Journal of Fluorine Chemistry 132 (2011) 131–137

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

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

Synthesis and biological evaluation of new 3-trifluoromethylpyrazolesulfonyl-urea and thiourea derivatives as antidiabetic and antimicrobial agents

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ARTICLE INFO

Article history:
Received 10 October 2010
Received in revised form 11 December 2010
Accepted 14 December 2010
Available online 21 December 2010

Keywords:
Fluorinated pyrazoles
Benzenesulfonylureas
Thioureas
Thiazolidines
Thiazines
Antidiabetic and antimicrobial activities

ABSTRACT

Fluorinated pyrazoles, and benzenesulfonylurea and thiourea derivatives as well as their cyclic sulfonylthioureas **2**–**18** were prepared as hypoglycemic and antibacterial agents. The chemistry involves the condensation of 4-hydrazino benzenesulfonamide hydrochloride with 1-trifluoromethyl diketones **1** to give pyrazole derivatives **2** which upon bromination gave the bromopyrazole **3**. Reaction of **2** or **3** with isocyanates and isothiocyanates gave the corresponding ureas **4** and **5** and thioureas **6** and **7**. Cyclization of thiourea derivatives with ethyl bromoacetate, ethyl β-bromopropionate, 1,3-dichloroacetone and α-bromoacetophenone yielded the corresponding 4-oxothiazolidines **8** and **9**, 4-oxo-5,6-dihydrothiazine **10**, 5-oxo-4,5-dihydrothiazines **11** and **12** and thiazolines **13** and **14**. Preliminary biological screening of the prepared compounds revealed significant antidiabetic and antibacterial activities.

1. Introduction

The presence of fluorine and trifluoromethyl group in particular, is recognized in medicinal chemistry as a substituent of distinctive qualities [1,2]. Insertion of fluorine in a strategic position of a molecule has emerged as a very powerful and versatile tool for the development of compounds endowed with biological activities. In heterocyclic compounds trifluoromethyl group plays a significant role to alter the physico-chemical and biological characteristics of these molecules [3,4]. The incorporation of fluorine into a drug modulates the steric and electronic parameters thereby influencing both the pharmacodynamic and pharmacokinetic properties of drugs. In terms of bioisosterism, trifluoromethyl group is smaller than the isopropyl, larger than the methyl, and rather similar to the ethyl group [5]. The presence of fluorine often leads to increased lipid solubility, thereby enhancing rates of absorption and transport of drugs *in vivo* [6]. Therefore, there has been greater effort towards the synthesis of biologically active pyrazoles having trifluoromethyl group as one of the substituents on either C-3 or C-5 [7–9]. Furthermore, 5-aminopyrazoles and 3-trifluoromethylpyrazoles with a wide array of groups at N-1 and C-4 were reported to be selective inhibitors of cyclooxygenase [10–12] and have antidiabetic [13], herbicidal [14] and antibacterial properties [15]. However, since several 3,5-dimethylpyrazoles possess hypoglycemic activities as much as 100 times that of tolbutamide in glucose-primed intact rats [16–19], studies have been conducted in our group on the synthesis of new 3,5-disubstituted pyrazoles [20–25]. In continuation of our previous work in the preparation of 3,5-disubstituted pyrazole [21–29] and fluorinated pyrazole [30,31] benzenesulfonylurea and thiourea derivatives as well as their cyclic sulfonylthioureas, many new trifluoromethyl pyrazole derivatives of these classes were synthesized and were tested for hypoglycemic and antimicrobial activities. Preliminary biological testing revealed that some compounds showed significant antibacterial and antidiabetic activities.

2. Results and discussion

2.1. Synthesis and spectral characterizations

Condensation of the key intermediates, *p*-sulfonylphenylhyrazine hydrochloride with fluorodiketones **1** afforded 5-substituted-3-trifluoromethyl-1-(*p*-sulfonylphenyl)pyrazoles **2** (Scheme 1 and Table 1). Bromination of **2** with bromine in chloroform afforded the corresponding 4-bromo-pyrazole **3**. The IR spectra of these pyrazoles displayed two absorption bands at 3225–3238 cm^{-1} and 3352–3368 cm^{-1} indicative of the NH_2 group, in

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doi:10.1016/j.jfluchem.2010.12.009