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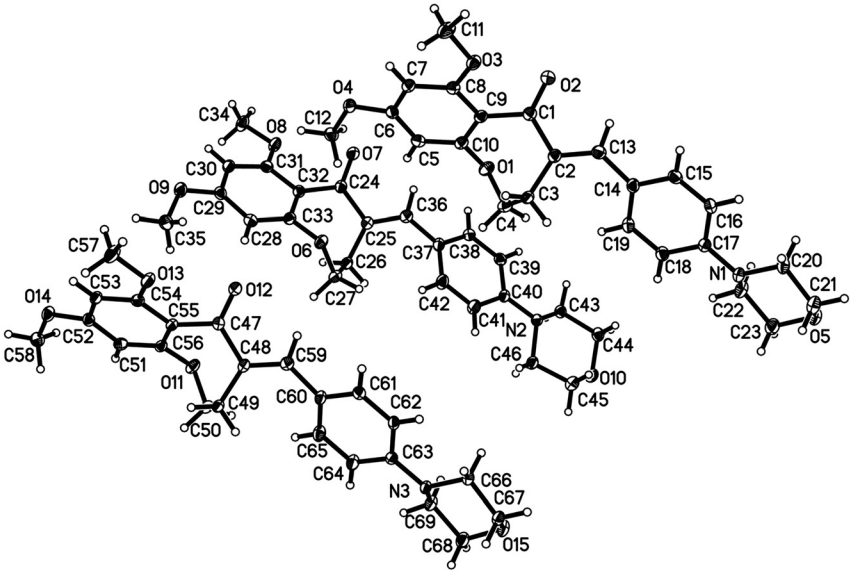
Crystal structure of (*E*)-6,8-dimethoxy-4-(4-morpholinobenzylidene)-3,4-dihydro-1-benzoxepin-5(*2H*)-one, $C_{23}H_{25}NO_5$



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Abstract

$C_{23}H_{25}NO_5$, monoclinic, *Cc* (no. 9), *a* = 21.2548(2) Å, *b* = 20.4713(1) Å, *c* = 16.7944(1) Å, *β* = 126.267(1)°, *V* = 5,891.79(10) Å^3, *Z* = 12, $R_{gt}(F)$ = 0.0240, $wR_{ref}(F^2)$ = 0.0649, T = 293 K.

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The crystal structure is shown in figure. Displacement ellipsoids are drawn at the 30 % probability level. There are three drug molecules.

Tables 1 and 2 contain details on crystal structure and measurement conditions and a list of the atoms including atomic coordinates and displacement parameters.

Table 1: Data collection and handling.

Crystal:	Yellow block
Size:	0.16 × 0.13 × 0.10 mm
Wavelength:	Cu *K*α radiation (1.54178 Å)
μ:	0.77 mm^{-1}
Diffractometer, scan mode:	Four-circle diffractometer, *ω*
θ_{max}, completeness:	74.3°, >99 %
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	16,377, 7,213, 0.013
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\sigma(I_{obs})$, 7,174
$N(param)_{refined}$:	791
Programs:	CrysAlis^{PRO},[1] SHELX[2,3]

1 Source of material

According to the literature synthetic strategies,[4,5] morpholine (13.94 g, 0.16 mol) and potassium carbonate (27.64 g, 0.20 mol) have been stirred overnight at 313 K with N,N-dimethylformamide (10 mL) as solvent. Then *p*-fluorobenzaldehyde (2.48 g, 0.02 mol) was added to the mixture and the temperature was raised to 393 K for 5 h reflux reaction. Thin-layer chromatography (TLC, dichloromethane: methanol = 15:1, *v*:*v*) was used to observe the reaction process. After the reaction, the system was purified by extraction, vacuum distillation and silica gel column (dichloromethane: methanol = 20:1, *v*:*v*) to obtain the intermediate. Using 25 % sodium hydroxide

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Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2).

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
C1	0.54398 (9)	0.35949 (7)	0.17591 (12)	0.0172 (3)
C2	0.61248 (9)	0.37213 (7)	0.28030 (11)	0.0167 (3)
C3	0.59643 (9)	0.37333 (7)	0.35678 (11)	0.0169 (3)
H3A	0.552902	0.402441	0.334431	0.020*
H3B	0.641730	0.390861	0.417946	0.020*
C4	0.57761 (10)	0.30619 (8)	0.37705 (11)	0.0202 (3)
H4A	0.625927	0.282273	0.420708	0.024*
H4B	0.553649	0.311751	0.410996	0.024*
C5	0.38819 (10)	0.27750 (8)	0.18550 (11)	0.0173 (3)
H5	0.385349	0.245559	0.222654	0.021*
C6	0.32083 (9)	0.30455 (8)	0.10286 (11)	0.0162 (3)
C7	0.32489 (9)	0.35432 (7)	0.04865 (11)	0.0162 (3)
H7	0.279526	0.373488	−0.004755	0.019*
C8	0.39724 (9)	0.37462 (7)	0.07556 (11)	0.0159 (3)
C9	0.46663 (9)	0.34612 (7)	0.15657 (11)	0.0157 (3)
C10	0.45983 (9)	0.29939 (7)	0.21119 (11)	0.0163 (3)
C11	0.33859 (10)	0.45167 (9)	−0.05637 (12)	0.0265 (4)
H11A	0.307544	0.470036	−0.037633	0.040*
H11B	0.308902	0.418934	−0.106124	0.040*
H11C	0.353232	0.485501	−0.082071	0.040*
C12	0.23896 (10)	0.24172 (8)	0.12622 (12)	0.0212 (3)
H12A	0.258069	0.199541	0.124895	0.032*
H12B	0.184952	0.238316	0.100369	0.032*
H12C	0.268513	0.257338	0.193016	0.032*
C13	0.68063 (9)	0.38524 (8)	0.29453 (12)	0.0189 (3)
H13	0.677337	0.387661	0.236869	0.023*
C14	0.75851 (9)	0.39625 (8)	0.38481 (12)	0.0179 (3)
C15	0.81178 (10)	0.43401 (8)	0.38076 (12)	0.0188 (3)
H15	0.794998	0.454044	0.321544	0.023*
C16	0.88841 (9)	0.44233 (8)	0.46206 (12)	0.0180 (3)
H16	0.921835	0.468016	0.456703	0.022*
C17	0.91622 (9)	0.41241 (7)	0.55248 (11)	0.0156 (3)
C18	0.86251 (9)	0.37606 (8)	0.55776 (12)	0.0183 (3)
H18	0.878749	0.357238	0.617511	0.022*
C19	0.78640 (10)	0.36780 (8)	0.47622 (12)	0.0187 (3)
H19	0.752710	0.342773	0.481900	0.022*
C20	1.04693 (10)	0.45739 (8)	0.62867 (12)	0.0207 (3)
H20A	1.023136	0.499309	0.599205	0.025*
H20B	1.057404	0.435442	0.586458	0.025*
C21	1.12287 (10)	0.46767 (8)	0.73070 (13)	0.0245 (4)
H21A	1.158562	0.492693	0.724576	0.029*
H21B	1.112460	0.492745	0.770744	0.029*
C22	1.03072 (9)	0.35719 (8)	0.69108 (12)	0.0217 (3)
H22A	1.039939	0.329113	0.652418	0.026*
H22B	0.995968	0.334443	0.701253	0.026*
C23	1.10725 (10)	0.37099 (9)	0.78990 (13)	0.0260 (4)
H23A	1.097306	0.395375	0.830924	0.031*
H23B	1.131749	0.329998	0.822889	0.031*
C24	0.30430 (9)	0.10507 (7)	0.27271 (11)	0.0171 (3)
C25	0.37854 (9)	0.10832 (8)	0.37533 (11)	0.0167 (3)
C26	0.37005 (9)	0.11826 (7)	0.45764 (11)	0.0172 (3)
H26A	0.418239	0.105499	0.519723	0.021*
H26B	0.328873	0.090040	0.446490	0.021*
C27	0.35121 (9)	0.18851 (8)	0.46562 (11)	0.0197 (3)
H27A	0.327716	0.189488	0.500570	0.024*
H27B	0.399180	0.213598	0.503629	0.024*
C28	0.16168 (10)	0.21327 (7)	0.28023 (11)	0.0167 (3)
H28	0.163417	0.249245	0.315305	0.020*
C29	0.09116 (9)	0.18700 (8)	0.20363 (11)	0.0168 (3)
C30	0.08817 (9)	0.13104 (8)	0.15340 (11)	0.0174 (3)
H30	0.040305	0.113844	0.102019	0.021*
C31	0.15708 (9)	0.10142 (7)	0.18080 (11)	0.0167 (3)
C32	0.23070 (9)	0.12890 (7)	0.25507 (11)	0.0161 (3)
C33	0.23001 (9)	0.18456 (7)	0.30355 (11)	0.0158 (3)
C34	0.08455 (10)	0.01270 (9)	0.07284 (13)	0.0258 (4)
H34A	0.060411	0.003914	0.105226	0.039*
H34B	0.092615	−0.027624	0.050878	0.039*
H34C	0.051311	0.040663	0.017047	0.039*
C35	0.01753 (10)	0.26150 (8)	0.22797 (12)	0.0228 (3)
H35A	0.042466	0.245701	0.294070	0.034*
H35B	−0.035776	0.272331	0.199639	0.034*
H35C	0.044332	0.299706	0.229313	0.034*
C36	0.44537 (9)	0.09920 (7)	0.38498 (12)	0.0184 (3)
H36	0.439314	0.091482	0.326226	0.022*
C37	0.52585 (9)	0.09955 (8)	0.47324 (12)	0.0180 (3)
C38	0.58103 (10)	0.05956 (8)	0.47722 (12)	0.0188 (3)
H38	0.564955	0.032979	0.423379	0.023*
C39	0.65846 (10)	0.05801 (8)	0.55801 (12)	0.0182 (3)
H39	0.692794	0.029938	0.557866	0.022*
C40	0.68625 (9)	0.09836 (7)	0.64075 (11)	0.0160 (3)
C41	0.63068 (10)	0.13844 (8)	0.63726 (13)	0.0227 (4)
H41	0.646427	0.164982	0.691016	0.027*
C42	0.55377 (10)	0.13920 (8)	0.55626 (13)	0.0224 (3)
H42	0.519124	0.166846	0.556425	0.027*
C43	0.81545 (9)	0.04824 (8)	0.73068 (12)	0.0177 (3)
H43A	0.806508	0.040821	0.667670	0.021*
H43B	0.802393	0.008376	0.749143	0.021*
C44	0.90069 (9)	0.06415 (8)	0.80789 (12)	0.0199 (3)
H44A	0.932090	0.026551	0.816953	0.024*
H44B	0.915531	0.100057	0.784479	0.024*
C45	0.87093 (10)	0.13710 (8)	0.88768 (12)	0.0209 (3)
H45A	0.884166	0.173433	0.863070	0.025*
H45B	0.882885	0.149701	0.950955	0.025*
C46	0.78463 (9)	0.12274 (8)	0.81608 (11)	0.0182 (3)
H46A	0.770381	0.089016	0.843290	0.022*
H46B	0.755063	0.161767	0.806675	0.022*
C47	0.16961 (9)	0.37269 (8)	0.46108 (12)	0.0192 (3)
C48	0.23909 (9)	0.38163 (8)	0.56663 (11)	0.0164 (3)
C49	0.22389 (9)	0.37692 (7)	0.64359 (11)	0.0154 (3)
H49A	0.178586	0.403183	0.622839	0.019*
H49B	0.268253	0.394731	0.705361	0.019*
C50	0.20997 (9)	0.30699 (8)	0.66056 (11)	0.0183 (3)
H50A	0.259718	0.284667	0.702138	0.022*
H50B	0.186202	0.307595	0.695170	0.022*
C51	0.02246 (10)	0.27728 (7)	0.47469 (11)	0.0169 (3)
H51	0.022896	0.243855	0.512507	0.020*
C52	−0.04731 (9)	0.30327 (7)	0.39494 (11)	0.0159 (3)
C53	−0.04799 (9)	0.35487 (7)	0.33958 (11)	0.0157 (3)
H53	−0.095119	0.372471	0.287162	0.019*

Table 2: (continued)

Atom	x	y	z	U_{iso}*/U_{eq}
C54	0.02190 (9)	0.37952 (8)	0.36337 (11)	0.0158 (3)
C55	0.09430 (9)	0.35283 (8)	0.44247 (11)	0.0166 (3)
C56	0.09162 (9)	0.30264 (7)	0.49639 (11)	0.0156 (3)
C57	−0.04716 (10)	0.45801 (9)	0.23444 (12)	0.0254 (4)
H57A	−0.075782	0.425675	0.183677	0.038*
H57B	−0.037447	0.495120	0.208190	0.038*
H57C	−0.077013	0.471412	0.257613	0.038*
C58	−0.12318 (10)	0.23662 (8)	0.42511 (13)	0.0210 (3)
H58A	−0.097688	0.196715	0.429220	0.032*
H58B	−0.176777	0.227791	0.397674	0.032*
H58C	−0.097578	0.254916	0.489968	0.032*
C59	0.30757 (9)	0.39553 (8)	0.58245 (11)	0.0183 (3)
H59	0.305050	0.400264	0.525548	0.022*
C60	0.38516 (9)	0.40436 (8)	0.67481 (11)	0.0171 (3)
C61	0.44016 (9)	0.44181 (8)	0.67419 (11)	0.0176 (3)
H61	0.425046	0.462172	0.615834	0.021*
C62	0.51608 (9)	0.44948 (8)	0.75738 (11)	0.0158 (3)
H62	0.550225	0.475732	0.754158	0.019*
C63	0.54251 (9)	0.41832 (7)	0.84660 (11)	0.0144 (3)
C64	0.48718 (9)	0.38152 (8)	0.84801 (12)	0.0198 (3)
H64	0.502012	0.361544	0.906492	0.024*
C65	0.41160 (10)	0.37442 (8)	0.76481 (12)	0.0206 (3)
H65	0.377058	0.349028	0.768377	0.025*
C66	0.67605 (9)	0.45531 (7)	0.92134 (11)	0.0162 (3)
H66A	0.654804	0.496325	0.886285	0.019*
H66B	0.686704	0.427738	0.883629	0.019*
C67	0.75132 (9)	0.46800 (8)	1.02316 (11)	0.0181 (3)
H67A	0.788915	0.488663	1.016244	0.022*
H67B	0.740980	0.497617	1.059263	0.022*
C68	0.72923 (9)	0.38139 (9)	1.09220 (12)	0.0227 (3)
H68A	0.720476	0.412274	1.128522	0.027*
H68B	0.751147	0.341938	1.131477	0.027*
C69	0.65217 (9)	0.36539 (8)	0.99507 (11)	0.0185 (3)
H69A	0.659883	0.330958	0.961956	0.022*
H69B	0.615695	0.349637	1.007532	0.022*
N1	0.99378 (8)	0.41800 (6)	0.63684 (10)	0.0163 (3)
N2	0.76499 (8)	0.10101 (6)	0.72043 (9)	0.0162 (3)
N3	0.61937 (7)	0.42330 (6)	0.93090 (9)	0.0148 (3)
O1	0.52608 (7)	0.26799 (5)	0.28881 (8)	0.0197 (2)
O2	0.54943 (7)	0.35885 (6)	0.10744 (8)	0.0226 (2)
O3	0.40724 (7)	0.42268 (6)	0.02809 (8)	0.0198 (2)
O4	0.24695 (7)	0.28638 (5)	0.06716 (8)	0.0190 (2)
O5	1.15881 (7)	0.40724 (6)	0.77905 (9)	0.0237 (3)
O6	0.29864 (6)	0.21822 (5)	0.36984 (8)	0.0187 (2)
O7	0.30364 (7)	0.08440 (6)	0.20379 (8)	0.0250 (3)
O8	0.15808 (6)	0.04423 (6)	0.14049 (8)	0.0215 (2)
O9	0.01990 (7)	0.21180 (6)	0.16954 (9)	0.0216 (2)
O10	0.91687 (7)	0.08155 (5)	0.90072 (8)	0.0207 (2)
O11	0.16029 (7)	0.27136 (5)	0.56949 (8)	0.0192 (2)
O12	0.17361 (7)	0.37980 (8)	0.39210 (9)	0.0327 (3)
O13	0.02569 (6)	0.43088 (6)	0.31485 (8)	0.0199 (2)
O14	−0.11947 (7)	0.28203 (6)	0.36316 (8)	0.0198 (2)
O15	0.78328 (7)	0.40850 (6)	1.07735 (9)	0.0211 (2)

solution (10 mL) as a catalyst, intermediate (0.96 g, 5.00 mmol) and 6,8-dimethoxy-3,4-dihydro-1-benzoxepin-5(*2H*)-one (1.11 g, 5.00 mmol) were dissolved in methanol (30 mL) for stirring about 5 h at 298 K. Then the mixture was filtered, and the residue was washed with 50 % methanol. The precipitate was collected and recrystallized from a dichloromethane and methanol solution (1:1, *v:v*) at room temperature to gain clear light yellow block crystals, (*E*)-6,8-dimethoxy-4-(4-morpholinobenzylidene)-3,4-dihydro-1-benzoxepin-5(*2H*)-one.

2 Experimental details

The H atoms were placed in idealized positions and treated as riding on their parent atoms, with *d*(C–H) = 0.96 Å (methyl), U_{iso}(H) = 1.5U_{eq}(C), and *d*(C–H) = 0.97 Å (methylene), U_{iso}(H) = 1.2U_{eq}(C), and *d*(C–H) = 0.93 Å (aromatic), U_{iso}(H) = 1.2U_{eq}(C).

3 Comment

In existing studies, 3,4-dihydro-1-benzoxepin-5(*2H*)-one derivatives have shown excellent anti-inflammatory activities.[4,5] It has been demonstrated that cytotoxicity can be decreased with the aid of introducing another pharmacophore, *α,β*-unsaturated ketone.[6,7] Based on these structural characteristics, a series of compounds obtained by the condensation reaction of aromatic aldehydes with 3,4-dihydro-1-benzoxepin-5(*2H*)-one have been reported.[8] Research shows that the better activity of the compound can be obtained by introducing the nitrogen-containing heterocycles.[9] So we introduced morpholine substituents at the C(17) position. In this study, intermediate was prepared by morpholine and *p*-fluorobenzaldehyde. Followed by a Claisen–Schmidt condensation reaction with 6,8-dimethoxy-3,4-dihydro-1-benzoxepin-5(*2H*)-one to afford the target compound, (*E*)-6,8-dimethoxy-4-(4-morpholinobenzylidene)-3,4-dihydro-1-benzoxepin-5(*2H*)-one.

Crystals were obtained by evaporation from an equal volume ratio solution of dichloromethane and methanol solution. The single-crystal structure analysis reveals that the title compound crystallizes in the monoclinic space group *Cc*. There are three molecules in the asymmetric unit (cf. figure). The pharmacophore of the compound is 3,4-dihydro-1-benzoxepin-5(*2H*)-one. In the C(2) position, it reacts with 4-morpholinobenzaldehyde to obtain *α,β*-unsaturated ketone. In first molecule, the bond lengths of O(2)=C(1) and C(2)=C(13)

are respectively 1.222(2) and 1.348(2) Å, which are within the normal range of olefinic bonds. The torsion angle of O(2)=C(1)–C(2)=C(13) is about 2.3(2)°. The dihedral angle between the 3,4-dihydro-1-benzoxepin-5(*2H*)-one and the benzene ring is about 21.08(3)°. In second molecule, the bond lengths of O(7)=C(24) and C(25)=C(36) are 1.225(2) and 1.344(2) Å, respectively. The torsion angle of O(7)=C(24)–C(25)=C(36) is about 11.9(2)°. The dihedral angle between the 3,4-dihydro-1-benzoxepin-5(*2H*)-one and the benzene ring is about 17.66(3)°. In third molecule, the bond lengths of O(12)=C(47) and C(48)=C(59) are 1.220(2) and 1.346(2) Å, respectively. The torsion angle of O(12)=C(47)–C(48)=C(59) is about −2.5(2)°. The dihedral angle between the 3,4-dihydro-1-benzoxepin-5(*2H*)-one and the benzene ring is about 22.60(3)°. Moreover, the morpholine ring connected to the benzene ring displays "chair" conformation and the whole molecule has a linear structure.[10,11] In first molecule, the torsion angle of N(1)–C(20)–C(21)–O(5) and N(1)–C(22)–C(23)–O(5) are 57.09(18)° and −56.19(19)°, respectively. In second molecule, the torsion angle of N(2)–C(43)–C(44)–O(10) and N(2)–C(46)–C(45)–O(10) are 53.66(17)° and −56.84(17)°, respectively. In third molecule, the torsion angle of N(3)–C(66)–C(67)–O(15) and N(3)–C(69)–C(68)–O(15) are 58.28(17)° and −55.58(18)°, respectively.

Author contribution: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

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