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Synthesis and Electronic Structure of New Aryl- and Alkyl-Substituted 1,3,4-Oxadiazole-2-thione Derivatives

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New 5-alkyl and 3-(2,4-dimethylphenyl) substituted 1,3,4-oxadiazole-2-thione derivatives were synthesized by the ring closure reactions of various acylhydrazides with carbon disulphide. Mannich bases for some of these compounds were also synthesized by condensation with benzaldehyde and primary amines. All new compounds were characterized by spectral data. Most of them were tested for their antibacterial and antituberculostatic activity.

Molecular orbital calculations at the HF/6-31G** level were also performed to determine the optimized geometrical structures. Results indicated electron delocalization over several atoms of the ring. An additional study on the tautomeric equilibrium between 1,3,4-oxadiazole-2-thione and its thiol form showed that the thione tautomer is favoured by 9.616 kcal/mole in the gas phase and by 12.123 kcal/mole in aqueous medium.

Introduction

Oxadiazole derivatives, which belong to an important group of heterocyclic compounds, have been the subject of extensive study in the recent past. Numerous reports have highlighted their chemistry and use[1−3]. Diverse biological activities, such as anti-tuberculostatic, antiinflamatory, analgesic, antipyretic and anticonvulsant, have been found to be associated with oxadiazole derivatives[4,5]. For this reason our aim was to synthesize various 1,3,4-oxadiazole-2-thione derivatives to make notable contributions to this class of heterocyclic compounds. We report the synthesis and characterization of some 5-alkyl substituted 1,3,4-oxadiazole-2-thiones (**3a-e**) and 5-alkyl substituted 3-(2,4-dimethylphenyl)-1,3,4-oxadiazole-2-thiones (**4a-d**) using the synthetic procedure based on the ring closure reactions of appropriate acid hydrazides with carbon disulphide[6] .We also synthesized some bis-Mannich bases by the reaction of **3a-e** with benzaldehyde and benzidine.

Although there have been many studies about the synthesis and biological activities of 1,3,4-oxadiazole-2-thiones, there are only a few articles concerning the structures of these compounds[7,8] and to our knowledge,

there are no articles on their complete structural analysis. On the other hand, since 1,3,4-oxadiazole-2-thiones are biologically active compounds, information about their 3-dimensional structures may be of great interest for rational drug design. Therefore, we also aimed to obtain and analyse the electronic structures of the 1,3,4-oxadiazole-2-thiones that we synthesized. For this purpose, molecular orbital calculations were employed. Ab initio Hartree-Fock theory with 6-31G** basis set was used since it is known to be quite a reliable method[9] .

1,3,4-Oxadiazole-2-thiones consist of an equilibrium mixture of its thione and thiol forms[7,8,10,11]but there is lack of information about the energetics of this process. Therefore, we also calculated the energy of each species involved in the tautomeric equilibrium.

Results and Discussion

Experimental Study

Acid hydrazides were reacted with carbon disulphide to give the corresponding 1,3,4-oxadiazole-2-thione compounds **3a-e** and **4a-d** (Figure 1). Compounds **3a-e** underwent condensation with benzaldehyde and aromatic amines to form their Mannich bases (Figure 2). All synthesized compounds were purified by recrystallization and their structures were elucidated on the basis of spectral data. The IR spectra of compounds **3a-e** and **5a-e** indicate NH stretching vibrations at 3259-3030 and 3250-3300 cm^{-1}, respectively. In the ^1H NMR spectra recorded in DMSO-d_6, the NH protons of **3a-e** are at 6.24-4.55 ppm as broad bands. For **4a-d** methyl signals are at 2.38-1.91 ppm as singlets. In the ^1H NMR spectra of **5a-e** the signals at 6.47-6.40 ppm belong to NH protons. The other protons have chemical shifts as expected.

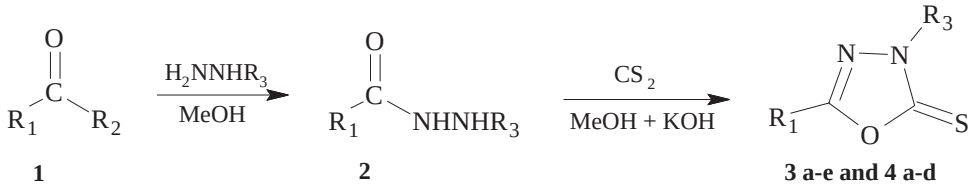
The ^{13}C NMR spectra of **3a-e** and **4a-e** in DMSO-d_6 show C=S signals at 171.5-194.3 ppm and C=N signals at 151.7-167.9 ppm. In addition to IR and NMR spectral data, the mass spectra of all the new compounds gave exact molecular ion peaks.

Except 3-(2,4-dimethylphenyl) substituted derivatives, all new compounds were examined for their antibacterial and antituberculostatic activity. The Mannich bases which contain benzidine were the most active, while the others had moderate activity.

Theoretical Study

The 3-dimensional structures optimized at the HF/6-31G** level and atom numbering are given in Figure 3. The bond distances and bond angles obtained from calculations were tabulated and are available upon request.

Inspection of the calculated bond distances gives evidence for some degree of delocalization in the 1,3,4-oxadiazole-2-thione ring. Shortened O-C bond distances (partial double bond) as in carboxylic acids are known to be 1.36 Å and C-N distances having a partial double bond character in heterocyclic systems e.g. C_5H_5N and in $HCONH_2$ are known to be 1.352 Å and 1.322 Å respectively[12]. These values are comparable to O-C and C2-N3 bond distances in 1,3,4-oxadiazole-2-thiones. O-C Distances vary between 1.329 Å and 1.354 Å, and C2-N3 distances vary between 1.320 Å and 1.336 Å. Thus, O1-C2, O1-C5 and C2-N3 bonds exhibit a partial double bond character. In addition, these compounds are known to exist as a tautomeric equilibrium[7,8,10,11] between the thiol and the thione. All this evidence shows that electrons are delocalized



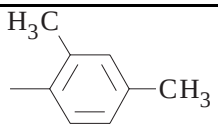
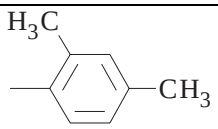
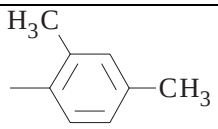
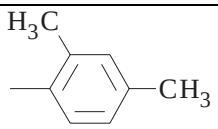
Compound Number	R_1	R_2	R_3
3a	OCH_3	Cl	H
3b	OC_2H_5	Cl	H
3c	CH_2COCH_3	OC_2H_5	H
3d	$CH_2COC_6H_5$	OC_2H_5	H
3e	$COOC_2H_5$	OC_2H_5	H
4a	CH_2Cl	OC_2H_5	
4b	OCH_3	Cl	
4c	CH_2COCH_3	OC_2H_5	
4d	C_6H_5	OCH_3	

Figure 1. Substituted 1,3,4-oxadiazole-2-thione compounds synthesized.

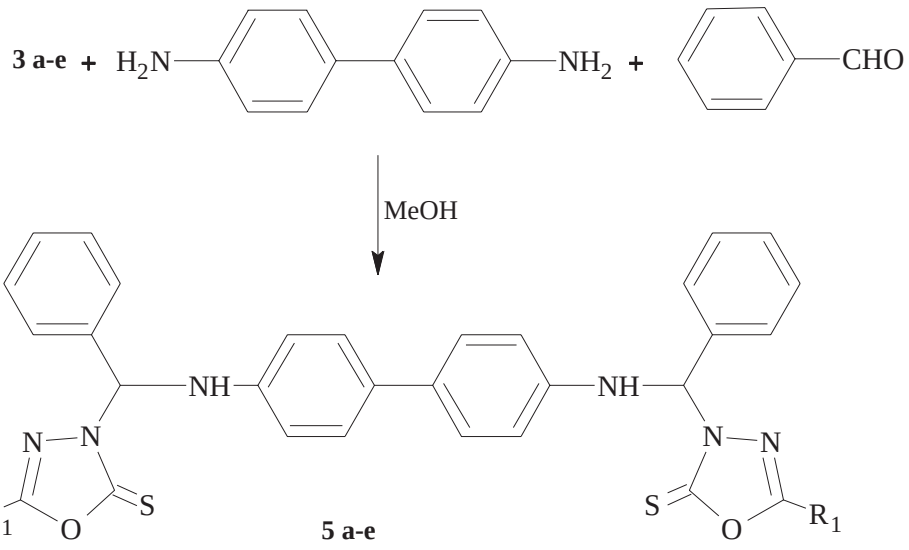


Figure 2. Synthesis of Mannich bases.

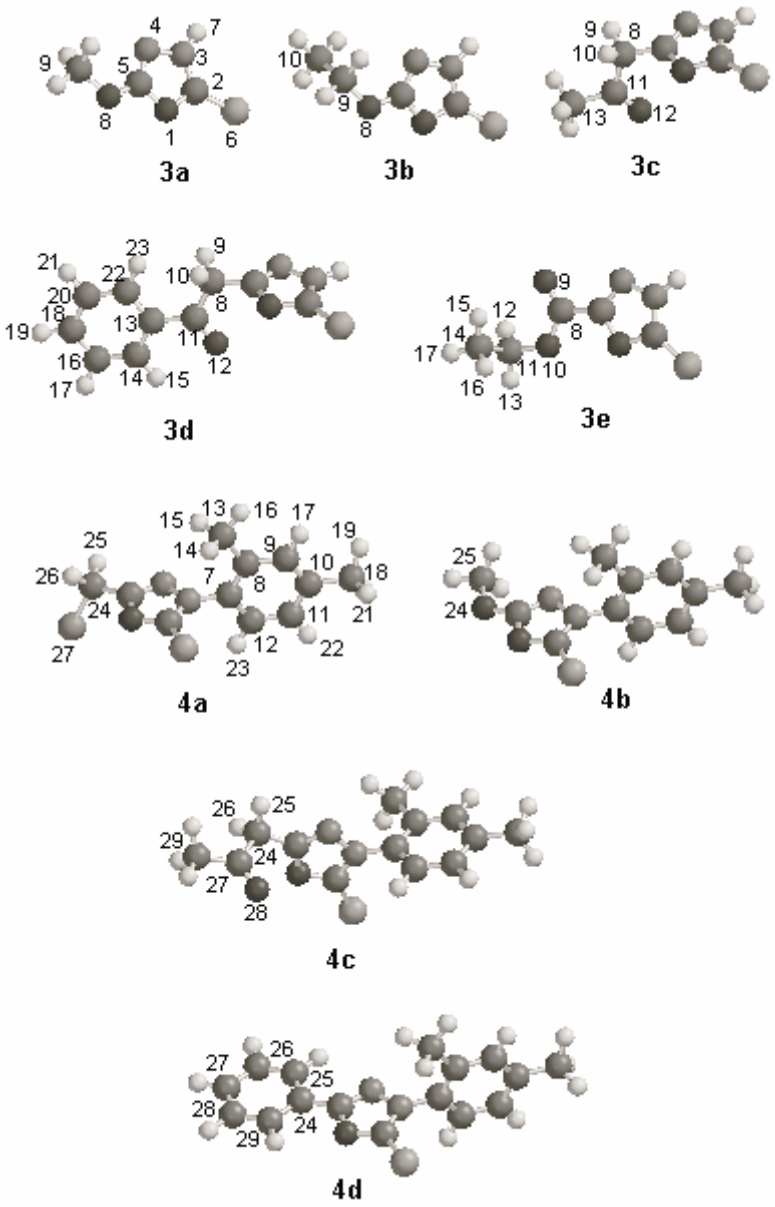


Figure 3. Atom numbering and 3-dimensional view of optimized structures.

on the ring through the pathways N3-C2-S6, O1-C2-S6 and O1-C5-N4. Another notable feature of the bond distances calculated is that compounds **3a**, **3b**, **4b** and **4d** having 5-alkoxy and 5-phenyl substituents show parallel tendencies in bond distances such that N4-C5 distances increase by 0.006 Å relative to the ones in the rest of the compounds. In alkoxy derivatives, the distances C5-O8 for **3a** and **3b** and C5-O24 for **4b** are shorter than the ether bonds (O8-C9 and C25-O24) by 0.14 Å. Likewise, for the 5-phenyl derivative **4d**, the lengthening of N4-C5 is accompanied by a shortening of C5-C24 by 0.15 Å as compared to the C-C single bonds C8-C13 and C10-C18 in compounds **4a-d**. These results can be rationalized in terms of π-electron donation from 5-methoxy and 5-phenyl substituents to the oxadiazole ring, which leads to a negative charge on N4 and a positive charge on ortho and para positions of the phenyl ring. The calculated electronic charges

in Table 1 also confirm this situation. In 5-alkoxy and 5-phenyl derivatives (**3a**, **3b**, **4b**, **4d**), the negative charge on N4 is greater than the one in the other compounds. A decrease in electron density at the ortho and para positions of the 5-phenyl ring is also observed. The negative charges on C25, C27 and C29 of compound **4d** decrease slightly, relative to the carbons at the meta positions.

Table 1. Electronic charges for selected atoms in 1,3,4-oxadiazole-2-thione derivatives

	3a	**3b**	**3c**	**3d**	**3e**	**4a**	**4b**	**4c**	**4d**
O1	-0.547	-0.547	-0.546	-0.543	-0.545	-0.537	-0.548	-0.548	-0.579
C2	0.502	0.502	0.505	0.505	0.497	0.509	0.510	0.514	0.515
N3	-0.456	-0.455	-0.454	-0.454	-0.447	-0.575	-0.572	-0.573	-0.566
N4	-0.378	-0.384	-0.308	-0.309	-0.250	-0.264	-0.355	-0.285	-0.322
C5	0.982	0.984	0.640	0.638	0.542	0.607	0.980	0.638	0.679
S6	-0.265	-0.269	-0.272	-0.275	-0.247	-0.264	-0.275	-0.282	-0.286
C7						0.241	0.242	0.240	0.242
O8	-0.617	-0.630							
C8			-0.382	-0.377	0.808	0.049	0.049	0.049	0.050
C9	-0.049	0.065				-0.191	-0.193	-0.194	-0.193
O9					-0.534				
C10		-0.365				0.021	0.021	0.021	
O10					-0.621				
O12			-0.492	-0.525					
O24							-0.620		
O28								-0.494	
C24									-0.118
C25									-0.113
C26									-0.160
C27									-0.132
C28									-0.158
C29									-0.121

Dihedral angles give information about the relative orientations of the atoms in space. The oxadiazole ring is known to be planar[7] and our calculations also predict a planar structure for the 1,3,4-oxadiazole-2-thione ring. Thus, in Tables 2 and 3, all the dihedral angles belonging the ring range from -0.51° to 0.73°. The planarity of the oxadiazole ring is expected to enhance delocalization, which supports the conclusion of our discussion above. Mrozek et al.[13] reported the X-ray structure analysis of 5-alkylthio-1,3,4-thiadiazol-2-thiones. They emphasized that electrons are delocalized over the atomic centres $S2_{exo}$-C2-S1-C5-$S5_{exo}$. Depending on the planarity, π-electron delocalization and HOMA index calculations, they concluded that the ring is aromatic. Since 1,3,4-thiadiazol-2-thione is the sulphur analogue of 1,3,4-oxadiazol-2-thione, 1,3,4-oxadiazol-2-thiones can also be considered to have an aromatic character.

Table 2. Selected dihedral (°) angles for 5-substituted 1,3,4-oxadiazole-2-thiones.

Dihedral angle	3a -OCH_3	3b -OCH_2CH_3	3c -CH_2COCH_3	3d -$CH_2COC_6H_5$	3e -$COOC_2H_5$
O1-C2-N3-N4	-0.08	-0.11	0.10	0.09	-0.08
O1-C2-N3-H7	-179.86	-179.86	-179.77	-179.67	-179.75
O1-C5-N4-N3	-0.03	-0.17	0.61	0.73	0.00
S6-C2-O1-C5	-179.91	-179.99	179.57	179.56	-179.92
S6-C2-N3-N4	179.88	179.88	-179.16	-179.08	179.92
S6-C2-N3-H7	0.10	0.13	0.97	1.16	0.24
C2-O1-C5-N4	-0.02	0.12	-0.59	-0.72	-0.04
C2-O1-C5-C8	179.92	-179.49	-179.89	-179.68	-179.97
C2-N3-N4-C5	0.07	0.17	-0.44	-0.51	0.05
N3-N4-C5-C8	-179.96	179.36	179.83	179.59	179.91
C5-N4-N3-H7	179.86	179.93	179.44	179.26	179.75
C5-O1-C2-N3	0.06	0.00	0.26	0.34	0.07
N4-C5-O8-C9	0.18	0.68			
N4-C5-C8-C11			108.11	106.42	
O1-C5-C8-C11			-72.71	-74.79	
C5-C8-C11-C13			170.95	176.63	
O12-C11-C8-C5			-9.60	-4.03	
C11-C13-C14-C16				179.74	
O12-C11-C13-C22				1.32	
C14-C13-C11-C8				0.93	
C22-C13-C11-C8				-179.35	
O1-C5-C8-O9					179.84
O1-C5-C8-O10					-0.34
N4-C5-C8-O9					-0.07
N4-C5-C8-O10					179.75
C5-C8-O10-C11					-179.92
O9-C8-C10-C11					-0.13

In compound **4d**, the phenyl substituent on C5 is coplanar with the oxadiazole ring, which is evident from the dihedral angles connecting these two ring systems (Table 3). All the calculated dihedral angles are either 0° or 180°. The oplanarity of the phenyl ring also confirms the π-electron donation discussed above.

On the other hand, in compounds **4a-d**, 2,4-dimethylphenyl rings do not contribute to the delocalization of the oxadiazole ring. As expected, 2,4-dimethyl phenyl rings lie almost perpendicular to the oxadiazole fragment since the values of dihedral angles C2-N3-C7-C8, C2-N3-C7-C12, N4-N3-C7-C8 and N4-N3-C7-C12 are all close to 90°. Our ^{1}H NMR data for compounds **4a-d** are in agreement with the above discussion. In

compounds **4a, 4b** and **4c**, signals belonging to aromatic protons vary between 6.63 and 7.71 ppm, whereas, in **4d**, they are at 6.82-8.03 ppm. Thus, in **4d**, more deshielded aromatic protons probably belong to the 5-phenyl ring as a result of electron donation to the oxadiazole ring. Moreover, the 3-dimethylphenyl ring is ortogonal to the oxadiazole ring and π-electron donation is not possible in this orientation. Therefore, the aromatic protons in the upfield region are expected to belong to the 3-dimethylphenyl ring.

Table 3. Selected dihedral angles (°) for 5-substituted 3-(2,4-dimethyl)-1,3,4-oxadiazole-2-thiones.

Dihedral angle	4a $-CH_2Cl$	4b $-OCH_3$	4c $-CH_2COCH_3$	4d $-C_6H_5$
O1-C2-N3-N4	0.01	-0.04	0.05	-0.20
O1-C2-N3-C7	-179.81	-178.93	177.88	-178.82
O1-C5-N4-N3	0.16	0.01	-0.62	-0.05
S6-C2-O1-C5	179.61	179.85	179.60	-179.94
S6-C2-N3-N4	-179.47	-179.83	179.16	179.91
S6-C2-N3-C7	1.61	1.28	-3.01	1.29
C2-O1-C5-N4	-0.17	-0.03	0.68	-0.08
C2-O1-C5-C24	-179.29		-179.75	179.83
C2-O1-C5-O24		179.95		
C2-N3-N4-C5	-0.10	0.02	0.34	0.16
C2-N3-C7-C8	-92.30	-90.19	-89.23	-87.92
C2-N3-C7-C12	88.72	91.09	-92.02	93.54
N3-C2-O1-C5	0.09	0.04	-0.41	0.17
N3-N4-C5-C24	179.20		179.86	-179.94
N3-N4-C5-O24		-179.96		
N3-C7-C8-C13	1.43	1.64	-1.43	1.73
N3-C7-C8-C9	-178.85	-178.76	178.88	-178.67
N3-C7-C12-C11	178.95	178.81	-178.87	178.65
N3-C7-C12-H23	-1.21	-1.33	1.21	-1.44
N4-N3-C7-C8	88.87	91.00	-93.12	93.57
N4-N3-C7-C12	-90.11	-87.71	85.63	-84.96
C5-N4-N3-C7	178.91	179.01	-177.67	178.90
N4-C5-O24-C25		-0.01		
O1-C5-O24-C25		-179.99		
C5-C24-C25-C26				179.94
C5-C24-C29-C28				-179.91
N4-C5-C24-C25				0.24
N4-C5-C24-C29				-179.83
O1-C5-C24-C25				-179.64
O1-C5-C24-C29				0.29
N4-C5-C24-C27			-107.15	
O1-C5-C24-C27			73.35	
C5-C24-C27-O28			10.90	
C5-C24-C27-C29			-169.75	
N4-C5-C24-Cl 27	110.94			
O1-C5-C24-Cl 27	-70.07			

The tautomeric equilibrium in Figure 4 was investigated both for isolated and for solvated species considering the aqueous medium. The results are given in Table 4. Tsoleridis et al.[8] studied the same equilibrium using semiempirical AM1 and PM3 methods and found that the thiol form is 4.44 kcal/mol more stable in the gas phase. However, this is contrary to the known experimental finding. On the basis

of UV and IR data, it is known that 5-methyl-1,3,4-oxadiazole-2-thione and the parent compound exist in solution in the thione rather than the thiol form[11]. Parallel to experimental data, our HF/6-31G** calculations predicted that the thione tautomer is 9.616 kcal/mole more stable than the thiol in the gas phase (Table 4). In aqueous solution, the equilibrium is even more favoured (by 12.123 kcal/mole) towards the thione because the thione is better solvated than the thiol. Note that it exhibits a larger solvation energy and a greater dipole moment.

Table 4. Relative energies[a], solvation energies (kcal/mole) and dipole moments (Debye) for 1,3,4-oxadiazole-2-thione and its thiol tautomer.

	Relative energy			
	In gas phase	In solution	Solvation energy	Dipole moment
Thione	0.000	0.000	-13.603	4.397
Thiol	9.616	12.123	-11.095	2.266

[a]Energies are relative to the energy of thione (-412983.51935 kcal/mole in gas phase and –412997.123115 kcal/mole in solution, respectively)

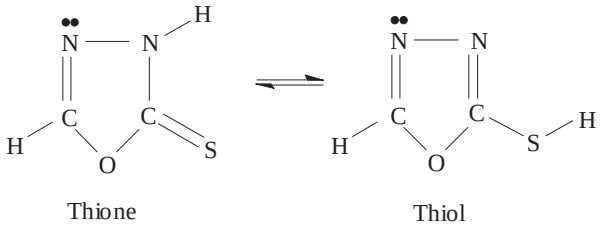


Figure 4. Thione-thiole tautomerization of 1,3,4-oxadiazole-2-thione.

Experimental

Melting points are uncorrected and were measured in open capillaries with an Electrothermal IA 9100 melting point apparatus. IR spectra were recorded on a Philips PU 9714 spectrometer as KBr pellets. NMR spectra were determined on a Nicolet 300 MHz spectrometer in DMSO-d_6 with TMS as the internal standard. Mass spectra were obtained with a Shimatzu GS/MS QP 200 spectrometer with 70 eV electron impact ionization. Thin layer chromatography was carried out using silica gel sheets with fluorescent indicator purchased from E. Merck AG (5554).

Synthesis of 5-substituted-1,3,4-oxadiazole-2-thiones (3a-e and 4a-d), general procedure: Acid hyrazides, **2** (1.0 mole), synthesized from corresponding esters, **1** (1.0 mole), via condensation with hydrazine hydrate (1.0 mole) or 2,4-dimethylphenylhyrazine hydrate (1.0 mole) in methanol, were cyclizated with carbon disulphide (2.5 mole) in methanol with the presence of potassium hydroxide (1 mole) for 5 to 9 hours. The solvent was evaporated and the residue was dissolved in ice-water. The resulting solution was filtered and the filtrate was acidified with 1 N hydrochloric acid and the solid obtained was extracted with a 1:1 mixture of diethyl ether and ethyl acetate. The organic layer was then dried over anhydrous sodium sulphate, filtrated and concentrated under reduced pressure. The residue was crystallized from ethanol.

5-Methoxy-1,3,4-oxadiazole-2-thione, 3a: Yield 71% ; m.p. 153-54°C; IR (KBr): ν = 3055, 1038 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 3.60 (s, 3H, OCH_3), 5.42 (b, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, δ, 300 MHz): 61.02 (OCH_3), 154.5 (C=N), 178.9 (C=S) ppm; MS: m/z= 132 (M^+) for $C_3H_4N_2O_2S$.

5-Ethoxy-1,3,4-oxadiazole-2-thione, 3b: Yield 61% ; m.p. 172-73°C; IR (KBr): ν = 3175, 1030 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 1.08-1.20 (t, 3H, CH_3), 4.07-4.11 (q, 2H, OCH_2), 5.51 (b, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, δ, 300 MHz): 15.01 (CH_3), 64.39 (OCH_2), 158.3 (C=N), 176.3 (C=S) ppm; MS: m/z = 146 (M^+) for $C_4H_6N_2O_2S$.

5-Acetylmethyl-1,3,4-oxadiazole-2-thione, 3c: Yield 83% ; m.p. 197°C (decomp.); IR (KBr): ν = 3259, 1063, 1712 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 2.46 (s, 3H, CH_3), 4.05 (s, 2H, CH_2), 5.70 (b, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, δ, 300 MHz): 29.92 (CH_3), 46.32 (CH_2), 160.20 (C=N), 181.5 (C=S), 201.67 (C=O) ppm; MS: m/z = 158 (M^+) for $C_5H_6N_2O_2S$.

5-Benzoylmethyl-1,3,4-oxadiazole-2-thione, 3d: Yield 65% ; m.p. 165-66°C; IR (KBr): ν = 3125, 1042, 1695 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 4.02 (s, 2H, CH_2), 4.55 (b, 1H, NH), 6.93-7.66 (m, 5H, Ar) ppm; ^{13}C NMR (DMSO-d_6, δ, 300 MHz): 44.39 (CH_2), 158.12-128.34 (aromatic), 151.7 (C=N), 184.3 (C=S), 195.01 (C=O) ppm; MS: m/z = 220 (M^+) for $C_{10}H_8N_2O_2S$.

5-Ethoxycarbonyl-1,3,4-oxadiazole-2-thione, 3e: Yield 68% ; m.p. 221-22°C; IR (KBr): ν = 3083, 1032 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 1.13-1.27 (t, 3H, CH_3), 3.96-4.07 (q, 2H, OCH_2), 6.24 (b, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, δ, 300 MHz):14.75 (CH_3), 62.01 (OCH_2), 153.4 (C=N), 158.01 (C=O), 197.3 (C=S) ppm; MS: m/z = 174 (M^+) for $C_5H_6N_2O_3S$.

5-Chloromethyl-3-(2,4-dimethylphenyl)-1,3,4-oxadiazole-2-thione, 4a: Yield 60% ; m.p. 195-96°C; IR (KBr): ν = 1045 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 1.91 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 4.14 (s, 2H, CH_2Cl), 6.63-7.21 (m, 3H, Ar) ppm; ^{13}C NMR (DMSO-d_6, δ, 300 MHz): 18.97 (CH_3), 21.02 (CH_3), 48.01 (CH_2), 136.92-119.45 (aromatic), 154.70 (C=N), 171.0 (C=S) ppm; MS: m/z = 254 (M^+) for $C_{11}H_{11}ClN_2OS$.

5-Methoxy-3-(2,4-dimethylphenyl)-1,3,4-oxadiazole-2-thione, 4b: Yield 72% ; m.p. 181-82°C; IR (KBr): ν = 1036 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 2.31 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.61 (s, 3H, OCH_3), 6.68-7.71 (m, 3H, Ar) ppm; ^{13}C NMR (DMSO-d_6, δ, 300 MHz): 18.96 (CH_3), 21.04 (CH_3), 57.99 (OCH_3), 138.76-118.15 (aromatic), 151.80 (C=N), 182.10 (C=S) ppm; MS: m/z = 236 (M^+) for $C_{11}H_{12}N_2O_2S$.

5-Acetylmethyl-3-(2,4-dimethylphenyl)-1,3,4-oxadiazole-2-thione, 4c: Yield 57% ; m.p. 169-70°C; IR (KBr): ν = 1065 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 2.02 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.30 (s, 3H, $COCH_3$), 4.02 (s, 2H, CH_2), 7.06-7.12 (m, 3H, Ar) ppm; ^{13}C NMR (DMSO-d_6, δ, 300 MHz): 19.01 (CH_3), 20.61 (CH_3), 31.26 (CH_3), 48.09 (CH_2), 139.23-118.56 (aromatic), 163.5 (C=N), 176.2 (C=S), 205.07 (C=O) ppm; MS: m/z = 262 (M^+) for $C_{13}H_{14}N_2O_2S$.

5-Phenyl-3-(2,4-dimethylphenyl)-1,3,4-oxadiazole-2-thione, 4d: Yield 68% ; m.p. 155-56°C; IR (KBr): ν = 1039 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 2.25 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 6.82-8.03 (m, 8H, Ar) ppm; ^{13}C NMR (DMSO-d_6, δ, 300 MHz):18.77 (CH_3), 21.02 (CH_3), 133.97-118.04 (aromatic), 167.9 (C=N), 179.34 (C=S) ppm; MS: m/z = 282 (M^+) for $C_{16}H_{14}N_2OS$.

Synthesis of N,N′-bis(3-benzylideno-5-alkyl-1,3,4-oxadiazole-2-thione)benzidines (5a-e), general procedure: Into the solution of **3a-e** (2.0 mole) in small amount methanol, benzaldehyde (2.0 mole) was added and stirred for 1 hour in an ice bath. Then the cold solution of benzidine (1.0 mole) was added dropwise while stirring. The resulting mixture was refluxed for 3-5 hours on a steam bath. The

residue obtained after the evaporation of solvent was recrystallized from ethanol.

N,N′-bis(3-benzylideno-5-methoxy-1,3,4-oxadiazole-2-thione)benzidine, 5a: Yield 65% ; m.p. 135-36°C; IR (KBr): ν = 3250, 1115 cm^{-1}; ^{1}H NMR (DMSO-d$_6$, δ, 300 MHz): 3.78 (s, 6H, OCH$_3$), 6.40 (d, 2H, NH), 6.83 (d, 2H, benzylic CH), 7.07-7.71 (m, 18H, aromatic) ppm; MS: m/z= 624 (M$^+$) for $C_{32}H_{28}N_6O_4S_2$.

N,N′-bis(3-benzylideno-5-ethoxy-1,3,4-oxadiazole-2-thione)benzidine, 5b: Yield 61% ; m.p. 167-68°C; IR (KBr): ν = 3275, 1075 cm^{-1}; ^{1}H NMR (DMSO-d$_6$, δ, 300 MHz): 1.46-1.43 (t, 6H, OCH$_2$C**H**$_3$), 4.29-4.25 (q, 4H, OC**H**$_2$CH$_3$), 6.43 (d, 2H, NH), 6.82 (d, 2H, benzylic CH), 6.35-7.72 (m, 18H, aromatic) ppm; MS: m/z= 652 (M$^+$) for $C_{34}H_{32}N_6O_4S_2$.

N,N′-bis(3-benzylideno-5-acetylmethyl-1,3,4-oxadiazole-2-thione)benzidine, 5c: Yield 51% ; m.p. 215°C; IR (KBr): ν = 3300, 1100, 1715 cm^{-1}; ^{1}H NMR (DMSO-d$_6$, δ, 300 MHz): 2.29 (s, 6H, CH$_3$), 3.71 (s, 4H, C**H**$_2$COCH$_3$), 6.45 (d, 2H, NH), 6.78 (d, 2H, benzylic CH), 6.87-7.33 (m, 18H, aromatic) ppm; MS: m/z= 676 (M$^+$) for $C_{36}H_{32}N_6O_4S_2$.

N,N′-bis(3-benzylideno-5-benzoylmethyl-1,3,4-oxadiazole-2-thione)benzidine, 5d: Yield 42% ; m.p. 243°C; IR (KBr): ν = 3280, 1065, 1692 cm^{-1}; ^{1}H NMR (DMSO-d$_6$, δ, 300 MHz): 4.28 (s, 4H, C**H**$_2$COC$_6$H$_5$), 6.42 (d, 2H, NH), 6.75 (d, 2H, benzylic CH), 6.95-7.96 (m, 28H, aromatic) ppm; MS: m/z= 800 (M$^+$) for $C_{46}H_{36}N_6O_4S_2$.

N,N′-bis(3-benzylideno-5-ethoxycarbonyl-1,3,4-oxadiazole-2-thione)benzidine, 5e: Yield 49% ; m.p. 189°C; IR (KBr): ν = 3270, 1095, 1705 cm^{-1}; ^{1}H NMR (DMSO-d$_6$, δ, 300 MHz):1.15-1.12 (t, 6H, OCH$_2$C**H**$_3$), 4.13-4.09 (q, 4H, OC**H**$_2$CH$_3$), 6.47 (d, 2H, NH), 7.01 (d, 2H, benzylic CH), 6.75-7.33 (m, 18H, aromatic) ppm; MS: m/z= 708 (M$^+$) for $C_{36}H_{32}N_6O_6S_2$.

Methods

Calculations were performed using the PC Spartan Pro[14] program package. For all the compounds, the following procedure was applied. Conformational searching was done with a semi-empirical PM3 method[15]. In order to determine the potential energy surface, all the bonds which possess free rotation were rotated 6-fold. The lowest energy conformer was then selected and subjected to full geometry optimization at the HF/6-31G** level of the theory[16]. Aqueous solvation energies for the tautomeric species were calculated using the SM5.4 solvation model developed by Cramer and Truhlar [17].

Biological Evaluation

Antitubercular activity: The in vitro tuberculostatic activity of 1,3,4-oxadiazole-2-thione derivatives was studied against *Mycobacterium tuberculosis* using Lowenstein Jensen's egg medium by serial twofold dilution and the retardation of the growth rate studied for six weeks at 37°C. The tuberculostatic concentration was 0.03 μg/ml.

Antibacterial activity: The antibacterial activity of the compounds was tested by agar plate diffusion against *Staphylococcus aureus* using tetracycline as the standard.

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