α-Substituted *N*-(Sulfonamido)alkyl-*β*-aminotetralins: Potent and Selective Neuropeptide Y Y5 Receptor Antagonists

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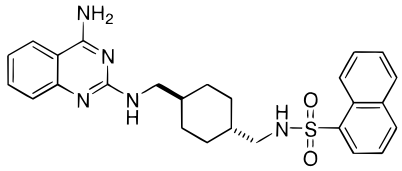
Introduction. Neuropeptide Y (NPY), first isolated from porcine brain,[1] is a powerful stimulant of food intake.[2−5] In landmark studies by Stanley and Leibowitz,[4,5] injection of 100 ng of NPY into the hypothalamic paraventricular nucleus of live rats caused satiated animals to overeat. A dose of 1 μg induced animals to consume, within 4 h, an amount of food approximately equivalent to the normal daily intake in an age-matched, vehicle-treated group.

Endogenous receptors that bind NPY and related peptides are members of the superfamily of G-protein-coupled receptors, and most NPY receptors have been cloned and expressed in viable functional cell lines. Five different NPY receptor subtypes (Y1, Y2, Y4(PP), Y5, and Y6 (formerly designated as a Y5 receptor and expressed as a pseudogene)) are recognized today based upon binding profile, pharmacology, and composition if identity is known.[6−16] Some studies have suggested that an "atypical Y1" receptor is responsible for invoking NPY-stimulated food consumption[17] in animals. For example, the NPY fragment NPY2−36 has been shown to be a potent inducer of feeding despite poor binding at the Y1 receptor.[18] In contrast, a potent and selective Y1 agonist has been reported to be ineffective at stimulating feeding in animals,[19] whereas the Y5 receptor agonist, [D-Trp[32]]NPY, stimulated food intake when injected into the hypothalamus of rats.[20] Since [D-Trp[32]]-NPY appears to be a full agonist of the Y5 receptor with no appreciable Y1 activity, the Y5 receptor is hypothesized to be at least partially responsible for the feeding response. Furthermore, antisense oligodeoxynucleotides to the Y5 receptor are reported to reduce food consumption in animal models of feeding.[21] Accordingly, compounds that antagonize the Y5 receptor should be effective in inhibiting food intake, particularly that stimulated by NPY.

With this premise in mind, a variety of small molecule Y5 antagonists have been developed within the past years. Arylsulfonamides and arylsulfamides derived from arylalkylamines are reported to be sub-micromolar Y5 antagonists.[22] Structurally related sulfonamides that contain heterocyclic systems such as a series of 2,4-diaminoquinazolines are being developed as well;[23−26] the nanomolar Y5 antagonist **1** is reported to reduce food consumption in animal models of feeding.[27] In addition, structurally diverse series of pyrazoles, aminopyridines, and various amide derivatives have been claimed as nanomolar Y5 receptor ligands.[28−31]



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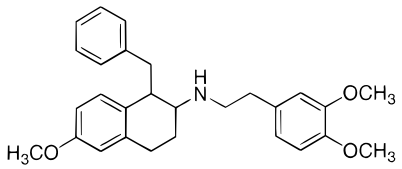
Herein we report on a novel series of α-substituted *N*-(sulfonamido)alkyl-*β*-aminotetralins and -*β*-amidotetralins that are among the most potent and selective NPY Y5 receptor antagonists identified to date. Certain members of this series possess good chemical and metabolic stability along with high aqueous solubility thus making these compounds extremely useful for elucidating the physiological role of the Y5 receptor. Furthermore, a prototypic compound was effective in reducing food consumption in an ad libitum fasted rat model of feeding.

Chemistry. Screening of our in-house chemical library identified novel aminotetralin **2** as having low micromolar binding affinity for the human Y5 receptor.[32] With this lead in-hand, we chose to construct the



2: hY5r IC_{50} ~ 0.9 μM

α-substituted *β*-aminotetralin nucleus and carry out acylations and alkylations of the nitrogen center in the hope of improving receptor binding affinity. Accordingly, *β*-tetralone **3** was reacted with pyrrolidine to give the corresponding enamine which underwent alkylation upon reaction with benzyl or alkyl halides to afford iminium salt **4**. Hydrolysis generated the corresponding tetralone **5** which was subjected to reductive amination to produce *cis*-α-substituted *β*-aminotetralin **6** (along with traces of the *trans*-product). Heteroaryl groups were introduced via condensation of *β*-tetralone **3** with heteroarylcarboxaldehydes in the presence of piperidine, followed by hydrogenolysis and/or reductive amination. Following these synthetic routes, a host of racemic α-substituted *β*-aminotetralins containing aralkyl, heteroaralkyl, alkyl, or alkenyl appendages were readily prepared (Scheme 1).

In keeping with the general structural features of our lead compound **2** and finding that aminotetralins lacking N-substitution are inactive in terms of Y5 receptor

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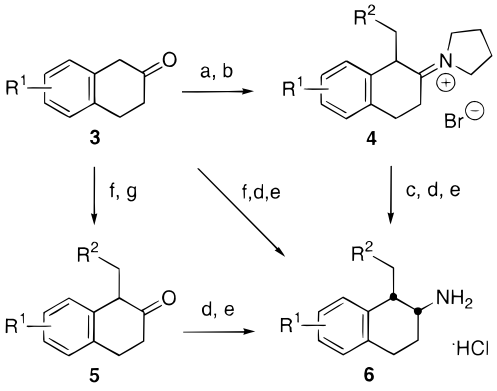
Scheme 1. Synthesis of *cis*-α-Substituted *β*-Aminotetralins



(a) pyrrolidine/PhH (-H_2O); (b) R^2CH_2Br/CH_3CN;
(c) HOAc, H_2O, CH_2Cl_2/MeOH;
(d) Na(BH_3)CN, NH_4OAc/MeOH reflux; (e) HCl/Et_2O;
(f) R^2CHO, cat. piperidine/PhH reflux (-H_2O); (g) H_2, Pd/ /MeOH

binding, we decided to tether terminal arylsulfonamido groups onto the aminotetralin nitrogen center. We chose to utilize Ω-sulfonamidocarboxylic acids derived from simple aliphatic amino acids to see if there was any preferred spacing between the aminotetralin ring system and the arylsulfonamido group. We also investigated constrained versions of the tether (L) thus leading to the *trans*-methyl(cyclohexyl)methyl scaffold present in other series of Y5 antagonists.[22,25] Using known peptide coupling protocols (i.e., HBTU/DMF), aminotetralins **6** underwent acylation to afford the corresponding amide adducts **7** which were subsequently reduced to aminotetralin sulfonamides **8** (Scheme 2).

We tailored our strategy to include scaffolds derived from lysine and cyclic amines in an attempt to lower lipophilicity and enhance aqueous solubility. Accordingly, N-Boc-protected aminopyrrolidines and aminopiperidines were reacted with ethyl bromoacetate and subsequently hydrolyzed to give the desired pyrrolidinyl- and piperidinylacetic acids. These substrates coupled smoothly with aminotetralins **6** to give the corresponding amides **9**. Treatment with acid removed the Boc group giving intermediates **10** which were sulfonylated to the desired acetylated aminotetralins **7** (Scheme 2). Similarly, an α-aminopentyl scaffold was introduced via reaction of aminotetralin **6** with sulfonylated lysine.

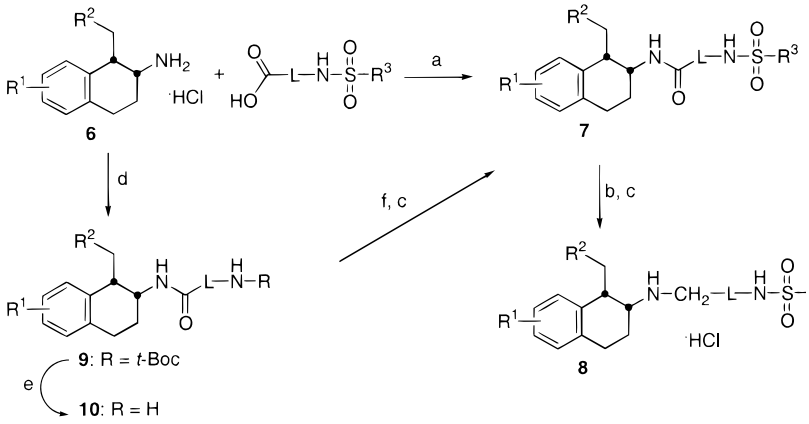
Results and Discussion. α-Substituted *N*-(sulfonamido)alkyl-*β*-aminotetralins **8** and -*β*-amidotetralins **7** were evaluated for binding affinity to the human NPY Y5 receptor using a stably transfected HEK293 cell line and measuring competitive inhibition of binding of [^{125}I]-PYY (Table 1).[32] Replacement of the *N*-phenethyl substituent found in the lead compound **2** (IC_{50} = 910 ± 153 nM, n = 4) with (arylsulfonamido)alkyl groups afforded aminotetralins **8** with enhanced binding affinity (e.g., **8a**: IC_{50} = 443 ± 155 nM). The length of the hydrocarbon tether (L group) was found to be important indicating that proper spacing between the aminotetralin nucleus and sulfonamide group is needed for potent binding. The optimum distance was demonstrated to be between five and six carbon atoms; compounds with shorter or longer alkyl tethers were poorly active (not shown).

In general, α-aralkylaminotetralin sulfonamides containing bulky hydrocarbon R^2 substituents such as phenyl (**8a**), substituted phenyl, and naphthyl (not shown) displayed weak receptor affinity and were typically plagued by poor physical properties (low aqueous solubility, high lipophilicity). For this reason, we chose to introduce smaller hydrocarbon groups and various heterocyclic systems. In particular, pyridine substituents afforded aminotetralins with enhanced solubility and the 3-pyridyl congeners maintained good affinity for the Y5 receptor (**8b**: IC_{50} = 337 nM). Rather surprisingly, replacement of the pyridyl (R^2) substituent with a simple allyl group also gave potent compounds.

A dramatic increase in potency was observed in going from naphthylsulfonamides to the smaller phenyl and substituted phenyl analogues (**8d**: IC_{50} = 10 nM). Substitution on the *ortho* position of the benzenesulfonamide was tolerated; for example, electron-withdrawing groups such as fluoro gave equipotent compounds. However, the introduction of substituents onto other positions of the benzenesulfonamide diminished binding affinity.

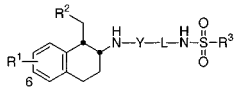
An additional enhancement of receptor binding was achieved by examining aminotetralin substituents (R^1). In general, substitution onto the aryl ring of the tetralin system was well-tolerated. However, the C-6 center was

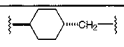
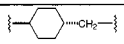
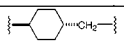
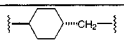
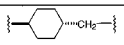
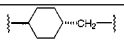
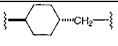
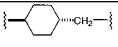
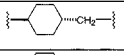
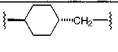
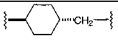
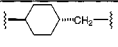
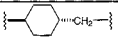
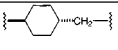
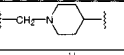
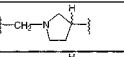
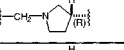
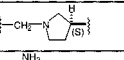
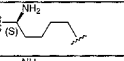
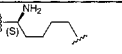
Scheme 2. Synthesis of α-Substituted *N*-(Sulfonamido)alkyl-*β*-aminotetralins **8** and -*β*-Amidotetralins **7**



(a) HBTU, DIEA / DMF; (b) BH_3-THF reflux or LAH / THF reflux; (c) HCl; (d) HOOC-CH_2-N(CH$_2$)$_{1-2}$ HBTU, DIEA / DMF; (e) TFA / DCM, trace H_2O; (f) $ArSO_2Cl$, DIEA / CH_3CN

Table 1. Y5 Receptor Affinities of *cis*-α-Substituted *β*-Aminotetralin Sulfonamides **8** (Y = $-CH_2-$) and *β*-Amidotetralins **7** (Y = C=O)



Entry	R^1	R^2	Y	L	R^3	Y5 IC_{50} ± SD (nM)
8a [a]	6-OMe	Ph	$-CH_2-$		2-naphthyl	443 ± 155 (n=10)
8b [a]	6-OMe	3-pyr	$-CH_2-$		2-naphthyl	337 ± 7 (n=2)
8c [a]	6-OMe	3-pyr	$-CH_2-$	$-(CH_2)_5-$	Ph	53 ± 30 (n=2)
7d [a]	6-OMe	3-pyr	C=O		Ph	11 ± 3 (n=2)
8d [a]	6-OMe	3-pyr	$-CH_2-$		Ph	10 ± 6 (n=2)
7e [a]	6-F	3-pyr	C=O		Ph	40 ± 27 (n=2)
8e [a]	6-F	3-pyr	$-CH_2-$		Ph	27 ± 15 (n=2)
7f [a]	6-F	3-pyr	C=O		(2-F)Ph	12 ± 4 (n=6)
8f [a]	6-F	3-pyr	$-CH_2-$		(2-F)Ph	19 ± 12 (n=2)
7g [a]	6-OMe	3-pyr	C=O		(2-F)Ph	11± 1 (n=2)
8g [a]	6-OMe	3-pyr	$-CH_2-$		(2-F)Ph	23 ± 9 (n=10)
8h [a]	6-OH	3-pyr	$-CH_2-$		(2-F)Ph	7 ± 2 (n=9)
7i [a]	6-F	$-CH=CH_2$	C=O		Ph	75 ± 13 (n=3)
8i [a]	6-F	$-CH=CH_2$	$-CH_2-$		Ph	21 ± 6 (n=22)
8j [a]	6-OH	$-CH=CH_2$	$-CH_2-$		Ph	5 ± 2 (n=23)
7k [a]	6-F	3-pyr	C=O		Ph	10 ± 9 (n=3)
7l [b]	6-F	3-pyr	C=O		Ph	11 ± 13 (n=3)
7m [b]	6-F	3-pyr	C=O		Ph	27 ± 2 (n=2)
7n [b]	6-F	3-pyr	C=O		Ph	5 ± 4 (n=3)
7o [c]	6-F	3-pyr	C=O		(2-F)Ph	22 ± 2 (n=2)
8p [c]	6-OH	3-pyr	$-CH_2-$		(2-F)Ph	1.0 ± 0.3 (n=4)
NPY	---	---	---	---	---	3 ± 2 (n=6)

[a] Compound is racemic mixture. [b] Compound is mixture of diastereomers; chiral center of known configuration is shown (L column). [c] Compound is single pure diastereomer of unknown absolute configuration; chiral center of known configuration is shown (L column). NPY (human) was purchased from Bachem (Torrance, CA).

a preferred site and the hydroxy group was an exceptional substituent that routinely gave a severalfold increase in potency compared to methoxy and fluoro analogues (**8h**: IC_{50} = 7 nM vs **8g**: IC_{50} = 23 nM and **8f**: IC_{50} = 19 nM; **8j**: IC_{50} = 5 nM vs **8i**: IC_{50} = 21 nM). Combining these structural features routinely gave α-(3-pyridylmethyl)-*β*-aminotetralin-derived sulfonamides that exhibited nanomolar binding affinity for the Y5 receptor.

Although the corresponding amides displayed good affinity (**7i**: IC_{50} = 75 nM; **7e**: IC_{50} = 40 nM; **7f**: IC_{50} = 12 nM; **7g**: IC_{50} = 11 nM), these compounds suffered from poor aqueous solubility (**7i**: <1 mg/mL; **7e**−**g**: ≤10 mg/mL) and were problematic in terms of isolating well-characterized salts suitable for dosing in animals. We attributed these undesired properties to the presence of the cycloalkyl tether, and for this reason, we investigated amine-containing variations which would be expected to impart lower lipophilicity and possibly enhance solubility.

To our satisfaction, the incorporation of aminopiperidinyl-, aminopyrrolidinyl-, or aminopentyl-derived scaffolds resulted in a slight augmentation of binding affinity (**7k**: IC_{50} = 10 nM, **7n**: IC_{50} = 5 nM vs **7e**: IC_{50} = 40 nM; **8p**: IC_{50} = 1 nM vs **8h**: IC_{50} = 7 nM), and water solubility was improved as well (**7n**: >50 mg/mL; **8p**: >50 mg/mL). Interestingly, *β*-amidotetralins containing these tethers are very potent Y5 receptor antagonists without the need to reduce to the amine. This finding differentiates our series of compounds from other known sulfonamide-based Y5 receptor antagonists and may be indicative of a unique binding motif with the receptor.

Chromatographic separation of racemic **8i** using a chiral stationary phase provided the individual enantiomers, and it was demonstrated that essentially all of the Y5 affinity resided in one enantiomer (**8i** *ent*-1: IC_{50} = 439 nM, $[\alpha]_D = +35.9°$, c = 0.81 g/dL (MeOH) vs **8i** *ent*-2: IC_{50} = 12 nM, $[\alpha]_D = -35.1°$, c = 0.67 g/dL (MeOH)). The *β*-amidotetralins containing aminopentyl and aminopyrrolidinyl scaffolds could be derived from lysine and aminopyrrolidines of known stereochemical configurations, and thus sets of diastereomers were readily obtained via chromatographic separation. Upon separation, a single diastereomer was shown to be responsible for Y5 receptor affinity (**7o** *diast*-1: IC_{50} = 22 nM vs **7o** *diast*-2: IC_{50} = 869 nM (not shown)), and in one case, a single pure diastereomer had exquisite affinity for the Y5 receptor (**8p**: IC_{50} = 1 nM).

Receptology studies of members of this series reveal that α-substituted *N*-(sulfonamido)alkyl-*β*-aminotetralins and -*β*-amidotetralins are highly selective Y5 antagonists. A panel of compounds (**8i**,**p** and **7n**) did not stimulate binding of labeled GTPγS in a Bowes melanoma cell line transfected with the human Y5 receptor but, in the presence of PYY, was able to inhibit incorporation of label. Several compounds of this series (e.g., **8g**,**i**) were screened against over 30 G-protein-coupled receptors and ion channels and found to have only weak (≥1 μM) affinity for the central muscarinic receptor and the L-type calcium channel. Members of this series are also Y receptor subtype specific and do not bind to either Y1 or Y2 receptors in radioligand ([^{125}I]PYY) displacement assays (e.g., **8g**: 0% vs hY1, 0% vs hY2; **8i**: 0% vs hY1, 30% vs hY2 @ 10 μM). In vitro metabolism studies reveal that these aminotetralins possess good stability when incubated with human (and rat) S9 hepatic fractions (**8g**: 92% unchanged and **8i**: 95% unchanged after 1 h).

A prototypic compound (**8i**) was evaluated in an animal model of feeding measuring food consumption as an endpoint.[33] Drug-treated, fasted male rats consumed statistically significant less chow than vehicle control group over a 6-h period (Table 2), suggesting that antagonism of the Y5 receptor can suppress feeding under certain conditions (i.e., food deprivation). Additional studies are underway to determine if this effect

Table 2. Inhibition of Food Consumption in a Fasted Rodent Model of Feeding

compd	dose (mg/kg) (no. rats)	cumulative food consumption (g) 0−2 h (% change)	0−4 h (% change)	0−6 h (% change)	2−6 h (% change)
vehicle PEG-200	ip $N = 8$	9.63	13.3	20.9	11.3
8i	30, ip $N = 8$	4.88 (−49%) $p = 0.003$	8.00 (−40%) $p = 0.010$	13.6 (−35%) $p = 0.025$	8.75 (−22%) $p = 0.252$

can be directly attributed to antagonism of the Y5 receptor. In general, the α-substituted *N*-(sulfonamido)-alkyl-*β*-aminotetralins and -*β*-amidotetralins are well-tolerated in animals at doses needed to inhibit feeding.

Conclusion. Collectively, these results indicate that the α-substituted *N*-(sulfonamido)alkyl-*β*-aminotetralins **8** and -*β*-amidotetralins **7** reported here are potent and selective antagonists of the human Y5 receptor which may be useful for the treatment of human feeding disorders and obesity.

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Supporting Information Available: Experimental protocols for the synthesis of compounds **8j**,**p** and **7l**, intermediates supported with NMR and MS data, and high-resolution and elemental analyses (C, H, N) of all compounds in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) **Stable Transfection.** The human NPY Y5 receptor cDNA (GenBank Accession number U66275) was inserted into the vector pCIneo (Invitrogen) and transfected into human embryonic kidney cells (HEK-293) via calcium phosphate method (Wigler et al. *Cell* **1977**, *11*, 223). Stably transfected cells were selected with G-418 (600 μg/mL) and served as the source for the membranes for the NPY Y5 receptor binding assay. **Membrane Preparation.** NPY Y5-transfected HEK-293 cells were grown to confluence in 150-cm^2 culture dishes. Cells were washed once with phosphate-buffered saline (Gibco cat# 14040-133) and then incubated in phosphate-buffered saline without calcium and without magnesium, supplemented with 2 mM EDTA. Cells were incubated for 10 min at room temperature, collected by repetitive pipeting, formed into pellets, and then

frozen at −80 °C until needed. Frozen pellets were homogenized with a polytron at full speed for 12 s in a homogenization buffer (20 mM Tris HCl, 5 mM EDTA, pH 7.4). Homogenates were centrifuged for 5 min at 4 °C at 200*g* and the supernatants were transferred to corex tubes and centrifuged for 25 min at 28000*g*. The pellets were resuspended in binding medium (20 mM HEPES, 10 mM NaCl, 0.22 mM KH_2PO_4, 1.3 mM $CaCl_2$, 0.8 mM $MgSO_4$, pH 7.4). Membranes were kept on ice until use. **Competition Binding Assay.** Aminotetralin sulfonamides and β-amidotetralins described herein compete with [^{125}I]PYY for binding to cell membranes containing the human Y5 receptor. The less [^{125}I]PYY bound to the membranes implies that a compound is a good inhibitor (competitor). Bound [^{125}I]PYY is determined by centrifugation of membranes, aspirating supernatant, washing away residual [^{125}I]PYY, and subsequently counting the bound sample in a γ-counter. Aminotetralin sulfonamides **8** and β-amidotetralins **7** were prepared as 10× stocks in binding buffer and added to assay tubes (RIA vials, Sarstedt). Twenty (20) μL of each 10× compound stock was transferred via pipet into separate vials along with 80 μL of [^{125}I]PYY (NEN cat# NEX240), which was diluted to a concentration of 200 pM in 0.25% BSA in binding buffer (final concentration of [^{125}I]PYY was 80 pM). To each tube was added 100 μL of membranes and the mixture was agitated by pipeting. Samples were incubated for 1 h at room temperature. Aluminum cast plates (Sarstedt) containing the vials were then centrifuged for 10 min at 3200 rpm in a Sorvall RT6000 and the supernatant was then aspirated. To each vial 400 μL of PBS was added followed by aspiration again. Vials were put in carrier polypropylene 12 × 75 tubes and counted in a γ-counter (Packard). Nonspecific binding was determined in the presence of 300 nM NPY. Percent inhibition of [^{125}I]PYY binding was calculated by subtracting nonspecific binding from the test samples (containing compound **7** or **8**), taking these counts and dividing by total binding, and multiplying by 100. Inhibitory concentration values (IC_{50}) of compounds were calculated by obtaining percent inhibition of [^{125}I]PYY binding values at different concentrations and using a graphing program such as GraphPad Prism to calculate the concentration of test compound that inhibits 50% of [^{125}I]PYY binding.

(33) Fasted male Long-Evans rats (180−200 g) were housed individually and maintained on a once-a-day feeding schedule (10 a.m. to 4 p.m.) for 5 days following quarantine to allow the animals to acclimate to feeding on powdered chow (#5002 PMI Certified Rodent Meal) during the allotted time. The chow was made available in an open jar, anchored in the cage by a wire, with a metal follower covering the food to minimize spillage. Water was available ad libitum. Animals were fasted for 18 h prior to testing. At the end of the fasting period, animals were administered compound **7** or **8** or vehicle. Vehicle and test compounds were administered 30 min prior to the experiment and given intraperitoneally (1 mL/kg). The test compound **7** or **8** was individually administered intraperitoneally as a solution or suspension in PEG 200; compound concentrations typically ranged from 1−100 mg/kg, preferably from 10−30 mg/kg. Food intake was measured at 2, 4, and 6 h after administration by weighing the special jar containing the food before the experiment and at the specified times. Percent reduction of food consumption was calculated by subtracting the grams of food consumed by the treated group from the grams of food consumed by the control group, divided by the grams of food consumed by the control group, multiplied by 100.

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