.3.9 Reactions with Schiff's bases	61
3.3.3.10 Reactions with azines	61
3.3.3.11 Reactions with sodium azide	62
3.3.4 Reactions with carbon nucleophiles	62
3.3.4.1 Reactions with Grignard reagents	62
3.3.4.2 Friedel-Crafts reactions	67
3.3.4.3 Reactions with active methylene containing compounds	68
4. DISCUSSION	72
1. Synthesis and reactions of N-(2-(4-chlorophenyl)-1-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)vinyl)-2-(1,3-dioxoisindolin-2-yl)acetamide	72
1.1 The structure of compound (2) was established from the following:	72
1.2 Chemical proven of compound (2)	75
1.2.1 Reaction with amines	75
1.2.1 Hydrazinolysis	79
2. Base catalyzed of 3,1-(4H)-benzoxazinone (2) with active methylene compounds	80
3. Action of sodium azide	80
4. Friedel-Crafts reaction	81
5. Reaction with 2-amino methyl benzimidazole	83
6. Diels-Alder reaction	83

7. Synthesis of quinazolinyl urea	85
8. Synthesis of triazino quinazolinone derivative	85
9. Ammonolysis	88
9.1 Chemical proven of compound (14)	89
9.1.1 Acylation of (14)	89
9.1.2 Acetylation of quinazol-4-one (14)	90
9.1.3 Action of phosphorus pentachloride - phosphorus oxychloride on quinazol-4-one (14)	91
10. Mannish reaction	91
11. Synthesis of ethyl 2-(2-(2-(4-chlorophenyl)-1-(2-(1,3-dioxoisindolin-2-yl)acetamido)vinyl)quinazolin-4-yloxy)acetate	93
11.1 Chemical proven of compound (19)	94
12. Action of phenyl isocyanate on quinazolinone (20)	94
13. Action of p-chlorobenzaldehyde on quinazolinone (20)	95
14. Base catalysed reaction with hydroxylamine hydrochloride	95
14.1 Chemical proven of compound (23)	96
14.1.1 Acetylation of 3-N-hydroxy-4-quinazolone	96
14.1.2 Reaction with ethyl chloroacetate	97
14.1.2.1 Chemical proven of compound (25)	97
15. Action of phenyl isocyanate on quinazolinone (26)	98
16. Action of p-chlorobenzaldehyde on quinazolinone (26)	98
5. BIOLOGICAL ACTIVITY	100
6. BIOLOGICAL ACTIVITY	105
7. EXPERIMENTAL	110
1. Synthesis and reactions of N-(2-(4-chlorophenyl)-1-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)vinyl)-2-(1,3-dioxoisindolin-2-yl)acetamide (2)	110
2. Action of primary amines on (2): formation of (3 _{a-h})	110
3. Action of hydrazines on (2): Formation of (4 _{a,b})	110
4. Action of active methylene on benzoxazinone (2): Formation of 1,4-quinolinone (5)	110
5. Action of sodium azide on benzoxazinone (2): Formation of tetrazole (6)	111
6. Action of aromatic substrates on benzoxazinone (2) in presence of anhydrous AlCl ₃ : Formation of o-arylanilides (7 _{a,b})	111
7. 2-Amino methyl benzimidazole (8)	111
8. Action of (8) on benzoxazinone (2): Formation of 2-substituted- 3-methyl-[2'-benzimidazolyl]-(4H)- 3,1-quinazolin-4-one (9)	111
9. Diels-Alder reaction on (2):	111

10. Synthesis of quinazolinylurea (11)	111
11. Cyclization of quinazolinylurea(12)	112
12. Action of thiosemicarbazide on benzoxazone (2)	112
13. Action of ammonium acetate or formamide on (2):Formation of quinazolone (14)	112
14. Acylation of (14): Formation of (15).....	112
15. Action of acetic anhydride on (14): Formation of 3N-acetyl quinazolone (16)	112
16. Action of phosphorus pentachloride - phosphorus oxychloride on quinazol-4-one (14)	112
17. Mannish reaction on quinazolone (14): Formation of Mannish bases (18).....	112
18. Action of ethyl chloroacetate on quinazolinone (14)	113
19. Action of hydrazine hydrate on quinazolinone (19).....	113
20. Action of phenyl isocyanate on quinazolinone (20).....	113
21. Action of aldehyde on quinazolinone (20)	113
22. Action of hydroxylamine hydrochloride on benzoxazone (2) Formation of 3-hydroxy-4-quinazolone (23)	113
23. Action of acetic anhydride 3-hydroxy quinazolone (23) Formation of (24).....	113
24. Action of ethyl chloroacetate on 3-hydroxy-4-quinazolone (23).....	113
25. Action of hydrazine hydrate on quinazolinone (25).....	114
26. Action of phenyl isocyanate on quinazolinone (26)	114
27. Action of aldehyde on quinazolinone (26)	114
8. REFERENCES.....	123

SUMMARY

This study presents the synthesis of the N-(2-(4-chlorophenyl)-1-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)vinyl)-2-(1,3-dioxoisindolin-2-yl)acetamide (2). It was synthesized by treatment of anthranilic acid with (Z)-2-((4-(4-chlorobenzylidene)-5-oxo-4,5-dihydrooxazol-2-yl)methyl)isoindoline-1,3-dione (1). Amminolysis of (2) gave 2-(substituted)-carbamoyl phenyl acetanilides (3_{a-h}).

The benzoxazinone (2) underwent ring fission of the hetero cyclic ring when heated with hydrazine hydrate and gave the amide derivative (4_a). On the other hand, reaction of (2) with phenyl hydrazine, yielded quinazolinone derivative (4_b).

While treatment of (2) with ethyl acetoacetate gave carbethoxy 3,4-dihydro-1,4-quinolinone derivative (5).

Benzoxazinone (2) reacted with sodium azide and yielded tetrazole (6). While treatment of (2) with anhydrous AlCl₃ in hydrocarbons under the Fridel-Crafts condition reaction gave o-substituted phenyl aryl ketones (7_{a,b}).

On the other hand, Mannich reaction of (2) gave Mannich base (9). While treatment of (2) with dimethyl maleate in dry xylene gave the corresponding Diels-Alder adducts (10).

Otherwise, benzoxazinone (2) was allowed to react with semicarbazide hydrochloride in boiling pyridine which afforded quinazolinyl urea derivative (11). On fusion of the above compound at its melting point it was cyclized to produce triazole quinazoline derivative (12).

Moreover, benzoxazinone (2) was treated with thiosemicarbazide in boiling pyridine and afforded (13).

While ammonolysis of (2) gave the corresponding 2-substituted-4(3H)-quinazol-4-one derivative (14). The lactam-lactim tautomerism of (14) was further demonstrated chemically by studies the effect of alkylating agent, acetic anhydride, a mixture of phosphorus pentachloride and phosphorus oxychloride and Mannich reaction to give 4-(substituted)-2-(substituted)-quinazolin-4-ones (15), 3N-acetyl-2-(substituted)-quinazolin-4-one (16), 2-(substituted)vinyl-4-chloroquinazolin-4-one (17) and the Mannich base 3N-(substituted)-quinazolin-4-one (18) respectively.

Quinazolinone (14) reacts with ethyl chloroacetate in dry acetone and in the presence of dry potassium carbonate to give compound (19) which was further

demonstrated chemically by hydrazinolysis of the ester by hydrazine hydrate to yield the hydrazide derivative (20).

Furthermore, the hydrazide derivative (20) was reacted with phenyl isocyanate in dioxane and p-chlorobenzaldehyde in absolute ethanol and 1ml pipridine to give (21) and (22) respectively.

Benzoxazinone (2) reacted with hydroxylamine hydrochloride in the presence of sodium acetate in boiling ethanol to give N-(2-(4-chlorophenyl)-1-(3-hydroxy-4-oxo-3,4-dihydroquinazolin-2-yl)vinyl)-2-(1,3-dioxoisindolin-2-yl)acetamide (22).

On the other hand, 3-N-hydroxy-4-quinazolone derivative (23) used as a key starting material for synthesis of some interesting heterocyclic compounds and it was further demonstrated chemically by studies the effect of acetic anhydride and ethyl chloroacetate to give 2-(2-(4-chlorophenyl)-1-(2-(1,3-dioxoisindolin-2-yl)acetamido)vinyl)-4-oxoquinazolin-3(4H)-yl acetate (24) and ethyl 2-(2-(2-(4-chlorophenyl)-1-(2-(1,3-dioxoisindolin-2-yl)acetamido)vinyl)-4-oxoquinazolin-3(4H)-yloxy)acetate (25) respectively.

The compound (25) was further demonstrated chemically by hydrazinolysis of the ester by hydrazine hydrate to yield the hydrazide derivative (26).

Moreover, the hydrazide derivative (26) was reacted with phenyl isocyanate in dioxane and p-chlorobenzaldehyde in absolute ethanol and 1ml pipridine to give (27) and (28) respectively.

The structure of all synthesized derivatives compounds is established by: (i) elemental analysis, (ii) IR, (iii) H^1 NMR, (iv) Mass spectra.

Biological activities of some synthesized compounds was investigated and the results are presented.

AIM OF THE WORK

Studying the behavior of 4H-3,1-benzoxazinone derivative towards nitrogen and carbon nucleophiles and with carbon electrophiles will give a good information about the extent of the reactivity for 4H-3,1-benzoxazinone derivative qualitatively .

Moreover, one of the most important features of 4H-3,1-benzoxazinone derivative in chemistry is its applications as a key starting material for further transformations. They are useful intermediates for the synthesis of 4(3H)-quinazolinone derivatives, which can be employed in biological applications.

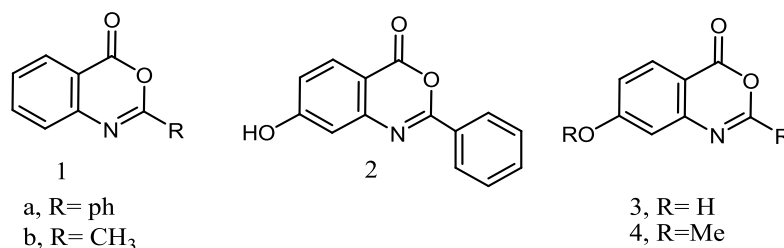
On the other hand, the behavior of the synthesized organic compounds as antibacterial was investigated.

INTRODUCTION

Studies on 4H-3,1-Benzoxazin-4-ones

INTRODUCTION

4H-3,1-benzoxazinones as a class have been known for more than a century. The phenyl derivative 1a was first synthesized [128] and the methyl analog 1b seventeen years later [54]. Members of this family have been given the common name “acylanthranils” presumably from their early synthesis from 2,1-benzisooxazole (anthranil) and an acylating agent. Compounds possessing this ring system are found in nature. e.g. Phytoalexins avenalumin [202] and Dianthalexins 2 [52,147], and some hydroxylated derivatives of this last compound 3,4 [224].



The present review will covers this important field of fused heterocycles with nearly all the chemistry (synthesis and reactions) as well as its applications. For 4H-3,1-benzoxazin-4-one derivatives only those with carbon substituents at 2-position will be mentioned.

1. Importance of 4H-3,1-benzoxazin-4-ones

1.1 Pharmaceutical applications of 4H-3,1-benzoxazin-4-ones

The 4H-3,1-benzoxazin-4-one core is a key structural fragment in a range of biologically active compounds. Work by medicinal chemists had led to a number of drugs. Related uses being found for this class of heterocyclic systems.

4H-3,1-benzoxazin-4-ones have attracted considerable attention as inhibitors of Serine proteases. The interaction of 3,1-benzoxazin-4-ones with serine proteases involves enzyme acylation due to the nucleophilic attack of the active site of serine on the lactone carbon, ring cleavage, and subsequent deacylation of the acylenzyme formed [139,295]. Hays et al. have screened a series of 2-substituted 4H-3,1-benzoxazin-4-ones as inhibitors of Clr serine protease of the complement system.

Particularly, 2-aryl-4H-3,1-benzoxazin-4-ones act as Clr Serine protease inhibitors [133]. Also it was converted into the corresponding 4(3H)-quinazolin-4-ones interaction with 4-amino-1-phenyl-2,3-dimethyl pyrazolin-5-one (aminoantipyrine), which act as Non-Steroidal anti-inflammatory agents [118, 123].

In a modern fashion, 4H-3,1-benzoxazin-4-ones core linked to heterocycle or heteroaryl were disclosed as Serine hydrolase inhibitors. They were evaluated in a human sputum neutrophil elastase assay [274].

Chiral 2-alkylamino 4H-3,1-benzoxazin-4-one derivatives were reported as inhibitors or potent inactivators of Standard Serine Proteases of the Chemotrypsin superfamily [215,289,180].

A series of 2-amino substituted 4H-3,1-benzoxazin-4-one derivatives was reported as inhibitors for human protease, and some of them demonstrate Anti-Viral activity in cell culture, with selectivities related to chemotrypsin and Elastase and stability with respect to hydrolysis in human plasma [8,137,138,149]. Also a combination of 4H-3,1-benzoxazin-4-one with 2-aminothiadiazole gives substituted quinazolinone which act as potent Anticonvulsants and Enzyme inhibitors [275].

5-Methyl-4H-3,1-benzoxazin-4-one derivatives are accomplished as specific inhibitors of Human. Leukocyte Elastase (HLE), where they showed strong and highly specific inhibition of Human Sputum Elastase (HSE), which is equivalent to HLE [302].

Moreover, 2-substituted-4H-3,1-benzoxazin-4-one derivatives showed good Cytotoxic activity [236], Herbicidal properties and inhibition of Herpes simplex virus type 1 (HSV-1) protease [145,167]. A series of 4H-3,1-benzoxazin-4-ones with different aromatic substitution pattern were evaluated as HIV-1 Reverse transcriptase inhibitors [244].

2-Aryl-substituted 4H-3,1-benzoxazin-4-ones act as novel active substances for the cardiovascular system. They exhibit relaxing effect on smooth musculature in particular and markedly increase coronary flow through Langendorff hearts [304]. Moreover, they are used in the treatment of Obesity and also found to be novel specific Puromycin sensitive aminopeptidase inhibitors [153,307]. Nevertheless, they exhibit biological activities towards anti-elastases. [69].

Clearly, some 2-substituted 4H-3,1-benzoxazin-4-ones have the ability to lower the levels of cholesterol and triglycerides in plasma, and to raise the proportion of total cholesterol carried by high-density lipoproteins [124].

The importance of these 4H-3,1-benzoxazin-4-one also resides in that, these compounds are useful precursors for the preparation of other pharmaceutically active heterocyclic compounds, mainly quinazoline derivatives [68].

For example, 2-styryl-4-(3R)-quinazolinone bearing 5-,6-, 7-, 8-Cl, 6-Br, 6-F, 6-NH₂, 6-OMe, 6-OH, 6-OEt act as new class of Anti-Mitotic Anti-Cancer agents which inhibited Tubulin polymerization. Extensive structure activity relationship studies suggest that, the entire quinazolinone structure was required, but activity was further enhanced by halides or small hydrophobic substituents at position-6 [169].

While, substituted 2-(1-adamantyl)-4H-3,1-benzoxazin-4-ones and 2-(1-adamantyl)-3-amino or alkyl-3,4-dihydroquinazolin-4-ones are found to exhibit a broad spectrum Anti-Tumor activity with full panel (MG-MID) median growth inhibition (GI_{50}), some of them showed moderate selectivity towards Leukemia Cell Lines, and some of them possess moderate Anti-HIV-1 potency [112].

1.2 Industrial applications

4H-3,1-benzoxazin-4-ones containing at 2-position Ph, m-, p-tolyl, p-chlorophenyl, m-nitrophenyl, or m-methoxyphenyl are additives comprising surfactants, carboxypolymers, polysaccharides and/or polyalicylene glycols. amount of 5-7% of this compounds have good storage stability in detergent components containing a peroxygen bleach, such as Na perborate tetrahydrate, dissolve rapidly in water, and provide good bleaching of stained textiles during laundering a dispersion of 100g sodium-Dedecylbenzene-sulfoflate in 800g molten 2-phenyl-4H-3,1-benzoxazin-4-one was prepared at 130 °C, cooled and milled to give particles with av. diameter 0.5-1mm [219,235].

2-Alkyl and 2-aryl-4H-3,1-benzoxazin-4-ones are widely used in the synthesis of polymeric materials and optical bleaching agents [41,127]. Some 4H-3,1-benzoxazin-4-ones bearing sulfonylamino groups are used as fluorescent dyes [181].

Recently, 4H-3,1-benzoxazin-4-one derivatives with (2-aryl) vinyl substituent at 2-position were reported as useful UV absorber having absorption in the long-wavelength region for cosmetics [293].

(2,2'-Di-(4H-3,1-benzoxazin-4-one))-m- or p-phenylenes were used for improving the light-fastness of textile materials, where they are used for increasing the light-fastness of textiles and producing textiles which protect the wearer from the solar UV radiation [220].

2. Synthesis of 4H-3,1-benzoxazin-4-ones

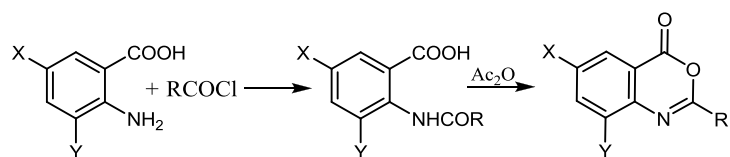
4H-3,1-benzoxazinones comprise a relatively large group of substances which have come to be known were synthesized as follows:

2.1 From anthranilic acids

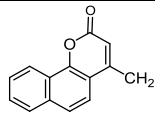
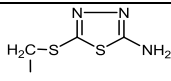
By far the most popular and versatile route to the 3,1-benzoxazinone nucleus relies on anthranilic acid or its derivatives as a convenient starting material.

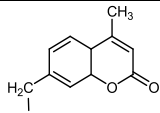
2.1.1 Via the action of acid chlorides on anthranilic acid

2-Alky, -aryl and -aryalkyl 4H-3,1-benzoxazinones 1 have been obtained by heating anthranilic acid or substituted anthranilic acid with acid chlorides. Here, a vast array of acid chlorides are either commercially available or easily prepared.

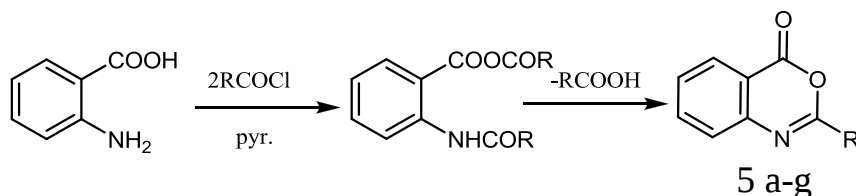
1 a-z₁₂

The compounds thus obtained are collected in the following table

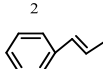
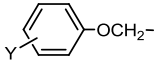
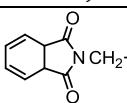
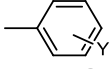
	X	Y	R	Reference
a	H	H	-C ₆ H ₅	[128, 36]
b	H	H	-CH ₃	[315, 75]
c	Br	H	-CH ₃	[266]
d	H	H	-C ₃ H ₇ (iso)	[121]
e	H	H	-CH ₂ COCH ₃	[96]
f	H	H	-CH ₂ C ₆ H ₅	[96]
g	H	H	-C ₃ H ₇ (n)	[119, 126]
h	H	H	-CH ₂ Cl	[256]
i	H	H	-C ₁₀ H ₇ (α)	[88]
j	Br	Br	-CH ₃	[161]
k	H	H		[110]
l	Br	Br	-C ₆ H ₅	[162]
m	I	H	-CH ₃	[213]
n	NO ₂	H	-C ₃ H ₇ (n)	[64]
o	CH ₃	H	-C ₆ H ₄ C ₄ H ₉ (t)(4)	[141]
p	H	H	C ₄ H ₃ S	[107]
q	I	H	C ₆ H ₅	[131]
r	H	H		[44]
s	H/Br Br/Cl	H/Br H	-C ₆ H ₄ .Cl(4)	[188]
t	H/Br	H/Br	C ₆ H ₅ - -C ₆ H ₄ Cl (o, m,p)	[188]
u	H	H	-C ₆ H ₄ .I(o)	[148]
v	I	H	-C ₆ H ₅	[4]
w	I	H	-CH ₂ Cl	[90]
x	H	H	-C ₂ H ₅	[30]
y	NHSO ₂ R	H	-CH ₃	[310]
z	H	H	-C ₆ H ₄ .NHSO ₂ R	[51]

	X	Y	R	Reference
z_1	H	H		[285]
Z_2	CH_3	H	$-C_6H_4 \cdot C_4H_9t(4)$	[141]
Z_3	H	H	$-CH=CH_2$	[176]
Z_4	H	H	$-C_{10}H_7(\beta)$	[210]
Z_5	Br	Br	C_4H_3S	[162]
Z_6	Br/H	Br/H	$-CH_3$	[171]
Z_7	Cl	Cl	$-C_6H_5$	[214]
Z_8	H	OCH_3	$C_6H_4Br(4),$ $C_6H_4Br(2),$ $C_6H_4Cl(3),$ $C_6H_4F(2),$ $C_6H_4Cl(4),$ $C_6H_4Cl(2)$	[155]
Z_9	H	OCH_3	$-CH_3, C_2H_5,$ $C_4H_9,$ $C_6H_5,$ $C_6H_4Br(4),$ $C_6H_4Cl(4),$ $-C_6H_4Br(2),$ $C_6H_4Cl(2),$ $C_6H_4F(2),$ $C_6H_4CH_3(2),$ $C_6H_4(OCH_3)(2)$	[156]
z_{10}	H	Cl/CH_3	$-C_6H_4Br(2),$ $C_6H_4Cl(2),$ $C_6H_4F(2),$ $C_6H_4CH_3(2),$ $C_6H_4(OCH_3)(2)$	[156]
	F	H	$-CH_2CH_2ph,$ Bu, Ph, 	[327]
z_{11}	H	H	C_4H_3O	[193]
z_{12}	2-aminobenzoic acid	Ph		
	CH_3	H		[61]

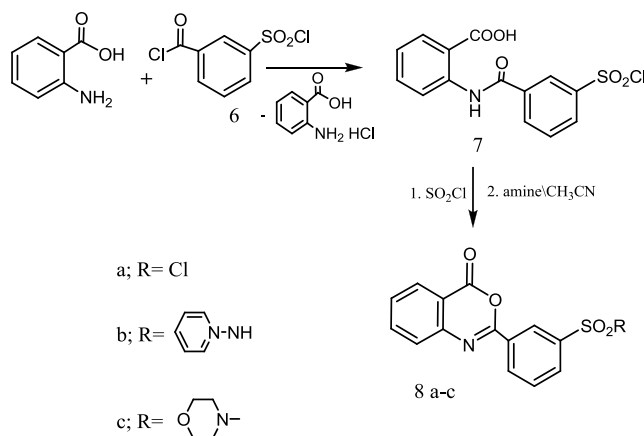
Although these methods provide benzoxazinones in a straight forward manner, the lack of a wide variety of readily available acid chlorides limits the generality of this method. As a modification of literature methods [326,313], 2-aryl-4H-3,1-benzoxazin-4-ones **5** were obtained via reaction of anthranilic acid with two equivalents of an acid chloride in pyridine solution.



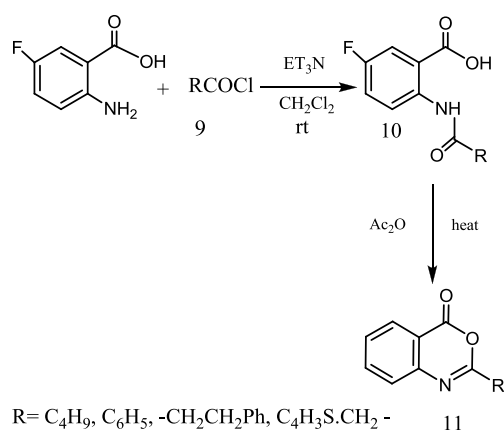
The compounds thus obtained are collected in the following table

	X	R	Ref.
a	H	 Y = H, Cl, Br, Me, OMe, CF ₃ , NO ₂ , COOH(at o-, m-, p-)	[36,147, 141,173,133,239]
b	H		[36,297,265,267]
c	H		[36]
d	H	 Y = H, Me, OMe, NO ₂	[36]
e	H		[277, 183]
f	H	 Y H, 3-F, 2-F, 3-OMe, 4-OMe, 2-OMe, 3-OH, 4-OH, 2,5-Di-OH, 2-OH	[273]
g	NO ₂	-C ₆ H ₅	[175]

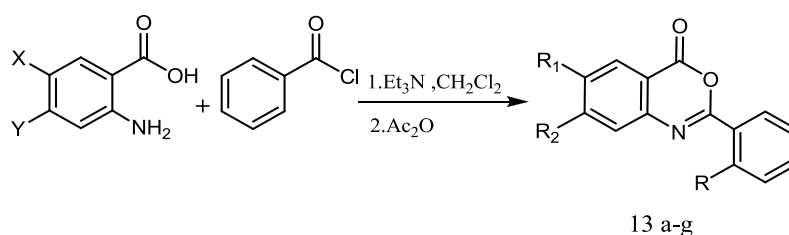
In contrast, the 3-chloro sulphonylbenzoyl chloride **6** reacts with 2 equivalents of anthranilic acid to give N-(3-chlorosulphonylbenzoyl)anthranilamide (**7**), which furnishes the 3-(4-oxo-4H-3,1-benzoxazin-2-yl)benzenesulphonyl chloride (**8a**) on treatment with thionyl chloride. 4H-3,1-benzoxazinones **8b,c** are obtained on treatment of **8a** with aniline and piperidine at 20 °C in acetonitrile [296].



On the other hand, 5-fluoroanthranilic acid reacts with acid chlorides 9 in the presence of triethylamine and methylene chloride at room temperature to afford 10, which on heating with acetic acid anhydride for 1 hour produces the 6-fluoro-2-substituted benzoxazinones 11 [327].



The reaction of acid chlorides with anthranilic acids can be performed as a one-pot reaction. Thus the reaction of substitute anthranilic acid with 2-substituted benzoyl chlorides 12 in presence of Et₃N and CH₂Cl₂ followed by addition of acetic acid anhydride and affords disubstituted benzoxazinones 13 [261].

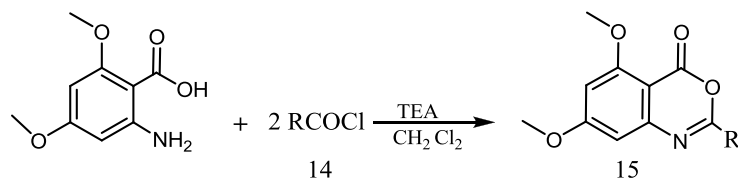


The compounds thus obtained are collected in the following table

	X	Y	R	R ₁	R ₂
a	Br	H	CH ₃	Br	H
b	Br	H	CH ₃	C ₆ H ₄ .Cl(4)	H
c	H	Br	H	H	Br
d	H	Br	H	H	C ₆ H ₄ .Cl(4)
e	H	H	CH ₃	H	H

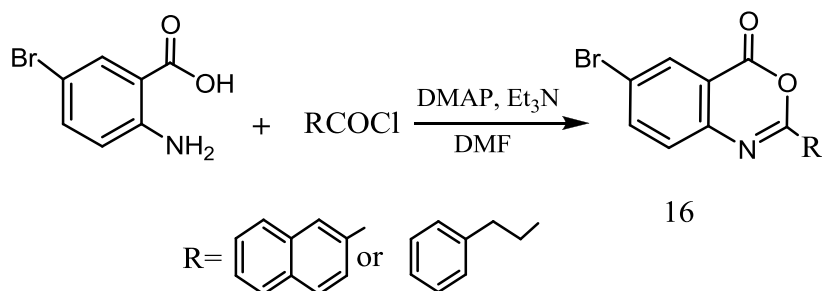
	X	Y	R	R ₁	R ₂
f	OCH ₃	H	OCH ₃	OCH ₃	H
g	OCF ₃	H	CH ₃	OCF ₃	H

If 4,6-dimethoxyanthranilic alkanoyl chlorides 14 in TEA and acid is reacted with CH₂Cl₂ at 40 °C, 4H-3,1-benzoxazin-4-one derivatives 15 is produced [136].

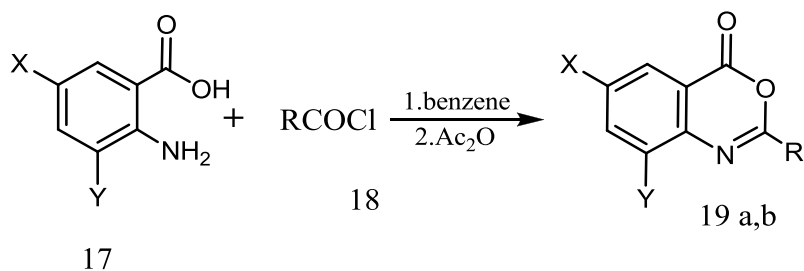


R= Me, Et, n-Pr, i-Pr, n-Bu, i-Bu

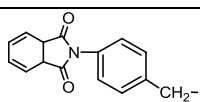
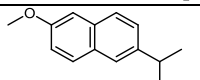
5-Bromoanthranilic acid is cyclized with 2- naphthoyl and/or phenethyloyl chloride by heating the mixture with DMPA and triethyl amine in DMF and furnishes 16 [322]



Moreover, reaction of anthranilic acids 17 with synthesized acid chlorides 18 was carried out in boiling benzene followed by refluxing in acetic acid anhydride to afford benzoxazinone derivatives 19.



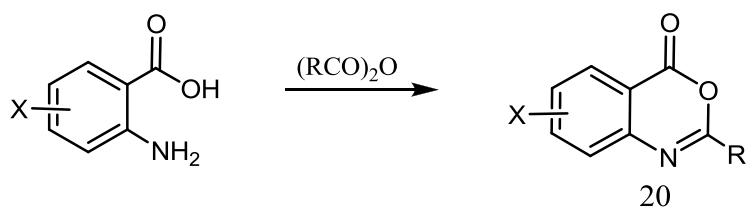
The compounds thus obtained are collected in the following table

	X	Y	R	Ref.
a	H	H		[42]
b	Cl	Cl		[14]

2.1.2 Via the action of acid anhydrides on anthranilic acid

Simple 2-substituted derivatives 20 are best prepared by reacting an anthranilic acid derivative with an appropriate anhydride at elevated temperatures. Lower

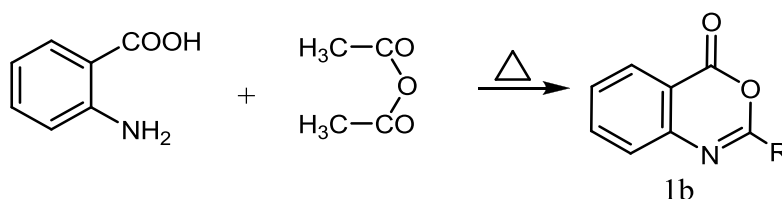
molecular weight anhydrides are usually employed as the solvents [57, 249, 243, 178, 23, 35, 111].



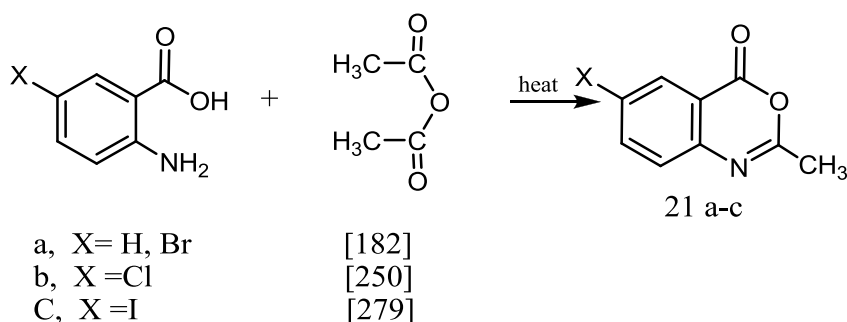
X=H, halogen, OMe, NO₂

R=Me, Et, n-Pr, Ph, CF₃

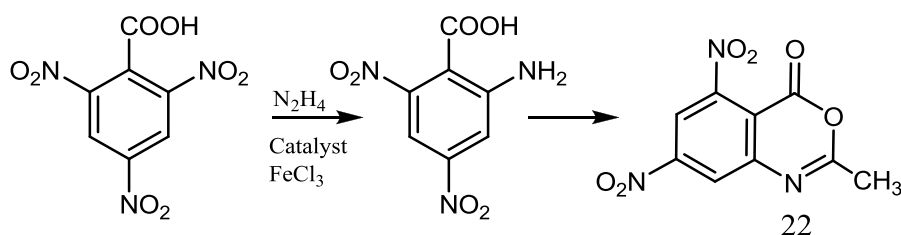
2-Methyl-4H-3,1-benzoxazin-4-one (1b) are obtained by heating anthranilic acid with acetic anhydride [200].



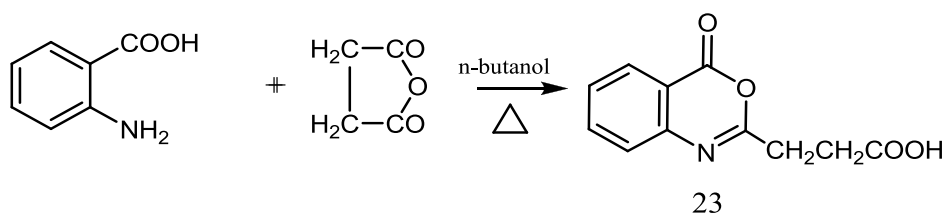
Recently, 2-methyl-6-halo-4H-3,1-benzoxazin-4-ones 21 are obtained by heating 5- haloanthranilic acid with acetic acid anhydride for two hours.



2-methyl-5,7-dinitro-4H-3,1- benzoxazin-4-one (22) is prepared in the same way by generating 4,6-dinitroanthranilic acid (catalytic reduction of 2,4,6-trinitrobenzoic acid) followed by heating with acetic acid anhydride [177].

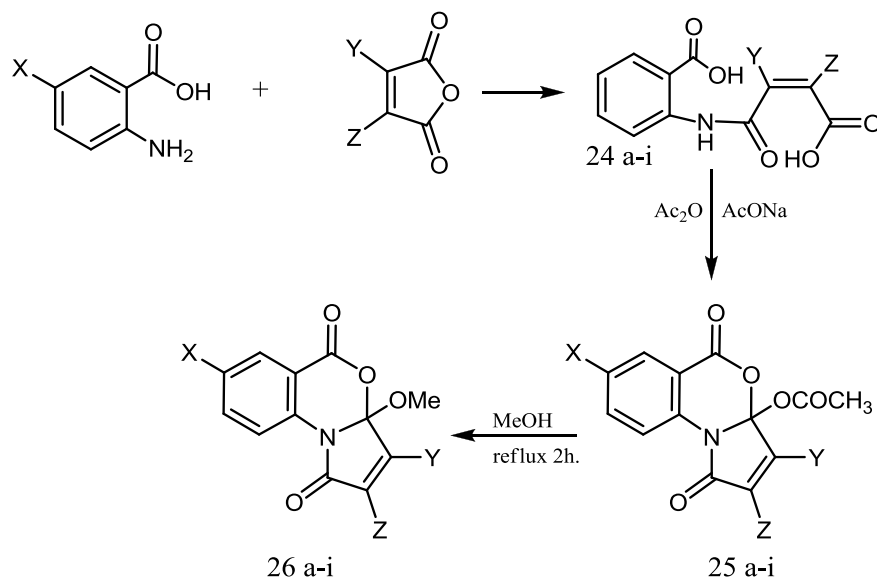


Similarly, 2-(β-carboxyethyl)-4H-3, 1-benzoxazin-4-one (23) has been obtained by heating anthranilic acid with succinic acid anhydride in n-butanol [119].



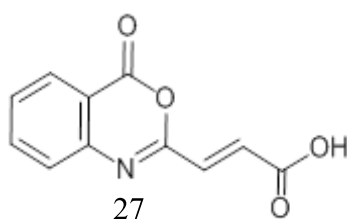
Also co-solvents as chloroform, dioxane, toluene, and orthoesters are used successfully as cyclizing agents [26, 45, 306].

In addition, a series of o-carboxymaleanilic acids 24 are prepared by reacting anthranilic acid with maleic anhydride, methylmaleic anhydride, or phenylmaleic anhydride, which intermolecularly dehydrated to afford pyrrolobenzoxazinones 25. Which underwent solvolysis via refluxing with anhydrous methanol furnishes 26 [40].



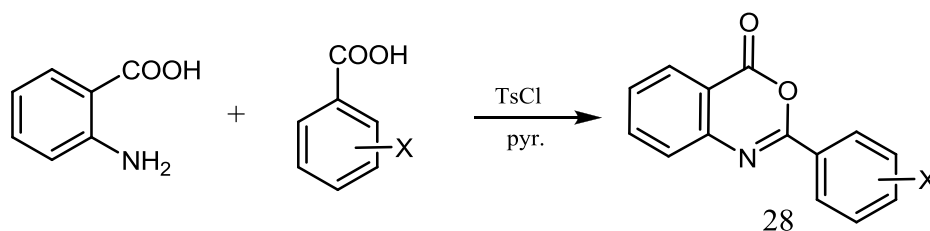
	X	Y	Z
a	H	H	H
b	Cl	H	H
c	Br	H	H
d	I	H	H
e	H	Me	H
f	H	H	Me
g	H	Ph	H
h	H	Me	Me
i	H	o-C ₄ H ₄	o-C ₄ H ₄

Under identical conditions, o-carboxyfumaranic acid afforded 2-carboxyvinylbenzoxazinone 27 which does not further cyclized due to its cis-geometry [40].

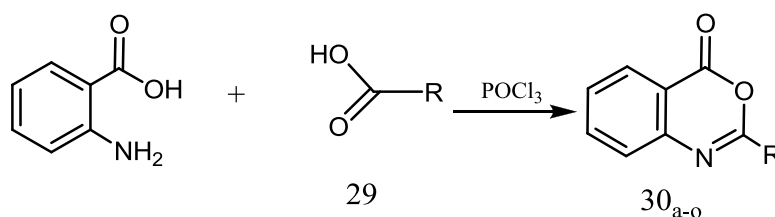


2.1.3 Via reaction of anthranilic acid with aromatic carboxylic acid

A closely related synthesis of 2-phenyl-4H-3,1-benzoxazin-4-one 28 uses the reaction of anthranilic acid with two equivalents of an ortho or para substituted benzoic acid ($X = \text{H, Cl, Me, OMe, NO}_2$) in the presence of tosyl chloride [255].

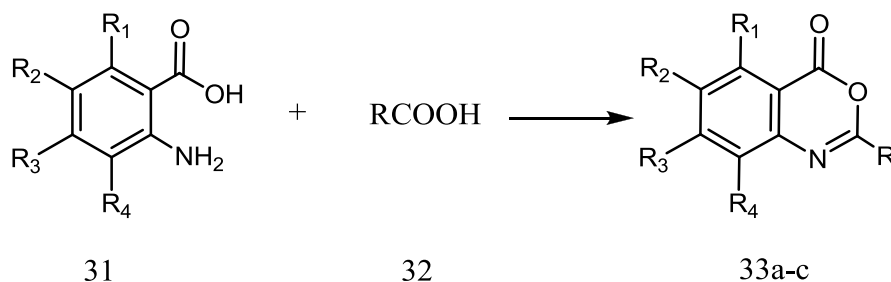


Starting from anthranilic acid on one hand and the aromatic carboxylic acids 29 on the other hand, where the preliminary chlorination to furnish the acid chloride is not necessary when the reaction proceed to yield benzoxazinone derivatives 30 a-o as a final product is performed in phosphoryl chloride under nitrogen atmosphere [260].



(a)	(b)	(c)	(d)
(e)	(f)	(g)	(h)
(i)	(j)	(k)	(l)
(m)	(n)	(o)	

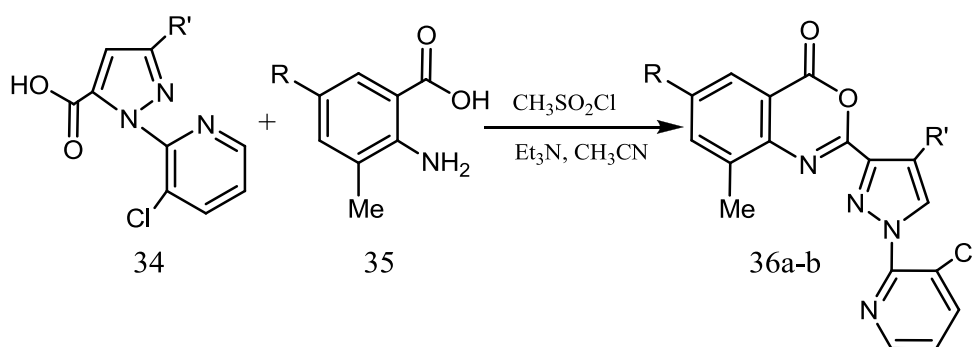
Recently, heteroarylbenzoxazinones 33 a-c were prepared by heterocyclization of heterocarboxylic acids 32a,b with substituted anthranilic acids 31a,b. If the benzoxazinone 33a is combined with 3-(dimethylamino) pyrrolidine gives 4H-3,1-benzoxazin-4-one derivative 33e.



The compounds thus obtained are collected in the following table

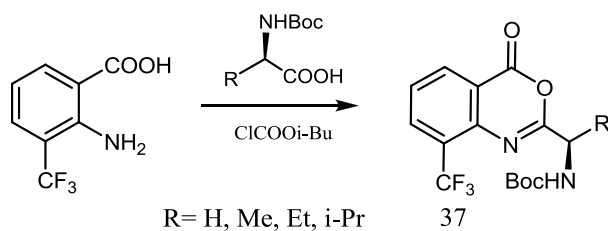
	R ¹	R ²	R ³	R ⁴	R	Ref.
a	Et	H	OMe	H		[274]
b	H	CN	H	Me		[190]
c	Et	H	OMe	H		[274]

Another variation of this method uses the coupling of the pyrazole acid 34 with anthranilic acids 35 in acetonitrile and triethyl amine in presence of methanesulphonyl chloride to obtain the 4H-3,1- benzoxazin-4-one derivatives 36.



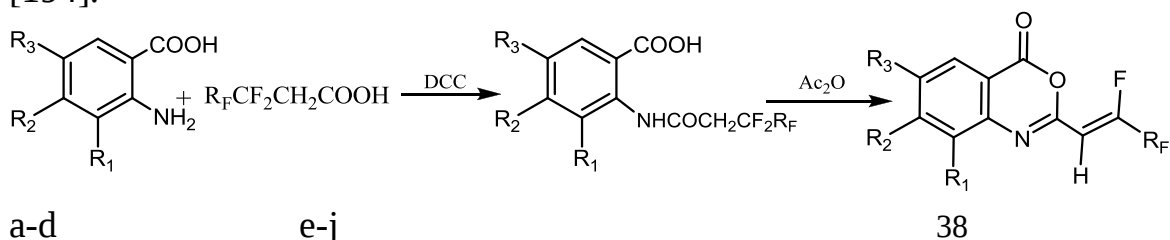
2.1.4 Reaction of substituted anthranilic acid with Boc-protected amino acids

The interesting aminobenzoxazinone derivative 37 was readily prepared from the reaction of equimolar quantities of 3-trifluoromethylantranilic acid and Bocprotected amino acid with two equivalents of isobutylformate in the presence of N-methylmorpholine with complete retention of the chiral information [66, 67].



2.1.5 Reaction of substituted anthranilic acid with 2,2-dihydro fluoroalkanoic acid

2-[(z)-1-hydrofluoro-1-alkenyl]-4H-3,1-benzoxazin-4-ones 38 are obtained via condensation of 2,2-dihydropolyfluoro alkanolic acid with anthranilic acid or its derivatives in the presence of N,N'-dicyclohexylcarbodiimide (DCC) in CH₂Cl₂ [194].



- a-d e-j
- a, R₁=R₂R₃=H b, R₁=H, R₂=R₃=OCH₃
- c, R₁=R=H, R₂=Cl d, R₁=R₃=Br, R₂=H

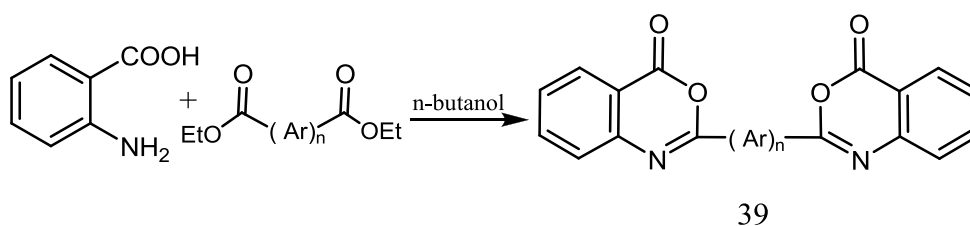
R_F, e=C₅F₁₁,
h=CF₂C₁,

f = CF₆C₁,
I = CF₂Br,

g = C₃F₇,
j = CF₃

2.1.6 Synthesis of Bis(411)-3,1-benzoxazin-4-one derivatives :-

Bis(4H)-3,1-benzoxazin-4-one derivatives 39 are prepared from interaction of terephthaloyl chloride with diethyloxalate or anthranilic acid [201].



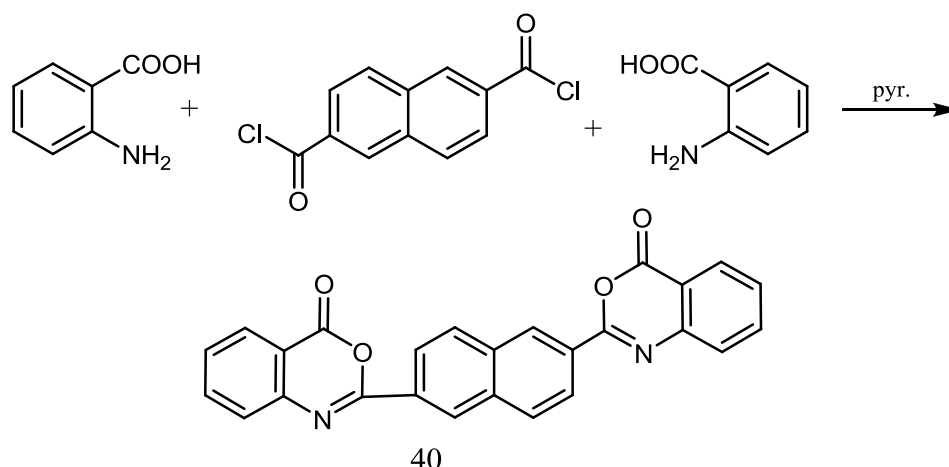
a, n= 0 in case of diethyloxalate

b,n=1 in case of terephthaloyl chloride which gave 2,2'-p-phenylene bis-(6-substituted)-3,1-benzoxazin-4-one.

General formula (39; R₁, R₂= C₁-C₁₀ hydrocarbyl, C₁-C₃ alkoxy, C₁-C₄ acyl, halogen, nitro, Ar C₆-C₁₂ aromatic hydrocarbon group n= 0,1) were prepared and used as light stabilizer for polyester fibers' [201].

Similarly a sunscreen contains a cyclic imino ester (40) (R = divalent aromatic hydrocarbyl) as a UV absorbent, has been obtained via interaction of 2,6-naphthalene dicarboxylic acid chloride with anthranilic acid in pyridine [324].

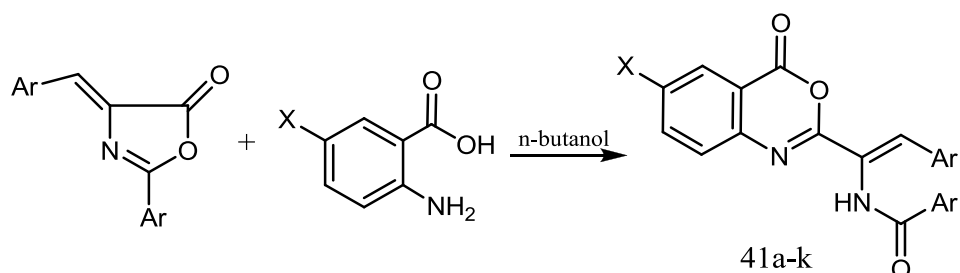
It is resistant to water, not readily soluble in organic solvents, fats, oils, and nonirritating to the skin. It prevents skin rash and acts as skin conditioner.



2.1.7 From interaction of anthranilic acid with heterocyclic compounds

2.1.7.1 From 4-arylidene-2-aryl-oxazolin-5-one

2-substituted-4H-3,1-benzoxazin-4-ones 41 were obtained via interaction of 4-arylidene-2-aryl-oxazolin-5-one with anthranilic acid in boiling butanol.



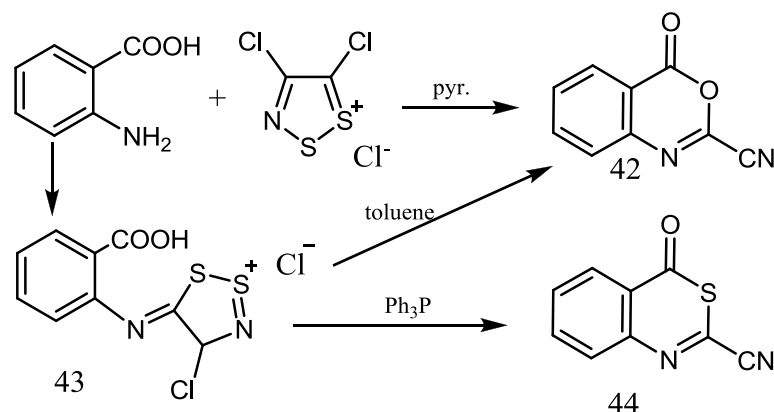
The compounds thus obtained are collected in the following table

	X	Ar	Ar	Ref
a	H	C ₆ H ₄ .(OCH ₃)(4)	C ₆ H ₅	[84]
b	H	C ₆ H ₄ .NO ₂ (3)	C ₆ H ₅	[84]
c	H	C ₆ H ₄ .(OCH ₃)(4)	C ₆ H ₄ .(OCH ₃)(4)	[84]
d	H	C ₆ H ₄ .C ₁₀ H ₇ (2)	C ₆ H ₅	[94]
e	H	C ₆ H ₂ .(OCH ₃) ₃ (3,4,5)	C ₆ H ₄ .Cl(2)	[94]
f	H	C ₆ H ₂ .(OCH ₃) ₃ (3,4,5)	C ₆ H ₄ .Cl(2)	[94]
g	H	C ₆ H ₂ .(OCH ₃) ₃ (3,4,5)	C ₆ H ₅	[99]
h	H	C ₆ H ₄ .Cl(4)	C ₆ H ₅	[99]
i	H	C ₆ H ₄ C ₁₀ H ₇ (1)	C ₆ H ₅	[6]
j	H	2-furyl	C ₆ H ₅	[6]
k	Br	C ₆ H ₅	C ₆ H ₅	[217]

2.1.7.2 From iminodithiazole

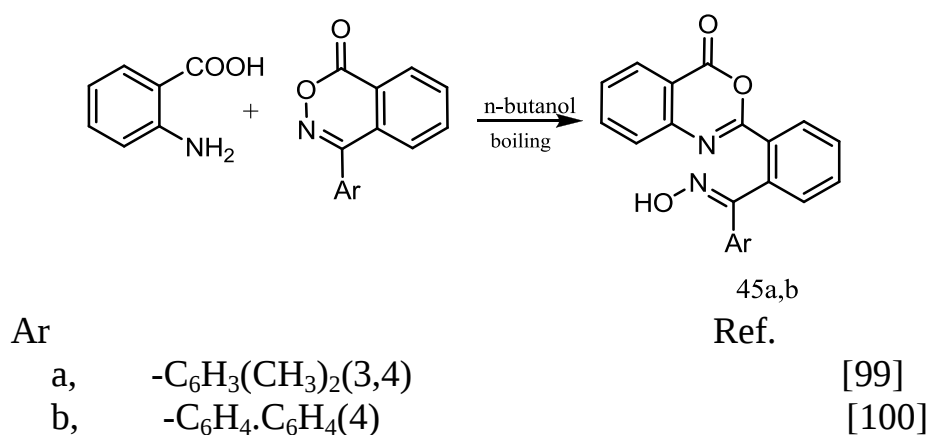
Iminodithiazole obtained from condensation of anilines with 4,5-dichloro-1,2,3-dithiazolium. Chloride were reacted with a solution of anthranilic acid (in

methylene chloride) in the presence of pyridine to produce 2-cyano-3,1-benzoxazin-4-one (42). A similar reaction of using triphenyl phosphine instead of pyridine yielded the analogous 3,1-benzothiazin-4-one 44. The delicate intermediate iminodithiazole 43 can be isolated if four equivalents of anthranilic acid are used without the addition of pyridine. Heating of 43 in toluene afforded 42, while treating 43 with two equivalents of triphenyl phosphine produces 44 [47, 48].



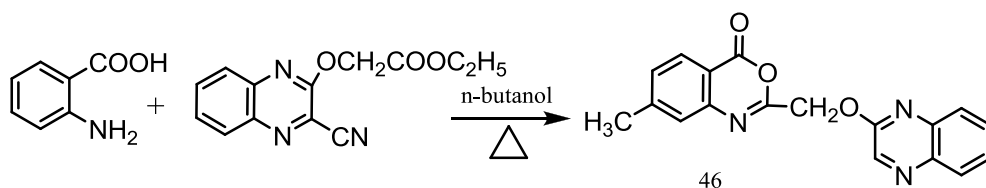
2.1.7.3 From (4H)-3,2-benzoxazin-4-one

2-substituted-4H-3,1-benzoxazin-4-ones 45 have been obtained when 1-substituted-4H-3,2-benzoxazin-4-one derivatives were allowed to react with anthranilic acid in boiling n-butanol.



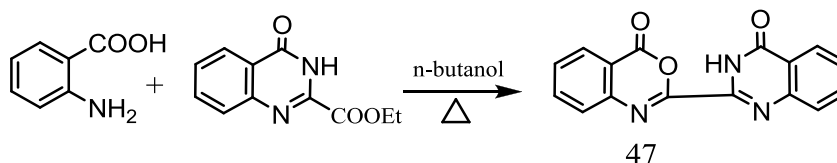
2.1.7.4 From 3-methyl-2-(ethoxycarbonylmethoxy) quinoxaline

Substituted-4H-3,1-benzoxazin-4-one 46, which bearing a hetaryl moiety at 2-position, are synthesized via interaction of 2-(ethoxycarbonylmethoxy)-3-methylquinoxaline with anthranilic acid in boiling butanol at 120 °C [210].



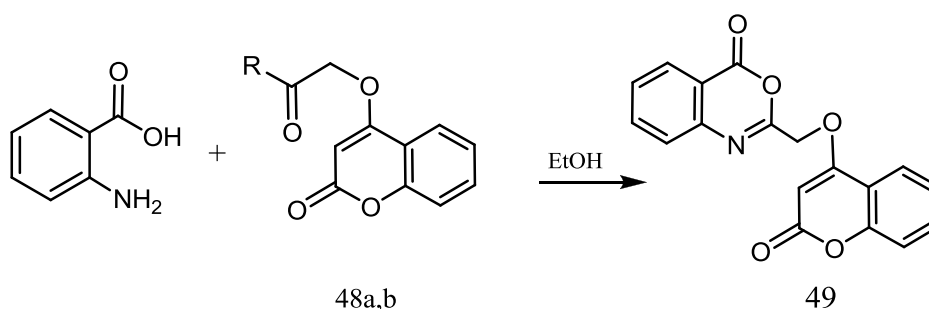
2.1.7.5 From 2-ethoxycarbonyl-4(3H)-quinazolin-4-one

2-[4(3H)-oxoquinazol-2-yl]-(4H)-3,1-benzoxazin-4-one (47) are synthesized via interaction of 2-ethoxycarbonyl-4(3H)-quinazolinone with anthranilic acid by fusion at 170 °C or by refluxing in n-butanol for 3 hr [19].



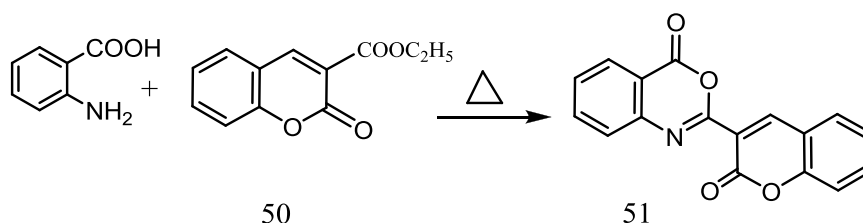
2.1.7.6 From substituted coumarin

4H-3,1-benzoxazin-4-one derivative 49 is resulted from the interaction of anthranilic acid with (2-oxo-2H-chromen-4-yloxy)acetyl chloride 48a or the ester 48b in boiling ethanol [27].

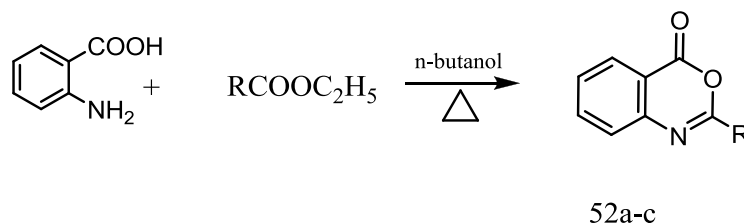


a; R= Cl b; R= OEt

While, 4H-3,1-benzoxazin-4-one 51 bearing coumarin-3-yl moiety at position-2 was obtained via interaction of 3-ethoxycarbonyl coumarin 50 with anthranilic acid by fusion at 150 °C or refluxing in n-butanol [102].



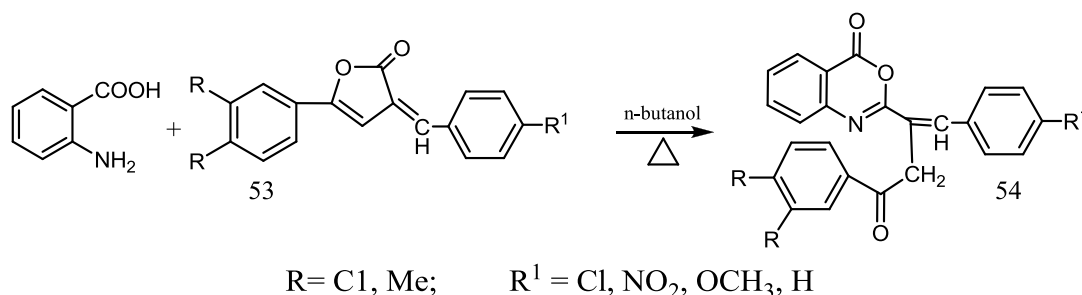
Similarly, 2-cyanomethyl, acetonyl andlor ethoxycarbonyl-4H-3,1-benzoxazin-4-one 52 were obtained via interaction of ethylcyanoacetate, ethylacetoacetate and diethyloxalate with anthranilic acid in boiling butanol.



	R	Ref.
a	-CH ₂ CN	[212]
b	-CH ₂ COCH ₃	[96]
c	-COOC ₂ H ₅	[19]

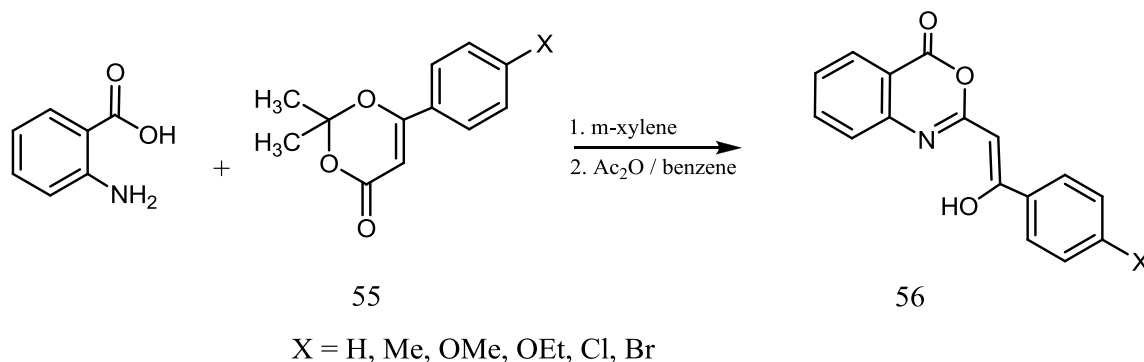
2.1.7.7 From hetero-ring opening of furanone derivatives

Hetero-ring opening of the furanone derivatives 53 with anthranilic acid in boiling butanol affords the 4H-3,1-benzoxazin-4-one derivatives 54 [284].



2.1.7.8 From hetero-ring opening of 1,3-dioxin-4-one derivatives

2-Substitutedphenylvinyl-4H-3,1-benzoxazin-4-one derivatives 56 were synthesized via refluxing anthranilic acid with 2,2-dimethyl-6-phenyl-[1,3]dioxin-4-one derivative 55 in *m*-xylene, followed by dehydration [309].

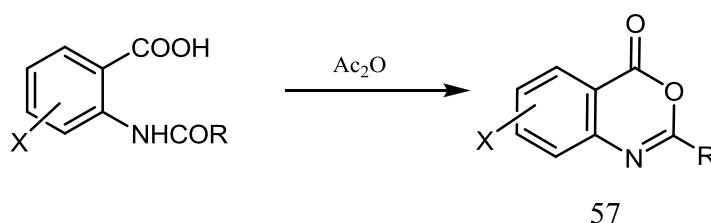


2.2 From N-acylanthranilic acid

Starting from an N-acylanthranilic acid a variety of reagents can be used to affect cyclodehydration to the benzoxazin-4-one.

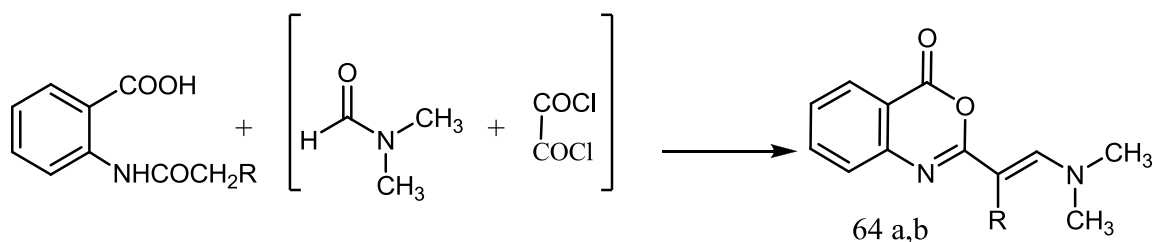
2.2.1 Acetic anhydride as cyclizing agent

Acetic anhydride is the most widely used reagent for this purpose, the cyclization can accommodate a wide variety of acyl groups (X = electron donating or withdrawing group, R = alkyl, substituted phenyl, CH_2Cl , $\text{CH}(\text{CH}_3)\text{Cl}$, styryl, trifluoromethyl, phthalimidomethyl, COOEt , 2-thienyl, pyridyl or thiadiazole) [71,163].



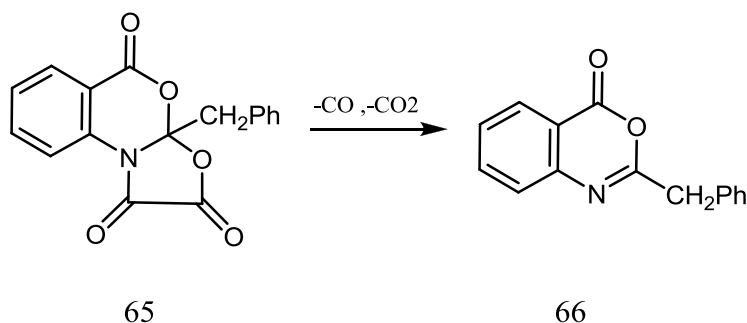
Also, aromatic systems containing thionylamino functionality at position-2 was introduced to obtain derivative 58 [15].

phenylacetyl anthranilic acid gave 2-(2'- dimethylamino-1'-phenyl)ethenyl-4H-3,1-benzoxazin-4- one (64b) [46].



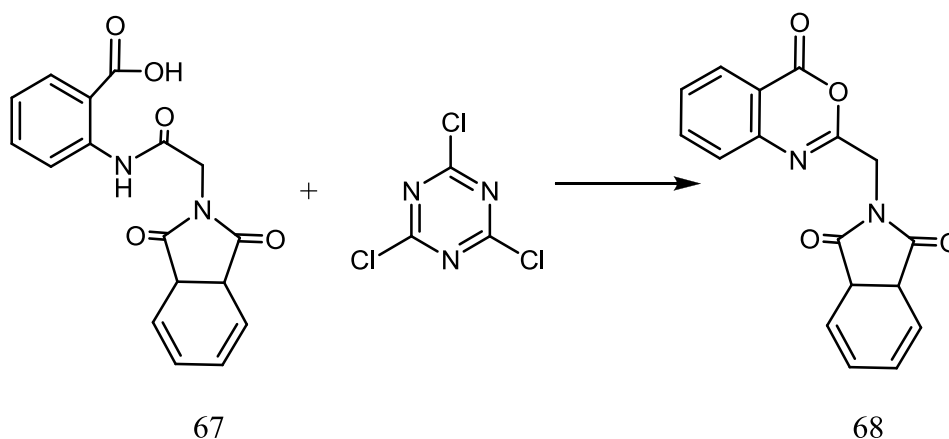
a, R=H b, R=Ph

Reaction of N-acetylated anthranilic acids and oxalyl chloride alone give the fused oxazolidine-4,5-dione (65) [46].



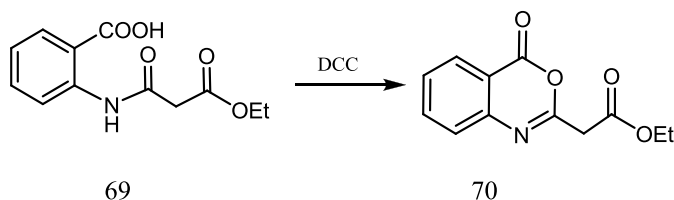
2.2.4 Cyanuric chloride as cyclizing agent

2-(N-phthaloylmethyl)-4H-3,1-benzoxazin-4-one 68 are prepared via reaction of the acyl chloride derivative N-phthaloylglycine with anthranilic acid in chloroform and N-phthaloylanthranilic acid 67 is generated. It reacted with cyanuric chloride to form the final product [272].

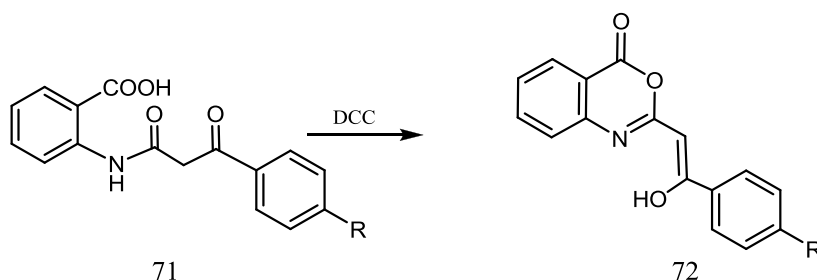


2.2.5 Dicyclohexylcarbodiimide as cyclizing agent

N,N'-dicyclohexylcarbodiimide (DCC) is used for dehydration of N-acylanthranilic acid 69 to obtain the 2- ethoxycarbonylmethyl-4H-3,1-benzoxazin-4-one 70. Where, N-acylanthranilic acid 69 was obtained via reaction of anthranilic acid with diethylmalonate [303].



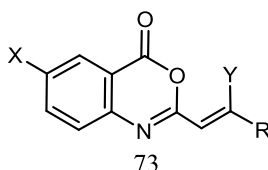
Dehydration of N-acylanthranilic acid 71 to benzoxazinone 72 using DCC is achieved in higher yield and shorter reaction time as compared to the conversion with acetic acid anhydride as dehydrating agent [309].



R= H, Me, OMe, OEt, Cl, Br

2.3 From 2-methyl-4H-3,1-benzoxazin-4-one

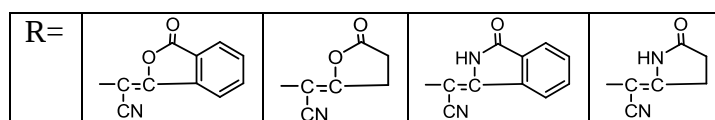
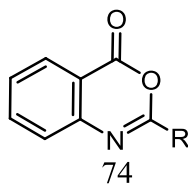
2-styryl or substituted styryl-4H-3,1-benzoxazin-4-ones 73 have been obtained, via interaction of 2-methyl-4H-3,1-benzoxazin-4-one with aromatic aldehydes and /or ketones in the presence of anhydrous zinc chloride at 170 °C.



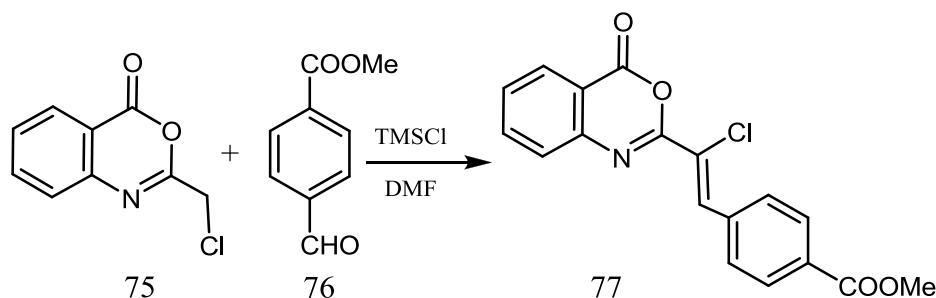
The compounds thus obtained are collected in the following table

	X	Y	R	Ref.
a	Br	H	C ₆ H ₅ , C ₆ H ₄ .OCH ₃ (4), C ₆ H ₄ .NO ₂ (4), C ₆ H ₃ (O ₂ CH ₂)(3,4), C ₆ H ₄ N(CH ₃) ₂ (4), -CH=CH-C ₆ H ₅	[266]
b	H	CH ₃ CO	C ₆ H ₅ , C ₆ H ₄ .OH(4), C ₆ H ₄ .NO ₂ (3), C ₆ H ₄ .OCH ₃ (4), -CH=CH- C ₆ H ₅ , C ₆ H ₃ (O ₂ CH ₂)(3,4)	[96]
c	H	C ₆ H ₅	C ₆ H ₄ .OCH ₃ (4), C ₆ H ₄ .OH(2), C ₆ H ₄ N(CH ₃) ₂ (4), -CH=CH- C ₆ H ₅	[92]
d	H	H	OC ₆ H ₄ .Cl(4) , C ₆ H ₅ , C ₆ H ₃ (O ₂ CH ₂)(3,4)	[101]
e	H	H	C ₄ H ₃ O(2)	[203]

Similarly, 2-cyanomethyl-(4H)-3,1-benzoxazin-4-one has been reacted with phthalic anhydride, succinic anhydride, phthalimide and succinimide to give the benzoxazinone derivatives 74 [212].



A more recent concept uses the idea of reaction of aldehydes with chloromethyl benzimidazole, meanwhile the 2-[(2-aryl-1-chloro)vinyl]-4H-3,1-benzoxazin-4-one 77 is obtained via interaction of 2-chloromethyl analog 75 with aldehyde 76 in presence of chlorotriethylsilane [262].

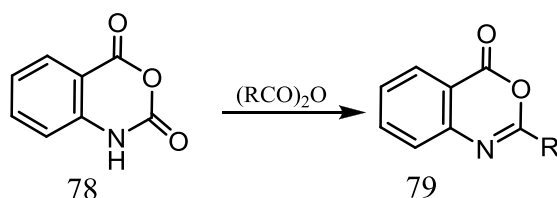


2.4 From isatoic anhydrides

Isatoic anhydrides are noted for their versatility in heterocyclic synthesis, so it is no surprise that 4H-3,1-benzoxazin-4-one heterocycle can be obtained from the closely related 2H-3,1-benzoxazin-2,4(1H)-dione (78) system.

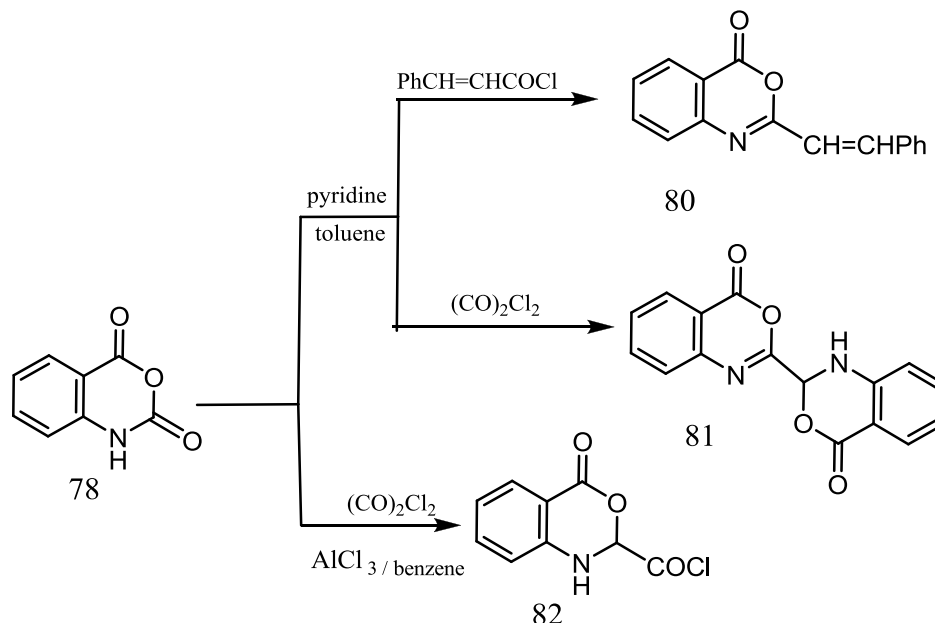
2.4.1 Reaction of isatoic anhydride with acid anhydrides

When isatoic anhydride 78 is refluxed in acetic anhydride [297], acetic acid anhydride/ pyridine [166, and 301] or stirred with trifluoro acetic acid anhydride/pyridine at room temperature [321] the corresponding benzoxazinone 79 is isolated in high yield.

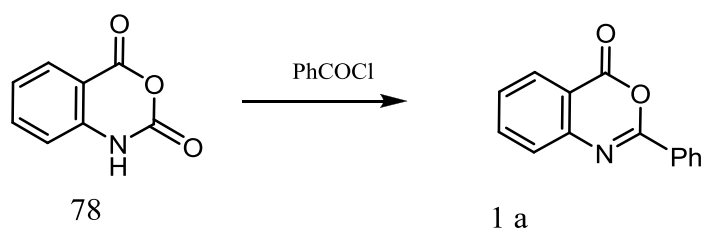


2.4.2 Reaction of isatoic anhydride with acid chlorides

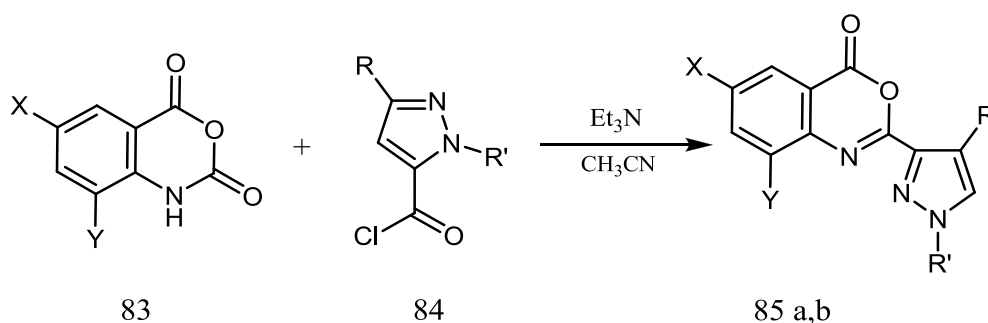
Likewise, refluxing a mixture of isatoic anhydride **78** and either cinnamoyl chloride or oxalyl chloride in pyridine/toluene solvent produces the 2-styryl analog **80** or the bis-3,1-benzoxazin-4-one **81** [166]. If the reaction with oxalyl chloride carried out in benzene using anhydrous aluminium chloride or 4-(dimethylamino)pyridine as an additive, the 2-chloroformyl derivative **82** is isolated [301].



Isatoic anhydride also reacts with acid chlorides at elevated temperature to give 3,1-benzoxazin-4-one. Thus, heating compound **78** and benzoyl chloride results in the 2-phenylbenzoxazinone **1a** [142, 143].

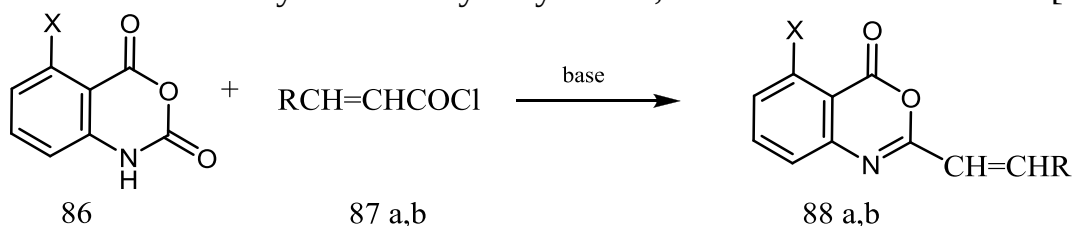


Coupling of trifluoromethyl-substituted isatoic anhydride **83** with pyrazole acid chlorides **84** affords benzoxazinones **85** in modest yield.



	X	Y	R	R'	Ref.
a	CF ₃	Me	OCR ₃ , CF ₃ , Br, Cl, OCF ₂ H, OCH ₂ CF ₃		[192]
B	H	H	CF ₃	C ₆ H ₅	[191]

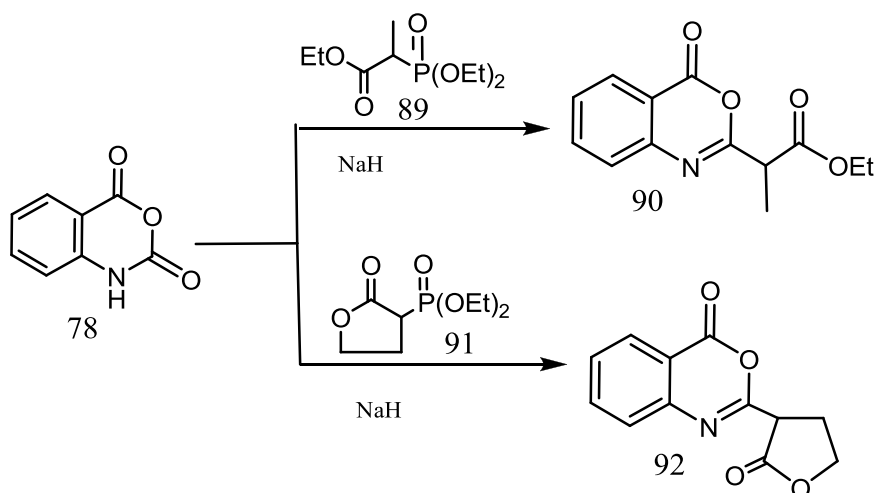
Condensation of isatoic anhydride **86** with 3-substituted-acryloyl chloride **87** under basic condition yields the arylvinyl-4H-3,1-benzoxazin-4-ones **88** [293].



	X	R
a	H	Ph, CH ₃ .C ₆ H ₄ (4), OCH ₃ .C ₆ H ₄ (4), Cl .C ₆ H ₄ (4), Br.C ₆ H ₄ (4), (OCH ₃) ₂ .C ₆ H ₃ (2,4), C ₄ H ₃ O(2)
b	Cl	Ph, CH ₃ .C ₆ H ₄ (4), OCH ₃ .C ₆ H ₄ (4)

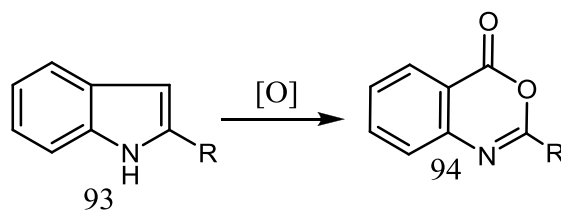
2.4.3 Reaction of isatoic anhydride with phosphoryl- stabilized anions

Reaction of isatoic anhydride **78** with phosphoryl-stabilized anions bearing no α -hydrogen atoms led to the formation of 3,1-benzoxazin-4-one. Consequently, when compound **78** is allowed to react with the anion of ethyl 2-diethylphosphonopropanoate (**89**) or α -diethyl phosphono--butyrolactone **91** in benzene, it produces **90** and **92** respectively [204, 205].



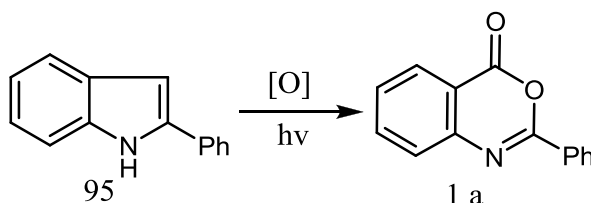
2.5 Oxidation of indoles

2-substituted indoles **93** were readily oxidized With *m*-chloroperoxybenzoic acid [55] or *p*-chloroperoxybenzoic acid [53] and the corresponding benzoxazinone **94** are produced.

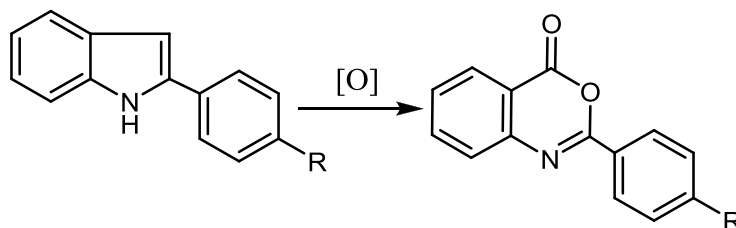


R= i-Pr, t-Bu, Ph, 2-pyridyl

A similar transformation is accomplished by the photooxygenation of 2-phenylindole 95 in methanol using Rose Bengal as a sensitizer [129].



In a closely related transformation, the oxidation of 2-phenylindolenin-3-one 96 with *m*-chlorobenzoic acid in chloroform affords 1a [259]. Whereas, oxidation of 4-dimethylamino analog 97 with hydrogen peroxide in *N,N*-dimethylformamide furnishes 98 [10].

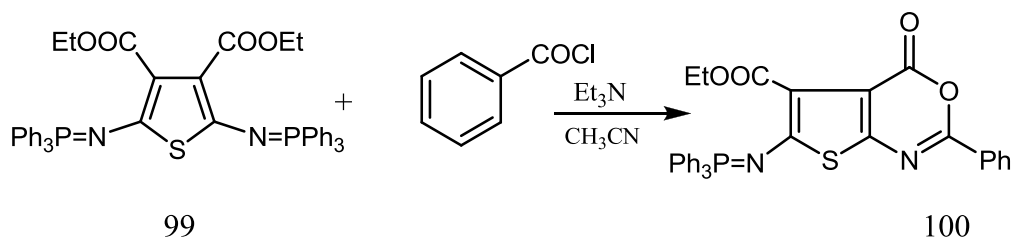


	R
1a	H
96	H
97	NMe ₂
98	NMe ₂

2.6 Miscellaneous

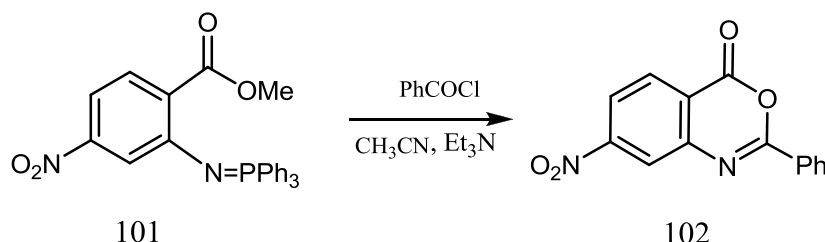
2.6.1 From β -(Triphenylphosphoranylidene)amino esters

β -(Triphenylphosphoranylidene)amino ester derivative 99 is treated with 1 equivalent of benzoyl chloride and triethylamine in acetonitrile and the oxazinone derivative 100 is generated [314].



2.6.2 From iminophosphorane

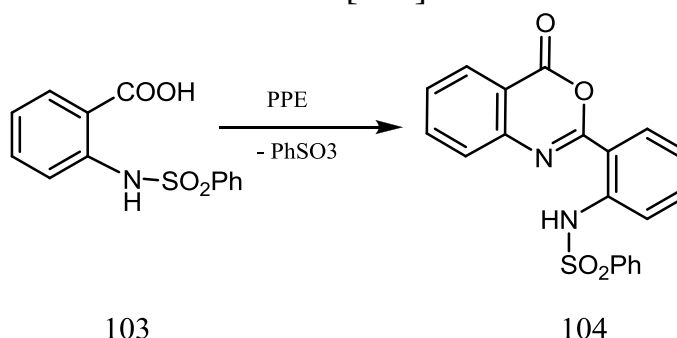
Similarly, treatment of iminophosphorane 101 with benzoyl chloride in acetonitrile in the presence of small excess of triethyl amine yielded 7-nitro-2-phenyl-4H-3,1-benzoxazin-4-one (102) [314].



This reaction is used for the production of heteroannulated 3,1-benzoxazin-4-ones, where the benzene ring is replaced with thiophene, thiazole, and pyridazine [314].

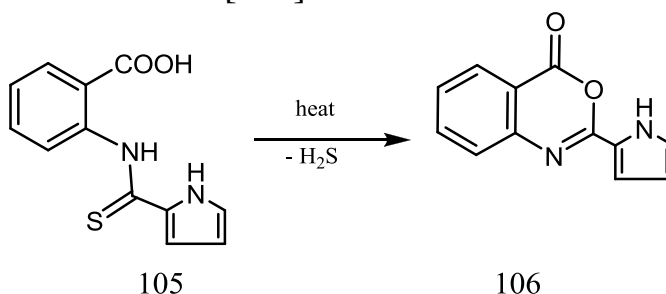
2.6.3 From N-benzenesulphonylanthranilic acid

The self condensation of 2-molecules of N-benzenesulphonyl anthranilic acid 103 in polyphosphate ester (PPE) results in the formation of 2-substituted phenyl-4H-3,1-benzoxazin-4-one 104 [312].



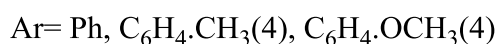
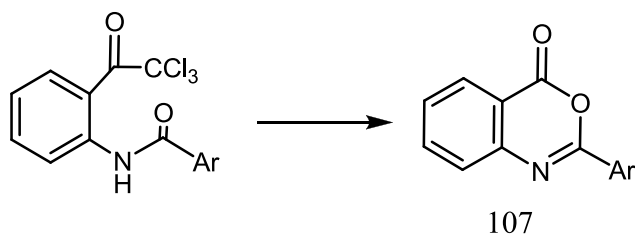
2.6.4 From thioamide derivatives

Heating thioamide derivative 105 in refluxing t-butylbenzene causes cyclization to occur with loss of hydrogen sulphide and produces 2-pyrrolyl-4H-3,1-benzoxazin-4-one 106 [195].



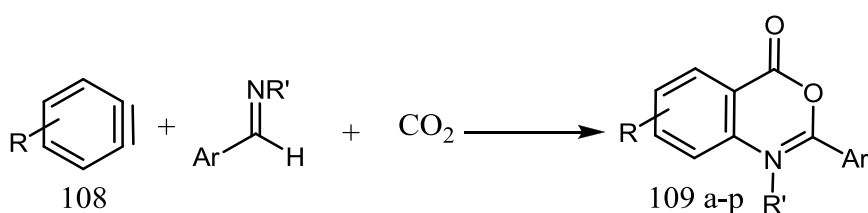
2.6.5 From electrochemical trichloroacetylanilides

The electrochemical reduction of several o-trichloroacetylanilides, 2-CCl₃CO.C₆H₄.NHCOAr (Ar = Ph, 4-MeC₆H₄, 4-MeOC₆H₄), on mercury pool in acetonitrile, yields 4H-3,1-benzoxazin-4-ones 107 [216].



2.6.6 CO₂ Incorporation reaction using arynes

The CO₂ incorporation reaction based upon three component assembly by the use of arynes and imines produced benzoxazinones 109. The reaction carried out by in situ generated benzyne 108 which reacted with aryl imines under a CO₂ atmosphere (1 atm) [323].

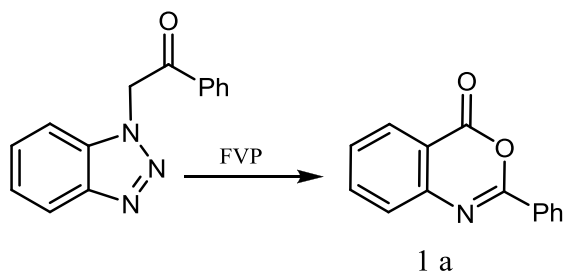


	R	R'	Ar
a	4- CH ₃	Me	2,4,6-(CH ₃) ₃ .C ₆ H ₂
b	4-F	Me	2,4,6-(CH ₃) ₃ .C ₆ H ₂
c	6- CH ₃	Me	2,4,6-(CH ₃) ₃ .C ₆ H ₂
d	3- OCH ₃	Me	2,4,6-(CH ₃) ₃ .C ₆ H ₂
e	4,5- (CH ₃) ₂	Me	2,4,6-(CH ₃) ₃ .C ₆ H ₂
F	3,6- (CH ₃) ₂	Me	2,4,6-(CH ₃) ₃ .C ₆ H ₂
g	H	H	2,4-(CH ₃ O) ₂ .C ₆ H ₃
h	H	H	2,4-(CH ₃) ₂ .C ₆ H ₃
i	H	H	4-(CH ₃ O).C ₆ H ₄
j	H	H	C ₆ H ₅
k	H	H	1-naphthyl
l	H	H	2-thienyl
m	H	H	4-CF ₃ .C ₆ H ₄
n	H	Bn	4-CH ₃ O.C ₆ H ₄
o	H	n-Bu	H
P	H	i-Pr	H

2.6.7 From 2-(1H-1,2,3-benzotriazol-1-yl)phenylethanone

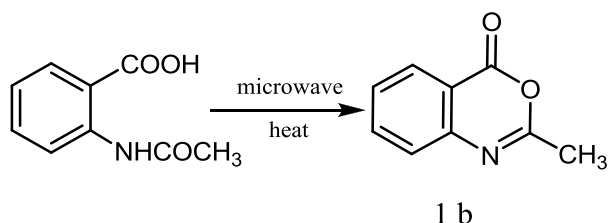
Homogenous flash vacuum pyrolysis reaction of 2-(1 H-1,2,3-benzotriazol-1-yl)phenyl ethanone is considered as one-pot synthesis of 2-phenyl-4H-3,1

benzoxazin-4-one (1a). Where the benzotriazole underwent acyl migration followed by elimination of diazomethane and rearrangement of the intermediate formed [218].

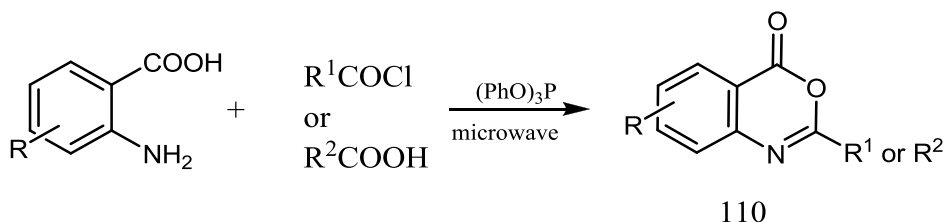


2.6.8 From heating of acetylanthranilic acid by microwave

The benzoxazinone 1b was obtained via heating of acetylanthranilic acid under microwave heating conditions [300].

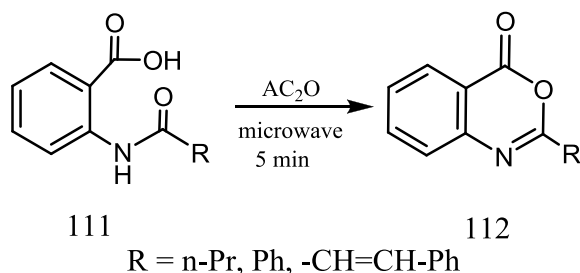


On the other hand, the 4H-3,1-benzoxazin-4-one derivatives 110 can be obtained via applying optimized microwave reaction conditions to a variety of anthranilic acids and both acyl chlorides ($R^1\text{COCl}$) and carboxylic acids ($R^2\text{CO}_2\text{H}$) in the presence of the coupling reagent triphenyl phosphite [193].



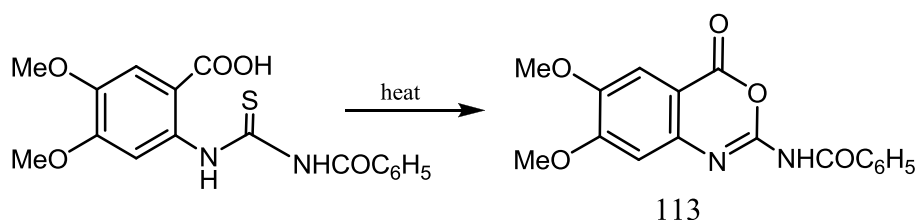
R	R^1	R^2
H	Ph	Ph
H	$\text{C}_4\text{H}_3\text{O}(2)$	Bn
H		$(\text{CH}_3)_3\text{CH}$
H		C_3H_5
H		Et
4- Me		Me
4-Cl		$(\text{CH}_3)_2\text{CHCH}_2$
2-amino nicotinic acid		Ph

A fast synthesis of 2-substituted-4H-3,1- benzoxazin-4-one 112 is achieved from the reaction of acetic acid anhydride with 2-acylaminobenzoic acid 111 under microwave and solvent-free conditions [251].



2.6.9 Thermolysis of 2-(3-benzoylthioureido)-4,5-dimethoxy benzoic acid

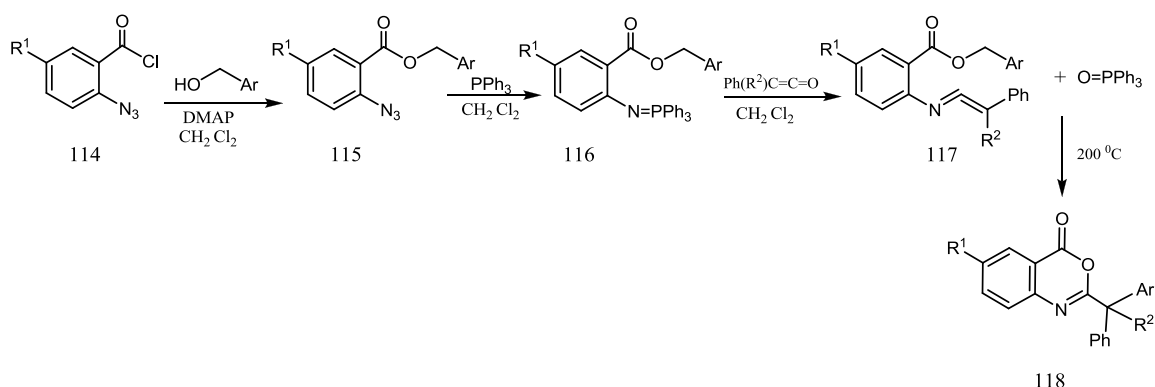
2-benzoylamino-6,7-dimethoxy-4H-3,1-benzoxazin-4-one (113) is prepared by thermal treatment of benzoic acid derivative [138].



The inactivation of Chymotrypsin and human Leukocyte elastase by compound 113 is reported [138].

2.6.10 Thermally induced cyclization of ketenimines

4H-3,1-benzoxazin-4-one 118 is prepared based on the thermally induced cyclization of N-(2-benzyloxycarbonyl)phenyl ketenimines 117, generated from the interaction of 2-azidobenzoyl chlorides 114 with benzylic alcohols [13].

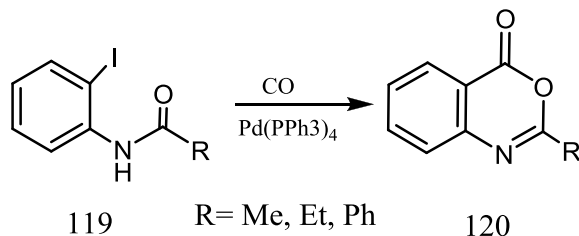


R ¹	R ²	Ar
H	Me	4-MeC ₆ H ₄
Cl	Ph	4-OMe C ₆ H ₄
		3,4-(OMe) ₂ C ₆ H ₄
		3,5-(OMe) ₂ C ₆ H ₄

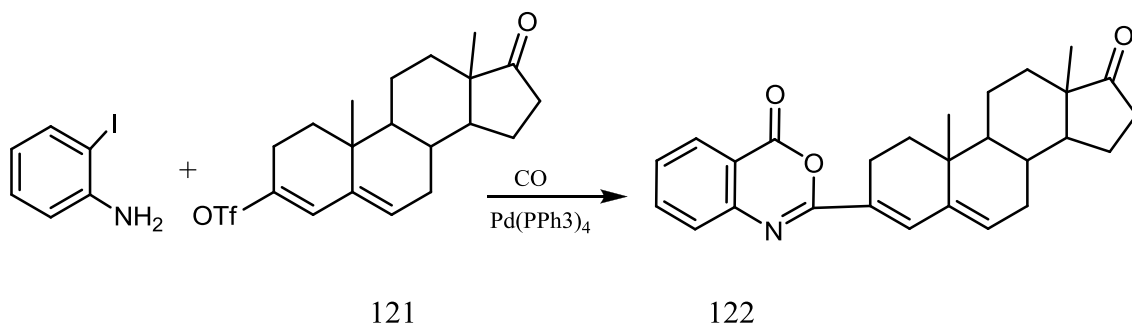
2.6.11 From o-iodoaniline

In all the syntheses of 4H-3,1-benzoxazin-4-ones presented so far the common scenario begins with materials which have the amine and carbonyl carbon

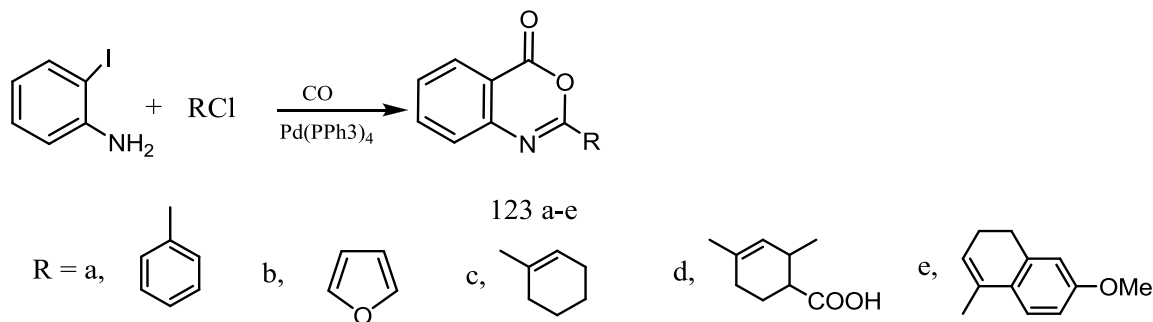
(which will ultimately become the 1- and 4-positions of the product) already positioned appropriately on the benzene ring. An alternate strategy takes advantage of carbonylation methodology which allows for the attachment of the carbonyl function onto a simpler aniline derivative. This is elegantly demonstrated by the reaction of an *o*-acylamidophenyl iodide **119** in the presence of potassium carbonate and palladium catalyst under an atmosphere of carbon monoxide which produces the benzoxazinone derivatives **120** [59].



A three-component reaction, using *o*-iodoaniline as the aromatic anchor, an aryl iodide or vinyl triflate (as precursors of the substituent at 2-position), and carbon monoxide to supply the 4-carbonyl, allows access to a variety of 2-aryl or 2-vinyl-4H-3,1-benzoxazin-4-ones [59]. A good example of this methodology at work is the reaction of *o*-iodoaniline with triflate **121** to give the steroidal benzoxazinone **122**.



Similarly, employing *o*-iodoaniline as building-block, unsaturated halides are used as precursors of the substituent at 2-position of oxazinone nucleus, and carbon monoxide in the presence of potassium carbonate and catalytic amount of $\text{Pd(PPh}_3)_4$. Such a process can be easily fulfilled to afford 4H-3,1-benzoxazin-4-one derivatives **123** containing an unsaturated unit, linked to C-2 [22].



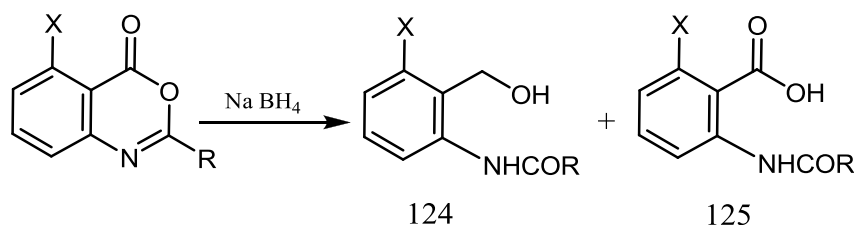
3. Reactions of 4H-3,1-benzoxazin-4-ones

4H-3,1-benzoxazin-4-one derivatives can be considered as semi-acid anhydrides formed by cyclodehydration of acylantranilic acids. They undergo many reactions of true acid anhydrides, but at slower rate [117].

Electrophilic reactions on the benzene ring of the benzoxazinone nucleus are rare and are probably unnecessary due to the plethora of diversely substituted anthranilic acids which are available. We will concern on the remaining reactive sites and feature the reactions at the C-4 and C-2 carbons of our heterocycle.

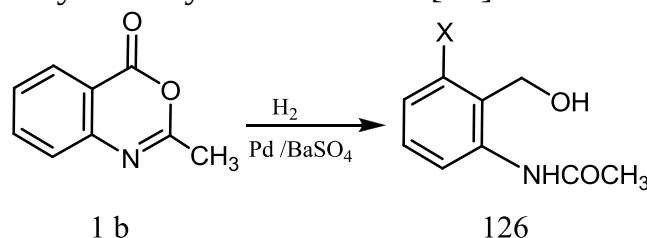
3.1 Reactions with Hydrogen nucleophiles

Benzoxazinone nucleus is susceptible to attack by hydride reagents as sodium borohydride and tend to give varying mixture of 2-acylaminobenzyl alcohol 124 and N-alkylantranilic acid 125 [24].

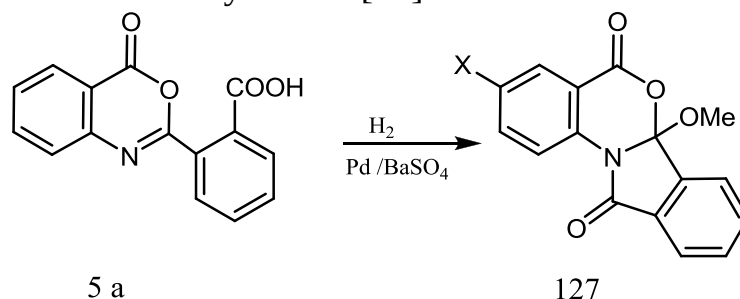


R = Me, t-Bu, CF₃, Ph, styryl, 2-thienyl

In contrast, catalytic hydrogenation of 2-methyl-4H-3,1-benzoxazin-4-one (1b) in acetic acid affords only N-acetyl toluidine 126 [56].



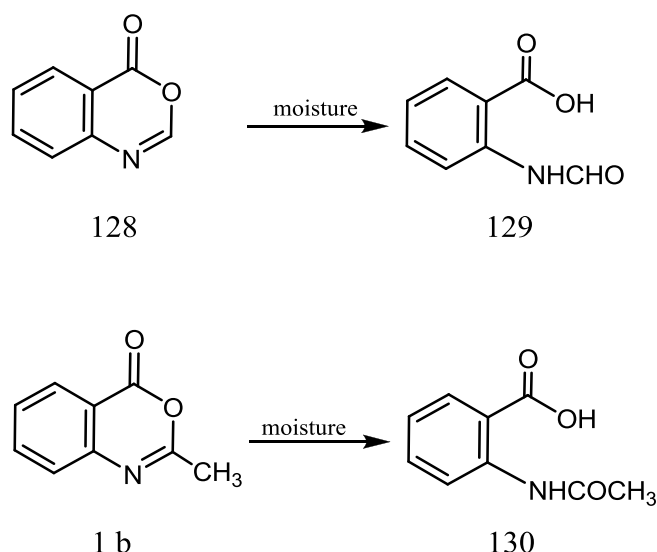
Similarly, hydrogenation of benzoxazinone 5a under neutral conditions resulted in the initial reduction of C=N bond then cyclization with o-carboxylic acid group and furnished the tetracycle 127 [56].



3.2 Reactions with Oxygen nucleophiles

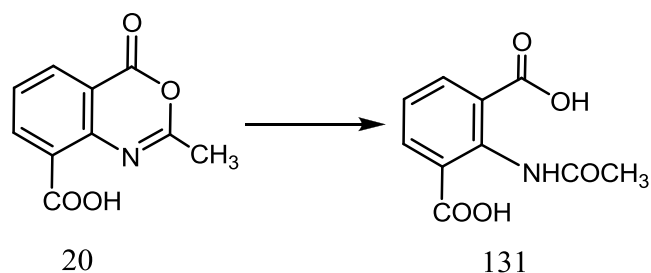
The simplest and sometimes the most unwanted reaction of some 4H-3,1-benzoxazin-4-ones is hydrolysis. Where, the 4H-3,1-benzoxazin-4-ones are exceedingly labile to hydrolysis and the initial cleavage to N-acylantranilic acids parallels that of benzoxazoles to acylaninophenol.

However, their sensitivities to hydrolysis vary greatly. 4H-3,1Benzoxazinone (formanthranil) 128 and acetanthi-anil 1b undergo cleavage by atmosphere moisture. The higher 2-alkylbenzoxazinones are increasingly stable and the 2-aryl/and 2-styrylbenzoxazinones can be handled without special precautions [75].



Kinetic studies for hydrolysis of 4H-3,1-benzoxazin-4-one in dilute buffers at 0.1 M ionic strength and D₂O was reported. The bases in the buffers were catalysts and the second order rate constants obeyed a Bronsted relation with isotope effect on the OH term. Hydrolysis under acidic and basic conditions in O-enriched H₂O indicated attack at C₂ and C₄, respectively. R-substituted 2-phenyl-4H-3,1-benzoxazin-4-one (R=H, p-Br, p-Me, p-MeO) showed Hammett ρ values under acidic and basic conditions (-0.38 and +0.71). Strong acid media inhibited hydrolysis of the phenyl and p-MeO derivatives in accordance with extensive protonation of N₁ and a lowering of the H₂O activity with the increased acidity [320].

Incorporation of a carboxylic acid at 8-position allows intramolecular protonation of N₁, which enhances susceptibility attack at C-2 and/or C-4 [80].

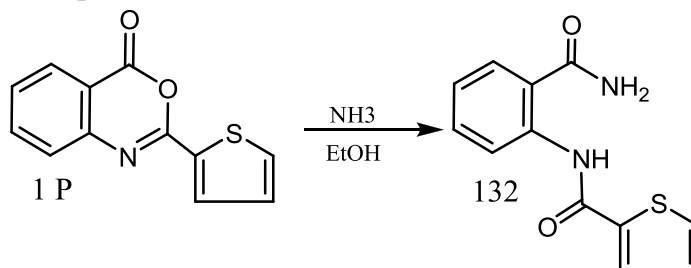


3.3 Reactions with nitrogen nucleophiles

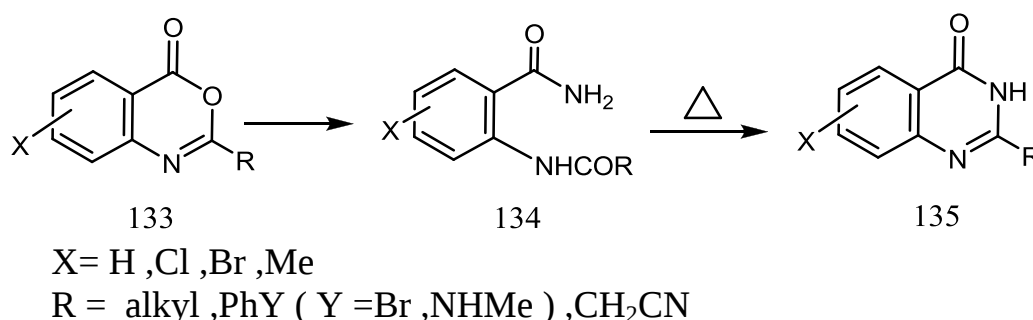
Reaction of 4H-3,1-benzoxazin-4-ones with amines is the most interesting, because of the wide range of heterocycles that can be produced either directly or through further transformations of the initially formed products.

3.3.1 Ammonolysis

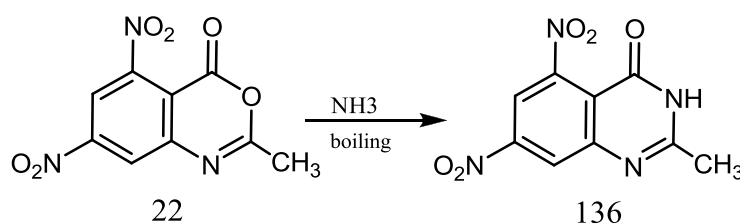
The interaction of 4H-3,1-benzoxazin-4-one derivative 1p with ammonia in ethanol produces compound 132 [76].



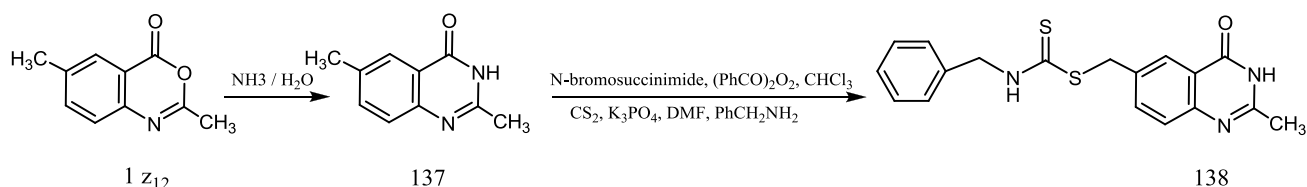
Ammonia (The simplest of amines) or ammonium hydroxide, when allowed to react with benzoxazinone derivative 133 over a period of 1-3 hours, the anthranilamide 134 is produced in good yield [233,230,317]. This in turn, can be cyclized to 3-unsubstituted-4(3H)-quinazolone 135 under thermal conditions (240-280 °C) or with acetic anhydride. quinazolone can also be produced after longer reaction times with ammonium hydroxide (6-24h.) [199,233,230] or by heating with formamide (170-175°C) [120, 119] or ammonium acetate at 130-135°C [37,169].



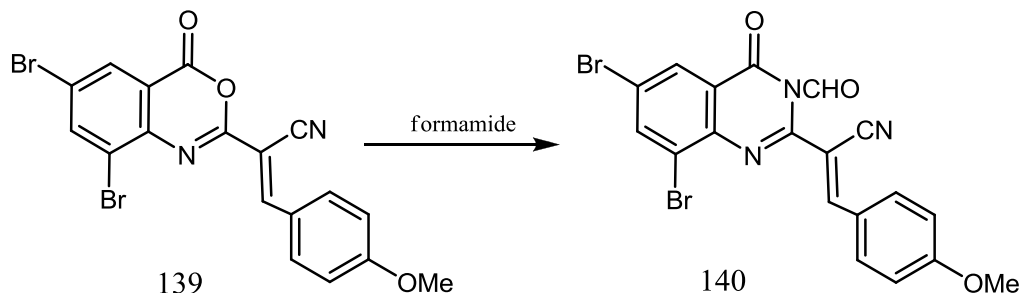
Boiling 4,6-dinitro-2-methyl-4H-3,1-benzoxazin-4-one (22) with aqueous ammonia; suffered recyclization into the corresponding quinazolone derivative 136 [177].



2,6-Dimethyl-4(3H)-quinazolinone (137) is produced via interaction of 2,6-dimethyl benzoxazinone 1z₁₂ with 25% aqueous ammonia in ethanol at room temperature for 48 hours. The obtained quinazolone 137 is converted to an interesting 6-substituted quinazolone derivative 138, which is known as a Cytotoxic active compound [61].



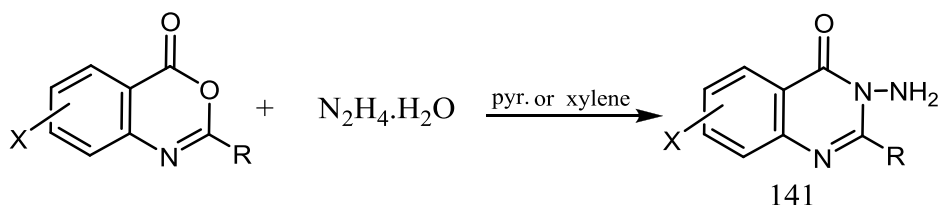
In contrast, 4H-3,1-benzoxazin-4-one derivative 139 is formylated on treatment with excess of formamide and yielded the N-formyl-quinazolinone derivative 140 [108].



3.3.2 Hydrazinolysis

3.3.2.1 Reactions with hydrazine hydrate

Heating 4H-3,1-benzoxazin-4-ones in neat hydrazine hydrate or in pyridine or xylene solutions produces the 3-amino-4-quinazolones 141 [57,26, 306, 305, 185, 270,271, 208, 78, 283].

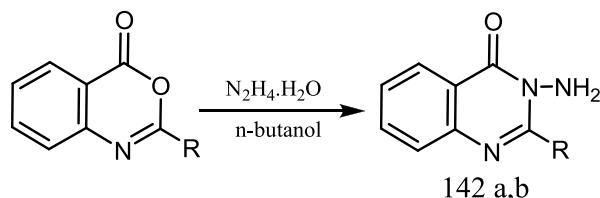


X=H, halo, Me, NO₂

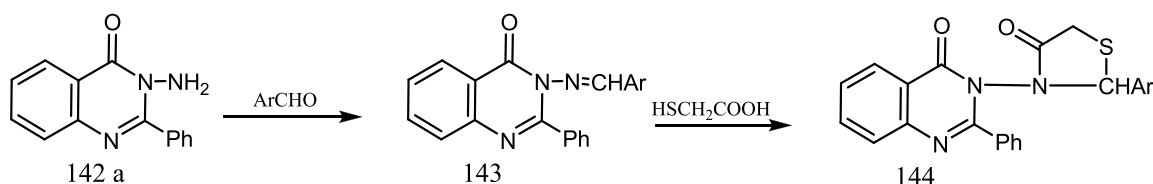
R=Me, Et, i-Pr, CF₃, Ph, 2-furyl

It was found that, cyclization on both nitrogens of the hydrazine to form a 1,3,4-benzotriazepin-5-one is not observed [305].

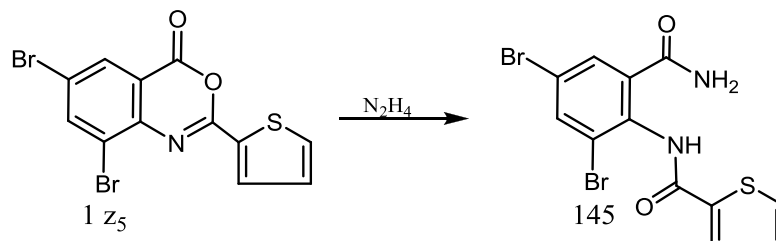
Similarly, heating benzoxazinone derivatives 1a,b with hydrazine hydrate in n-butanol afford 3-aminoquinazolinone derivatives 142 [211,210,158].



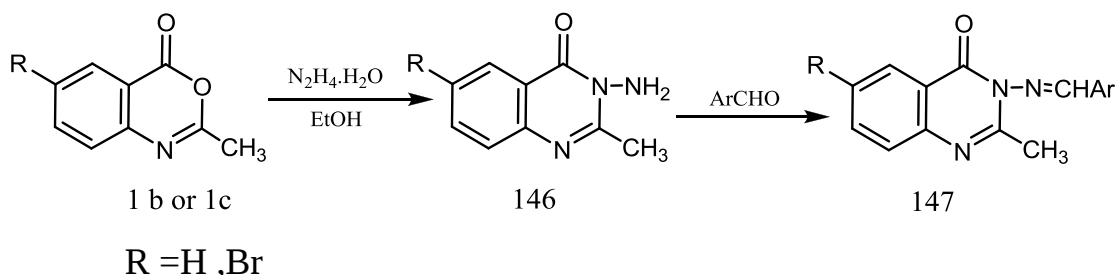
The quinazolinone 142a is reacted with aromatic aldehydes and produces the corresponding benzylidene aminoquinazolinone derivatives 143, which in turn cyclized to thiazolinone derivative 144 by its interaction with thioglycolic acid [158].



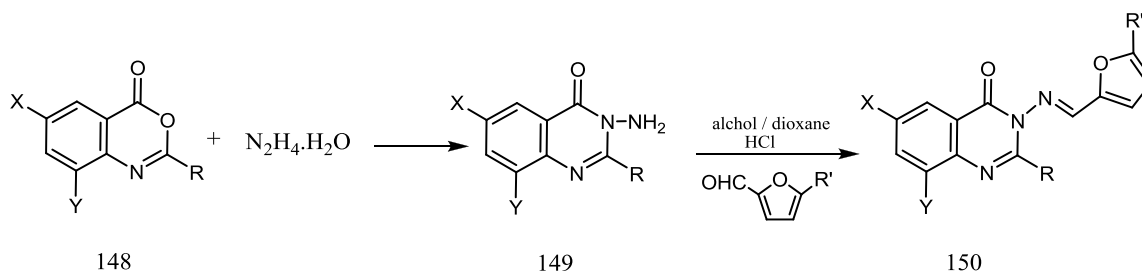
On the other hand, treatment of the benzoxazinone derivative 1z₅ with hydrazine hydrate in ethanol affords the (thienoylamino) dibromobenzamide 145 [162].



Compounds 1b and 1c undergo heteroring opening with hydrazine and give 2-methyl-3-amino-4(3H)-quinazolinone. Compounds 146 condensed with aromatic and aldehydes and give 2-styryl-3-benzyidene imino-4(3H)-quinazolinone derivatives 147 (Ar=phenyl, substituted phenyl R=H, Br) [29].

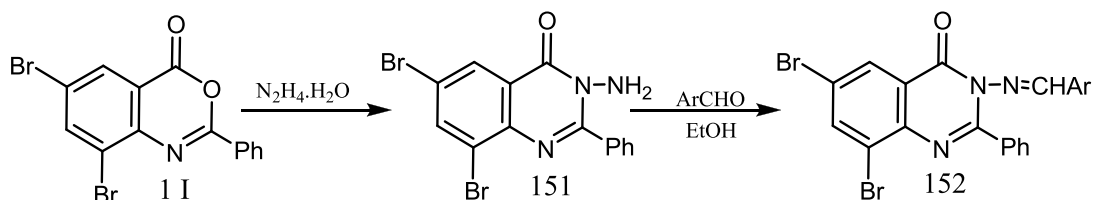


Condensation of substituted 4H-3,1-benzoxazin-4-ones 148 with hydrazine hydrate produce 3-amino-substituted quinazolinone 149. This compounds 149 treated with furan-2-aldehydes in the presence of acid catalyst forming substituted-furyl-quinazolin-4(3H)-ones 150 [254].



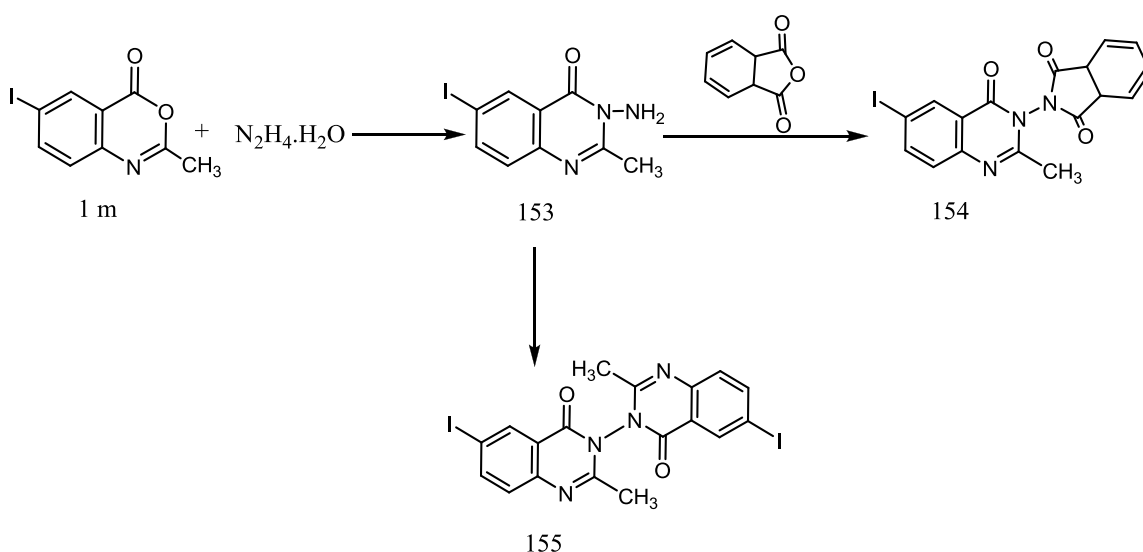
X/Y = H, Br & R = Ph, Me, n-Pr & R' = H, Me, NO₂

A series of novel hydrazones 152 are synthesized by condensation of 3-amino-6,8-dibromo-2-phenylquinazolin-4(3H)-ones 151 with different aromatic aldehydes via cyclized intermediate 6,8-dibromo-2-phenyl-4H-3,1-benzoxazin-4-one(11). The obtained hydrazones 152 are screened for its Antimicrobial activity [242].

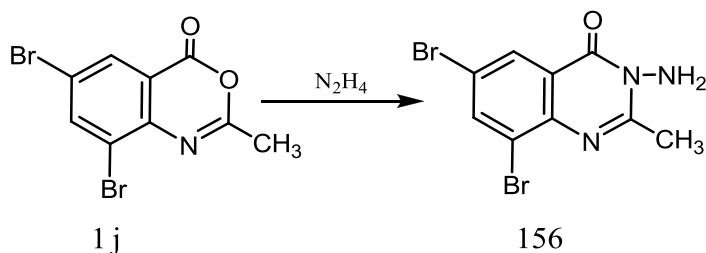


Ar = Ph, C₆H₄.OCH₃(4), C₆H₄.OH(2), C₆H₄.N(CH₃)₂(4), C₆H₄.NO₂(3),
C₆H₄.CH₃(4), C₆H₄.OH(4), C₆H₄.Cl(4), C₆H₄.NO₂(4), C₆H₂(OCH₃)₃(3,4,5),
C₆H₃.OH(4).OCH₃(3), -CH=CHPh

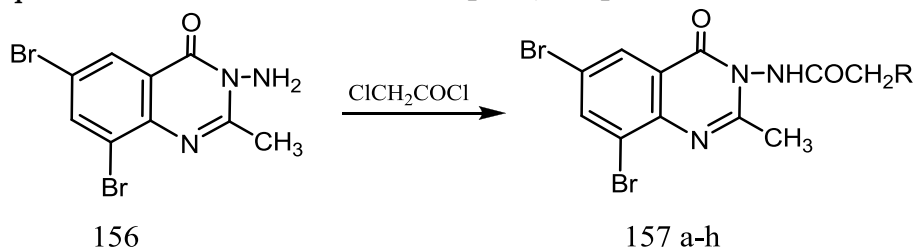
Also compound 1m reacts with hydrazine hydrate in ethanol and yields aminoidomethyl quinazolinone 153, which reacts with phthalic anhydride and gives phthalimidoquinazolinone 154. And with a second molecule of 6-iodo-2-methyl-4H-3,1-benzoxazin-4-one 1m yields 4-oxoquinazolinylquinazolinone 155 [213].



6,8-Dibromo-2-methyl-4H-3,1-benzoxazin-4-one (1j) reacts with hydrazine hydrate in ethanol and gives 3-amino- 6 ,8-dibromo-2-methyl-4(3H)-quinazolinone (156) [270,271].



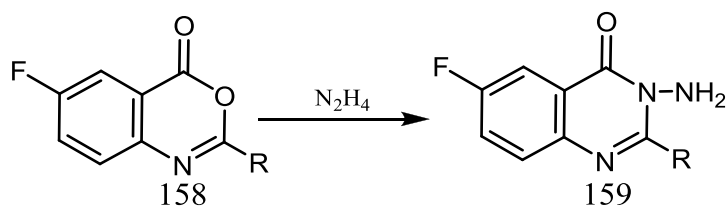
Compound 156 reacts with chloro acetyl chloride and gives N-chloroacetyl quinazolinone derivative 157a [270,271].



a	R=Cl	e	R=Et ₂ N
b	R=BuS	f	R=morpholinyl
c	R=t-BuS	g	R= piperidinyl
d	R=Me ₂ N	h	R= N ⁴ phenylpiperazinyl

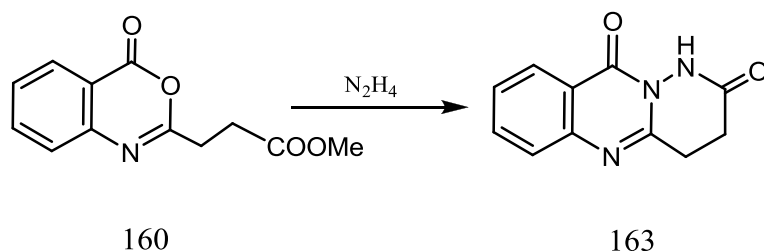
Compounds 157b-h are prepared by eventual reaction of 157a with the appropriate mercaptan or secondary amines, are tested for lethal toxicity in mice, antifungal activity in vitro (*Currularia lunata* and *Dreschlera halodis*), Analgesic activity in mice and Antiflammatory activity in rats [270,271].

In similar way as mentioned above, 6-fluoro-2- substituted 4H-3,1-benzoxazine-4-ones 158 has reacted with hydrazine hydrate and compound 159 is generated [325, 327].

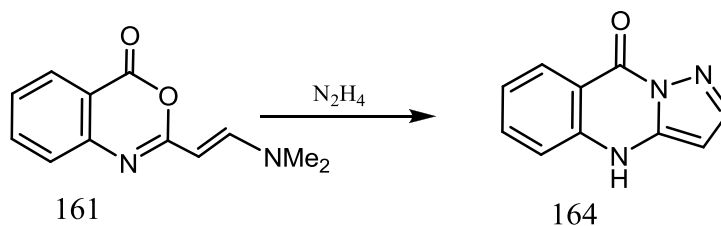


R = PhCH₂CH₂, Bn, Ph, 2-thiophenemethylene

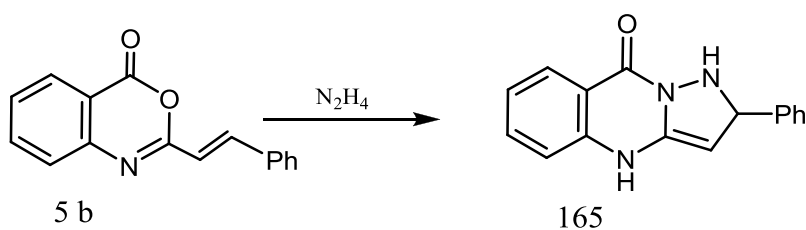
4H-3,1-benzoxazin-4-ones with additional reactive functionalities at 2-position undergo further cyclization when exposed to hydrazine hydrate, and form a variety of interesting heterocycles 163-167.



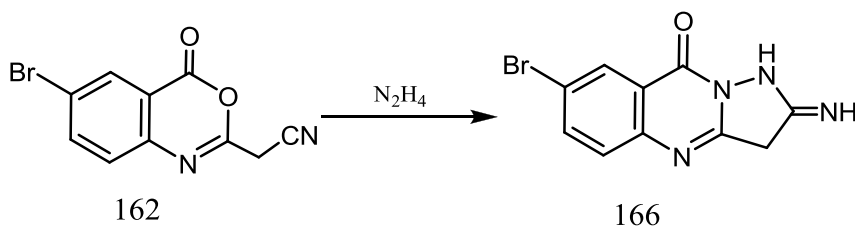
[38]



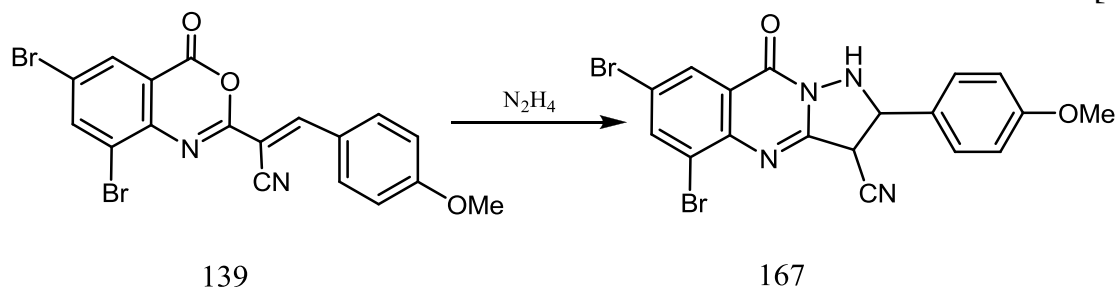
[46]



[169]

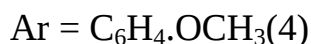
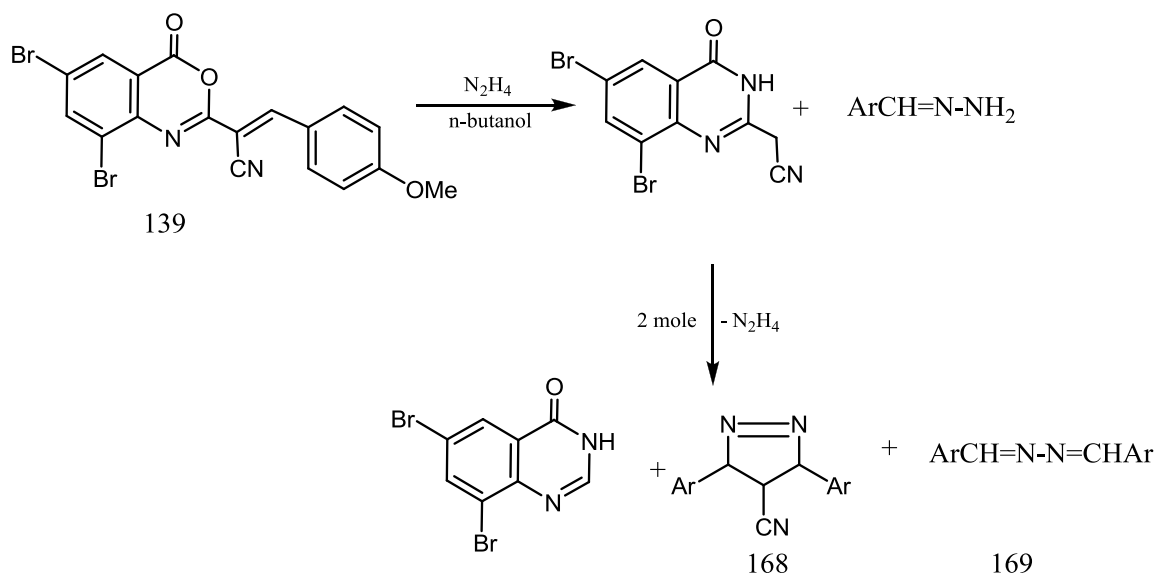


[16,17]



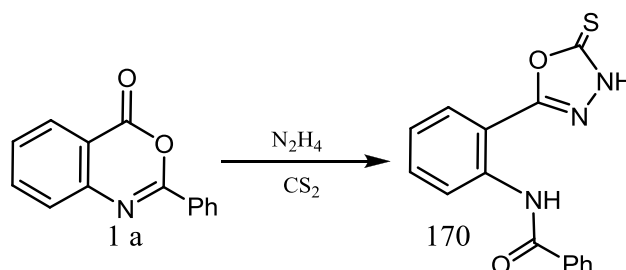
[108]

On the other hand, when the reaction of 4H-3,1- benzoxazin-4-one 139 with hydrazine hydrate is conducted in n-butanol, a mixture of 3,5 -bis-(4-methoxyphenyl)-1H-pyrazole-4-carbonitrile (168) and N,N-bis-(4-methoxybenzylidene)hydrazine (169) is obtained [108].



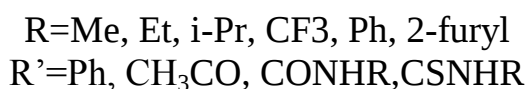
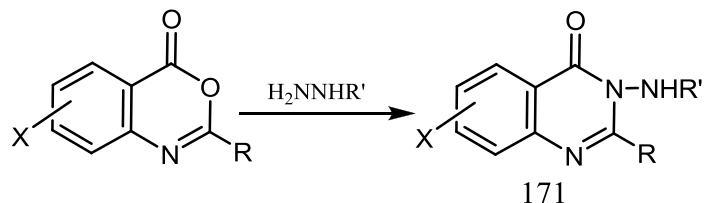
3.3.2.2 Reaction with hvdrazine hydrate in presence of carbondisulphide

When the reaction of 4H-3,1-benzoxazin-4-one 1a with hydrazine hydrate is conducted in the presence of carbon disulphide in alcoholic potassium hydroxide, the 1,3,4-oxadiazolin-5-thione 170 is produced directly [164].

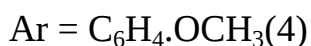
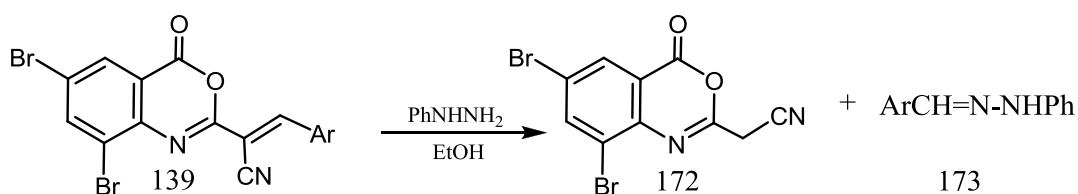


3.3.2.3 Reaction with substituted hydrazines

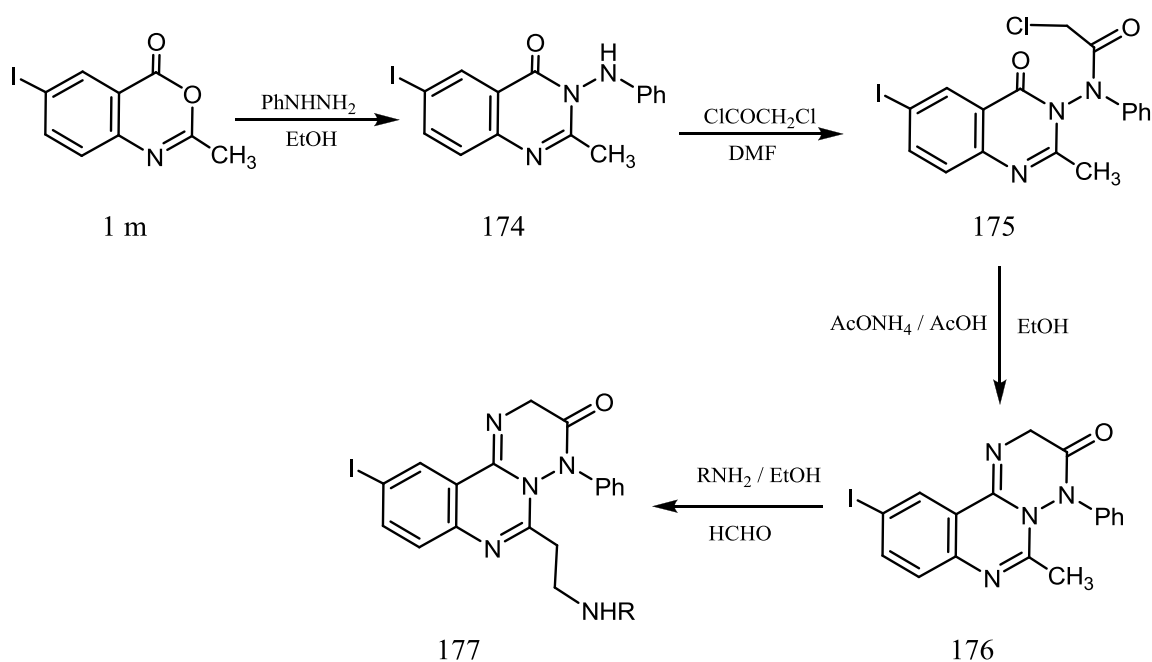
Substituted hydrazines react likewise in solvents such as benzene, pyridine, ethanol, or acetic acid to furnish 3-N-substituted quinazolinone derivatives 171, where R can be phenyl [213], acyl [5], ($C=XNHR$ ($X=O$ or S) [158], and others [9,299].

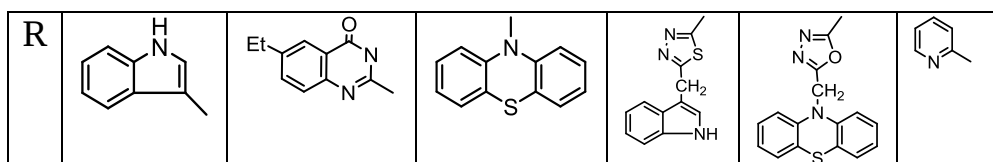


4H-3,1-benzoxazin-4-one 139 is reacted with phenyl hydrazine in the same manner like reaction with hydrazine hydrate, it gives a mixture of carbonitrile 172 and hydrazine derivative 173 [108].

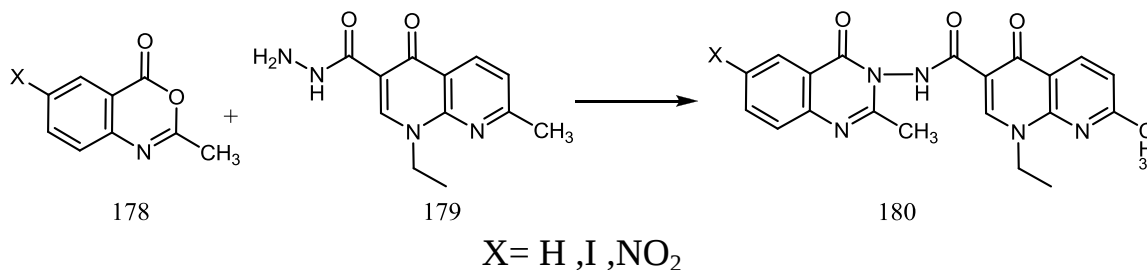


Hydrazinolysis of benzoxazinone derivative 1m using phenyl hydrazine furnishes the quinazolinone derivative 174. It is used in synthesizing some triazino-quinazoline derivatives 177 by introducing aromatic nuclei via Mannich reaction with arylamines [279].

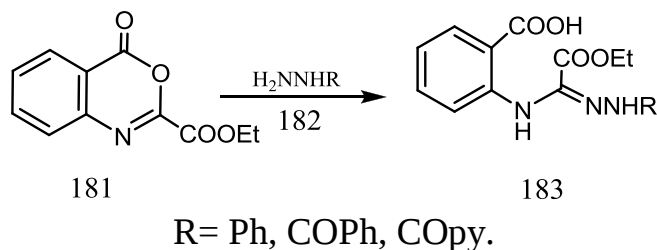




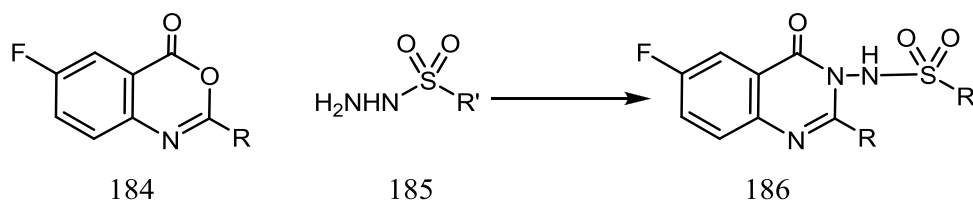
Interaction of 2-methyl-4H-3,1-benzoxazin-4-one derivatives 178 with nalidixic acid hydrazide 179 yield substituted 3,1-quinazol-4-one derivatives of nalidixic acid 180, which exhibited inhibitory activity against *A. hydrophila* [135].



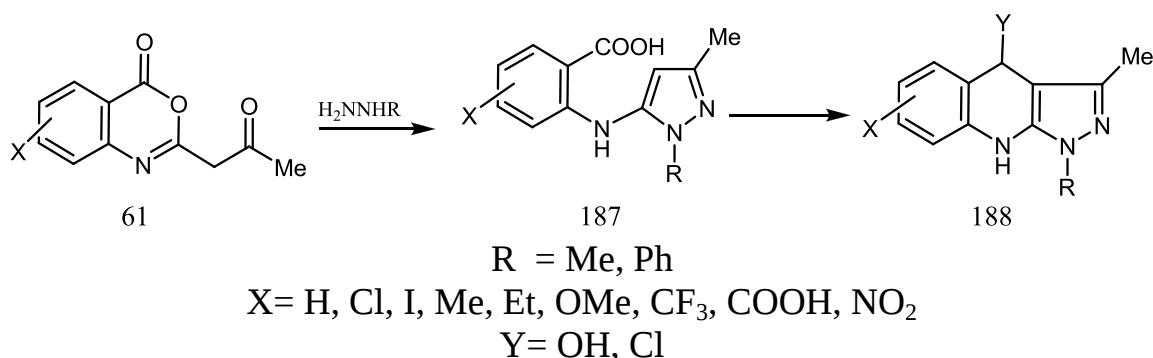
When 2-ethoxycarbonyl-4H-3,1-benzoxazine-4-one (181) treated with substituted hydrazines 182, the hydrazones 183 are isolated [229].



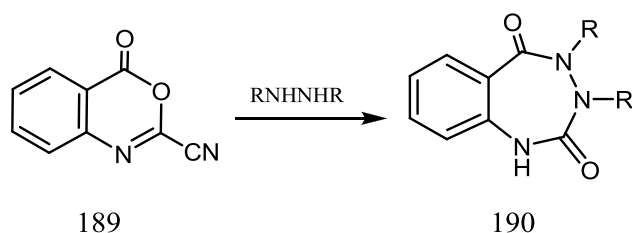
Combining 4H-3,1-benzoxazin-4-ones 184 acid substituted sulphonylhydrazides 185 devoid of solvents, followed by heating at 160 °C (oil bath) gave compounds 186 as the major products [327].



Reactions of acetyl benzoxazinones 61 with methylhydrazine or various phenylhydrazines affording the pyrazolyl anthranilic acids 187. Cyclization of these intermediates with a mixture of phosphorus pentoxide and polyphosphoric acid providing the 4-hydroxypyrazolo [3,4- d]quinazoline 188 (Y = OH) [63,288], whereas cyclization with phosphorus oxychloride gives the 4-chloro analog 188 (Y = Cl) [73,72].



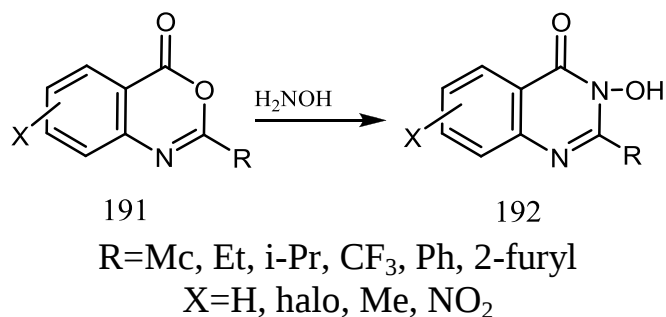
Symmetrically disubstituted hydrazines are reacted with cyano derivative 189 with loss of HCN to produce 1,3,4- benzotriazepin-2,5-diones 190 [292].



$\text{R} = \text{Me, Et, i-Pr}$

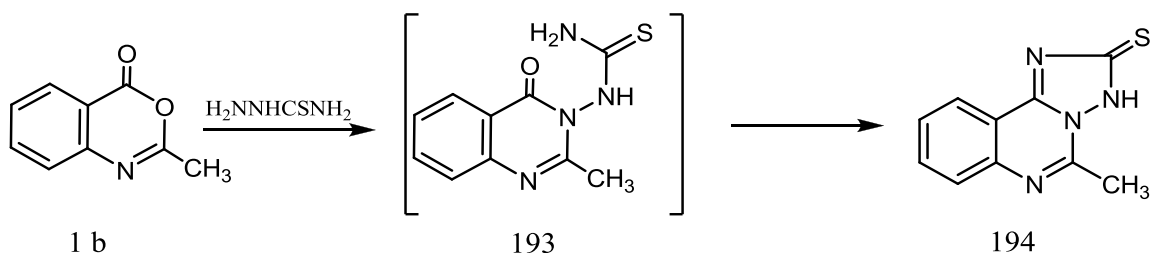
3.3.2.4 Reactions with hydroxylamine hydrochloride

Reaction of 4H-3,1-benzoxazine-4-one derivatives 191 with hydroxylamine hydrochloride in refluxing pyridine afford 3-hydroxy-4-quinazolinone derivatives 192 [50, 92, 121, 161].

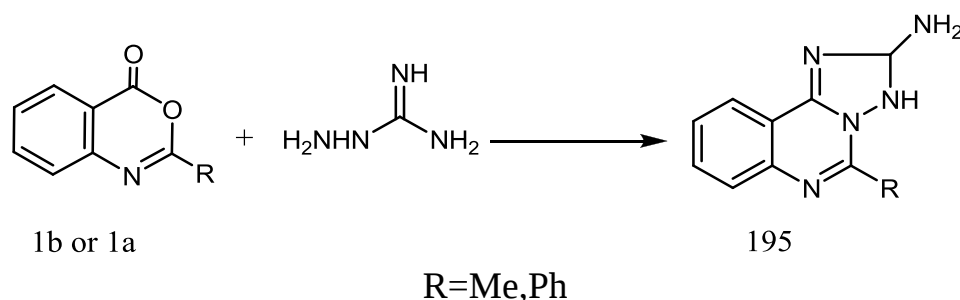


3.3.2.5 Reactions with thiosemicarbazide and aminoguanidines

If heating 2-methyl-4H-3,1-benzoxazin-4-one (1b) with thiosemicarbazide in acetic acid in the presence of fused sodium acetate, the conversion does not stop at the thiocarbamide intermediate 193 but continues to cyclodehydrate providing 194 [159].



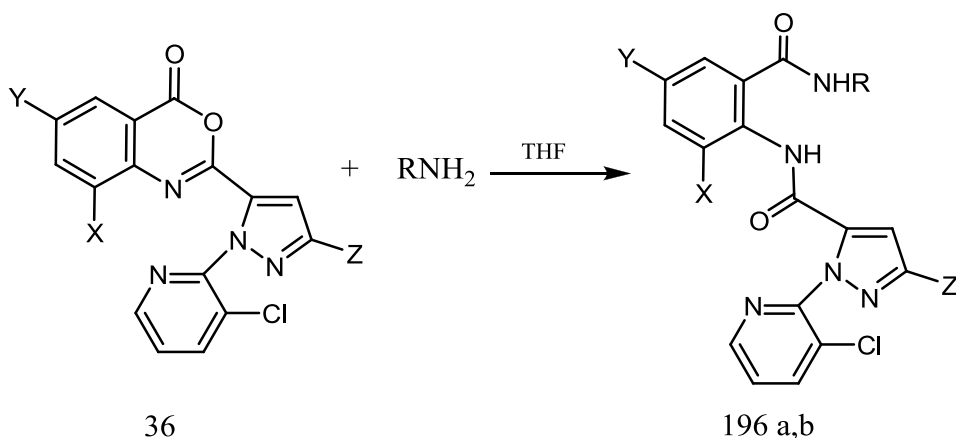
In a similar fashion, refluxing 2- phenyl (or methyl)-4H-3,1-benzoxazin-4-ones (1a or 1b) with aminoguanidine in pyridine to afford the amino derivatives 195 [71].



3.3.3 Aminolysis

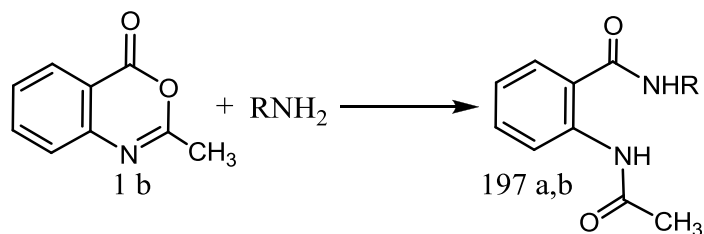
3.3.3.1 Reactions with primary nonaromatic amines

In many cases, acylantranilamides are the products of the interaction of 4H-3,1-benzoxazin-4-ones with primary amines (due to the weak nucleophilicity of primary amines in comparison with aromatic amines and consequently depend on the mode of attacking the benzoxazinone moiety). Reaction of 4H-3,1-benzoxazinone 36 with isopropyl amine and/or methylamine in THF produced the corresponding pyridylpyrazole anthranilic diamides 196. Compounds 196 have insecticidal potency and a Calcium mobilization threshold (CMT).



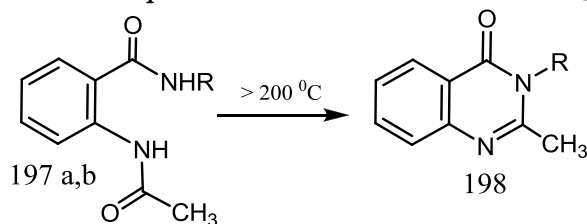
a; X= Cl, Me	[190,192]
Y=H,Cl	
Z=CF ₃	
R=i-Pr	
b ; X=CH ₃	[191]
Y=H,Cl,Br,I,CF ₃	
Z=Br,Cl, CF ₃ , OCH ₃ , OCF ₂ H,	
OCH ₂ CF ₃ R = Me, i-Pr	

Reactions of 4H-3,1-benzoxazin-4-one 1b with isopropyl amine and/or t-butylamine produces N-acylantranilamide 197 [114,118].

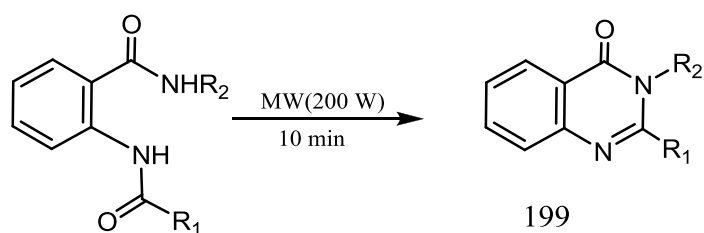


a, R = $-\text{CH}(\text{CH}_3)_2$ b, R = $-\text{C}(\text{CH}_3)_3$

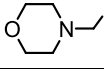
N-acylantranilamide **197** requires temperatures above 200°C to affect cyclization into 3-substituted quinazolinone derivative **198** [115, 117].



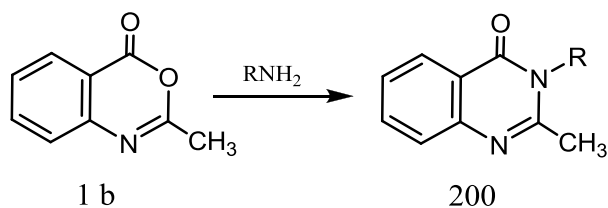
Instead of using high temperature to effect cyclization, microwave-assisted cyclocondensation is used to obtain 2,3-disubstituted quinazolinone **199** [179].



R1 = Me, Et

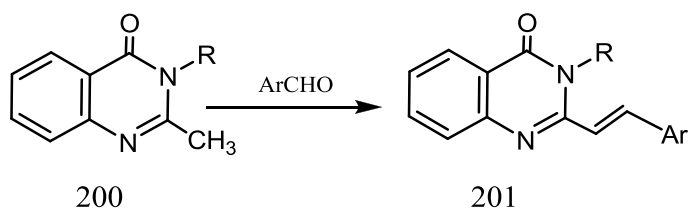
R2 = Me, n-Bu, Et_3N , , 

Simple straight-chain alkylamines as methyl and n-butyl amines react with benzoxazinone **1b** to afford 3-substituted-4-quinazolinones **200** [207].



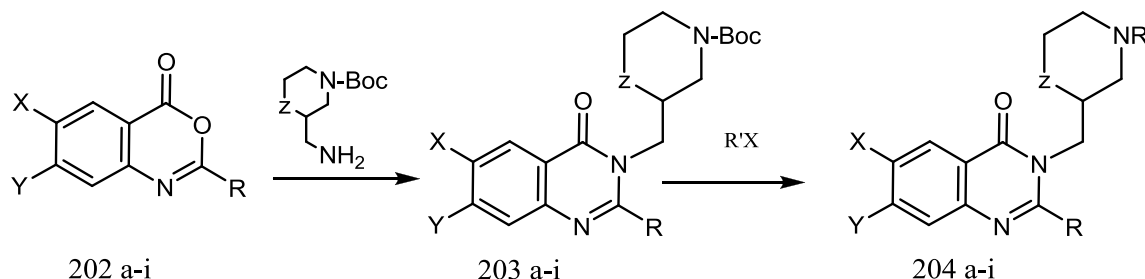
R = Me, n-Bu

2-Methylquinazolinone **200** can be easily homologated to styryl derivative **201** by refluxing it with an appropriate aldehyde [32].



R = Me, n-Bu Ar = Ph, naphthyl, 2-furyl

4H-3,1-benzoxazin-4-one 202 furnishing 3-substituted quinazolin-4(3H)-one 204 via insertion of Boc-protected aminomethylpiperidine or 3-aminomethylmorpholine, led to intermediate 203 which is deprotected and subsequently is alkylated using reductive amination or nucleophilic substitution conditions [261].

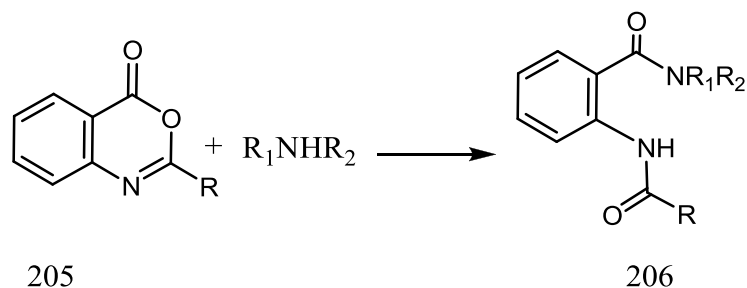


The compounds thus obtained are collected in the following table

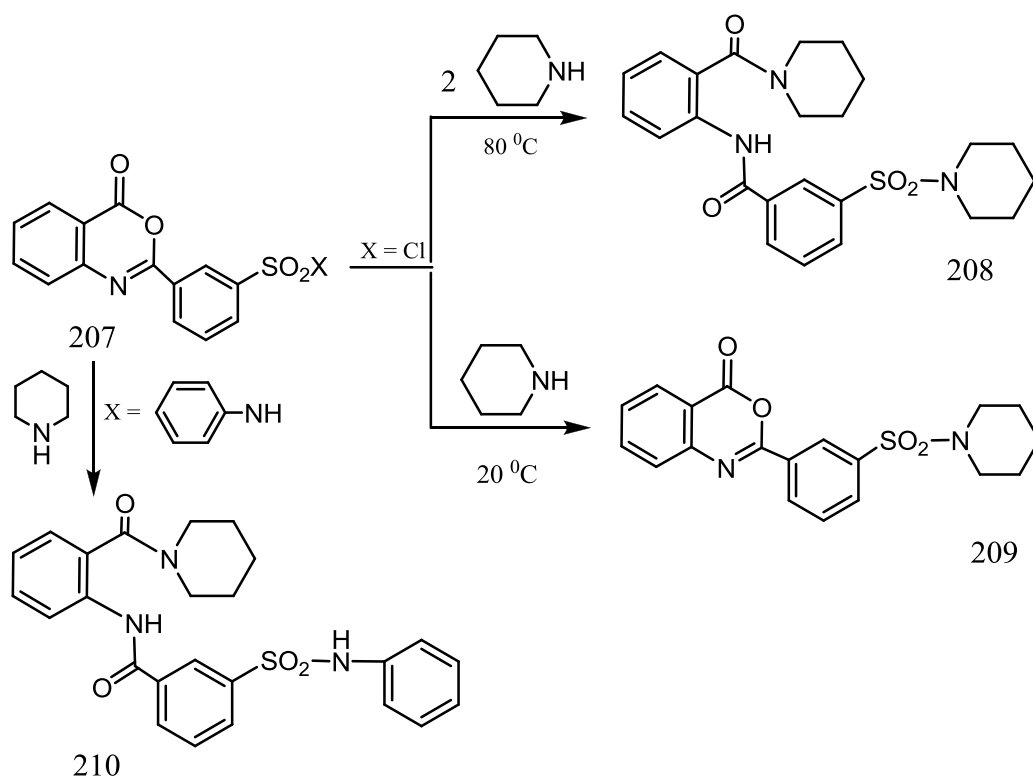
	X	Y	Z	R	R'
a	C ₆ H ₄ Cl(4)	H	CH ₂	C ₆ H ₄ CH ₃ (2)	Et, i-Pr, (CH ₂) ₃ CH-, (CH ₂) ₂ OCH ₃ , (CH ₂) ₂ F, EtCF ₃ , n-Pr-CF ₃
b	C ₆ H ₄ Cl(4)	H	CH ₂	C ₆ H ₄ OCH ₃ (2)	Et
c	F.C ₆ H ₄ (4)	H	CH ₂	i-Pr	Et
d	H	H	CH ₂	C ₆ H ₄ CH ₃ (2)	i-Pr
e	OCH ₃	H	CH ₂	C ₆ H ₄ OCH ₃ (2)	Et
f	OCH ₃	H	CH ₂	C ₆ H ₄ CH ₃ (2)	Et
g	F.C ₆ H ₄ (4)	H	CH ₂	C ₆ H ₄ CH ₃ (2)	H, i-Pr
h	Br	H	O	C ₆ H ₄ CH ₃ (2)	Bn, H, i-Pr
i	H	C ₆ H ₄ Cl(4)	CH ₂	C ₆ H ₄ OCH ₃ (2)	Et

3.3.3.2 Reactions with secondary amines

In a similar fashion, as isopropyl and/or t-butylamines are reacted with 4H-3,1-benzoxazin-4-ones 205 and produce N-acylanthranilamides 206. Also secondary amines such as dimethylamine, morpholine, piperidine, and pyrrolidine are reacting and produce N-acylanthranilamides 206 [71].



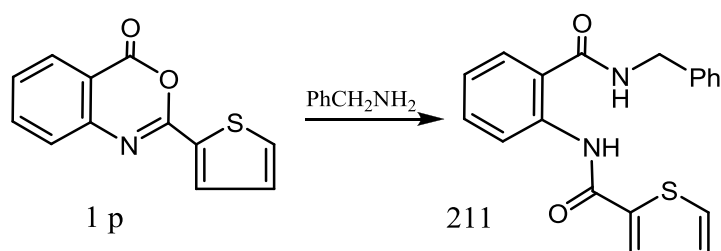
4H-3,1-benzoxazin-4-ones 207 with sulphonyl group introduced at 2-position are reacting with piperidine under different reaction conditions leading to 208-210. It gives an idea about the extent of the reactivity of the benzoxazinone fragment, where the chlorosulphonyl group is more reactive than the benzoxazinone fragment toward amines [294].



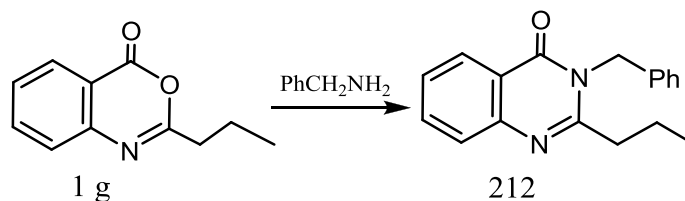
3.3.3.3 Reactions with alkylamines

3.3.3.3.1 Reactions with benzylamine

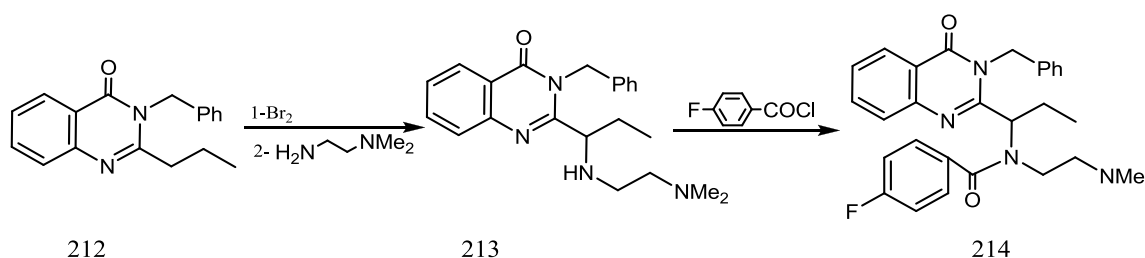
Treatment of benzoxazinone 1p with benzylamine in ethanol affords N-acetylanthranilamides 211 [76].



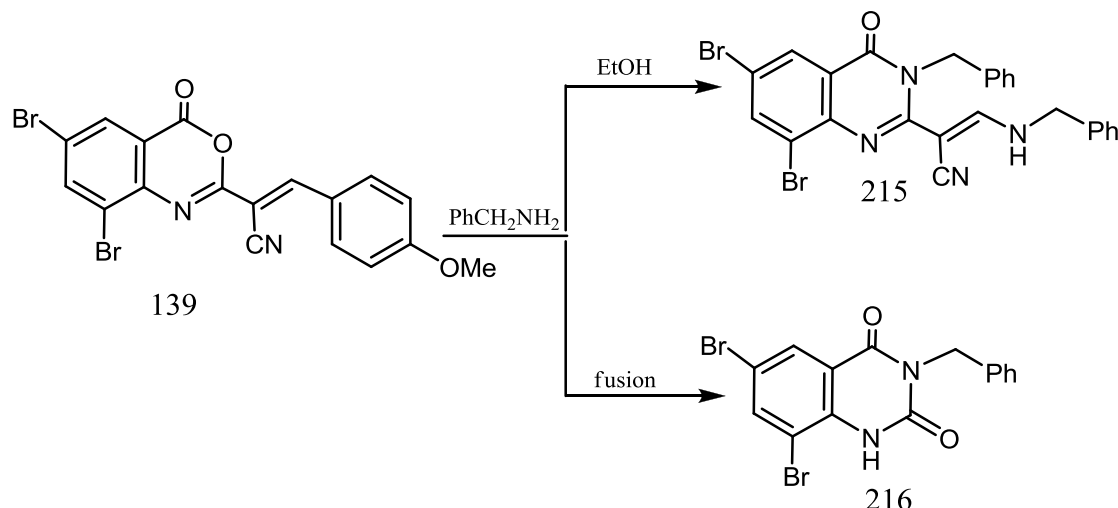
On the other hand, treatment of 2-propyl-4H-3,1-benzoxazin-4-one (1g) with benzylamine yields 3-benzyl quinazolinone 212 [126].



Bromination of quinazolinone 212 followed by addition of N,N-dimethyl ethylene diamine produces 213. The latter quinazolinone 213 reacts with 4-fluorobenzoyl chloride to furnish 214. Compound 214 is a biologically active compound and useful in treatment of Cancer, Hyperplasia, Restenosis immune disorders and inflammation [126].

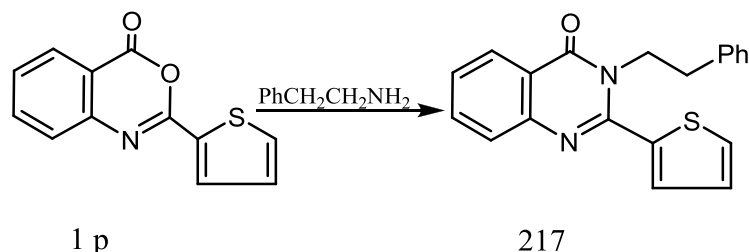


2-Substituted acrylonitril-4H-3,1-benzoxazin-4-one 139 reacts with benzylamine under different reaction conditions in order to give a mixture of N-benzylquinazolinone derivative 215 and quinazolin-2,4-dione 216 [108].

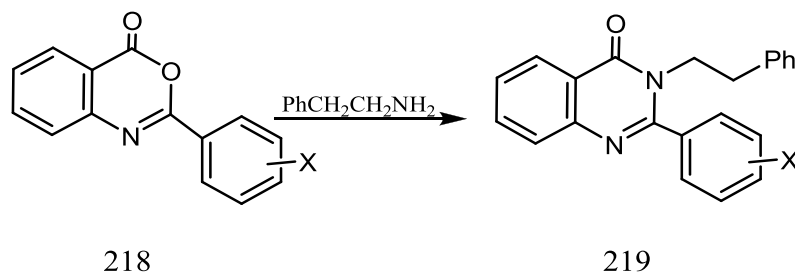


3.3.3.3.2 Reactions with phenylethylamine

Search for novel drug-like Calcilytics identified a new quinazolinone derivative 217 formed via heating 4H-3,1- benzoxazin-4-one 1p with phenethylamine [319].

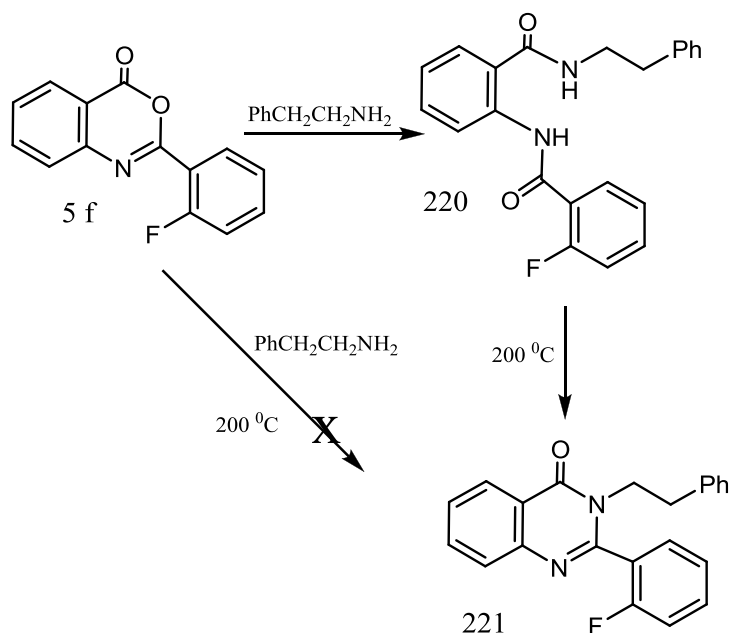


Similarly, refluxing 2-phenyl (or substituted phenyl)-4H- 3,1-benzoxazin-4-ones 218 with a 10 fold excess of phenethylamine for 2-3 hours at 200 °C produce the corresponding 4(3H)-quinazolin-4-one derivatives 219 [273].



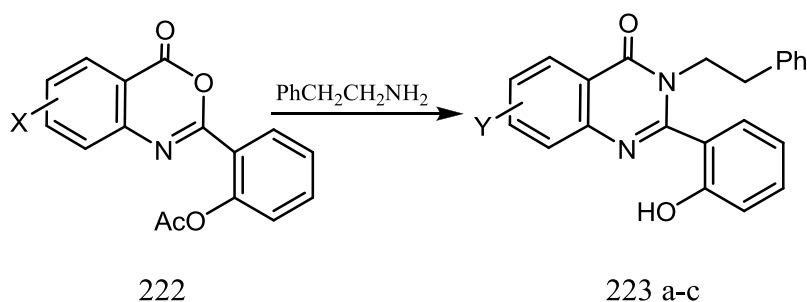
X = H, 3-F, 3-OMe, 4-OMe, 2-OH, 3-OH, 4-OH, 2,5-di-OH

Similarly, fusion of 2-(2-fluorophenyl)-substituted benzoxazinone 5f and phenethylamine at 200 °C, resulted in the dominant nucleophilic displacement of fluorine substituent with the amino moiety .For preservation of the 2-(2-fluorophenyl) fragment, synthesis of the intermediate bisamide 220 was carried out in pyridine at 120 °C followed by thermal cyclization to 2-(2-fluorophenyl)-3-phenethyl-3H-quinazolin-4-one (221) [273, 313].



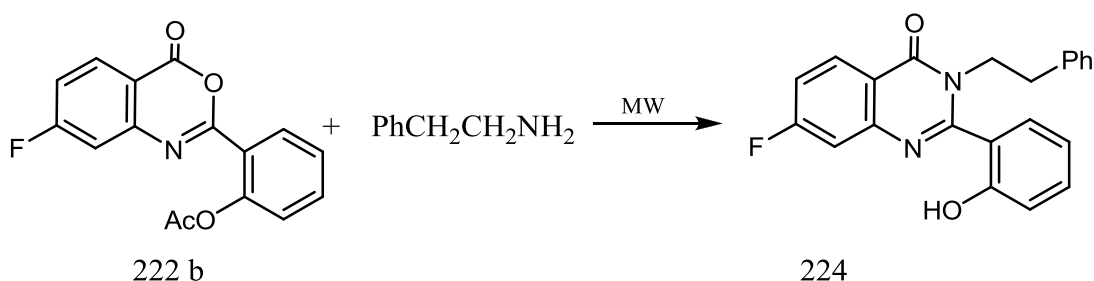
Benzoxazinones 222 bearing fluorine at 5, 7, or 8- position are submitted to the latter reaction with phenethylamine lead to amino-substituted quinazolinones 223 (where undesired nucleophilic displacement of the fluorine by the amine

occurs), probably due to the reaction conditions (elevated temperature and absence of solvent) [273].

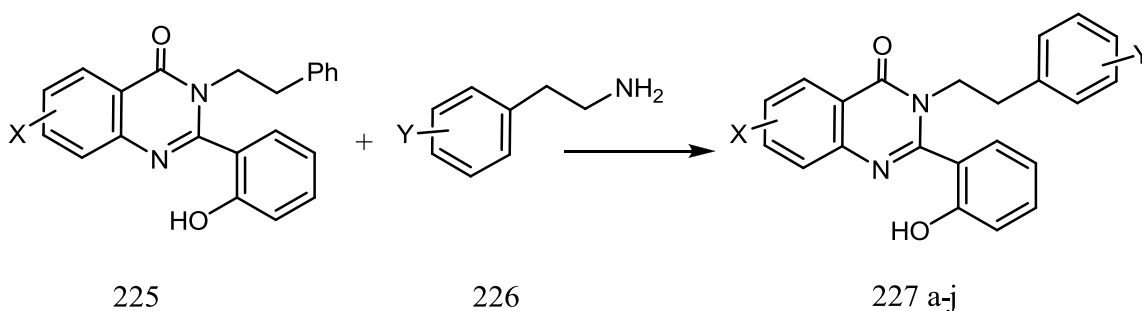


a	X= 5-F	Y= 5-PhCH ₂ CH ₂ NH
b	X= 7-F	Y= 7- PhCH ₂ CH ₂ NH
c	X= 8-F	Y= 8- PhCH ₂ CH ₂ NH

Applying microwave irradiation to the above benzoxazinone 222b results 7-fluoro-substituted quinazolinone 224, whereas 5- and 8-fluoro-substituted benzoxazinones 222a,c still produce products of nucleophilic displacement 223 a,c [273].



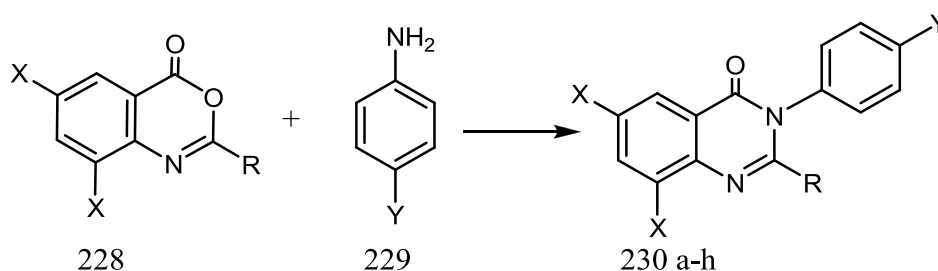
A series of 2-(2-hydroxyphenyl)-3-phenethylquinazolin-4(3H)-one 227 are prepared in the same fashion starting from 2-(2-hydroxyphenyl) substituted benzoxazinones 225 and phenethyl amines 226 [273].



	X	Y
a	8-Me	H
b	7-F	H
c	7-Cl	3-F
d	6-Cl	H
e	5-Me	3-F
f	H	3-Cl
g	6-Me	H
	X	Y
h	5-Me	3-F
i	6-F	H
j	6-F	3-F

3.3.3.4 Reactions with anilines

Several experimental conditions for the reactions of anilines with 4H-3,1-benzoxazin-4-ones are reported. The reactants can be combined neat at room temperature [249], at elevated temperature ranging from 150- 220 °C [287, 282, 152, 157] or at 150-180°C in the presence of zinc chloride [87, 214, 7]. Alternatively, the reaction can be performed in solvents such as pyridine [296,280], dioxane [90,16,17], acetic acid [206], dimethylformamide or ethanol [90,154]. Substituted anilines 229 afforded quinazolinones 230 when reacted with substituted benzoxazinones 228.



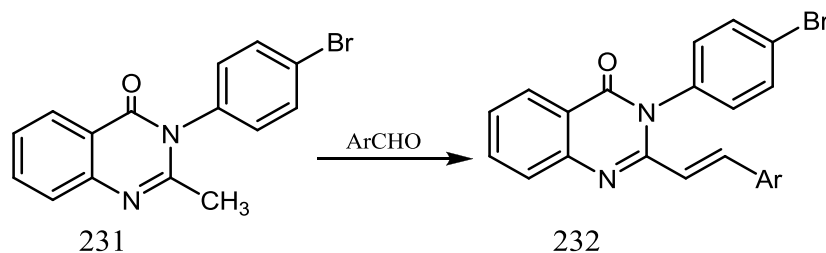
X=H, halo

R= Me, CH₂Cl, Ph, CH₂Ph, COOEt

	Y	Ref.
a	Halo	[90]
b	Me	[154]
c	OH	[183, 281, 182]
d	OMe	[258]
e	Phenoxy	[33]
f	NO ₂	[11,286]
g	SO ₂ NH ₂	[231,232,33]
h	COOEt	[23,207]

3.3.3.4.1 Reactions with p-bromoanilines

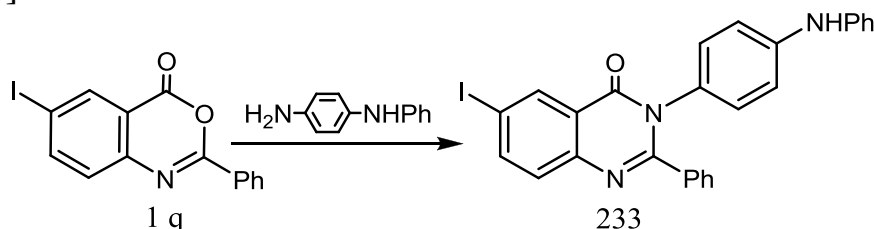
p-Bromoaniline for example, reacts with benzoxazinone 1b in ethanol and affords 3-(bromophenyl)-2-methyl-3H-quinazolin-4-one (231) [122].



Ar = Ph, 4-Cl-Ph, 2-thienyl, 4-OMePh

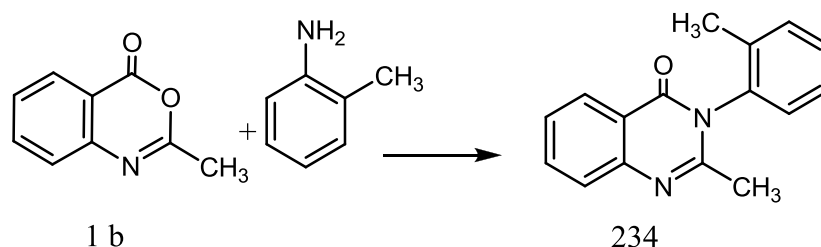
3.3.3.4.2 Reactions with p-aminodiphenylamine

In similar fashion, interaction of 2-phenyl-6-iodo-4H-3,1-benzoxazin-4-one (1q) with p-aminodiphenylamine yields 6-iodo-2-phenyl-3-(4'-phenylaminophenyl)-quinazolin-4-one (233) [131].

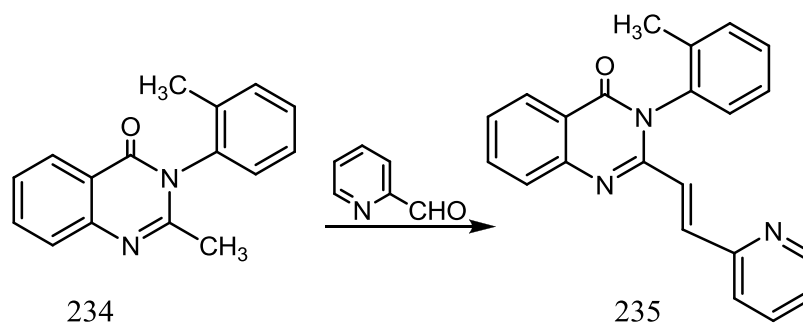


3.3.3.4.3 Reactions with o-toluidine

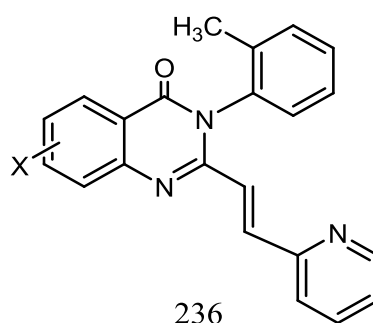
Refluxing a mixture of benzoxazinone 1b and o-toluidine in toluene under azeotropic conditions furnishes the CNS agent Methaqualone 234 [257].



The above reaction also can be conducted in acetic acid followed by condensation of the produced quinazolinone 234 with 2-pyridinecarboxaldehyde in the presence of zinc chloride and provided 2-[(pyridine-2-yl)vinyl]-3-(2-methylphenyl)-quinazolin-4(3H)-one (235), which is known as Piriqualone and it was tested as anticonvulsant agent [318].

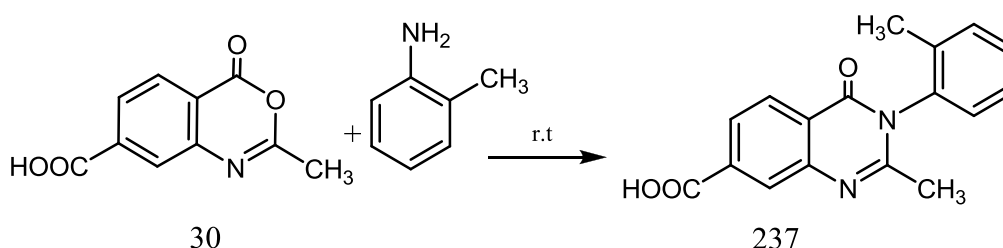


Starting from substituted 2-methyl-4H-3,1-benzoxazin-4-ones, a series of 3-(2-methylphenyl)-2-[(2-pyridyl)vinyl] quinazolones 236 is obtained [318].



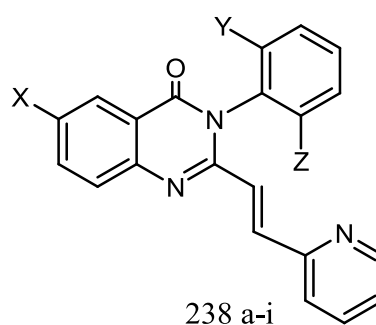
X = 6-CR₃, 6-F, 6-Cl, 7-Cl, 8-Cl, 6,8-Cl₂, 6-Br, 8-OCR₃, 6,7-(OCH₃)₂

7-Carboxyquinazolinone 237 is synthesized by mixing benzoxazinone 20 and o-toluidine at room temperature for 3-4 hours [249].



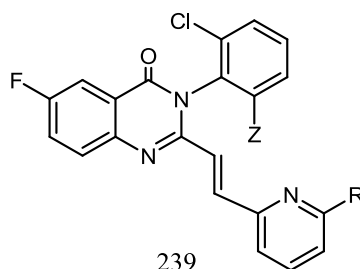
3.3.3.4.4 Reactions with 2-substituted and/or 2,6-disubstituted anilines

A variety of 2-substituted and/or 2,6-disubstituted anilines interact with substituted 4H-3,1-benzoxazin-4-ones to produce quinazolinone derivatives 238 [318].



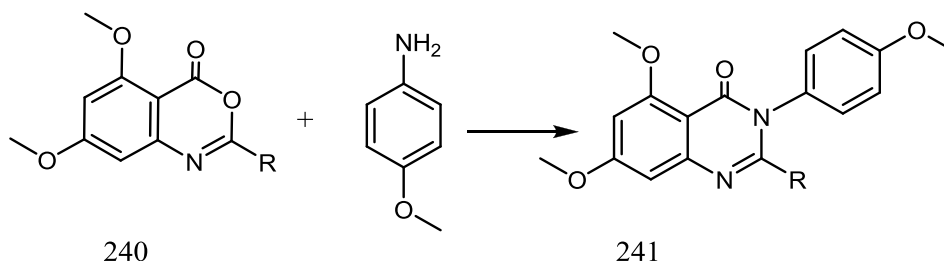
	X	Y	Z		X	Y	Z
a	H	F	H	g	F	Cl	H
b	H	Cl	H	h	F	Br	H
c	H	Br	H	i	H	H	H
d	H	CF ₃	H	j	H	CH ₃	CH ₃
e	H	OCH ₃	H	k	H	Cl	Cl
f	F	F	H	L	F	F	F

In a similar fashion, a series of 3-(2-chlorophenyl)-2- substituted quinazolones 239 is prepared and their biological activity are tested. They are identified as antagonist template for AMPA receptors (play an important role in pharmacological studies of glutamate receptors) [65].



R		
H	CH ₃ OCH ₂	piperidine
CH ₃	CH ₃ CH ₂ OCH ₂	(CH ₃) ₂ CHNHCH ₂
CHO	CH ₂ F	(CH ₃) ₂ NCH ₂ CH ₂ N(CH ₃)CH ₂
CH ₂ NH ₂	CN	(C ₂ H ₅) ₂ NCH ₂
COOH	COOCH ₃	(CH ₃) ₂ NCH ₂
CH ₂ OH	C ₂ H ₅ NCH ₂	CH ₃ NHCH ₂
AcOCH ₂	pyrrolidine	

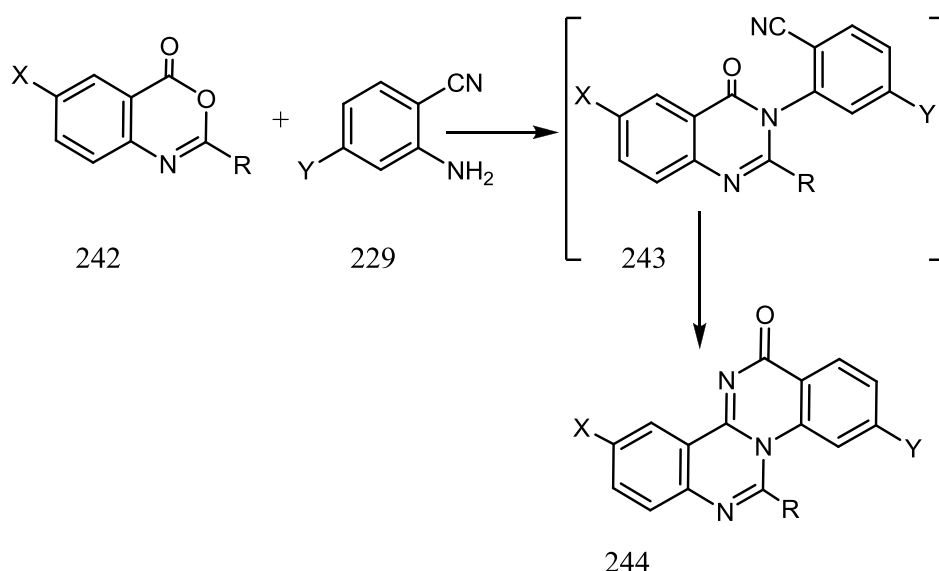
5,7-Dimethoxy-2-substituted benzoxazinones 240 are reacted with p-methoxyaniline either via refluxing in xylene for 4 hours or in acetic acid at 60 °C for 24 hours and afforded 3-(4-methoxy phenyl)-4(3H)-quinazolinone 241 [136].



R = H, Me, Et, n-Pr, n-Bu, i-Bu

3.3.3.4.5 Reactions with anilines containing reactive function groups

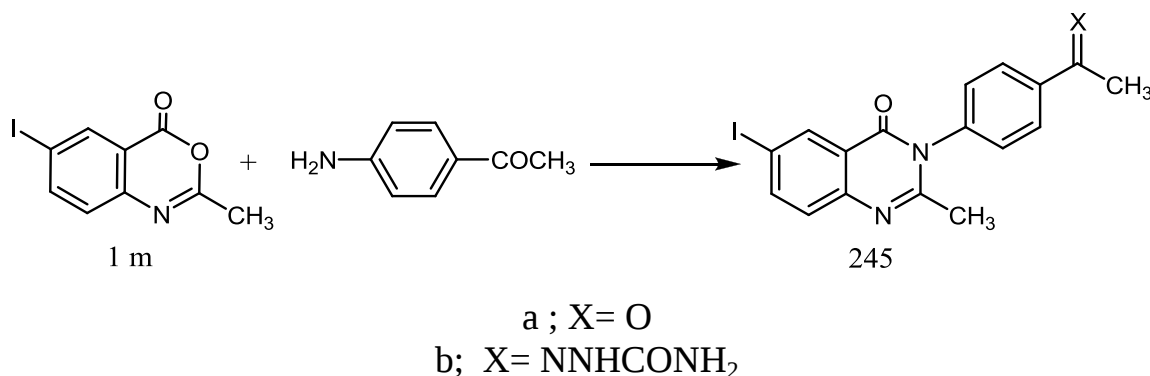
3.3.3.4.5.1 Reaction with 2-cyanoanilines



X = H, Cl, Me & Y = H, Cl, Me & R = Me, n-Pr, i-Pr

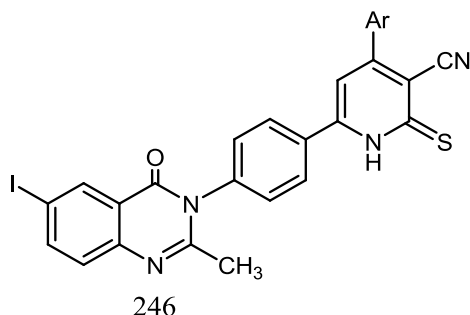
3.3.3.4.5.2 Reactions with p-aminoacetophenone

Benzoxazinone 1m condenses with 4-amino acetophenone in n-butanol and gives 2-methyl-6-iodo-3-(4'- acetylphenyl)-quinazol-4-one (245a,b) [130].



The semicarbazone 245b was obtained from 245a by refluxing with an equimolar amount of semicarbazide hydrochloride in ethanol [130].

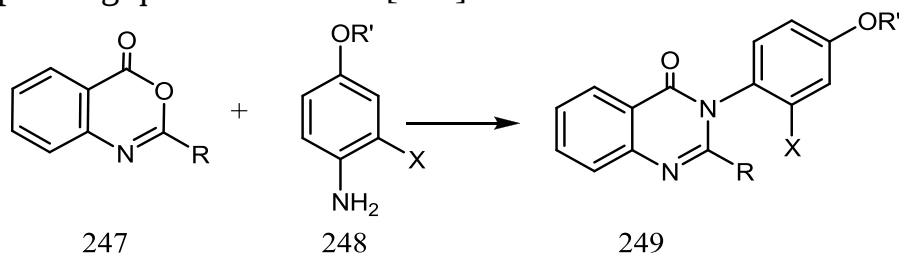
Cyanopyridin-2-(1H)-thione derivatives were obtained via the reaction of arylmethylene-cyanothioacetamide ($\text{ArCH}=\text{C}(\text{CN})\text{CSNH}_2$) with the active methylene carbonyl quinazolone 245b. An assay for Antitumor activity showed that compound 246 ($\text{Ar} = 4\text{-OCH}_3\text{C}_6\text{H}_4$) has a significant activity against Ehrlich Acites Carcinoma tumor cells (in vitro) and displayed a significant percent of the nonviable tumor cells to about 40% and 80% at concentration of 10 and 100mg, respectively [130].



Ar= Ph, 4-pyridyl, 2-thienyl

3.3.3.4.5.3 Reactions with 4-hydroxyanilines

Treatment of 4H-3,1-benzoxazin-4-ones 247 with 4- hydroxyanilines 248 yield the corresponding quinazolone 249 [245].

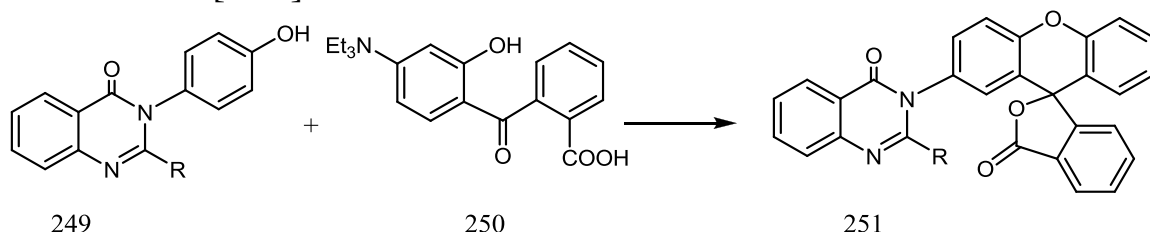


R = Me, Ph, CH₂Cl, CH₂Ph

a; R' = H, X = H

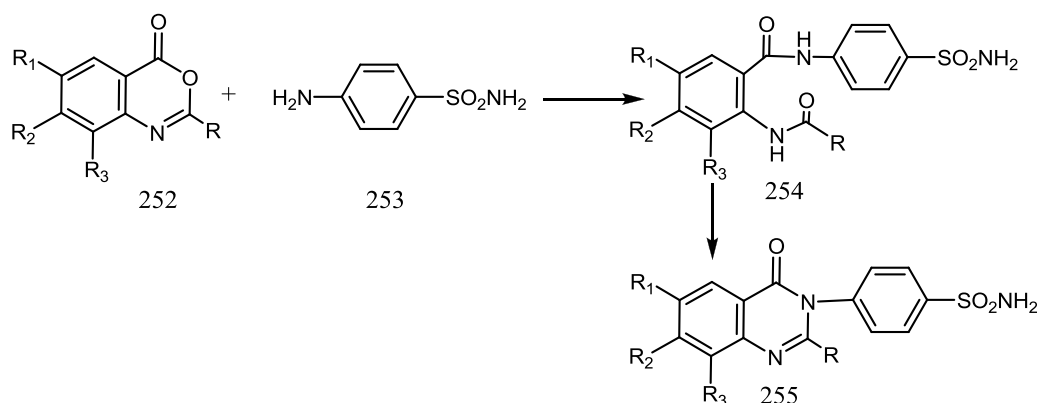
b; R' = Me, X = NO₂

The latter quinazolones 249 react with 2-(4- diethylamino-2-hydroxybenzoyl)benzoic acid (250) in the presence of sulphuric acid to produce fluorans 251 [245].

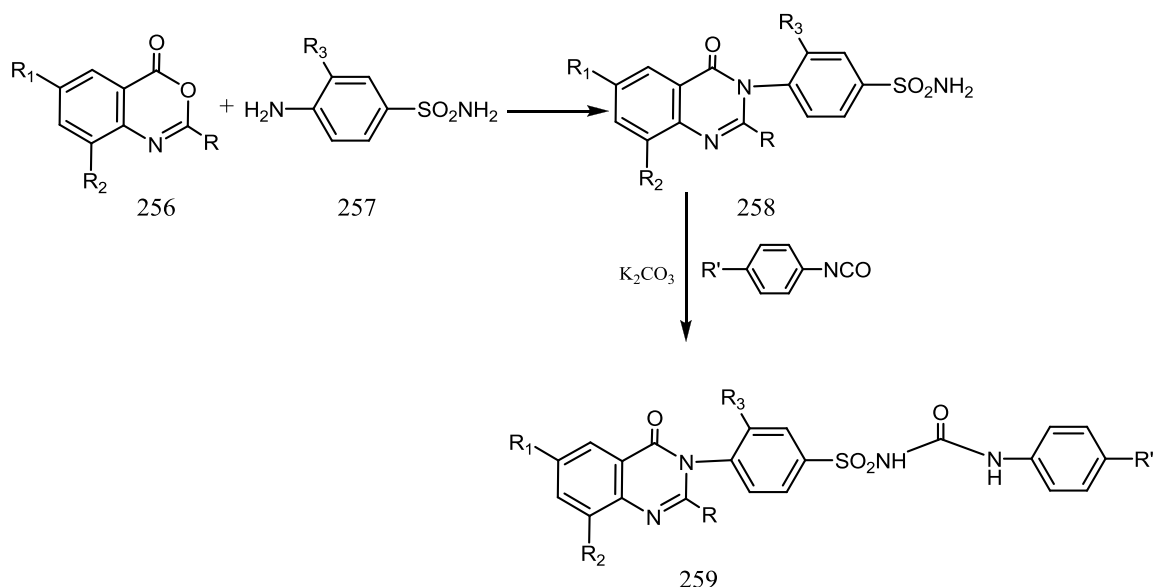


3.3.3.4.5.4 Reactions with sulphanilamide

3-(4-sulphamoylphenyl)-4(3H)-quinazolin-4-ones (255; R = alkyl; R¹ = H, Me, halo; R² = H, Cl, NO₂ R³ = H, halo) are synthesized by condensation of sulphanilamide with various 4H-3, 1-benzoxazin-4-ones 252. 2-amido-N-(4-sulphamoyl phenyl)benzamides are isolated as reaction intermediates. Some of quinazolone derivatives 255 showed significant anticonvulsant effects against pentetrazoll- induced avulsions [111].



Similarly, 1- [4-(4'-oxo-2-methyl/ phenyl-4-(3H)-quinazolin-yl)-3-aryl] ureas (259; R = Me, Ph; R³ = H, Me; R² = H, Me; R¹, R² = H, Br) are prepared by reaction of corresponding quinazolinone-sulphanilamides 258 with aryl isocyanates in the presence of K₂CO₃ in acetone solution. the corresponding quinazolinones are obtained from interaction the corresponding 4H-3,1-benzoxazin-4-ones 256 [221].

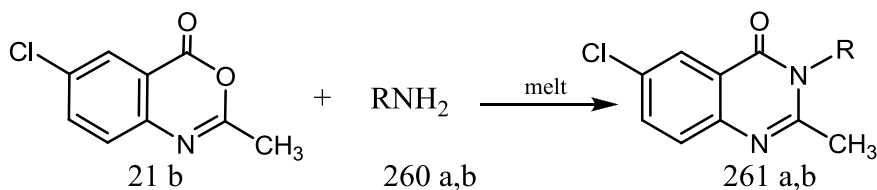


Both the oral and i.p. LD⁽⁵⁰⁾ values for 259 in mice were 1600 to >2000 and 600 to 800 mg/Kg. This compounds were evaluated for their hypoglyceamic activity against the streptozotocin induced diabetic rats. (259; R = Ph; R³ = H, Me; R¹ = R² = H) decreased the blood sugar level significantly both in normal and streptozotocin-induced diabetic rats. The other compounds showed significant hypoglyceamic activity [221].

3.3.3.5 Reactions with amino heterocyclic compounds

Amino heterocycles such as pyridine, pyrimidine [277,31], pyrazole [247], thiazole [277,113], or 1,3,4-thiadiazole [243, 298, 238] have been successfully useful to prepare 3-heterosubstituted quinazolinone with high biological activity [11, 276, 187].

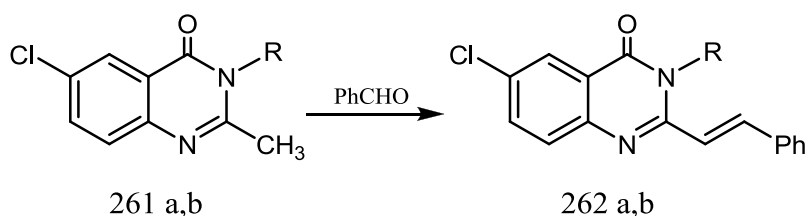
Fusion of 6-chloro-2-methyl-4H-3,1-benzoxazin-4-one **21b** with heterocyclic amines **260** produces 3-heterocyclic-2-methylquinazolone derivatives **261** [252].



a; R=5-indazolyl

b; R= 1-ethyl-5-pyrazolyl

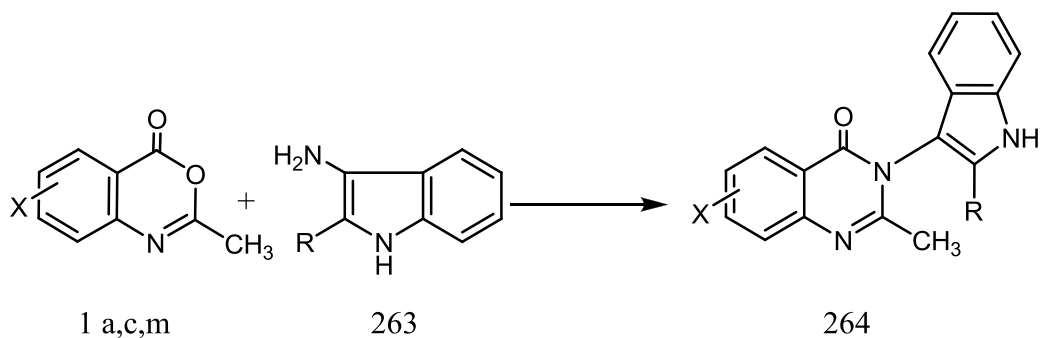
Refluxing equimolar amounts of 2-methyl quinazolone **261** and benzaldehyde in glacial acetic acid; the 3-heterocyclo-2-styrylquinazolinones **262** are generated [253].



a; R= 5-indazolyl

b; R= 1-ethyl-5-pyrazolyl

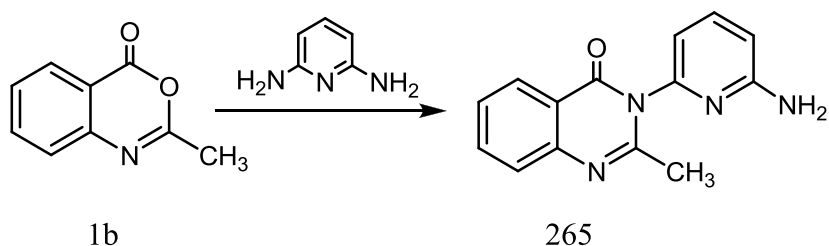
Reaction of 4H 3,1-benzoxazin-4-ones **1a,c,m** with 2-substituted-3-aminoindoles **263** in dry pyridine produce 2-methyl-3-(2'-substitutedindol-3-yl)-4(3H)-quinazolinone **264** [184].



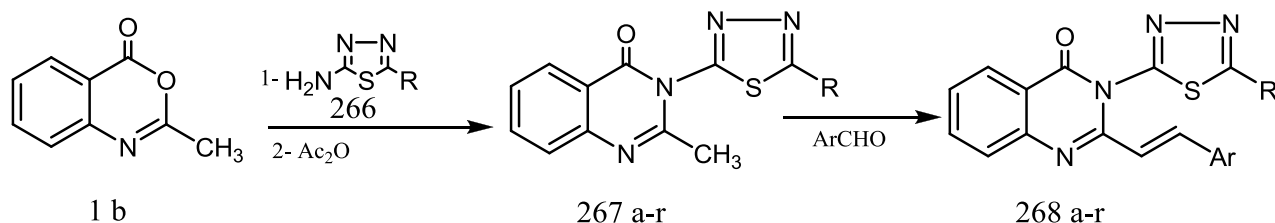
X= H, 6-I, 6-Br

R= H, Me

Also 4H-3,1-benzoxazin-4-one **1b** is reacted with 2,6-pyridindiamine to furnish 3-substituted quinazolone **265** [290].



Synthesis of 3-(1',3',4'-thiadiazolyl)-2-styrylquinazolin-4(3H)-ones (268) is accomplished by a three-step procedure, the intermediate 3-(1,3 4-thiadiazolyl)-2-methyl quinazolinones 267 is obtained by refluxing 2-methyl-4H-3,1-benzoxazin-4-one 1b with thiadiazole-amino derivatives 266 [168].

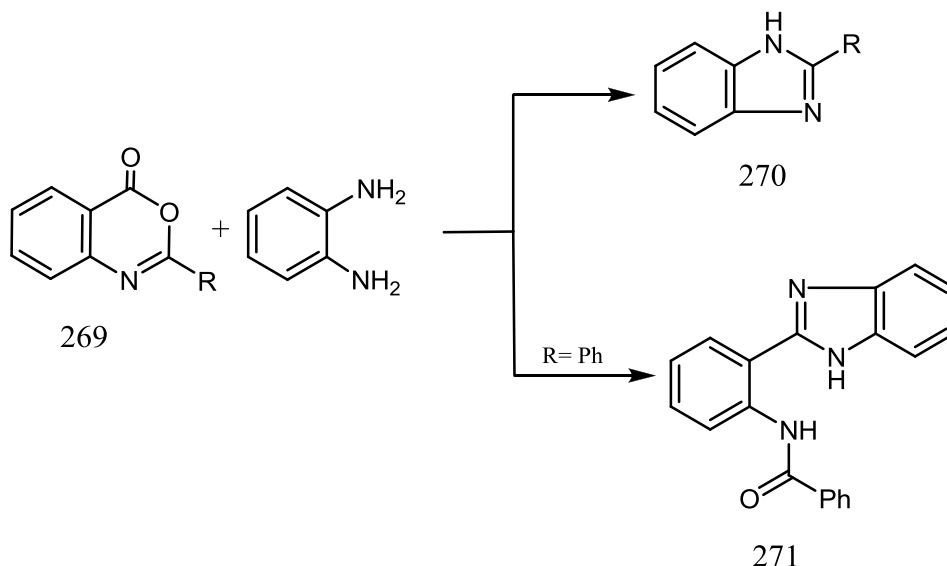


	R	Ar		R	Ar		R	Ar
a	Ph	4-ClC ₆ H ₄	g	Ph	3-ClC ₆ H ₄	m	Ph	4-pyridyl
b	4-OCH ₃ C ₆ H ₄	4-ClC ₆ H ₄	h	4-OCH ₃ C ₆ H ₄	3-ClC ₆ H ₄	n	4-OCH ₃ C ₆ H ₄	4-pyridyl
c	4-CH ₃ C ₆ H ₄	4-ClC ₆ H ₄	i	4-CH ₃ C ₆ H ₄	3-ClC ₆ H ₄	o	4-CH ₃ C ₆ H ₄	4-pyridyl
d	4-ClC ₆ H ₄	4-ClC ₆ H ₄	j	4-ClC ₆ H ₄	3-ClC ₆ H ₄	p	4-ClC ₆ H ₄	4-pyridyl
e	3-ClC ₆ H ₄	4-ClC ₆ H ₄	k	3-ClC ₆ H ₄	3-ClC ₆ H ₄	q	3-ClC ₆ H ₄	4-pyridyl
f	-CH=CHPh	4-ClC ₆ H ₄	l	-CH=CHPh	3-ClC ₆ H ₄	r	-CH=CHPh	4-pyridyl

3.3.3.6 Reactions with diamines

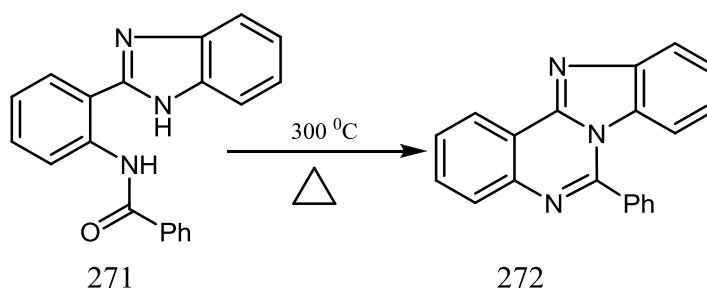
3.3.3.6.1 Reactions with o-phenylenediamine

If refluxing benzoxazinone derivatives 269 with o-phenylenediamine in chloroform, 2-substituted benzamidazoles 270 are formed. Conversely, heating the above mixture in polyphosphoric acid at 200 °C provided 271 [250,163].

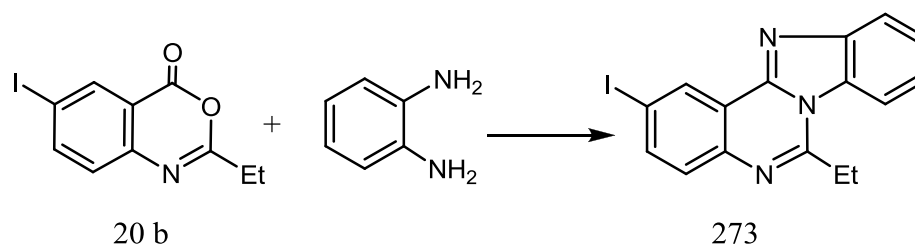


R = Me, Ph, CH₂Ph

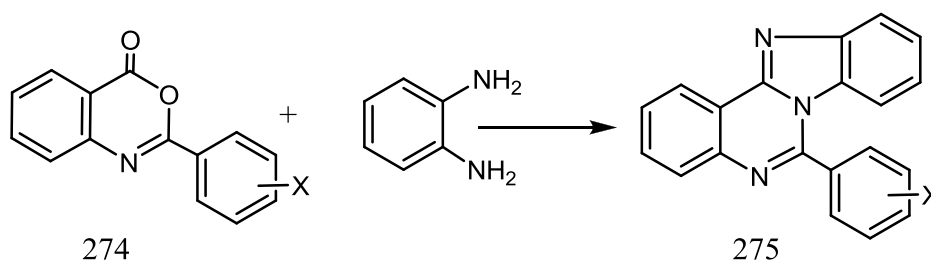
If compound 271 is heated at 300 °C in a sublimation apparatus it cyclodehydrates and benzimidazo quinazoline 272 is produced [250].



Refluxing a mixture of 2-ethyl-6-iodo-4H-3,1- benzoxazin-4-one (20b) and o-phenylenediamine in acetic acid in the presence of fused sodium acetate resulted the formation of tetracyclic compound 273 [30].

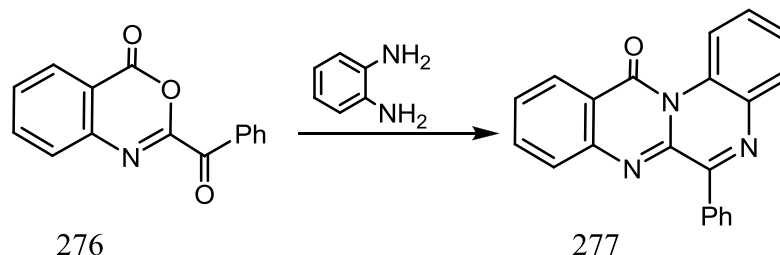


Cyclocondensation of 2-aryl benzoxazinones 274 (R = Ph or substituted Ph) with o-phenylenediamine catalyzed by orthophosphoric acid yields analogs benzoimidazo quinazolinones 275 [237].



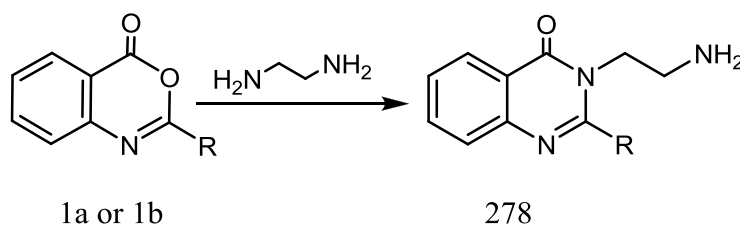
X= H, 2-OH, 4-NO₂

4H-3,1-benzoxazin-4-ones (276) reacts with o-phenylenediamine to afford 277 [250].



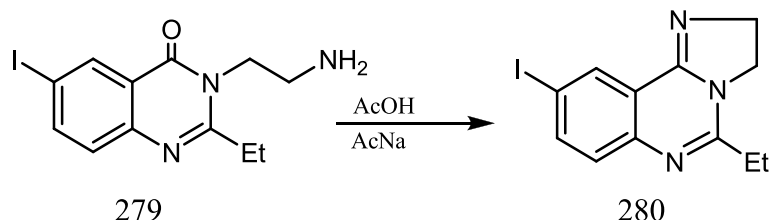
3.3.3.6.2 Reactions with ethylenediamine

2-Methyl-4H-3,1-benzoxazin-4-one 1b as well as 2- phenyl analog 1a are reacting with ethylenediamine and produce the conespoding 3-functionalized quinazolones 278 [239,114,118, 74].



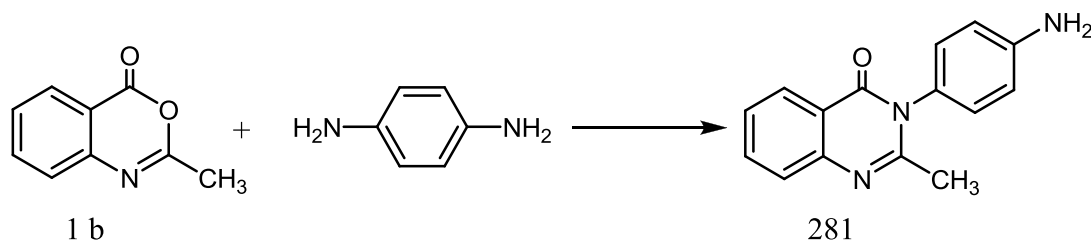
R = Me, Ph

Analogs such as this have the added capability to react further and generated more complex heterocyclic systems [250]. For example, heating quinazolinone 279 in acetic acid in the presence of fused sodium acetate, cyclodehydration occurred and the imidazolo quinazoline 280 is generated [30].



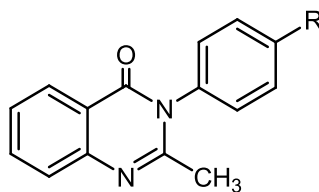
3.3.3.6.3 Reactions with p-phenylenediamine

Interaction of 2-methyl-4H-3,1-benzoxazin-4-one (1b) with p-phenylenediamine affords quinazolinone 281 [146].



Treatment of quinazolinone 281 with alkyl isocyanates followed by cyclocondensation with phenacyl bromides or chloroacetic acid furnished

quinazolinones 282 bearing heterocyclic moieties with high biological activities [146].

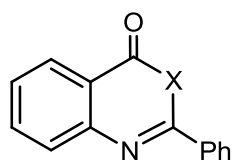


282 a-c

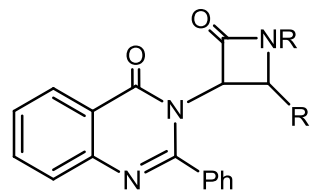
a	b	c
R = NHCSNHR ¹	R = 3-alkyl- 4-aryl-2, 3-dihydrothiazol-2-ylideneamino	R=3-alkyl-4-oxo-thiazolidin-2-ylideneamino
R ¹ = Me, Et, Bu, CH ₂ Ph		

3.3.3.7 Reactions with aminoacids

1,4-Disubstituted 3-[3'-(2'-phenyl-4-oxo-quinazolinyl)]- 2-azetidinones 284 [240], were prepared by cyclocondensation of Schiff's bases RN= CHR₁ (same R groups) with ketenes, the ketene was prepared by treating 1a (X =O) with H₂NCH₂COOH to give 283b (X = NCH₂COOH) which was converted to the acid chloride 283c (X = NCH₂COCl). Treatment of the acid chloride with Et₃N gave 283d (X = NCH=CO) in situ. Compounds 284 showed antiimplantation activity in rats [240].



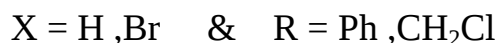
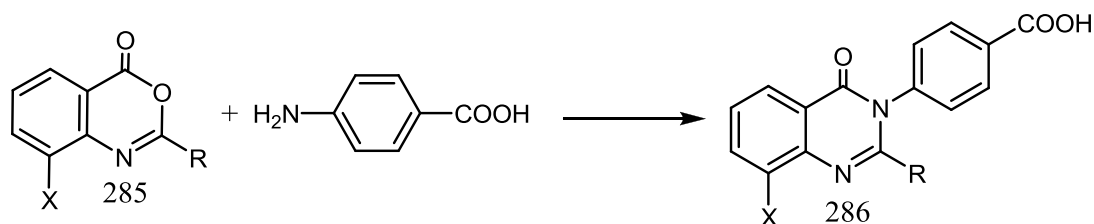
283 a-d



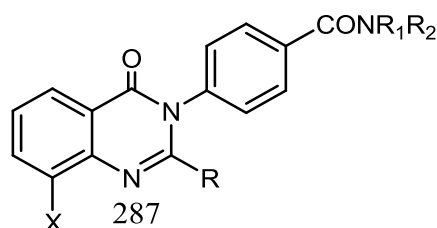
284

R	R ₁
Ph	Ph
4-OMeC ₆ H ₄	2-CH ₃ C ₆ H ₄
2-NO ₂ C ₆ H ₄	3-CH ₃ C ₆ H ₄
2-FC ₆ H ₄	4-ClC ₆ H ₄

In the same manner, carboxyphenylquinazolones 286 has been obtained via cyclocondensation of 2-aryl or alkyl-8-bromo-4H-3,1-benzoxazin-4-one 285 with p-aminobenzoic acid [225].



2(phenyl/chloromethyl)-3-[4-(N,N-disubstituted amino carbonyl)Phenyl]-8-substituted 4(3H)quinazolinones 287 are synthesized by treating carboxyquinazolinone 286 with SOCl_2 in benzene and with the different secondary amines. All quinazolinones 287 are screened for toxicity, central nervous system, cardiovascular and anti-inflammatory activities. Most of these compounds are found to be non-toxic and stimulant in nature. Some of these compounds also exhibited cardiovascular and anti-inflammatory activities [225].



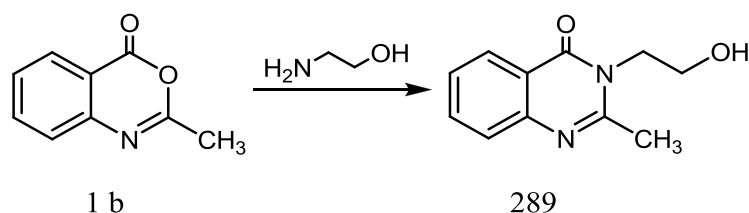
$X = \text{H, Br}$

$R = \text{Ph, CH}_2\text{Cl}$

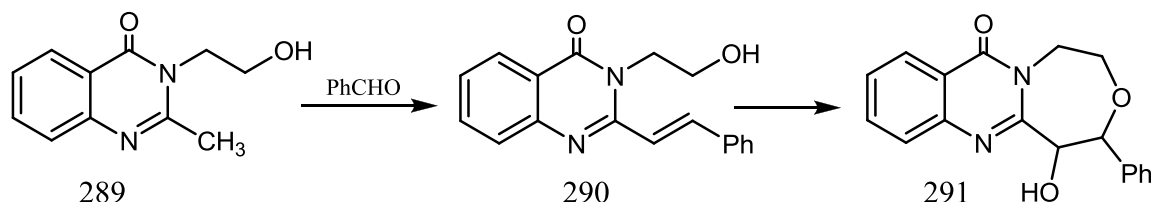
$R_1R_2N =$ morpholino, N-Me piperazino, Et₂N, (HOCH₂CH₂)₂N, piperidino, N-phenylpiperazino

3.3.3.8 Reactions with aminoalcohols

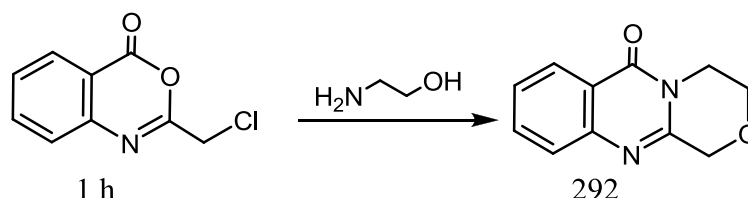
2-Methyl-4H-3,1-benzoxazin-4-one 1b reacts with ethanolamine to produce the corresponding 3-hydroxyethyl quinazolinone 289 [71].



Heating of the resulting quinazolinone 289 with benzaldehyde yields the styryl derivative 290. Epoxidation of the double bond, then treatment of the product with sodium methoxide afforded 291 as a result of intramolecular attack of ethanol group on the epoxide [81].

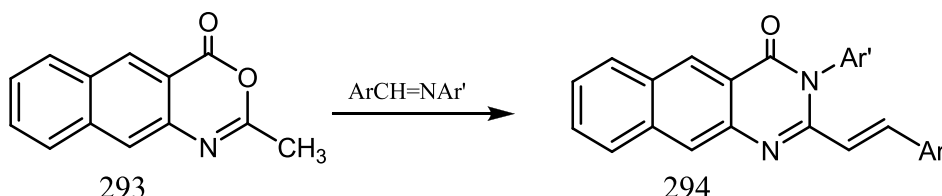


Heterocondensed quinazolones 1,4-oxazino[3,4-b]quinazolin-6-one 292 has been obtained (chloromethyl)-4H-3,1-benzoxazin-4-one 1h with ethanol amine followed by base-catalyzed cyclization [227].

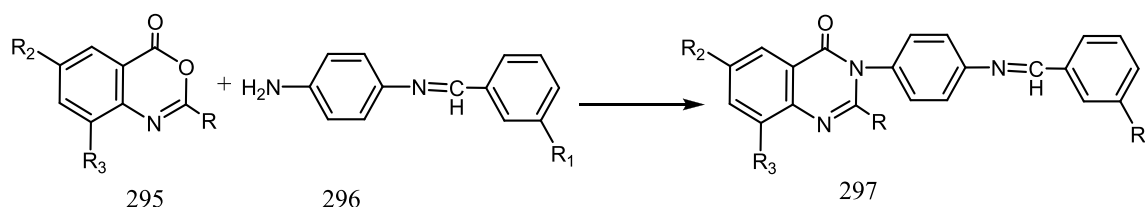


3.3.3.9 Reactions with Schiff's bases

Condensation of methylnaphthoxazinone 293 with $\text{ArCH}=\text{NAr}'$ (Ar, Ar' substituted phenyl) in acetic acid yield benzoquinazolones 294 [186].



Similarly, compounds 297 are prepared by reaction of 4H-3,1-benzoxazin-4-one derivatives 295 with Schiff's base 296. Compounds 297 are tested for Anthelmintic, Virucidal and Bactericidal activity [278].



$\text{R} = \text{Me, Ph}$

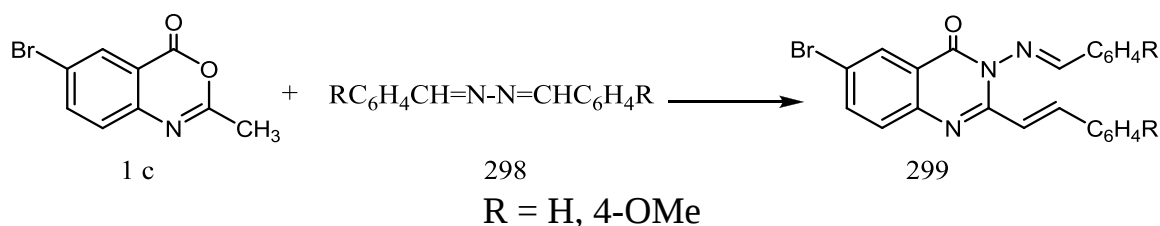
$\text{R}_1 = 3\text{-NO}_2, 4\text{-OH}, 4\text{-NMe}_2, 2\text{-OH}, 4\text{-Cl}$

$\text{R}_2 = \text{H, Br}$

$\text{R}_3 = \text{H, Br}$

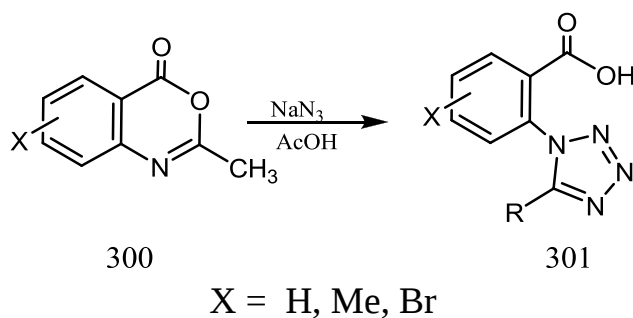
3.3.3.10 Reactions with azines

6-Bromo-2-methyl-4H-3,1-benzoxazin-4-one (1c) undergoes hetero-ring opening followed by recyclization and condensation when treated with azines 298 and yielded 3-arylideneamino-substituted quinazolin-4-(3H)one 299. The reaction involves a cleavage of the azine into its amine and arylidene moieties which are smoothly incorporated into 1c via nucleophilic attack of the amine at position-4 and condensation of the aldehyde with a reactive methyl group at position-2 respectively [77].

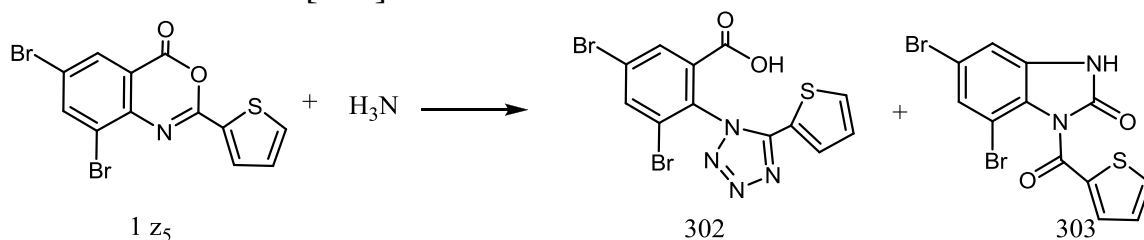


3.3.3.11 Reactions with sodium azide

Treatment of 4H-3, 1-benzoxazin-4-ones **300** with hydrazoic acid (generated with sodium azide in acetic acid) [163, 203, 28, 119, 109, 43, 86] or directly with sodium azide in dimethylformamide [132] resulted in the formation of the tetrazolyl benzoic acids **301**.



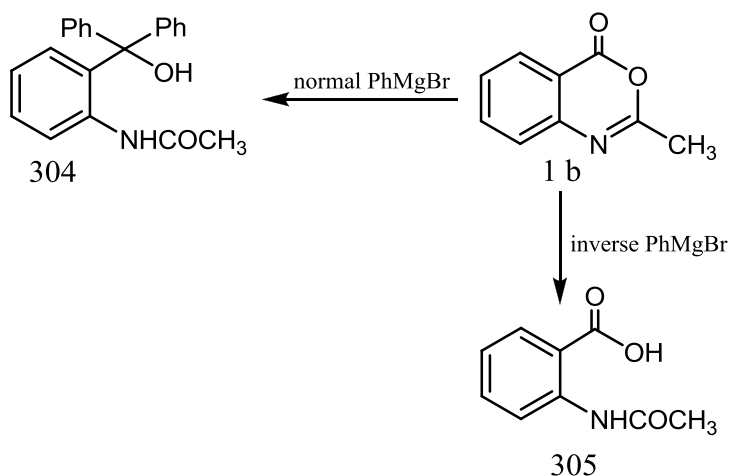
Reaction of compound **1z₅** with HN_3 gave the tetrazole **302** along with the benzimidazolone **303** [162].



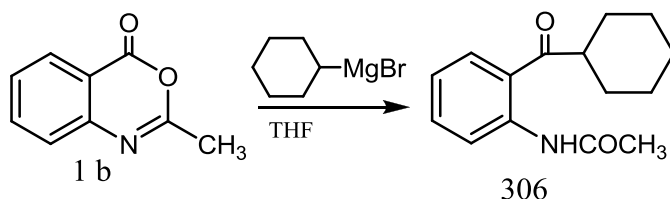
3.3.4 Reactions with carbon nucleophiles

3.3.4.1 Reactions with Grignard reagents

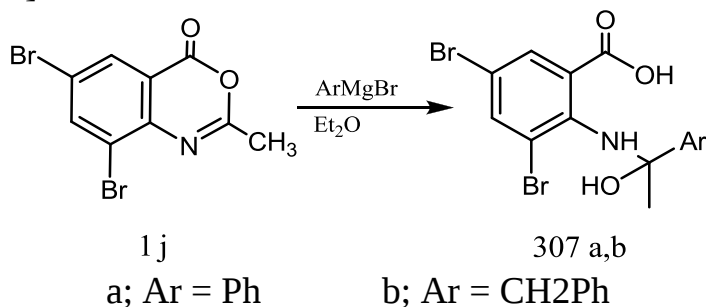
The benzoxazinone **1b** reacts with Grignard reagents in a fashion determined by the manner in which the reaction is carried out [315].



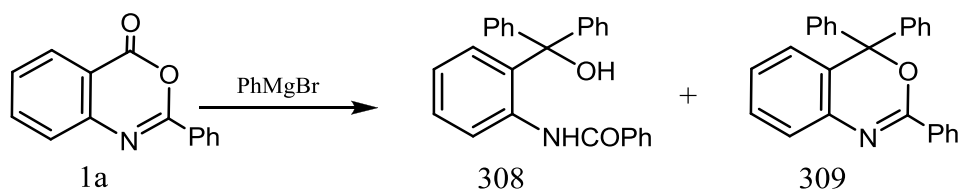
While this benzoxazinone **1b** reacts with cyclohexyl magnesium bromide in THF to afford ketone **306** [62].



6,8-Dibromo analog **1j** reacts with Grignard reagent and provide the unexpected products **307** [196].

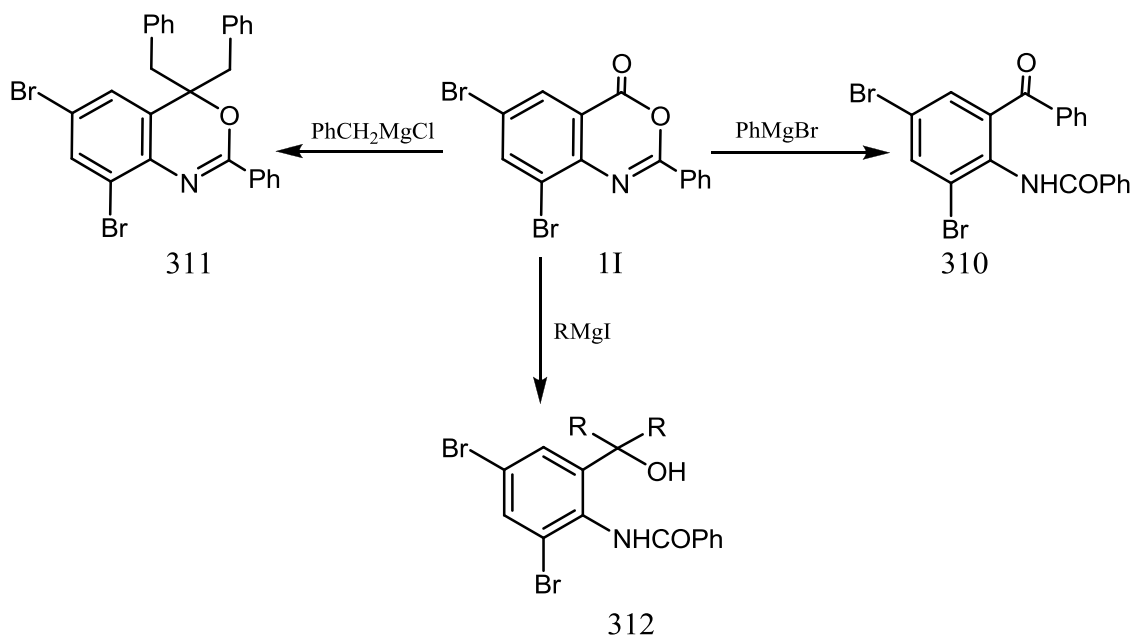


On the other hand, 2-phenyl-4H-3,1-benzoxazin-4-one **1a** on reaction with phenyl magnesium bromide by either the normal or inverse addition method providing only 2-benzamidophenyl diphenyl carbinol **308** and its dehydration product 2,4,4-triphenyl-3,1-benzoxazine **309** [12].



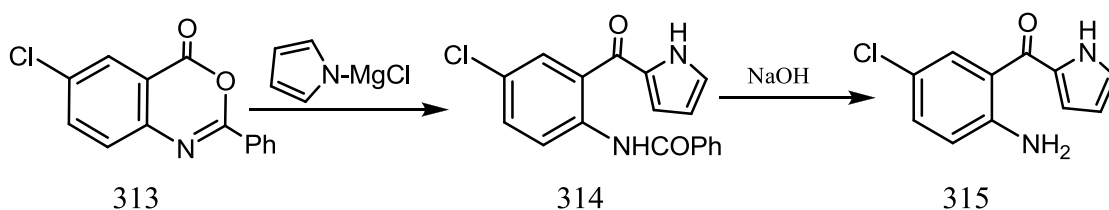
Similarly, 2-methyl-7-methoxy-4H-3,1-benzoxazin-4-one reacts with p-methoxyphenyl magnesium bromide to give 2-acetamido-4,4-dimethoxybenzophenone [150].

6,8-Dibromo-2-phenyl-4H-3,1-benzoxazin-4-one (**1I**) reacts with different Grignard reagents affording different products **310-312** depending on the nature of the reagent and not on the reaction conditions [163].

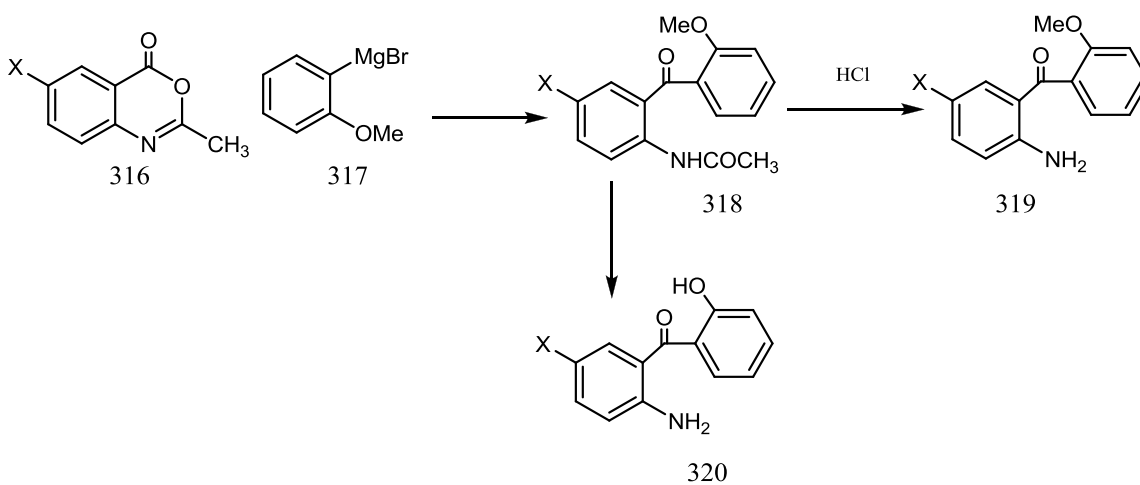


$\text{R} = \text{Et}, 4\text{-OMePh}$

Benzoxazinones 313 reacting with pyrrolyl Grignard reagent followed by hydrolysis to afford 2-amino-5-chlorophenyl-2'-pyrrylketone 315 which is used as a key intermediate in the synthesis of HIV Tat-Antagonists [226].

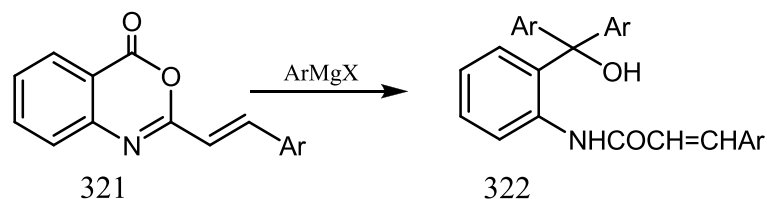


6-Halo-2-methyl-4H-3,1-benzoxazin-4-one 316 reacts with Grignard reagent 317 and produces ketone 318, which by hydrolysis gives the amines 319 and 320 [268].

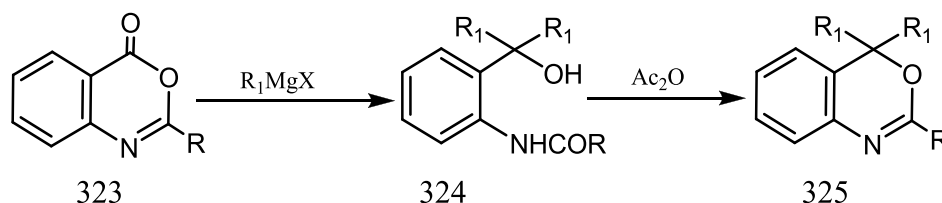


$\text{X} = \text{F}, \text{Cl}, \text{Br}$

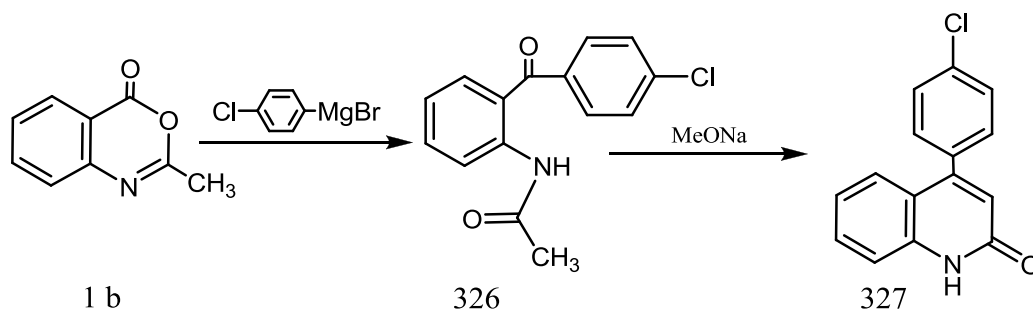
The benzoxazinone 321 is reacted with Grignard reagents and gave the carbinols 322 which are identified as o-(cinnamoylamidophenyl)diarylcarbinols [**Error! eference source not found.**].



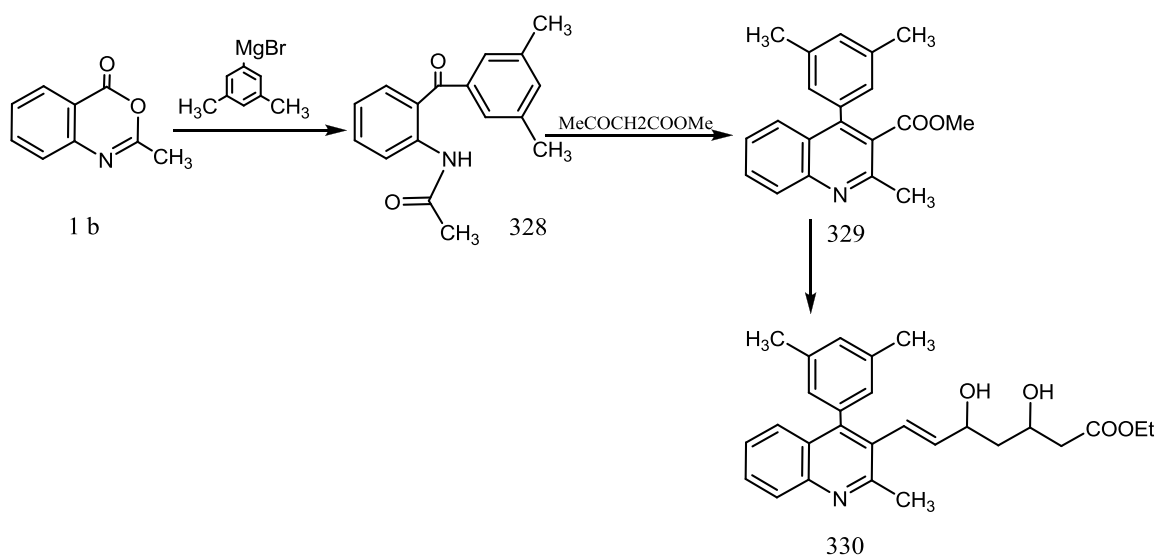
As a point of interest, 2-p-tolyl and/or p-chlorophenyl-4H-3,1-benzoxazin-4-ones 323 are reacted with PhMgBr or CH_3I and gave the carbinols o-[$\text{HOC}(\text{R}^1)_2$] $\text{C}_6\text{H}_4\text{NHCOR}$ [324; $\text{R}^1 = \text{CH}_3, \text{C}_6\text{H}_5$; $\text{R} = \text{C}_6\text{H}_4.\text{CH}_3(4), \text{C}_6\text{Cl}(4)$] which on heating with Ac_2O - AcONa are cyclized to 4,4-(diphenyl or dimethyl)-2-(p-tolyl or p-chlorophenyl)-3,1-benzoxazines 325 [329].



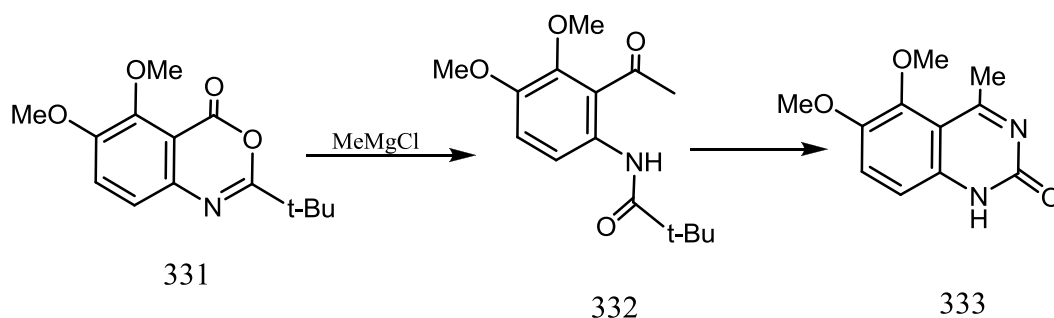
Reaction product 326 of benzoxazinone 1b and 4-chlorophenylmagnesium bromide are treated with sodium ethoxide and are cyclized to the 4-phenylcarbostyryl 327 [151,197].



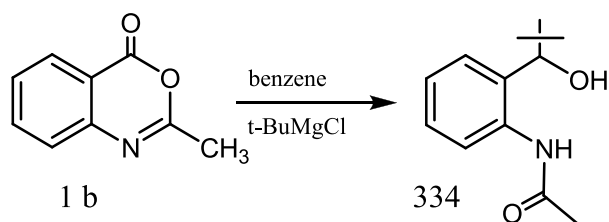
Benzoxazinone 1b reacts with 3,5-dimethylphenyl magnesium bromide and produces 328a. The acyl group of 328a is removed under acidic conditions and resulting 2-aminobenzophenone 328b. It condenses with methyl acetoacetate to afford the quinoline 329, which is then elaborated by using Wittig methodology to the 4-arylquinolin heterocycle 330. Compound 330 comprises the hydrophobic domain of reductase inhibitors [316].



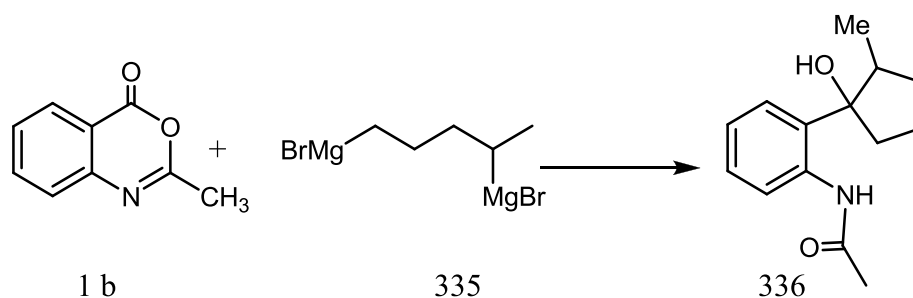
Cardiotonic bemarkinone, 5,6-Dimethoxy-4-methyl-2(1H)-quinazolinone 333 is readily prepared from 4H-3,1-benzoxazinone 331 [70].



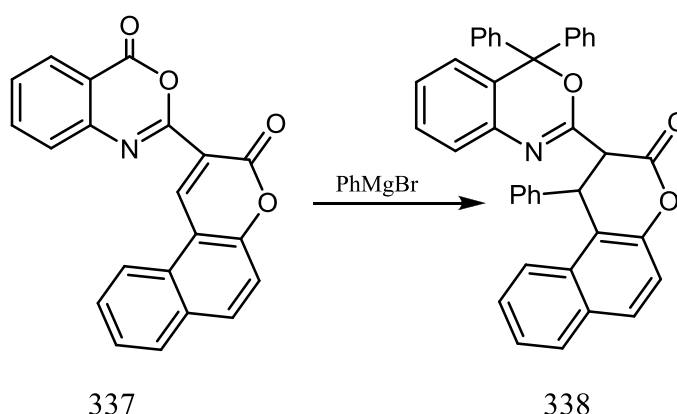
Addition of 2-methyl benzoxazinone 1b to an excess of t-butyl magnesium chloride produces the secondary alcohol 334. The first equivalent of Grignard reagent adds normally to 1b to generate N-acetylbenzophone derivative, then the second equivalent of the reagent instead of adding to the newly formed ketone, it reduces the keto group presumably because of highly steric interactions between both ketone and organometallic [328].



BisGrignard reagents such as 335 add to 2-methyl benzoxazinone 1b to give tertiary alcohol 336 [60].

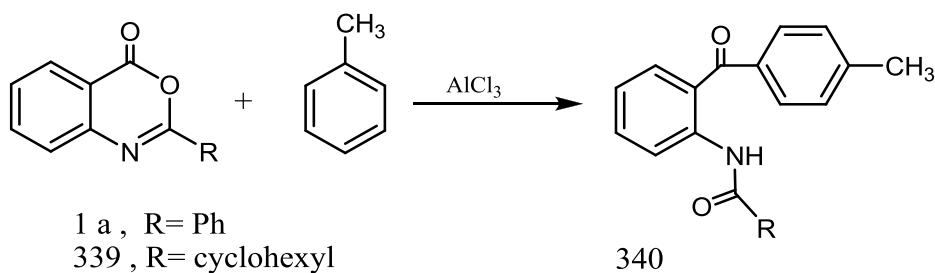


4H-3,1-Benzoxazin-4-ones 337 have bulky group at 2- position also react with Girgnard reagent PhMgBr and produce compound 338 [263].

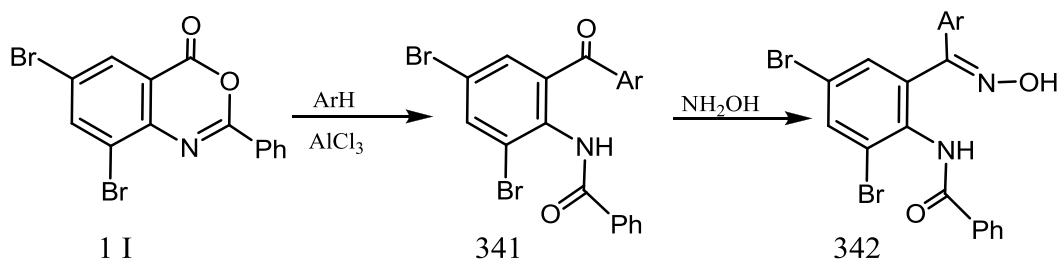


3.3.4.2 Friedel-Crafts reactions

2-Phenyl-4H-3,1-benzoxazin-4-one 1a and cyclohexyl-(4H)-3,1-benzoxazin-4-one 339 are reacted with toluene in the presence of anhydrous AlCl_3 under Friedel-Crafts conditions to give 2-benzamido and 2-cyclohexylamido-p-methyl benzophenone 340 [265,267].

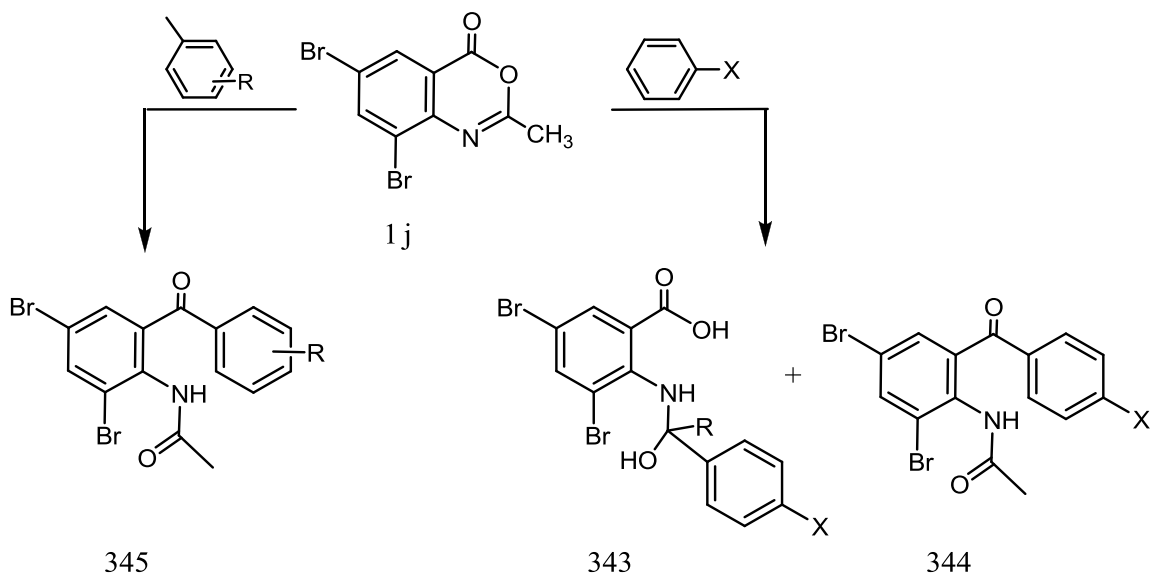


6,8-Dibromobenzoxazinone 1I is submitted to arylation by applying Friedel-Crafts reaction conditions, benzophenone derivatives 341 are afforded. Compound 341a is reacted with hydroxylamine hydrochloride to yield oxime 342 [163].

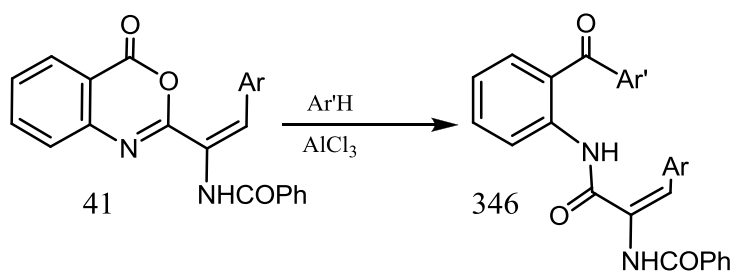


Ar = Ph, 4-CH₃C₆H₄, 3,4-di-MeC₆H₃, 2,4-di-MeC₆H₃, 2,6-di-MeC₆H₃

In contrast, 6,8-dibromo-2-methyl-4H-benzoxazin-4-one **1j** arylated in different fashion; where it reacts with hydrocarbons namely, benzene, ethylbenzene, m- and p-xylene to afford either two benzophenone derivatives **343** and **344** in case of less bulky hydrocarbons (benzene, ethylbenzene) or only one product **345** in case of more bulky m- and p-xylene [196].



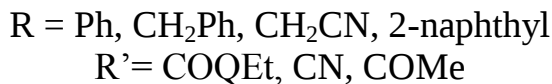
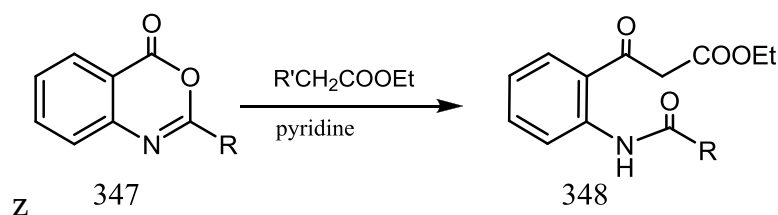
Also 4H-3,1-benzoxazin-4-ones **41** with bulky groups at 2-position arylated when submitted to react with hydrocarbons under Friedel-Crafts reaction conditions producing benzophenone derivatives **346**.



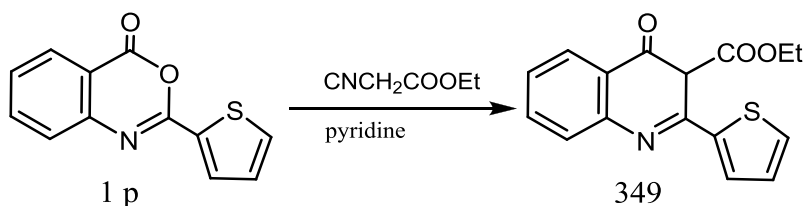
	Ar		Ar'		Ref.
a	4-OCH ₃ C ₆ H ₄	3-NO ₂ C ₆ H ₄	3-indolyl		[86]
b	1-naphthyl	2-furyl	2,4-di-MeC ₆ H ₃	2,5-di-MeC ₆ H ₃	[6]

3.3.4.3 Reactions with active methylene containing compounds

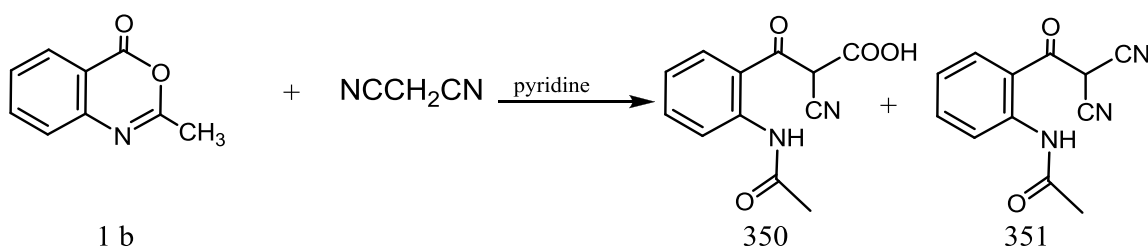
Reaction of benzoxazinones with active methylene containing compounds provide a variety of interesting results. Heating the benzoxazinones **347** with diethyl malonate, ethyl cyanoacetate, or ethyl acetoacetate in dry benzene produce one and the same product **348** as the consequence of the loss of the R' group [210, 265, 267, 292, 212].



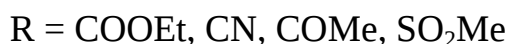
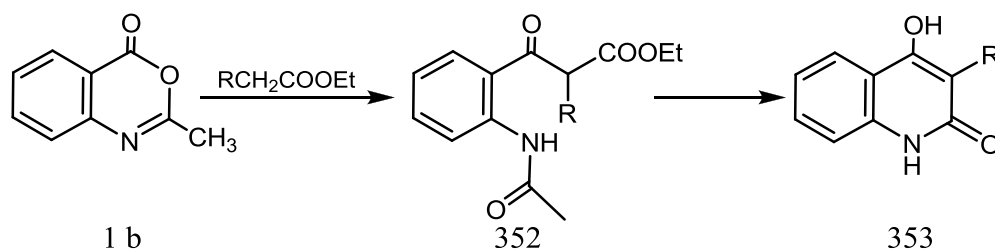
An analogous reaction of thienyl derivative 1p with ethyl cyanoacetate affording the cyclized product 349 [163].



Under the same conditions, benzoxazinone 1b with malononitrile and a mixture of 350 and 351 is furnished [209].



Using potassium *t*-butoxide to generate the anion of the active methylene and running the reaction at room temperature, allow the R' group to be retained giving compound 352. That in turn, can be cyclized to the 4-hydroxy-2-quinoline 353 with either sodium alkoxide or 8% alcoholic hydrochloric acid [79].



Recently, [274] showed that the hit-to-lead optimization of the HNE inhibitor 5-methyl-2-(2-phenoxy-pyridin-3-yl)-benzo[d][1,3]oxazin-4-one is described. A structure–activity relationship study that focused on the 5 and 7 benzoxazinone positions yielded the optimized 5-ethyl-7-methoxy- benzo[d][1,3]oxazin-4-one core structure. 2-[2-(4-Methyl-piperazin-1-yl)-pyridin-3-yl] derivatives of this core were shown to yield HNE inhibitors of similar potency with significantly different stabilities in rat plasma.

More recently, Waisser et al. [311] showed that the new 3-benzyl-4-thioxo-2H-1,3-benzoxazine-2(3H)-ones and 3-benzyl-2H-1,3-benzoxazine-2,4(3H)-dithiones were synthesized. The compounds were tested for in vitro antimycobacterial activity against *Mycobacterium tuberculosis*, *Mycobacterium kansasii* and *Mycobacterium avium*. The replacement of the carbonyl group by the thiocarbonyl group increased the antimycobacterial activity. The most active derivatives were more active than isonicotinhydrazide (INH). The cytotoxicity and the antiproliferative activity were studied as well.

DISCUSSION

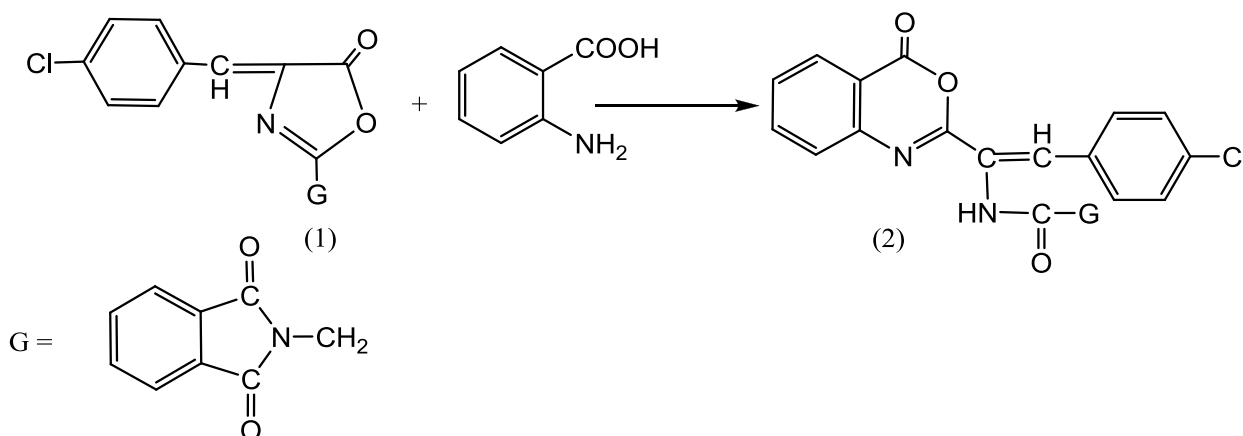
DISCUSSION

1. Synthesis and reactions of N-(2-(4-chlorophenyl)-1-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)vinyl)-2-(1,3-dioxoisindolin-2-yl)acetamide

The present work deals with synthesis of N-(2-(4-chlorophenyl)-1-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)vinyl)-2-(1,3-dioxoisindolin-2-yl)acetamide (2), as a key starting material for many benzoxazinone derivatives.

It is well known [105] that 2-substituted 4(H)-3,1-benzoxazin-4-ones undergo ring opening by moisture and many research groups have provided the correlation of stability of benzoxazinones with various steryl derivatives in position-2.

Thus compound (2) was prepared by treatment of anthranilic acid with (Z)-2-((4-(4-chlorobenzylidene)-5-oxo-4,5-dihydrooxazol-2-yl)methyl)isoindoline-1,3-dione (1).



1.1 The structure of compound (2) was established from the following:

1. Correct analytical data.
2. Infrared spectrum of (2) exhibited absorption bands at 1614 cm^{-1} (ν CO of α,β - unsaturated amide), at $1774\text{--}1720\text{ cm}^{-1}$ (ν CO of benzoxazinone and ν CO of cyclic imide) and at $3475, 3370\text{ cm}^{-1}$ (ν NH) .
3. The ^1H -NMR spectrum of (2) (δ ; DMSO- d_6) showed signals at 4.45(s, 2H, NCH_2CO), at 6.75 (s, 1H, olefinic proton), at 7.22-7.91 (m, 12H, Ar-H) and at 9.08 (s, 1H, NH) .
4. The mass spectrum of (2) (cf. Figs.3 and chart 1) showed the molecular ion peak $[\text{M}]^+$ $m/z = 485$ and the molecular ion peak $[\text{M}+2]^+$ at $m/z = 487$.

Table 1 The mass spectrum fragmentation of compound (2)

m/z	abundance
485	0.17
353	0.15
355	0.09
325	0.15
327	0.11
282	0.23
284	0.10
171	0.26
160	100.00
146	0.90
132	19.52
102	2.84

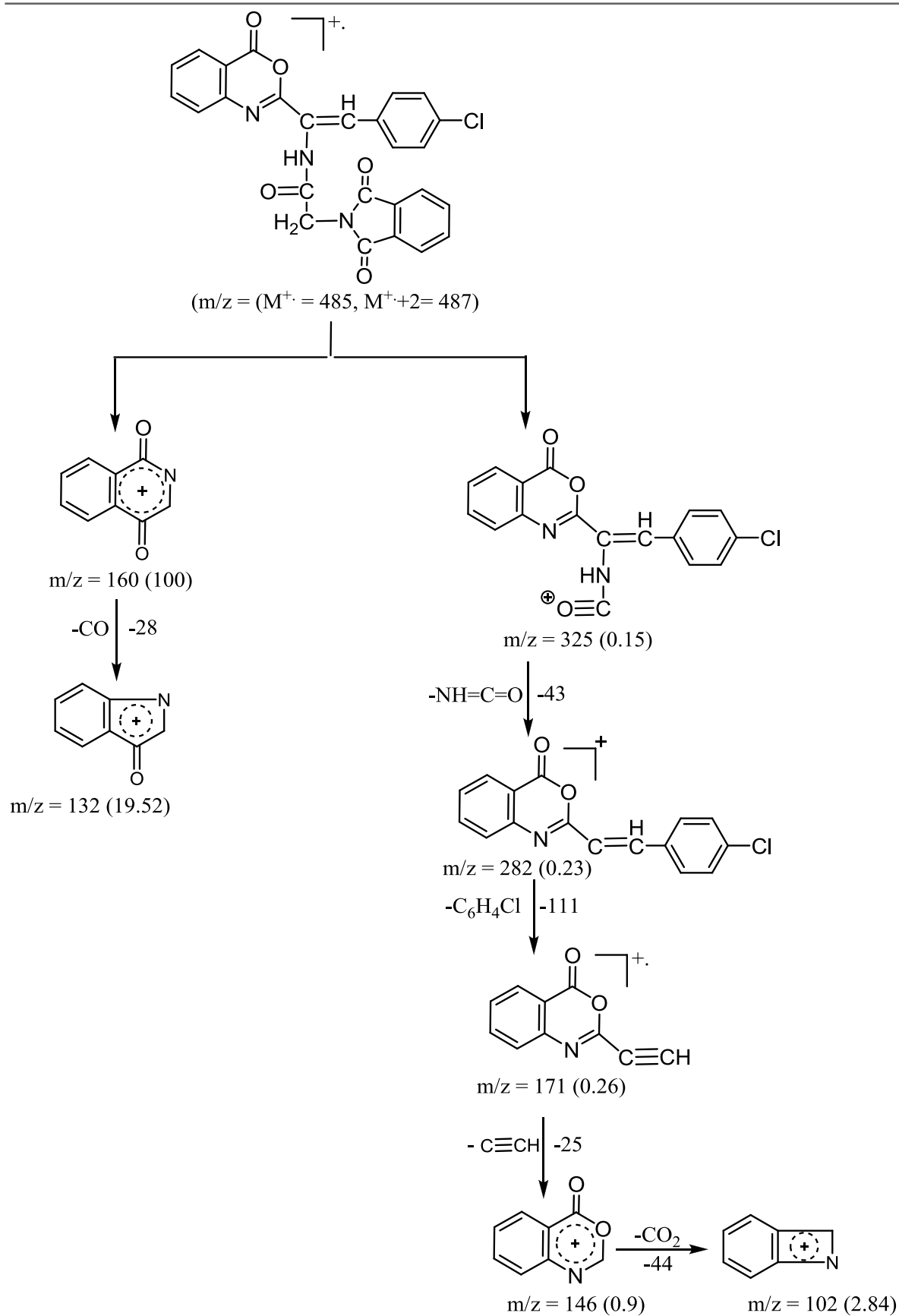
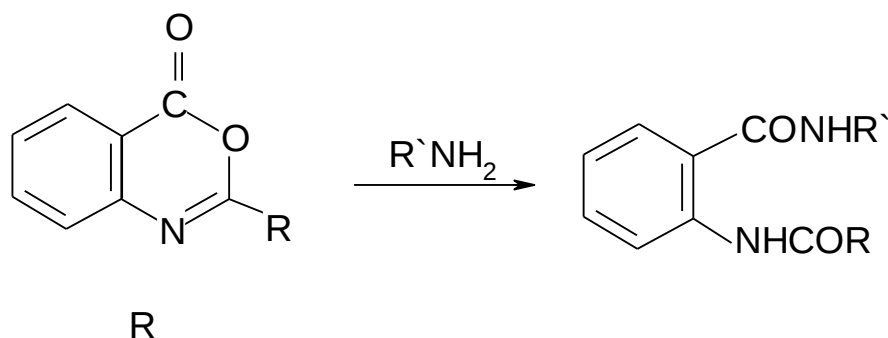


Chart 1

1.2 Chemical proven of compound (2)

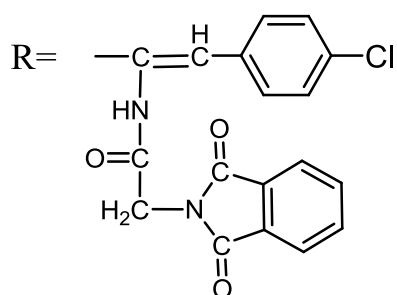
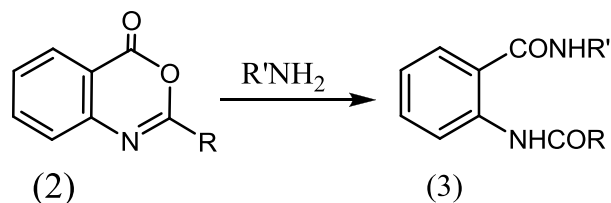
1.2.1 Reaction with amines

It has been reported that 2-substituted (4H)-3,1-benzoxazin-4-ones reacted with primary amines, amino acids or aminophenols in boiling ethanol to give 2-substituted)-carbamoyl phenyl acetanilides [291].



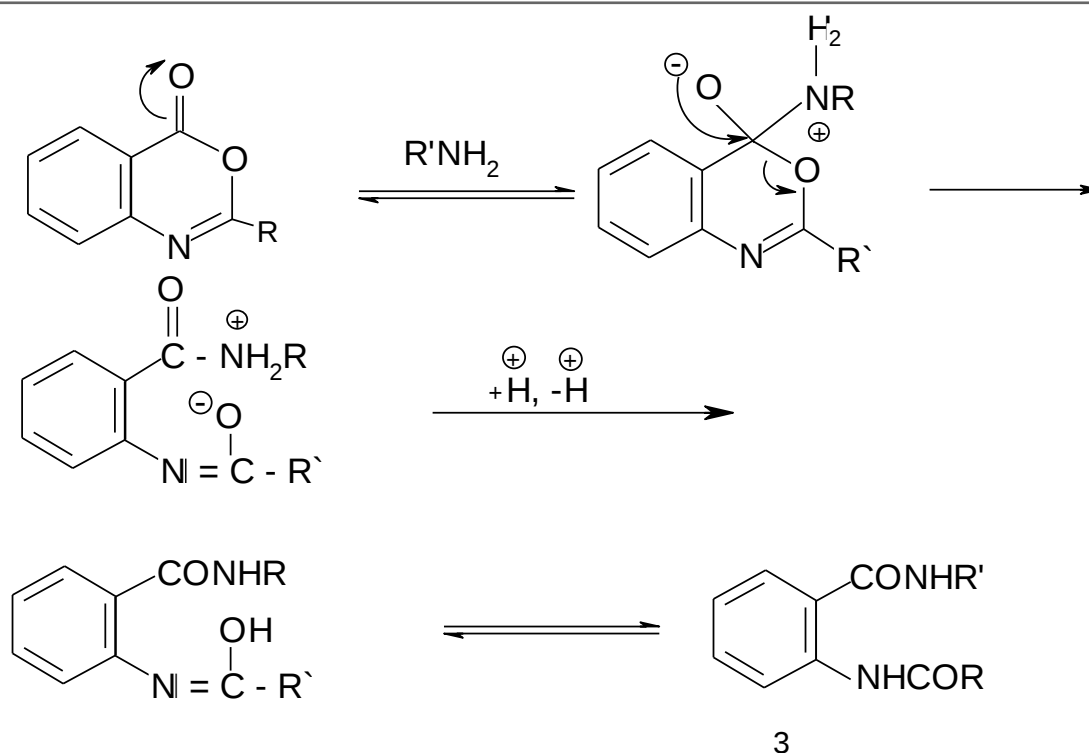
- R
- CH₂Ph
 - CH = CHAr

The present investigation deals with the reaction of (2) with methylamine, ethylamine, butylamine, hexylamine, glycine, p-anisidine and o-phenylenediamine in boiling ethanol to give the corresponding 2-(substituted) carbamoyl phenyl acetanilides (3_{a-h}).



- R' =
- | | |
|---|--|
| a, CH ₃ | b, CH ₂ CH ₃ |
| c, (CH ₂) ₃ CH ₃ | d, (CH ₂) ₄ CH ₃ |
| e, (CH ₂) ₅ CH ₃ | f, CH ₂ COOH |
| g, (C ₆ H ₄)OCH ₃ | h, (C ₆ H ₄)NH ₂ |

The formation of (3_{a-h}) may be interpreted from the fact that amines or amino acids react via the mechanism outlined below, in which the nucleophilic attack by lone pair of electrons on the nitrogen of amino group upon carbon of carbonyl group in benzoxazinone nucleus took place leading to ring opening of the heterocyclic ring.



The structure of (**3_a**) was proved from:

1. Correct analytical data.
2. Infrared spectrum showed bands for compound (**3_a**) at 1647 cm^{-1} (νCO of acyclic amides), at $1774\text{--}1713\text{ cm}^{-1}$ ($\nu\text{ CO}$ of cyclic imide) and at $3317, 3133\text{ cm}^{-1}$ ($\nu\text{ NH}$).
3. The mass spectrum of (**3_a**) (chart 2) showed the molecular ion peak $[M]^+$ $m/z = 516.45$ (0.02) and the molecular ion peak $[M+2]^+$ at $m/z = 518.5$ (0.02).

Table 2 mass spectrum fragmentation of compound (3a**)**

m/z	abundance
518.50	0.02
516.45	0.02
356	0.02
313	0.07
202	0.18
177	0.11
160	100.00
134	4.78
132	20.16
104	44.21
76	50.68

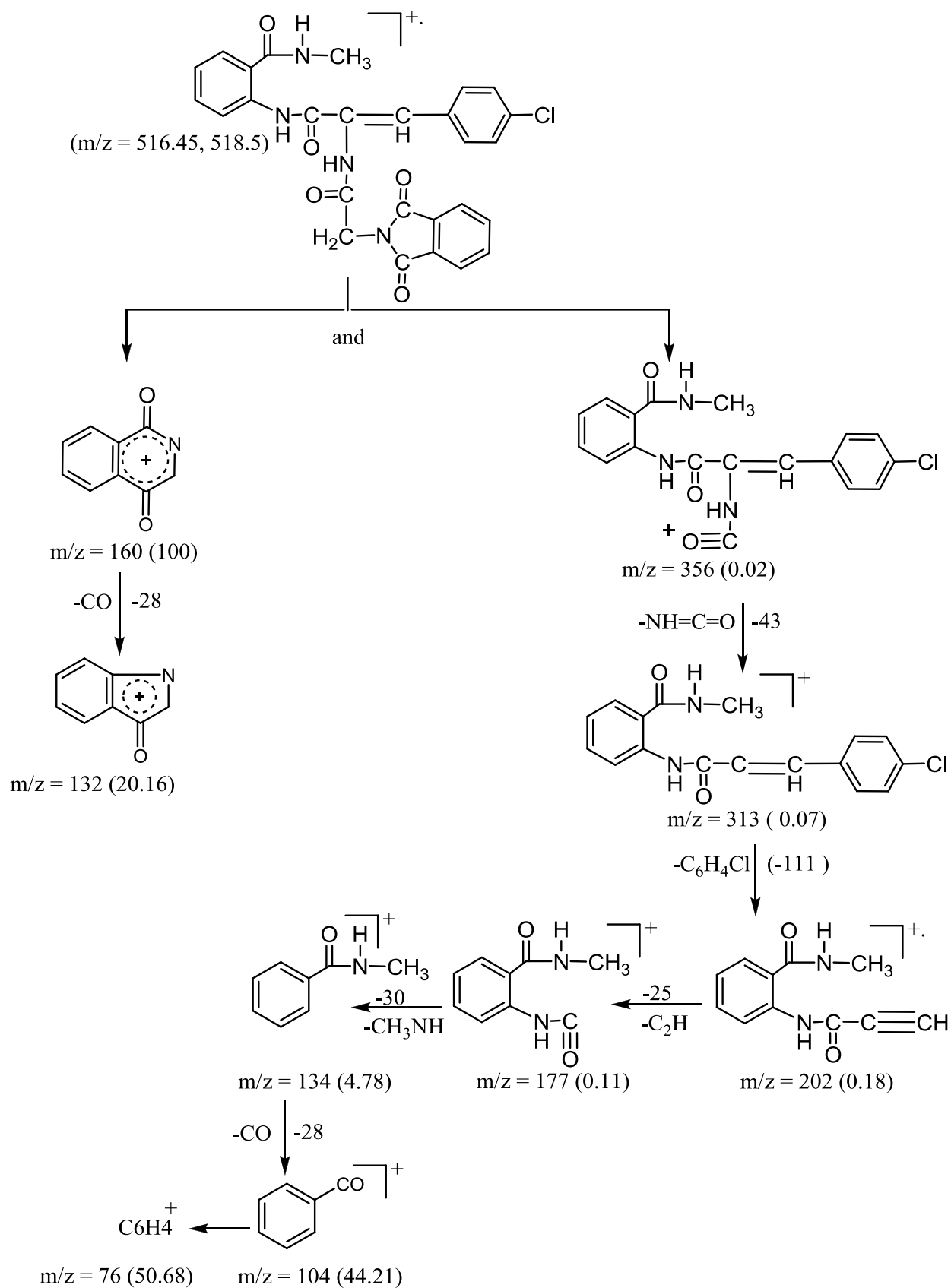


Chart 2

The structure of (**3_b**) was proved from:

1. Correct analytical data.
2. Infrared spectrum showed bands for compound (**3_b**) at 1645 cm^{-1} (νCO of acyclic amides), at 1774-1715 cm^{-1} (νCO of cyclic imide) and at 3473, 3220 cm^{-1} (νNH).
3. The ^1H -NMR spectrum of (**3_b**) (δ ; DMSO- d_6) showed band at δ 1.2(t, 3H, CH_3), at 4.1(q, 2H, CH_2), at 4.43(s, 2H, NCH_2CO), at 6.74(s, 1H, olefinic proton), at 7.2-7.92 (m, 12H, Ar-H) and 9.80-10.38(s, broad, 3H, $3\times\text{NH}$) disappeared by addition of D_2O .

The structure of (**3_c**) was proved from:

1. Correct analytical data.
2. Infrared spectrum showed bands for compound (**3_c**) at 1645 cm^{-1} (νCO of acyclic amides), at 1774-1719 cm^{-1} (νCO of cyclic imide) and at 3360 cm^{-1} (νNH).
3. The mass spectrum of (**3_c**) showed the molecular ion peak $[\text{M}+1]^+$ at $m/z = 560$ (50%) and the molecular ion peak $[\text{M}+2]^+$ at $m/z = 561$ (20%).

The structure of (**3_d**) was proved from:

1. Correct analytical data.
2. Infrared spectrum showed bands for compound (**3_d**) at 1641 cm^{-1} (νCO of acyclic amides), at 1774-1719 cm^{-1} (νCO of cyclic imide) and at 3475, 3240 cm^{-1} (νNH).

The structure of (**3_e**) was proved from:

1. Correct analytical data.
2. Infrared spectrum showed bands for compound (**3_e**) at 1650 cm^{-1} (νCO of acyclic amides), at 1774-1720 cm^{-1} (νCO of cyclic imide) and at 3448, 3350 cm^{-1} (νNH).

The structure of (**3_f**) was proved from:

1. Correct analytical data.
2. Infrared spectrum showed bands for compound (**3_f**) at 1640 cm^{-1} (νCO of acyclic amides), at 1774-1712 cm^{-1} (νCO of cyclic imide) and at 3360 cm^{-1} (νNH) and at 3300-2400 cm^{-1} (νOH broad).

The structure of (**3_g**) was proved from:

1. Correct analytical data.
2. Infrared spectrum showed bands for compound (**3_g**) at 1644 cm^{-1} (νCO of acyclic amides), at 1774-1716 cm^{-1} (νCO of cyclic imide) and at 3455, 3360 cm^{-1} (νNH).

The structure of (**3_h**) was proved from:

1. Correct analytical data.
2. Infrared spectrum showed bands for compound (**3_h**) at 1640 cm^{-1} (νCO of acyclic amides), at $1774\text{--}1711\text{ cm}^{-1}$ ($\nu\text{ CO}$ of cyclic imide) and at $3330, 3310\text{ cm}^{-1}$ ($\nu\text{ NH}$).

1.2.1 Hydrazinolysis

Recently [2], it has been shown that the reaction of 3,1-(4H)-benzoxazinones with hydrazine hydrate affected the fission of the heterocyclic ring. This promoted us to study the proclivity of N-(2-(4-chlorophenyl)-1-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)vinyl)-2-(1,3-dioxoisindolin-2-yl)acetamide (**2**) towards hydrazines such as hydrazine hydrate and phenylhydrazine.

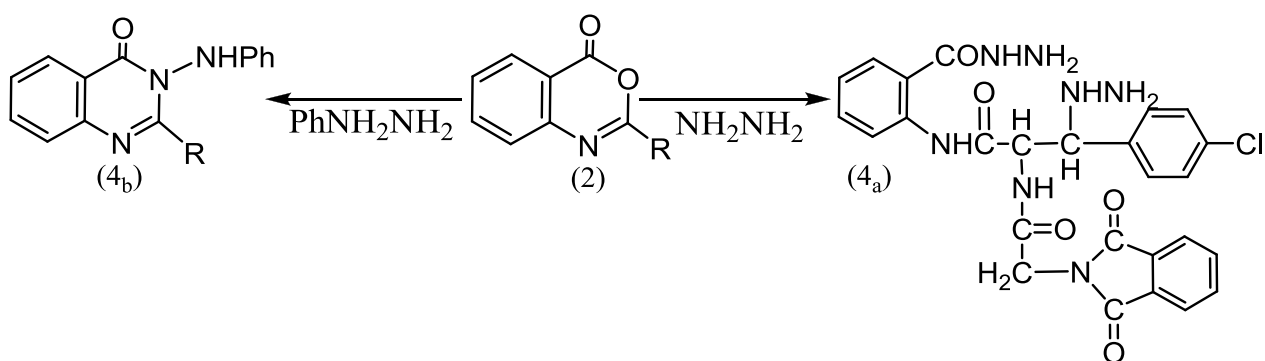
Hydrazinolysis of (**2**) with an excess amount of hydrazine hydrate gave the hydrazide derivative (**4_a**). On the other hand, reaction of (**2**) with phenyl hydrazine, yielded quinazolinone derivative (**4_b**).

The infrared spectrum of (**4_a**) exhibited bands at 1617 cm^{-1} ($\nu\text{ CO}$ of α,β -unsaturated amide), at $1774\text{--}1720\text{ cm}^{-1}$ ($\nu\text{ CO}$ of cyclic imide) and at 3445 cm^{-1} ($\nu\text{ NH}$).

The mass spectrum of (**4_a**) showed the molecular ion peak $[M]^+$ $m/z = 549$ (16.7%).

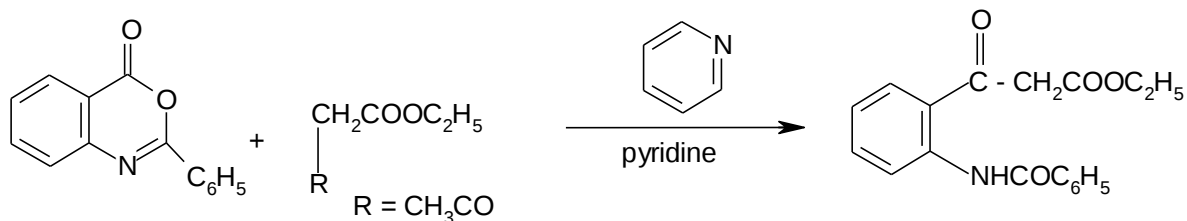
The infrared spectrum of (**4_b**) exhibited bands at 1646 cm^{-1} (νCO of cyclic and acyclic amides), at $1774\text{--}1714\text{ cm}^{-1}$ ($\nu\text{ CO}$ of cyclic imide) and at $3460\text{--}3380\text{ cm}^{-1}$ ($\nu\text{ NH}$).

The mass spectrum of (**4_b**) showed the molecular ion peak $[M-2]^+$ $m/z = 574$ (40%).

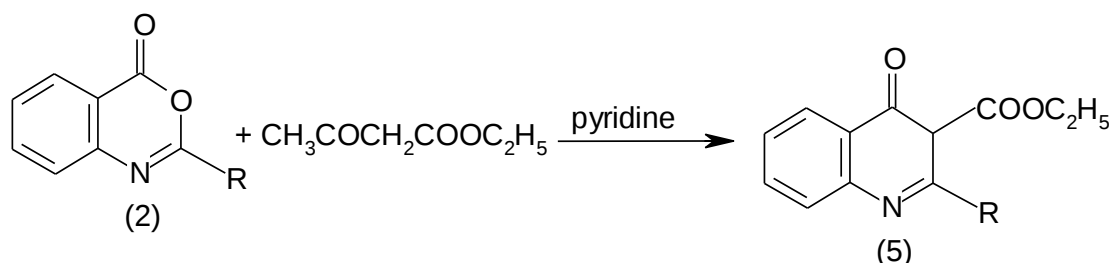


2. Base catalyzed of 3,1-(4H)-benzoxazinone (2) with active methylene compounds

Sammour et al [1] reported that 2-phenyl-3,1-benzoxazinone reacted with ethyl acetoacetate to give o-ethyl-o-benzamido benzoyl acetate.



In the present investigation, the reaction of (2) with ethyl acetoacetate gave carbethoxy 3,4-dihydro-1,4-quinolinone derivative (5).



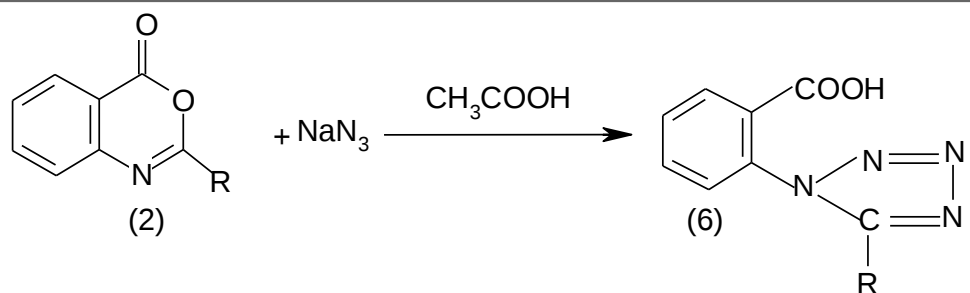
This result can be explained by the opening of the heterocyclic ring with the carbanion of active methylene group followed by ring closure with deacetylation.

The following support the structure assigned for the product (5)

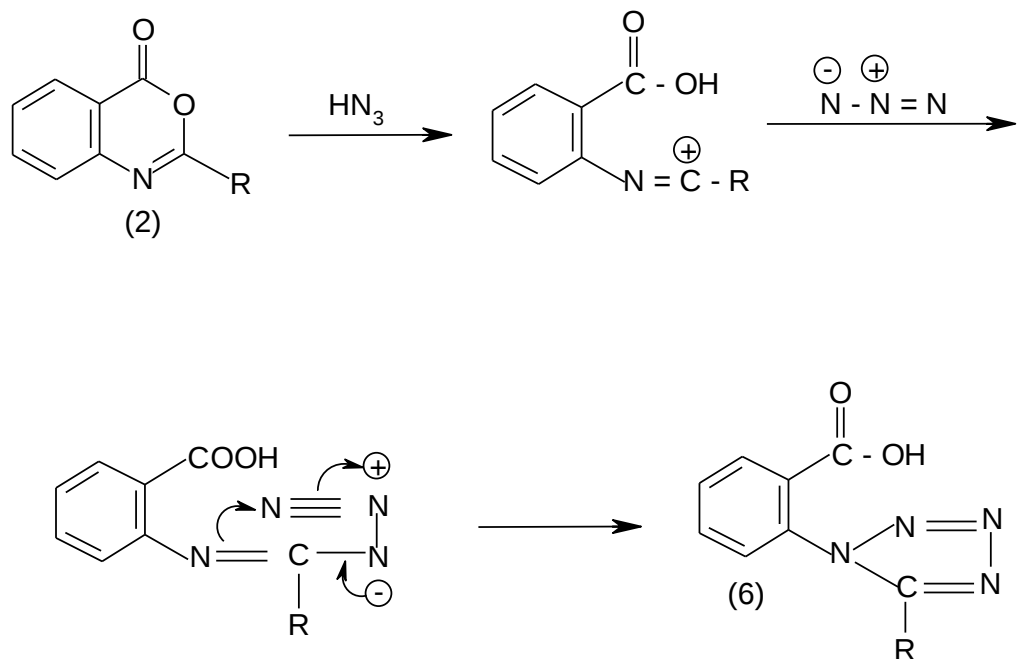
1. Correct analytical data.
2. Infrared spectrum which showed bands at 1611cm^{-1} of (ν CO of α,β -unsaturated amide), at 1725cm^{-1} (ν CO of ester), at 1774 (ν CO of imide) and at 3479cm^{-1} (ν NH).
3. The ^1H -NMR spectrum of (5) (δ ; DMSO-d_6) showed band at δ 1.2-2.49 (m, with interference, 5H, $\text{COOCH}_2\text{CH}_3$), at 4.42 (s, 2H, NCH_2), at 3.37 (s, 2H, CH_2), at 6.74 (s, 1H, olefinic proton), at 7.89- 7.91 (m, 12H, Ar-H) and 9.5-10.2 (s, broad, 1H, NH) disappeared by addition of D_2O .

3. Action of sodium azide

Benzoxazinone (2) reacted with sodium azide in boiling acetic acid and yielded 2-(5-(2-(4-chlorophenyl)-1-(2-(1,3-dioxoisindolin-2-yl)acetamido)vinyl)-1H-tetrazol-1-yl)benzoic acid (6).



The formation of (6) possibly takes place according to the following mechanism:

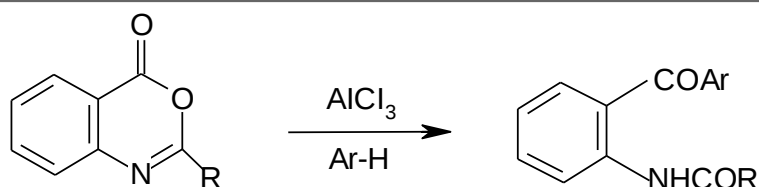


The infrared spectrum of (6) was consistent with the proved structure which exhibited bands at 1111 cm^{-1} attributable to tetrazole nucleus, at 1614 cm^{-1} (ν CO of α,β -unsaturated amide), at 1718 (ν CO of carboxylic), at $1774\text{-}1760\text{ cm}^{-1}$ (due to coupling carbonyl bands of cyclic imide), at $3455, 2928\text{ cm}^{-1}$ (ν OH and NH).

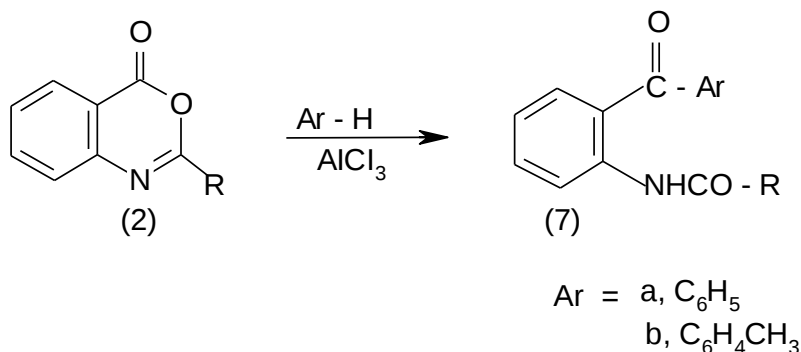
The ^1H -NMR spectrum of (6) (δ ; DMSO-d_6) showed signals at 4.55(s, 2H, NCH_2CO), at 6.85 (s, 1H, olefinic proton), at 7.25-8.20 (m, 12H, Ar-H) and at 9.98-10.69(s, broad, 1H, NH) and at 13.84 (s, 1H, OH).

4. Friedel-Crafts reaction

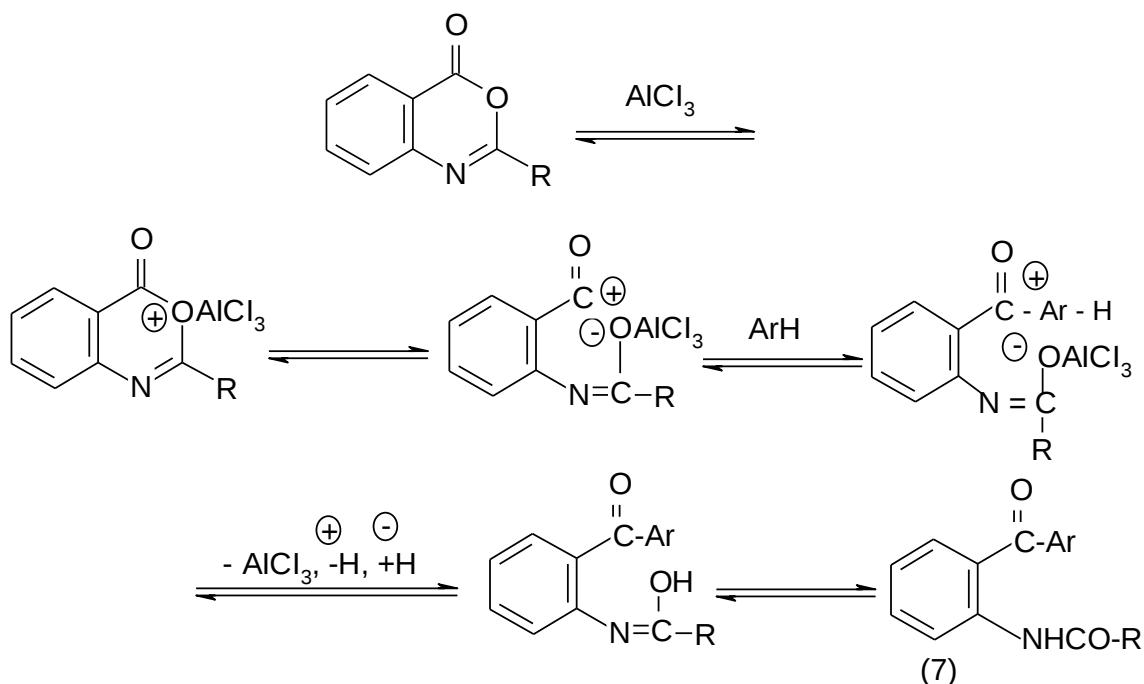
2-Substituted-4H-3,1-benzoxazinones reacted with AlCl_3 in hydrocarbons under the Friedel-Crafts condition reaction to give 2-aryl (alkyl) imido (substituted) benzophenones [3].



Thus, N-(2-(4-chlorophenyl)-1-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)vinyl)-2-(1,3-dioxoisindolin-2-yl)acetamide (2) reacted with benzene, toluene in the presence of anhydrous aluminium chloride under Friedel-Crafts conditions to give o-substituted phenyl aryl ketone (7_{a,b}).



The reaction possibly takes place according to the following mechanism:



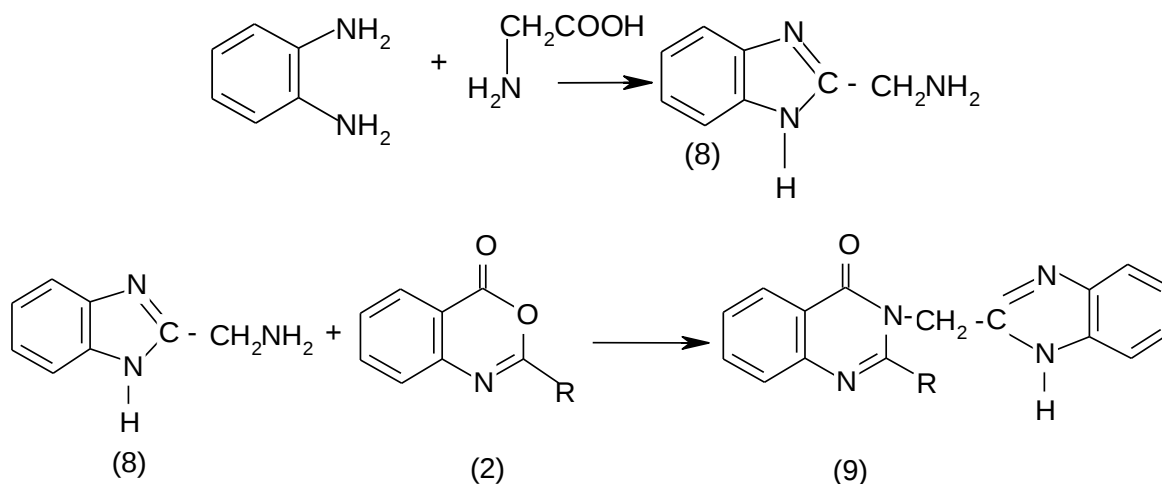
The structure of (7_{a,b}) were confirmed from their infrared spectra which showed bands at $1675\text{--}1657\text{cm}^{-1}$ (ν CO of ketone and α,β -unsaturated amide), at $1774\text{--}1725\text{cm}^{-1}$ (ν CO of cyclic imide) and at $3401, 3208\text{cm}^{-1}$ (ν NH).

The $^1\text{H-NMR}$ spectrum of (7_a) showed signals (δ ; DMSO-d_6) at 4.43(s, 2H, NCH_2), 6.58(s, 1H, olefinic proton), 7.56–8.0(m, 17H, Ar-H) and 9.2–10.2(s, broad, 2H, $2\times\text{NH}$) disappeared by addition of D_2O .

The mass spectrum of (7b) showed the molecular ion peak $[M]^+$. $m/z = 578$ (14.75).

5. Reaction with 2-amino methyl benzimidazole

It was reported [241] that o-phenylenediamine reacts with glycine in presence of concentrated hydrochloric acid to give 2-amino methyl benzimidazole (8). Benzoxazinone (2) react with (8) to give 3-N-substituted quinazolinone derivative (9).

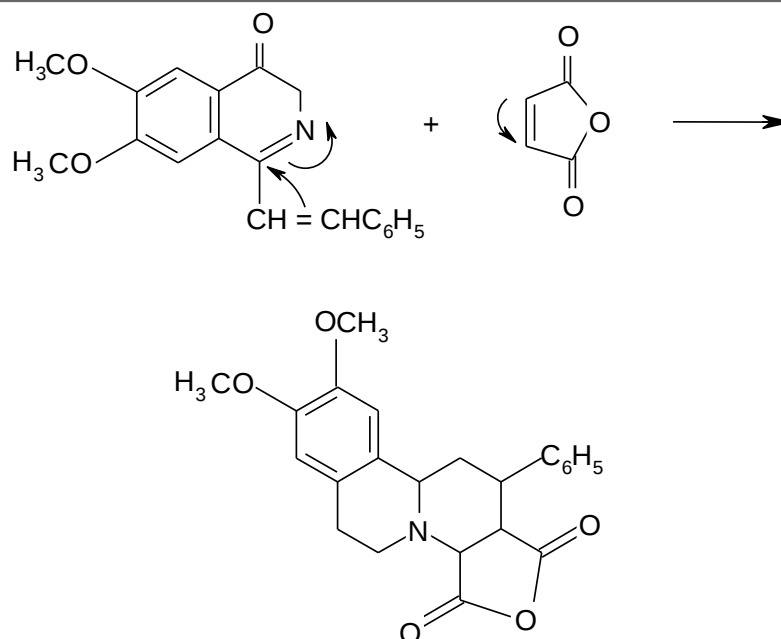


The structure of and (9) was proved from:

1. Analytical data.
2. Infrared spectra showed bands at 1666 cm^{-1} (νCO of acyclic amide), at $1774\text{-}1719\text{ cm}^{-1}$ ($\nu\text{ CO}$ of cyclic imide), at 3431 cm^{-1} ($\nu\text{ NH}$).
3. The ^1H -NMR spectrum of (9) showed signals (δ ; DMSO-d_6) at 4.43(s, 2H, NCH_2), at 6.76(s, 1H, olefinic proton), at 7.05-8.68 (m, 16H, Ar-H), at 9.08 (s, broad, 1H, NH), at 13.01(s, broad, 1H, NH, exchangeable with D_2O).

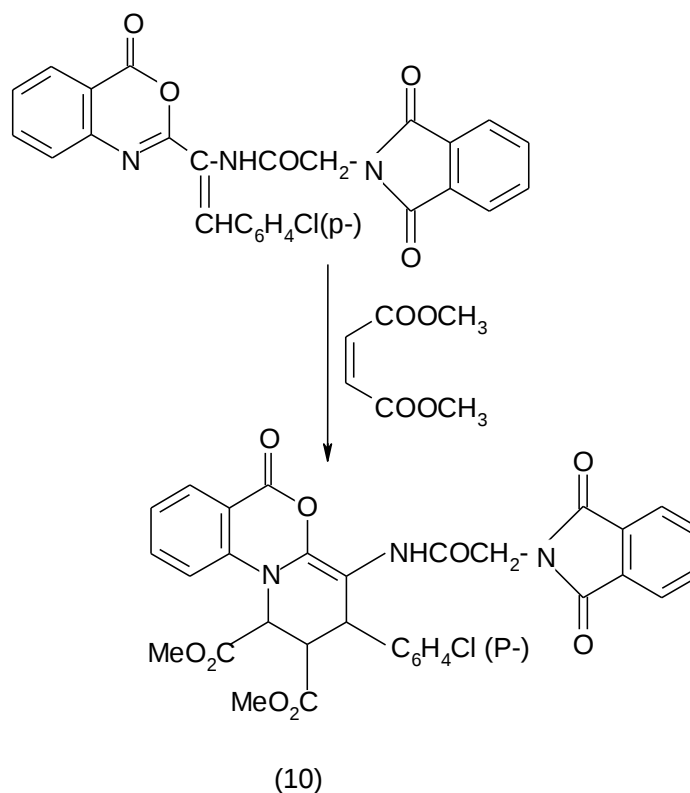
6. Diels-Alder reaction

The Schiff base of 2-styryl pyridine was found to react smoothly as a diene with a number of dienophilic compounds [222]. Hydroquinazine adducts was formed by addition of maleic anhydride to the diene-1-styryl-6,7-dimethoxy-3,4-dihydro-isoquinoline according to the following equation:



In the present work the reaction of dimethyl maleate with N-(2-(4-chlorophenyl)-1-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)vinyl)-2-(1,3-dioxoisindolin-2-yl)acetamide (**2**) was investigated.

Thus (**2**) reacted with dimethyl maleate in dry xylene to give the corresponding Diels-Alder adducts (**10**).



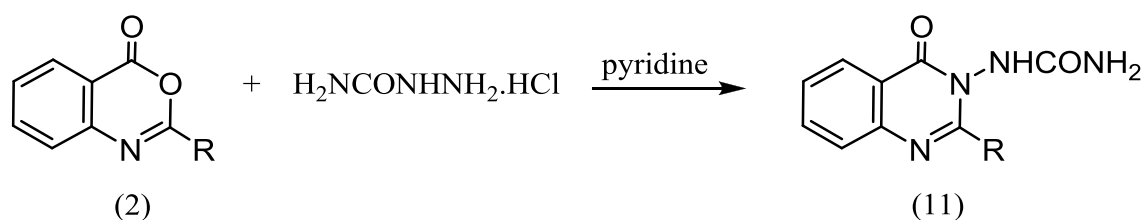
The structure of (**10**) was established from:

1. Correct analytical data.

2. Infrared spectra which showed bands at 1642 cm^{-1} of (ν CO of amide), at $1774\text{--}1760\text{ cm}^{-1}$ of (ν CO of imide), at 1731 cm^{-1} (ν CO of ester), at 1720 cm^{-1} (ν CO of sat. benzoxazinone ring), and at 3446 cm^{-1} (ν NH).
3. The ^1H -NMR spectrum of (**10**) showed signals (δ ; DMSO- d_6) at 2.5(s, 6H, COOH_3), at 4.1(m, 3H, cyclic protons), at 4.50(s, 2H, NCH_2), at 7.35–8.85(m, 12H, Ar-H), 9.2–10.2(s, broad, 2H, 2NH) disappeared by addition of D_2O .

7. Synthesis of quinazolinyl urea

When benzoxazinone (**2**) was allowed to react with semicarbazide hydrochloride in boiling pyridine afforded quinazolinyl urea derivative (**11**).

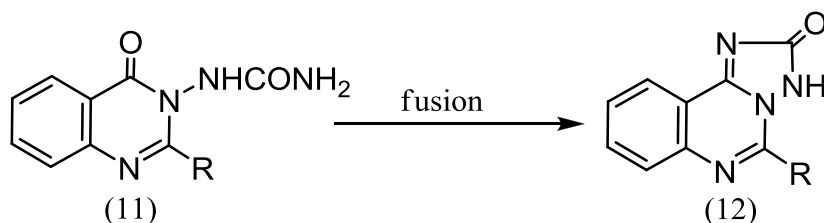


Infrared spectrum of (**11**) showed bands at 1615 cm^{-1} of (ν CO of amides), at $1774\text{--}1722\text{ cm}^{-1}$ of (ν CO of cyclic imide) and at 3424 cm^{-1} (ν NH).

The ^1H -NMR spectrum of (**11**) showed signals (δ ; DMSO- d_6) at 4.43 (s, 2H, NCH_2), at 5.8(s, broad, 2H, NH_2), at 6.8 (s, 1H, olefinic proton), at 7.5–8.0(m, 12H, Ar-H) and 9.8–10.9(s, broad, 2H, $2\times\text{NH}$) disappeared by addition of D_2O .

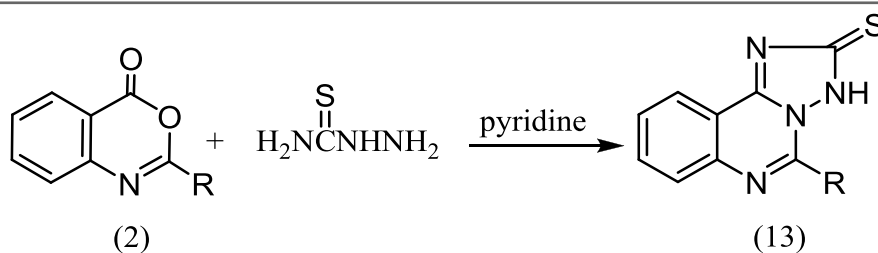
On fusion of the above compound at its melting point it was cyclized to produce triazole quinazoline derivative of (**12**) which shows the bands in IR-spectrum at 1658 cm^{-1} of (ν CO of cyclic and acyclic amides), at $1774\text{--}1725\text{ cm}^{-1}$ of (ν CO of cyclic imide) and at 3468 cm^{-1} (ν NH).

The ^1H -NMR spectrum of (**12**) showed signals (δ ; DMSO- d_6) at 4.43 (s, 2H, NCH_2), at 6.74 (s, 1H, olefinic proton), at 7.87–8.0(m, 12H, Ar-H) and 9.6–10.4(s, broad, 2H, $2\times\text{NH}$) disappeared by addition of D_2O .



8. Synthesis of triazino quinazolinone derivative

When benzoxazinone (**2**) was treated with thiosemicarbazide in boiling pyridine afforded N-(2-(4-chlorophenyl)-1-(2-thioxo-2,3-dihydro-[1,2,4]triazolo[1,5-c]quinazolin-5-yl)vinyl)-2-(1,3-dioxoisindolin-2-yl)acetamide (**13**).



Infrared spectrum of **(13)** showed bands at 1309 of (ν CS of cyclic thio amide), at 1610cm^{-1} of (ν CO of α,β - unsaturated amide), at $1774\text{-}1719\text{cm}^{-1}$ of (ν CO of cyclic imide) and at 3462cm^{-1} (ν NH) .

The mass spectrum of **(13)** showed the molecular ion peak $[\text{M}-3]^+$ at $m/z = 537$ (chart 3).

Table 3 The mass spectrum fragmentation of compound (13)

m/z	abundance
537.40	0.09
352	0.25
354	0.18
293	0.31
295	0.27
188	31.17
160	100.00
153	1.24
151	1.78
142	0.36
138	2.44
116	1.80
113	2.51
111	7.34
76	46.79

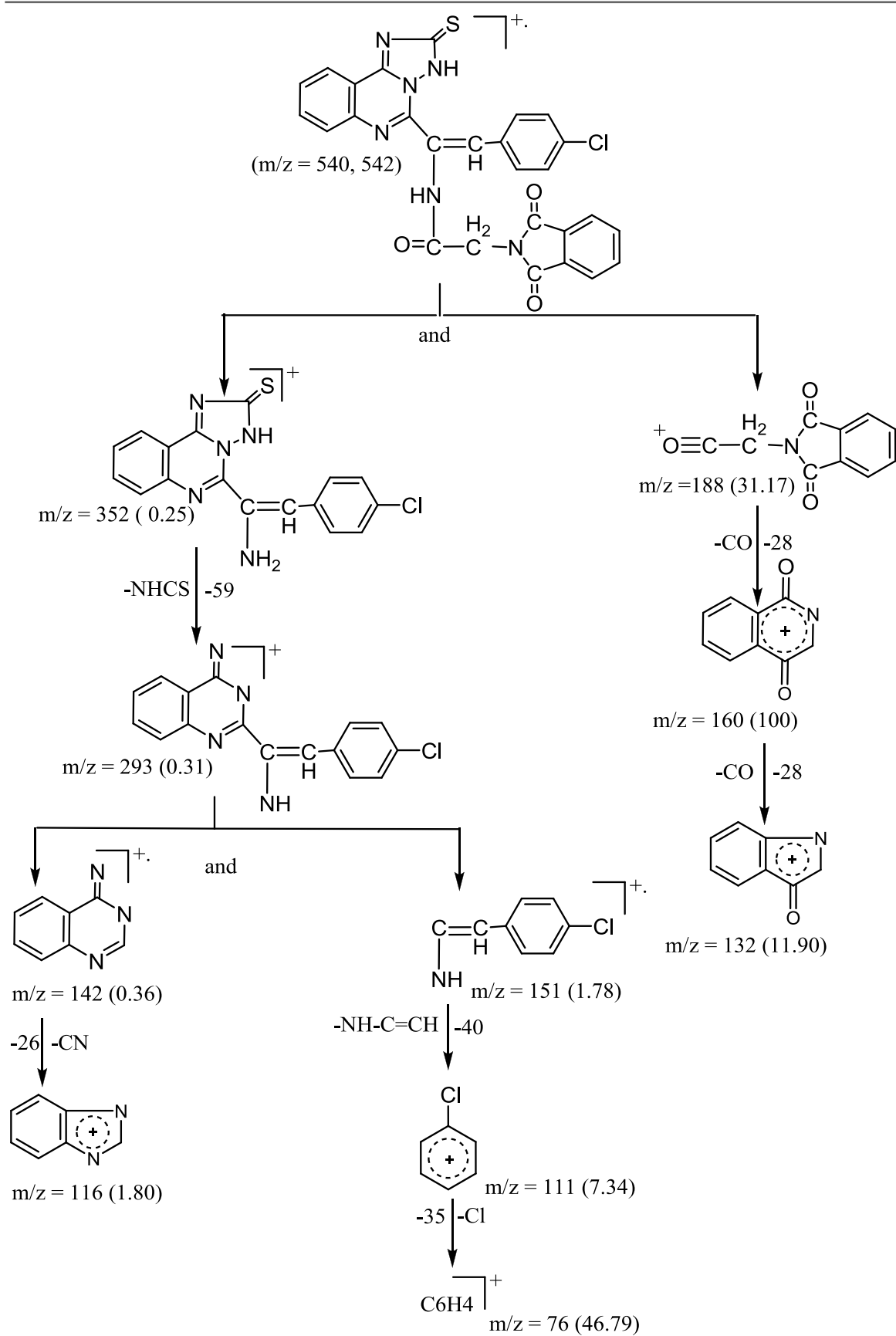
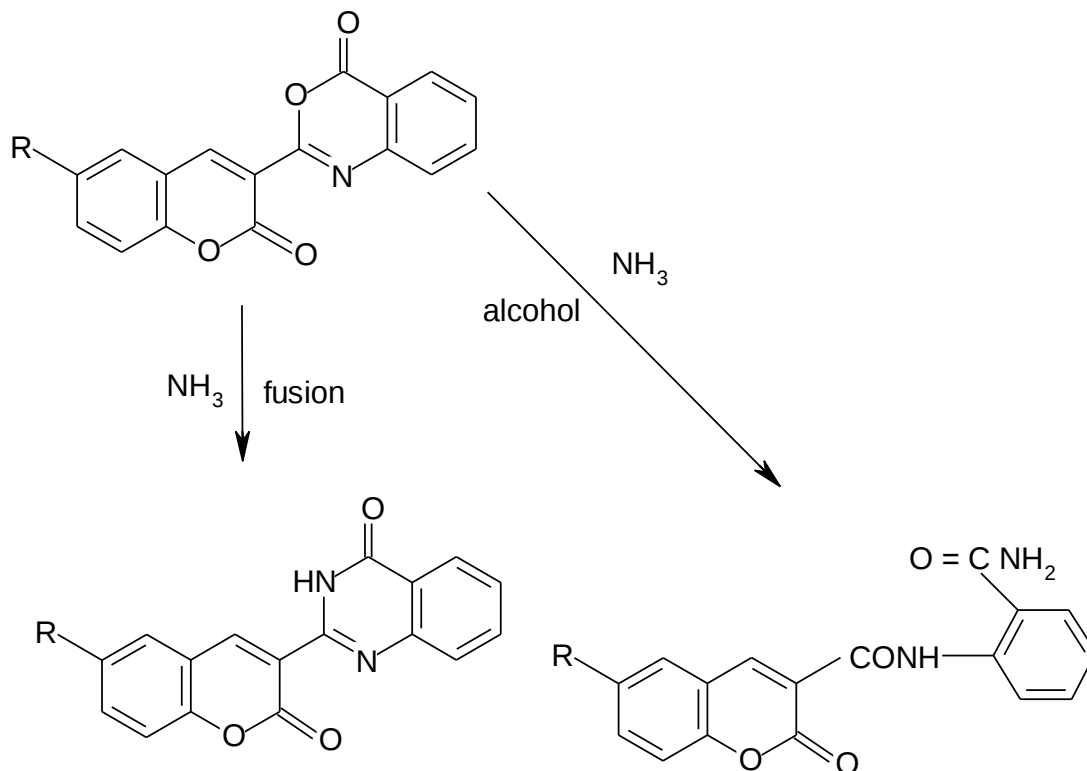


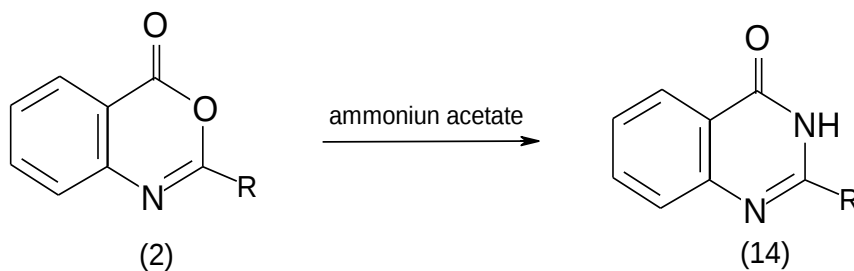
Chart 3

9. Ammonolysis

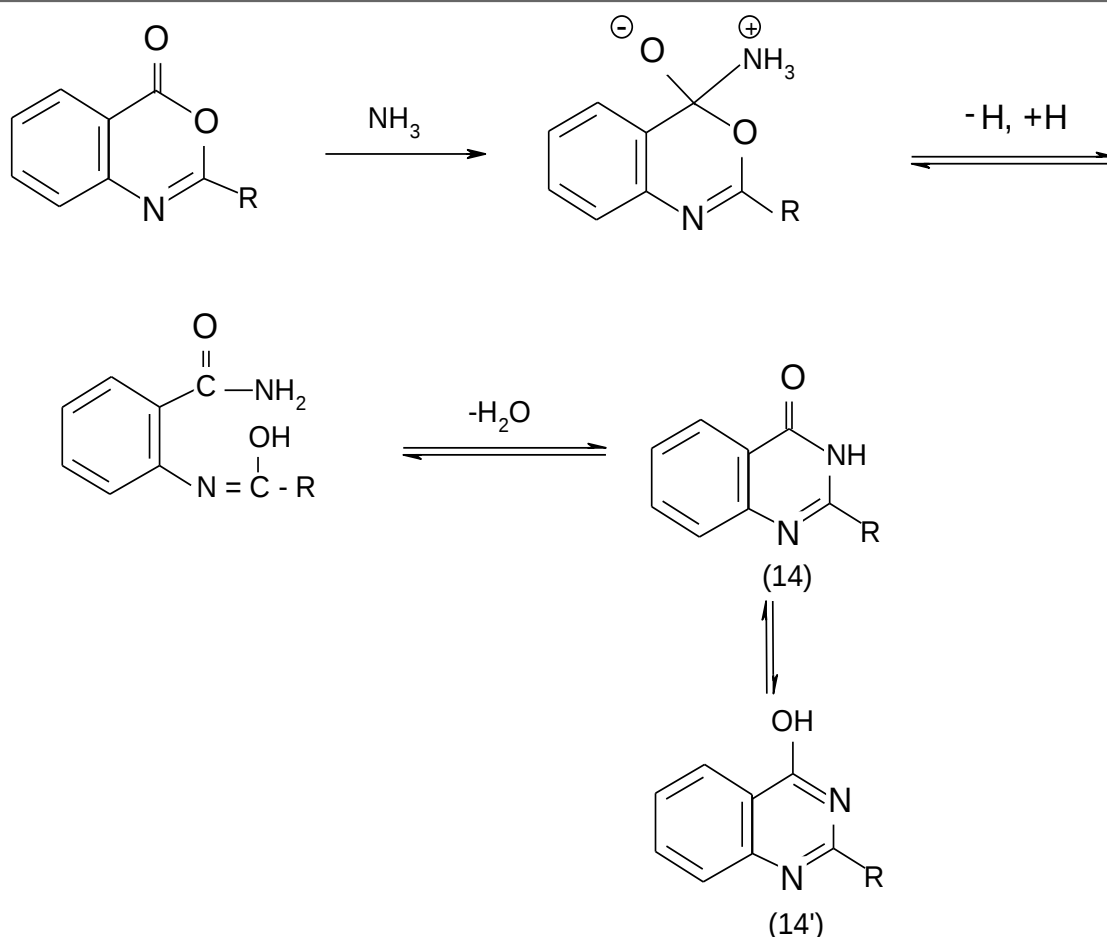
It was reported[104] that 3,1-(4H)-benzoxazinone derivatives underwent ring fission with ammonia furnished from ammonium acetate or urea in alcohol to give N-(substituted) anthranilic acid amide, while by fusion in oil bath or in the presence of anhydrous zinc chloride the corresponding 2-(substituted)-4-quinazolones were obtained.



The present investigation deals with ammonolysis of (2) with ammonia furnished from ammonium acetate by fusion at 170°C to give the corresponding 2-substituted-4(3H)-quinazol-4-one derivative (14).



The reaction possibly takes place via ammonolysis followed by cyclization according to the following mechanism:



The structure of (14) was established from:

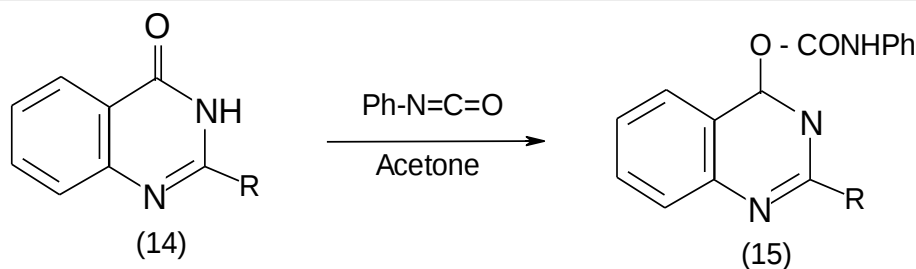
1. Correct analytical data.
2. Infrared spectrum of (14) showed bands at 1624 cm^{-1} (ν CO of α,β -unsaturated amide), at $1774\text{--}1718\text{ cm}^{-1}$ (ν CO of cyclic imide) and at $3470, 3362\text{ cm}^{-1}$ (ν NH).
3. The ^1H -NMR spectrum of (14) (δ ; DMSO-d_6) showed signals at 4.42(s, 2H, NCH_2), at 6.51 (s, 1H, olefinic proton), at 7.86–8.0(m, 12H, Ar-H), 9.7–10.5(s, broad, 2H, 2NH) disappeared by addition of D_2O .

9.1 Chemical proven of compound (14)

The lactam-lactim tautomerism of (14) was further demonstrated chemically by the following:

9.1.1 Acylation of (14)

While treatment of (14) with phenylisocyanates in presence of anhydrous potassium carbonate and dry acetone gave 4-substituted-2-substituted quinazolin-4-ones (15).

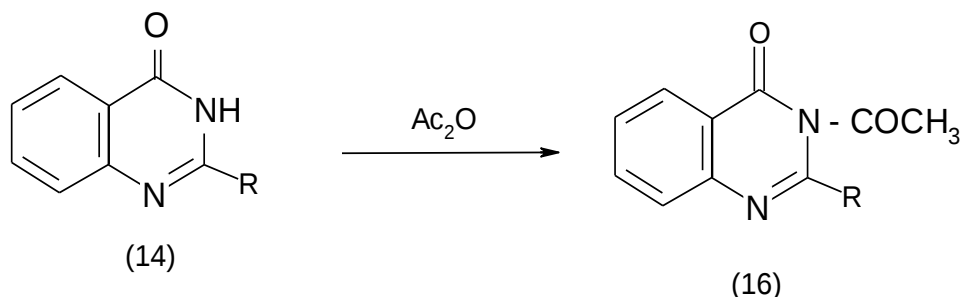


The structure of (15) was proved from the following:

1. The infrared spectrum of (15) showed bands at $1670\text{--}1645\text{ cm}^{-1}$ (ν CO of acyclic amide), at 1731 cm^{-1} (ν CO of carbamate ester), $1774\text{--}1740\text{ cm}^{-1}$ (ν CO of cyclic imide) and at $3360\text{--}3170\text{ cm}^{-1}$ (ν NH).
2. The ^1H -NMR spectrum of (15) (δ ; DMSO- d_6) showed signals at 4.44 (s, 2H, NCH_2), 6.94 (s, 1H, olefinic proton), 7.2-8.7 (m, 17H, Ar-H), 9.8-10.95 (s, broad, 2H, $2\times\text{NH}$) disappeared by addition of D_2O .

9.1.2 Acetylation of quinazolin-4-one (14)

Treatment of N-(2-(4-chlorophenyl)-1-(4-oxo-3,4-dihydroquinazolin-2-yl)vinyl)-2-(1,3-dioxoisindolin-2-yl)acetamide (14) with acetic anhydride afforded N-(1-(3-acetyl-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(4-chlorophenyl)vinyl)-2-(1,3-dioxoisindolin-2-yl)acetamide (16).

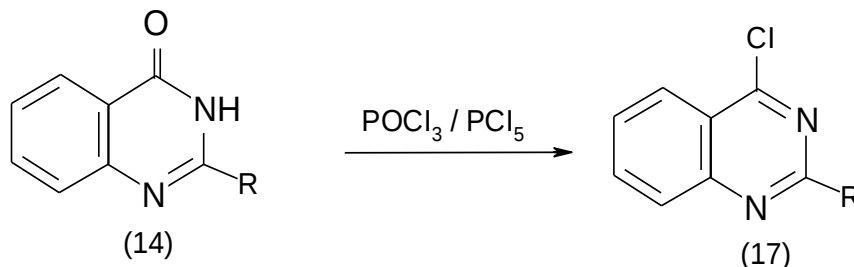


The structure of (16) was established from the following:

1. The infrared spectrum of (16) showed bands at 1617 cm^{-1} (ν CO of α,β -unsaturated amide), at $1774\text{--}1718\text{ cm}^{-1}$ (ν CO of cyclic imide) and at $3474, 3370\text{ cm}^{-1}$ (ν NH).
2. The ^1H -NMR spectrum of (16) (δ ; DMSO- d_6) showed signals at 2.49 (s, 3H, COCH_3), at 4.42 (s, 2H, NCH_2), at 6.76 (s, 1H, olefinic proton), at 7.87-8.0 (m, 12H, Ar-H) and 9.65-10.5 (s, broad, 1H, 1NH) disappeared by addition of D_2O .

9.1.3 Action of phosphorus pentachloride - phosphorus oxychloride on quinazol-4-one (14)

The reaction of (14) with a mixture of phosphorus pentachloride and phosphorus oxychloride gave N-(2-(4-chlorophenyl)-1-(4-chloroquinazolin-2-yl)vinyl)-2-(1,3-dioxoisindolin-2-yl)acetamide (17).

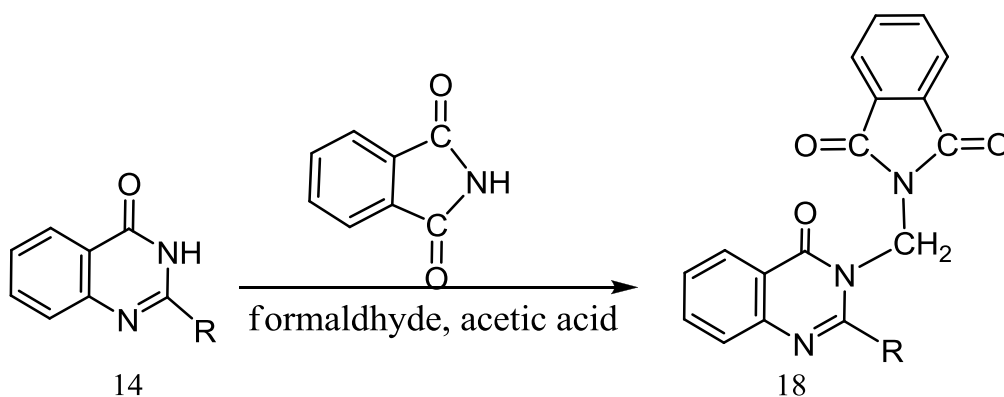


The structure of (17) was established from the following:

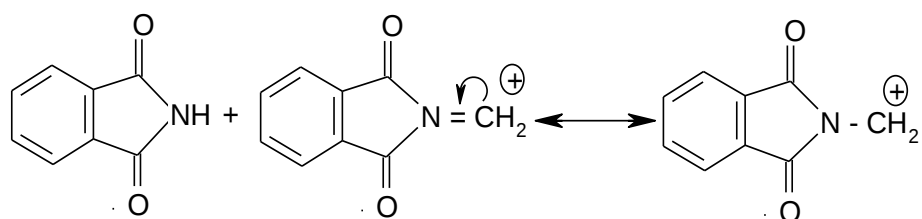
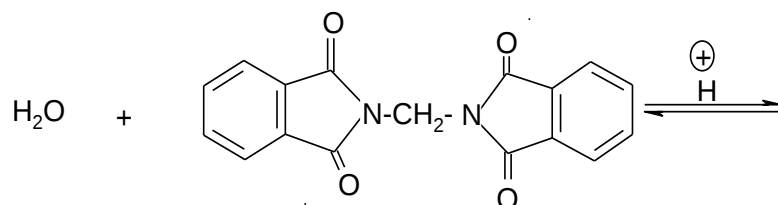
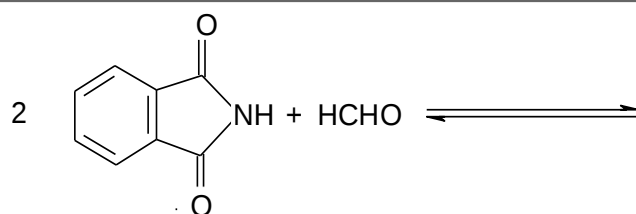
1. Correct analytical data.
2. The infrared spectrum showed bands at 1618 cm^{-1} (ν CO of α,β -unsaturated amide), at $1774\text{--}1715\text{ cm}^{-1}$ (due to coupling carbonyl bands of cyclic imide) and at 3470 cm^{-1} (νNH).
3. The ^1H -NMR spectrum of (17) (δ ; DMSO-d_6) showed signals at 4.44(s, 2H, NCH_2), at 6.74 (s, 1H, olefinic proton), at 7.2-8.0(m, 12H, Ar-H) and at 9.9-10.7(s, broad, 1H, NH) disappeared by addition of D_2O .

10. Mannish reaction

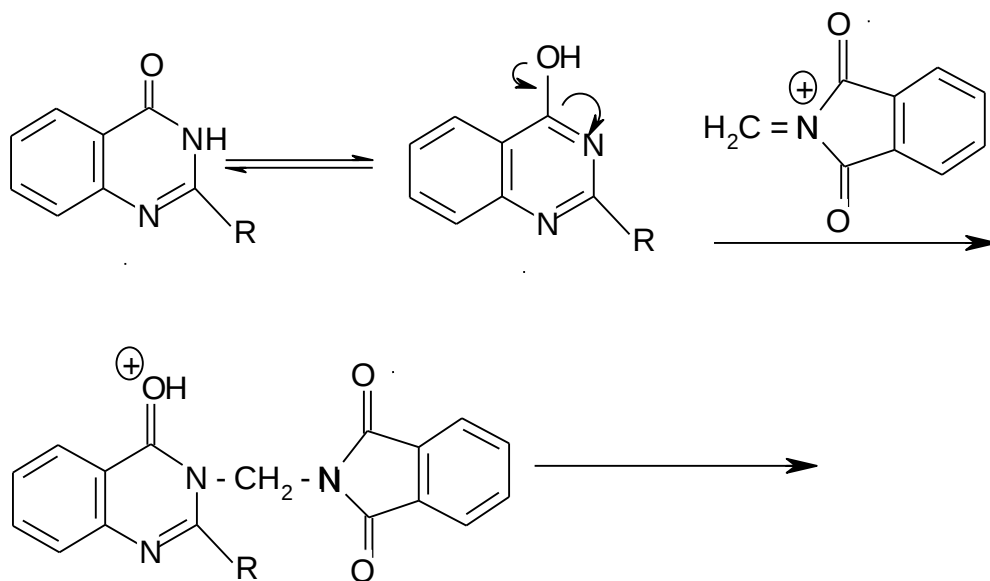
Alcoholic solution of 2-substituted quinazol-4-one (14) was condensed with formaldehyde in the presence imides namely, phthalimide to give the corresponding Mannish bases 3N-(substituted) quinazol-4-ones (18).

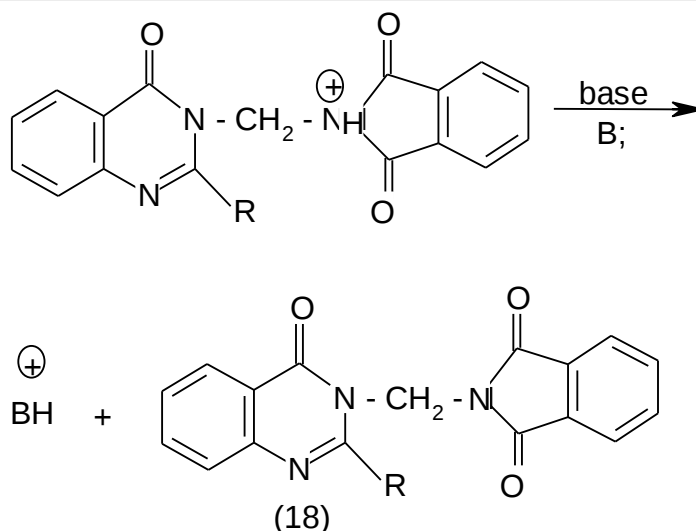


The Mannich intermediate may be formed as follows, taking phthalimide as an example:



The reaction possibly takes place according to the following mechanism:



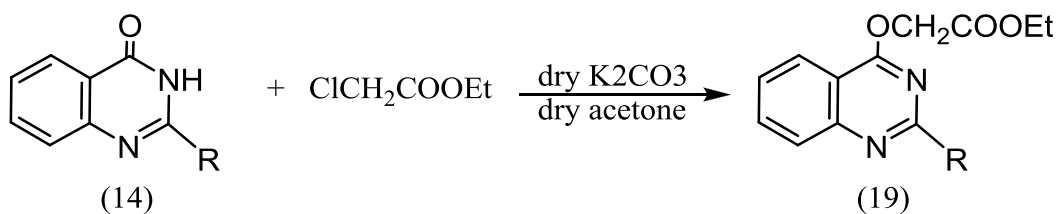


The structure of **(18)** was proved from:

1. Analytical data
2. The infrared spectrum showed bands at 1613 cm^{-1} (ν CO of α,β - unsaturated amide), at $1774\text{-}1721\text{ cm}^{-1}$ (ν CO of cyclic imides) and at 3432 cm^{-1} (ν NH) .
3. The ^1H -NMR spectrum of **(18)** (δ ; DMSO- d_6) showed signals at 4.09 (s, 2H, CH_2), at 4.42(s, 2H, NCH_2), at 5.82 (s, 1H, olefinic proton), at 7.91-7.93(m, 16H, Ar-H) and at 9.9-10.7(s, broad, 1H, NH) disappeared by addition of D_2O .

11. Synthesis of ethyl 2-(2-(2-(4-chlorophenyl)-1-(2-(1,3-dioxoisindolin-2-yl)acetamido)vinyl)quinazolin-4-yloxy)acetate

Quinazolinone (**14**) reacts with ethyl chloroacetate in dry acetone and in the presence of dry potassium carbonate to give compound **(19)**.



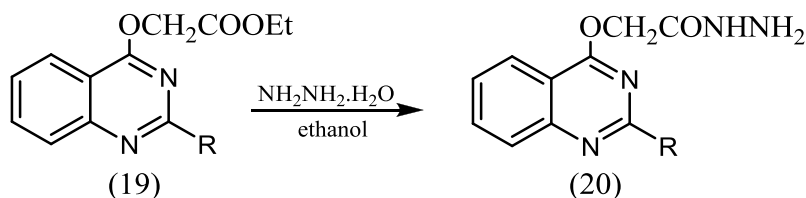
The structure of **(19)** was established from:

1. Correct analytical data.
2. The infrared spectrum showed bands at 1660 cm^{-1} (ν CO of acyclic amide), at $1774\text{-}1719\text{ cm}^{-1}$ (ν CO of cyclic imide), 1731 cm^{-1} (ν CO of ester) and at $3440, 3328\text{ cm}^{-1}$ (ν NH).
3. The ^1H -NMR spectrum of **(19)** (δ ; DMSO- d_6) showed band at δ 1.1-2.5 (m, with interference, 5H, $\text{COOCH}_2\text{CH}_3$), at 4.43 (s, 2H, NCH_2), at 4.83(s, 2H, OCH_2COO), at 6.63(s, 1H, olefinic proton), at 7.86-7.95 (m,

12H, Ar-H) and 9.5-10.2 (s, broad, 1H, NH) disappeared by addition of D₂O .

11.1 Chemical proven of compound (19)

From hydrazinolysis of the ester by hydrazine hydrate to yield the hydrazide derivative (20).

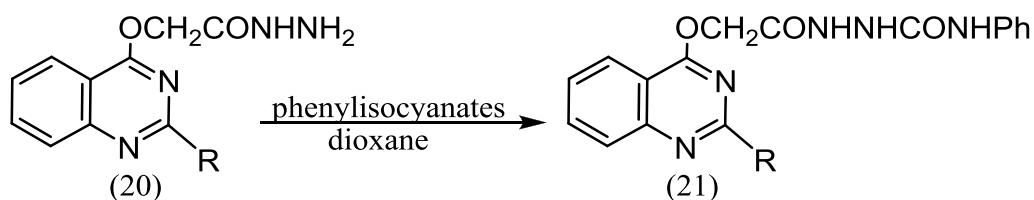


The structure of (20) was established from:

1. Correct analytical data.
2. The infrared spectrum showed bands at 1623 cm⁻¹(ν CO of α,β-unsaturated amide) , at 1774-1719 cm⁻¹ (ν CO of cyclic imide) and at 3426 cm⁻¹ (νNH) .
3. The H¹-NMR spectrum of (20) (δ; DMSO-d₆) showed signals at 4.76 (s, 2H, NCH₂), at 4.82(s, 2H, OCH₂CO), at 6.72 (s, 1H, olefinic proton), 7.84-8.1(m, 12H, Ar-H), 9.65-10.5(s, broad, 2H, 2×NH) disappeared by addition of D₂O .

12. Action of phenyl isocyanate on quinazolinone (20)

Quinazolinone (20) reacts with phenyl isocyanate in dioxane to give 2-(2-(2-(2-(4-chlorophenyl)-1-(2-(1,3-dioxoisindolin-2-yl)acetamido)vinyl)quinazolin-4-yloxy)acetyl)-N-phenylhydrazinecarboxamide (21).

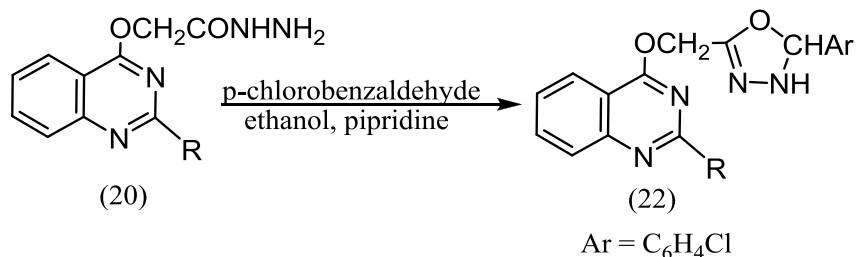


The structure of (21) was established from:

1. Correct analytical data.
2. The infrared spectrum showed bands at 1615cm⁻¹(ν CO of α,β-unsaturated amide), at 1774-1719 cm⁻¹ (ν CO of cyclic imide) and at 3366 cm⁻¹ (νNH) .
3. The H¹-NMR spectrum of (21) (δ; DMSO-d₆) showed signals at 4.43(s, 2H, NCH₂), at 6.51 (s, 1H, olefinic proton), at 7.85-8.1(m, 12H, Ar-H), 9.65-10.5(s, broad, 4H, 4×NH) disappeared by addition of D₂O .

13. Action of p-chlorobenzaldehyde on quinazolinone (20)

Quinazolinone (20) reacts with p-chlorobenzaldehyde in absolute ethanol and 1ml pipridine to give (22).

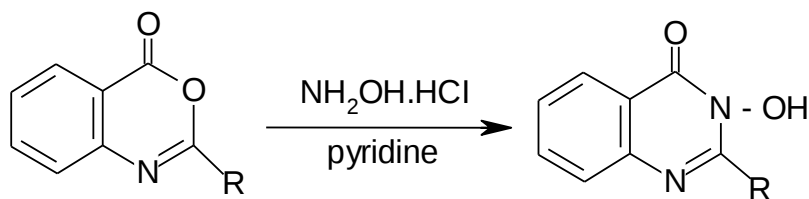


The structure of (22) was established from:

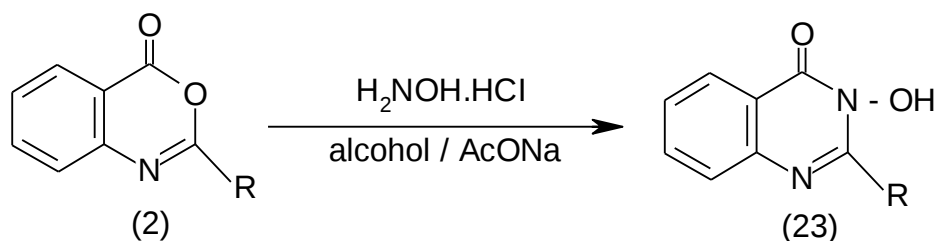
1. Correct analytical data.
2. The infrared spectrum showed bands at 1615 cm⁻¹ (ν CO of α,β-unsaturated amide), at 1774-1722 cm⁻¹ (ν CO of cyclic imide) and at 3424 cm⁻¹ (νNH) .
3. The H¹-NMR spectrum of (22) (δ; DMSO-d₆) showed signals at 4.6(s, 2H, NCH₂), at 6.6 (s, 1H, olefinic proton), at 6.74 (s, 1H, N=CH), at 7.74-8.09(m, 16H, Ar-H) and at 9.6-10.2(s, broad, 2H, 2×NH) disappeared by addition of D₂O .

14. Base catalysed reaction with hydroxylamine hydrochloride

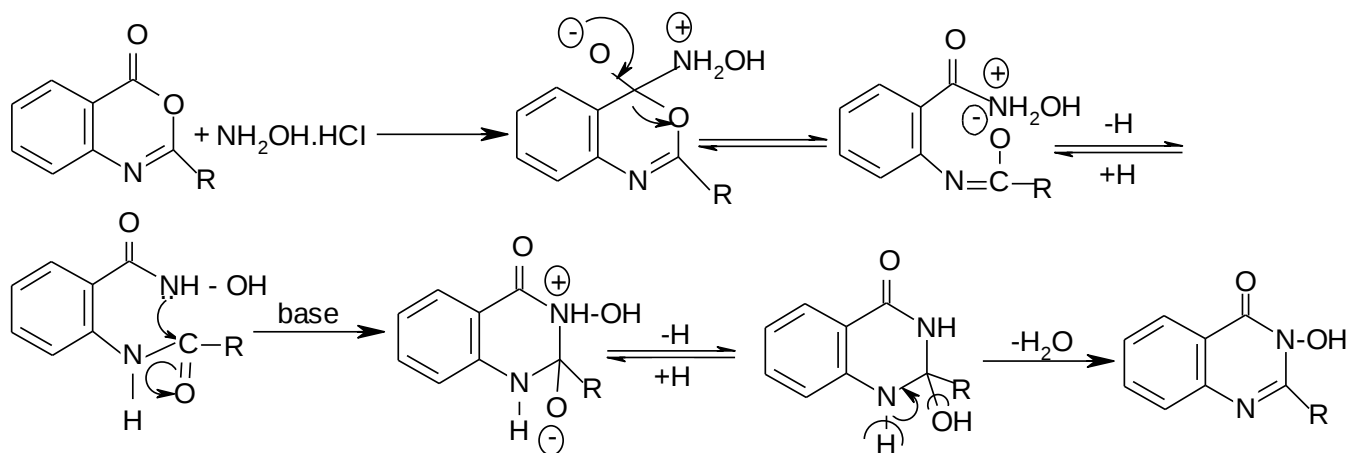
Recently, [103] it was reported that 2-substitutedbenzoxazinones reacted with hydroxylamine hydrochloride in refluxing pyridine to give 2-substituted 3-hydroxy-4-quinazoline.



In pursuit the above result, the author investigated the reaction of hydroxylamine hydrochloride with N-(2-(4-chlorophenyl)-1-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)vinyl)-2-(1,3-dioxoisindolin-2-yl)acetamide (2) in the presence of sodium acetate in boiling ethanol to give N-(2-(4-chlorophenyl)-1-(3-hydroxy-4-oxo-3,4-dihydroquinazolin-2-yl)vinyl)-2-(1,3-dioxoisindolin-2-yl)acetamide.



The formation of (23) possibly takes place according to the following mechanism:



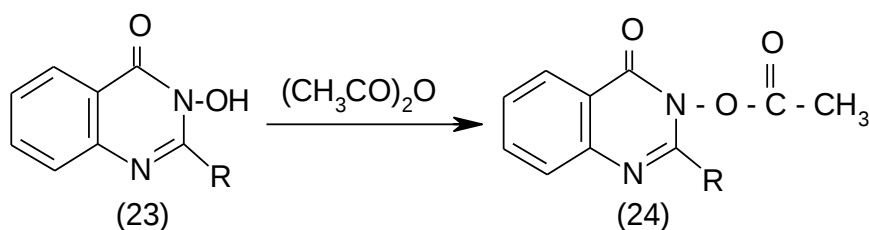
The structure of (23) was established from:

1. Correct analytical data.
2. Infrared spectrum for (23) showed bands at 1617 cm^{-1} (ν CO of cyclic and a cyclic amide), at $1774\text{--}1720\text{ cm}^{-1}$ (ν CO of cyclic imide), and at 3848 , 3743 , 3485 cm^{-1} (νOH and NH).
3. The ^1H -NMR spectrum of (23) (δ ; DMSO-d_6) showed signals at $4.43(\text{s}, 2\text{H}, \text{NCH}_2)$, at $6.75(\text{s}, 1\text{H}, \text{olefinic proton})$, $7.3\text{--}7.95(\text{m}, 12\text{H}, \text{Ar-H})$, at $8.68(\text{s}, \text{broad}, 1\text{H}, \text{NH})$ and at $10.69(\text{s}, 1\text{H}, \text{OH})$.

14.1 Chemical proven of compound (23)

14.1.1 Acetylation of 3-N-hydroxy-4-quinazolone

The acylation of the readily available (23) investigated thus, treatment of (23) with excess of acetic anhydride gave 2-(2-(4-chlorophenyl)-1-(2-(1,3-dioxoisindolin-2-yl)acetamido)vinyl)-4-oxoquinazolin-3(4H)-yl acetate (24).



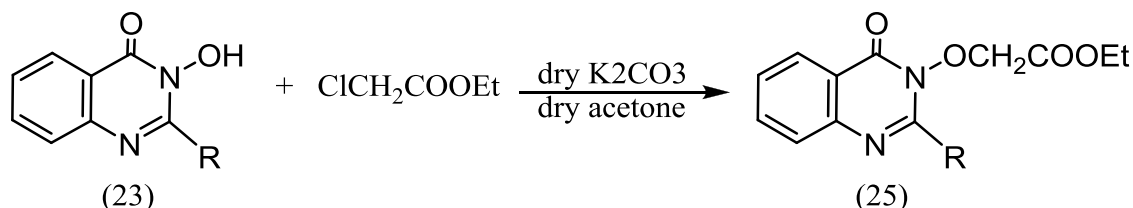
The structure of (24) was established from:

1. Correct analytical data.
2. Infrared spectrum for (24) showed bands at 1660 cm^{-1} (ν CO of cyclic and acyclic amide), at $1774\text{--}1720\text{ cm}^{-1}$ (ν CO of cyclic imide), 1731 cm^{-1} (ν CO of ester), and at 3462 , 3328 cm^{-1} (νNH).

3. The ^1H -NMR spectrum of (24) (δ ; DMSO- d_6) showed signals at 2.49 (s, 3H, OCOCH_3), 4.42(s, 2H, NCH_2), at 6.75 (s, 1H, olefinic proton), 7.87-7.95(m, 12H, Ar-H) and at 9.6-10.2(s, broad, 1H, NH) disappeared by addition of D_2O .

14.1.2 Reaction with ethyl chloroacetate

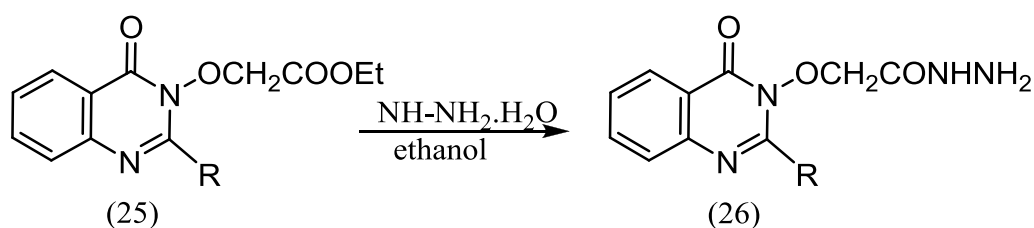
Another reaction which confirm the presence of hydroxyl group is the reaction with ethyl chloroacetate in dry acetone which leads to formation of ethyl 2-(2-(2-(4-chlorophenyl)-1-(2-(1,3-dioxoisindolin-2-yl)acetamido)vinyl)-4-oxoquinazolin-3(4H)-yloxy)acetate (25).



1. The structure of compound (25) were supported by their infrared spectrum which showed bands at 1660 cm^{-1} (ν CO of cyclic and acyclic amide), at $1774\text{-}1722\text{ cm}^{-1}$ (ν CO of cyclic imide), 1732 cm^{-1} (ν CO of ester) and at $3440, 3324\text{ cm}^{-1}$ (νNH).
2. The ^1H -NMR spectrum of (25) (δ ; DMSO- d_6) showed signals at δ 1.2(t, 3H, CH_3), at 4.1(q, 2H, CH_2 of ester), at 4.42 (s, 2H, NCH_2), at 4.83(s, 2H, OCH_2COO), at 6.63(s, 1H, olefinic proton), at 7.4-7.9 (m, 12H, Ar-H) and 9.5-10.2 (s, broad, 1H, NH) disappeared by addition of D_2O .

14.1.2.1 Chemical proven of compound (25)

From hydrazinolysis of the ester by hydrazine hydrate to yield the hydrazide derivative (26).

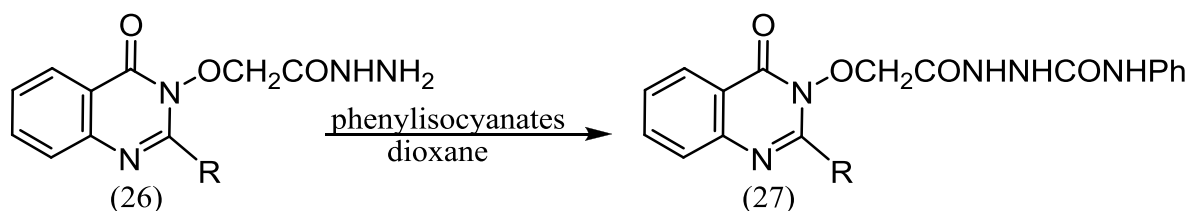


The structure of (26) was established from:

1. Correct analytical data.
2. The infrared spectrum showed bands at $1680\text{-}1660\text{ cm}^{-1}$ (ν CO of amides and hydrazide), at $1774\text{-}1723\text{ cm}^{-1}$ (ν CO of cyclic imide) and at $3480\text{-}3220\text{ cm}^{-1}$ (νNH and NH_2).
3. The ^1H -NMR spectrum of (26) (δ ; DMSO- d_6) showed signals at 4.42(s, 2H, NCH_2), at 4.82(s, 2H, OCH_2CO), at 6.6(s, 1H, olefinic proton), 7.09-8.06(m, 12H, Ar-H), 9.65-10.5(s, broad, 2H, $2\times\text{NH}$) disappeared by addition of D_2O .

15. Action of phenyl isocyanate on quinazolinone (26)

Quinazolinone (26) reacts with phenyl isocyanate in dioxane to give 2-(2-(2-(2-(4-chlorophenyl)-1-(2-(1,3-dioxoisindolin-2-yl)acetamido)vinyl)quinazolin-4-yloxy)acetyl)-N-phenylhydrazinecarboxamide (27).

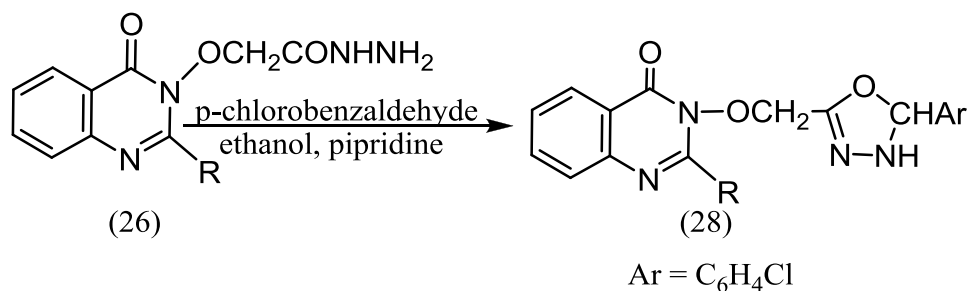


The structure of (27) was established from:

1. Correct analytical data.
2. The infrared spectrum showed bands at 1662 cm⁻¹ (ν CO of amides), at 1774-1718 cm⁻¹ (ν CO of cyclic imide), and at 3462, 3320 cm⁻¹ (νNH).
3. The H¹-NMR spectrum of (27) (δ; DMSO-d₆) showed signals at 4.43(s, 2H, NCH₂), at 5.82 (s, 1H, olefinic proton), at 7.85-8.08 (m, 12H, Ar-H), 9.65-10.5(s, broad, 4H, 4×NH) disappeared by addition of D₂O.

16. Action of p-chlorobenzaldehyde on quinazolinone (26)

Quinazolinone (26) reacts with p-chlorobenzaldehyde in absolute ethanol and 1ml pipridine to give (28).



The structure of (28) was established from:

1. Correct analytical data.
2. The infrared spectrum showed bands at 1666 cm⁻¹ (ν CO of amides), at 1774-1716 cm⁻¹ (ν CO of cyclic imide) and at 3445 cm⁻¹ (νNH).
3. The H¹-NMR spectrum of (28) (δ; DMSO-d₆) showed signals at 4.43 (s, 2H, NCH₂), at 6.5 (s, 1H, olefinic proton), at 6.7 (s, 1H, N=CH), at 7.78-8.09 (m, 16H, Ar-H) and at 9.6-10.2(s, broad, 2H, 2×NH) disappeared by addition of D₂O.

BIOLOGICAL ACTIVITY

Studies on 4H-3,1-Benzoxazin-4-ones

BIOLOGICAL ACTIVITY

The behavior of the synthesized organic compounds as antibacterial was investigated at the Micro analytical unit, Cairo University, Egypt.

The antimicrobial activity of synthesized derivatives was examined in vitro by hole plate and filter paper disc methods. Some compounds were tested for activity Gram-positive, Gram-negative bacteria and fungi using tetracycline and amphotericin B as a reference standard.

The results show the effectively of compounds **2**, **4a**, **5**, **7a**, **14** and **23** against bacteria, *Escherichia Coli*(G⁻) (cf. Fig.1,2,3), *Staphylococcus Aureus* (G⁺) (cf. Fig. 4,5,6) and *Candida albicans* (fungus) (cf. Fig.10,11,12) and the ineffectively against *Aspergillus Flavus* (fungus) (cf. Fig.7,8,9)

On the other hand, for compounds **3b**, **3f** and **15** the results show its effective against bacteria, Es (cf. Fig. 1, 3), and St (cf. Fig.4, 6), and its ineffective against fungi As (cf. Fig.7,9), and Ca (cf. Fig. 10, 12).

Moreover, the results show the effectively of compounds **9**, **10**, **11**, **12**, **14**, **17**, **18**, **19**, **20**, **22**, **25**, **27** and **28** against bacteria, *Escherichia Coli*(G⁻), *Staphylococcus Aureus* (G⁺) and *Candida albicans* (fungus) and the ineffectively against *Aspergillus Flavus* (fungus).

For compounds **6**, **16**, **21**, **24** and **26** the results show its effective against bacteria, Es and St and its ineffective against fungi As and Ca. The results are summarized in (Table 4).

Es: *Escherichia Coli*

St: *Staphylococcus Aureus*

As: *Aspergillus Flavus*

Ca: *Candida albicans*

Table 4 Relative activity of the some compounds against (G⁺),(G⁻) bacteria and fungi

Sample		Inhibition zone diameter (mm/mg sample)			
		Escherichia Coli (G ⁻)	Staphylococcus Aureus(G ⁺)	Aspergillus Flavus (Fungus)	Candida albicans (Fungus)
Control : DMSO		0.0	0.0	0.0	0.0
Standard	Tetracycline Antibacterial agent	34	32	--	--
	Amphotericin B Antifungal agent	--	--	18	20
2		15	15	0.0	12
3 _b		15	16	0.0	0.0
3 _f		14	14	0.0	0.0
4 _a		12	13	0.0	10
5		14	13	0.0	13
6		12	13	0.0	0.0
7 _a		11	10	0.0	10
9		12	13	0.0	10
10		14	13	0.0	13
11		11	10	0.0	10

Sample		Inhibition zone diameter (mm/mg sample)			
		Escherichia Coli (G ⁻)	Staphylococcus Aureus(G ⁺)	Aspergillus Flavus (Fungus)	Candida albicans (Fungus)
Control : DMSO		0.0	0.0	0.0	0.0
Standard	Tetracycline Antibacterial agent	34	32	--	--
	Amphotericin B Antifungal agent	--	--	18	20
12		15	15	0.0	12
13		15	16	0.0	0.0
14		13	14	0.0	12
15		11	10	0.0	0.0
16		15	16	0.0	0.0
17		14	13	0.0	12
18		13	12	0.0	10
19		12	13	0.0	10
20		14	13	0.0	13
21		12	10	0.0	0.0
22		15	16	0.0	10

Sample		Inhibition zone diameter (mm/mg sample)			
		Escherichia Coli (G ⁻)	Staphylococcus Aureus(G ⁺)	Aspergillus Flavus (Fungus)	Candida albicans (Fungus)
Control : DMSO		0.0	0.0	0.0	0.0
Standard	Tetracycline Antibacterial agent	34	32	--	--
	Amphotericin B Antifungal agent	--	--	18	20
23		15	15	0.0	12
24		15	16	0.0	0.0
25		13	14	0.0	12
26		11	10	0.0	0.0
27		14	13	0.0	13
28		11	10	0.0	10

FIGURES

Studies on 4H-3,1-Benzoxazin-4-ones

BIOLOGICAL ACTIVITY

Escherichia coli (G⁻)

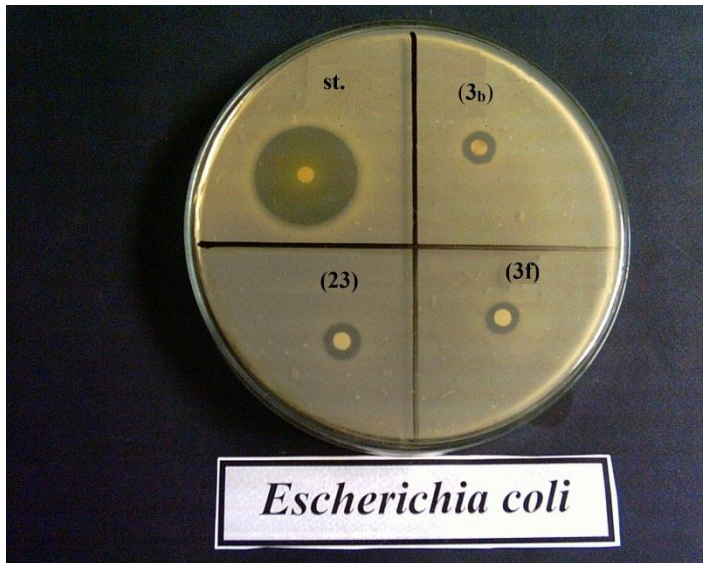


Figure 1

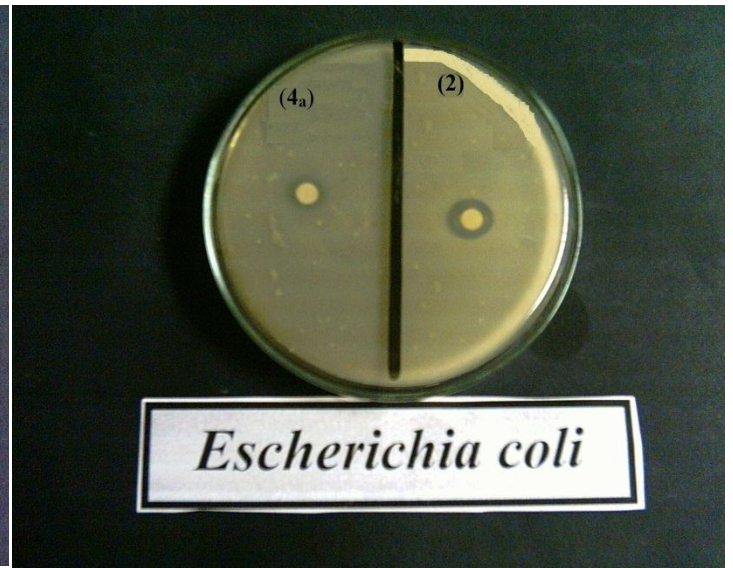


Figure 2

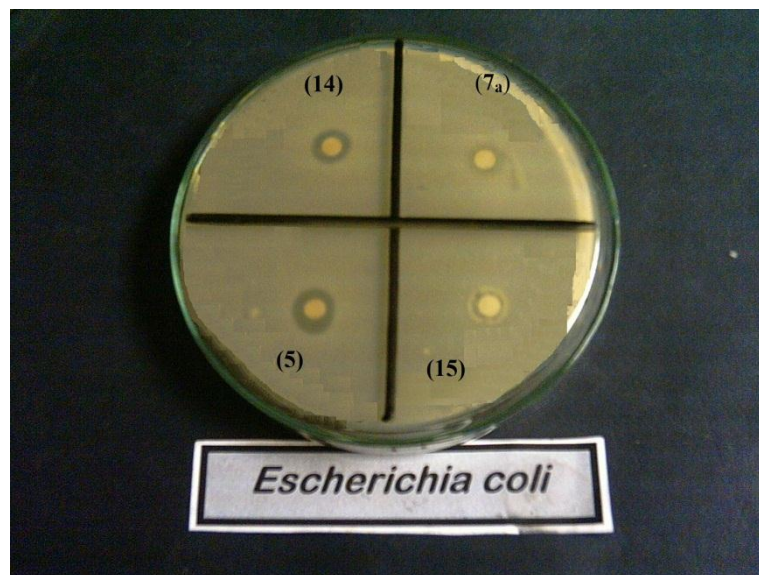


Figure 3

Staphylococcus aureus (G⁺)

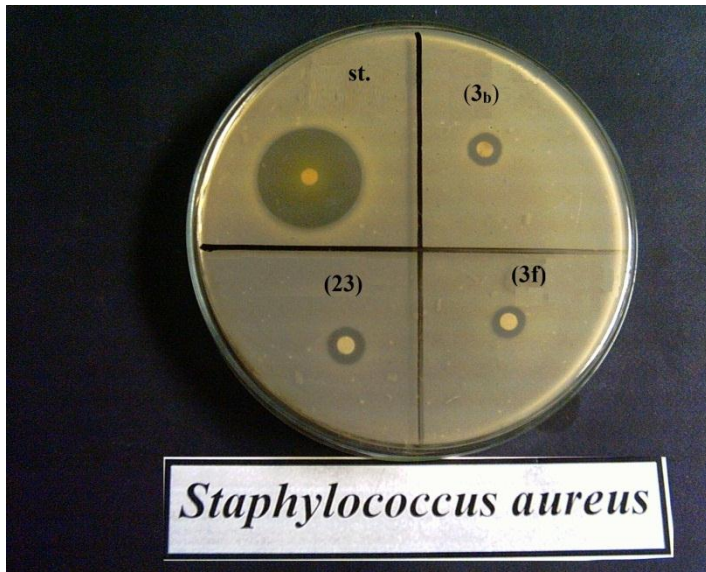


Figure 4

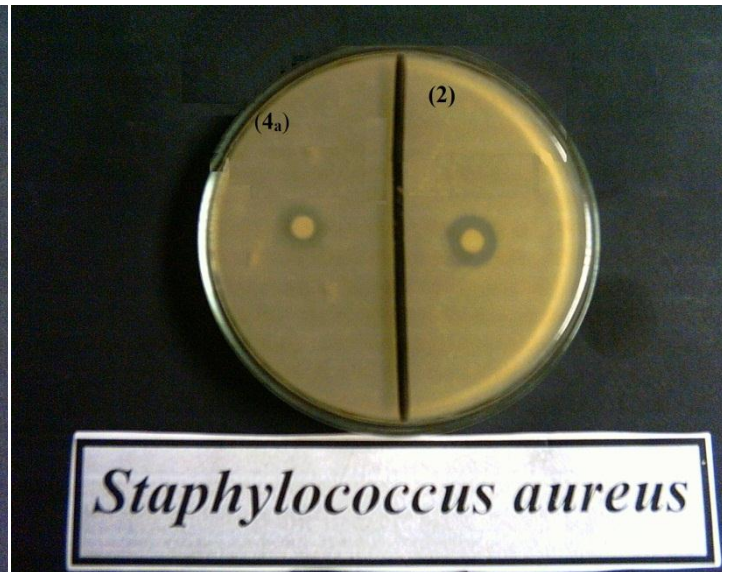


Figure 5

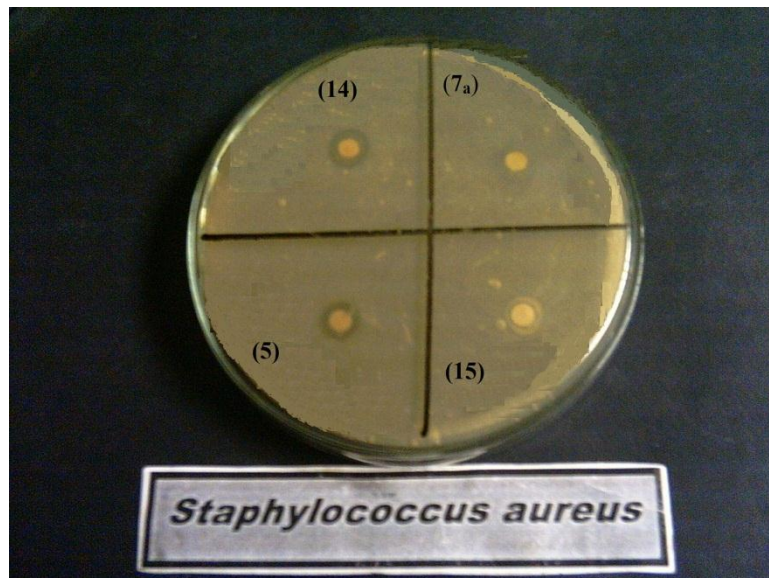


Figure 6

Aspergillus flavus(fungus)

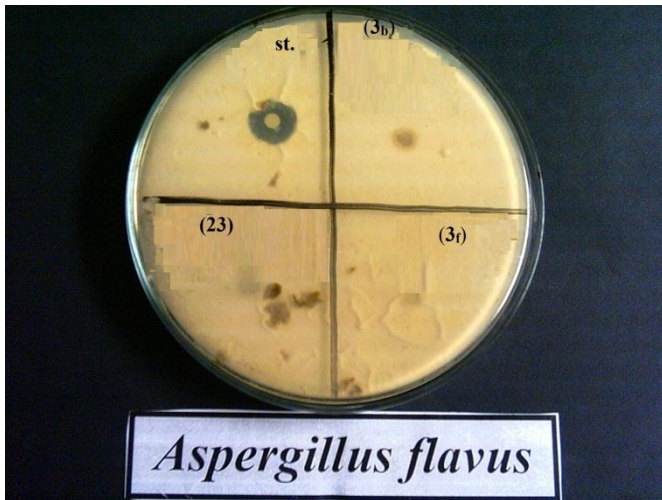


Figure 7

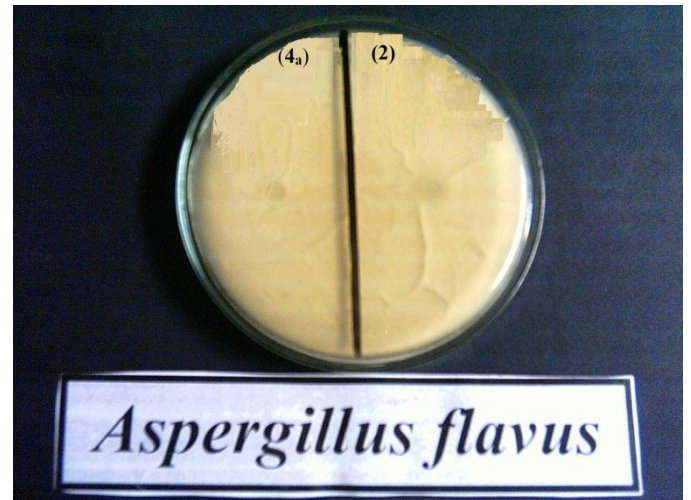


Figure 8

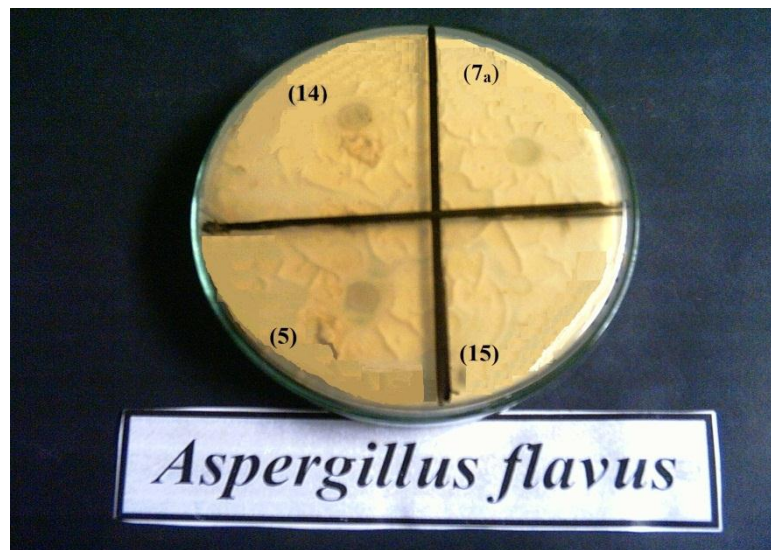


Figure 9

Candida albicans (fungus)

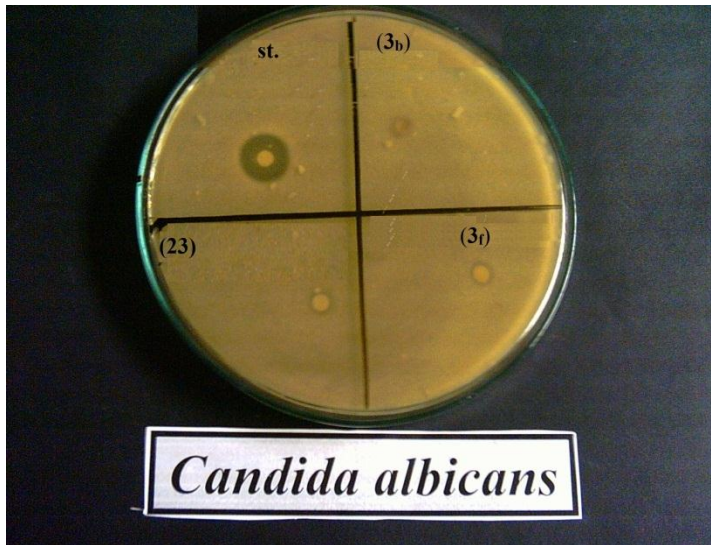


Figure 10

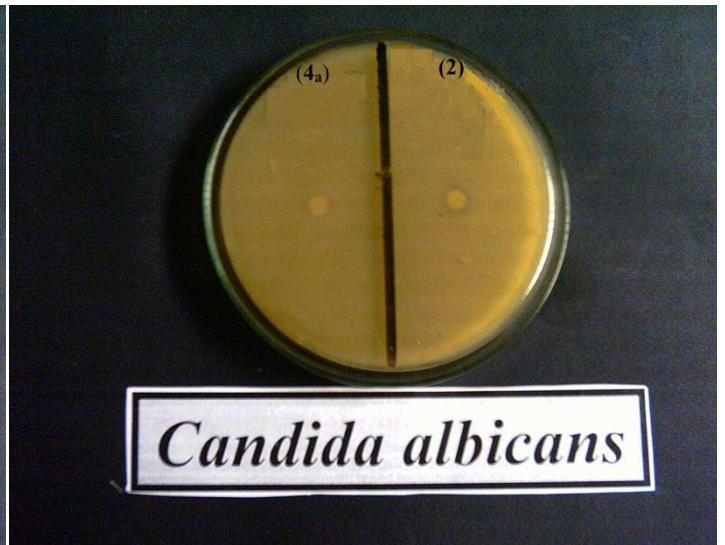


Figure 11

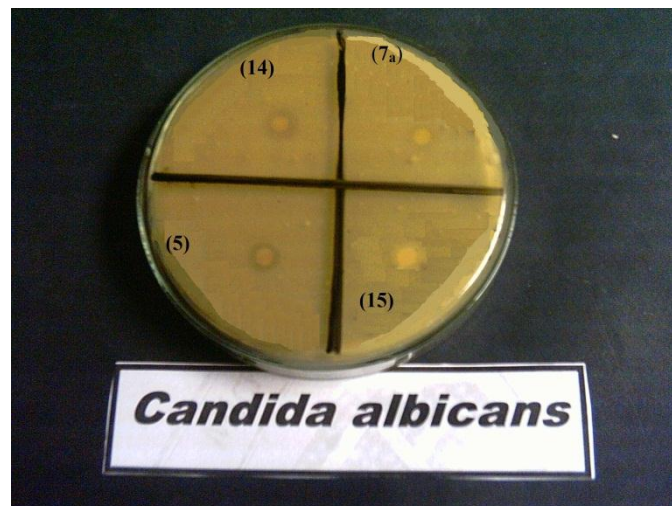


Figure 12

EXPERIMENTAL

Studies on 4H-3,1-Benzoxazin-4-ones

EXPERIMENTAL

Melting points were measured on electrothermal melting point apparatus and are uncorrected. IR model 550 spectrophotometers. Mass spectra were recorded at 70 eV with a Varian MAT 311. ¹H-NMR spectra were determined on Bruker Wpsy 200 MHz spectrometer with TMS as internal standard. The chemical shifts are in ppm. Solvent was DMSO. All analysis was carried out at MicroAnalytical Center, Faculty of Science, Cairo University, Egypt. The chemicals and reagents were purchased from EL-Gomhouria Company, Egypt. Physical data and analytical data for the synthesized compounds have been summarized in (Table 5, 6).

1. Synthesis and reactions of N-(2-(4-chlorophenyl)-1-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)vinyl)-2-(1,3-dioxoisindolin-2-yl)acetamide (2)

A mixture of (Z)-2-((4-(4-chlorobenzylidene)-5-oxo-4,5-dihydrooxazol-2-yl)methyl)isindoline-1,3-dione (**1**) (0.05 mol) and anthranilic acid (0.035 mol) in boiling n-butanol was heated under reflux for 10 hrs. The solid product obtained was crystallized from benzene to give compound (**2**).

2. Action of primary amines on (2): formation of (3_{a-h})

A solution of (**2**) (0.01 mol) and primary amines, namely methylamine, ethylamine, butyl amine, pentylamine, hexyl amine, glycine, p-anisidine and o-phenylenediamine (0.01 mol) in (50 ml) ethanol was refluxed for 4 hrs. The solid product was separated on cooling and crystallized from the proper solvent to give (**3_{a-h}**).

3. Action of hydrazines on (2): Formation of (4_{a,b})

A solution of benzoxazinone (**2**) (0.01 mol) with hydrazine hydrate (0.02 mol) in ethanol (30 ml) was refluxed for 4 hrs, the product that separated on cooling was crystallized from the pet. ether (40-60) to give the hydrazide derivative (**4_a**). On the other hand, reaction of (**2**) (0.01 mol) with phenyl hydrazine (0.02 mol) in ethanol (30 ml) was refluxed for 4 hrs. The product that separated on cooling was crystallized from benzene to give quinazolinone derivative (**4_b**).

4. Action of active methylene on benzoxazinone (2): Formation of 1,4-quinolinone (5)

A solution of (**2**) (0.01 mol) and ethyl acetoacetate (0.03 mol) in pyridine (50 ml) was refluxed for 4 hrs. The reaction mixture was cooled and poured into ice / HCl. The separated product was filtered off and crystallized from ethanol to give (**5**).

5. Action of sodium azide on benzoxazinone (2): Formation of tetrazole (6)

A mixture of benzoxazinone (2) (0.01 mol) and sodium azide (0.05 mol) in boiling acetic acid (50 ml) was refluxed for 3 hrs. The separated product obtained after concentration was crystallized from ethanol to give tetrazole derivative (6).

6. Action of aromatic substrates on benzoxazinone (2) in presence of anhydrous AlCl_3 : Formation of o-aroylanilides (7_{a,b})

Anhydrous AlCl_3 (0.03 mol) was added under stirring to (2) (0.01 mol) in dry aromatic substrate namely benzene and toluene at room temperature. The reaction mixture was stirred for 3 hrs, and the resultant complex formed decomposed with ice/dilHCl. The solvent was steam distilled and the residual solid filtered and crystallized from the proper solvent to give (7_{a,b}).

7. 2-Amino methyl benzimidazole (8)

A mixture of the equimolar amounts of o-phenylenediamine and glycine was heated for 2.5 hrs under reflux in the presence of conc. HCl subsequently reaction mixture was concentrated and the desired product separated out on cooling crystallized, from ethanol to give (8).

8. Action of (8) on benzoxazinone (2): Formation of 2-substituted- 3-methyl-[2'-benzimidazolyl]-(4H)- 3,1-quinazolin-4-one (9)

A mixture of 2-Amino methyl benzimidazole (8) (0.01 mol) and benzoxazin-4-one (2) (0.01 mol) in (30 ml) dry pyridine was refluxed for 6 hrs. The reaction mixture was poured into ice/HCl. The solid product that separated out was washed repeated with water and crystallized from ethanol to give (9).

9. Diels-Alder reaction on (2):

A mixture of benzoxazinone (2) (0.01 mol) and dimethyl maleate (0.01 mol) in dry xylene (50 ml) was refluxed for 20 hrs. The reaction mixture was filtered upon hot, the filtration was concentrated and cooled. The separated product obtained was crystallized from benzene to give (10).

10. Synthesis of quinazolinylurea (11)

A solution of benzoxazinone (2) (0.01mol) in (40 ml) pyridine with semicarbazide hydrochloride (0.01mol) was refluxed for 6hrs, left to cool , poured into cold water with stirring ,the solid that separated out was filtered off , washed with cold water, dried and crystallized from ethanol to give (11).

11. Cyclization of quinazolinylurea(12)

On fusion of quinazolinylurea derivative for 2 hrs on sand bath above melting point. The solid product after cooling was crystallized from pet-ether(40-60) to give (12).

12. Action of thiosemicarbazide on benzoxazone (2)

A mixture of benzoxazinone (2) (0.01 mol) and thiosemicarbazide (0.01 mol) in dry pyridine (30 ml) was refluxed for 4 hrs, left to cool , poured into ice/HCl, filtered off and crystallized from methanol to give (13).

13. Action of ammonium acetate or formamide on (2):Formation of quinazolone (14)

(0.01 mol) of benzoxazinone (2) was fused with (0.02 mol) ammonium acetate on sand bath above the melting point for 3hrs. The reaction mixture after cooling was poured into water, filtered off and crystallized from benzene to give (14).

14. Acylation of (14): Formation of (15)

A mixture of (14) (0.01 mol) , anhydrous potassium carbonate (0.04mol) and phenyl isocyanate (0.042 mol) was heated for 24 hrs under reflux in (50 ml) dry acetone. The reaction mixture after removing the excess solvent was poured into cold water, the solid that separated out was filtered off, dried and crystallized from ethanol solvent to give (15).

15. Action of acetic anhydride on (14): Formation of 3N-acetyl quinazolone (16)

Treatment of (14) with excess acetic anhydride (20 ml) was refluxed for 3 hrs. After cooling the product obtained was washed with water; filtered off, dried and crystallized from ethanol to give (16).

16. Action of phosphorus pentachloride - phosphorus oxychloride on quinazol-4-one (14)

(0.01 mol) quinazolinone (14) and a mixture of PCl_5 (0.01 mol), POCl_3 (2 ml) was heated in water bath for 5 hrs. After cooling the reaction mixture was poured into ice , filtered off and crystallized from benzene to give (17).

17. Mannish reaction on quinazolone (14): Formation of Mannish bases (18)

A mixture of (14) (0.01 mol), formaldehyde (5 ml) and phthalimide (0.01mol) in boiling acetic acid and (30 ml) was refluxed for 4hrs, after cooling the separated product was crystallized from ethanol to give Mannish base (18).

18. Action of ethyl chloroacetate on quinazolinone (14)

A mixture of (14) (0.01mol) , anhydrous potassium carbonate (0.04mol) and ethyl chloroacetate (0.04mol) in (60 ml) dry acetone was refluxed for 24hrs. The product obtained after removing the excess solvent was poured into cold water, the solid that separated out was filtered off , dried and crystallized from methanol to give (19).

19. Action of hydrazine hydrate on quinazolinone (19)

A mixture of (19) (0.01mol) and hydrazine hydrate (0.01mol) in (40 ml) ethanol was refluxed for 3hrs, after cooling , the solid that separated out was filtered off , dried and crystallized from dioxane to give (20).

20. Action of phenyl isocyanate on quinazolinone (20)

An equimolecular quantity of amino carbonyl derivative (20) (0.01mol) and phenyl isocyanate (0.01mol) in dioxane (40 ml) was refluxed for 6hrs. On cooling at room temperature, the fine crystals which appeared, filtered off and dried and crystallized from ethanol to give (21).

21. Action of aldehyde on quinazolinone (20)

A mixture of (20) (0.01mol) and p-chlorobenzaldehyde (0.012mol) in (50 ml) ethanol containing (1ml) piperidine was refluxed for 3hrs, after cooling, the solid that separated out was filtered off , dried and crystallized from ethanol to give (22).

**22. Action of hydroxylamine hydrochloride on benzoxazone (2)
Formation of 3-hydroxy-4-quinazolone (23)**

A mixture of (2) (0.01 mol), hydroxylamine hydrochloride (0.03 mol) and sodium acetate (0.03 mol) in ethyl alcohol (50 ml) was heated under reflux for 5 hrs. The reaction mixture after cooling was poured into water, filtered off and crystallized from benzene to give (23).

**23. Action of acetic anhydride 3-hydroxy quinazolone (23)
Formation of (24)**

Treatment of (23) (0.01 mol) with excess of acetic anhydride (25 ml) was refluxed for 2 hrs. After cooling the solid product obtained was washed with water, filtered off, dried and crystallized from benzene to give (24).

24. Action of ethyl chloroacetate on 3-hydroxy-4-quinazolone (23)

A mixture of (23) (0.01mol), anhydrous potassium carbonate (0.04mol) and ethyl chloroacetate (0.04mol) in (60 ml) dry acetone was refluxed for 24hrs. The product obtained after removing the excess solvent was poured into cold

Experimental

water, the solid that separated out was filtered off, dried and crystallized from ethanol to give (25).

25. Action of hydrazine hydrate on quinazolinone (25)

A mixture of (25) (0.01mol) and hydrazine hydrate (0.01mol) in (40 ml) ethanol was refluxed for 3hrs, after cooling, the solid that separated out was filtered off, dried and crystallized from dioxane to give (26).

26. Action of phenyl isocyanate on quinazolinone (26)

An equimolecular quantity of amino carbonyl derivative (26) (0.01mol) and phenyl isocyanate (0.01mol) in dioxane (40 ml) was refluxed for 6hrs. On cooling at room temperature, the fine crystals which appeared, filtered off, dried and crystallized from ethanol to give (27).

27. Action of aldehyde on quinazolinone (26)

A mixture of (26) (0.01mol) and p-chlorobenzaldehyde (0.012mol) in (50 ml) ethanol containing (1ml) piperidine was refluxed for 3hrs, after cooling, the solid that separated out was filtered off, dried and crystallized from ethanol to give (28).

Table 5 Characteristics and Physical Data for the Synthesized Compounds

Compound	Empirical formula	M.wt	Solvent	Yield %	Calculated/ Found, %						m.p, °C
					C	H	O	N	Cl	S	
2	C ₂₆ H ₁₆ ClN ₃ O ₅	485.88	benzene	72	64.27 64.23	3.32 3.64	16.46 16.49	8.65 8.32	7.30 7.26	-	150-152
3 _a	C ₂₇ H ₂₁ ClN ₄ O ₅	516.93	benzene	76	62.73 62.41	4.09 4.23	15.48 15.63	10.48 10.44	6.86 7.15	-	230-232
3 _b	C ₂₈ H ₂₃ ClN ₄ O ₅	530.96	ethanol	75	63.34 63.07	4.37 4.28	15.07 15.22	10.55 10.05	6.68 6.97	-	218-220
3 _c	C ₃₀ H ₂₇ ClN ₄ O ₅	559	ethanol	65	64.46 64.16	4.87 5.02	14.31 13.99	10.02 10.05	6.34 6.02	-	250-252
3 _d	C ₃₁ H ₂₉ ClN ₄ O ₅	573	ethanol	67	64.97 64.08	5.10 5.39	13.96 13.63	9.78 9.46	6.19 6.22	-	220-222
3 _e	C ₃₂ H ₃₁ ClN ₄ O ₅	587	ethanol	62	65.47 65.5	5.32 4.99	13.63 13.92	9.54 9.58	6.04 6.01	-	270-272
3 _f	C ₂₈ H ₂₁ ClN ₄ O ₇	560.94	ethanol	80	59.95 59.98	3.77 3.45	19.97 20.3	9.99 10.27	6.32 6.06	-	180-182
3 _g	C ₃₃ H ₂₅ ClN ₄ O ₆	609.03	benzene	70	65.08 65.11	4.14 3.71	15.76 16.05	9.20 9.49	5.82 5.47	-	60-62
3 _h	C ₃₂ H ₂₄ ClN ₅ O ₅	594.02	benzene	85	64.70 64.73	4.07 4.39	13.47 13.04	11.79 11.38	5.97 5.94	-	100-102
4 _a	C ₂₆ H ₂₄ ClN ₇ O ₅	549.97	Pet-ether 40-60	70	56.78 56.74	4.40 4.43	14.55 13.22	17.83 17.79	6.45 6.74	-	98-100

Experimental

Compound	Empirical formula	M.wt	Solvent	Yield %	Calculated/ Found, %						m.p, °C
					C	H	O	N	Cl	S	
4 _b	C ₃₂ H ₂₂ ClN ₅ O ₄	576	benzene	75	66.73 66.69	3.85 4.18	11.11 10.79	12.16 11.88	6.16 6.19	-	75-77
5	C ₃₀ H ₂₂ ClN ₃ O ₆	555.97	ethanol	60	64.81 64.53	3.99 3.56	17.27 17.3	7.56 7.88	6.38 5.49	-	240-242
6	C ₂₆ H ₁₇ ClN ₆ O ₅	528.9	ethanol	65	59.04 59.36	3.24 2.96	15.13 15.16	15.89 15.63	6.70 7.02	-	222-224
7 _a	C ₃₂ H ₂₂ ClN ₃ O ₅	563.99	benzene	75	68.15 68.12	3.93 3.61	14.18 13.92	7.45 7.42	6.29 5.96	-	190-192
7 _b	C ₃₃ H ₂₄ ClN ₃ O ₅	578	benzene	78	68.57 68.89	4.19 3.76	13.84 13.56	7.27 7.56	6.13 5.81	-	170-172
8	C ₈ H ₉ N ₃	147.18	ethanol	65	65.29 65.26	6.16 5.73	-	28.25 28.54	-	-	245-247 (lit)
9	C ₃₄ H ₂₃ ClN ₆ O ₄	615.04	ethanol	67	66.40 66.38	3.77 3.45	10.41 10.13	13.66 13.95	5.76 5.79	-	190-192
10	C ₃₂ H ₂₄ ClN ₃ O ₉	630	benzene	50	61.01 60.99	3.84 3.43	22.86 23.19	6.67 6.95	5.63 5.31	-	230-232
11	C ₂₇ H ₁₉ ClN ₆ O ₅	542.93	ethanol	60	59.73 59.41	3.53 3.25	14.73 15.02	15.48 15.81	6.53 6.1	-	60-62
12	C ₂₇ H ₁₇ ClN ₆ O ₄	524.91	Pet-ether 40-60	60	61.78 61.52	3.26 3.22	12.19 12.52	16.01 15.66	6.75 6.78	-	222-224
13	C ₂₇ H ₁₇ ClN ₆ O ₃ S	540.98	Methanol	75	59.94 60.26	3.17 3.6	8.87 8.46	15.53 15.27	6.55 6.88	5.93 6.25	190-192
14	C ₂₆ H ₁₇ ClN ₄ O ₄	484.89	benzene	68	64.40 64.08	3.53 3.51	13.20 14.53	11.55 11.23	7.31 7.6	-	218-220
15	C ₃₃ H ₂₂ ClN ₅ O ₅	603.13	ethanol	58	65.62 65.91	3.67 3.99	13.24 12.81	11.59 11.33	5.87 5.9	-	210-212
16	C ₂₈ H ₁₉ ClN ₄ O ₅	526.10	ethanol	62	63.82 63.54	3.63 3.3	15.18 14.92	10.63 10.66	6.73 7.02	-	205-207
17	C ₂₆ H ₁₆ Cl ₂ N ₄ O ₃	503.34	benzene	72	64.04 64.33	3.20 2.79	9.54 9.57	11.13 11.42	14.09 13.74	-	190-192
18	C ₃₅ H ₂₂ ClN ₅ O ₆	643.13	ethanol	55	65.27 64.94	3.44 3.76	14.91 14.5	10.87 11.16	5.50 5.15	-	195-197
19	C ₃₀ H ₂₃ ClN ₄ O ₆	570.98	Methanol	75	63.11 62.85	4.06 3.73	16.81 15.92	9.81 9.84	6.21 6.5	-	165-167
20	C ₂₈ H ₂₁ ClN ₆ O ₅	556.13	Dioxane	65	60.38 60.71	3.80 4.12	14.36 14.39	15.09 14.74	6.37 6.11	-	175-177
21	C ₃₅ H ₂₆ ClN ₇ O ₆	573	ethanol	67	62.18 62.51	3.88 3.56	14.20 14.49	14.50 14.07	5.24 5.27	-	210-212
22	C ₃₅ H ₂₆ Cl ₂ N ₆ O ₅	587	ethanol	62	65.47 65.5	5.32 4.99	13.63 13.92	9.54 9.51	6.04 6.01	-	270-272
23	C ₂₆ H ₁₇ ClN ₄ O ₅	500.89	benzene	62	62.34 62.01	3.42 3.71	15.97 15.94	11.19 11.48	7.08 6.76	-	220-222
24	C ₂₈ H ₁₉ ClN ₄ O ₆	542.10	benzene	63	61.94 61.62	3.53 3.2	17.68 17.97	10.32 10.04	6.53 6.86	-	230-232

Experimental

Compound	Empirical formula	M.wt	Solvent	Yield %	Calculated/ Found, %						m.p, °C
					C	H	O	N	Cl	S	
25	C ₃₀ H ₂₃ ClN ₄ O ₇	586.13	ethanol	58	61.39 61.36	3.95 3.91	19.08 19.06	9.54 9.51	6.04 6.01	-	155-157
26	C ₂₈ H ₁₉ ClN ₄ O ₅	572.96	Dioxane	62	58.70 58.66	3.69 3.67	16.75 16.78	14.67 14.93	6.19 5.84	-	180-182
27	C ₃₅ H ₂₆ ClN ₇ O ₇	692.08	ethanol	55	60.74 61.06	3.79 4.22	16.18 16.44	14.17 14.14	5.12 4.8	-	230-232
28	C ₂₆ H ₁₇ ClN ₄ O ₅	697.52	ethanol	62	60.27 59.98	3.76 3.43	13.76 14.05	12.05 12.08	10.17 9.91	-	260-262

Table 6 H¹-NMR, MS and IR data of prepared compounds

Compd.No.	H ¹ -NMR (δ in ppm)	MS (m/z, %)	IR cm ⁻¹	
			$\nu_{\text{N-H}}$	$\nu_{\text{C=O}}$
2	4.45(s, 2H, NCH ₂ CO), at 6.75 (s, 1H, olefinic proton), at 7.22-7.91 (m, 12H, Ar-H) and at 9.08 (s, 1H, NH)	[M] ⁺ . 485.55, [M+2] ⁺ . 487	3475, 3370	1614 cm ⁻¹ (ν CO of α,β -unsaturated amide), at 1774-1720 cm ⁻¹ (ν CO of benzoxazinone and ν CO of cyclic imide)
3_a	—	[M] ⁺ . 516.45, [M+2] ⁺ . 518.5	3317, 3133	1647 (acyclic amides) 1774-1713 (cyclic imide)
3_b	1.2(t, 3H, CH ₃), at 4.1(q, 2H, CH ₂), at 4.43(s, 2H, NCH ₂ CO), at 6.74(s, 1H, olefinic proton), at 7.2-7.92 (m, 12H, Ar-H) and 9.80-10.38(s, broad, 3H, 3×NH) disappeared by addition of D ₂ O	—	3473, 3220	1645 (acyclic amides) 1774-1715(cyclic imide)
3_c	—	[M+1] ⁺ . 560, [M+2] ⁺ . 561	3465, 3322	1643 (acyclic amides) 1774-1717(cyclic imide)
3_d	—	—	3475, 3240	1641 (acyclic amides) 1774-1719(cyclic imide)
3_e	—	—	3448, 3350	1650 (acyclic amides) 1774-1720(cyclic imide)
3_f	—	—	3360	1640 (acyclic amides) 1774-1712(cyclic imide)
3_g	—	—	3455, 3360	1644 (acyclic amides) 1774-1716(cyclic imide)
3_h	—	—	3330, 3310	1640 (acyclic amides) 1774-1711(cyclic imide)

Experimental

Compd.No.	^1H -NMR (δ in ppm)	MS (m/z, %)	IR cm^{-1}	
			$\nu_{\text{N-H}}$	$\nu_{\text{C=O}}$
4 _a	–	$[\text{M}]^+$ 549	3445	1617 (α,β -unsaturated amide) 1774-1720 (cyclic imide)
4 _b	–		3460, 3380	1646 (cyclic and acyclic amides) 1774-1714 (of cyclic imide)
5	1.2-2.49 (m, with interference, 5H, $\text{COOCH}_2\text{CH}_3$), at 4.42 (s, 2H, NCH_2), at 3.37(s, 2H, CH_2), at 6.74(s, 1H, olefinic proton), at 7.89-7.91 (m, 12H, Ar-H) and 9.5-10.2 (s, broad, 1H, NH) disappeared by addition of D_2O	–	3479	1611 (α,β -unsaturated amide) 1725 (ester) 1774 (imide)
6	4.55(s, 2H, NCH_2CO), at 6.85 (s, 1H, olefinic proton), at 7.25-8.20 (m, 12H, Ar-H) and at 9.98-10.69(s, broad, 1H, NH) and at 13.84 (s, 1H, OH)	–	3455-2928 For OH and NH	1614 (α,β -unsaturated amide) 1718 (ν CO of carboxylic) 1774-1760 (due to coupling carbonyl bands of cyclic imide)
7 _a	4.43(s, 2H, NCH_2), 6.58(s, 1H, olefinic proton), 7.56-8.0(m, 17H, Ar-H) and 9.2-10.2(s, broad, 2H, $2\times\text{NH}$) disappeared by addition of D_2O	–	3401, 3208	1657cm^{-1} (α,β -unsaturated amide) 1774-1725 (cyclic imide)
7 _b	–	$[\text{M}]^+$ 578	3401, 3208	1657cm^{-1} (α,β -unsaturated amide) 1774-1725 (cyclic imide)
9	4.43(s, 2H, NCH_2), at 6.76(s, 1H, olefinic proton), at 7.05-8.68 (m, 16H, Ar-H), at 9.08 (s, broad, 1H, NH), at 13.01(s, broad, 1H, NH, exchangeable with D_2O)	–	3431	1666 (acyclic amide) 1774-1719 (cyclic imide)

Experimental

Compd.No.	$^1\text{H-NMR}$ (δ in ppm)	MS (m/z, %)	IR cm^{-1}	
			$\nu_{\text{N-H}}$	$\nu_{\text{C=O}}$
10	2.5(s, 6H, COOH_3), at 4.1(m, 3H, cyclic protons), at 4.50(s, 2H, NCH_2), at 7.35-8.85(m, 12H, Ar-H), 9.2-10.2(s, broad, 2H, 2NH) disappeared by addition of D_2O	—	3446	1642 (amide) 1774-1740 (imide) 1731 (ester) 1720 (sat. benzoxazinone ring)
11	4.43 (s, 2H, NCH_2), at 5.8(s, broad, 2H, NH_2), at 6.8 (s, 1H, olefinic proton), at 7.5-8.0(m, 12H, Ar-H) and 9.8-10.9(s, broad, 2H, 2 $\times$ NH) disappeared by addition of D_2O	—	3424	1615 (amides) 1774-1722 (cyclic imide)
12	4.43 (s, 2H, NCH_2), at 6.74 (s, 1H, olefinic proton), at 7.87-8.0(m, 12H, Ar-H) and 9.6-10.4(s, broad, 2H, 2 $\times$ NH) disappeared by addition of D_2O	—	3468	1658 (cyclic and acyclic amides) 1774-1725 (cyclic imide)
13	—	$[\text{M}-3]^+$ 537	3462	1610 (α,β -unsaturated amide) 1774-1719 (cyclic imide)
14	4.42(s, 2H, NCH_2), at 6.51 (s, 1H, olefinic proton), at 7.86-8.0(m, 12H, Ar-H), 9.7-10.5(s, broad, 2H, 2NH) disappeared by addition of D_2O	—	3470, 3362	1624 (α,β -unsaturated amide) 1774-1718 (cyclic imide)
15	4.44 (s, 2H, NCH_2), 6.94 (s, 1H, olefinic proton), 7.2-8.7(m, 17H, Ar-H), 9.8-10.95(s, broad, 2H, 2 $\times$ NH) disappeared by addition of D_2O	—	3360, 3170	1645 (acyclic amide) 1731 (carbamate ester) 1774-1740 (cyclic imide)
16	2.49(s, 3H, OCOCH_3), at 4.42(s, 2H, NCH_2), at 6.76 (s, 1H, olefinic proton), at 7.87-8.0(m, 12H, Ar-H) and 9.65-10.5(s, broad, 1H, 1NH) disappeared by addition of D_2O	—	3474, 3370	1617 (α,β -unsaturated amide) 1774-1718 (cyclic imide)
17	4.44(s, 2H, NCH_2), at 6.74 (s, 1H, olefinic proton), at 7.2-8.0(m, 12H, Ar-H) and at 9.9-10.7(s, broad, 1H, NH) disappeared by addition of D_2O	—	3470	1618 (α,β -unsaturated amide) 1774-1715 (due to coupling carbonyl bands of cyclic imide)

Experimental

Compd.No.	^1H -NMR (δ in ppm)	MS (m/z, %)	IR cm^{-1}	
			$\nu_{\text{N-H}}$	$\nu_{\text{C=O}}$
18	4.09 (s, 2H, CH_2), at 4.42(s, 2H, NCH_2), at 5.82 (s, 1H, olefinic proton), at 7.91-7.93(m, 16H, Ar-H) and at 9.9-10.7(s, broad, 1H, NH) disappeared by addition of D_2O	—	3432	1613 (α,β -unsaturated amide) 1774-1721 (cyclic imides)
19	1.1-2.5 (m, with interference, 5H, $\text{COOCH}_2\text{CH}_3$), at 4.43 (s, 2H, NCH_2), at 4.83(s, 2H, OCH_2COO), at 6.63(s, 1H, olefinic proton), at 7.86-7.95 (m, 12H, Ar-H) and 9.5-10.2 (s, broad, 1H, NH) disappeared by addition of D_2O	—	3440, 3328	1660 (acyclic amide) 1774-1719 (cyclic imide) 1731 (ester)
20	4.76 (s, 2H, NCH_2), at 4.82(s, 2H, OCH_2CO), at 6.72 (s, 1H, olefinic proton), 7.84-8.1(m, 12H, Ar-H), 9.65-10.5(s, broad, 2H, $2\times\text{NH}$) disappeared by addition of D_2O	—	3426	1623 (α,β -unsaturated amide) 1774-1719 (cyclic imide)
21	4.43(s, 2H, NCH_2), at 6.51 (s, 1H, olefinic proton), at 7.85-8.1(m, 12H, Ar-H), 9.65-10.5(s, broad, 4H, $4\times\text{NH}$) disappeared by addition of D_2O	—	3366	1615 (α,β -unsaturated amide) 1774-1719 (cyclic imide)
22	4.6(s, 2H, NCH_2), at 6.6 (s, 1H, olefinic proton), at 6.74 (s, 1H, N=CH), at 7.74-8.09(m, 16H, Ar-H) and at 9.6-10.2(s, broad, 2H, $2\times\text{NH}$) disappeared by addition of D_2O	—	3424	1615 (α,β -unsaturated amide) 1774-1722 (cyclic imide)
23	4.43(s, 2H, NCH_2), at 6.75 (s, 1H, olefinic proton), 7.3-7.95(m, 12H, Ar-H), at 8.68 (s, broad, 1H, NH) and at 10.69(s, 1H, OH)	—	3848, 3743, 3485 (OH and NH)	1617 (cyclic and a cyclic amide) 1774-1720 (cyclic imide)
24	2.49 (s, 3H, OCOCH_3), 4.42(s, 2H, NCH_2), at 6.75 (s, 1H, olefinic proton), 7.87-7.95(m, 12H, Ar-H) and at 9.6-10.2(s, broad, 1H, NH) disappeared by addition of D_2O	—	3462, 3328	1660 (cyclic and acyclic amide) 1774-1720 (cyclic imide) 1731 (ester)

Experimental

Compd.No.	$^1\text{H-NMR}$ (δ in ppm)	MS (m/z, %)	IR cm^{-1}	
			$\nu_{\text{N-H}}$	$\nu_{\text{C=O}}$
25	1.2(t, 3H, CH_3), at 4.1(q, 2H, CH_2 of ester), at 4.42 (s, 2H, NCH_2), at 4.83(s, 2H, OCH_2COO), at 6.63(s, 1H, olefinic proton), at 7.4-7.9 (m, 12H, Ar-H) and 9.5-10.2 (s, broad, 1H, NH) disappeared by addition of D_2O	—	3440, 3324	1660 (cyclic and acyclic amide) 1774-1722 (cyclic imide) 1732 (ester)
26	4.42(s, 2H, NCH_2), at 4.82(s, 2H, OCH_2CO), at 6.6(s, 1H, olefinic proton), 7.09-8.06(m, 12H, Ar-H), 9.65-10.5(s, broad, 2H, $2\times\text{NH}$) disappeared by addition of D_2O	—	3480-3220 (NH and NH_2).	1680, 1660 (amides and hydrazide) 1774-1723 (cyclic imide)
27	4.43(s, 2H, NCH_2), at 5.82 (s, 1H, olefinic proton), at 7.85-8.08 (m, 12H, Ar-H), 9.65-10.5(s, broad, 4H, $4\times\text{NH}$) disappeared by addition of D_2O	—	3462, 3320	1662 (amides) 1774-1718 (cyclic imide)
28	4.43 (s, 2H, NCH_2), at 6.5 (s, 1H, olefinic proton), at 6.7 (s, 1H, N=CH), at 7.78-8.09 (m, 16H, Ar-H) and at 9.6-10.2(s, broad, 2H, $2\times\text{NH}$) disappeared by addition of D_2O	—	3445	1666 (amides) 1774-1716 (cyclic imide)

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Studies on 4H-3,1-Benzoxazin-4-ones

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ARABIC SUMMERY

Studies on 4H-3,1-Benzoxazin-4-ones

وعلاوة على ذلك، يتفاعل البنزواوكزازينون (٢) مع هيدروكلوريد هيدروكسيلامين في وجود خلات الصوديوم الامائيه ليعطى ٣ن-هيدروكسي-كينازولين-٤-اون (٢٣) وقد أمكن دراسة الاتزان الديناميكي للمركب (٢٣) بتفاعله مع انهيدريد حمض الخليك، خلات كلوريد الإيثيل ليعطى المركبات (٢٤) و (٢٥) علي الترتيب.

من ناحية أخرى ، قد أمكن دراسة الاتزان الديناميكي للمركب (٢٥) بتفاعله مع الهيدرازين هيدرات لتعطى المركب (٢٦) وقد تم تفاعل المركب (٢٦) مع فينيل ايزو سيانات، بارا-كلورو- بنزالدهيد ليعطى المركبات (٢٧) و (٢٨) علي الترتيب. وقد تم اختبار النشاط البيولوجي للمركبات.

الملخص العربي

تشبيد و تفاعلات بعض المركبات الحلقية غير متجانسة الحلقة والمتوقع لها نشاطا بيولوجيا

تقدم هذه الدراسة تحضير مشتق البنزواوكزازين-٤-أون (٢) وذلك بتفاعل حمض الانثرانيليك مع مشتق الاكزازولون (١) وتنتج مشتقات كربامويل فينيل اسيتانيدات (3a-h) بالتحلل الاميني للمركب (٢) وتم فتح حلقة البنزواوكزازينون (٢) بتسخينها مع الهيدرازين هيدرات لتعطى مشتق ن-هيدرازيد حمض الانثرانيليك (4a) بينما تفاعل المركب (٢) مع الفينيل هيدرازين وأعطى مشتق الكينازولينون (4b) وبمعالجة البنزواوكزازينون (٢) بأستيتو خلا تا لايشيل ينتج المركب (٥) اعتمادا على عامل الوقت للتفاعل .

من ناحية أخرى ، يتفاعل البنزواوكزازينون (٢) مع أزيد الصوديوم ليعطى مشتق تترازول (٦) ويتفاعل المركب (٢) تحت ظروف فريدل كرافتز مع كل من البنزين و الطولوين معطيا الكيتونات المقابلة (7a,b) .

خلاف ذلك ، يتفاعل البنزواوكزازينون (٢) تحت ظروف مانس ليعطى قاعدة مانس (٩). وكذلك يتفاعل المركب (٢) معماليات ثنائي الميثيل ليعطى ناتج ديلز ألدر (١٠).

من ناحية أخرى ، يتفاعل البنزواوكزازينون (٢) مع هيدروكلوريد الكربازيد ليعطى مشتق الترايازول كينازولين (١١) و بصهر هذا المركب عند درجة حرارة أعلى من درجة انصهار يعطى المركب (١٢) و يتفاعل البنزواوكزازينون (٢) مع ثيو الكربازيد ليعطى المركب (١٣) .

وعلاوة على ذلك ، أمكن الحصول علي ٢- (مشتق)-٤- الكينازولينون (١٤) بصهر المركب (٢) مع خلا تا لا أمونيوم وقد أمكن دراسة الاتزان الديناميكي للمركب (٥) بتفاعله مع عامل الألكلة، انهيدريد حمض الخليك، مخلوط من خامس كلوريد الفسفور و اكسي كلوريد الفسفور، وتفاعله مانس ليعطى ٤- (مشتق)-٢- (مشتق)- كينازولين-٤-أون (١٥)، ٣-اسيتيل-٢- (مشتق)- كينازولين-٤-أون (١٦)، ٢- (مشتق)- فينيل -٤-كلورو كينازولين-٤-أون (١٧)، ٣- (مشتق)- كينازولين-٤-أون (١٨) علي الترتيب.

من ناحية أخرى ، يتفاعل المركب (١٤) مع خلا تا كلوريد الإيثيل في الأستيتون الجاف وفي وجود كربونات البوتاسيوم الجافة ليعطى المركب (١٩) وقد أمكن دراسة الاتزان الديناميكي

للمركب (١٩) بتفاعله مع الهيدرازين هيدرات لتعطى المركب (٢٠) وقد تم تفاعل المركب (٢٠) مع فينيل ايزو سيانات، بارا- كلورو- بنزالد هيد ليعطى المركبات (٢١) و (٢٢) علي الترتيب.

قرار لجنة الحكم

اسم الباحث/ إسرائ عزمي عبد الوهاب

عنوان الرسالة : تشييد و تفاعلات بعض المركبات الحلقية غير متجانسة الحلقة
والمتوقع لها نشاطا بيولوجيا

لجنة الحكم والمناقشة

م	الاسم	الوظيفة	التوقيع
١			
٢			
٣			
٤			

تاريخ المناقشة:

تقدير الرسالة:

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جامعة بنها
كلية العلوم
قسم الكيمياء

اسم الباحث : إسماعيل عزمي عبد الوهاب

عنوان الرسالة : تشييد و تفاعلات بعض المركبات الحلقية غير متجانسة
الحلقة والمتوقع لها نشاطا بيولوجيا

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تشبيد و تفاعلات بعض المركبات الحلقية غير متجانسة الحلقة
والمتوقع لها نشاطا بيولوجيا

رسالة مقدمة كجزء متمم للحصول على
درجة الماجستير فى العلوم
(كيمياء عضوية)

مقدمة من
إسراء عزمى عبد الوهاب
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