A Review on Medicinal Importance and Synthesis of benzothiazolo-[2, 3b]-quinazolin-1-one Derivatives via Multi-Component Reactions

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Abstract: Synthesis of benzothiazolo-[2, 3b]-quinazolin-1-ones and their derivatives offered important biological and pharmaceutical applications in Chemistry research field. Multi-component reactions in recent days gained a new aspect in designing methods to produce sophisticated libraries of biologically active heterocyclic compounds. Green Chemistry has become a powerful tool in Chemistry in the last decade and recent areas of interest are the production of organic bioactive molecules via MCRs with an environmentally friendly solvent system such as water, ionic liquids etc. Multi-component methodologies contribute remarkable advantages over conventional reactions due to maintaining their atom economy, convergence, easy work up procedure, structural multiplicity and short reaction time. The present review expresses various synthetic methods and medicinal importance of benzothiazolo-[2, 3b]-quinazolin-1-ones and their derivatives.

Keywords: - Biological activity, [2, 3b]-quinazolin-1-ones, multi-component reactions, organic transformations, synthesis.

I. INTRODUCTION

Multi-component reactions (MCRs) is an important subclass of tandem reactions, in which three or more accessible components react to form a single product that incorporates essentially most or all atoms of the reactants used. Multi-component methodologies contribute remarkable advantages over conventional reactions due to maintaining their atom economy, convergence, easy work up procedure, structural multiplicity and short reaction time. In recent year heterocyclic compounds analogues of benzothiazoles and their derivatives have attracted strong interest due to their biological and pharmacaological properties [1].

Heterocyclic systems have emerged as a useful tool in the designing of new molecular frameworks for biological active drugs with various pharmacological activities [2]. Benzothiazolo-quinazolines are remarkable heterocyclic compounds [3] used as building blocks in several synthetic products and numerous natural that reveal a broad spectrum of pharmacological and biological activities. Thiazoloquinazolines is a significant class of heterocycles used in drug fields; as they include both quinazoline and biodynamic hetero systems thiazole which shown considerable anticancer activities [4]. Furthermore, thiazoloquinazolines have also been identified as glycogen synthase kinase-3 inhibitors and cyclin dependent kinase [5]. The Chemistry of benzothiazolo-[2,3b]-quinazolin-1-one is interested because of its biological significance; many of them showed antifungal [6], antibacterial [7], anti-inflammatory [8], anticonvulsant [9] and antiproliferative activities as well as inhibitory effects for thymidylate synthase and poly-(ADP-ribose) polymerase (PARP) [10]. Benzothiazolo-[2,3b]-quinazolin-1-one derivatives are also found to be tranquilizer, antiallergic, antiulcer and antiasthmatic agent [11]. The common methods used for the preparation of these compounds are using ionic liquid, PTSA, DMF-K2CO3, THF, microwave irradiation. Using anhydrous zinc chloride catalyst, the corresponding Benzothiazolo-[2,3b]-quinazolin-1-one was formed in excellent yields. The ZnCl2-DMF system is found to be more suitable because of shorter reaction time and easy workup. Thus, we prepared this review on medicinal importance and the synthesis of Benzothiazolo-[2,3b]-quinazolin-1-one derivatives.

Benzothiazolo-[2,3b]-quinazolin-1-one derivatives represent an important class of heterocycles that possess an atom of carbonyl group at 1 position, atoms of nitrogens at 5 and 11.

Figure-1: General structure for Benzothiazolo-[2,3b]-quinazolin-1-one derivatives.

General Procedure for Benzothiazolo-[2,3b]-quinazolin-1-ones derivatives
Our previous research reported the synthesis of Benzothiazolo-[2,3b]-quinazolin-1-one derivatives using the mixture of 2-aminobenzothiazole (1 mmol), substituted aromatic benzaldehyde (1 mmol), 1,3-cyclohexanone (1 mmol) and anhydrous zinc chloride (5 mol %) in N,N-dimethyl formamide (5 mL) solvent was added. The reaction mixture was refluxed at 120 °C in oil bath for appropriate time. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured onto ice-cold water with constant stirring. The separated solid product was filtered, washed with cold water and dried. The obtained crude was purified by column chromatography using dichloromethane and ethyl acetate in 3:1 ratio as an eluent (Scheme-1).

**Possible Mechanism of Benzothiazolo-[2,3b]-quinazolin-1-ones:**

In the first step Keto-enol tautomerism of 1,3 cyclohexanone takes place. The catalyst plays vital role in the proposed mechanism, anhydrous ZnCl₂ activate the carbonyl oxygen of 1, 3 cyclohexanone. In second step activated 1, 3 cyclohexanone reacts with 2-aminobenzothiazole for the formation of intermediate (A); 1, 3 shift take places in intermediate (A), to which further aromatic aldehydes is added. By elimination of water molecule from intermediate (B), finally the formation of quinazolin-1-one product takes place.

**II. MEDICINAL IMPORTANCE OF BENZOTHIAZOLO-[2,3B] QUINAZOLIN-1-ONES:**

MCRs have received considerable attention because of its wide range of applications in pharmaceutical Chemistry for the creation of structural diversity and combinatorial libraries for drug discovery [12]. The heterocyclic ring containing benzothiazoles are considered as significant goal in medicinal Chemistry because of the presence of the benzothiazole structural moiety in numerous biologically active compounds with a range of biological activities such as antitumor, antimalarial, anti-HIV, antiviral, antihelmintic etc [13]. Synthesized hybrid pharmacophores of isatin-benzothiazoles and they exhibited anti-breast cancer activity reported by Solomon V. R. et al [14]. In recent, Henriksen G. et al has been developed radio-labeling of benzothiazole derivatives for PET imaging in the detection of Alzheimer’s disease [15]. 2-(4’-Amino-3’-methylphenyl) benzothiazole (AMBP) Yoshida M. et al has been reported to exhibit anticancer activity against a variety of cancers, including breast, ovary and kidney cancers, in animal studies [16]. Liqiang Wu, et al. were described the antiproliferative activities of 13-aryl-13H benzo(g) benzothiazolo[2,3-b]quinazoline-5,14-diones synthesized compounds were evaluated on two different human cancer cell lines (HepG2 and Hela), and the results showed that most of the new compounds showed good to potent cytotoxic activities. All the synthesized compounds were subjected to in vitro Antiproliferative evaluation using the MTT assay in two human cancer cell lines representative of major cancer HepG2 (liver) and Hela (cervix), and IC50 (IM) [17]. Mhran M. A. et al was described synthesis and in vitro evaluation of some new benzothiazole derivatives as schistosomical agents [18]. Akhtar, T et al described in vitro antitumor and antiviral activities of new benzothiazole and 1,3,4-oxadiazole-2-thione derivatives [19]. Gaslonde, T. et al has been reported the synthesis and cytotoxic activity of dimeric analogs of acrycine in the Benzol[h]pyrano [3, 2-h]acridin-7-one series has been studied [20]. Galarce, G. D. et al. were reported 6- Arylbenzimidazo[1,2-c]quinazoline derivatives as a potential anti-inflammatory agents [21]. Kandeel, M. M. et al. were reported synthesis and biological activity of some pyrimido[2,1-b]benzothiazol-8-yl-sulphones starting from bis[2-aminobenzothiazol-6-yl] sulphone [22]. Derivatives of 6-amino-2-phenylbenzothiazole by Racane, L. et al. bearing different substituents (amino, dimethylamino or fluoro) on the phenyl ring were prepared and found to exert cytostatic activities against malignant human cell lines [23].

**III. METHODS FOR THE SYNTHESIS OF BENZOTHIAZOLO-[2,3B]-QUINAZOLIN-1-ONES DERIVATIVES:**
The common methods used for the preparation of such compounds are using tetramethylguanidinium trifluoroacetate ionic liquid [24], PTSA [25], THF [26], microwave irradiation [27]. Our continuing efforts in laboratory towards the development of environmentally friendly and cheap methodologies for organic reactions using ZnCl₂-DMF [28].

Cui-Ting Ma, et al (2017): were studied the environmentally benign reaction medium for one-pot Synthesis of 13-aryl-13H-benzo[g]benzothiazolo[2,3-b]quinazoline-5,14-diones in Oxalic acid/proline via three-component reaction of aromatic aldehydes, 2-aminobenzothiazole and 2-hydroxy-1,4-naphthoquinone under microwave irradiation [29].

Ali Maleki, et al (2017): was reported a green approach for the ultrasound-enhanced one-pot multicomponent synthesis of tetraheterocyclic imidazo(thiazolo) pyrimidines is described via the condensation of a 2-aminobenzimidazole or 2-aminobenzothiazole, dimedone and various aldehydes in the presence of Fe₃O₄@clay as an environmentally benign and reusable core/shell nanocomposite catalyst [30].

Ali Maleki, et al (2015): were synthesized tetracyclic benzimidazolo[2,3-b]quinazoliones via the condensation of 2-aminobenzimidazoles or 2-aminobenzothiazoles, dimedone, and various aldehydes using Fe₃O₄@chitosan as an environmentally benign and reusable nanocomposite catalyst [33].

S. Nazneen, et al (2014): were described the preparation of 4H-pyrrolo[2,1-b]benzothiazoles derivatives under solvent-free condition by using iron fluoride catalyst assisted convenient and efficient strategy [34].

Manmeet Koura, et al (2016): were reported a series of novel and highly efficient Lewis acids covalently grafted over sulfonic acid functionalized carbon@titania composites were successfully synthesized via sulfonation of carbon@titania composites followed by treatment with different Lewis acids like AlCl₃, FeCl₃, SnCl₂, Cu(OAc)₂ and Bi(NO₃)₃. The utility of the developed catalysts was explored for the synthesis of a diverse range of 4H-pyrrolo[2,1-b]benzothiazoles and benzoxanthenones, and among various catalysts, C/TiO₂-SO₃H-SbCl₃ was found to be the most active [31].

Razieh Talaei, et al (2016): was studied the synthesis of 4H-pyrrolo[2,1,b]benzimidazoles and 4H-pyrrolo[2,1,b]benzothiazoles through one-pot three-component cyclocondensation reactions of 2-aminobenzimidazole or 2-aminobenzothiazole with dimedone and aromatic aldehydes in the presence of guanidinium chloride under solvent-free conditions [32].

Ali Maleki, et al (2013): were has been developed the synthesis of tetraheterocyclic benzimidazolo[2,3-b]quinazolin-1-ones via a multi-component reaction, which involves the condensation of 2-aminobenzimidazole, dimedone and different aldehydes using chitosan-supported metal nano-composite as a catalyst [37].

Pramod Kumar Sahu, et al (2012): was prepared the 4H-pyrimido[2,1-b][1,3]benzothiazolo, 1,2,4-triazoloquinazolines, octahydroquinazolines and fused thiazolo[2,3-b]quinazolinone by multicomponent reactions using aldehydes, dicarbonyl and 2-aminobenzothiazole/3-amino-1,2,4-triazole/urea/thiorea has been carried out in the presence of Mg-Al CO3 and Ca-Al CO3 hydrotalcite as a heterogeneous catalyst [38].

Kidwai, M.; et al (2012): has been recently developed the synthesis of tetraheterocyclic benzothiazolo[2,3-b]-quinazolin-1-ones methodology, involves condensation of 2-aminobenzothiazole, cyclic β-diketones and aldehydes using Amberlyst-15 in PEG 400 [39].

Anand Kumar Arya et al (2011): have been synthesized spiro-heterocyclic derivatives with fused hetro systems; spiro[benzothiazolo[2,3-b]chromeno [3,4-e]pyrimidine-7,3’-indoline]-2’,6-diones, spiro [benzothiazolo[2,3-b]pyrimido[5,4-e] pyrimidine-5,3’-indoline]-2’,4-triones, spiro[benzothiazolo[2,3-b]quinazolin-5,3’-indoline]-2’,4-diones and spiro[bienzo thiazolo [2,3-b]pyran[3,4-e]-pyrimidine-5,3’-indoline] -2’,4-diones incorporating medicinally privileged hetro systems by an environmentally benign, efficient and convenient methodology involving the sulfamic acid-catalyzed multicomponent domino reaction of

2-aminobenzothiazoles with isatin and cyclic 1,3-diketones in an aqueous medium [40].

Sharma B. K. et al (2010) was studied the synthesis of benzothiazolo[2,3-b]quinazolin-1-ones was achieved by a multicomponent reaction of substituted 2-aminobenzothiazoles, cyclic β-diketone and aromatic aldehydes in the presence of absolute ethanol [41].

Wu L et al (2010): were studied Sulfamic acid catalyzed synthesis of 4-aryl-3-methyl-1-phenyl-1H-benzo[g]pyrazolo [3,4-b]-quinoline-5,10-diones was achieved from three-component condensation reaction of 3-methyl-1-phenyl-1H-pyrazol-5-amine, aromatic aldehydes and 2-hydroxy-1,4-naphthoquinone under solvent-free [42a].

Wu L et al (2010): has been reported Silica sulfuric acid promoted synthesis of benzo[4,5]imidazo [1,2-a]pyrimidine was achieved by the reaction of 2-amino- benzimidazole, aldehydes and dicarbonyl compounds under solvent free conditions [42b].

Heravi M. M. et al (2008): has been synthesized the [1,2,4]-triazolo/benzimidazolo-quinazolinone derivatives was achieved by the condensation of 2-amino benzimidazole and 3-amino-1,2,4-triazole as amine with dimedone and different aldehydes in the presence of H9P2W18O62·18H2O catalyst and acetonitrile [43].
Shaabani A. et al (2007): was reported the synthesis of 3,4-dihydrobenzimidazo[2,1-b]quinazolin-1(2H)-ones in the presence of 3-butyl-1-methyl imidazolium bromide as ionic liquid at 120°C were reported [44].

Shaabani A. et al (2006): was studied the synthesis of tetrahydrocyclic benzimidazo[1,2-a]quinazolin-4(1H)-one and tetrahydro-1,2,4-triazolo[5,1-b]quinazolin-8(4H)-one was reported by the condensation reaction of an aldehyde, cyclic β-diketone, 2-aminobenzimidazole and 2-aminobenzimidazole or 3-amino-1,2,4-triazole under solvent free conditions [45].

Pavlenko A. A. et al (2005): has been reported the reaction of aminobenzothiazole with benzaldehyde and cyclohexane-1,3-dione, leading to 12-phenyl-2,3,4,12-tetrahydro-1H-benzon-[4,5]-[1,3]thiazolo[2,3-b] quinazolin-1-one were described [46].

Shah, N. K. et al (2009): were described the synthesized series of 12-(2-chloro-6-quinoline-3-y1)-3,3,8-substituted-2,3,4,12-tetrahydro-benz[4,5]thiazolo [2,3-b] quinazolin-1-ones in ethanol. All the synthesized compounds were screened for their antibacterial activity against Grampositive bacterial species Bacillus cereus and Bacillus subtilis, Gram-negative bacteria species Escherichia coli, and their fungicidal activity against Aspergillus niger, Fusarium oxysporum, and Rhizopus species were described [47].

elvam, T. P. et al (2010): was studied series of 6,7,8,9-tetrahydro-5H-5-(2'-hydroxyphenyl)-2- (4'-some substituted benzylidine) thiazolo (2, 3-b) quinazolin-3-phenyl hydrazones derivatives were synthesized and tested for anti-microbial activity [48].

Dandia, A. et al (2010): has been described synthesis of medicinally important substituted tetrahydro-3,3-dimethyl-1H-benzothiazolo[2,3-b]quinazlin-1-ones compounds under microwave irradiation, sonication and classical heating. The reaction was facilitated by the presence of DMF as solvent [49].

ti, K. G. et al (2002): has been reported the preparation of 4H-Pyrimido[2,1-b]benzothiazole-2-thiomethyl-3-cyano-4-one by the reaction of 2-aminobenzothiazole with ethyl-2-cyano-3,3-bismethyl thioacrylate in the presence of dimethyl formamide and anhydrous potassium carbonate [50].

Pingle, M. S. et al (2006): was reported the synthesis of 3-cyano-4-imino-2-methylthio-4H-pyrimido [2,1-b][1,3]benzothiazole from 2-aminobenzothiazole and bis(methylthio) methylene malononitrile in DMF and anhydrous potassium carbonate [51].

Wahe, H. et al (2003): has been described the synthesis 2H-pyrimido[2,1-b]benzo thiazol-2-ones via conjugate addition of 2-aminobenzothiazoles to the acetylenic acids, followed by cyclocondensation in 1-butanol for 48 hours [52].
IV. CONCLUSION

In this present review article, Medicinal Importance and Synthesis of benzothiazolo-[2,3-b]-quinazolin-1-one Derivatives via Multi-Component Reactions have been described in order to improve the reactions conditions and yield products. The benzothiazolo-[2,3-b]-quinazolin-1-one and their derivatives of heterocyclic compounds are biologically active such as antifungal, antibacterial, anti-inflammatory, anticonvulsant, anti-proliferative activities as well as inhibitory effects for thymidylate synthase and polynucleotide phosphorylase (PARP). Benzothiazolo-[2,3-b]-quinazolin-1-one derivatives are also found to be tranquilizer, antiallergic, antilucer and antiasthmatic agent. Therefore, Benzothiazolo-[2,3-b]-quinazolin-1-one derivatives represent shows potential compounds in the further search of novel drugs.

These methods have been implemented for the synthesis of Benzothiazolo-[2,3-b]-quinazolin-1-one derivatives due to

- Excellent yield of products
- Short reaction time
- Easy work up procedure.
- Moderate the reaction condition
- Environmental friendly approach.

V. ACKNOWLEDGMENTS

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