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Mini-review

Synthetic approaches, functionalization and therapeutic potential of quinazoline and quinazolinone skeletons: The advances continue

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ABSTRACT

The presence of *N*-heterocycles as an essential structural motif in a variety of biologically active substances has stimulated the development of new strategies and technologies for their synthesis. Among the various *N*-heterocyclic scaffolds, quinazolines and quinazolinones form a privileged class of compounds with their diverse spectrum of therapeutic potential. The easy generation of complex molecular diversity through broadly applicable, cost-effective, practical and sustainable synthetic methods in a straightforward fashion along with the importance of these motifs in medicinal chemistry, received significant attention from researchers engaged in drug design and heterocyclic methodology development. In this perspective, the current review article is an effort to recapitulate recent developments in the eco-friendly and green procedures for the construction of highly challenging and potentially bioactive quinazoline and quinazolinone compounds in order to help medicinal chemists in designing and synthesizing novel and potent compounds for the treatment of different disorders. The key mechanistic insights for the synthesis of these heterocycles along with potential applications and manipulations of the products have also been conferred. This article also aims to highlight the promising future directions for the easy access to these frameworks in addition to the identification of more potent and specific products for numerous biological targets.

1. Introduction

Nitrogen-containing heterocyclic compounds are the most abundant and integral scaffolds that occur ubiquitously in a variety of synthetic drugs, bioactive natural products, pharmaceuticals and agrochemicals. Owing to their widespread applications, these skeletons have long been a subject of immense interest, and substantial efforts have been made to the development of synthetic strategies which could lead to the discovery of new bioactive compounds in medicinal chemistry [1]. 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 [2].

Quinazoline and quinazolinone derivatives have attracted significant attention due to their diverse pharmacological activities such as antimicrobial [3], antimalarial [4], anti-inflammatory [5], antihypertensive [6], anticonvulsant [7], anti-diabetic [8], anticancer [9], cholinesterase inhibition [10], dihydrofolate reductase inhibition [11], and kinase inhibitory activity [12]. Quinazolines also exhibit a wide variety of biological functions like cellular phosphorylation inhibition [13], ligands for benzodiazepine and GABA receptors in the central nervous system [14], and some of them have acted as DNA binding agents [15]. They also act as effective α-adrenergic blocker, prazosin [16], bunazosin [17], and doxazosin [18], are useful medicines for antihypertensives, proquazone and fluproquazone as non-steroidal anti-inflammatory drugs, afloqualone as muscle relaxant, and diproqualone with sedative analgesic effects. KF31327 was developed as a heart disease remedy and an impotence medicine [19]. In a recent report, 3,4-dihydroquinazoline derivatives have been found to perform excellent T-type calcium channel blocking activity [20]. Some representative examples are displayed in Fig. 1.

Quinazolinone and their derivatives [21] are also building block for approximately 150 naturally occurring alkaloids isolated from a number of families of the plant kingdom, from microorganisms and animals. Some of the compounds incorporating quinazolinone

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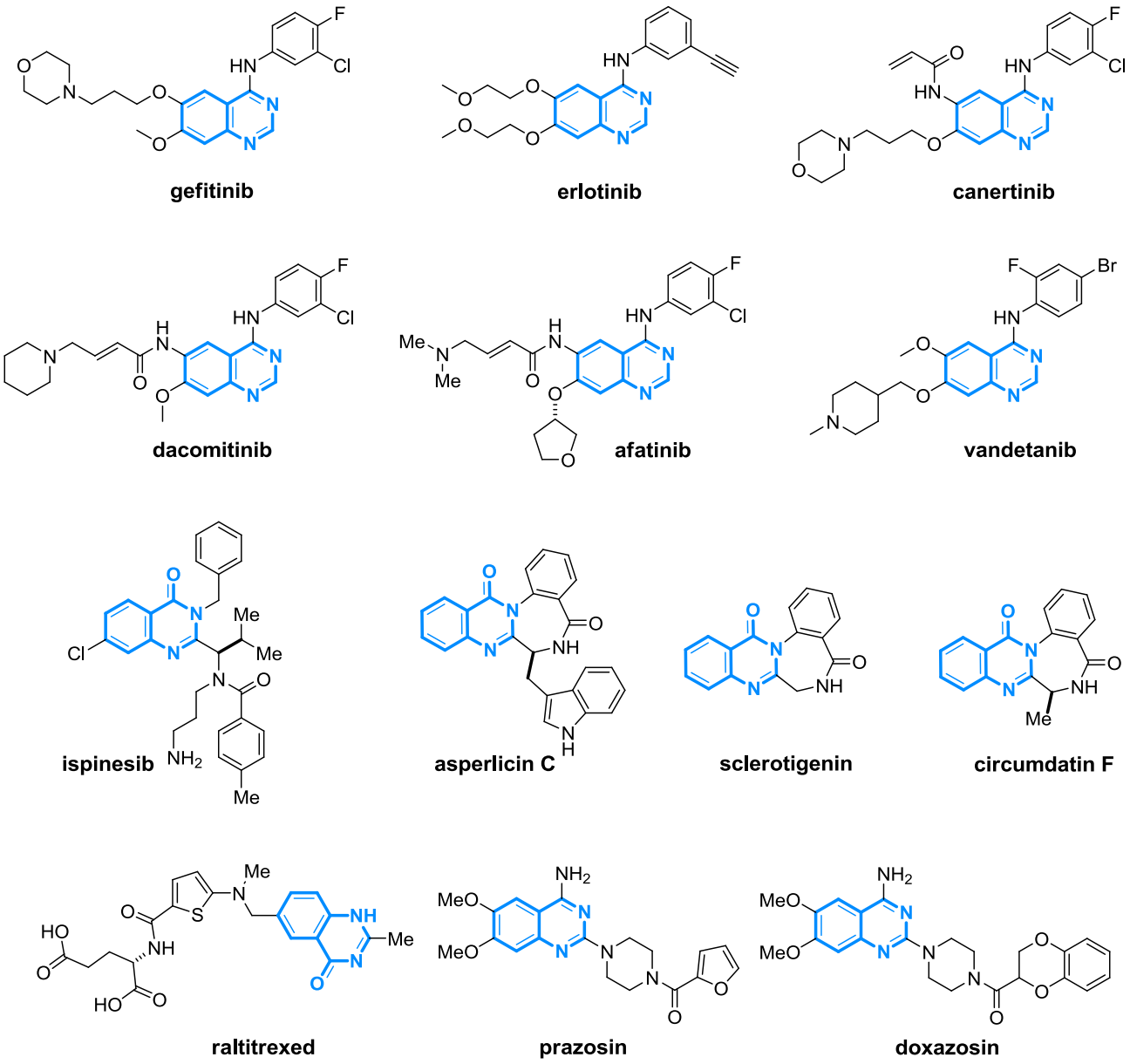

Fig. 1. Selected structures of some commercial drugs and alkaloids incorporating quinazoline and quinazolinone motifs.

motif like raltitrexed and thymitaq possess antitumor activities [22].

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 [23] and monographs [24] on quinazoline and quinazoline alkaloids. Recently, we have documented a formal collection of significant developments (2013) [25] on the synthetic methods through which these heterocycles (quinazolines and quinazolinones) could be accessed, along with diverse biological profile which they possess. Some other groups also published independently the synthesis of quinazolinones [26] and bioactive quinazolines [27], respectively. There has been no discussion on the mechanistic aspects of key transformations. So, in corollary of these fascinating findings as well as part of a programme aimed at discovering heterocyclic structures with various pharmacological properties, in general [28], and in continuation of our previous work [25] on these skeletons, we report here the very recent developments (2014) in the environmentally benign, green, and efficient synthetic protocols (in most cases) to access quinazoline and quinazolinone derivatives from cheap and readily available commercial feedstocks. This review also focuses on the mechanistic insights for the synthesis of these cores for key reactions, while presenting successful synthetic applications and product manipulations along with an array of pharmaceutical and agrochemical applications.

2. Progress in synthetic methods

The number of new methodologies regarding the synthesis of quinazoline and quinazolinone cores has dramatically increased from year to year. All these transformations provide rapid access to new and original quinazoline and quinazolinone compounds, affording the possibility of increasing structural diversity in a straightforward fashion starting from simple and common substrates. The subject matter of current review is aimed at providing a comprehensive overview of recent (2014) developments.