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ORIGINAL ARTICLE

Synthesis and biological evaluation studies of novel quinazolinone derivatives as antibacterial and anti-inflammatory agents

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Synthesis

Abstract Some novel 6,8-diiodo-2-methyl-3-substituted-quinazolin-4(3H)-ones bearing sulfonamide derivatives (4–11) were synthesized in good yields and evaluated for their possible antibacterial, anti-inflammatory activities and acute toxicity. The structures of the synthesized compounds were confirmed on the basis of their spectral data and elemental analysis. Their antibacterial activities were evaluated by the agar well diffusion method while their anti-inflammatory activities were evaluated by the carrageenan-induced hind paw edema test. All the tested compounds showed considerable antibacterial activities and high to moderate anti-inflammatory activities that last for 12 h compared to ibuprofen. All the tested compounds showed no toxic symptoms or mortality rates 24 h post-administration at tested anti-inflammatory doses. In addition, LD_{50} for all tested compounds was higher than that for ibuprofen implying their good safety margin. The obtained results showed that the most active compounds could be useful as a template for future design, modification and investigation to produce more active analogs.

1. Introduction

There is a strong relationship between bacterial infection and inflammation (Sy et al., 2011). Bacterial infection often produces pain and inflammation. Inflammation remains a common with poorly controlled clinical problem which can be life threatening in extreme form of allergy, autoimmune diseases and rejection of transplanted organs (Gounon and Huerre, 1996). The treatment options which can be used for inflammatory diseases are unsatisfactory and complicated

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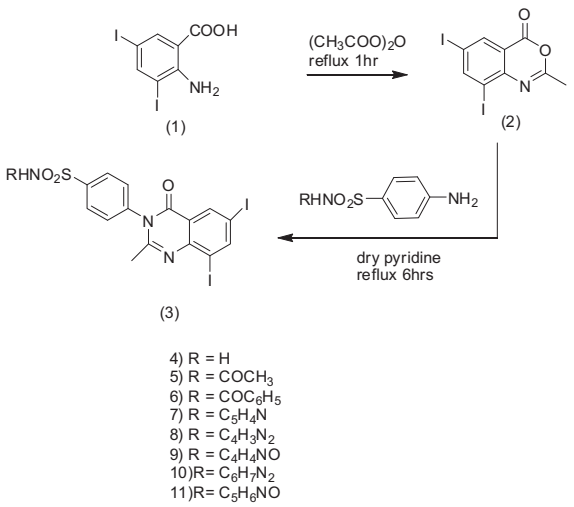
due to their lack of efficacy and adverse effect profile. It seemed worthwhile to look for candidates acting on more than one pathway involved in inflammatory conditions (Bot et al., 2011).

Quinazolin-4-one ring system has been consistently rewarded as a promising molecule because of its broad spectrum of pharmaceutical activities like antihistaminic (Lemura et al., 1989), anti inflammatory (Amin et al., 2010), antibacterial (Kini and Grover, 2006), antidiabetic (Ram et al., 2003), anticancer (Abbas et al., 2012), antifungal (Liu et al., 2006), anthelmintics (Connolly et al., 2005) and antiviral activities (Dinakaran et al., 2003). In addition to that, anti-inflammatory quinazolines possess remarkable anti-inflammatory activity through inhibition of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) (Rajan et al., 2010).

On the other hand, sulfonamide derivatives have been reported to possess significant antibacterial activities through competitive inhibition of dihydropteroate synthetase enzyme (DHPS) which is involved in folate synthesis (Skold, 2000). Moreover, some sulfonamides work as ant-inflammatory drugs like celecoxib which works as a COX-2 inhibitor (Gassani et al., 2010) and acetazolamide which works by diuretic mechanism (Jaiswal et al., 2004). On light of these findings, we planned to prepare the target compounds as hybrid molecules. These molecules contain the quinazolinone ring system and fused with sulfonamide derivatives to form a group of compounds resembling and collecting both features of nitrogen heterocyclic moiety and sulfonamide moiety. In addition, iodine atoms exist at 6th and 8th positions from quinazoline nucleus. Iodine was selected because it has received considerable attention in organic synthesis due to its high tolerance to air and moisture, low-cost, nontoxic nature and ready availability. Presence of iodine increases the lipophilicity of the molecules, the surface of contact, the absorption and the distribution (Laznicek et al., 1985; Yanming et al., 2003).

1.1. Rationale of the study

A literature survey revealed that the presence of quinazoline moiety, which can undergo substitution at the heteroatom or the distal aromatic ring, is a necessary requirement for the antibacterial and anti-inflammatory activities such as compounds [A] (Kini and Grover, 2006), [B] (Ali et al., 2010) and [C] (Panneerselvam et al., 2009). Moreover, quinazoline derivatives with the appropriate substituent mainly amine or substituted amine at 4th position and either halogen or electron rich substituent at 6th or 8th position are known to promote against bacteria and inflammation (Tiwari et al., 2006). In view of the previous rationale, it was thought worthwhile to study the effects of two pharmacophoric moieties like quinazolinone and sulfonamide in a single molecule on the antibacterial and anti-inflammatory activities. The target compounds have been designed to contain different substituents with different electronic environments. As shown in Scheme 1, these substituents joined to the fixed moiety (3) start with hydrogen from sulfanilamide in compound (4), acetamide from sulfacetamide in compound (5), benzamide from sulfabenzamide in compound (6), pyridine from sulfapyridine in compound (7), pyrimidine from sulfadiazine in compound (8), 5-methylisoxazole from sulfamethoxazole in compound (9), 4,6-dimethylpyrimidin from sulfamethazine in compound (10) and 3,4-dimethyl-1,2-oxazole from sulfafurazole in compound (11). These varied substituents allow us to study the effect of hydrophilic and hydrophobic



Scheme 1 Synthesis of the target compounds (4–11).

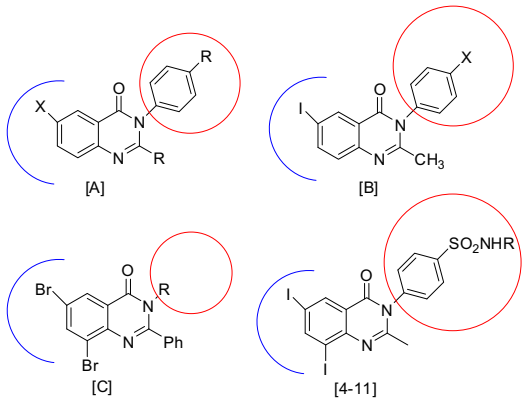


Figure 1 Similarities between reported compounds as antibacterial, anti-inflammatory and target compounds (4–11).

changes on the biological activity of the target compounds. Fig. 1 represents the similarities between the reported antibacterial and anti-inflammatory quinazolinones and our designed compounds.

2. Materials and methods

2.1. Chemistry

The tested compounds were analyzed at the Analytical Center, College of Science, Cairo University, Egypt. All melting points were measured on a Griffin melting point apparatus (Griffin) and are uncorrected. The Infrared spectra were recorded as KBr disks on a Nicolet IR 200 (Thermo Fisher Scientific). The ^{1}HNMR and ^{13}CNMR spectra were run using TMS as an internal standard (Sigma–Aldrich) on Varian Mercury VXr-300 NMR (Varian). Mass spectra were obtained on a JEOL-SX-102 instrument using electron impact ionization. Elemental analyses (C, H, N) were performed on a Perkin–Elmer 240C analyzer (Perkin–Elmer). All compounds were within ±0.4% of the theoretical values. All chemicals used for synthesis were purchased from (Sigma–Aldrich).