Tebogo M. L. Mokoto, Andreas Lemmerer, Yasien Sayed and Mark G. Smith*

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)

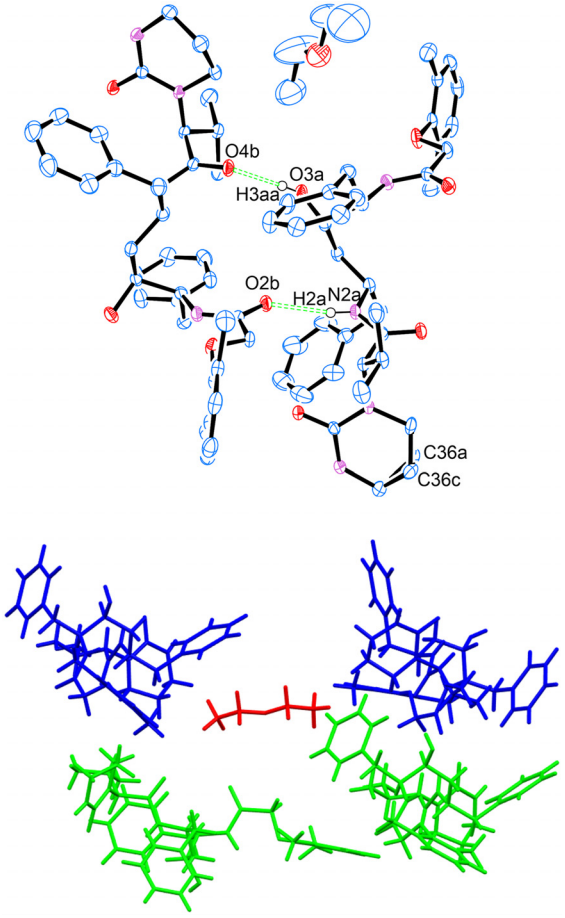

Table 1: Data collection and handling.

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
θ_{max}, completeness:	73.1°, >99 %
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	167390, 15008, 0.045
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 14592
$N(param)_{refined}$:	926
Programs:	Bruker (*1*), SHELX (*2*, *3*), WinGX/ORTEP (*4*), Mercury (*5*), PLATON (*6*)

https://doi.org/10.1515/ncrs-2023-0515
Received November 22, 2023; accepted December 31, 2023; published online January 19, 2024

Abstract

$2(C_{37}H_{48}N_4O_5)$, $C_4H_{10}O$, 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) Å^3, Z = 4, $R_{gt}(F)$ = 0.0355, w$R_{ref}(F^2)$ = 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.

***Corresponding author: Mark G. Smith**, Department of Chemistry, University of South Africa, Unisa Science Campus, 28 Pioneer Avenue, Florida, Roodepoort, Gauteng, South Africa, E-mail: smithm2@unisa.ac.za. https://orcid.org/0000-0003-2553-2540

Tebogo M. L. Mokoto and Yasien Sayed, Protein Structure-Function Research Unit, School of Molecular and Cell Biology, University of the Witwatersrand, Johannesburg, Gauteng, South Africa. https://orcid.org/0000-0001-7326-7118 (T.M.L. Mokoto). https://orcid.org/0000-0002-1781-2115 (Y. Sayed)

Andreas Lemmerer, Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, Johannesburg, Gauteng, South Africa. https://orcid.org/0000-0003-1569-2831

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

Atom	*x*	*y*	*z*	U_{iso}*/U_{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)
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	x	y	z	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	x	y	z	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)*

[a]Occupancy: 0.695 (7), [b]Occupancy: 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 KALETRAŏ00174 (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 viron 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 encaspulated 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 losely in the centre of the host molecule, it is able to vibrate within that space, resulting in large elipsoids 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 %.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: This work was supported by the National Research Foundation (NRF) Doctoral General Scholarship Grant number PMDS22071841801, the University of the Witwatersrand and the University of South Africa.
Competing interests: The authors declare no conflicts of interest regarding this article.

References

1. Bruker. *Apex3*, *Saint–Plus and Sadabs*; Bruker AXS Inc.: Madison, Wisconsin, USA, **2016**.
2. Sheldrick G. M. Crystal Structure Refinement with SHELXL. *Acta Crystallogr.* **2015**, *C71*, 3–8.
3. Sheldrick G. M. *SHELXL2018*; Universität Göttingen: Göttingen, Germany, **2018**.
4. Farrugia L. J. WinGX and ORTEP for Windows: an Update. *J. Appl. Crystallogr.* **2012**, *45*, 849–854.
5. Macrae C. F., Edgington P. R., McCabe P., Pidcock E., Shields G. P., Taylor R., van der Streek T. Mercury 4.0: From Visualization to Analysis, Design and Prediction. *J. Appl. Crystallogr.* **2020**, *39*, 453–457.
6. Spek A. L. Structure Validation in Chemical Crystallography. *Acta Cryst* **2009**, *D65*, 148–155.
7. Kaletra |C74H96N10O10S2 |CID 11979606 – PubChem [Internet]. https://pubchem.ncbi.nlm.nih.gov/compound/lopinavir%2Fritonavir (accessed Aug 3, 2023).
8. Cvetkovic R. S., Goa K. L., Perrin L., Van Heeswijk R. P. G., Ziegler J. B. Lopinavir/Ritonavir – A Review of its Use in the Management of HIV Infection. *Drugs* **2003**, *63*, 769–802.
9. Liu Z., Yedidi R. S., Wang Y., Dewdney T. G., Reiter S. J., Brunzelle J. S., Kovari I. A., Kovari L. C. Crystallographic Study of Multi-Drug Resistant HIV-1 Protease Lopinavir Complex: Mechanism of Drug Recognition and Resistance. *Biochem. Biophys. Res. Commun.* **2013**, *437*, 199–204.
10. Jeffrey G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: New York, **1997**.