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7-Methoxy-4-morpholino-6-(3-morpholinopropoxy)quinazoline trihydrate

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.007 Å
R factor = 0.080
wR factor = 0.205
Data-to-parameter ratio = 15.9

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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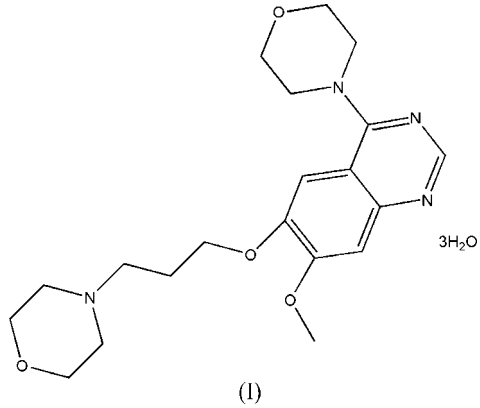
In the title compound, $C_{20}H_{28}N_4O_4\cdot 3H_2O$, the two morpholine rings adopt chair conformations. The crystal packing is stabilized by intermolecular O—H···N and O—H···O hydrogen bonds involving the water moleucles.

Comment

Epidermal growth factor receptor (EGFR) has become one of the significant target proteins in drug discovery (Kamath & Buolamwini, 2006), since its excess always leads to a variety of cancers. Among the small molecular inhibitors of EGFR, the quinazoline ring system, including 4-anilinoquinazoline and its derivatives, has been widely investigated. Many small molecular inhibitors of EGFR are used as anticancer drugs (Speake *et al.*, 2005), such as gefitinib (Levin *et al.*, 2002) and erlotinib (Sorbera *et al.*, 2002). As part of our studies in this area, we have focused our attention on 4-aminoquinazoline derivatives, and now report the synthesis and structure of the title compound, (I) (Fig. 1).



(I)

In compound (I), the two morpholine rings adopt chair conformations. For the C17–C20/N4/O4 ring, N4 and O4 deviate from the mean plane of C17/C18/C19/C20 by 0.627 (6) and −0.641 (6) Å, respectively. Atoms N1 and O1 deviate from the plane of C1–C4 by 0.655 (7) and −0.624 (7) Å, respectively.

In the crystal structure of (I), the constituent species interact by way of O—H···N and O—H···O hydrogen bonds (Table 1 and Fig. 2), involving the water molecules.

Experimental

Potassium iodide (0.1 g) was added to a solution of 4-chloro-6-(3-chloropropoxy)-7-methoxyquinazoline (0.51 g, 1.8 mmol) in morpholine (10 ml) and the mixture was stirred at 343 K for 15 min.

Water (50 ml) was added to the reaction mixture, which was then extracted with chloroform (3 × 10 ml), washed with brine (10 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was crystallized from ethyl acetate, to afford the title compound as a crystalline solid. Crystals of (I) were obtained from ethyl acetate, by slow evaporation at room temperature (m.p. 372–373 K). Analysis calculated for $C_{20}H_{34}N_4O_7$: C 54.28, H 7.74, N 12.66%; found C 54.37, H 7.82, N 12.80%.

Crystal data

$C_{20}H_{28}N_4O_4\cdot 3H_2O$
M_r = 442.51
Monoclinic, $P2_1/c$
a = 10.437 (2) Å
b = 10.438 (2) Å
c = 21.004 (4) Å
β = 97.17 (3)°
V = 2270.3 (8) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.10 mm^{-1}
T = 293 (2) K
0.40 × 0.20 × 0.10 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.962, T_{max} = 0.990
4457 measured reflections
4457 independent reflections
2267 reflections with $I > 2\sigma(I)$
3 standard reflections
every 200 reflections
intensity decay: ?

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.080
$wR(F^2)$ = 0.205
S = 1.01
4457 reflections
280 parameters
23 restraints
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.93 e Å^{-3}
$\Delta\rho_{min}$ = −0.42 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
OW2—HW2B···OW3	0.85	2.22	2.787 (5)	125
OW3—HW3B···OW1	0.85	2.14	2.747 (5)	128
OW3—HW3A···N2	1.01	1.84	2.836 (5)	167
OW1—HW1A···OW2^{i}	0.85	2.15	2.715 (5)	123
OW1—HW1B···N1^{ii}	1.06	1.95	2.899 (5)	148
OW2—HW2A···O1^{iii}	0.85	2.11	2.834 (5)	143

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

The H atoms bonded to C atoms were placed in calculated positions, with C—H = 0.96–0.97 Å, and refined as riding, with U_{iso}(H) = 1.2U_{eq}(C) or 1.5U_{eq}(methyl C). The water H atoms were located in a difference map and refined as riding in their as-found relative positions with U_{iso}(H) = 1.2U_{eq}(O). Atoms C5, C6 and C7 were restrained so that their U^{ij} components approximated to isotropic behavior.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989); cell refinement: *CAD-4 Software*; data reduction: *XCAD4* (Harms & Wocadlo, 1995); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997*a*); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997*a*); molecular graphics: *SHELXTL* (Sheldrick, 1997*b*); software used to prepare material for publication: *SHELXL97*.

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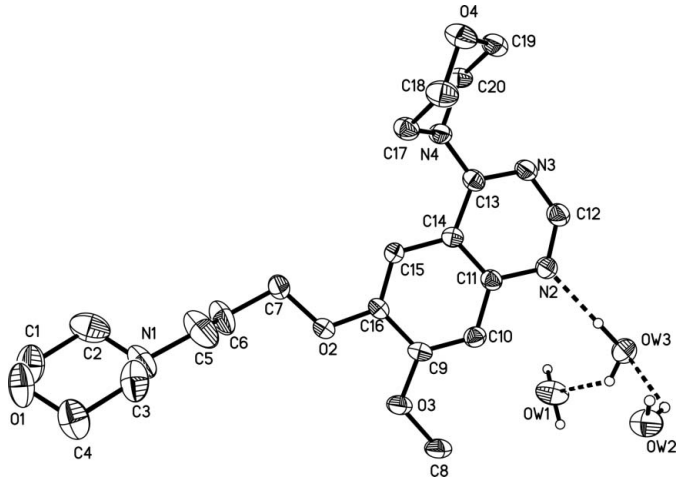

Figure 1
The molecular structure of (I) showing 40% displacement ellipsoids (arbitrary spheres for the water H atoms; other H atoms omitted for clarity). Dashed lines indicate hydrogen bonds.

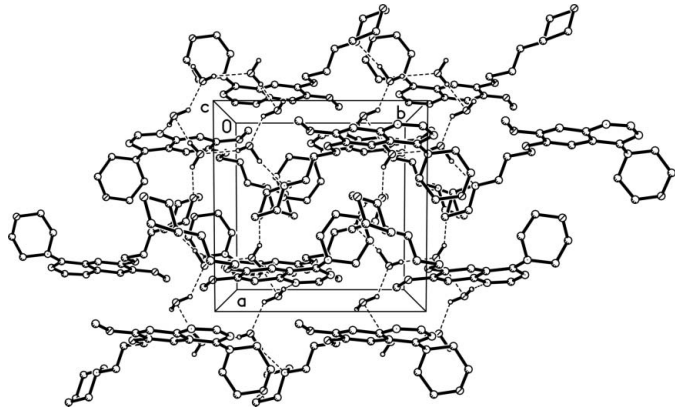

Figure 2
The packing of (I). Hydrogen bonds are shown as dashed lines, and the H atoms not involved in the hydrogen bonds have been omitted for clarity.

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