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Synthesis and SAR of selective small molecule Neuropeptide Y Y2 receptor antagonists

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Abstract

Highly potent and selective small molecule Neuropeptide Y Y2 receptor antagonists are reported. The systematic SAR exploration of a hit molecule *N*-(4-ethoxyphenyl)-4-[hydroxy(diphenyl)methyl]piperidine-1-carbothioamide, identified from HTS, led to the discovery of highly potent NPY Y2 antagonists **16** (CYM 9484) and **54** (CYM 9552) with IC₅₀ values of 19 nM and 12 nM respectively.

Keywords

Neuropeptide Y Y2; Antagonist; Structure Activity Relationship; Thiourea; Carbamate

Neuropeptide Y (NPY) is a highly conserved 36-amino acid peptide neurotransmitter, structurally and functionally related to the 36-amino acid pancreatic peptide (PYY) and pancreatic polypeptide (PP) and one of the most abundant neuropeptides in the mammalian brain.^{1,2} NPY is involved in a variety of physiological processes such as regulation of energy balance, anxiety, food intake, water consumption, circadian rhythms, learning, memory, anxiety, cell proliferation, and angiogenesis.^{3–6} Four different receptor subtypes^{7,8} (Y1, Y2, Y4, Y5) have been identified as endogenous receptors in humans that bind to NPY and are expressed in both the central and peripheral nervous systems. All NPY receptor subtypes belong to the family of G protein coupled receptors (GPCR) and mediate their biological responses via Gαi signaling pathways.

The NPY Y2 receptor has attracted considerable interest since it has been associated with various physiological and pathological processes such as affective disorders, infertility, bone mass formation, responses to ethanol and drugs of abuse, angiogenesis, and food intake.⁹ Doods et al¹⁰ reported a highly potent (IC₅₀ = 3.3 nM) peptide-like NPY Y2 antagonist BIIE0246, which decreased ethanol consumption in rats and induced antidepressant-like effects in mice¹¹ following intracerebroventricular (icv) administration. However, the potential therapeutic application of this compound is limited due to its peptide-like structure, high molecular weight, poor brain penetration and off-target selectivity.^{12,13} While most of

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the efforts in the literature have been focused on the discovery and development of NPY Y1 and Y5 receptor antagonists as potential therapeutic agents for obesity and feeding disorders, there are only few reports on the identification of selective NPY Y2 receptor antagonists.^{14–18} Therefore, selective NPY Y2 antagonists with good physicochemical properties, suitable for *in vivo* studies are desired.

With an aim to identify selective, brain-penetrant, non-peptidic NPY Y2 antagonists that are suitable for *in vivo* studies, we performed whole-cell based high throughput screening of a library of small molecules available through the auspices of the National Institutes of Health. From the screening, we identified four distinct chemotypes (SF-11, SF-21, SF-31 and SF-41) that are novel, brain-penetrant, and selective against the NPY Y1 and 38 off-target receptors, including GPCRs, transporters and ion-channels.¹⁹ The four chemotypes (Figure 1) exhibited antagonism at the NPY Y2 receptor with IC₅₀ values ranging from 0.19 to 4.4 μ M. The hits are being followed up to further improve the potency, brain-penetration and drug-likeness. Here, we report the synthesis and SAR investigations of one of the hit molecules SF-11.

The hit molecule SF-11 was divided into three parts **A** (phenyl ring), **B** (diphenylcarbinol) and **C** (linker) to explore the SAR systematically (Figure 1). The preliminary SAR, observed from a tiny set of SF-11 analogues from the HTS campaign, indicated that the NPY Y2 antagonist activity may depend on both the position and type of the substituent present on the phenyl ring (**A**).¹⁹ Therefore, we have primarily explored the substitution on the aryl ring (**A**). The desired analogues (**1–30**, Table 1) were prepared by the coupling of commercially available α,α -diphenylpiperidino-4-methanol with a variety of aryl isothiocyanates (Scheme 1). The non-commercially available aryl isothiocyanates were prepared from appropriate anilines and thionating reagent di-2-pyridyl thionocarbonate.²⁰ All compounds were determined to be >95% pure by ¹H NMR and LC-MS.²¹ The compounds were tested against NPY Y2 and Y1 receptors using the cAMP biosensor assay as previously described.¹⁹ The activity data is presented in Table 1.

To determine the minimal structural requirements for the antagonist activity, the ethoxy group of the hit molecule SF-11 was removed as exemplified by **1**, which resulted in complete loss of activity, suggesting a substitution on the aryl ring is essential. The replacement of the ethoxy group with a methoxy (**2**), isopropoxy (**3**) or trifluoromethoxy (**4**) resulted in decreased potency, which indicates the presence of a hydrophobic pocket with steric-constraints at the binding site. Interestingly, the *n*-propyl analogue **5** was less potent than the ethoxy analogue SF-11, suggesting the presence of both a hydrogen-bond acceptor and optimal hydrophobic group at this position would improve the antagonist activity. We have consequently investigated a variety of hydrogen-bond acceptor containing groups such as dialkylamines, esters, carboxamides, and sulfonamides. The diethylamine analogue **8** showed nearly 3-fold increase in the potency compared to SF-11. The dimethyl amine analogue **7**, as well as cyclic amines **9** and **10** were less potent than the diethyl amine analogue **8** and SF-11, corroborating the SAR. The ethyl ester analogue **11** and ethyl amide analogue **13** exhibited similar potency to SF-11. The *N,N*-dialkylamide analogues **14** and **15** were more potent than the monoalkylamides **12** and **13**, of which *N,N*-diethylamide analogue **15** was 4-fold more potent than *N,N*-dimethylamide analogue **14**. In contrast to *N,N*-dialkylamide analogues **14** and **15**, *N,N*-dimethyl sulfonamide analogue **16** (CYM 9484) displayed higher potency (IC₅₀ = 19 nM) than *N,N*-diethyl sulfonamide analogue **17** and was 10-fold more potent than the hit molecule SF-11.

The importance of the position of the substituent on the phenyl ring (**A**) was studied subsequently. The 3-substituted analogues **20** and **21** were less potent than the corresponding 4-substituted analogues **2** and **6**, except compound **22** which displayed

similar potency to **11**, but exhibited partial antagonism. To understand the effect of an additional substituent on the antagonist activity, we also explored 3, 4- and 2, 4-disubstitutions on the phenyl ring (**A**) as exemplified by **23–30**. The chloro (**24**) and cyano (**25** and **26**) groups were tolerated at the 3-position, but did not improve the potency significantly compared to the corresponding 4-substituted analogues **8**, SF-11 and **3**. The incorporation of methyl (**27**), trifluoromethyl (**28**) and chloro (**29**) groups at the 2-position resulted in complete loss of activity, whereas the fluoro (**30**) group was tolerable, but nearly 7-fold less potent than the corresponding analogue SF-11. The SAR exploration of groups on phenyl ring (**A**) suggests that a substitution at the 4-position of phenyl ring is important for antagonist activity, of which the *N,N*-dimethyl sulfonamide group is optimal.

We then performed SAR studies on the diphenylcarbinol (**B**) of the hit molecule (Table 2). The removal of either one of the phenyl rings (**31**) or hydroxyl group of the diphenylcarbinol (**34–36**) was detrimental to the activity. The hydroxyl group was methylated to identify the necessity of a hydrogen-bond donor for the antagonist activity. The methylated analogue **35** displayed no activity, signifying the essentiality of a hydrogen-bond donor. Interestingly, the piperazine analogue **36** retained the activity in contrast to the piperidine analogue **32**, supporting the requirement of a hydrogen-bond donor. Subsequently, we focused our efforts on modification of one of the phenyl rings of the diphenylcarbinol. The replacement of one of the phenyl rings with a cyclohexyl group (**38**) resulted in complete loss of activity. The heteroaryl analogues such as pyridin-2-yl **40** and thiophen-3-yl **41** were tolerable, whereas the furan-3-yl **42**, 3-pyridin-3-yl **39** and 3,5-dimethylisoxazol-4-yl **43** analogues significantly lost the activity. The substitution of a fluorine at the 4-position (**44**) of one of the phenyl rings of diphenylcarbinol was tolerable, but not beneficial. We also explored the conformationally-constrained tricyclic moieties as exemplified by **45** and **46** to investigate the conformational requisite of the phenyl rings of diphenylcarbinol. Notably, the dibenzoazepinone analogue **46** displayed higher potency than the corresponding analogue **37**, whereas the less-constrained tricyclic analogue **45** was inactive. The SAR studies of part B of the hit molecule suggest that a hydrogen-bond donor and the conformation of phenyl rings of diphenylcarbinol are important for the antagonist activity.

The synthesis of analogues **32–34** was carried out as shown in scheme 2. Dehydration of commercially available α,α -diphenylpiperidino-4-methanol using TFA gave the 4-(diphenylmethylene)piperidine, which was then reduced with trimethyl silane to yield the 4-benzhydrylpiperidine. Both, 4-(diphenylmethylene)piperidine and 4-benzhydrylpiperidine were coupled with aryl isothiocyanates to yield the target compounds **32–34**.

The synthesis of analogues **38–44** is outlined in scheme 3. The addition of cyclohexyl or various heteroaryl groups to the benzyl or ethyl-4-benzoylpiperidine-1-carboxylate was achieved by reacting with cyclohexylmagnesium bromide or heteroaryl lithiums that were generated *in situ* by treating the appropriate heteroaryl bromides with *n*-BuLi. The resulting benzyloxycarbonyl- or ethoxycarbonyl- protected 4-bis-arylcarbinolpiperidines, after deprotection by hydrogenation using Pd/C or basic conditions using K₂CO₃, were reacted with appropriate aryl isothiocyanates to afford the target compounds.

Compound **46** was prepared according to the scheme 4. The anthraquinone was transformed into 5*H*-dibenzo[*b,e*]azepine-6,11-dione²² (**47**), by treating with conc. H₂SO₄ and NaN₃, which was then reduced to the alcohol **48** with sodium borohydride in MeOH. The resulting alcohol **48** was converted into the chloro derivative, 11-chloro-5*H*-dibenzo[*b,e*]azepin-6(11*H*)-one (**49**) by refluxing in thionyl chloride. The chloro group of the corresponding compound was displaced with piperazine using microwave irradiation to obtain 11-piperazin-1-yl-5,11-dihydrodibenzo[*b,e*]azepine-6-one (**50**), which was subsequently reacted with 4-isothiocyanato-*N,N*-dimethylbenzenesulfonamide to afford the

desired compound **46**. Compound **45** was prepared similarly to compound **46**, starting from commercially available 5-chloro-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulene.

We subsequently modified the thiourea linker (**C**) of the hit molecule by replacing it with urea and carbamate functionalities. A variety of urea derivatives (not shown) that had different groups at 4-position of phenyl ring (**A**) were prepared and found to be inactive at 10 μ M. Notably, the carbamate linker was very well tolerated (Table 3). In the carbamate series, we explored the groups that were good in the thiourea series at the 4-position of phenyl ring (**A**). In contrast to the thiourea series, the *N,N*-diethylsulfonamide analogue **54** (CYM 9552) was more potent (IC_{50} = 12 nM) than its corresponding *N,N*-dimethylsulfonamide analogue **53**. The *N,N*-diethylamide analogue **60** was 18-fold less potent than the *N,N*-diethyl sulfonamide analogue **54**. We also explored sulfones **56–59** at the 4-position, which displayed similar potency to the corresponding sulfonamide analogues **53** and **54**. While the reverse sulfonamide analogue **63** retained the antagonist activity, the reverse carboxamide analogues **61** and **62** completely lost the activity. The 3-substituted analogues **64** and **65** displayed no activity, which suggests that in both the carbamate and thiourea series the substitution at the 4-position of phenyl ring (**A**) is important for the antagonist activity.

The carbamate analogues **51–65** were prepared by reacting the α,α -diphenylpiperidino-4-methanol with aryl chloroformates, obtained from the reaction of phenols with triphosgene, in the presence of *i*Pr₂EtN. The non-commercially available phenols were prepared by conversion of the appropriate aryl fluoride into the corresponding phenol with 2-butyne-1-ol and potassium *tert*-butoxide in DMSO (Scheme 5).²³

In summary, we systematically explored the SAR of the hit molecule SF-11 that led to the identification of selective and highly potent small molecule NPY Y2 receptor antagonists **16** (CYM 9484; IC_{50} =19 nM) and **54** (CYM 9552; IC_{50} =12 nM). The investigation of *in vivo* PK and further lead optimization of the series of compounds will be reported in due course.

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21. Spectral data for compound **16**: ^1H NMR (400 MHz, DMSO- d_6) δ : 7.64 – 7.62 (m, 2H), 7.57 – 7.54 (m, 6H), 7.29 (t, J = 8.0 Hz, 4H), 7.15 (t, J = 8.0 Hz, 2H), 4.75 – 4.66 (m, 2H), 3.12 (t, J = 12 Hz, 2H), 2.99 – 2.89 (m, 1H), 2.59 (s, 6H), 1.59 – 1.46 (m, 2H), 1.40 – 1.31 (m, 2H). LC–MS (m/z): 510 $[\text{M}+\text{H}]^+$. Compound **54**: ^1H NMR (300 MHz, CDCl_3) δ : 7.78 (d, J = 8.4 Hz, 2H), 7.49 – 7.46 (m, 4H), 7.32 (t, J = 7.5 Hz, 4H), 7.25 – 7.19 (m, 4H), 4.31 – 4.27 (m, 2H), 3.21 (q, J = 7.1 Hz, 4H), 3.04 – 2.83 (m, 2H), 2.64 (t, J = 11.7 Hz, 1H), 1.66 – 1.61 (m, 2H), 1.43 – 1.39 (m, 2H), 1.12 (t, J = 7.3 Hz, 6H). LC–MS (m/z): 523 $[\text{M}+\text{H}]^+$.
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Figure 1.
Structures of four different chemotypes identified from HTS.

Scheme 1.

Reagents and conditions: (a) CH₂Cl₂, rt, 2–3 h; (b) di-2-pyridyl thionocarbonate, CH₂Cl₂, rt, 2 h.

Scheme 2.

Reagents and conditions: (a) TFA, CH₂Cl₂, rt, 6 h; (b) (CH₃)₃SiH, CH₂Cl₂, 3 days, rt; (c) aryl isothiocyanate, CH₂Cl₂, rt, 2–3 h

Scheme 3.

Reagents and conditions: (a) i) ethyl or benzylchloroformate, Et_3N , CH_2Cl_2 , rt, 12 h; ii) cyclohexylmagnesium bromide, THF, -78°C , 1 h or heteroaryl bromide, THF, $n\text{-BuLi}$, -78°C , 30 min, then addition of ketones, -78°C , 3 h; (b) H_2 , 10% Pd/C, MeOH, 3 h or K_2CO_3 , MeOH, reflux, 24 h; (c) aryl isothiocyanate, CH_2Cl_2 , 2–3 h, rt.

Scheme 4.

Reagents and conditions: (a) NaN_3 , H_2SO_4 , CHCl_3 , reflux, 12 h; (b) NaBH_4 , MeOH , 0°C to rt, 3 h; (c) SOCl_2 , CHCl_3 , reflux, 4 h; (d) piperazine, $i\text{Pr}_2\text{EtN}$, DMF , 145°C , microwave, 1 h; (e) 4-isothiocyanto-*N,N*-dimethylbenzenesulfonamide, CH_2Cl_2 , rt, 3 h.

Scheme 5.

Reagents and conditions: (a) 2-butyne-1-ol, KO^tBu, DMSO, 125 °C microwave, 15 min.; (b) triphosgene, NaOH, CH₂Cl₂/H₂O, 0 °C to rt, 3 h; (c) α,α-diphenylpiperidino-4-methanol, ^tPr₂EtN, CH₂Cl₂, rt, 6 h.

Table 1

Exploration of substitutions on the phenyl ring (A)

Compd	R ¹	R ²	R ³	Y2 IC ₅₀ ^a (μM)
SF-11	H	H	OC ₂ H ₅	0.199
1	H	H	H	NA
2	H	H	OCH ₃	1.1
3	H	H	O ⁱ Pr	1.77
4	H	H	OCF ₃	1.047
5	H	H	<i>n</i> C ₃ H ₇	0.777
6	H	H	CF ₃	0.178
7	H	H	N(CH ₃) ₂	0.612
8	H	H	N(C ₂ H ₅) ₂	0.072
9	H	H	Pyrrolidin-1-yl	1.2
10	H	H	Piperidin-1-yl	0.271 ^b
11	H	H	CO ₂ C ₂ H ₅	0.207
12	H	H	CONHCH ₃	1.419
13	H	H	CONHC ₂ H ₅	0.206
14	H	H	CON(CH ₃) ₂	0.301
15	H	H	CON(C ₂ H ₅) ₂	0.078
16	H	H	SO ₂ N(CH ₃) ₂	0.019
17	H	H	SO ₂ N(C ₂ H ₅) ₂	0.136
18	H	H	SO ₂ -pyrrolidin-yl	0.117
19	H	H	SO ₂ NHC ₂ H ₅	0.121
20	H	OCH ₃	H	8.162 ^b
21	H	CF ₃	H	NA
22	H	CO ₂ C ₂ H ₅	H	0.238 ^b
23	H	CF ₃	OCH ₃	6.079 ^b
24	H	Cl	N(C ₂ H ₅) ₂	0.085
25	H	CN	OC ₂ H ₅	0.323

Compd	R ¹	R ²	R ³	Y2 IC ₅₀ ^a (μM)
26	H	CN	O ^t Pr	0.899
27	CH ₃	H	OC ₂ H ₅	NA
28	CF ₃	H	OC ₂ H ₅	NA
29	Cl	H	CF ₃	NA
30	F	H	OC ₂ H ₅	1.35

^a All compounds were inactive at NPY Y1 receptor; the highest concentration tested in the assay was 10 μM, (NA = not active);

^b exhibited partial antagonism.

Table 2

SAR exploration of the part **B**.

Compd	R ⁵	X	R ³	Y2 IC ₅₀ ^a (μM)
31		CH	OC ₂ H ₅	NA
32		CH	OC ₂ H ₅	>10
33		CH	COOC ₂ H ₅	6.76
34		C	OC ₂ H ₅	NA
35		CH	SO ₂ N(CH ₃) ₂	NA
36		N	OC ₂ H ₅	0.371
37		N	SO ₂ N(CH ₃) ₂	0.483

Compd	R^5	X	R^3	Y2 IC ₅₀ ^a (μ M)
38		CH	OC ₂ H ₅	NA
39		CH	SO ₂ N(CH ₃) ₂	NA
40		CH	SO ₂ N(CH ₃) ₂	0.098
41		CH	SO ₂ N(CH ₃) ₂	0.248
42		CH	SO ₂ N(CH ₃) ₂	NA

Compd	R ⁵	X	R ³	Y2 IC ₅₀ ^a (μM)
43		CH	OC ₂ H ₅	3.3
44		CH	SO ₂ N(CH ₃) ₂	0.089
45		N	SO ₂ N(CH ₃) ₂	NA
46		N	SO ₂ N(CH ₃) ₂	0.067

^aAll compounds were inactive at NPY Y1 receptor; the highest concentration tested in the assay was 10 μM, (NA = not active).

Table 3

SAR of the carbamate analogues.

Compd	R ²	R ³	Y2 IC ₅₀ ^a (μM)
51	H	OCH ₃	2.68
52	H	OC ₂ H ₅	1.58
53	H	SO ₂ N(CH ₃) ₂	0.061
54	H	SO ₂ N(C ₂ H ₅) ₂	0.012
55	H	SO ₂ -pyrrolidine	0.049
56	H	SO ₂ CH ₃	0.141
57	H	SO ₂ C ₂ H ₅	0.059
58	H	SO ₂ (CH ₃) ₂	0.057
59	H	SO ₂ (C ₂ H ₅) ₂	0.043
60	H	CON(C ₂ H ₅) ₂	0.22
61	H	NHCOCH ₃	NA
62	H	NHCOC ₂ H ₅	NA
63	H	NHSO ₂ CH ₃	0.394
64	CON(C ₂ H ₅) ₂	H	NA
65	SO ₂ N(C ₂ H ₅) ₂	H	NA

^a All compounds were inactive at NPY Y1 receptor; the highest concentration tested in the assay was 10 μM, (NA = not active).