Discovery of PF-04457845: A Highly Potent, Orally Bioavailable, and Selective Urea FAAH Inhibitor


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ABSTRACT Fatty acid amide hydrolase (FAAH) is an integral membrane serine hydrolase that degrades the fatty acid amide family of signaling lipids, including the endocannabinoid anandamide. Genetic or pharmacological inactivation of FAAH leads to analgesic and anti-inflammatory phenotypes in rodents without showing the undesirable side effects observed with direct cannabinoid receptor agonists, indicating that FAAH may represent an attractive therapeutic target for the treatment of inflammatory pain and other nervous system disorders. Herein, we report the discovery and characterization of a highly efficacious and selective FAAH inhibitor PF-04457845 (23). Compound 23 inhibits FAAH by a covalent, irreversible mechanism involving carbamylation of the active-site serine nucleophile of FAAH with high in vitro potency (k_{inact}/K_{i} and IC_{50} values of 40300 M^{-1} s^{-1} and 7.2 nM, respectively, for human FAAH). Compound 23 has exquisite selectivity for FAAH relative to other members of the serine hydrolase superfamily as demonstrated by competitive activity-based protein profiling. Oral administration of 23 at 0.1 mg/kg results in efficacy comparable to that of naproxen at 10 mg/kg in a rat model of inflammatory pain. Compound 23 is being evaluated in human clinical trials.

KEYWORDS FAAH, endocannabinoid, irreversible inhibitor, clinical candidate

Fatty acid amide hydrolase (FAAH) is an integral membrane enzyme that degrades the fatty acid amide family of signaling lipids, including the endocannabinoid anandamide.1–3 FAAH is a serine hydrolase that employs an unusual serine→serine→lysine catalytic triad to efficiently hydrolyze both amides and esters.4 Genetic or pharmacological inactivation of FAAH leads to elevated endogenous levels of fatty acid amides5 and a range of analgesic effects in various animal models of inflammation and chronic pain.6–9 Importantly, these behavioral phenotypes occur in the absence of the undesirable side effects observed with direct cannabinoid receptor agonists, indicating that FAAH may represent an attractive therapeutic target for the treatment of inflammatory pain and related conditions.

Several classes of reversible and irreversible covalent FAAH inhibitors have been reported (Figure 1).8,10 Electrophilic ketone inhibitors such as OL-135 (1) reversibly form an enzyme-stabilized hemiketal between the active-site Ser241 and the electrophilic carbonyl.11–12 Carbamates such as URB597 (2) irreversibly inhibit FAAH by carbamylation of Ser241 with the alcohol group serving as the leaving group.13–15 We and others have previously reported a series of piperidine/piperazine urea FAAH inhibitors (e.g., 3–7).16–21 Mechanistic studies revealed that PF-750 (4) inhibited FAAH in a time-dependent manner by covalently modifying the enzyme’s active site nucleophile, despite the inherent stability of the urea functional group.16 PF-750 was confirmed to be covalently attached to the Ser241 of FAAH through a carbamate linkage by a X-ray crystal structure of humanized rat (h/r) FAAH in complex with PF-750.22 Additional medicinal chemistry efforts led to the identification of a more potent series of FAAH inhibitors based on a biaryl ether piperazine/piperidine urea scaffold (e.g., 6 and 7).17,21 The prototype from this series, PF-3845 (7), inhibits FAAH by covalently modifying the enzyme’s active site serine nucleophile as expected and is selective for FAAH relative to other mammalian serine hydrolases as demonstrated by activity-based protein profiling (ABPP).17 In addition, several groups have recently...
reported apparent noncovalent FAAH inhibitors with no obvious serine-interacting groups (i.e., 8).  

![Image](https://example.com/image.png)

We reasoned that in the case of a target like FAAH, where inhibition leads to elevated levels of endogenous N-acyl ethanolamine (NAE) substrates by up to 10–20-fold in central tissues, an irreversible inhibitor may be beneficial because the nonequilibrium binding mechanism limits the competition with high endogenous substrate concentrations leading to increased biochemical efficiency.  

Furthermore, the pharmacodynamic effect resulting from covalent inhibition often outlasts the pharmacokinetics of the inhibitor, because enzyme activity can be recovered only by synthesis of new enzyme or, in some cases, by slow hydrolysis of the covalent enzyme adduct. To minimize the risk associated with developing a covalent inhibitor, two critical design/screening principles were emphasized—selectivity to avoid off target toxicity and potency to achieve as low a dose as possible.  

In this manuscript, we describe the evolution of a series of benzylidine piperidine urea FAAH inhibitors with improved potency and pharmaceutical properties, culminating in the clinical candidate PF-04457845 (23). Given the lipophilic nature of the fatty acid amide substrates of FAAH (i.e., clog P of anandamide = 6.2), it is not surprising that adding lipophilicity to FAAH inhibitors in the acyl chain binding region improves potency.  

The major challenge is balancing potency with appropriate physicochemical properties to identify FAAH inhibitors with high oral bioavailability that are suitable for clinical development. During the evolution of 23 from 7, we focused on improving the potency without compromising essential druglike properties. One strategy was to rigidify the conformation of the molecule within the acyl chain binding domain to reduce the entropic penalty of binding by having less rotatable bonds and lowering the conformational energy of the active conformer.  

Another key area of investigation was focused on finding optimal places in the molecule to incorporate polarity for modulating parameters such as clog P and pH_{50}, while simultaneously optimizing lipophilic interactions within the acyl chain binding pocket.  

We initially sought to explore piperidine isosteres with different ring sizes and conformational constraints with the goal of optimally projecting the biaryl ether moiety into the acyl chain binding channel. Because these ureas inhibit FAAH irreversibly, the potency was measured as the second order rate constant $k_{\text{inact}}/K_i$ using an enzyme-coupled human FAAH (hFAAH) and rat FAAH (rFAAH) assay as described previously.  

Unlike IC_{50} values, $k_{\text{inact}}/K_i$ values are independent of preincubation times and substrate concentrations and are considered the best measure of potency for irreversible inhibitors. We found that incorporating a methyleneepiperidine into the previous quinoline (i.e., 4) and benzothioephene (i.e., 5) urea series to give analogues 9 and 10 resulted in improved FAAH potency, particularly against the rat enzyme. Therefore, we made the corresponding methyleneepiperidine analogue in the PF-3845 biaryl ether piperidine series (Table 1). We were gratified to see that methyleneepiperidine 11 was approximately 2- and 4-fold more potent than the corresponding methylpiperidine 7 for hFAAH and rFAAH, respectively. Furthermore, 11 was equipotent against the hFAAH and rFAAH enzymes. We also prepared the corresponding pyrrolidine (12–14) and azetidine (15) analogues, but these were considerably less active. We do not know the precise reason why the activity drops off with smaller ring sizes, but we speculate that the urea is not able to be activated to the same extent upon binding in the FAAH active site.  

In addition, we prepared the (E)- and (Z)-3-methyleneepiperidine analogues (16 and 17). The (E)-isomer 16 was approximately 19-fold less potent than 11 for hFAAH, while the activity was almost completely abolished in the case of the

Table 1. Human and Rat FAAH Potency ($k_{\text{inact}}/K_i$ values) for Piperidine Spacer Analogues

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>hFAAH $k_{\text{inact}}/K_i$ (M$^{-1}$s$^{-1}$)</th>
<th>rFAAH $k_{\text{inact}}/K_i$ (M$^{-1}$s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td></td>
<td>12,600 ± 3000</td>
<td>3900 ± 780</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>21,600 ± 6600</td>
<td>15,100 ± 3400</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>88</td>
<td>NA</td>
</tr>
<tr>
<td>13</td>
<td>&lt;16</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>144 ± 47</td>
<td>NA</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>298 ± 110</td>
<td>173 ± 31</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>1150 ± 57</td>
<td>233 ± 17</td>
</tr>
<tr>
<td>17</td>
<td></td>
<td>35 ± 6</td>
<td>22 ± 4</td>
</tr>
</tbody>
</table>

*a Each $k_{\text{inact}}/K_i$ value corresponds to an average of at least two independent determinations (±SD) and was obtained using the method described in the Supporting Information.*
We next examined the structure–activity relationship (SAR) of the 3-aminopyridyl portion of the molecule, which constitutes the leaving group upon carbamylation of the FAAH active site serine. Our previous work on benzothio- phene FAAH inhibitors indicated that a heteroaryl group was preferred at this position. We were especially interested in introducing substituents next to the pyridyl nitrogen as well as exploring other heterocycle replacements, because of the potential cytochrome P450 metabolic liability associated with unsubstituted pyridines. Indeed, compound 11 exhibited moderate CYP2D6 and CYP3A4 inhibition (Table 2). As observed with previous urea FAAH inhibitors, the 3-aminopyridine analogue (11) was superior to the 2-aminopyridine (18) and aniline (19) analogues. Introduction of a methyl (20) or methoxy (21) substituent at the 6-position of the 3-aminopyridine provided analogues with slightly reduced potency. The methylpyridine analogue (20) had less CYP3A4 inhibition, but the CYP2D6 inhibition was unaffected. We next explored similar heterocycles with reduced basicity while maintaining the position of the nitrogen relative to the 3-aminopyridine. As expected, replacement of the pyridine with the less basic pyrazine (22) or pyridazine (23) removed any potential CYP liabilities. Unexpectedly, compounds 22 and 23 displayed a 2-fold higher \( k_{\text{inact}}/K_i \) value for hFAAH as compared to 11. We also assessed several 5-membered and 5,6 fused heterocycles (e.g., 24 and 25). These compounds generally showed reduced potency for hFAAH but increased potency for rFAAH. For example, the dimethylisoxazole 24 was 5-fold less potent for hFAAH but 2-fold more potent for rFAAH as compared to 23. This highlights the importance of screening compounds against both the hFAAH and the rFAAH enzymes. Thus, the benzylidenepiperidine pyridazine urea scaffold appears to be optimal.

We next surveyed the importance of the pyridyl nitrogen as well as the position and nature of the substituent on the left-hand side biaryl ether moiety (Table 3). Removal of the pyridine nitrogen (i.e., compound 26) resulted in a 2-fold reduction in potency for hFAAH. An additional 10-fold loss in potency resulted from removal of the trifluoromethyl substituent as observed for compound 27. The trifluoromethyl group at the 5-position of the 2-pyridyl ring makes key van der Waals contacts in the acyl chain-binding pocket that are important for potency in an analogous fashion to that described for PF-3845 (7). In contrast, substituents at the 6-position (34), 4-position (32), or 5-position (35) impair potency, demonstrating that steric bulk is not accommodated in that region. The position of the nitrogen in the pyridine ring is also important. Interestingly, the potency of 28 for hFAAH was within 2-fold of

### Table 2. Human and Rat FAAH Potency (\( k_{\text{inact}}/K_i \) Values) and CYP IC\(_{50} \) Values for Heteroaryl Urea Analogues

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>hFAAH ( k_{\text{inact}}/K_i ) (M(^{-1})s(^{-1}))</th>
<th>rFAAH ( k_{\text{inact}}/K_i ) (M(^{-1})s(^{-1}))</th>
<th>CYP inhibition IC(_{50} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td></td>
<td>21,600 ± 6000</td>
<td>15,100 ± 3400</td>
<td>2D6 1.4 μM</td>
</tr>
<tr>
<td>18</td>
<td>Ph</td>
<td>6090 ± 3000</td>
<td>563 ± 98</td>
<td>3A4(^a) 4.3 μM</td>
</tr>
<tr>
<td>19</td>
<td>Ph</td>
<td>4800 ± 230</td>
<td>584 ± 34</td>
<td>3A4(^b) 0.8 μM</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td>13,100 ± 5100</td>
<td>5210 ± 1200</td>
<td>2D6 1.6 μM</td>
</tr>
<tr>
<td>21</td>
<td></td>
<td>16,000 ± 3100</td>
<td>11,400 ± 2900</td>
<td>3A4(^c) 3.0 μM</td>
</tr>
<tr>
<td>22</td>
<td></td>
<td>42,600 ± 16,000</td>
<td>23,700 ± 3800</td>
<td>2D6 25.1 μM</td>
</tr>
<tr>
<td>23</td>
<td></td>
<td>40,300 ± 11,000</td>
<td>32,400 ± 8600</td>
<td>3A4(^b) 30 μM</td>
</tr>
<tr>
<td>24</td>
<td></td>
<td>7990 ± 1600</td>
<td>54,400 ± 14,000</td>
<td>3A4(^c) 30 μM</td>
</tr>
<tr>
<td>25</td>
<td></td>
<td>3930 ± 380</td>
<td>30,200 ± 7200</td>
<td>2D6 14.5 μM</td>
</tr>
</tbody>
</table>

\(^{a}\) Each \( k_{\text{inact}}/K_i \) value corresponds to an average of at least two independent determinations (±SD) and was obtained using the method described in the Supporting Information. Midazolam was used as the CYP3A4 substrate. Testosterone was used as the CYP2A substrate. 23, but the potency for rFAAH was dramatically reduced. Finally, several other substituents were shown to be tolerated at the 5-position (i.e., 29–31), and the trifluoromethyl group proved to be optimal.

These medicinal chemistry efforts culminated in the discovery of PF-04457845 (compound 23, Table 2), a benzylidenepiperidine pyridazine urea that displayed a 3- and 8-fold higher \( k_{\text{inact}}/K_i \) value for hFAAH and rFAAH, respectively, as compared to PF-3845 (7). We also measured FAAH potency for 23 by determining IC\(_{50} \) values with a 60 min preincubation time, and the IC\(_{50} \) was 7.2 ± 0.63 nM for hFAAH and 7.4 ± 0.62 nM for rFAAH (see the Supporting Information). Key features of 23 that contribute to its potency include the p-trifluoromethyl substituent and the pyridyl nitrogen on the biaryl ether moiety, the benzylidenepiperidine urea, and the 3-aminopyridazine leaving group. It is worthwhile to note that not only did the pyridine and pyridazine heterocycles contribute to the improved potency, but they also served to lower the lipophilicity and improve the physicochemical properties (i.e., \( clog P = 3.9 \), PSA = 80) and ADME parameters (vide supra) for 23.

PF-04457845 (23) was synthesized in six linear steps with a 40% overall yield from commercially available starting...
materials (Scheme 1). The synthesis began with a nuclo-
philic aromatic substitution of 3-(hydroxymethyl)phenol
with 2-chloro-5-(trifluoromethyl)pyridine in the presence
of K₂CO₃ to form biaryl ether 35. Treatment of benzyl
alcohol 35 with thionyl chloride provided the correspond-
ing benzyl chloride, which was reacted with triethyl
phosphite to give the benzylphosphonate 36. Horner–Wadsworth–Emmons olefination of 1-Boc-4-piperidone
with 36 in the presence of potassium tert-butoxide
followed by removal of the Boc protecting group using HCl in dioxane afforded the benzylidinepiperidine 37
as the hydrochloride salt. Finally, reaction of 37 with
phenyl pyrazidin-3-ylcarbamate in the presence of
dissopropylethyl amine provided the urea 23.

We next assessed the selectivity of PF-04457845 (23)
against the serine hydrolase superfamily of enzymes (> 200
members in humans) of which FAAH is a member.₁₆⁻₁₈
Compound 23 was profiled at 10 and 100 μM utilizing
a functional proteomic screen based on competitive
activity-based protein profiling (ABPP)³¹ in brain membrane
and soluble liver proteomes derived from both human
and mouse. We used a rhodamine-tagged fluorophosphonate
(FP) ABPP probe, which serves as a general activity-based
profiling tool for the serine hydrolase superfamily.³² Serine
hydrolases that show significant reductions in FP probe
labeling intensity in the presence of inhibitor are scored as
targets of the compound. The selectivity of 23 was compared
to that of the carbamate FAAH inhibitor URB597 (2)
(Figure 1). Both 23 and 2 completely inhibited FAAH in
human and mouse membrane proteomes at both 10 and
100 μM with no off targets. However, in soluble proteomes
of liver, the profile of 23 was drastically different than that of 2.
Compound 23 was completely selective as none of the
other FP-reactive serine hydrolases were inhibited even at 100 μM.
In contrast, 2 displayed multiple off targets as it blocked FP
labeling of several additional serine hydrolases, particularly
among FP-labeled proteins migrating between 55 and 65 kDa.
Several off targets were completely inhibited even at 10 μM 2.
Thus, 23 is exquisitely selective for FAAH relative to other
mammalian serine hydrolases. In addition, 23 exhibited a
favorable selectivity profile when screened against a 68 target
CEREP panel (Table S1 in the Supporting Information).

PF-04457845 (23) has an excellent pharmacokinetic
profile in rats and dogs as well as in human in vitro assays.
The permeability of 23 (A-B, 15.2 × 10⁻⁶ cm/s; and B-A, 20.2 ×
10⁻⁶ cm/s) across MDCK cells was moderate, with no
apparent efflux due to Pgp (B/A ratio is 1.33). Compound
23 has low clearance and moderate volume of distribution
in rats and dogs (Table 4). Compound 23 was rapidly absorbed
following oral administration of a methylcellulose suspension
of the crystalline material with a bioavailability of 88 %
in rats and 58 % in dogs. Low risk for drug–drug interactions
is anticipated based on in vitro CYP inhibition studies in
human liver microsomes using relevant substrates (Table S2
in the Supporting Information). The potential of 23 to form
reactive metabolites was investigated, and no glutathione
conjugate of 23 was observed from in vitro rat or human
hepatocyte incubations. The half-life of 23 in human liver
microsomal experiments was determined to be 105 min
tested at 0.8 mg/mL protein concentration. The microsomal
protein binding of 23 was 90 %. Human blood clearance
based on these in vitro experiments was predicted to be
0.6 mL/min/kg. On the basis of this data, 23 is predicted to be
suitable for once a day oral administration in humans.

Table 3. Human and Rat FAAH Potency (kiact/Ki, Values) of Biaryl
Ether Analogues

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>bFAAH Kᵢact/Kᵢ (M⁻¹s⁻¹)</th>
<th>rFAAH Kᵢact/Kᵢ (M⁻¹s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>F₃C</td>
<td>40,300 ± 11,000</td>
<td>32,400 ± 8600</td>
</tr>
<tr>
<td>26</td>
<td>F₃C</td>
<td>18,900 ± 3500</td>
<td>22,900 ± 7600</td>
</tr>
<tr>
<td>27</td>
<td>Ph</td>
<td>1530 ± 300</td>
<td>1900 ± 220</td>
</tr>
<tr>
<td>28</td>
<td>F₃C</td>
<td>26,600 ± 5100</td>
<td>2020 ± 450</td>
</tr>
<tr>
<td>29</td>
<td>Δ</td>
<td>28,800 ± 5400</td>
<td>46,300 ±19,000</td>
</tr>
<tr>
<td>30</td>
<td>EtO</td>
<td>9230 ± 2200</td>
<td>11,700</td>
</tr>
<tr>
<td>31</td>
<td></td>
<td>21,500 ± 9200</td>
<td>5530 ± 1800</td>
</tr>
<tr>
<td>32</td>
<td></td>
<td>1580 ± 590</td>
<td>-</td>
</tr>
<tr>
<td>33</td>
<td></td>
<td>2200 ± 240</td>
<td>256 ± 75</td>
</tr>
<tr>
<td>34</td>
<td></td>
<td>1090 ± 260</td>
<td>586 ± 100</td>
</tr>
</tbody>
</table>

*Each Kᵢact/Kᵢ value corresponds to an average of at least two independent determinations (±SD) and was obtained using the method described in the Supporting Information.*

Δ

**Scheme 1.** Synthesis of PF-04457845 (23)

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\[
\text{\textit{a}} \quad \text{SOCl}_2, \text{CICH}_2, \text{room temperature, } 2 \text{ h, quant.} \\
\text{\textit{b}} \quad \text{K}_2\text{CO}_3, \text{DMF, } 90 \text{°C, } 16 \text{ h, quant.} \\
\text{\textit{c}} \quad \text{P}(/\text{OEt})_2, \text{CICH}_2, \text{room temperature, } 2 \text{ h, quant.} \\
\text{\textit{d}} \quad \text{N-Boc-piperidin}-4\text{-one, } t\text{-BuOK, THF, } 69 \% \\
\text{\textit{e}} \quad \text{HCl, dioxane, } 84 \%
\]```
Figure 1. Selectivity profiling of PF-04457845 (23) and URB597 (2) by competitive ABPP. Gel images of proteomes labeled with FP-rhodamine in the presence or absence of FAAH inhibitors (lane 1, DMSO; lane 2, 2 at 100 μM; lane 3, 2 at 10 μM; lane 4, 23 at 100 μM; lane 5, 23 at 10 μM; and lane 6, DMSO). Gel profiles of FP-rhodamine-labeled mouse and human (A) liver soluble serine hydrolases and (B) brain membrane serine hydrolases in the presence or absence of 23 and 2. The band on the gel corresponding to the FAAH enzyme is highlighted by the black arrow. Note that 2, but not 23, blocks FP-rhodamine labeling of several liver serine hydrolases (red arrows and bracket). For both A and B, fluorescent gel images are shown in gray scale.

We next assessed in vivo efficacy of PF-04457845 (23) in a rat model of inflammatory pain. Subcutaneous injection of complete Freund’s adjuvant (CFA) into the plantar surface of the hind paw produced a significant decrease in mechanical paw withdrawal threshold (PWT) after 5 days postinjection as previously described (Figure 2).17 Oral administration of 23 caused a significant inhibition of mechanical allodynia measured after 4 h with a minimum effective dose (MED) of 0.1 mg/kg, which is ~30-fold lower than PF-5845 (7) (MED of 5 mg/kg). Furthermore, at 0.1 mg/kg (p.o.), 23 inhibited the pain response to a comparable degree as the nonsteroidal anti-inflammatory drug naproxen at 10 mg/kg (Figure 2). It has been reported that a near-complete blockade of FAAH activity is required to maintain elevated anandamide levels in vivo.14,17 In full agreement with this observation, the robust in vivo efficacy by 23 was accompanied by near complete inhibition of FAAH activity with concomitant elevations in anandamide and other fatty acid amides in brain and plasma (details will be described elsewhere). The degree of inhibition in pain response by 23 was similar at all efficacious doses likely because near complete FAAH inhibition is necessary to obtain in vivo efficacy, which was achieved at all doses starting at 0.1 mg/kg.

In conclusion, PF-04457845 (23) is a potent FAAH inhibitor that covalently modifies the active-site serine nucleophile of FAAH with exquisite selectivity relative to other members of the serine hydrolase superfamily. The compound has excellent pharmacokinetic properties and is suitable for once a day oral administration. It is efficacious in the CFA model of inflammatory pain in rats. Compound 23, at 0.1 to 10 mg/kg, produced a reduction of mechanical allodynia (hyperalgesia) in rats (black bars). The effect of the nonsteroidal anti-inflammatory drug naproxen (10 mg/kg, po, hatched bar) is shown for comparison. The antihyperalgesic responses were determined at 4 h following drug treatment and were significantly different for 23 (0.1–10 mg/kg, po) and naproxen (10 mg/kg, po) as compared to vehicle-treated groups (p<0.05), n=8 rats per group.

has excellent pharmacokinetic properties and is suitable for once a day oral administration. It is efficacious in the CFA model of inflammatory pain in rats. Compound 23 is currently being evaluated in human clinical trials with the potential to treat chronic pain and other nervous system disorders.

**SUPPORTING INFORMATION AVAILABLE** Experimental procedures for the synthesis of 11–34, assay protocols, and two supplementary tables. This material is available free of charge via the Internet at http://pubs.acs.org.

**AUTHOR INFORMATION**
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**REFERENCES**


(4) Patricelli, M. P.; Cravatt, B. F. Fatty acid amide hydrolase competitively degrades bioactive amides and esters through...


(30) We have proposed that the urea may be activated upon binding in the active site of FAAH by undergoing a conformational change that diminishes conjugation of the nitrogen lone pair with the carbonyl, which would activate the urea for attack by the serine nucleophile (see refs 16 and 18).


NOTE ADDED AFTER ASAP PUBLICATION This paper was published on the Web on November 15, 2010 with an error in structure PP-750 (4). The corrected version was reposted on January 19, 2011.