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Mini-review

Recent advances in the structural library of functionalized quinazoline and quinazolinone scaffolds: Synthetic approaches and multifarious applications

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ABSTRACT

Drug development has been a principal driving force in the rapid maturation of the field of medicinal chemistry during the past several decades. During this period, the intriguing and challenging molecular architectures of nitrogen-containing heterocycles with potential bioactive properties have received significant attention from researchers engaged in the areas of natural product synthesis and heterocyclic methodology, and constituted a continuous stimulus for development in bio(organic) chemistry. In this perspective, the current review article is an effort to summarize recent developments in the environmentally benign synthetic methods providing access to quinazoline and quinazolinone scaffolds with promising biological potential. This article also aims to discuss potential future directions on the development of more potent and specific analogues for various biological targets.

1. Introduction

Heterocycles occupy a central position in organic chemistry [1–3], and are of particular interest and significant importance in the search for new bioactive scaffolds in both the agrochemical and pharmaceutical industries. Indeed, with particular reference to the pharmaceutical industry, heterocyclic motifs are especially prevalent with over 60% of the top retailing drugs containing at least one heterocyclic nucleus as part of the overall topography of the compound [4]. In addition, the exploitation of a small molecule to a desirable extent is a valuable contribution in the field of synthetic organic and medicinal chemistry [5]. In this context, nitrogen heterocycles in particular exhibit diverse biological and pharmacological activities due in part to the similarities with many natural and synthetic molecules with known biological activity [6]. Furthermore, compounds that contain heterocyclic moieties often exhibit improved solubilities and can facilitate salt formation properties, both of which are known to be important for oral absorption and bioavailability [7].

Quinazoline **1** is 1,3-diazanaphthalene. It is also known as 5,6-benzopyrimidine or benzo[*a*]pyrimidine, or phenmiazine [8], and its 4-oxo derivative is called 4(3*H*)-quinazolinone **2** [9–11] (Fig. 1).

Quinazoline and quinazolinone derivatives have attracted significant attention due to their diverse pharmacological activities such as antimalarial [12], antimicrobial [13], anti-inflammatory [14], anticonvulsant [15], antihypertensive [16], anti-diabetic [17], cholinesterase inhibition [18], and anticancer activities [19]. Moreover, several of these compounds like **3**–**7** and TMQ, exhibited dihydrofolate reductase inhibition [20] (Fig. 2), and also used as kinase inhibitors [21] such as gefitinib, erlotinib, caneratinib, dacomitinib, afatinib, vandetanib, ispinesib and compounds **8** and **9** (Fig. 3). Some quinazoline derivatives interact with tubulin [22] and interfere with its polymerization, others act by modulating aurora kinase activity [23] or have an effect in critical phases in the cell cycle [24] or act as apoptosis inducers [25].

Quinazolinone and their derivatives [26] are also building block for approximately 150 naturally occurring alkaloids isolated from a number of families of the plant kingdom, from microorganisms and animals (Fig. 4). Some of the compounds incorporating quinazolinone motif like raltitrexed, thymitaq and compounds **10** and **11** possess antitumor activities [27] (Fig. 5).

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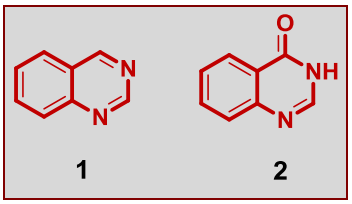

Fig. 1. Chemical structures of quinazoline 1 and 4(3*H*)-quinazolinone 2.

Quinazolines also exhibit a variety of biological functions like cellular phosphorylation inhibitors [28], ligands for benzodiazepine and GABA receptors in the central nervous system [29] and some of them have acted as DNA binding agents [30]. They have also shown to possess effective α-adrenergic blocking activity. Moreover, these derivatives are core motifs of prazosin [31], bunazosin [32], and doxazosin [33], useful medicines for antihypertensives. Some other drugs like proquazone and fluproquazone possess non-steroidal anti-inflammatory potential, afloqualone as muscle relaxant, and diproqualone with sedative analgesic effects. KF31327 was developed as a heart disease remedy and an impotence medicine [34]. In a recent report, 3,4-dihydroquinazoline derivatives have been found to possess excellent T-type calcium channel blocking activity [35] (Fig. 6).

A vast number of quinazoline derivatives have been synthesized to provide synthetic drugs and to design more effective medicines. There are a number of reviews [36] and monographs [37] on quinazoline and quinazoline alkaloids. But, owing to the number of publications reporting an extremely high output of results, there has been no formal collection of recent advances encompassing the synthetic methods through which these heterocycles (quinazolines and quinazolinones) can be accessed, along with diverse biological profile which they possess. So, in corollary of these fascinating findings as well as part of a programme aimed at finding heterocyclic structures with various pharmacological properties [38], we have targeted the libraries of these novel heteroaromatic scaffolds with broad spectrum of biological actions. The purpose of this review is to demonstrate that quinazoline and quinazolinone derivatives are privileged motifs which can be accessed through a variety of synthetic efforts/methodologies starting from cheap and readily available starting materials, and are core structures found in various commercial drugs.

2. Progress in synthetic methods

In the past decade, a variety of synthetic methods have been employed for the preparation of functionalized quinazoline and quinazolinone motifs and the level of interest in the current domain is clearly shown by the number of publications reporting an extremely high output of results as well as the presence of these scaffolds in numerous marketed medicines as core structures. The subject matter of current review are aimed at providing a comprehensive overview of recent (2013) practical, extremely mild, and operationally simple methodologies used to construct quinazoline and quinazolinone skeletons of pharmaceutical as well as agrochemical interest.

Fu and co-workers [39] developed an easy and efficient method for the synthesis of pyrazolo[1,5-*c*]quinazolines **13** via one-pot two-step process involving readily available substituted 1-(2-halophenyl)-3-alkylprop-2-yn-1-ones **12**, hydrazine hydrochloride and amidine hydrochlorides under mild conditions (Scheme 1). With the optimized conditions in hand, the substrate scope was examined using inexpensive CuI as a catalyst which afforded the corresponding pyrazolo[1,5-*c*]quinazolines in good to excellent yields. This novel method affords a new strategy for the construction of diverse and useful *N*-fused heterocyclic compounds for combinatorial and medicinal chemistry.

Pal and co-workers [40] were able to develop an elegant, versatile, rapid and a new one-pot Cu-mediated synthetic methodology for the assembly of six membered fused *N*-heterocyclic ring, 5*H*-isoquinolino[2,3-*a*]quinazoline-5,12(6*H*)dione **16** (Scheme 2). The starting material **14** was prepared via amide bond formation between 2-halo (het)aryl carboxylic acid chloride and 2-amino (het)aryl carboxylate ester which was coupled with ethyl cyanoacetate **15** to afford the required compound. The scope of this domino reaction was also examined which revealed that a diverse variety of substituents like alkynyl, phenyl, 2-thienyl or NO_2 are compatible under optimized conditions providing access to target compounds in good to excellent yields.

Menéndez and co-workers [41] described an efficient, user-friendly, one-pot synthetic protocol involving the combination of MCR methodology and microwave heating affording 5,6-dihydroquinazolin-4-ones **23** (Scheme 3). The reaction involves readily available materials such as chalcones **17**, 1,3-dicarbonyl compounds **18**, butylamine **19**, ammonium formate and formamide via intermediate anthranilate derivatives **20**, **21** and **22**.

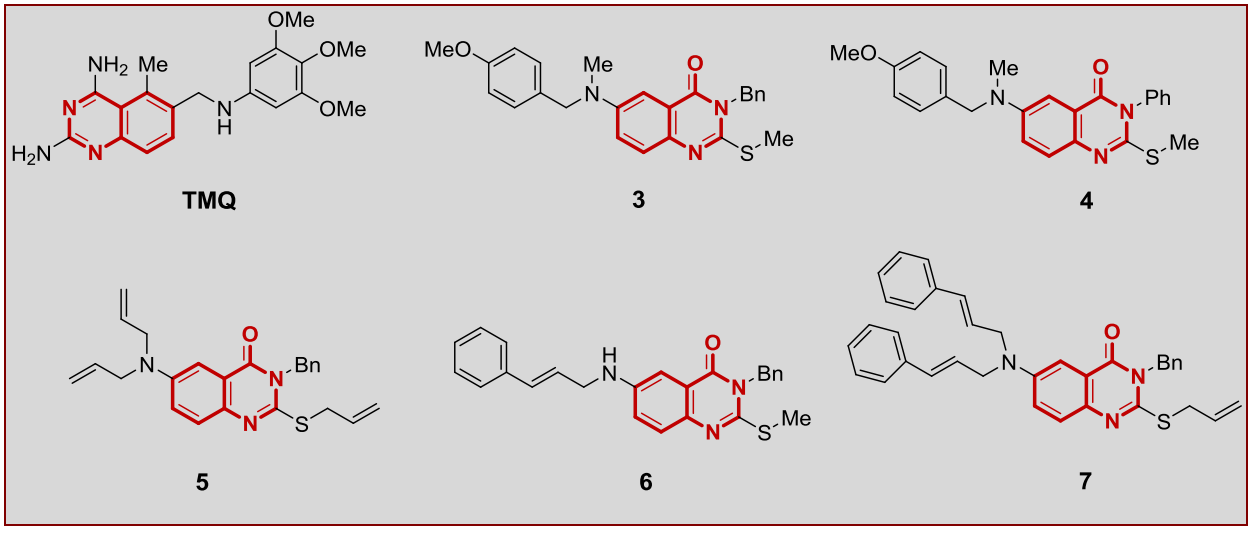

Fig. 2. Structures of lead antifolate compounds.