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Some 2-(2-(p-chlorophenyl)benzimidazol-1-ylmethyl)-5-substituted amino-[1,3,4]-thiadiazoles were synthesized and their in vitro antimicrobial activities were tested against *Staphylococcus aureus*, *Bacillus subtilis, Escherichia coli, Candida albicans* and *Candida krusei*. Compounds **1b** and **12b** which possess remarkable activity against *C. albicans* and marginal activity against *C. krusei* were found to be the most active compounds in this series. Single crystal X-ray diffraction analysis was performed for compound **8b**.

Key Words: Benzimidazoles, thiadiazoles, antimicrobial activity, X-ray.

Introduction

The development of resistance to current antibacterial therapy continues to drive the search for more effective agents. In addition, primary and opportunistic fungal infections continue to increase the number of immunocompromised patients, those suffering from such as AIDS or cancer or who have undergone organ transplantation. It is well known that benzimidazoles exhibit antimicrobial[1−6], antitubercular[7], anticancer[8−9], anthelmintic[10], antiallergic[11−14], antioxidant[15], anticonvulsant[16] and analgesic[17] activities. It is also well known that thiadiazoles possess anti-inflammatory[18−19] and antimicrobial [4,20] activities. We designed and prepared a series of thiadiazole containing benzimidazoles in an effort to investigate their antimicrobial activities (Figure 1).

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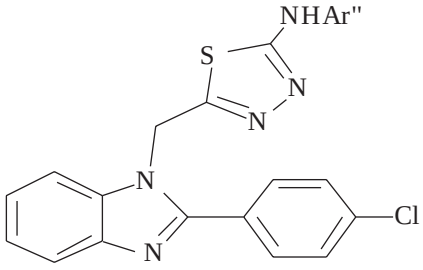


1b-12b

Ar": phenyl, 4-tolyl, 2-tolyl, 4-fluorophenyl, 3-fluorophenyl, 2-fluorophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 4-bromophenyl, 3-bromophenyl, 2-bromophenyl.

Figure 1

Experimental

Chemistry

Melting points were determined with a Büchi SMP-20 melting point apparatus and are uncorrected. IR spectra were recorded on a Jasco FT/IR 420 spectrometer as potassium bromide disks. ^{1}H NMR spectra were measured with a Bruker GmbH DPX-400, 400 MHz instrument using TMS internal standard and DMSO-d_6. All chemical shifts were reported as δ (ppm) values. EIMS were obtained with a VG Platform II, micromass spectrometer with ionization energy maintained at 70 eV. Elemental analyses (C, H, and N) were determined on a Leco CHNS 932 instrument (St. Joseph, USA), and were within ± 0.4% of the theoretical values. All instrumental analyses were performed at the Scientific and Technical Research Council of Turkey (TÜBİTAK). The chemical reagents used in synthesis were purchased from Merck (Darmstadt, Germany) and Aldrich (Milwaukee, USA).

General procedure for the preparation of the 2-(2-(p-chlorophenyl) benzimidazol-1-yl methyl)-5-substituted amino-[1,3,4]-thiadiazoles **(1b-12b)**

The appropriate thiosemicarbazide **1a-12a (**3.4 mmol) was stirred for 10 min. in 10 mL ice-cold concentrated sulfuric acid and was then left for another 10 min. at room temperature. The resulting solution was poured slowly into ice-cold water and made alkaline to pH 8 with aqueous ammonia. The precipitated product was filtered, washed with water and crystallized from ethanol.

X-ray analysis

The intensity reflections were measured using an Enraf-Nonius CAD4 diffractometer using graphite monochromatized MoK$_\alpha$ radiation [$\lambda = 0.71073$ Å] and $\omega/2\theta$ scan mode to $2\theta = 52.58°$ (h: -13 → 13, k:-20 → 0 and l: -15 → 0): 4285 reflections were used for refinement on F^2. An empirical absorption correction[21] was applied to the data. The structure was solved by direct methods[22] and subjected to full-matrix refinement[23].

The refinement was made with anisotropic displacement factors for all non-hydrogen atoms. The hydrogen atom of N5 was found from the difference map and was refined isotropically. All other hydrogen atoms were calculated to their idealized positions and were refined as riding atoms. Crystal data and a

summary of intensity data collection and structure refinement are presented in Table 1 and the selected bond lengths, bond angles and torsion angles are given in Table 2.

Table 1. Crystal data and details of the structure determination of (**8b**).

Chemical formula	$C_{22}H_{15}N_5Cl_2S_1$
Formula weight	452.35
Space group; crystal system	$P2_1/c$; monoclinic
Crystal dimensions (mm)	0.48 × 0.24 × 0.51
a (Å)	10.7118 (15)
b (Å)	16.4630 (12)
c (Å)	12.3489 (10)
β (°)	97.044 (9)
Volume (Å^3); Z	2161.3 (4); 4
D_c (g cm^{-3}); μ (mm^{-1})	1.39; 0.416
λ (Å); Scan type	0.71073; ω - 2θ
Absorption correction type	Empirical psi-scan
T_{min}; T_{max}	0.816; 0.907
Range of θ (°)	2.28; 26.29
Reflections collected	4484 [R_{int}=0.0298]
Reflns. used in refinement	4285
Weighting scheme	w = 1/[σ^2 (Fo^2) + (0.0545P)^2+ 0.1527P] where P = (Fo^2+2Fc^2)/3
R and R_w values	0.0482; 0.131
Goodness of fit	1.002
Final shift/error	0.000
Max. and min. electron density (e Å^{-3})	0.177, -0.352

Antimicrobial activity

The in vitro antimicrobial activity of the compounds was tested using the tube dilution technique[24]. All of the test compounds and the standards ampicillin trihydrate and fluconazole were dissolved in 12.5% DMSO, at concentrations of 100 μg/ mL, and further dilutions of the compounds and standards in the test medium were prepared at the required quantities of 50, 25, 12.5, 6.25, 3.12, 1.56 and 0.78 μg/ mL concentrations. The final inoculum size was 10^5 CFU/mL. The minimum inhibitory concentrations (MIC) were defined as the lowest concentrations of the compounds that prevented visible growth. It was determined that the solvent had no antimicrobial activity against any of the test microorganisms.

All the compounds were tested for their in vitro growth inhibitory activity against *Staphylococcus aureus* ATCC 25923 and *Bacillus subtilis* ATCC 6633 as Gram positive bacteria and *Escherichia coli* ATCC 25922 as Gram negative bacteria and *Candida albicans* ATCC 10231 and *Candida krusei* ATCC 6258 as fungi.

Antibacterial activity assay

The cultures were obtained in Mueller-Hinton Broth (Difco) for all the bacteria after 18-24 h of incubation at 37 ± 1 °C. Testing was carried out in Mueller-Hinton Broth at pH 7.4 and the 2-fold dilution was applied. A set of tubes containing only inoculated broth were kept as controls. After incubation for 18-24 h at 37 ± 1 °C, the last tube with no microorganism growth was recorded to represent MIC expressed in μg/mL.

Table 2. Selected geometric parameters (Å, °) of (**8b**).

S1 —	C18	1.739(3)		
Cl1 —	C13	1.738(3)		
Cl2 —	C21	1.736(4)		
C2 —	N2	1.307(3)		
C2 —	N1	1.379(3)		
C2 —	C10	1.468(4)		
N1 —	C8	1.385(3)		
N1 —	C16	1.456(3)		
N3 —	C17	1.276(3)		
N3 —	N4	1.385(3)		
N2 —	C9	1.385(4)		
N5 —	C18	1.356(4)		
N5 —	C19	1.398(4)		
N4 —	C18	1.295(4)		
C17—	C16	1.493(4)		
C17—	S1 —	C18	86.24(15)	
N2 —	C2 —	N1	112.7(3)	
N1 —	C2 —	C10	122.1(3)	
C2 —	N1 —	C8	105.9(2)	
C2 —	N1 —	C16	127.0(2)	
C2 —	N2 —	C9	105.6(3)	
C18 —	N5 —	C19	127.6(3)	
C18 —	N4 —	N3	112.0(2)	
N4 —	C18 —	S1	114.1(2)	
N5 —	C18 —	S1	120.0(2)	
N3 —	C17 —	S1	114.5(2)	
N1 —	C16 —	C17	110.0(2)	
C18 —	S1 —	C17—	N3	0.0(3)
C17 —	N3 —	N4 —	C18	1.4(4)
N3 —	N4 —	C18 —	S1	-1.4(4)
C17—	S1 —	C18 —	N4	0.8(3)
C8 —	N1 —	C16 —	C17	93.5(4)
N2 —	C2 —	C10 —	C15	49.2(5)
N1 —	C16 —	C17 —	S1	-50.0(4)
C19 —	N5 —	C18 —	S1	-165.2(3)
C18 —	N5 —	C19 —	C24	-173.4(4)

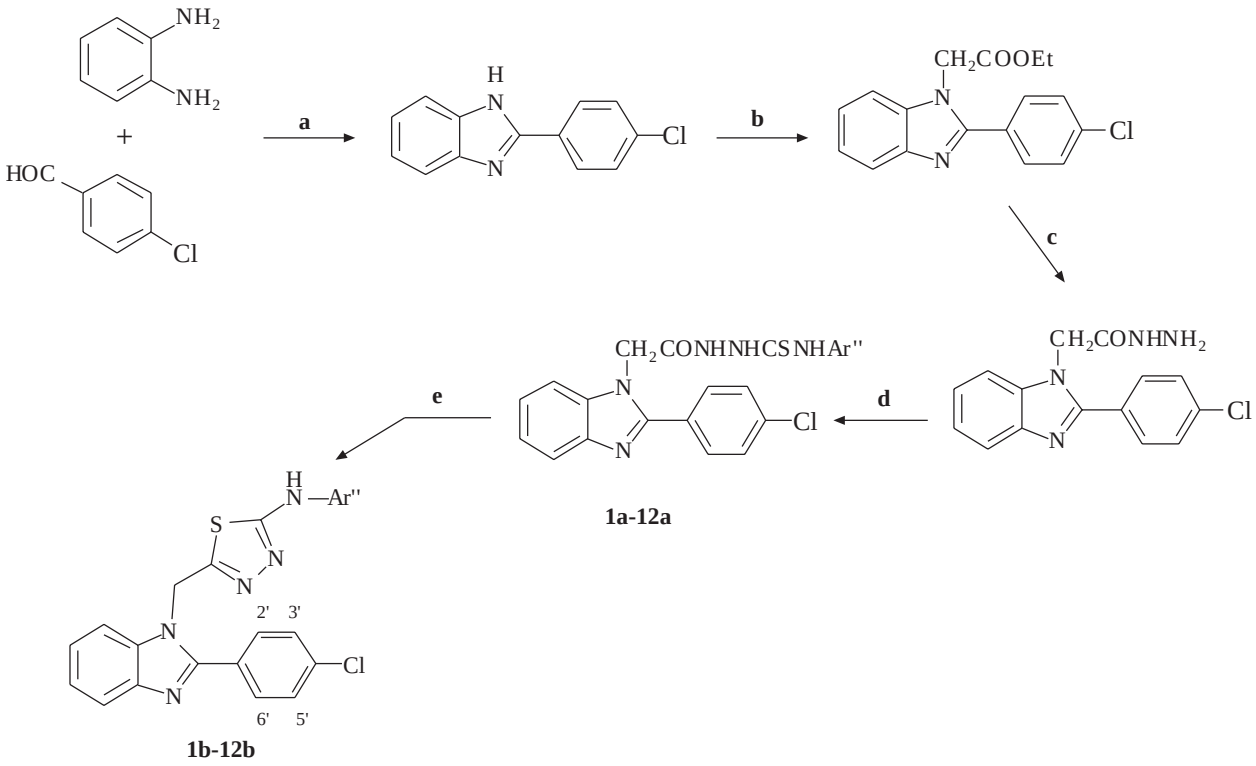
Antifungal activity assay

The yeasts were maintained in Sabouraud Dextrose Broth (Difco) after incubation for 48 h at 25 ± 1 °C. Testing was performed in Sabouraud Dextrose Broth at pH 7.4 and the 2-fold dilution was applied. A set of tubes containing only inoculated broth were kept as controls. After incubation for 48 h at 25 ± 1 °C, the last tube with no yeast growth was recorded to represent MIC expressed in μg/mL.

Results and Discussion

For the synthesis of the target compounds the reaction sequences outlined in Scheme 1 were followed. 2-Phenyl-1*H*-benzimidazole was prepared via oxidative condensation of o-phenylenediamine, benzaldehyde and

sodium metabisulfite[25]. Treatment of 2-phenyl-1*H*-benzimidazole with ethyl chloroacetate in KOH/DMSO gave the N-alkylated product (2-phenyl-benzimidazol-1-yl)-acetic acid ethyl ester[26]. Hydrazine hydrate and the ester in ethanol were refluxed for 4 h to give the desired hydrazide compound (2-phenyl-benzimidazol-1-yl)-acetic acid hydrazide, in a 94% yield[27]. The thiosemicarbazides (**1a-12a**) (Scheme 1) were obtained upon the reaction of acid hydrazide with aryl isothiocyanates in ethanol[28]. Cyclization of thiosemicarbazides with sulfuric acid, according to the method described in reference previously[29], resulted in the formation of 2-(2-(p-chlorophenyl) benzimidazol-1-yl methyl)-5-substituted amino-[1,3,4]-thiadiazoles **1b-12b**. Melting points, % yields and spectral data are given in Table 3. The structure of compound **8b** was also elucidated by the X-ray diffraction (Tables 1 and 2).



Scheme. Synthetic route for the preparation of the compounds.

Reagents a: $Na_2S_2O_5$ **b:** $ClCH_2COOEt$ / KOH-DMSO **c:** $NH_2NH_2.H_2O$ / EtOH **d:** appropriate phenylisothiocyanate **e:** H_2SO_4

Technical details of the structure determination are given in the experimental section. An ORTEP[30] drawing of the structure with atomic numbering is shown in Figure 2. This drawing clearly establishes the structural formula and also shows the conformation of the molecule. The benzimidazole ring system is almost planar; the displacements of all 9 atoms contained in the ring are less than 0.054 (3) Å (for C2) from the least-squares plane. The orientation of the thiadiazolylmethyl substituent at N1 is defined by the torsion angles of C8-N1-C16-C17 93.5(4) and N1-C16-C17-S1–50.0(4)°. The thiadiazole ring is also planar [maximum deviation 0.007 (3) Å for C18] and forms a dihedral angle of 77.74(6)° with the best plane of the benzimidazole ring system. The phenylamino group attached to the thiadiazole ring is not coplanar with this ring and makes a dihedral angle of 21.69(10)° with the thiadiazole ring plane. The planar p-chlorophenyl

Table 3. Physical and spectral data of compounds **1b-12b.**

No.	Formulae	M.P. (°C)	Yield	^{1}H NMR data (δ ppm)	Mass data (70 eV)
1b	$C_{22}H_{16}ClN_5S$	232	85	5.8 (s, 2H, *CH*$_2$), 6.96 (td, 1*H*, J_o=7.28 Hz, 7.32 Hz,'*H-4''*), 7.27-7.34 (m, 4H, H-5,6,3'',5''), 7.52 (d, 2H, H-2'',6'', J_o=8.23 Hz), 7.66 (d, 2H, H-3', 5', J_o= 8.33 7.69-7.74 (m, 2H, H-4,7), 7.88 (d, 2H, H-2', 6', J_o= 8.36 Hz), 10.89 (br s, 1H, NH)
2b	$C_{23}H_{18}ClN_5S$	249	68	2.31 (s, 3H, *CH*$_3$), 5.83 (s, 2H, *CH*$_2$), 7.09 (d, 2H, H-2'',6'', J_o=8.17 Hz), 7.28-7.33 (m, 2H, H-5,6), 7.40 (d, 2H, H-3'',5'', J_o= 8.24 Hz), 7.66 (d, 2H, J_o= 8.38 Hz, H-3', 5'), 7.68-7.73 (m, 2H, H-4,7), 7.88 (d, 2H, H-2',6', J_o=8.35 Hz), 10.3 (br s, 1H, NH)
3b	$C_{23}H_{18}ClN_5S$	228	50	2.18 (s, 3H, *CH*$_3$), 5.82 (s, 2H, *CH*$_2$), 6.98 (td, 1*H*, J_o=7.36 Hz, 7.35 Hz H-4''), 7.13-7.18 (m, 2H, H-3'', 5''), 7.28-7.34 (m, 2H, H-5,6), 7.64 (d, 2H, H-3',5', J_o=8.47 Hz), 7.69-7.73 (t, 2H, H-4,7), 7.77 (d, 1H, H-6'', J_o=7.92 Hz), 7.88 (d, 2H, H-2',6', J_o=8.45 Hz), 9.48 (br s, 1H, NH)
4b	$C_{22}H_{15}ClFN_5S$	226	65	5.85 (s, 2H, *CH*$_2$), 7.14 (td, 2H, J_o=8.87 Hz, 8.82 Hz H-2'',6''), 7.28-7.34 (m, 2H, H-5,6), 7.53-7.56 (m, 2H, H-3'',5''), 7.65 (d, 2H, H-3',5', J_o= 8.46 Hz), 7.68-7.73 (m, 2H, H-4,7), 7.87 (d, 2H, H-2',6', J_o= 8.46 Hz),10.25 (br s, 1H, NH)
5b	$C_{22}H_{15}ClFN_5S$	259	54	5.87 (s, 2H, *CH*$_2$), 6.76-6.78 (m, 1H, H-4''), 7.18-7.21 (m, 1H, H-6''), 7.28-7.33 (m, 3H, H-5,6,5''), 7.57-7.74 (m, 5H, H-4,7,3',5', 2'') 7.88 (d, 2H, H-2',6', Jo= 8.45 Hz), 10.29 (br s, 1H, NH)
6b	$C_{22}H_{15}ClFN_5S$	237	85	5.86 (s, 2H, *CH*$_2$), 6.98-7.34 (m, 5H, H-5,6,3'',4'',5''), 7.63-7.74 (m, 4H, H-4,7, 3',5'), 7.88 (d, 2H, H-2',6', J_o=8.55 Hz), 8.26 (m, 1H, H-6''), 10.14 (br s, 1H, NH)
7b	$C_{22}H_{15}Cl_2N_5S$	239	81	5.78 (s, 2H, *CH*$_2$), 6.98 (td, 1H, J_o=7.80 Hz, 7.51 Hz), 7.21-7.27 (m, 3H), 7.38 (d, 1H), 7.57 (d, 2H, H-3', 5', J_o=8.50 Hz), 7.63 (t, 2H, H-4,7), 7.80 (d, 2H, H-2',6', Jo= 8.49 Hz), 8.12 (d, 1H), 9.79 (s, 1H, NH)
8b	$C_{22}H_{15}Cl_2N_5S$	257	78	5.87 (s, 2H, *CH*$_2$), 7.00-7.03 (m, 1H, H-4''), 7.28-7.34 (m, 4H, H-5,6,5'',6''), 7.65 (d, 2H, H-3',5', Jo= 8.53 Hz), 7.68-7.73 (m, 2H, H-4,7), 7.81 (s, 1H, H-2''), 7.87 (d, 2H, H-2',6', J_o= 8.52 Hz), 10.54 (s, 1H, NH)
9b	$C_{22}H_{15}Cl_2N_5S$	244	89	5.85 (s, 2H, *CH*$_2$), 7.05 (td, 1H, J_o=7.70 Hz, 7.61 Hz H-4''), 7.26-7.34 (m, 3H, H-5,6,5''), 7.44 (d, 1H, H-3'', J_o= 8.27 Hz), 7.65 (d, 2H, H-3',5', J_o= 8.39 Hz), 7.69-7.73 (t, 2H, H-4,7), 7.88 (d, 2H, H-2',6', J_o=8.25 Hz), 8.2 (d, 1H, -H-6'', Jo=8.10 Hz), 9.87 (s, 1H, NH)
10b	$C_{22}H_{15}BrClN_5S$	243	69	5.86 (s, 2H, *CH*$_2$), 7.28-7.32 (m, 2H, H-5,6), 7.46 (d, 2H, H-2'',6'', J_o= 8.66 Hz), 7.51 (d, 2H, H-3'',5'', J_o= 8.62 Hz), 7.64-7.73 (m, 4H, H-4,7,3',5'), 7.87 (d, 2H, H-2',6', J_o=8.10 Hz), 10.46 (s, 1H, NH)
11b	$C_{22}H_{15}BrClN_5S$	260	60	5.87 (s, 2H, *CH*$_2$), 7.14 (d, 1H, H-4'', J_o= 8.60 Hz), 7.23-7.38 (m, 4H, H-5,6,5'', 6''), 7.65 (d, 2H, H-3',5', J_o=8.42 Hz), 7.68-7.73 (m, 2H, H-4,7), 7.87(d, 2H, H-2',6', J_o=8.39 Hz), 7.96 (s, 1H), 10.47 (br s, 1H, NH)
12b	$C_{22}H_{15}BrClN_5S$	232	82	5.84 (s, 2H, *CH*$_2$), 6.99 (td, 1H, J_o=7.76 Hz, 7.67 Hz H-4''), 7.26-7.36 (m, 3H, H-5,6,5''), 7.6-7.7 (m, 5H, H-4,7,3',5',3''), 7.87 (d, 2H, H-2',6', J_o=8.43 Hz), 8.03 (d, 1H, H-6'', J_o=7.58 Hz), 9.64 (s, 1H, NH)	497.77 ($M^{+\cdot}$) (3.22), 325 (5.54), 299 (8.79), 267 (87.27), 228 (45.21), 188 (25), 164 (8.96), 137 (66.84), 102 (36.36), 90 (55.08), 50 (100)

moiety at C2 makes a dihedral angle of 51.26(8)° with the benzimidazole ring; the orientation of the phenyl moiety is also defined by the torsion angle N2-C2-C10-C15 49.2(5)°.

The crystal structure is stabilized by one intramolecular hydrogen bond between N4 and C20 [C20...N4 2.917(4), C20-H20 0.93(3) Å and C20-H20...N4 121.7(2)°] and one inter-molecular hydrogen bond between N5.. N2 [N5.. $N2^{i}$ 2.872(4), N5-H5' 0.87(3) Å and N5 -H5'...N2 165(3); symmetry code: (i) -x+1,-y,-z+1].

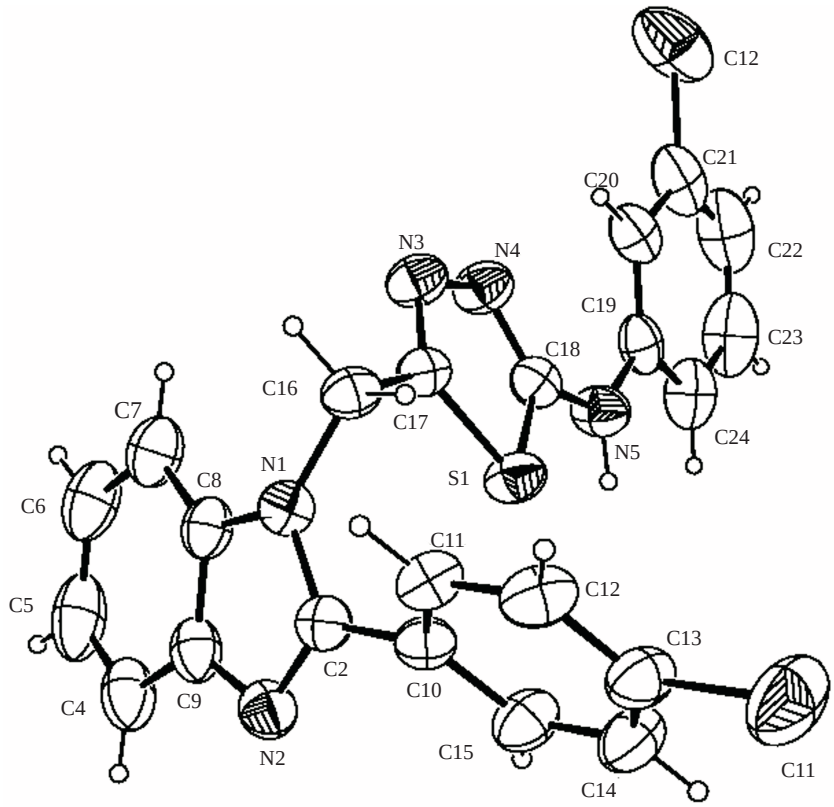
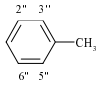
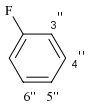
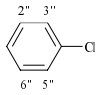
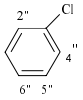


Figure 2. An Ortep II drawing of compound (**8b**) with the displacement ellipsoids drawn at the 35% probability level.

All of the compounds were evaluated for their in vitro antimicrobial activity against *S. aureus, B. subtilis, E. coli, C. albicans and C. krusei.* MIC values of the compounds and the standards are presented in Table 4. All the tested compounds showed less activity than ampicillin against *E. coli.* Compounds **1b, 5b, 8b, 9b, 11b** and **12b** were moderately active against *B. subtilis* (MIC:25μg/mL). Compounds **9b** and **10b** were more effective against *S. aureus* (MIC: 12.5 μg/mL) compared with the other derivatives. However, none of the compounds was superior to the ampicillin used as standard against *S. aureus, B. subtilis and E. coli.* Among the compounds tested, it was observed that compounds **1b**, **3b**, **8b** and **12b** possessed comparable activity to fluconazole against *C. albicans* with a MIC value of 12.5 μg/mL and compounds **1b** and **12b** showed remarkable activity against *C. krusei* with a 6.25 μg/mL MIC value.

Table 4. The in vitro antimicrobial activity of the compounds **1b-12b** (MIC, μg/mL).

	Ar''	*S. aureus*	*E. coli*	*B. subtilis*	*C. albicans*	*C. krusei*
1b		50	50	25	12.5	6.25
2b		100	>100	100	100	100
3b		12.5	50	50	12.5	12.5
4b		50	50	50	50	50
5b		100	50	25	50	25
6b		100	50	50	25	12.5
7b		50	12.5	50	25	12.5
8b		25	50	25	12.5	25
9b		12.5	50	25	25	25
10b		12.5	50	50	50	25
11b		50	50	25	25	25
12b		50	50	25	12.5	6.25
Ampicillin		6.25	1.78	6.25	*	*
Fluconazole		*	*	*	12.5	3.125

*: not tested

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