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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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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.

*4.1.2. 3,5-Di(trifluoromethyl)-4-p-sulfonamidophenyl-1,2,4-triazoles (**3a–d**)*

A solution of the appropriate *N*-di(trifluoroacetyl)sulfonamide derivative **2** (10 mmol) in THF (25 mL) was refluxed with hydrazine hydrate (12 mmol) for 2 h. The reaction mixture was then, cooled poured onto ice and the obtained solid was recrystallized from ethanol as needles.

*4.1.3. p-(3,5-Di(trifluoromethyl)-1,2,4-triazol-4-yl)benzenesulfonylureas (**4a–c**)*

A mixture of the 1,2,4-triazole derivative **3** (10 mmol) and anhydrous K_2CO_3 (20 mmol) in dry acetone (25 mL) was stirred and refluxed for 1 h. At this temperature, a solution of the appropriate isocyanate (15 mmol) in dry acetone (5 mL) was added dropwise. After the mixture was stirred and refluxed overnight, acetone was removed under pressure, and the solid residue was dissolved in water. The crude product was isolated by acidification with 2 N HCl and purified by recrystallization from ethanol as needles.

*4.1.4. p-(3,5-Di(trifluoromethyl)-1,2,4-triazol-4-yl)benzenesulfonylthioureas (**5a–f**)*

A mixture of **3** (10 mmol) and anhydrous K_2CO_3 (20 mmol) in dry acetone (25 mL) was stirred and treated with the appropriate isothiocyanate (12 mmol). After the mixture was stirred and refluxed for 10 h, acetone was removed under pressure, and the solid mass dissolved in water and acidified with 2 N HCl. The crude product was purified by recrystallization from ethanol as needles. Alternatively, compounds **5** has been prepared by refluxing the appropriate thiourea derivative **6** (10 mmol) with equimolar amount of hydrazine hydrate in ethanol (20 mL) for 2 h.

*4.1.5. N^1-Subistituted N^3-[p-di(trifluoroacetylamino)benzenesulfonylthioureas (**6a–d**)*

A mixture of **2** (10 mmol) and anhydrous K_2CO_3 (20 mmol) in dry acetone (25 mL) was stirred and treated with the appropriate isothiocyanate (12 mmol). After the mixture was stirred and refluxed for 10 h, acetone was removed under pressure, and the solid mass dissolved in water and acidified with 2 N HCl. The crude product was purified by recrystallization from ethanol as needles.

*4.1.6. 3-Substituted-2-[p-(3,5-di(trifluoromethyl)-1,2,4-triazol-4-yl)benzenesulfonylimino]-4-oxothiazolidines (**7a–e**)*

A mixture of **5** (10 mmol), ethyl bromoacetate (10 mmol) and sodium acetate (20 mmol) in absolute ethanol (30 mL) was refluxed for 2 h. The reaction mixture was then filtered while hot, concentrated and allowed to cool. The product obtained was recrystallized from ethanol as needles.

*4.1.7. 3-Substituted-2-[p-(3,5-di(trifluoromethyl)-1,2,4-triazol-4-yl)benzenesulfonylimino]thiazolidines (**8a–c**)*

A solution of **5** (10 mmol) in absolute ethanol (20 mL) was refluxed with 1,2-di-iodoethane (10 mmol) and sodium acetate (20 mmol) for 2 h. The reaction mixture was then cooled and poured into water; the precipitated thiazine was recrystallized from ethanol as needles.

*4.1.8. 3-Substituted-2-[p-(3,5-di(trifluoromethyl)-1,2,4-triazol-4-yl)benzenesulfonylimino]-4,5-dioxothiazolidines (**9a–c**)*

A mixture of the appropriate thiourea, **5** (10 mmol), diethyl oxalate (10 mmol) and sodium acetate (20 mmol) in absolute ethanol (25 mL) was refluxed for 2 h. The thiazine which separated on cooling was recrystallized from ethanol as needles.

*4.1.9. 3,4-Disubstituted-2-[p-(3,5-di(trifluoromethyl)-1,2,4-triazol-4-yl)benzenesulfonylimino]-1,3-thiazolines (**10a–g**)*

A solution of the corresponding thiourea derivative **5** (10 mmol) in absolute ethanol (25 mL) was refluxed with the appropriate α-bromoacetophenone (10 mmol) and sodium acetate (20 mmol) for 2 h. The reaction mixture was then cooled and poured into water; the precipitated thiazoline was recrystallized from ethanol as needles.

*4.1.10. N-Disubstituted sulfonamides (**11a–c**)*

A mixture of the appropriate sulfonamide **1** (10 mmol) and the proper anhydride (5 mL) was refluxed for 4 h. The reaction mixture was then, cooled poured onto ice and the obtained solid was recrystallized from ethanol as needles.

*4.1.11. 3,5-Disubstituted-4-p-sulfonamidophenyl-1,2,4-triazoles (**12a–c**)*

A solution of the appropriate N-disubstituted sulfonamide derivative **11a–c** (10 mmol) in THF (25 mL) was refluxed with hydrazine hydrate (12 mmol) for 2 h. The reaction mixture was then, cooled poured onto ice and the obtained solid was recrystallized from ethanol as needles.

4.2. Procedure for biological activity

4.2.1. Procedure for anti-microbial activity

The preliminary anti-microbial activities of new fluorinated 1,2,4-triazole and pyrimidine derivatives were measured in a concentration of 50 mg/L by disc diffusion method [29,30]. The prepared compounds were tested for their antimicrobial activity against two types of bacterium, *S. aureus* (ATCC 25923) as Gram positive bacteria, *E. coli* (ATCC 25922) as an example of Gram negative bacteria, and the antifungal activity was tested using the pathogenic yeast strain *C. albicans* and *A. niger*. DMSO was used as a solvent control and the standard drugs used were Ampicillin and Griseofulvin. The disc diffusion method was performed using Muller–Hinton agar (Hi-Media) medium. The inhibition zones were measured in mm at the end of an incubation period of 24 h at 37 °C for bacteria and 72 h at 24 °C for fungi.

4.2.2. Procedure for anti-microbial activity using UV (366 nm) light

This test was performed as mentioned before but the Petri-discs containing microorganisms and the testing compounds were subjected to UV light (366) for 3 h before transferred to the incubation periods.

4.2.3. Procedure for antidiabetic activity

Compounds **2a**,**b**, **3a**,**c**,**d**, **4a–c**, **5b**,**c**, **6b**, **7a**,**b**, **8a**,**b**, **10a**,**c**,**f**,**g** were tested for hypoglycemic activity using alloxan-treated female albino mice weighing 20 g. Alloxan 100 mg/kg was injected into the tail vein in a 10 mg/ml saline solution. Three days later the mice were given the test compounds orally in suspension in 1% carboxymethylcellulose solution at the rate of 0.2 mmol/kg of the body weight. Each day a group of four mice was used as a control group and one group of five mice was given the standard 100 mg of phenformine/kg. Up to six groups of four mice received the test compounds. Blood samples were collected into 0.04% NaF solution at 0, 1 and 3 h.

Glucose was determined by the micro-colorimetric copper reduction technique of Haslewood and Strookman [31]. Results are expressed as a percentage reduction of the plasma glucose levels compared to the control value. Statistical significance was assessed by a student *t*-test. Statistical significance was accepted where the calculated *t*-value exceeded the tabulated *t*-value at the $p = 0.05$ level.

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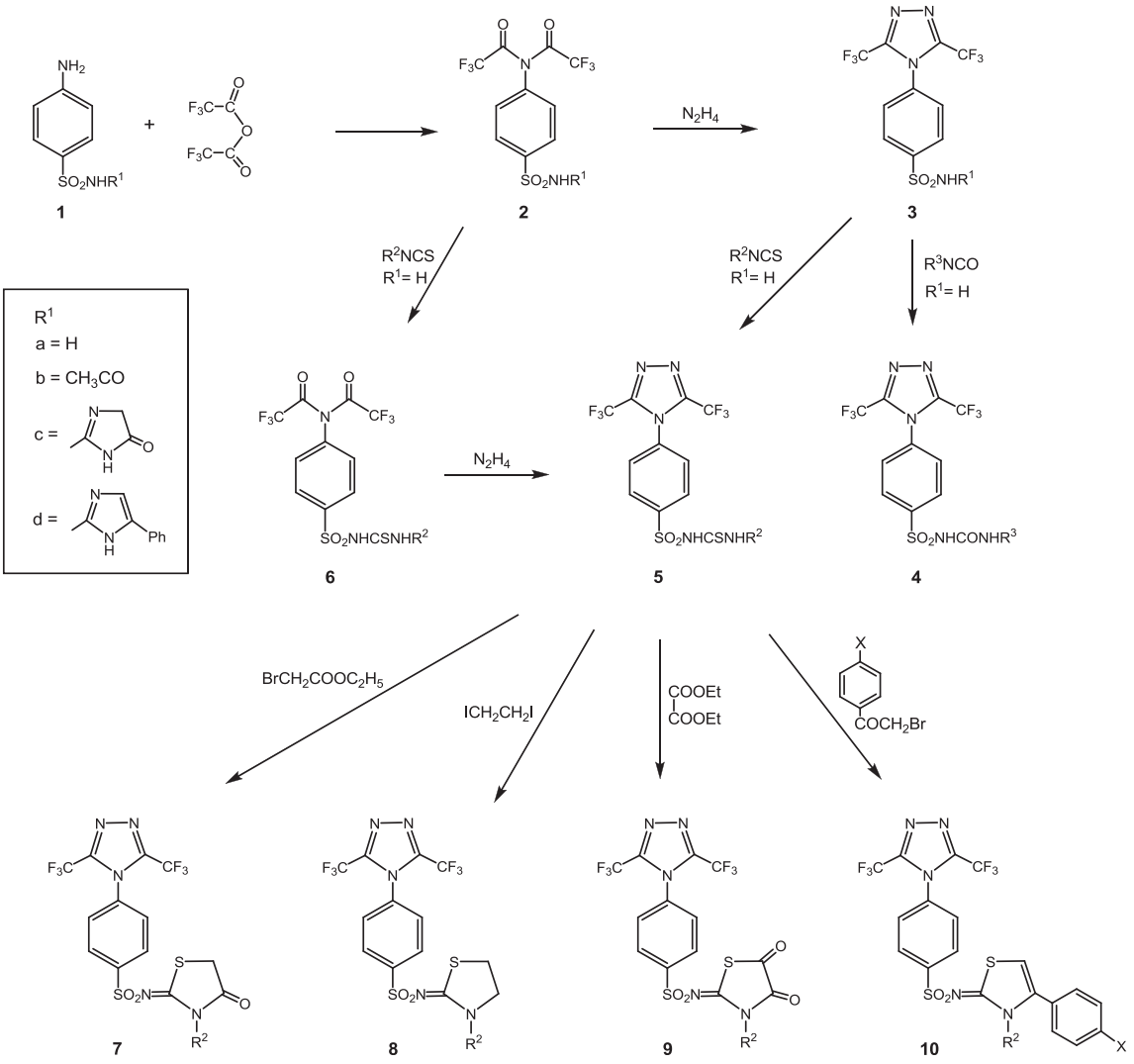
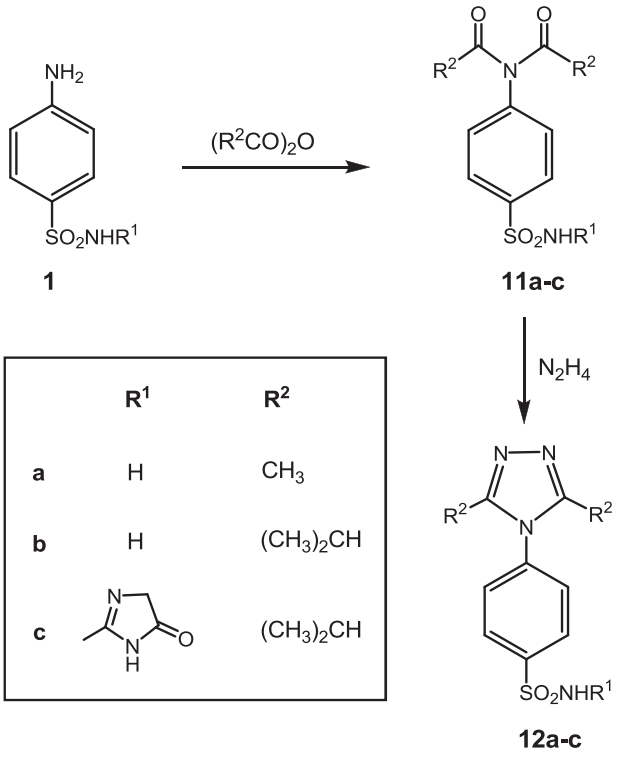
Appendix A

See Schemes 1 and 2.



Scheme 1.



Scheme 2.

Appendix B

See Tables 1–5.

Table 1
Characterization data of compounds **2**–**13**.

Compd.	R^1, R^2 or R^3	X	Yield (%)	m.p. (°C)	Mol. formula	Calc. %			Found %		
						C	H	N	C	H	N
2a	–[a]		80	211–213	$C_{10}H_6F_6N_2O_4S$	32.98	1.66	7.69	33.01	1.59	7.62
2b	–[a]		70	229–230	$C_{12}H_8F_6N_2O_5S$	35.48	1.98	6.90	35.51	2.03	6.81
2c	–[a]		74	178–180	$C_{13}H_8F_6N_4O_5S$	34.99	1.81	12.55	34.04	1.92	12.58
2d	–[a]		78	150–152	$C_{19}H_{12}F_6N_4O_4S$	45.07	2.39	11.06	45.13	2.41	11.17
3a	–[a]		94	194–196	$C_{10}H_6F_6N_4O_2S$	33.34	1.68	15.55	33.19	1.72	15.60
3b	–[a]		82	162–164	$C_{12}H_8F_6N_4O_3S$	35.83	2.00	13.93	35.91	1.98	13.89
3c	–[a]		84	150–152	$C_{13}H_8F_6N_6O_3S$	35.30	1.82	19.00	35.42	1.76	18.97
3d	–[a]		87	124–126	$C_{19}H_{12}F_6N_6O_2S$	45.42	2.41	16.73	45.52	2.38	16.72
4a	Cyclohexyl		76	184–186	$C_{17}H_{17}F_6N_5O_3S$	42.06	3.53	14.43	42.12	3.64	14.42
4b	C_6H_5		78	180–181	$C_{17}H_{11}F_6N_5O_3S$	42.60	2.31	14.61	42.45	2.29	14.60
4c	4-ClC_6H_4		80	220–222	$C_{17}H_{10}ClF_6N_5O_3S$	39.74	1.96	13.63	39.88	2.02	13.75
5a	CH_3		68	182–184	$C_{12}H_9F_6N_5O_2S_2$	33.26	2.09	16.16	33.17	2.11	16.17
5b	Cyclohexyl		70	128–130	$C_{17}H_{17}F_6N_5O_2S_2$	40.72	3.42	13.97	40.81	3.35	14.03
5c	C_6H_5		74	150–152	$C_{17}H_{11}F_6N_5O_2S_2$	41.21	2.24	14.14	41.25	2.19	14.21
5d	4-$CH_3C_6H_4$		72	120–122	$C_{18}H_{13}F_6N_5O_2S_2$	42.44	2.57	13.75	42.48	2.62	13.82
5e	4-ClC_6H_4		78	172–174	$C_{17}H_{10}ClF_6N_5O_2S_2$	38.53	1.90	13.22	38.56	2.02	13.35
5f	4-FC_6H_4		76	126–128	$C_{17}H_{10}F_7N_5O_2S_2$	39.77	1.96	13.64	39.82	2.11	13.70
6a	CH_3		70	172–173	$C_{12}H_9F_6N_3O_4S_2$	32.96	2.07	9.61	33.11	2.14	9.66
6b	Cyclohexyl		72	180–182	$C_{17}H_{17}F_6N_3O_4S_2$	40.40	3.39	8.31	40.51	3.40	8.45
6c	4-$CH_3C_6H_4$		78	202–204	$C_{18}H_{13}F_6N_3O_4S_2$	42.11	2.55	8.18	42.21	2.71	8.21
6d	4-FC_6H_4		80	125–127	$C_{17}H_{10}F_7N_3O_4S_2$	39.46	1.95	8.12	39.55	2.13	8.17
7a	Cyclohexyl		66	167–169	$C_{19}H_{17}F_6N_5O_3S_2$	42.14	3.16	12.93	42.01	3.18	13.04
7b	C_6H_5		76	230–232	$C_{19}H_{11}F_6N_5O_3S_2$	42.62	2.07	13.08	42.73	2.20	12.99
7c	4-$CH_3C_6H_4$		70	130–132	$C_{20}H_{13}F_6N_5O_3S_2$	43.72	2.38	12.75	43.82	2.41	12.72
7d	4-ClC_6H_4		78	222–224	$C_{19}H_{10}ClF_6N_5O_3S_2$	40.04	1.77	12.29	40.15	1.82	12.31
7e	4-FC_6Hv		75	170–172	$C_{19}H_{10}F_7N_5O_3S_2$	41.23	1.82	12.65	41.25	1.79	12.74
8a	Cyclohexyl		62	202–204	$C_{19}H_{19}F_6N_5O_2S_2$	43.26	3.63	13.28	43.28	3.71	13.33
8b	C_6H_5		66	228–230	$C_{19}H_{13}F_6N_5O_2S_2$	43.76	2.51	13.43	43.67	2.62	13.48
8c	4-ClC_6H_4		68	218–220	$C_{19}H_{12}ClF_6N_5O_2S_2$	41.05	2.18	12.60	41.21	2.20	12.73
9a	Cyclohexyl		64	160–162	$C_{19}H_{15}F_6N_5O_4S_2$	41.08	2.72	12.61	41.11	2.83	12.56
9b	C_6H_5		67	180–182	$C_{19}H_9F_6N_5O_4S_2$	41.53	1.65	12.75	41.64	1.74	12.84
9c	4-ClC_6H_4		69	148–150	$C_{19}H_8ClF_6N_5O_4S_2$	39.08	1.38	11.99	39.12	1.42	12.06

Table 1 (*Continued*)

Compd.	R^1, R^2 or R^3	X	Yield (%)	m.p. (°C)	Mol. formula	Calc. %			Found %		
						C	H	N	C	H	N
10a	C_6H_5		72	232–234	$C_{25}H_{15}F_6N_5O_2S_2$	50.42	2.54	11.76	50.41	2.63	11.84
10b	4-$CH_3C_6H_4$		68	248–250	$C_{26}H_{17}F_6N_5O_2S_2$	51.23	2.81	11.49	51.31	2.67	11.60
10c	4-ClC_6H_4		74	186–187	$C_{25}H_{14}ClF_6N_5O_2S_2$	47.66	2.24	11.12	47.81	2.31	11.24
10d	4-FC_6H_4		73	136–138	$C_{25}H_{14}F_7N_5O_2S_2$	48.94	2.30	11.41	49.12	2.38	11.52
10e	Cyclohexyl	Br	64	130–132	$C_{25}H_{20}BrF_6N_5O_2S_2$	44.13	2.96	10.29	44.18	3.12	10.33
10f	C_6H_5	Br	74	120–122	$C_{25}H_{14}BrF_6N_5O_2S_2$	44.52	2.09	10.38	44.64	2.11	10.44
10g	4-ClC_6H_4	Br	72	125–127	$C_{25}H_{13}BrClF_6N_5O_2S_2$	42.36	1.85	9.88	42.45	1.92	9.78
11a	–[b]		68	262–264	$C_{10}H_{12}N_2O_4S$	46.87	4.72	10.93	46.92	4.80	11.10
11b	–[b]		70	178–179	$C_{14}H_{20}N_2O_4S$	53.83	6.45	8.97	53.77	6.56	9.02
11c	–[b]		59	186–188	$C_{17}H_{22}N_4O_5S$	51.76	5.62	14.20	51.82	5.54	14.17
12a	–[b]		70	216–218	$C_{10}H_{12}N_4O_2S$	47.61	4.79	22.21	47.72	4.81	22.24
12b	–[b]		74	226–228	$C_{14}H_{20}N_4O_2S$	54.52	6.54	18.71	54.55	6.61	18.85
12c	–[b]		65	198–200	$C_{17}H_{22}N_6O_3S$	52.29	5.68	21.52	52.30	5.78	21.63

[a] For R^1 see Scheme 1.
[b] For R^2 see Scheme 2.

Table 2
^{1}H and ^{13}C NMR spectral data (δ/ppm)[c] of compounds **2–13**.

Compd.	R^1, R^2 or R^3	X	^{1}H NMR			^{13}C NMR		
			Ar-*H* (*m*)	NH_2 or N*H*	Other *H*	Ar-*C*	*C*O or *C*S	Other *C*
2a	–[a]		6.85–7.71 (4H)	8.12		120.1, 125.7, 134.9, 144.0	166.3	122.2 (CF_3)
2b	–[a]		7.05–7.82 (4H)	8.03	2.02 (*s*, CH_3)	120.7, 126.1, 135.3, 145.6	167.7	16.8 (CH_3), 123 (CF_3)
2c	–[a]		6.99–7.92 (4H)	8.00, 8.13	2.24 (*s*, CH_3)	120.8, 126.1, 133.9, 143.2, 163.8	166.2, 173.8	53.4 (CH_2), 114.8 (CF_3)
2d	–[a]		7.12–7.84 (10H)	8.17, 11.24		120.5, 122.1, 123.5, 125.6, 127.0, 128.5, 129.0, 134.9, 136.4, 136.9, 144.0	165.9	122.6 (CF_3)
3a	–[a]		6.98–7.46 (4H)	8.07		126.3, 129.1, 132.4, 139.3, 161.6		114.3 (CF_3)
3b	–[a]		7.24–7.92 (4H)	8.24	2.15 (*s*, CH_3)	126.1, 128.9, 131.8, 138.9, 161.3	173.3	16.6 (CH_3), 114.9 (CF_3)
3c	–[a]		7.68–7.91 (4H)	8.14, 8.34	2.36 (*s*,CH_2)	1321.3, 125.9, 135.0, 144.6, 161.0, 163.2	174.1	53.1 (CH_2), 115.2 (CF_3)
3d	–[a]		7.08–7.91 (10H)	8.10, 12.02		121.3, 122.2, 122.9, 125.1, 127.2, 128.9, 129.2, 135.1, 136.7, 137.0, 143.8		
4a	Cyclohexyl		7.46–7.76 (4H)	8.03, 8.32	[1.44–1.65 (m, 10H), 3.54 (m, 1H); cyclohexyl]	126.1, 129.3, 132.2,139.4, 160.1	161.3	21.6, 27.1, 32.7, 47.0 (cyclohexyl C), 114.1 (CF_3)
4b	C_6H_5		7.00–7.90 (9H)	8.16, 8.24		120.4, 124.1, 126.3, 128.6, 129.4, 132.0, 138.2, 139.5, 161.1	159.9	114.6 (CF_3)
4c	4-ClC_6H_4		7.25–7.88 (9H)	8.25, 8.40		121.8, 126.0, 129.1, 129.4, 130.3, 132.2, 136.4, 139.2, 161.4	160.2	114.9 (CF_3)
5a	CH_3		7.61–7.91 (4H)	8.12, 8.64	2.47 (*s*, CH_3)	126.2, 129.2, 132.4, 139.4, 161.5	186.3	33.7 (CH_3), 113.9 (CF_3)
5b	Cyclohexyl		7.68–7.90 (4H)	8.18, 8.34	[1.36–1.52 (m,10H), 2.56 (m, 1H); cyclohexyl]	125.8, 129.1, 133.3, 140.1, 161.3	186.1	27.6, 27.3, 33.4, 52.0 (cyclohexyl C), 114.2 (CF_3)
5c	C_6H_5		6.62–7.71 (9H)	8.14, 8.20		124.5, 125.3, 126.1, 128.7, 129.4, 132.3, 139.3, 140.2, 162.3	187.4	115.1 (CF_3)
5d	4-$CH_3C_6H_4$		6.58–7.77 (8H)	8.11, 8.42	2.35 (*s*, CH_3)	125.2, 126.3, 128.9, 129.5, 132.4, 133.7, 136.4, 139.6, 161.2	185.9	20.9 (CH_3), 114.5 (CF_3)
5e	4-ClC_6H_4		6.64–7.82 (8H)	8.30, 8.56		123.9, 125.2, 126.7, 128.5, 129.2, 129.8, 137.6, 161.9	188.2	114.9 (CF_3)
5f	4-Fv		6.68–7.87 (4H)	8.23, 8.51		115.8, 126.0, 126.9, 129.2, 132.8, 135.6, 139.5, 158.1, 161.7	187.4	114.1 (CF_3)
6b	Cyclohexyl		7.82–7.90 (4H)	8.01, 8.18	[1.38–1.59 (m, 10H), 2.43 (m, 1H); cyclohexyl]	120.6, 124.9, 135.0, 143.8	167.3	22.6, 27.4, 33.2, 53.1 (cyclohexyl C), 123.2 (CF_3)
6c	4-$CH_3C_6H_4$		6.64–7.89 (8H)	8.13, 8.19	2.36 (*s*, CH_3)	120.8, 125.6, 125.2, 129.3, 134.4, 135.7, 136.2, 143.8	168.6	20.9 (CH_3), 124.3 (CF_3)
6d	4-FC_6H_4		6.70–7.91 (8H)	8.04, 8.19				
7b	C_6H_5		7.00–7.86 (9H)		3.81 (*s*,CH_2)	120.4, 124.3, 126.4, 128.7, 129.1, 132.5, 138.8, 140.6	168.9	32.8 (CH_2), 114.7 (CF_3)
7c	4-$CH_3C_6H_4$		7.04–7.91 (9H)		2.40 (*s*, CH_3), 3.62 (*s*,CH_2)	120.2, 126.8, 129.3, 129.4, 132.4, 133.3, 137.8, 139.7, 161.7	169.3	21.5 (CH_3), 33.1 (CH_2), 113.8 (CF_3)
7d	4-ClC_6H_4		7.25–7.88 (8H)		3.80 (*s*,CH_2)			
7e	4-FC_6H_4		6.95–7.90 (8H)		3.79 (*s*,CH_2)	115.9, 122.0, 126.2, 129.4, 132.2, 136.4, 140.1, 156.6, 161.6	167.3	32.8 (CH_2), 114.6 (CF_3)
8a	Cyclohexyl		7.12–7.65 (4H)		[1.43–1.52 (m, 10H), 2.55 (m, 1H); cyclohexyl], 2.99 (*s*,CH_2), 3.22 (*s*,CH_2)			
8b	C_6H_5		6.63–7.76 (9H)		2.80 (*s*,CH_2), 3.14 (*s*,CH_2)	112.3, 116.9, 126.0, 129.1, 129.3, 132.4, 138.9, 143.5, 163.2		31.6 (C-5), 54.6 (C-4), 114.6 (CF_3)

Table 2 (*Continued*)

Compd.	R^1, R^2 or R^3	X	^{1}H NMR			^{13}C NMR		
			Ar-*H* (*m*)	NH_2 or N*H*	Other *H*	Ar-*C*	*C*O or *C*S	Other *C*
8c	4-ClC_6H_4		6.45–7.81 (8H)		2.90 (*s*,CH_2), 3.26 (*s*,CH_2)	113.7, 122.2, 126.3, 129.2, 129.6, 132.6, 139.9, 141.2, 162.9		30.7 (C-5), 56.6 (C-4), 114.2 (CF_3)
9a	Cyclohexyl		7.62–7.93 (4H)		[1.48–1.62 (m, 10H), 3.36 (m,1H); cyclohexyl]	126.3, 129.4, 132.9, 139.2, 162.1	164.2, 185.4	22.1, 26.9, 31.0, 40.2 (cyclohexyl C), 114.1 (CF_3)
9b	C_6H_5		7.01–7.79 (9H)			120.4, 124.1, 126.3, 128.7, 129.2, 132.1, 138.2, 139.3, 163.0	165.1, 186.3	114.2 (CF_3)
9c	4-ClC_6H_4		7.23–7.81 (8H)			121.8, 126.1, 129.2, 129.3, 129.6, 132.7, 136.1, 139.4, 163.0	164.9, 187.1	114.6 (CF_3)
10a	C_6H_5		6.68–7.90 (14H)		5.73 (*s*, H-5)	89.4, 115.1, 118.5, 125.9, 126.2, 127.6, 128.4, 129.2, 129.4, 132.6, 134.7, 139.1, 148.0, 151.2, 163.1		114.1 (CF_3)
10b	4-$CH_3C_6H_4$		6.38–7.88 (13H)		2.33 (*s*, CH_3), 5.80 (*s*, H-5)	84.6, 115.0, 126.3, 126.7, 127.4, 127.7, 128.3, 130.5, 132.3, 134.2, 139.1, 142.8, 150.1, 162.8		20.9 (CH_3), 114.5 (CF_3)
10c	4-ClC_6H_4		6.44–7.91 (13H)		5.77 (*s*, H-5)			
10d	4-FC_6H_4		6.58–7.82 (13H)		5.80 (*s*, H-5)	87.6, 116.3, 116.8, 126.0, 126.3, 127.7, 128.2, 129.4, 131.9, 134.0, 138.7, 141.8, 152.2, 153.1, 161.4		115.1 (CF_3)
10e	Cyclohexyl	Br	6.63–7.90 (8H)		[1.40–1.68 (m, 10H), 2.62 (m, 1H); cyclohexyl], 6.77 (*s*, H-5)	88.1, 126.2, 126.8, 127.7, 128.5, 129.3, 132.6, 134.8, 139.1, 151.6, 160.2		22.4, 27.1, 31.2, 42.9 (cyclohexyl C), 114.3 (CF_3)
10f	C_6H_5	Br	6.54–7.90 (13H)		6.72 (*s*, H-5)			
10g	4-ClC_6H_4	Br	7.19–7.82 (12H)		6.62 (*s*, H-5)	86.1, 116.3, 122.2, 123.8, 126.3, 128.1, 129.0, 129.7, 131.9, 132.0, 133.4, 139.1, 144.2, 157.0, 163.4		114.8 (CF_3)
11a	–[b]		7.91–7.92 (4H)		2.40 (*s*, 6H,$2CH_3$)	120.7, 125.8, 134.7, 144.1	168.2	14.9 (CH_3)
11b	–[b]		7.82–7.95 (4H)		1.19 (*d*, 12H, $4CH_3$), 2.78 (m, 2H, CH_2)	121.2, 125.9, 135.3, 145.4	167.4	18.0 (CH_3), 33.1 (CH)
11c	–[b]		7.78–7.80 (4H)		1.16 (*d*, 12H, $4CH_3$), 2.23 (s, 2H, CH_2), 2.70 (m, 2CH)	120.9, 125.7, 134.2, 143.8	166.8, 173.2	18.2 (CH_3), 33.4 (CH)
12a	–[b]		7.75–7.92 (4H)		2.35 (*s*, 6H,$2CH_3$)	126.1, 129.3, 133.4, 139.2		7.4 (CH_3), 161.1 (C-3, triazole)
12b	–[b]		7.70–7.86 (4H)		1.29 12H, $4CH_3$), (d, 3.12 (m, 2CH)	125.9, 128.9, 132.8, 138.9		24.4 (CH_3), 25.6 CH), 160.7 (C-3, triazole)
12c	–[b]		7.87–7.91 (4H)		1.29 12H, $4CH_3$), 2.28 (s, CH_2), 3.16 (m, 2CH)	–	–	–

[a] For R^1 see Scheme 1.
[b] For R^2 see Scheme 2.
[c] Solution in a mixture of $CDCl_3$ and DMSO-d_6.

Table 3
Anti-bacterial and anti-fungal data of trifluoromethyltriazole derivatives.

Compd.	Zone of inhibition in mm Anti-bacterial activity		Zone of inhibition in mm Anti-fungal activity	
	Escherichia coli	*Staphylococcus aureus*	*Aspergillus niger*	*Candida albicans*
2a	11	12	10	12
2b	14	13	12	14
2c	13	15	14	16
2d	15	14	16	15
3a	14	11	12	10
3b	13	12	10	8
3c	19	16	18	16
3d	18	15	17	15
4a	12	14	11	10
4b	13	12	12	11
4c	19	17	18	16
5a	14	12	13	12
5b	15	14	10	12
5c	18	17	16	19
5d	17	16	18	18
5e	22	20	19	17
5f	25	23	22	21
6b	14	12	10	8
6d	20	22		16
7a	9	8	7	8
7b	11	10	9	8
7c	15	13	12	11

Table 3 (*Continued*)

Compd.	Zone of inhibition in mm Anti-bacterial activity		Zone of inhibition in mm Anti-fungal activity	
	Escherichia coli	*Staphylococcus aureus*	*Aspergillus niger*	*Candida albicans*
7d	19	18	17	16
7e	20	22	20	19
8a	11	13	15	14
8b	15	14	11	12
8c	20	19	20	21
9a	14	15	13	14
10b	12	13	11	10
10a	14	7	7	6
10b	13	11	10	13
10c	15	13	11	10
10d	13	10	12	13
10e	13	11	11	12
10f	22	23	20	21
10g	26	22	21	22
11a	8	7	6	9
11b	9	6	7	6
11c	10	11	7	8
12a	9	10	8	6
12b	10	9	6	7
12c	11	10	8	9
Ampicillin	33	29	–	–
Griseofulvin	–	–	30	28

Table 4
Anti-bacterial and anti-fungal data of trifluoromethyltriazole derivatives using UV (366) light.

Compd.	Zone of inhibition in mm Anti-bacterial activity		Zone of inhibition in mm Anti-fungal activity	
	Escherichia coli	*Staphylococcus aureus*	*Aspergillus niger*	*Candida albicans*
2a	11	–	–	13
2b	15	–	–	14
2c	–	16	–	17
2d	16	15	17	16
3a	16	–	–	–
3b	–	–	–	–
3c	22	17	19	17
3d	19	16	–	16
4a	–	–	–	–
4b	–	–	–	12
4c	20	–	–	17
5a	16	13	14	–
5b	17	–	12	12
5c	20	18	–	–
5d	19	18	–	19
5e	24	21	–	18
5f	26	–	23	22
6b	15	–	10	–
6d	22	23	–	–
7a	–	8	–	–
7b	–	–	–	9
7c	16	–	–	12
7d	20	19	18	18
7e	21	24	22	21
8a	12	–	–	15
8b	18	–	–	16
8c	–	–	–	22
9a	–	–	–	–
10b	–	–	12	–
10a	15	–	–	–
10b	–	–	–	14
10c	16	15	–	11
10d	15	11	12	15
10e	–	–	–	13
10f	23	24	–	22
10g	–	–	–	–

–, no activity.

Table 5
Antidiabetic activity of triazole derivatives.

Compd.	Reduction in plasma glucose level, %	*P*
Phenformin	10	<0.01[a]
2a	<1	<0.05
2b	<1	0.05
3a	5	<0.01[a]
3c	7	<0.01[a]
3d	6	<0.01[a]
4a	9	<0.01[a]
4b	8	<0.01[a]
4c	7	<0.01[a]
5b	6	<0.01[a]
5c	4	<0.05
6b	3	0.05
7a	1.5	0.05
7b	2	0.05
8a	1	0.05
8b	2	0.05
10a	5	0.01[a]
10c	4	0.05
10f	8	0.01[a]
10g	9	0.01[a]

[a] Statistically significant.

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