Molecular Basis for Kv1.5 Channel Block

CONSERVATION OF DRUG BINDING SITES AMONG VOLTAGE-GATED K⁺ CHANNELS

Niels Decher‡§, Bernard Pirard¶, Florian Bundis¶, Stefan Peukert¶, Karl-Heinz Baringhaus¶, Andreas E. Busch¶, Klaus Steinmeyer¶, and Michael C. Sanguinetti‡¶

From the ‡Aventis Pharma Deutschland GmbH, D-65926 Frankfurt am Main, Germany and ¶University of Utah, Department of Physiology, Eccles Institute of Human Genetics, Salt Lake City, Utah 84112

Kv1.5 channels conduct the ultrarapid delayed rectifier current (I_{Kur}) that contributes to action potential repolarization of human atrial myocytes. Block of these channels has been proposed as a treatment for atrial arrhythmias. Here we report a novel and potent inhibitor of Kv1.5 potassium channels, N-benzyl-N-pyridin-3-yl-methyl-2-(toluene-4-sulfonylamino)-benzamide hydrochloride (S0100176), which exhibits features consistent with preferential block of the open state. The IC_{50} of S0100176 for Kv1.5 expressed in Xenopus oocytes was 0.7 μM. Ala-scanning mutagenesis within the pore helix and the S6 segment, regions that form the walls of the central cavity, was combined with voltage clamp analysis to identify point mutations that altered drug affinity. This approach identified Thr-479, Thr-480, Val-505, Ile-508, and Val-512 as the most important residues for block by S0100176. Mutations of these key residues to Ala or other amino acids caused marked changes in the IC_{50} of S0100176 (p < 0.01). For example, the IC_{50} of S0100176 increased 362-fold for T480A, 26-fold for V505A, 150-fold for I508A, and 99-fold for V512A. We used modeling to dock S0100176 into the inner cavity of a Kv1.5 pore homology model that was generated based on the crystal structure of KcsA. The docking predicted that the five residues identified by the Ala scan were positioned less than 4.5 Å from the compound. Based on the homology models, the positions of the five amino acids identified to interact with S0100176 face toward the central cavity and overlap with putative binding sites for other blockers and voltage-gated potassium channels.

Atrial fibrillation is the most common chronic arrhythmia in humans and represents a major clinical problem with serious morbidity in the elderly (1). However, current drug therapies for this arrhythmia are unsatisfactory. Kv1.5 channels are highly expressed in human atria (but not ventricle) and conduct the ultrarapid delayed rectifier current (I_{Kur}) that contributes to action potential repolarization of human atrial myocytes (2–4). Thus, Kv1.5 is an important molecular target for treatment of atrial fibrillation or atrial flutter, particularly because inhibition of Kv1.5 should selectively prolong atrial but not ventricular action potential duration. Therefore, a significant effort has been made to identify novel blockers of Kv1.5 (5) and to characterize their binding site (6–9).

The intracellular approach identified Thr-507, Leu-510, and Val-514 of the S6 segment (7, 8) by interaction with residues in the S6 domain (6–11). The residues Thr-507, Leu-510, and Val-514 of the S6 segment (7, 8) and Thr-479 near the selectivity filter (8, 11) were identified as potential binding sites for these drugs. Previous studies have shown that blockers of Na⁺, Ca²⁺, and K⁺ channels also bind to residues within the S6 segment and/or regions near the selectivity filter (12–18). In addition, open channel blockers such as tetraethyl ammonium, other quaternary amines, and Kv1.5 subunits or the inactivation gate itself are thought to bind to the central cavity of voltage-gated K⁺ channels (12, 19–22). For quaternary amines, this binding presumably involves an interaction with two different sites, including one near the selectivity filter and a second site in the S6 segment (12, 13, 23).

Residues located in the S6 domain and the base of the pore helix are predicted to face toward the central cavity of K⁺ channels (24–26). Ala scanning of the residues in these regions in Kv1.5 combined with voltage clamp experiments of mutant channels identified four residues as putative binding sites for N-benzyl-N-pyridin-3-ylmethyl-2-(toluene-4-sulfonylamino)-benzamide hydrochloride (S0100176), an antranilic acid derivative that reduced current with properties characteristic of open channel block. The positions of the residues correspond to important residues responsible for drug binding to other K⁺ channels such as HERG (human ether-a-go-go-related gene) (18), KCNQ1 (27), and Kv1.3 (28), indicating a conservation of drug binding sites among different K⁺ channel families.

EXPERIMENTAL PROCEDURES

Site-directed Mutagenesis of Human Kv1.5—PCR-based site-directed mutagenesis was used to introduce mutations into the human Kv1.5 (KCNAS) cDNA. Kv1.5 was cloned from human heart and differs from the GenBank™ data base entry NM_002234 by two residues, K418R and K565E. The newer data base entry of the Kv1.5 sequence (NM_002234) has an N terminus with two additional residues. This results in a shift of the amino acid numbering of +2 when compared with literature referring to the previous entry (M60451). PCR products were fully sequenced (ABI 3100, Applied Biosystems).

For Xenopus oocyte expression, the Kv1.5 cDNA was cloned into the oocyte expression vector pSGEM (29), and capped cRNA was synthesized using the T7 mMessage mMACHINE kit (Ambion, Austin, TX) after linearization of the plasmid with NheI (Roche Applied Science).

Isolation and Electrophysiological Recordings from Xenopus Oocytes—Methods for isolation and injection of Xenopus oocytes were as described in Ref. 30. Oocytes were injected with 50 nl of cRNA using a microinjector (A203XVZ, World Precision Instruments, Sarasota, FL). This paper is available on line at http://www.jbc.org
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Oocytes were incubated with gentle shaking at 18 °C in a ND96 buffer containing (in mM): NaCl 96, KCl 2, CaCl2 1.8, MgCl2 1, and HEPES 5, titrated to pH 7.5 with NaOH. In addition, sodium pyruvate 2.5, theophylline 0.5, and gentamycin 50 μg/ml were added to this solution. Oocytes were used for experiments 1–3 days after injection. A two-electrode voltage clamp of oocytes (31) bathed in ND96 solution was performed at room temperature. The microelectrodes had a resistance of 0.3–1.3 MΩ after filling with a 3 M KCl solution. Data were recorded with a Turbo Tec 10CD amplifier using an ITC-16 interface (NPI, Tamm, Germany) and Pulse software (Heka Elektronik, Lambrecht, Germany) and stored on a PC for analyses.

Voltage Clamp Protocols—To activate Kv1.5, oocytes were clamped at a holding potential of −50 mV and pulsed to voltages ranging from −60 to +60 mV for 1.5 s. The ratio of current in the presence of drug divided by current before drug (I_drug/I_control) was determined to calculate the fraction of unblocked current as a function of time. The time constant of block (τ_b) was determined by fitting I_dracf/I_control to a monoexponential function. The frequency dependence of peak current block was analyzed by stepping for 250 ms to 0 mV at a pulse frequency that ranged from 1 to 3 Hz. At 4 Hz, a pulse duration of 200 ms was used. The voltage dependence of Kv1.5 channel activation in the absence and presence of 1 μM S0100176 was determined from peak current amplitudes at each test potential (Vt) and the current reversal potential (Erev). These values were corrected for the transmembrane K+ driving force (Vt − Erev) and normalized to the peak current measured at +60 mV to obtain the normalized current, I0. The resulting relationship was fit to a Boltzmann equation to obtain the half-point (V1/2) and slope factor (k): I0 = I1/2 + exp[(Vt − V1/2)/k].

Data Analysis—Pulse (Heka) and Origin version 5 software (Microcal Software) were used for data acquisition and analysis on a Pentium II PC. All fitting procedures were based on the simplex algorithm. The concentration required for 50% block of current (IC50) was determined from Hill plots using 3–5 concentrations of drug for each mutant (3–10 oocytes/point). Results are reported as mean ± S.E. (n = number of oocytes). Statistical differences between wild-type and mutant channels were evaluated by a Student's unpaired t test. Significance was assumed for p < 0.05.

Drugs—S0100176 was synthesized by the medicinal chemistry department of Aventis Pharma Deutschland GmbH. It was prepared as a 50 mM stock solution in Me2SO and stored at room temperature.

Homology Modeling of the Kv1.5 Pore and Docking of S0100176—The pore-forming domains (S5–S6) of Kv1 channels share 54% sequence homology with the bacterial K+ channel KcsA in which three-dimensional structure has been solved by x-ray crystallography (24). An open state molecular model of the S5–S6 region of Kv1.3 (kindly provided by Ying-Duo Gao), generated using the crystal structure of the KcsA channel (28) from the Protein Data Bank file (1BL8), was used as a template for docking S0100176. The S5 and S6 domains and the pore helix of Kv1.3 and Kv1.5 share 100% sequence similarity. Kv1.3 differs from the sequence of Kv1.5 only in the external S5-P loop and P-S6 loop.

We proceeded in three steps to dock S0100176 into the homology model of the Kv1.3/1.5 pores. First, S0100176 was manually docked to the putative site in the central cavity. Second, to remove severe steric clashes with the protein, the manually docked S0100176 was submitted to a short sequence of energy minimizations involving 100 steps of steepest descent minimization followed by 100 steps of conjugate gradient minimization. At each step, the energy was evaluated with the SYBYL 6.7 implementation of the MMFF94S force field (Tripos Inc.). Finally, the minimized complex served as input for QXP (32), which searched for alternative binding modes. QXP (quick explore) uses fast Monte Carlo searches and energy minimizations for flexible docking to a binding site. During a QXP run, the ligand is flexible while the user can define a few flexible amino acids. In this work, we considered as flexible the amino acids Thr-479, Thr-480, Val-505, Ile-508, and Val-512, in which the side chains pointed toward the docked ligand. A docking search of 1,000 steps was performed. All of the S0100176 binding orientations produced by QXP were visually analyzed and grouped into clusters. For each cluster, the top scoring solution (QXP score) was inspected for contacts between S0100176 and both Val-505 and Ile-508. A cutoff of 4.5 Å between the ligand and any of the side chain atoms of the corresponding amino acids was defined as a potential contact. If these contacts were not observed, then the second best solution of the corresponding cluster was considered. If none of the members of a cluster showed contact with both Val-505 and Ile-508, then this cluster was discarded. For a docking solution that passed this filtering step, we identified the Kv1.5 residues found within 4.5 Å of S0100176. QXP generated multiple solutions. The one that gave a high QXP score and passed all the filters is presented here.

RESULTS

Voltage- and Frequency-dependent Block of Kv1.5 Channels by S0100176—S0100176 is a derivative of anthranilic acid (Fig. 1A). The effect of 1 μM S0100176 on Kv1.5 was characterized by eliciting currents with step changes in voltage to potentials ranging from −60 to +60 mV applied in 10-mV increments from a holding potential of −80 mV. In the absence of drug, Kv1.5 slowly inactivates during the test pulse (Fig. 1B). In the presence of drug, the current appeared to inactivate much faster and more thoroughly, but this effect more likely represents open channel block rather than an increased rate of inactivation. The voltage dependence of peak currents was shifted by about +10 mV by the compound (Fig. 1A) with greater block at the less depolarized potentials. However, for currents measured at the end of the 1.5-s pulse, after attaining a pseudo steady-state level, the reduction was more substantial and not voltage-dependent (Fig. 1C). The lack of an increase in block at higher potentials suggests that this compound does not preferentially block Kv1.5 channels in the inactivated state. The concentration of compound required to reduce current by 50% (IC50) at the end of a 1.5-s pulse to +40 mV was 0.7 ± 0.2 μM with a Hill coefficient of 1.09 (n = 5). There was no shift in

![Figure 1](http://www.jbc.org/)

**A.** Current-voltage relationship for peak Kv1.5 currents in the absence (○) and presence (□) of 1 μM S0100176. Inset shows the chemical structure of S0100176. **B.** Kv1.5 currents induced by depolarization to potentials ranging from −60 to +60 mV in the absence and presence of 1 μM S0100176. Inset shows the voltage clamp protocol used to elicit currents. E0, holding potential. **C.** Percent inhibition of Kv1.5 at the end of a 1.5-s voltage step to the indicated test potential induced by 1 μM S0100176 (n = 8).
the voltage dependence of activation for currents measured at the end of the 1.5-s pulse; the $V_{1/2}$ was $-4.2 \pm 1.2$ mV before and $-5.9 \pm 1.8$ mV after 1 mM S0100176 ($n = 7$; data not shown).

To determine whether block of Kv1.5 by S0100176 is dependent on channel opening, we recorded currents in oocytes before and after a pulse-free period of incubation with the compound. The inset of Fig. 2A presents Kv1.5 currents elicited at a test potential of $+40$ mV before and after exposure of an oocyte to 1 mM S0100176 for 8 min without pulsing at a holding potential of $-80$ mV. The initial value of the $I_{\text{drug}}/I_{\text{control}}$ relationship for pulses to the indicated test potentials of $-10$ to $+60$ mV. The inset shows current traces of Kv1.5 before (right) and after (left) addition of 1 mM S0100176. C, initial value of $I_{\text{drug}}/I_{\text{control}}$ versus test potential obtained from experiments similar to the one depicted in panel B ($n = 5$). D, time constant ($\tau_b$) for onset of block by 1 mM S0100176 derived from fitting $I_{\text{drug}}/I_{\text{control}}$ traces shown in panel B.

A common property of an open channel blocker is use dependence that reflects the dynamics of the on and off rates for drug binding. Consistent with open channel block, the inhibition of peak Kv1.5 was dependent on the pulse frequency. Currents were recorded in the absence or presence of 1 mM S0100176 during voltage steps applied at a frequency of 2 Hz to a potential of 0 mV (Fig. 3, A and B), a voltage at which channels did not exhibit measurable inactivation during the 250-ms pulses (Fig. 3A). Pulse trains were also applied at 1, 3, and 4 Hz, and the normalized peak current amplitudes were plotted as a function of the pulse number (Fig. 3C). In the absence of S0100176, Kv1.5 currents decreased by $4.1 \pm 2.8\%$, $7.6 \pm 3.1\%$, $10.1 \pm 4.8\%$, and $11.2 \pm 6.4\%$ ($n = 5$) when recorded with trains of pulses applied at 1, 2, 3, and 4 Hz,
respectively. In the presence of 1 μM S0100176, peak current was reduced by 39.4 ± 8.1% (n = 5) when pulses were applied at the very slow frequency of 0.0333 Hz. The additional block induced by a train of pulses increased with the pulsing rate. The normalized currents were suppressed by an additional 28.2 ± 3.8%, 45.5 ± 3.1%, 53.8 ± 2.7%, and 54.3 ± 2.9% (n = 5), at 1, 2, 3, and 4 Hz, respectively. Thus, S0100176 blocks Kv1.5 channels in a frequency-dependent manner, and at high pacing rates, the percentage block approximates the value obtained at the end of 1.5-s pulses applied at 0.0333 Hz. Frequency-dependent block of Kv1.5 would be an advantageous property for an antifibrillatory drug, because channels would be least affected during normal heart rates and most affected during tachycardia.

**Ala-scanning Mutagenesis of Kv1.5 Pore Residues**—Residues located in the K⁺ signature sequence and the S6 domain were chosen for the Ala scan based on their proximity to the central cavity. The 23 amino acids that were mutated to Ala; the two Ala residues in this region (Ala-501, Ala-509) were mutated to Val. S0100176 was applied at a single concentration of 15 μM, and inhibition of Kv1.5 currents was analyzed at the end of 1.5-s test pulses to +40 mV. At this concentration, wild-type Kv1.5 channels were inhibited by 95% (Fig. 4B). With the exceptions of L510A and P513A, the same pulse protocol was used to evaluate mutant channels. Because L510A Kv1.5 channels exhibited pronounced inactivation, we analyzed the inhibition of peak current amplitudes at +40 mV for this mutant. Because the P513A mutation caused a large rightward shift in the voltage of half-maximal activation (V1/2), near +70 mV, block was assessed at a test potential of +60 mV. The potency of drug block was significantly reduced (p < 0.05) by I502A, L506A, and V516A and even more (p < 0.01) by T479A, T480A, V505A, I508A, and V512A mutations (Fig. 4B). The latter five residues face the central cavity of the channel and were chosen for further characterization. Two are located at the base of the pore helix near the selectivity filter (Thr-479, Thr-480), and three residues reside in the S6 segment (Val-505, Ile-508, Val-512). The IC_{50} was determined for conservative mutations (T479S, T480S, V505A, I508(V/L), V512A) and Ala mutations (T479A, T480A, I508A) of these residues. As an example, the effects of S0100176 on T480A Kv1.5 currents at multiple potentials are shown in Fig. 5A. At +40 mV and a concentration of 60 μM, the current was only decreased by 8.7 ± 2.0% (n = 6). The IC_{50} of S0100176 was increased 3.5-fold for T479S, 88-fold for T480S, 26-fold for V505A, 9-fold for I508L, 27-fold for I508V, and 99-fold for V512A (Fig. 5B, *left side*). Mutation of Thr-479, Thr-480, and Ile-508 to the nonconservative Ala residue resulted in more pronounced increases in IC_{50} (Fig. 5B, *right side*). For example, the IC_{50} was increased 362-fold for T480A and 150-fold for I508A.

**Changes in Drug Affinity Are Independent of Kv1.5 Inactivation**—The point mutations of Kv1.5 caused significant variation in the extent of C-type inactivation of Kv1.5 and provided an opportunity to examine the potential link between inactivation and channel block by S0100176. There was no apparent linear relationship (r = 0.23) between the fold change in IC_{50}
and percent inactivation determined at a test potential of +40 mV for wild-type and mutant channels (Fig. 6).

Model of S0100176 Docking to Channel Pore—The results of the docking solution that passed several filtering steps (described under “Experimental Procedures”) is presented in Fig. 7. The docking of the compound is illustrated from three vantage points including views from the intracellular (Fig. 7A) or extracellular (Fig. 7B) sides of the membrane and a side view (Fig. 7C) facilitated by removal of one of the subunits. The side chains of residues Thr-480, Ala-501, Val-508, Ala-509, and Val-512 from at least one subunit of the tetramer were predicted to be located within less than a 4.5-Å distance to S0100176. This can be seen more clearly in a magnified stereoview (Fig. 7D) of the area outlined by the dashed lines in Fig. 7C.

If S0100176 blocks Kv1.5 channels at the site predicted by our experiments and as corroborated by the modeling, then the compound should be an equally effective inhibitor of other Kv1 channels. Accordingly, the IC$_{50}$ for Kv1.3 channels expressed in oocytes was 0.9 ± 0.1 μM (n = 4), not significantly different from the IC$_{50}$ for Kv1.5.

DISCUSSION

Atrial fibrillation is the most common chronic arrhythmia in humans. Prolongation of atrial refractoriness determines the efficacy of class III and contributes to the activity of class 1c antiarrhythmic drugs against atrial fibrillation and atrial flutter (33). However, prolongation of ventricular action potentials by these drugs can also induce long QT syndrome. One approach to minimize this side effect is the development of drugs that block potassium channels expressed in the atrium but not in the ventricle. In the human heart, the ultra-rapid delayed rectifier potassium current (I$_{Kur}$) was identified in atrial but not in ventricular tissues (2, 34). The Kv1.5 α-subunit cloned from the human heart (4) forms K$^+$ channels that conduct I$_{Kur}$ and is a key mediator of atrial repolarization (3). Thus, potent and selective blockers of Kv1.5 are of potential interest for treatment of atrial fibrillation and atrial flutter. It was well recognized previously that Kv1.5 is expressed in tissues other than the atria (e.g. vascular smooth muscle), suggesting that discovery of a cardiac-specific Kv1.5 blocker would be a difficult goal to attain. Our findings add another level of potential difficulty in the drug discovery process. The key residues in Kv1.5 that interact with S0100176 are shared in common with other Kv1 channels. This has obvious clinical implications because Kv1 channels are expressed in many tissues other than atrial muscle. In addition, a specific Kv1.5 blocker may require activity at a binding site other than the one located in the central cavity.

The crystal structures of the bacterial channels, KcsA and MthK, are believed to represent the closed and open state of the channel, respectively. However, both KcsA and MthK lack the PVP motif in the S6 domain that was proposed to be an important structural determinant for the gating of Kv channels (28), including Kv1.5. Hanner et al. (28) developed a homology model of Kv1.3, which was based on the KcsA structure that also considered the potential importance of the PVP motif in determining the open state conformation of the channel. The docking of S0100176 to this homology model indicates several residues in the pore loop (Thr-479, Thr-480) and the S6 segment (Val-505, Ile-508, Val-512) that could constitute drug binding sites. These residues face toward the inner cavity of the pore and are the same sites identified using a site-directed mutagenesis approach. However, with the exception of Thr-479, these residues were not previously reported to influence the pharmacology of Kv1.5. Based on a more limited mutagenesis approach, the S6 segment residues, Thr-507, Leu-510, and Val-514, were identified as potential sites of drug-channel interactions for quinidine, benzocaine, and bupivacaine (7, 8, 11). However, the Kv1.3/1.5 homology model predicts that these residues point away from the central cavity. Further studies are required to determine whether these drugs also interact with the residues we identified here as important for channel block by S0100176.

An emerging theme from several recent studies is that the few residues, located in the S6 domain and base of the pore helix and that face the inner cavity, form the binding site for drugs or peptides that block the open state of voltage-gated K$^+$ channels. For example, Val-551 and Ile-554 (in the S6 domain of Kv1.4) form important receptor sites for both the N-terminal inactivation gate and quaternary ammonium compounds (22). Val-551, Ile-554, Val-558, and Val-562 line the inner cavity of Kv1.4 and are homologous to Val-505, Ile-508, Val-512, and Val-516 of Kv1.5. It is also noteworthy that Ile-508 and Val-512 of Kv1.5 are located in positions equivalent to Tyr-652 and Phe-656 of HERG, which are the key residues that determine the pharmacological properties of this channel (18, 35–38). There are also several examples of the importance of the Thr residues located at the base of the pore helix and part of the K$^+$...
signature sequence. The T479S mutation is equivalent to the T441S mutation in Shaker channels, which reduced internal TEA affinity 10-fold (12). This residue is also important for binding of bupivacaine (8), benzocaine (11), and S0100176. Interestingly, the IC<sub>50</sub> of S0100176 was increased even more by mutation of Thr-480 to Ser. The highly conserved Thr (or Ser) residues of the K<sup>H11001</sup> signature sequence are also reported to be important sites of interaction with blockers of HERG, Shaker, and KCNQ1 channels (12, 19–22, 27, 36).

There are several limitations of the approach we used to identify the putative binding site for S0100176. First, we measured the effect of mutations on the block of Kv1.5 channel current rather than directly assaying for altered ligand binding. Second, altered drug sensitivity caused by mutation of a specific amino acid may have been caused by an allosteric effect. This is especially possible for Val-512, which is located between the two Pro residues that are predicted to contribute to significant rearrangement of the S6 domain during gating. Third, the potency of drug block is usually underestimated when currents are measured in intact oocytes. Nonetheless, our approach identified residues that face the central cavity and would, therefore, be expected to be potential interaction sites for a drug that preferentially blocks open channels.

In summary, we have identified the residues Thr-479, Thr-480, Val-505, Ile-508, and Val-512 as the most important components of the putative binding site for a novel Kv1.5 open channel blocker. It is becoming increasingly clear that the few residues located at the base of the pore helix and on the S6 domains that directly face the inner cavity are important components of the binding sites for compounds of diverse structures that preferentially block Kv channels in the open state. Blockers of Na<sup>+</sup>/Ca<sup>2+</sup> channels also bind to pore-lining residues within the S6 segment and/or regions near the selectivity filter (14–17). Future studies will analyze whether Kvβ-related changes in pharmacology correlate to interactions with these specific residues.

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REFERENCES

FIG. 7. Pore homology models of Kv1.5/Kv1.3 and docking of S0100176. S5–S6 domains of the open state channel as viewed from the intracellular side (A) or extracellular side (B) of the membrane. S0100176 is shown as a Corey-Pauling-Koltun space-filling model in the docked position predicted by QXP. C, homology model of three channel subunits with docked drug as viewed from the side with the intracellular solution at the bottom. The dotted red box represents the area that is magnified in panel D. The residues identified as most important for drug interaction are shown as colored sticks (green: Thr-479 and Thr-480; yellow: Val-505, Val-512; orange: Ile-508). D, stereoview of the region outlined in panel C with S0100176 shown as Corey-Pauling-Koltun sticks. The pyridine group of the drug faces downward and is within 4.3 Å of Ile-508 in the right subunit. The phenyl of the benzamide group faces upward and is 2.6–4.0 Å from the Thr-479 and Thr-480 residues of all 3 subunits. The sulfonylamino group faces Val-505 of the left subunit, and the toluene group faces downward and is 3.6 Å away from Val-512 of the left subunit.
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