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NOVEL 1,2,4-TRIAZOLE-3-MERCAPTOACETIC ACID DERIVATIVES AS POTENTIAL ANTI-MYCOBACTERIAL AND ANTIMICROBIAL AGENTS

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تم تشييد قواعد شيف الجديدة لمركب ٤ ميثيل ٤,٢,١ تريازول ٣ ميركابتو إسيتيك أسيد هيدرازيد وتم التعرف على هذه المُركبات بالتحاليل الدقيقة والأشعة تحت الحمراء والرنين النووى المغناطيسى لعُنصرى الهيدروجين والكربون المُشع بالإضافة إلى مطياف الكُتلة وتم تعيين نسبة النظائر الهندسية باستخدام الرنين النووى المغناطيسى لعُنصر الهيدروجين وقد أختُبرت هذه المُركبات ضد ميكروب الدرن وأظهرت فاعلية متوسطة عند تركيز ٦,٢٥ ميكرو جرام / ملى وأختُبرت الفاعلية كمُضادات للبكتيريا ووجد أن المُركب 4g له فاعلية مُماثلة للأمبسيلين ضد *S. aureus*.

*Novel Schiff bases of 4-methyl-1,2,4-triazole-3-mercaptoacetic acid hydrazide were synthesized. Their chemical identities were elucidated by elemental analyses, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data. The percentage of the geometrical isomers was also elucidated using the ^{1}H-NMR. The synthesized compounds were selected for screening at the Tuberculosis Antimicrobial Acquisition and Coordination Facility (TAACF) against Mycobacterium tuberculosis $H_{37}R_{v}$ strain in which they showed moderate activity at a concentration of 6.25 μg/ml. Moreover, antimicrobial screenings against E. coli (ATCC 25922), S. aureus (ATCC 19433) and C. albicans identified compound **4g** as the most effective showing similar antibacterial activity as ampicillin against S. aureus.*

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INTRODUCTION

The rapid emergence of drug resistant bacterial pathogens such as the multidrug-resistant (MDR) strains of *Mycobacterium tuberculosis* emphasizes the need for new classes of antibacterial agents. These new antibacterial agents should preferably consist of chemical characteristics that clearly differ from those of existing agents.[1-3] Over the past few decades, certain small heterocyclic molecules such as quinolones, and oxazolidinones served as highly functionalized scaffolds and known pharmacophores of a number of antibacterial agents.[4-7] Furthermore, heterocyclic mercaptoacetic acid derivatives[8&9] and Schiff bases[10&11] are well known for their antimycobacterial and antimicrobial activity. In the last few years, 1,2,4-triazoles have been studied extensively for their diverse biological activities.[12-14] As the Schiff bases formation enhanced the antimycobacterial activity of both isoniazide[11] and 5-(2-furyl)-1,2,4-triazole-3-meracaptoacetic acid hydrazide,[8] we expected that compounds combining 1,2,4-triazole-3-mercaptoacetic acid and different Schiff bases will have potential antimycobacterial and antimicrobial activities. Therefore, the synthesis of planned series of such compounds will aim to confirm essential requirements for the antibacterial activities of this pharmacophore.

EXPERIMENTAL

Melting points were determined on Electrothermal Melting Point Apparatus and are uncorrected. Elemental microanalyses were performed on Perkin-Elmer, 240 Elemental Analyzer, at the central laboratory, Assiut University. TLC was carried out using silica gel 60 F_{254} precoated sheets (E. Merck, Germany) and was visualized using UV lamp at 254 nm. IR spectra were recorded as KBr disks on a 470-Shimadzu Spectrophotometer.

^{1}H-NMR spectra were recorded on a JEOL JNM-AL 300 FT NMR system. Coupling constants (*J*) are reported in hertz, and chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (TMS) as internal standard. DMSO-d_6 was used as solvent unless otherwise specified. ^{13}C-NMR spectra were recorded on JEOL-JNM-EX 300, 75.45 MHz. Liquid chromatographic-mass spectra (LC-MS) were determined on a Finnigan Electrospray Ionization-Mass spectrometer (ESI-MS) at Atmospheric Pressure Ionization (API) on the positive ion mode.

4-Methyl-1,2,4-triazole-3-mercapto-acetic acid methyl ester (2)

To a stirred solution of 3-mercapto-4-methyl-1,2,4-triazole (**1**) (0.1 mol) in DMF (25 ml), anhydrous K_2CO_3 (0.1 mol) was added at 0° and stirring was continued for 1 h. Methyl 2-chloroacetate (0.12 mol) was added, and the reaction mixture was stirred at

room temperature for 10 h. The solvent was evaporated; the residue extracted with AcOEt, washed with 5% $NaHCO_3$ and brine. The organic layer dried over anhydrous Na_2SO_4, filtered, and the filtrate was evaporated under reduced pressure. The residue was dried in desiccator to yield titled ester as a white powder. Yield 90%, m.p 65-66°. ^{1}H-NMR ($CDCl_3$) δ: 8.16 (s, 1H, C_5 of triazole), 4.05 (s, 2H, SCH_2), 3.75 (s, 3H, OCH_3), 3.67 (s, 3H, NCH_3). IR (KBr) cm^{-1} 3465, 1731, 1514, 1432. The resulted compound was directly used for the next step.

4-Methyl-1,2,4-triazole-3-mercapto-acetic acid hydrazide (3)

A mixture of **2** (0.01 mol), hydrazine monohydrate (0.05 mol, 100%) and ethanol (40 ml) was heated under reflux for 3 h. After cooling, the formed precipitate was collected by filtration and recrystallized from absolute ethanol to give **3**. Yield 65%, m.p 174-175°. ^{1}H-NMR δ: 9.27 (s, 1H, CONH), 8.64 (s, 1H, C_5 of triazole), 4.28-4.16 (hump, 2H, NH_2)**,** 3.73 (s, 2H, SCH_2), 3.56 (s, 3H, NCH_3). ^{13}C-NMR δ: 166.23, 148.57, 146.17, 35.05, 30.76. IR (KBr) cm^{-1} 3405, 3265, 1671, 1538, 1515, 1471. *Anal.* Calcd. for $C_5H_9N_5OS$: C, 32.08; H, 4.85; N, 37.41; Found; C, 31.96; H, 4.55; N, 37.67.

General method for the synthesis of Schiff bases (4a-h)

To a stirred solution of **3** (0.72 mol) in ethanol (25 ml), the appropriate aldehyde or ketone (0.76 mol) was added followed by three drops of conc HCl and stirring was continued overnight at room temperature. The formed precipitate was filtered off and recrystallized from aqueous ethanol. Physical data of the synthesized compounds are shown in Table 1.

N-Benzylidene-2-(4-methyl-4H-1,2,4-triazol-3-ylthio)aceto-hydrazide (4a)

^{1}H-NMR δ: 11.68, 11.61 (2s, 1H, CONH), 8.55, 8.50 (2s, 1H, C_5 of triazole), 8.16, 7.99 (2s, 1H, N=CH), 7.66-7.63 (m, 2H, ArH), 7.42-7.41 (m, 3H, ArH), 4.36, 3.95 (2s, 2H, SCH_2), 3.59 (s, 3H, NCH_3). IR (KBr) cm^{-1}: 3410, 3235, 1683, 1635, 1613. ESI-MS: m/z 276.10 $(M+1)^+$, 297.80 $(M+Na)^+$. *Anal*. Calcd. for $C_{12}H_{13}N_5OS$: C, 52.35; H, 4.76; N; 25.44; Found; C, 51.90, H; 4.56; N, 25.30.

N-(4-Chlorobenzylidene)-2-(4-methyl-4H-1,2,4-triazol-3-ylthio)-acetohydrazide (4b)

^{1}H-NMR δ: 11.69 (s, 1H, CONH), 8.54, 8.50 (2s, 1H, C_5 of triazole), 8.16, 7.98 (2s, 1H, CH=N), 7.71-7.65 (d, 2H, ArH), 7.58-7.47 (d, 2H, ArH), 4.35, 3.95 (2s, 2H, S-CH_2), 3.59 (s, 3H, N-CH_3). IR (KBr) cm^{-1}: 3410, 3230, 1670, 1634, 1613. ESI-MS: m/z 309.90 (M^+), 331.90 $(M+Na)^+$. *Anal.* Calcd. for $C_{12}H_{12}ClN_5OS.0.5H_2O$: C, 45.21; H, 4.11; N; 21.97; Found; C, 45.35, H; 3.99; N, 21.82.

N-(4-Methoxybenzylidene)-2-(4-methyl-4H-1,2,4-triazol-3-ylthio)-acetohydrazide (4c)

^{1}H-NMR δ: 11.49 (s, 1H, CONH), 8.53, 8.50 (2s, 1H, C_5 of triazole), 8.09, 7.93 (2s, 1H, CH=N), 7.63-7.57 (d, 2H, ArH), 6.99-6.96 (d, 2H, ArH), 4.33, 3.93 (2s, 2H, S-CH_2), 3.78 (s, 3H, OCH_3), 3.59 (s, 3H, NCH_3). ^{13}C-NMR δ: 168.47, 146.18, 146.08, 143.57, 128.67, 128.37, 114.24, 55.23, 35.26, 30.75. IR (KBr) cm^{-1}: 3410, 3235, 1662, 1634, 1600, 1241. ESI-MS: m/z 305.90 (M^+), 328.00 $(M+Na)^+$. *Anal.* Calcd. for $C_{13}H_{15}N_5O_2S$: C, 51.13; H, 4.95; N; 22.9; Found; C, 51.34, H; 4.68; N, 22.3.

N-(3,5-Dimethoxybenzylidene)-2-(4-methyl-4H-1,2,4-triazol-3-yl thio)acetohydrazide (4d)

^{1}H-NMR δ: 11.57, 11.49 (2s, 1H, CONH), 8.55, 8.50 (2s, 1H, C_5 of triazole), 8.08, 7.91 (2s, 1H, CH=N), 7.28-7.25 (m, 1H, ArH), 7.16-7.13 (m, 1H, ArH), 6.99-6.96 (m, 1H, ArH), 4.33, 3.94 (2s, 2H, S-CH_2), 3.81-3.79 (s, 6H, OCH_3), 3.59 (s, 3H, N-CH_3). ^{13}C-NMR δ: 168.58, 163.29, 150.53, 148.91, 147.43, 146.10, 143,81, 126.60, 121.83, 121.09, 111.46, 111.38, 55.48, 55.40, 35.74, 30.76. IR (KBr) cm^{-1}: 3410, 3235, 1670, 1634, 1613, 1262. ESI-MS: m/z 335.80 (M^+), 357.90 $(M+Na)^+$. *Anal.* Calcd. for $C_{14}H_{17}N_5O_3S$. C, 50.14; H, 5.11; N; 20.88; S, 9.56; Found; C, 50.51, H; 5.12; N, 19.12; S, 9.12.

N-(4-Hydroxy-3-methoxybenzylidene)-2-(4-methyl-4H-1,2,4-triazol-3-ylthio)acetohydrazide (4e)

^{1}H-NMR δ: 11.43 (s, 1H, CONH), 9.52 (s, 1H, OH), 8.55, 8.50 (2s, 1H, C_5 of triazole), 8.03, 7.87 (2s, 1H, CH=N), 7.24-7.21 (m, 1H, ArH), 7.06-7.03 (m, 1H, ArH), 6.82-6.79 (m, 1H, ArH), 4.32, 3.92 (2s, 2H, S-CH_2), 3.75 (s, 3H, OCH_3), 3.60 (s, 3H, N-CH_3). IR (KBr) cm^{-1}: 3410, 3235, 1680, 1636, 1613, 1212. ESI-MS: m/z 321.70 (M^+), 344.10 $(M+Na)^+$. *Anal.* Calcd. for $C_{13}H_{15}N_5O_3S$: C, 48.59; H, 4.70; N, 21.79; Found; C, 48.02; H, 4.51; N, 21.33.

N-(4-(Dimethylamino)benzylidene)-2-(4-methyl-4H-1,2,4-triazol-3-yl thio)acetohydrazide (4f)

^{1}H-NMR δ: 11.37, 11.31 (2s, 1H, CONH), 8.54, 8.51 (2s, 1H, C_5 of triazole), 8.00, 7.85 (2s,1H, CH=N), 7.49-7.43 (m, 2H, ArH), 6.73-6.59 (m, 2H, ArH), 4.31, 3.90 (2s, 2H, S-CH_2), 3.59 (s, 3H, N-CH_3), 2.94 (s, 6H, $N(CH_3)_2$). ESI-MS: m/z 319.00 $(M+1)^+$, 341.00 $(M+Na)^+$. *Anal.* Calcd. for $C_{14}H_{18}N_6OS.1H_2O$: C, 49.98; H, 5.99; N; 24.98; Found; C, 49.96, H; 6.03; N, 25.09.

2-(4-Methyl-4H-1,2,4-triazol-3-yl thio)-N-((pyridin-3-yl)methylene)-acetohydrazide (4g)

^{1}H-NMR δ: 11.86, 11.77 (2s, 1H, CONH), 8.82 (s, 1H, pyr), 8.59-8.50 (m, 2H, pyr, C_5 of triazole), 8.10-8.02 (m, 2H, pyr), 7.48-7.44 (2s, 1H, CH=N), 4.36, 3.97 (2s, 2H, S-CH_2), 3.60 (s, 3H, N-CH_3). IR (KBr) cm^{-1}:

3410, 3230, 1678, 1634, 1612. ESI-MS: m/z 277.10 $(M+1)^+$, 575.21 $(2M+Na)^+$. *Anal.* Calcd. for $C_{11}H_{12}N_6OS.1.5H_2O$: C, 43.55; H, 4.98; N; 27.70; Found; C, 43.64, H; 4.46; N, 27.27.

N-(1-(4-Chlorophenyl)ethylidene)-2-(4-methyl-4H-1,2,4-triazol-3-yl thio)acetohydrazide (4h)

^{1}H-NMR δ: 10.88 (s, 1H, CONH), 8.56, 8.50 (2s, 1H, C_5 of triazole), 7.93-7.90 (d, 2H, ArH), 7.79-7.76 (d, 2H, ArH), 4.39, 4.05 (2s, 2H, S-CH_2), 3.59 (s, 3H, N-CH_3), 2.25 (s,3H,CH_3). IR (KBr) cm^{-1}: 3410, 3235, 1673, 1635, 1613. ESI-MS: m/z 323.80 (M^+), 346.10 $(M+Na)^+$. *Anal.* Calcd. for $C_{13}H_{14}ClN_5OS$: C, 48.22; H, 4.36; N; 21.63; S, 9.90 Found; C, 47.85, H; 4.20; N, 21.11; S, 9.61.

Antimycobacterial Assay

The primary antimycobacterial evaluation was performed at the National Hansen's Disease Programs (NHDP) TAACF facilities, Baton Rouge, LA, USA. The screening was conducted at a single concentration of 6.25 μg/ml against *Mycobacterium tuberculosis* H_{37}Rv (ATCC 27294) in BACTEC 12B medium using the Microplate Alamar Blue Assay (MABA). Compounds exhibiting fluorescence are tested in the BACTEC 460-radiometric system.[15] Compounds effecting <90% inhibition in the primary screen are not evaluated further.

Antimicrobial assay

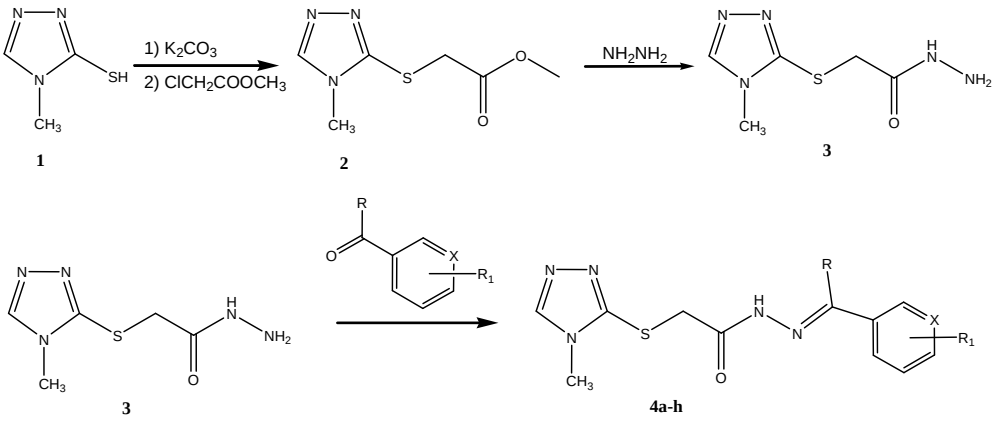
The microdilution susceptibility test in Müller-Hinton Broth (Oxoid) and Sabouraud Liquid Medium (Oxoid) were used for the determination of antibacterial and antifungal activity.[16] The utilized test organisms were: *Escherichia coli* (*E. coli*) ATCC 25922 as an example of Gram-negative bacteria, *Staphylo-coccus aureus* (*S. aureus*) ATCC 19433 as an example of Gram-Positive bacteria and *Candida albicans* (*C. albicans*) as yeast-like fungi. Ampicillin trihydrate and clotrimazole were used as standard antibacterial and antifungal agents, respectively. Solutions of the test compounds, ampicillin trihydrate and clotrimazole were prepared in DMSO at concentration of 1600 μg/ml. The twofold dilution of the compounds were prepared (800, 400,...6.25 μg/ml). The microorganism suspensions at 10^6 CFU/ml (Colony Forming Unit / ml) concentration were inoculated to the corresponding wells. Plates were incubated at 36° for 24 h to 48 h. The incubation chamber was kept sufficiently humid. At the end of the incubation period, the minimal inhibitory concentrations (MICs) were determined which were defined as the minimum concentrations of a compounds that visually inhibits the growth of tested microorganisms.

RESULTS AND DISCUSSION

Chemistry

All the new compounds were synthesized according to Chart 1. Reaction of the commercially available 3-mercapto-4-methyl-1,2,4-triazole **1** with methyl 2-chloroacetate afforded 4-methyl-1,2,4-triazole-3-mercaptoacetic acid methyl ester **2** that consequently give hydrazide **3** when reacted with hydrazine hydrate. Condensation of hydrazide **3** with aromatic aldehydes or ketone gave the corresponding Schiff bases **4a-h**. The identities of the compounds obtained were confirmed by elemental analyses, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data. Some physical data of the synthesized compounds are shown in Table 1.

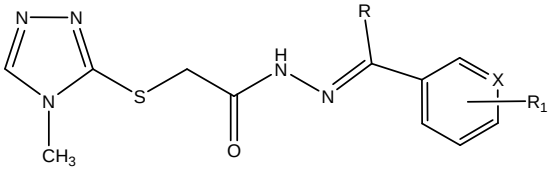
In the IR spectra, significant bands due to N-H, hydrazide C=O, and C=N appeared at 3410-3200 cm^{-1}, 1683-1660 cm^{-1} and 1635-1610 cm^{-1}, respectively. In the ^{1}H-NMR spectra, the presence of two geometric isomers in different ratios is clearly confirmed not only by the appearance of the SCH_2, N=CH, and CONH peaks as pairs of singlets but also the triazole C_5 proton showing the same pattern (Table 2). For the N=CH, CONH, and triazole C_5 proton, the resonances of the isomers with higher percentage in the mixture appear at higher fields while in case of the SCH_2 protons an opposite pattern is observed (Table 2) As it is reported that the azomethine proton (N=CH) of the Z isomers of the enamine compounds appears at lower fields



N.B.: For X, R, and R_1 see Table 1.

Chart 1. Synthesis of the 4-methyl-1,2,4-triazole-3-mercaptoacetic acid derivatives.

Table 1: Structures and physical data of compounds **4a-h**.



Compd. No	R	X	R_1	m.p°	Yield %	Mol. Formula Mol. Wt
4a	H	C	H	194-95	62	$C_{12}H_{13}ON_5S$ 275.3295
4b	H	C	4-Cl	186	70	$C_{12}H_{12}ClON_5S$ 309.7746
4c	H	C	4-OCH_3	146	65	$C_{13}H_{15}O_2N_5S$ 305.3555
4d	H	C	3,5-OCH_3	100-02	98	$C_{14}H_{17}O_3N_5S$ 335.3815
4e	H	C	3-OCH_3, 4-OH	226	95	$C_{13}H_{15}O_3N_5S$ 321.3549
4f	H	C	4-$N(CH_3)_2$	162-63	84	$C_{14}H_{18}ON_6S$ 318.3973
4g	H	N	H	160-61	60	$C_{11}H_{11}ON_6S$ 276.3176
4h	CH_3	C	4-Cl	184-85	60	$C_{13}H_{14}ClON_5S$ 323.8012

Table 2: ^{1}H-NMR chemical shifts and the ratios of peak intensities of selected peaks in compounds **2, 3, 4a-h**.

Compd. No[a)]	^{1}H-NMR (ppm)			
	S-CH_2 (Ratio %)[b)]	N=CH(Ratio %)[b)]	CONH[c)]	Triazole (C_5-H)[c)]
2	4.05	-	-	8.16
3	3.73	-	9.27	8.53
4a	3.95, 4.36 (33:67)	7.99, 8.16 (67:33)	11.61, 1168	8.50, 8.55
4b	3.95, 4.35 (33:67)	7.98, 8.16 (67:33)	11.69	8.50, 8.54
4c	3.93, 4.33 (35:65)	7.93, 8.09 (67:35)	11.49	8.50, 8.53
4d	3.94, 4.33 (40:60)	7.91, 8.08 (60:40)	11.49, 11.57	8.50, 8.55
4e	3.92, 4.32 (39:61)	7.87, 8.03 (61:39)	11.43	8.50, 8.55
4f	3.90, 4.31 (39:61)	7.85, 8.00 (61:39)	11.31, 11.37	8.51, 8.54
4g	3.97, 4.36 (33:67)	8.03, 8.23 (67:33)	11.77, 11.86	8.50, 8.55
4h	4.05, 4.39 (36:64)	-	10.88	8.50, 8.56

[a)] For the structures see Table 1 and Chart 1., [b)] Approximate ratio as determined from peak integration, [c)] The same ratios as N=CH.

compared to the E isomers,[17] we concluded that the E isomer is the predominant in agreement with already reported data of this type of compounds.[8] All other aromatic and aliphatic protons were observed at expected regions. Liquid chromatographic-mass spectra (LC-MS) by Electrospray Ionization (ESI-MS) of the prepared compounds showed $(M+1)^+$ or $(M+Na)^+$ peaks, which were in agreement with their molecular formula.[18]

Antimycobacterial Activity

Compounds **4a-h** were tested for their primary antimycobacterial activity against *Mycobacterium tuberculosis* $H_{37}R_v$ at a single concentration of 6.25 μg/ml. As Shown in Table 3, all compounds exhibited a growth inhibition in the range 19–24%. Furthermore, compounds **4a-h** exhibited antimycobacterial activity comparable to that of 1,2,4-triazole-3-mercaptoacetic acid derivatives tested at the same concentration of 6.25 μg/ml.[8] Although no observed variations of the biological activities of all the tested compounds, compound **4e** is the most effective in this series. Comparing the activity of the 4-methoxyphenyl Schiff base **4c** (20% inhibition) and that previously reported[8] for the 4-methoxyphenyl Schiff base of 5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptoacetic acid hydrazide (18% inhibition) indicates that the 5-(2-furyl) moiety on the 1,2,4-triazole ring is not essential for the antimycobacterial activity. From the above results we can conclude that the 1,2,4-triazole-3-mercapto-acetic acid Schiff base as a whole unit appears to be a useful scaffold for the antimycobacterial agents.

Antimicrobial activity

Compounds **3**, **4a-h** were tested for their *in vitro* antimicrobial activity against *Escherichia coli* (*E. coli*) ATCC 25922, *Staphylococcus aureus* (*S. aureus*) ATCC 19433, and *Candida albicans* (*C. albicans*) by the method shown in the experimental part.[16] Ampicillin trihydrate and clotrimazole were used as standard antibacterial and antifungal agents, respectively. As shown in Table 4, the MIC values of the tested compounds are generally within the range of 12.5-200 $\mu g.ml^{-1}$ against all evaluated strains. Against *Staphylococcus aureus*, compound **4g** showed similar activity to ampicillin, and **4d, 4f** showed good activity while other compounds are moderately active. Only compound **4b** showed moderate activity against *Candida albicans* when compared to clotrimazole whereas all other compounds are less active.

Furthermore, the most active compound **4g** has similar lipophilicity as that of ampicillin as already shown by comparing their CLog P (Table 4). Also the presence of the pyridine ring may be a contributing factor for the high antibacterial activity of compound **4g** against *S. aureus*. Further progress in this area of compounds will be the subject of future reports.

Table 3: Antitubercular *in vitro* activity of test compounds expressed as % inhibition of *Mycobacterium tuberculosis* $H_{37}R_v$ at a single concentration of 6.25 μg/ml.

No (Code)	TAACF ID	% inhibition	MIC (μg/ml)
4a (TTC-1)	298315	20	> 6.25
4b (TTC-2)	298316	21	> 6.25
4c (TTC-3)	298317	20	> 6.25
4d (TTC-4)	298318	21	> 6.25
4e (TTC-5)	298319	24	> 6.25
4f (TTC-6)	298320	20	> 6.25
4g (TTC-7)	298321	19	> 6.25
4h (TTC-8)	298322	19	> 6.25

Table 4: Minimal inhibitory concentrations (MIC μg/ml) of test compounds.

Compd. No	*E. coli*	*S. aureus*	*C. albicans*	CLog P[a)]
3	100	100	>200	-2.4578
4a	200	100	>200	0.1468
4b	>200	>200	100	0.8598
4c	100	100	>200	0.3658
4d	100	50	>200	0.4343
4e	200	100	>200	-0.0621
4f	200	25	>200	0.6778
4g	100	12.5	200	-1.1702
4h	>200	>200	>200	1.7668
Ampicillin	25	12.5	---	-1.2045
Clotrimazole	---	---	12.5	5.254

[a)] Calculated values using ChemDraw ultra 8.0 software.

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REFERENCES

1- K. M. Overbye and J. F. Barrett, Drug Discovery Today, 10, 45 (2005).
2- N. H. Georgopapadakou, Drug Resistance Updates, 5, 181 (2002).
3- T. Thomas Scior, I. M. Morales, S. J. G. Eisele, D. David Domeyer and S. Stefan Laufer; Arch. Pharm. Pharm. Med. Chem., 11, 511 (2002).
4- N. Anand and W. E. Remers, in "Burger's Medicinal Chemistry and Drug Discovery", 6th Ed, Vol. 5, "John Wiley and Sons", New York, 2003, pp. 582-587.
5- M. Brands, Y. C. Grande, R. Endermann, R. Gahlmann, J. Kruger and S Raddatz, Biorg. Med. Chem. Lett., 13, 2641 (2003).
6- R. Tokuyama, Y. Takahashi, Y. Tomita, M. Tsubouchi, T. Yoshida, N. Iwasaki, N. Kado, E. Okezaki and O. Nagata, Chem. Pharm. Bull., 49, 353 (2001).
7- L. Ballell, R. A. Field, K. Duncan and R. J. Young, Antimicrob. Agents Chemother., 49, 2153 (2005).
8- N. Ulusoy, A. Gursoy and G. Otuk, Farmaco, 56, 947 (2001).
9- I. A. Shehata, Saudi Pharmaceutical Journal, 11, 87 (2003).
10- P. Panneerselvam, R. R. Nair, G. Vijayalakshmi, E. H. Subramanian and S. K. Dridhar, Eur. J. Med. Chem., 40, 225 (2005).
11- M. J. Hearn and M. H. Cynamon, J. Antimicrob. Chemother., 53, 185 (2004).
12- A. Shafiee, A. Sayadi, M. H. Roozbahani, A. Foroumadi and F. Kamal, Arch. Pharm. Pharm. Med. Chem., 10, 495 (2002).
13- K. Colanceska-Ragenovic, V. Dimova, V. Kakurinov and D. M.Gabor, J. Heterocycl. Chem., 40, 905 (2003).
14- P. Marakos, S. Papakonstantinou-Garoufalias, E. Tani, P. N. Kourounakis, G. Athanasiou and A. Chytyroglou-Lada, Arzneim.-Forsch/Drug Res., 52, 572 (2002).
15- L., Collins and S. G.Franzblau, Antimicrob. Agents Chemother., 41, 1004 (1997).
16- B. Henderson In: M. M. Dale, J. C. Foreman and T-P. D. Fan. (Eds), "Textbook of Immunopharmacology", 3rd Ed., Blackwell Scientific Publications, London, 1994, pp. 16 and 193.
17- E. Pretsch, P. Buhlmann and C. Affolter, "Structure Determination of Organic Compounds: Tables of Spectral Data", Springer-Verlag Berlin Heidelberg, 2000, pp. 211-212.
18- C.-K. Lim and G. Lord, Biol. Pharm. Bull., 25, 547 (2002).