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Review

Trifluoromethylpyrazoles as anti-inflammatory and antibacterial agents: A review

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ABSTRACT

In the recent past trifluoromethylpyrazoles have gained much attention, particularly as anti-inflammatory and antibacterial agents, in the field of medicinal chemistry. The location of trifluoromethyl group, specially on 3- or 5-position of pyrazole nucleus, is greatly associated with variation in activity profile of the compounds. Therefore, the main objective of this article is to highlight the importance of trifluoromethylpyrazoles as anti-inflammatory and antibacterial agents on a single front. The present review covers the literature from 2000 to 2015 and would certainly be proven as a great help to the medicinal chemists to explore some novel anti-inflammatory and antibacterial agents with better action profiles with minimal side effects.

Contents

1. Introduction

1.1. Medicinal importance of fluorinated heterocycles

Heterocyclic compounds have been drawn scientific attention over the years due to their remarkable biological properties [1–5]. Literature survey revealed that presence of fluorine or trifluoromethyl group on the heterocyclic core, particularly azole or azine, resulted in the development of a large number of synthetically, medicinally and agrochemically potent compounds. Some important examples include: capecitabine (RG-340) **1**, a *N*-4 carbamate pyrimidine prodrug, used for treatment of breast and colorectal cancers [6]; fluazinam **2** which displayed very high potential against diseases in field crops [7]; ARN-509 **3**, a non-steroidal anti-androgen compound, inhibited prostate cancer cell proliferation (under clinical trials) [8]; sitagliptin **4** (an inhibitor of dipeptidyl peptidase 4) and (*S*)-6-(3-cyclopentyl-2-(4-(trifluoromethyl)-1*H*-imidazol-1-yl)propanamido)nicotinic acid **5** (hepatoselective glucokinase activator) were used as promising drug candidates for the treatment of type-2 diabetes mellitus

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[9,10]. 3-(4-Nitrophenoxy)-5-(trifluoromethyl)-4*H*-1,2,4-triazol-4-amine **6**, thifluzamide **7** and metsulfovax **8** were used as an efficient fungicidal agents [11,12], and (*R*,*S*)-2-amino-3-(3-hydroxy-5-trifluoromethyl-4-isoxazolyl)propanoic acid **9**, a highly potent AMPA receptor agonist [13] (Fig. 1).

1.2. Medicinal importance of trifluoromethylpyrazoles

Among fluorinated heterocycles, trifluoromethylpyrazole derivatives are known to possess interesting bioactivities (Fig. 2). Some of the important examples of such compounds include: celecoxib **10**, acts as an anti-inflammatory as well as antibacterial agent [5,14]; 3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide derivative **11**, used as an activator of the M2 isoform of pyruvate kinase [15]; 5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-trifluoromethylpyrazole **12**, acts as growth suppressor in human lung cancer cells [16]; 1-(2-aminomethylphenyl)-3-trifluoromethyl-N-[3-fluoro-2′-(aminosulfonyl)[1,1′-biphenyl)]-4-yl]-1*H*-pyrazole-5-carboxyamide hydrochloride (DPC-602) **13**, acts as a potent, selective and orally bioavailable factor Xa inhibitor (serine protease inhibitor) which was used to provide an effective treatment for both venous and arterial thrombosis [17]. High medicinal value of trifluoromethylpyrazoles is might be due to presence of CF_3 group which makes these molecules more lipophilic and thereby increases the bioavailability of the drugs at the targeted site [18]. They are also used as agrochemicals, for instance fluorinated tebufenpyrad derivative **14** was used as a herbicide and penthiopyrad **15** was found as an efficient fungicidal agent [19,20].

1.3. Scope in inflammation and bacterial infections

It has been found that the treatment of various disorders involving inflammation and bacterial infections is the major challenge in the field of drug discovery. Inflammation and infection are not equal, even when infection is primary cause of inflammation [21]. Inflammation may cause accumulation of fluid in the injured area which may result into increase in bacterial growth [21]. Literature survey revealed that non selective and non steroidal anti-inflammatory drugs (NSAIDs) using in treatment of inflammation may enhance the progression of bacterial infection [21]. These drugs are known to inhibit the activity of both the isoforms of enzyme cyclooxygenase (COX), *i.e.* COX-1 and COX-2. The anti-inflammatory effect of NSAIDs comes as a result of COX-2 inhibition, whereas many side effects including gastric ulceration were observed due to inhibition of COX-1 isoform [22,23] (Fig. 3). In order to overcome limitations of the non selective NSAIDs some selective COX-2 inhibitors (coxibs) came in demand. These coxibs are regarded as safe agents to treat the bacterial infection in comparison to non selective NSAIDs [14]. Moreover, due to increase in antibiotic resistance developed by the pathogens in the last few decades, there is also a need to develop an efficient class of antibacterial agents [24]. After discovery of the drug, celecoxib, as a selective COX-2 inhibitor as well as an efficient antibacterial agent several other trifluoromethylpyrazole derivatives have been designed and synthesized to explore their application in the field of medicinal chemistry. Therefore, the main objective of the present review is to highlight the importance and development of trifluoromethylpyrazole derivatives as an efficient class of anti-inflammatory and antibacterial agents.

1.4. Common synthetic routes toward trifluoromethylpyrazoles

Owing to broad applications in various research fields, synthetic chemistry of trifluoromethylpyrazoles has also become a matter of great interest among the chemists worldwide [25–32]. The reaction of trifluoromethyl β-carbonyl compounds **16** with various *N*-substituted hydrazines **17** is the most commonly used method to achieve 3- and/or 5-trifluoromethylpyrazole derivatives **18**–**20** (Scheme 1) [33].

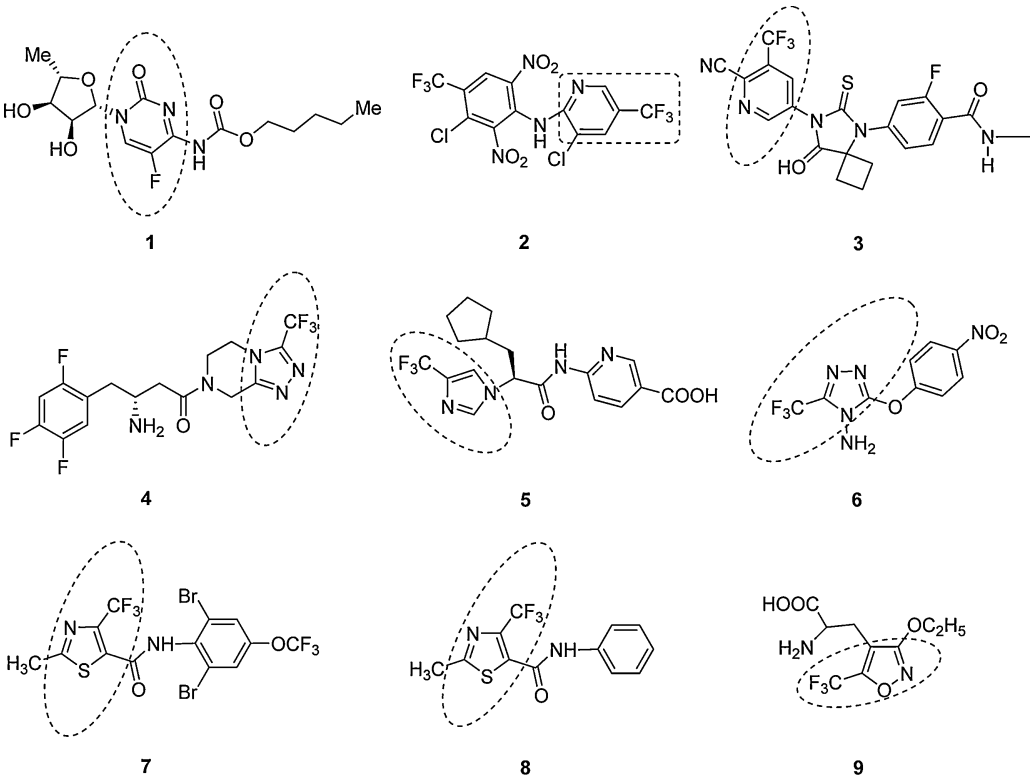

Fig. 1. Some important fluorine or trifluoromethyl-substituted azole or azine compounds.