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Graphical Abstract

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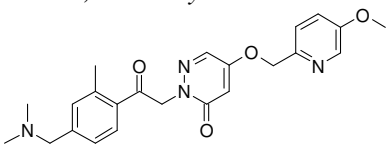

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Design, synthesis and evaluation of MCH Receptor 1 antagonists – Part III: Discovery of pre-clinical development candidate BI 186908

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ABSTRACT

Although overweight and obesity are highly prevalent conditions, options to treat them are still very limited. As part of our search for safe and effective MCH-R1 antagonists for the treatment of obesity, two series of pyridones and pyridazinones were evaluated. Optimization was aimed at improving DMPK properties by increasing metabolic stability and improving the safety profile by reducing inhibition of the hERG channel and reducing the potential to induce phospholipidosis. Steric shielding of a labile keto moiety with an *ortho*-methyl group and fine-tuning of the polarity in several parts of the molecule resulted in BI 186908 (**11g**), a potent and selective MCH-R1 antagonist with favorable DMPK and CMC properties. Chronic administration of BI 186908 resulted in significant body weight reduction comparable to sibutramine in a 4 week diet-induced obesity model in rats. Based on its favorable safety profile, BI 186908 was advanced to pre-clinical development.

Obesity is a major risk factor in the modern world and associated with many serious diseases of the metabolic syndrome such as type 2 diabetes, dyslipidemia, coronary heart disease, and stroke. Consequently, the pharmaceutical industry has made major efforts over the last decades to develop new effective and safe treatments of obesity; nevertheless, current treatment options are still limited. A number of approaches have targeted central mechanisms regulating food consumption and energy homeostasis. The melanin-concentrating hormone (MCH), a cyclic 19-amino acid polypeptide, has been a focus of obesity research since the turn of the millennium. Despite many efforts of the pharmaceutical industry to develop MCH-R1 antagonists as potential anti-obesity agents, only few compounds have been advanced to the clinical stage[1]. Safety concerns such as hERG inhibition, potentially leading to cardiac liabilities, or phospholipidosis[2] were among the prominent reasons for the discontinuation of research programs in the past[3,4]. Thus, in order to assess the full therapeutic potential of the MCH-R1 antagonist therapeutic concept, potent and safe antagonists with adequate DMPK properties are required.

Our group has previously reported on a novel series of potent and selective pyridazines **2**[5] that was originally derived from the alkyne class 1 (Figure 1)[6]. Based on two-dimensional structural considerations, we reasoned that a molecular topology similar to the pyridazine class **2** could be obtained by replacing the central 4-atom linker with a 2-atom linker and attaching the right-hand-side phenyl via a 2-atom linker to an aryl or heteroaryl group. Based on the lesson from the pyridazine series that polarity reduces the risk for potent inhibition of the hERG channel and phospholipidosis, we aimed to incorporate polar heteroaryl groups. This strategy ultimately led to the pyridone series **3** and pyridazinone series **4** of MCH-R1 antagonists. This letter describes the synthesis and optimization towards pre-clinical development candidate BI 186908 (**11g**) and its pharmacological profile.

< FIGURE 1>

<SCHEME 1>

The synthesis of MCH-R1 antagonists described herein is outlined in Scheme 1. Pyridone prototype **7** bearing a central ethylene linker was synthesized starting from **5** in an alkylation,

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bromination, amination sequence. Pyridone series **10** and pyridazinone series **11** bearing a central oxoethylene linker (–C(=O)–CH_2–) were synthesized in similar fashion from the corresponding benzyl alcohols **9** (sequence B). The latter ones were prepared from the corresponding substituted acetophenones **8** by α-bromination and subsequent alkylation of the corresponding right-hand side pyrid(azin)one intermediates **15** and **18**. The acetophenone precursor **13** bearing an *ortho*-methyl substituent was prepared from (4-bromo-3-methyl-phenyl)-methanol (**12**) by bromine-iodine exchange, Heck reaction with butyl vinyl ether and acidic hydrolysis of the vinyl ether intermediate. Right-hand side pyridones **15** were prepared by regio-selective alkylation of 2,4-dihyroxypyridine. The corresponding pyridazinone precursors **18** were typically prepared by Mitsunobu reaction of THP-protected 5-hydroxy-pyridazin-3-one **20** (accessible from commercially available building block **19**) with the corresponding substituted aryl or heteroaryl methanol precursors **16** followed by acidic removal of the THP protecting group. The above reactions proceeded in good-to-acceptable yields and full experimental details have been reported elsewhere[8].

< TABLE 1>

In support of the original design hypothesis (Figure 1), pyridone prototype **7** bearing a central ethylene linker was found to be a single-digit nanomolar antagonist of the MCH-R1 (Table 1). Similar to the previously disclosed pyridazine and alkyne class, a large variety of left-hand side benzylic amine moieties are tolerated with tertiary amines typically exhibiting less undesirable P-gp efflux than secondary amines (data not shown)[5,6]. As *in vivo* pharmacological profiling in this project was performed in rats, we routinely tested metabolic stability of potent MCH-R1 antagonists in a rat microsome assay; unfortunately, **7** as well as other close analogs bearing tertiary amines exhibited only very poor stability in this assay (data not shown). Metabolic instability of structurally similar pyridone derivatives bearing an ethylene linker was also reported by others[7].

We hypothesized that oxidation of the benzylic position in the central linker may contribute to the observed metabolic instability; thus, we designed and synthesized analog **10a** which features an oxoethylene (–C(=O)–CH_2–) instead of the ethylene linker. **10a** retained potent binding to MCH-R1 and exhibited somewhat improved stability in rat liver microsomes. However, in a human hepatocyte assay, **10a** was found to be unstable. Analysis of metabolites after incubation with human hepatocytes revealed that the ketone moiety is rapidly reduced to the corresponding alcohol (data not shown). In order to block the carbonyl group from attack by reductases we prepared compound **10b** which features a sterically demanding methyl group in *ortho*-position potentially preventing the attack. Gratifyingly, **10b** not only retained acceptable potency and metabolic stability in the rat microsome assay but also exhibited strongly improved metabolic stability / reduced clearance in the human hepatocyte assay, supporting our original design hypothesis and defining **10b** as lead for further evaluation.

<TABLE 2>

In vitro selectivity profiling of pyridone analogs **10a** and **10b** revealed favorable selectivity (>200-fold, data not shown) for MCH-R1 *vs.* M1 and 5HT2a, two receptors which had been critical in the optimization of the alkyne and pyridazine class[5,6]; however, both compounds exhibited significant blockage of the hERG channel at 10 μM and first effects at ≤100 μM in a phospholipidosis assay[9]. Following the strategy that had proven successful in the pyridazine class[5], we decided to increase the polarity / reduce the logP by employing pyridinyl groups on the right-hand side. Table 2 summarizes the structure-activity relationships that were established in the pyridone class by means of several key compounds. Replacing the right-hand side phenyl with a 5-chloro-pyridin-2-yl or 5-bromo-pyridin-2-yl group furnished MCH-R1 antagonists with slightly reduced logP and acceptable potency and rat microsomal stability; in these cases, the installation of the methyl group *ortho* to the metabolically labile ketone moiety also led to improved stability in human hepatocytes (**10d** *vs.* **10c** and **10f** *vs.* **10e**) underlining the generalizability of the steric shielding strategy. The more polar 5-fluoro-pyridin-2-yl and 5-methoxy-pyridin-2-yl analogs **10g** and **10h** were hampered by a drop in potency. While there was a slight reduction in hERG affinity, first effect concentrations in the phospolipidosis assay remained below 100 μM for two representative compounds.

<TABLE 3>

Encouraged by the promising metabolic stability achieved in the pyridone series, we applied the learnings to the pyridazinone series (Table 3). We were pleased to find that prototypes **11a** and **11b** retained potency in the 10 nM range, and we also confirmed the beneficial effect of the *ortho*-methyl group on human hepatocyte stability in this series. Still, compound **11b** displayed potent hERG inhibition and exhibited first effects below 100 μM in the phospholipidosis assay. The corresponding 5-halogen-pyridine-2-yl analogs **11c**-**11f** retained acceptable potency and – in the case of the *ortho*-methyl analogs **11d** and **11f** – exhibited acceptable rat microsomal as well as human hepatocyte stability, but did not exhibit any advantages with respect to hERG inhibition or phospholipidosis-inducing potential. In contrast to the pyridone series, it was the most polar 5-methoxy-pyridine-2-yl analog **11g** in the pyridazinone series that eventually provided the desired balance of potency (MCH-R1 IC_{50} = 22 nM, ~3-fold improvement over pyridone analog **10h**), acceptable metabolic stability in rat liver microsomes as well as human hepatocytes, and favorable *in vitro* safety properties (M1, 5HT2a, hERG IC_{50} >10 μM, no phospholipidosis at 100 μM). Encouraged by this attractive initial profile, we initiated in-depth pharmacological and DMPK studies for **11g** (BI 186908).

<TABLE 4>

BI 186908 (**11g**) was shown to bind with comparably high affinity to the recombinant human, cynomolgus monkey, dog and rat MCH-R1 (Table 4). A broad radioligand binding affinity screen on 164 receptors revealed a favorable selectivity profile; substantial binding was detected only to the histamine H3 receptor at concentrations which were regarded as noncritical; the hERG channel was blocked with an IC_{50} of 16 μM in a patch clamp assay.

BI 186908 (**11g**) was shown to have low metabolic stability in hepatocytes from rats and dogs and moderate stability in hepatocytes from monkeys and humans (Table 4). A good correlation was found between *in vitro* metabolic stability and *in vivo* clearance in the animal species investigated. The low bioavailability observed in dog is most likely caused by first pass elimination (in accordance with the high plasma clearance) and not by poor absorption. Plasma protein binding is comparable across species with a slightly lower value observed in dogs. There is no indication that transporters significantly influence absorption or brain penetration (efflux in the Caco-2 model 1.0; concentrations in cerebrospinal fluid were comparable to unbound plasma concentrations). BI 186908 (**11g**) causes a moderate inhibition of CYP 3A4 and exhibits a moderate CYP induction potential (only at 30 µM, PXR screening assay). BI 186908 (**11g**) tested negative in the AMES screening assay, and the phospholipidogenic potential was considered to be low as no effects were observed at 100 µM in the screening assay. The crystalline hydrochloride salt of BI 186908 (**11g**) exhibted favorable aqueous solubility (Table 4).

<FIGURE 2>

Pharmacological efficacy of BI 186908 (**11g**) was assessed in a 4-week study in diet-induced obese female Wistar rats made obese by feeding a simplified cafeteria diet (high-fat chow, chocolate and peanuts) for four months (baseline body weight 440-450 g). In this study, a twice daily oral dosing regimen of 3, 6 and 10 mg/kg BI 186908 (**11g**) was chosen in comparison to the marketed oral anorexiant sibutramine (5 mg/kg once daily). The dose chosen for sibutramine is the maximally tolerated dose in rat. Whereas sibutramine showed a rapid onset of efficacy, all other treatments resulted in a more gradual weight loss which was sustained after 4 weeks of dosing (Figure 2). Placebo-corrected body weight reduction was 7.7% (3 mg/kg bid BI 186908), 10.1% (6 mg/kg bid BI 186908), 10.2% (10 mg/kg bid BI 186908), and 10.9% (5 mg/kg qd sibutramine). This can be attributed exclusively to a decrease in body fat content. The content of water and protein was unchanged. All treatments were well tolerated. The efficacious human dose was conservatively estimated (data not shown) based on the exposure observed in the fully efficacious 6 mg/kg bid dosing regimen ($AUC_{0\text{-}24h}$ ~ 2,600 nM·h).

Cardiovascular effects of BI 186908 (**11g**) were assessed in the conscious cynomolgus monkey after oral administration of 3, 10 and 30 mg/kg (corresponding to 2.4, 8 and 24-fold estimated human C_{max}, respectively). In summary, BI 186908 exhibited a favorable cardiovascular safety profile (data not shown); no effects on systolic and diastolic blood pressure, left ventricular pressure, or myocardial contractility were observed at any dose. For the 30 mg/kg dose, there was a significant slight decrease in heart rate, a trend towards increase in the PR interval and a trend towards reduction in body temperature. When corrected for heart rate and body temperature, there was no significant increase in the QTc-interval.[10]

In conclusion, optimization of metabolic stability employing steric shielding of a labile keto moiety and *in vitro* safety parameters employing property-based design yielded BI 186908 (**11g**), a potent and selective antagonist of the MCH-R1 with favorable DMPK, CMC and pharmacological properties. Based on its favorable safety profile, BI 186908 was advanced to pre-clinical development.

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8. Oost, T.; Lotz, R.; Stenkamp, D. WO13131935, **2013**; Stenkamp, D. et al.WO09103478, **2009**; Stenkamp, D. et al. WO08022979, **2008**; MCH-R1 binding assay: Membranes from CHO/Galpha16 cells stably transfected with human MCH-R1 are re-suspended using a syringe (needle 0.6 x 25 mm) and diluted in test buffer (50 mM HEPES, 10 mM $MgCl_2$, 2 mM EGTA, pH 7.00; 0.1 % bovine serum albumin (protease-free), 0.021 % bacitracin, 1 µg/ml aprotinin, 1 µg/ml leupeptin and 1 µM phosphoramidone) to a concentration of 5 to 15 µg/ml. 200 µL of this membrane fraction (contains 1 to 3 µg of protein) are incubated for 60 minutes at ambient temperature with 100 pM of ^{125}I-tyrosyl melanin concentrating hormone (^{125}I-MCH commercially obtainable from NEN) and increasing concentrations of the test compound in a final volume of 250 µL. After the incubation the reaction is filtered using a cell harvester through 0.5% PEI treated fibreglass filters (GF/B, Unifilter Packard). The membrane-bound radioactivity retained on the filter is then determined after the addition of scintillator substance (Packard Microscint 20) in a measuring device (TopCount of Packard). The non-specific binding is defined as bound radioactivity in the presence of 1 µM MCH during the incubation period. The analysis of the concentration binding curve is carried out on the assumption of one receptor binding site. IC_{50} values are the mean of at least two separately performed experiments. Standard: Non-labelled MCH competes with labelled ^{125}I-MCH for the receptor binding with an IC_{50} value of 0.06 - 0.15 nM. The K_D value of the radioligand is 0.16 nM; HPLC-based logP determinations according to: Donovan, S. F.; Pescatore, M. C. *J. Chromatogr. A* **2002**, *952*, 47.
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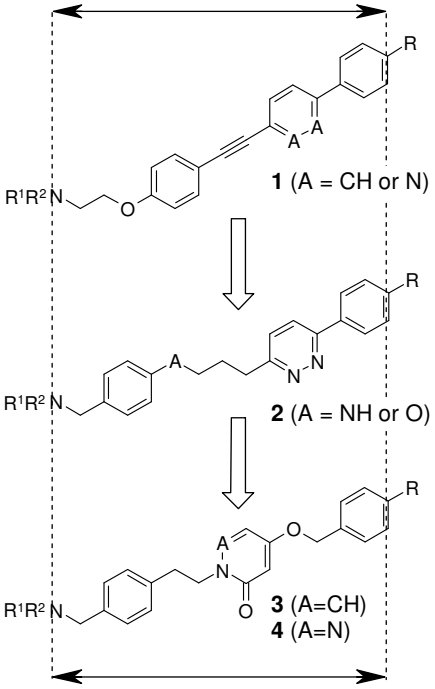
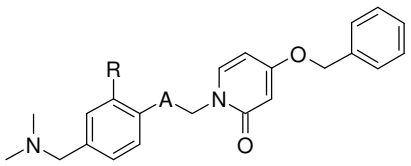


Figure 1. Molecular tailoring of the pyridone series **3** and pyridazinone series **4**.

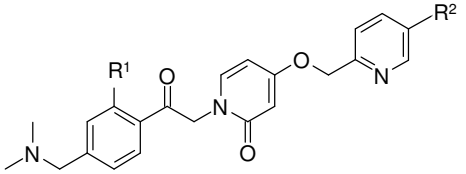
Table 1. Discovery of pyridone lead with improved human metabolic stability[a]



	A	R	logP	MCH-R1 IC_{50} [nM]	Rat Microsomes $T_{1/2}$ [min]	Human Hepatocytes Cl_{int} [µL/(min*10^6 cells)]	hERG Patch Clamp Blockage @ 10 µM	Phospholipidosis First effect conc. [µM]
7	CH_2	H	3.2	7	5	NT	NT	100
10a	CO	H	3.0	13	23	24	63%	100
10b	CO	CH_3	3.3	17	24	4	67%	50

[a] For the description of assay methods, see reference 8; NT: not tested.

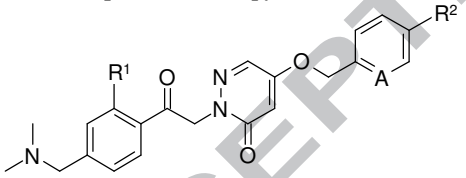
Table 2. Optimization of pyridone series towards improved metabolic stability[a]



	R^1	R^2	logP	MCH-R1 IC_{50} [nM]	Rat Microsomes $T_{1/2}$ [min]	Human Hepatocytes Cl_{int} [µL/(min*10^6 cells)]	hERG Patch Clamp Blockage @ 10 µM	Phospholipidosis First effect conc. [µM]
10c	H	Cl	2.3	41	>45	69	NT	NT
10d	CH_3	Cl	2.7	33	44	14	41%	50
10e	H	Br	2.5	28	32	66	NT	NT
10f	CH_3	Br	2.8	17	45	21	42%	50
10g	CH_3	F	NT	70	NT	NT	NT	NT
10h	CH_3	OCH_3	NT	57	NT	NT	NT	NT

[a] For the description of assay methods, see reference 8; NT: not tested.

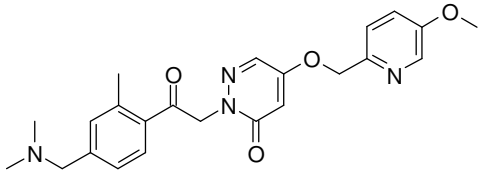
Table 3. Optimization of pyridazinone series towards improved metabolic stability and *in vitro* safety parameters[a]



	R^1	R^2	A	logP	MCH-R1 IC_{50} [nM]	Rat Microsomes $T_{1/2}$ [min]	Human Hepatocytes Cl_{int} [µL/(min*10^6 cells)]	hERG Patch Clamp Blockage @ 10 µM	Phospholipidosis First effect conc. [µM]
11a	H	H	CH	3.6	10	6	17	NT	NT
11b	CH_3	H	CH	3.8	8.7	15	4.8	88%	50
11c	H	Cl	N	2.9	25	14	NT	39%	50
11d	CH_3	Cl	N	3.1	24	>45	NT	NT	50
11e	H	Br	N	3.1	22	7	58	NT	NT
11f	CH_3	Br	N	3.4	16	29	12	85%	50
11g	CH_3	OCH_3	N	2.3	22	>45	3.3	17%	200

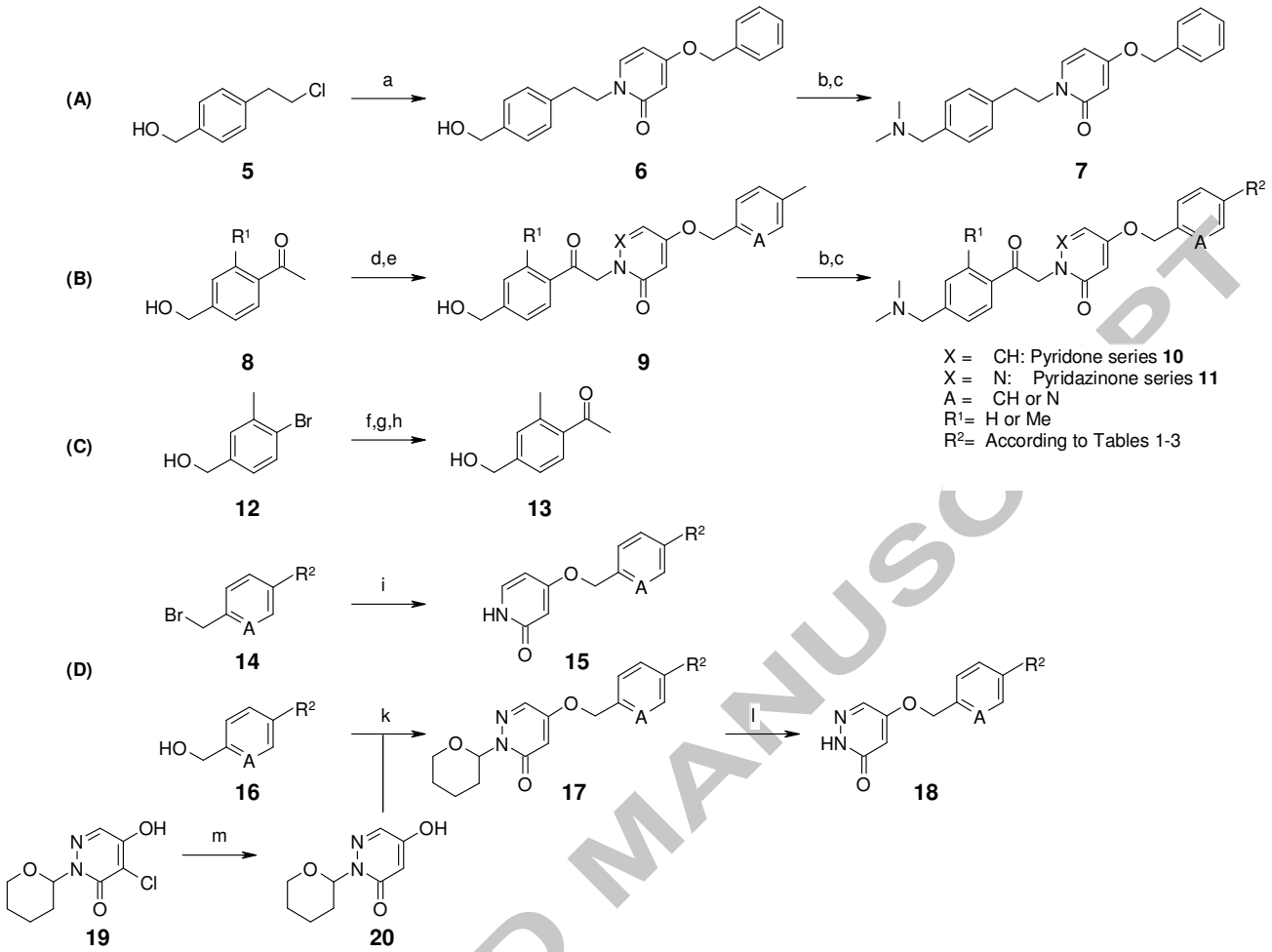
[a] For the description of assay methods, see reference 8; NT: not tested.

Table 4. Properties of pre-clinical development candidate BI 186908 (**11g**)



***In vitro* pharmacology**	
MCH-R1 IC_{50} / K_i	22 / 14 nM
Ricerca panel of 164 receptors	H3 receptor: 78% inhibition @ 10 µM; others <50% inhibition @ 10 µM
Rat / Dog / Cynomolgus IC_{50}	18 / 23 / 18 nM
ADME properties	
Hepatocyte Stability Human / Rat / Dog / Cynomolgus	26 / 78 / 98 / 43 $\%Q_h$
Plasma protein binding Human / Rat / Dog / Cynomolgus	93 / 90 / 80 / 90 %
Caco-2 P_{app} (a-b), 10 µM	$52 \cdot 10^{-6}$ cm/s
Caco-2 efflux ratio, 10 µM	1.0
Clearance Rat / Dog / Cynomolgus	164 / 229 / 40 $\%Q_h$
V_{ss} Rat / Dog / Cynomolgus	3.3 / 2.9 / 1.3 L/kg
MRT_{disp} Rat / Dog / Cynomolgus	0.5 / 0.7 / 1.2 h
MRT_{tot} Rat / Dog / Cynomolgus	3.4 / 2.9 / 2.2 h
F_{oral} Rat / Dog / Cynomolgus	53 / 1.4 / 44 %

***In vitro* safety properties**	
CYP inhibition IC_{50} 3A4/2C8/2C9/2C19/2D6	3A4: 18 µM, others > 50 µM
CYP 3A4: Time-dependent inhibn.	85% CTRL (30 min @ 25 µM)
CYP induction PXR	17% of rifampicin induction @ 10 µM
AMES screen	Negative
Cytotoxicity (U-937 cells)	IC_{50} = 506 µM
Phospholipidosis (Nile red uptake in U-937 cells)	No effect at 100 µM; first effect at 200 µM
hERG patch clamp IC_{50}	16 µM
Physicochemical properties	
logP, logD, pKa	2.3, 1.4, 8.3 / 2.8
Aqueous solubility (pH 2.2 / 4.5 / 6.8 / 7.4)	> 1 mg/mL



Scheme 1. Reagents and conditions: (a) 4-Benzyloxy-1H-pyridin-2-one, K_2CO_3, DMF, 100°C; (b) PBr_3, CH_2Cl_2, r.t.; (c) $NHMe_2$, DMF, 20-50°C; (d) Bu_4NBr_3, CH_2Cl_2/MeOH, r.t.; (e) Cs_2CO_3, DMF or DMSO, **15** or **18**; (f) CuI, NaI, *N*,*N*'-dimethylethylenediamine, dioxane, 120°C; (g) butyl vinyl ether, $Pd(OAc)_2$, 1,3-bis(diphenylphosphino)propane, K_2CO_3, LiCl, DMF/H_2O, 90°C; (h) 1M aq. HCl, r.t.; (i) 2,4-dihydroxypyridine, K_2CO_3, acetonitrile, r.t.; (k) polymer-bound PPh_3, diisopropyl azodicarboxylate, CH_2Cl_2/THF, 0°C→r.t.; (l) 12M aq. HCl in MeOH; (m) H_2 (1700 hPa), 10% Pd/C, MeOH, Et_3N, r.t.

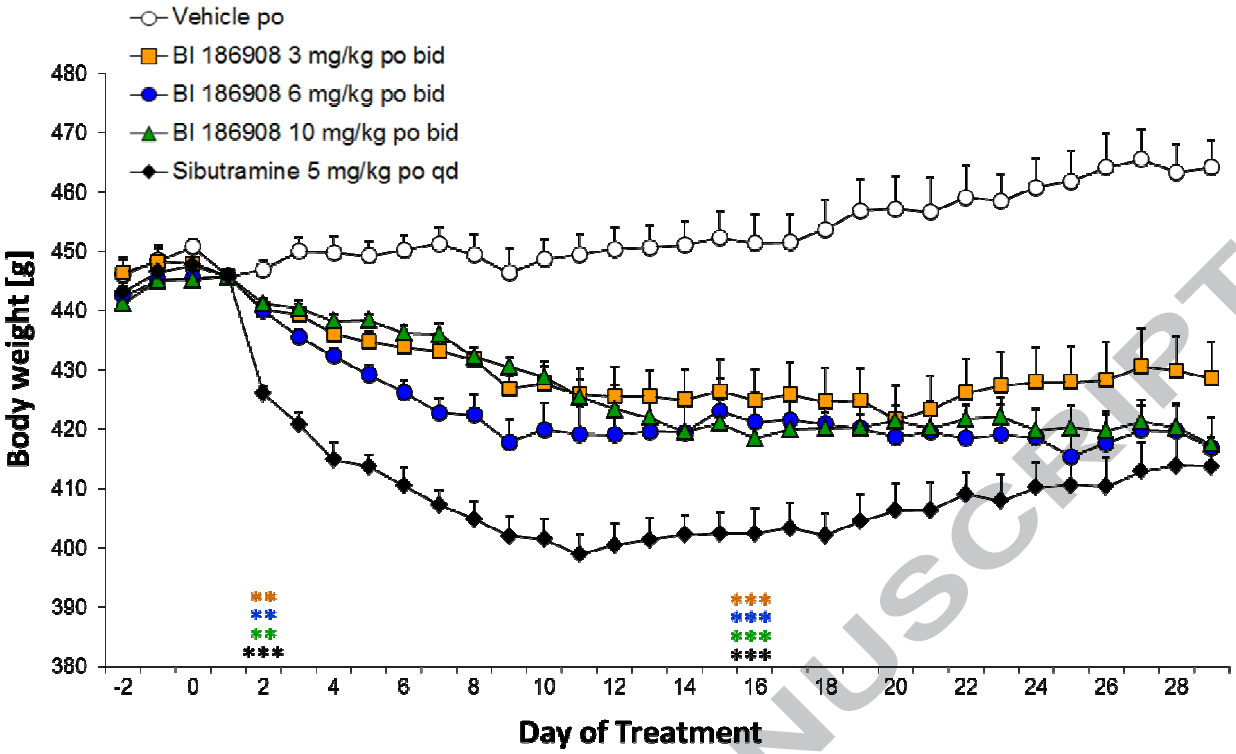


Figure 2. Effect of administration of BI 186908 (**11g**) and sibutramine on body weight in dietary-induced obese Wistar rats. Results are means + SEM. Significant differences from the control group are denoted by **p<0.01 and ***p<0.001.