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Review Article

AN UPDATE ON THE SYNTHESIS OF BENZOXAZOLES

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ABSTRACT

Benzoxazoles being structurally similar to bases adenine and guanine interact with biomolecules present in living systems. These compounds possess antimicrobial, central nervous system activities, antihyperglycemic potentiating activity, analgesic, and anti-inflammatory activity. It can also be used as starting material for other bioactive molecules. Modifications in structure and the biological profiles of new generations of benzoxazoles were found to be more potent with enhanced biological activity. Considering all these, we have prepared this review and discussed the synthesis and biological activities of benzoxazoles.

Keywords: Benzoxazoles, Chemistry synthesis, Biological activities.

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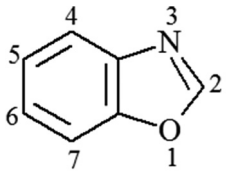
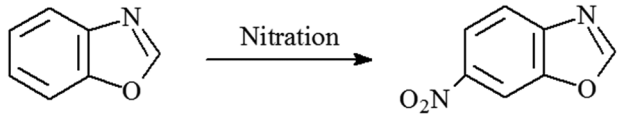
INTRODUCTION TO CHEMISTRY

Benzoxazole (1) (m.p. 27-30°C; b.p. 182°C), is a planar molecule with aromatic chemical properties [1].



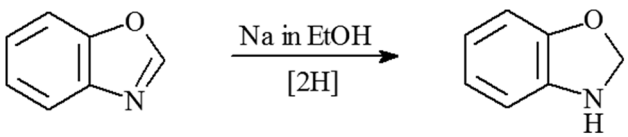
(1)

Benzoxazoles tend to react mainly at C-6 in electrophilic substitutions and to a lesser extent at C-5. Nitration of benzoxazole affords the 6-nitro products (2).

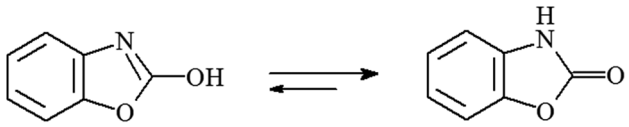


(2)

Benzoxazoles are stable toward a range of reductive conditions, but the reduction of the ring to oxazolidines can be effected with sodium in ethanol.

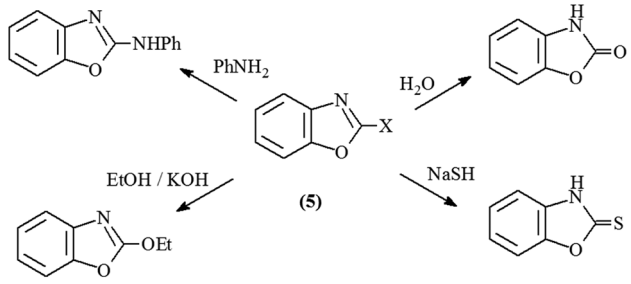


2-Arylbenzoxazoles undergo photo-fries rearrangements. 2-Hydroxy-benzoxazoles (3) exist predominately in the 2-keto form (4).



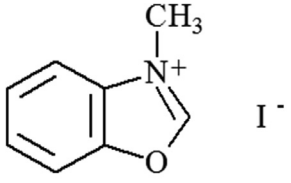
(3) **(4)**

Halogenobenzoxazoles (5) undergo a range of nucleophilic displacements which are summarized in the scheme.



(5)

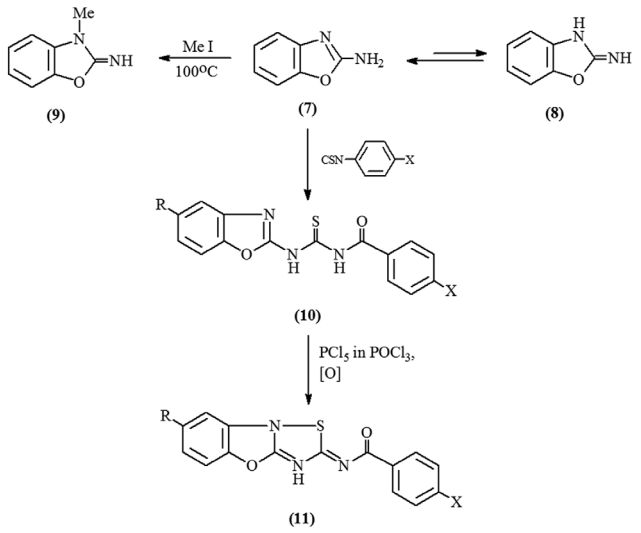
Benzoxazole quarternizes to give the methiodide (6), but under more vigorous conditions may suffer ring cleavage.



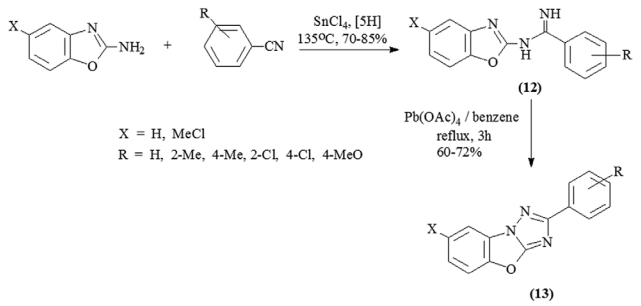
(6)

The 2-amino benzoxazole (7) exists as the amine tautomers (8). The aminobenzoxazole (7) protonate on the ring nitrogen and reacts with methyl iodide at 100°C to give the N^3-alkylated product (9). The reaction

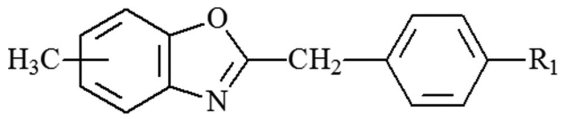
of 2-aminobenzoxazole with aroyl isothiocyanates gives N-aroyl-N'-(benzoxazolo-2yl) thioureas (10) [2]. The product (11) obtained on reaction with PCl_5 in $POCl_3$ and with oxidizing agents have been identified as 3-aroyliminobenzoxazolo [3,2-b] [1,2,4]-thiazolidines.



The reaction o-aminobenzoxazoles with benzonitriles gives N-(benzoxazol-2-yl) benzamidines in high yields. Lead (12) acetate affords 2-aryl[1,2,4]triazolo[5,1-b]benzoxazoles (13) in good yields when cyclodehydrogenation takes place [3].

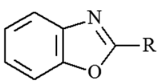


A new series of 5 (or 6) methyl-2-substituted benzoxazoles (14) were described by Oren *et al.* [4]. Some of these compounds showed significant activity against *Pseudomonas aeruginosa* having MIC 2.5 mg/ml, providing higher potencies than the reference drugs.

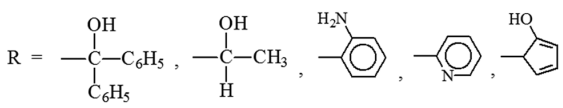


(14)

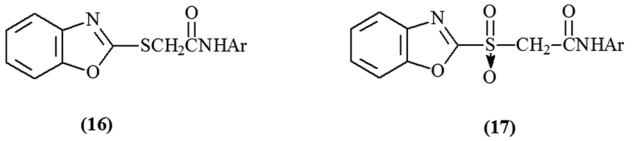
The *in vitro* antibacterial and antifungal activities of six benzimidazole and benzoxazole derivatives (15) were tested on clinical isolates where two of the benzoxazoles were found to be active [5].



(15)

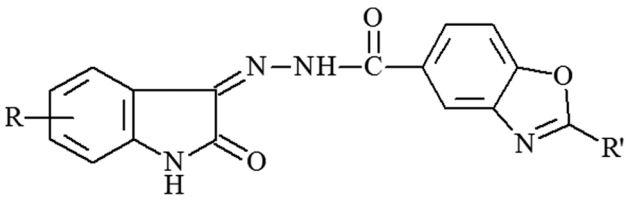


Some 2-(N-Aryl-carboxamidomethylthio)benzoxazoles (16) and corresponding sulfones (17) were prepared, and their antimicrobial activity was assayed against some bacteria and fungi and was found to exhibit 20-70% inhibition at a concentration of 0.1 mg/ml [6].



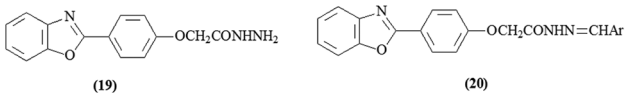
(16) **(17)**

Sarangapani and Reddy [7] synthesized some new isatin-[N^2-(2-alkylbenzoxazol-5-carbonyl)]hydrazones (18) from our laboratory and found them to exhibit a moderate antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus, Escherichia coli* and *Proteus vulgaris* and mild antifungal activity against *Aspergillus niger,* and *Cola verticillata*.



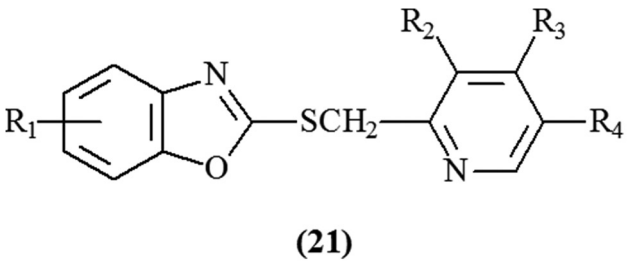
(18)

Bahadur and Pandey [8] reported the synthesis and antiviral activity of *p*-(2-benzoxazolyl) phenoxy acetic acid hydrazides (19) and corresponding arylidene hydrazides (20). These compounds were found to exhibit a significant antiviral activity *in vitro* but not *in vivo*.



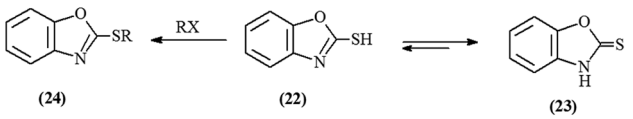
(19) **(20)**

Katsura *et al.* [9] reported the synthesis and antiulcer activity of compounds (21).



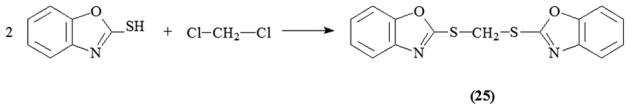
(21)

2-Mercaptobenzoxazoles (22) exist predominantly in the thione form (23). Alkylation can occur at sulfur to yield compound (24).



(24) **(22)** **(23)**

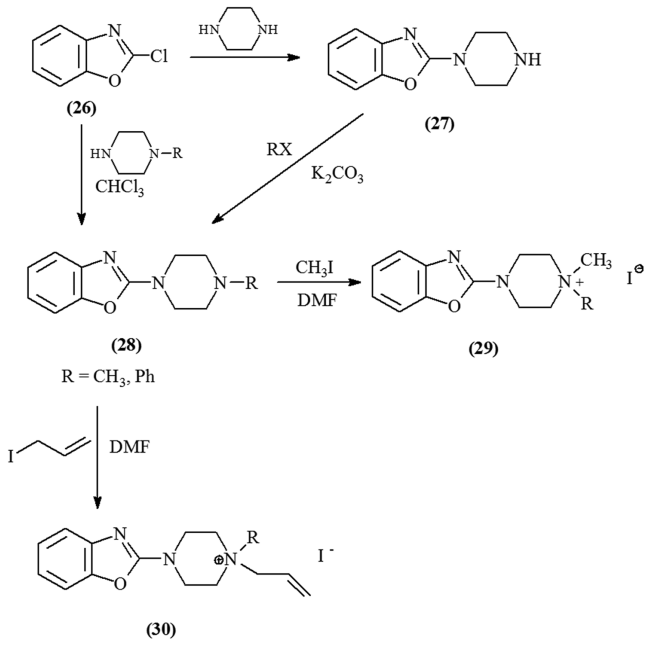
Reaction of Z-X-Z (ex; X = CH_2, Z = Cl), with 2-mercaptobenzoxazole.



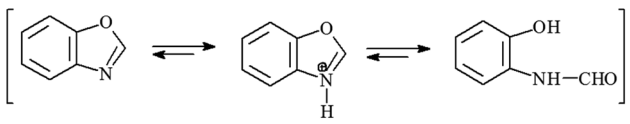
(25)

(14) Affords the corresponding thioether linked bis heterocycles [10] (25).

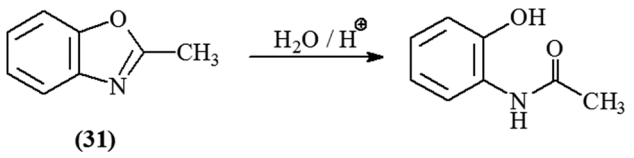
Reactions of piperazines with 2-chlorobenzoxazole (26) result in the formation of compounds (27) and (28) [11]. Alkylation (28) with methyl iodide results in the quaternary salt (29).



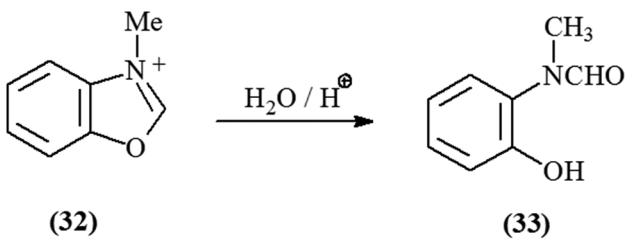
Similarly, compound (28) on allylation with allyl iodide in dimethyl form amide results in the corresponding quaternary salt (30). Benzoxazoles react with two moles of diphenyl keten in a [2+2+2] cyclo addition involving the C=N double bond, affording an oxazine-fused benzoxazole. Benzoxazoles are resistant to alkaline hydrolysis but are readily cleaved by acids, probably because of nucleophilic attack.



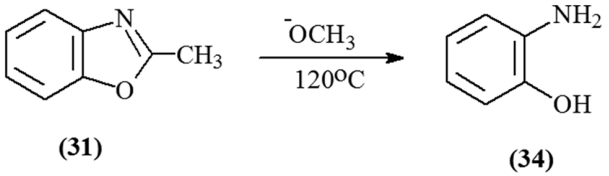
Benzoxazole hydrolysis is relatively easy, 2-methyl benzoxazole giving o-acetamido phenol in hot water, although the reaction is more rapid in dilute acid.



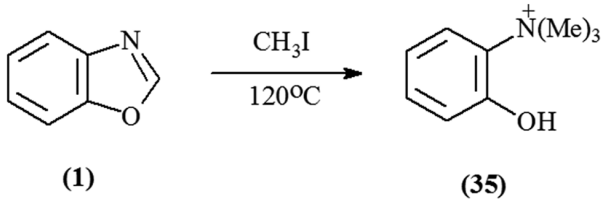
Quaternary salts are hydrolyzed more readily as shown by the hydrolysis of N-methyl benzoxazole (32).



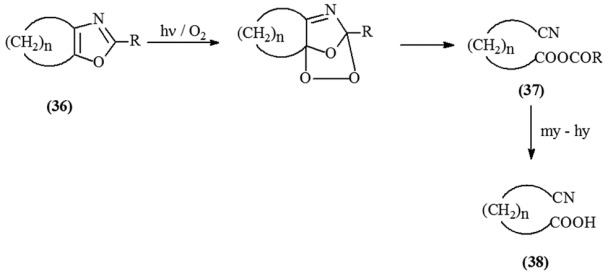
Although 2-methylbenzoxazole (31) can be cleaved by methoxide at 120°C to give o-amino phenol (34).



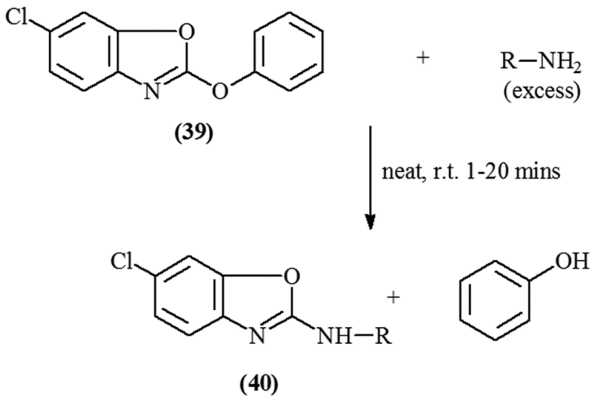
Quaternization of benzoxazole (35) with methyl iodide at 120°C leads to 2-hydroxytrimethyl aniline.



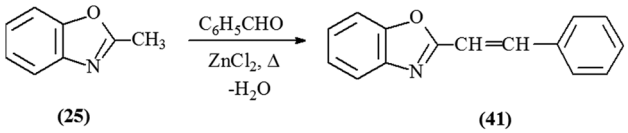
Benzoxazole affords an excellent synthetic route to w-nitrilo acids (38).



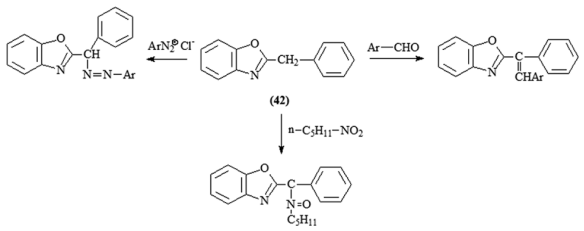
6-Chloro-2-phenoxybenzoxazole (39) reacts smoothly with a series of aliphatic primary amines to give 6-chloro-2-(substituted amino) benzoxazoles (40), at room temperature, in the presence of an excess of amines [12]. Thus, 2-phenoxy group of the benzoxazole system nucleophilically move susceptible than its 6-chloro group.



2-Methylbenzoxazole (31) reacts with benzaldehyde in the presence of zinc chloride to give the 2-benzylidene derivative (41) indicating the reactivity of the methyl group linked to azomethine system.

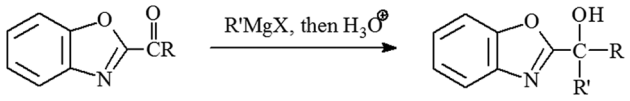


2-Benzylbenzoxazole (42) is reactive enough to couple with diazonium salts and reacts at the 2-methylene group with aldehydes, nitroso compounds, and amyl nitrite.



(42)

Benzoxazoles with acyl substituents at C-2 may undergo Grignard reactions.

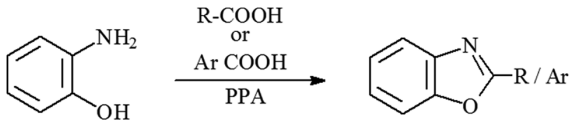


(43)

Benzoxazoles react with two moles of diphenyl keten in a [2+2+2] cyclo addition involving the C=N double bond, affording an oxazine-fused benzoxazole.

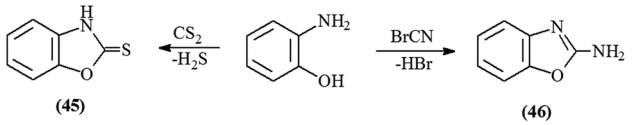
Synthesis

Benzoxazoles (44) have been obtained by heating o-aminophenol and carboxylic acids in the presence of PPA [13].



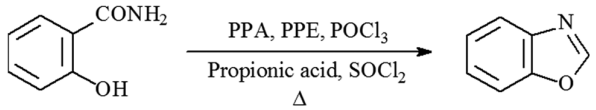
(44)

The condensation of carbon disulfide or cyanogen bromide with o-aminophenol leads to benzoxazole thione (45) or 2-aminobenzoxazole (46), respectively.



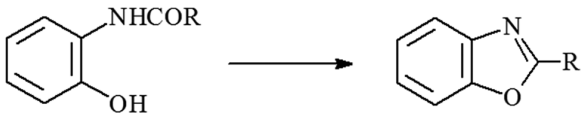
(45) (46)

Thermal cyclization with acid catalysts is commonly employed to synthesize benzoxazoles (1).



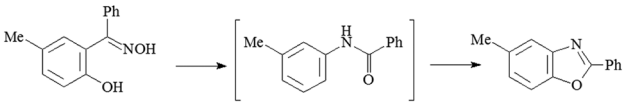
(1)

Thermal dehydration [14] of o-(acylamino) phenols is most widely used for the preparation of these compounds (47).



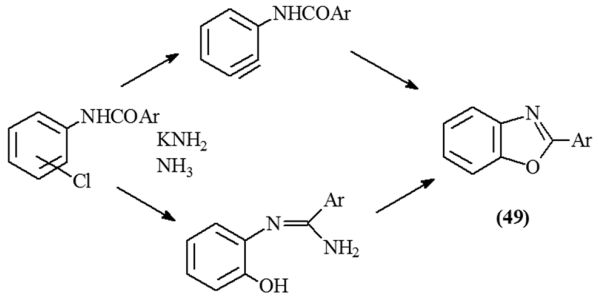
(47)

Beckmann rearrangement of oximes of o-hydroxybenzophenones leads to the formation of benzoxazoles (48).



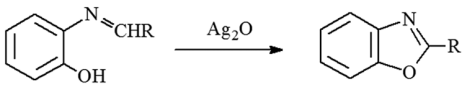
(48)

Benzoxazoles (49) can also be prepared by the action of potassium amide in liquid ammonia.

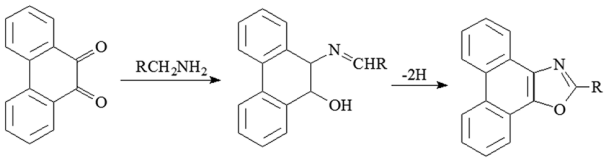


(49)

Benzoxazoles (47) are obtained by the oxidative ring closure of some Schiff's bases. E.g., phenanthro-oxazoles (50) formation.

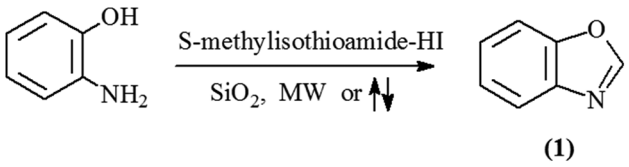


(47)



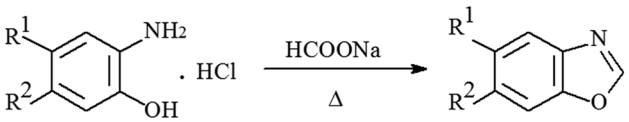
(50)

The synthesis of benzoxazoles (1) by the cyclocondensation reaction of o-aminophenol with S-methyl isothioamide hydroiodides on silica gel under microwave irradiation and also in a solvent under reflux [15].



(1)

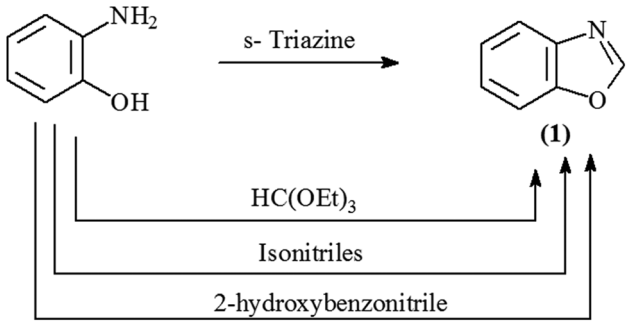
Different substituted benzoxazoles (51) are synthesized [16] by distillation of aminocresol hydrochlorides with sodium formate.



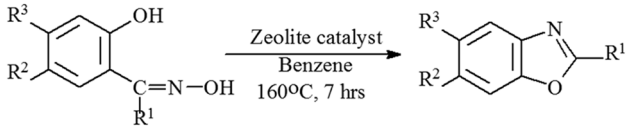
$R^1 = CH_3, \; R^2 = H$ (51)

$R^1 = H, \; R^2 = CH_3$

An advanced method involves cyclization of a 2-aminophenol with s-triazines, triethyl orthoformate or isonitriles and 2-hydroxybenzonitrile, photochemically to yield benzoxazole (1) [17-22].



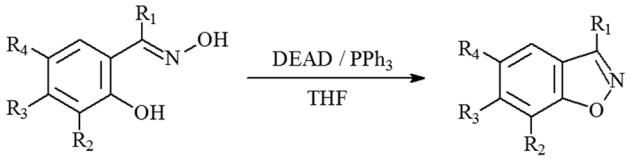
Bhawal *et al*. [23] reported the mild and simple method (52) via Beckmann rearrangement of o-acyl phenol oximes.



(52)

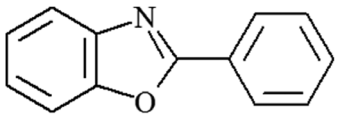
R^1 = Me or Et, R^2 = Me, H, Cl, R^3 = H, OH

1,2-benzoxazoles (53) are also prepared from salicylaldoximes and ortho-hydroxy phenyl ketoximes via intramolecular Mitsunobu reaction [24].



(53)

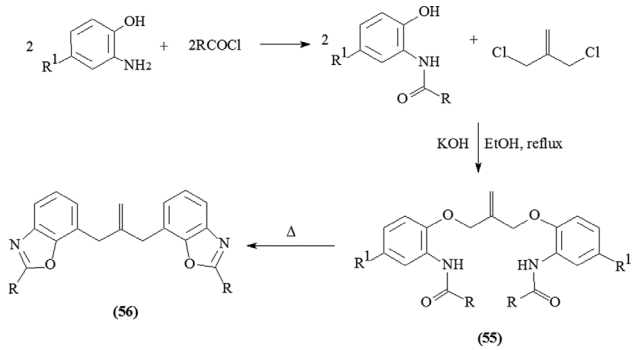
However, the reaction with o-hydroxyphenyl ketoxime led to a 7/3 mixture of 1,2-benzoxazole and 1,3-benzoxazole (54).



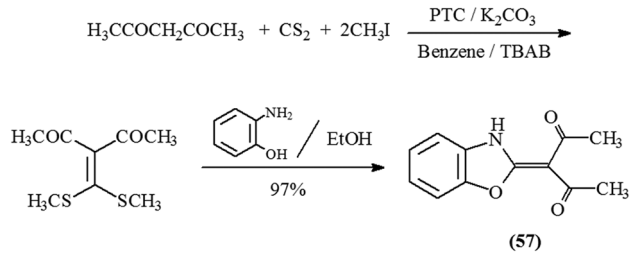
(54)

The one-pot thermal reaction of 1,3-bis(o-acylaminophenyloxy)-2-methylene propane derivatives gave the bis(benzoxazole) derivatives (55) in good yields [25].

2-Amino-4-methyl phenols, when treated with the corresponding acid chlorides, gave bis(o-acylaminophenyloxy)-2-methylene propane (55). The thermal bulk reaction of (55) gives the corresponding bis(benzoxazoles) [26] (56).

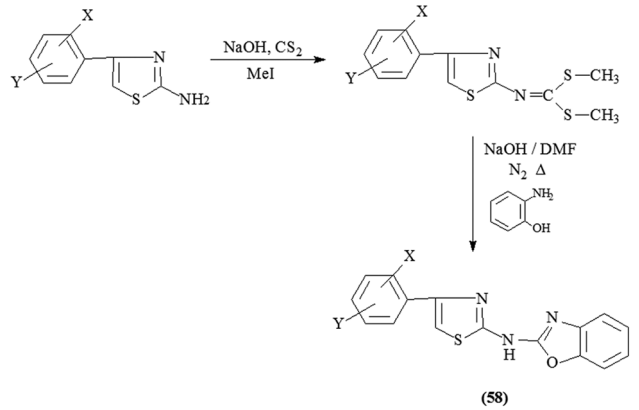


Synthesis of some new spiro-(pyran-4,2'-benzoxazole) derivatives are reported by El-Saghier and Khodairy [27] Ketene S,S-acetal reacts with 2-amino phenol to afford 2-(1-acetyl-2-oxopropylidene) benzoxazole (57), which was allowed to react with a variety of active methylenes having an α-cyano of α-keto group to give spiro(pyran-4,2'-benzoxazole)derivatives.



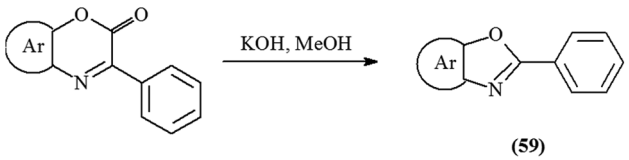
(57)

Synthesis of 2-(4-aryl-2-thiazolylamino)benzoxazoles is reported by Khan and Rastogi [28]. The reaction of 2-amino-4-arylthiazoles with CS_2 and MeI in DMF in the presence of strong sodium hydroxide solution gives the corresponding dimethyl N-(4-aryl-2-thiazolyl) dithiocarbonimidodithioates. These compounds on reaction with 2-aminophenol in refluxing DMF, in the presence of one equivalent sodium hydroxide affords the 2-(4-aryl-2-thiazolylamino)-benzoxazoles (58).



(58)

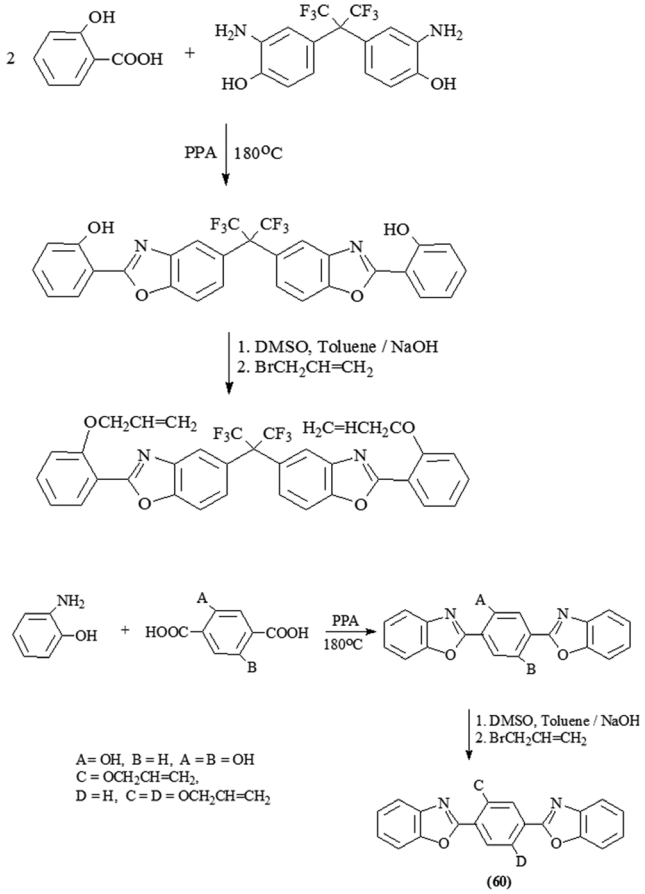
New synthesis of naphtho- and benzoxazoles (59) was reported by Saitz *et al.* [29]. The method consists of a decomposition of naphtho and benzoxazinones with KOH.



(59)

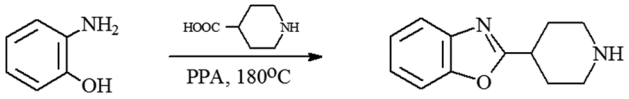
Ar = 1,2-benzo-, 1,2-naphtho-, 2,1-naphtho-, 2,3-naphtho-

Synthesis of aromatic benzoxazoles containing allyl ether groups (60) reported by Dang *et al.* [30].



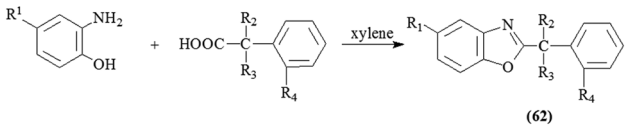
(60)

Piperidine-4-carboxylic acid and o-aminophenol were heated with polyphosphoric acid to afford [31] (61).



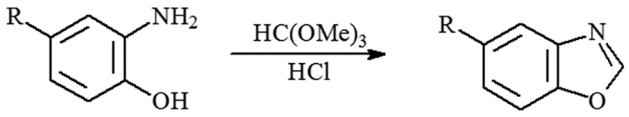
(61)

The compounds (62) prepared by direct condensation of suitable aminophenol with substituted phenyl acetic acid [32].



(62)

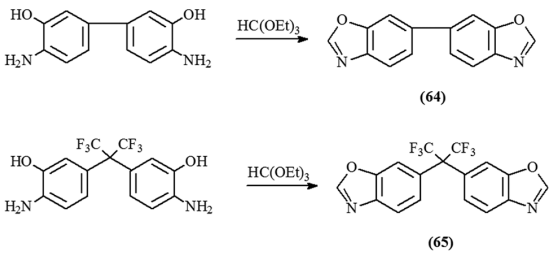
A simple and convenient synthesis of 5-substituted benzoxazoles has been reported by Kunz *et al.* [33]. 5-Substituted benzoxazoles (63) are prepared from 4-substituted 2-aminophenols by the treatment with trimethyl orthoformate and concentrated aqueous hydrochloric acid.



(63)

R = Acetamido, benzoyl, bromo, chloro, cyano, iodo, methoxy, methyl, nitro, propionyl.

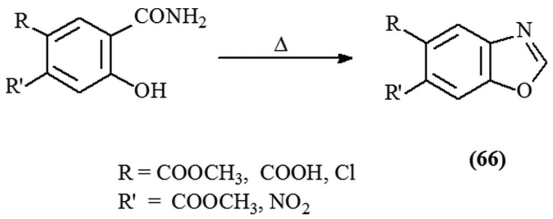
New bis(benzoxazoles) (64, 65) have been synthesized in excellent yield from the corresponding bis(o-aminophenol) by refluxing with triethyl orthoformate [34].



(64)

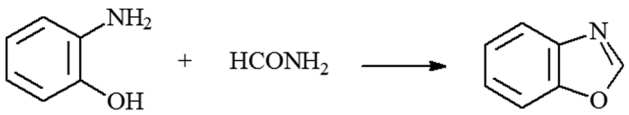
(65)

The oldest method in the synthesis of benzoxazoles [35] (66) is heating or distilling 2-formamidophenols at elevated temperatures.



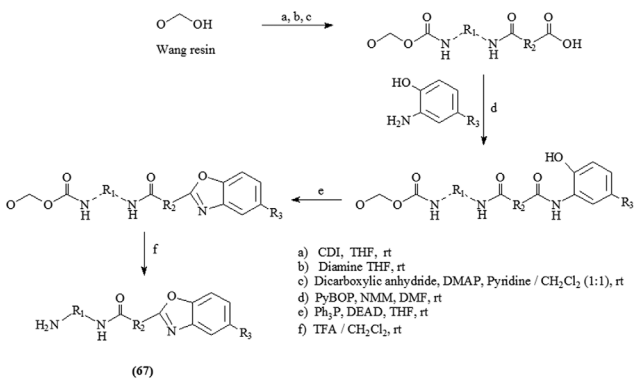
(66)

Benzoxazole (1) is also obtained from the dry distillation of formamide and 2-aminophenol [36].



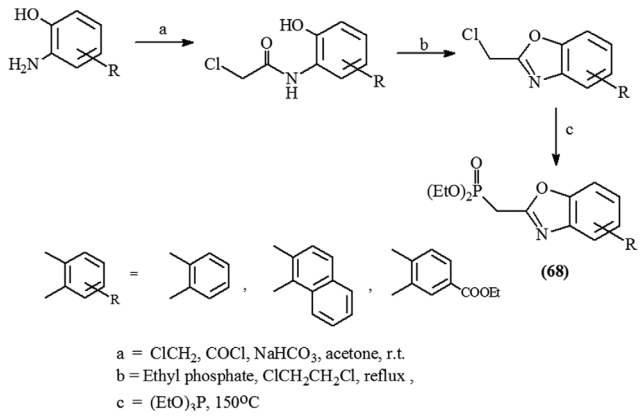
(1)

Solid phase synthesis of benzoxazoles was reported by Wang and Hauske [37]. 2-Aminophenol attached to a solid support can be converted to the corresponding benzoxazole (67) by the treatment with triphenylphosphine and diethyl azodicarboxylate in THF at room temperature, in high yield and purity.

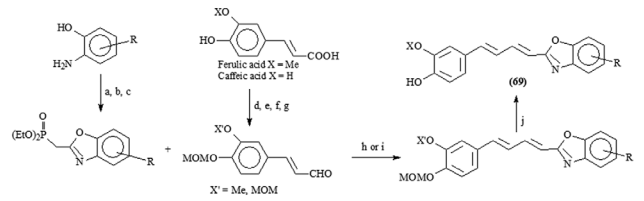


(67)

Phosphoryl methyl benzoxazoles (68) were prepared in three steps from o-aminophenols by: (i) Chloroacetylation with chloroacetyl chloride in the presence of $NaHCO_3$, (ii) oxazole formation by treatment with ethyl polyphosphate, and (iii) Arbuzov reaction with triethyl phosphate [38].

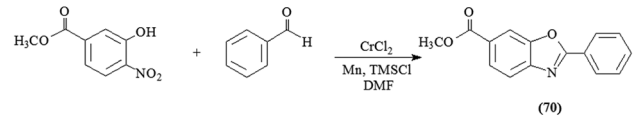


A novel series of 2-Aryldienylbenzoxazoles were prepared by Kosaka *et al*. [39]. The compounds (69) were prepared from o-aminophenols which were chloroacetylated, cyclized by ethyl polyphosphate and subjected to the Arbuzov reaction to give phosphonates. The condensation of an aldehyde with phosphates by Hormer-Wadsworth-Emmons reaction and compounds were deprotected under acid conditions.



a = $ClCH_2COCl$, $NaHCO_3$, acetone, r.t.f = NIBAH, THF, −78°C.
b = Ethyl polyphosphate, $ClCH_2CH_2Cl$, reflux g = MnO_2, CH_2Cl_2, r.t.
c = $(EtO)_3P$, 150°C, h = NaH, 4A sieves, THF −10°C.
d = EtOH, H_2SO_4, reflux, i = NaOH, nBu_4NBr, H_2O, CH_2Cl_2, r.t.
e = MOMCl, ipr_2 NET, CH_2Cl_2, r.t.j = aq, 4M HCl, THF, r.t.

A one-pot synthesis of benzoxazoles by chromium-manganese redox coupled reactions reported by Hari *et al*. [40]. The reaction in which a chromium-manganese redox couple is employed both to catalytically reduce an o-hydroxy nitroarene and to oxidatively cyclize a subsequently formed imine (70).

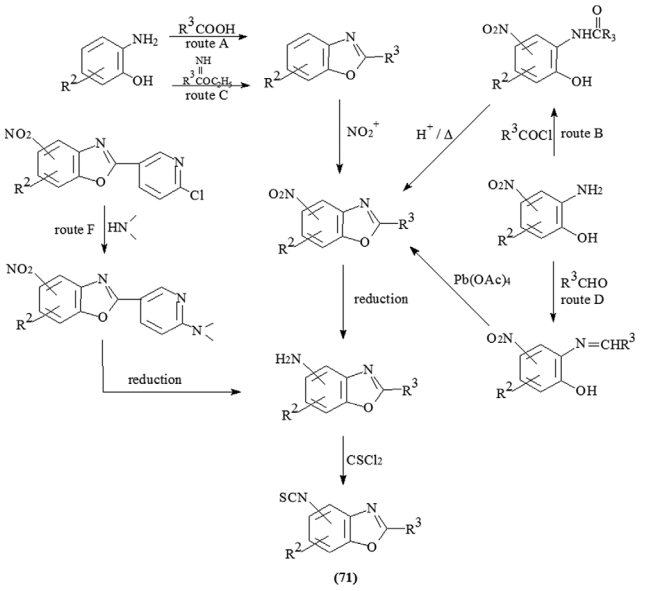


2-Hetero aromatic substituted isothiocyanatobenzoxazoles were synthesized by Haugwitz *et al*. [41].

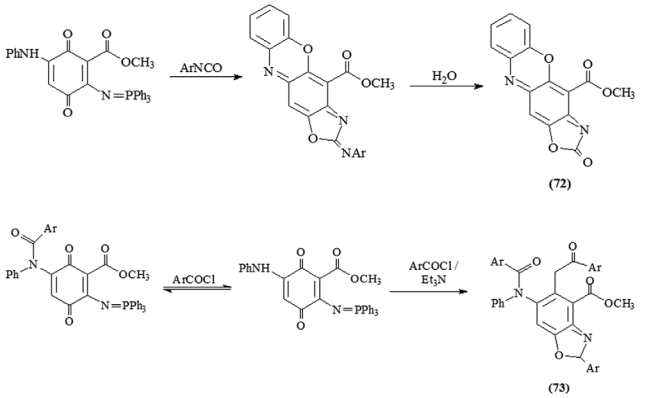
The intermediates of 5 and 6-nitrobenzoxazoles were prepared by the following routes:

a. PPA-catalyzed ring closure of o-aminophenols with the appropriate carboxylic acids followed by nitration of benzoxazoles
b. Acylation of nitroaminophenols with carboxylic acid chlorides and subsequent thermally induced cyclodehydration of the amides
c. Oxidation cyclization of Schiff bases using lead (IV) acetate and
d. Reaction of imino ethers derived from 2-cyanopyrazine or cyano--nitropyridine with o-aminophenols and nitration of corresponding benzoxazoles.

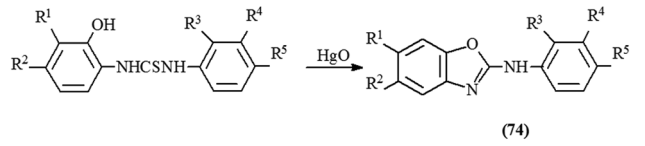
Followed by thiocarbonylation of resulting amines using thiophosgene, completed the synthesis of 5 and/or 6-isothiocyanatobenzoxazoles (71).



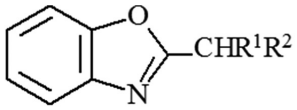
Salome Rodreguez Morgade Gouloumis *et al*. [42] reported the synthesis of benzoxazole derivatives. The aza-Wittig reaction of the triphenyl phosphoranylideneamino-1,4-benzoquinone with aryl isocyanates and aryl chlorides allows the preparation of benzoxazole derivatives (72). The same reaction using aminophosphorano-quinone provides substituted benzoxazoles (73).



Qian *et al*. [43] reported, yellow HgO as an efficient cyclodesulfurizing agent in the synthesis of 2-(substituted amino)benzoxazoles from N-(2-hydroxy phenyl)-N'-phenylthioureas. 2-(Substituted amino) benzoxazoles (74) (R_1, R_2 = H, F; R_3, R_4 = H, Cl, F; R_5 = H, F, OH) were prepared in good yields by cyclodesulfurization of N-(2-hydroxyphenyl)-N'-phenyl thioureas with yellow HgO.



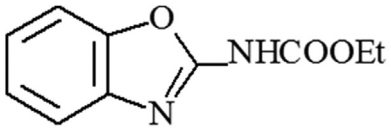
Facile synthesis of 2-substituted benzoxazoles via ketenes reported by Olagbemiro *et al*. [44]. The generation of diphenyl-, phenyl-, phenoxy-, and chloroketenes by the treatment of corresponding acid chlorides with triethylamine in the presence of 2-aminophenol resulted in good yields of 2-substituted benzoxazoles (75).



(75)

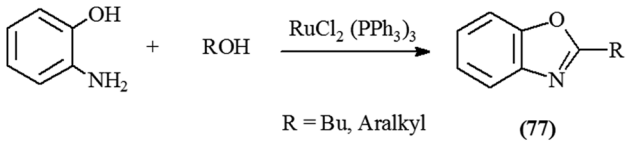
R^1, R^2 = Ph, Ph; Ph, H; PhO, H; Cl, H

Omar *et al.* [45] reported the synthesis of several 2-ethoxycarbonyl- benzoxazoles (76). They are synthesized in high yield by cyclodesulfurization of the corresponding thioureas and thiosemicarbazide derivatives with dicyclohexylcarbodiimide.



(76)

Ruthenium complex-catalyzed facile synthesis of 2-substituted benzoxazoles (77) reported by Kondo *et al.* [46] $RuCl_2$ $(PPh_3)_3$ shows high catalytic activity for the reaction of o-aminophenol.



With ROH (R = Bu, aralkyl) to give the corresponding benzoxazoles. Benzoxazoles being structurally similar to bases adenine and guanine possess significant biological activities [47-49] and structural modifications can result in molecules with enhanced biological activity.

CONCLUSIONS

Considering the biological and pharmacological importance of these molecules, the synthetic strategies of various benzoxazoles were discussed and reviewed in this article.

REFERENCES

1. Barton D, Ollis WD. Comprehensive Organic Chemistry. Vol. 1. England: Pergamon Press; 1979. p. 641.
2. Chaudhary M, Pareek D, Pareek PK, Kant R, Ojha KG, Pareek A. Synthesis of some new biologically active benzothiazole derivatives containing benzimidazole and imidazoline moieties. Chem Inf 2011;42(23):131-6.
3. Sambaiah T, Reddy KK. Synthesis of 2-Aryl [1, 2, 4] triazolo [5, 1-b] benzoxazoles by oxidative cyclization of N-(benzoxazol-2-yl) benzamidines. Synthesis 1990;1990(5):422-4.
4. Oren I, Temiz O, Yalçin I, Sener E, Akin A, Uçartürk N. Synthesis and microbiological activity of 5(or 6)-methyl-2-substituted benzoxazole and benzimidazole derivatives. Arzneimittelforschung 1997;47(12):1393-7.
5. Elnima EI, Zubair MU, Al-Badr AA. Antibacterial and antifungal activities of benzimidazole and benzoxazole derivatives. Antimicrob Agents Chemother 1981;19(1):29-32.
6. El-Sherief HA, Mahmoud AM, Abdel-Rahman AE, El-Naggar GM. Synthesis of some new benzoxazole, benzothiazole and benzimidazole derivatives with biological activity. Chem Inform 1983;14(31):28-37.
7. Sarangapani M, Reddy VM. Phramacological evaluation of 1-(N, N-disubstituted aminomethyl)-3-Imino-(2-phenyl-3, 4-dihydro-4-oxo-quinazolin-3-Yl) indolin-2-ones. Indian J Pharm Sci 1996;58(4):147.
8. Bahadur S, Pandey K. Synthesis of ethyl P-(2-benzoxazolyl) phenoxyacetate and corresponding hydrazides. Chem Inform 1982;13(3):46-54.
9. Katsura Y, Inoue Y, Tomoi M, Takasugi H. Studies on antiulcer drugs. V. Synthesis and antiulcer activity of aralkylbenzazoles. Chem Pharm Bull (Tokyo) 1992;40(8):2062-74.
10. Matthews CJ, Leese TA, Clegg W, Elsegood MR, Horsburgh L, Lockhart JC. A route to bis (benzimidazole) ligands with built-in asymmetry: Potential models of protein binding sites having histidines of different basicity. Inorg Chem 1996;35(26):7563-71.
11. Yamada M, Sato Y, Kobayashi K, Konno F, Soneda T, Watanabe T. A new 5-HT3 receptor ligand. II. Structure-activity analysis of 5-HT3 receptor agonist action in the gut. Chem Pharm Bull 1998;46(3):445-51.
12. Kövér J, Tímár T, Tompa J. Novel and efficient synthesis of 6-chloro-2-(substituted amino) benzoxazoles. Synthesis 1994;1994(11):1124-6.
13. Hein DW, Alheim RJ, Leavitt JJ. The use of polyphosphoric acid in the synthesis of 2-aryl-and 2-alkyl-substituted benzimidazoles, benzoxazoles and benzothiazoles1. J Am Chem Soc 1957;79(2):427-9.
14. Katritzky AR. Highlights from 50 years of heterocyclic chemistry. J Heterocycl Chem 1994;31(3):569-602.
15. Rostamizadeh S, Housaini SG. Microwave-assisted preparation of 2-substituted benzothiazoles. Phosphorus Sulfur Silicon Relat Elem 2005;180(5-6):1321-6.
16. Larina L, Lopyrev V. Synthesis of nitrobenzazoles. In: Nitroazoles: Synthesis, Structure and Applications. New York: Springer; 2009. p. 81-156.
17. Grundmann C, Kreutzberger A. Triazines. XIII. The ring cleavage of s-triazine by primary amines. A new method for the synthesis of heterocycles1, 2. J Am Chem Soc 1955;77(24):6559-62.
18. Jenkins G, Knevel A, Davis C. Notes. A new synthesis of the benzothiazole and benzoxazole rings. J Org Chem 1961;26(1):274.
19. Hojati SF, Maleki B, Beykzadeh Z. 1, 3-dibromo-5, 5-dimethylhydantoin as an efficient homogeneous catalyst for synthesis of benzoxazoles, benzimidazoles, and oxazolo [4, 5-b] pyridines. Monat Chem Chem Mon 2011;142(1):87-91.
20. Ito Y, Inubushi Y, Zenbayashi M, Tomita S, Saegusa T. Synthetic reactions by complex catalysts. XXXI. Novel and versatile method of heterocycle synthesis. J Am Chem Soc 1973;95(13):4447-8.
21. Ito Y, Ito I, Hirao T, Saegusa T. Synthetic reactions by complex catalysts XXXV. A facile synthetic method of cyclic imino ethers and imino thioethers. Synth Commun 1974;4(2):97-103.
22. Ferris JP, Antonucci FR, Trimmer RW. Mechanism of the photoisomerization of isoxazoles and 2-cyanophenol to oxazoles. J Am Chem Soc 1973;95(3):919-20.
23. Bhawal BM, Mayabhate SP, Likhite AP, Deshmukh AR. Use of zeolite catalysts for efficient synthesis of benzoxazoles via Beckmann rearrangement. Synth Commun 1995;25(21):3315-21.
24. Poissonnet G. A simple and convenient synthesis of 1, 2-benzoxazoles via intramolecular mitsunobu reaction from salicylaldoximes and orthohydroxyarylketoximes. Synth Commun 1997;27(22):3839-46.
25. Koyama E, Yang G, Hiratani K. A novel synthesis of bis (benzoxazole) derivatives via tandem claisen rearrangement. Tetrahedron Lett 2000;41(42):8111-6.
26. Novel Heteroaryl Substituted Benzoxazoles No. WO/2007/149030.
27. El-Saghier AM, Khodairy A. New synthetic approaches to condensed and spiro coumarins: Coumarin-3-thiocarboxamide as building block for the synthesis of condensed and spiro coumarins. Phosphorus Sulfur Silicon Relat Elem 2000;160(1):105-19.
28. Khan RH, Rastogi RC. Synthesis and biological activity of 2-(4-aryl-2-thiazolylamino) benzothiazoles/benzoxazoles/benzimidazoles/ imidazolidines. Chem Inform 1989;20(43):529-31.
29. Saitz C, Rodríguez H, Márquez A, Canete A, Jullian C, Zanocco A. New synthesis of naphtho-and benzoxazoles: Decomposition of naphtho-and benzoxazinones with KOH. Synth Commun 2001;31(1):135-40.
30. Dang TD, Hudson LS, Feld W. Synthesis and characterization of aromatic benzoxazoles containing allylether pendent groups. Polym Prepr (USA) 2000;41(1):103-4.
31. Sato Y, Yamada M, Yoshida S, Soneda T, Ishikawa M, Nizato T, *et al.* Benzoxazole derivatives as novel 5-HT3 receptor partial agonists in the gut. J Med Chem 1998;41(16):3015-21.
32. Skinner WA, Gualtiere F, Brody G, Fieldsteel AH. Antiviral agents. 1. Benzothiazole and benzoxazole analogs of 2-(alpha.-hydroxybenzyl) benzimidazole. J Med Chem 1971;14(6):546-9.
33. Kunz KR, Taylor EW, Hutton HM, Blackburn BJ. A simple and convenient synthesis of 5-substituted benzoxazoles. Org Prep Proced Int 1990;22(5):613-8.
34. Konda S. Development of Biologically Active Benz Oxazole Derivatives. US: Lulu; 2015.

35. Jois YH, Gibson HW. Difunctional heterocycles: A convenient one pot synthesis of novel bis (benzoxazoles) from bis (o-aminophenols). J Heterocycl Chem 1992;29(5):1365-8.
36. Niementowski S. New methods for the preparation of the anhydro compounds. Ber Deutsch Chem Ges 1897;30(3):3062-71.
37. Wang F, Hauske JR. Solid-phase synthesis of benzoxazoles via mitsunobu reaction. Tetrahedron Lett 1997;38(37):6529-32.
38. Watanabe KA. The chemistry of C-nucleosides. In: Chemistry of Nucleosides and Nucleotides. US: Springer; 1994. p. 421-535.
39. Kosaka T, Ochiai K, Ohba S, Wakabayashi T, Murota SI. A novel series of highly potent 5-lipoxygenase inhibitors; 2-aryldienylbenzoxazoles. Bioorg Med Chem Lett 1995;5(1):35-8.
40. Hari A, Karan C, Rodrigues WC, Miller BL. Extending the scope of chromium-manganese redox-coupled reactions: A one-pot synthesis of benzoxazoles. J Org Chem 2001;66(3):991-6.
41. Haugwitz RD, Angel RG, Jacobs GA, Maurer BV, Narayanan VL, Cruthers LR, *et al*. Antiparasitic agents. 5. Synthesis and anthelmintic activities of novel 2-heteroaromatic-substituted isothiocyanatobenzoxazoles and-benzothiazoles. J Med Chem 1982;25(8):969-74.
42. Gouloumis A, Liu SG, Sastre A, Vazquez P, Echegoyen L, Torres T. Synthesis and electrochemical properties of phthalocyanine-fullerene hybrids. Chemistry 2000;6(19):3600-7.
43. Qian X, Li Z, Song G, Li Z. Yellow HgO as an efficient cyclodesulfurising agent in the synthesis of 2-substituted aminobenzoxazoles from N-(2-hydroxyphenyl)-N'-phenylthioureas. J Cheml Res 2001;4:138-9.
44. Olagbemiro TO, Agho MO, Abayeh OJ, Amupitan JO. Facile synthesis of 2-substituted benzoxazoles via ketenes. Rec Trav Chim Pays Bas 1996;115(6):337-8.
45. Omar AM, Mohsen ME, Ashour FA, Bourdais J. The cyelodesulfurization of thio-compounds. Part XVII. Synthesis of some novel 2-substituted amino-3, 4-dihydro-5H-1, 3, 4-benzotriazepin-5-ones by cyelodesulfurization of thiosemicarbazides with dicyclohexylearbodiimide (DCCD). J Heterocycl Chem 1979;16(7):1435-8.
46. Kondo T, Yang S, Huh KT, Kobayashi M, Kotachi S, Watanabe Y. Ruthenium complex-catalyzed facile synthesis of 2-substituted benzo-azoles. Chem Lett 1991;20(7):1275-8.
47. Katritzky AR, Rees CW. Comprehensive Heterocyclic Chemistry. Oxford: Pergamon Press; 1984.
48. Kaur A, Sharad W, Pathak DP. Benzoxazole: The molecule of diverse pharmacological importance. Int J Pharm Pharm Sci 2014;7(1):16-23.
49. Paralapalli AD, Kishore A, Cidda M, Manda S. Antiinflammatory and antioxidant activities of 2-amino-N-(substituted alkyl) benzoxazole-5-carboxamide derivatives. Int J Pharm Pharm Sci 2014;6(7):311-4.