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ORIGINAL PAPER

Synthesis, Characterization, Crystal Structure and Biological Study of Carboxamides Obtained from 2-Aminothiazole Derivatives

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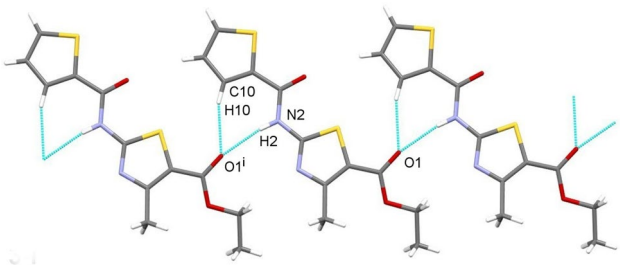
Abstract

Two series of novel thiazolylcarboxamide derivatives were synthesized by the reaction of ethyl 2-amino-4-methylthiazole-5-carboxylate or 1-(2-amino-4-methylthiazol-5-yl)ethan-1-one with four substituted carbonyl chlorides at 0 °C in excellent yield. All products were characterized by FTIR, ^{1}H NMR spectroscopy and mass spectrometry. Crystal structures of four compounds were studied by X-ray analysis. All the synthesized compounds were screened against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus pyogenes* for antibacterial activity and against *Candida albicans*, *Aspergillusniger* and *Aspergillus clavatus* for antifungal activity.

Graphic Abstract

Present study describes the biological activity and crystal structure study of carboxamides obtained from 2-aminothaizol derivatives. Owing to the insolubility of these amides in single volatile solvent, crystals were grown in a mixture of solvents.



Keywords Thiazolylcarboxamides · Aminothiazole · Carbonyl chloride · Amidation · Antibacterial and antifungal activity · Single crystal X-ray study

Introduction

The amides of 2-aminothiazoles are pharmaceutically very important from drug discovery point of view and are found in many important disease-intervening substances. For example, meloxicam is a selective cyclooxygenase-2 inhibitor from the group of non-steroidal anti-inflammatory drugs (NSAID) [1–4] and thiazotropsin A is binding to the minor groove of duplex DNA [5, 6]. Sulfur and nitrogen containing 1,3-thiazoles are very important class of heterocyclic compounds [7, 8]. They are well known for their biological activities [9–12]. Structures are shown in Scheme 1. Ethyl 2-amino-4-methylthiazole-5-carboxylate and its 2-substituted derivatives are building blocks in organic synthesis in making biologically and medicinally useful moieties [13, 14]. Also 1-(2-amino-4-methylthiazol-5-yl)ethan-1-one is used as an intermediate for synthesis of 4-methyl-5-formylthiazole, a key intermediate for cefditoren pivoxil [15–17]. Derivatives of ethyl 2-amino-4-methylthiazole-5-carboxylate have been reported to have shown significant

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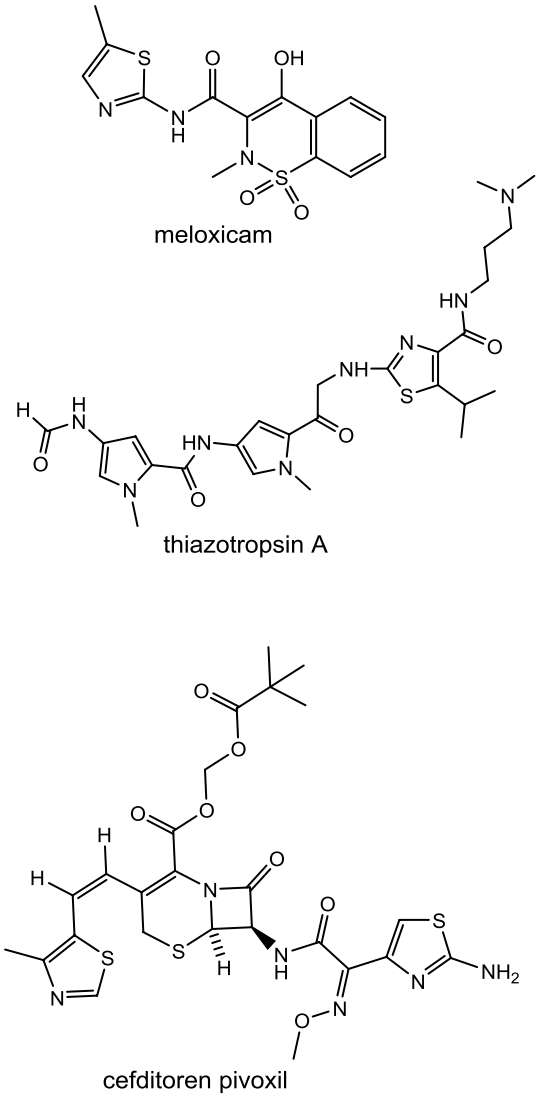


Scheme 1 Structures of drugs showing presence of 2-aminothiazole amide linkage

antileukemic activity on various human cells and exhibited a promising antineoplastic potential [13]. Amidation of 2-aminothiazol is of great interest to the researchers due to the weak nucleophilicity of the amino group. 2-benzamido-4-methylthiazole-5-carboxylic acid derivatives were studied as potential xanthine oxidase inhibitors and free radical scavengers [18].

Result and Discussion

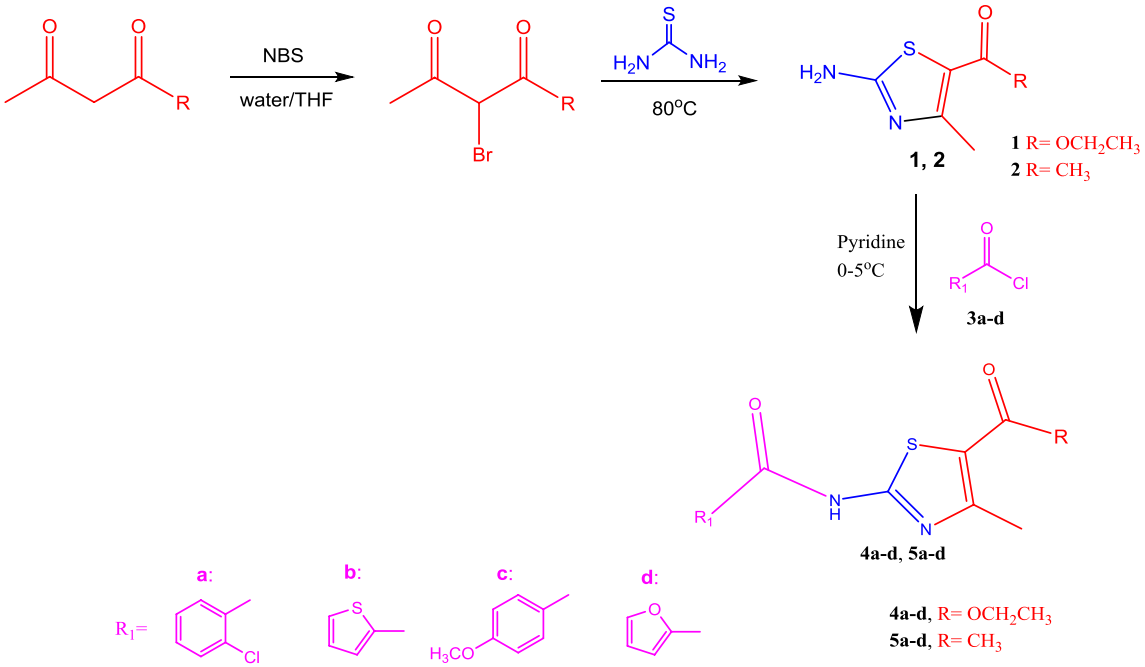
The starting compounds **1** and **2** were synthesized and characterized by FTIR and ^{1}H NMR spectroscopy. The IR spectrum of **1** and **2** shows characteristic υ(–NH) absorption band in the region 3260–3300 cm^{-1} and υ(–CO–) absorption band in the region 1662 cm^{-1}. The ^{1}H NMR spectra of **1** and **2** in DMSO exhibit characteristic singlet showing three protons at 2.37–2.40 ppm for thiazolylmethyl group. A singlet showing two protons around 7.68 ppm reveals –NH_2 group of aminothiazole which confirms the structure of **1** and **2** (Scheme 2).

Synthesized compounds **4a**–**d** and **5a**–**d** show characteristic ^{1}H NMR singlet around 12.60–13.00 ppm attributed to –NH group. A triplet in the range of 1.20–1.30 ppm is attributed to O–CH_2–CH_3 group of **4a**–**d** while a singlet around 2.32 ppm for three protons is attributed CO–CH_3 group of **5a**–**d**. The IR spectrum of compounds **4a**–**d** show one *υ*(C=O) absorption band in the range of 1643 to 1687 cm^{-1} range and another *υ*(C=O) absorption band in the range of 1511 to 1533 cm^{-1} range. Similarly compounds **5a**–**d** show *υ*(C=O) absorption band at 1662 cm^{-1} and 1599 cm^{-1}. Strong absorption band at 1643 to 1687 cm^{-1} for **4a**–**d** and at 1662 cm^{-1} for **5a**–**d** may be attributed to the carbonyl group of amide. Absorption due to *υ*(C=N) band in the region 1500–1600 cm^{-1} and *υ*(–NH) stretching band around 3200 cm^{-1} is observed which confirm the formation of desired products.

We were able to obtain crystals suitable for X-ray structural analysis of **4b** and **5b**–**d** (Fig. 1). Crystallographic data is listed in Table 1. Compounds **4b** and **5b**, differing only in the substituent on position 5 of the thiazol ring (ethoxycarbonyl vs. acetyl group), both crystallize in monoclinic *C*2/*c* space group with very similar cell parameters. Although compound **5d** is a close analogue of **5b**, it crystallizes in monoclinic $P2_1/c$ space group suggesting different packing mode. Compound **5c** crystallizes in triclinic *P*–1 space group. X-ray crystal structures of studied compounds show that all the bond lengths are within normal ranges [19]. All analyzed molecules are nearly planar with the dihedral angle between thiazole ring and thiophene (**4b**, **5b**), phenyl (**5c**) and furan (**5d**) ring (Fig. 1) is in the range of 5.02(9)–9.36(14)°. The ethoxycarbonyl group in **4b** and acetyl group in **5b**–**d** are almost coplanar with the thiazole ring showing dihedral angles in the range of 7.43(15)–10.87(6)°.

Supramolecular structures of studied compounds have a common motif with a hydrogen-bonded chain formed through the N2–H2···O1 bonding between the amide NH group as a hydrogen-bond donor and the carbonyl O atom of ethoxycarbonyl substituent in **4b** and acetyl substituent in **5b**–**d** as a hydrogen-bond acceptor supported by a C–H···O1 hydrogen bond forming a $R_2^1(7)$ ring motif [20] (Table 2, Figs. 2, 3, 4).

Supramolecular structures are achieved through C–H···π and π···π interactions. In **4b**, a stack of chains is formed due to π···π interactions between thiazole rings of two adjacent molecules with centroid-to-centroid distance of 3.9177(11) Å, and dihedral angle between the rings of 7.53(7)°, and also by C–H···π interactions between the methyl group or the methylene hydrogen atom of the ethyl group and the



Scheme 2 Synthesis of thiazolylcarboxamides of **4a–d** and **5a–d**

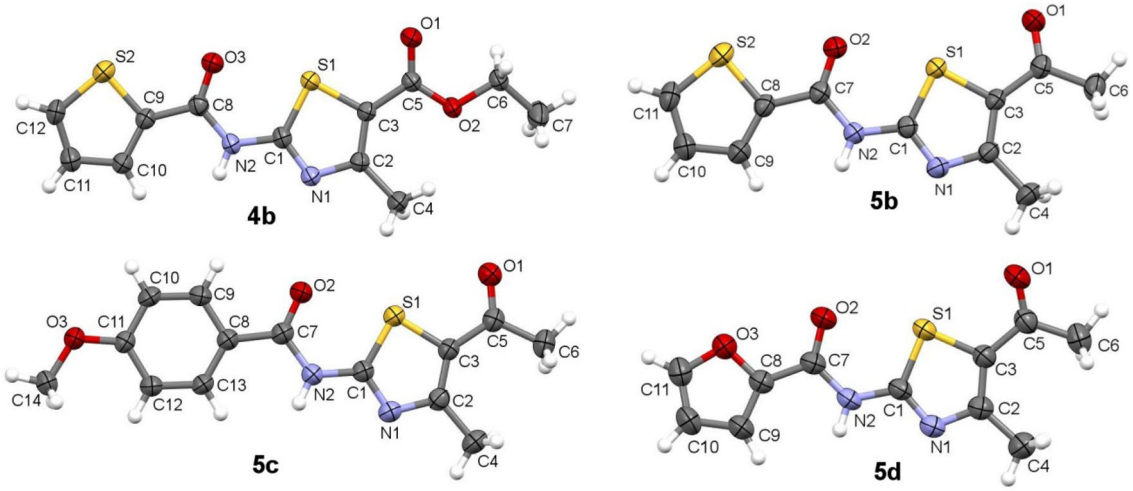


Fig. 1 Molecular structures and atom numbering schemes for **4b** and **5b–d**. Probability ellipsoids are drawn at the 50% level

thiophene ring (Fig. 2a–d). The presence of acetyl group in **5b** at the position 5 of the thiazole ring in comparison to the ethyl carboxylato group in **4b** doesn't alter the chain formation via N2–H2···O1 and C–H···O1 hydrogen bonding (Figs. 2a and 3a). However, it has a significant influence on the supramolecular structure even though both compounds **4b** and **5b** crystallize in monoclinic *C*2/*c* space group. Contrary to **4b** with stacks of chains, in **5b** C–H···π and π···π interactions connect only two adjacent molecules via π···π interaction between two thiazole rings with centroid-to-centroid distance of 4.1453(9) Å and ring slippage of 2.174 Å, and C–H···π interactions between methyl hydrogen of acetyl group and the thiophene ring (Table 3, Figs. 2 and 3).

The chain formation in **5c** is further enhanced by a C12–H12···O2 hydrogen-bond between the phenyl moiety and the carbonyl O atom of the amide group forming a $R_2^2(12)$ ring motif, while in **5d** the chain formation is enhanced by a C9–H9···S1 hydrogen-bonding between the furanyl moiety and the thiazole S atom forming a $R_1^2(5)$ ring

Table 1 Crystallographic data for **4b** and **5b–d**

Compound code	**4b**	**5b**	**5c**	**5d**
CCDC number	1826821	1826822	1826823	1826824
Molecular formula	$C_{12}H_{12}N_2O_3S_2$	$C_{11}H_{10}N_2O_2S_2$	$C_{14}H_{14}N_2O_3S$	$C_{11}H_{10}N_2O_3S$
Molecular weight	296.36	266.33	290.33	250.27
Crystal system	Monoclinic	Monoclinic	Triclinic	Monoclinic
Space group	*C*2/*c*	*C*2/*c*	*P*–1	$P2_1/c$
a (Å)	13.7498 (8)	13.5566 (6)	7.9860 (5)	7.5438 (14)
b (Å)	8.0735 (4)	8.1496 (4)	8.2593 (5)	20.7257 (14)
c (Å)	23.7840 (11)	21.432 (9)	11.0646 (6)	7.9241 (9)
α (°)	90	90	74.674 (5)	90
β (°)	96.347 (5)	95.793 (4)	81.594 (5)	115.377 (18)
γ (°)	90	90	77.941 (5)	90
Z	8	8	2	4
V (Å^3)	2624.1 (2)	2355.83 (19)	685.11 (7)	1119.4 (3)
D_{calc} (g cm^{-3})	1.500	1.502	1.407	1.485
μ (mm^{-1})	0.410	0.442	0.245	0.286
F(000)	1232	1104	304	520
Reflections collected	7757	6700	6024	7110
Independent reflections	3023	2703	3151	2564
R_{int}	0.0203	0.0182	0.0206	0.0320
Parameters	174	156	184	156
R_1, wR_2 [$I > 2\sigma(I)$][a]	0.0512, 0.1419	0.0348, 0.0953	0.0438, 0.1048	0.0442, 0.0442
R_1, wR_2 (all data)[a]	0.0563, 0.1473	0.0403, 0.0993	0.0649, 0.1171	0.0442, 0.1151
GOF[b]	1.094	1.060	1.049	1.038
$\Delta\rho_{min}$, $\Delta\rho_{max}$ (e Å^{-3})	− 0.229, 1.329	− 0.275, 0.316	− 0.175, 0.254	− 0.239, 0.233

[a] $R = \sum||F_o| - |F_c||/\sum|F_o|$; $wR_2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{1/2}$. [b] $S = \{\sum[(F_o^2 - F_c^2)^2]/(n/p)\}^{1/2}$ where *n* is the number of reflections and *p* is the total number of parameters refined

motif. Additionally, two adjacent chains in **5c** and **5d** are connected into a belt in a antiparallel and parallel fashion (Fig. 4), respectively, via hydrogen-bonding through the centrosymmetric C10–H10···O3 hydrogen-bond between the phenyl moiety and the methoxy group of the adjacent molecule with a $R_2^2(8)$ ring motif (in **5c**), and via hydrogen-bonding through the C11–H11···O2 hydrogen-bonding between the furanyl moiety and the carbonyl O atom of the amide group with a $R_3^3(16)$ ring motif (in **5d**) (Table 2, Fig. 4).

The alteration of thiophene group in **5b** with a methoxyphenyl (**5c**) and furanyl (**5d**) groups enables the belt formation (Fig. 4). It also changes the mode of π···π interactions. In **5c**, two adjacent molecules form π···π interactions between a thiazole and phenyl rings in a head-to-tail orientation with centroid-to-centroid distance of 3.8621(11) Å, and dihedral angle between the rings of 5.02(9)° (Table 3). Such dimeric units are connected into a pillar through the C4–H4A···π interactions between the methyl substituent and phenyl ring leading to a stack of belts (Fig. 5).

In **5d**, π···π stacking interactions through two different interactions of the aromatic rings are present. Two adjacent molecules connect in a similar fashion as in **5b** through the π···π interaction between two thiazole rings with centroid-to-centroid distance of 4.0513(15) Å and with slightly smaller ring slippage of 1.970 Å in comparison to **5b** (2.174 Å) (Table 3). Due to smaller slippage the formation of additional π···π interaction is enabled between the thiazole and furan ring with centroid-to-centroid distance of 4.1617(16) Å, and dihedral angle between the rings of 9.36(14)°. Thus, the pillar structure is formed leading to a stack of belts (Fig. 6).

It can be also observed in the studied structures that heteroatoms N and S of the thiazole ring are not involved as hydrogen bond acceptors with the only exception of compound **5d** where sulfur atom S1 is involved in bifurcated hydrogen bonding of the C9–H9 moiety. Heteroatoms in thiofuran and furan (**5b** and **5d**, respectively) are also not involved as hydrogen bond acceptors. As revealed by a search of the Cambridge Structural Database (CSD, Version 5.40, plus updates [21]), 7 entries were found with the thiazole moiety possessing amido group at the position 2 and keto or alkoxycarbonyl group at the position 5. In 6 out of 7 entries the alkoxycarbonyl group (–COOR, R = Me, Et, tBu) is present and only one entry possesses the keto group at the position 5. In all those 7 entries hydrogen bonding motifs are different than in **4b** and **5b–d**. Similar

Table 2 Hydrogen bond geometry of **4b** and **5b–d**

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)	Symmetry code
4b					
N2–H2···O1	0.86	2.15	3.003 (2)	170.4	$x, y+1, z$
C4–H4C···O2	0.96	2.35	2.938 (3)	119.3	x, y, z
C10–H10···O1	0.93	2.33	3.230 (3)	161.4	$x, y+1, z$
C4–H4A···*Cg*2	0.96	2.97	3.801 (3)	146	$-x+½, y-½, -z+½$
C6–H6A···*Cg*2	0.97	2.94	3.678 (3)	133	$-x+1, y-1, -z+½$
5b					
N2–H2···O1	0.86	2.02	2.8755 (18)	172.7	$x-½,y-½, z$
C9–H9···O1	0.93	2.27	3.139 (2)	156.0	$x-½,y-½, z$
C6–H6B···*Cg*2	0.96	2.94	3.593 (2)	127	$-x+1, -y+1, -z+1$
5c					
N2–H2···O1	0.86	2.13	2.981 (2)	169.3	$x-1, y, z$
C10–H10···O3	0.93	2.58	3.508 (2)	174.4	$-x, -y+1, -z+2$
C12–H12···O2	0.93	2.57	3.481 (2)	167.6	$x-1, y, z$
C13–H13···O1	0.93	2.37	3.287 (2)	170	$x-1, y, z$
C4–H4A···*Cg*2	0.96	2.86	3.607 (3)	135	$-x+1, -y, -z+1$
5d					
N2–H2···O1	0.86	2.05	2.901 (2)	171.6	$x, y, z-1$
C9–H9···S1	0.93	2.84	3.551 (2)	133.8	$x, y, z-1$
C9–H9···O1	0.93	2.29	3.132 (3)	149.8	$x, y, z-1$
C11–H11···O2	0.93	2.48	3.400 (3)	169.1	$x, -y+½, z-½$

*Cg*2 is S2/C9–12 (for **4b**), S2/C8–111 (for **5b**) and C8–C13 (for **5c**) ring centroid

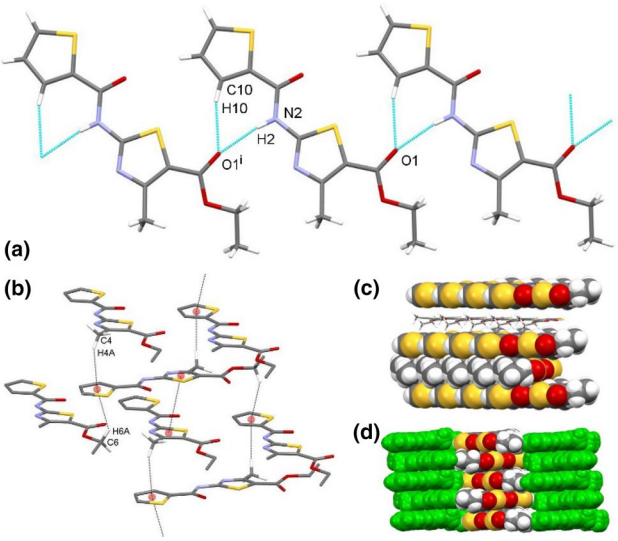


Fig. 2 **a** Chain formation in **4b** generated by N2–H2···O1 and C10–H10···O1 hydrogen bonding. Hydrogen-bonding is indicated by blue dashed lines. **b** C4–H4A···π, C6–H6A···π and π···π interactions. Interactions are indicated by black dashed lines. **c** Stacking of chains into a stack due to C–H···π and π···π interactions. **d** Packing of stacks; adjacent stacks are shown in green color (Color figure online)

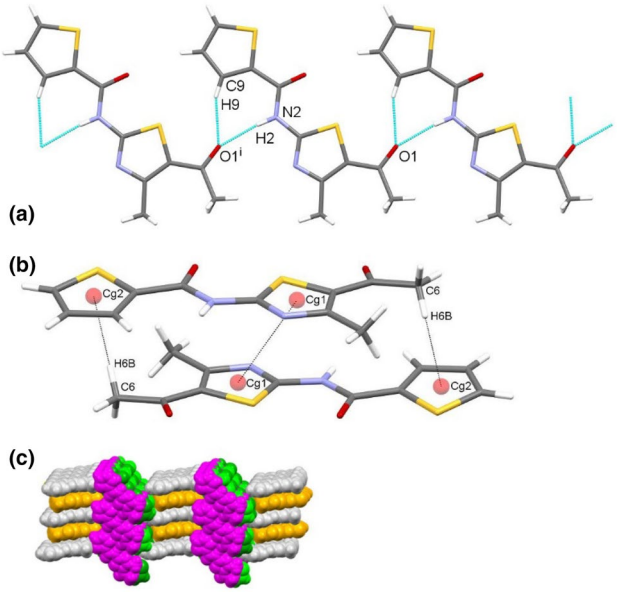


Fig. 3 **a** Chain formation in **5b** generated by N2–H2···O1 and C9–H9···O1 hydrogen bonding. Hydrogen-bonding is indicated by blue dashed lines. **b** C6–H6B···π and π···π interactions between two adjacent molecules. Interactions are indicated by black dashed lines. **c** Packing of chains (arbitrary colors) (Color figure online)

hydrogen-bonded chain formation through the N–H···O bonding between the amide NH group and the carbonyl O atom of ethoxycarbonyl or acetyl substituent as in **4b** and **5b–d** can be observed in only one entry; however, zig-zag chains are formed (Chandra L, 2011 CSD communication,

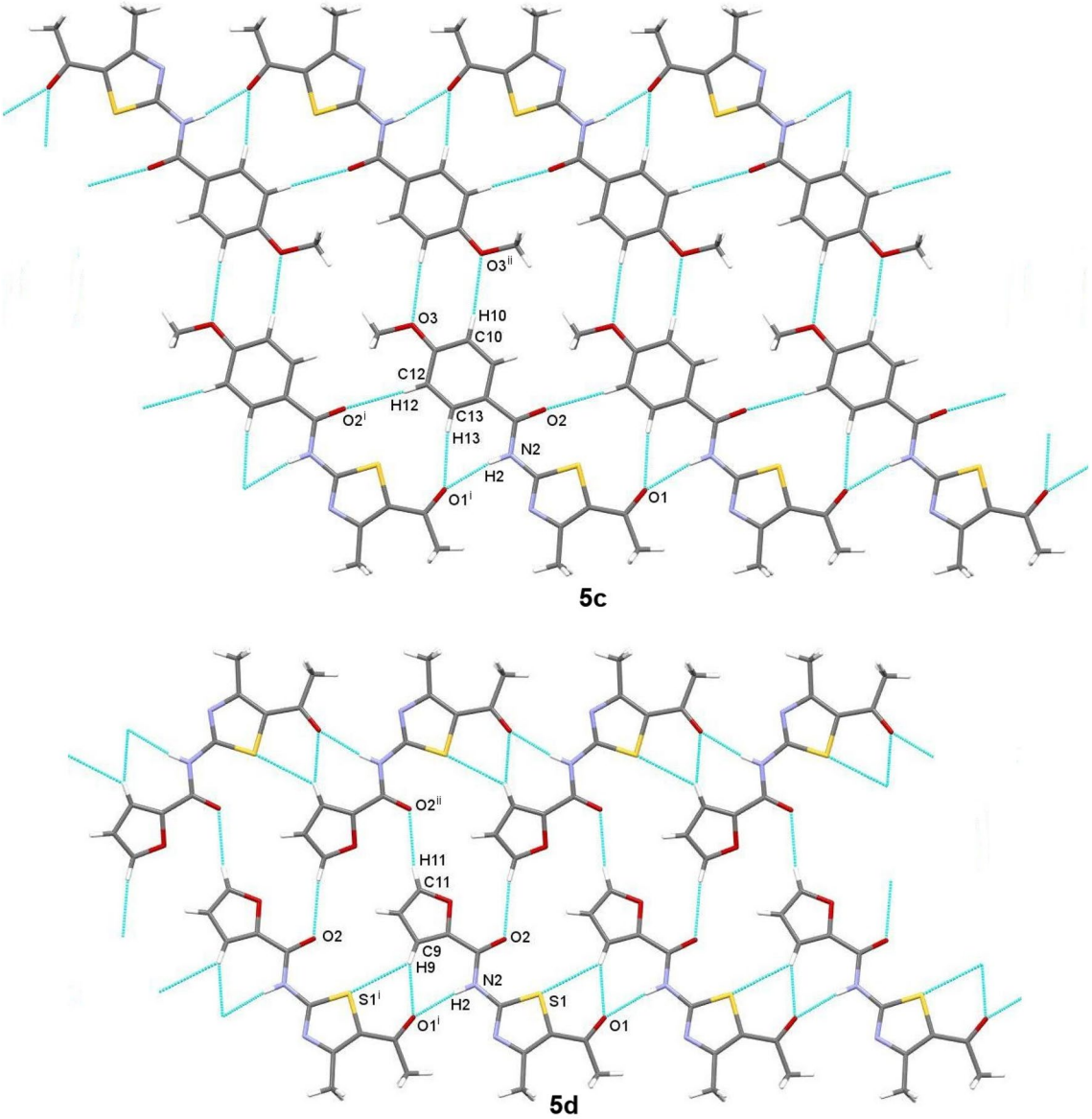


Fig. 4 Belt formation in **5c** and **5d** generated by N2–H2···O1 and C–H···O1 hydrogen bonding and by C12–H12···O2 and C10–H10···O3 (in **5c**) and by C9–H9···S1 and C11–H11···O2 (in **5d**). Hydrogen-bonding is indicated by blue dashed lines (Color figure online)

Private communication). In two entries chains are formed by N–H···O bonding, however, not with oxygen atom of alkoxycarbonyl or acetyl group as in **4b** and **5b–d** [22, 23]. In three entries nitrogen atom of the thiazole ring is involved in hydrogen bonding forming centrosymmetric hydrogen-bonded dimers through N–H···N(thiazole) [24, 25] or chains through N–H···N(thiazole) and N–H···O(amide) interactions [26]. In one entry compound crystallizes as a hydrate leading to very different hydrogen bonding motif (Borges F, Gomes LR, Low JN, 2017, CSD communication, Private communication).

All synthesized compounds were screened for antibacterial and antifungal activity against *E. coli*, *P. aeruginosa, S. aureus* and *S. pyogenus* as bacterial strain and *C. albicans, A. niger* and *A. clavatus* as fungal strain. It was found that all synthesized thiazolylcarboxamides **4a–d** and **5a–d** show activity against *S. aureus* close to standard ampicillin with **4b** and **5a–b** being more active than ampicillin. Activity of compound **4b** against *E.coli* and *S. pyogenus* was found to be close to activity of standard drugs like ampicillin, chloramphenicol, ciprofloxacin and activity against *P. aeruginosa* and *S. aureus* was found to be close to values of chloramphenicol and ampicillin, respectively. Compounds **4c** and **5b** show the activity against *E. coli* and *S. aureus* similar to ampicillin. **5d** was found to be active against *E. coli*, *S. aureus* and *S. pyogenus* similar as ampicillin (Table 4).

Table 3 Geometrical parameters (Å, °) for π···π stacking interactions in **4b** and **5b–d**

*Cg*I···*Cg*J	*Cg*I···*Cg*J	*α*	*β*	*Cg*I-Perp	Ring slippage	Symmetry code
4b						
*Cg*1···*Cg*1	3.9177 (11)	7.53 (7)	27.81	3.4652 (8)	–	$-x+1, y, -z+½$
5b						
*Cg*1···*Cg*1	4.1453 (9)	0	31.64	− 3.5292 (6)	2.174	$-x+1, -y+1, -z+1$
5c						
*Cg*1···*Cg*2	3.8621 (11)	5.02 (9)	26.01	3.5249 (7)	–	$-x+1, -y+1, -z+1$
5d						
*Cg*1···*Cg*1	4.0513 (15)	0	29.09	3.5404 (10)	1.970	$-x+1, -y+1, -z+1$
*Cg*1···*Cg*2	4.1617 (16)	9.36 (14)	31.48	− 3.6910 (9)	–	$-x, -y+1, -z$

C*g*I···C*g*J, α, β and C*g*I-Perp are, respectively, the centroid-to-centroid distance between rings I and J, the inter-ring dihedral angle, slip angle and the perpendicular distance of C*g*I from ring J. *Cg*1 is S1/C1/N1/C2–C3 and *Cg*2 is C8–C13 (for **5c**) and O3/C8–C11(for **5d**) ring centroids, respectively

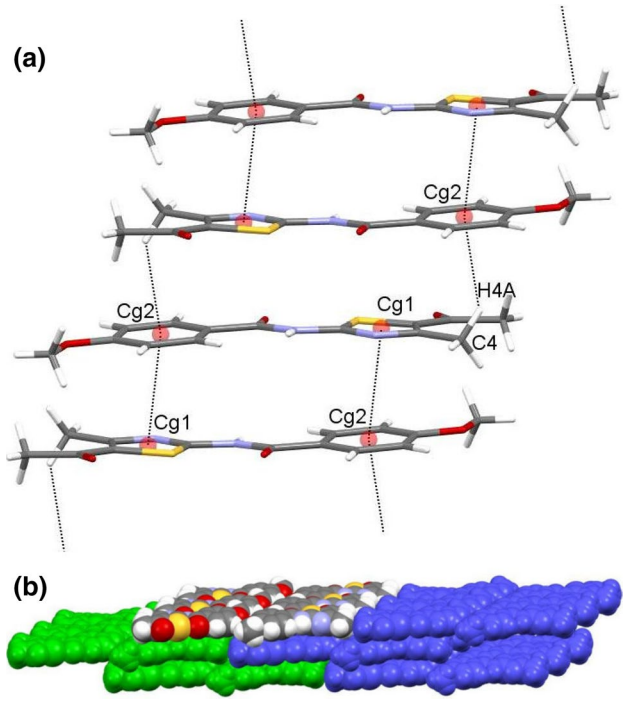


Fig. 5 **a** C4–H4A···π and π···π interactions in **5c**. Interactions are indicated by black dashed lines. **b** Packing of hydrogen-bonded belts (arbitrary colors) (Color figure online)

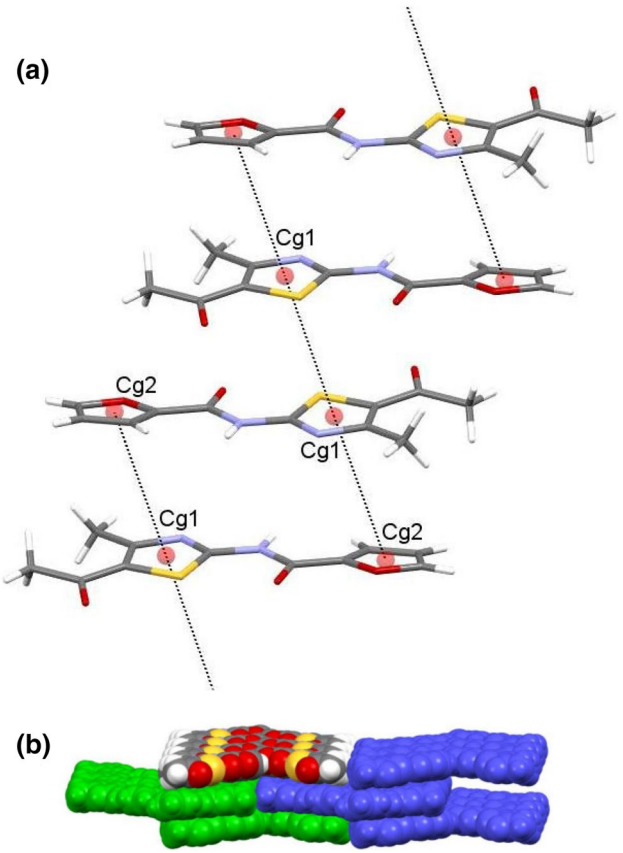


Fig. 6 **a** π···π stacking interactions in **5d**. Interactions are indicated by black dashed lines. **b** Packing of hydrogen-bonded belts (arbitrary colors) (Color figure online)

Compounds **4a**, **4b** and **5c** were found to be active against fungal strain *C. albicans* similar to griseofulvin, whereas **4d** and **5a** were found to be more active than griseofulvin. Compound **5d** shows activity against *C. albicans* similar to nystatin and griseofulvin (Table 5).

Conclusions

Thiazolylcarboxamide derivatives were synthesized by the reaction of ethyl 2-amino-4-methylthiazole-5-carboxylate or 1-(2-amino-4-methylthiazol-5-yl)ethan-1-one with four

Table 4 Antibacterial activity of **4a–d** and **5a–d** along with standard drugs

Minimal inhibition concentration (μg/mL)					
S. no.	Code given	*E. coli* (MTCC443)	*P. aeruginosa* (MTCC1688)	*S. aureus* (MTCC96)	*S. pyogenus* (MTCC442)
1	**4a**	50	100	250	125
2	**4b**	25	50	100	50
3	**4c**	100	125	250	500
4	**4d**	250	100	250	250
5	**5a**	250	500	62.5	125
6	**5b**	100	250	125	125
7	**5c**	250	125	250	250
8	**5d**	100	62.5	250	100
9	Gentamycin	0.05	1	0.25	0.5
10	Ampicillin	100	–	250	100
11	Chloramphenicol	50	50	50	50
12	Ciprofloxacin	25	25	50	50
13	Norfloxain	10	10	10	10

Table 5 Antifungal activity of **4a–d** and **5a–d** along with standard drugs

Minimal inhibition concentration (μg/mL)				
S. no.	Code given	*C. albicans* (MTCC227)	*A. niger* (MTCC282)	*A. clavatus* (MTCC1323)
1	**4a**	500	> 1000	> 1000
2	**4b**	500	1000	500
3	**4c**	1000	> 1000	> 1000
4	**4d**	250	500	500
5	**5a**	250	1000	500
6	**5b**	> 1000	500	500
7	**5c**	500	1000	1000
8	**5d**	100	500	500
9	Nystatin	100	100	100
10	Griseofulvin	500	100	100

substituted carbonyl chlorides in pyridine as a solvent at 0–5 °C in excellent yield. Single-crystal X-ray structures of **4b** and **5b–d** were determined. Owing to the insolubility of synthesized amides it was difficult to obtain the crystals using any volatile solvent alone. But this was overcome by use of a mixture of solvents. This method resulted in good quality crystals of amides. It helped in revealing structural features of this class of compounds. Compounds form hydrogen-bonded chains (**4b**, **5b**) and belts (**5c**, **d**) and are further connected through C–H···π and/or π···π interactions. Compound **4b** shows antibacterial activity comparable to ciprofloxacin on *E. coli*. **4b** also shows higher antibacterial activity than chloramphenicol in case of *E. coli* and it shows activity equivalent to chloramphenicol in case of *P. aerugenosa*, *S. aureus* and *S. pyogenus*. All compounds show considerable antifungal activity only against *C. albicans*. Compounds **4d** and **5a** have higher activity towards *C. albicans* as compared to griseofulvin. Compounds **5a**, **5b** and **5c** show activity equivalent to griseofulvin against *C. albicans*, while **5d** shows activity higher than griseofulvin and equivalent to nystatin against *C. albicans*.

Experimental

Materials and Method

All the starting materials and solvents (ethyl acetoacetate, acetylacetone, thiourea, *N*-bromosuccinimide, 2-chlorobenzoic acid, thiophene-2-carboxylic acid, 4-methoxybenzoic acid, furoic acid, pyridine, thionyl chloride, tetrahydrofuran) were purchased from commercial sources and were used without further purification. Melting points were determined in open capillaries using Electro thermal melting point apparatus and are uncorrected. Infrared (FTIR) spectra (4000–600 cm^{-1}) of the samples were recorded using a Perkin–Elmer Spectrum 100, equipped with a Specac Golden Gate Diamond ATR as a solid sample support. ^{1}H NMR spectra were recorded with a Bruker Avance III 500 NMR spectrometer with TMS as internal reference. MS spectra were recorded with an Agilent 6624 Accurate Mass TOF LC/MS instrument (ESI ionization).

Experimental Procedure

Synthesis

Synthesis of Ethyl 2-Amino-4-methylthiazole-5-carboxylate(1) and 1-(2-Amino-4-methylthiazol-5-yl)ethan-1-one

(2) Compounds **1** and **2** were synthesized according to the earlier reported procedure [27] (Scheme2).

General Procedure for Amidation of 1 and 2 Substituted carbonyl chlorides (**3a–d**) were prepared by the reaction of substituted carboxylic acid (50 mmol) and thionyl chloride (5.5 mL, 75 mmol) at about 50 °C. **3a–d** was added to cooled mixture of 50.0 mmol of **1** or **2** in pyridine (10 mL) respectively with continuous stirring for about 10 min at 0-5 °C to give dark yellow precipitate of corresponding carboxamides **4a–d** and **5a–d** respectively (Scheme 2). The product obtained was filtered and washed with dilute solution of sodium bicarbonate to remove unreacted carboxylic acid if any. It was then washed with water and dried. The compounds obtained were recrystallized using hot ethyl acetate [28].

Crystal Growth Using Combination of Three Solvents

It was observed that the compounds **4a–d** and **5a–d** were insoluble in ethanol, chloroform as well as ethyl acetate at room temperature. Crystals of **4b** and **5b–d** suitable for single-crystal x-ray analysis were obtained by adding about 1 g of compound in a mixture of ethanol, chloroform and ethyl acetate (1:1:1 v/v) 3 mL each. The mixture was heated slowly in water bath till complete dissolution of the compound, and allowed for slow evaporation in a dark chamber for about 6–8 days.

Spectral and Physical Data

Ethyl 2-Amino-4-methylthiazole-5-carboxylate (1) Yield-83%, pale yellow solid, melting point: 178–179 °C, Solubility: Ethanol, ^{1}H NMR (DMSO, 500 MHz, δ ppm): 1.22 (t, 3H, OCH_2CH_3), 2.37 (s, 3H, thiazole-4-CH_3), 4.14 (q, 2H, OCH_2CH_3), 7.68 (s, 2H, $–NH_2$).IR (cm^{-1}): 3362 (amine), 2984 (alkyl C–H), 1662 (C=O), 1501 (CH=N), 1366 (C=C).

1-(2-Amino-4-methylthiazol-5-yl)ethan-1-one (2) Yield-85%, pale yellow solid, melting point: 230 °C, Solubility: Ethanol, ^{1}H NMR (DMSO, 500 MHz, δ ppm): 2.31 (s, 3H, $COCH_3$), 2.40 (s, 3H, thiazole-4-CH_3), 7.79 (s, 2H, $–NH_2$). IR (cm^{-1}): 3264 (amine), 2989 (alkyl), 1662 (C=O), 1491 (CH=N), 1304 (C=C).

Ethyl 2-(2-Chlorobenzamido)-4-methylthiazole-5-carboxylate (4a) Yield-74%, pale yellow solid, melting point: 140 °C, Solubility: ethyl acetate. MS (ESI+) *m/z*: 325 (MH^+). HRMS: calcd. for $C_{14}H_{14}ClN_2O_3S$: 325.0408. Found: 325.0416. ^{1}H NMR (500 MHz, DMSO, δ ppm): 1.30 (t, 3H, OCH_2CH_3), 2.58 (s, 3H, thiazole–4–CH_3), 4.27 (q, 2H, OCH_2CH_3), 7.78–7.43 (m, 4H, –Ar), 13.09 (s, 1H, NH). IR (cm^{-1}): 3160 (NH), 1687 (C=O), 1533 (C=O), 1377 (C=C), 1273 (C–O).

Ethyl 4-Methyl-2-(thiophene-2-carboxamido)thiazole-5-carboxylate (4b) Yield: 76%, pale yellow solid, melting point: 218 °C Solubility: ethyl acetate. MS (ESI+) *m/z*: 297 (MH^+), HRMS: calcd. for $C_{12}H_{13}N_2O_3S_2$: 297.0362. Found: 297.0372.^{1}H NMR (500 MHz, DMSO, δ ppm): 1.29 (t, 3H, OCH_2CH_3), 2.59 (s, 3H, thiazole-4-CH_3), 4.26(q, 2H, OCH_2CH_3), 7.26 (t, 1H, thiophene), 8.01 (s, 1H, thiophene), 8.27(s, 1H, thiophene),13.11(s, 1H, NH). IR (cm^{-1}): 3273 (NH), 1643 (C=O), 1511 (C=O), 1413 (C=C), 1278 (C–O).

Ethyl 2-(4-methoxybenzamido)-4-methylthiazole-5-carboxylate (4c) Yield-73%, pale yellow solid, melting point: 160 °C, Solubility: ethyl acetate. MS (ESI+) *m/z*: 321 (MH^+), HRMS: calcd. for $C_{15}H_{17}N_2O_4S$: 321.0904. Found: 321.0913.^{1}H NMR (500 MHz, DMSO, δ ppm): 1.29 (t, 3H, OCH_2CH_3), 2.60 (s, 3H, thiazole-4-CH_3), 3.82 (s, 3H, $ArOCH_3$), 4.26 (q, 2H, OCH_2CH_3), 7.01 (d, 2H, Ar) 7.89 (d, 2H, Ar–H), 12.64 (s, 1H, NH).IR (cm^{-1}): 2984 (NH), 1674 (C=O), 1517 (C=O), 1423 (C=C), 1294 (C–O).

Ethyl 2-(Furan-2-carboxamido)-4-methylthiazole-5-carboxylate (4d) Yield-71%, pale yellow solid, melting point: 215 °C, Solubility: ethyl acetate. MS (ESI+) *m/z*: 281 (MH^+), HRMS: calcd. for $C_{12}H_{13}N_2O_4S$: 281.0591. Found: 281.0595. ^{1}H NMR (500 MHz, DMSO, δ ppm): 1.29 (t, 3H, OCH_2CH_3), 2.58 (s, 3H, thiazole-4-CH_3), 4.26 (q, 2H, OCH_2CH_3), 6.75-6.76 (m, 1H, furanyl), 7.72 (s, 1H, furanyl), 8.64 (s, 1H, furanyl), 12.99 (s, 1H, NH). IR (cm^{-1}): 3266 (NH), 1652 (C=O), 1517 (C=O), 1470 (C=C), 1275 (C–O).

***N*-(5-Acetyl-4-methylthiazol-2-yl)-2-chlorobenzamide (5a)** Yield-76%, pale yellow solid, melting point: 185 °C, Solubility: ethyl acetate. MS (ESI+) *m/z*: 295 (MH^+), HRMS: calcd. for$C_{13}H_{12}ClN_2O_2S$: 295.0303. Found: 295.0297. ^{1}H NMR (500 MHz, DMSO, δ ppm): 2.32 (s, 3H, $COCH_3$), 2.59 (s, 3H, thiazol-4-CH_3), 7.47–7.67 (m, 4H, –Ar), 13.07 (s, 1H, NH). IR (cm^{-1}): 3253 (NH), 1662 (C=O), 1599 (C=O), 1496 (C=C), 1309 (C–O).

***N*-(5-Acetyl-4-methylthiazol-2-yl)thiophene-2-carboxamide (5b)** Yield-74%, pale yellow solid. melting point: 195 °C, Solubility: ethyl acetate. MS (ESI+) *m/z*: 267 (MH^+), HRMS: calcd. for $C_{11}H_{11}N_2O_2S_2$: 267.0256. Found: 267.0252. ^{1}H NMR (500 MHz, DMSO, δ ppm): 2.32 (s, 3H, $COCH_3$), 2.61 (s, 3H, thiazol-4-CH_3), 7.26–8.26 (m, 3H, thiophene), 13.10 (s, 1H, NH). IR (cm^{-1}): 3264 (NH), 1662 (C=O), 1599 (C=O), 1491 (C=C), 1309 (C–O).

***N*-(5-Acetyl-4-methylthiazol-2-yl)-4-methoxybenzamide (5c)** Yield-72%, pale yellow solid. melting point: 175 °C, Solubility: ethyl acetate. MS (ESI+) *m/z*: 291 (MH^+), HRMS: calcd for $C_{14}H_{15}N_2O_3S$: 291.0798. Found: 291.0792. ^{1}H NMR (500 MHz, DMSO, δ ppm): 2.32 (s, 3H, $COCH_3$), 2.61 (s, 3H, thiazol-4-CH_3), 3.85 (s, 3H, –OCH_3) 7.08 (d, 2H, –Ar),8.12 (d, 2H, –Ar), 12.82 (s, 1H, NH). IR (cm^{-1}): 3264 (NH), 1662 (C=O), 1599 (C=O), 1496 (C=C), 1247(C–O).

***N*-(5-Acetyl-4-methylthiazol-2-yl)furan-2-carboxamide (5d)** Yield-70%, pale yellow solid melting point: 190 °C, Solubility: ethyl acetate. MS (ESI+) *m/z*: 251 (MH^+), HRMS: calcd for $C_{11}H_{11}N_2O_3S$: 251.0485. Found: 251.0483. ^{1}H NMR (500 MHz, DMSO, δ ppm): 2.31 (s, 3H, $COCH_3$), 2.60 (s, 3H, thiazol-4-CH_3), 7.47–7.67 (m, 3H, furanyl), 12.97(s, 1H, NH). IR (cm^{-1}): 3253 (NH), 1662 (C=O), 1599 (C=O), 1377 (C=C), 1288 (C–O).

X-Ray Crystallographic Study

Single-crystal X-ray diffraction data for all compounds were collected on an Agilent Technologies SuperNova Dual diffractometer with an Atlas detector using Mo-Kα radiation (λ = 0.71073 Å) at room temperature. The data were processed using CrysAlis Pro [29]. Structures were solved by direct methods using the program ShelXS and refined by a full-matrix least-squares procedure based on F^2 with ShelXL [30] using Olex2 program suite [31]. All the non-hydrogen atoms were refined anisotropically. Hydrogen atoms were readily located in difference Fourier maps and were subsequently treated as riding atoms in geometrically idealized positions with C–H = 0.93 Å (aromatic), 0.97 Å (methylene) or 0.96 Å (methyl), N–H = 0.86 Å and with $U_{iso}(H) = kU_{eq}(C,N)$, where $k = 1.5$ for methyl group and 1.2 for all other H atoms. Crystallographic data is listed in Table 1. Crystal structure data are deposited with the Cambridge Crystallographic Data Centre under CCDC 1826821–1826824 and can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk).

Determination of Minimum Inhibitory Concentrations by Micro Broth Dilution for Antibacterial and Antifungal Activity

All the synthesized drugs were used for antibacterial and antifungal test procedures. Minimal Inhibition Concentration (MIC) was determined according to the standard procedure proposed by the clinical and laboratory standard institute [32–36].

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