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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.

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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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2. Results and discussion

2.1. Synthesis and spectral characterizations

Bi-nucleophlic attack on the 1,3-bicarbonyl compounds under mild conditions is an important process in synthetic organic chemistry, especially primary bi-nitrogen reagent led to formation of functionalized 1,2,4-triazoles which easily form a type of complexes with transition metals as antifungal agents [25].

Thus, condensation of sulfanilamide derivatives **1a–d** with trifluoroacetic anhydride afforded *N*-di(trifluoroacetyl)sulfanilamides **2a–d** which in turn react with hydrazine hydrate to give 3,5-di(trifluoromethyl)-4-*p*-sulfonamidophenyl-1,2,4-triazoles **3a–d** (Scheme 1). The IR spectra of **2a–d** displayed carbonyl band at 1700–1710 cm^{-1}, two absorption bands at 3265–3272 cm^{-1} and 3368–3384 cm^{-1} indicative of the NH_2 group, in addition to the strong bands at 1330–1352 cm^{-1} and 1145–1156 cm^{-1} for the SO_2N moiety. On the other hand The IR spectra of the triazole derivatives **3a–d** lacked the CO band and showed the NH_2 absorption bands at 3258–3268 and 3365–3376 cm^{-1} as well as the two SO_2 bands at 1148 cm^{-1} and 1362 cm^{-1}. The ^{13}C NMR spectra of **2** exhibited a carbonyl carbon signal at δ 166.5 which is in agreement with the suggested structures. The same peak was absent in the ^{13}C NMR spectra of compounds **3** (Table 2). Condensation of triazole derivative **3a** with the appropriate isocyanate and isothiocyanate in dry acetone yielded the corresponding benzene urea **4** and thiourea **5** derivatives respectively. Furthermore, condensation of **2** with appropriate isothiocyanate afforded the thiourea derivative **6**. Compound **5** can alternatively be prepared from **6** by refluxing the latter with equimolar amount of hydrazine hydrate in ethanol. The IR spectra of these compounds exhibited two bands at 1330–1362 cm^{-1} and 1144–1156 cm^{-1} due to SO_2N group as well as a urea carbonyl band at 1654–1660 cm^{-1} in case of compounds **4** and a thiourea carbonyl absorption at 1133–1148 cm^{-1} for compounds **5**. The structures of the above compounds **4** and **5**, were further supported by their elemental analyses (Table 1), ^1H NMR and ^{13}C NMR spectra (Table 2).

It has been reported that condensation of N,N′-disubstituted thiourea with chloroacetic acid, its chloride or α-bromo esters afforded 2-imino-4-oxothiazolidines, and the reaction proceeds through the intermediate formation of the cyclic pseudothiohydantoic acid [26–28]. In the present study, cyclization of the thiourea derivatives **5** with ethyl bromoacetate, 1,2-diiodoethane, diethyl oxalate and α-bromoacetophenone derivatives afforded the corresponding 4-oxothiazolidine **7**, thiazolidine **8**, 4,5-di-oxothiazolidine **9** and 4-subistituted thiazoline **10** derivatives respectively. IR spectra of compounds **7** and **9** showed cyclic carbonyl absorptions at 1720–1740 cm^{-1} and two other absorption bands at 1335–1344 cm^{-1} and 1150–1164 cm^{-1} for the SO_2N group. The structures of the above fluorinated compounds **7–10** and the non-fluorinated analogs **11** and **12** were further supported by their ^1H NMR and ^{13}C NMR data (Table 2).

2.2. Anti-microbial activity

Compounds **2–12** were screened *in vitro* for their antimicrobial and antifungal activity against *Escherichia coli*, *Staphylococcus aureus*, *Aspergillus niger* and *Candida albicans*. The zones of inhibition formed for the compounds against bacteria and fungi are summarized in Table 3. All compounds were found to possess mild to moderate activity. Compounds **3c**,**d**, **4c**, **5c–f**, **6d**, **7d**,**e**, **8c** and **10f**,**g** were however, significantly active when compared with rest of the series. Moreover, after using UV–vis light, most of the tested compounds showed an additional activity especially towards *E. coli* and *C. albicans* (Table 5). All test data in Tables 3 and 4 were of average values from triplicate runs and the test compounds showed reduced antimicrobial activities when compared with their respective standards. In a related study of the non-fluorinated analogs (**11a–c** and **12a–c**; Scheme 2) when compared with their fluorinated counterparts, the former could not exhibit the same degree of zone inhibition thereby suggesting the trifluoromethyl substitution in the triazole ring to be an activity enhancer in the present study (Table 3).

2.3. Antidiabetic activity

From the data presented in Table 5, it is implied that tested compounds possess mild hypoglycemic activity. The potency of these compounds is less than that of phenformine. Introduction of bromine atom into the phenyl ring of compounds **10** slightly increases the hypoglycemic activity of these derivatives.

3. Conclusions

In this paper, several new 3,5-di(trifluoromethyl)-4-*p*-sulfonamidophenyl-1,2,4-triazole derivatives were synthesized by the condensation of 4-hydrazino benzenesulfonamide hydrochloride with *N*-di(trifluoroacetyl)sulfonamides. Moreover, many new urea and thiourea derivatives were prepared from the reaction of the above triazoles with the appropriate isocyanate and isothiocyanate. Cyclization of the thiourea derivatives with the appropriate reagent afforded the corresponding cyclic compounds. The structures of the prepared compound were confirmed by elemental analysis, IR ^1H and ^{13}C NMR spectral analysis. Preliminary biological testing of some of these compounds revealed that some triazole derivatives exhibited significant antimicrobial activities but weak antidiabetic activity. Further, the incorporation of trifluoromethyl group is justified by a comparative study with the non-fluorinated analogs. The fluorinated analogs were found to be more active than their non-fluorinated counterparts.

4. Experimental

4.1. Chemicals and methods

Melting points were determined in open glass capillaries on a Gallenkamp melting point apparatus and were uncorrected. The infrared (IR) spectra were recorded on Perkin-Elmer 297 infrared spectrophotometer using the plate technique. The ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 as a solvent on Bruker DPX-400-FT spectrometer using tetramethylsilane as the internal standard. Elemental analyses were performed at the Microanalytical Unit, Faculty of Science, Cairo University, Cairo, Egypt. Follow up of the reactions and checking the homogeneity of the compounds were made by TLC on silica gel-protected aluminum sheets (Type 60 F254, E. Merck) and the spots were detected by exposure to UV lamp at λ 254. Biological testing was performed in the Faculty of Medicine University of Alexandria, Egypt. Reagents were of analytical grade and were used without further purification.

4.1.1. N-Di(trifluoroacetyl)sulfonamides (2a–d)

A mixture of the appropriate sulfonamide **1** (10 mmol) in THF (30 mL) and trifluroacetic anhydride (10 mmol) was refluxed for 2 h. The solid which separated on cooling was recrystallized from ethanol as needles.

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