Anti-Tubercular Activity and Molecular Docking Studies of Indolizine Derivatives

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1. Energy framework calculation

The software *Crystal Explorer 17.5* program has been used to assess the interaction energies for diethyl 3-(4-chlorobenzoyl)indolizine-1,2-dicarboxylate (4b). The supramolecular nature of molecular crystal structures has an intense and unusual way of imagining energy frameworks. At the B3LYP/6-31G(d,p) level, the interaction energies between the molecules are obtained using monomer wave functions. In all the energy frameworks, the tube size (scale factor) used was 80, and the energy threshold (cut off) value was set to zero. For the corresponding interaction, the diameter of the tube cylinder represents the interaction energy in the molecular packaging in the 3D-topological images. Interaction between the molecule selected and the molecules present in the 1x1x1 unit cell dimensions of a 3.8 Å° cluster around it, as shown in Figure S10. Energies between molecular pairs are described as cylinders which connect centroids of molecular pairs with a cylindrical radius proportional to the magnitude of the energy interaction. The energy framework was modelled as red cylinders for $E_{\text{elec}}$, $E_{\text{dis}}$ as green, and $E_{\text{tot}}$ as blue [Figure S11a-S11c], and the relative strength of molecular packing in various directions is expressed by these tubes. Therefore, energy structures precisely imagine the supramolecular nature of the crystal structure. Interaction Energies as obtained colourwise from the *Crystal Explorer 17.5* software in the form of KJ/mol as shown in Table S1. As shown in Figure S12, the crystal void generates a promolecule surface, including all the atoms in the cluster present in the crystal packing. The void surface is known as an isosurface of procrystal electron density in *Crystal Explorer* program and calculated for a whole unit cell [1-3]. The default value is 0.002 a.u. The void volume in Figure S12 is 104.53 Å³, and the surface area is 309.58 Å². The observed value of void volume for compound 4b in Figure S12 shows that there are no large cavities found in the anhydrous form. Crystal voids present in the title compound 4b along with ac plane, bc plane and ab plane respectively as shown in the Figure S13.
**Table S1.** Single crystal X-ray data of title compound diethyl 3-(4-chlorobenzoyl)indolizine-1,2-dicarboxylate (4b).

| Parameter                                              | Value                        |
|--------------------------------------------------------|------------------------------|
| CCDC Number                                            | 2002636                      |
| Molecular Formula                                      | C₂₁H₁₈Cl₁N₁O₅                |
| Molecular weight                                       | 399.81                       |
| Temperature                                            | 100(2)                       |
| Crystal Size (mm)                                      | 0.15, 0.15, 0.14             |
| Absorption coefficient (mm⁻¹)                          | 0.238                        |
| T_min, T_max                                           | 0.966, 1.000                 |
| Crystal system                                         | Triclinic                    |
| Lattice parameters: a (Å), b (Å), c (Å)                 | 8.6556(4), 10.1462(5), 11.8762(6) |
| α, β, γ (°)                                            | 71.173(2), 73.631(2), 76.169(2) |
| Space Group, Density, Z, Z′                            | P-1, 2, 1                    |
| h_min, max; k_min, max; l_min, max;                     | -11, 11; -13, 13; -15, 15     |
| Number of total/unique/observed reflections             | 23691, 4643, 3311             |
| No of parameters                                       | 255                          |
| R_{int}                                                | 0.0608                       |
| R_{all}, R_{obs}                                       | 0.0788, 0.0454               |
| wR2_{all}, wR2_{obs}                                   | 0.1043, 0.0879               |
| Δρ_{min, max} (eÅ⁻³)                                   | -0.390, 0.317                |
| G.o.F                                                  | 1.050                        |
Table S2. Interaction energies as obtained from the *Crystal Explorer 17.5* (in KJ/mol).

| Colour   | N | Symop       | R    | E_ele | E_pol | E_dis | E_rep | E_tot |
|----------|---|-------------|------|-------|-------|-------|-------|-------|
| Red      | 2 | x, y, z     | 8.66 | 0.1   | -0.2  | -11.5 | 3.6   | -7.8  |
| Orange   | 1 | -x, -y, -z  | 5.94 | -28.3 | -10.1 | -58.6 | 51.8  | -56.4 |
| Yellow   | 1 | -x, -y, -z  | 7.58 | -9.8  | -1.5  | -59.4 | 32.2  | -43.3 |
| Lime     | 1 | -x, -y, -z  | 15.68| 0.6   | -0.1  | -4.2  | 1.3   | -2.3  |
| Green    | 2 | x, y, z     | 11.88| -0.1  | -0.1  | -5.6  | 1.3   | -4.3  |
| Aquamarine | 1 | -x, -y, -z  | 6.67 | -19.0 | -5.7  | -118.5| 70.3  | -84.2 |
| Cyan     | 2 | x, y, z     | 10.15| -13.4 | -3.1  | -24.0 | 21.3  | -24.2 |
| Blue     | 1 | -x, -y, -z  | 11.66| -8.3  | -1.0  | -25.1 | 26.0  | -15.3 |
| Violet   | 1 | -x, -y, -z  | 8.97 | -12.3 | -3.5  | -15.0 | 16.3  | -18.6 |
| Orchid   | 2 | x, y, z     | 12.57| -3.4  | -1.2  | -14.7 | 8.8   | -11.9 |
| Pink     | 1 | -x, -y, -z  | 8.02 | -19.3 | -9.1  | -27.4 | 19.6  | -38.9 |
Figure S1: FT-IR of diethyl-3-(4-fluorobenzoyl)indolizine-1,2-dicarboxylate (4a)
Figure S2: \(^1\)H-NMR of diethyl-3-(4-fluorobenzoyl)indolizine-1,2-dicarboxylate (4a)
Figure S3: $^{13}$C-NMR of diethyl-3-(4-fluorobenzoyl)indolizine-1,2-dicarboxylate (4a)
Figure S4: FT-IR of diethyl-3-(4-chlorobenzoyl)indolizine-1,2-dicarboxylate (4b)
Figure S5: $^1$H-NMR of diethyl-3-(4-chlorobenzo)indolizine-1,2-dicarboxylate (4b)
Figure S6: $^{13}$C-NMR of diethyl-3-(4-chlorobenzoyl)indolizine-1,2-dicarboxylate (4b)
Figure S7: FT-IR of diethyl-3-(4-nitrobenzoyl)indolizine-1,2-dicarboxylate (4c)
Figure S8: $^1$H-NMR of diethyl-3-(4-nitrobenzoyl)indolizine-1,2-dicarboxylate (4c)
Figure S9: $^{13}$C-NMR of diethyl-3-(4-nitrobenzoyl)indolizine-1,2-dicarboxylate (4c).
Figure S10. Energy frameworks corresponding to the total interaction energy between the selected molecule 4b and the molecules present in a 3.8 Å cluster around it.

(a) Coulombic energy, (b) dispersion energy and (c) total energy.

Figure S11. $d_{\text{norm}}$ mapped on Hirshfeld surface of the molecule 4b with energy framework in the form of (a) Coulombic energy, (b) dispersion energy and (c) total energy.
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