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# Synthesis and biological evaluation of new 3,5-di(trifluoromethyl)-1,2,4-triazolesulfonylurea and thiourea derivatives as antidiabetic and antimicrobial agents

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ABSTRACT

Fluorinated 1,2,4-triazoles **3** and benzenesulfonyl urea and thiourea derivatives as well as their cyclic sulfonylthioureas **4**–**10** were prepared as antimicrobial agents. The chemistry involves the condensation of sulfanilamide derivatives **1** with trifluoroacetic anhydride to give *N*-di(trifluoroacetyl)sulfonamides **2** which upon reaction with hydrazine hydrate afforded the corresponding triazole derivatives **3**. Reaction of triazole derivative **3a** with isocyanates and isothiocyanates gave the corresponding ureas **4** and thioureas **5**. Cyclization of thiourea derivatives with ethyl bromoacetate, 1,2-diiodoethane, diethyl oxalate and α-bromoacetophenone derivatives yielded the corresponding 4-oxothiazolidines **7**, thiazolidines **8**, 4,5-dioxothiazolidines **9** and thiazolines **10**. Preliminary biological screening of the prepared compounds revealed significant antimicrobial and mild antidiabetic activities.



## 1. Introduction

The introduction of fluorine or appropriate fluorinated functions into a molecule has become an invaluable tool for medicinal chemists [1,2]. Replacing hydrogen and other functional groups with fluorine can have a dramatic effect on the modulation of electronic, lipophilic and steric parameters, all of which can critically influence both the pharmacodynamic and pharmacokinetic properties of drugs [3,4]. Substitution of fluorine into a potential drug molecule not only alters the electronic environment, but it also influences the properties of neighboring functional groups. It exerts a substantial effect on the molecule's dipole moment, the acidity or basicity of other groups nearby, not to mention the overall reactivity and stability of the molecule [5,6].

Trifluoromethyl group is recognized in medicinal chemistry as a substituent of distinctive qualities and it is one of the most lipophilic functional groups known. It provides an extremely useful way of making a molecule more easily delivered to the active site in the body. Some of the best known drugs have trifluoromethyl substitution. These include the SSRI anti-depressant fluoxetine and fluvoxamine [7,8], the COX-2 inhibitor celecoxib [9], the antimalarial drug mefloquine [10], HIV protease inhibitor tipranavir [11], anticancer drug bicalutamide [12], and antiemetic drug aprepitant [13].

Substituted 1,2,4-triazoles constitute an important class of organic compounds with wide-ranging pharmacological activities such as antibacterial [14], antifungal [15], antimycobacterial [16], anti-inflammatory [17], and anticancer [18,19] activities. Some of the fluoro substituted and trifluoromethyl substituted 1,2,4-triazoles, Fluconazole [20] and Fluotrimazole [21] respectively, are well known drugs in use. However, none of them have a trifluoromethyl group in the triazole ring. Furthermore, fluoro- and trifluoromethyl pyrazoles, benzenesulfonyl urea and thiourea derivatives as well as their cyclic sulfonylthioureas were reported by our group to possess hypoglycemic and antimicrobial activities [22–24]. Therefore, it was considered worthwhile to introduce trifluoromethyl groups in triazole ring. The current study involves the preparation of fluorinated 1,2,4-triazoles and benzenesulfonyl urea and thiourea derivatives as well as their cyclic sulfonylthioureas as possible antimicrobial and antidiabetic agents.

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