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

Hassan M. Faidallah [a,*], Khalid A. Khan [a], Abdullah M. Asiri [a,b]

[a] Department of Chemistry, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia
[b] Center of Excellence for Advanced Materials Research, King Abdulaziz University, P.O. Box 80203, Jeddah 21589, Saudi Arabia

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.

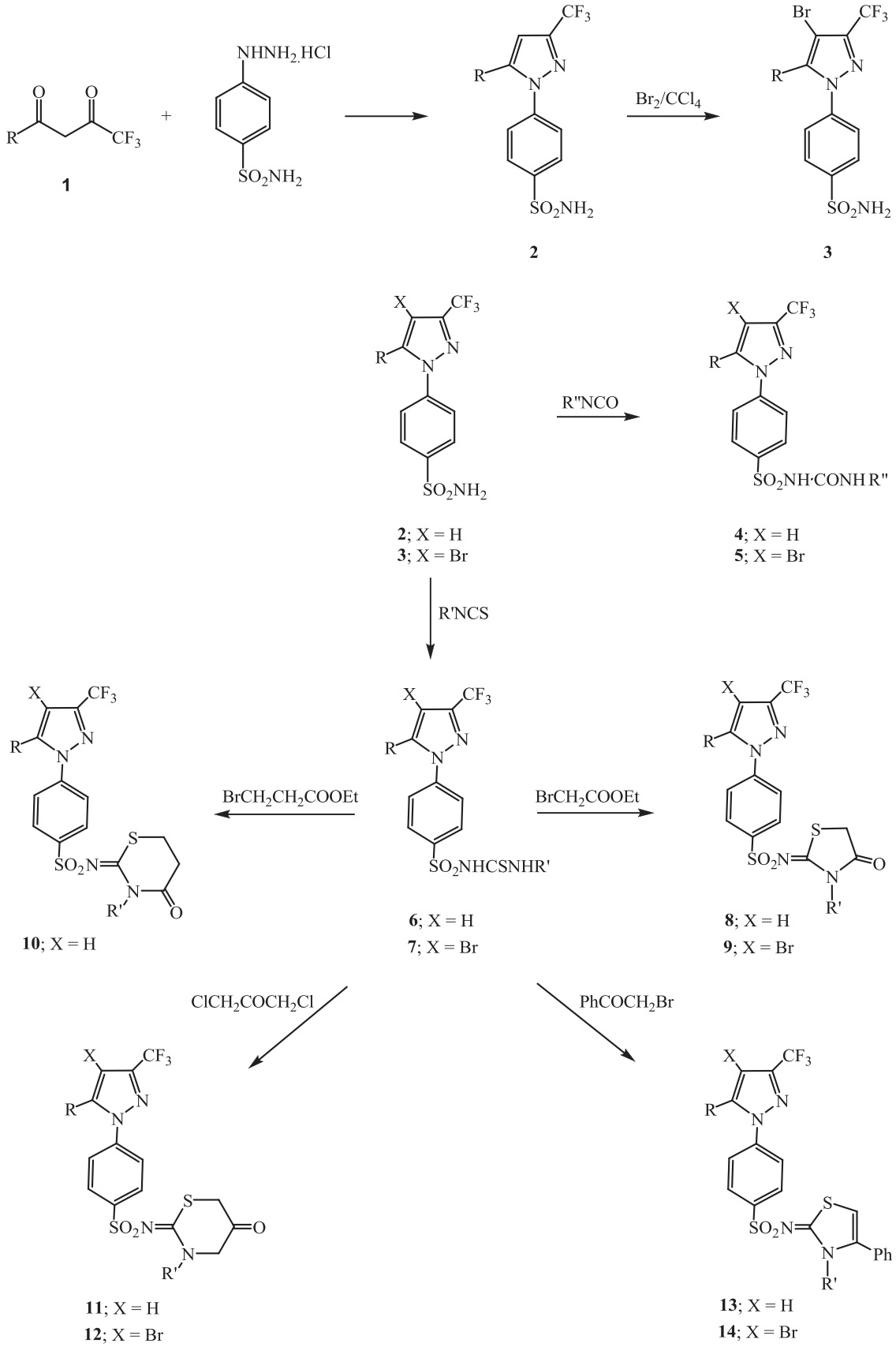
2. Results and discussion

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

* Corresponding author at: Department of Chemistry, P.O. Box 80203, Faculty of Science, King Abdulaziz University, Jeddah 21589, Saudi Arabia.
Tel.: +966 567743180.
E-mail address: hfaidallahm@hotmail.com (H.M. Faidallah).

0022-1139/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2010.12.009


1
2
3
2; X = H
3; X = Br
4; X = H
5; X = Br
6; X = H
7; X = Br
8; X = H
9; X = Br
10; X = H
11; X = H
12; X = Br
13; X = H
14; X = Br
R''NCO
R'NCS
Br2/CCl4
BrCH2CH2COOEt
BrCH2COOEt
ClCH2COCH2Cl
PhCOCH2Br

Scheme 1.

Table 1
Physical and analytical data of pyrazole derivatives.

Compd.	R	R′	Yield (%)	mp (°C)	Mol. formula	Found %				Calc.			
						C	H	N	S	C	H	N	S
2a	CH_3		86	144[a]									
2b	Furyl		82	194	$C_{14}H_{10}F_3N_3O_3S$	47.18	2.91	11.66	8.75	47.07	2.82	11.76	8.97
3a	CH_3		80	164–166	$C_{11}H_9BrF_3N_3O_2S$	34.28	2.45	11.02	8.21	34.39	2.36	10.94	8.34
3b	Furyl		88	207	$C_{14}H_9BrF_3N_3O_3S$	38.75	2.11	9.48	7.42	38.55	2.08	9.63	7.35
4a	CH_3	Cyclohexyl	70	166–168	$C_{18}H_{21}F_3N_4O_3S$	50.36	4.71	13.15	7.51	50.26	4.88	13.02	7.44
4b	CH_3	Ph	75	143–145[b]									
4c	CH_3	Naphthyl	72	139–140	$C_{22}H_{17}F_3N_4O_3S$	55.92	3.76	11.91	6.81	55.71	3.61	11.81	6.76
4d	CH_3	*p*-Cl C_6H_4	78	244–245	$C_{18}H_{14}ClF_3N_4O_3S$	47.34	3.12	12.21	7.05	47.12	3.07	12.21	6.99
4e	Furyl	Cyclohexyl	72	200–202	$C_{21}H_{21}F_3N_4O_4S$	52.39	4.47	11.55	6.72	52.28	4.38	11.61	6.64
4f	Furyl	Ph	76	180–182	$C_{21}H_{15}F_3N_4O_4S$	53.05	4.62	11.88	6.89	52.95	4.44	11.76	6.73
4g	Furyl	Naphthyl	73	124–125	$C_{15}H_{17}F_3N_4O_4S$	57.15	3.38	10.77	6.21	57.04	3.25	10.64	6.09
5a	CH_3	Ph	75	181–183	$C_{18}H_{14}BrF_3N_4O_3S$	43.06	2.91	11.24	6.51	42.96	2.81	11.13	6.37
5b	CH_3	*p*-Cl C_6H_4	77	248–251	$C_{18}H_{13}BrClF_3N_4O_3S$	40.35	2.56	10.56	6.01	40.21	2.44	10.42	5.96
5c	Furyl	Cyclohexyl	70	163–164	$C_{21}H_{20}BrF_3N_4O_4S$	44.79	4.01	9.78	5.71	44.93	3.59	9.98	5.71
5d	Furyl	Ph	70	141–143	$C_{21}H_{14}BrF_3N_4O_4S$	45.45	2.61	10.12	5.88	45.42	2.54	10.09	5.77
5e	Furyl	*p*-Cl C_6H_4	76	186–188	$C_{21}H_{13}BrClF_3N_4O_4S$	42.75	2.25	9.61	5.48	42.77	2.22	9.51	5.43
6a	CH_3	Ph	72	133–135	$C_{18}H_{15}F_3N_4O_2S_2$	49.22	3.35	12.81	14.52	49.12	3.41	12.72	14.54
6b	CH_3	Benzyl	68	144[c]									
6c	Furyl	Ph	72	147–148	$C_{21}H_{15}F_3N_4O_3S_2$	51.25	3.15	11.52	13.01	51.23	3.07	11.38	13.02
6d	Furyl	Benzyl	63	134–136	$C_{22}H_{17}F_3N_4O_3S_2$	52.21	3.35	11.15	12.78	52.18	3.38	11.06	12.66
6e	Furyl	Benzoyl	65	179–180	$C_{22}H_{15}F_3N_4O_5S_2$	50.85	3.01	10.91	12.42	50.78	2.91	10.77	12.32
7a	CH_3	Ph	69	131–132	$C_{18}H_{14}BrF_3N_4O_2S_2$	41.77	2.84	10.85	12.41	41.63	2.72	10.79	12.35
7b	CH_3	Benzyl	62	151–153	$C_{19}H_{16}BrF_3N_4O_2S_2$	42.82	3.14	10.65	12.15	42.79	3.02	10.51	12.02
7c	Furyl	Cyclohexyl	66	174–176	$C_{21}H_{20}BrF_3N_4O_3S_2$	43.71	3.52	9.82	11.21	43.68	3.49	9.71	11.11
7d	Furyl	Ph	72	152–154	$C_{21}H_{14}BrF_3N_4O_3S_2$	44.25	2.61	9.92	11.25	44.15	2.47	9.81	11.22
7e	Furyl	*p*-Cl C_6H_4	74	140–142	$C_{21}H_{13}BrClF_3N_4O_3S_2$	41.75	2.27	9.41	10.52	41.64	2.16	9.25	10.58
8a	CH_3	Ph	76	212–215	$C_{20}H_{15}F_3N_4O_3S_2$	50.21	3.26	11.71	13.48	50.01	3.15	11.66	13.34
8b	CH_3	Benzyl	70	205[d]									
8c	Furyl	Ph	76	184–186	$C_{23}H_{15}F_3N_4O_4S_2$	51.92	2.95	10.66	12.15	51.88	2.84	10.52	12.04
8d	Furyl	Benzyl	65	137–138	$C_{24}H_{17}F_3N_4O_4S_2$	52.88	3.24	10.36	11.85	52.75	3.13	10.25	11.73
8e	Furyl	Benzoyl	68	182	$C_{24}H_{15}F_3N_4O_5S_2$	51.52	2.81	10.11	11.61	51.43	2.71	9.99	11.44
9a	CH_3	Ph	71	248–250	$C_{20}H_{14}BrF_3N_4O_3S_2$	43.01	2.64	10.15	11.41	42.95	2.52	10.02	11.46
9b	Furyl	Ph	72	254	$C_{23}H_{14}BrF_3N_4O_4S_2$	45.21	2.41	9.31	10.55	45.19	2.31	9.16	10.49
9c	Furyl	*p*-Cl C_6H_4	75	225	$C_{23}H_{13}BrClF_3N_4O_4S_2$	42.84	2.13	8.76	9.84	42.78	2.03	8.67	9.93
10a	Furyl	Ph	62	147–148	$C_{24}H_{17}F_3N_4O_4S_2$	52.82	3.21	10.31	11.82	52.75	3.13	10.25	11.73
11a	CH_3	Ph	76	140–142	$C_{21}H_{17}F_3N_4O_3S_2$	51.12	3.56	11.42	13.01	51.01	3.46	11.33	12.97
11b	Furyl	Ph	77	210	$C_{24}H_{17}F_3N_4O_4S_2$	52.88	3.22	10.38	11.82	52.75	3.13	10.25	11.73
11c	Furyl	Benzyl	70	125–128	$C_{25}H_{19}F_3N_4O_4S_2$	53.67	3.32	9.88	11.43	53.57	3.41	9.99	11.44
12a	CH_3	Ph	68	187–188	$C_{21}H_{16}BrF_3N_4O_3S_2$	44.01	3.43	9.86	11.21	43.99	3.34	9.77	11.18
13a	CH_3	Ph	73	149–150	$C_{26}H_{19}F_3N_4O_2S_2$	57.88	3.62	10.41	11.92	57.77	3.54	10.36	11.86
13b	CH_3	Benzyl	69	134[e]									
13c	Furyl	Ph	70	156–158	$C_{29}H_{19}F_3N_4O_3S_2$	58.87	2.24	9.61	10.93	58.78	3.23	9.45	10.82
13d	Furyl	Benzyl	66	121–122	$C_{30}H_{21}F_3N_4O_3S_2$	59.35	3.51	9.35	10.62	59.41	3.49	9.24	10.57
14a	CH_3	Ph	69	159–161	$C_{26}H_{18}BrF_3N_4O_2S_2$	50.55	2.81	9.12	10.51	50.41	2.93	9.04	10.35
15	Furyl		62	188	$C_{24}H_{15}F_3N_6O_3S_2$	51.92	3.02	15.21	11.62	51.81	2.91	15.11	11.52
16	Furyl		58	192	$C_{25}H_{17}F_3N_6O_3S_2$	52.75	2.98	14.82	11.31	52.63	3.01	14.73	11.24
17	Furyl		56	132–134	$C_{30}H_{21}F_3N_6O_3S_2$	56.82	3.43	13.35	10.21	56.78	3.33	13.24	10.11
18	CH_3		54	155–156	$C_{27}H_{20}BrF_3N_6O_2S_2$	49.12	3.18	12.82	9.71	49.02	3.05	12.71	9.69

Lit. [31].
[a] mp 142 °C.
[b] mp 144 °C.
[c] mp 145 °C.
[d] mp 204 °C.
[e] mp 132 °C.

addition to the strong bands at 1330–1352 cm^{-1} and 1145–1156 cm^{-1} for the SO_2N moiety. Their ^1H NMR spectra exhibited the aromatic and NH_2 protons as multiplets at δ 6.53–8.20 (Table 2). Condensation of pyrazole derivatives **2** or **3** with the appropriate isocyanate and isothiocyanate in dry acetone yielded the corresponding benzene urea **4** and **5** and thiourea **6** and **7** derivatives respectively. The IR spectra of these compounds exhibited two bands at 1330–1362 cm^{-1} and 1148–1158 cm^{-1} due to SO_2N group as well as a urea carbonyl band at 1652–1658 cm^{-1} in case of compounds **4** and **5** and a thiourea carbonyl absorption at 1134–1145 cm^{-1} in the case of compounds **6** and **7**. The structures of the above compounds (**4–7**) were further supported by their elemental analyses (Table 1), ^1H NMR (Table 2) and ^{13}C NMR spectra (Table 3).

It has been reported that condensation of N,N-disubstituted thiourea with chloroacetic acid, its chloride or bromide esters afforded 2-imino-4-oxothiazolidines, and the reaction proceeds through the intermediate formation of the cyclic pseudothiohydantoic acid [32–34]. In the present study, cyclization of the thiourea derivatives **6** and **7** with ethyl bromoacetate, ethyl β-bromopropionate, 1,3-dichloroacetone and α-bromoacetophenone afforded the corresponding 4-oxothiazolidine **8** and **9**, 4-oxo-5,6-dihydrothiazine **10**, 5-oxo-4,5-dihydrothiazine **11** and **12**, and thiazoline **13** and **14** derivatives respectively. IR spectra of compounds **8–12** showed cyclic carbonyl absorption 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 compounds **8–14** were further supported by their ^1H NMR

Table 2
^{1}H NMR[a] spectral data (δ) of pyrazole derivatives.

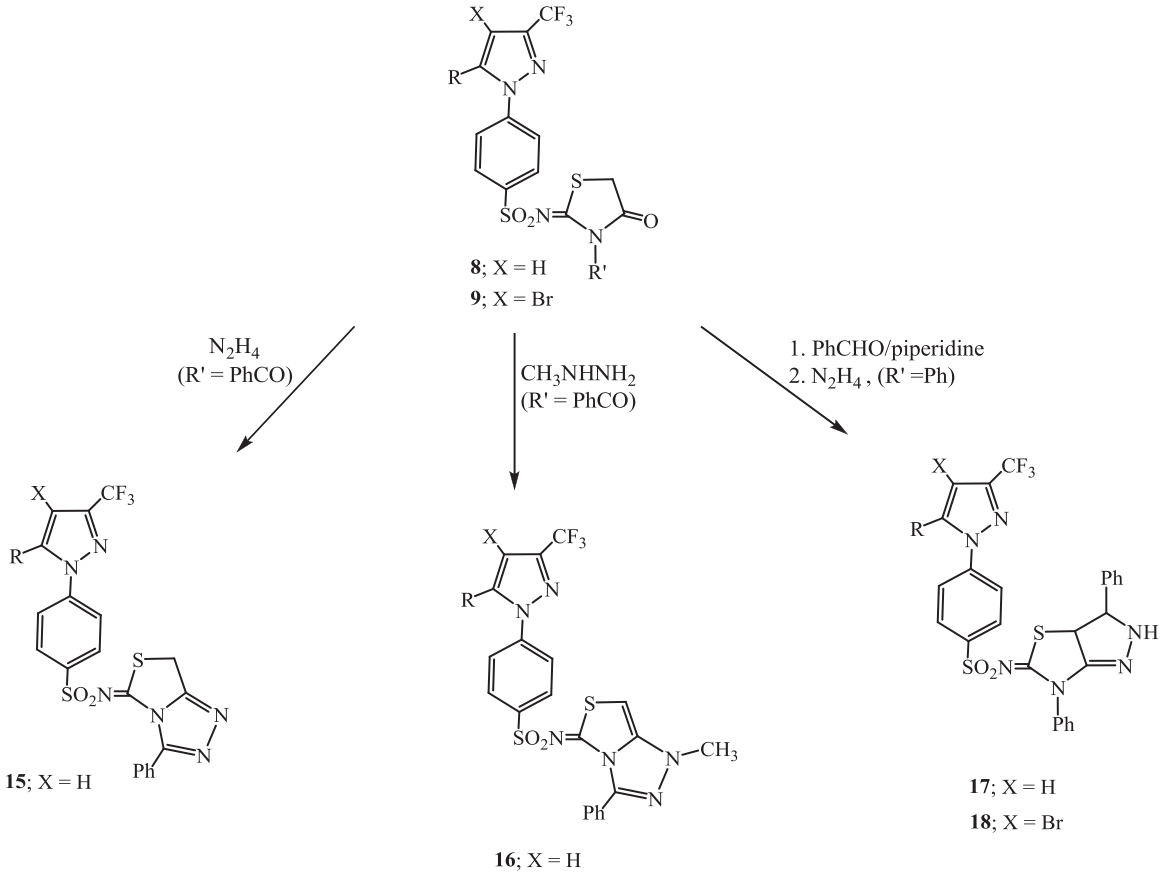
Compd.	R	R′	ArH and NH (*m*)	Others
2a			6.70–8.12 (7H)	3.35 (*s*, 3H, CH_3)
2b	Furyl		6.64–8.02 (10H)	
3a	CH_3		6.62–8.20 (6H)	3.38 (*s*, 3H, CH_3)
3b	Furyl		6.53–8.14 (9H)	
4a	CH_3	Cyclohexyl	7.12–8.38 (6H)	3.32 (*s*, 3H, CH_3); 8.65 (*s*, 1H, NH)
4b	CH_3	Ph	7.00–8.10 (11H)	3.40 (*s*, 3H, CH_3); 8.56 (*s*, 1H, NH)
4d	CH_3	*p*-Cl C_6H_4	6.98–7.99 (10H)	3.29 (*s*, 3H, CH_3); 8.75 (*s*, 1H, NH)
4e	Furyl	Cyclohexyl	6.78–8.17 (9H)	0.92–1.85 (*m*, 11H, cyclohexyl); 8.55 (*s*, 1H, NH)
4f	Furyl	Ph	7.02–8.04 (13H)	8.60 (*s*, 1H, NH); 8.75 (*s*, 1H, NH)
4g	Furyl	Naphthyl	7.11–8.12 (15H)	8.78 (*s*, 1H, NH); 9.01 (*s*, 1H, NH)
5a	CH_3	Ph	6.85–7.97 (9H)	3.32 (*s*, 3H, CH_3); 8.56 (*s*, 1H, NH); 8.78 (*s*, 1H, NH)
5b	CH_3	*p*-Cl C_6H_4	7.02–8.03 (8H)	3.28 (*s*, 3H, CH_3); 8.62 (*s*, 1H, NH); 8.81 (*s*, 1H, NH)
5c	Furyl	Cyclohexyl	6.92–8.12 (7H)	0.88–1.76 (*m*, 11H, cyclohexyl); 8.58 & 8.82 (2*s*, 1H, NH)
5d	Furyl	Ph	6.87–8.02 (12H)	8.59 (*s*, 1H, NH); 8.80 (*s*, 1H, NH)
6a	CH_3	Ph	6.92–7.89 (10H)	3.35 (*s*, 3H, CH_3); 8.45 (*s*, 1H, NH); 8.70 (*s*, 1H, NH)
6b	CH_3	Benzyl	6.89–8.01 (10H)	3.29 (*s*, 3H, CH_3); 8.56 (*s*, 1H, NH); 8.78 (*s*, 1H, NH)
6c	Furyl	Ph	6.99–8.01 (13H)	8.55 (*s*, 1H, NH); 8.80 (*s*, 1H, NH)
6d	Furyl	Benzyl	7.00–8.14 (13H)	4.52 (*d*, 2H, CH_2); 8.62 (*s*, 1H, NH); 8.85 (*s*, 1H, NH)
6e	Furyl	Benzoyl	7.12–8.05 (13H)	8.49 (*s*, 1H, NH); 8.72 (*s*, 1H, NH)
7a	CH_3	Ph	7.02–7.98 (9H)	3.30 (*s*, 3H, CH_3); 8.52 (*s*, 1H, NH); 8.68 (*s*, 1H, NH)
7c	Furyl	Cyclohexyl	7.01–8.08 (7H)	0.95–1.82 (*m*, 11H, cyclohexyl); 8.60 & 8.75 (2*s*, 1H, NH)
7d	Furyl	Ph	7.00–7.98 (12H)	8.60 (*s*, 1H, NH); 8.90 (*s*, 1H, NH)
8a	CH_3	Ph	7.10–8.05 (10H)	3.32 (*s*, 3H, CH_3); 3.85 (*s*, 2H, CH_2); 4.42 (*s*, 2H, CH_2)
8b	CH_3	Benzyl	7.05–8.11 (10H)	3.30 (*s*, 3H, CH_3); 3.80 (*s*, 2H, CH_2); 4.51 (*s*, 2H, CH_2)
8c	Furyl	Ph	6.82–8.02 (13H)	3.90 (*s*, 2H, CH_2); 4.52 (*s*, 2H, CH_2)
8e	Furyl	Benzoyl	6.79–8.13 (13H)	3.84 (*s*, 2H, CH_2); 4.46 (*s*, 2H, CH_2)
9a	CH_3	Ph	6.88–8.02 (12H)	3.29 (*s*, 3H, CH_3); 3.87 (*s*, 2H, CH_2); 4.50 (*s*, 2H, CH_2)
9b	Furyl	Ph	6.92–8.10 (12H)	3.79 (*s*, 2H, CH_2); 4.48 (*s*, 2H, CH_2)
10a	Furyl	Ph	6.89–8.00 (13H)	3.52–4.12 (*m*, 4H, $2CH_2$)
11a	CH_3	Ph	6.92–8.01 (10H)	3.30 (*s*, 3H, CH_3); 3.72 (*s*, 2H, CH_2); 4.02 (*s*, 2H, CH_2)
11b	Furyl	Ph	6.82–8.12 (13H)	3.84 (*s*, 2H, CH_2); 4.15 (*s*, 2H, CH_2)
11c	Furyl	Benzyl	6.80–8.09 (13H)	3.75 (*s*, 2H, CH_2); 4.09 (*s*, 2H, CH_2)
12a	CH_3	Ph	6.89–8.05 (9H)	3.32 (*s*, 3H, CH_3); 3.78 (*s*, 2H, CH_2); 4.08 (*s*, 2H, CH_2)
13a	CH_3	Ph	6.90–8.12 (16H)	3.30 (*s*, 3H, CH_3); 4.35 (*s*, 2H, CH_2)
13b	CH_3	Benzyl	7.09–8.19 (16H)	3.29 (*s*, 3H, CH_3); 4.38 (*s*, 2H, CH_2)
13d	Furyl	Benzyl	7.00–8.01 (19H)	4.42 (*s*, 2H, CH_2)
14a	CH_3	Ph	6.82–8.12 (15H)	3.35 (*s*, 3H, CH_3)
15	Furyl		6.92–8.07 (13H)	3.75 (*s*, 2H, CH_2)
16	Furyl		6.84–8.11 (14H)	3.62 (*s*, 3H, CH_3)
17	Furyl		6.62–8.13 (19H)	4.50 (*d*, 1H, CH); 5.20 (*m*, 1H, CH)
18	CH_3		6.67–8.09 (18H)	4.42 (*d*, 1H, CH); 3.80 (*m*, 1H, CH)

[a] Solutions in a mixture of $CDCl_3$ and DMSO-d_6, δ in ppm.

Table 3
^{13}C NMR[a] spectral data (δ) of pyrazole derivative.

Compd.	R	R′	Ar and pyrazole *C*	CH_3	Other C
2a	CH_3		148.9, 141.2, 138.7, 126.2, 124.1, 122.4, 114.5	14.6	
2b	Furyl		147.8, 140.9, 142.6, 139.5, 128.1, 127.2, 124.2, 123.2, 121.1, 112.5, 109.3		
3a	CH_3		146.7, 140.4, 136.5, 127.8, 125.5, 121.4, 110.3	14.8	
4a	CH_3	Cyclohexyl	145.0, 142.3, 137.8, 128.2, 125.3, 120.2, 112.6	14.5	176.2 (CO); 23.0, 29.1, 34.5, 49.6 (cyclohexyl)
4b	CH_3	Ph	146.0, 141.2, 138.6, 129.3, 128.4, 127.9, 126.4, 125.1, 123.5, 122.1, 110.3	14.3	175.0 (CO)
4f	Furyl	Ph	146.3, 144.5, 142.6, 140.3, 138.2, 129.5, 128.4, 128.2, 127.4, 125.1, 123.0, 122.6, 120.1, 113.5, 108.6		178.0 (CO)
5a	CH_3	Ph	149.0, 143.4, 140.6, 137.2, 129.0, 128.3, 128.1, 127.5, 126.3, 120.6, 109.2	14.2	177.4 (CO)
5d	Furyl	Ph	147.0, 145.6, 143.2, 141.3, 139.6, 129.4, 128.2, 128.0, 127.3, 126.2, 122.6, 121.0, 112.6, 110.4		176.5 (CO)
6b	CH_3	Benzyl	146.4, 142.3, 140.0, 136.9, 129.2, 128.4, 128.0, 127.6, 125.6, 122.4, 110.3	14.6	204 (CS); 63.2 (CH_2)
7c	Furyl	Cyclohexyl	147.7, 143.2, 141.0, 138.9, 128.6, 127.6, 124.2, 123.0, 122.6, 112.5, 108.6		201 (CS); 22.9, 28.8, 34.2, 48.6 (cyclohexyl)
8a	CH_3	Ph	146.2, 142.8, 140.4, 137.6, 134.2, 129.5, 128.3, 128.2, 127.8, 125.3, 121.8, 109.2	14.6	192 (CO); 38.6 (CH_2)
8c	Furyl	Ph	147.6, 142.9, 140.5, 139.2, 134.0, 133.2, 129.4, 128.6, 128.3, 127.5, 126.4, 123.6, 122.6, 121.4, 113.5, 106.5		194 (CO); 39.2 (CH_2)
11a	CH_3	Ph	146.8, 143.6, 141.2, 138.6, 135.4, 133.3, 129.8, 128.2, 128.0, 127.6, 125.0, 116.5	14.2	189 (CO); 38.8, 36.4 (CH_2)
14a	CH_3	Ph	149.2, 147.6, 146.4, 142.2, 140.6, 139.8, 138.7, 136.5, 134.2, 133.6, 129.8, 128.3, 128.2, 127.6, 126.4, 124.2, 122.3, 116.6	14.2	
15	Furyl		148.9, 147.2, 145.4, 142.3, 140.6, 138.8, 136.4, 134.0, 130.5, 129.8, 128.4, 128.3, 126.9, 125.4, 123.8, 122.4, 120.5, 108.2		39.5 (CH_2)

[a] Solutions in a mixture of $CDCl_3$ and DMSO-d_6, δ in ppm.



Scheme 2.

(Table 2) and ^{13}C NMR data (Table 3). Moreover, some new condensed ring systems namely 3-phenyl-7H-thiazolo [3,4-*c*][1,2,4]triazoles **15** and **16** (Scheme 2), starting from the appropriate 3-benzoyl-2-(substituted benzenesulfonylimino)thiazolidin-4-one **8e** were prepared by reacting such compounds with the suitable hydrazine refluxing in ethanol. On the other hand, the targeted pyrazolo [3,4-*d*]thiazole fused ring system **17** and **18** was achieved by condensing the thiazolidinones **8c** and **9a** with benzaldehyde followed by reaction with hydrazine hydrate. The IR spectra of the above compounds **15**–**18** were characterized by the absence of the carbonyl absorption band of thiazolidinones. The ^{1}H NMR and ^{13}C NMR spectra of the above compound are listed in Tables 2 and 3 respectively.

2.2. Antidiabetic activity

Compounds **2a**, **3a**, **4a**,**b**,**c**, **5a**,**c**,**d**, **6a**,**c**, **7a**,**c**, **8a**,**c**, **9a**, **11a**, **12a**, **13a**,**d** and **15** 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. 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.

From the data presented in Table 4, it is obvious that the 3,5-disubstituted-benzenesulfonylurea derivatives **4** and **5** possess marked hypoglycemic activity. The potency of these compounds is more than that of phenformine, and they are much more active than the parent compound 3,5-dimethylpyrazole. Introduction of bromine at position 4 of the pyrazole ring increases the

Table 4
Antidiabetic activity of pyrazole derivatives.

Compd.	Reduction in plasma glucose level (%)	*P*
Phenformin	10	<0.01[a]
3,5-Dimethylpyrazole	4	<0.05
2a	<1	0.05
3a	<1	0.05
4a	17	<0.01[a]
4b	14	<0.01[a]
4e	13	<0.01[a]
5a	20	<0.01[a]
5c	16	<0.01[a]
5d	18	<0.01[a]
6a	1.5	0.05
6c	2	0.05
7a	3	0.05
7c	2.5	0.05
8a	8	0.01[a]
8c	5	0.01[a]
9a	10	0.01[a]
11a	7.5	0.01[a]
12a	9	0.01[a]
13a	7	0.01[a]
13d	8.5	0.01[a]
15	<1	0.05

[a] Statistically significant.

Table 5
Anti-bacterial and anti-fungal data of trifluoromethylpyrazole 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	14	12	11	12
2b	15	13	14	13
3a	16	18	19	16
3b	19	20	18	21
4a	9	10	8	6
4b	8	7	10	11
4d	12	13	11	12
4e	6	8	10	7
4f	8	10	9	10
5a	10	8	11	9
5b	11	10	12	13
5c	10	11	10	8
6a	14	15	13	16
6b	15	17	14	15
6c	12	13	14	13
6d	16	14	12	11
6e	17	18	20	19
7a	15	16	12	11
7c	14	15	13	12
7e	20	18	21	19
8a	10	9	11	10
8b	6	7	7	6
9c	8	10	9	11
10a	8	7	6	8
11a	9	8	9	10
11b	11	10	11	12
12a	12	13	14	12
13a	14	12	16	15
13b	13	14	15	12
14a	15	16	14	13
15	10	11	10	8
16	8	10	7	6
17	11	9	11	8
18	13	12	10	11
Ampicillin	33	29	–	–
Griseofulvin	–	–	30	28

hypoglycemic activity of the urea derivative. On the other hand although the hypoglycemic activity of the thioureas is low, their cyclic thio-analogs showed potent antidiabetic activity (Table 4).

2.3. Anti-microbial activity

Compounds **2**–**18** were screened *in vitro* for their anti-microbial and antifungal activity against *Escherichia coli*, *Staphylococcus aureus*, against *Aspergillus niger* and *Candida albicans*. The zones of inhibition formed for the compounds against bacteria and fungi are summarized in Table 5. Compounds **3a**, **3b**, **6e** and **7e** exhibited significant activities against various strains of micro-organisms. All test data in Table 5 were of average values from triplicate runs and the test compounds showed reduced antimicrobial activities when compared with their respective standards.

3. Conclusions

In this paper, several new 3-trifluoropyrazole derivatives were synthesized by the condensation of 4-hydrazino benzenesulfonamide hydrochloride with 1-trifluoromethyl diketones. 4-Bromopyrazoles were prepared by the bromination of the corresponding pyrazole derivative. Furthermore, many new urea and thiourea derivatives were prepared from the reaction of the above pyrazoles 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 ^{1}H and ^{13}C NMR spectral analysis. Preliminary biological testing of some of these compounds revealed that **3a**, **3b**, **6e** and **7e** exhibited significant antimicrobial activities and compounds **4** and **5** showed marked hypoglycemic activities.

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 ^{1}H 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. 3-Trifluoromethyl-5-substituted-1-(p-sulfamylphenyl)pyrazoles (2)

A solution of the appropriate diketone **1** (10 mmol) in ethanol (50 mL) was refluxed with 4-hydrazinobenzenesulfonamide hydrochloride (10 mmol) for 4 h, cooled and diluted with water. The precipitated crude product was filtered and recrystallized from ethanol as needles.

4.1.2. 4-Bromo-3-trifluoromethyl-5-substituted-1-(p-sulfamylphenyl)pyrazoles (3)

A solution of the appropriate pyrazole **2** (10 mmol) in chloroform (30 mL) was refluxed and stirred with bromine (10 mmol) for 1 h. The crude product that separated during heating was filtered and recrystallized from ethanol as needles.

4.1.3. p-(3-Trifluoromethyl-5-substituted-pyrazole-1-yl)benzenesulfonylureas (4 and 5)

A mixture of the appropriate pyrazole **2** or **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-Trifluoromethyl-5-substituted-pyrazol-1-yl)benzenesulfonylthioureas (6 and 7)

A mixture of **2** or **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.

4.1.5. 3-Substituted-2-[p-(3-trifluoro-5-substituted-pyrazol-1-yl)benzenesulfonylimino]- and 3-subsituted-2-[p-(4-bromo-3-trifluoro-5-substituted-pyrazol-1-yl)benzenesulfonylimino]-4-oxothiazolidines (8 and 9)

A mixture of **6** or **7** (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.

*4.1.6. 3-Substituted-2-[p-(3-trifluoro-5-substituted-pyrazol-1-yl)benzenesulfonylimino]-4-oxo-5,6-dihydro-1,2-thiazines (**10**)*

A solution of **6** (10 mmol) in absolute ethanol (20 mL) was refluxed with ethyl β-bromopropionate (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.

*4.1.7. 3-Substituted-2-[p-(3-trifluoro-5-substituted-pyrazol-1-yl)benzenesulfonylimino]- and 3-substituted-2-[p-(4-bromo-3-trifluoro-5-substitued-pyrazol-1-yl)benzenesulfonylimino]-5-oxo-4,6-dihydrothiazines (**11** and **12**)*

A mixture of the appropriate thiourea, **4** or **10** (10 mmol), 1,3-dichloroacetone (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.

*4.1.8. 3-Substituted-2-[p-(3-trifluoro-5-substituted-pyrazol-1-yl)benzenesulfonylimino]- and 3-substituted-2-[p-(4-bromo-3-trifluoro-5-substitued-pyrazol-1-yl)benzenesulfonylimino]-1,3-thiazolines (**13** and **14**)*

A solution of the corresponding thiourea derivative **6** or **7** (10 mmol) in absolute ethanol (25 mL) was refluxed with 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.

*4.1.9. 3-Phenyl-7H-thiazolo[3,4-c]-1,2,4-triazoles (**15** and **16**)*

A mixture of 3-benzoyl-2-(substituted benzenesulfonylimino)thiazolidin-4-one **8e** (10 mmol) and the appropriate hydrazine (10 mmol) in ethanol (15 mL) was heated under reflux for 2 h. The solid product obtained on cooling was filtered and recrystallized from ethanol.

*4.1.10. 3,6-Diphenylpyrazolo[3,4-d]thiazoles (**17** and **18**)*

To a solution of the appropriate thiazolidinone **8** or **9** (5 mmol) and piperidine (3 drops) in absolute ethanol (15 mL) was added benzaldehyde (5 mmol). The mixture was refluxed for 6 h, where the solid product was partially crystallized out. The reaction mixture left to cool to room temperature and the separated solid product was collected by filtration, dissolved in ethanol (20 mL) and treated with hydrazine hydrate (1 mL). The mixture was refluxed for 1 h. The solid product obtained on cooling was filtered and recrystallized from ethanol.

4.2. Procedure for anti-microbial activity

The preliminary anti-microbial activities of new trifluoromethylpyrazoles were measured in a concentration of 50 mg/L by disc diffusion method [35,36]. The prepared compounds were tested for their antimicrobial activity against two types of bacterium, one gram-positive *S. aureus* and one gram-negative bacterium *E. coli* 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.

Acknowledgement

The authors wish to thank Department of Pharmacology, Faculty of Pharmacy, University of Alexandria for their helpful contribution and for facilities.

References

[1] R. Filler, Y. Kobayashi, Biomedical Aspects of Fluorine Chemistry, Kodansha/Elsevier, New York, 1982.
[2] A.V. Fokin, A.F. Kolomiyets, J. Fluorine Chem. 40 (1988) 247–259.
[3] B.E. Smart, J. Fluorine Chem. 109 (2001) 3–11.
[4] H.G. Bonacorso, A.P. Wentz, R.V. Lourega, C.A. Cechinel, T.S. Moraes, H.S. Coelho, N. Zanatta, M.A.P. Martins, M. Hoerner, S.H. Alves, J. Fluorine Chem. 127 (2006) 1066–1072.
[5] M. Jagodzinska, F. Huguenot, G. Candiani, M. Zanda, Chem. Med. Chem. 4 (2009) 49–51.
[6] R. Filler, R. Saha, Future Med. Chem. 1 (2009) 777–791.
[7] F.M.D. Ismail, J. Fluorine Chem. 118 (2002) 27–33.
[8] Y. Yonetoku, H. Kubota, Y. Okamoto, J. Ishikawa, M. Takeuchi, M. Ohta, S. Tsukamoto, Bioorg. & Med. Chem. 14 (2006) 5370–5383.
[9] D.-J. Wang, L. Fan, C.-Y. Zheng, Z.-D. Fang, J. Fluorine Chem. 131 (2010) 584–586.
[10] G.R. Desiraju, B. Gopalakrishinan, R.K.R. Jetti, D. Raveendra, J.A.R.P. Sarma, H.S. Subramanya, Molecules 5 (2000) 945–955.
[11] C. Cusan, G. Spalluto, M. Prato, M. Adam, A. Bodensieck, R. Bauer, A. Tubaro, P. Bernardi, T. Da Ros, Il Farmaco 60 (2005) 327–332.
[12] M.V.R. Reddy, V.K. Billa, V.R. Pallela, M.R. Mallireddigari, R. Boominathan, J.L. Gabriel, E.P. Reddy, Bioorg. & Med. Chem. 16 (2008) 3907–3916.
[13] K.L. Kees, J.J. Fitzgerald Jr., K.E. Steiner, J.F. Mattes, B. Mihan, T. Tosi, D. Mondero, M.L. Mc Caled, J. Med. Chem. 39 (1996) 3920–3928.
[14] N. Kudo, S. Furuta, M. Taniguchi, T. Endo, K. Sato, Chem. Pharm. Bull. 47 (1999) 857–868.
[15] J.L. Kane Jr., B.H. Hirth, D. Laing, B.B. Gourlie, S. Nahill, G. Barsomian, Bioorg. Med. Chem. Lett. 13 (2003) 4463–4466.
[16] J.B. Wright, W.E. Dulin, J.H. Markillie, J. Med. Chem. 7 (1964) 102–105.
[17] G.C. Gerritsen, W.E. Dulin, Diabetes 14 (1965) 507–515.
[18] G.C. Gerritsen, W.E. Dulin, J. Pharmacol. Exp. Ther. 150 (1965) 491–498.
[19] D.L. Smith, A.A. Forist, W.E. Dulin, J. Med. Chem. 8 (1965) 350–353.
[20] R. Soliman, H. Mokhtar, E.S. El-Ashry, Pharmazie 33 (1978) 184–185.
[21] R. Soliman, H.M. Faidallah, J. Pharm. Sci. 70 (1981) 602–605.
[22] R. Soliman, H.M. Faidallah, S.K. El-Sadany, H.F. Mohamed, J. Pharm. Sci. 70 (1981) 606–610.
[23] R. Soliman, H.M. Faidallah, H.F. Mohamed, J. Pharm. Sci. 70 (1981) 952–956.
[24] H.M. Faidallah, H.M. Mokhtar, R. Soliman, J. Heterocycl. Chem. 18 (1981) 1561–1564.
[25] R. Soliman, H.M. Faidallah, S.K. El-Sadany, J. Pharm. Sci. 76 (1987) 626–632.
[26] M.S. Al-Saadi, H.M. Faidallah, S.A. Rostom, Arch. Pharm. Chem. Life Sci. 341 (2008) 424–434.
[27] H.M. Faidallah, M.S. Al-Saadi, S.A. Rostom, H.T.Y. Fahmy, Med. Chem. Res. 16 (2007) 300–318.
[28] H.M. Faidallah, M.S. Al-Saadi, S.A. Rostom, Saudi Pharm. J. (SPI) 16 (2008) 33–42.
[29] H.M. Faidallah, E.M. Sharshira, M.S. Al-Saadi, Heterocyclic Commun. 15 (2009) 43–50.
[30] H.M. Faidallah, H.M. Mokhtar, A.M.G. Nassar, M. Morsi, Bull. Fac. Sci. Assiut Univ. 24 (1995) 187–195.
[31] A.M. Asiri, H.M. Faidallah, H.M. Albar, E.M. Sharshira, Heterocyclic Commun. 9 (2003) 483–488.
[32] P.N. Bhargava, J. Amer. Chem. Soc. 73 (1951) 2353–2354.
[33] F.B. Dians, F.A. Eberly, J. Amer. Chem. Soc. 58 (1936) 2544–2547.
[34] E.R.H. Jones, F.A. Robinson, H.N. Starchan, J. Chem. Soc. (1946) 91–92.
[35] W.R. Kirkpatrick, T.M. Turner, A.W. Fothergill, D.I. McCarthy, S.W. Redding, M.G. Rinaldi, T.F. Patterson, J. Clin. Microbiol. 36 (1998) 3429–3432.
[36] T. Premkumar, S. Govindarajan, World J. Microbiol. Biotechnol. 21 (2005) 479–480.