Olanzapine

(Last updated 28 October 2024)



Figure . The molecular diagram of Olanzapine.

# CSP studies

|  |  |
| --- | --- |
| REFCODE | UNOGIN |
| Formula | C17 H20 N4 S1 |
| Study\_ID | 20 |
| Common Name | Olanzapine |
| IUPAC Systematic Name | 2-Methyl-10-(4-methyl-1-piperazinyl)-4H-3-thia-4,9-diaza-benzo[f]azulene |
| CSD Refcodes | UNOGIN03, UNOGIN04, UNOGIN06, UNOGIN05 |
| Scientist | Louise Price |
| Date | 2013 |
| Publication | Bhardwaj RM, Price LS, Price SL, Reutzel-Edens SM, Miller GJ, Oswald IDH, Johnston B, Florence AJ 2013. Cryst Growth Des 13, 1602-1617. |
| Programs | Flexible CrystalPredictor (1.x), dmaflex-Quick, DMACRYS (2.0.4) |
| Location on S Drive | \CHEMISTRY\_CPOSS\Olanzapine\CrystalPredictor |
| Potential Description | GDMA2.2(MP2/6-31G(d,p))multipoles rotated from gas phase local minimum + FIT with isotropic S |
| Programs | Study\_ID=20, CrystalOptimizer, DMACRYS (2.0.4) |
| Location on S Drive | \CHEMISTRY\_CPOSS\Olanzapine\CrystalOptimizer |
| Potential Description | GDMA2.2(PBE0/6-31G(d,p)) + FIT with isotropic S |
| Programs | Study\_ID=11, DMACRYS (2.0.4) |
| Location on S Drive | \CHEMISTRY\_CPOSS\Olanzapine\PCM |
| Potential Description | GDMA2.2(PCMdielectric3(PBE0/6-31G(d,p))) + FIT with isotropic S |

CrystalPredictor was run – this is energy model 1

CrystalOptimizer refinement was carried out (with a 30 Å cutoff) – this is energy model 2

The multipoles within the PCM were evaluated, and the unit cells reoptimized with DMACRYS (rigid molecule refinement). Second derivative properties were evaluated for the optimized unit cell with a 15 Å cutoff. These are energy model 3.

|  |  |
| --- | --- |
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|  |

Figure . Crystal energy landscape of Olanzapine from previous work. Top left, energy model 1 (CrystalPredictor search), bottom left, energy model 2 (CrystalOptimizer refinement), right, energy model 3 (rigid molecule refinement within PCM). Free energy approximations are also available for energy model 3 – see the spreadsheet.

# CSD structures (CSD version 5.44 with Jun and Sep 2023 updates)

The recently published structure for form III is included, although it is not yet on the CSD.

Table . Crystallographic information for CSD entries for Olanzapine. Different polymorphs are coloured differently.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| REFCODE | space group | Z’ | a / Å | b / Å | c / Å | α / ° | β / ° | γ / ° | density / g cm-3 | Form |
| UNOGIN | P21/c | 1 | 10.388 | 14.839 | 10.567 | 90 | 100.64 | 90 | 1.296 | I |
| UNOGIN01 | P21/c | 1 | 10.383 | 14.826 | 10.56 | 90 | 100.616 | 90 | 1.299 | I |
| UNOGIN02 | P21/c | 1 | 9.913 | 16.5329 | 9.9992 | 90 | 98.023 | 90 | 1.279 | II |
| UNOGIN03 | P21/c | 1 | 10.3411 | 14.521 | 10.5314 | 90 | 100.291 | 90 | 1.334 | I |
| UNOGIN04 | P21/c | 1 | 9.8544 | 16.314 | 9.9754 | 90 | 98.304 | 90 | 1.308 | II |
| UNOGIN05 | P21/n | 1 | 8.6555 | 15.4441 | 12.5558 | 90 | 95.284 | 90 | 1.242 | IV |
| UNOGIN06 | P21/c | 1 | 10.708 | 16.476 | 10.065 | 90 | 90 | 110.43 | 1.247 | III |

Table . Experimental information for CSD entries for Olanzapine.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| REFCODE | space group | R factor | T / K | Year | Comments |
| UNOGIN | P21/c | 3.33 | 293 | 2004 | Slow evaporation of a toluene solution at room temperature1 (The title of the paper refers to this polymorph as form II, due to the misleading patent literature. It is actually form I by the current nomenclature.) |
| UNOGIN01 | P21/c | 4.3 | 293 | 2003 | Olanzapine (270 g) was suspended in ethyl acetate (2.6 L). The stirred suspension was heated to 76 °C to dissolve the solids. The solution was then cooled to ambient temperature, at which time a crystal slurry formed. The solid product was isolated by vacuum filtration and dried in vacuo at 50 °C.2 |
| UNOGIN02 | P21/c | 4.66 | 298 | 2011 | Cocrystallization of olanzapine with nicotinamide in a 1:1 ratio from ethyl acetate afforded block-shaped pale-yellow crystals of olanzapine form IV in the space group P21/c. The expected cocrystal with nicotinamide was not obtained.3 (Again the form name is incorrect due to the misleading patent literature.) |
| UNOGIN03 | P21/c | 3.34 | 123 | 2013 | Form I was most frequently observed under all conditions (417 individual crystallizations) and the only nonsolvated form which could be obtained directly from solution recrystallization as a pure phase.4 |
| UNOGIN04 | P21/c | 5.42 | 123 | 2013 | Form II single crystals were obtained through vapor phase via sublimation of olanzapine.4 |
| UNOGIN05 | P21/n | 10.5 | 443 | 2019 | synchrotron powder  An olanzapine-PVP (Kollidon K90F) solid dispersion (70:30 w/w drug/polymer) was prepared using a spray drying method. A simultaneous DSC–PXRD analytical platform, similar to that described by Clout et al., was used to heat and crystallize the amorphous dispersion and concurrently capture heat flow and diffraction data.5 |
| UNOGIN06 | P21/c | 11.39 | 293 | 2024 | electron diffraction  a mixture of OLZP forms I, II and III with a higher content of the latter was obtained using a slightly modified method of crystallization than that published by Reutzel-Edens et al.2 3D ED data were collected over 32 crystals and their indexing confirmed the presence of three different polymorphs.6 |

# Other notes

The study was originally done with two conformational regions named eq(uatorial) and ax(ial) relating to the manner in which the benzodiazepine group linked to the nitrogen atom. Susan was not happy with these terms being used for a nitrogen atom, so they were changed to A and B respectively. (A is the conformation seen in the experimental crystal structures and is the lower in energy.) Crystal structures have been given to other groups with the old names, and hence these are occasionally referred to in the literature.

A125 was originally thought to be the best match for form III, although Rajni noted that there were problems with it and it wasn’t perfect.

1. I. Wawrzycka-Gorczyca, A. E. Koziol, M. Glice and J. Cybulski, *Acta Crystallographica Section E - Structure Reports Online*, 2004, **60**, o66-o68.

2. S. M. Reutzel-Edens, J. K. Bush, P. A. Magee, G. A. Stephenson and S. R. Byrn, *Crystal Growth & Design*, 2003, **3**, 897-907.

3. R. Thakuria and A. Nangia, *Acta Crystallographica Section C-Crystal Structure Communications*, 2011, **67**, O461-O463.

4. R. M. Bhardwaj, L. S. Price, S. L. Price, S. M. Reutzel-Edens, G. J. Miller, I. D. H. Oswald, B. Johnston and A. J. Florence, *Crystal Growth & Design*, 2013, **13**, 1602-1617.

5. S. Askin, J. K. Cockcroft, L. S. Price, A. D. Goncalves, M. Zhao, D. A. Tocher, G. R. Williams, S. Gaisford and D. Q. M. Craig, *Crystal Growth & Design*, 2019, **19**, 2751-2757.

6. G. Anyfanti, E. Husanu, I. Andrusenko, D. Marchetti and M. Gemmi, *IUCrJ*, 2024, **11**, 843-848.