Review

Chemistry of 4*H*-3,1-Benzoxazin-4-ones

Ahmed El-Mekabaty

Department of Chemistry, Faculty of Science, Mansoura University, ET-35516 Mansoura-Egypt

E-Mail: a_el_m11@yahoo.com; elmekabaty@mans.edu.eg; Tel: (+2010)03677361.

Abstract: This review presents a systematic and comprehensive survey of the methods of preparation and the chemical reactivity of benzoxazinone derivatives. This literature survey also implies study of the behavior of benzoxazinone derivatives toward hydrogen, oxygen, nitrogen, sulphur and carbon nucleophiles. Due to their selective transformations with different reagents they have been attracting increasing attention in view of their high reactivity as building blocks for the preparation of compounds of various classes. The most eye catching features of these compounds are their greatest utility resides in pharmaceuticals (analgesic, antibacterial, antifungal, antagonists, antiinflammatory, antimicrobial, antidiabetic, antihyperglycemic and anxiolytic).

Keywords: Benzoxazinone; quinazolinone; reactions; heterocycles; antimicrobial activity.

1. Introduction

Benzoxazinone derivatives are considered to be important chemical synthons of various physiological significances and pharmaceutical utilities. They possess a variety of biological effects including antitubercular [1], antifungal [2-5], antimalarial, anticancer, anti-HIV [3,7], antiviral and antibacterial activities [4,6,8]. On the other hand, quinazolinones constitute one of the most significant

groups among CNS active agents and act as CNS depressants, anticonvulsants and anti-inflammatory agents. They are also reported to possess anti-spermatogenic and anti-adjuvant polyarthritic activities in rats and anti-inflammatory, analgesic and antipyretic activities in mice [4,5]. Several compounds containing quinazolone nucleus have recently been introduced for the treatment of infections caused by different intestinal nematodes and cestodes [4]. Moreover, many quinazolines contributed to the quest for an ultimate antitumor chemotherapeutic agent [6,8]. The aim of the present investigation is to study in some details the synthesis, reactions and biological activity of some derivatives of these classes of compounds.

2. Synthesis

The various methods that have been used for the preparation of 3,1-(4*H*)-benzoxazin-4-one derivatives are discussed as follows:

2.1. From Anthranilic Acids

2.1.1. Reaction of anthranilic acids with acetic anhydride

Heating of anthranilic or substituted anthranilic acids with acetic anhydride lead to the formation of 2-methyl-3,1-(4*H*)-benzoxazin-4-one derivatives **1a-e**.
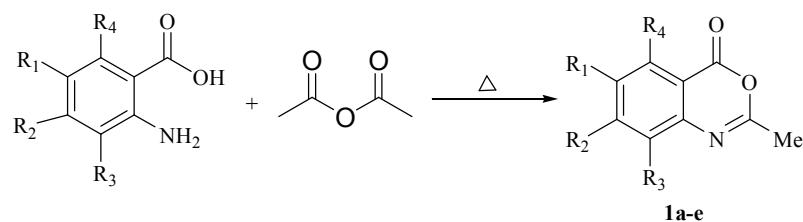

**Table 1:** Preparation of 2-methyl-3,1-(4*H*)-benzoxazin-4-one derivatives **1a-e**.

Comp. No. **1**	R_1	R_2	R_3	R_4	Ref.
a	H	H	H	H	[1,6,10,14,15]
b	Br	H	Br	Cl	[7]
c	Br	H	Br	H	[9,11]
d	I, Cl	H	H	H	[1,6]
e	NO_2	H	H	H	[1]

Hassan *et. al*. found that 2-acetonyl benzoxazinone **2** [12] was obtained by heating of anthranilic acid with excess acetic anhydride in the presence of anhydrous sodium acetate.


2
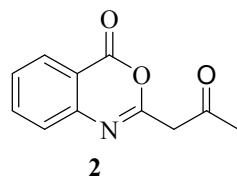
### 2.1.2. Reaction of anthranilic acid with acid chlorides

Anthranilic acid reacts with two equivalents of acid chlorides in pyridine solution to give 2-aryl-3,1-benzoxazin-4-one derivatives.
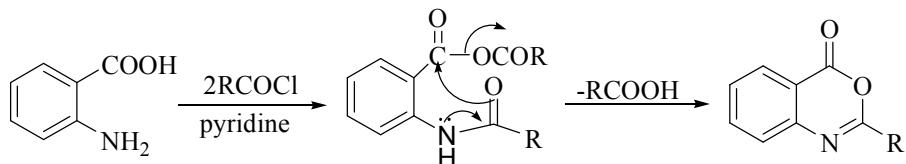

The formation of benzoxazinone can be explained by the well established mechanism in which one mole of the acid chloride acylated the amino group and the second mole reacts with the carboxylic group of anthranilic acid with the formation of a mixed anhydride followed by a loss of a molecule of the acid to give the benzoxazinone derivative. In a similar way, benzoxazinone derivatives **3-8** [13,16-25] have been reported.


X= H, Me, OMe, NO$_2$
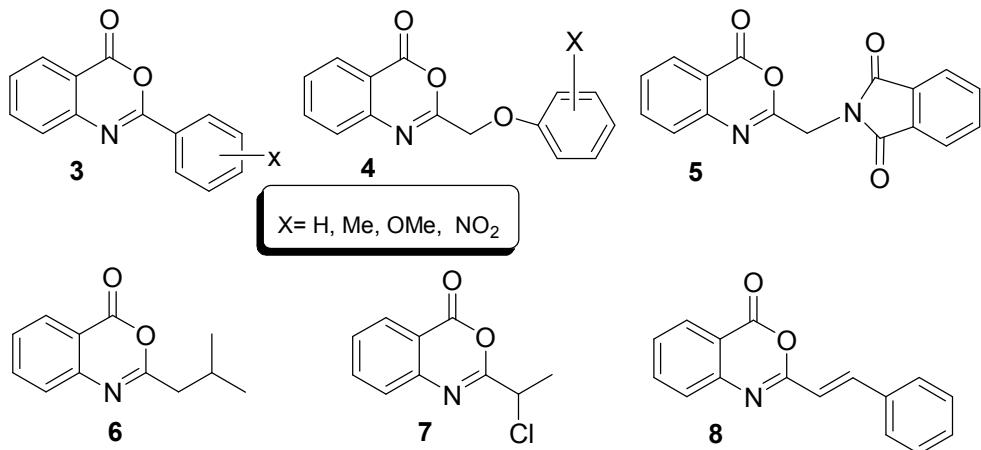
2-(*o*-arylideneaminophenyl)-3,1-benzoxazin-4-ones **9** [27] were prepared by the reaction of anthranilic acid with *o*-arylideneaminobenzoyl chlorides.
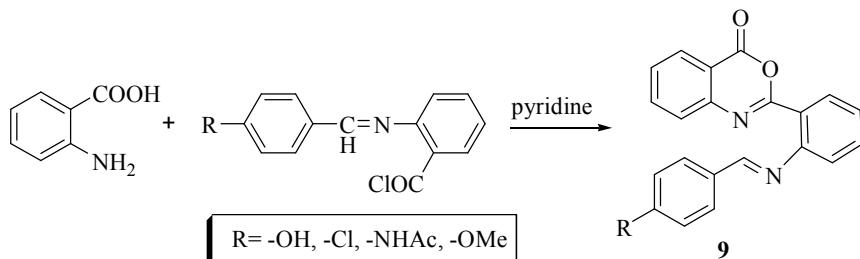
The reaction of equimolar quantities of anthranilic acid with nicotinic acid derivatives in the presence of phosphorusoxychloride produced pyridyl derivatives **10** [26].
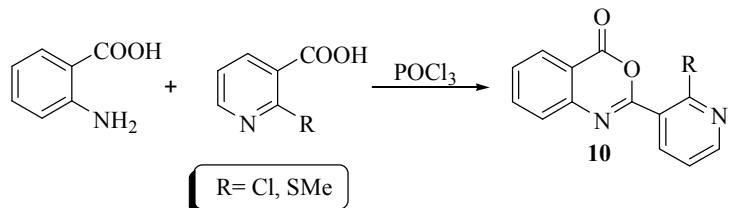

Bis-benzoxazinone **11** has been obtained *via* interaction of 2,6-naphthalene dicarboxylic acid chloride with anthranilic acid in pyridine [28].
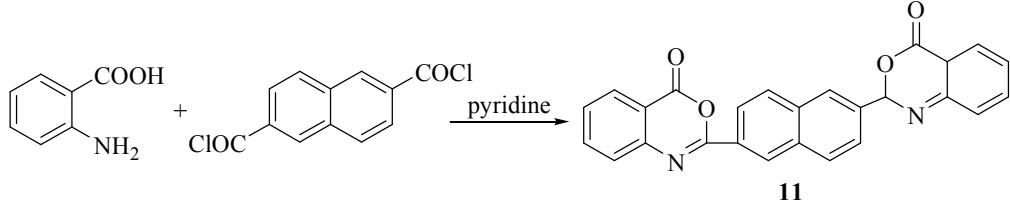
β-(2,4,6-trimethylbenzoyl)-acryloylchloride reacts with anthranilic acid to give the corresponding amide which easily cyclizes in acetic anhydride affording 2-[2-(2,4,6-trimethylbenzoyl) vinyl]-(4*H*)-3,1-benzoxazin-4-one **12** [29].
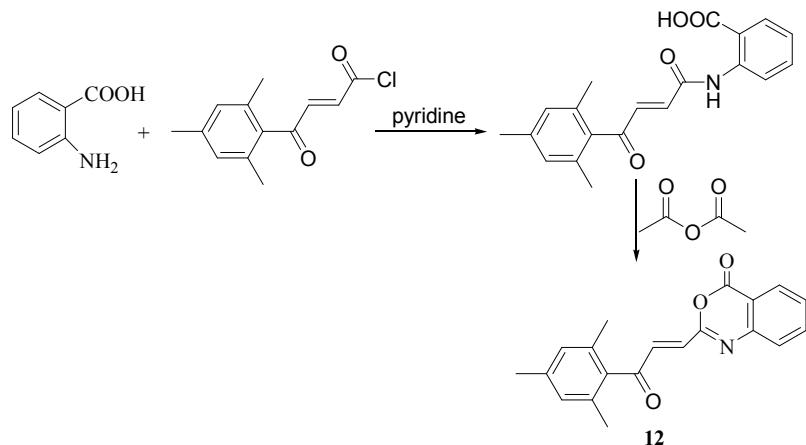
Finer *et.al.* reported that, treatment of anthranilic acid with butyryl chloride in pyridine afforded the corresponding amide **13** which was converted into the corresponding benzoxazinone derivative**14** upon treatment with acetic anhydride[30].
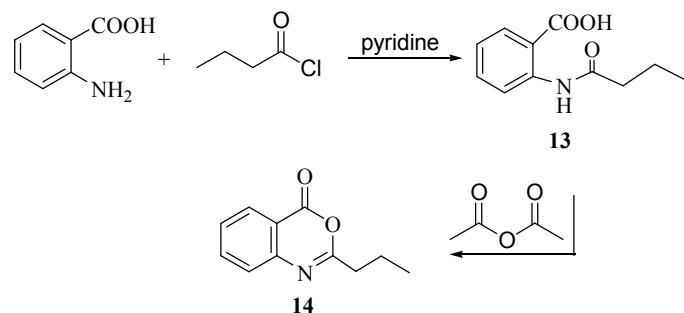

2.1.3. Reaction of anthranilic acid with oxazolone derivatives

It was stated by many investigators that, reaction of anthranilic acid with 4-arylidene-2-phenyl-5-(4*H*)-oxazolones gives the benzoxazinone derivatives **15** [31-34].
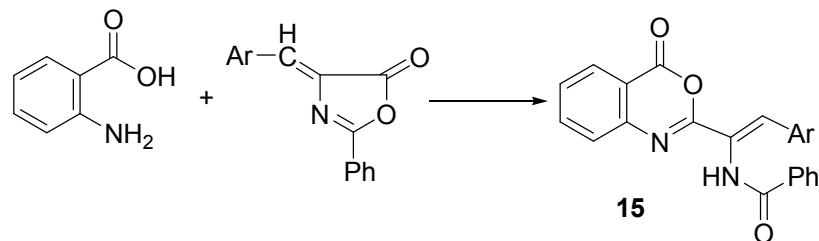

2.1.4. Reaction of anthranilic acid with 2-aminothiophenol

Reaction of anthranilic acid with 2-aminothiophenol in the presence of triphenylphosphate-pyridine mixture gives a mixture of 2-phenyl-3,1-(4*H*) benzoxazin-4-one **3** and 2-phenyl benzothiazole **3'** respectively[35].
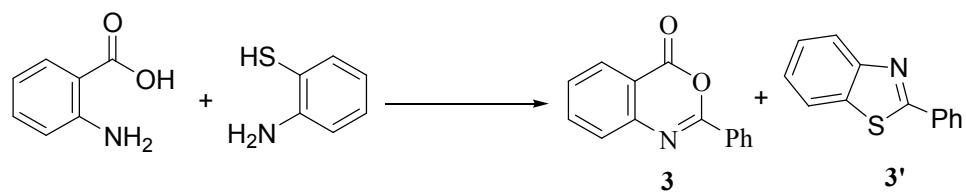

2.1.5. Reaction of anthranilic acid with hippuric acid

It was found that treatment of 2-(benzamido)acetyl chloride with substituted anthranilic acids (R= H, Br) gave the corresponding benzoxazinones **16** [36].

16
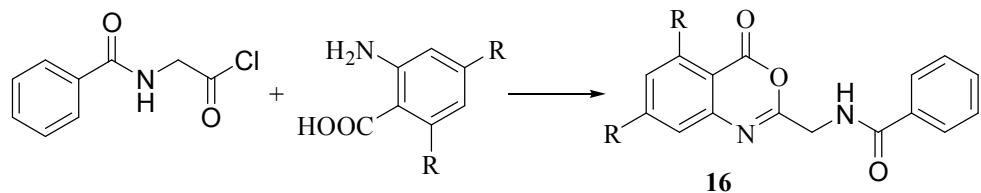
2.1.6. Reaction of anthranilic acid with diethyloxalate or terphthaloyl chloride

Bis-(4*H*)-3,1-benzoxazine-4-one derivatives (n= 0,1) **17a,b** were prepared from the interaction of diethyl oxalate or terephthaloylchloride with anthranilic acid [37].

17a,b
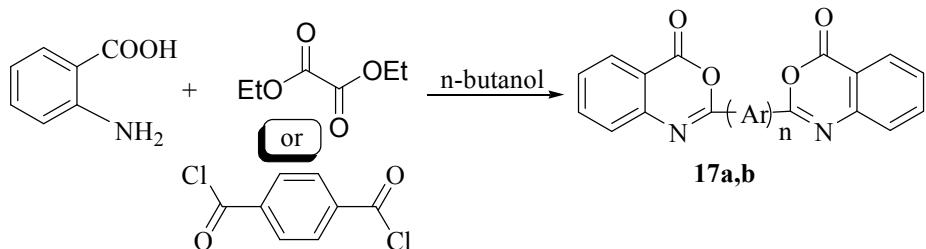
2.1.7. By self condensation of anthranilic acid

Heating of anthranilic acid with polyphosphoric acid gives a mixture of compounds **18**, **19** and **20**, respectively [38].

18   **19**   **20**
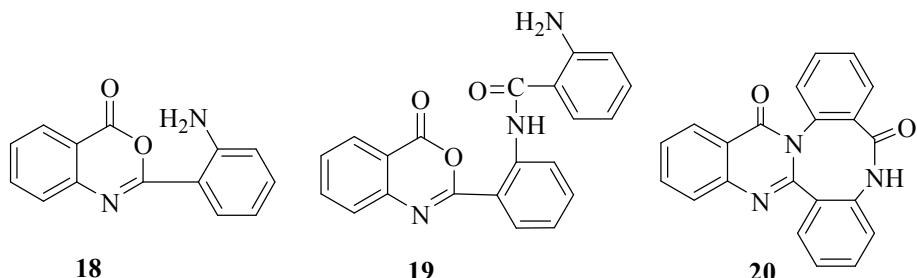
2.2. From N-acyl Anthranilic Acids

2–Substituted benzoxazinones **21a-d** were prepared *via* refluxing the corresponding *N*-acyl anthranilic acids with acetic anhydride as shown in Table 2.
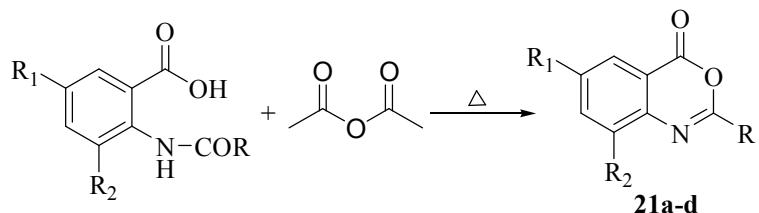

21a-d

Table 2: Preparation of 2–substituted benzoxazinones **21a-d** from *N*-acyl anthranilic acids and acetic anhydride**.**

Comp. No. **21**	R	R_1	R_2	Ref.
a	-CH$_2$C$_6$H$_5$	H	H	[39]
b	H, Me, NH$_2$, Ph, C$_6$H$_4$NO$_2$-*m*	H, NO$_2$	H	[40,41,42]
c	PhCONH-C=CH-C$_6$H$_4$-OCH$_3$-*p*	Br	Br	[43]
d	CH$_2$Cl, Chloroalkyl	H	H	[44,45,46,47]

Acylation of anthranilic acid with succinic anhydride affords the corresponding amide **22** which up on esterification with methyl alcohol followed by refluxing in acetic anhydride leads to formation of the 3-(4-oxo-4*H*-benzo[*d*][1,3]oxazin-2-yl)-propionic acid methyl ester derivative **23** [48].
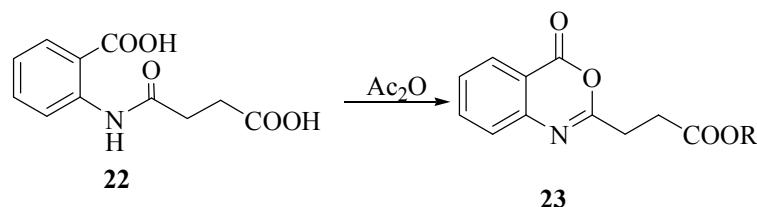
Anthranilic acids were also acylated with 2,2,6-trimethyl-(4*H*)-1,3-dioxin-4-one to give **24** which treated with acetic anhydride to afford the 2-acetonyl derivatives **2** [49].

X= H, Me, Cl, OMe, CF$_3$, NMe$_2$, NO$_2$
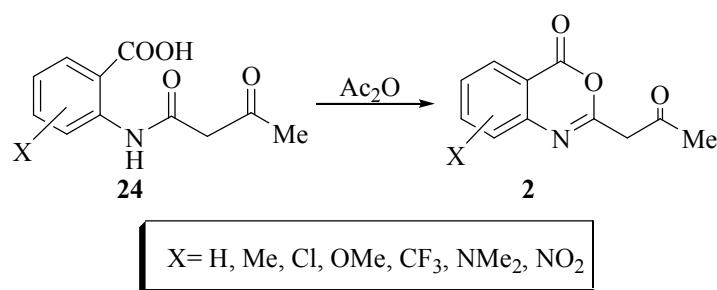
Similarly, refluxing of *N*-(2-bromo propionoyl) anthranilic acid **25** in acetic anhydride afforded 2-(1-bromoethyl)-3,1-benzoxazin-4-one **26**[45].
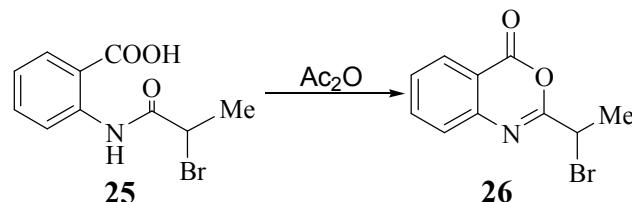
Likewise cyclocondensation of *N*-thienoyl anthranilic acid **27** with acetic anhydride yielded 2-(2'-thienyl)-3,1-(4*H*)-benzoxazine-4-one **28** [50,51].
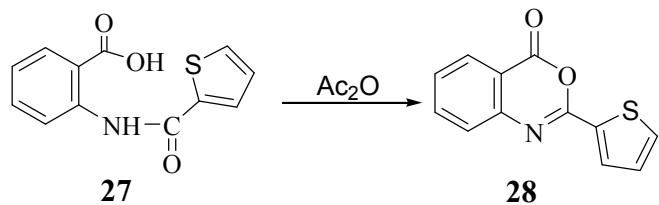
2.3. From Isocyanate Derivatives

Reaction of anthranilic acid with alkyl or aryl isocyanates in benzene [52] or pyridine [53] afforded the corresponding benzoxazinone derivatives **29**.

29

R= Me, Ph
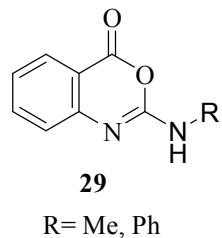
On the other hand, reaction of anthranilic acids or their esters **30** with alkyl isocyanates gave *N*-substituted anthranilic acids **31** which upon cyclization using concentrated sulfuric acid yielded 2-aminoalkyl-benzoxazin-4-ones **32** [54-60].
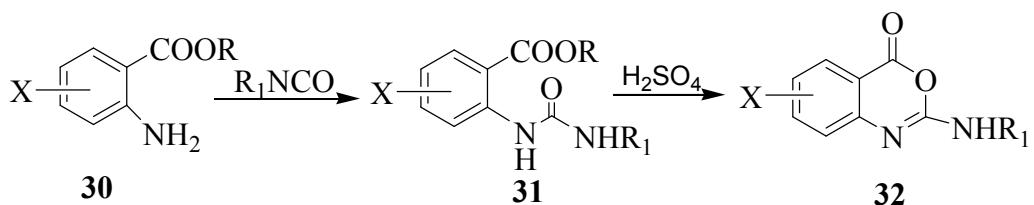
R= H, Me
R_1= alkyl, aryl, CH_2COOEt, $(CH_2)_3Cl$
X= H, Me, Cl, OMe, CF_3, NMe_2, NO_2

The reaction of amino acid esters **34** with isocyanates **33** was used as a route for the synthesis of substituted benzoxazinones **35** *via* the cyclization of *N*-substituted anthranilate [61].
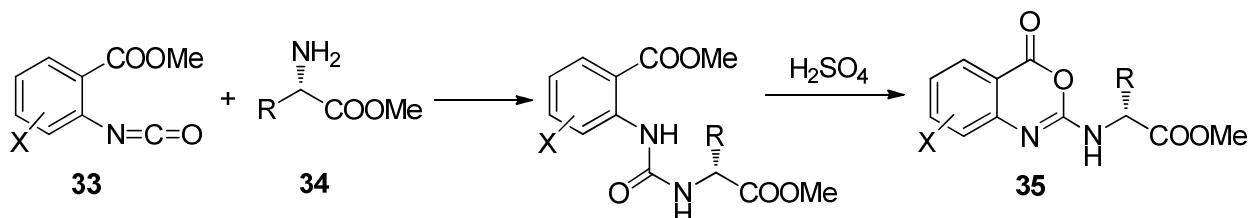
In a similar manner, methyl 2-isocyanatobenzoate **33** reacted with thiophene in the presence of anhydrous $SnCl_4$ to produce 2-(2-thienyl)-(*4H*)-3,1-benzothiazin-4-one **36** which undergoes ring opening in aqueous NaOH to give carboxylic acid **37**. Refluxing the latter in *t*–butyl benzene, looses hydrogen sulfide and gives 2-(2-thienyl)-3,1-(*4H*)-benzoxazin-4-one **28** [62].
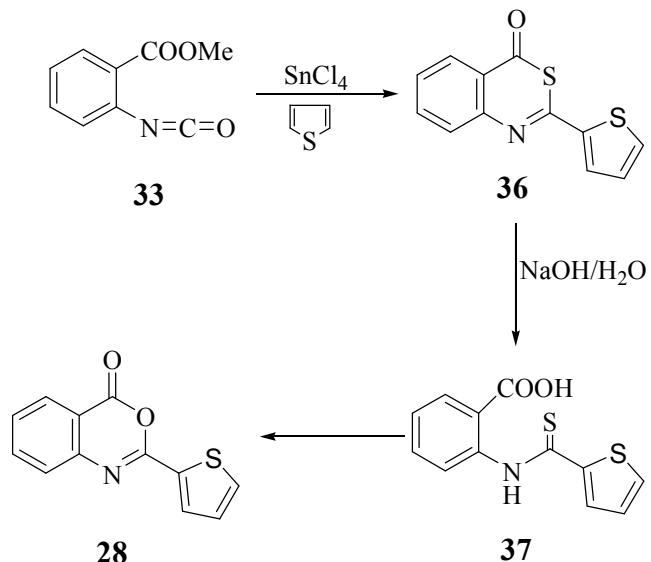
Treatment of 2-isocyanatobenzoyl chloride with nitromethane in benzene gave the corresponding tetracyclic **38** [63].
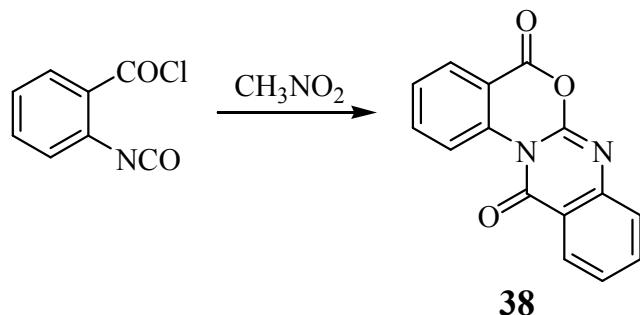
Once more, 2-dialkylamino-3,1-(*4H*)-benzoxazinone derivatives **39** were obtained from the reaction of 2-isocyanatobenzoyl chloride with dialkylamines [64].
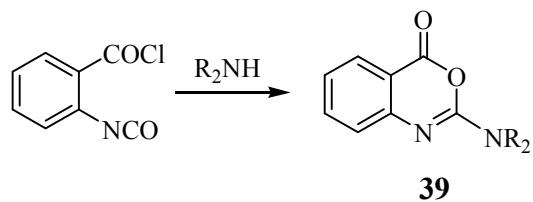
On the other hand, 2-substituted benzoxazinone derivatives **32** were prepared by the action of phenylisocyanates on 1,2,3-triazin-4-one [65].
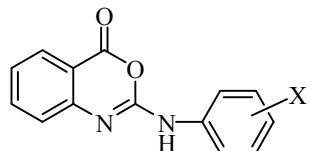
32

2.4. By Ring Expansion

Davis *et. al.* [65] reported that, benzoylation of 5-substituted-1*H*-benzo[*c*]isothiazol-3-one **40** in pyridine gave *o*-benzoyl derivatives **41** which rapidly extrude sulphur and form 2-phenyl–3,1 -(4*H*)-benzoxazinones **3**.

40   **41**   **3**

R= H, Cl, NO$_2$
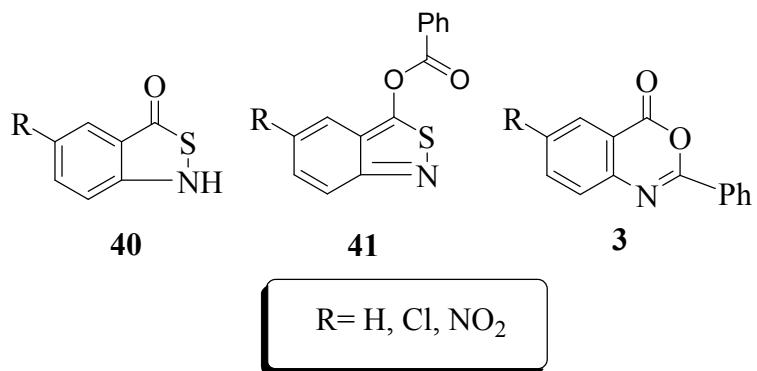
2.5. From 2–Substituted-3,1-Benzothiazin-4–Thione

Boiling 2-substituted-3,1-benzothiazin-4-thione derivatives with alcoholic potassium hydroxide solution result in the formation of unstable intermediates **42** which on heating with acetic acid give the corresponding 2-substituted-3,1-benzoxazin-4-ones **43** [67].

42

43

X= 6-Cl
R= Ph, 4-ClC$_6$H$_4$
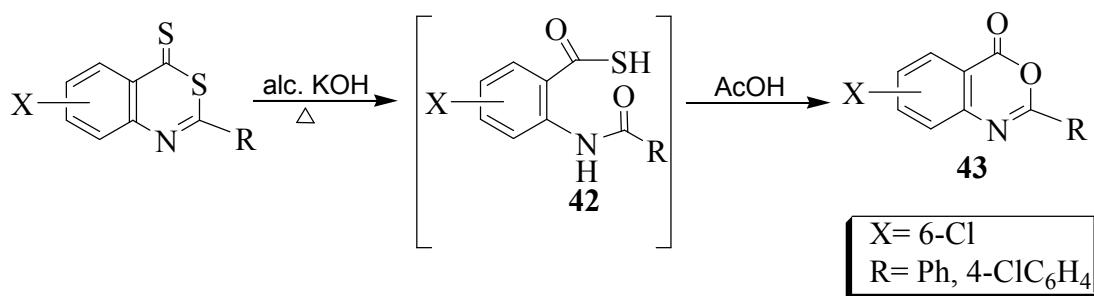
2.6. Via Cyclization of o-Substituted Aryl Azides

Benzoxazinone derivatives **3** were prepared by cyclization of *o*-substituted aryl azides with aromatic aldehydes [68].

R= H, Cl, OMe
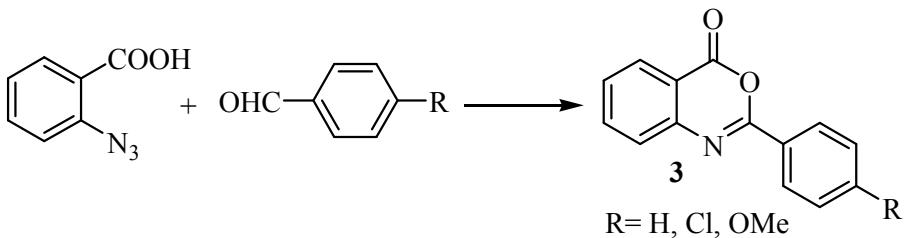
2.7. Via Photomerization of 2-Aryl Isatogens

Irradiation of 2-aryl isatogens gave 2-phenyl-(4*H)*-benzoxazin-4-one derivative **3** through the intermediate epoxide [69].
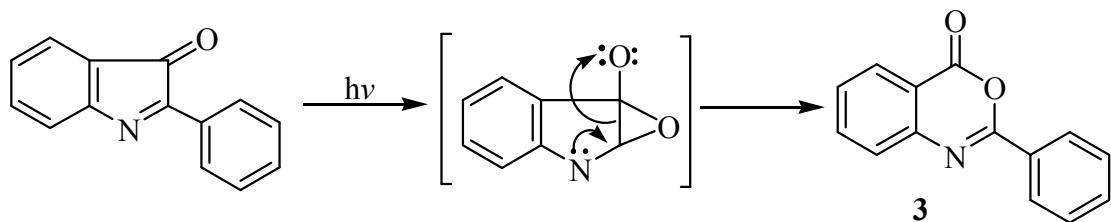
2.8. Via Intramolecular Rearrangement

2.8.1. 1,4-benzodiazepin-2,5-dione derivative

7-Chloro-1,4-benzodiazepin-2,5-dione underwent intramolecular rearrangement on refluxing with acetic anhydride in the presence of pyridine to give 6-chloro-2-methyl-(4*H*)-3,1-benzoxazin-4-one derivative **1** [70].
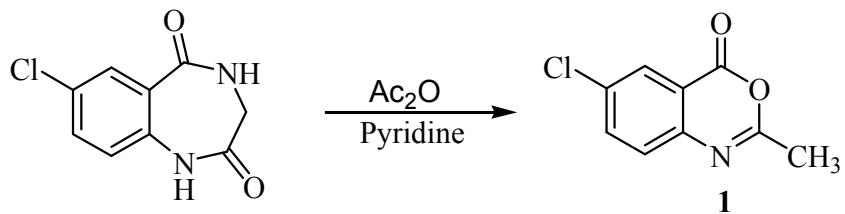
2.8.2. Carboxymaleanilic acid and/or fumaranilic acids

Pyrrolo benzoxazinones **44** were obtained by intramolecular cyclization of maleanilic acid derivatives (R= H, Cl; R$_1$= H, Me; R$_2$= H, Me, Ph; R$_3$= COOH) with acetic anhydride containing sodium

acetate. On the other hand, under these conditions fumaranilic acid derivatives (R= R_1= R_3= H; R_2= COOH) gave only 3,1-benzoxazinone derivative **45** [71].
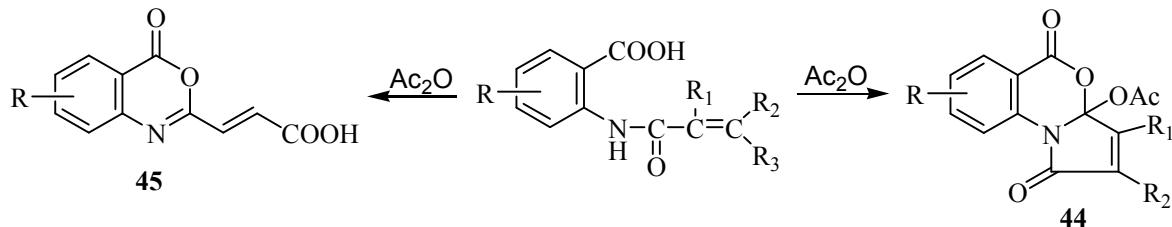
2.9. Miscellaneous Methods

Reaction of anthranilic acid with a slight excess of ethyl chloroformate in tetrahydrofuran (THF) in the presence of potassium carbonate [72] yielded the 2-carboalkoxyamino benzoic acid which cyclizes to produce **46**.
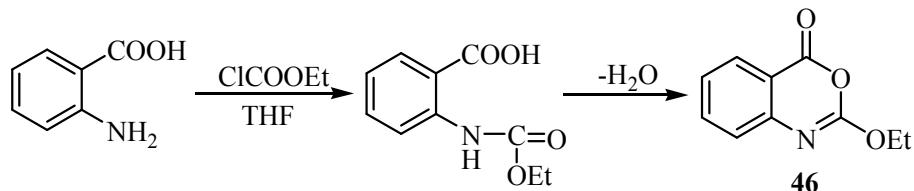
Treatment of iminophosphorane **47** with benzoyl chloride in acetonitrile in the presence of triethylamine gives 7-nitro-2-phenyl benzoxazinone **48** [73].
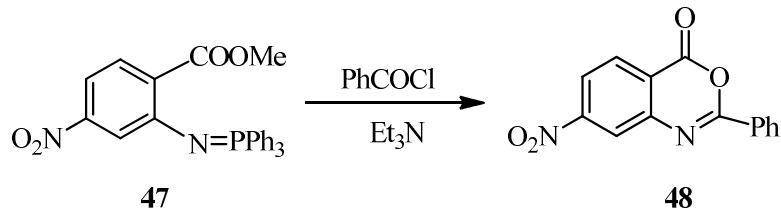
Oxidation of 2-isopropyl indole with monoperphthalic acid gave 2-hydroxy indole derivative **49** and isopropylindolyl indoxyl **50**. When the reaction time increased, the benzoxazinone **51** was formed [74].
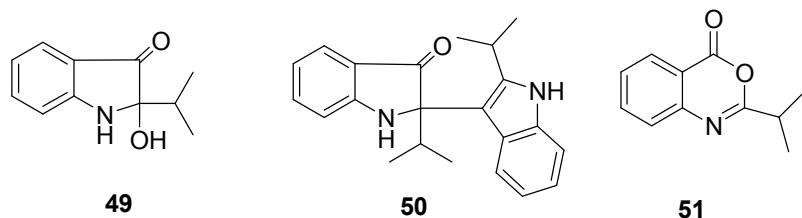
3. Reactions

3.1. Reactions with Hydrogen Nucleophiles

The benzoxazine nucleus is susceptible to attack by hydride reagents such as sodium borohydride. When the reaction was performed in alcohol or tetrahydrofuran afforded a mixture of *N*-alkylanthranilic acids **52** and 2-(*N*-acetylbenzyl alcohol) derivatives **53**, respectively [75].
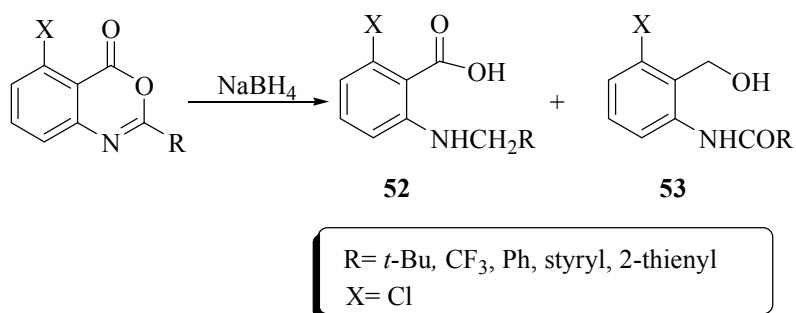
Catalytic hydrogenation of **1** in acetic acid affords 2-(*N*-acetylbenzyl alcohol) **54** in 41% yield. Similarly, hydrogenation of **55** under neutral conditions results in the initial reduction of C=N bond then cyclizes with the *o*-carboxylic group to furnish **56** in 40% yield [76].
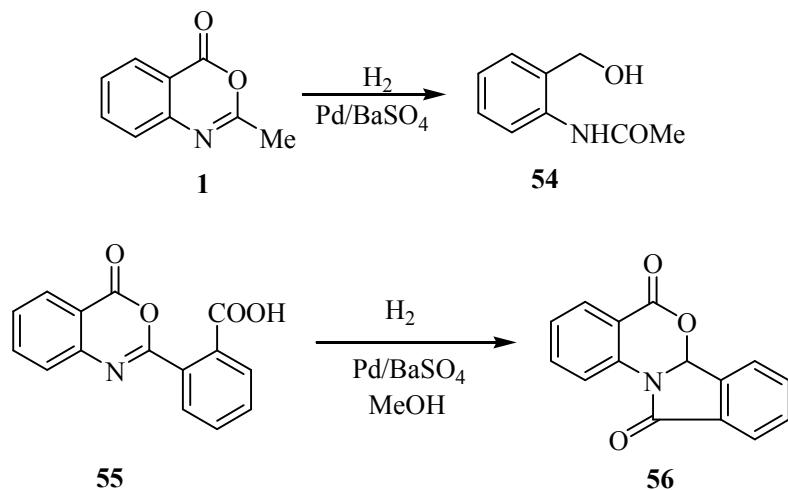
3.2. Reactions with Oxygen Nucleophiles

Exposure of benzoxazinones **1** to air resulted in the quantitative formation of *N*-aceylanthranilic acids **57** [77].
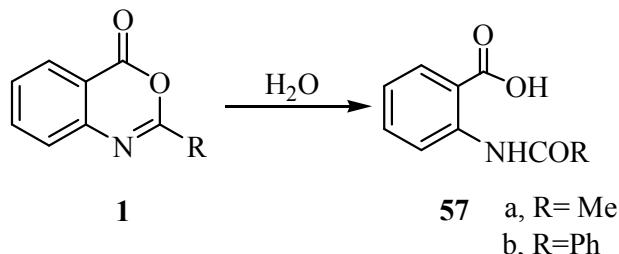
Refluxing of a solution of **58** in aqueous acetone for one hour results in the formation of ureidobenzoic acid **59** in 74% yield [57].
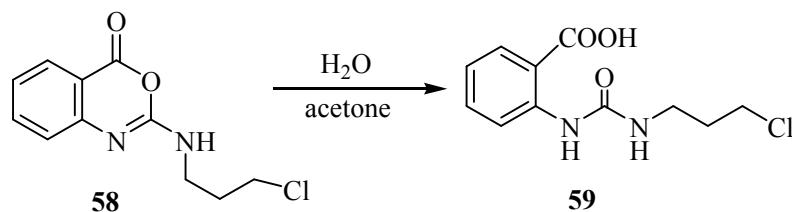
Likewise, heating of benzoxazine derivative **60** in water for two hours resulted in hydrolysis followed by cyclization of the resulting ureidobenzoic acid to the quinazoline-2,4-dione system which on further hydrolysis furnished **61** in 83% yield [78].
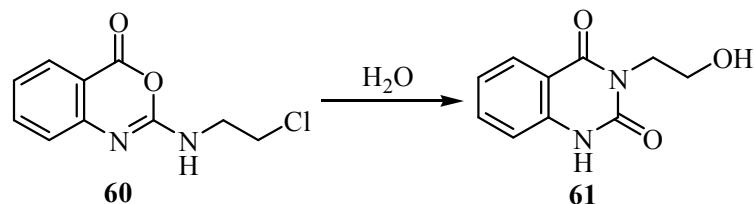
On the other hand, heating of **60** with concentrated hydrochloric acid for one hour gave 3-chloroethylquinazoline-2,4-dione **62** in 90% yield which on treatment with 10% aqueous sodium hydroxide in ethanol affords **63** in 72% yield [78].
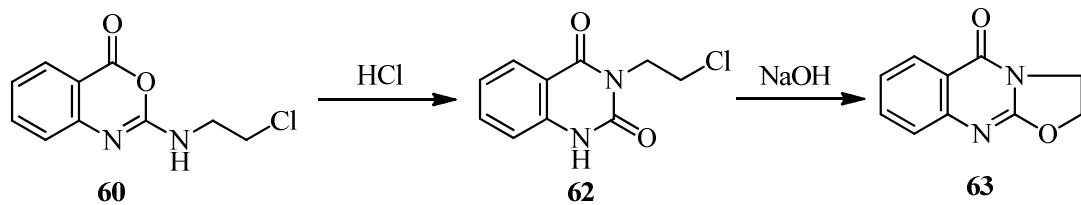
In a likewise fashion, treatment of **64** with dilute hydrochloric acid for 2-3 minutes, furnishes **65** in a quantitative yield. However, heating of **64** in concentrated hydrochloric acid for 15 minutes or allowing the mixture to stand at room temperature for 15 hours, the quinazoline-3,4-dione **66** was obtained in 70% yield [55].
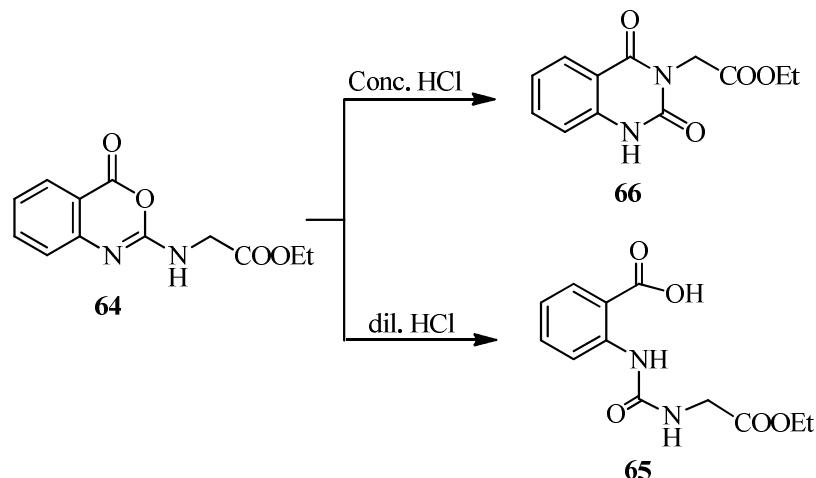
Moreover, treatment of 2-Alkoxybenzoxazin-4-one derivative **67** with hydrochloric acid (4*N*) in tetrahydrofuran for 15 minutes affords **68a** in 74% yield [79,80].
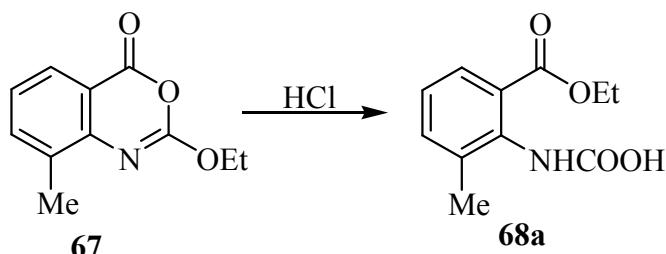
Furthermore, treatment of **67** with sodium ethoxide at 0°C for 3 hours results in the formation of ethyl anthranilate derivative **68b** [81].
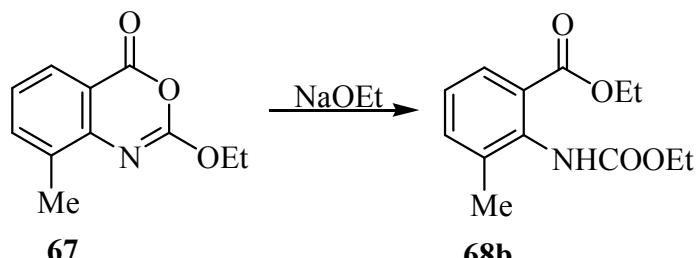
Benzoxazinone derivative **28** undergoes hydrolysis to produces *N*-thienoylanthranilic acid **27**, while its reaction with sodium methoxide results in the formation of ester **69** [82].
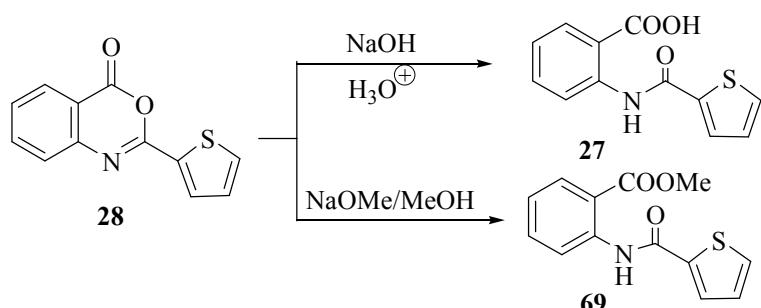
3.3. Reaction with Nitrogen Nucleophiles

3.3.1. With ammonia and aliphatic amines

It has been stated that, reaction of **28** with NH_3/EtOH takes place *via* ring opening of the benzoxazinone ring to produce **70** [62].
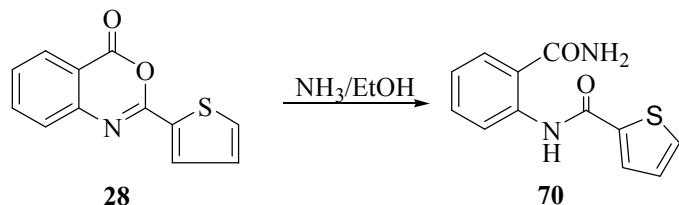
Ammonia or ammonium hydroxide, when allowed to react with **1** over a period of 1-3 hours produces anthranilamides **71** in good yield which cyclizes to 4-quinazolones **72** under thermal conditions (240-280°C) or on heating with acetic anhydride [83,84]. Quinazolones **72** can be also produced from **1** by longer reaction times with ammonium hydroxide (16-24 hours) and also by heating with formamide (170-175°C) [85,86], or ammonium acetate at 130-135°C [87].

X= H, Cl, Br, Me
R= alkyl, PhY(Y= Br, NHMe), CH_2CN
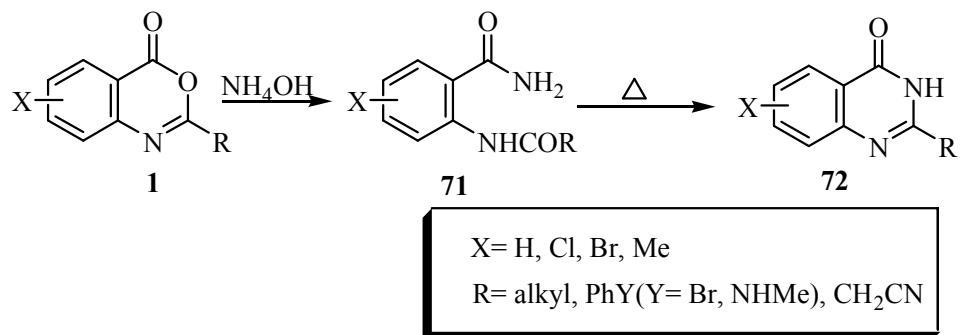
Fusion of **73** with ammonium acetate or formamide at 150°C gives 2-anilino-4-quinazolone **74** in 50% yield [88,89].
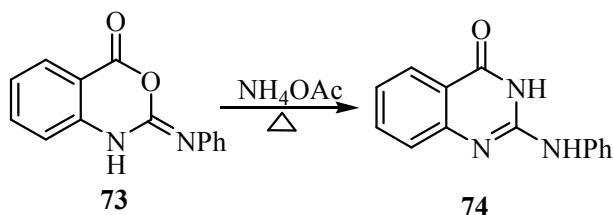
On the other hand, the benzoxazinone ring of **28** undergoes ring opening upon treatment with benzyl amine to give **75** [62].

28 → **75**
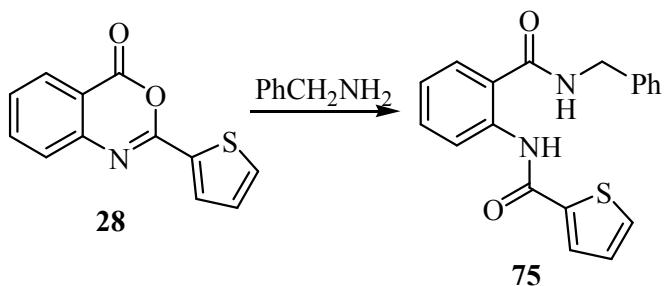
Moreover, aminolysis of **28** with *n*-propylamine gives the quinazolinone derivative **76** [90].

28   **76**
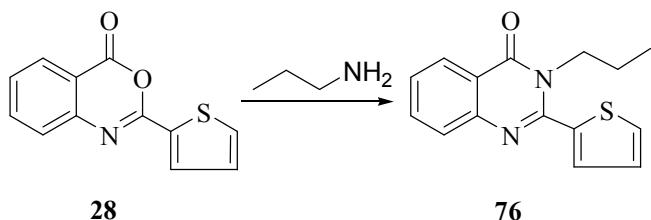
Similary, benzoxazinones **77** react with benzyl amine to afford **78** [91,92].

77   **78**

a, R_1= H, Br
b, R_2= H, Br
c, R_3= CHClMe,
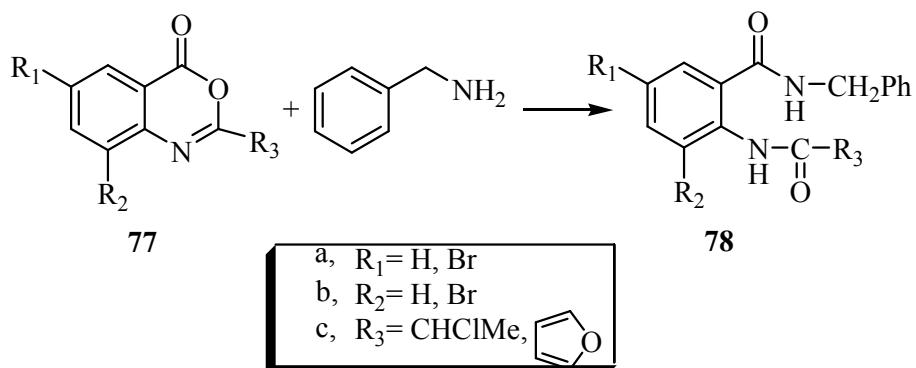
Also, treatment of arylpyrazolinyl benzoxazinones **79a** with aliphatic amines gives the quinazolones **79b** or the corresponding anilides **80** [93].

79 a,b
a) X= O
b) X= NR$_3$

80
R_1= H, Cl
R_2= Me, Br
R_3= Me
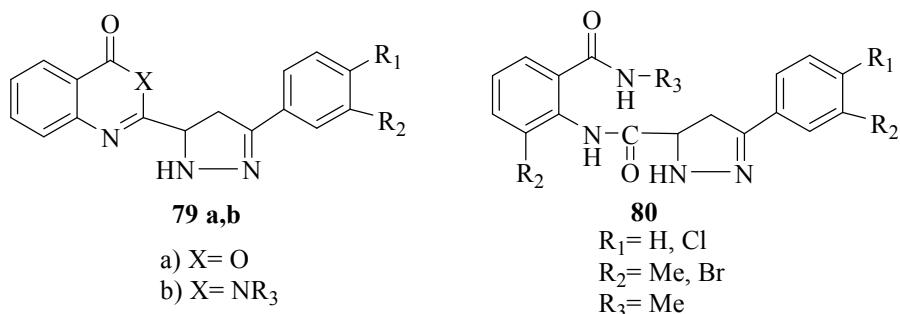
In view of the growing biological importance of quinazolone derivatives, reaction of 2-propyl-3,1-(4*H*)-benzoxazin-4-one **81** with benzylamine gives 2-propyl-3-benzyl quinazolin-4-one **82** which undergoes bromination followed by addition of *N,N*-dimethyl ethylene diamine to give **83**.

The latter was reacted with 4-fluorobenzoyl chloride to give compound **84** which is useful for treating cancer, hyperplasia and inflammation [30].
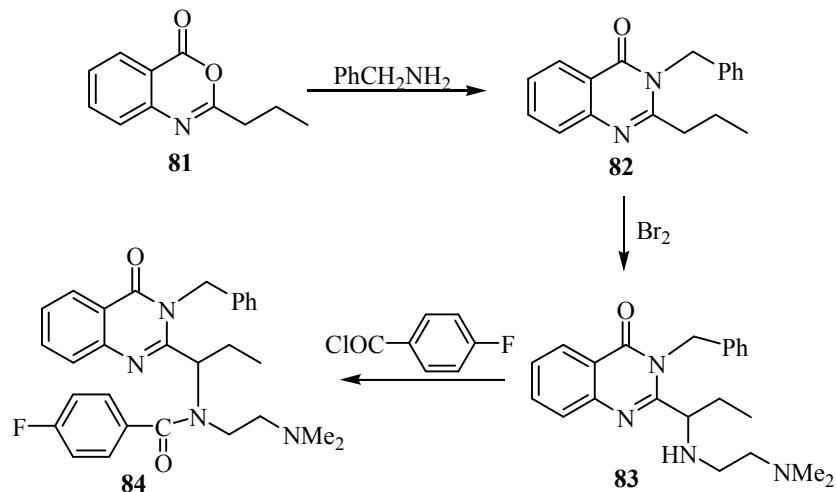
3.3.2. With secondary amines

It has been reported that, 2-methyl-3,1-(4*H*)-benzoxazin-4-one reacts with pyrolidine in diethyl ether to give a mixture of the acetamidinium salt **85** and 2-acetamido-*N*-pyridinobenzamide **86** respectively[94].

NR$_1$R$_2$= 1-pyrrolidinyl
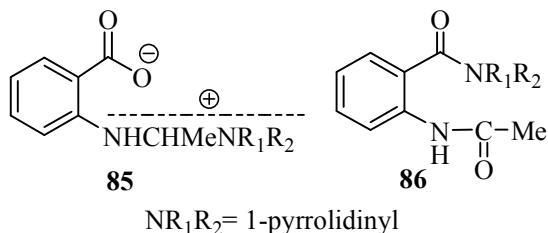
Treatment of 6,8-dibromobenzoxazinone derivatives **77c** with morpholine or piperidine affords **87** [92]. Similarly, treatment of 2-ethoxy-5-methyl-3,1-benzoxazinone **46** with morpholine in acetone produces **88** in 90% yield [95].
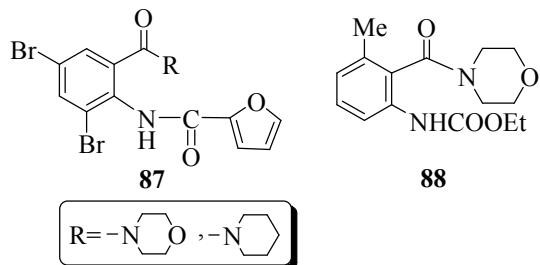
3.3.3. With heterocyclic amines

2-Substituted benzoxazinones react with some heterocyclic amines, namely, 2-aminothiazoles [34], 2-amino-5-*t*-butyl-1,3,4-thiadiazole [7], 2-amino-5-trifluoromethyl-1,3,4-thiadiazol [7],

2–methyl-3-aminoindole [15], 4-aminoantipyrine [98], 2,6-pyridindiamine [97] and nalidixic acid hydrazide [1,96] to afford the corresponding quinazolone derivatives **89a-g**, respectively as shown in Table 3.
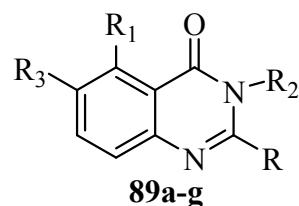
89a-g

Table 3: Preparation of quinazolone derivatives **89a-g** from 2-substituted benzoxazinones with some heterocyclic amines**.**

Comp. No. **89**	R	R_1	R_2	R_3	Ref.
a		H		H	[34]
b	Me	H		Br	[7]
c	Me	F		H	[7]
d	Me	H		H	[15]
e	H	H		H	[98]
f	Me	H		H	[97]
g	Me	H		H, I, NO$_2$	[1,96]

3.3.4. With aromatic amines

Several authors stated that, reaction of 2–substituted benzoxazinone derivatives with primary aromatic amines give the corresponding quinazolones **90a-g** [12,44,90,99-102], as shown in Table 4.
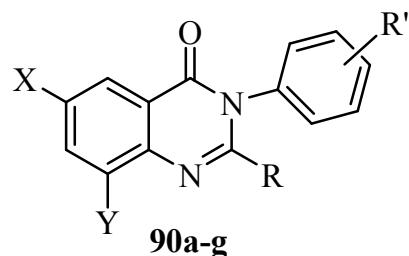
90a-g

Table 4: Preparation of quinazolone derivatives **90a-g** from 2-substituted benzoxazinones with some primary aromatic amines.

Comp. No. **90**	R	R'	X	Y	Ref.
a	—CH₂—C(Me)=NCH₂OC₆H₅	4-NO₂	H, Br, I	H, Br	[12]
b	—CH₂—C(Me)=NCH₂OC₆H₄CH₃	4-NO₂	H, Br, I	H, Br	[99]
c	thieno[2,3-d]pyrimidine (4,5-diMe, 2-Ph)	H, 4-Br, 4-OCH₃	H	H	[100]
d	-CH₂Cl	2-MeC₆H₄, 2-OHC₆H₄, 3–MeC₆H₄	H	H	[44]
e	—CH=CH-C(O)-C₆H₄-OMe-*p*	2-Me	H	H	[101]
f	-Me	4-Br	H	H	[102]
g	2-methylthiophene	4-OCH₃	H	H	[90]

Likewise, treatment of 3,1-(4*H*)-benzoxazin-4-one **1** with sulfanilamide and/or sulfa-methoxazole affords 2,3-disubstituted 4-(3*H*)-quinazolinones **91** and **92**, respectively[9,103,104].
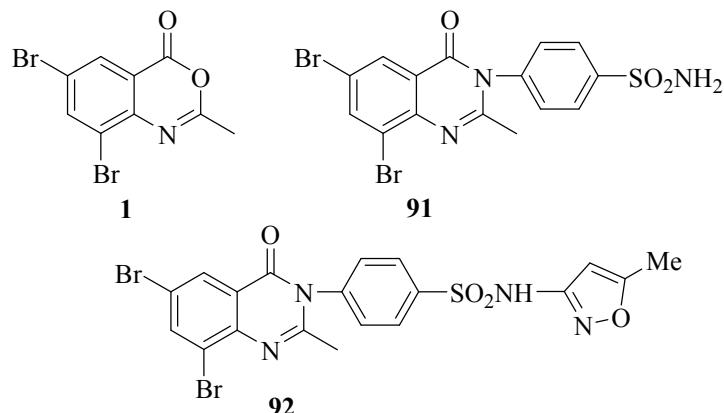
In a similar way, benzoxazinones **1** were condensed with 4–aminoacetophenone in *n*-buanol or ethanol to give quinazolone derivatives **93** [9,105].

93
R_1= I, Br
R_2= H, Br
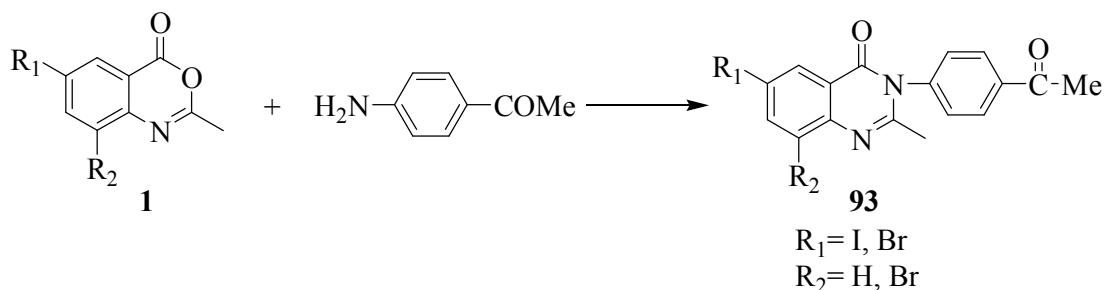
It has been reported that, benzoic and cinnamic acid hydrazides condensed with *p*-amino benzaldehyde to give the corresponding hydrazones which on treatment with benzoxazinones gave the quinazolone derivatives **94** [106].

R= Ph, 2-ClC$_6$H$_4$, PhCH=CH, 4-O$_2$NC$_6$H$_4$,
R'= Ph, PhCH=CH

94
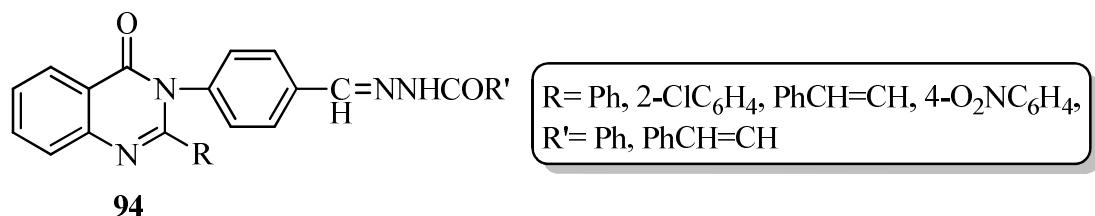
Moreover, reaction of benzoxazinones with arylideno aniline derivatives yielded the corresponding quinazolones **95** [107].

R= Me, Ph; R'= 3-NO$_2$, 4-OH, 4-NMe$_2$;
R_2= H, Br, I; R_3= H, Br

95
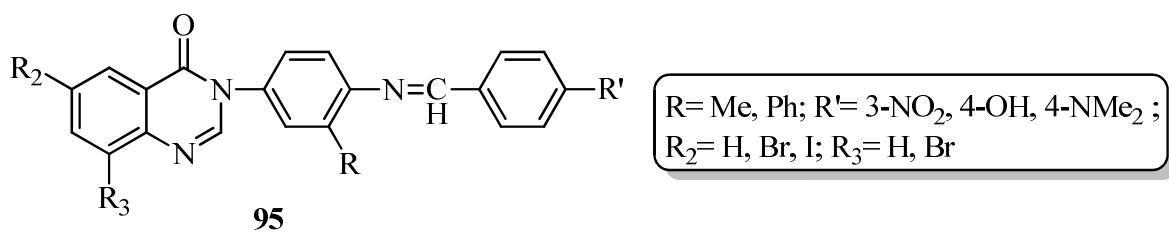
Furthermore, condensation of benzoxazinones with *p*-aminophenol gave the corresponding 3-(*p*-hydroxyphenyl)quinazolone derivatives **96a-c** [12,108,109], as shown in Table 5.
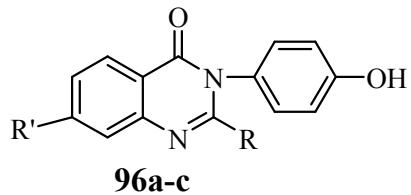
96a-c

Table 5: Preparation of quinazolone derivatives **96a-c** from condensation of benzoxazinones with
p-aminophenol.

Comp. No. **96**	R	R'	Ref.
a	CH_3	NO_2	[108]
b	$-H_2C-\underset{\underset{Me}{\mid}}{C}=N-C_6H_4OH\text{-}p$	H	[12]
c	CH_3	NO_2	[109]

3.3.5. With diamines

Reaction of 2-methyl-3,1-(4*H*)-benzoxazinone **1** with *p*-phenylenediamine affords the
corresponding 3-(4'-aminophenyl) quinazolone derivative **97** [108,109].

97
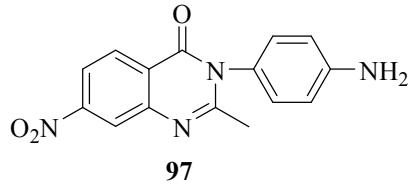
In a similar manner, 2-acetonylbenzoxazinone **2** condenses with excess *p*-phenylenediamine in
acetic acid and anhydrous sodium acetate to give *p*-phenylene-di-3-(*p*-aminophenyl)-2-isopropyl-imino
-(4*H*)-quinazolone **98** [12].

98
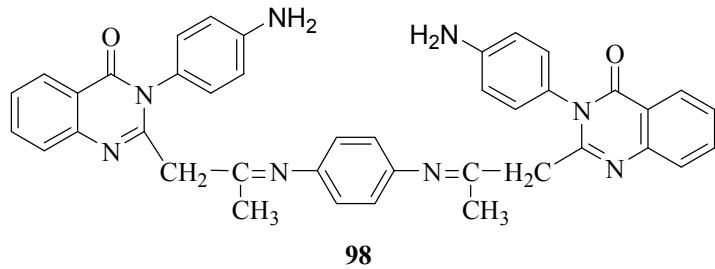
Condensation of 6,8–dibromo-2-methyl-3,1-benzoxazin-4-one **1c** with *o*-phenylenediamine
gave 3,5-dibromoanthranilic acid **99**, benzimidazole **100** and 3-(*o*-aminophenyl) -6,8-dibromo-2-methyl
quinazolin-4-one **101**, respectively. However, when the reaction was carried out in ethanol or in the
absence of solvents at elevated temperature, a mixture of **99** and **100** were obtained [110].

99   **100**   **101**
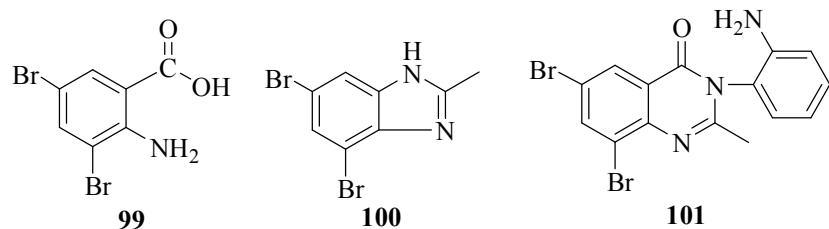
On the other hand, reaction of *o*-phenylenediamine with 6,8-dibromo-2-phenyl-3,1-benzoxazin-4-one **3** gave 3-(*o*-aminophenyl)-6,8-dibromo-2-phenyl-quinazolin-4-one **102** or 2-benzoylamino-3,5-dibromo-*N*-(*o*-aminophenyl)benzamide **103** [110,111], depending upon the reaction conditions.

102   **103**
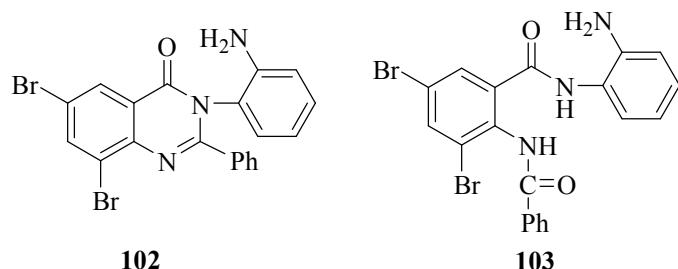
Refluxing a mixture of **104** and *o*-phenylenediamine in acetic acid in the presence of fused sodium acetate resulted in the formation of **105** [112].

104   **105**
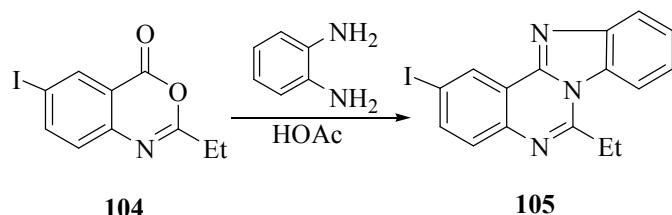
3.3.6. With ethanol amine

Treatment of 6,7-dimethoxy-2-substituted-3,1-(4*H*)-benzoxazinones with ethanolamine gave 3-hydroxyethyl-6,7-dimethoxy-2-substituted quinazolones **106** [113]. Similarly, 2-phenyl-3,1-benzoxazinone reacts with ethanolamine in pyridine to give the quinazolone derivative **107** [114].

106   **107**
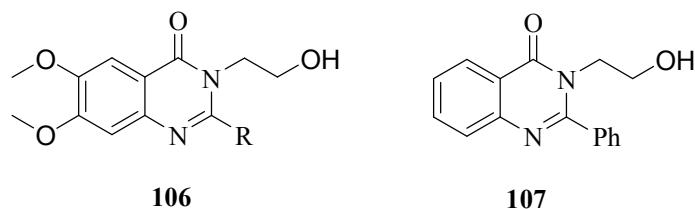
R= C$_{1-3}$ alkyl, unsubstituted aryl

Reaction of 2-ethyl-benzoxazine-4-one with ethanolamine gave **108** which reacted with Br$_2$ in acetic acid followed by NaOH affording 1-Methyl-3,4-dihydro-(1*H*,6*H*)-1,4-oxazino-(3,4-b)-quinazolin –6–one **109** [45].
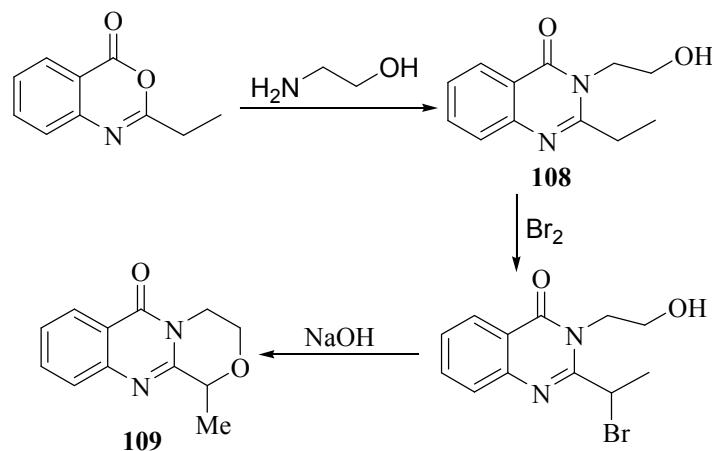
3.3.7. *With hydroxylamine hydrochloride*

It has been stated that, benzoxazinone derivatives react with hydroxylamine hydrochloride to give the corresponding 3-hydroxy quinazolone derivatives **110a-e,** respectively [9,50,92,115], as shown in Table 6.
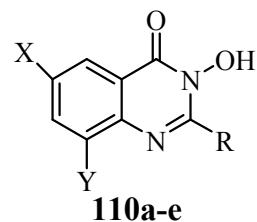
110a-e

Table 6: Preparation of 3-hydroxy quinazolone derivatives **110a-e** from the reaction of benzoxazinone derivatives with hydroxylamine hydrochloride**.**

Comp. No.**110**	R	X	Y	Ref.
a	2–thienyl	H	H	[50]
b	(furyl)O	Br	Br	[92]
c	Me	Br	Br	[9]
d	Me	H	H	[92]
e	(cyclohexyl)	H	H	[115]

3.3.8. With amino acids

Condensation of benzoxazinones **21** with *p*-amino benzoic acid afforded carboxyphenyl quinazolone **111** in high yield[116].

R= H, Br
R$_1$= Ph, CH$_2$Cl
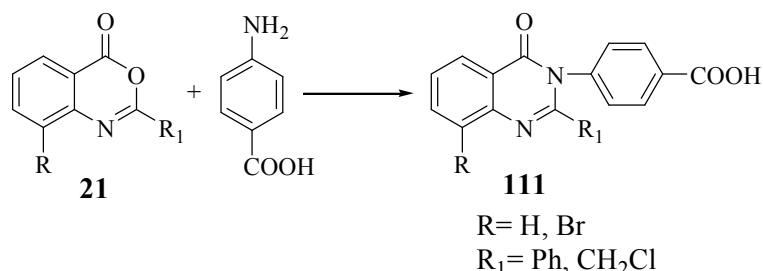
When benzoxazinones react with amino acid under fusion conditions at 190°C or by refluxing in pyridine/water mixture, produce quinazolone-3-acetic acid derivatives **112** in high yield. Glycine [117], longer chain amino acids (H$_2$N(CH$_2$)$_n$COOH) [118] and many of the natural α-alkyl amino acids [119], have been used in this reaction. The methyl ester (**113**; R$_1$= H) is prepared by refluxing a mixture of the benzoxazinone, glycine methylester hydrochloride and triethylamine in benzene [120] or by esterification of the acid **112** with methanol in the presence of thionyl chloride [121].

R= Me, Pr, Ph
R$_1$= H, alkyl
X= H, halogen

R$_2$= H   **112**
R$_2$= Me   **113**   MeOH / H$^+$
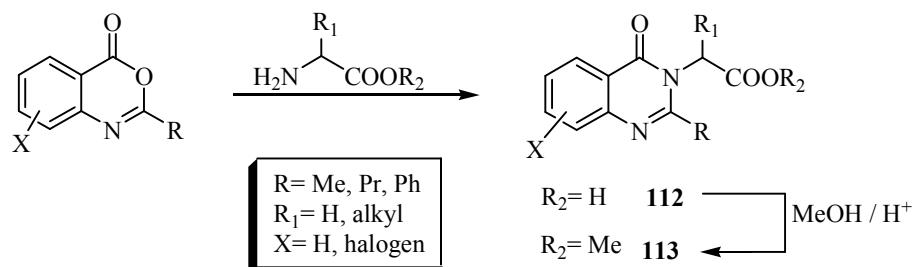
3.3.9. With hydrazine hydrate

Reaction of hydrazine hydrate with 2-substituted-(4*H*)-3,1-benzoxazinones results in the formation of 3-amino quinazolinone derivatives [103]. Similarly, when benzoxazinone **114** was allowed to react with hydrazine hydrate in boiling ethanol gave 3-amino-4(3*H*)-quinazolinone **115** which undergo condensation with aromatic aldehydes affording 3-arylideneamino-4-(3*H*)-quinazolinones **116** [9].

Ar= Ph,4-(OMe)C$_6$H$_4$, 4-(Cl)C$_6$H$_4$
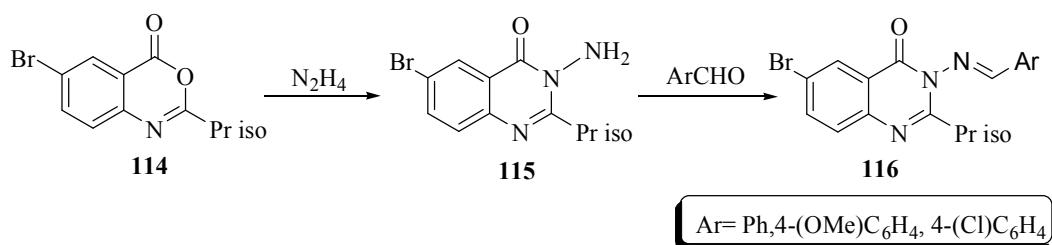
Cyclocondensation of **116** with 2-mercapto acetic acid in the presence of few drops of piperidine gave the thiazolidin-4-one derivative **117** [122]. Once more, compound **116** was allowed to react with thiophenol in the presence of piperidine as a basic catalyst to afford **118** [123].
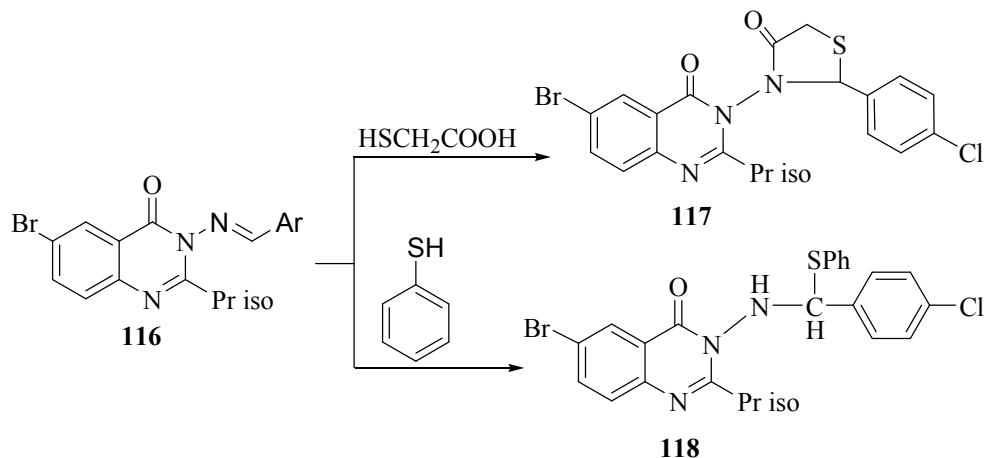
Reddy *et. al.* stated that, reaction of 2-substituted-3,1-(4*H*)-benzoxazin-4-ones with hydrazine hydrate depends on the reaction conditions. Thus, refluxing in xylene gave 2-substituted-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones **119** [124], while in basic solvents, the products have been proved to be 2-substituted-3-amino quinazolin-(4*H*)-one derivatives **120** [124].
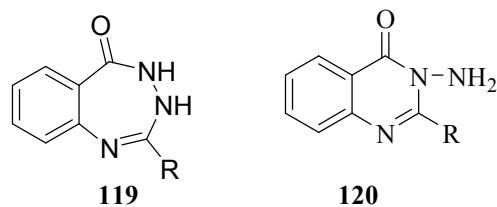
R= C_6H_5, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, 4-ClC$_6$H$_4$, ⌐O

Likewise, reaction of 2-methyl-6-iodo-1,3-benzoxazinone (**1d**) with hydrazine hydrate in ethanol [125] yielded the 3-amino derivative **121** which upon reaction with both phthalic anhydride and 6-iodo-2-methyl-*4H*-3,1-benzoxazin-4-one afforded phthalimidoquinazolinone **122** and 4-oxo quinazolinyl quinazolinone **123**, respectively.
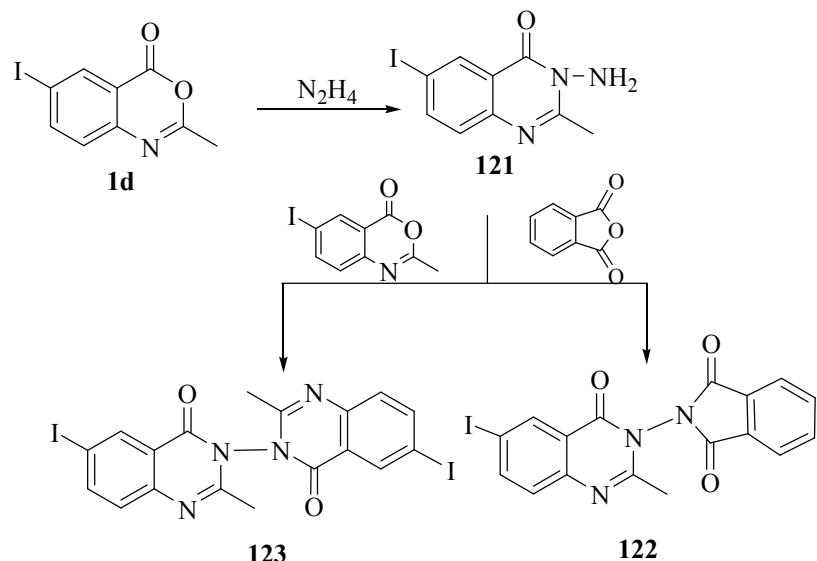
In the same way, treatment of 2–substituted benzoxazinones **1** (R= Me, PhCH$_2$) with both hydrazine hydrate and hydrazide derivatives R'CONHNH$_2$ (R'=Me, Ph, PhCH$_2$, 4–NO$_2$C$_6$H$_4$CH$_2$) afforded the quinazolone derivatives **124** and **125**, respectively [126].
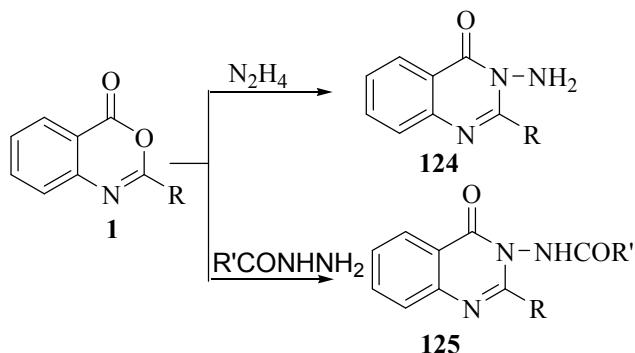
Once more, 2-phenyl-3,1-benzoxazin-4-one reacts with a mixture of hydrazine hydrate and carbon disulfide in the presence of potassium hydroxide to give 2-(*o*-benzoylaminophenyl) -1,3,4-oxadiazoline-5-thione **126** [127].
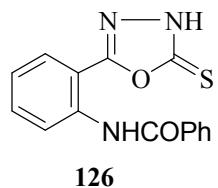
3.3.10. With semicarbazide

Successful attempt to construct a third heterocyclic ring condensed with quinazolin was achieved *via* reaction of benzoxazinone derivative **1** with semicarbazide hydrochloride in dry pyridine to furnish triazolo(2,3-*c*)quinazoline **127**[9].
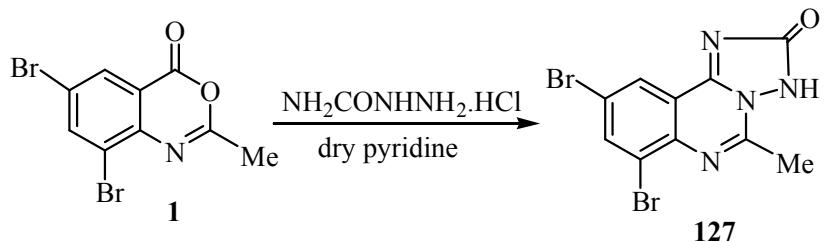
3.3.11. With thiosemicarbazide

Similar to the above reaction, treatment of 2-substituted-3,1-benzoxazin-4-ones with thiosemicarbazide yielded 2-substituted -3-triazolo-(1',5'-c)-quinazoline derivatives **128** [128-130].

X= H; R= Ph, PhCH=CH, methyl phthalimido, *p*-$O_2NC_6H_4$;
X= Cl, R= Me;
X= Br, R= Me.

128
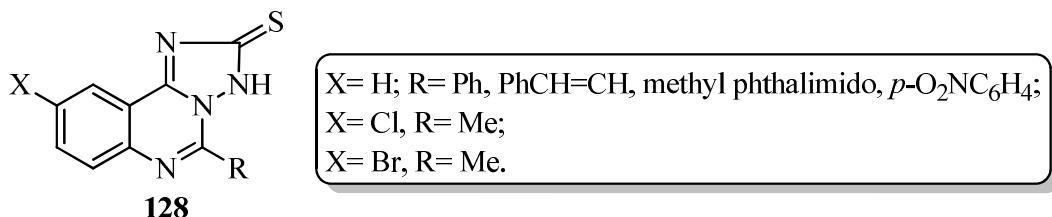
3.4. Reaction with Sulphur Nucleophiles

Various benzothiazin-4-thione derivatives **129a-e** [23,34,131-133] were prepared by treatment of 2-substituted-3,1-(4*H*)-benzoxazin-4-ones with phosphorous pentasulfide in dry xylene or pyridine as shown in Table (7).
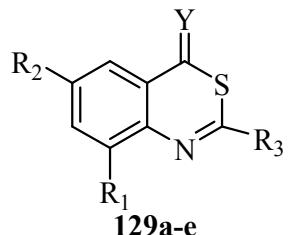
129a-e

Also, treatment of benzoxazinone derivatives **1** (R= H, Me, Et, CHMe$_2$, CMe$_3$, PH; R^1= H) with the thiolating agent **130** gave the benzothiazine derivatives **131** [134].
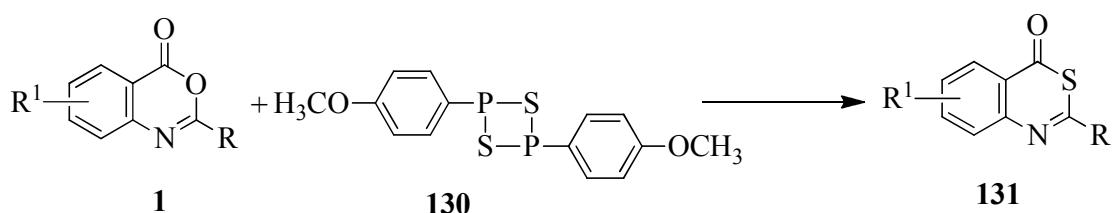
Table 7: Preparation of benzothiazin-4-thione derivatives **129a-e** from 2-substituted-3,1-(4*H*) benzoxazin-4-ones with phosphorous pentasulfide.

Comp. No. **129**	R	Y	Ref.
a	$-C=C-\langle\rangle-Cl$ (H on second C), NHCOC$_6$H$_5$	S	[34]
b	$-\overset{H}{\underset{Cl}{C}}-CH_3$	O	[23]
c	$-CH(CH_3)_2$	S	131
d	furan-2-yl	S	[132]
e	$-\overset{\parallel}{\underset{CHC_6H_5}{C}}-OC_6H_4Cl\text{-}p$	S	[133]

On the other hand, ethyl anthranilate derivatives **132** (R= H, Me, Et, CHMe$_2$, Me$_3$C, Ph) reacted with the thiolating agent **133** to give the corresponding benzothiazine thione derivatives **134** [134].
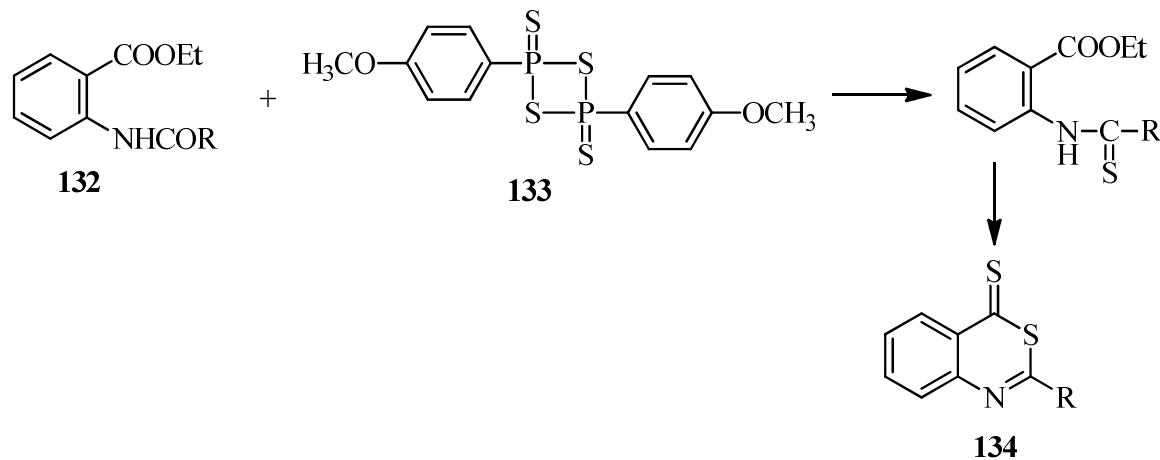
Treatment of 2-phenyl-3,1-benzoxazin-4-one with aromatic thiols leads to heteroring opening with the formation of thioanthranilates **135** [135].
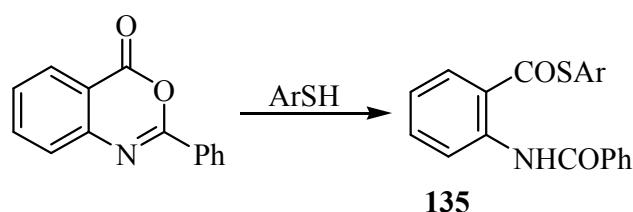
3.5. Reaction with Grignard Reagents

It was reported that, treatment of 2-substituted-3,1-benzoxazinones **1** with phenylmagnesium bromide lead to opening of heteryl ring with the formation of the corresponding carbinols **136** [136].
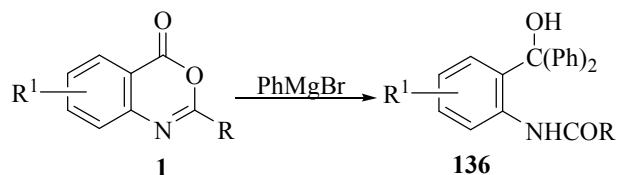
The 4-arylquinoline heterocyclic **140** was prepared by the reaction of 2-methyl-3,1-benzoxazinone **1** with 3,5-dimethyl phenylmagnesium bromide. The acyl group of **137** was removed under acidic conditions and the resulting compound **138** was condensed with methylacetoacetate to afford the quinoline **139** [137].
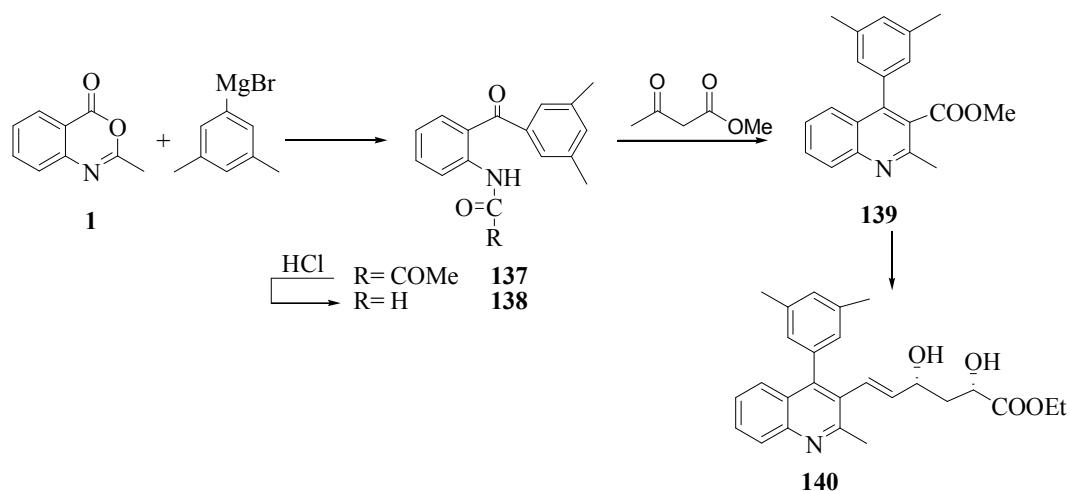
As a point of interest, it was found that the reaction of the benzoxazinone derivative **1** with phenylmagnesium bromide gave the substituted aminocarbinols **136**. Carrying out the reaction with benzylmagnesium chloride or bromide gave the corresponding aroyl ketone **141** [138].
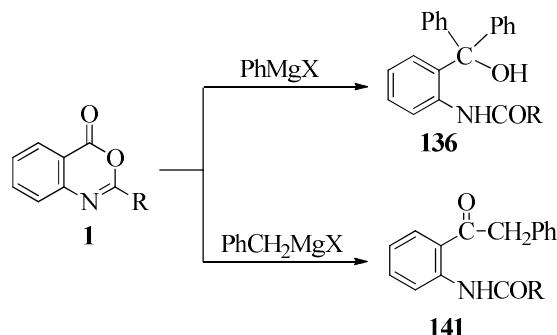
3.6. Reaction with Sodium Azide

2-Substituted-3,1-(4*H*)-benzoxazinone derivatives react with sodium azide in boiling acetic acid to give a mixture of the corresponding tetrazole **142a-c** and benzimidazole derivatives **143a-c** [51,85,132]. Under the same conditions 3,1-(4*H*)-benzoxazinones containing bulky groups at the 2-position were reacted with sodium azide to give only the corresponding 2-carboxyphenyl tetrazole derivatives **142d-f** [33,131,139] as shown in Table (8).
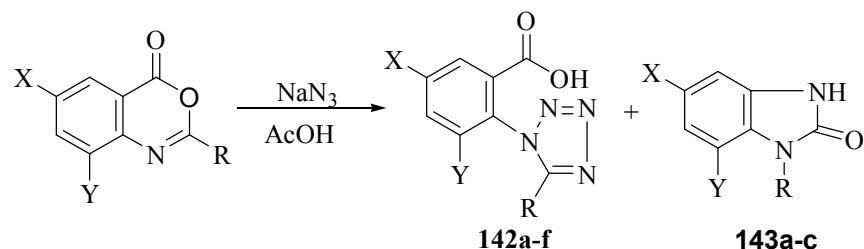
Table 8: Preparation of tetrazole **142a-f** and benzimidazole derivatives **143a-c** from 2-substituted-3,1-(4*H*)- benzoxazinone derivatives with sodium azide.

Comp. No. **142,143**	R	X	Y	Ref.
a	(thiophene)	Br	Br	[51]
b	(furan)	H	H	[132]
c	$-CH_2CH_2CH_3$	H	H	[85]
d	$-C=C-C_6H_4$-OMe-*p* | H | NHCOC$_6$H$_4$Cl-*o*	H	H	[33]
e	(chromanone)	H	H	[139]
f	$-CH(CH_3)_2$	H	H	[131]

3.7. Reaction with Carbon Nucleophiles

Reaction of 2-methyl-3,1-benzoxazin-4-one **1** with active methylene compounds under basic conditions gave the intermediate **144** which underwent cyclization to furnish 3-substituted 4-hydroxy quinolin-2(1*H*)-ones **145** [140].

Y, Z= CN, COOMe, COOEt, COMe, SO₂Me.
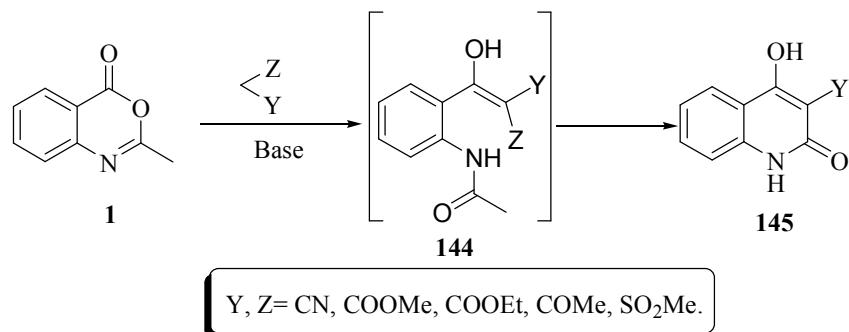
Similarly, reaction of 2-ethoxy-3,1-benzoxazinone with methylcyanoacetate under basic conditions leads to the formation of the intermediate **146** which undergoes cyclization to give 3-cyano-4-hydroxyquinolin-2-ones **145** [141].
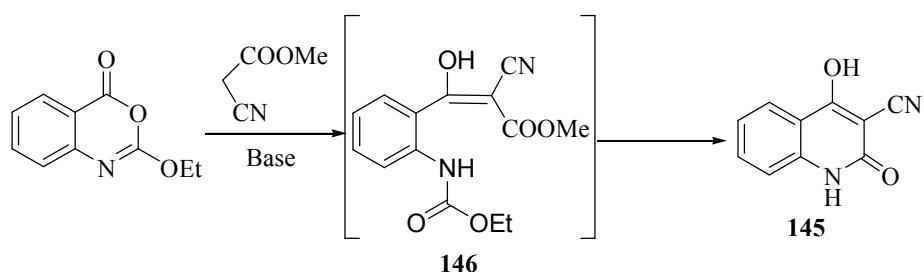
On the other hand, reaction of benzoxazinone derivatives containing bulky or thienyl groups at the 2-position with the same reagents in pyridine yielded the same product, namely 2-(substituted) -3-carboxy(or carboethoxy)-4-quinolinone derivatives **147a-b** [33,50] as shown in Table (9). This result was explained by the opening of heterocyclic ring followed by ring closure then deacylation or elimination of carboethoxy or cyano groups.
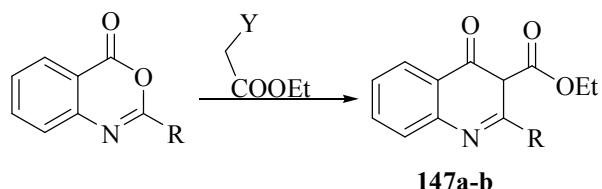
Table 9: Preparation of 2-(substituted) -3-carboxy(or carboethoxy)-4-quinolinone derivatives **147a-b**.

Comp. No **147**	R	Y	Ref.
a	2-thienyl	CN	[50]
b	—C=C–C₆H₄OMe-*p* H NHCOPh	COCH₃, CN, COOEt	[33]

4. Biological Activity

4*H*-3,1-benzoxazin-4-ones can be considered as semi acid anhydrides which undergo many of the reactions of true acid anhydrides but at a slower rate. This special reactivity allows this class of compounds to be quite useful as serine protease inhibitors, inactivating enzymes such as chymotrypsin [3-8], human leucocytes elastase [5-9], porcine pancreatic elastase, cathepsin G [6,8] and CIr serine protease [4-6]. Mechanistically, the inactivation involves nucleophilic attack of the active site of serine hydroxyl group on the C-4 carbonyl of the benzoxazinone which leads to ring opening and formation of an acylated enzyme. The chemical stability and potency of the benzoxazinones can be turned by choosing substituents (R) which influence the reactivity of the carbonyl by electronic and steric effects. A variety of 2-alkoxy-4*H*-3,1-benzoxazin-4-ones have been designed to inhibit enzymes such as chymotrypsin [142,143], thrombin [143,144], cathepsin G [71], HSV-1 protease[16], protac[R] [13], human leukocyte proteinase [145], HLE [146,147] and pancreatic elastase [148].

2-Aryl-4*H*-3,1-benzoxazin-4-ones act as Cirserine protease inhibitors [13]. Also it converted to the corresponding 4(3*H*)-quinazolinones via interaction with 4-amino-1-phenyl-2,3 dimethylpyrazolin-5-one (aminoantipyrine), which acts as non-steroidal anti-inflammatory agents [97]. Combination of benzoxazin-4-ones with 2-aminothiazole, 2-aminobenzothiazole or 2-aminothiadiazole give substituted quinazolinones which act as potent anticonvulsant and enzyme inhibitors [149]. Moreover, 2-styryl-4(3*H*) quinazolinones bearing 5-, 6-, 7-, 8-Cl, 6-Br, 6-F, 6-NH$_2$, 6-OMe, 6-OH, 6-OEt act as a new class of antimitotic, anticancer agents which inhibit tubulin polymerization [86].

2-Amino benzoxazinones are useful for the treatment of viral infections. Compounds **148** (R, R$_2$= H, halo, alkyl, NH$_2$; R$_1$= H, alkyl, alkoxy; R$_3$= H, alkyl, alkyl-aminoalkyl; R$_4$= H, alkyl, cycloalkyl, aryl, heterocycle, carbamoylalkyl, hydroxyalkyl, aminoalkyl) are viral protease inhibitors and useful for treatment of infection by CMV, HSV-1, HSV-2. L-alanine tert-Bu ester HCl was coupled with 2-amino-6-methylbenzoic acid using CDI in pyridine followed by cyclization using Et$_3$N in CH$_2$Cl$_2$ to give **149**. Compounds **148** act as inhibitors HCMV protease, Chymotrypsin and human leukocyte elastase as well as cell culture assay results for antiviral activity [148].

148

149
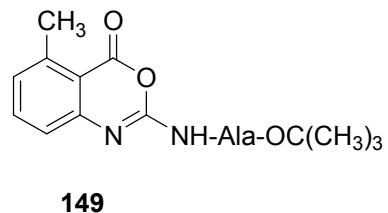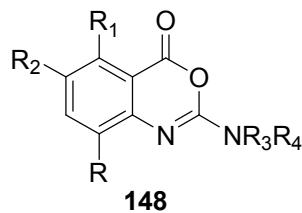
2-(6-Methoxy-3,4-dihydro-1-naphthyl)-4*H*-3,1-benzoxazin-4-one **150** has been synthesized and tested for inhibitory activity against human leukocyte elastase. It was shown activities both *in vitro* toward human sputum elastase and *in vivo* in a hemorrhagic assay [147-148].

150
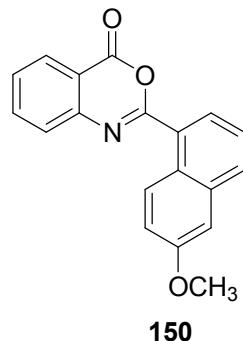
5. Conclusion

This review provides detailed methods for the synthesis and chemical reactions of 4*H*-3,1-benzoxazin-4-ones. The greatest utilities of benzoxazinones and quinazolinones in biological and industrial applications have shown interesting developments in the very last years. It is sure that, as it has been until now, the use of these compounds will show a continuous flow of applications in the next years and will continue to be an indispensable synthetic tool in organic chemistry.

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