Olanzapine

(Last updated 28 October 2024)



Figure . The molecular diagram of Olanzapine.

# CSP studies

This work was carried out in collaboration with Susan Reutzel-Edens and Rajni Miglani-Bhardwaj when they were working at Eli Lilly and the University of Strathclyde, respectively. A rigid molecule MOLPAK search was carried out in 2010, but this has not been published. This is called search B. A flexible CrystalPredictor search was carried out in 2013. This is called search A.

There were second derivative properties which could not be uploaded to the database, but the free energy corrections derived from these could.

|  |  |
| --- | --- |
| REFCODE | UNOGIN |
| Formula | C17 H20 N4 S1 |
| 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 |
|  |  |
| Search Identifier | A |
| 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. |
| Energy Model | 3 |
| Study\_ID | 30 (published) |
| 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 |
| Energy Model | 1 |
| Study\_ID | 20 |
| 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 |
| Energy Model | 2 |
| Study\_ID | 11 |
| 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 |
|  |  |
| Search Identifier | B |
| Scientist | Louise Price |
| Date | 2010 |
| Publication | Early search - not published |
| Energy Model | 1 |
| Study\_ID | 0 |
| Programs | Molpak, DMAREL (4.1.1) |
| Location on S Drive | \CHEMISTRY\_CPOSS\0-EarlySearches\home\louise\_price.eminerals\olanzapine |
| Potential Description | SCF 6-31G(d,p) DMA(v1.2)+ fit.pots+iso S |
| Energy Model | 2 |
| Study\_ID | 10 |
| Programs | Study\_ID=0, dmaflex, DMAREL (4.1.1) |
| Location on S Drive | \CHEMISTRY\_CPOSS\0-EarlySearches\home\louise\_price.eminerals\Olanzapine\_dmaflex |
| Potential Description | SCF 6-31G(d,p DMA(v1.2)+ fit.pots+iso S |

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

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 5.45 with Mar, Jun and Sep 2024 updates)

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 | 110.43 | 90 | 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 Reutzel-Edenswas 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.

A162 was originally thought to be the best match for form III, although Rajni Miglani Bhardwaj noted that there were problems with it and it wasn’t perfect which it is referred to it as a model for form III in that paper.4

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.