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Synthesis and biological evaluation of piperazinyl carbamates and ureas as fatty acid amide hydrolase (FAAH) and transient receptor potential (TRP) channel dual ligands

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ABSTRACT

The evaluation of a series of piperazinyl carbamates and ureas, designed on the basis of previously reported TRPV1 antagonists and FAAH inhibitors, led to the identification of some 'dual-action' compounds targeting both FAAH and TRPV1 or TRPA1 receptors.

The endocannabinoid system, which comprises at least two G-protein coupled receptors (CB_1 and CB_2), their endogenous ligands (endocannabinoids), and a series of proteins involved in endocannabinoid metabolism,[1] has emerged as a particularly promising target for the treatment of wide array of human disorders, in particular neuropathic and inflammatory pain.[2] Indeed, the endocannabinoid *N*-arachidonoylethanolamine (anandamide, AEA), and the endocannabinoid-like molecules, *N*-arachidonoylglycine (NAGly) and *N*-palmitoylethanolamine (PEA), exert potent analgesic and anti inflammatory activities in vivo.[3]

AEA, NAGly, and PEA are all inactivated by enzymatic hydrolysis catalyzed by amidases, the best characterized of which is the fatty acid amide hydrolase (FAAH).[4] The past 10 years have witnessed the discovery of an ever increasing number of FAAH inhibitors with analgesic activity in a variety of pain models through mechanisms that are not uniquely mediated by cannabinoid receptors.[5]

The transient receptor potential vanilloid type-1 (TRPV1) channel represents another possible new answer to the ever increasing demand for analgesic drugs.[6] TRPV1 is a nonselective cation channel localized in neurons of C- and Aδ-sensory fibers and considered to be a key polymodal integrator of noxious stimuli.[7] Its activation by noxious heat, acidic pH, plant toxins and endogenous lipid mediators such as AEA (which can thus be considered also a true endovanilloid)[8] causes calcium influx, neuron depolarization, and an initial sensation of pain. The analgesic profile generated in animal pain models by TRPV1 receptor genetic or pharmacological blockade has provided compelling data for the therapeutic use of TRPV1 antagonists, the identification of which has become a focus of major attention within the pharmaceutical industry.[9]

A popular and logic approach to developing inhibitors of FAAH has been the modification of its substrates, and early work in this area identified a number of such compounds including *N*-arachidonoylserotonin (AA-5-HT).[5a] AA-5-HT was recently found to also antagonize TRPV1 receptors, a property that might explain the high efficacy of this compound against neuropathic pain and anxiety, thus prompting the development of additional therapeutically useful dual FAAH/TRPV1 blockers.[10] Simultaneous blockade of FAAH and TRPV1 channels might cause analgesic effects stronger then the targeting of each single system, due to the different respective roles in the control of nociception.[11]

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As a continuation of our efforts to identify new molecules able to target simultaneously both FAAH and TRPV1 receptors,[12] we have selected as lead compounds BCTC,[9c] the most studied member of the piperazine carboxamide class of TRPV1 antagonists, and PF-622,[13] a piperazinyl urea recently described as the prototype of a novel mechanistic class of FAAH inhibitors (Fig. 1).

In view of the well documented efficacy of *O*-arylcarbamates as FAAH inhibitors,[5] a first series of compounds was synthesized in which the ureic function of BCTC and PF-622 was replaced by a carbamate moiety (compounds **1**–**18**). According to the pharmacophore model developed for pyridyl piperazine carboxamides and related structures that can be traced back to the prototypical TRPV1 antagonist capsazepine,[7b] compounds **1**–**18** should retain the ability to interact with TRPV1 channels. In fact, two carbamates structurally related to compounds **1**–**18** have been claimed in the patent literature to exhibit TRPV1 antagonism.[14] A second series of compounds was designed through the combination of the pyridinyl (or quinolinyl) piperazine moiety of BCTC and PF-622 with the serotonin portion of AA-5-HT (compounds **19**–**22**).

The synthesis of compounds **1**–**14** is shown in Scheme 1. The piperazinyl moieties **25** and **26**, obtained by condensation of the commercially available pyridines **23** or **24** with an excess of piperazine,[15] were reacted with the appropriately substituted phenyl chloroformates, generated by treatment of the corresponding phenols with phosgene. Compounds **15**–**18** were obtained by reacting 1-Cbz-piperazine[16] with substituted phenyl chloroformates. Deprotection of the Cbz group by hydrogenolysis afforded the piperazine derivatives, which were subsequently coupled with the appropriate 2-chloromethylheterocycles (Scheme 2). Ureas **19** and **20** were synthesized by treatment of the 1-pyridin-2-ylpiperazines **25** or **26** with phosgene followed by reaction of the resulting carbamoyl chlorides with serotonin hydrochloride (Scheme 3).

Finally, the synthesis of compounds **21**–**22** is outlined in Scheme 4. The 1-Cbz-piperazinyl chloroformate, obtained by reaction of 1-Cbz-piperazine with phosgene, was condensed with serotonin hydrochloride; deprotection of the Cbz group by hydrogenolysis and alkylation of the resulting piperazine derivative with 2-(chloromethyl)pyridine and 2-(chloromethyl)quinoline afforded **21** and **22**, respectively.[17]

All compounds were evaluated in assays of FAAH and TRPV1 activity as well as on transient receptor potential ankyrin type-1 (TRPA1). TRPA1 is another member of the transient receptor potential family of ion channels and is restrictively expressed in sensory neurons of dorsal root and trigeminal ganglia, and in hair cells of the inner ear. The TRPA1 channel is activated by a variety of noxious stimuli including cold temperatures, pungent natural compounds, and environmental irritants and, like TRPV1, with which it is very often co-localized, plays an important role in pain sensing.[18] The effects of carbamates **1**–**18** and ureas **19**–**22** on [^{14}C]anandamide hydrolysis by rat brain membranes (which express FAAH as the only AEA hydrolyzing enzyme) and on intracellular Ca^{2+} elevation mediated by TRPV1 and TRPA1 channels overexpressed in HEK293 cells, are shown in Table 1.[19] Data for the lead compounds, namely AA-5-HT, BCTC, and PF-622, are also included in the Table as controls.

The most important results were as follows. Almost all carbamates **1**–**18** showed fairly good FAAH inhibitory activities (**2**–**7** and **9**–**18**). Compounds with *meta* substituted aromatic rings were more potent than *para* substituted analogues, with only one exception (**3** and **4**), independent of the nature of the substituent and similar to previously reported results for AA-5-HT analogues[12] and alkylcarbamic acid aryl esters.[20] The presence of a methylene

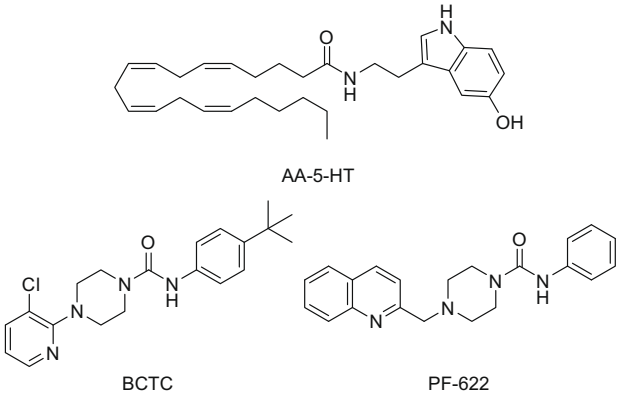
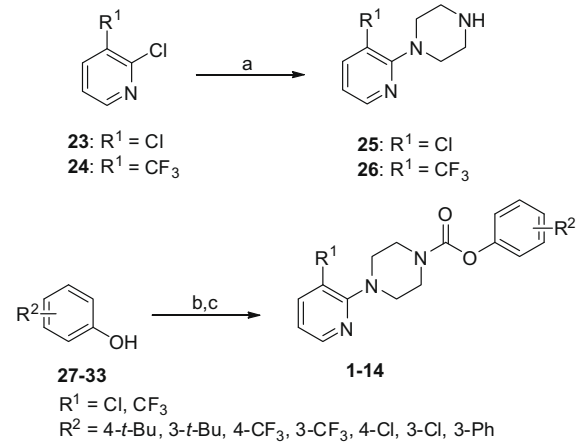
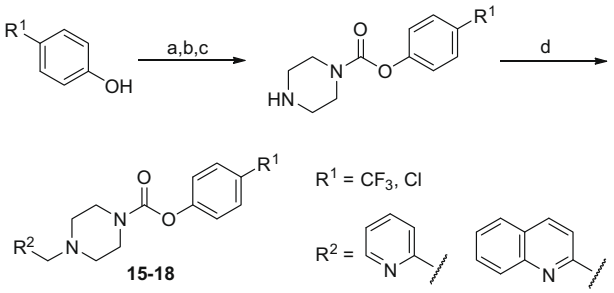


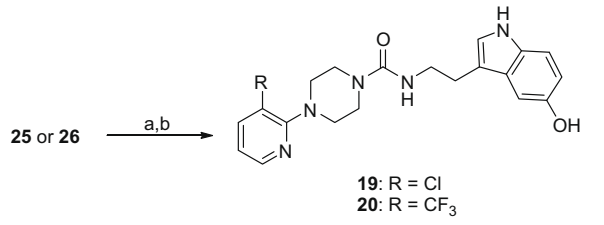
Figure 1. Structures of some reported FAAH and/or TRPV1 ligands.



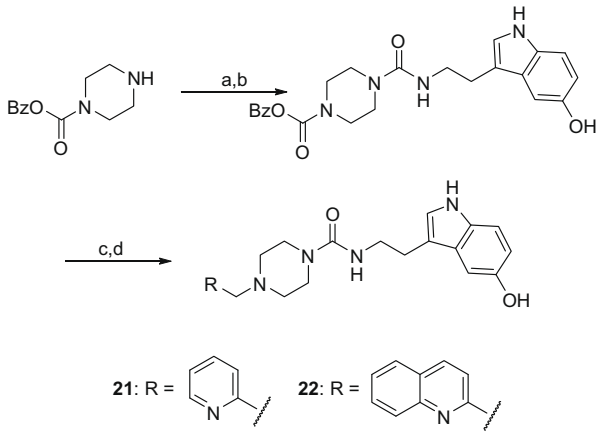
Scheme 1. Synthesis of compounds **1**–**14**. Reagents and conditions: (a) piperazine, *n*-butanol, reflux, 20 h, 91–94%; (b) 20% $COCl_2$ in toluene, Et_3N, toluene, 0 °C, then 2 h at 25 °C; (c) **25** or **26**, Et_3N, DMF–CH_2Cl_2 1:1, 15 h, 25 °C, 32–63%.



Scheme 2. Synthesis of compounds **15**–**18**. Reagents and conditions: (a) 20% $COCl_2$ in toluene, Et_3N, toluene, 0 °C, then 2 h at 25 °C; (b) 1-Cbz-piperazine, Et_3N, DMF–CH_2Cl_2 1:1, 15 h, 25 °C, 47–54%; (c) 10% Pd/C, H_2 (1 atm), MeOH, 2 h, 25 °C, 63–78%; (d) 2-(chloromethyl)pyridine hydrochloride or 2-(chloromethyl)quinoline hydrochloride, KI, Et_3N, DMF, 80 °C, 15 h, 35–72%.



Scheme 3. Synthesis of compounds **19**, **20**. Reagents and conditions: (a) 20% $COCl_2$ in toluene, Et_3N, CH_2Cl_2, 0 °C, then 3 h at 25 °C; (b) serotonin hydrochloride, Et_3N, DMF–CH_2Cl_2 1:1, 15 h, 25 °C, 74–77%.

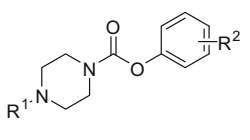


Scheme 4. Synthesis of compounds **21**, **22**. Reagents and conditions: (a) 20% $COCl_2$ in toluene, Et_3N, CH_2Cl_2, 0 °C, then 3 h at 25 °C; (b) serotonin hydrochloride, Et_3N, DMF–CH_2Cl_2 1:1, 15 h, 25 °C, 100%; (c) 10% Pd/C, H_2 (1 atm), MeOH/AcOEt 1:1, 3 h, 25 °C, 72%; (d) 2-(chloromethyl)pyridine hydrochloride or 2-(chloromethyl)quinoline hydrochloride, KI, Et_3N, DMF, 80 °C, 15 h, 27–47%.

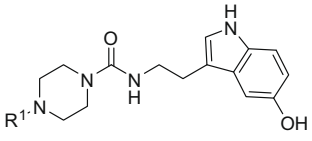
group between the piperazine and the pyridine (or quinoline) rings did not affect critically the FAAH inhibitory activity. Some of the carbamates also exhibited significant TRPV1 antagonist (**1**, **4**, **8**, **10**, **12**) and/or TRPA1 agonist (**1**–**6**, **13**, **14**) activity. A stronger TRPV1 antagonist activity was observed with *para* substituted derivatives (in particular **1** and **8**). Among carbamates, particularly interesting appears to be compound **10**, which was 2.4-fold more potent as FAAH inhibitor and 3.7-fold less potent as TRPV1 antagonist than AA-5-HT,[12] and compounds **2**, **3**, **5**, **6**, **13** and **14**, which exhibited dual inhibitory and stimulatory activity at FAAH and TRPA1, respectively, and are potentially able to covalently bind to electron donor aminoacid residues in TRPA1 channels,[21] thereby desensitising them to the action of other nociceptive stimuli. It is worth mentioning in this context that URB597, a potent FAAH inhibitor, was also reported to activate TRPA1 channels with a potency 6.6–40.8-fold lower than that of **2**, **3**, **5**, **6**, **13** and **14**,[22] and that most of TRPA1 agonists so far identified are either highly reactive, nonselective, or not potent or efficacious and, therefore, do not represent optimal tools for pharmacological studies. Conversely, none of the serotonin ureic derivatives (**19**–**22**) showed significant activity on the selected targets. This result was rather unexpected in view of the potent and selective FAAH inhibitory activity of PF-622 and of the hypothesis that the aniline moiety of PF-622 is accommodated in the hydrophilic cytoplasmatic access channel of FAAH,[13] which should have allowed for a stronger interaction with the enzyme following introduction of serotonin moiety.

In conclusion, we have synthesized and assayed a series of piperazinyl carbamates and ureas designed on the basis of previously reported TRPV1 antagonists and FAAH inhibitors, and have identified some piperazinyl carbamates that inhibit FAAH with fairly good potency and interact also with excitatory TRP ionotropic receptors involved in nociception. Promising hits proved to be in particular: (a) carbamates **10** and **12**, able to act as dual FAAH/TRPV1 blockers with a potency slightly lower than that of the prototypical 'hybrid' blocker AA-5-HT, but with likely higher chemical stability than this arachidonic acid-containing compound; and (b) FAAH/TRPA1 ligands **2**, **3**, **5**, **6**, **13** and **14**, which could conceivably

Table 1
Results of FAAH, TRPV1, and TRPA1 assays of carbamates **1**–**18** and ureas **19**–**22**[a]



1-18



19-22

Compound	R^1	R^2	AEA hydrolysis (IC_{50}, μM)	% Inhibition (c = 50 μM)	TRPV1 (IC_{50}, μM)	TRPA1 (EC_{50}, μM)
1	3-Chloropyridin-2-yl	4-*t*-Bu	19.19	72.9	0.48	1.6
2	3-Chloropyridin-2-yl	3-*t*-Bu	1.27	97.5	>10	1.8
3	3-Chloropyridin-2-yl	4-CF_3	3.90	97.4	>10	3.1
4	3-Chloropyridin-2-yl	3-CF_3	6.56	98.3	3.9	2.0
5	3-Chloropyridin-2-yl	4-Cl	6.44	78.6	>10	0.6
6	3-Chloropyridin-2-yl	3-Cl	0.91	97.7	>10	1.0
7	3-Chloropyridin-2-yl	3-Ph	0.75	97.7	>10	>25
8	3-Trifluoromethylpyridin-2-yl	4-*t*-Bu	30.11	63.1	0.26	>25
9	3-Trifluoromethylpyridin-2-yl	3-*t*-Bu	0.77	97.0	>10	>25
10	3-Trifluoromethylpyridin-2-yl	4-CF_3	3.36	69.4	1.0	>25
11	3-Trifluoromethylpyridin-2-yl	3-CF_3	0.61	98.2	>10	>25
12	3-Trifluoromethylpyridin-2-yl	4-Cl	2.19	97.5	4.6	>25
13	3-Trifluoromethylpyridin-2-yl	3-Cl	0.74	98.5	>10	3.7
14	3-Trifluoromethylpyridin-2-yl	3-Ph	0.38	97.4	>10	1.0
15	Pyridin-2-ylmethyl	4-CF_3	2.9	92.4	>10	>25
16	Quinolin-2-ylmethyl	4-CF_3	9.3	98.0	>10	>25
17	Pyridin-2-ylmethyl	4-Cl	4.1	90.1	>10	>25
18	Quinolin-2-ylmethyl	4-Cl	5.9	90.0	>10	>25
19	3-Chloropyridin-2-yl		>50	21.5	>10	>25
20	3-Trifluoromethylpyridin-2-yl		>50	35.4	>10	>25
21	Pyridin-2-ylmethyl		>50	34.0	>10	>25
22	Quinolin-2-ylmethyl		>50	32.6	>10	>25
AA-5-HT			8.0[b]	92.0	0.27[b]	>25
BCTC			>50	24.6	0.0067	4.5
PF-622			0.50	98.8	>10	>25

[a] Data are means of n = 4 separate determinations. Standard errors are not shown for the sake of clarity and were never higher than 10% of the means.
[b] Data from Ref. 12.

represent useful pharmacological tools for the study of TRPA1 channels.

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17. *Data for selected compounds*: Compound **6**: yield 63%; oil; IR ($CHCl_3$) 2925, 2847, 1717, 1578, 1421, 1238 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.38–3.43 (m, 4H), 3.74–3.82 (m, 4H), 6.89 (dd, J = 7.6, 4.6 Hz, 1H), 7.02–7.08 (m, 1H), 7.17–7.21 (m, 2H), 7.27 (d, J = 8 Hz, 1H), 7.62 (dd, J = 7.8, 1.6 Hz, 1H), 8.20 (dd, J = 4.8, 1.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 44.13, 44.51, 48.89, 118.54, 120.11, 122.43, 122.86, 125.58, 129.94, 134.53, 138.92, 145.93, 151.93, 153.23, 158.05. Compound **10**: yield 43%; mp 106–109 °C; IR (KBr) 2921, 2869, 1717, 1591, 1450, 1417, 1324, 1212 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.33 (br s, 4H), 3.73–3.83 (m, 4H), 7.09 (dd, J = 7.8, 4.8 Hz, 1H), 7.26 (d, J = 8.2 Hz, 4H), 7.64 (d, J = 8.4 Hz), 7.92 (dd, J = 7.8, 1.6 Hz, 1H), 8.48 (dd, J = 4.6, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.19, 44.76, 50.68, 117.83 (q, J = 31 Hz), 118.10, 122.14, 123.59 (q, J = 271 Hz), 123.82 (q, J = 271 Hz), 126.68, 127.69 (q, J = 33 Hz), 137.26, 151.30, 153.03, 153.94, 159.78. Compound **12**: yield 55%; mp 103–105 °C; IR (KBr) 2904, 2865, 1715, 1590, 1577, 1444, 1417, 1249, 1218, 1121 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.32–3.33 (m, 4H), 3.71–3.81 (m, 4H), 7.07 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 7.91 (dd, J = 7.8, 1.6 Hz, 1H), 8.47 (dd, J = 4.6, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.13, 44.66, 50.67, 117.76 (q, J = 31 Hz), 118.00, 123.12, 123.82 (q, J = 271 Hz), 129.33, 130.70, 137.26, 149.89, 151.26, 153.45, 159.79. Compound **13**: yield 45%; oil; IR ($CHCl_3$) 2927, 2850, 1718, 1592, 1445, 1421, 1311, 1238 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.32 (br s, 4H), 3.72–3.80 (m, 4H), 7.04–7.30 (m, 5H), 7.91 (dd, J = 7.8, 1.6 Hz, 1H), 8.47 (dd, J = 4.6, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.12, 44.68, 50.66, 117.72 (q, J = 31 Hz), 118.02, 120.15, 122.45, 123.68 (q, J = 271 Hz), 125.63, 130.00, 134.52, 137.21, 151.27, 151.89, 153.24, 159.75. Compound **14**: yield 45%; oil; IR ($CHCl_3$) 2927, 2850, 1709, 1592, 1446, 1311, 1240, 1183 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.32 (br s, 4H), 3.73–3.83 (m, 4H), 7.02 (dd, J = 7.6, 4.6 Hz, 1H), 7.11–7.13 (m, 1H), 7.31–7.42 (m, 6H), 7.57–7.59 (m, 2H), 7.88 (dd, J = 7.8, 1.6 Hz, 1H), 8.45 (dd, J = 4.6, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.07, 44.66, 50.69, 117.77 (q, J = 31 Hz), 117.90, 120.53, 122.01, 123.88 (q, J = 271 Hz), 124.11, 127.15, 127.57, 128.75, 129.57, 137.21, 140.31, 142.69, 151.24, 151.77, 153.79, 159.77.
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