Review

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Synthesis of fused heterocycles derived from 2*H*-1,4-benzoxazin-3(4*H*)-ones

Abstract: The synthesis of 1,4-benzoxazine fused heterocycles has been reviewed.

Keywords: imidazo[1,4]benzoxazines; indolo[1,4]benzoxazines; pyrazolopyrimido[1,4]benzoxazines; pyrrolo[1,4]benzoxazines; thieno[1,4]benzoxazines; triazolo[1,4]benzoxazines.

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Introduction

The past few decades have seen the emergence of a number of 1,4-benzoxazin-3(4*H*)-one **1** derivatives including a cardiotonic agent **2** [1], antihypertensive agent **3** [2], antidiabetic agent **4** [3], anticancer agent **5** [4], laxative **6** [5], aldose reductase inhibitor **7** [6], antianxiety agent **8** [7], antiemetic agent **9** [8] and antiparasitic agent **10** [9]. A number of these simple benzofused 1,4-oxazines are a part of natural products with antituberculosis **11** [10] and anticancer **12** [11] activities. 2,4-Dihydroxy-7-methoxy-1,4-benzoxazinone **13** [12] isolated from corn seedling is an active compound in the resistance of maize to the *European corn borer. Blepharin* **14** is a biologically significant 1,4-benzoxazinone glycoside [13]. *Ofloxacin* **15**, a 1,4-benzoxazine fused heterocycle, is an active antibacterial agent and presently in clinical use [14] (Figure 1). In view of these findings, an attempt was made to review the synthesis of various 1,4-benzoxazine fused heterocycles in the present article. To the best of our knowledge, no review has appeared on 1,4-benzoxazine fused systems and the literature available is very limited.

Synthetic methods of 2,3-dihydro-1,4-benzoxazin-3(4*H*)-ones

The most convenient and commonly used method for the synthesis of 1,4-benzoxazinones **1** has been reported by Shridhar et al. [15] by reaction of 2-aminophenol with chloroacetyl chloride in refluxing methylisobutylketone (MIBK) in the presence of aqueous sodium bicarbonate in a single step (Scheme 1).

Another strategy involves reduction of nitro ethers **16** with Fe/AcOH [16] and Zn/NH_4Cl [17], which gives the desired benzoxazinones in moderate yields. The nitro ethers can be prepared by the alkylation of potassium nitrophenoxides with a 2-bromoester (Scheme 2).

1,4-Benzoxazinones **17** with acetic acid substitution in 2-position have been prepared in a single step by the reaction of 2-aminophenols with maleic anhydride [18] (Scheme 3).

In another method, 2-hydroxyethyl-2,3-dihydro(2*H*)-1,4-benzoxazinones **18** [19] have been prepared by the reaction of 2-aminophenols with α-bromo-γ-butyrolactone in *N*,*N*-dimethylformamide in the presence of potassium carbonate or sodium hydride at room temperature followed by reduction [14] (Scheme 4).

Reactions and classification of 1,4-benzoxazine fused heterocyclic systems

In the present review, the heterocycles are classified according to the site of the reaction, as shown below, followed by cyclocondensation to form the fused heterocycle. This classification is purely based on convenience and is not general.

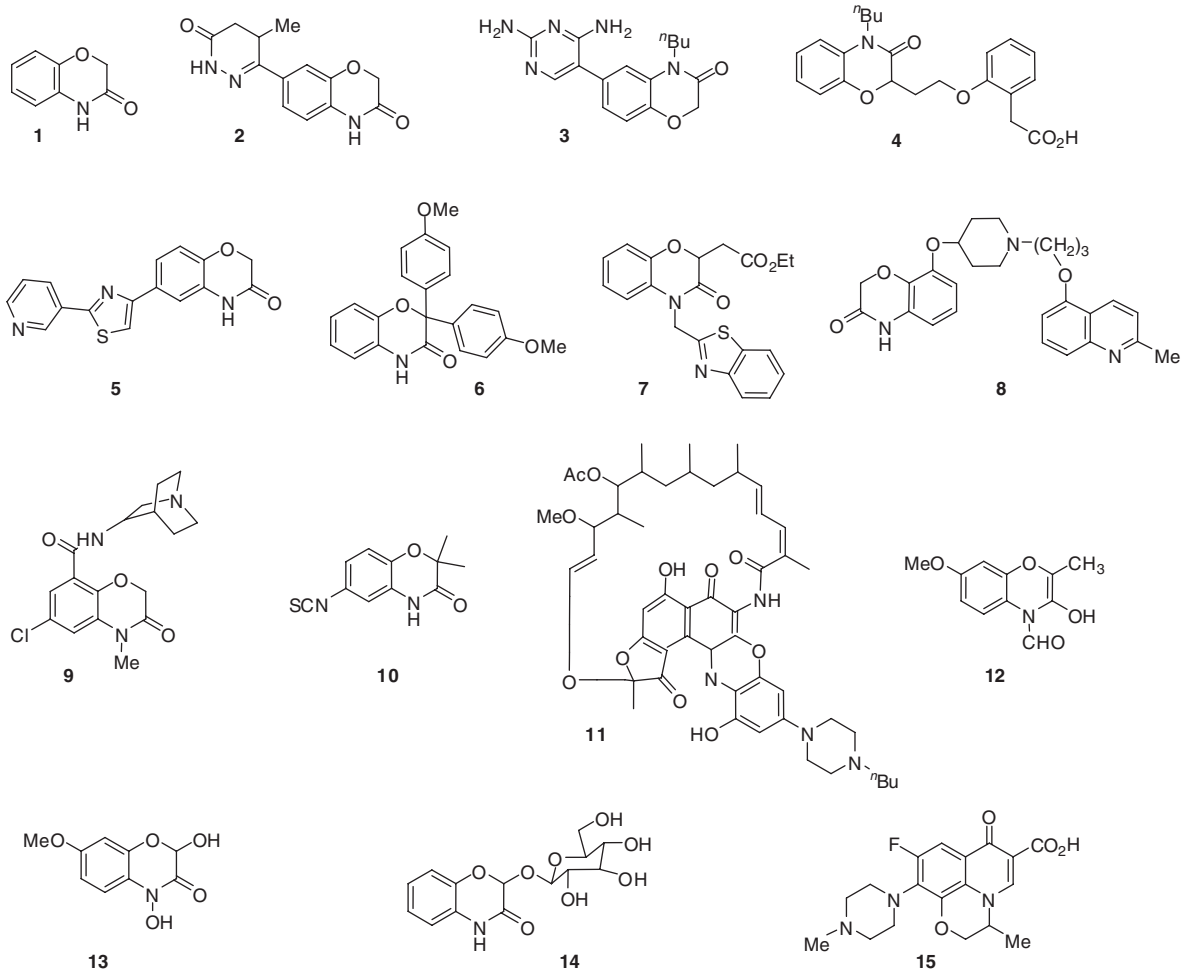
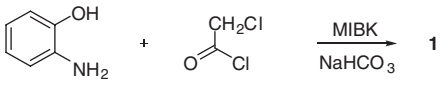
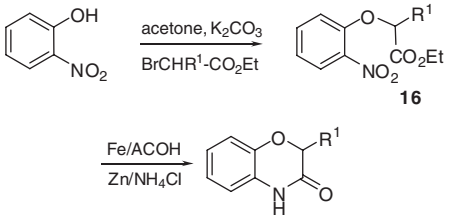


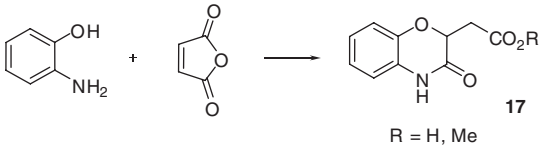
Figure 1 1,4-Benzoxazin-3(4*H*)-one (**1**) and its biologically active derivatives.



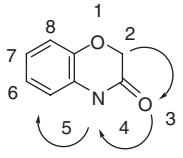
Scheme 1



Scheme 2



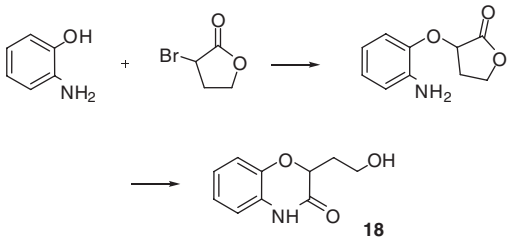
Scheme 3



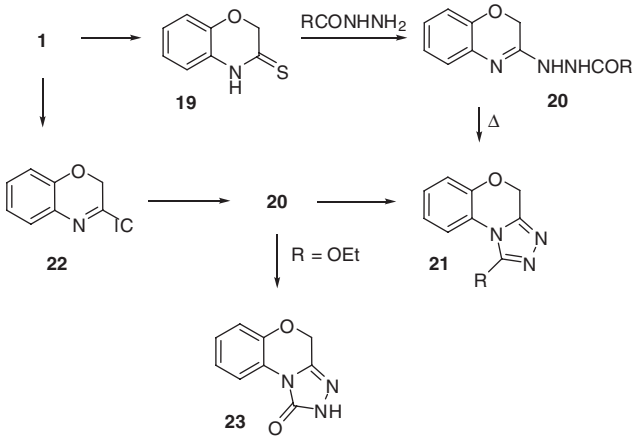
- Reaction at C-3 followed by cyclocondensation at **4** (3–4 fused system).
- Reaction at ring nitrogen (**4**) followed by cyclocondensation at C-3 (4–3 fused system).
- Reaction at ring nitrogen (**4**) followed by cyclocondensation at C-5 (4–5 fused system).
- Reaction at C-2 and C-3 (2–3 fused system).
- Benzofused system (6–7 fused system).

3–4 Fused systems

1,2,4-Triazolo[3,4-c][1,4]benzoxazines A wide range of medicinal properties such as anti-inflammatory [20],



Scheme 4

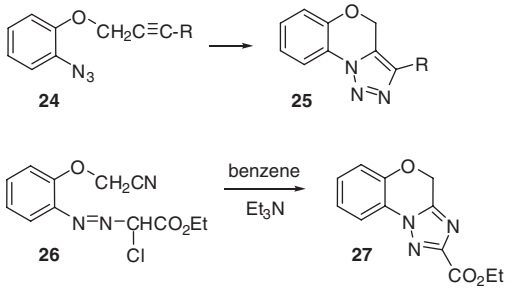


Scheme 5

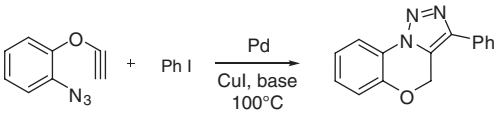
central muscle relaxant [21] and diuretic activities [22] have been reported for these systems. Compounds have been prepared by thiation of **1** with Lawesson's reagent to give **19** followed by reaction with alkyl/aryl hydrazones to give **20**. Thermal cyclization of **20** has furnished the triazolo-1,4-benzoxazines **21** as crystalline solids (Scheme 5).

Hydrazones **20** have also been prepared conveniently via iminochloride **22** obtained by reaction of **1** with phosphorous oxychloride in the presence of CH_3CN/Et_3N [23]. Hydrazones obtained *in situ* undergo cyclocondensation under PTC conditions to give 1-oxo-triazolobenzoxazines **23** in good yields (Scheme 5).

The isomeric triazolobenzoxazines **25** and **27** have been prepared as outlined in Scheme 6. Thus, compounds **25** have been prepared by an intramolecular



Scheme 6



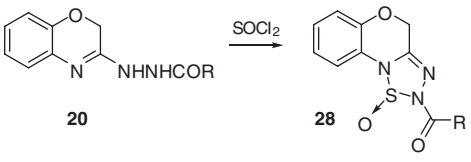
Scheme 7

cyclocondensation of the azido group [24] to the acetylenic function of *O*-azido-acetylenic derivative **24**, whereas the other isomer **27** was obtained by refluxing *O*-phenoxyacetonitrile-nitrile imide **26** in benzene in the presence of triethylamine [25].

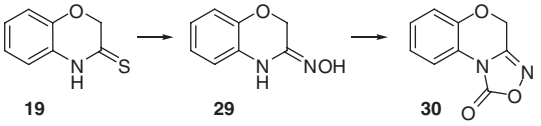
Chowdary et al. [26] have reported a palladium-copper catalyzed synthesis of 1,2,3-triazolo[5,1-*c*]benzoxazines through C-C bond formation followed by intramolecular cycloaddition of aromatic azide with internal alkyne generated *in situ* (Scheme 7).

4*H*-[1,2,3,5]–Thiatriazolo[4,5-*c*][1,4]benzoxazine Hydrazones **20** undergo reaction with thionyl chloride forming sulfur containing *C*-annulated benzoxazines **28** via intermolecular ring formation [27] (Scheme 8)

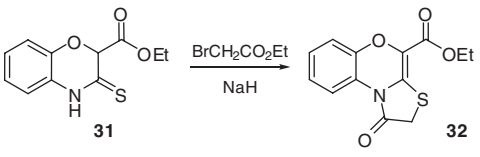
4*H*-[1,2,4]–Oxadiazolo[3,4-*c*][1,4]benzoxazine Bartsch et al. [28] have synthesized another interesting system starting from thioxobenzoxazine **19**. Thus, reaction of **19** with hydroxylamine hydrochloride in the presence of triethylamine gives the oxime **29**. Cyclocondensation of **29** with carbonyl di-imidazole yields oxadiazolo[1,4]benzoxazine **30** in approximately 45% yield (Scheme 9).



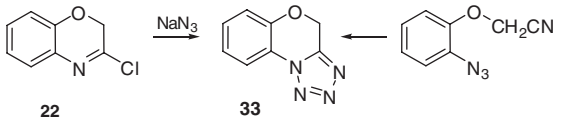
Scheme 8



Scheme 9



Scheme 10



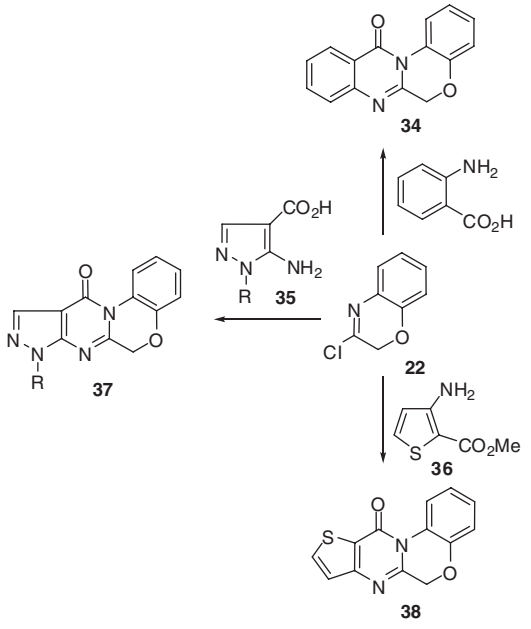
Scheme 11

Thiazolo[2,3-*c*][1,4]benzoxazine The reaction of 2-ethoxycarbonyl-3-thioxobenzoxazine **31** with ethyl bromoacetate in the presence of sodium hydride gives thiazolo[2,3-*c*][1,4]benzoxazine **32** ring system [29] in approximately 50% yield (Scheme 10).

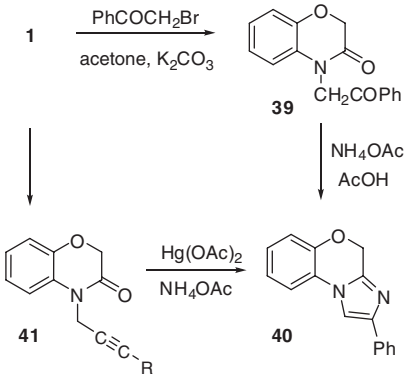
4*H*-Tetrazolo[5,1-*c*][1,4]benzoxazines The synthetic utility of iminochloride **22** derived from **1** is further exemplified in the synthesis of tetrazolobenzoxazine system **33**. The treatment of iminochloride **22** *in situ* with sodium azide gives the tetrazolobenzoxazine **33** in 40–60% yield [30] (Scheme 11).

An alternative synthetic route to this system involves a 1, 3-dipolar addition of *O*-azidophenoxyacetonitrle [24].

Pyrimido[2,3-*c*][1,4]benzoxazines A number of pyrimidobenzoxazines have been synthesized utilizing the reactivity of iminochloride **22**. It undergoes reaction with anthranilic acid in refluxing acetonitrile to give quinazolino[2,3-*c*][1,4]benzoxazine **34** in a single step [31]. A multistep synthesis of this system has been reported by Kulkarni and Abdi [32]. Similarly, **22** undergoes cyclocondensation with 5-aminopyrazole-4-carboxylic-acids **35** and 3-amino-thiophene-2-carboxylates **36** to give pyrazolo



Scheme 12



Scheme 13

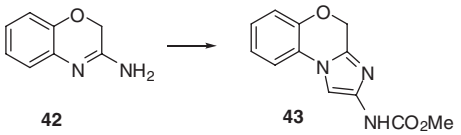
[3′,4′:4,5] pyrimido [2,3-c] [1,4] benzoxazines [33] **37** and thieno[3′,2′:4,5] pyrimido[2,1-*c*][1,4]benzoxazines [34] **38**, respectively (Scheme 12).

4–3 Fused systems

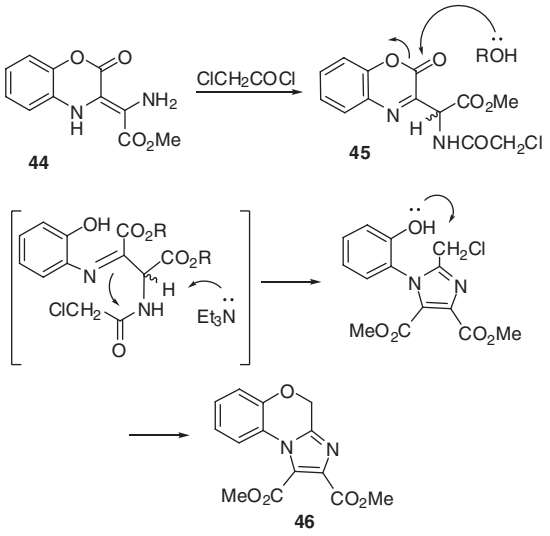
4*H*–Imidazo[2,1-*c*][1,4]benzoxazines A number of substituted imidazobenzoxazines have been reported to exhibit antiallergic and bronchodilator activities [35]. Sundara Murthy et al. [36] have reported a two-step synthesis of imidazobenzoxazines. Alkylation of **1** with phenacyl bromide in refluxing acetone in the presence of potassium carbonate gives *N*-substituted benzoxazine **39**, which was cyclocondensed in glacial acetic acid in the presence of ammonium acetate to give imidazobenzoxazine **40** in good yield. In another strategy, propynyl-substituted benzoxazines **41** have been cyclocondensed in the presence of mercuric acetate and ammonium acetate (Scheme 13).

Shridhar et al. [37] have reported the synthesis of antiparasitic imidazobenzoxazinyl carbamates **43** starting from 3-aminobenzoxazine **42** (Scheme 14). Substrate **42** has been prepared by amination of thioxobenzoxazine **19**.

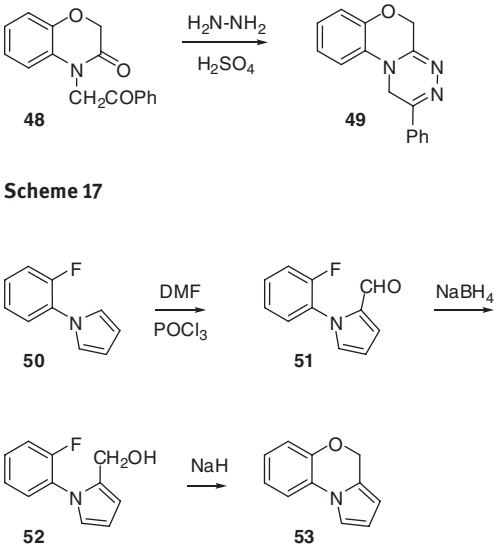
Rowlands et al. [38] have reported the synthesis of antiallergic imidazo[2,1-*c*][1,4] benzoxazines **46** by a different method. Thus, the reaction of benzoxazine derivative **44** with chloroacetyl chloride gives acetamido intermediate **45**. This compound in refluxing methanol in the presence of triethylamine undergoes an interesting rearrangement giving **46** in approximately 80% yield. The mechanism is depicted in Scheme 15.



Scheme 14



Scheme 15



Scheme 17

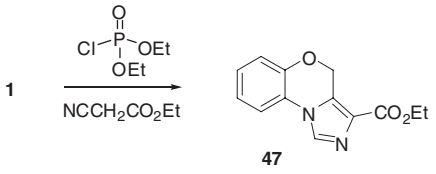
Scheme 18

Bartch et al. [27] have reported the synthesis of isomeric imidazo[5,1-*c*][1,4] benzoxazines **47** from **1** after activation with diethyl chlorophosphate and subsequent treatment with ethyl isocyanoactate (Scheme 16).

4*H*–[1,2,4]Triazino[3,4-*c*][1,4]benzoxazines *N*-Acylbenzoxazinones **48** undergo cyclocondensation with hydrazine hydrate in the presence of catalytic amount of sulfuric acid to give triazino benzoxazines **49** in good yields [39]. These compounds have been found to exhibit significant anti-inflammatory activities (Scheme 17).

Pyrrolo[2,1-*c*][1,4]benzoxazines Sanohez and Pujol [40] have synthesized this interesting system starting from *N*-(2-fluorophenyl) pyrrole **50**. Vilsmeyer formylation of **50** with phosphorous oxychloride/dimethyl formamide gives the formylpyrrole derivative **51**, which on sodium borohydride reduction has been transformed into the alcohol **52**. In the presence of NaH, this compound has been cyclized to pyrrolo[2,1][1,4]benzoxazine ring system **53** (Scheme 18).

Azaindolo[2,1-*c*][1,4]benzoxazines Bhuniya et al. [41] have reported a two-step one-pot synthesis of an azaindolo[2,1-*c*][1,4]benzoxazine ring system. Thus,



Scheme 16

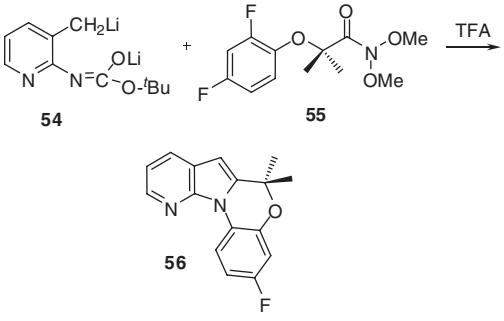
reaction of dilithiated reagent **54** with Weinreb amide derivative **55** followed by treatment with trifluoroacetic acid (TFA) gave the new tetracyclic ring system **56** (Scheme 19).

2–3 Fused systems

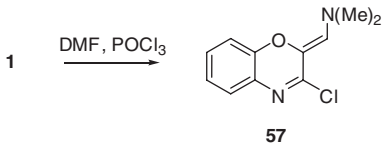
Pyrazolo[4,3-*b*] and pyrazolopyrimido[4,5-*b*][1,4] benzoxazines Reaction of **1** with phosphorous oxychloride in the presence of *N,N*-dimethylformamide under Vilsmeyer-Hack conditions [42] results in the formation of 2-dimethylamino-formylidene-3-chloro[1,4]benzoxazine **57** with reactive centers at positions 2 and 3. Bifunctional nucleophiles undergo reaction with **57** leading to the formation of fused 1,4-benzoxazines (Scheme 20).

Combs [43] has reported the synthesis of pyrazolobenzoxazine analog **58** (Scheme 21) of cardiotonic agent *Bemoradon* **2** (Figure 1).

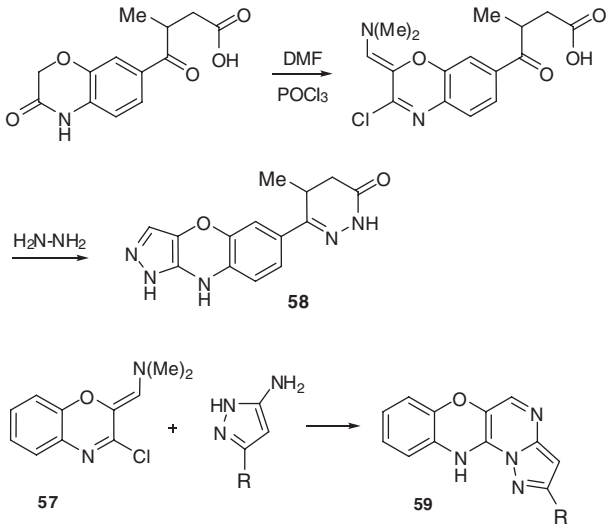
Jagath Reddy et al. [44] have reported the cyclocondensation of **57** with a variety of 5(3)-aminopyrazoles



Scheme 19



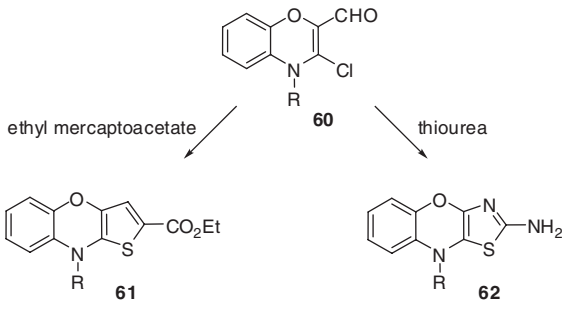
Scheme 20



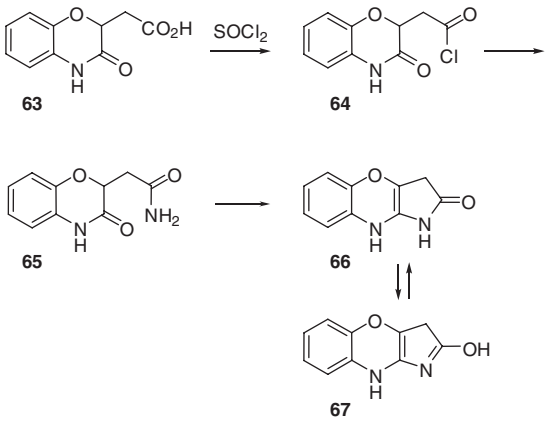
Scheme 21

to give a new tetracyclic ring system pyrazolo[5,′1′:2,3] pyrimido[4,5-*b*][1,4] benzoxazine **59**.

Thieno[3,2-*b*][1,4]benzoxazines and thiazolo[2,3-*b*][1,4]benzoxazines *N*-substituted benzoxazinones undergo reaction with phosphorous oxychloride in *N,N*-dimethylformamide to give 3-chloro 1,4-benzoxazin-2-yl-carboxaldehydes **60**. Compounds **60** undergo cyclocondensation with ethyl mercaptoacetate and thiourea to give thieno- and thiazolo-fused benzoxazines **61** and **62**, respectively, in approximately 58% yields [45] (Scheme 22). Reaction of **62** with phenacyl bromide results in the formation of benzoxazine fused imidazothiazole system [46].



Scheme 22

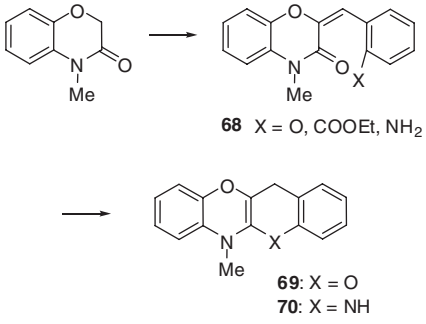


Scheme 23

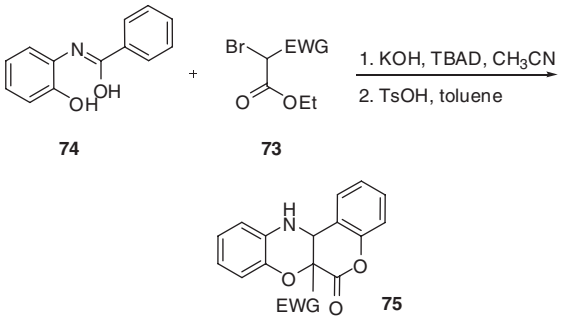
1*H*,9*H*–Pyrrolo[3,2-*b*][1,4]benzoxazines Okafor and Akpuaka [47] have reported the construction of this ring system starting from benzoxazin-2-yl-acetic acid **63**. The acid chloride **64** was obtained by reaction of **63** with thionyl chloride. The corresponding amide **65** then undergoes cyclization when treated with polyphosphoric acid at 120–130°C to give **67** in good yields (Scheme 23).

Benzopyranobenzoxazines and quinolinobenzoxazines Bartsch et al. [48] have reported the synthesis of these systems utilizing the reactivity of an active methylene group at position 2 of benzoxazinone ring system. *N*-Substituted benzoxazinones undergo electrophilic substitution with salicylaldehyde, methyl salicylate and methyl anthranilates giving the corresponding benzylidene derivatives **68**, which then undergo cyclocondensation to form fused benzoxazine systems **69** and **70** (Scheme 24).

Moustafa [49] has reported the synthesis of new thieno- and pyrano-fused 1,4-benzoxazines starting from 4-methylbenzoxazin-3-ones. A series of coumarino[3,4-*b*][1,4]benzoxazines **75** has been reported by Ruzhang et al. [50] via domino [5+1] annulation of 2-halo-1,3-dicarbonyl

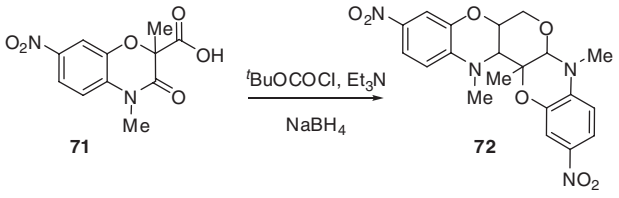


Scheme 24



74 73 75

Scheme 25



71 72

Scheme 26

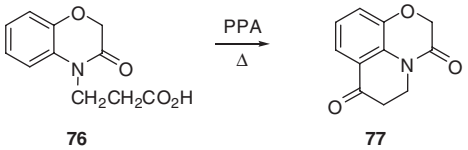
compounds **73** with imines **74** under mild conditions (Scheme 25).

Pyrano-bis-benzoxazine A novel pentacyclic compound **72** has been reported by Kikelji et al. [51]. Thus, the attempted sodium borohydride reduction of a mixed anhydride of 2,4-dimethyl-7-nitro-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-ylcarboxylic acid **71** resulted in the formation of a novel pyranobis-benzoxazine ring system **72** (Scheme 26).

4–5 Fused systems

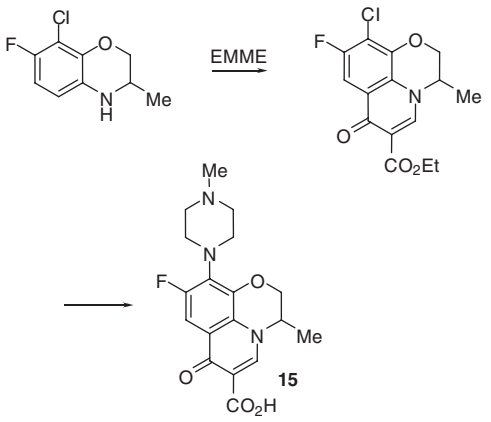
Oxazino[2,3,4-*ij*]quinoline Katekar [52] has reported the synthesis of oxajulolidene, which is 3,7-dioxo-2,3,6,7-tetrahydro-5*H*-[1,4]oxazino[2,3,4,*ij*]quinoline **77**, via polyphosphoric acid cyclization of benzoxazin-4-yl-propionic acid **76** (Scheme 27) in approximately 67% yield.

Ofloxacin **15** is a 4,5-fused 1,4-benzoxazine derivative discovered and developed as a broad-spectrum antibacterial agent that is currently in clinical use. The synthesis of **15** is depicted in Scheme 28.



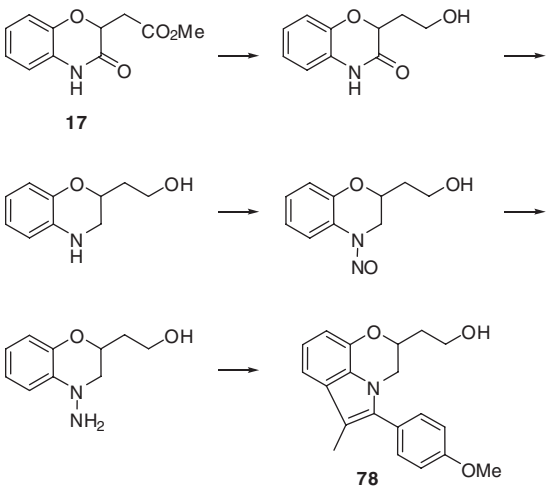
76 77

Scheme 27



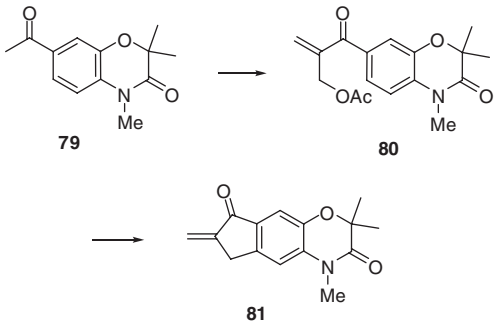
15

Scheme 28



17 78

Scheme 29

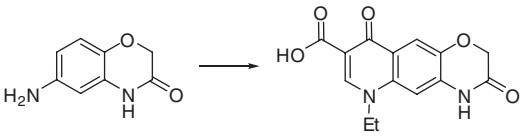


79 80 81

Scheme 30

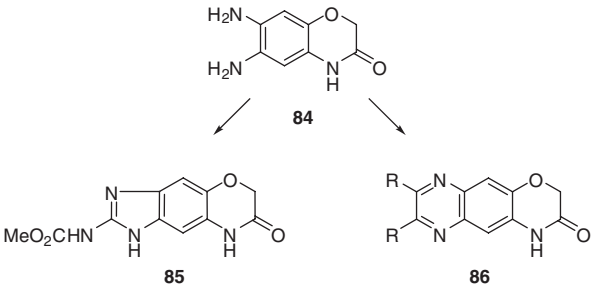
The asymmetric synthesis of levofloxacin, which is less toxic than the racemic drug ofloxacin, has also been developed [53].

Pyrrolo[1,2,3,-*de*][1,4]benzoxazines A series of pyrrolobenzoxazines **78** has been reported as anti-



82 83

Scheme 31



84 85 86

Scheme 32

inflammatory and antiallergic agents [54]. The synthesis of this ring system starts from the substrate **17** as shown in Scheme 29.

6–7 Benzo-fused systems

Cyclopenta[*g*]-2,3-dihydro[1,4]benzoxazines Depreux et al. [55] have synthesized these derivatives for evaluation as antiparasitic agents. 7-Acetyl–3-oxo–2,2,4-trimethyl[1,4]benzoxazine **79** has been transformed into product **80** in 55% yield. On heating with sulfuric acid at 40°C this compound undergoes cyclization to cyclopenta[*g*][1,4]benzoxazine **81** in approximately 50% yield (Scheme 30).

Pyridobenzoxazines Carboxylic acid **83** and a number of its analogs have been synthesized starting from 6-aminobenzoxazin-3-one **82** and evaluated as antibacterial agents [56] (Scheme 31).

Imidazo and pyrazinobenzoxazines The systems **85** and **86** have been prepared starting from 6,7-diaminobenzoxazin-3-one **84**. Product **85** and its derivatives have been evaluated for their anthelmintic activity [57, 58] (Scheme 32).

Conclusion

During the past decade, a number of substituted benzoxazinones have been synthesized and evaluated for their medicinal properties. The present article reviews some of the known fused 1,4-benzoxazine systems.

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