RECENT ADVANCES IN SYNTHESIS AND BIOLOGICAL ACTIVITY EVALUATION OF CONDENSED THIAZOLOQUINAZOLINES: A REVIEW

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Abstract. In the review we systematize the theoretical and experimental data concerning methods of condensed thiazoloquinazolines synthesis, with respect to compile the literature on synthetic approaches utilized for thiazolo[2,3-b]quinazolines, thiazolo[4,3-b]quinazolines, thiazolo[3,2-a]quinazolines, thiazolo[3,4-a]quinazolines, and thiazolo[5,4-f]quinazolines construction. This paper also reviews the current knowledge with regard of prospects and challenges of condensed thiazoloquinazolines use in the targeted synthesis of biologically active substances and analysis of recent advances in this heterocyclic compounds pharmacology screening. Generalization of the published data gives reason to consider thiazoloquinazolines scaffold as an important pharmacophore in compounds which are characterized with diverse biological activity.

Graphical abstract

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Inroduction
The fundamental aspects of 4-thiazolidinones chemistry and pharmacology are summarized in a few survey articles [1-4] however most intensive researches concerning the chemistry of condensed thiazoles (with the condensed benzo-thiazoles exception) have a sporadic character. The number of review and original articles within the development of 4-thiazolidinone derivatives efficient preparation methods and their biological activity evaluations as novel chemotherapeutical agents is quite limited, while almost all of them were published over the last three decades.

The thiazolidinone core imparts an important function in medicinal chemistry and serves as a powerful biophore template for the rational design of "drug-like" molecules as the prototypes of various therapeutic agents development. Therefore condensed heterocyclic systems obtained with 4-thiazolidinones as synthetic precursors, have gained considerable attention and motivated research aimed at novel biologically active substances development.

In the light of thiazolidinone derivatives importance their molecules structural rigidity strengthening may appear as enormously essential variable for the pharmacological activities extensive spectrum. Such structural rigidity may be considered as the first precondition for these compounds selectivity increasing towards different possible biological targets, and the number of possible substitution positions increasing can be evaluated as a platform for the thiazolidinone-based combinatorial libraries creating.

Quinazoline derivatives also have always been among the most important research areas in medicinal chemistry. In particular, quinazolines have been on the forefront of attention due to their numerous uses in pharmaceutical applications as biologically active compounds and effective drugs [5]. Listed advantages present the highlights of recent developments with the interest maintaining in obtaining compounds containing a thiazolidinone ring annulated with quinazoline one. The combination of these heterocyclic systems into a tricyclic scaffold commonly provides much more interest in the enhanced activity profile of its analogs than their parent constituents. A crucial role in broadening the scope of such condensed system derivatives is displayed as novel qualitatively features appearance for annulated molecules, increasing the possibility of pharmacoforic groups different dispositions and the ability of their interaction with a wider range of receptors.

In the present review we highlight recent advances in the fast growing research area of thiazoloquinazolines chemistry summarizing the existing literature information with respect of condensed thiazoloquinazolines construction synthetic approaches (thiazolo[2,3-b]quinazolines, thiazolo[4,3-b]quinazolines, thiazolo[3,2-a]quinazolines, thiazolo[3,4-a]quinazolines, thiazolo[5,4-f]quinazolines):

The review is also aimed to report the biological activities evaluation of thiazoloquinazolines during past years.
Synthesis of Thiazolo[2,3-b]quinazolines

In 1955 M.S. Dhatt and K.S. Narang reported 7-methyl-2, 3-dihydrothiazolo [2,3-b] quinazolin-5-on obtaining produced from 2-carbethoxy-4-methylthiourea by its 1.5 h refluxing in dibromoethane medium on an oil heater (Scheme 1).

Scheme 1.

Similar reaction of 2-carbethoxy-4-methylthiourea with α-halogenketones in aqueous ethanol medium was reported to give the respective 2, 3-dialkyl-7-methylthiazolo[2,3-b]quinazolin-5-ones [6].

H. A. Daboun and co-workers (1983) [7] had introduced 5-aryliden- or 5-arylazo-2-ethylsulfanylthiazolidin-4-ones into the reaction with anthranilic acid in acetic acid medium led to respective 2-aryliden- and 2-arylazo-thiazolo[2,3-b]quinazoline-3,5-diones preparation in moderate yields (Scheme 2).

Scheme 2.

In 1983 Georgiev and co-workers [8] reported 2,3-dihydro - 5H - thiazolo - [2,3-b] quinazoline derivatives obtaining by introducing anthranilic acid amide as the initial compound, whose interaction with lithiumaluminium hydride resulted in the formation of o-aminobenzylamine. On the next stage o-aminobenzylamine undergo cyclization under its treating with thiophosgene yielding thiazolo[2,3-b]quinazoline. The latest generated target products via its condensation with acetylenedicarbonic acid esters (Scheme 3).
Scheme 3.

A.I. Khodair (2002) described a mild and efficient method of 2-(4-oxo-thiazolinedine-2-ylideneamino)benzoic acid synthesis, followed by its further cyclization led to $S\text{-thiazolo}[2,3-b]\text{quinazoline-3,5}[2H]$-diones preparation as it is shown in Scheme 4 [9].

Scheme 4.

In 2006 B. Karpiak and co-workers demonstrated the convenient method for tricyclic condensed system of 2,3-dihydro-$5H$-[1,3]thiazolo[2,3-\text{b}] quinazolin-5-one construction by reaction of 3-aryl-2-chloropropylisothiocyanates with methylanthranylate under long-term heating in ethanol medium [10] according to Scheme 5.

Scheme 5.
In 2007 Isabelle Bouillon and Viktor Krchňák proposed an efficient method to provide novel thiazolo[2,3-\textit{b}]quinazolin-5-ones based on solid-phase linkers application [11] (Scheme 6).

Scheme 6.

A series of novel compounds with thiazolo-[2,3-\textit{b}]quinazoline moiety genetarion was reported in 2010 by Yu Feng and co-authors [12] as depicted in Scheme 7.
The same year A. Mobinikhaledia and co-authors suggested one-pot three-component reaction of thioxoquinazoline with ethylchloroacetic acid and aromatic aldehydes leading to novel thiazolo-[2,3-b]quinazolines generation. Ethanol medium with sodium hydride introducing to the reaction mixture under refluxing were deemed to be the optimum reaction conditions [14] (Scheme 9).

Scheme 9.

In 2011 Z. J. Quan et al. reported octahydroquinazoline-2-thione cyclization with α-bromoketones to afford novel thiazolo-[2,3-b]-quinazolines [15]. The proposed approach provided a simple and facile method of condensed quinazoline framework construction readily available for its further functionalization (Scheme 10).

Scheme 10.

G. Hassan employed cyclohexanone or cycloheptanone and aromatic aldehydes to yield the appropriate diarylidene derivatives [16]. Their interaction with thiazole derivatives resulted in thiazolo-[2,3-b]quinazoline or thiazolo-[3,2-a]-pyrimidines formation, respectively (Scheme 11).
The new, environmentally friendly two stages synthetic protocol was employed by Yadav A. K. with co-authors in 2013 to obtain 5\(H\)-[1,3]-thiazolo-[2,3-b]-quinazoline-3,5(2\(H\))-dione and 5\(H\) - thiazolo-[2,3-b]-quinazolin-5-one and its derivatives [17]. Appropriately substituted 2-aminobenzoic acid derivatives under condensation with thiourea in 1-butyl-3-methylimidazolium bromide at moderate temperatures in nitrogen atmosphere afforded the synthesis of 2-thioxo-1\(H\)-4-quinazoline as an intermediate (Scheme 12).
The final products were generated in high yields via cyclisation in the reactions with 2-chloroacetic acid or 2-chloropropionic acid, respectively.

Silvana Grasso and co-authors [18] demonstrated novel, facile and efficient synthetic method for 1-aryl-1H, 3H-thiazolo[4,3-b]quinazoline obtaining. The target product was afforded as a result of 2-aminobenzylamine mixture with various aromatic aldehydes and the excess of merkaptoacetic or 2-mercapto-propionic acids boiling in anhydrous benzene medium (Figure 14).
Regio-selective synthesis of $4H$-3,3a-dihydrothiazolo-[4,3-$b$]quinazolines and 7-methyl-$4H$-3,3a-dihydrotiazolo-[4,3-$b$]quinazolines proposed by E.A. Adegoke and co-workers [19] is shown in Scheme 15.

Scheme 15.

N-substituted thiazolidinecarboxylic acid derivatives were transformed firstly into respective chloroanhydrides. Final thiazolo-quinazolines were achieved via their further reductive cyclization.

Synthesis of Thiazolo[3,2-$a$]quinazolines

The proposed method appeared to proceed as the reaction between methyl-2-(2-cyanoacetamide)benzoate and various arylidene malononitriles.

**Synthesis of Thiazolo[3,4-a]quinazolines**

O. O. Parkhomenko and co-authors [21] described a new heterocyclic system - 1-thioxo[1,3]thiazolo[3,4-a]quinazolin-5(4H)-one construction as it is depicted in Scheme 17:

They employed three-component condensation of methyl-2-isothiocyanobenzoate, sulfur and cyanoacetamide or cyanacetic acid ester to yield the above mentioned system.

**Synthesis of Thiazolo[5,4-f]quinazolines**

A. Foucourt performed synthesis of new thiazolo[5,4-f]quinazolines [22] by using a microwave-assisted reactions (Scheme 18).
The proposed methodology included the Dimroth's rearrangement with 4,5-di-chloro-1,2,3-ditiazole chloride (Apple's salt) implementation.

**Pharmacological Potential of Condensed Quinazolines**

The combining of combinatorial chemistry methods and high-throughput pharmacological screening afforded to identify a large group of biological cell targets. This fact contributed considerably to a deeper discovering and understanding of the mechanisms of pharmacological agents action in details, as well as significant extension of chemical compounds arsenal as potential drug candidates. The above mentioned strategies employment became a key factor in the rapid pharmacological potential development of condensed thiazole and thiazolidone derivatives and was resulted in novel pharmacological effects revealing of these compounds and early evaluated ones broadening realized in "ligand-receptor interaction" terms.

It is found that quinazolines and their condensed derivatives demonstrated biological activity, including anti-tumor [23-26], antioxidant [27], analgesic [28], anti-inflammatory [24,29], anticonvulsant [30], anti-HIV, anti-bacterial, antifungal [31-34], antihypertensive [35], anti-leishmaniasive [36] and antidepressant effects [37]. On the other hand, thiazole derivatives also possess a significant biological activity, that causes permanent interest of researchers to this class of compounds for a long-time period. In particular, antibacterial, antifungal [38-41], anti-inflammatory [42], antituberculous [43,44], anticancer [45-51], antidiabetic [52], anti-HIV [53], antioxidant [54], antitypanosomal activities [55] were evaluated for thiazole and thiazolidones derivatives. As a result, based on these noted conclusions, the quinazolines and thiazoles may be considered as privileged structures according the "double-drugs" concept.

**Conclusions**

In the present review we performed the literature search and highlighted recent advances in the fast growing research area of thiazoloquinazolines chemistry. References obtained were considered to review and summarize the existing information with respect of condensed thiazoloquinazolines construction synthetic approaches and their pharmacological actions spectrum. Thus, broad synthetic possibilities of condensed thiazoloquinazolines generation and functionalization, their high pharmacological potential found a strong basis for the systematic research of these compounds.

**References**


8. Georgiev VS., Bennett GA., Radov LA., Kamp DK., Trusso L.A. 2-Substituted


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