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Organic and Inorganic Chemistry 2018: Syntheses and crystal structures of two adamantly substituted 1,2,4-triazole-5-thione N-Mannich bases-Monirah Al-Alshaikh-King Saud University

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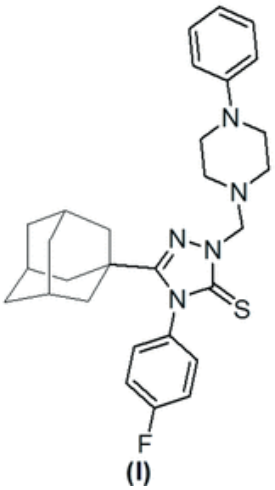
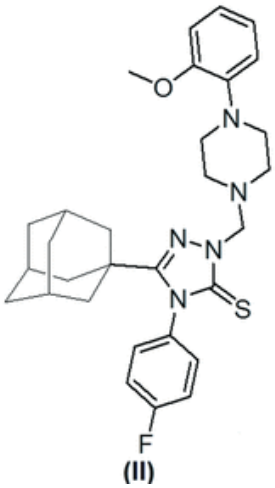
In the title N-Mannich bases, 3-(adamantan-1-yl)-4-(4-fluorophenyl)-1- [(4-phenylpiperazin-1-yl)methyl]-4,5-dihydro-1H-1,2,4-triazole-5-thione (C29H34FN5S) (I), and 3-(adamantan-1-yl)-4-(4-fluorophenyl)-1-{[4-(2-methoxyphenyl)piperazin-1-yl]-methyl}-4,5-dihydro-1H-1,2,4-triazole-5-thione (C30H36FN5OS) (II), fluorophenyl, adamantane and piperazine moieties are linked to a planar triazole ring. There is an additional phenyl ring on the piperazine ring in (I) and a methoxyphenyl ring in (II). In compound (I), the fluorophenyl and phenyl rings are inclined to the triazole ring by 86.55 (13) and 60.52 (12), respectively, and the two aryl rings are inclined to one another by 66.37 (13). In compound (II), the corresponding dihedral angles are 83.35 (13), 71.38 (15) and 11.97 (16), respectively. The crystal structure of (I) shows pairs of C—HF hydrogen bonds forming inversion dimers, while in the crystal of compound (II), in addition to the C—HF hydrogen bonds that generate chains parallel to the b axis, there are C—H interactions present that link the chains to form layers parallel to the ab plane.

Chemical context:

The incorporation of an adamantyl moiety into various bioactive molecules results in compounds with relatively high lipophilicity, which in turn modifies the bioavailability and modulates the therapeutic indices through various mechanisms (Liu et al., 2011; Lamoureux & Artavia, 2010). Several adamantane-based drugs have been developed as antiviral (Davies et al., 1964; Togo et al., 1968; Rosenthal et al., 1982; ElEmam et al., 2004; Burstein et al., 1999; Balzarini et al., 2009), anti-Parkinsonian (Schwab et al., 1969) and hypoglycaemic (Villhauer et al., 2003; Augeri et al., 2005) drugs. In addition, numerous adamantane-based analogues have promising anticancer (Sun et al., 2002), bactericidal (Protopopova et al., 2005; El-Emam et al., 2013; Kadi et al., 2010; Al-Abdullah et al.; 2014; Al-Deeb et al., 2006) and fungicidal (Omar et al., 2010) activities. In a continuation of our ongoing studies on the pharmacological and structural properties of adamantyl 1,2,4- triazole derivatives (Al-Abdullah et al., 2012; Al-Tamimi et al., 2014; El-Emam et al.; 2013; 2014), we report herein on the synthesis and crystal structures of the title adamantyl-substituted 1,2,4-triazole-5-thione N-Mannich bases, (I) and (II).



(I)



(II)

Structural commentary:

The molecular structures of the title compounds, (I) and (II), are illustrated in Figs. 1 and 2, respectively. In both molecules the piperazine rings have a chair conformation, with the Nbound substituents occupying equatorial positions. In (I), the fluorophenyl ring (C13–C18) and the phenyl ring (C24–C29) are inclined to the triazole ring (N1–N3/C11/C12) by 86.55 (13) and 60.52 (12), respectively. The two aryl rings are inclined to one another by 66.37 (13). In compound (II), the fluorophenyl ring (C13–C18) and the phenyl ring (C24–C29) are inclined to the triazole ring (N1–N3/C11/C12) by 83.35 (13) and 71.38 (15), respectively, while the two aryl rings are inclined to one another by only 11.97 (16). This difference in conformation is illustrated by the structural overlap diagram, shown in Fig. 3.

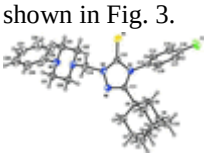


Figure 1-The mol¬ecular structure of compound (I) , with the atom labelling and 30% probability displacement ellipsoids.

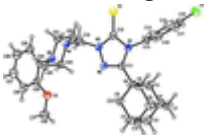


Figure 2-The mol¬ecular structure of compound (II) , with the atom labelling and 30% probability displacement ellipsoids.

Supramolecular features

In the crystal of compound (I), molecules are linked by pairs of C—HF hydrogen bonds, forming inversion dimers

(Table 1 and Fig. 4). In compound (II), molecules are linked by C—HF hydrogen bonds, forming chains parallel to the baxis direction. The chains are linked by C—H interactions, forming layers parallel to the ab plane

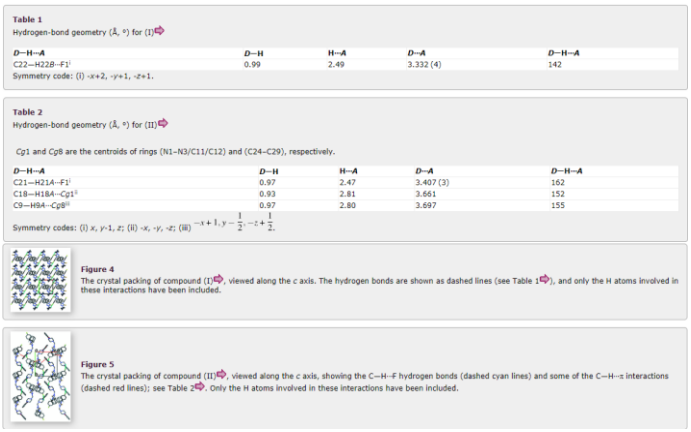


Table 1
Hydrogen-bond geometry (Å, °) for (I)

D—H···A	D—H	H···A	D···A	D—H···A
C22—H22B···F1^{i}	0.99	2.49	3.332 (4)	142

Symmetry code: (i) -x+2, -y+1, -z+1.

Table 2
Hydrogen-bond geometry (Å, °) for (II)

Cg1 and Cg8 are the centroids of rings (N1–N3/C11/C12) and (C24–C29), respectively.

D—H···A	D—H	H···A	D···A	D—H···A
C21—H21A···F1^{i}	0.97	2.47	3.407 (3)	162
C18—H18A···Cg1^{ii}	0.93	2.81	3.661	152
C9—H9A···Cg8^{iii}	0.97	2.80	3.697	155

Symmetry codes: (i) $x, y-1, z$; (ii) $-x, -y, -z$; (iii) $-x+1, y-\frac{1}{2}, -z+\frac{1}{2}$.

Figure 4
The crystal packing of compound (I), viewed along the c axis. The hydrogen bonds are shown as dashed lines (see Table 1), and only the H atoms involved in these interactions have been included.

Figure 5
The crystal packing of compound (II), viewed along the c axis, showing the C—H···F hydrogen bonds (dashed cyan lines) and some of the C—H···π interactions (dashed red lines); see Table 2. Only the H atoms involved in these interactions have been included.

Database survey:

A search of the Cambridge Structural Database (Version 5.38, last update May 2017; Groom et al., 2016) for the 3-(adamantan-1-yl)-4-[(piperazin-1-yl) methyl]-1,2,4-triazole3(3H)-thione moiety gave 14 hits. One compound, 3-(adamantan-1-yl)-4-phenyl-1-[(4-phenylpiperazin-1-yl)methyl]-1H-1,2,4-triazole-5(4H)-thione (GAPWUR; Al-Abdullah et al., 2012), is very similar to compound (I). It has a phenyl ring substituent on the piperazine ring and a phenyl ring substituent on the triazole ring, which are inclined to one another by 72.4 (2), and by 89.0 (2) and 74.4 (2), respectively, to the triazole ring. In compound (I), the corresponding dihedral angles are 66.37 (13), 86.55 (13) and 60.52 (12), respectively. Two compounds have a 2-methoxyphenyl ring substituent on the piperazine ring, viz. (3-(1-adamantyl)-1-{[4- (2-methoxyphenyl)piperazin-1-yl]methyl}-4-methyl-1H-1,2,4-triazole 5(4H)-thione (YUPVIP; El-Emam et al., 2014), with a methyl substituent on the triazole ring, and 3-(adamantan-1-yl)-4-ethyl-1-{[4-(2-methoxyphenyl)piperazin-1-yl]methyl}-1H-1, 2,4-triazole-5(4H)-thione (RITMUE; Al-Tamimi et al., 2010) with an ethyl substituent on the triazole ring. In these two compounds the methoxyphenyl rings are inclined to the triazole ring by 67.1 (1) and 59.4 (1), respectively. In compound (II), the corresponding dihedral angle is 71.38 (15).

Synthesis and crystallization:

The title compounds, (I) and (II), were synthesized via the reaction of 3-(adamantan-1-yl)-4-(4-fluoromethyl)-4H-1,2,4-triazole-5-thiol (Al-Deeb et al., 2006) with the appropriate monosubstituted piperazie and a formaldehyde solution, as outlined in Fig. 6.

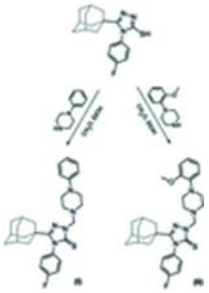


Figure 6:Reaction schemes for the syntheses of compounds (I) and (II) .x

Compound (I): 1-Phenylpiperazine (325 mg, 2 mmol) and a 37% formaldehyde solution (1 ml) were added to a solution of 3-(adamantan-1-yl)-4-(4-fluoromethyl)-4H-1,2,4-triazole-5-thiol (659 mg, 2 mmol) in ethanol (10 ml), and the mixture was heated under reflux for 1 h then allowed to stand overnight. Cold water (3 ml) was slowly added and the mixture was stirred for 20 min. The precipitated crude product was filtered, washed with water, dried, and crystallized from ethanol to yield 846 mg (84%) of compound (I) as colourless plateshaped crystals (m.p. 469–471 K). 1 H NMR (700.17 MHz): 1.47–1.49 (m, 3H, adamantane-H), 1.60–1.62 (m, 3H, adamantane-H), 1.80 (s, 6H, adamantane-H), 1.89 (s, 3H, adamantane-H), 2.89–2.91 (m, 4H, piperazine-H), 3.14–3.15 (m, 4H, piperazine-H), 5.14 (s, 2H, CH2), 6.77–6.79 (m, 1H, Ar-H), 6.94 (d, 2H, Ar-H, J = 8.4 Hz), 7.20–7.22 (m, 2H, Ar-H), 7.41–7.49 (m, 4H, Ar-H). 13C NMR (125.76 MHz): 27.61, 36.07, 39.62, 39.74 (adamantane-C), 48.73, 50.30 (piperazineC), 69.06 (CH2), 116.0, 116.78, 119.41, 129.37, 132.80, 133.10, 151.48, 156.28 (Ar-C), 162.17 (triazole C-3), 170.95 (C S).

Compound (II): 1-(2-Methoxyphenyl)piperazine (385 mg, 2 mmol) and a 37% formaldehyde solution (1 ml) were added to a solution of 3-(adamantan-1-yl)-4-(4-fluoromethyl)-4H1,2,4-triazole-5-thiol (659 mg, 2 mmol) in ethanol (10 ml), and the mixture was heated under reflux for 1 h then allowed to stand overnight. The precipitated crude product was filtered, washed with cold ethanol, dried, and crystallized from ethanol to yield 865 mg (81%) of compound (II) as colourless blocklike crystals (m.p. 462–464 K). 1 H NMR (700.17 MHz): 1.49– 1.50 (m, 3H, adamantane-H), 1.61–1.63 (m, 3H, adamantaneH), 1.83 (s, 6H, adamantane-H), 1.90 (s, 3H, adamantane-H), 2.89–2.90 (m, 4H, piperazine-H), 2.96–2.98 (m, 4H, piperazineH), 3.78 (s, 3H, OCH3), 5.11 (s, 2H, CH2), 6.88–6.96 (m, 4H, Ar-H), 7.42–7.52 (m, 4H, Ar-H). 13C NMR (125.76 MHz): 27.61, 35.77, 36.07, 39.61 (adamantane-C), 50.54, 50.58 (piperazine-C), 55.65 (OCH3), 69.39 (CH2), 112.08, 116.78,118.51, 121.23, 123.02, 132.79, 133.13, 141.53, 152.36, 156.32 (Ar-C), 162.17 (triazole C-3), 171.0 (C S). Suitable single crystals of compounds (I) and (II) were obtained by slow evaporation of CHCl3:EtOH solutions (1:1, 5 ml) at room temperature.

Refinement :

Crystal data, data collection and structure refinement details are summarized. The C-bound H atoms were positioned

geometrically and treated as riding atoms: C—H = 0.93–1.00 A˚ with Uiso(H) = 1.5Ueq(C-methyl) and 1.2Ueq(C) for other H atoms.

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