Synthesis of New Benzoxazinone Derivatives as Neuropeptide Y5 Antagonists for the Treatment of Obesity[#]

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Screening of our internal chemical collection against the neuropeptide Y5 (NPY Y5) receptor allowed the identification of a benzoxazine derivative **5f** as a hit that showed moderate affinity (IC_{50} = 300 nM). With the aim of improving the in vitro potency, a series of 2-benzoxazinone derivatives have been synthesized and tested for NPY Y5 activity. Most of the compounds were found to be potent and selective NPY Y5 antagonists having nanomolar binding affinities for the NPY Y5 receptor and showing functional antagonism in the forskolin-induced cyclic AMP test. Prelimminary studies in order to understand the structure−activity relationship were undertaken. Selected compounds were further evaluated for in vivo efficacy, affording the lead compound 2-[4-(8-methyl-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]-*N*-(9-oxo-9*H*-fluoren-3-yl)acetamide **5p**, which displayed in vivo activity reducing food intake in rodents.

Introduction

Pharmacological research in appetite control has been a hot field during the past decade because obesity is recognized as a fast growing and spreading disease. Obesity and related diseases such as type II diabetes are clearly escalating not only in the U.S. but also in many other countries.[1,2] Neuropeptide Y (NPY) is a 36 amino acid peptide originally discovered in extracts of porcine brain.[3] The peptide belonging to a broad family of peptides (which includes peptide YY and pancreatic polypeptide) has a wide distribution in the central[4−6] and peripheral nervous system.[7−9]

Neuropeptide Y has a number of physiological effects, and on the basis of experimental studies in primates and rodents, it has repeatedly been suggested that there is a relationship of NPY and its receptors with several pathological disorders including depression, anxiety-related disorders, seizures in epilepsy, and potentiation of vasoconstriction.[10−16] NPY is expressed in hypothalamic regions thought to be important in the regulation of feeding, its expression is sensitive to energy status, while its administration reduces energy expenditure,[17,18] and one of the most profound ability of NPY is to acutely stimulate feeding.[19−22] Although this body of results has led to the recognition of NPY as a key regulator of food intake, the real implication of the peptide is still controversial,[23,24] and targeted gene deletion of NPY provides limited evidence to support this idea.[25,26]

The biological effects of NPY are mediated through its interaction with at least five different cloned receptors known as the Y_1, Y_2, Y_4, Y_5, and y_6 subtypes.[27−30] All these receptors have been cloned[31−37] and are expressed in several species except for the y_6 subtype, which has been shown to be expressed in mouse and rabbit but not in rat and primates. On the other hand, the subtype Y3 has not yet been cloned and its real existence still remains to be fully established. NPY Y1 and NPY Y5 receptors have been recognized as strong candidates for the mediation of NPY in food intake.[17,18] The involvement of NPY Y5 has been suggested by pharmacological results on feeding in rodents,[38−45] by the inhibitory effects of NPY Y5 receptor antisense oligonucleotides, and by using NPY Y5 antagonists.

On the basis of all these data and having as a hypothesis that an agent with antistarvation properties would be valuable to control food intake, many groups have postulated different and selective NPY Y5 antagonists (Chart 1) as potential drugs for the treatment of obesity.[46a−f] Since in vivo specificity of those compounds is unclear, additional structurally diverse NPY Y5 antagonists are important in order to probe the role of NPY Y5 receptor.

In the present study, we focus on the preparation of non-peptide antagonists to the NPY Y5 receptor as part of our antiobesity program, and we report the discovery of a novel benzoxazinone class of NPY Y5 antagonists.[47]

Chemistry

As a result of the screening of the NPY Y5 receptor performed with our internal compound collection, benzoxazinone **5f** (Chart 2) was identified as a hit displaying moderate binding affinity (IC_{50} = 300 nM). Compound **5f** provided us with a lead for further optimization that had common structural features with benzimidazolone derivatives described by Bayer[46f] (Chart 1). In this report, we describe the synthesis and biological activity of analogues of **5f** and report our preliminary SAR studies that were undertaken in an effort to improve the in vitro potency of this series.

[#] Dedicated to the memory of Paul Janssen.

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Chart 1. Examples of NPY Y5 Receptor Antagonists

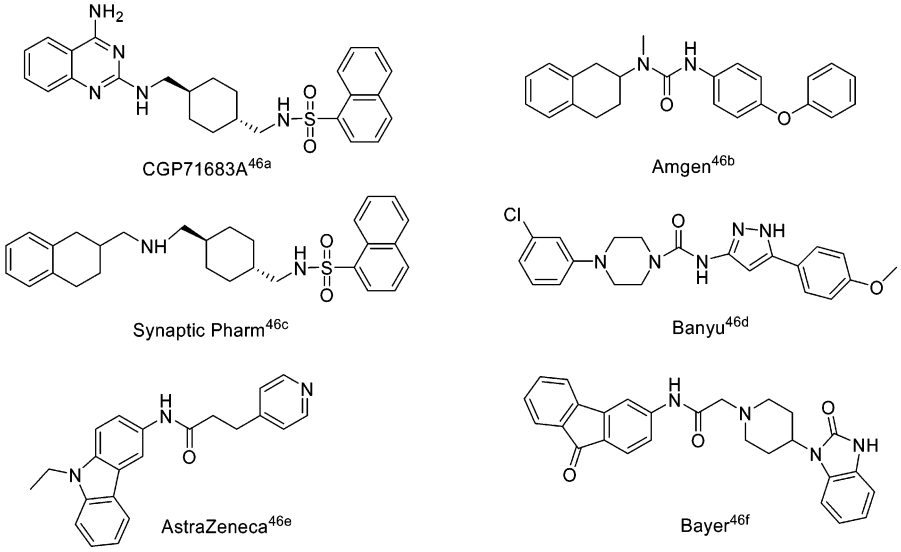
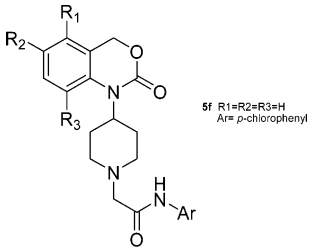
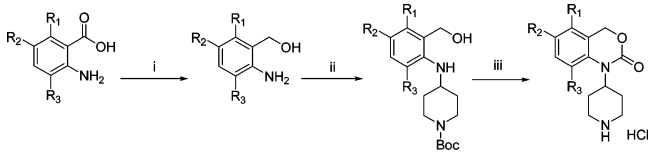


Chart 2. General Structure of Benzoxazinone Series



Scheme 1[a]



Compd	a	b	c	d	e	f	g
R1	Cl	H	H	H	H	H	H
R2	H	F	H	H	Me	H	Cl
R3	H	H	OMe	H	H	Me	H

[a] Reagents: (i) $LiAlH_4$/THF; (ii) *N*-Boc-4-piperidone, $NaBH_3CN$; (iii) (a) triphosgene, (b) HCl.

We were interested in targets in which the benzoxazinone ring and the amide moiety are varied to explore the effect of these substituents on the affinity. The diversity of the benzoxazinone ring (R1−R3) is introduced at the beginning of the synthetic pathway. Further diversification then focuses on the amide moiety (Ar), which is introduced in the final step. Several anthranilic acids **1a**−**c**, with the appropriate substitution patterns, were chosen as starting materials to investigate the effect of the benzoxazinone substituents on the binding and functionality properties. The diversity of the amide moiety was achieved by introduction of selected arylamines, which in some cases need to be previously synthesized.

The preparation of the benzoxazinone scaffold (Scheme 1) started with reduction of commercial anthranilic acids **1a**−**c** to the corresponding alcohols **2**. The transformation was performed under standard conditions employing $LiAlH_4$ as reducing agent in THF. The procedure proved to be very efficient, in most cases affording the amino alcohols **2a**−**c** in excellent yields. In addition, the efficiency of this method allowed the reactions to be performed in parallel on scales ranging from 5 to 10 g of the starting materials. In most cases the crude products were sufficiently pure and were used in next step without further purification. On the other hand, amino alcohols **2d**−**g** are commercially available.

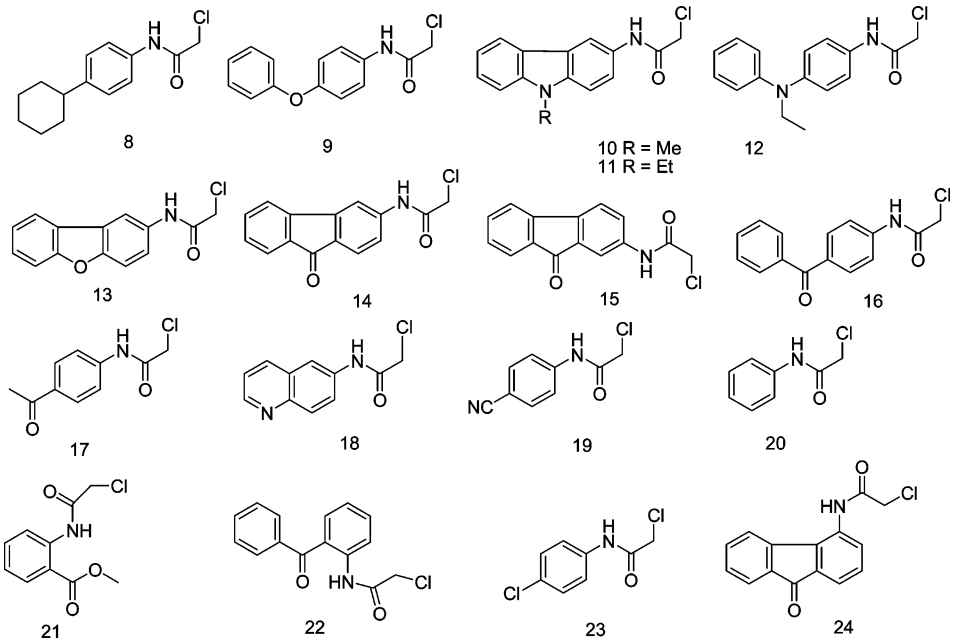
A reductive amination reaction on compounds **2a**−**g** was carried out to introduce the piperidine moiety (Scheme 1). Initial condensation of the amino alcohols with the *N*-Boc-4-piperidone and subsequent reduction of the generated imino functionality with $NaBH_3CN$ under acidic conditions generally afforded the products **3a**−**g** in good yields.

The benzoxazinone ring system **4** is formed via carbonylative cyclization of intermediates **3**. This process (Scheme 1) was performed in parallel using triphosgene as the CO equivalent. It was found that the efficiency of this reaction depended very much on the nature of the ring substituents. Although the expected products were formed in most cases, the yields were moderate and the reaction mixtures were often very complex, requiring further purification by column chromatography or by recrystallization.

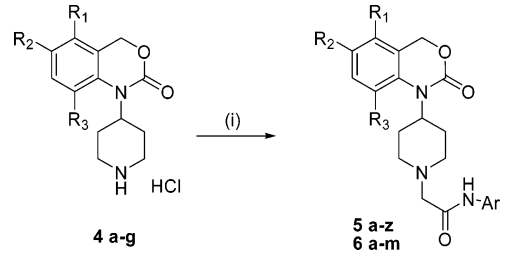
Removal of the Boc protecting group was performed by slow addition of acetyl chloride to a solution of piperidine derivatives **4a**−**g** in methanol or by treatment with hydrochloric acid in ethanol or diethyl ether (Scheme 1). As expected, these reactions are easily performed in parallel and afforded the products as hydrochloride salts in high yields and purity.

Chloroacetamide derivatives were required for the preparation of the final targets. These compounds have been prepared using the general procedure described in the experimental part. Essentially, chloroacetyl chloride was reacted with a selection of amines to yield the desired alkylating agents (Chart 3). Most of the amines required for the preparation of compounds **8**−**24** are commercially available. The amines that are not commercially available were prepared following literature procedures (see experimental part).

Chart 3. Chloroacetamides **8**−**24**

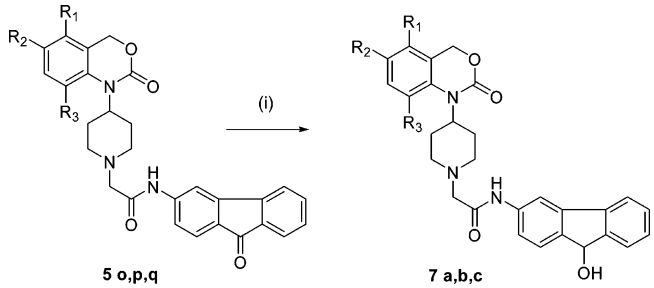


Scheme 2. Synthesis of Compounds **5a**−**z** and **a**−**m**[a]



[a] Reagents: (i) $ArNHCOCH_2Cl$, DMF, K_2CO_3.

Scheme 3. Synthesis of Compounds **7a**−**c**[a]



[a] Reagents: (i) $NaBH_4$, EtOH.

Reaction conditions were tested for the alkylation step. The conditions that proved to be the most efficient and most suitable for performing the alkylation reactions in parallel employed K_2CO_3 as a base and DMF as a solvent (Scheme 2). All products were purified by parallel chromatography or were transformed further to HCl salts and recrystallized. The structures of compounds **5a**−**z** and **6a**−**m** synthesized by this procedure are depicted in Table 1.

To obtain the hydroxy derivatives **7a**−**c**, an additional step was carried out. The reduction of the keto group of compounds **5o**−**q** was performed with $NaBH_4$ under standard conditions, affording the desired final products with excellent yields (Scheme 3).

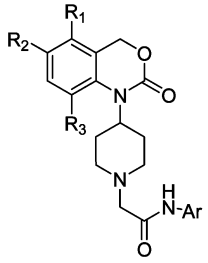
Results and Discussion

Screening of our internal chemical collection against the NPY Y5 receptor resulted in the identification of the novel benzoxazinone class lead **5f**. This lead had an IC_{50} value of 300 nM and obviously needed to be further optimized in terms of potency. For this purpose, an exploratory library using parallel synthesis was prepared.[47] In this report we describe the preparation and biological results of selected compounds from this library and our understanding of the structure−activity relationship.

The binding affinities at the NPY Y5 receptor were determined in a filter binding assay using [^{125}I]-PYY. The activity of the compounds as putative agonists or antagonists was studied in an in vitro system using C6 cells overexpressing the receptor. The NPY Y5 receptor is known to be negatively coupled to the adenylyl cyclase system, so agonists of the receptor would decrease in a significant way the levels of intracellular cyclic AMP (cAMP). As depicted in Figure 1, our compounds clearly showed antagonistic activity because they were able to reverse the effect of PYY on cyclic AMP levels. The binding affinity for the NPY Y5 receptor and functionality results of selected compounds are illustrated in Table 1.

In discussing the initial SAR within the series, we have divided the structure into two main parts: the amide moiety (Ar) and the substitution (R_1, R_2, R_3) in the benzoxazinone scaffold (Table 1). With the aim of enhancing affinity, initial efforts were focused on the modification of the *p*-chloroaniline group present in **5f**. Diverse simple monocyclic anilines were used in the first approach. Removing the *p*-chloro group as in **6k**, using aniline itself, led to a dramatic loss of activity. Among all the substituted anilines used, *p*-cyano (**6i**, IC_{50} = 132 nM) and mainly *p*-acetyl (**6a**, IC_{50} = 17.3 nM) groups afforded the highest affinities. It seemed that the presence of a carbonyl group could be important. To explore this hypothesis, we introduced several groups containing this function in a different position of the phenyl ring with disappointing results (i.e., a 2-COOMe ester group **5w**, IC_{50} > 1000 nM). We then examined

Table 1. NPY5 Binding Affinity and Functional Inhibition of the NPY Y5 Agonist Induced CAMP Accumulation[a]



Cpd	R1	R2	R3	Salt	Ar	IC_{50} (nM)[b]	% Inh cAMP[c]
5a	H	H	H	HCl		20	100.0
5b	H	Me	H	HCl		104	94.5
5c	H	Cl	H	HCl		60.7	99.2
5d	H	H	Me	HCl		>1000	n.d.
5e	H	H	Me	HCl		>1000	n.d.
5f	H	H	H	HCl		300	n.d.
5g	H	Cl	H	HCl		112.4	98.4
5h	H	H	H	HCl		>1000	n.d.
5i	H	H	H	HCl		9.6	88.7
5j	Cl	H	H	HCl		54.6	83.4
5k	H	Cl	H	HCl		100	99.3
5l	H	H	Me	HCl		50	96.9
5m	H	H	OMe	HCl		765.1	19.2
5n	H	H	OMe	----		55.7	23.6
5o	H	H	H	HCl		23.3	100
5p	H	H	Me	HCl		50	93.8
5q	H	Cl	H	HCl		25	100.0
5r	H	H	H	HCl		>1000	n.d.
5s	H	Me	H	HCl		86.7	93.9
5t	H	Cl	H	HCl		69	94.0
5u	H	H	Me	HCl		39.6	100.0
5v	H	Cl	H	HCl		11.2	97.4
5w	H	H	H	----		>1000	n.d.
5x	H	H	Me	----		>1000	n.d.
5y	H	Cl	H	----		>1000	n.d.
5z	H	Me	H	----		>1000	n.d.
6a	H	H	H	HCl		17.3	95.4
6b	H	Cl	H	HCl		21	99.9
6c	H	Me	H	HCl		26	89.4
6d	H	H	H	HCl		>1000	n.d.
6e	H	H	Me	HCl		>1000	n.d.
6f	H	Cl	H	HCl		>1000	n.d.
6g	H	F	H	----		7.7	93.3
6h	H	Cl	H	----		148	71.9
6i	H	H	H	HCl		132	88.7
6j	H	Cl	H	HCl		199	91.5
6k	H	H	H	HCl		>1000	n.d.
6l	H	H	H	----		7.6	n.d.
6m	H	H	H	HCl		138.2	n.d.
7a	H	Cl	H	HCl		8	100.0
7b	H	H	H	HCl		8.7	96.1
7c	H	H	Me	HCl		30	100

[a] Table shows the effect of compounds **5a**−**z, 6a**−**m,** and **7a**−**c.** [b] [125 I]-PYY binding to the rat NPY Y5 receptor. [c] Reversal of PYY inhibition of forskolin-stimulated cyclic AMP production. n.d.: not determined.

the introduction of a second phenyl ring attached to the 4-carbonyl group, with excellent results (i.e., **6l**, IC_{50} = 7.6 nM). Interestingly, the same substitution pattern in position 2 failed to give activity (i.e., **6d**, IC_{50} > 1000

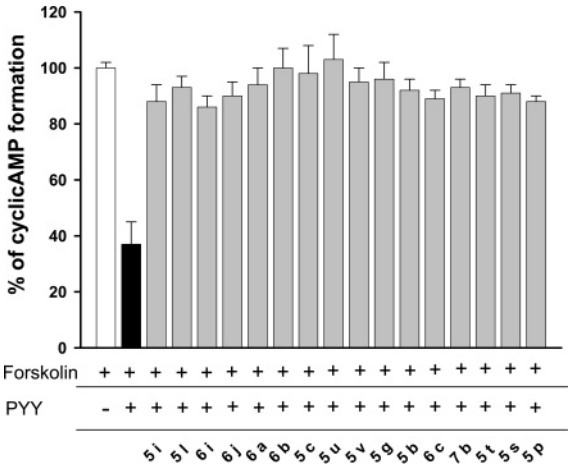


Figure 1. Functional activity of selected compounds. The antagonistic properties of these compounds were demonstrated by their ability to reverse the inhibitory effects of PYY on the forskolin-stimulated cyclic AMP formation in C6 cells stably expressing the rat NPY Y5 receptor. Bars express the mean ± SEM of the percentage of cyclic AMP formation in the presence of PYY compared to controls (forskolin-stimulated cyclic AMP formation in C6 cells in the absence of PYY). Experiments were performed at least three times in separate experiments.

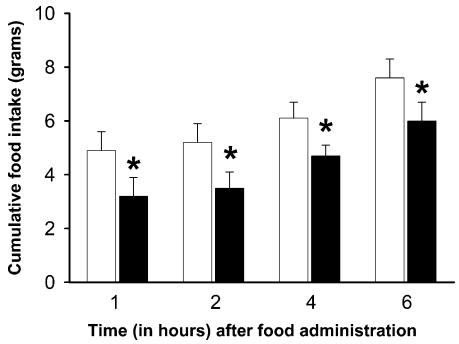


Figure 2. Acute feeding effects of compound **5p**, a NPY Y5 receptor antagonist. Wistar rats were food-deprived for 24 h. Vehicle or **5p** were intraperitoneally administered, and food intake was measured 1, 2, 4, and 6 h after the administrations. Open bars show food intake in vehicle-treated animals, and filled bars show food intake in compound-treated animals at a dose of 10 mg/kg. Bars show the mean ± SEM: (∗) $P < 0.05$, $n = 10-12$ for each group.

nM), suggesting that the substitution in position 4 is necessary for the affinity. With these results in our hands, we turned our attention to structurally related arylamines used by others in the NPY Y5 described antagonists. Thus, incorporation of 3-aminofluorenone[46f] gave **5o** (IC_{50} = 23.3 nM), **5p** (IC_{50} = 50 nM), and **5q** (IC_{50} = 25 nM), which could be considered constrained analogues of **6l**, **5u**, and **5v**, respectively. It is noted that 2-amino and 4-aminofluorenone groups failed to provide affinity. This fact can be observed by comparing compound **5o** (IC_{50} = 23.3 nM) with **5r** (IC_{50} >1000 nM) and **6m** (IC_{50} = 138.2 nM). On the other hand, introduction of 3-amino-9-ethylcarbazole[46e] (i.e., **5l**, IC_{50} = 50 nM) and 4-phenyloxyaniline[46b] (i.e., **5a**, IC_{50} = 20 nM) afforded in both cases compounds with remarkable affinities. To study the influence of the carbonyl function of fluorenone derivative **5o**, we prepared the corresponding hydroxyl group by $NaBH_4$ reduction. Surprisingly, **7b** showed higher potency (IC_{50} = 8.7 nM) than the parent compound. The analysis of these data could suggest that the presence of the carbonyl is not essential for affinity. To determine the influence of the hydroxyl group, the preparation of new compounds in a lead optimization process is currently ongoing.

With this set of data, we focused our efforts to study the influence of different substituents in the benzoxazinone phenyl ring. After preparation of several monosubstituted analogues with R1 = H, Cl or R2 = H, Cl, Me, F, or R3 = H, Me, MeO, some differences in terms of binding results could be observed. Thus, we tried to determine the role of these substituents by studying pairs of compounds with a single substitution change at R1 or R2 or R3. On the basis of the results displayed in Table 1, in the case of R2 being Cl or H, a comparison between compounds **5r** and **5t** and also between **5h** and **5g** showed a preference for Cl substitution, whereas a comparison between **5c** and **5a** showed a preference for H. Similar results were obtained when we studied pairs of compounds with Me or H at R2. As an example, a comparison of **5a** and **5b** could suggest that H is better for affinity, but on the other hand, looking to **5r** and **5s** could lead to the conclusion that Me is preferred. The same could be applied to position R3 comparing Me and H. While pairs of compounds **5e** and **5f** and **5p** and **5o** seem to demonstrate that H at R3 leads to more active products, the differences between **7b** and **7c** indicate the opposite. Therefore, substitution in this part of the molecule is tolerated, but no clear correlation between the presence of a particular group and the binding affinity could be established.

Selected compounds with high affinity were profiled in a commercially available panel of more than 50 radioligand binding assays (MSD, Taiwan). These comprise the characterization of potential interactions at the ligand binding site of a wide range of mainly G-protein-coupled receptors (GPCRs) and ligand-gated ion channels, plus a limited number of modulatory sites on voltage-gated ion channels. Binding results showed a marked selectivity of our compounds for the NPY Y5 receptor with respect to other NPY receptors (NPY Y1, NPY Y2), and only a certain degree of affinity for the 5-HT_2 receptor, the monoamine transporter, and for the sodium channel site 2 was observed, determined at 10 μM.

The antagonistic nature of the compounds is shown in Figure 1, and their ability to reverse the effect of the NPY Y5 receptor agonist PYY on cyclic AMP levels in an in vitro cell system was clearly established.

The in vivo activity of the compounds on food intake in rats was studied in animals that fasted for 24 h and then allowed to eat with no restrictions. Figure 2 shows the profile of one the compounds with antagonistic activity at the NPY Y5 receptor on food consumption in fasted rats. Among several compounds tested, **5p**, when administered intraperitoneally, clearly reduced food intake after a fasting period, and the effect lasts for at least 6 h.

Compound **5p** clearly shows hypophagic capacities in a rat model. Although it does not have the highest affinity for the NPY Y5 receptor, its demonstrated antagonistic properties and its excellent behavior in in vivo tests make **5p** a potential candidate for profiling. Further studies in order to establish its metabolic and

pharmacokinetic characteristics are currently ongoing. Future results should help the optimization of our series and to throw some more light on the controversial subject of the real implication of the NPY Y5 receptor in feeding behavior.

Conclusion

Because the physiological role of the NPY Y5 receptor still remains unclear, the evaluation of structurally diverse new classes of compounds could be critical to address the real importance of the Y5 receptor in food intake related diseases.

We have synthesized a novel series of benzoxazinone derivatives that have been identified as highly potent and selective Y5 antagonists. Initial studies of the structure−activity relationship looking at the effect of benzoxazinone phenyl ring substitution have shown that introduction of a methyl or a halogen group is tolerated but not relevant for affinity. On the other hand, incorporation of several arylamine groups in the other part of the structure has led to the conclusion that 3-aminofluorenone and the corresponding hydroxy derivatives are preferred.

The new prepared compounds should prove useful for further pharmacological characterization of the role of the NPY Y5 receptor. Although compound **5p** does not display the highest affinity and although more pharmacological studies are needed on its convenient antagonistic profile and its remarkable activity in acute feeding tests, 2-[4-(8-methyl-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]-*N*-(9-oxo-9*H*-fluoren-3-yl)acetamide hydrochloride (**5p**) could be considered as a potential drug candidate for the treatment of obesity.

Experimental Section

General Methods. Melting points were determined in open capillary tubes on a Büchi 535 melting point apparatus and are uncorrected. Proton NMR spectra were obtained on a Varian Unity 300 (300 MHz) spectrometer. Elemental analysis for carbon, hydrogen, and nitrogen for target compounds were carried out by Serveis Cientificotècnics of Parc Científic of Barcelona (PCB). HPLC analysis was performed using Agilent 1100 (software Chemstation A.06.03) equipment with a Waters XTerra MS C8 3.9 mm × 150 mm, 5 μm column, eluting with a mixture of acetonitrile containing 0.05% TFA and water containing 0.05% TFA. HPLC/MS analyses were recorded on a ThermoFinnigan instrument equipped with a Surveyor pump, a Waters XTerra MS C18 4.6 mm × 50 mm, 5 μm column and a LCQ DECA XP ion trap analyzer working in positive atmospheric pressure chemical ionization (ApcI). Eluents were 10 mM ammonium acetate and acetonitrile. Analytical thin-layer chromatography (TLC) was conducted on precoated silica gel 60 F254 plates (Merck). Chromatography was conducted on silica gel 60, 220−400 mesh. All starting materials were obtained from commercial sources and used as received.

The aminobenzyl alcohols **2d**−**g** were obtained from commercial suppliers.

Chemistry Methods. 2-Amino-6-chlorobenzyl Alcohol (2a). Under a nitrogen atmosphere, a solution of commercial 2-amino-6-chlorobenzoic acid **1a** (13.72 g, 80 mmol) in dry THF (100 mL) was added dropwise to a 1 M solution of $LiAlH_4$ in THF (160 mL) while the temperature was maintained at 0 °C. The resulting mixture was allowed to reach room temperature and was stirred for 2 h. The mixture was hydrolyzed by addition of water (6.5 mL) and 5% NaOH (20 mL). The resulting suspension was filtered; the precipitate was washed with ethyl acetate, washed once with water and brine, dried over Na_2SO_4, filtered, and evaporated. The residue was triturated with ether and vacuum-dried, giving the title compound as a yellow solid (mp 76−78 °C; 10.33 g, 82%). IR (KBr) 3389, 1601, 1578, 1451, 1399, 1244, 1004, 780 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 4.63 (d, J = 5.42 Hz, 2 H), 5.09 (t, J = 5.42 Hz, 1 H), 5.40 (s, 2 H), 6.65 (m, 2 H), 7.02 (t, J = 7.98 Hz, 1 H).

2-Amino-5-fluorobenzyl Alcohol (2b). Following the procedure described for the synthesis of **2a**, compound **2b** was prepared from commercial 2-amino-5-fluorobenzoic acid (**1b**) (21.98 g, 142 mmol) to give a brown solid (mp 103−108 °C; 14.60 g, 73%). IR (KBr) 3385, 1508, 1430, 1251, 1017, 882, 821 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 4.32 (d, J = 5.42 Hz, 2 H), 4.73 (s, 2 H), 5.11 (t, J = 5.42 Hz, 1 H), 6.56 (dd, J = 8.64, 4.98 Hz, 1 H), 6.75 (td, J = 8.64, 3.08 Hz, 1 H), 6.89 (dd, J = 9.81, 3.08 Hz, 1 H).

2-Amino-3-methoxybenzyl Alcohol (2c). Following the procedure described for the synthesis of **2a**, compound **2c** was prepared from commercial 2-amino-3-methoxybenzoic acid (**1c**) (15.13 g, 90 mmol) to give a brown solid (mp 42−46 °C; 12.1 g, 88%). IR (KBr) 3398, 1483, 1442, 1278, 1238, 1022, 740 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 3.74 (s, 3 H), 4.38 (d, J = 5.42 Hz, 2 H), 4.50 (s, 2 H), 5.00 (t, J = 5.42 Hz, 1 H), 6.51 (t, J = 7.76 Hz, 1 H), 6.72 (m, 2 H).

General Procedure for the Synthesis of Substituted 1-Piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-ones (4a−g). 1-Piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-ones (**4a**−**g**) were synthesized, as shown in Scheme 1, according to the method described by Ian M. Bell et al.[49] by reductive amination of 2-aminobenzyl alcohols (**2a**−**g**) treated with *N*-(*tert*-butyloxycarbonyl)-4-piperidone and $NaBH_3CN$, followed by cyclization using triphosgene and final elimination of the protective group by treatment in acidic media.

6-Chloro-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]-oxazin-2-one Hydrochloride (4g). A solution of 1-(*tert*-butyloxycarbonyl)-4-piperidone (9.96 g, 50 mmol), 2-amino-5-chlorobenzyl alcohol (8.66 g, 55 mmol), and acetic acid (6.3 mL, 110 mmol) in dry toluene (200 mL) was refluxed with azeotropic removal of water for 6 h, then cooled at room temperature and concentrated under reduced pressure to about one-half of the original volume. To the solution were added $NaBH_3CN$ (10.37 g, 165 mmol) and dry THF (150 mL). Acetic acid (4.9 mL, 85 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in EtOAc (350 mL). The EtOAc layer was washed with saturated aqueous $NaHCO_3$ (4 × 125 mL) and brine (125 mL). The EtOAc layer was dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography using 30% EtOAc in hexanes, affording 1-(*tert*-butyloxycarbonyl)-4-[4-chloro-(2-hidroxymethylphenylamine)]piperidine (**3g**) as a syrup (16.30 g, 96%). ^1H NMR ($CDCl_3$) δ ppm 1.32 (d, J = 11.2 Hz, 2H), 1.41 (s, 9H), 1.92 (d, J = 11.2 Hz, 2H), 2.92 (t, J = 12.0 Hz, 1H), 3.10 (s, 1H), 3.37 (m, 1H), 3.88 (d, J = 13.7 Hz, 2H), 4.49 (s, 2H), 4.75 (s, 1H), 6.52 (d, J = 8.6 Hz, 1H), 6.96 (s, 1H), 7.07 (d, J = 8.6 Hz, 1H).

This intermediate **3g** (13.50 g, 39.5 mmol) was dissolved in dry THF (150 mL) and cooled to 0 °C. To the solution were added *N*,*N*-diisopropylethylamine (21.5 mL, 125 mmol) and triphosgene (4.35 g, 14.6 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 72 h. Diethyl ether (150 mL) was added, the mixture was cooled to 0 °C for 2 h, and the hydrochloride salt of DIEA was removed by filtration. The solvents were removed under reduced pressure, and the residue was dissolved in EtOAc (300 mL). The EtOAc solution was washed with 5% aqueous citric acid (2 × 250 mL), water (100 mL), and saturated aqueous $NaHCO_3$ (2 × 200 mL). The EtOAc layer was dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. The residue was crystallized from boiling diethyl ether to afford 1-(*tert*-butyloxycarbonyl)-4-(piperidinyl)-6-chloro-1,4-dihydrobenz[*d*][1,3]oxazin-2-one **4d** as a white solid (mp 177−179 °C; 14.45 g, 67%). ^1H NMR ($CDCl_3$) δ ppm 1.46 (s, 9H), 1.79 (d, J = 10.1 Hz, 1H), 2.54 (m, 2H), 2.78 (m, 2H), 3.96 (m,

1H), 4.28 (m, 2H), 5.02 (s, 2H), 6.98 (d, J = 8.7 Hz, 1H), 7.13 (d, J = 2.4 Hz, 1H), 7.28 (dd, J = 8.7 Hz, 2.4 Hz, 1H).

A stirred solution of 1-(*tert*-butyloxycarbonyl)-4-(piperidinyl)-6-chloro-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one (12.0 g, 32.5 mmol) in EtOAc (200 mL) was cooled to 0 °C. A 5 M solution of hydrogen chloride in diethyl ether (500 mL) was then added, and the resulting mixture was stirred at 0 °C for 4 h. The precipitate formed was collected by filtration, washed with ether, and vacuum-dried, giving the title compound **4g** as a white solid (mp 254−257 °C; 8.48 g, 97%). IR (KBr) 2945, 2732, 1717, 1494, 1199,1047, 759 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.92 (d, J = 13.18 Hz, 2 H), 2.65 (m, 2 H), 3.05 (m, 2 H), 3.30 (m, 2 H), 4.21 (tt, J = 11.95, 3.57 Hz, 1 H), 5.14 (s, 2 H), 7.39 (m, 3 H), 8.65 (s, 1 H), 9.30 (s, 1 H).

5-Chloro-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]-oxazin-2-one Hydrochloride (4a). Following the procedure described for the synthesis of **4g**, compound **4a** was prepared from 2-amino-6-chlorobenzyl alcohol (**2a**) to afford a white solid in 47% overall yield, mp 281−284 °C. IR (KBr) 2956, 2732, 1722, 1599, 1461, 1190, 1047, 778 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.93 (d, J = 13.32 Hz, 2 H), 2.67 (m, 2 H), 3.06 (m, 2 H), 3.30 (m, 2 H), 4.22 (t, J = 11.86 Hz, 1 H), 5.26 (s, 2 H), 7.23 (m, 1 H), 7.40 (m, 2 H), 8.69 (s, 1 H), 9.34 (s, 1 H).

6-Fluoro-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]-oxazin-2-one Hydrochloride (4b). Following the procedure described for the synthesis of **4g**, compound **4b** was prepared from 2-amino-5-fluorobenzyl alcohol (**2b**) to afford a brown solid in 23% overall yield, mp 254−256 °C. IR (KBr) 3136, 2718, 1686, 1500, 1458, 1382, 1045, 758, 615 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.92 (d, J = 12.59 Hz, 2 H), 2.65 (m, J = 12.70, 3.88 Hz, 2 H), 3.06 (m, 2 H), 3.29 (m, 2 H), 4.20 (tt, J = 11.81, 3.64 Hz, 1 H), 5.13 (s, 2 H), 7.19 (m, 2 H), 7.41 (m, 1 H), 8.63 (s, 1 H), 9.25 (s, 1 H).

8-Methoxy-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]-oxazin-2-one Hydrochloride (4c). Following the procedure described for the synthesis of **4g**, compound **4c** was prepared from 2-amino-3-methoxybenzyl alcohol (**2c**) to afford a white solid in 42% overall yield, mp 228−230 °C. IR (KBr) 2697, 1708, 1390,1293, 1233,1082, 1028, 783, 737 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.03 (d, J = 12.01 Hz, 2 H), 2.59 (m, 2 H), 2.90 (m, 2 H), 3.29 (m, 2 H), 3.87 (m, 4 H), 5.06 (s, 2 H), 6.88 (dd, J = 6.52, 1.83 Hz, 1 H), 7.10 (m, 2 H), 8.45 (s, 1 H), 9.40 (s, 1 H).

1-Piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one Hydrochloride[49] (4d). Following the procedure described for the synthesis of **4g**, compound **4d** was prepared from commercial 2-aminobenzyl alcohol (**2d**) to afford a white solid in 55% overall yield, mp 253−256 °C. IR (KBr) 3442, 2945, 2735,1701, 1497,1387, 1292, 1204, 1036, 774 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.92 (d, J = 12.89 Hz, 2 H), 2.69 (m, 2 H), 3.08 (m, 2 H), 3.32 (d, J = 12.15 Hz, 2 H), 4.23 (m, J = 11.88, 3.48 Hz, 1 H), 5.14 (s, 2 H), 7.14 (m, 1 H), 7.28 (d, J = 7.17 Hz, 1 H), 7.37 (m, 2 H), 8.69 (s, 1 H), 9.36 (s, 1 H).

6-Methyl-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]-oxazin-2-one Hydrochloride (4e). Following the procedure described for the synthesis of **4g**, compound **4e** was prepared from commercial 2-amino-5-methylbenzyl alcohol **2e** to afford a white solid in 72% overall yield, mp 259−261 °C. IR (KBr) 2941, 1701, 1508, 1300, 1216, 1047, 766 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.90 (d, J = 12.59 Hz, 2 H), 2.26 (s, 3 H), 2.68 (m, 2 H), 3.05 (m, 2 H), 3.32 (d, J = 12.89 Hz, 2 H), 4.19 (tt, J = 11.82, 3.70 Hz, 1 H), 5.09 (s, 2 H), 7.08 (s, 1 H), 7.16 (m, 1 H), 7.26 (m, 1 H), 8.68 (s, 1 H), 9.32 (s, 1 H).

8-Methyl-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]-oxazin-2-one Hydrochloride (4f). Following the procedure described for the synthesis of **4g**, compound **4f** was prepared from commercial 2-amino-3-methylbenzyl alcohol (**2f**) to afford a white solid in a 68% overall yield, mp 257−262 °C. IR (KBr) 2949, 2716, 1713, 1477, 1410, 1227, 1025, 772 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.04 (d, J = 13.62 Hz, 2 H), 2.38 (s, 3 H), 2.65 (m, J = 12.89, 3.51 Hz, 2 H), 2.98 (m, 2 H), 3.28 (d, J = 12.15 Hz, 2 H), 3.76 (ddd, J = 11.49, 8.27, 3.51 Hz, 1 H), 5.06 (s, 2 H), 7.11 (m, 2 H), 7.23 (dd, J = 7.25, 1.39 Hz, 1 H), 8.50 (s, 1 H), 9.48 (s, 1 H).

General Procedure for the Synthesis of *N*-Chloroacetamides (8−24). The chloroacetamides were obtained from commercial suppliers or prepared as follows. To a solution of starting amine (10 mmol) and triethylamine (15 mmol) in dry dichloromethane (25 mL) was slowly added 2-chloroacetyl chloride (10.5 mmol) in dry dichloromethane (10 mL). The reaction mixture was stirred for 1−12 h at room temperature. The reaction mixture was washed with 2 N HCl (1 × 30 mL) and water (2 × 30 mL) and dried with sodium sulfate. The solution was concentrated under reduced pressure.This crude material was used without further purification.

2-Chloro-*N*-(9-methyl-9*H*-carbazol-3-yl)acetamide (10). Reduction of 3-nitro-9-methylcarbazole gave 3-amino-9-methylcarbazole in good yield.[50] To a solution of 3-amino-9-methylcarbazole (1.96 g, 10 mmol) and triethylamine (2.07 mL, 15 mmol) in dry dichloromethane (25 mL), a solution of chloroacetyl chloride (1.18 g, 10.5 mmol) in dry dichloromethane (10 mL) was added. The reaction mixture was stirred for 16 h at room temperature. The reaction mixture was washed with 2 N HCl (1 × 30 mL) and water (2 × 30 mL) and dried with sodium sulfate and the solvent evaporated, giving the title compound as a brown solid (2.59 g, 95%). ^1H NMR (300 MHz, DMSO-d_6) δ ppm 3.64 (s, 3 H), 4.28 (s, 2H), 7.18 (m, 1 H), 7.44 (t, J = 7.14 Hz, 1 H), 7.55 (m, 3 H), 8.06 (d, J = 7.7 Hz, 1 H), 8.04 (s, 1H), 10.32 (s, 1 H).

2-Chloro-*N*-[(4-aminophenyl)ethylphenylamine]acetamide (12). According to the general method, compound **12** was obtained from (4-aminophenyl)ethylphenylamine[51] in 97% yield. This crude material was used without further purification. ^1H NMR ($CDCl_3$) δ ppm 1.21 (t, J = 7.14 Hz, 3H), 3.76 (d, J = 7.14 Hz, 2H), 4.18 (s, 2H), 6.98 (m, 5H), 7.26 (m, 2H), 7.42 (d, J = 8.8 Hz, 2H), 8.23 (s, 1H).

2-Chloro-*N*-dibenzofuran-2-ylacetamide (13). According to the general method, compound **13** was obtained from 2-aminodibenzofuran[52] in 86% yield. This crude material was used without further purification. MS ($APCI^+$) *m/z*: 260 ($M + H^+$).

2-Chloro-*N*-(3-amino-9-fluorenone)acetamide (14). According to the general method, compound **14** was obtained from commercial 3-amino-9-fluorenone in 94% yield. This crude material was used without further purification. ^1H NMR ($CDCl_3$) δ ppm 4.18 (s, 2 H), 7.28 (m, 2 H), 7.45 (m, 2 H), 7.58 (m, 2 H), 7.98 (d, J = 1.76 Hz, 1 H), 9.07 (s, 1 H).

2-Chloro-*N*-(2-amino-9-fluorenone)acetamide (15). According to the general method, compound **15** was obtained from commercial 2-amino-9-fluorenone in 73% yield. This crude material was used without further purification. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 4.26 (s, 2 H), 7.28 (m, 1 H), 7.54 (m, 2 H), 7.67 (m, 3 H), 7.89 (s, 1 H), 10.55 (s, 1 H).

2-Chloro-*N*-(4-aminobenzophenone)acetamide (16). According to the general method, compound **16** was obtained from commercial 4-aminobenzophenone in 97% yield. This crude material was used without further purification. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 4.30 (s, 2 H), 7.54 (m, 2 H), 7.68 (m, 7 H), 10.67 (s, 1 H).

2-Chloro-*N*-(4-amino-9-fluorenone)acetamide (24). According to the general method, compound **24** was obtained from commercial 4-amino-9-fluorenone in 73% yield. This crude material was used without further purification. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 4.44 (s, 2 H), 7.39 (m, 2 H), 7.51 (m, 2 H), 7.61 (m, 2 H), 7.70 (d, J = 7.51 Hz, 1 H), 10.39 (s, 1 H).

General Procedure for the Synthesis of Compounds 5a−z and 6a−m. The corresponding chloroacetamide (1.10 mmol) was added to a suspension of benzoxazinone (**4a**−**g**) (1 mmol) and K_2CO_3 (3 mmol) in dry DMF (10 mL) at room temperature. After the reaction mixture was stirred overnight, the solvent was removed under reduced pressure, and the residue was partitioned in ethyl acetate and water and extracted twice with ethyl acetate. The organic layer was washed with brine, dried, filtered, and evaporated. The crude products were purified by crystallization or column chroma-

tography. Hydrochloride salt formation was usually a convenient method for the purification of these compounds.

2-[4-(2-Oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]-*N*-(4-phenoxyphenyl)acetamide Hydrochloride (5a). To a suspension of 1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]-oxazin-2-one hydrochloride (**4d**) (0.268 g, 1 mmol) and K_2CO_3 (0.414 g, 3 mmol) in dry DMF (25 mL) 2-chloro-*N*-(phenoxyphenyl)acetamide (**9**) (0.28 g, 1.10 mmol) was added at room temperature. After the reaction mixture was stirred overnight, the solvent was removed under reduced pressure, and the residue was partitioned in ethyl acetate (15 mL) and water (15 mL) and extracted twice with ethyl acetate (2 × 15 mL). The organic layer was washed with brine (1 × 25 mL), dried, filtered, and evaporated. The crude was dissolved in ethanol (10 mL), and 0.36 mL of a 2.8 M solution of hydrochloric acid in absolute ethanol was added to collect a brown solid after it was filtrated, washed with ethanol, and dried under vacuum (0.37 g, 75%), mp 242−248 °C. IR (KBr) 3044, 1703, 1686, 1506, 1487, 1392, 1226, 1040, 751, 694 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.01 (d, J = 12.8 Hz, 2H), 2.90 (m, J = 12.1 Hz, 2H), 3.41 (m, 2H), 3.63 (m, 2H), 4.18 (s, 2H), 4.29 (m, 1H), 5.16 (s, 2H), 6.96 (m, 2H), 7.03 (m, 2H), 7.12 (m, 2H), 7.35 (m, 5H), 7.67 (d, J = 8.8 Hz, 2H), 10.26 (s, 1H), 11.13 (s, 1H). Anal. free base ($C_{27}H_{27}N_3O_4 \cdot 0.5H_2O$) C, H, N.

2-[4-(6-Methyl-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]-*N*-(4-phenoxyphenyl)acetamide Hydrochloride (5b). Following the procedure described for the synthesis of **5a**, compound **5b** was prepared from 6-methyl-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4e**) and 2-chloro-*N*-(phenoxyphenyl)acetamide (**9**) to afford a white solid (yield 54%), mp 234−237 °C. IR (KBr) 3148, 2970, 2449, 1691, 1541, 1507, 1233, 1038 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.0 (d, J = 14.1 Hz, 2 H), 2.2 (s, 3 H), 2.9 (m, 2 H), 3.3 (m, 2 H), 3.6 (d, J = 12.1 Hz, 2 H), 4.1 (s, 2 H), 4.2 (m, 1 H), 5.1 (s, 2 H), 7.0 (m, 6 H), 7.2 (m, 2 H), 7.3 (t, J = 7.8 Hz, 2 H), 7.6 (d, J = 9.0 Hz, 2 H), 10.1 (s, 1 H), 10.6 (s, 1 H). Anal. ($C_{28}H_{29}N_3O_4 \cdot HCl \cdot 0.25H_2O$) C, H, N.

2-[4-(6-Chloro-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]-*N*-(4-phenoxyphenyl)acetamide Hydrochloride (5c). Following the procedure described for the synthesis of **5a**, compound **5c** was prepared from 6-chloro-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4g**) and 2-chloro-*N*-(phenoxyphenyl)acetamide (**9**) to afford a white solid (yield 49%), mp 262−267 °C. IR (KBr) 2990, 1714, 1560, 1488, 1231, 1039, 950, 871, 751 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.0 (d, J = 13.2 Hz, 2 H), 2.9 (m, 2 H), 3.3 (m, 2 H), 3.6 (d, 2 H), 4.1 (s, 2 H), 4.3 (m, 1 H), 5.1 (s, 2 H), 7.0 (m, 4 H), 7.1 (t, J = 7.4 Hz, 1 H), 7.3 (m, 5 H), 7.6 (d, J = 9.0 Hz, 2 H), 10.2 (s, 1 H), 10.6 (s, 1 H). Anal. ($C_{27}H_{26}ClN_3O_4 \cdot HCl \cdot H_2O$) C, H, N.

2-[4-(8-Methyl-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]-*N*-phenylacetamide Hydrochloride (5d). Following the procedure described for the synthesis of **5a**, compound **5d** was prepared from 8-methyl-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4f**) and 2-chloro-*N*-phenylacetamide (**20**), giving a white solid (yield 61%), mp 232−239 °C. IR (KBr) 3190, 1696, 1599, 1556, 951, 773, 726, 694 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.1 (d, J = 13.7 Hz, 2 H), 2.4 (s, 3 H), 3.0 (m, 2 H), 3.2 (s, 2 H), 3.6 (m, 2 H), 3.8 (m, 1 H), 4.1 (s, 2 H), 5.0 (s, 2 H), 7.1 (m, 3 H), 7.2 (d, J = 7.8 Hz, 1 H), 7.3 (t, J = 6.5 Hz, 2 H), 7.6 (d, J = 8.1 Hz, 2 H), 10.1 (s, 1 H), 10.6 (s, 1 H).

***N*-(4-Chlorophenyl)-2-[4-(8-methyl-2-oxo-4*H*-benzo[*d*]-[1,3]oxazin-1-yl)piperidin-1-yl]acetamide Hydrochloride (5e).** Following the procedure described for the synthesis of **5a**, compound **5e** was prepared from 8-methyl-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4f**) and 2-chloro-*N*-(4-chlorophenyl)acetamide (**23**), giving a white solid (yield 57%), mp 245−253 °C. IR (KBr) 3277, 2991, 1726, 1681, 1597, 1541, 1492, 1280, 1255, 1201 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.1 (d, J = 13.2 Hz, 2 H), 2.4 (s, 3 H), 2.9 (m, 2 H), 3.3 (m, 2 H), 3.6 (d, J = 2.9 Hz, 2 H), 3.8 (m, 1 H), 4.1 (s, 2 H), 5.0 (s, 2 H), 7.1 (m, 2 H), 7.2 (d, J = 7.1 Hz, 1 H), 7.3 (d, J = 7.1 Hz, 2 H), 7.6 (m, 2 H), 10.2 (s, 1 H), 10.8 (s, 1 H).

***N*-(4-Chlorophenyl)-2-[4-(2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]acetamide Hydrochloride (5f).** Following the procedure described for the synthesis of **5a**, compound **5f** was prepared from 1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4d**) and 2-chloro-*N*-(4-chlorophenyl)acetamide (**23**), giving a white solid (yield 71%), mp 272−276 °C. IR (KBr) 3454, 3057, 1701, 1610, 1552, 1492, 1394, 1292, 1254, 1024 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.99 (d, J = 12.4 Hz, 2H), 2.90 (m, J = 11.5 Hz, 2H), 3.40 (m, 2H), 3.63 (d, J = 11.0 Hz, 2H), 4.20 (s, 2H), 4.28 (m, 1H), 5.15 (s, 2H), 7.12 (m, 1H), 7.29 (d, J = 7.3 Hz, 1H), 7.40 (m, 4H), 7.69 (d, J = 8.8 Hz, 2H), 10.28 (s, 1H), 11.35 (s, 1H).

2-[4-(6-Chloro-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]-*N*-(4-cyclohexylphenyl)acetamide Hydrochloride (5g). Following the procedure described for the synthesis of **5a**, compound **5g** was prepared from 6-chloro-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4g**) and 2-chloro-*N*-(4-cyclohexylphenyl)acetamide (**8**), giving a white solid (yield 67%), mp 249−256 °C. IR (KBr) 2929, 1692, 1607, 1547, 1293, 1201, 1043, 830 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.3 (m, 4 H), 1.7 (m, 6 H), 2.0 (d, J = 15.7 Hz, 2 H), 2.4 (m, 1 H), 2.9 (q, J = 12.5 Hz, 2 H), 3.3 (t, J = 11.9 Hz, 2 H), 3.6 (d, J = 10.3 Hz, 2 H), 4.1 (s, 2 H), 4.2 (t, J = 12.1 Hz, 1 H), 5.1 (s, 2 H), 7.1 (d, J = 8.6 Hz, 2 H), 7.4 (m, 3 H), 7.5 (d, J = 8.6 Hz, 2 H), 10.1 (br, 1 H), 10.5 (s, 1 H). Anal. ($C_{27}H_{32}ClN_3O_3 \cdot HCl \cdot 0.25H_2O$) C, H, N.

***N*-(4-Cyclohexylphenyl)-2-[4-(2-oxo-4*H*-benzo[*d*][1,3]-oxazin-1-yl)piperidin-1-yl]acetamide Hydrochloride (5h).** Following the procedure described for the synthesis of **5a**, compound **5h** was prepared from 1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4d**) and 2-chloro-*N*-(4-cyclohexylphenyl)acetamide (**8**) to afford a white solid (yield 68%), mp 256−260 °C. IR (KBr) 3422, 1701, 1609, 1550, 1393, 1292, 1260, 1205, 1043 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.29 (m, 5H), 1.72 (m, 5H), 2.00 (d, J = 13.2 Hz, 2H), 2.45 (m, 1H), 2.91 (m, J = 11.7 Hz, 2H), 3.39 (m, 2H), 3.64 (m, 2H), 4.16 (s, 2H), 4.30 (m, 1H), 5.15 (s, 2H), 7.13 (m, 3H), 7.29 (d, J = 7.3 Hz, 1H), 7.38 (m, 2H), 7.54 (d, J = 8.2 Hz, 2H), 10.28 (s, 1H), 10.96 (s, 1H).

***N*-(9-Methyl-9*H*-carbazol-3-yl)-2-[4-(2-oxo-4*H*-benzo[*d*]-[1,3]oxazin-1-yl)piperidin-1-yl]acetamide Hydrochloride (5i).** Following the procedure described for the synthesis of **5a**, compound **5i** was prepared from 1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4d**) and 2-chloro-*N*-(9-methyl-9*H*-carbazol-3-yl)acetamide (**10**) to afford a white solid (yield 63%), mp 191−193 °C. IR (KBr) 3425, 3048, 1709, 1686, 1607, 1496, 1248, 1040, 771, 750 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.03 (d, J = 12.4 Hz, 2H), 2.93 (m, J = 11.2 Hz, 2H), 3.42 (m, 2H), 3.69 (d, J = 11.2 Hz, 2H), 3.86 (s, 3H), 4.22 (s, 2H), 4.32 (m, 1H), 5.17 (s, 2H), 7.13 (m, 1H), 7.20 (d, J = 7.3 Hz, 1H), 7.30 (d, J = 7.3 Hz, 1H), 7.43 (m, 3H), 7.58 (d, J = 10.2 Hz, 2H), 7.65 (d, J = 8.6 Hz, 1H), 8.06 (d, J = 7.7 Hz, 1H), 8.47 (s, 1H), 10.29 (s, 1H), 11.09 (s, 1H). Anal. ($C_{28}H_{28}N_4O_3 \cdot HCl$) C, H, N.

2-[4-(5-Chloro-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]-*N*-(9-ethyl-9*H*-carbazol-3-yl)acetamide Hydrochloride (5j). Following the procedure described for the synthesis of **5a**, compound **5j** was prepared from 5-chloro-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4a**) and 2-chloro-*N*-(9-ethyl-9*H*-carbazol-3-yl)acetamide (**11**) to give a white solid (yield 65%), mp 234 °C. IR (KBr) 1692, 1589, 1462, 1301, 1229, 1047, 783 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.3 (t, J = 6.8 Hz, 3 H), 2.1 (d, J = 11.1 Hz, 2 H), 2.9 (m, 2 H), 3.4 (m, 2 H), 3.7 (d, J = 11.6 Hz, 2 H), 4.2 (s, 2 H), 4.3 (m, 1 H), 4.4 (q, J = 6.6 Hz, 2 H), 5.3 (s, 2 H), 7.2 (t, J = 7.3 Hz, 1 H), 7.3 (d, J = 7.1 Hz, 1 H), 7.5 (m, 3 H), 7.6 (m, 3 H), 8.1 (d, J = 7.6 Hz, 1 H), 8.5 (s, 1 H), 10.2 (s, 1 H), 10.9 (s, 1 H). Anal. ($C_{29}H_{29}ClN_4O_3 \cdot HCl$) C, H, N.

2-[4-(6-Chloro-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]-*N*-(9-ethyl-9*H*-carbazol-3-yl)acetamide Hydrochloride (5k). Following the procedure described for the synthesis of **5a**, compound **5k** was prepared from 6-chloro-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochlo-

ride (**4g**) and 2-chloro-*N*-(9-ethyl-9*H*-carbazol-3-yl)acetamide (**11**) to give a white solid (yield 47%), mp 265−268 °C. IR (KBr) 2970,1712, 1691, 1492, 1376, 1294, 1201, 1043 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.28 (t, J = 7.0 Hz, 3H), 2.01 (d, J = 12.4 Hz, 2H), 2.90 (m, 2H), 3.43 (m, 2H), 3.68 (m, 2H), 4.27 (m, 3H), 4.41 (q, J = 7.0 Hz, 2H), 5.16 (s, 2H), 7.17 (t, J = 7.4 Hz, 1H), 7.44 (m, 4H), 7.61 (m, 3H), 8.05 (d, J = 7.9 Hz, 1H), 8.47 (s, 1H), 10.33 (s, 1H), 11.16 (s, 1H). Anal. ($C_{29}H_{29}ClN_4O_3$·HCl) C, H, N.

***N*-(9-Ethyl-9*H*-carbazol-3-yl)-2-[4-(8-methyl-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]acetamide Hydrochloride (5l).** Following the procedure described for the synthesis of **5a**, compound **5l** was prepared from 8-methyl-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4f**) and 2-chloro-*N*-(9-ethyl-9*H*-carbazol-3-yl)acetamide (**11**) to afford a white solid (yield 41%), mp 229−232 °C. IR (KBr) 3449, 2976, 1710, 1685, 1490, 1384, 1326, 1225, 953, 745 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.28 (t, J = 7.0 Hz, 3H), 2.13 (d, J = 12.8 Hz, 2H), 2.40 (s, 3H), 2.92 (m, 2H), 3.40 (m, 2H), 3.64 (d, J = 11.0 Hz, 2H), 3.84 (m, 1H), 4.17 (s, 2H), 4.41 (q, J = 7.0 Hz, 2H), 5.09 (s, 2H), 7.13 (m, 3H), 7.25 (d, J = 7.3 Hz, 1H), 7.44 (m, 1H), 7.60 (m, 3H), 8.05 (d, J = 7.7 Hz, 1H), 8.43 (s, 1H), 10.18 (s, 1H), 11.09 (s, 1H). Anal. ($C_{30}H_{32}N_4O_3$·HCl) C, H, N.

***N*-[4-(Ethylphenylamino)phenyl]-2-[4-(8-methoxy-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]acetamide Hydrochloride (5m).** Following the procedure described for the synthesis of **5a**, compound **5m** was prepared from 8-methoxy-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4c**) and 2-chloro-*N*-[(4-aminophenyl)-ethylphenylamine]acetamide (**12**) to afford a white solid (yield 54%), mp 216−218 °C. IR (KBr) 3422, 2980, 1701, 1510, 1492, 1388, 1287, 1252, 1088, 1029 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.2 (t, J = 7.1 Hz, 3 H), 2.2 (d, J = 12.1 Hz, 2 H), 2.9 (m, 2 H), 3.3 (m, 2 H), 3.7 (d, J = 11.1 Hz, 2 H), 3.8 (q, J = 7.1 Hz, 2 H), 4.0 (s, 3 H), 4.1 (m, 1 H), 4.2 (s, 2 H), 5.2 (s, 2 H), 6.9 (m, 4 H), 7.1 (d, J = 8.6 Hz, 2 H), 7.2 (m, 2 H), 7.3 (m, 2 H), 7.6 (d, J = 8.6 Hz, 2 H), 10.2 (s, 1 H), 11.0 (s, 1 H). Anal. ($C_{30}H_{34}N_4O_4$·HCl·H_2O) C, H, N.

***N*-Dibenzofuran-2-yl-2-[4-(8-methoxy-2-oxo-4*H*-benzo-[*d*][1,3]oxazin-1-yl)piperidin-1-yl]acetamide (5n).** Following the procedure described for the synthesis of **5a**, base **5n** was prepared from 8-methoxy-1-piperidin-4-yl-1,4-dihydrobenzo-[*d*][1,3]oxazin-2-one hydrochloride (**4c**) and 2-chloro-*N*-dibenzofuran-2-ylacetamide (**13**) to afford a cream solid (yield 62%), mp 88−92 °C. IR (KBr) 1718, 1483, 1286, 1223, 1191, 1079, 1037 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 2.0 (d, J = 11.6 Hz, 2 H), 2.4 (t, J = 10.9 Hz, 2 H), 2.9 (qd, J = 12.3, 4.0 Hz, 2 H), 3.1 (d, J = 11.6 Hz, 2 H), 3.2 (s, 2 H), 3.8 (m, 1 H), 3.9 (s, 3 H), 5.0 (s, 2 H), 6.8 (d, J = 7.1 Hz, 1 H), 6.9 (d, J = 7.6 Hz, 1 H), 7.1 (m, 1 H), 7.3 (t, J = 7.6 Hz, 1 H), 7.5 (t, J = 7.8 Hz, 1 H), 7.6 (m, 3 H), 8.0 (d, J = 7.1 Hz, 1 H), 8.4 (d, J = 2.0 Hz, 1 H), 9.4 (s, 1 H). Anal. ($C_{28}H_{27}N_3O_5$·0.5H_2O) C, H, N.

2-[4-(2-Oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]-*N*-(9-oxo-9*H*-fluoren-3-yl)acetamide Hydrochloride (5o). Following the procedure described for the synthesis of **5a**, compound **5o** was prepared from 1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4d**) and 2-chloro-*N*-(3-amino-9-fluorenone)acetamide (**14**), giving a yellow solid (yield 72%), mp >275 °C. IR (KBr) 3433, 1705, 1609, 1557, 1467, 1451, 1297, 1253, 1111, 769 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.02 (d, J = 12.6 Hz, 2H), 2.91 (m, J = 12.6 Hz, 2H), 3.43 (m, 2H), 3.67 (d, J = 9.9 Hz, 2H), 4.26 (m, 3H), 5.16 (s, 2H), 7.13 (m, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.40 (m, 3H), 7.64 (m, 5H), 8.06 (s, 1H), 10.29 (s, 1H), 11.46 (s, 1H). Anal. ($C_{28}H_{25}N_3O_4$·HCl) C, H, N.

2-[4-(8-Methyl-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]-*N*-(9-oxo-9*H*-fluoren-3-yl)acetamide Hydrochloride (5p). Following the procedure described for the synthesis of **5a**, compound **5p** was prepared from 8-methyl-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4f**) and 2-chloro-*N*-(3-amino-9-fluorenone)acetamide (**14**), giving a yellow solid (yield 63%), mp 233−236 °C. IR (KBr) 3410, 3014, 1701, 1609, 1561, 1450, 1371, 1285, 1237, 1109, 916, 768, 731 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.13 (d, J = 12.8 Hz, 2H), 2.40 (s, 3H), 2.91 (m, 2H), 3.42 (m, 2H), 3.63 (d, J = 10.2 Hz, 2H), 3.84 (m, 1H), 4.25 (s, 2H), 5.09 (s, 2H), 7.10 (m, 2H), 7.25 (d, J = 6.8 Hz, 1H), 7.38 (t, J = 7.4 Hz, 1H), 7.62 (m, 5H), 8.07 (s, 1H), 10.27 (s, 1H), 11.75 (s, 1H). Anal. free base ($C_{29}H_{27}N_3O_4$·0.5H_2O) C, H, N.

2-[4-(6-Chloro-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]-*N*-(9-oxo-9*H*-fluoren-3-yl)acetamide Hydrochloride (5q). Following the procedure described for the synthesis of **5a**, compound **5q** was prepared from 6-chloro-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4g**) and 2-chloro-*N*-(3-amino-9-fluorenone)acetamide (**14**), giving a yellow solid (yield 68%), mp 245−249 °C. IR (KBr) 3421, 1701, 1609, 1560, 1371, 1298, 1201 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.01 (d, J = 11.8 Hz, 2H), 2.88 (m, 2H), 3.42 (m, 2H), 3.66 (d, J = 11.8 Hz, 2H), 4.30 (m, 3H), 5.16 (s, 2H), 7.39 (m, 4H), 7.60 (m, 5H), 8.08 (s, 1H), 10.39 (s, 1H), 11.75 (s, 1H). Anal. ($C_{28}H_{24}ClN_3O_4$·HCl·2H_2O) C, H, N.

2-[4-(2-Oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]-*N*-(9-oxo-9*H*-fluoren-2-yl)acetamide Hydrochloride (5r). Following the procedure described for the synthesis of **5a**, compound **5r** was prepared from 1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4d**) and 2-chloro-*N*-(2-amino-9-fluorenone)acetamide (**15**) to afford a yellow solid (yield 70%), mp 276−280 °C. IR (KBr) 3241, 1696, 1608, 1560, 1463, 1391, 1293, 1259, 1206, 739 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.00 (d, J = 12.6 Hz, 2H), 2.90 (m, J = 12.6 Hz, 2H), 3.43 (m, 2H), 3.66 (d, J = 9.7 Hz, 2H), 4.21 (s, 2H), 4.28 (m, 1H), 5.16 (s, 2H), 7.13 (m, 1H), 7.34 (m, 4H), 7.59 (d, J = 7.0 Hz, 2H), 7.76 (m, 3H), 8.00 (s, 1H), 10.26 (s, 1H), 11.36 (s, 1H).

2-[4-(6-Methyl-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]-*N*-(9-oxo-9*H*-fluoren-2-yl)-acetamide Hydrochloride (5s). Following the procedure described for the synthesis of **5a**, compound **5s** was prepared from 6-methyl-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4e**) and 2-chloro-*N*-(2-amino-9-fluorenone)acetamide (**15**) to afford a yellow solid (yield 43%), mp 281−285 °C. IR (KBr) 2985, 1701, 1604, 1561, 1466, 1300, 1262 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.0 (d, J = 11.7 Hz, 2 H), 2.3 (s, 3 H), 2.9 (m, 2 H), 3.2 (m, 2 H), 3.6 (d, 2 H), 4.2 (m, 3 H), 5.1 (s, 2 H), 7.1 (s, 1 H), 7.3 (m, 3 H), 7.6 (m, 2 H), 7.7 (m, 3 H), 8.0 (s, 1 H), 10.3 (s, 1 H), 11.4 (s, 1 H). Anal. free base ($C_{29}H_{27}N_3O_4$) C, H, N.

2-[4-(6-Chloro-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]-*N*-(9-oxo-9*H*-fluoren-2-yl)acetamide Hydrochloride (5t). Following the procedure described for the synthesis of **5a**, compound **5t** was prepared from 6-chloro-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4g**) and 2-chloro-*N*-(2-amino-9-fluorenone)acetamide (**15**) to afford a yellow solid (yield 59%), mp >300 °C. IR (KBr) 2999, 1707, 1603, 1561, 1490, 1463, 1298, 1200 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.0 (d, J = 11.7 Hz, 2 H), 2.8 (m, 2 H), 3.1 (m, 2 H), 3.5 (d, 2 H), 4.3 (m, 3 H), 5.2 (s, 2 H), 7.3 (m, 1 H), 7.4 (m, 3 H), 7.6 (m, 2 H), 7.7 (m, 3 H), 8.0 (s, 1 H), 10.3 (s, 1 H), 11.4 (s, 1 H). Anal. free base ($C_{28}H_{24}ClN_3O_4$) C, H, N.

***N*-(4-Benzoylphenyl)-2-[4-(8-methyl-2-oxo-4*H*-benzo[*d*]-[1,3]oxazin-1-yl)piperidin-1-yl]acetamide Hydrochloride (5u).** Following the procedure described for the synthesis of **5a**, compound **5u** was prepared from 8-methyl-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4f**) and 2-chloro-*N*-(4-aminobenzophenone)acetamide (**16**), giving a white solid (yield 71%), mp 217−220 °C. IR (KBr) 3432, 2894, 1701, 1649, 1597,1541, 1281, 1033, 925, 857 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.1 (d, J = 13.4 Hz, 2 H), 2.4 (s, 3 H), 2.9 (m, 2 H), 3.3 (m, 2 H), 3.6 (d, J = 11.4 Hz, 2 H), 3.8 (m, 1 H), 4.1 (s, 2 H), 5.0 (s, 2 H), 7.1 (m, 2 H), 7.2 (d, J = 7.5 Hz, 1 H), 7.5 (m, 2 H), 7.6 (dd, J = 6.9, 2.1 Hz, 1 H), 7.7 (dd, J = 8.2, 1.3 Hz, 2 H), 7.8 (s, 4 H), 10.2 (s, 1 H), 10.9 (s, 1 H). Anal. ($C_{29}H_{29}N_3O_4$·HCl·0.5H_2O) C, H, N.

***N*-(4-Benzoylphenyl)-2-[4-(6-chloro-2-oxo-4*H*-benzo[*d*]-[1,3]oxazin-1-yl)piperidin-1-yl]acetamide Hydrochloride (5v).** Following the procedure described for the synthesis of **5a**, compound **5v** was prepared from 6-chloro-1-piperidin-4-

yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4g**) and 2-chloro-*N*-(4-aminobenzophenone)acetamide (**16**), giving a white solid (yield 60%), mp 256−259 °C. IR (KBr) 3449, 3051, 1708, 1599, 1541, 1315, 1203, 1041, 949, 702 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.0 (d, J = 13.2 Hz, 2 H), 2.9 (m, 2 H), 3.3 (m, 2 H), 3.6 (d, J = 9.9 Hz, 2 H), 4.2 (s, 2 H), 4.2 (m, 1 H), 5.1 (s, 2 H), 7.3 (m, 3 H), 7.5 (t, J = 7.3 Hz, 2 H), 7.6 (t, J = 7.9 Hz, 1 H), 7.7 (m, 2 H), 7.7 (m, 4 H), 10.2 (s, 1 H), 10.9 (s, 1 H). Anal. ($C_{28}H_{26}ClN_3O_4$·HCl·H_2O) C, H, N.

2-{2-[4-(2-Oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]acetylamino}benzoic Acid Methyl Ester (5w). Following the procedure described for the synthesis of **5a**, compound **5w** was prepared from 1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4d**) and methyl-*N*-(chloroacetyl)antranilate (**21**) to afford the base as a white solid (yield 42%), mp 180−182 °C. IR (KBr) 3232, 1702, 1583, 1521, 1450, 1385, 1262, 1204, 1090, 1045, 772, 749 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.9 (d, J = 11.7 Hz, 2 H), 2.4 (td, J = 11.6, 1.8 Hz, 2 H), 3.0 (qd, J = 12.4, 3.9 Hz, 2 H), 3.1 (d, J = 11.3 Hz, 2 H), 3.2 (s, 2 H), 4.0 (s, 3 H), 4.2 (qd, J = 12.3, 3.8 Hz, 1 H), 5.1 (s, 2 H), 7.1 (q, J = 7.1 Hz, 2 H), 7.2 (t, J = 6.1 Hz, 1 H), 7.3 (m, 1 H), 7.5 (d, J = 8.2 Hz, 1 H), 7.5 (m, 1 H), 8.0 (dd, J = 8.0, 1.6 Hz, 1 H), 8.8 (m, 1 H), 12.1 (s, 1 H).

2-{2-[4-(8-Methyl-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]acetylamino}benzoic Acid Methyl Ester (5x). Following the procedure described for the synthesis of **5a**, compound **5x** was prepared from 8-methyl-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4f**) and methyl-*N*-(chloroacetyl)antranilate (**21**) to afford the base as a white solid (yield 34%), mp 169−171 °C. IR (KBr) 3202, 1727, 1705, 1508, 1449, 1270, 1215, 1089, 1033, 765 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.9 (d, J = 12.3 Hz, 2 H), 2.3 (t, J = 12.7 Hz, 2 H), 2.4 (s, 3 H), 3.0 (m, 4 H), 3.2 (s, 2 H), 3.4 (m, 1 H), 4.1 (s, 3 H), 5.0 (s, 2 H), 7.1 (m, 3 H), 7.2 (d, J = 7.3 Hz, 1 H), 7.5 (m, 1 H), 8.0 (dd, J = 8.0, 1.7 Hz, 1 H), 8.8 (d, J = 8.4 Hz, 1 H), 12.2 (s, 1 H).

2-{2-[4-(6-Chloro-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]acetylamino}benzoic Acid Methyl Ester (5y). Following the procedure described for the synthesis of **5a**, compound **5y** was prepared from 6-chloro-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4g**) and methyl-*N*-(chloroacetyl)antranilate (**21**) to afford the base as a white solid (yield 22%), mp 153−156 °C. IR (KBr) 1702, 1508, 1448, 1259, 1201, 1090, 756 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.9 (d, J = 11.4 Hz, 2 H), 2.5 (t, J = 11.4 Hz, 2 H), 2.9 (m, 2 H), 3.1 (d, J = 11.5 Hz, 2 H), 3.2 (s, 2 H), 4.0 (s, 3 H), 4.2 (qd, J = 12.6, 3.9 Hz, 1 H), 5.1 (s, 2 H), 7.1 (m, 2 H), 7.3 (m, 1 H), 7.4 (d, J = 8.8 Hz, 1 H), 7.6 (m, 1 H), 8.1 (dd, J = 7.9, 1.6 Hz, 1 H), 8.8 (d, J = 8.4 Hz, 1 H), 12.1 (s, 1 H).

2-{2-[4-(6-Methyl-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]acetylamino}benzoic Acid Methyl Ester (5z). Following the procedure described for the synthesis of **5a**, compound **5z** was prepared from 6-methylpiperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4e**) and methyl-*N*-(chloroacetyl)antranilate (**21**) to afford a white solid (yield 38%), mp 152−155 °C. IR (KBr) 1701, 1509, 1448, 1265, 1219, 1091, 756 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.9 (d, J = 11.4 Hz, 2 H), 2.3 (s, 3 H), 2.4 (m, 2 H), 2.9 (qd, J = 12.4, 3.8 Hz, 2 H), 3.1 (d, J = 11.4 Hz, 2 H), 3.2 (s, 2 H), 4.0 (s, 3 H), 4.2 (m, 1 H), 5.0 (s, 2 H), 7.0 (s, 1 H), 7.1 (m, 2 H), 7.3 (d, J = 8.4 Hz, 1 H), 7.6 (t, J = 7.0 Hz, 1 H), 8.1 (dd, J = 8.1, 1.6 Hz, 1 H), 8.8 (m, 1 H), 12.1 (s, 1 H).

***N*-(4-Acethylphenyl)-2-[4-(2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]acetamide Hydrochloride (6a).** Following the procedure described for the synthesis of **5a**, compound **6a** was prepared from 1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4d**) and *N*-(acetylphenyl)-2-chloroacetamide (**17**) to afford a white solid (yield 70%), mp >280 °C. IR (KBr) 3448, 3044, 1708, 1600, 1395, 1261, 1043, 948, 842, 771 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.0 (d, J = 13.5 Hz, 2 H), 2.5 (s, 3 H), 2.9 (m, 2 H), 3.3 (m, 2 H), 3.6 (d, J = 11.4 Hz, 2 H), 4.1 (s, 2 H), 4.3 (m, 1 H), 5.1 (s, 2 H), 7.1 (m, 1 H), 7.2 (d, J = 7.3 Hz, 1 H), 7.3 (m, 2 H), 7.7 (d, J = 8.8 Hz, 2 H), 7.9 (d, J = 8.8 Hz, 2 H), 10.2 (s,1 H), 10.8 (s, 1 H). Anal. ($C_{23}H_{25}N_3O_4$·HCl·1.5H_2O) C, H, N.

***N*-(4-Acethylphenyl)-2-[4-(6-chloro-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]acetamide Hydrochloride (6b).** Following the procedure described for the synthesis of **5a**, compound **6b** was prepared from 6-chloro-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4g**) and *N*-(acetylphenyl)-2-chloroacetamide (**17**) to afford a white solid (yield 40%), mp >244 °C (dec). IR (KBr) 3579, 3475, 2992, 1717, 1667, 1600, 1545, 1263, 1041, 948 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.0 (d, J = 13.7 Hz, 2 H), 2.5 (s, 3 H), 2.9 (m, 2 H), 3.4 (m, 2 H), 3.7 (d, J = 11.9 Hz, 2 H), 4.2 (s, 2 H), 4.3 (m, 1 H), 5.1 (s, 2 H), 7.4 (m, 3 H), 7.7 (d, J = 8.6 Hz, 2 H), 8.0 (d, J = 8.6 Hz, 2 H), 10.2 (s, 1 H), 11.0 (s, 1 H). Anal. ($C_{23}H_{24}ClN_3O_4$·HCl·H_2O) C, H, N.

***N*-(4-Acethylphenyl)-2-[4-(6-methyl-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]acetamide Hydrochloride (6c).** Following the procedure described for the synthesis of **5a**, compound **6c** was prepared from 6-methylpiperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4e**) and *N*-(acetylphenyl)-2-chloroacetamide (**17**) to afford a white solid (yield 54%), mp 273−277 °C. IR (KBr) 2927, 1705, 1666, 1594, 1595, 1508, 1267, 1117, 946, 839 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.0 (d, J = 13.2 Hz, 2 H), 2.2 (s, 3 H), 2.5 (s, 3 H), 2.9 (m, 2 H), 3.4 (m, 2 H), 3.6 (d, J = 12.1 Hz, 2 H), 4.2 (m, 3 H), 5.1 (s, 2 H), 7.1 (s, 1 H), 7.2 (m, 2 H), 7.7 (d, J = 8.8 Hz, 2 H), 7.9 (d, J = 8.8 Hz, 2 H), 10.2 (br, 1 H), 10.9 (s, 1 H). Anal. free base ($C_{24}H_{27}N_3O_4$·1.2H_2O) C, H, N.

***N*-(2-Benzoylphenyl)-2-[4-(2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]acetamide Hydrochloride (6d).** Following the procedure described for the synthesis of **5a**, compound **6d** was prepared from 1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4d**) and *N*-(2-benzoylphenyl)-2-chloroacetamide (**22**) to afford a white solid (yield 58%), mp 211−216 °C. IR (KBr) 3260, 3058, 1681, 1610, 1296, 1036, 954, 772 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.9 (d, J = 13.7 Hz, 2 H), 2.8 (m, 2 H), 3.1 (m, 2 H), 3.3 (d, J = 10.6 Hz, 2 H), 3.9 (s, 2 H), 4.2 (t, J = 10.3 Hz, 1 H), 5.1 (s, 2 H), 7.1 (t, J = 7.1 Hz, 1 H), 7.4 (m, 8 H), 7.6 (m, 2 H), 7.7 (d, J = 7.1 Hz, 2 H), 10.1 (br, 1 H), 10.8 (s, 1 H).

***N*-(2-Benzoylphenyl)-2-[4-(8-methyl-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]acetamide Hydrochloride (6e).** Following the procedure described for the synthesis of **5a**, compound **6e** was prepared from 8-methyl-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4f**) and *N*-(2-benzoylphenyl)-2-chloroacetamide (**22**) to afford a white solid (yield 45%), mp 168−176 °C. IR (KBr) 3413, 2961, 1686, 1606, 1282, 1033, 951, 775 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.0 (d, J = 13.4 Hz, 2 H), 2.3 (s, 3 H), 2.8 (m, 2 H), 3.0 (m, 2 H), 3.3 (d, J = 10.8 Hz, 2 H), 3.7 (t, J = 12.2 Hz, 1 H), 3.8 (s, 2 H), 5.0 (s, 2 H), 7.0 (m, 2 H), 7.2 (d, J = 7.7 Hz, 1 H), 7.3 (t, J = 7.5 Hz, 1 H), 7.4 (m, 4 H), 7.6 (m, 2 H), 7.7 (d, J = 7.7 Hz, 2 H), 10.0 (s, 1 H), 10.7 (s, 1 H).

***N*-(2-Benzoylphenyl)-2-[4-(6-chloro-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]acetamide Hydrochloride (6f).** Following the procedure described for the synthesis of **5a**, compound **6f** was prepared from 6-chloro-1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4g**) and *N*-(2-benzoylphenyl)-2-chloroacetamide (**22**) to afford a white solid (yield 56%), mp 167−178 °C. IR (KBr) 3259, 1686, 1491, 1299, 1205, 1041, 956, 770 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.9 (d, J = 12.8 Hz, 2 H), 2.7 (m, 2 H), 3.1 (m, 2 H), 3.3 (d, J = 10.6 Hz, 2 H), 3.9 (s, 2 H), 4.2 (m, 1 H), 5.1 (s, 2 H), 7.4 (m, 5 H), 7.5 (m, 3 H), 7.6 (m, 2 H), 7.7 (d, J = 8.1 Hz, 2 H), 10.0 (s, 1 H), 10.8 (s, 1 H).

2-[4-(6-Fluoro-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]-*N*-quinolin-6-ylacetamide (6g). Following the procedure described for the synthesis of **5a**, compound **6g** was prepared from 6-fluoropiperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]-oxazin-2-one hydrochloride (**4b**) and 2-chloro-*N*-quinolin-6-ylacetamide[53] (**18**) to afford the base as a cream solid (yield 71%), mp 84 °C. IR (KBr) 1701, 1500, 1458, 1272, 1205, 1044, 768 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.9 (d, J = 12.1 Hz, 2 H), 2.5 (t, J = 11.1 Hz, 2 H), 2.9 (qd, J = 12.5, 4.0 Hz,

2 H), 3.1 (d, J = 11.6 Hz, 2 H), 3.3 (s, 2 H), 3.8 (m, 1 H), 5.1 (s, 2 H), 6.9 (dd, J = 7.6, 2.5 Hz, 1 H), 7.0 (m, 2 H), 7.4 (dd, J = 8.1, 4.0 Hz, 1 H), 7.8 (dd, J = 8.8, 2.3 Hz, 1 H), 8.1 (d, J = 9.1 Hz, 1 H), 8.1 (d, J = 8.6 Hz, 1 H), 8.3 (d, J = 2.0 Hz, 1 H), 8.8 (m, 1 H), 9.4 (s, 1 H). Anal. ($C_{24}H_{23}FN_4O_3 \cdot 0.5H_2O$) C, H, N.

2-[4-(6-Chloro-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]-*N*-quinolin-6-ylacetamide (6h). Following the procedure described for the synthesis of **5a**, compound **6h** was prepared from 6-chloropiperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]-oxazin-2-one hydrochloride (**4g**) and 2-chloro-*N*-quinolin-6-ylacetamide[53] (**18**) to afford the base as a cream solid (yield 64%), mp 87−89 °C. IR (KBr) 3410, 1718, 1604, 1527, 1497, 1379, 1199, 1043 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.9 (d, J = 10.1 Hz, 2 H), 2.5 (m, 2 H), 2.9 (qd, J = 12.5, 4.0 Hz, 2 H), 3.1 (d, J = 11.6 Hz, 2 H), 3.3 (s, 2 H), 3.8 (m, 1 H), 5.1 (s, 2 H), 7.1 (s, 1 H), 7.1 (m, 2 H), 7.4 (dd, J = 8.6, 4.0 Hz, 1 H), 7.8 (dd, J = 9.1, 2.5 Hz, 1 H), 8.1 (d, J = 9.1 Hz, 1 H), 8.2 (d, J = 8.1 Hz, 1 H), 8.4 (d, J = 2.5 Hz, 1 H), 8.8 (d, J = 2.5 Hz, 1 H), 9.4 (s, 1 H). Anal. ($C_{24}H_{23}ClN_4O_3 \cdot 0.5H_2O$) C, H, N.

***N*-(4-Cyanophenyl)-2-[4-(2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]acetamide Hydrochloride (6i).** Following the procedure described for the synthesis of **5a**, compound **6i** was prepared from 1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4d**) and 2-chloro-*N*-(4-cyanophenyl)acetamide (**19**) to afford a white solid (yield 37%), mp 268 °C (dec). IR (KBr) 3401, 2992, 2217, 1708, 1600, 1538, 1391, 1042, 950, 842 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.0 (d, J = 12.7 Hz, 2 H), 2.9 (m, 2 H), 3.4 (m, 2 H), 3.7 (d, J = 11.5 Hz, 2 H), 4.3 (m, 3 H), 5.1 (s, 2 H), 7.1 (m, 1 H), 7.3 (d, J = 7.8 Hz, 1 H), 7.4 (m, 2 H), 7.8 (m, 4 H), 10.2 (s, 1 H), 11.1 (s, 1 H). Anal. ($C_{22}H_{22}N_4O_3 \cdot HCl \cdot 1.2H_2O$) C, H, N.

2-[4-(6-Chloro-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]-*N*-(4-cyanophenyl)acetamide Hydrochloride (6j). Following the procedure described for the synthesis of **5a**, compound **6j** was prepared from 6-chloropiperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4g**) and 2-chloro-*N*-(4-cyanophenyl)acetamide (**19**) to afford a white solid (yield 82%), mp 274−278 °C. IR (KBr) 3414, 2986, 2219, 1721, 1602, 1541, 1313, 1200, 1040, 842 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.0 (d, J = 12.6 Hz, 2 H), 2.9 (m, 2 H), 3.3 (m, 2 H), 3.6 (d, J = 12.2 Hz, 2 H), 4.2 (s, 2 H), 4.3 (m,1H), 5.1 (s, 2 H), 7.4 (m, 3 H), 7.8 (s, 4 H), 10.2 (s, 1H), 11.0 (s, 1 H). Anal. ($C_{22}H_{21}ClN_4O_3 \cdot HCl \cdot 0.5H_2O$) C, H, N.

2-[4-(2-Oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)-piperidin-1-yl]-*N*-phenylacetamide Hydrochloride (6k). Following the procedure described for the synthesis of **5a**, compound **6k** was prepared from 1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4d**) and 2-chloro-*N*-phenylacetamide (**20**)-to afford a white solid (yield 69%), mp 262−272 °C. IR (KBr) 3405, 3068, 1707, 1609, 1557, 1259, 1043, 947 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.0 (d, J = 13.4 Hz, 2 H), 2.9 (m, 2 H), 3.3 (m, 2 H), 3.6 (d, J = 11.7 Hz, 2 H), 4.1 (s, 2 H), 4.3 (m, 1 H), 5.1 (s, 2 H), 7.1 (dd, J = 7.3, 5.9 Hz, 2 H), 7.3 (m, 5 H), 7.6 (d, J = 8.5 Hz, 2 H), 10.1 (s, 1 H), 10.6 (s, 1 H). Anal. ($C_{21}H_{23}N_3O_3 \cdot HCl \cdot 0.5H_2O$) C, H, N.

***N*-(4-Benzoylphenyl)-2-[4-(2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]acetamide (6l).** Following the procedure described for the synthesis of **5a**, compound **6l** was prepared from 1-piperidin-4-yl-1,4-dihydro-benzo[*d*][1,3]oxazin-2-one hydrochloride (**4d**) and 2-chloro-*N*-(4-aminobenzophenone)acetamide **(16)** to afford a white solid (yield 66%), mp 133−137 °C. IR (KBr) 3630, 3449, 3249, 1682, 1600, 1516, 1498, 1316, 1282, 1045, 757, 697 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.73 (d, J = 11.7 Hz, 2 H), 2.36 (m, J = 11.2 Hz, H), 2.61 (m, J = 11.7 Hz, 2 H), 2.98 (d, J = 10.8 Hz, 2 H), 3.22 (s, 2H), 3.87 (m, J = 11.7 Hz, 1 H), 5.11 (s, 2 H), 7.09 (t, J = 7.3 Hz, 1 H), 7.27 (d, J = 7.3 Hz, 2 H), 7.36 (t, J = 7.7 Hz, 1 H), 7.54 (t, J = 7.3 Hz, 2 H), 7.69 (m, 5 H), 7.83 (s, 1 H), 10.18 (s, 1 H). Anal. ($C_{28}H_{27}N_3O_4 \cdot 1H_2O$) C, N. H: calcd, 6.00; found, 5.51.

2-[4-(2-Oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]-*N*-(9-oxo-9*H*-fluoren-4-yl)acetamide Hydrochloride (6m). Following the procedure described for the synthesis of **5a**, compound **6m** was prepared from 1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one hydrochloride (**4d**) and 2-chloro-*N*-(4-amino-9-fluorenone)acetamide **(24)** to afford a white solid (yield 75%), mp 270−273 °C. IR (KBr) 1710, 1698, 1608, 1541, 1466, 1390, 1292, 1263, 1201, 737 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.03 (d, J = 12.1 Hz, 2H), 2.90 (m, J = 11.2 Hz, 2H), 3.49 (m, 2H), 3.70 (d, J = 11.2 Hz, 2H), 4.29 (m, 1H), 4.40 (s, 2H), 5.16 (s, 2H), 7.14 (m, 1H), 7.30 (d, J = 7.3 Hz, 1H), 7.42 (m, 4H), 7.61 (m, 4H), 7.82 (d, J = 7.1 Hz, 1H), 10.29 (s, 1H), 10.96 (s, 1H). Anal. ($C_{28}H_{25}N_3O_4 \cdot HCl \cdot 0.3H_2O$) C, H, N.

General Procedure for the Synthesis of Compounds 7a−c by Reduction of Fluorenones Derivatives 5o−q. To the ketone (0.15 mmol) dissolved in methanol (4 mL), a sodium borohydride (0.30 mmol) solution in methanol (2 mL) was added dropwise. After the mixture was stirred for 30 min at room temperature, a further aliquot of sodium borohydride (0.30 mmol) was added. After the mixture was stirred for 30 min, the solvent was evaporated and the residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated. The crude products were purified by crystallization or column chromatography. The hydrochloride salt is a good method for purification of these compounds.

2-[4-(6-Chloro-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]-*N*-(9-hydroxy-9*H*-fluoren-3-yl)acetamide Hydrochloride (7a). Compound **7a** was prepared in a similar manner as described in the general procedure by reduction of compound **5q** to give a yellow solid (yield 72%), mp 219−222 °C. IR (KBr) 3422, 3045, 1701, 1559, 1491, 1295, 1200, 1042 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.01 (d, J = 11.9 Hz, 2H), 2.88 (m, 2H), 3.39 (m, 2H), 3.66 (d, J = 9.8 Hz, 2H), 4.27 (m, 3H), 5.16 (s, 2H), 5.45 (s, 1H), 5.86 (broad, 1H), 7.36 (m, 5H), 7.54 (m, 3H), 7.64 (d, J = 7.2 Hz, 1H), 8.06 (s, 1H), 10.28 (s, 1H), 11.17 (s, 1H). Anal. ($C_{28}H_{26}ClN_3O_4 \cdot HCl \cdot 1.2H_2O$) C, H, N.

***N*-(9-Hydroxy-9*H*-fluoren-3-yl)-2-[4-(2-oxo-4*H*-benzo[*d*]-[1,3]oxazin-1-yl)piperidin-1-yl]acetamide Hydrochloride (7b).** Compound **7b** was prepared in a similar manner as described in the general procedure by reduction of compound **5o** to give a yellow solid (yield 68%), mp 270−273 °C. IR (KBr) 3328, 3071, 2547, 1715, 1691, 1606, 1259, 1045, 775 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.0 (d, J = 11.5 Hz, 2 H), 2.9 (m, 2 H), 3.4 (m, 2 H), 3.7 (d, J = 12.3 Hz, 2 H), 4.2 (s, 2 H), 4.3 (m, 1 H), 5.1 (s, 2 H), 5.4 (s, 1 H), 7.1 (m, 1 H), 7.3 (m, 2 H), 7.3 (m, 3 H), 7.5 (dd, J = 8.2, 1.8 Hz, 1 H), 7.6 (m, 2 H), 7.6 (d, J = 7.1 Hz, 1 H), 8.0 (d, J = 1.6 Hz, 1 H), 10.1 (s, 1 H), 10.7 (s, 1 H). Anal. ($C_{28}H_{27}N_3O_4 \cdot HCl$) C, H, N.

***N*-(9-Hydroxy-9*H*-fluoren-3-yl)-2-[4-(8-methyl-2-oxo-4*H*-benzo[*d*][1,3]oxazin-1-yl)piperidin-1-yl]acetamide Hydrochloride (7c).** Compound **7c** was prepared in a similar manner as described in general procedure by reduction of compound **5p** to give a yellow solid (yield 64%), mp 207−212 °C. IR (KBr) 3435, 1679, 1390, 1263, 774 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.13 (d, J = 13.3 Hz, 2H), 2.40 (s, 3H), 2.91 (m, J = 12.0 Hz, 2H), 3.36 (m, 2H), 3.63 (d, J = 10.8 Hz, 2H), 3.83 (m, 1H), 4.18 (s, 2H), 5.09 (s, 2H), 5.45 (s, 1H), 5.86 (broad, 1H), 7.11 (m, 2H), 7.33 (m, 3H), 7.55 (m, 3H), 7.64 (d, J = 7.3 Hz, 1H), 8.05 (s, 1H), 10.19 (s, 1H), 11.22 (s, 1H). Anal. ($C_{29}H_{29}N_3O_4 \cdot HCl \cdot 0.75H_2O$) C, H, N.

Biological Methods. In Vitro NPY Y5 Membrane Binding Assays. A modification of the method previously described by Hu[48] was used. C6 cells were transfected with the rat Y5 receptor and grown under standard culture conditions in 150 cm^2 dishes. Cells harvested from five dishes were collected and centrifuged, and the pellets were washed, homogenized, and centrifuged again. The pellet was resuspended in 8 mL of membrane buffer (Tris-HCl 25 mM, NaCl 120 mM, KCl 5 mM, KH_2PO_4 1.2 mM, $CaCl_2$ 2.5 mM, $MgSO_4$ 1.2 mM, BSA 0.15 mg/mL, bacitracin 0.5 mg/mL, pH 7,4) and rehomogenized. [^{125}I]-PYY (100 pM) was used as the radioligand in a total incubation volume of 200 μL (protein concentration was 40 μg/mL). Following incubation at 25 °C for 2 h, the reaction was stopped by addition of 5 mL of ice-cold buffer (Tris-HCl 25 mM, NaCl 120 mM, KCl 5 mM, KH_2PO_4 1.2 mM, $CaCl_2$ 2.5 mM,

$MgSO_4$ 1.2 mM, pH 7,4) and rapid filtration onto glass fiber filters (Schleicher & Schnell 3362) pretreated with 0.5% polyethyleneimine. Filters were then washed once with ice-cold buffer and placed into plastic scintillation vials with scintillation cocktail Ecoscint H. The radioactivity present was determined in a Wallac Winspectral 1414 counter. Nonspecific binding was determined in the presence of 1 μM pNPY. All binding assays were done in triplicate.

Adenylyl Cyclase Activity Assay. The activation or inhibition of adenylyl cyclase activity was studied by measuring levels of cAMP in 96-well plates by the FlashPlate method (Perkin-Elmer). Briefly, C6 cells overexpressing the NPY Y5 receptor were grown to 80% confluency in Dulbecco's modified Eagle's medium with L-glutamine, penicillin, and streptomycin, without fetal bovine serum. Two hours prior to the assay, the medium was removed and cells were dissociated with trypsin and centrifuged and the resulting resuspended pellets were added to the wells (50 000 cells/well approximately). Testing compounds were then added (in the presence or absence of PYY), and after 30 min, the reaction was stopped by the addition of detection solution ([^{125}I]succinyl cAMP tracer). After 2 h, plates can be measured. Data are expressed as the percentage of cAMP accumulation above the basal level and represent the mean ± SEM of three different experiments in duplicate.

Food Intake Measurements. Male Wistar rats (200−270 g) obtained from Harlan were used in these experiments. Animals were housed in the animal facility for at least 5 days before being subjected to any experimental procedure. During this period, animals were housed (in groups of five) in translucid cages and provided with food and water ad libitum. At least 24 h before the experiments, animals were adapted to single-housing conditions.

To study the acute effects of selected compounds on food intake in fasted rats, animals were fasted for 23 h in home cages, and after this period, either vehicle or selected compounds were administered intraperitoneally. One hour later preweighed food was left on top covers and cumulative food consumption was measured 1, 2, 4, and 6 h later.

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Supporting Information Available: Results from elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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