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The crystal structure of the host-guest complex: *N'*-{5-[2-(2,6-dimethylphenoxy)acetamido]-4-hydroxy-1,6-diphenylhexan-2-yl}-3-methyl-2-(2-oxo-1,3-diazinan-1-yl)butanamide-diethyl ether (2/1)

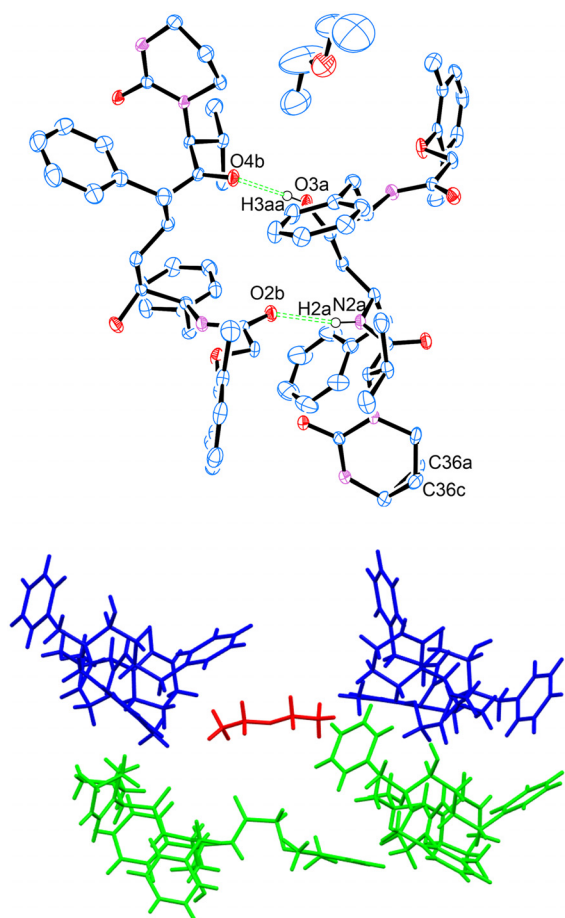


Table 1: Data collection and handling.

Crystal:	Colourless needle
Size:	0.59 × 0.08 × 0.05 mm
Wavelength:	CuKα radiation (1.54178 Å)
μ :	0.62 mm ⁻¹
Diffractometer, scan mode:	Bruker D8 Venture Photon CCD, ω
$\theta_{\max}$, completeness:	73.1°, >99 %
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	167390, 15008, 0.045
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 14592
$N(\text{param})_{\text{refined}}$:	926
Programs:	Bruker (1), SHELX (2, 3), WinGX/ORTEP (4), Mercury (5), PLATON (6)

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Abstract

2(C₃₇H₄₈N₄O₅), C₄H₁₀O, orthorhombic, $P2_12_12_1$ (no. 19), $a = 11.8629(3)$ Å, $b = 23.3541(6)$ Å, $c = 27.4519(7)$ Å, $V = 7605.5(3)$ Å³, $Z = 4$, $R_{\text{gt}}(F) = 0.0355$, $wR_{\text{ref}}(F^2) = 0.0979$, $T = 123$ K.

CCDC no.: 2227179

Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

1 Source of materials

All reagents are commercially available without the need of further purifications. Approximately 0.010 g of Lopinavir (0.0159 mmol) was added into an 8 mL glass polytop vial and dissolved in 5 mL diethyl ether solvent. The vial was closed with a hole on the top of the vial, the solution was left to allow slow evaporation at temperatures between 10 to 15 °C for 24 h. Colourless needles were formed and were observed the following day.

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Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($\text{\AA}^2$).

Atom	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
C1A	0.11299 (15)	0.71769 (8)	0.61258 (7)	0.0208 (4)
C2A	0.10626 (16)	0.76316 (9)	0.64529 (8)	0.0271 (4)
C3A	0.07929 (18)	0.81682 (9)	0.62704 (10)	0.0348 (5)
H3A	0.073857	0.848531	0.648591	0.042*
C4A	0.06036 (18)	0.82457 (9)	0.57809 (10)	0.0365 (5)
H4A	0.0414	0.86151	0.566143	0.044*
C5A	0.06866 (17)	0.77906 (10)	0.54607 (8)	0.0310 (5)
H5A	0.056074	0.785171	0.512294	0.037*
C6A	0.09515 (16)	0.72455 (8)	0.56267 (7)	0.0234 (4)
C7A	0.1319 (2)	0.75478 (13)	0.69863 (9)	0.0476 (7)
H7AA	0.211703	0.762887	0.704655	0.071*
H7AB	0.115246	0.715129	0.707867	0.071*
H7AC	0.085258	0.780862	0.718032	0.071*
C8A	0.1071 (2)	0.67534 (10)	0.52758 (9)	0.0363 (5)
H8AA	0.046019	0.647822	0.533021	0.055*
H8AB	0.179851	0.656434	0.532787	0.055*
H8AC	0.103186	0.689757	0.494093	0.055*
C9A	0.05476 (16)	0.62734 (8)	0.64240 (8)	0.0239 (4)
H9AA	0.0118	0.617085	0.612735	0.029*
H9AB	0.003089	0.647217	0.665114	0.029*
C10A	0.10040 (16)	0.57359 (8)	0.66619 (7)	0.0207 (4)
C11A	0.26996 (15)	0.52296 (8)	0.69411 (7)	0.0206 (4)
H11A	0.220602	0.504813	0.719285	0.025*
C12A	0.29090 (17)	0.47918 (8)	0.65303 (7)	0.0251 (4)
H12C	0.221398	0.475796	0.633274	0.03*
H12D	0.351096	0.494085	0.631514	0.03*
C13A	0.32438 (17)	0.42023 (8)	0.67039 (7)	0.0250 (4)
C14A	0.24209 (18)	0.37791 (9)	0.67410 (8)	0.0281 (4)
H14A	0.165596	0.387013	0.66741	0.034*
C15A	0.27100 (19)	0.32267 (9)	0.68746 (8)	0.0318 (5)
H15A	0.214508	0.293905	0.689128	0.038*
C16A	0.38183 (19)	0.30910 (9)	0.69843 (8)	0.0319 (5)
H16A	0.401524	0.271105	0.707401	0.038*
C17A	0.46377 (19)	0.35133 (9)	0.69622 (9)	0.0352 (5)
H17A	0.53946	0.342662	0.704786	0.042*
C18A	0.43512 (18)	0.40635 (9)	0.68146 (9)	0.0317 (5)
H18A	0.492064	0.434792	0.67892	0.038*
C19A	0.37911 (15)	0.54270 (8)	0.71865 (7)	0.0211 (4)
H19A	0.41901	0.508714	0.732566	0.025*
C20A	0.36202 (16)	0.58749 (8)	0.75879 (7)	0.0221 (4)
H20C	0.435053	0.593307	0.775519	0.027*
H20D	0.341496	0.624217	0.743121	0.027*
C21A	0.27357 (16)	0.57394 (8)	0.79713 (7)	0.0221 (4)
H21A	0.199644	0.569325	0.780069	0.027*
C22A	0.26037 (18)	0.62282 (9)	0.83484 (8)	0.0290 (4)
H22C	0.238261	0.658146	0.817339	0.035*
H22D	0.198029	0.612805	0.857247	0.035*
C23A	0.36399 (18)	0.63552 (9)	0.86479 (7)	0.0278 (4)
C24A	0.4332 (2)	0.68207 (11)	0.85471 (9)	0.0440 (6)
H24A	0.415686	0.706202	0.827904	0.053*
C25A	0.5274 (3)	0.69409 (15)	0.88298 (10)	0.0602 (9)
H25A	0.573169	0.726291	0.875495	0.072*
C26A	0.5546 (3)	0.65940 (15)	0.92184 (10)	0.0568 (8)
H26A	0.619119	0.667488	0.941176	0.068*
C27A	0.4883 (3)	0.61343 (12)	0.93227 (9)	0.0482 (7)

Table 2: (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
H27A	0.507308	0.589171	0.958809	0.058*
C28A	0.3929 (2)	0.60154 (9)	0.90450 (8)	0.0368 (5)
H28A	0.346754	0.569746	0.91281	0.044*
C29A	0.22001 (15)	0.48919 (8)	0.84371 (6)	0.0194 (4)
C30A	0.26100 (15)	0.43698 (8)	0.87215 (6)	0.0193 (4)
H30A	0.341842	0.430376	0.863493	0.023*
C31A	0.19511 (16)	0.38253 (8)	0.85942 (8)	0.0245 (4)
H31A	0.114213	0.388746	0.868192	0.029*
C32A	0.20207 (18)	0.37122 (10)	0.80472 (8)	0.0325 (5)
H32D	0.170522	0.403918	0.786977	0.049*
H32E	0.159113	0.336618	0.796777	0.049*
H32F	0.281056	0.365872	0.7953	0.049*
C33A	0.2390 (2)	0.33126 (9)	0.88855 (10)	0.0370 (5)
H33D	0.31812	0.32427	0.880175	0.055*
H33E	0.194141	0.297265	0.880662	0.055*
H33F	0.232844	0.339424	0.923468	0.055*
C34A	0.35445 (15)	0.45805 (8)	0.94969 (6)	0.0188 (4)
C35A	0.14625 (17)	0.45706 (11)	0.94810 (8)	0.0339 (5)
H35C ^a	0.121094	0.418888	0.959403	0.041*
H35D ^a	0.090275	0.471302	0.924254	0.041*
H35E ^b	0.119939	0.497116	0.944913	0.041*
H35F ^b	0.091188	0.432201	0.931159	0.041*
C36A ^a	0.1507 (2)	0.49715 (15)	0.99064 (10)	0.0320 (9)
H36E ^a	0.077414	0.497061	1.007889	0.038*
H36F ^a	0.165963	0.536595	0.979195	0.038*
C36C ^b	0.1486 (6)	0.4420 (4)	0.9986 (2)	0.041 (2)
H36C ^b	0.163894	0.40055	1.002137	0.049*
H36D ^b	0.074574	0.450337	1.013655	0.049*
C37A	0.24400 (18)	0.47772 (13)	1.02503 (8)	0.0400 (6)
H37C ^a	0.254265	0.506198	1.051377	0.048*
H37D ^a	0.223715	0.440568	1.040023	0.048*
H37E ^b	0.22188	0.518532	1.026961	0.048*
H37F ^b	0.255201	0.463214	1.058572	0.048*
N1A	0.21147 (13)	0.57278 (7)	0.67413 (6)	0.0223 (3)
N2A	0.29987 (13)	0.51946 (7)	0.82116 (6)	0.0196 (3)
N3A	0.25580 (13)	0.45154 (7)	0.92420 (6)	0.0213 (3)
N4A	0.34713 (15)	0.47194 (8)	0.99741 (6)	0.0258 (4)
O1A	0.14606 (11)	0.66429 (6)	0.62985 (6)	0.0299 (3)
O2A	0.03559 (11)	0.53452 (6)	0.67748 (5)	0.0264 (3)
O3A	0.45040 (12)	0.56988 (6)	0.68359 (5)	0.0258 (3)
O4A	0.11947 (11)	0.50353 (6)	0.84354 (5)	0.0248 (3)
O5A	0.44766 (11)	0.45256 (6)	0.92974 (5)	0.0211 (3)
C1B	0.61132 (15)	0.29326 (8)	0.86633 (7)	0.0201 (4)
C2B	0.63111 (16)	0.30061 (8)	0.91587 (7)	0.0237 (4)
C3B	0.62162 (18)	0.25264 (9)	0.94573 (8)	0.0297 (4)
H3B	0.634773	0.256303	0.979722	0.036*
C4B	0.59336 (18)	0.19978 (9)	0.92666 (9)	0.0323 (5)
H4B	0.588497	0.167382	0.947475	0.039*
C5B	0.57212 (17)	0.19388 (8)	0.87736 (9)	0.0296 (4)
H5B	0.552435	0.157435	0.864564	0.035*
C6B	0.57936 (16)	0.24096 (8)	0.84630 (8)	0.0249 (4)
C7B	0.66156 (19)	0.35805 (9)	0.93661 (8)	0.0308 (4)
H7BA	0.592592	0.379162	0.944583	0.046*
H7BB	0.705347	0.379698	0.912582	0.046*
H7BC	0.706618	0.352787	0.966192	0.046*
C8B	0.5515 (2)	0.23579 (10)	0.79301 (9)	0.0362 (5)

Table 2: (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	U_{iso}^*/U_{eq}
H8BA	0.490459	0.262406	0.784867	0.054*
H8BB	0.527475	0.196522	0.785876	0.054*
H8BC	0.618336	0.24507	0.773588	0.054*
C9B	0.54505 (15)	0.38132 (8)	0.83265 (7)	0.0202 (4)
H9BA	0.513601	0.387222	0.865671	0.024*
H9BB	0.483175	0.368513	0.811036	0.024*
C10B	0.59340 (16)	0.43704 (8)	0.81381 (6)	0.0193 (4)
C11B	0.76684 (15)	0.48839 (8)	0.79054 (7)	0.0202 (4)
H11B	0.722091	0.505404	0.763273	0.024*
C12B	0.78071 (17)	0.53417 (8)	0.83061 (7)	0.0246 (4)
H12A	0.707807	0.539377	0.847601	0.03*
H12B	0.836468	0.520587	0.854827	0.03*
C13B	0.81883 (17)	0.59084 (8)	0.81048 (7)	0.0235 (4)
C14B	0.73955 (17)	0.62833 (9)	0.79103 (8)	0.0278 (4)
H14B	0.661791	0.618654	0.791869	0.033*
C15B	0.7735 (2)	0.67994 (9)	0.77037 (8)	0.0326 (5)
H15B	0.718667	0.705178	0.757179	0.039*
C16B	0.8854 (2)	0.69479 (9)	0.76883 (9)	0.0345 (5)
H16B	0.908113	0.729999	0.754524	0.041*
C17B	0.96440 (19)	0.65818 (9)	0.78820 (10)	0.0388 (5)
H17B	1.041979	0.668216	0.787263	0.047*
C18B	0.93163 (18)	0.60658 (9)	0.80915 (9)	0.0325 (5)
H18B	0.986981	0.581865	0.822688	0.039*
C19B	0.87981 (15)	0.46779 (8)	0.77006 (7)	0.0208 (4)
H19B	0.923329	0.501346	0.75747	0.025*
C20B	0.86936 (16)	0.42250 (8)	0.72979 (7)	0.0226 (4)
H20A	0.943692	0.418654	0.713722	0.027*
H20B	0.851985	0.385281	0.745328	0.027*
C21B	0.78160 (16)	0.43357 (8)	0.69069 (7)	0.0221 (4)
H21B	0.707656	0.43935	0.707483	0.027*
C22B	0.76776 (18)	0.38231 (9)	0.65557 (8)	0.0284 (4)
H22A	0.734881	0.349978	0.674059	0.034*
H22B	0.712765	0.393173	0.630065	0.034*
C23B	0.87387 (18)	0.36139 (9)	0.63074 (8)	0.0295 (4)
C24B	0.9204 (2)	0.30871 (10)	0.64328 (9)	0.0360 (5)
H24B	0.886944	0.286748	0.668569	0.043*
C25B	1.0150 (2)	0.28777 (11)	0.61937 (10)	0.0435 (6)
H25B	1.045085	0.251548	0.628241	0.052*
C26B	1.0655 (2)	0.31904 (12)	0.58296 (9)	0.0453 (6)
H26B	1.129713	0.304438	0.566468	0.054*
C27B	1.0216 (2)	0.37208 (13)	0.57057 (9)	0.0447 (6)
H27B	1.057063	0.394339	0.545987	0.054*
C28B	0.9262 (2)	0.39288 (11)	0.59389 (8)	0.0367 (5)
H28B	0.896085	0.428977	0.584654	0.044*
C29B	0.72508 (15)	0.51502 (8)	0.64091 (6)	0.0191 (4)
C30B	0.76320 (15)	0.56162 (8)	0.60560 (6)	0.0196 (4)
H30B	0.842852	0.571878	0.613718	0.024*
C31B	0.69178 (16)	0.61604 (8)	0.60930 (7)	0.0236 (4)
H31B	0.610917	0.605876	0.603724	0.028*
C32B	0.70432 (18)	0.64051 (9)	0.66052 (8)	0.0302 (4)
H32A	0.678202	0.612263	0.68439	0.045*
H32B	0.659083	0.675457	0.663416	0.045*
H32C	0.783729	0.649533	0.666681	0.045*
C33B	0.7277 (2)	0.66011 (10)	0.57139 (9)	0.0367 (5)
H33A	0.808021	0.66865	0.575349	0.055*
H33B	0.683721	0.695273	0.575782	0.055*

Table 2: (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	U_{iso}^*/U_{eq}
H33C	0.714298	0.644755	0.538677	0.055*
C34B	0.86114 (15)	0.53272 (8)	0.53104 (6)	0.0186 (3)
C35B	0.65410 (17)	0.52092 (10)	0.53394 (7)	0.0303 (5)
H35A	0.623641	0.554676	0.516539	0.036*
H35B	0.59922	0.509588	0.559336	0.036*
C36B	0.67089 (18)	0.47197 (10)	0.49840 (8)	0.0328 (5)
H36A	0.696161	0.437352	0.516119	0.039*
H36B	0.598761	0.463019	0.481938	0.039*
N1B	0.70562 (13)	0.43881 (7)	0.80928 (6)	0.0215 (3)
N2B	0.80707 (13)	0.48635 (7)	0.66383 (6)	0.0196 (3)
N3B	0.76223 (13)	0.53563 (7)	0.55667 (6)	0.0211 (3)
N4B	0.85861 (15)	0.50924 (7)	0.48614 (6)	0.0233 (3)
O1B	0.63071 (11)	0.33848 (5)	0.83436 (5)	0.0225 (3)
O2B	0.53035 (11)	0.47723 (6)	0.80365 (5)	0.0242 (3)
O3B	0.94222 (12)	0.44069 (6)	0.80821 (5)	0.0265 (3)
O4B	0.62397 (11)	0.50261 (6)	0.64562 (5)	0.0250 (3)
O5B	0.95121 (11)	0.54979 (6)	0.54902 (5)	0.0235 (3)
C37B	0.75820 (17)	0.48892 (9)	0.46116 (7)	0.0283 (4)
H37A	0.777311	0.455579	0.440479	0.034*
H37B	0.727904	0.519538	0.439923	0.034*
O1	0.2965 (2)	0.28377 (11)	0.50825 (8)	0.0659 (6)
C3	0.2582 (5)	0.2565 (2)	0.46612 (15)	0.1054 (17)
H3C	0.211961	0.284164	0.447472	0.127*
H3D	0.32453	0.246882	0.445821	0.127*
C1	0.3959 (4)	0.3570 (2)	0.55116 (15)	0.0855 (12)
H1D	0.330685	0.360061	0.572946	0.128*
H1E	0.427244	0.395217	0.545327	0.128*
H1F	0.453339	0.332642	0.56624	0.128*
C2	0.3599 (7)	0.3314 (3)	0.50416 (19)	0.153 (3)
H2D	0.316629	0.360475	0.485716	0.183*
H2E	0.428081	0.322118	0.484914	0.183*
C4	0.1952 (6)	0.2070 (3)	0.4726 (2)	0.136 (2)
H4C	0.242867	0.173474	0.466608	0.204*
H4D	0.131819	0.206903	0.449672	0.204*
H4E	0.166361	0.205718	0.506016	0.204*
H1A	0.254 (2)	0.6027 (10)	0.6622 (8)	0.021 (5)*
H3AA	0.494 (2)	0.5477 (12)	0.6724 (10)	0.031 (7)*
H2A	0.364 (2)	0.5068 (10)	0.8199 (8)	0.023 (6)*
H4AA	0.407 (3)	0.4713 (12)	1.0130 (10)	0.040 (7)*
H1B	0.746 (2)	0.4079 (10)	0.8184 (8)	0.023 (5)*
H2B	0.874 (2)	0.4992 (11)	0.6603 (9)	0.031 (6)*
H4BA	0.916 (2)	0.5157 (9)	0.4702 (8)	0.014 (5)*
H3BA	0.992 (3)	0.4608 (13)	0.8175 (12)	0.048 (9)*

^aOccupancy: 0.695 (7), ^bOccupancy: 0.305 (7).

2 Experimental details

The collection method involved ω -scans of 0.5° width. The data was reduced using SAINT-Plus version 6.02.6 software. SADABS was then used to process the empirical absorption corrections (1). The crystal structure was solved using SHELXT (2). Hydrogen atoms were geometrically positioned

and $U_{iso}(H) = 1.2U_{eq}(C)$. All diagrams were prepared for publication using Ortep (4), WinGX (4), MERCURY (5) PLATON (6).

3 Comment

Lopinavir is a protease targeting antiretroviral drug marketed as KALETRA[®]000174 (Lopinavir/ritonavir) for the treatment of HIV infections (7). Lopinavir is both potent and selective in its mechanism of action, this is due to its ability to inhibit the maturation of the HIV-1 virion within a host cell. Subsequently, this renders the HIV-1 protease itself ineffective and therefore prevents cells that were initially not infected from being infected (8). In this paper Lopinavir was crystallised as a solvated host-guest complex with diethyl ether.

The asymmetric unit of the molecule is shown in the figure, this unit exists as two molecules of *N*-[5-[2-(2,6-dimethylphenoxy)acetamido]-4-hydroxy-1,6-diphenylhexan-2-yl]-3-methyl-2-(2-oxo-1,3-diazinan-1-yl)butanamide (Lopinavir) and one molecule of diethyl ether. All the bond angles and lengths were as expected (9). The secondary amine moiety is attached by an N2a–H2a···O2b to the carbonyl group with a hydrogen bond, at a bond length of 2.946 Å. The hydroxyl group is hydrogen bonded by O3a–H3aa···O4b to the carbonyl group, at a bond length of 2.792 Å. The hydrogen bond lengths presented in this compound are between the typical lengths reported by (10). Hydrogen bond lengths that fall between 2.5 to 3.3 Å are considered to be moderately strong hydrogen bonds (10). The moderate hydrogen bonds are observed between the Lopinavir molecules to form a host molecule that has encapsulated the diethyl ether solvent (the guest). This guest molecule is held in the centre of four host molecules (Lopinavir) by weak intermolecular forces. Due to the guest molecule (diethyl ether) being held loosely in the centre of the host molecule, it is able to vibrate within that space, resulting in large ellipsoids that are present on the diethyl ether. It can also be observed that the C36 carbon is

disordered, C36a has an occupancy of 30.5 % and C36b has an occupancy of 69.5 %.

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