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Review article

Quinazolines and quinazolinones as ubiquitous structural fragments in medicinal chemistry: An update on the development of synthetic methods and pharmacological diversification

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ABSTRACT

Nitrogen-rich heterocycles, particularly quinazolines and quinazolinones, represent a unique class of diversified frameworks displaying a broad spectrum of biological functions. Over the past several years, intensive medicinal chemistry efforts have generated numerous structurally functionalized quinazoline and quinazolinone derivatives. Interest in expanding the biological effects, demonstrated by these motifs, is growing exponentially, as indicated by the large number of publications reporting the easy accessibility of these skeletons in addition to the diverse nature of synthetic as well as biological applications. Therefore, the main focus of the present review is to provide an ample but condensed overview on various synthetic approaches providing access to quinazoline and quinazolinone compounds with multifaceted biological activities. Furthermore, mechanistic insights, synthetic utilization, structure–activity relationships and molecular modeling inputs for the potent derivatives have also been discussed.

Contents

Abbreviations: BPO, Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate; BSA, bovine serum albumin; BZD, benzodiazepine; DBU, 1,8-diazabicycloundec-7-ene; DIPEA, *N,N*-Diisopropylethylamine; DMAD, dimethyl acetylenedicarboxylate; DNA, Deoxyribonucleic acid; EGFR, Epidermal growth factor receptor; GABA, Gamma-aminobutyric acid; MAO, monoamine oxidase; MES, maximal electroshock seizure; MTT, 3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium; MW, microwave; NIS, *N*-Iodosuccinimide; PARP, poly ADP ribose polymerase; PTZ, pentylenetetrazole; RBV, ribavirin; RT, room temperature; SAR, structure–activity relationship; TBAF, tetra-*n*-butylammonium fluoride; TBHP, *tert*-Butyl hydroperoxide; TG, triglyceride; TMEDA, Tetramethylethylenediamine; TFA, Trifluoroacetic acid; *p*-TSA, *p*-toluenesulfonic acid; ZNMR, zanamivir.

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1. Introduction

Nitrogen-containing heterocycles are ubiquitous and integral pharmacophoric units prevalent in a diverse variety of bioactive natural products, synthetic drugs, pharmaceutical and agrochemicals.[1] Among these heterocycles, quinazoline and quinazolinone cores, and their derivatives constitute an imperative class of compounds with a diverse therapeutic and pharmacological properties such as antimicrobial,[2] anticonvulsant,[3] anticancer,[4] antimalarial,[5] antihypertensive,[6] anti-inflammatory,[7] anti-diabetic,[8] antitumor,[9] anti-cholinesterase,[10] dihydrofolate reductase inhibition,[11] cellular phosphorylation inhibition,[12] and kinase inhibitory activities.[13] A variety of quinazoline derivatives have been synthesized to provide synthetic drugs and to design more effective medicines for several disorders.[14–17] Some representative examples of drugs and natural products containing quinazoline and quinazolinone motifs are displayed in Figure 1.

Owing to the widespread biological properties, a vast number of synthetic approaches have been developed to synthesize quinazoline and quinazolinone derivatives, and we have recently documented a formal collection of significant developments in this field of research.[18,19] Recognizing the importance of quinazoline and quinazolinone skeletons in synthetic and medicinal chemistry arena, and as part of a larger drug discovery program,[20] it was considered worthwhile to update the recent literature findings comprising of efficient synthetic protocols to access these aza-heterocyclic skeletons, key mechanistic investigations, synthetic utility along with an array of pharmaceutical and agrochemical applications. In addition, the aim of this review is not only to present some fundamental methodological principles used for the design and synthesis of new *N*-heterocycles but also to provide some insights and inspiration for future medicinal chemistry research.

2. Advancements in synthetic methods

The volume of new synthetic methodologies regarding the synthesis of quinazoline and quinazolinone cores has dramatically increased from year to year. All these transformations generally provide straightforward access to new and effective quinazoline and quinazolinone compounds with increased structural diversity from easily accessible and affordable substrates.

2.1. Synthesis of quinazolines

In this part, we outline examples dealing with the synthesis of quinazoline skeleton from readily available and cheap starting material.

2.1.1. Rhodium-catalyzed *ortho*-amidation cyclocondensation

Harrity and co-workers[21] developed a mild and regioselective *ortho*-amidation cyclocondensation sequence delivering a range of 4-aminoquinazolines **3** in good yield (Scheme 1). The study