Bulletin of Faculty of Pharmacy, Cairo University xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Bulletin of Faculty of Pharmacy, Cairo University

journal homepage: www.elsevier.com/locate/bfopcu

Original Article

Quinazolino-thiadiazoles as antimicrobial agents

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ARTICLE INFO

Keywords:
Synthesis
Quinazolino-thiadiazoles
Antimicrobial activity
Quinazolin-4(3H)-one

ABSTRACT

In the present research, we report the synthesis and *in vitro* antimicrobial activity of a new series of novel quinazolino-thiadiazoles as fused pharmacophore (3–20). In general, the results of the *in vitro* antibacterial activity are encouraging, as out of 18 compounds tested, Compounds 3 and 8 with a 4-chlorophenyl and 4-nitro phenyl at C-2 of thiadiazole and chloromethyl substituent at C-2 of quinazolinone displayed a broad spectrum antimicrobial activity against all the strains, while compounds 13 and 16 again with a 4-chlorophenyl and 4-nitrophenyl at C-2 of thiadiazole and ethyl substituent at C-2 of quinazolinone showed the same potency but with a narrower spectrum (Bacterial and Fungal strains) with MIC values of 62.5 μg/ml. The structures of the compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR and Mass analysis. It is worth to mention that the combination of two biologically active moieties quinazoline and thiadiazole profoundly influences the biological activity.

1. Introduction

Quinazolines are a class of fused heterocycles that are of considerable interest because of their diverse pharmacological profile [1]. Quinazolines attracted the scientist since 1888, with the discovery of the first natural representative of them –(+)-preganine (vasicine) [2]. Quinazolinones and quinazolines are very interesting molecules and their pharmacological activities are well documented. It has been reported as antihypertensive [3] antimicrobial [4–8], antiviral [9,10], anti-HIV [11] anticonvulsant [12,13], anti-inflammatory [14] and anticancer [15–18] activity, *etc*. The rapid rise in bacterial resistance to the traditional antibiotics has encouraged a continuing search for new classes of compounds with novel modes of antimicrobial activity. To overcome this rapid development of drug resistance, new agents should preferably consist of chemical characteristics that clearly differ from those of existing agents [19].

Quinazolinones show a wide spectrum of chemotherapeutic activity and a considerable amount of work has been done on the synthesis of new potent antibacterial and antifungal quinazolinones. Albaconazole (UR-9825) chemically known as 7-chloro-3-[(2R,3R)-3-(2,4-difluoro phenyl)-3-hydroxy-4-(1,2,4-triazol-1-yl)butan-2-yl]quinazolin-4-one, is a triazole antifungal. It has potential broad-spectrum antibacterial activity [2].

Among the heterocyclic systems, thiadiazole template represents one of the privileged structure fragments in the modern medicinal chemistry. 1,3,4-thiadiazoles are associated with diverse biocidal activities probably by the virtue of a toxophoric –N=C-S- grouping. Abdel-Wahab et al. reported the synthesis of new 1,3,4-thiadiazole derivatives of 5-(benzofuran-2-yl)-1-phenylpyrazole moiety [7]. All the synthesized compounds were screened against bacterial strains and found to possess significant activity against *E. coli* and *C. albicans* (Fig. 1). Kadi *et al* synthesized of a new series of 5-(1-adamantyl)-1,3,4-thiadiazole derivatives and evaluated them for their antimicrobial activity which revealed that all the synthesized compounds exhibited better activity than reference drugs (gentamicin and ampicillin) on *E. coli* and *Pseudomonas aeuroginosa*. SAR studies have shown that introduction of a benzyl- or 4-substituted benzyl and adamantly moiety on C-5 of thiadiazole nucleus enhances the antibacterial and antifungal activity respectively, as shown in Fig. 1 [8].

Based on the above facts and in continuation to our research for new antimicrobial agents [20–24], in the present study we planned to synthesize novel compounds that are hybrids of the 2 biologically active ring systems: quinazoline and 1,3,4 thiadiazole. This combination aims to get antimicrobial agents with better activity than those agents containing only one ring of them.

Peer review under responsibility of Faculty of Pharmacy, Cairo University.
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https://doi.org/10.1016/j.bfopcu.2018.03.001
Received 14 January 2017; Received in revised form 16 January 2018; Accepted 3 March 2018

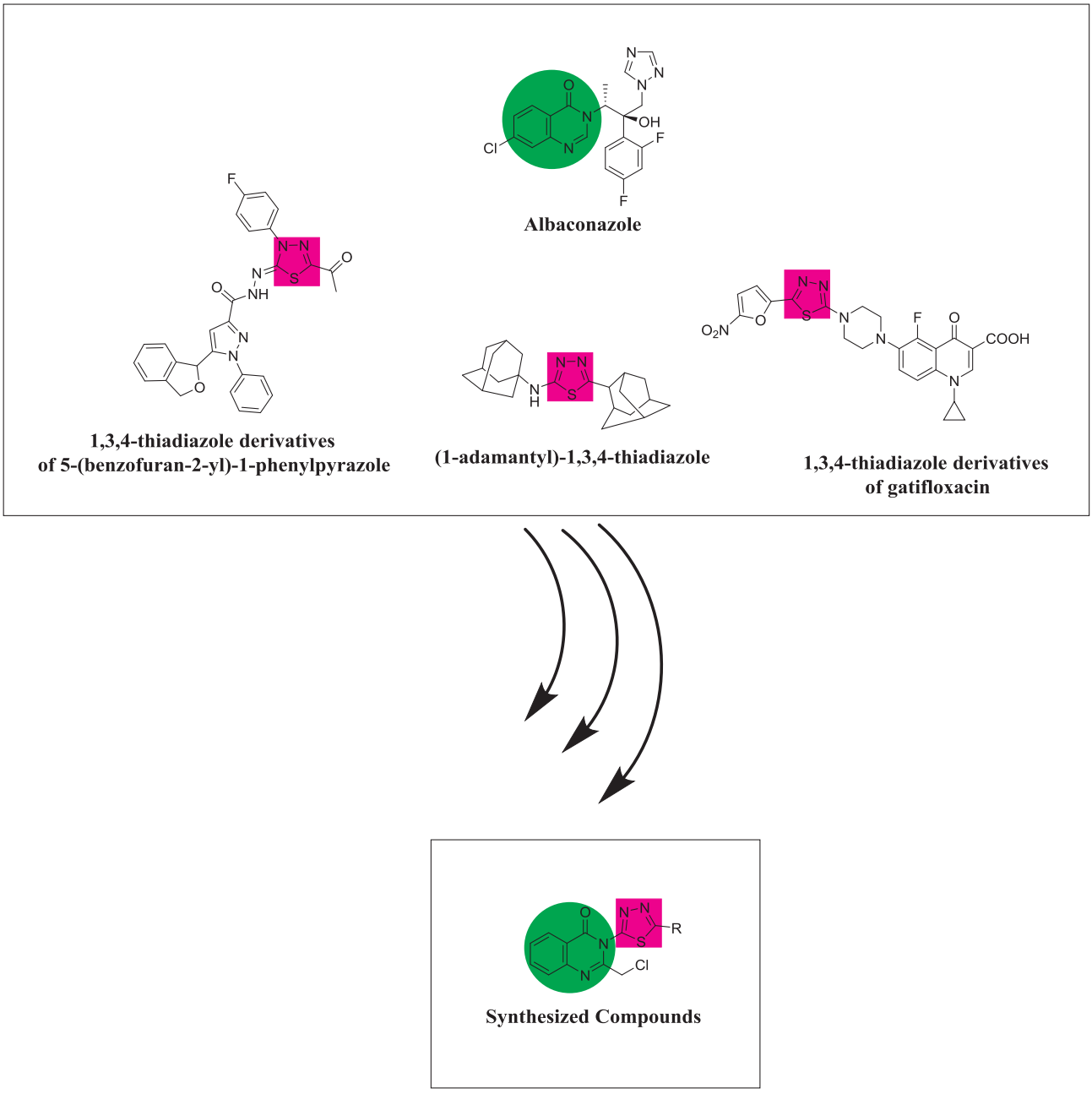

Fig. 1. Rationale for the synthesis of compounds.

2. Materials and methods

2.1. Experimental

All the chemicals and solvents were supplied by Loba, S. D. Fine, E-Merck, and Rankem chemicals, Sigma-Aldrich and Spectrochem Pvt. Ltd. Solvents were distilled and dried before use as required. The reactions were monitored with the help of thin-layer chromatography using pre-coated aluminum sheets with GF_{254} silica gel, 0.2 mm layer thickness (Merck) by using solvent systems benzene : acetone (7:3 and 9:1), toluene: ethyl acetate: formic acid (5:4:1) and chloroform: methanol (9:1). The spots were visualized under UV lamp. Melting points of the synthesized compounds were determined and are uncorrected using one end open capillary tubes on a scientific melting point apparatus Analab Scientific Instruments. FTIR spectrum was recorded using KBr on FTIR-8400S Shimadzu spectrometer. Both ^{1}H NMR (DMSO) and ^{13}C NMR spectra of the synthesized compounds were performed with Bruker Avance-II 400 NMR spectrometer operating at 400 MHz in SAIF, Punjab University, Chandigarh. Chemical shifts were measured relative to internal standard TMS and are reported in (δ ppm). Mass spectra of the synthesized compounds were recorded at MAT 120 in SAIF, Punjab University.

2.1.1. Synthesis of 2-(chloromethyl)-4H-benzo[d][1,3]oxazin-4-one (2a)

It is prepared as the reported procedure [25].

2.1.2. Synthesis of 2-ethyl-4H-benzo[d][1,3]oxazin-4-one (2b)

Equimolar quantities of anthranilic acid and propionic anhydride were refluxed for 3 h, after cooling solid was obtained. The obtained product was filtered and washed with methanol. Recrystallization of final the product was done from ethanol to get pure compound [26].