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CYCLOPENTYLAMINE SUBSTITUTED TRIAZOLO[4,5-*D*]PYRIMIDINE: IMPLICATIONS FOR BINDING TO THE ADENOSINE RECEPTOR

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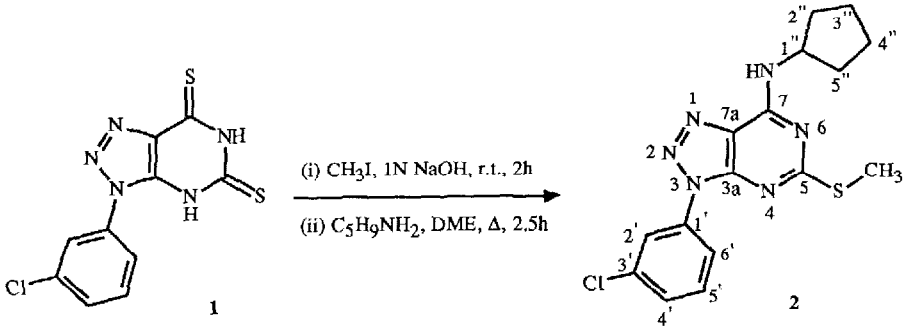
Summary. 3-(3-chlorophenyl)-7-(N-cyclopentylamino)-5-methylthio-1,2,3-triazolo[4,5-*d*]pyrimidine was found to have restricted rotation around the exocyclic C-N bond. This has implications for the orientation of hydrophobic substituents relative to the plane of the heterocyclic ring of adenosine receptor ligands.

We have recently proposed a model of the adenosine A1 and A2 receptors that defines the receptors as having three binding domains; a hydrophobic binding domain, an aromatic binding domain and a ribose binding domain.[1] We have provided evidence for a conserved 6 membered ring with the synthesis of 4-(n-butylthio)-6-(phenylamino)-2-propionamidylthiopyrimidine.[2] We now report evidence for the orientation of the hydrophobic domain relative to the aromatic binding domain. Restricted rotation has been observed in 3-(3-chlorophenyl)-7-(N-cyclopentylamino)-5-methylthio-1,2,3-triazolo[4,5-*d*]pyrimidine indicating two possible orientations of the hydrophobic cyclopentyl group relative to the plane of the heterocyclic ring.

Treatment of 3-phenyl-1,2,3-triazolo[4,5-*d*]pyrimidine-5,7-dithione (**1**)[3] in 1N NaOH with methyl iodide (4.0 equiv, dropwise) at r.t. gave a precipitate which was collected by suction filtration after 2 hrs. Washing with water, drying and recrystallization from hexane afforded bismethylated compound (66% yield) which was refluxed in DME with cyclopentylamine (7 equiv) for 2.5 hrs. Cooling to 0°, addition of water and recrystallisation of the precipitate from ether gave **2** in 67% yield.[4] The presence of two isomers was apparent from both ^{1}H and ^{13}C NMR which showed signals integrating for one proton in the ratio of 2.7:1 for the N**H** proton (δ6.20 and 6.74) and the methine proton of the cyclopentyl (δ4.64 and 5.16) and doubling of many of the carbon signals. Significant double bond character of the exocyclic C-N bond (1.343Å compared to C-N bond lengths in the ring of 1.313, 1.349, 1.356, 1.357, 1.359 and 1.382Å) was evident from X-ray crystallographic analysis. Crystal/refinement data: $C_{16}H_{17}ClN_6S$, M = 360.9, Monoclinic, space group $C2/c$ (No. 15), a = 16.609(11), b = 16.893(4), c = 13.826(6)Å, β = 116.78(2)°, V= 3463(3) Å^3. D_c (Z = 8) = 1.383g cm^{-3}. $F(000)$ = 1504. Monochromatic MoK_α radiation, λ = 0.71073Å, large colorless crystal aggregates were cleaved to give a specimen 0.30 x 0.24 x 0.13 mm, μ_{Mo} = 3.4cm^{-1}, no absorption or extinction corrections. $2\theta_{max}$ = 50°, N_{indept}= 2439, N_{obs} = 1244; R_F = 0.037, R_W = 0.039 (statistical weights). Anisotropic thermal parameter refinement for non-hydrogen atoms; $(x,y,z,U_{iso})_H$ constrained at estimated values in full matrix least squares refinement.[5] The refinement model is consistent with the spectroscopic evidence. The observed restricted rotation has important implications for receptor-ligand binding of N^6-substituted adenosine analogues.



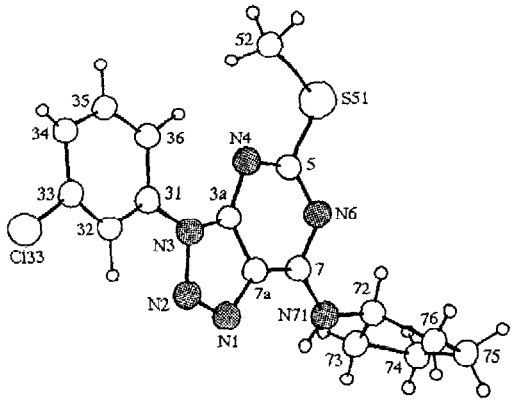


Figure 1 Molecule of **2** showing crystallographic numbering scheme. Hydrogens were located by difference methods and their positional and isotropic parameters refined. The heterocyclic ring and atoms N(71) and C(72) are approximately co-planar [torsion angle N(6)-C(7)-N(71)-C(72), +0.9(4)°].

Table 1. Non-hydrogen atom coordinate

Atom	x	y	z
N(1)	0.3337(2)	0.3293(2)	0.0449(
N(2)	0.3504(2)	0.4049(2)	0.0552(
N(3)	0.4425(2)	0.4157(2)	0.1018(
N(4)	0.5731(2)	0.3281(2)	0.1659(
C(5)	0.5859(2)	0.2512(3)	0.1714(
N(6)	0.5269(2)	0.1897(2)	0.1403(
C(7)	0.4381(2)	0.2092(3)	0.0948(
C(3a)	0.4841(2)	0.3443(3)	0.1206(
C(7a)	0.4148(2)	0.2892(3)	0.0848(
S(51)	0.6979(1)	0.2161(1)	0.2300(
C(52)	0.7604(3)	0.3077(3)	0.2606(
C(31)	0.4774(3)	0.4944(3)	0.1155(
C(32)	0.4185(3)	0.5570(3)	0.0909(
C(33)	0.4507(4)	0.6329(3)	0.1022(
Cl(33)	0.3784(1)	0.7123(1)	0.0728(
C(34)	0.5418(4)	0.6479(4)	0.1376(
C(35)	0.5984(3)	0.5837(4)	0.1625(
C(36)	0.5689(3)	0.5070(3)	0.1527(
N(71)	0.3777(2)	0.1499(2)	0.0643(
C(72)	0.3999(2)	0.0667(3)	0.0774(
C(73)	0.3640(4)	0.0204(4)	-0.0275(
C(74)	0.3682(4)	-0.0653(4)	0.0053(
C(75)	0.3666(4)	-0.0644(4)	0.1124(
C(76)	0.3602(3)	0.0215(3)	0.1406(

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References and Notes

1. R. J. Quinn, M. J. Dooley, A. Escher, F. A. Harden and H. Jayasuriya, *Nucleosides and Nucleotides*, press
2. M. J. Dooley, R. J. Quinn, W. C. Patalinga and A. H. White, *Tetrahedron Lett.*, **31**, 6103 (1990).
3. prepared following the method of A. Albert and C. J. Lin, *J. Chem. Soc. Perkin Trans. I*, 210 (1977).
4. Spectral data for **2:** m.p.: 153°C; chemical shifts of minor rotamer in { } where distinguishable from ma rotamer 1H-NMR (250MHz, $CDCl_3$): δ 1.5-1.8 (m) and 2.1-2.3 (m) (8H, H2",H3",H4",H5 2.60 (s, 3H, SCH_3); 4.54-4.73 {5.07-5.26} (m, 1H, H1"); 6.20 {6.74} (br d, J 7.0Hz, 1H, NI 7.35 (br d, J 8.0 Hz, 1H, H4'); 7.48 (br t, J *ca* 8Hz, 1H, H5'); 8.20 (br d, J 7.5Hz, 1H, H6 8.35 (t, J 2.0Hz, 1H, H2'); 13C NMR ($CDCl_3$): δ 14.5 {14.2} (SCH_3), 23.7 (C3",C4"), 32.9 {33. (C2",C5"), 52.5 {55.5} (C1"), 118.4 (C6'), 120.7 (C2'), 123.8 {123.0} (C-7a), 127.8 (C4'), 13((C5'), 135.1 (C3'), 137.5 (C1'), 148.9 (C3a), 153.1 {153.6} (C7), 172.7 {171.7} (C5); I.R. 3270 (N broad), 2950, 1610, 1590, 1490, 1320 cm^{-1}; UV (ethanol): λ_{max} = 257, 309 nm (ε = 14500, 11200).
5. Tables of structure factor amplitudes, thermal and hydrogen parameters and molecular geometries have be deposited at the Cambridge Crystallographic Centre.

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