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8-AMINO-6-(ARYLSULPHONYL)-5-NITROQUINOLINES: NOVEL NONPEPTIDE NEUROPEPTIDE Y1 RECEPTOR ANTAGONISTS

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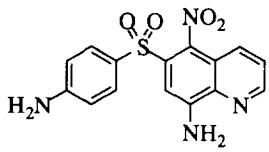
Abstract. A novel series of 8-amino-6-(arylsulphonyl)-5-nitroquinoline neuropeptide Y1 (NPY) receptor antagonists is reported. The 8-amino and 5-nitro groups were important for NPY1 binding affinity as changes caused large drops in potency. The 6-arylsulphonyl group was necessary; however, substitution on the phenyl was tolerated. The 2-isopropyl analog **21** was a moderately potent, highly selective NPY1 receptor antagonist.

Neuropeptide Y (NPY) is a 36 amino acid polypeptide isolated in 1982 from porcine brain.[1] It is a member of the pancreatic polypeptide (PP) family of peptides and shares high structural similarity and sequence homology with PP and peptide YY (PYY).[2] NPY is present in a highly conserved manner across species[3] and is the most abundant peptide yet discovered in mammalian brain. Accordingly, NPY is involved in many peripheral and central processes such as vasoconstriction, analgesia, anxiolysis, and feeding regulation.[4]

NPY analogs have defined NPY1, NPY2, and NPY3 receptor subtypes.[5] The NPY1 and NPY2 receptors have been cloned along with a new receptor, tentatively labelled NPY4/PP1.[6] To date, two potent, peptoid NPY1 receptor antagonists have been reported, BIBP 3226[7] and SR 120819A.[8] In this paper we report a novel series of nonpeptide NPY1-selective antagonists.

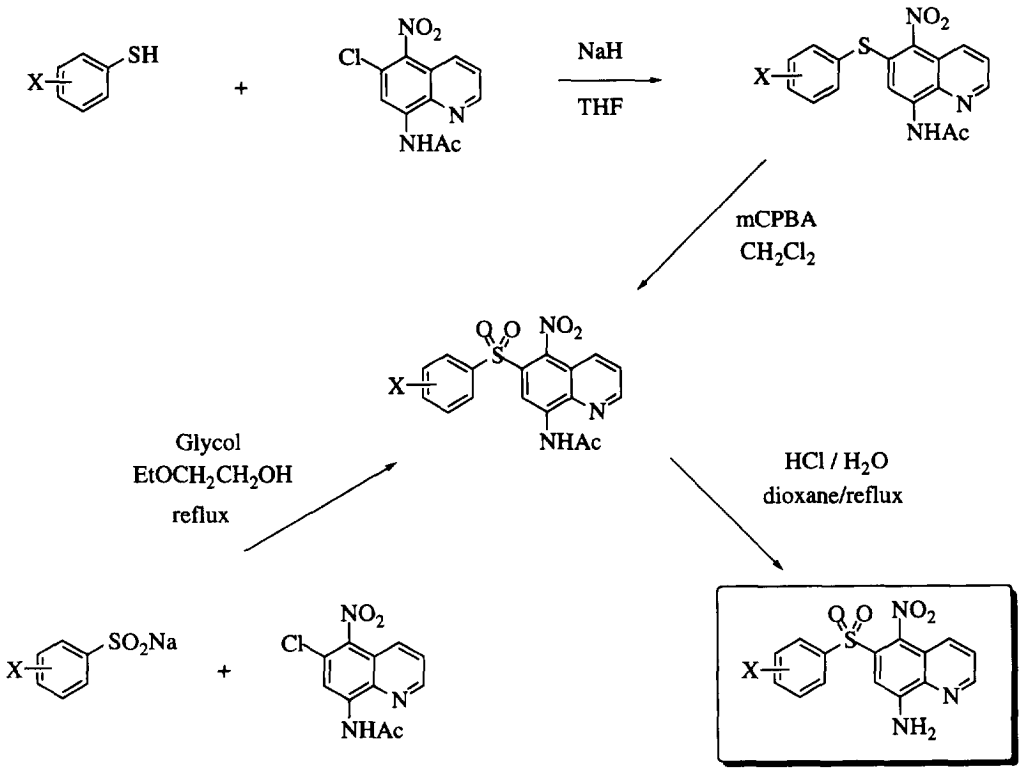


PD 9262 (**1**)

High volume screening of our chemical library for compounds with NPY receptor binding activity revealed that PD 9262 (**1**) bound to NPY1 receptors (K_i = 282 nM) but had weak affinity for NPY2 receptors (K_i >10,000 nM).[9] We prepared analogs of **1** with the goal of improving NPY1 receptor binding affinity. The synthesis of these analogs is shown in Scheme 1.[10] 8-Acetamido-6-chloro-5-nitroquinoline was prepared as described by Gilman et al.[11] and it reacted readily with arylthiol sodium salts at room temperature in THF.

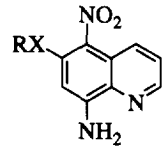
Subsequent oxidation to the sulphone was achieved in good yield with m-chloroperoxybenzoic acid (mCPBA). However, 2-substituents on the aryl ring slowed this oxidation and increased the amount of competing quinoline N-oxidation, lowering yields. This problem could be circumvented by addition of the sodium salts of sulphinic acids as described by Gilman. Unfortunately, the lower nucleophilicity of the sulphinic acids versus the thiols meant that much higher temperatures were necessary for the addition, often resulting in lower yields.

Scheme 1



To initiate our SAR study, we examined the importance of the anilino-sulphone portion of **1** (Table 1) for NPY1 binding affinity. The aniline could be replaced by phenyl (compound **2**) with no significant change in binding. However, an aryl group was necessary; replacement with methyl (compound **3**) markedly reduced receptor affinity. In addition, the sulphone analog **2** was more potent than the sulphoxide, sulphide, and sulphonamide analogs **4–6**.

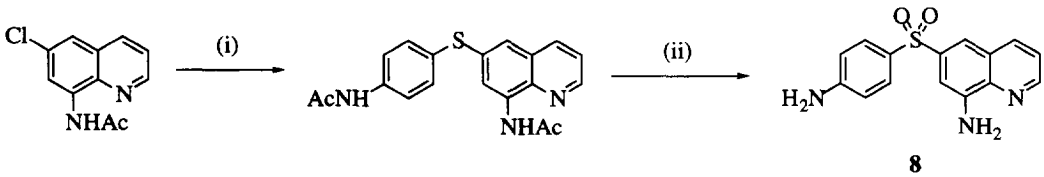
Table 1: NPY1 receptor binding for arylsulphone analogs of **1**



Compound	RX	NPY1 Binding (K_i nM)
1	4-NH_2PhSO_2	282
2	$PhSO_2$	297
3	$MeSO_2$	>10,000
4	4-NH_2PhSO	1250
5	4-NH_2PhS	>10,000
6	$PhSO_2NH$	>10,000

In Table 2 the importance of the quinoline 5-nitro and 8-amino groups was evaluated. For SAR studies on the quinoline system, we kept the 6-substituent constant as either 4-anilinosulphonyl or phenylsulphonyl. We assumed that either of these groups would produce equipotent analogs. Hydrogenation of compound **1** (10% Pd-C/EtOH) gave the 5,8-diaminoquinoline **7**, which had weaker affinity for NPY1 receptors. The des-nitro analog **8**, prepared as shown in Scheme 2 using Gilman's intermediate,[11] also showed no significant NPY1 binding affinity. Exposure of 6-chloro-5-nitroquinoline[12] or 6-chloro-8-methyl-5-nitroquinoline[13] to phenylsulphinic acids as in Scheme 1 gave analogs of **1** and **2** in which the 8-amino group was replaced by hydrogen (compound **9**) or methyl (compound **10**). Monomethylation of **2** with aqueous formaldehyde and sodium cyanoborohydride in acetonitrile gave compound **11**. All these changes to the 8-amino substituent of **2** dramatically reduced NPY1 receptor affinity. It was clear that both the 5-nitro and 8-amino groups were essential for NPY1 receptor activity.

Scheme 2



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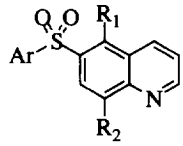
(i) 4-AcNHPhSH, K_2CO_3, NMP, 150 °C, 18 h; (ii) H_2O_2, AcOH; HCl, dioxane, reflux.

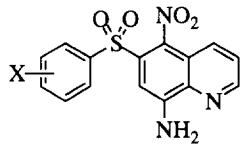
Table 2: NPY1 receptor binding for analogs of **1**



Compound	Ar	R_1	R_2	NPY1 Binding (K_i nM)
1	4-NH_2Ph	NO_2	NH_2	282
7	4-NH_2Ph	NH_2	NH_2	>10,000
8	4-NH_2Ph	H	NH_2	>10,000
9	4-NH_2Ph	NO_2	H	>10,000
10	Ph	NO_2	Me	>10,000
11	Ph	NO_2	NHMe	>10,000

Table 3 lists substitutions made on the phenyl system. While 4-aminophenyl was equipotent with phenyl (**1** vs **2**; Table 1), other 4-substitutions reduced NPY1 binding activity. The position seemed most sensitive to substituent size; larger groups decreased activity. However, moving a chlorine substituent around the ring increased activity. The 2-chloro analog **16** was more potent than our lead, PD 9262 (**1**).

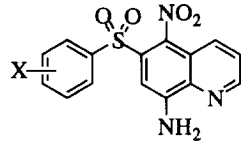
Table 3: NPY1 receptor binding for aryl analogs of **2**



Compound	X	NPY1 Binding (K_i nM)
12	4-methyl	594
13	4-methoxy	1135
14	4-chloro	1750
15	3-chloro	892
16	2-chloro	93

The 2-substituted phenyl analogs in Table 4 revealed that this effect was general. Every example was more potent at NPY1 receptors than parent phenyl compound **2**. For the 2-halo analogs **16–18**, potency increased as size decreased. However, the opposite effect was seen with the 2-alkyl analogs **19–21**. In this case, increasing size led to increased NPY1 binding affinity.

Table 4: NPY1 receptor binding for aryl analogs of **2**



Compound	X	NPY1 Binding (K_i nM)
17	2-bromo	234
16	2-chloro	93
18	2-fluoro	58
19	2-methyl	119
20	2-ethyl	129
21	2-isopropyl	48

Compound **21** (PD 160170)[14] was the most potent analog and was chosen for further evaluation. It showed less than 50% inhibition of PYY binding to NPY2 receptors at 10,000 nM. Compound **21** showed no significant activity in a variety of other receptor binding and enzyme assays. NPY inhibits forskolin-stimulated cAMP accumulation in SK-N-MC cells (IC_{50} 0.3 nM). Like many examples of this series, compound **21** (10 μM) caused a rightward shift of the NPY dose-response curve (IC_{50} 8.2 nM) without having any influence on basal or forskolin-stimulated cAMP accumulation in the absence of NPY.

In conclusion, we have discovered a novel series of selective NPY1 antagonists. Any changes made to the 8-amino-5-nitroquinoline system caused a dramatic loss in NPY1 binding affinity. The arylsulphone was also needed; however, aryl substitution was possible and led to a series of compounds more potent than the lead PD 9262 (**1**). Unlike earlier compounds, which are believed to mimic part of the C-terminal region of NPY, it is difficult to see how these new compounds overlap NPY at all. In any event, they should be useful in the quest to understand the physiological roles of NPY and its receptors.

References and Notes

1. Tatemoto, K. *Proc. Natl. Acad. Sci. U.S.A* .**1982**, *79*, 5485.

2. Tatemoto, K.; Carlquist, M.; Mutt, V. *Nature (London)* **1982**, *296*, 659.

3. Larhammar, D.; Blomqvist, A. G.; Soderberg, C. *Comp. Biochem. Physiol.* **1993**, *106C*, 743.

4. Grundemar, L.; Håkanson, R. *Trends Pharmacol. Sci.* **1994**, *15*, 153. For reviews see: Dhanoa, D. S. *Exp. Opin Ther Patents* **1995**, *5*, 391; Wettstein, J. G.; Earley, B.; Junien, J. L. *Pharmac. Ther.* **1995**, *65*, 397.

5. Beck-Sickinger, A. G.; Jung, G. *Biopolymers* **1995**, *37*, 123; Michel, M. C. *Trends Pharmacol. Sci.* **1991**, *12*, 389.

6. NPY1: Herzog, H.; Hort, Y. J.; Ball, H. J.; Hayes, G.; Shine, J.; Selbie, L. A. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 5794; NPY2: Gerald, C.; Walker, M. W.; Vaysse, P. J.-J.; He, C.; Branchek, T. A.; Weinshank, R. L. *J. Biol. Chem.* **1995**, *270*, 26758; NPY4/PP1: Bard, J. A.; Walker, M. W.; Branchek, T. A.; Weinshank, R. L. *J. Biol. Chem.* **1995**, *270*, 26762

7. Rudolf, K.; Eberlein, W.; Engel, W.; Wieland, H. A.; Willim, K. D.; Entzeroth, M.; Wienen, W.; Beck-Sickinger, A. G.; Doods, H. N. *Eur. J. Pharmacol.* **1994**, *271*, R11.

8. Serradeil-Le Gal, C.; Valette, G.; Rouby, P.-E.; Pellet, A.; Oury-Donat, F.; Brossard, G.; Lespy, L.; Marty, E.; Neliat, G.; de Cointet, P.; Maffrand, J.-P.; Le Fur, G. *FEBS Lett.* **1995**, *362*, 192.

9. NPY1 receptor binding was assayed by displacement of [^{125}I]PYY from SK-N-MC membranes. Compounds with K_is <10,000 nM were repeated at least once and the average calculated. NPY2 receptor binding was assayed by displacement of [^{125}I]PYY from membranes derived from rat hippocampi.

10. All new compounds had satisfactory ^{1}H NMR, IR, MS, and microanalysis.

11. Gilman, H.; Benkeser, R. A.; Gainer, G. C.; Lindblad, A. E.; Marshall, F. J.; Massie, S. P.; Myers, J. E.; Tolman, L. *J. Am. Chem. Soc.* **1946**, *66*, 1577.

12. McCarthy, P. A.; Hamanaka, E. S.; Marzetta, C. A.; Bamberger, M. J.; Gaynor, B. J.; Chang, G.; Kelly, S. E.; Inskeep, P. B.; Mayne, J. T.; Beyer, T. A.; Walker, F. J.; Goldberg, D. I.; Savoy, Y. E.; Davis, K. M.; Diaz, C. L.; Freeman, A. M.; Johnson, D. A.; LaCour, T. G.; Long, C. A.; Maloney, M. E.; Martingano, R. J.; Pettini, J. L.; Sand, T. M.; Wint, L. T. *J. Med. Chem.* **1994**, *37*, 1252.

13. Bailey, D. M.; Archer, S.; Wood, D.; Rosi, D.; Yarinsky, A. *J. Med. Chem.* **1970**, *13*, 598.

14. Data for **21** [6-(2-isopropylbenzenesulphonyl)-5-nitroquinolin-8-ylamine]: mp 216-217 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6, referenced by residual DMSO = 2.52 ppm) δ 9.00 (1H, d, J = 4.2 Hz), 8.21 (1H, d, J = 8.6 Hz), 7.93 (1H, d, J = 8.1 Hz), 7.82 (1H, dd, J = 4.2, 8.8 Hz), 7.76 (1H, t, J = 7.6 Hz), 7.67 (1H, d, J = 7.8 Hz), 7.52 (1H, t, J = 7.7 Hz), 7.47 (2H, broad s), 7.24 (1H, s), 3.59 (1H, heptet, J = 5.4 Hz), 1.01 (6H, d, J = 6.8 Hz); MS (CI$^+$) *m/z* 372 (M+H$^+$, 100%).

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