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# Selective antagonists of mouse trace amine-associated receptor 1 (mTAAR1): Discovery of EPPTB (RO5212773)

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ABSTRACT

High throughput screening of the Roche compound library identified benzanilides such as **1** and **2** as antagonists of TAAR1. Optimisation of this hit series led to the first selective TAAR1 antagonist (*N*-(3-Ethoxy-phenyl)-4-pyrrolidin-1-yl-3-trifluoromethyl-benzamide **EPPTB** (**RO5212773**, **9f**) having $IC_{50}$ of 28 nM at mouse TAAR1.



Trace amine-associated receptor 1 (TAAR1) is a G protein-coupled receptor (GPCR) which is activated by endogenous metabolites of amino acids such as *p*-tyramine, β-phenethylamine, octopamine and tryptamine,[1,2] that are found in low concentrations in the brain.[3] TAAR1 is considered a promising drug target for the treatment of psychiatric and neurodegenerative disorders.[4–6] The availability of selective agonists and antagonists of TAAR1 is key for obtaining critical information with regard to the therapeutic potential of this target.[7] Here we report the discovery and the identification of EPPTB, that was recently described to be a competitive TAAR1 antagonist and inverse agonist.[8]

A high throughput screening (HTS) of the Roche compound library (~788'000 compounds at 10 μM) was performed using a functional cAMP assay employing a chimeric human/rat TAAR1 receptor.[9] The cAMP assay was run in both antagonist ($IC_{50}$) and agonist ($EC_{50}$) mode. The resulting primary hit set was clustered[10] according to substructure similarity and based on this analysis a hit expansion was performed. The extended primary hit set was then tested at mouse TAAR1 (mTAAR1) in antagonist and agonist dose–response mode. The switch from the human/rat chimeric to the mouse TAAR1 for dose–response determination was due to a licensing issue and considered as reasonable due to the good homology between human and mouse TAAR1.[11] With 25 representatives, benzanilides were the most prominent chemical class found and represented not only the largest set but also the most active compounds; all were antagonists at mTAAR1 ($IC_{50}$ <16 μM, 12 compounds had $IC_{50}$ <1 μM, all compounds had $EC_{50}$ >20 μM, data not shown). Furthermore, selected primary hits were also tested for functional activity at human TAAR1 (hTAAR1) resulting in comparable values to human/rat chimeric TAAR1. The profiles of two representative benzanilides are shown in Figure 1. The values reported are the average of at least two independent experiments and typically duplicate values are within a twofold margin.[12] Compound **1** was one of the most active hits found in the HTS.

The binding assay data for **1** and **2** reveal high affinity for mTAAR1 ($K_i$ 2–4 nM) resulting in ligand efficiency (LE) around 0.4 but only weak affinity at rat TAAR1 (rTAAR1) ($K_i$ 1.4 μM) and no detectable affinity for hTAAR1 ($K_i$ >20 μM). These results are reflected in the functional assay data: at mTAAR1 **1** had $IC_{50}$ 0.006 μM (28% residual stimulation by endogenous agonist β-PEA, partial agonist) and **2** had $IC_{50}$ 0.060 μM (full antagonist), whereas at hTAAR1 **1** had $IC_{50}$ >10 μM and **2** had $IC_{50}$ 3.79 μM. Regardless of the chemical series, we observed significant species differences in binding affinity at TAAR1 for all the HTS hits. Whereas many compounds were potent at mTAAR1, the majority of compounds were inactive at hTAAR1 and only weakly active at rTAAR1. Therefore the focus of chemical optimisation narrowed to the search for a tool compound suitable for mechanistic in vitro pharmacology experiments and in vivo behavioural studies in mice.

All compounds from the HTS hit series having high functional activity at mTAAR1 had high lipophilicity ($c\log P$ >4; $\log D$ >3), poor aqueous solubility (<1 μg/ml at pH 6.5), and high clearance in human and mouse microsomes. A medicinal chemistry

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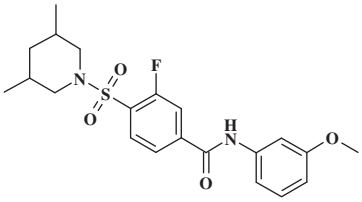
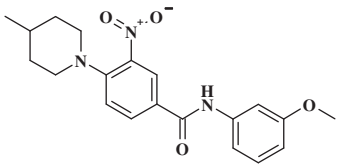


**1 [rac/meso] (RO4467280-000)**



**2 (RO4534926-000)**

| | Functional assay [i] | Binding | Functional assay [i] | Binding |
|---|---|---|---|---|
| hTAAR1 : | $IC_{50}$ >10 μM | $K_i$ > 20 μM | $IC_{50}$ 3.79 μM (0%) | $K_i$ > 20 μM |
| mTAAR1: | $IC_{50}$ 0.006 μM (28%) | $K_i$ 0.004 μM; LE 0.40 | $IC_{50}$ 0.060 μM (0%) | $K_i$ 0.002 μM; LE 0.44 |
| rTAAR1 : | $IC_{50}$ --- μM | $K_i$ 1.39 μM | $IC_{50}$ --- μM | $K_i$ --- μM |
| | **Phys-chem. prop.** | **Microsomes** | **Phys-chem. prop.** | **Microsomes** |
| | MW: 420.5 | Clearance [ii] | MW: 369.4 | Clearance [ii] |
| | PSA: 62.8 | h 538 | PSA: 72.7 | h 154 |
| | clogP : 4.6 | m 1705 | clogP : 4.3 | m 396 |
| | solubility: <1μg/ml [iii] | | solubility: <1μg/ml [iii] | |

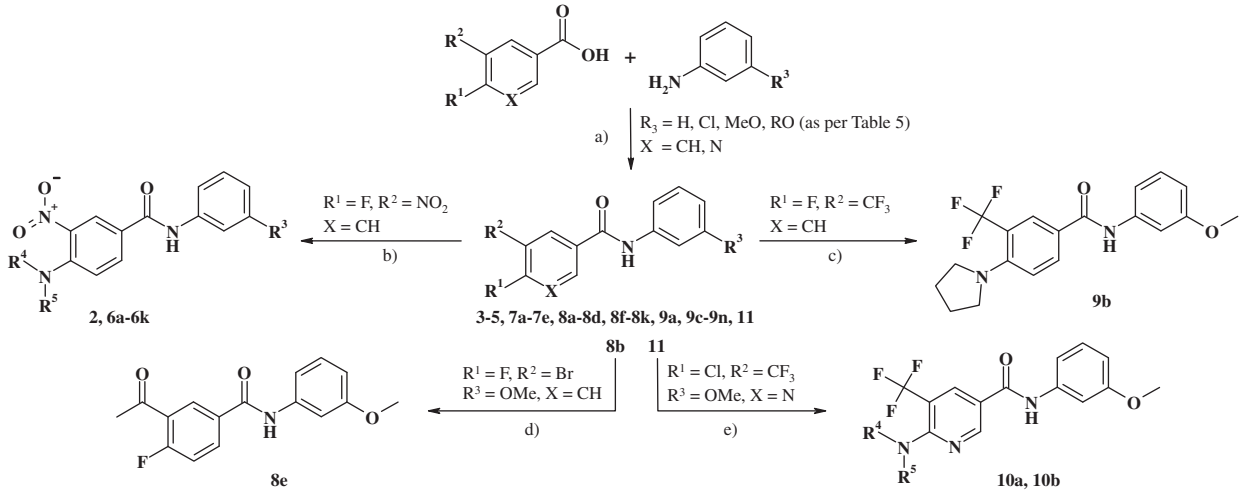
**Figure 1.** Profile of benzanilides **1** and **2** found in HTS. hTAAR1 = human TAAR1, mTAAR1 = mouse TAAR1, rTAAR1 = rat TAAR1, LE = ligand efficiency; (i) antagonistic efficacy: reversal of effect of endogenous agonist β-PEA (in vitro cAMP functional assay; 100% efficacy = 0% min% stim.); (ii) intrinsic clearance in vitro in mouse (m) and human (h) liver microsomes, μg/min/mg protein; (iii) aqueous solubility at pH 6.5.

optimisation programme was initiated focusing on the improvement of physicochemical properties and metabolic stability.

Our synthetic approach allowed a rapid modification of the exit vectors around the central benzanilide core (Scheme 1). The benzanilides or nicotinanilides were obtained in one step from the benzoic or nicotinic acid derivatives by condensation with anilines (Scheme 1, step a). In cases where $R^2$ was an electron-withdrawing group ($CF_3$ or $NO_2$), halogens in *para* position of the benzoyl moiety could be substituted with amines leading to compounds **2**, **6a–6k** and **9b**. *meta*-Acetyl compound **8e** was prepared by Heck type reaction of the corresponding *meta*-bromo compound **8b** with vinyl butyl ether followed by hydrolysis of the intermediate vinyl ether. Compounds **10a** and **10b** were obtained by substitution with amines of the 6-chloro substituent in 6-chloro-*N*-(3-methoxy-phenyl)-5-trifluoromethyl-nicotinamide **11**.

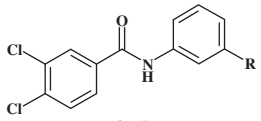
The structure–activity relationship (SAR) for substituents on the aniline moiety (e.g., MeO, F, Cl, Me, Et, phenyl, $CF_3$, acetyl, $MeSO_2$) was examined first. Monosubstitution in *ortho* or *para* positions, or *meta*,*meta'*-disubstitution led to compounds with weaker affinity (mTAAR1 $K_i \gg 100$ nM; data not shown), whereas monosubstitution in the *meta* position afforded compounds with high affinity with the exception of phenyl, $CF_3$ and $MeSO_2$: these displayed a binding affinity at mTAAR1 of $K_i$ >200 nM. Small substituents are preferred at the *meta* position, especially methoxy (**3**) and chloro (**4**) residues (Table 1). Aniline derivative **5** proved to be equipotent with the chloro compound **4**. However, benzanilides derived from aniline showed in most cases a clearly lower binding affinity than the corresponding *meta*-chloro or *meta*-methoxy aniline derivatives (data not shown).

The 3-methoxy-aniline motif was selected as optimal at this stage and structural modification was then directed towards the benzoyl residue. Starting from **2**, a first effort modifying or replacing the amino residue was undertaken (Tables 2 and 3). Replacement of the 4-methyl-piperidin-1yl residue in **2** by an amino group led to significant loss of affinity (**6a**: $K_i$ 1.92 μM) but activity could be recovered by mono N-alkylation (**6b**–**6e**). The best




**Scheme 1.** Synthesis of benz- and nicotin-anilides **2**–**11**. Reagents and conditions: (a) EDC, DMAP, $CH_2Cl_2$, rt, 18 h, 16–99%; (b) $HNR^4R^5$, DMF, rt, 2.5 h or THF, 60 °C, 70 h, 43–99%; (c) pyrrolidine, DMF, rt, 20 h, 98%; (d) (i) $H_2C{=}CH{-}O{-}n$Bu, $Pd(OAc)_2$, dppp, $i Pr_2NH$, DMSO/[bmim][$BF_4$] 10:1, 170 °C (microwave), 15 min, 31%; (ii) 5% aq HCl, rt, 30 min 65%; (e) $HNR^4R^5$, NMP, **10a**:150 °C (microwave), 15 min, 53%; **10b**: 250 °C (microwave), 15 min, 71%.

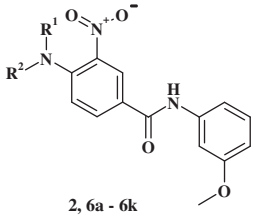
**Table 1**
Binding affinity at mTAAR1 for 3-substituted anilines



3 - 5

| Entry | R | m$K_i$ (μM) |
|---|---|---|
| **3** | MeO | 0.025 |
| **4** | Cl | 0.060 |
| **5** | H | 0.054 |

**Table 2**
In vitro binding affinity and functional activity at mTAAR1 for 4-amino-benzoyl derivatives



2, 6a - 6k

| Entry | $R^1$ | $R^2$ | m$K_i$ (μM) | m$IC_{50}$ (μM) | min% stim.[a] |
|---|---|---|---|---|---|
| **2** | –$(CH_2)_2$–CH(Me)–$(CH_2)_2$– | | 0.002 | 0.060 | 0 |
| **6a** | H | H | 1.92 | nt | |
| **6b** | H | Et | 0.024 | 0.075 | 23 |
| **6c** | H | *n*Pr | 0.004 | 0.013 | 14 |
| **6d** | H | *i*Pr | 0.012 | 0.142 | 0 |
| **6e** | H | Benzyl | 0.005 | 0.014 | 3 |
| **6f** | H | Phenyl | 0.029 | 0.175 | 0 |
| **6g** | –$(CH_2)_3$– | | 0.029 | 0.200 | 9 |
| **6h** | –$(CH_2)_4$– | | 0.013 | 0.017 | 0 |
| **6i** | –$(CH_2)_5$– | | 0.012 | 0.019 | 0 |
| **6j** | –$(CH_2)_2$–O–$(CH_2)_2$– | | 0.103 | 0.079 | 0 |
| **6k** | –$(CH_2)_2$–NMe–$(CH_2)_2$– | | 0.164 | nt | |

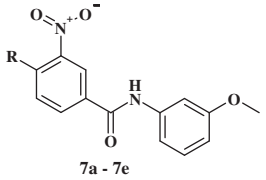
[a] Residual stimulation by endogenous agonist β-PEA at maximum concentration of test compound; Antagonistic efficacy: reversal of effect of endogenous agonist β-PEA (in vitro cAMP functional assay; 100% efficacy = 0% min % stim.).

binding affinity and functional activity was observed for *n*Pr (**6c**: $K_i$ 0.004 μM, $IC_{50}$ 0.013 μM) and for benzyl (**6e**: $K_i$ 0.005 μM, $IC_{50}$ 0.014 μM) substituents, both displaying similar affinity and functional activity at mTAAR1. For the phenyl derivative (**6f**) a drop in affinity and activity was observed. Cyclic secondary amine substituents (**6g**–**6k**) displayed a high affinity for mTAAR1 ($K_i$ 0.012–0.164 μM), with the pyrrolidine (**6h**) or piperidine (**6i**) derivatives being optimal in terms of functional activity ($IC_{50}$ 0.017–0.019 μM). However, in terms of binding affinity, **2** still remained the most potent compound in our hands, although in the functional assay, **2** ($IC_{50}$ 0.060 μM) was inferior to the pyrrolidine and piperidine derivatives **6h** and **6i**, respectively. All three compounds are full antagonists of mTAAR1.

Omitting the 4-amino residue furnished **7a** (Table 3), a significantly less active compound with $K_i$ 0.189 μM and $IC_{50}$ 0.665 μM. The amino moiety may be replaced with halogen substituents, whereby increasing size leads to increasing affinity: from $K_i$ 0.090 μM for fluoro derivative **7b** to 0.021 μM for bromo compound **7d**. In the functional assay at mTAAR1, the chloro compound **7c** ($K_i$ 0.037 μM) displayed an $IC_{50}$ of 0.012 μM. Substitution of bromine with a larger and non-basic substituent like pyrazole-1-yl in **7e** resulted in a strong drop of binding affinity to $K_i$ 0.262 μM.

Based on **7a** and **7b**, replacement options for the nitro group were explored next. The nitro group, a potential toxicophore, is

**Table 3**
In vitro binding affinity and functional activity at mTAAR1 for non-basic benzoyl derivatives



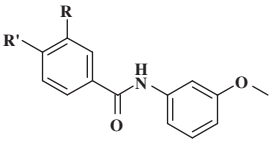
7a - 7e

| Entry | R | m$K_i$ (μM) | m$IC_{50}$ (μM) | min % stim.[a] |
|---|---|---|---|---|
| **7a** | H | 0.189 | 0.665 | 0 |
| **7b** | F | 0.090 | nt | |
| **7c** | Cl | 0.037 | 0.012 | 0 |
| **7d** | Br | 0.021 | 0.043 | 0 |
| **7e** | Pyrazol-1-yl | 0.262 | nt | |

[a] Residual stimulation by endogenous agonist β-PEA at maximum concentration of test compound; Antagonistic efficacy: reversal of effect of endogenous agonist β-PEA (in vitro cAMP functional assay; 100% efficacy = 0% min % stim.).

often replaced by a strong electron-withdrawing group like CN, $SO_2Me$ or $SO_2NH_2$.[13,14] In our series substitution of the nitro residue with these functional groups led to compounds with inferior binding affinity for mTAAR1 (Table 4). While binding affinity of the nitrile derivative **8f** was only weakly attenuated, the methylsulfonyl (**8k**) and sulfonylamide (**8j**) derivatives proved to be substantially weaker. As demonstrated with sulfonamide **8h**, introduction of a large and lipophilic substituent led to recovery of binding affinity compared to the less lipophilic **8j**. Replacement of the nitro group in **7b** with a lipophilic non-polarizing moiety like Me (**8i**) led to significant loss of activity, whereas replacement with polarizing substituents like acetyl (**8e**) or polarizing and lipophilic substituents like fluoro (**8g**) or trifluoromethoxy (**8d**) resulted in only a slight drop in activity. Substitution of the nitro residue with chloro (**8c**) led to an equipotent compound. Replacing chloro with a more lipophilic substituent such as bromo (**8b**) or trifluoromethyl (**8a**) improved the binding affinity at mTAAR1 up to threefold. Only compound **7a** and **8a** were tested in the functional assay: at mTAAR1 **7a**

**Table 4**
In vitro binding affinity at mTAAR1 for benzanilides with replacements for *meta*-nitro residue



7a, 7b, 8a-8k

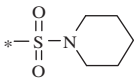
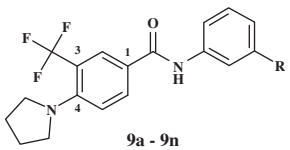
| Entry | R′ | R | $K_i$ (μM) | *c* log *P* |
|---|---|---|---|---|
| **7a** | H | $NO_2$ | 0.189 | 2.8 |
| **7b** | F | $NO_2$ | 0.090 | 2.7 |
| **8a** | F | $CF_3$ | 0.030 | 4.0 |
| **8b** | F | Br | 0.056 | 3.9 |
| **8c** | F | Cl | 0.100 | 3.7 |
| **8d** | F | $CF_3O$ | 0.138 | 4.0 |
| **8e** | F | COMe | 0.139 | 2.3 |
| **8f** | F | CN | 0.149 | 2.7 |
| **8g** | F | F | 0.229 | 3.1 |
| **8h** | F |  | 0.694 | 3.6 |
| **8i** | F | Me | 1.58 | 3.5 |
| **8j** | F | $SO_2NH_2$ | 7.43 | 1.5 |
| **8k** | H | $SO_2Me$ | 6.00 | 1.6 |

**Table 5**
2nd Optimisation of aniline part: in vitro binding affinity at mTAAR1



**9a - 9n**

| Entry | R | $K_i$ (μM) | *c* log *P* | $IC_{50}$ (μM) | min % stim[a] |
|---|---|---|---|---|---|
| **9a** | Me | 0.016 | 4.8 | 0.070 | 0 |
| **9b** | OMe | 0.003 | 4.3 | 0.067 | 0 |
| **9c** | $OCHF_2$ | 0.012 | 4.7 | 0.187 | 0 |
| **9d** | $OCF_3$ | 0.101 | 5.4 | nt | |
| **9e** | Et | 0.021 | 5.4 | 0.470 | 0 |
| **9f** | OEt | 0.0009 | 4.8 | 0.028 | −12 |
| **9g** | $OCF_2CHF_2$ | 0.039 | 6.2 | 0.364 | 0 |
| **9h** | *i*Pr | 0.065 | 5.8 | nt | |
| **9i** | O*i*Pr | 0.004 | 5.1 | 0.027 | 0 |
| **9j** | OPh | 0.082 | 6.4 | nt | |
| **9k** | Ac | 0.026 | 4.0 | 0.120 | 0 |
| **9l** | F | 0.009 | 4.6 | 0.020 | 0 |
| **9m** | Cl | 0.020 | 5.1 | 0.245 | 0 |
| **9n** | Br | 0.046 | 5.3 | 0.568 | 0 |

[a] Residual stimulation by endogenous agonist β-PEA at maximum concentration of test compound; Antagonistic efficacy: reversal of effect of endogenous agonist β-PEA (in vitro cAMP functional assay; 100% efficacy = 0% min % stim.).

had $IC_{50}$ 0.665 μM (full antagonist) and **8a** had $IC_{50}$ 0.028 μM (full antagonist).

Based on the results compiled in Table 4, the trifluoromethyl group (as in **8a**) was chosen as a suitable bioisosteric replacement of the nitro group. Combined with the preferred pyrrolidinyl residue (cf. Table 2) we obtained **9b** which displayed $K_i$ 0.003 μM at mTAAR1 (Table 5).

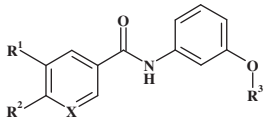
With the 4-pyrrolidinyl-3-trifluoromethyl benzoyl residue as the optimized left hand part, a second optimization of the 3-substituent on the aniline moiety was undertaken (Table 5). Replacing the methoxy group in **9b** by an alkyl moiety, that is, **9a**, **9e** or **9h**, or by a halogen, that is, **9l**–**9n**, led to loss of binding affinity. Among these compounds the least lipophilic fluoro compound **9l** (*c* log *P* 4.6) displayed the highest binding affinity with $K_i$ 0.009 μM. Substitution of the methoxy group by a fluoroalkoxy, that is, **9c**, **9d**, or **9g**, or by a phenoxy residue, that is, **9j**, provided compounds with $K_i$ in the range 0.012 μM (*c* log *P* 4.7) to 0.082 μM (*c* log *P* 6.4), whereby a decrease of binding affinity with increasing lipophilicity was again observed. Substitution of the methoxy group by other alkoxy substituents afforded the best results. Compound **9i** bearing a 3-isopropoxy residue was equipotent with methoxy derivative **9b**, and the highest affinity of all with $K_i$ 0.0009 μM was shown by 3-ethoxy compound **9f** (*c* log *P* 4.8). In the functional assay at mTAAR1 all tested compounds proved to be full antagonists.

Attempts to reduce the lipophilicity of **9b** by replacing the benzoyl part by a nicotinoyl moiety led to a compound having an excellent binding affinity of $K_i$ 0.002 (Table 6, **10a**). Note that the more lipophilic analogue **10b** with $IC_{50}$ 0.22 μM and log *D* >4 (*c* log *P* 4.7) had significantly lower functional activity compared to the less lipophilic **10a** with $IC_{50}$ 0.006 μM (*c* log *P* 3.7).

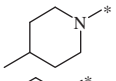
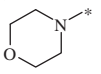
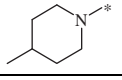
The most promising compounds arising from our SAR exploration work, compounds **2**, **6j**, **9b**, **9f**, **10a** and **10b**, were tested for their in vitro metabolic stability in mouse microsomes (Table 6). Benzanilide **2** and the nicotinoyl derivatives **10a** and **10b** unfortunately proved to be rapidly metabolized during the microsomal incubation. The 4-(1-morpholinyl)-3-nitro-benzoyl derivative **6j** having low lipophilicity (log *D* 2.7) displayed a medium clearance of 18 μg/min/mg protein in mouse microsomes and had an acceptable $IC_{50}$ 0.079 μM but unfortunately proved to be unstable in mouse plasma. We therefore focused our attention on compound **9f** having a *meta*-ethoxy residue on the aniline part which, compared to methoxy analogue **9b**, not only showed a higher binding affinity and functional activity but also a lower microsomal clearance. Compound **9f** was therefore selected for profiling in single dose in vivo pharmacokinetic (PK) experiments in mice comparing different routes of parenteral administration (Fig. 2).[15]

In the event, **9f** displayed a high clearance after iv administration to mice but achieved good bioavailability (74%) after ip application, reaching a maximum plasma concentration of 590 ng/ml following a dose of 5 mg/kg ip (Fig. 2). With a measured brain/

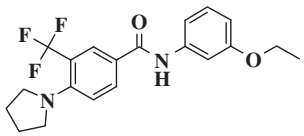
**Table 6**
Microsomal clearance and lipophilicity of key compounds, compared to in vitro binding affinity and functional activity at mTAAR1



**2, 6j, 9b, 9f, 10a, 10b**

| Entry | X | $R^1$ | $R^2$ | $R^3$ | $K_i$ (μM) | $IC_{50}$ (μM) | min % stim.[a] | Clearance[b] | log D | *c* log *P* |
|---|---|---|---|---|---|---|---|---|---|---|
| **2** | CH | $NO_2$ |  | Me | 0.002 | 0.060 | 0 | 396 | >3 | 4.3 |
| **6j** | CH | $NO_2$ |  | Me | 0.103 | 0.079 | 0 | 18 | 2.7 | 2.4 |
| **9b** | CH | $CF_3$ |  | Me | 0.003 | 0.067 | 0 | 341 | | 4.3 |
| **9f** | CH | $CF_3$ |  | Et | 0.0009 | 0.028 | −12 | 109 | | 4.8 |
| **10a** | N | $CF_3$ |  | Me | 0.002 | 0.006 | 0 | 321 | | 3.7 |
| **10b** | N | $CF_3$ |  | Me | 0.002 | 0.220 | 0 | 107 | >4 | 4.7 |

[a] Residual stimulation by endogenous agonist β-PEA at maximum concentration of test compound; Antagonistic efficacy: reversal of effect of endogenous agonist β-PEA (in vitro cAMP functional assay; 100% efficacy = 0% min % stim.).
[b] Intrinsic clearance in mouse liver microsomes, μg/min/mg protein.



**EPPTB (RO5212773, 9f)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **mTAAR1** | $K_i$ | 0.0009 | µM | $IC_{50}$ | 0.028 µM | (-12%) [i] |
| **rTAAR1** | $K_i$ | 0.942 | µM | $IC_{50}$ | 4.54 µM | |
| **hTAAR1** | Ki | > 5 | µM | $IC_{50}$ | 7.49 µM | |

**SDPK (mouse)**

| *i.p.* (5 mg/kg) | | *i.v.* (2.5 mg/kg) | |
|---|---|---|---|
| $C_{max}$ | 590 ng/mL | Clearance | 87 mL/min/kg |
| F | 74 % | t1/2 | 1.9 h |
| brain/plasma | 0.5 | Vss | 3.7 L/kg |
| | | brain/plasma | 0.5 |

**Figure 2.** In vitro activity at TAAR1 and single dose PK data for **9f** (**RO5212773** = **EPPTB**); (i) residual stimulation by endogenous agonist β-PEA at maximum concentration of test compound; Antagonistic efficacy: reversal of effect of endogenous agonist β-PEA (in vitro cAMP functional assay; 100% efficacy = 0% min% stim.).

plasma ratio of 0.5, exposure of **9f** in the brain was considered sufficient for in vivo behavioural pharmacology experiments.

A Cerep ExpressProfile® screen of 56 receptors, ion channels and enzymes[16] showed that at a concentration of 10 µM **9f** had no relevant affinity for any of the included targets with the exception of the sodium channel (site 2) and the adenosine A3 receptor (cf. Supplementary data), confirming that **9f** is a selective antagonist of mTAAR1. The first in vitro mechanistic studies with **9f** (*N*-(3-ethoxy-phenyl)-4-pyrrolidin-1-yl-3-trifluoromethyl-benzamide: **EPPTB = RO5212773**) have recently been published.[8] This selective competitive antagonist was shown to be an inverse agonist and has enabled the elucidation of TAAR1-mediated regulatory mechanisms in dopaminergic neurons of the mesolimbic system. Further in vitro and in vivo studies with **EPPTB** are ongoing and will be published in due course.

In summary, a series of benzanilide TAAR1 antagonists was identified in a HTS and was optimized for potency in binding, functional activity, and selectivity versus other biological targets. **EPPTB (RO5212773, 9f)** was identified as a highly potent and selective full antagonist of mTAAR1 which is suitable for use as a pharmacological tool for in vitro and in vivo investigations. To the best of our knowledge, **EPPTB** is the first selective TAAR1 antagonist disclosed.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.12.075. These data include MOL files and InChiKeys of the most important compounds described in this article.

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