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Crystal Structure Analysis and Molecular Docking Studies of Acylthiourea Derivatives against mycobacterium tuberculosis DprE1 Inhibitor

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ABSTRACT

*Single crystals of two acylthiourea derivatives, namely N-((4-methoxyphenyl) carbamothioyl) cyclohexanecarboxamide (**1**) and N-(dibenzylcarbamothioyl) cyclohexane carboxamide (**2**), have been carried out using X-ray diffraction methods. The acylthiourea group in both the derivatives adopts an extended conformation. Docking studies demonstrate that acylthiourea derivatives can bind to mycobacterium tuberculosis DprE1 enzyme and to evaluate whether these molecules can be used as potential inhibitor for tuberculosis (TB) infectious diseases.*

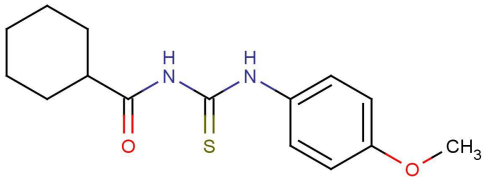
INTRODUCTION

During the past two decades, there has been a tremendous research focus on the preparation, characterization and functional studies of thioruea compounds. Thiourea derivatives are the versatile building blocks for the synthesis of heterocyclic compounds and exhibit a wide spectrum of biological activities. Thiourea moieties have long been known as versatile ligands after the successful synthesis [**1, 2**]. Thiourea possess herbicidal, fungicidal, bactericidal, anticancer, antimalarial, insecticidal and plant growth regulatory activity, and also patented as anti-diabetic, anti-arthritic, anti-neoplastic and anti-coagulant agents for the treatment of cognitive problems and prostate disorders [**3-12**]. Acylthiourea motif forms an intramolecular hydrogen bond, and this makes the derivatives highly selective receptors for basic anions such as F^- and AcO− [**13-15**]. As an anion transporter considerable attention has been given on the development of chiral thiourea ligands and their metal complexes, which are used as ligands in asymmetric catalysis [**16-22**].

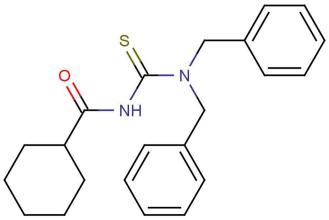
MATERIALS AND METHODS

Synthesis

Cyclohexanecarbonyl chloride (1.4661 g, 10 mmol) dissolved in acetone (80 mL), was added drop wise with stirring to potassium thiocyanate (0.9718g, 10 mmol) dissolved in acetone (80 mL), in a round bottom flask. The mixture was heated to reflux for 30 minutes and then allowed to cool. A solution of 4-methoxy aniline or dibenzylamine (1.2315 or 1.987 g, 10 mmol) in acetone (80 mL) was added to the reaction mixture and the resulting mixture was stirred for 2 hours. Hydrochloric acid (0.1 N, 300 ml) was added and the resulting white solid was filtered off, washed with water and dried *in vacuo*. Yield: 87-90%.



Comp 1



Comp 2

X-Ray Crystallographic Studies

Intensity Data Collection

X-ray diffraction intensity data were collected for Comp 1 and Comp 2 on Bruker axs SMART APEXII single crystal X-ray diffractometer equipped with graphite monochromated Mo*Kα* (λ=0.7103 Å) radiation and CCD detector. Crystals were cut to suitable size and mounted on a glass fibre using cyanoacrylate adhesive. The unit cell parameters were determined from 36 frames measured (0.5° phi-scan) from three different crystallographic zones and using the method of difference vectors. The intensity data were collected with an average four-fold redundancy per reflection and optimum resolution (0.75 Å). The intensity data collection, frames integration, Lorentz and polarization correction and decay correction were done using *SAINT-NT* (version 7.06a) software. Empirical absorption correction (multi-scan) was performed using *SADABS* [23] program.

Structure Solution and Refinement

Crystal structures were solved by direct methods using *SHELXS-97* [24]. The structures were refined by the full-matrix least-squares method using *SHELXL-97* [24]. All the non-hydrogen atoms were first refined isotropically and then with anisotropic displacement parameters for Comp 1 and Comp 2, respectively. For Comp 1 and Comp 2, all the hydrogen atoms were placed in calculated positions with C—H = 0.93 Å, refined in the riding model with fixed isotropic displacement parameters: Uiso(H) = 1.2 Ueq(C). The refinement converged to a final R-factor of 0.0404 for Comp 1 and 0.0409 for Comp 2, respectively.

Molecular Docking Studies

Molecular docking can be categorized into two main kinds: Rigid docking is the molecular docking which allows only ligand (donor or small molecule) to change its orientation (depending on its torsional degree of freedom) and consider the receptor to be rigid during docking calculation. In Flexible docking or induced fit docking, in addition to rigid docking, where the ligand is considered to be flexible, the macromolecule (protein/enzyme) also changes its orientation (flexible), especially around the active site.

The molecular docking studies presented in the paper follows *Induced fit Docking* protocol using *Maestro* Graphical User Interface of the *Glide* software of Schrödinger [25].

RESULTS AND DISCUSSION

Structure Description

The perspective view of the molecules (Comp 1 & Comp 2) with the numbering scheme are shown in Figs. 1 & 2. In Comp 1, there are two crystallographically independent molecules in the asymmetric unit. The crystal data and other relevant details of Comp 1 & Comp 2 are given in Table 1. The selected bond lengths, bond angles and selected torsion angles for the non-hydrogen atoms of Comp 1 & Comp 2 are given in Tables 2, 3, 4 & 5, respectively.

The bond lengths [C8—S1] 1.672(2)Å/1.662(2)Å; [C7—N1] 1.376(3)Å/1.383(3)Å; [C8—N1] 1.389(3)Å/1.387(3)Å and [C8—N2] 1.322(3)Å/1.327(3)Å for molecules A/B of Comp 1 and 1.6704(16)Å, 1.389(2)Å, 1.404(2)Å and

1.325(2)Å, for Comp 2, are comparable with the related literature values [C—S] 1.662 (2)Å, [C8—N1] 1.386 (3) Å and [C8—N2] 1.331 (3) Å [26]. The central thiourea group makes dihedral angles of 53.01(1)° & 40.62(2)° (molecule A), 72.66(2)° & 49.51(1)° (molecule B) of Comp 1 and 75.18(1)°, 88.48(6)° & 84.00(2)° of Comp 2 with the terminal benzene rings.

The central carbonyl thiourea moiety (N2/C8/S1/N1/C7/O1), the 2-methoxyphenyl group (C9–C14/O2/C15) and the phenyl rings (C10–C14, C10–C15 and C17–C22) are individually planar in both Comp 1 & 2, respectively.

Packing Features

In the crystal structure of Comp 1, an intramolecular N—H…O hydrogen bond plays a role in functional activities. A couple of weak intermolecular N—H…S & C—H…S hydrogen bonds are useful in stabilizing the molecules in the unit cell. The overall crystal packing with N—H…S, N—H…O and C—H…S hydrogen bonds as shown in Fig. 3.

In Comp 2, the molecules are linked by two parallel independent N–H…S and C–H…S hydrogen bonds (Table 6). Atoms C9 & C15 in the molecule at (x, y, z) act as donors and make hydrogen bond to atom O1 (1-x,-y,1-z), linking the two molecules into a dimer to generate a centrosymmetric $R^2_2(8)$ motif. Atom O1 bifurcates with atom C9 and C15 to form $R^2_2(6)$ motif [27] as shown in Fig. 4. Relevant hydrogen bond details are given in Table 5.

Molecular Docking Studies

In the past several years, treatment for active tuberculosis (TB) infections has relied on a moderately small set of chemotherapeutic agents, including the widely used lead drugs isoniazid, ethambutol, rifampicin, and pyrazinamide [28].

The need of novel inhibitors of sufficient efficacy has favored the emergence of multidrug-resistant (MDR) and extensive drug-resistant (XDR) strains of the tubercle bacillus, radically increasing the cost and duration of treatment and threatening to undermine World Health Organization-led efforts to contain the global TB pandemic [29, 30]. Responding to the urgent need for new antibiotics, partnerships between academic institutions, research charities, and industry have been able to feed a modest pipeline of drug leads, with two candidates currently in phase III clinical trials [31].

The three-dimensional representations of flexible docked complexes of Mycobacterium tuberculosis DprE1-ligands are shown in Fig. 5. Molecular docking studies show that the thiomorpholine derivatives bind well in the active site pocket of Mycobacterium tuberculosis DprE1 and interact with the active site amino acid residues.

The structures of thiourea derivatives (Comp1 & Comp 2) have been shown to be effective inhibitors. In Comp 1, hydophobic interactions only play major role while docking the molecules against the target. In Comp 2, the oxygen atom interacts with the hydroxyl group of THR184 at a distance of 2.83Å.

The docking score and energy of the compounds of Comp 1 & Comp 2 are compared with the co-crystal ligand. In both the complexes, the non-bonded interactions limit is varied from 2.5Å to 3.5Å (Table 7), which reveal that the ligands favour for a strong inhibition.

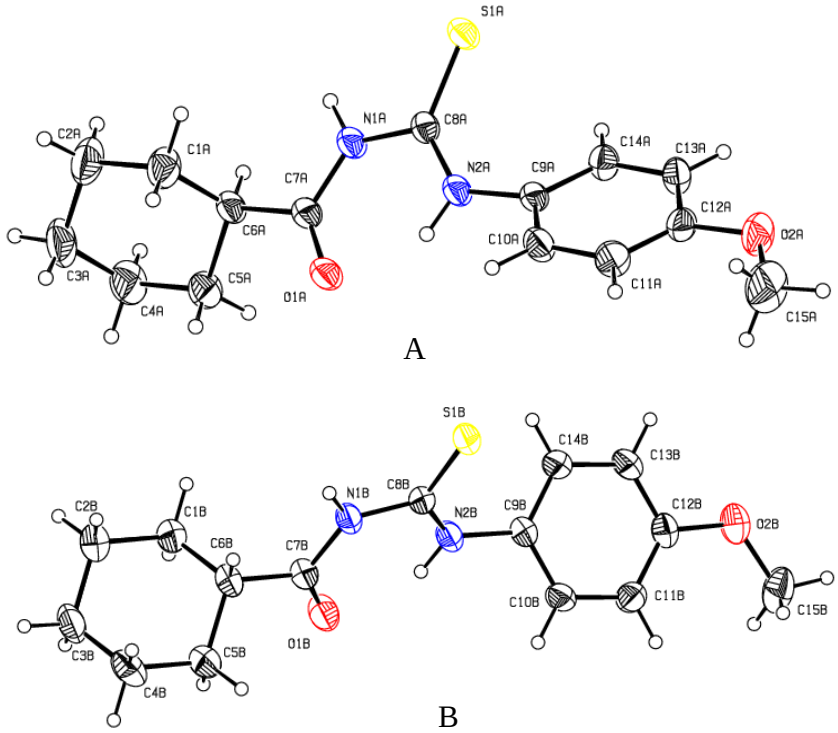


Figure 1. The molecular structure of the Comp1 (A & B), the displacement ellipsoids are drawn at 30% probability level. H atoms are shown as spheres of arbitrary radius

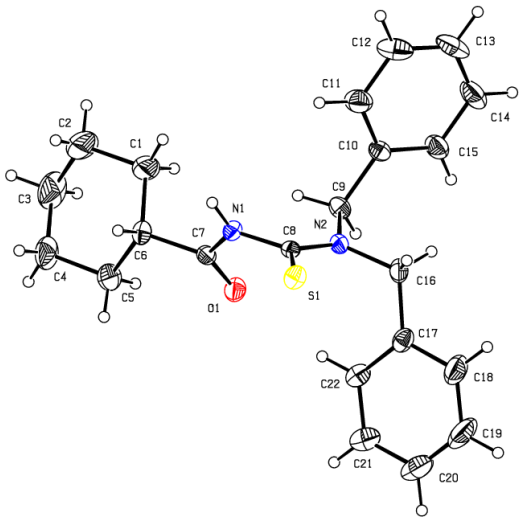


Figure 2. The molecular structure of the Comp 2, the displacement ellipsoids are drawn at 30% probability level. H atoms are shown as spheres of arbitrary radius

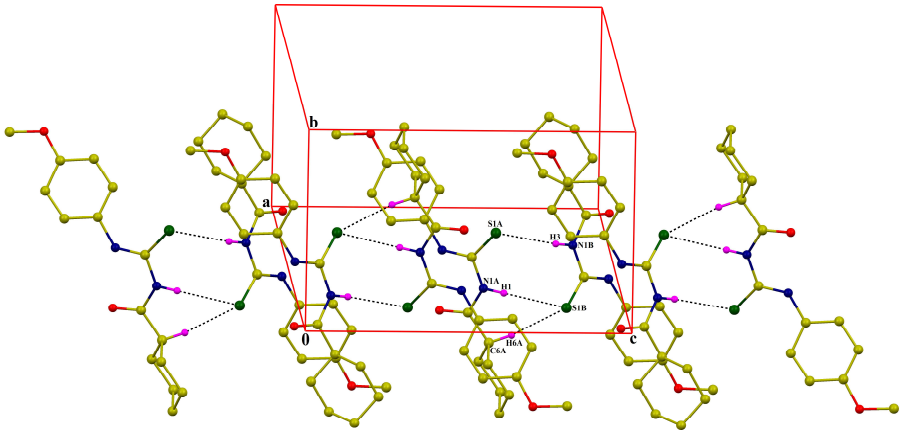


Figure 3. The crystal packing of the Comp 1 showing the chain formed by molecules linked by $R^1_2(6)$ and $R^2_2(8)$ rings motif. H–atoms not involved in hydrogen bonds have been excluded for clarity.

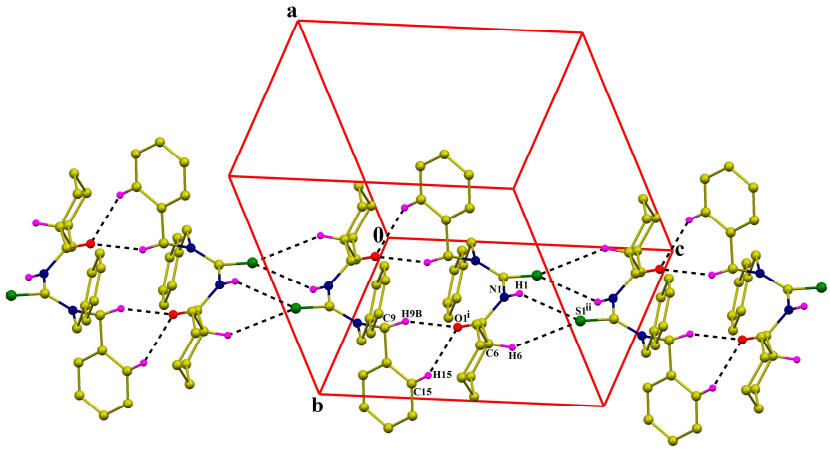


Figure 4. The crystal packing of the Comp 2 showing the chain formed by molecules linked by $R^1_2(6)$ and $R^2_2(16)$ rings motif. H–atoms not involved in hydrogen bonds have been excluded for clarity

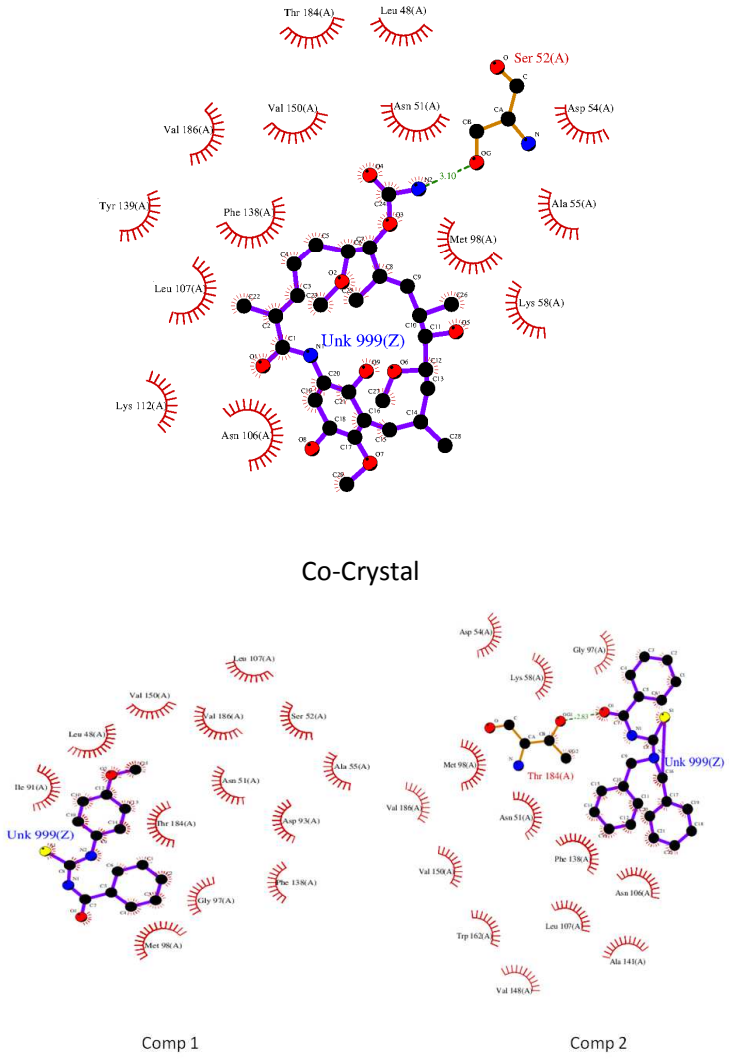


Figure 5. Hydrogen bond contacts (Comp 1 & 2 and co-crystal) with the active residues of Mycobacterium tuberculosis DprE1 inhibitor

Table 1 Crystal data and structure refinement for Comp 1 & Comp 2

Compound	(1)	(2)
Molecular formula	C_{15} H_{20} N_2 O_2 S	C_{22} H_{26} N_2 O S
Formula weight	292.39	366.51
Temperature (K)	296(2)	293(2)
Wavelength(Å)	0.71073	0.71073
Crystal system	Triclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1/n$
Unit cell dimensions		
a(Å)	9.123(5)	9.809(5)
b(Å)	13.278(5)	19.159(8)
c(Å)	13.432(5)	11.541(5)
α(°)	96.356(5)	90
β(°)	91.747(4)	111.679(2)
γ(°)	107.251(6)	90
Volume($Å^3$)	1540.9(12)	2015.60(16)
Z	4	4
Calculated density (Mg/m^3)	1.260	1.208
Absorption coefficient (mm^{-1})	0.213	0.173
F(000)	624	784
Crystal size(mm)	0.30 x 0.30 x 0.25	0.30 x 0.25 x 0.20
θ- range for data collection (°)	1.62 to 25.00	2.13 to 25.00
Index ranges	-10< = h < = 10 -15< = k < = 15 -15 < = l < = 15	-11< = h < = 11 -22< = k < = 22 -13 < = l < = 13
Reflections collected / unique	20363 / 5423 [R(int) = 0.0287]	18474 / 3556 [R(int) = 0.0227]
Completeness to theta (%)	100	100
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0404 wR2 = 0.1035	R1 = 0.0409 wR2 = 0.1047
R indices (all data)	R1 = 0.0653 wR2 = 0.1227	R1 = 0.0487 wR2 = 0.1111
Largest diff. peak and hole ($e.Å^{-3}$)	0.390 and -0.210	0.434 and -0.429

Table 2 Bond lengths (Å) for Comp 1 & Comp 2

Bond lengths (Å)	(1)		Bond lengths (Å)	(2)
	Molecule A	Molecule B		
C1-C6	1.503(3)	1.511(3)	C1-C2	1.525(3)
C1-C2	1.517(3)	1.524(3)	C3-C2	1.513(4)
C2-C3	1.511(4)	1.514(4)	C4-C3	1.494(4)
C3-C4	1.498(4)	1.504(4)	C5-C4	1.513(3)
C4-C5	1.525(3)	1.519(4)	C6-C1	1.523(3)
C5-C6	1.521(3)	1.523(3)	C6-C5	1.519(3)
C6-C7	1.505(3)	1.504(3)	C7-C6	1.504(2)
C7-O1	1.220(2)	1.216(3)	C10-C9	1.505(2)
C7-N1	1.376(3)	1.383(3)	C10-C15	1.370(3)
C8-N2	1.322(3)	1.327(3)	C11-C10	1.377(3)
C8-N1	1.389(3)	1.387(3)	C12-C11	1.377(3)
C8-S1	1.672(2)	1.662(2)	C13-C14	1.366(4)
C9-C10	1.368(3)	1.371(3)	C13-C12	1.363(4)
C9-C14	1.382(3)	1.383(3)	C14-C15	1.383(3)
C9-N2	1.426(3)	1.432(3)	C17-C16	1.511(3)
C10-C11	1.384(3)	1.380(3)	C17-C18	1.383(3)
C11-C12	1.371(3)	1.373(3)	C18-C19	1.384(4)
C12-O2	1.372(3)	1.372(3)	C20-C19	1.368(4)
C12-C13	1.379(3)	1.383(3)	C20-C21	1.363(3)
C13-C14	1.372(3)	1.373(3)	C22-C17	1.374(3)
C15-O2	1.398(3)	1.421(3)	C21-C22	1.386(3)
N1-H1	0.899(15)	0.874(16)	O1-C7	1.2088(19)
N2-H2	0.878(16)	0.879(16)	N1-C7	1.389(2)
			N1-C8	1.404(2)
			N2-C8	1.325(2)
			N2-C9	1.477(2)
			N2-C16	1.465(2)
			S1-C8	1.6704(16)

Table 3 Bond angles (°) for Comp 1 & Comp 2

Bond angles (°)	(1)		Bond angles (°)	(2)
	Molecule A	Molecule B		
C6-C1-C2	111.0(2)	111.0(2)	C8-N2-C9	124.86(13)
C3-C2-C1	111.7(2)	111.0(2)	C16-N2-C9	115.21(13)
C4-C3-C2	111.4(2)	111.5(2)	C7-N1-C8	123.39(13)
C3-C4-C5	111.3(2)	110.8(2)	C12-C13-C14	119.8(2)
C6-C5-C4	110.7(2)	111.3(2)	C13-C12-C11	120.3(2)
C1-C6-C7	110.52(19)	110.28(19)	C12-C11-C10	120.5(2)
C1-C6-C5	111.13(19)	111.4(2)	C15-C10-C11	118.95(17)
C7-C6-C5	111.66(18)	110.6(2)	C15-C10-C9	121.62(16)
O1-C7-N1	122.59(19)	122.7(2)	C11-C10-C9	119.43(16)
O1-C7-C6	123.59(19)	123.4(2)	N2-C9-C10	111.17(13)
N1-C7-C6	113.81(19)	113.8(2)	N2-C8-N1	117.38(13)
N2-C8-N1	115.20(18)	114.78(19)	N2-C8-S1	123.51(12)
N2-C8-S1	126.73(16)	126.44(17)	N1-C8-S1	119.11(11)
N1-C8-S1	118.07(15)	118.76(17)	O1-C7-N1	121.27(15)
C10-C9-C14	119.36(19)	119.6(2)	O1-C7-C6	123.03(15)
C10-C9-N2	117.60(19)	117.89(19)	N1-C7-C6	115.63(14)
C14-C9-N2	122.86(19)	122.4(2)	C7-C6-C5	110.93(15)
C9-C10-C11	121.2(2)	121.1(2)	C7-C6-C1	108.75(15)
C12-C11-C10	119.3(2)	119.4(2)	C5-C6-C1	110.92(17)
C11-C12-O2	124.9(2)	124.5(2)	C4-C5-C6	112.10(18)
C11-C12-C13	115.5(2)	115.9(2)	C3-C4-C5	111.2(2)
O2-C12-C13	119.6(2)	119.6(2)	C4-C3-C2	110.2(2)
C14-C13-C12	120.9(2)	120.9(2)	C21-C20-C19	119.6(2)
C13-C14-C9	119.6(2)	119.4(2)	C20-C21-C22	120.0(2)
C7-N1-C8	129.05(19)	128.8(2)	C18-C17-C16	118.12(19)
C8-N2-C9	129.03(18)	127.28(19)	N2-C16-C17	114.61(14)
C12-O2-C15	117.5(2)	117.1(2)	C8-N2-C16	119.75(13)

Table 4 Torsion angles (°) for Comp (1)

Torsion angles (°)	(1)	(2)
	Molecule A	Molecule B
C6A-C1A-C2A-C3A	55.2(4)	-55.8(3)
C1A-C2A-C3A-C4A	-55.1(4)	55.7(3)
C2A-C3A-C4A-C5A	55.2(4)	-55.8(3)
C3A-C4A-C5A-C6A	-55.6(3)	56.1(3)
C2A-C1A-C6A-C7A	179.7(2)	179.6(2)
C2A-C1A-C6A-C5A	-55.7(3)	55.9(3)
C4A-C5A-C6A-C1A	55.9(3)	-179.3(2)
C4A-C5A-C6A-C7A	179.8(2)	-56.3(3)
C1A-C6A-C7A-O1A	96.5(3)	-84.2(3)
C5A-C6A-C7A-O1A	-27.8(3)	39.0(3)
C1A-C6A-C7A-N1A	-82.2(2)	94.7(2)
C5A-C6A-C7A-N1A	153.5(2)	-142.1(2)
C14A-C9A-C10A-C11A	-0.2(3)	0.8(3)
N2A-C9A-C10A-C11A	175.1(2)	177.0(2)
C9A-C10A-C11A-C12A	0.2(4)	0.5(3)
C10A-C11A-C12A-O2A	180.0(2)	179.1(2)
C10A-C11A-C12A-C13A	0.5(4)	-1.3(3)
C11A-C12A-C13A-C14A	-1.2(3)	1.0(4)
O2A-C12A-C13A-C14A	179.2(2)	-179.4(2)
C12A-C13A-C14A-C9A	1.3(3)	0.2(4)
C10A-C9A-C14A-C13A	-0.6(3)	-1.1(4)
N2A-C9A-C14A-C13A	-175.61(19)	-177.1(2)
O1A-C7A-N1A-C8A	3.2(4)	-5.2(4)
C6A-C7A-N1A-C8A	-178.04(19)	175.9(2)
N2A-C8A-N1A-C7A	2.2(3)	7.4(3)
S1A-C8A-N1A-C7A	-177.17(18)	-171.01(18)
N1A-C8A-N2A-C9A	174.15(19)	-176.7(2)
S1A-C8A-N2A-C9A	-6.6(3)	1.5(3)
C10A-C9A-N2A-C8A	146.0(2)	130.8(2)
C14A-C9A-N2A-C8A	-38.9(3)	-53.1(3)
C11A-C12A-O2A-C15A	4.0(4)	-7.4(4)
C13A-C12A-O2A-C15A	-176.4(3)	173.0(2)

Table 5 Torsion angles (°) for Comp (2)

Torsion angles (°)	(2)	Torsion angles (°)	(2)
C1-C6-C5-C4	53.6(3)	C13-C12-C11-C10	-0.1(4)
C6-C5-C4-C3	-56.3(3)	C12-C11-C10-C15	2.0(3)
C5-C4-C3-C2	57.5(3)	C12-C11-C10-C9	-178.4(2)
C7-C6-C5-C4	174.62(19)	C22-C17-C18-C19	0.3(3)
C8-N2-C9-C10	-110.25(17)	C16-C17-C18-C19	179.2(2)
C8-N2-C16-C17	-76.8(2)	C21-C20-C19-C18	0.1(4)
C9-N2-C16-C17	107.88(16)	C17-C18-C19-C20	-0.5(4)
C7-C6-C1-C2	-175.2(2)	C22-C17-C16-N2	-7.1(2)
C5-C6-C1-C2	-53.0(3)	C18-C17-C16-N2	174.07(17)
C4-C3-C2-C1	-57.7(4)	C16-N2-C9-C10	64.80(18)
C6-C1-C2-C3	55.6(4)	C15-C10-C9-N2	-106.53(19)
C9-C10-C15-C14	178.26(18)	C16-N2-C8-N1	171.26(14)
C9-N2-C8-N1	-13.9(2)	C16-N2-C8-S1	-8.6(2)
C7-N1-C8-N2	-57.1(2)	C9-N2-C8-S1	166.27(12)
C7-N1-C8-S1	122.72(14)	C19-C20-C21-C22	0.4(4)
C8-N1-C7-O1	7.7(2)	C20-C21-C22-C17	-0.7(3)
C8-N1-C7-C6	-175.42(14)	C21-C22-C17-C18	0.3(3)
C12-C13-C14-C15	1.5(4)	C21-C22-C17-C16	-178.59(18)
C11-C10-C15-C14	-2.2(3)	O1-C7-C6-C5	-23.2(2)
C11-C10-C9-N2	73.9(2)	N1-C7-C6-C5	159.96(16)
C13-C14-C15-C10	0.5(3)	O1-C7-C6-C1	99.1(2)
C14-C13-C12-C11	-1.6(4)	N1-C7-C6-C1	-77.8(2)

Table 6 Hydrogen-bonding geometry (Å, °) for Comp 1 & Comp 2

Compound	D-H…A	D-H (Å)	H…A (Å)	D…A (Å)	D-H…A (°)
(1)	N2A—H2...O1A O1A 0.88(2) 1.92(2) 2.647(3) 139(2) ----- N2B H4 O1B 0.88(2) 1.91(2) 2.641(3) 140(2) ----- N1A H1 S1B 0.899(18) 2.619(18) 3.491(3) 163.8(17) ----- N1B H3 S1A 0.874(16) 2.636(18) 3.478(2) 162(2) -----	0.88(2)	1.92(2)	2.647(3)	139(2)
	N2B—H4...O1B	0.88(2)	1.91(2)	2.641(3)	140(2)
	N1A—H...S1B	0.899(18)	2.619(18)	3.491(3)	163.8(17)
	N1B—H3...S1A	0.874(16)	2.636(18)	3.478(2)	162(2)
(2)	C6A—H6A...S1B	0.98	2.86	3.687(3)	142
	C1A—H1A ...Cg2[i]	0.97	2.68	3.520(3)	146
	C3B—H3D...Cg4[ii]	0.97	2.91	3.758(4)	147
	C22—H22...O1	0.93	2.52	3.445(2)	171
	N1—H1...S1[iii]	0.86	2.75	3.4281(14)	137
	C6—H6...S1[iii]	0.98	2.95	3.8141(17)	147.8
	C9—H9B...O1[iv]	0.97	2.42	3.340(2)	159
	C15—H15...O1[iv]	0.93	2.52	3.358(2)	150
	C4—H4A ...Cg3[v]	0.97	2.89	3.822(3)	162

Symmetry Equivalent Positions:

i. -x+1,-y,-z+1
ii. -x,-y,-z
iii. -x+1,-y+2,-z
iv. -x+1, -y+2, -z+1
v. -x+3/2, y−1/2, -z+1/2

Table 7 Hydrogen bond interactions with amino acids at the active site of mycobacterium tuberculosis DprE1 (Å, °) for Comp 1 & Comp 2

Compound	Docking Score	Glide Energy	Interaction	Distance
Comp 1	-6.439	-45.943	-	-
Comp 2	-10.007	-50.789	O*-THR184	2.83
Co-Crystal	-8.645	-58.787	N*-SER52	3.10

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Supplementary Information

The crystallographic data for the structural analyses have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 1040800 for **(Comp 1)** and 1403523 for **(Comp 2)**. The Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk orhttp://www.ccdc.cam.ac.uk).

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