Synthesis and crystal structure of 2-{5-[2-(2,6-dichlorophenylamino)benzyl]-4-p-tolyl-4H-1,2,4-triazol-3-ythio}acetate

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1,2,4-Triazole derivative; Crystal structure; C–H…N; C–H…O/N–H…N weak interactions

Abstract The compound 2-{5-[2-(2,6-dichlorophenylamino)benzyl]-4-p-tolyl-4H-1,2,4-triazol-3-ythio}acetate has been prepared and characterized by IR, 1H NMR, 13C NMR and mass spectra. The crystal and molecular structure were further confirmed using single crystal X-ray diffraction. The crystal structure has been found to be stabilized by intermolecular C–H…O interaction generating bifurcated hydrogen bonds whereas the C–H…N interactions generate chain of molecules. The intramolecular N–H…N hydrogen bond forms a ring with S(7) graph-set motif.

1. Introduction

1,2,4-Triazoles are among the most promising heterocyclic compounds playing an important role in medicinal, agricultural and industrial fields. Some of them are used as analytical reagents for the determination of boron, cobalt and antimony. A few triazoles find synthetic application as halogenating agents, as activating polymeric reagents and are also used as photographic reagents. Substituted-1,2,4-triazoles, are among the various heterocyclic compounds that have received considerable attention during the last two decades for their potential antibacterial (Andotra et al., 1986), antifungal (Khan et al., 1987), antiviral (Somorai et al.,1986), antifungal (Khan et al., 1987), antiviral (Somorai et al., 1986), antiHIV (Ikizler et al., 1998), anticancer (Ronghui et al., 2005), diuretic (Shah et al., 1969), antihypertensive (Emilsson et al., 1987; Kuzmierkiwicz et al., 1985), anti-inflammatory and analgesic (Bozo et al., 1989; Pignatellol et al., 1991; Mullican et al., 1993), hypoglycemic (Agarwal, 1991), anticonvulsant (Khanum et al., 2004), and antimycobacterial (Vera et al., 2004) activities. Many antifungal agents containing 1,2,4-triazoles are in clinical use (Frank et al., 2003; Kelly, 1997). Ribavirin, the antiviral agent is a synthetic nucleoside derivative containing 1,2,4-triazole moiety and is active against a wide verity of RNA/DNA virus. It is used in the treatment of severe lower respiratory infections caused by RS virus. Guanazole, a very old compound bearing triazole moiety, is recently found to be active against tumors.
Anastrozole is a non-steroidal aromatase inhibitor having triazole moiety, decreases the estrogen synthesis in the body and thereby prevents or inhibits the growth of many types of breast cancer cells that need estrogen to grow.

Various 3-substituted-4-amino-5-mercapto-1,2,4-triazoles have been reported for their wide spectrum of biological activities. In recent years, the focus has been on the molecular modification of the triazole moiety to obtain a lead molecule with better biological activity and lesser side effects. Substitutions have been carried out primarily on the 3rd position of the 1,2,4-triazole ring by substituting groups such thiol, alkylthiol and alkenylthiol (Eldeen et al., 1991) in order to enhance the biological activity.

The synthesis of the compound was followed by subsequent spectroscopic analysis using IR, $^1$H NMR and $^{13}$CNMR techniques to confirm the presence of the supposed ring systems, as well as the signals for the existence of various protons. The compound was subjected to single crystal X-ray diffraction analysis so that its supramolecular structure could be investigated in terms of possible intermolecular interactions.

2. Experimental

2.1. Materials

All chemicals were obtained from a commercial source. Solvents were dried and purified with known conventional methods.
-4-p-tolyl-4H-1,2,4-triazole-3-thiol (5). 5-(2,6-Dichlorophenylamino)benzyl]-4-p-tolyl-4H-1,2,4-triazole-3-thiol (5) when treated with ethyl chloroacetate, in the presence of anhydrous potassium carbonate yields 2-[5-(2,6-dichlorophenylamino)benzyl]-4-p-tolyl-4H-1,2,4-triazol-3-ylthio]acetate (6). Yield 71% (3.65 g).

2.4. Physical measurements

2.4.1. 2-[5-[2-(2,6-Dichlorophenylamino)benzyl]-4-p-tolyl-4H-1,2,4-triazol-3-ylthio]acetate (6)

White crystalline solid (DMF), yield 71%, m.p. 158–160 °C; IR (KBr) v cm⁻¹: 3250 (–NH) 2980 (CH’), 1738 (C’O ester, 1583 C–N, 750 (–Cl).

¹H NMR (DMSO) δ ppm: 1.20–1.27 (t, 3H, alk-CH₃), 2.19 (s, 3H, Ar–CH₃), 4.01 (s, 2H, Ar–CH₂), 4.05 (s, 2H, –SCH₂), 4.15–4.22 (q, 2H, –OCH₂), 6.38 (s, Ar–NH), 6.5–7.43 (m, 11H, Ar).

¹³C NMR (DMSO) δ ppm: 14.12 (alk-CH₃), 21.08 (Ar–CH₃), 28.77 (Ar–CH₂), 34.64 (–SCH₂), 62.01 (–OCH₂), 115.11–150.91 (C of 3Ars), 155.61 (C₅ of triazole ring), 160.90 (C₃ of triazole ring), 168.28 (C’O).

MS m/z: (M+1) 528, the other major fragments 523, 499 and 465.

3. X-ray analysis

Single crystals of the compound were obtained from the solvent DMF. Transparent white plate crystals were selected for X-ray diffraction analysis. The X-ray diffraction data for compound 6 were collected on a Bruker Smart CCD Area Detector System, using MoKα (0.71073 Å) radiation for the crystal. Intensity data were collected using a single crystal with dimensions 0.40 × 0.35 × 0.30 mm up to a maximum of 28.40° in the ω-ϕ scan mode. The data were reduced using SAINTPLUS (Bruker, 1998). The structure was solved by direct methods using SHELXS97 (Sheldrick, 2008) and difference Fourier synthesis using SHELXL97 (Sheldrick, 2008). The positions and anisotropic displacement parameters of all non-hydrogen atoms were included in the full-matrix least-square refinement using SHELXL97 (Sheldrick, 2008) and the procedure was carried out for a few cycles until convergence was reached. A total of 15,519 reflections were collected, out of which were 6055 [R(int) = 0.0845] independent reflections. The number of reflections satisfying I > 2σ(I) criteria were 4013. These were treated as observed. The H atoms were placed at the calculated positions in the riding model approximation (C–H 0.93 Å), with their temperature factors set to 1.2 times those of the equivalent isotropic temperature factors of the parent atoms. All the other non-H atoms were refined anisotropically. The R factor for the observed data finally converged to R = 0.0658. The maximum and minimum values of residual electron density were 0.566 and −0.588 e Å⁻³. Molecular diagrams were generated using ORTEP (Farrugia, 1997). The mean plane calculation was done using the program PARST (Nardelli, 1983).
4. Result and discussion

Fig. 1 shows the ORTEP diagram of the molecule with thermal ellipsoids drawn at 50% probability. Figs. 2 and 3 show hydrogen bond interactions and crystal packing of the compound. The details of crystal data and refinements are given in Table 1.

Table 1 shows the respective hydrogen bond interactions for compound 6.

Compound 6 comprises 1,2,4-triazole, dichlorophenylamino benzyl group and the p-tolyl ring. The non-coplanarity between triazole and p-tolyl and that between triazole and dichlorophenylamino benzyl rings is obvious from the dihedral angle values of 68.93° and 58.36° respectively. The triazole ring is essentially planar (La Keya et al., 2006; Buzykin et al., 2008), the maximum deviation of atoms from their mean statistical planes being 0.0161 Å.

The bond lengths and angles for the 1,2,4-triazole moiety in the molecule are in good agreement, within experimental errors, with those observed in other 1,2,4 triazole derivatives (La Keya et al., 2006; Buzykin et al., 2008). The N(1)–N(2) bond length in the triazole ring is shorter (1.418(6) Å) than the distance characteristics of a single N–N bond (1.47 Å). The N–C and N–N distances in the triazole ring vary from 1.30(6) to 1.41(6) Å.

The molecular structure is primarily stabilized by strong intramolecular N2–H3...N3 hydrogen bond [N3–H3 = 0.864(4) Å, H3–N2 = 2.256(4) Å, N3–N2 = 3.018(6) Å] and the angle N3–H3–N2 = 147.63(2)° leading to the formation of a seven-membered hydrogen bonded pattern corresponding to graph set S(7) (Bernstein et al., 1995), thus locking the molecular conformation and eliminating the conformational flexibility. The crystal structure is further stabilized by some interesting features that comprise intermolecular interactions C–H–O and C–H–N. The C–H–O...N

Figure 3  Packing of the molecules in crystal of 6 viewed along ‘a’ axis. Dotted lines indicate, C–H...N intermolecular interactions.

Table 2  Non-bonded interactions and possible hydrogen bonds (Å, °) for compound 6. (D-donor; A-acceptor; H-hydrogen.)

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<thead>
<tr>
<th>D–H–A</th>
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<th>H–A</th>
<th>D–A</th>
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<td></td>
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<tr>
<td>N3–H3...N2</td>
<td>0.860(4)</td>
<td>2.256(4)</td>
<td>3.018(6)</td>
</tr>
<tr>
<td>C4–H4...O2</td>
<td>0.930(6)</td>
<td>2.963(4)</td>
<td>3.865(7)</td>
</tr>
<tr>
<td>C24–H24...O2ii</td>
<td>0.930(5)</td>
<td>2.450(4)</td>
<td>3.633(6)</td>
</tr>
<tr>
<td>C18–H18B...N2iii</td>
<td>0.970(6)</td>
<td>2.688(4)</td>
<td>3.594(8)</td>
</tr>
<tr>
<td>Symmetry code: (0) x, y, z (i) x, y+1, z+1 (ii) x+1, y+2, z+1/2 (iii) x, y+1, z−1</td>
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The angle characteristics of a single N–N bond (1.47 Å). The N–C and N–N distances in the triazole ring vary from 1.30(6) to 1.41(6) Å. The orientation of thioester group is characterized by the torsion angle N(1)–C(3)–S(1)–C(16) = 22.04(4)°.

The crystal structure is further stabilized by some interesting features that comprise intermolecular interactions C–H–O and C–H–N. The C–H–O...N...O hydrogen bond network is a prevalent feature of the crystal structure.
interaction forms a bifurcated bond from two donors C4 and C24 to the same acceptor O2, linking the molecule in a cohesive manner along ‘b’ axis (Fig. 2). On the other hand the C–H–N interaction results in one dimensional chain along ‘a’ axis (Fig. 3).

5. Conclusion

The synthesis of the substituted-1,2,4-triazole is described. Additionally, the X-ray analysis was carried out in order to extrapolate the results observed for structure activity correlations. Weak interactions and supramolecular assembly, involving several hydrogen bonding interactions of dichlorophenylamino and triazolo groups with thioester group have been demonstrated. The structure analysis of this compound provides an insight into the correlation between the molecular structures and intermolecular interactions in the compounds for drug development. Hydrogen bonds are the main non-covalent interactions in the structure of 1,2,4 triazole derivative and have great influence on the crystal packing. The compound has been made with the specific aim of assessing a new donor–acceptor-type of hydrogen-bonded interactions to control the architecture of organic solids for further investigation of supramolecular assembly in solid-state.

6. Supplementary data

Crystallographic data for the structure (6) reported in this paper have been deposited with the Cambridge data centre. The deposition number is CCDC 795601.

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References