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Benzothiophene piperazine and piperidine urea inhibitors of fatty acid amide hydrolase (FAAH)

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ABSTRACT

The synthesis and structure–activity relationships (SAR) of a series of benzothiophene piperazine and piperidine urea FAAH inhibitors is described. These compounds inhibit FAAH by covalently modifying the enzyme's active site serine nucleophile. Activity-based protein profiling (ABPP) revealed that these urea inhibitors were completely selective for FAAH relative to other mammalian serine hydrolases. Several compounds showed in vivo activity in a rat complete Freund's adjuvant (CFA) model of inflammatory pain.

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] Genetic[1g] or pharmacological[1f] inactivation of FAAH leads to elevated endogenous levels of fatty acid amides and a range of behavioral effects including analgesic and anti-inflammatory phenotypes in rodents. Importantly, these behavioral phenotypes occur in the absence of alterations in motility, weight gain, or body temperature that are typically observed with direct cannabinoid receptor 1 (CB1) agonists, indicating that FAAH may represent an attractive therapeutic target for the treatment of inflammatory pain and related conditions.[2] Several classes of FAAH inhibitors have been reported including electrophilic ketones (e.g., OL-135[3]), carbamates (e.g., URB597[4] and SA-47[5]) and, more recently, piperidine/piperazine ureas (e.g., PF-750[6] and Takeda-25/JNJ-1661010[7]) (Fig. 1). We recently reported that PF-750 inhibits FAAH by covalently modifying the enzyme's active site serine nucleophile and is completely selective for FAAH relative to other mammalian serine hydrolases.[6a] In this Letter, we describe the synthesis and structure–activity relationships (SAR) of a series of benzothiophene piperazine and piperidine urea FAAH inhibitors.

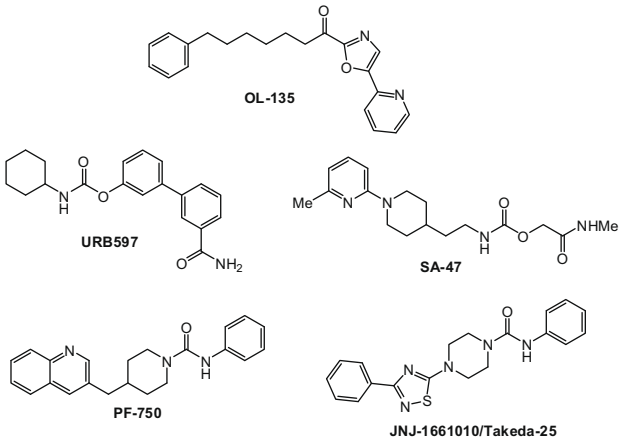

Figure 1. Structures of FAAH inhibitors.

A series of piperazine phenyl ureas, exemplified by **1**, was discovered by high throughput screening of the Pfizer chemical file

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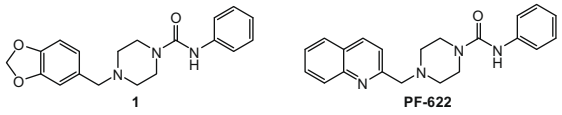


Figure 2. Structures of HTS lead (**1**) and PF-622.

against human FAAH (Fig. 2). We prepared piperazine phenyl urea intermediate **2** and performed a series of reductive aminations with various aromatic aldehydes (Scheme 1, Eqs. 1 and 2). This allowed us to easily vary the aldehyde component and resulted in the identification of several bicyclic cores including PF-622[6a] and a series of benzothiophenes represented by **4h** which is the subject of this manuscript (Scheme 1, Eq. 2).

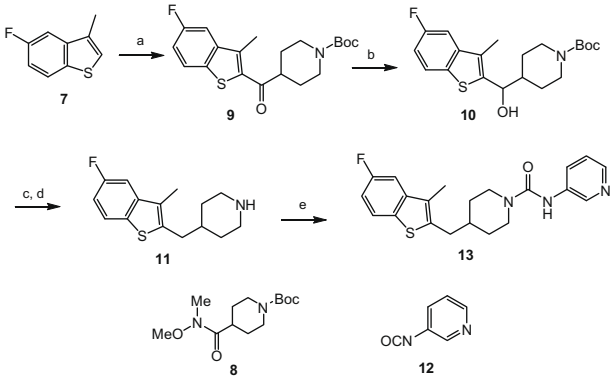
We then explored the benzothiophene lead **4h** in more detail. Therefore, the benzothiophene piperazine intermediate **5** was prepared according to equation 3 and reacted with various commercially available alkyl and aryl isocyanates or phenyl carbamates of heterocyclic amines[8] to give the corresponding piperazine ureas **4** and **6** (Scheme 1).

Schemes 2 and 3 outline the synthesis of representative piperidine urea FAAH inhibitors utilized in the current studies. Lithiation of benzothiophene **7** followed by reaction with Weinreb amide **8** provided ketone **9** in good yield.[9] Ketone **9** was reduced with sodium borohydride to give alcohol **10** which underwent elimination when treated with *p*-toluene sulfonic acid (TsOH). The resulting double bond was hydrogenated to give piperidine **11** which was treated with isocyanate **12** as described previously to give the desired urea **13**.[8]

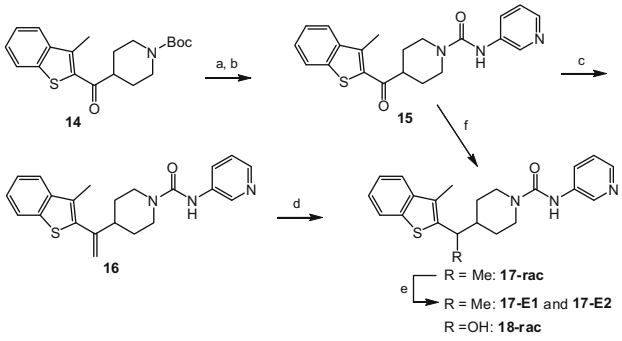
The linker analogs **15–18** were synthesized according to Scheme 3. Deprotection of Boc-piperidine **14** with TFA followed by reaction with isocyanate **12** afforded urea **15** with a ketone linker. Wittig olefination of ketone **15** provided compound **16** with a methylene substituted linker. Hydrogenation of the double bond gave **17** with a methyl substituted linker as the racemate and the enantiomers were separated by chiral chromatography. Furthermore, ketone **15** was reduced to give racemic **18** with a hydroxy substituted linker.

As previously reported, these piperidine/piperazine ureas inhibit FAAH by covalent carbamylation of the catalytic Ser241 nucleophile.[6a,b] Therefore, the potency of these benzothiophene piperidine/piperazine urea inhibitors were determined by the second order rate constants k_{inact}/K_i values using an enzyme-coupled FAAH assay as described previously.[6b,10] Unlike IC_{50} values, k_{inact}/K_i values do not change with various preincubation times and have been described as the best measure of potency for irreversible inhibitors.[11]

Table 1 shows the SAR of the right hand portion of the urea. The alkyl ureas (**4a–g**) had very low potency for FAAH, which is similar

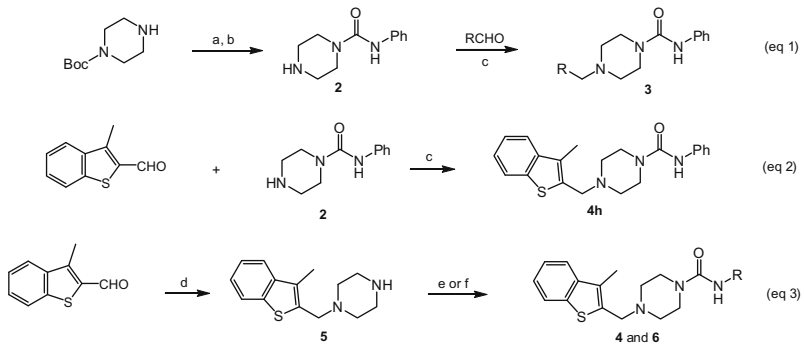


Scheme 2. Synthesis of piperidine urea **13**: (a) *n*-BuLi, THF, −78 °C; then add **8**, 70%, (b) $NaBH_4$, EtOH, quant; (c) TsOH, toluene, quant; (d) H_2(g), 20% Pd/C, MeOH, 87%; (e) **12**, CH_2Cl_2, 60%.



Scheme 3. Synthesis of linker analogs **15–18**: (a) TFA, CH_2Cl_2, 99%; (b) **12**, CH_2Cl_2, 85%; (c) Ph_3PCH_3Br, *n*-BuLi, THF, −20 °C to rt, 97%; d) H_2(g), Pd/C, MeOH, 76%; (e) chiral chromatography (CHIRALCEL® OD); (f) $NaBH_4$, EtOH, quant.

to what has been observed for *N*-alkyl urea analogs of URB597.[4a] In contrast, we found that aryl ureas such as phenyl urea **4h** were potent FAAH inhibitors. Next, we investigated a series of heteroaromatic ureas (**4i–l**, **6a**) in part to avoid the generation of aniline upon covalent binding to FAAH. The 3-aminopyridyl group (**6a**) was preferred over the 2-aminopyridyl (**4i**) and 3-aminopyridazinyl (**4j**) groups in the benzothiophene series. The SAR of the heterocyclic group was highly sensitive. For example, isoxazole **4k** retained potency, while the potency was lost with methylthiazole **4l**, which is consistent with observations made by Keith et al. in a related thiadiazolopiperazinyl urea series.[7b] Boger and co-workers also observed that subtle changes in the central heterocycle of α-ketoheterocycle FAAH inhibitors greatly influence inhibitor activ-



Scheme 1. Synthesis of piperazine ureas **4** and **6**: (a) PhNCO, CH_2Cl_2, 92%; (b) TFA, CH_2Cl_2, 80–99% (c) $NaBH(OAc)_3$, DCE, 50–95%; (d) *N*-Boc-piperazine, $NaBH(OAc)_3$, CH_2Cl_2; then TFA, CH_2Cl_2, 64%; (e) RNCO (R = alkyl, Ph, 3-pyr; ie. **4d–g**, **4h**, **6a**), CH_2Cl_2, 50–90%; (f) $RNHCO_2Ph$ (R = heterocycle, ie. **4j–1**, **6**), DMSO, 60 °C, 50–80%.