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Efficient Synthesis of a Highly Selective NPY-5 Receptor Antagonist: A Drug Candidate for the Treatment of Obesity

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Abstract:

A concise and practical synthesis of highly selective NPY-5 receptor antagonist 1 is described. The animopyrazine intermediate 3 was synthesized via either monobromination of aminopyrazine or palladium-catalyzed regioselective debromination of dibromopyrazine followed by an efficient Suzuki−Miyaura coupling. For the preparation of the spirolactone piperidine 2, significantly improved yield was achieved by using a combination of *n*-BuMgCl and *n*-BuLi. This protocol also dramatically increased the thermal stability of the aryllithium intermediate and eliminated the requirement for costly cryogenic conditions. The union of the spirolactone piperidine 2 and aminopyrazine 3 via a carbonyl group was accomplished using phenyl chloroformate delivering the target molecule in high yield.

Introduction

Obesity is a growing epidemic and is currently affecting approximately 30% of the adult population in the Western world. It is caused by a chronic imbalance between energy intake and energy expenditure. A body-mass-index (BMI) above 30 kg/m^2 significantly increases the risk of numerous diseases particularly diabetes, hypertension, and dyslipidemia and reduces life expectancy. Obesity is imposing an increasingly severe burden to the healthcare systems. Neuropeptide Y (NPY) is a highly conserved peptide that is involved in regulating feeding behavior.[1] Thus far six types of NPY receptors have been identified with the Y5 type dominant. It has been shown that chronic administration of NPY leads to obesity in rodents,[2] while injection of NPY antisense oligonucleotides or NPY antibodies acutely decreases feeding.[3]

Compound **1** is a highly selective NPY receptor antagonist with >4000-fold selectivity for the human Y5 receptors over other types of NPY receptors. It is being investigated for the prevention and treatment of diabetes, obesity, and obesity-related disorders.[4]

Structurally, the target molecule **1** consists of a spirolactone moiety **2** and a phenylpyrazine subunit **3** connected via a urea linkage (Scheme 1). The most efficient approach to the spirolactone fragment **2** appeared to be via aryllithium addition to protected piperidone **5** followed by in situ lactonization. Potential complications include quenching of the aryllithium by the carboxylic acid and enolization of the piperidone. The phenylpyrazine **3** could be synthesized by bromination of aminopyrazine **6** followed by a Pd-catalyzed Suzuki−Miyaura coupling with phenylboronic acid.

Results and Discussion

Selective monobromination of aminopyrazine is a long standing problem. In the literature, it has been reported[5] to be a low yielding reaction. In our hands, adding solid NBS to a solution of aminopyrazine **6** afforded the bromopyrazine **7** in 50−65% yields on a small scale. However, on a larger scale, whereas NBS was added slowly or in portions to control the exothermic reaction, the yield dropped precipitously (30%). Large amounts of a dark gummy solid appeared in the reaction mixture which further complicated the workup and isolation of the product.

With *N*-bromoacetamide, the reaction initially appeared to be much slower based on the rate of increase of the

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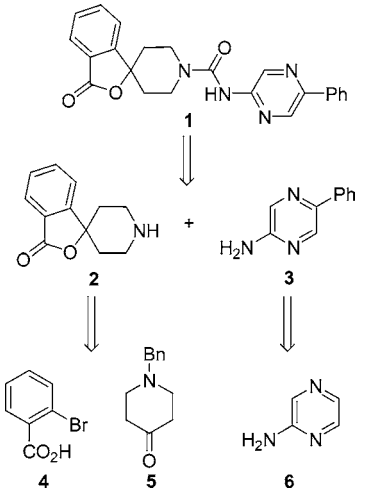
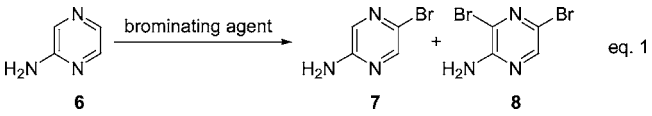
Scheme 1. **Retrosynthetic analysis**



reaction temperature and was thus added in one portion. Surprisingly, the temperature of the reaction mixture started to increase rapidly by 15 °C after a few minutes of induction period. To our surprise, the assay yield was 78%, the highest observed thus far! However, on scale-up, whereas the *N*-bromoacetamide was added slowly, the yield dropped back to 35%. Other brominating agents such as 1,3-dibromo-5,5-dimethylhydantoin (DBH) behaved similarly. Unfortunately, rapid addition would create a serious safety hazard on scale-up for the highly exothermic reaction. The other alternative for controlling the exothermic reaction was to slowly add the substrate to the brominating agent. However, this mode of addition produced large amounts of dibromopyrazine **8**. The barrier for the second bromination was surprisingly low. In fact, dibromopyrazine **8** could be obtained cleanly by simply adding the substrate to 2 equiv of brominating agent.



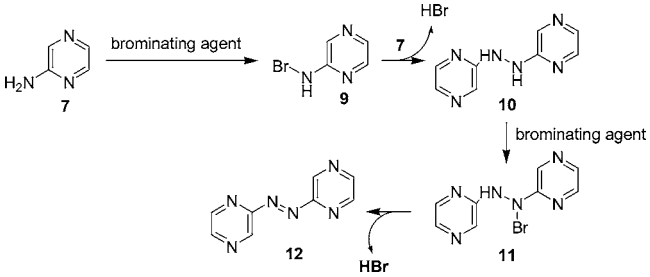
eq. 1

We hypothesized that the low yield on slow addition was due to competitive *N*-bromination followed by dimerization with the starting material to give **10** (Scheme 2). The presence of excess starting material favored this side reaction. Further *N*-bromination of the dimer followed by eliminating HBr gave an azo-dye type compound, 2,2′-azobispyrazine **12**, observed by LC−MS analysis.[6] Compound **6** could also participate in analogous side reactions, further aggravating the problem. This hypothesis was supported by the fact that decreased yields were accompanied by increased acidity of the reaction mixture as well as the appearance of large amounts of dark precipitate.

We reasoned that simultaneous addition of the substrate and the brominating agent should substantially reduce this N−N bond forming side reactions by minimizing the presence of excess starting material. This mode of addition required a reasonable stable solution of the brominating

(6) (a) 2,2′-Azobispyrazine: Carlucci, L.; Ciani, G.; Proserpio, D. M.; Rizzato, S. *New J. Chem.* **2003**, *27*, 483−489. (b) Brown, E. V.; Granneman, G. R. *J. Am. Chem. Soc.* **1975**, *97*, 621−627.

Scheme 2. **Bromination side reactions**



agent. We found that both NBS and DBH were unstable in THF, DMSO, DME, dioxane, NMP, and various aqueous/organic systems. The most promising solvents were DMF and MeCN. DBH was selected due to its higher solubility and more robust solution stability. It should be pointed out that both bromine atoms were utilized. *N*-Bromoacetamide was much more expensive and not readily available on scale. Thus, by simultaneously adding solutions of DBH and aminopyrazine **7** in MeCN/DMF to a reaction flask at 0−5 °C, the bromination became reproducible and the yield was significantly improved to 70%. While this procedure was convenient and scalable, it was still not optimal. As the reaction progressed, the accumulated product led to its increased participation in the above-mentioned side reactions. A flow-cell reactor, where the substrate and DBH solutions are rapidly mixed and then pushed out of the reactor, should eliminate this problem. Thus, the reaction was conducted in a simple flow-cell reactor prepared from a syringe and a coil of polypropylene tube. Solutions of the substrate and the brominating agent were added simultaneously to the syringe with stirring and then pushed through the coil. With this setup, the yield was further improved to 80%. This protocol was successfully demonstrated on a kilogram scale using a small round-bottom flask as the flow-cell reactor. Careful calibration of the pumps to maintain a proper reagent/substrate ratio was critical for optimal results.

Alternatively, selective reduction of dibromopyrazine **8**, obtained by simply adding aminopyrazine to 2.0 equiv of brominating agents (*vide supra)*, would provide the desired bromopyrazine **7**. Literature precedence on palladium-catalyzed regioselective Stille and Sonogashira couplings of **8** at the 3-position provided further impetus for investigating this approach.[7]

Screenings of various hydride donors, palladium sources, ligands, bases, and solvents for the regioselective debromination were carried out (Table 1). Initial results indicated that formic acid was the best hydride donor and $Pd(OAc)_2$ was a good palladium source for the reaction. Other palladium catalysts such as $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ also gave acceptable results. Polar aprotic solvents such DMAc and DMSO were the preferred solvents, and the best ligand appeared to be P(2-furyl)$_3$, which was unfortunately rather expensive (entry 3). The much more economical Ph_3P performed almost as well (91% yield). Triethylamine and *i*-Pr_2NEt afforded essentially the same results (entries 6, 7).

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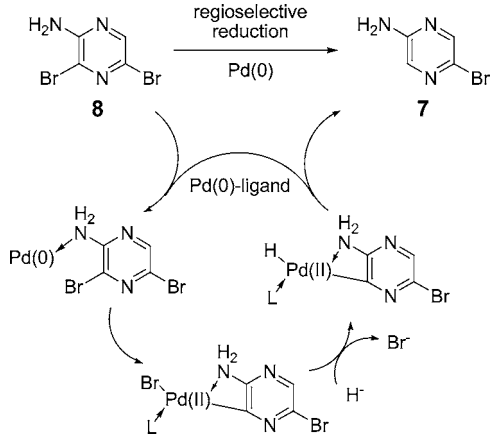
Table 1. **Effect of ligand, base, and solvent for regioselective reduction of 8**

entry	palladium/ligand	base	solvent	7	6
1	$Pd(OAc)_2/P(o\text{-tol})_3$	Et_3N	DMAc	33	5
2	$Pd(OAc)_2/P(t\text{-Bu})_3$	Et_3N	DMAc	39	10
3	**$Pd(OAc)_2$/P(2-furyl)$_3$**	**Et_3N**	**DMAc**	**97**	**2**
4	$Pd(OAc)_2/PPh_3$	Et_3N	DMAc	88	3
5	**$Pd(OAc)_2/PPh_3$**	**Et_3N**	**DMSO**	**90**	**1**
6	$Pd(OAc)_2/PPh_3$	Et_3N	MeCN	61	0.3
7	**$Pd(OAc)_2/PPh_3$**	***i*-Pr_2NEt**	**DMSO**	**91**	**2**
8	$Pd(OAc)_2/PPh_3$	DBU	DMSO	87	10
9	$Pd(OAc)_2/PPh_3$	$n\text{-}Bu_3N$	DMSO	68	1

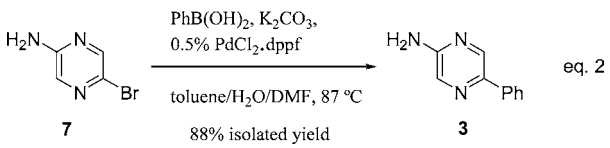
Scheme 3. **Mechanism of the regioselective debromination**



DBU gave a somewhat lower yield and more overreduction product **6** (entry 8). Longer chain tertiary amine n-Bu_3N gave a substantially lower yield (entry 9).

Interestingly, bidentate ligands such as DPPF and BINAP were much less effective than monodentate ligands. This observation supports our hypothesis that participation of the neighboring amino groups as a ligand was the key for the observed high regioselectivity (Scheme 3).

With the bromopyrazine **7** in hand, its coupling[8] with phenylboronic acid was investigated. It was found that excellent results were obtained with 0.5 mol % $PdCl_2$·dppf as the catalyst. The reaction went to completion in 2−8 h to give the coupling product **3** in 93% assay yield (eq 2). The

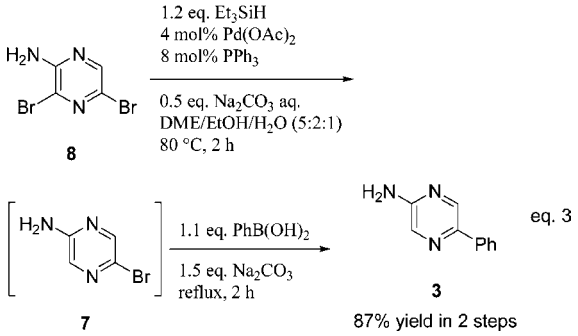


presence of water appeared to promote the reaction as the reaction was very sluggish in the absence of water. The product was crystallized from toluene/heptane in 88% yield.

Since palladium was used for the regioselective debromination step, it would be very advantageous to perform the Suzuki−Miyaura coupling in a one-pot fashion using the residual palladium catalyst. However, directly carrying forward the debromination reaction mixture to the next step failed. Therefore, a search for reaction conditions compatible with both steps was carried out in DME/EtOH/H_2O (5/2/1), the preferred solvent system for the Suzuki−Miyaura coupling (Table 2).

It was ound that formic acid, ammonium formate, sodium formate, or $(EtO)_3SiH$ gave poor results in the absence of a base (entries 1−3). A reasonable yield of the desired product **6** was obtained using $NaBH_4$ as the hydride source (entry 4). Triethylsilane appeared to be the best hydride donor for the debromination affording 95% yield of bromopyrazine **7** (entry 5). Expensive commercial $Pd(PPh_3)_4$ or a more economical in situ prepared catalyst from $Pd(OAc)_2$ and PPh_3 were very effective for the reactions. On the other hand, $PdCl_2/PPh_3$ was much less so (entry 7). Simple Pd/C was almost completely ineffective (entry 8). We also observed that 2.0 equiv of Et_3SiH were required for the reaction in the absence of base. By adding 0.5 equiv of Na_2CO_3 to neutralize the generated HBr, the Et_3SiH charge could be reduced to 1.2 equiv.

Thus, dibromopyrazine **8** was treated with 1.2 equiv of Et_3SiH in the presence of 4 mol % of $Pd(OAc)_2$, 8 mol % PPh_3, and 0.5 equiv of Na_2CO_3 in DME/EtOH/H_2O (5/2/1) at 80 °C for 2 h to give bromopyrazine **7**. The reaction mixture was then treated with 1.1 equiv of $PhB(OH)_2$ and 1.5 of equiv Na_2CO_3 at 80 °C for 2 h affording 2-amino-5-phenylpyrazine (**3**). The yield for the reduction step was as high as 96%, and the overall isolated yield of **3** was 87% (eq 3). Thus we have developed an efficient and high yielding



one-pot procedure for the synthesis of 2-amino-5-phenylpyrazine **3** from dibromopyrazine employing sequential palladium-catalyzed regioselective reduction and a Suzuki−Miyaura coupling reaction.

Subsequently, we also developed two alternative synthetic routes to the phenylpyrazine **3** via condensation of isonitrosoacetophenone with aminomalononitrile and aminoacetonitriles, respectively. The results have been published elsewhere.[9]

For the synthesis of spirolatone fragment **2**, aryllithium addition to *N*-protected piperidone appeared to be the most efficient approach (eq 4). Treatment of 2-bromobenzoic acid with 2.2 equiv of n-BuLi at −78 °C followed by *N*-benzyl piperidone and acidification afforded the desired spirolactone **7** albeit in rather low yield. The best yield (58% by HPLC

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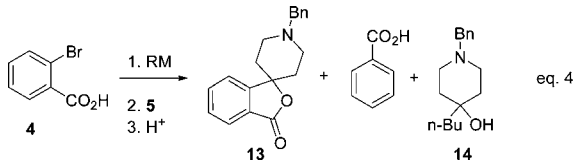
Table 2. **Screening of reducing agents and palladium catalysts for reduction**

entry	reductant (equiv)	palladium/ligand	base (equiv)	**7**	**6**
1	HCO_2H (2.0)	$Pd(PPh_3)_4$	none	19%	trace
2	HCO_2NH_4 (2.0)	$Pd(PPh_3)_4$	none	16%	trace
3	$(EtO)_3SiH$ (2.0)	$Pd(PPh_3)_4$	none	8%	ND
4	$NaBH_4$ (2.0)	$Pd(PPh_3)_4$	none	70%	1%
5	**Et_3SiH (2.0)**	**$Pd(PPh_3)_4$**	**none**	**95%**	**2%**
6	Et_3SiH (2.0)	$Pd(OAc)_2/PPh_3$	none	86%	7%
7	Et_3SiH (2.0)	$PdCl_2/PPh_3$	none	59%	7%
8	Et_3SiH (2.0)	Pd/C	none	13%	1%
9	**Et_3SiH (1.2)**	**$Pd(OAc)_2/PPh_3$**	**Na_2CO_3 aq. (0.5)**	**96%**	**2%**
10	Et_3SiH (1.2)	$Pd(OAc)_2/PPh_3$	Et_3N (1.0)	66%	28%
11	Et_3SiH (1.2)	$PdCl_2/PPh_3$	Na_2CO_3 aq. (0.5)	38%	3%

assay) was obtained by slow addition of *n*-BuLi.[10] As expected, quench of the aryllithium by the carboxylic acid was a major side reaction. Another side reaction was the enolization of piperidone. Various amounts of compound **8** via direct *n*-BuLi addition to the piperidone were also observed. Furthermore, the reaction required cryogenic conditions which would drive up the cost significantly for large scale production.



To avoid the premature halogen−metal exchange and the resulting internal quench, the feasibility of performing the deprotonation step with a less active alkylmagnesium reagent followed by subsequent metal−halogen exchange with *n*-BuLi was investigated. We also envisioned that, in the presence of Mg^{2+}, the aryllithium should be rapidly converted to the thermally more stable arylmagnesium and thus could potentially obviate the costly cryogenic conditions. This approach proved to be quite successful. Sequential treatment of 2-bromobenzoic acid with 0.52 equiv of *n*-Bu_2Mg and 1.1 equiv of *n*-BuLi followed by *N*-benzyl piperidone afforded the spirolactone **13** in 67% yield after in situ lactonization. The reaction could be successfully carried out at −20 to 0 °C without any instability problems. This procedure proved to be of general utility, and the detailed results were disclosed recently.[11]

Subsequently, various other alkylmagnesium reagents were examined, and the results are summarized in Table 3. We found that MeMgBr gave a somewhat lower yield than *n*-Bu_2Mg (entry 3). *i*-PrMgCl afforded quite good results (71% yield, entry 4). The best yield (76%) was obtained with 0.9−1.0 equiv of *n*-BuMgCl (entries 6 and 7). The reaction has been successfully scaled up to a multikilogram scale affording the spirolactone in 74% isolated yield.

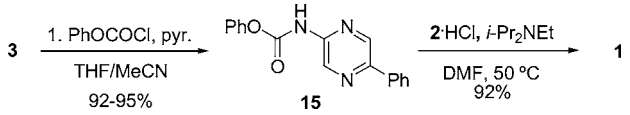
Removal of the benzyl protective group was accomplished by a simple hydrogenolysis of **13** in MeOH at 20−30 °C with Pd/C as the catalyst. The desired product **2** was isolated

Table 3. **Effect of alkylmagnesium reagents**

			yield (%) by HPLC		
entry	reagent (equiv)	*n*-BuLi (equiv)	**13**	$PhCO_2H$	**14**
1[a]	none	2.2	58	19	
2	*n*-Bu_2Mg (0.5)	1.05	67	28	
3	MeMgBr (1.0)	1.5	63	20	
4	*i*-PrMgCl (1.1)	1.5	71	17	
5	*n*-BuMgCl (0.8)	1.3	73	10	16
6	***n*-BuMgCl (0.9)**	**1.3**	**76**	**13**	**7**
7	*n*-BuMgCl (1.0)	1.3	76	11	13

[a] Reaction was carried out at −78 °C.

Scheme 4. **Final product**



in excellent yield (91%). Thus we have developed a very concise and economical synthesis of the spirolactone **2**. All raw materials were very inexpensive, and the requirement for cryogenic conditions was eliminated.

With both the spirolactone **2** and the phenylpyrazine **3** in hand, their coupling to the target molecule **1** was investigated. A number of methods for the synthesis of unsymmetrical ureas have been reported.[12] We decided to use the phenyl chloroformate protocol[12g] for ease of operation, low cost, and mildness of reaction conditions. The aminopyrazine **3** was chosen as the first coupling partner instead of the spirolactone amine **2**, as the latter should be more active and thus should proceed under milder conditions for the formation of a urea linkage. This consideration was important as the urea moiety in the final product was somewhat labile to hydrolysis under strong basic conditions. For the preparation of the activated carbamate **15**, aqueous workup and isolation should be avoided if possible as it is prone to hydrolysis. Ideally, the

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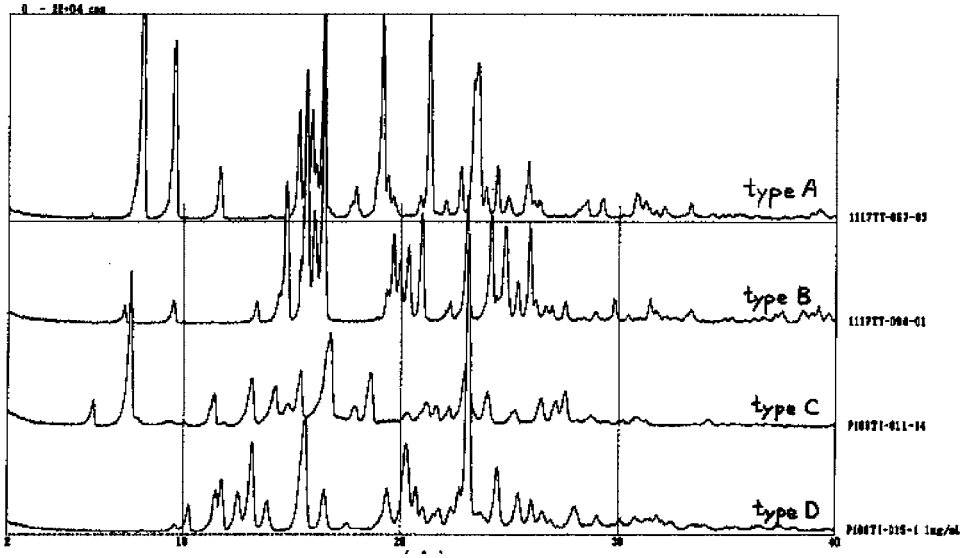

Figure 1. **XRPD chart of each crystal forms of 1.**

product would crystallize from the reaction media while the hydrochloride salt of the organic base remained in the mother liquor. Thus, proper selection of base and solvent was crucial. When pyridine was used as the base and THF was used as the solvent, a thick gel was obtained. After switching to acetonitrile as the solvent, the product **15** precipitated as a very slow-filtering fine suspension. Fortunately, excellent results were obtained when a THF/MeCN mixed solvent system was employed. The product crystallized nicely and was directly filtered in 92−95% yield while pyridine hydrochloride salt remained in the mother liquor.

The final coupling of the carbamate **15** with the spirolactone **2** is quite facile in solvents such as MeCN, THF, DMF, DMSO, etc. DMF was selected owing to the higher solubility of the substrate and product in this solvent. By adding *i*-Pr_2NEt as the base, the hydrochloride salt of the spirolactone could be used directly. The order of addition was quite important as the carbamate **15** was unstable to base (*i*-Pr_2NEt) in the absence of the coupling partner. Thus, the reaction was carried out by mixing the HCl salt of spirolactone **2** and *i*-Pr_2NEt for 0.5 h followed by addition of the carbamate **15**. The mixture was then heated to 40−45 °C and stirred for 2−4 h affording the final product **1** in 92% isolated yield (Scheme 4).

Compound **1** has four crystal forms; form A, B, C, and D (Figure 1). The most stable polymorph is usually preferable for pharmaceutical purposes because the crystalline form might affect the mechanical stability of tablets and the bioavailability of the active compound. It was necessary to minimize the possibility of subsequent polymorphic changes for the development of the drug. As deduced from many polymorph studies, we found that forms A and C were less thermodynamically stable than forms B and D (Figure 2). Form D is the most thermodynamically stable form and exists in hydrous and anhydrous forms. The results of the hygroscopic analysis showed that the vacuum-dried form D was converted to the hydrous form under high humidity, and the hydrous form D was converted to the hemihydrate form D under low humidity. Also form D was easily converted to

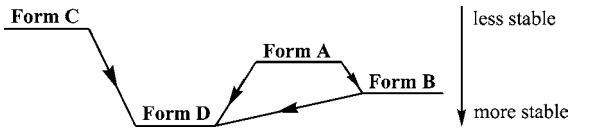

Figure 2. **Correlation of polymorphism for thermodynamic stability.**

form B under anhydrous slurry state conditions. The bioavailability of the anhydrous form D was nearly equal to that of form B. However, it was necessary to mill form D finely to acquire the same bioavailability as form B. As mentioned above, form D was not a good candidate for clinical study due to absorption and desorption of water reversibly depending on the relative humidity and technical issues of milling. But form B was a metastable form under aqueous conditions, so that the chemical stability tests of form B were investigated. As a result, form B was not converted to form D under high humidity, and the conversion from B to D was kinetically very slow under aqueous slurry state conditions. With these data in hand, it was clear that form B was the more preferable form than form D for clinical study. After the coupling reaction, **1** was obtained as form D by crystallization from a DMF/H_2O system. Then, form D was easily converted to form B by the slurry state transformation in MeCN.

In summary, we have developed a very concise and practical synthesis of the highly selective NPY-5 receptor antagonist **1**. A much improved monobromination of aminopyrazine by using a flow-cell reactor was developed. Alternatively, sequential palladium-catalyzed regioselective debromination of dibromopyrazine and Suzuki−Miyaura coupling gave the phenylpyrazine fragment **3**. A practical and economical synthesis of the spirolactone fragment **2** and a high-yielding coupling with the aminopyrazine **3** complete the synthesis of the target molecule **1**.

Experimental Section

General. All reagents were purchased and used without any further purification. Organic solvents were dried over 4

Å molecular sieves. ^{1}H and ^{13}C NMR spectra were taken in DMSO-d_6 at 400 and 100 MHz, respectively. Hydrogen multiplicity (C, CH, CH_2, CH_3) information was obtained from DEPT spectra.

2-Amino-5-bromopyrazine (7). (a) Simultaneous addition mode: A solution of 2-aminopyrazine **6** (3.5 kg, 36.8 mol) in DMF/MeCN (7 L/22.8 L) and a solution of DBH (5.5 kg, 19.3 mol) in DMF/MeCN (3.5 L/33.9 L) were added simultaneously to a flask containing 3.5 L of MeCN at 0 °C over 1 h. The reaction mixture was stirred for 0.5 h, quenched with aq. $Na_2S_2O_3 \cdot 5H_2O$ (10%, 7.0 L), and concentrated in vacuo. Solka-Floc (filter aid, 1.1 kg) and aq. Na_2CO_3 (2.0 wt %, 33.0 L) were added, and the mixture was stirred for 1 h and then filtered. The filtrate was saturated with solid NaCl (~10.0 kg) and then extracted with 3/2 EtOAc/*n*-heptane (35.0 L, 2 × 16.0 L). The combined organic extract was washed with brine and then treated with Darco-KB overnight. The product was crystallized by a solvent switch to heptane furnishing 4.48 kg of **7** as a yellow solid (65% yield corrected for 93% purity). (b) Flow-cell reaction: A small flow-cell reactor was made by connecting a 20 mL syringe with polypropylene tubing coiled to a ~70 mL internal volume. A magnetic stir bar is placed in the syringe reactor, and the latter was capped with a rubber septum. Both the syringe and the coil were immersed in a cooling bath (−20 °C). The outlet of the coil led to a 2 L flask maintained at 0 °C. A solution of 2-aminopyrazine **6** (35.0 g, 368 mmol) in DMF/MeCN (70/228 mL) and a solution of DBH (55.2 g, 193 mmol) in DMF/MeCN (35/339 mL) were added simultaneously via a syringe pump to the flow-cell reactor at a rate of 3.0 and 3.7 mL/min, respectively, with vigorous stirring. After completing the addition, the system was purged by pumping through acetonitrile. Following the workup and isolation, the procedure above gave 51.0 g of **7** as a yellow solid (75% yield corrected for 94% purity). Mp 114.5−115.5 °C; ^{1}H NMR (DMSO-d_6) δ 8.00 (d, J = 1.5 Hz, 1H), 7.68 (d, J = 1.5 Hz, 1H), 6.60 (brd, 2H); ^{13}C NMR (DMSO-d_6) δ 155.7 (C), 144.0 (CH), 132.6 (CH), 124.1 (C); IR (KBr, cm^{-1}) 3309, 3167, 1631, 1567, 1531, 1460, 1380, 1206, 1105, 1009, 863. Anal. Calcd for $C_4H_4N_3Br$: C, 27.61; H, 2.32; Br, 45.92; N, 24.15. Found: C, 27.52; H, 2.19; Br, 45.58; N, 24.03.

2-Amino-5-phenylpyrazine (3). (a) Synthesis from **6**: A mixture of toluene (13.4 L), water (9.5 L), DMF (2.38 L), K_2CO_3 (2.47 kg, 17.9 mol), 2-amino-5-bromopyrazine **6** (2.2 kg, 94 wt %, 11.9 mol), $PhB(OH)_2$ (1.6 kg, 13.1 mol), and $PdCl_2 \cdot dppf \cdot CH_2Cl_2$ (87.1 g, 0.12 mol) was degassed by vacuum/nitrogen-fill cycles and then heated to reflux (~87 °C) until the reaction was complete (5−8 h). It was cooled to <40 °C, and then THF (11.8 L) was added to dissolve the product. The organic layer was washed with brine (11.3 L, twice). It was then treated with Darco-KB (414 g) and Na_2SO_4 (2.07 kg) for overnight. The mixture was filtered, and the filter cake was washed with 1/1 toluene/THF (6.0 L). The filtrate was concentrated under reduced pressure to 8.5 L, and then *n*-heptane (7.5 L) was added over 1 h. After aging for 2 h, the product was collected by filtration and washed with 1/1 toluene/*n*-heptane (3.8 L) and then dried overnight to give 1.82 kg (88% yield) of **3** as a yellow solid. (b) One-pot debromination/Suzuki−Miyaura coupling procedure: A mixture of the dibromopyrazine **8** (100 g, 395 mmol), Et_3SiH (75.7 mL, 1.2 equiv), 1.5 M aq. Na_2CO_3 (132 mL, 0.5 equiv), and DME/EtOH/H_2O (5/2/1, 1.5 L) was degassed by vacuum/N_2-fill cycles. $Pd(OAc)_2$ (4 mol %) and PPh_3 (8 mol %) were added, and the mixture was degassed twice more. The mixture was heated to 80 °C and aged for 2 h. After confirming the completion of the reaction by HPLC, the reaction mixture was cooled to 30−40 °C. $PhB(OH)_2$ (53.0 g, 435 mmol) and solid Na_2CO_3 (62.8 g, 593 mmol) were added, and the mixture was degassed by vacuum/N_2-fill cycles. It was heated to refluxing temperature and aged for 2 h. After confirming the completion of the reaction by HPLC, it was cooled to ambient temperature and THF (500 mL) was added to dissolve the product. The organic layer was separated, washed with brine (500 mL × 2), treated with Darco-KB (5.0 g) and Na_2SO_4 (10.0 g) overnight, and then filtered and washed with toluene/THF (1/1, 300 mL). The filtrate was concentrated under reduced pressure to 400 mL, and then heptane (350 mL) was added over 1 h. After aging for 2 h, the product was filtered, washed with toluene/*n*-heptane (1/1, 200 mL), and dried to give 58.9 g of **3** as a yellow solid in 87% yield corrected for purity. Mp 147.5−148.0 °C; ^{1}H NMR (DMSO-d_6) δ 8.51 (d, 1H, J = 1.5 Hz), 8.00 (d, 1H, J = 1.5 Hz), 7.91 (d, 2H, J = 7.5 Hz), 7.40 (d, 2H, J = 7.7, 0.5 Hz), 7.29 (d, 1H, J = 7.7 Hz), 6.56 (brd s, 2H); ^{13}C NMR (DMSO-d_6) δ 155.4 (C), 139.6 (C), 139.3 (CH), 137.6 (C), 131.9 (CH), 129.1 (CH), 127.8 (CH), 125.2 (CH); IR (KBr, cm^{-1}) 3343, 3177, 1651, 1588, 1538, 1479, 1447, 1389, 1216, 1025, 1010, 883, 783, 751, 694. Anal. Calcd for $C_{10}H_9N_3$: C, 70.16; H, 5.30; N, 24.54. Found: C, 69.90; H, 4.97; N, 24.53.

1′-Benzylspiro[isobenzofuran-1(3*H*),4′-piperidin]-3-one Hydrochloride (13). *n*-BuMgCl (2.0 M in THF, 4.5 L, 9.0 mol) was added slowly to a solution of 2-bromobenzoic acid **4** (2.0 kg, 9.95 mol) in THF (20 L) followed by *n*-BuLi (1.56 M in *n*-hexane, 8.3 L, 12.9 mol) at −15 to −5 °C. The mixture was stirred for 0.5 h, and then a solution of 1-benzyl-4-piperidone (2.02 L, 10.9 mol) in *n*-heptane (6.0 L) was added over 1 h. After aging for 1 h, methyl *tert*-butyl ether (MTBE, 10.0 L) and AcOH (3.14 L, 54.8 mol) in water (20 L) were added sequentially. The mixture was heated to 35 to 40 °C and stirred for 3 h to affect the lactonization. It was then cooled to 25 °C, and the layers separated. The aqueous layer was extracted with MTBE (10.0 L) and then combined with the organic layer. The combined organic layer was then washed sequentially with NaOH (2.0 N, 10.0 L), K_2CO_3 (1.0 kg, 7.24 mol in 5.0 L of H_2O), and H_2O (10.0 L) and then concentrated and flushed with MeOH (24.0 L) until residual water was <0.2 wt %. A solution of HCl in EtOAc (4.0 N, 2.32 L, 9.28 mol) was slowly added followed by methyl *tert*-butyl ether (24.4 L) to crystallize the spirolactone **13** as its HCl salt. The solid was collected by filtration, washed with MeOH/MTBE (1/5), and then dried to give 2.4 kg of **13** HCl salt (74% yield). Mp 275 °C; ^{1}H NMR (DMSO-d_6) δ 11.5−11.8 (br s, 1H), 7.75−7.9 (2H, m), 7.6−7.75 (m, 3H), 7.4−7.55 (m, 4H), 4.76 (d, J = 5

Hz, 0.2H), 4.45 (d, J = 5.0 Hz, 1.8H), 3.1−3.5 (m, 4H), 2.83 (t, J = 13.0 Hz, 2H), 1.94 (d, J = 14 Hz, 2H). Free base: mp 106.5−107.5 °C; ^{1}H NMR (DMSO-d_6) δ 7.80 (d, J = 7.6 Hz, 1H), 7.78−7.73 (m, 2H), 7.61−7.55 (m, 1H), 7.36−7.31 (m, 4H), 7.29−7.22 (m, 1H), 3.58 (s, 2H), 2.84 (brd d, J = 11 Hz, 2H), 2.35 (td, J = 12.5, 2.0 Hz, 2H), 2.23 (td, J = 13.3 Hz, 4.3 Hz, 2H), 1.60 (d, J = 11.8 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 168.7 (C═O), 153.6 (C), 138.2 (C), 134.4 (CH), 129.4 (CH), 128.9 (CH), 128.1 (CH), 126.9 (CH), 125.1 (CH), 124.8 (C), 121.9 (CH), 84.5 (C), 62.1 (CH_2), 49.2 (CH_2), 35.4 (CH_2); IR (cm^{-1}) 1763 (C═O), 1071, 932, 731, 694. Anal. Calcd for $C_{19}H_{29}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.66; H, 6.22; N, 4.70.

Spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-one hydrochloride Monohydrate (2). A solution of **13** HCl salt (2.0 kg, 6.06 mol) in 10/1 methanol/water (35.2 L) was hydrogenated under 25 psi of hydrogen in the presence of 10% Pd/C (50 wt % wet, 400 g) at 30 °C for 6 h. The catalyst was filtered off and rinsed with MeOH (8.0 L). The filtrate was concentrated and flushed with methanol at 45−50 °C until a water content of 6−9% and a final volume of 6.4 L were achieved. The mixture was cooled to 30 °C, and then MTBE (4.8 L) was added over 2 h to crystallize the product. The product was filtered, washed with 1/5 MeOH/MTBE (3.2 L, twice), and dried at 25 °C to give 1.46 kg of **2** (93% yield corrected for purity, 6.4% water). Mp 268 °C (dec); ^{1}H NMR (DMSO-d_6) δ 9.59 (brd s, 2H), 7.85 (d, J = 7.6 Hz, 1H), 7.83 (dt, J = 7.5, 1.0 Hz, 1H), 7.64 (dd, J = 7.5, 1.0 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 3.44−3.39 (m, 4H), 3.12 (dt, J = 13.0, 2.8 Hz, 2H), 2.60 (dt, J = 14.2, 4.6 Hz, 2H), 1.85 (d, J = 14.3 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 168.7 (C), 152.6 (C), 135.5 (CH), 130.5 (CH), 126.0 (CH), 125.0 (C), 121.9 (CH), 82.5 (C), 40.6 (CH_2), 32.05 (CH_2); IR (cm^{-1}) 3600−2500 (brd), 1769, 1637, 1581, 1465, 1445, 1319, 1263, 1079, 1018, 957, 932, 764, 693. Anal. Calcd for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; Cl, 14.79; N, 5.84. Found: C, 59.90; H, 5.88; Cl, 15.06; N, 5.78.

(5-Phenyl-pyrazin-2-yl)-carbamic Acid Phenyl Ester (15). Phenyl chloroformate (1.36 kg, 1.09 L, 8.69 mol) was added to a mixture of **3** (1.45 g, 98 wt %, 8.28 mol) and pyridine (786 g, 804 mL, 1.2 equiv) in THF (6.1 L) and MeCN (8.2 L) at 20−30 °C over 3 h. The mixture was stirred for 1 h, filtered, washed with 2/1 MeCN/THF (4.5 L), and dried to give 2.22 kg (92% yield) of the carbamate **15** as a white solid. Mp 199.5−200.5 °C; ^{1}H NMR (DMSO-d_6) δ 11.17 (s, 1H), 9.15 (d, J = 1.5 Hz, 1 H), 9.00 (d, J = 1.5 Hz, 1H), 8.09 (dd, J = 7.1, 1.5 Hz, 2H), 7.53−7.43 (m, 5H), 7.31−7.25 (m, 3H); ^{13}C NMR (DMSO-d_6) δ 152.3 (C), 150.7 (C), 147.8 (C), 146.6 (C), 139.8 (CH), 136.2 (C), 135.0 (CH), 130.0 (CH), 129.6 (CH), 129.4 (CH), 126.5 (CH), 126.3 (CH), 122.4 (CH); IR (cm^{-1}) 3196, 2978, 1754, 1560, 1444, 1365, 1298, 1238, 1213, 1164, 1075, 1059, 1012, 928, 910. Anal. Calcd for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.42. Found: C, 69.92; H, 4.43; N, 14.34.

1′-{[(5-Phenyl-2-pyrazinyl)amino]carbonyl}-spiro-[isobenzofuran-1(3*H*),4′-piperidin]-3-one (1). A mixture of **2**·HCl monohydrate (1.68 kg, 7.5 mol), *i*-Pr_2NEt (990 mL, 5.67 mol), and DMF (13.9 L) was stirred for 0.5 h, and then carbamate **15** (1.98 kg, 6.8 mol) was added. (Carbamate **15** should be added last. Otherwise, it would decompose upon mixing with *i*-Pr_2NEt.) The mixture was heated to 40−45 °C for 2 h, cooled to ambient temperature, and then quenched with AcOH (119 mL, 2.08 mol). Water (4.2 L) was added, and the mixture was stirred for 1 h to initiate the crystallization. More water (5.1 L) was added over 2−4 h, and the mixture was stirred for 2 h. The product was filtered and washed with DMF/H_2O (1:1) and water to give the 2.76 kg (97% yield) of **1** (monohydrate, form D). It was converted into the anhydrous form by suspending in MeCN (7.9 L) overnight to give 2.5 kg of **1** (92% yield). Mp 207−207.6 °C; ^{1}H NMR (DMSO-d_6) δ 9.77 (s, 1H), 9.19 (d, J = 1.5 Hz, 1H), 8.90 (d, J = 1.5 Hz, 1H), 8.07 (td, J = 7.2, 1.5 Hz, 1H), 8.07 (d, J = 7.2 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.78 (dd, J = 7.4, 0.8 Hz, 1H), 7.76 (dt, J = 7.2, 0.8 Hz, 1H), 7.59 (dt, J = 7.3, 0.8 Hz, 1H), 7.48 (tt, J = 7.4, 1 Hz, 2H), 7.41 (tt, J = 7.3, 1.5 Hz, 1H), 4.37 (brd d, J = 13.7 Hz, 2H), 3.23 (t, J = 12.2 Hz, 2H), 2.27 (dt, J = 13.7, 4.5 Hz, 2H), 1.68 (d, J = 13.4 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 169.1 (C), 154.4 (C), 153.6 (C), 149.9 (C), 145.1 (C), 139.1 (CH), 136.6 (C), 136.3 (CH), 135.0 (CH), 130.0 (CH), 129.3 (CH), 129.2 (CH), 126.3 (CH), 125.7 (CH), 125.2 (C), 122.5 (CH), 85.1 (C), 41.4 (CH_2), 35.5 (CH_2); IR (cm^{-1}) 3291 (brd), 3058, 2951, 2871, 1765, 1668, 1542, 1502, 1446, 1358, 1230, 1064, 930, 790, 694. Anal. Calcd for $C_{23}H_{20}N_4O_3$: C, 68.99; H, 5.03; N, 13.99; O, 11.99. Found: C, 68.78; H, 4.88; N, 13.93.

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Supporting Information Available

One-pot debromination/Suzuki−Miyaura coupling procedure and ^{1}H and ^{13}C NMR data for **1**, **2**, **3**, **13**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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