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Exploration of a fundamental substituent effect of α-ketoheterocycle enzyme inhibitors: Potent and selective inhibitors of fatty acid amide hydrolase

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ABSTRACT

A series of C4 substituted α-ketooxazoles were examined as inhibitors of the serine hydrolase fatty acid amide hydrolase in efforts that further define and generalize a fundamental substituent effect on enzyme inhibitory potency. Thus, a plot of the Hammett σ_m versus $-\log K_i$ provided a linear correlation ($R^2 = 0.90$) with a slope of 3.37 ($\rho = 3.37$), that is of a magnitude that indicates that of the electron-withdrawing character of the substituent dominates its effects (a one unit change in σ_m provides a >1000-fold change in K_i).

Fatty acid amide hydrolase (FAAH)[1,2] is the enzyme that serves to hydrolyze endogenous lipid amides[3,4] including anandamide (**1a**)[5] and oleamide (**1b**),[6] Fig. 1. Its distribution is consistent with its role in degrading and regulating such signaling fatty acid amides at their sites of action.[3] Although it is a member of the amidase signature family of serine hydrolases, for which there are a number of prokaryotic enzymes, it is currently the only characterized mammalian enzyme bearing the family's unusual Ser–Ser–Lys catalytic triad.[7,8]

Due to the therapeutic potential of inhibiting FAAH[9] especially for the treatment of pain,[10] inflammation,[11] or sleep disorders,[12] there has been increasing interest in the development of selective and potent inhibitors of the enzyme.[9] Early studies shortly following the initial discovery and characterization of FAAH led to the demonstration that the endogenous sleep-inducing molecule 2-octyl α-bromoacetoacetate is an effective FAAH inhibitor,[13] the disclosure of a series of nonselective, reversible inhibitors bearing an electrophilic ketone (e.g., trifluoromethyl ketone-based inhibitors),[14,15] and the reports of a set of irreversible inhibitors[16] (e.g., fluorophosphonates and sulfonyl fluorides). To date, two classes of inhibitors have been disclosed that provide opportunities for the development of inhibitors with therapeutic potential. One class is the reactive aryl carbamates and ureas[17–24] that irreversibly acylate a FAAH active site serine.[25] A second class is the α-ketoheterocycle-based inhibitors[26–29] that bind to FAAH via reversible hemiketal formation with an active site serine. Many of these latter competitive inhibitors are not only potent and extraordinarily selective for FAAH versus other mammalian serine hydrolases,

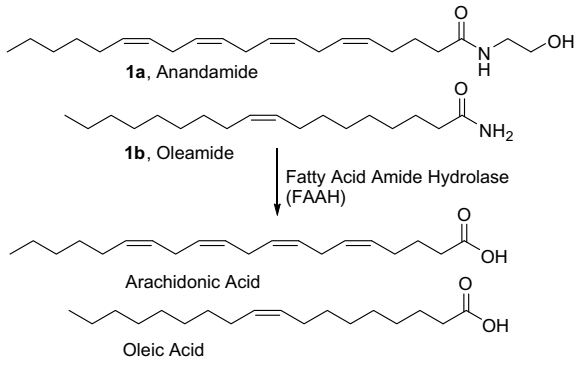

Figure 1. FAAH Substrates.

but also members of this class have been shown to be efficacious analgesics in vivo.[28]

In the course of these latter studies, we disclosed a fundamental substituent effect in which a well-defined correlation between the electronic character of a para substituent (Hammett σ_p) and the inhibitor potency ($-\log K_i$) was observed.[27] Thus, the inhibitor potency was found to smoothly increase as the electron-withdrawing character of the substituent increased, and the magnitude of the effect was remarkably large ($\rho = 2.7–3.0$)[26,27] indicating that a unit change in σ_p leads to nearly a 1000-fold increase in K_i. Presumably this reflects the electronic effect of the substituent on activating the electrophilic carbonyl toward nucleophilic attack by the FAAH active site catalytic Ser. Herein, we further generalize this fundamental effect to include meta substituents on the α-ketoheterocycle.

Whereas the former para substituents are directly conjugated with the electrophilic carbonyl, the meta substituents would exert

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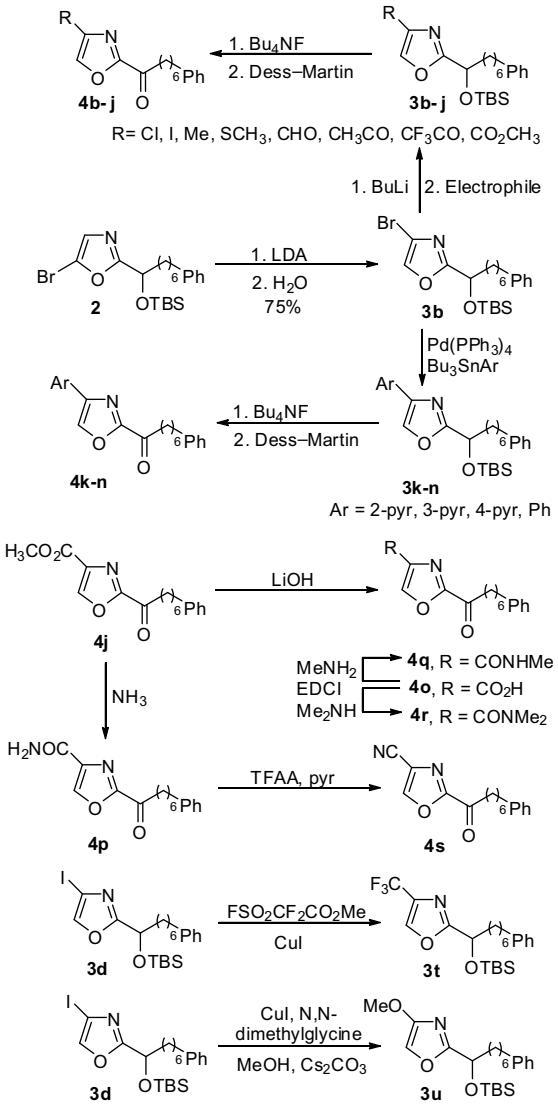
their effects through their inductive electron-withdrawing properties. Moreover and although intuitive expectations might suggest that such a non-conjugated substituent effect might be small, a comparison of Hammett σ_p and σ_m constants suggests that the magnitude of the effects may be surprisingly similar and, in some instances, even enhanced (e.g., F, Cl, Br, and I).

The candidate inhibitors bearing a varied C4 oxazole substituent were accessed from the readily available **2**,[26] enlisting its in situ conversion to the isomeric 4-bromooxazole via a halogen dance rearrangement, Scheme 1.[30] Thus, C4-lithiation of **2** followed by its in situ rearrangement to the more stable 5-lithio-4-bromooxazole[31] and its quench with water provided **3b**, the requisite precursor for the series of derivatives to be examined. These were accessed by metallation of **3b** with *n*-BuLi or *t*-BuLi followed by reaction with appropriate electrophiles (NCS, I_2, CH_3I, $(MeS)_2$, DMF, CH_3CONMe_2, CF_3CO_2Et, $NCCO_2Me$). Similarly, the C4 pyridine (**3k**, **3l**, and **3m**) and phenyl (**3n**) derivatives were prepared from bromide **3b** using a Stille coupling reaction with the respective pyridyl or phenyl tributylstannanes. Many of these derivatives served as precursors to additional candidate inhibitors bearing further modified C4 substituents. Methyl ester **4j** was directly converted to its corresponding carboxylic acid **4o** and carboxamide **4p** using LiOH and methanolic ammonia, respectively. Carboxylic acid **4o** was also coupled with methylamine and dimethylamine to give the substituted carboxamides **4q** and **4r**. Carboxamide **4p** was dehydrated with TFAA and pyridine to provide nitrile **4s**. The trifluoromethyl derivative **3t** was prepared from iodide **3d** using the method developed by Chen et al.[32] and iodide **3d** also served as the precursor to methyl ether **3u**.[33] In each case, deprotection of the TBS ether followed by Dess–Martin periodinane oxidation[34] of the liberated alcohol yielded the corresponding α-ketooxazole (**4b–u**).

The FAAH inhibition derived from the examination of the series of inhibitors and the correlation derived from a plot of $-\log K_i$ versus σ_m ($\rho = 3.37$, $R^2 = 0.90$ excluding **4e**, **4m**, **4p**, **4u**) are provided in Fig. 2. The magnitude of the effect defined by the correlation is large ($\rho = 3.37$) and satisfyingly comparable to that observed with σ_p ($\rho = 3.0$)[27] where a unit change in σ_m leads to an increase in the K_i of more than 1000-fold. As such and although the substituents may engage in additional, more subtle interactions at the enzyme active site, the magnitude of the electronic effect indicates that it dominates the behavior of the FAAH inhibitors.

Importantly, this allows one to quantitatively predict a K_i from the correlation based on the Hammett substituent constant (σ_p and σ_m) or use the measured K_i to draw inferences about active site binding that might not be known a priori. As an example of the latter, we can confidently establish that **4o** binds the FAAH active site as its deprotonated carboxylate ($\sigma_m = 0.02$) versus carboxylic acid ($\sigma_m = 0.35$) from the measured K_i, and this conclusion is reasonable given the pH of the enzyme assay conditions (pH = 9.0).[26] More subtly, we were able to establish that aldehyde **4g** (and trifluoromethyl ketone **4i**) exists in protic solution as a gem diol (at C4, not C2; ^1H and ^{13}C NMR, data in Supporting Information) and that it inhibits FAAH with a potency at a level more consistent with this C4 substituent gem diol versus carbonyl active site binding. Although the latter $C(OH)_2CF_3$ gem diol most likely suffers significant destabilizing steric interactions at the enzyme active site com-



Scheme 1.

cmpd	R	K_i, nM	cmpd	R	K_i, nM
4a	H	48	**4k**	2-Pyr	1.9
4b	Br	3.0	**4l**	3-pyr	18
4c	Cl	4.0	**4m**	4-pyr	1.6
4d	I	6.5	**4n**	Ph	65
4e	CH_3	520	**4o**	CO_2H	53
4f	SCH_3	29	**4p**	$CONH_2$	1.6
4g	CHO	55	**4q**	CONHMe	1.8
4h	$COCH_3$	2.0	**4r**	$CONMe_2$	35
4i	CF_3CO	470	**4s**	CN	0.5
4j	CO_2CH_3	3.4	**4t**	CF_3	3.7
			4u	OMe	740

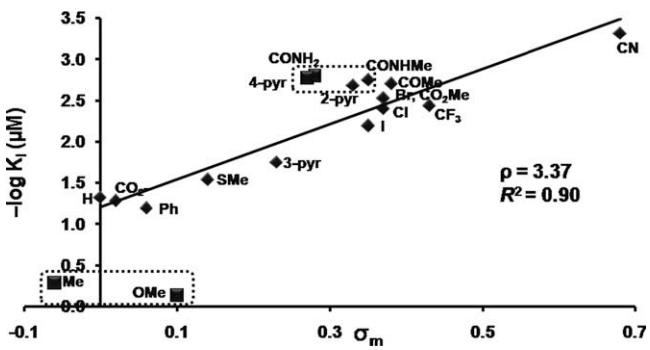


Figure 2. Rat FAAH inhibition (K_i, nM) and plot of σ_m versus $-\log K_i$.

parable to that of a *t*-butyl substituent, the measured K_i of the hydrated aldehyde ($CH(OH)_2$) is of a magnitude that suggests it may provide a good estimate of the σ_m for this substituent (0.02 for $CH(OH)_2$ vs 0.35 for CHO). That is, the correlation between σ_m and K_i is sufficiently dependable that deviations from the expectations can be utilized to establish features of active site binding not a priori known.

In this correlation, there are several inhibitors (**4m**, **4k**, **4p**, and **4q**) that deviate productively from expectations being more potent than predicted. All four could benefit from additional H-bonding at the active site that may increase affinity beyond that expected. Based on their relative K_i's, the 4-pyridyl derivative **4m** and, to a lesser extent, the 2-pyridyl derivative **4k** may interact with H-bond donors including the mobile catalytic Lys142 at the FAAH active site[26] where such a potential H-bond may be regarded not only as a conventional H-bond stabilizing interaction, but also as a partial protonation of the pyridyl nitrogen enhancing its electron-withdrawing properties. Similarly, the primary carboxamide **4p** and, to a lesser extent, the secondary carboxamide **4q** productively deviate from correlation expectations, whereas the tertiary carboxamide **4r** falls below extrapolated[35] expectations. Attractive explanations for this behavior include questions on the accuracy of the carboxamide σ_m, a productive H-bonding interaction of RCONHR at the FAAH active site for **4p** and **4q** (but not **4r**) that further increase affinity, and/or destabilizing steric interactions that emerge only with the tertiary amide **4r**. Two substituents (–Me, –OMe) display substantial nonproductive deviations from the correlation. Although we do not yet have attractive explanations for their behavior, both represent electron-donating and electron-rich substituents whose activity is predicted to be among the poorest. Thus, while additional substituent features can and will modulate the binding affinity of the candidate inhibitors (e.g., H-bonding, hydrophobic, or steric interactions), the magnitude of the electronic effect of the substituent ($\rho = 3.37$) indicates that the latter will typically dominate, especially for small and simple substituents.

Finally, the oxazole substituents in such inhibitors not only influence the FAAH inhibitor potency, but they can have an equally remarkable impact on the FAAH inhibition selectivity.[26] Although there are no other characterized mammalian members of the serine hydrolase family that bear the amidase signature sequence and its unusual Ser–Ser–Lys catalytic triad and no resulting close family of enzymes against which to counter-screen the candidate inhibitors, a close collaboration with Professor Cravatt led to the implementation of a proteome-wide assay capable of simultaneously interrogating all mammalian serine hydrolases applicable to assessing the selectivity of reversible enzyme inhibitors.[36] This assay, which requires no modification of the inhibitor, no purified protein for conventional substrate assay, no knowledge of candidate off-site targets or even the function or substrate of the enzymes, can globally detect, identify, and quantitate all potential competitive enzyme targets in the human proteome for such inhibitors.[37] To date, two enzymes have emerged at potential competitive targets for inhibitors in this class: triacylglycerol hydrolase (TGH) and a previously uncharacterized membrane-associated hydrolase that lacked known substrates or function at the time (KIAA1363), but has since been characterized by Cravatt and coworkers.[38] Enlisting this proteome selectivity assay, we have been able to simultaneously optimize inhibitors for both FAAH potency and selectivity, identifying key features of candidate inhibitors that can increase binding at the FAAH active site while simultaneously disrupting KIAA1363 and TGH affinity. This multidimensional SAR optimization is highlighted beautifully with the inhibitors **4t**, **4s**, **4k**, **4m,** and **4o** with the results summarized in Fig. 3. Like observations made with the 5-substituted oxazoles,[26] the addition of a 4-substituent to **4a** enhances the FAAH versus

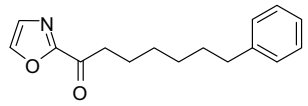
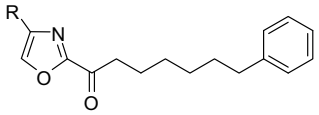
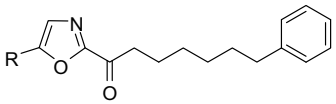
Cmpd	FAAH K_i, nM	FAAH IC_{50}, μM	KIAA1363 IC_{50}, μM	TGH IC_{50}, μM
				
4a (H)	48	2.5	20 (8)	0.02 (0.008)
				
4t (CF_3)	3.7	0.4	10 (25)	0.06 (0.15)
4s (CN)	0.6	0.02	30 (1500)	0.03 (1.5)
4k (2-pyr)	1.9	0.03	>100 (>3000)	10 (330)
4m (4-pyr)	1.7	0.14	>100 (>700)	0.7 (5)
4o (CO_2H)	53	0.5	>100 (>200)	2.5 (5)
				
5a (CF_3)	0.8	0.07	>100 (>1400)	0.2 (3)
5b (CN)	0.4	0.007	>100 (>14000)	0.02 (3)
5c (2-pyr)	4.7	0.002	>100 (>50000)	0.6 (300)
5d (CO_2H)	30	0.9	>100 (>100)	>100 (>100)

Figure 3. Selectivity screening, IC_{50}, μM (selectivity).

KIAA1363 selectivity (>25-fold selective vs eightfold for **4a**), but not always as substantially as the 5-substituted oxazoles (>100-fold) where such inhibitors typically fail to inhibit KIAA1363. Similarly, the addition of a 4-substituent converts the TGH selective inhibitor **4a** (>100-fold selective for TGH vs FAAH) into inhibitors that are modestly selective for FAAH (up to fivefold selective). The exception to this is **4k** which like OL-135 (**5c**) was found to be >300-fold selective for FAAH versus TGH. This enhancement in FAAH selectivity, while remarkable (typically >100-fold, but >40,000 for **4k**), is generally not as great as that observed in the 5-substituted oxazole series.

One additional feature of this study merits highlighting. In earlier studies,[26] we found that either a 4-substituent or 5-substituent on the oxazole can be utilized to enhance FAAH inhibitor potency, but candidate inhibitors bearing both were significantly less active. Although not extensively investigated, analogous observations were made in the course of these studies.[39] This suggests that the two classes of oxazole-based inhibitors may bind at the FAAH active site in a manner that places the substituent in a comparable location. This simply requires a flipped orientation of the oxazole at the active site reversing the location of the N and O of the heterocycle (Fig. 4). Consistent with this suggestion, related inhibitors[26] bearing a C5 substituent have been shown to exhibit a significant sensitivity to steric hindrance surrounding the analogous oxazole C4 center (potency: N > O > CH) indicating that there may be ample room for one, but not two such substituents. Provocatively and while this flipped orientation of the oxazole between the two series has little impact on the FAAH inhibitor potency, it

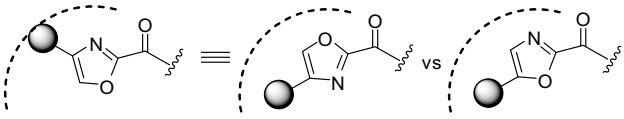


Figure 4. Binding models.

may have a more significant impact on the FAAH selectivity which often, but not always, appears to erode with the 4-substituted series disclosed herein.

A series of C4-substituted α-ketooxazoles were examined as inhibitors of the serine hydrolase fatty acid amide hydrolase in efforts that further define and generalize a fundamental substituent effect on enzyme inhibitory potency. A plot of the Hammett σ_m versus $-\log K_i$ provided a linear correlation ($R^2 = 0.90$) with a slope of 3.37 ($\rho = 3.37$), that is of a magnitude that indicates that the electron-withdrawing character of the substituent dominates its effects (a one unit change in σ_m provides a >1000-fold change in K_i). Moreover, this meta substituent effect is comparable, essentially identical, to that we previously defined for para substituents ($\rho = 2.7–3.0$, $R^2 = 0.91–0.97$)[26,29] confirming both its generality and magnitude independent of the site of substitution. Importantly, the correlation provides a useful and predictive design principle for enzyme inhibitors and is of a sufficient accuracy that subtleties of active site binding that are not known a priori may be established from a measured K_i. These observations may prove useful not only to extend to other enzyme classes, but also have provided herein an additional and useful class of potent and selective FAAH inhibitors.

Acknowledgments

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Appendix Supplementary. data

Full experimental details on the preparation and characterization of the inhibitors, the FAAH inhibition assay, and FAAH assay measurement errors are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.06.084.

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