Supplementary Material (ESI) for Chemical Communications


# Tautomeric polymorphism in omeprazole

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**Supplementary Material (ESI)**
(15 pages)

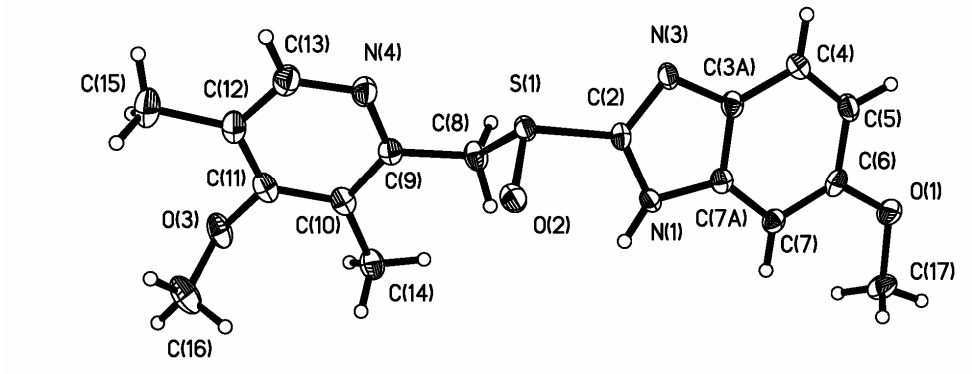


**Figure 1.** ORTEP diagram of omeprazole (**I**) at 50% probability level

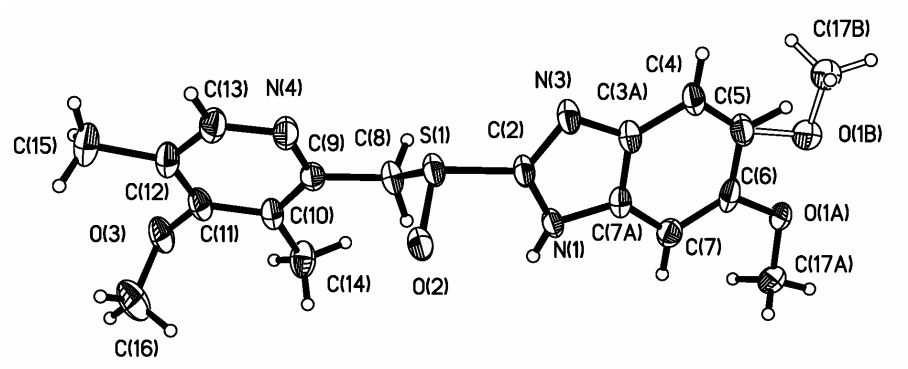


**Figure 2.** ORTEP diagram of omeprazole (**II**) at 50% probability level

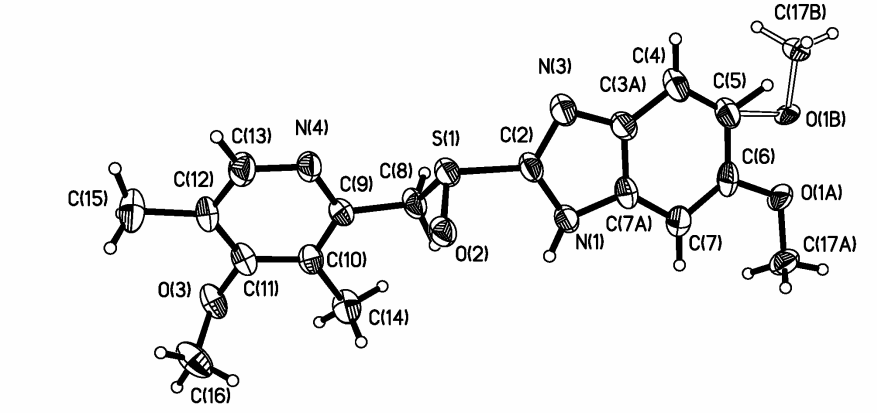


**Figure 3.** ORTEP diagram of omeprazole (**III**) at 50% probability level

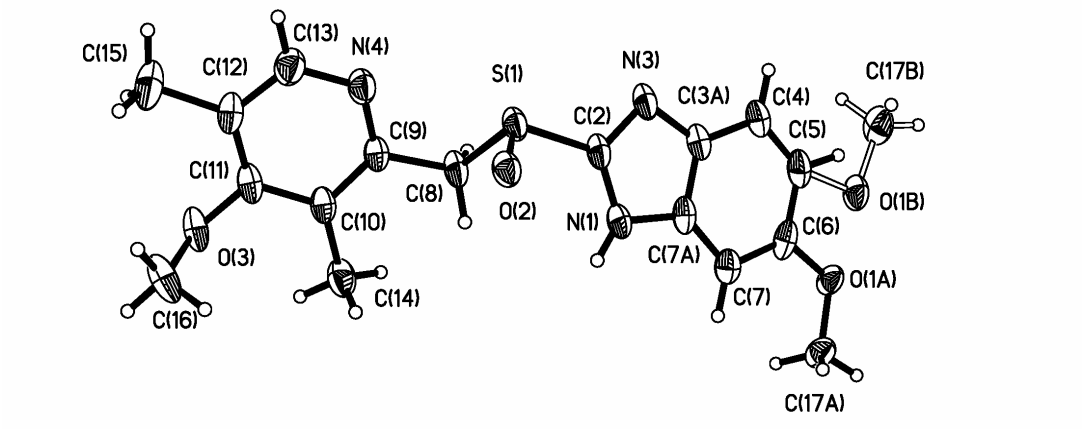


**Figure 4.** ORTEP diagram of omeprazole (**IV**) at 50% probability level

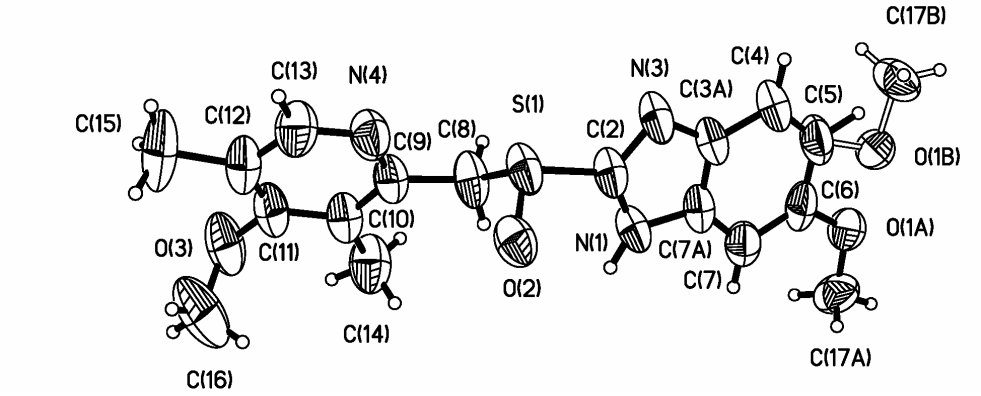


**Figure 5.** ORTEP diagram of omeprazole (**V**) at 50% probability level

**Simulated PXRD:** PXRDs were simulated from crystal structures using the Powder Cell 2.3 software. The wavelength 0.1540598 nm (Cu Kα) was used to generate simulated PXRD plots. For comparison of simulated PXRD with experimental PXRD, a temperature correction was made in the former by replacing the low temperature unit cell parameters with the room temperature ones.

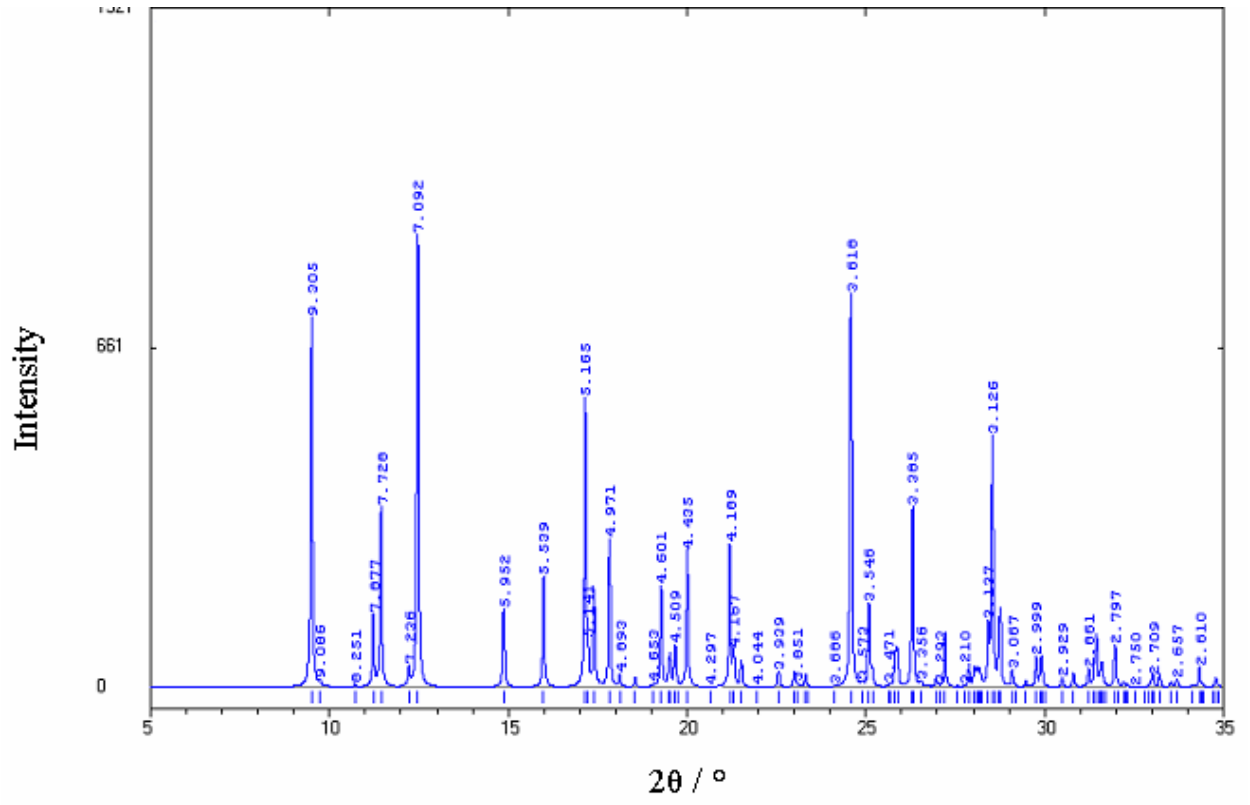


**Figure 6.** Simulated PXRD from single crystal X-ray data of omeprazole (**I**)

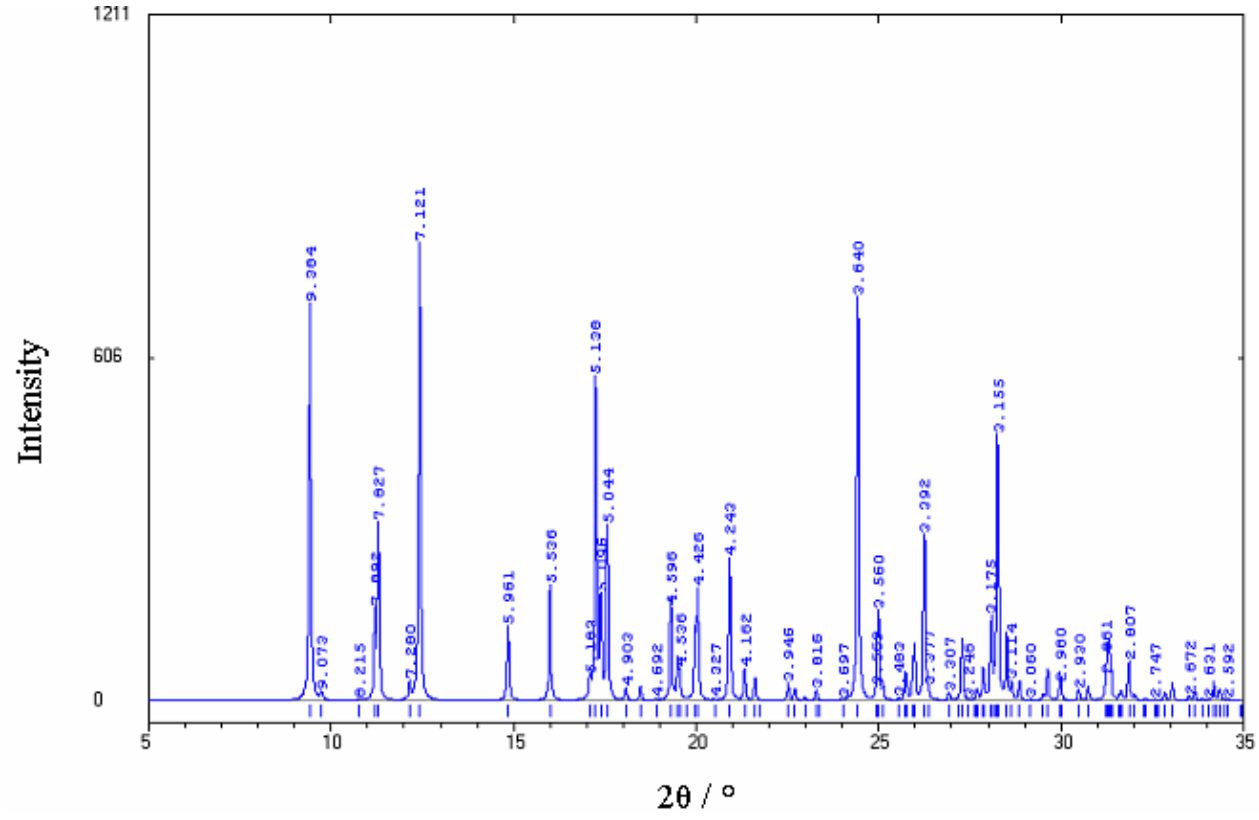


**Figure 7.** Simulated PXRD from single crystal X-ray data of omeprazole (**II**)

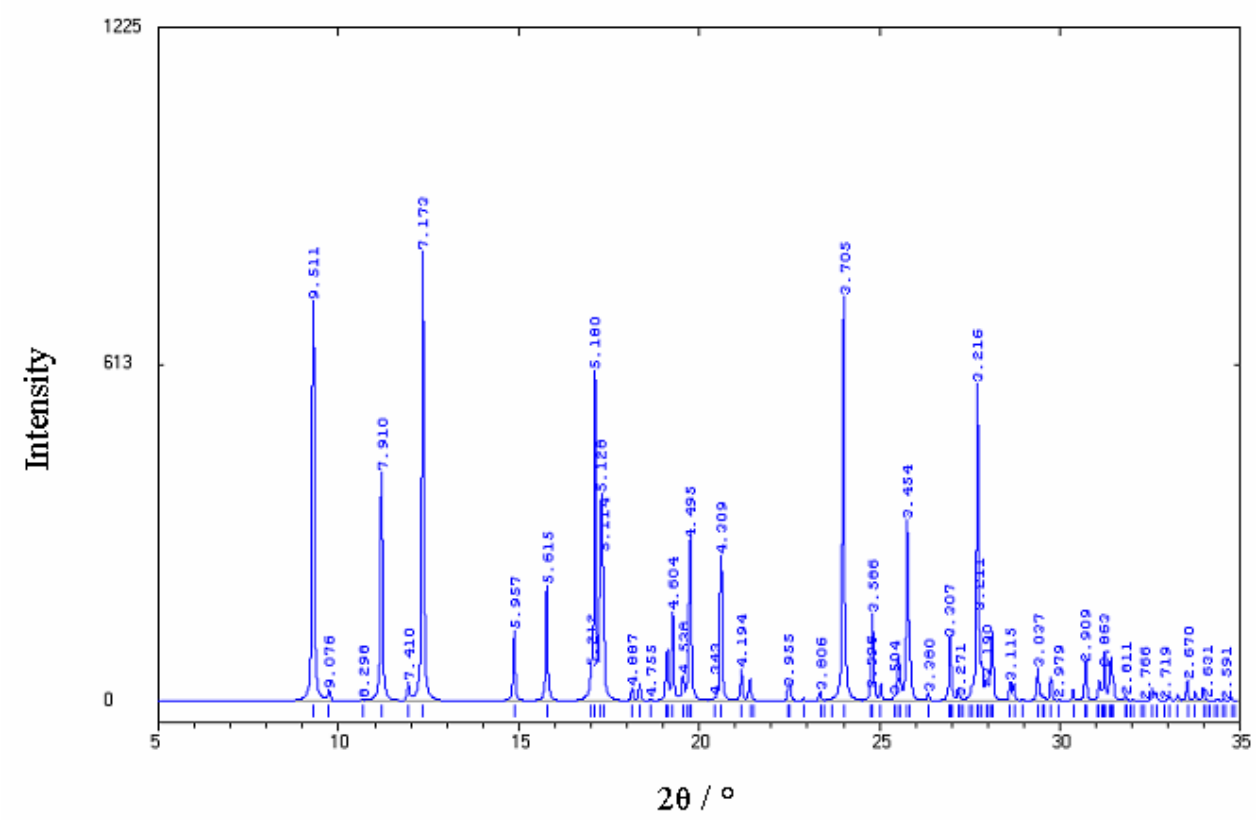


**Figure 8.** Simulated PXRD from single crystal X-ray data of omeprazole (**III**)

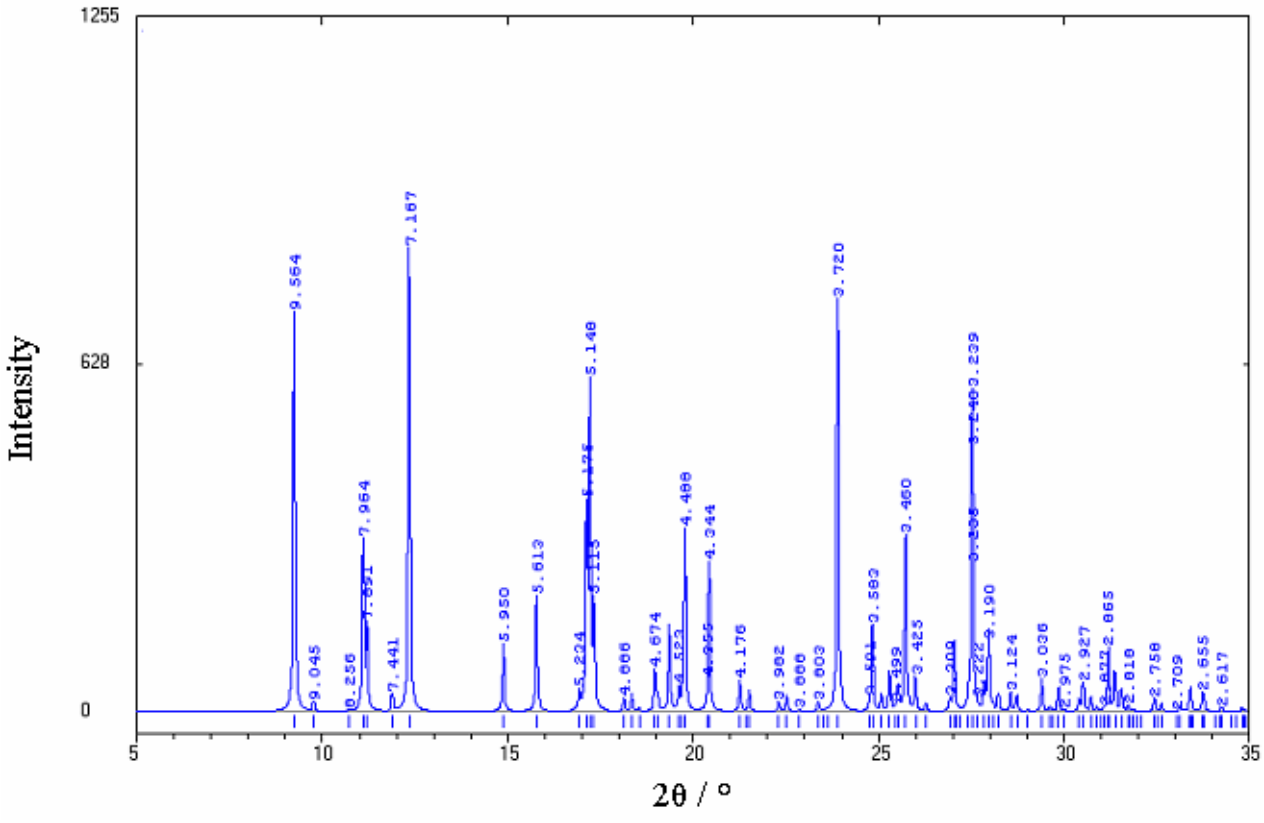


**Figure 9.** Simulated PXRD from single crystal X-ray data omeprazole (**IV**)

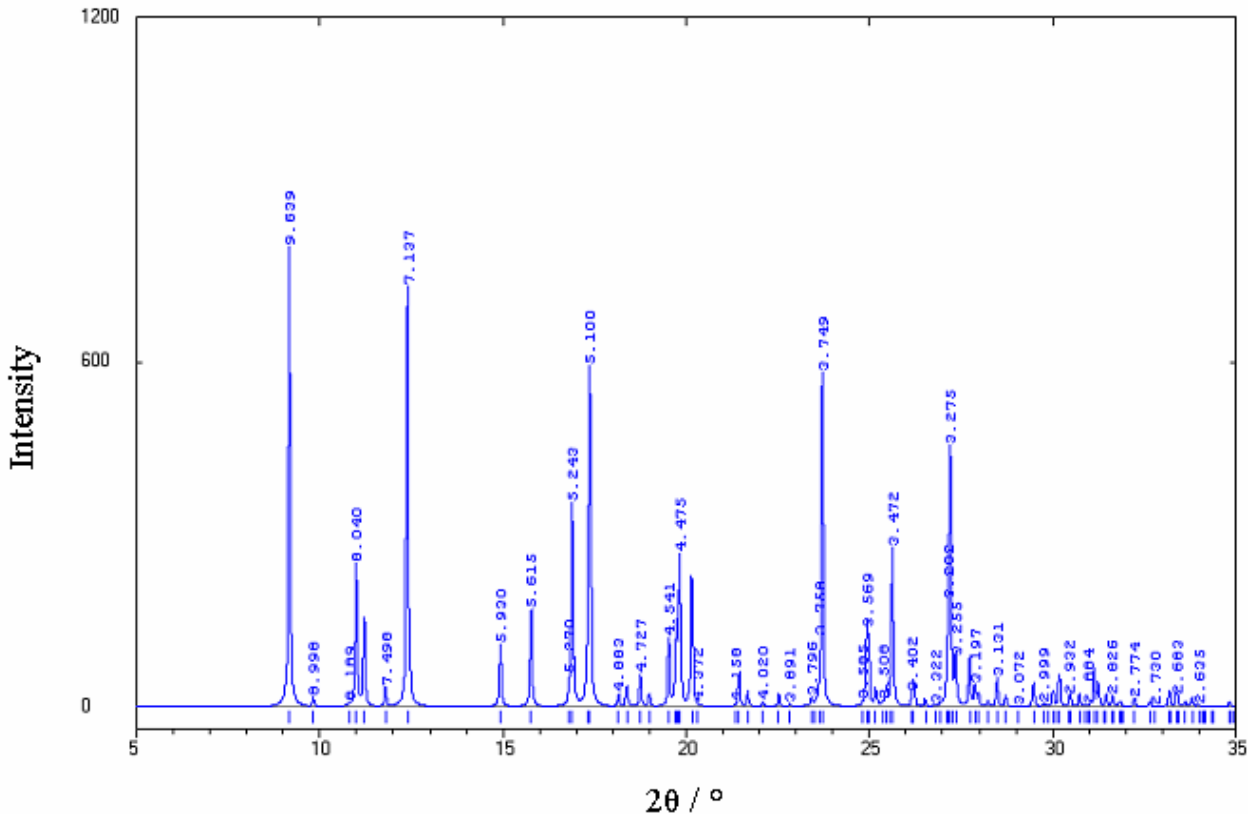


**Figure 10.** Simulated PXRD from single crystal X-ray data omeprazole (**V**)

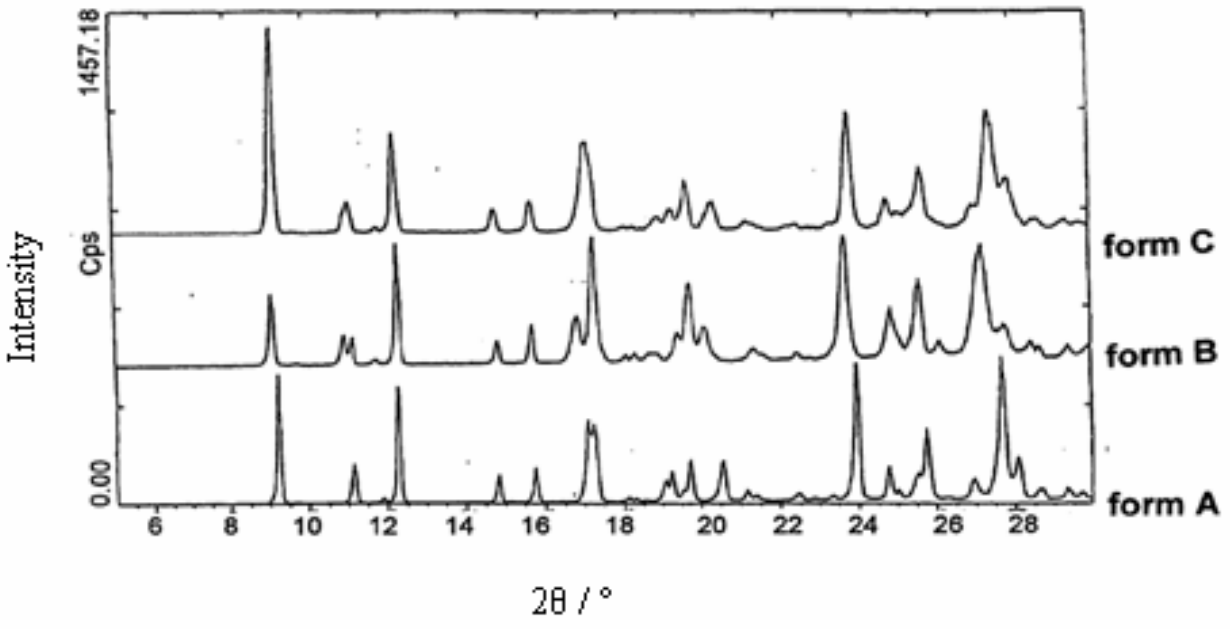


**Figure 11.** PXRD spectra of forms A, B and C given in the patent application US 2004/0122056 A1.

**Table 1.** d-values of PXRD pattern of form A, B and C reported in the patent application US 2004/0122056 A1.

d-values of omeprazole form C, form A and form B

| FORM C d-values (Å) | relative intensity | FORM A d-values (Å) | relative intensity | FORM B d-values (Å) | relative intensity |
|---|---|---|---|---|---|
| 9.5–9.6 | very strong | 9.5 | very strong | 9.6 | very strong |
| 7.9–8.0 | strong | 7.9 | strong | 8.0 | medium |
| 7.4–7.5 | weak | 7.4 | weak | 7.9 | medium |
| 7.2 | very strong | 7.2 | very strong | 7.5 | weak |
| 5.9–6.0 | medium | 6.0 | medium | 7.1 | very strong |
| 5.6 | medium | 5.6 | strong | 5.9 | medium |
| 5.1–5.2 | very strong | 5.2 | strong | 5.6 | medium |
| 4.88–4.90 | weak | 5.1 | strong | 5.3 | strong |
| 4.81–4.84 | weak | 4.89 | weak | 5.1 | strong |
| 4.65–4.67 | medium | 4.64 | medium | 4.54 | medium |
| 4.57–4.60 | medium | 4.60 | medium | 4.48 | strong |
| 4.48–4.51 | strong | 4.53 | weak | 4.41 | medium |
| 4.34–4.36 | medium | 4.49 | medium | 4.14 | weak |
| 4.16–4.19 | weak | 4.31 | medium | 3.75 | strong |
| 3.94–3.97 | weak | 4.19 | weak | 3.57 | medium |
| 3.72–3.73 | strong | 4.15 | weak | 3.47 | strong |
| 3.58–3.59 | medium | 3.95 | weak | 3.40 | weak |
| 3.46–3.47 | strong | 3.71 | strong | 3.28 | strong |
| 3.29–3.30 | medium | 3.59 | medium | 3.22 | medium |
| 3.23–3.25 | strong | 3.48 | medium | 3.02 | weak |
| 3.19–3.20 | medium | 3.45 | strong | | |
| 3.11–3.12 | weak | 3.31 | weak | | |
| 3.03–3.04 | weak | 3.22 | strong | | |
| | | 3.17 | medium | | |
| | | 3.11 | weak | | |
| | | 3.04 | weak | | |
| | | 3.00 | weak | | |

**Crystallisation Procedures:**

(1) Crystals of **I** were grown by dissolving 30 mg of omeprazole in 10 ml 2 % methanolic solution of NaOH in a 25 conical flask and then allowing it to evaporate slowly for a period of 2 days at ambient condition.

(2) Crystals of **II** were grown by dissolving 30 mg of omeprazole in 10 ml methanol containing 8-9 drops of 25% ammonia solution in a 25 ml conical flask and then allowing it to stand for a period of 3 days at ambient condition.

(3) Crystals of **III** were grown by dissolving 30 mg of omeprazole in10 ml methanol containing 4-5 drops of 25% ammonia solution in a 25 ml conical flask and then allowing it to stand for a period of 3 days in a refrigerator at around 5 °C.

(4) Crystals of **IV** were grown by dissolving 20 mg of omeprazole in 10 ml acetone in a 25 ml conical flask and then allowing it to stand for a period of 3 days in a refrigerator at around 5 °C.

(5) Crystals of **V** were grown by dissolving 30 mg of omeprazole in 10 ml chloroform in a 25 ml conical flask and then allowing it to stand for a period of 3 days at ambient temperature.

**Reported structures of omeprazole in literature:**

The crystals of omeprazole were obtained from chloroform by Ohishi *et al*. in 1989 communication (see ref. 20 in text). This structure was solved and refined as if it contains only **2.** However, the simulated PXRD matches with the sample containing 15% tautomer **1** which was also obtained by us from chloroform, as well as with the experimental PXRD of form B reported in the patent application. The simulated PXRD of the 1989 structure is shown below in fig 12. The crystals of omeprazole were obtained from butanone by Deng *et al*. in their 2000 paper (see ref. 21 in text). This structure also did not consider the possibility of tautomer **1** and the refinement was carried out as if the crystal contains only tautomer **2**. The simulated PXRD of the structure is similar to that of the 1989 structure except for a few peaks around d-

spacing 5.1-5.0, 3.5-3.4 and 3.3-3.2. The simulated PXRD of the 2000 structure is shown below in fig 13.

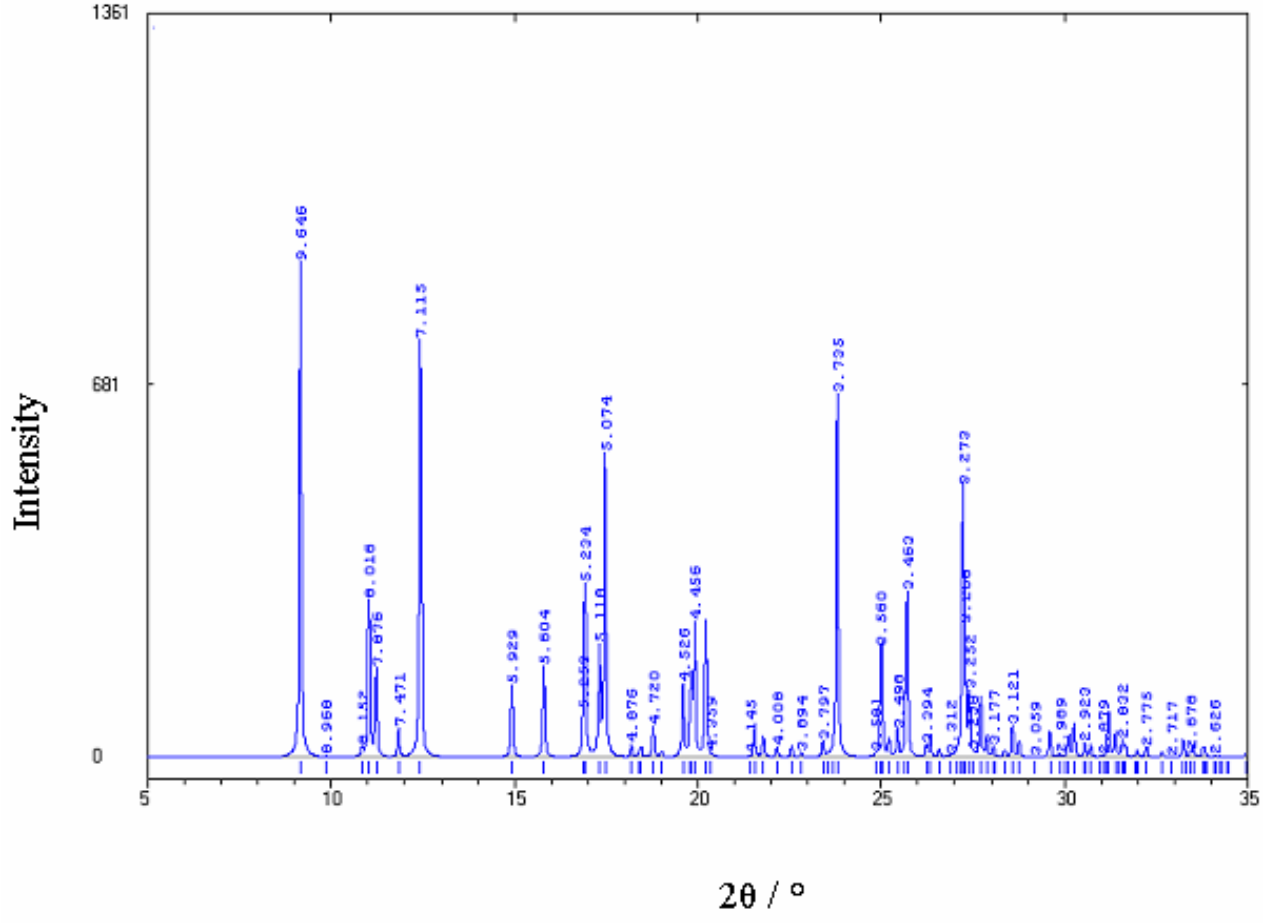


**Figure 12.** Simulated PXRD of the 1989 omeprazole structure (Ohishi *et al*.).

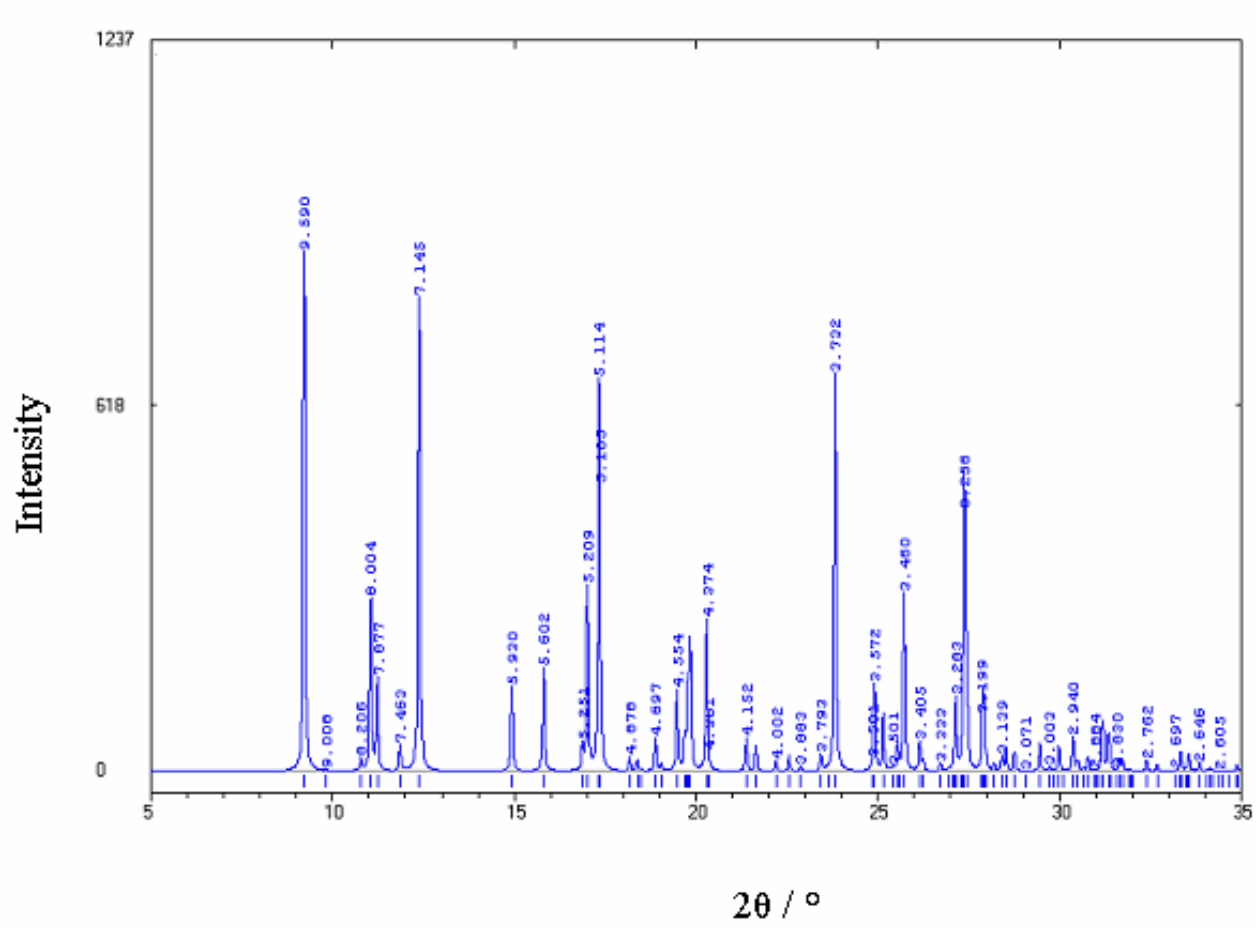


**Figure 13.** Simulated PXRD of the 2000 omeprazole structure (Deng *et al*.).

**Crystal packing of Omeprazole**

The crystal structure of omeprazole is mainly made up of N–H…O=S dimers. The modeling of the structure is done so that either tautomer may be present at any site in the crystal. Inspection of the packing reveals that there is enough space in the structure so that the change in the position of the methoxy group can be accommodated. In the 6-methoxy dimer, the 6-methoxy group of one molecule close packs with the methoxy group on the benzene ring of the other molecule (see fig 14) while in the 5-methoxy dimer, the 5-methoxy group of one molecule is on the opposite side of the methoxy group on the benzene ring of the other molecule (see

fig 15). There are no strong interactions in the structure except for the N–H…O hydrogen bonds. However, there is a weak C–H…O dimer between the hydrogen of the methylene group of one molecule and the oxygen of the sulfoxide group of the other molecule.

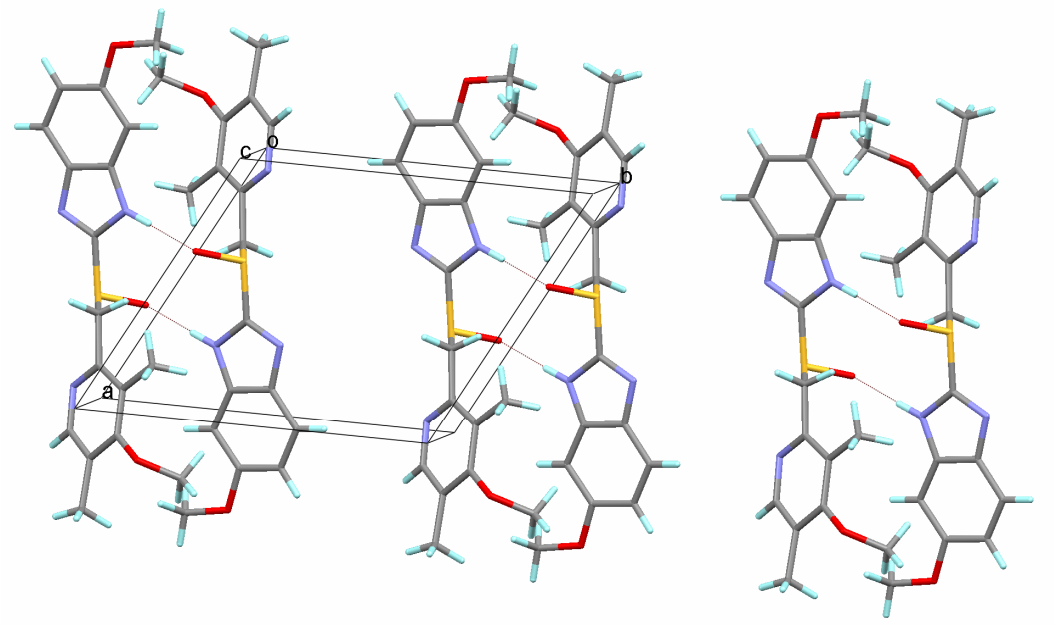


**Figure 14.** Dimers of the 6-methoxy tautomer. View down c-axis.

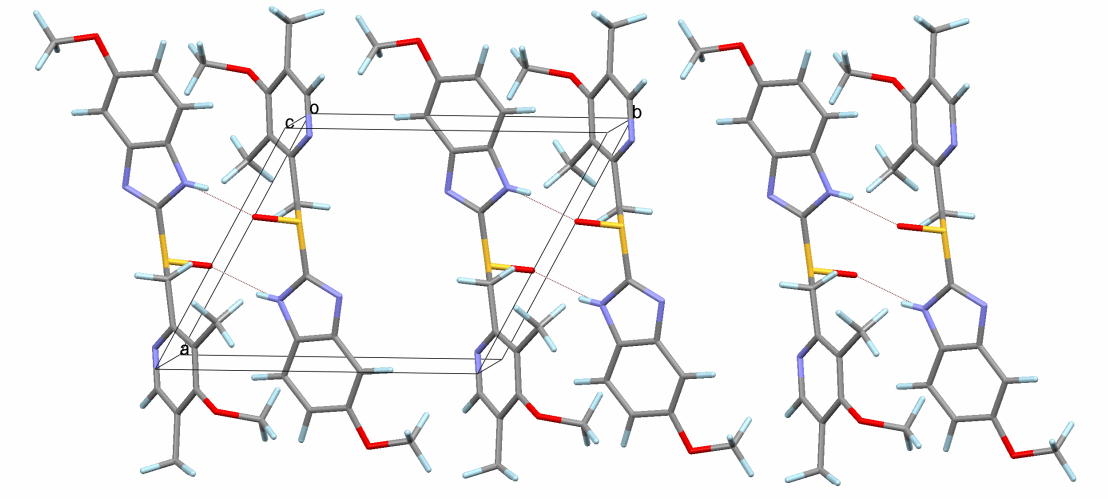


**Figure 15.** Idealised dimers of the 5-methoxy tautomer. View down c-axis.

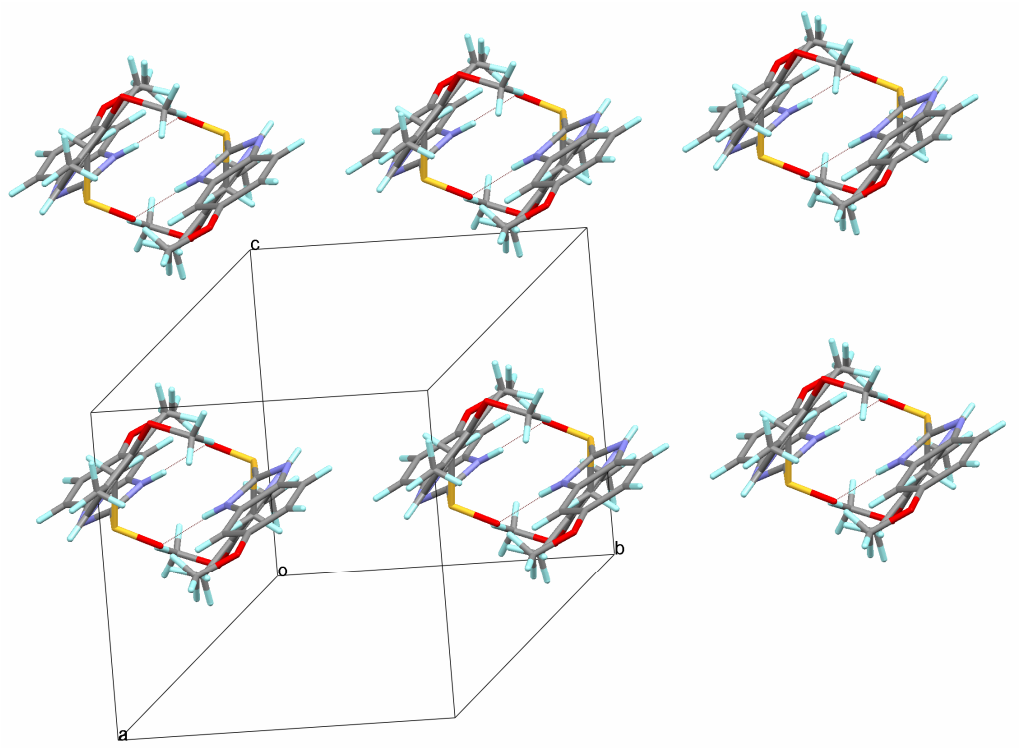


**Figure 16.** Packing of 6-methoxy dimers. Viewed perpendicular to the dimers.

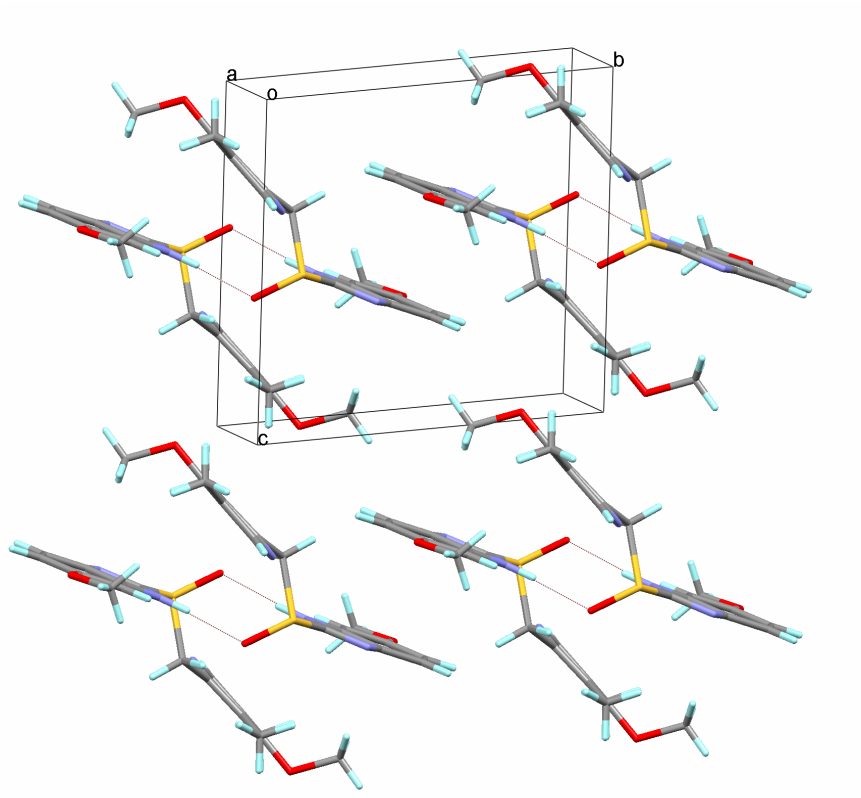


**Figure 17.** Packing of 6-methoxy dimers. Viewed down the a-axis.

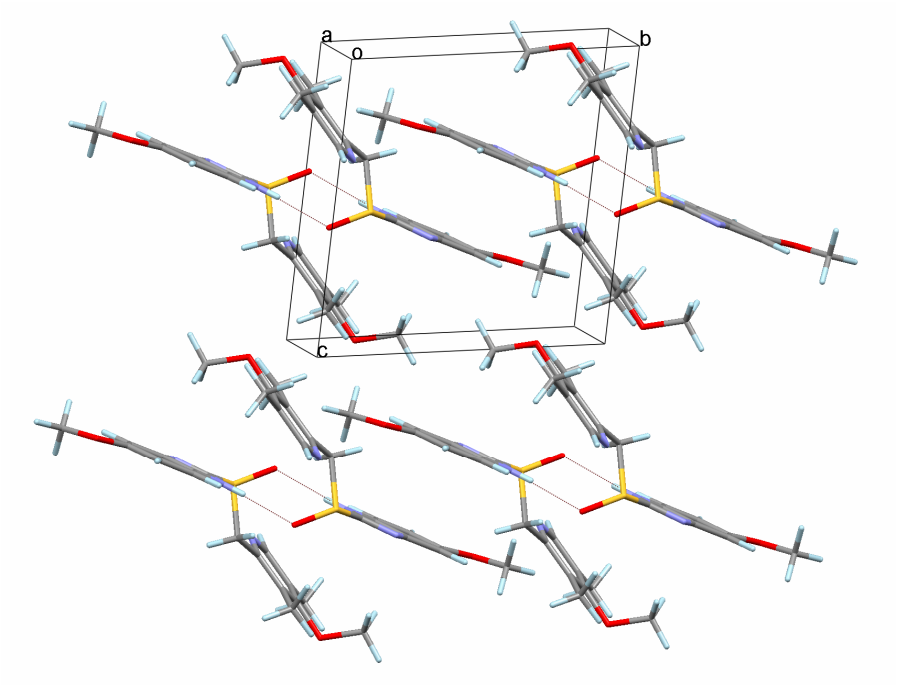


**Figure 18.** Packing of idealised 5-methoxy dimers. Viewed down the a-axis.

**Res. File of the idealised 5-methoxy structure.**

```
TITL ppp in P-1
CELL 0.71073 9.7014 10.2585 10.6942 91.72 112.117 115.642
ZERR 2 0.003 0.003 0.003 0.004 0.004 0.004
LATT 1
SFAC C H N O S
UNIT 34 38 6 6 2
FVAR       1.00000
C17B  1   1.29000   0.89500   0.82000   1.00000   0.20013
H4    2   0.71555   0.17164   0.52984   1.00000   0.02910
H6    2   0.36358   0.22753   0.34050   1.00000   0.07358
H7    2   0.41078   0.08566   0.36825   1.00000   0.14087
S1    5   0.41245   0.17489   0.54396   1.00000   0.04457   0.06009 =
     0.06332  -0.01042   0.02281   0.00362
O2    4   0.39242   0.03415   0.58967   1.00000   0.05685   0.05928 =
     0.07144   0.00405   0.03482   0.01266
N1    3   0.73360   0.24535   0.56675   1.00000   0.05556   0.04649 =
     0.05521  -0.00837   0.01624   0.00385
N3    3   0.06818   0.05377   0.34500   1.00000   0.05367   0.06867 =
     0.07689   0.00331   0.02727   0.01493
C1    1   0.89293   0.36975   0.62248   1.00000   0.04179   0.06024 =
     0.04556   0.00791   0.01261   0.01000
C2    1   0.87410   0.48046   0.67779   1.00000   0.04896   0.05497 =
     0.04784  -0.00591   0.00955   0.00630
O3    4  -0.16944  -0.25846  -0.02362   1.00000   0.07527   0.10150 =
     0.04326   0.00099   0.01202  -0.00110
N2    3   0.70948   0.42911   0.65961   1.00000   0.05101   0.06388 =
     0.05457  -0.01275   0.01638   0.00509
C3    1   0.63179   0.28996   0.59218   1.00000   0.04077   0.05951 =
     0.05737  -0.00309   0.01789   0.00342
C4    1   1.04269   0.38794   0.62581   1.00000   0.05806   0.05727 =
     0.06223   0.01003   0.01890   0.01882
C5    1   0.15725   0.02924   0.28519   1.00000   0.04504   0.05808 =
     0.05884   0.00832   0.02049   0.00897
C6    1   0.34929   0.12972   0.35974   1.00000   0.04581   0.07373 =
     0.06183   0.00139   0.01840   0.00230
C7    1   0.08484  -0.07576   0.16492   1.00000   0.04640   0.06594 =
     0.04604   0.01107   0.01536   0.01187
C8    1   1.16276   0.64457   0.74212   1.00000   0.05378   0.06415 =
     0.07232  -0.00445   0.00407  -0.00176
C9    1  -0.18814  -0.13359   0.15662   1.00000   0.04585   0.08577 =
     0.06376   0.01880   0.01826   0.00845
C10   1   1.17867   0.52883   0.68647   1.00000   0.03564   0.07219 =
     0.06348   0.01691   0.01002   0.00990
C11   1  -0.09842  -0.02560   0.28092   1.00000   0.05708   0.08414 =
     0.09194   0.02087   0.03569   0.02121
C12   1   1.01415   0.62369   0.73850   1.00000   0.05663   0.06002 =
     0.06883  -0.01216   0.01267   0.00802
```

C13 1 -0.08950 -0.15611 0.10192 1.00000 0.05731 0.06420 =
0.04725 0.01269 0.01080 0.00469
C14 1 0.18978 -0.10689 0.10265 1.00000 0.07783 0.11556 =
0.06669 4.00000 0.03683 0.03044
C15 1 -0.38108 -0.21022 0.08581 1.00000 0.03726 0.16998 =
0.10209 0.03351 0.00773 0.00801
C16 1 -0.20136 -0.41034 -0.01006 1.00000 0.16903 0.06891 =
0.08224 -0.00739 0.04244 -0.00059
O1B 4 1.31932 0.77445 0.78235 1.00000 0.34767
H 2 1.19006 0.89751 0.73115 1.00000 0.06000
H 2 1.40533 0.99986 0.85250 1.00000 0.06000
H 2 1.25286 0.87702 0.90427 1.00000 0.06000
H 2 -0.08204 -0.40890 0.04895 1.00000 0.06000
H 2 -0.26361 -0.48243 -0.11219 1.00000 0.06000
H 2 -0.28186 -0.45124 0.04303 1.00000 0.06000
H 2 0.26697 -0.00665 0.07908 1.00000 0.06000
H 2 0.10538 -0.19368 0.00839 1.00000 0.06000
H 2 0.27096 -0.14227 0.17658 1.00000 0.06000
H 2 -0.43057 -0.26748 0.15502 1.00000 0.06000
H 2 -0.42726 -0.28966 -0.00829 1.00000 0.06000
H 2 -0.42264 -0.12803 0.06035 1.00000 0.06000
H 2 1.30051 0.55081 0.69134 1.00000 0.06000
H 2 1.05363 0.29749 0.58353 1.00000 0.06000
H 2 -0.17100 -0.00579 0.32786 1.00000 0.06000
H 2 1.00300 0.71397 0.78083 1.00000 0.06000

END