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Discovery of melanin-concentrating hormone receptor R1 antagonists using high-throughput synthesis

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Abstract—A structure–activity study on benzylpiperidine **1** was accomplished by utilizing high-throughput synthesis. Three focused libraries were designed and synthesized to quickly develop SAR. Further optimization led to the discovery of compound **2**, an MCH receptor R1 antagonist with over 400-fold improvement in biological activity over the original lead.

1. Introduction

Melanin-concentrating hormone (MCH), first isolated from the *chum* salmon pituitaries, is a cyclic 19-amino acid neuropeptide responsible for color changes in fish skin.[1] MCH is present in the brains of all vertebrate species examined so far and it appears to be involved in feeding behavior based on the following observations: direct icv administration of MCH in rats results in increases in food intake in a dose dependent manner;[2] MCH mRNA is overexpressed in ob/ob mice and in fasted mice;[3a] MCH overexpressing mice are hyperphagic, mildly obese, hyperglycemic, and insulin resistant;[3b] MCH knockout mice are leaner than wild-type mice.[4] These discoveries prompted considerable interest in the MCH receptor as a potential target for the treatment of obesity and resulted in the identification of MCH receptors by several independent groups in a short time.[5,6] It is generally believed that MCH receptor R1 mediates the orexigenic effects of MCH and reports on MCH receptor R1 antagonists for the potential treatment of obesity have also appeared explosively in recent years.[7–49] In this paper, we describe the identification of highly potent MCH receptor R1 antagonists by using the high-throughput solid phase synthesis approach.[50]

2. Chemistry and results

Several lead structures such as **1** were identified in our initial in-house screening for antagonists of MCH receptor R1. Subsequent screening of the individual enantiomers of **1** revealed the R enantiomer to be more active with a eudesmic ratio of 10/1 (K_i 430, 4000 nM, respectively). To rapidly develop SAR, we decided to utilize solid phase chemistry to optimize the lead and our strategy was to explore modifications of the amide substituent on the left-hand side (LHS), the benzylpiperidine core, and the piperidine nitrogen substituent on the right-hand side (RHS) of the lead in a combinatorial manner. As shown in Scheme 1, different amines would be first anchored to the Argopore-MB-CHO resin by reductive alkylation.[51] These resins would then be acylated with acid chloride cores followed by the deprotection of the piperidine nitrogen atom and subsequently modified by reductive alkylation with aldehydes or ketones.[52] Final products would be cleaved off the resins under acidic conditions.

After successful validation of the three-step solid phase synthesis, we designed our first library to cover a wide range of inputs (Scheme 2): 10 (R^1) × 4 (R^2) × 10

Keywords: Melanin-concentrating hormone receptor R1 (MCH R1); Antagonist; Obesity; High-throughput synthesis.
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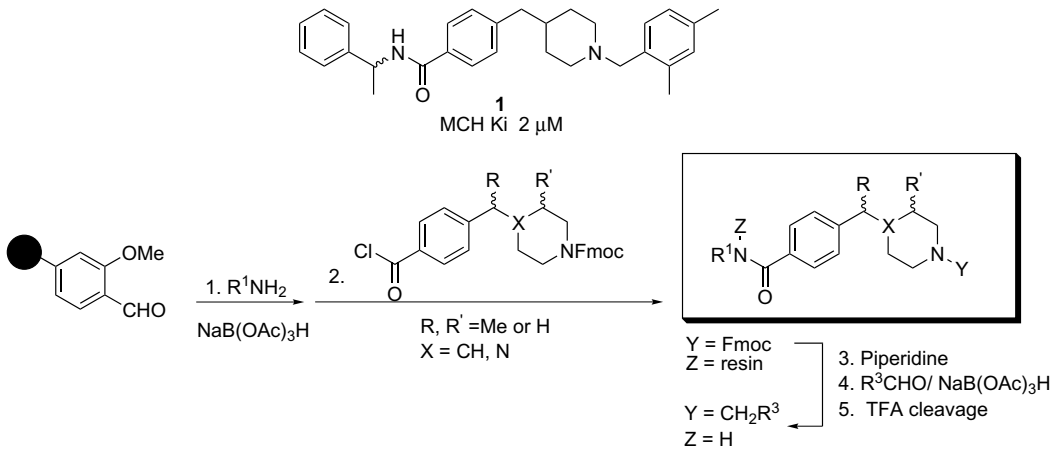
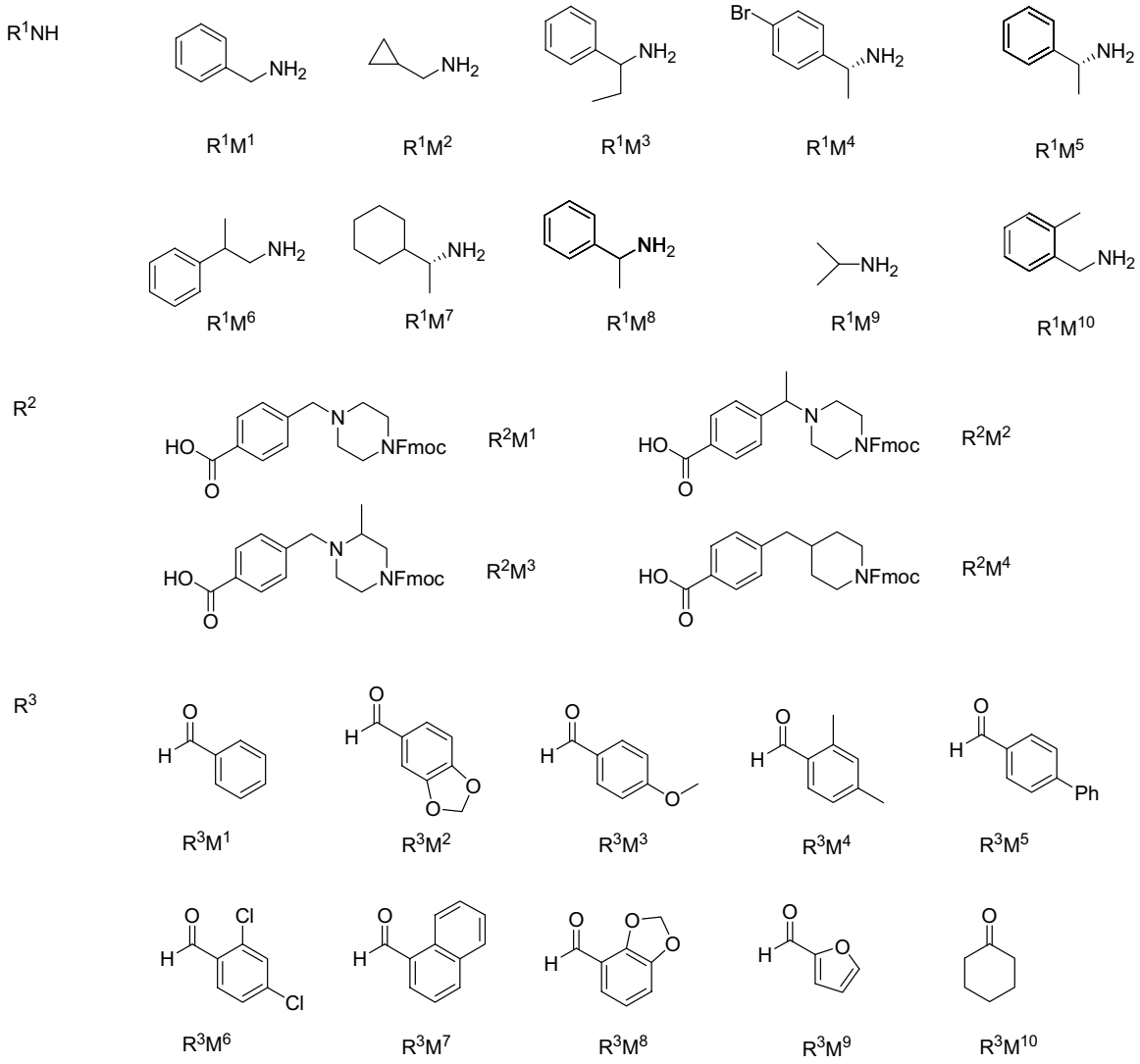


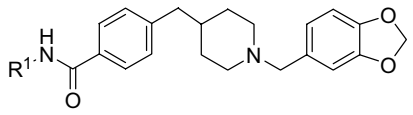
Scheme 1. Combinatorial synthesis of the first library.



Scheme 2. Reagents used for the first combinatorial library of 400 compounds.

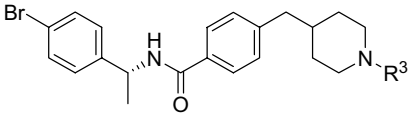
(R^3) = 400 (members). The 10 amines included several racemic amines (R^1M^3, R^1M^6, and R^1M^8), chiral amines (R^1M^4, R^1M^5, R^1M^7) of (*R*)-configuration as well as other alkyl amines. The core structures cover a benzylpiperidine (R^2M^4) and benzylpiperazines with or without a methyl group (R^2M^1, R^2M^2, R^2M^3). These modifications of the core structure were designed to allow us to probe a range of conformations and the effect of changing the basicity of the nitrogen atom on the biological activity. Similar modifications have been previously

Table 1. Selected SAR of the LHS modification of lead **1** from the first library



R^1NH	Compound	MCH K_i (nM)
R^1M^1	**3**	5642
R^1M^2	**4**	13,890
R^1M^3	**5**	1831
R^1M^4	**6**	101
R^1M^5	**7**	3473
R^1M^6	**8**	11,765
R^1M^7	**9**	3567
R^1M^8	**10**	4135
R^1M^9	**11**	Inactive
R^1M^{10}	**12**	9332

Table 3. Selected SAR of the RHS modifications of lead **1** from the third library

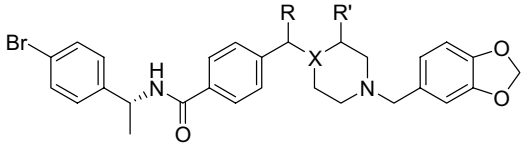


R^3	Compound	MCH K_i (nM)
R^3M^1	**16**	2584
R^3M^2	**6**	101
R^3M^3	**17**	149
R^3M^4	**18**	105
R^3M^5	**19**	5114
R^3M^6	**20**	Inactive
R^3M^7	**21**	1413
R^3M^8	**22**	17,380
R^3M^9	**23**	15,606
R^3M^{10}	**24**	36,588

shown to be important in the development of other GPCR antagonists such as M2 and CCR5 receptors.[53,54] Based on the initial lead, the majority of R^3 groups were derived from substituted aromatic aldehydes.

The synthesis of this library commenced with 10 individual reductive alkylations of amines with the Argopore-MB-CHO resin to prepare 10 resin bound amines. After the amine resins were distributed into 400 Irori™ minikans, the subsequent synthesis was carried out using the Irori technology. According to Scheme 1, 400 discrete compounds in 10–20 mg amounts were readily obtained in 3 weeks. Overall, the solid phase synthesis provided the desired products in excellent yields (85% on average) with high purity. Among the 400 compounds that were synthesized and screened, 93% of them were at least 70% pure by LC/MS. The rest of the 7% were at least 50% pure. The screening of this library provided us some very clear-cut SAR trends. Tables 1–3 show some of the SAR for the LHS, the core and the RHS, respectively. On the LHS, benzyl amines were more active than other alkyl amines (compound **3** vs **4** and **11**). The introduction of a substituent at the benzylic position further improved the activities (compound **3** vs **5** and **10**). The best amine in this region was (*R*)-4-bromo-α-methylbenzylamine (R^1M^4, compound **6**). It was 35-fold more active than the analog R^1M^5 (compound **7**), which lacked the bromine, suggesting the significance of the *para* substitution. Also noteworthy was compound **5** with racemic α-ethylbenzylamine fragment (R^1M^3). It was 2-fold more active than its corresponding α-methylbenzylamine analog **10** (R^1M^8) in all cases. As shown in Table 2, compound **13** with the benzylpiperidine core (R^2M^4) was at least 20-fold more active than the benzylpiperazine analogs. On the RHS, three compounds with *para* substitution on the phenyl ring were equally potent (compound **6**, **17**, and **18**), which suggested that a *para* substitution was very important in this region. These compounds were resynthesized, purified and submitted for assay. The fact that their original K_i values were within 2-fold of the new K_i values confirmed the high quality of the first library. The (*S*)-enantiomer of compound **6** was independently synthesized and its K_i was 1335 nM, again confirming the importance of the (*R*)-configuration on the LHS.

Table 2. Selected SAR of the core modifications of lead **1** from the second library



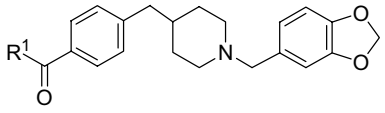
Core	Compound	MCH K_i (nM)
R^2M^1	**13**	1951
R^2M^2	**14**	2334
R^2M^3	**15**	4560
R^2M^4	**6**	101

Encouraged by the results of our first library, we expanded the SAR exploration of the substituent on the basic nitrogen on the RHS by incorporating a much greater variety of aromatic aldehydes in the second library. Keeping the optimized LHS (R^1M^4) and the benzylpiperidine core (R^2M^4), a total of 146 compounds of high quality were readily prepared by parallel solid phase synthesis using the Bohdan™ miniblock system. Although the biological activity of the best compound from this series remained at 100 nM, some useful SAR information was revealed by the following: (a) 3,4-disubstitution on the phenyl ring was important; (b) a small fused ring formed by these two substituents was preferred; (c) a heteroatom at the 4-position was particularly favored.[55]

Our third solid phase library was based on the Suzuki coupling reaction of compound **6** to explore the *para* substitution on the LHS. The synthesis was carried out using Advanced ChemTech™ platform and a 60-membered library was finished within a week. Most reactions worked very well and those that failed either had no reaction or gave the corresponding dehalogenated products. Biological evaluation of this series revealed that the biphenyl unit is not favored on the LHS as none of the substituents introduced on the phenyl ring improved activity over the lead compound **6**.

The successful synthesis of the three libraries allowed us to quickly develop SAR and led us to the new lead **6**. We then began to examine further optimization of this lead by synthesizing individual compounds in the traditional manner. On the LHS, a variety of substituents on the phenyl ring were introduced and the representative modifications were shown in Table 4. The biological results indicated that *para* substitution was far better than *meta* or *ortho* substitution (compound **25**–**27**). It was also found that halogen substituents were better than alkyl groups (compound **28**, **31**, **32**) and iodo- was the most active one (compound **32**, K_i 51 nM).[56] Since the data in the first library suggested that the α-ethylbenzylamine was more active than the α-methylbenzylamine (compound **5** vs **10**, Table 1), compound **33** was synthesized and the activity was indeed improved to 20 nM. However, increasing the size of the α-substituent further led to a drop in K_i (compound **34**, K_i 191 nM).

Table 4. Optimization of the LHS of lead **6**



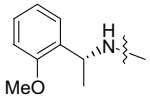
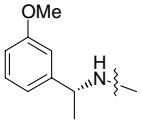
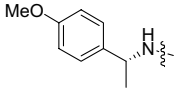
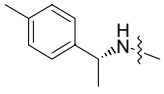
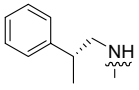
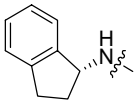
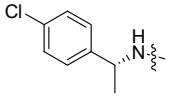
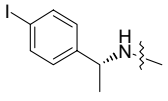
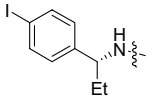
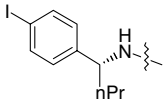
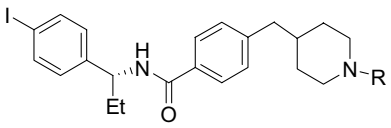
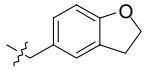
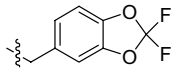
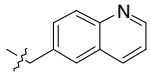
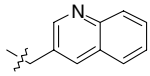
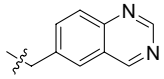
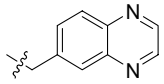
R^1	Compound	MCH K_i (nM)
	**25**	2056
	**26**	776
	**27**	266
	**28**	1078
	**29**	Inactive
	**30**	4678
	**31**	108
	**32**	51
	**33**	20
	**34**	191

Table 5. Optimization of the RHS of lead **6**



R	Compound	MCH K_i (nM)
	**35**	133
	**36**	795
	**2**	5
	**37**	312
	**38**	30
	**39**	40

Further optimization on the RHS was carried out based on the SAR information from the second library and representative examples are shown in Table 5. The 6-quinoline **2** emerged as the best compound in this series with K_i 5 nM. The position of the nitrogen atom was critical as the isomer 3-quinoline **37** was 60-fold less active. The quinazoline **38** and quinoxaline **39** were less active possibly due to the decrease in basicity of the nitrogen atom.

3. Summary

In this report we have focused on the SAR development using high-throughput solid phase synthesis to identify MCH receptor R1 antagonists. Using readily available commercial equipment, and a combination of combinatorial and parallel synthesis, over 600 compounds were prepared in high yields with excellent purity. These three libraries quickly provided very useful SAR information for three regions of the molecule: the LHS amide, the center core and the RHS. Based on these results, further fine tuning of the led to additional improvements in the biological activity and a potent new lead **2** (K_i 5 nM) has been identified.

4. Experimental

4.1. General methods

All reagents were used as received. ^1H and ^{13}C NMR spectra were obtained on a Varian XL-400 (400 MHz)

instrument and were reported as ppm downfield from Me_4Si. LCMS analysis was performed on an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column: Altech platinum C18, 3 μm, 33 mm × 7 mm ID; gradient flow: 0 min, 10% CH_3CN; 5 min, 95% CH_3CN; 7 min, 95% CH_3CN; 7.5 min, 10% CH_3CN; 9 min, stop. Chromatography was performed with Selecto Scientific flash silica gel, 32–63 μM.

4.2. MCH receptor binding assay

The K_i values of MCH receptor R1 antagonists were determined using a SPA-based radioligand binding assay. Membranes from CHO cells expressing MCH-R1 (0.1 mg/mL) were incubated with SPA beads (1 mg/mL) in binding buffer (25 mM HEPES, 10 mM $MgCl_2$, 5 mM $MnCl_2$, 0.1% BSA, pH 7.4) for 5 min on ice forming a bead/membrane mixture. The bead/membrane mixture was centrifuged (4 min at 300*g*) and resuspended in binding buffer. The bead/membrane mixture was then pelleted again (4 min at 300*g*), resuspended in binding buffer, and set aside. Binding buffer (50 μL/well) containing vehicle alone (2% DMSO), various compound concentrations, or 4 μM MCH (for non-specific binding) was added to a 96-well plate. Subsequently, 50 μL of binding buffer containing 0.5 nM ^{125}I-MCH was added to each well of the 96-well plate. Finally, 100 μL of the bead/membrane mixture was added to each well of the 96-well plate. The binding reactions were incubated for 2–4 h at room temperature. Binding of ^{125}I-MCH to the bead/membrane mixture was detected using a TOPCOUNT (Packard). K_i Values were determined using nonlinear regression analysis.

4.3. General procedures for chemical synthesis

Loading amines onto Argopore-MB-CHO resin.

To 6 g of Argopore-MB-CHO resin (0.76 mmol/g, 4.56 mmol, 1 equiv)/40 mL dichloroethane (DCE) was added an amine (18.24 mmol, 4 equiv). The mixture was agitated at room temperature under N_2 for 0.5 h followed by the addition of $NaBH(OAc)_3$ (3.84 g, 4 equiv). After 36 h of agitation, 50 mL of MeOH was added to the mixture and gas evolution was observed. The solvent was decanted and the residue was stirred with 50 mL 2 N NH_3 in MeOH for 10 min, followed by washing with dichloromethane (DCM) 100 mL × 1, MeOH 100 mL × 1, and DCM 100 mL × 2. The resin was collected and dried in a vacuum oven for 36 h.

Synthesis of cores: synthesis of the cores was carried out according to Refs. 57 and 58.

R^2M^1: ^{1}H NMR (DMSO-d_6): δ 2.30 (br s, 4H), 3.30 (br s, 6H), 4.22 (m, 1H), 4.40 (d, 2H, J = 5.8 Hz), 7.24–7.50 (m, 6H), 7.60 (d, 2H, J = 7.6 Hz), 7.90 (m, 4H). ^{13}C NMR (DMSO-d_6): δ 45.07, 48.45, 53.79, 63.02, 68.00, 121.59, 126.40, 128.56, 129.08, 130.30, 130.76, 142.21, 144.63, 145.25, 151.90, 154.80, 168.47. HRMS for (MH^+) $C_{27}H_{27}N_2O_4$ Calcd 443.1971. Found 443.1968. Elemental analysis: C, 73.28; H, 5.92; N, 6.33. Found: C, 72.74; H, 5.76; N, 6.27.

R^2M^2: ^{1}H NMR (DMSO-d_6): δ 1.30 (d, 3H, J = 6.6 Hz), 2.20 (br s, 4H), 3.2 (br s, 2H), 3.44 (m, 1H), 3.60 (br s, 2H), 4.20 (m, 1H), 4.40 (d, 2H, J = 6.2 Hz), 7.20–7.40 (m, 6H), 7.60 (d, 2H, J = 7.5 Hz), 7.85 (d, 2H, J = 7.8 Hz), 7.90 (d, 2H, J = 8.3 Hz). ^{13}C NMR (DMSO-d_6): δ 20.40, 32.36, 45.26, 48.45, 51.01, 64.77, 67.96, 121.56, 126.42, 128.53, 129.06, 130.76, 136.77, 142.19, 145.24, 148.00, 149.56, 155.57, 168.50. HRMS for (MH^+) $C_{28}H_{29}N_2O_4$ Calcd 457.2127. Found 457.2124. Elemental analysis: C, 73.66; H, 6.18; N, 6.14. Found: C, 70.34; H, 6.56; N, 5.20.

R^2M^3: ^{1}H NMR ($CDCl_3$): δ 1.10 (br d, 3H), 2.00 (br s, 1H), 2.40 (br s, 1H), 2.60 (br s, 1H), 2.95 (br s, 1H), 3.20 (br s, 2H), 3.60 (br s, 1H), 3.80 (br s, 1H), 4.00 (br s, 1H), 4.20 (br s, 1H), 4.40 (br s, 2H), 7.20–7.40 (m, 6H), 7.50 (d, 2H, J = 7.9 Hz), 7.76 (d, 2H, J = 7.6 Hz), 8.05 (d, 2H, J = 7.9 Hz). ^{13}C NMR (DMSO-d_6): δ 16.2, 45.12, 48.52, 51.04, 55.75, 58.47, 61.37, 67.83, 121.55, 126.39, 129.06, 130.13, 130.72, 142.27, 144.10, 145.28, 145.71, 146.20, 155.62, 168.51. HRMS for (MH^+) $C_{28}H_{29}N_2O_4$ Calcd 457.2127. Found 457.2119. Elemental analysis: C, 73.66; H, 6.18; N, 6.14. Found C, 71.72; H, 6.42; N, 5.30.

R^2M^4: ^{1}H NMR (DMSO-d_6): δ 0.9 (br s, 2H), 1.46 (br s, 2H), 1.75 (br s, 1H), 2.58 (d, 2H, J = 6.9 Hz), 3.3 (br s, 2H), 3.6–3.8 (br s, 2H), 4.2 (m, 1H), 4.40 (br s, 2H), 7.20–7.40 (m, 6H), 7.60 (d, 2H, J = 7.9 Hz), 7.90 (m, 4H). ^{13}C NMR (DMSO-d_6): δ 32.85, 38.54, 43.57, 45.18, 48.54, 67.74, 121.57, 126.39, 128.53, 129.04, 129.85, 130.67, 130.97, 142.24, 145.33, 146.88, 155.68, 168.55. HRMS for (MH^+) $C_{28}H_{28}NO_4$ Calcd 442.2018. Found: 442.2026. Elemental analysis: C, 76.17; H, 6.16; N, 3.17. Found C, 75.76; H, 6.21; N, 2.95.

Coupling of resin bound amines with acid chlorides R^2 and subsequently aldehyde/ketone R^3. A resin bound amine (40 mg, 0.7 mmol/g, 0.028 mmol, 1 equiv) was treated with freshly prepared acid chloride R^2 (2 equiv) in the presence of Hunig's base (5 equiv) in 5 mL DCM. The mixture was stirred at rt overnight and the resin was washed sequentially with MeOH, THF, DCM, MeOH, and DCM. The above resin was stirred in 20 mL 20% piperidine in DMF at rt for 1 h. After washing with THF, DCM, MeOH, DCM, the resin was reacted with 10 equiv of an aldehyde R^3 (or a ketone), 10 equiv of $NaBH(OAc)_3$ in 10 mL DCE for 24 h. The resin was washed with 2 N NH_3 in MeOH, THF, MeOH, and DCM several times and dried in a vacuum oven overnight.

Cleavage from the resin.[51]

The resin was stirred with 3 mL 30% TFA in DCM for 1 h and then filtered. The procedure was repeated and the filtrates were combined and the solvent was evaporated using GeneVac™ or SpeedVac™. The average yield for the above three steps was 85%.

N-[1(*R*)-(4-Bromophenyl)ethyl]-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**6**): ^{1}H NMR ($CDCl_3$): δ 1.20–1.38 (m, 3H), 1.42–1.50 (m,

2H), 1.58 (d, 2H, $J = 6.6$ Hz), 1.80 (t, 2H, $J = 11$ Hz), 2.58 (d, 2H, $J = 7.5$ Hz), 2.81 (d, 2H, $J = 11$ Hz), 3.40 (s, 2H), 5.22 (m, 1H), 5.92 (s, 2H), 6.70 (s, 2H), 6.82 (s, 1H), 7.18 (d, 2H, $J = 8.5$ Hz), 7.22 (d, 2H, $J = 8.5$ Hz), 7.42 (d, 2H, $J = 8.3$ Hz), 7.63 (d, 2H, $J = 8.0$ Hz). ^{13}C NMR ($CDCl_3$): δ 23.00, 30.02, 30.94, 37.18, 42.90, 49.96, 53.10, 61.67, 102.74, 109.74, 111.96, 122.05, 122.75, 126.23, 128.25, 128.98, 130.12, 132.66, 133.54, 143.49, 143.80, 149.33, 150.00, 153.29, 167.34. HRMS for $C_{29}H_{32}BrN_2O_3$ (MH^+) Calcd 535.1596. Found: 535.1587. Elemental analysis: C, 65.05; H, 5.84; N, 5.23. Found C, 62.79; H, 5.60; N, 4.86.

N-Benzyl-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**3**): MS (MH^+) 443.

N-Cyclopropylmethyl-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**4**): MS (MH^+) 407.

N-(1-Phenylpropyl)-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**5**): MS (MH^+) 471.

N-[1(*R*)-Phenylethyl]-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**7**): MS (MH^+) 457.

N-(2-Phenylpropyl)-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**8**): MS (MH^+) 471.

N-[1(*R*)-Cyclohexylethyl]-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**9**): MS (MH^+) 463.

N-(1-Phenylethyl)-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**10**): MS (MH^+) 457.

N-(1-Methylethyl-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**11**): MS (MH^+) 395.

N-(2-Methylbenzyl)-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**12**): MS (MH^+) 457.

N-[1(*R*)-(4-bromophenyl)ethyl]-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperazinyl]methyl]benzamide (**13**): MS (MH^+) 536.

N-[1(*R*)-(4-Bromophenyl)ethyl]-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperazinyl]-1-ethyl]benzamide (**14**): MS (MH^+) 550.

N-[1(*R*)-(4-Bromophenyl)ethyl]-4-[[1-(1,3-benzodioxol-5-ylmethyl)-3-methyl-4-piperazinyl]methyl]benzamide (**15**): MS (MH^+) 550.

N-[1(*R*)-(4-Bromophenyl)ethyl]-4-[[1-benzyl-4-piperidinyl]methyl]benzamide (**16**): MS (MH^+) 491.

N-[1(*R*)-(4-Bromophenyl)ethyl]-4-[[1-(4-methoxybenzyl)-4-piperidinyl]methyl]benzamide (**17**): MS (MH^+) 521.

N-[1(*R*)-(4-Bromophenyl)ethyl]-4-[[1-(2,4-dimethylbenzyl)-4-piperidinyl]methyl]benzamide (**18**): MS (MH^+) 519.

N-[1(*R*)-(4-Bromophenyl)ethyl]-4-[[1-(4-phyenylbenzyl)-4-piperidinyl]methyl]benzamide (**19**): MS (MH^+) 567.

N-[1(*R*)-(4-Bromophenyl)ethyl]-4-[[1-(2,4-dichlorobenzyl)-4-piperidinyl]methyl]benzamide (**20**): MS (MH^+) 560.

N-[1(*R*)-(4-Bromophenyl)ethyl]-4-[[1-naphthylmethyl-4-piperidinyl]methyl]benzamide (**21**): MS (MH^+) 541.

N-[1(*R*)-(4-Bromophenyl)ethyl]-4-[[1-(1,3-benzodioxol-4-ylmethyl)-4-piperidinyl]methyl]benzamide (**22**): MS (MH^+) 535.

N-[1(*R*)-(4-Bromophenyl)ethyl]-4-[[1-(2-furylmethyl)-4-piperidinyl]methyl]benzamide (**23**): MS (MH^+) 481.

N-[1(*R*)-(4-Bromophenyl)ethyl]-4-[[1-cyclohexyl-4-piperidinyl]methyl]benzamide (**24**): MS (MH^+) 483.

N-[1(*R*)-(2-Methoxyphenyl)ethyl]-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**25**): MS (MH^+) 487.

N-[1(*R*)-(3-Methoxyphenyl)ethyl]-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**26**): MS (MH^+) 487.

N-[1(*R*)-(4-Methoxyphenyl)ethyl]-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**27**): MS (MH^+) 487.

N-[1(*R*)-(4-Methylphenyl)ethyl]-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**28**): MS (MH^+) 471.

N-[2(*R*)-Phenylpropyl]-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**29**): MS (MH^+) 471.

N-[1(*R*)-Indanyl]-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**30**): MS (MH^+) 469.

N-[1(*R*)-(4-Chlorophenyl)ethyl]-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**31**): MS (MH^+) 491.

N-[1(*R*)-(4-Iodophenyl)ethyl]-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**32**): MS (MH^+) 483.

N-[1(*R*)-(4-Iodophenyl)propyl]-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**33**): ^{1}H NMR ($CDCl_3$): δ 1.00 (t, 3H, $J = 7.3$ Hz), 1.20–1.40 (m, 2H), 1.42–1.60 (m, 3H), 1.80–2.00 (m, 4H), 2.58 (d, 2H, $J = 6.6$ Hz), 2.82 (d, 2H, $J = 11.7$ Hz), 3.40 (s, 2H), 5.00 (q, 1H, $J = 7.4$ Hz), 5.90 (s, 2H), 6.24 (d, 1H, $J = 8.0$ Hz), 6.70 (s, 2H), 6.80 (s, 1H), 7.10 (d, 2H, $J = 8.0$ Hz), 7.20 (d, 2H, $J = 8.0$ Hz), 7.62 (d, 4H, $J = 8.0$ Hz). ^{13}C NMR (CD_3OD): δ 10.6, 29.0, 29.3, 35.6, 41.7, 52.5, 55.8, 60.6, 91.8, 102.2, 108.7, 111.0, 122.6, 125.7, 127.6, 128.9, 129.3, 132.9, 137.6, 143.5, 143.6, 148.8, 149.7, 168.8. HRMS for $C_{30}H_{34}IN_2O_3$

(MH^+) Calcd 597.1614. Found 597.1597. Elemental analysis: C, 56.93; H, 5.41; N, 4.43. Found C, 55.15; H, 5.54; N, 4.16.

N-[1(*R*)-(4-Iodophenyl)butyl]-4-[[1-(1,3-benzodioxol-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**34**): MS (MH^+) 611.

N-[1(*R*)-(4-Iodophenyl)propyl]-4-[[1-(2,3-dihydrobenzofuran-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**35**): MS (MH^+) 595.

N-[1(*R*)-(4-Iodophenyl)propyl]-4-[[1-(2,2-difluoro-benzo-[1,3]dioxol-5-ylmethyl)-4-piperidinyl]methyl]benzamide (**36**): MS (MH^+) 633.

N-[1(*R*)-(4-Iodophenyl)propyl]-4-[[1-(quinolin-3-ylmethyl)-4-piperidinyl]methyl]benzamide (**37**): MS (MH^+) 604.

N-[1(*R*)-(4-Iodophenyl)propyl]-4-[[1-(quinazolin-6-ylmethyl)-4-piperidinyl]methyl]benzamide (**38**): MS (MH^+) 605.

N-[1(*R*)-(4-Iodophenyl)propyl]-4-[[1-(quinoxalin-6-ylmethyl)-4-piperidinyl]methyl]benzamide (**39**): MS (MH^+) 605.

N-[1(*R*)-(4-Iodophenyl)propyl]-4-[[1-(quinolin-6-ylmethyl)-4-piperidinyl]methyl]benzamide (**2**): ^{1}H NMR ($CDCl_3$): δ 1.00 (t, 3H, J = 7.3 Hz), 1.30–1.43 (m, 2H), 1.45–1.62 (m, 3H), 1.80–2.10 (m, 4H), 2.60 (d, 2H, J = 7.0 Hz), 2.99 (d, 2H, J = 10.7 Hz), 3.70 (s, 2H), 5.00 (q, 1H, J = 7.3 Hz), 6.30 (d, 1H, J = 8.0 Hz), 7.08 (d, 2H, J = 8.3 Hz), 7.18 (d, 2H, J = 8.3 Hz), 7.38 (m, 1H), 7.60–7.80 (m, 5H), 8.02 (d, 1H, J = 8.0 Hz), 8.10 (d, 1H, J = 8.3 Hz), 8.90 (d, 1H, J = 4.4 Hz). ^{13}C NMR ($CDCl_3$): δ 10.6, 29.0, 29.2, 35.5, 41.5, 53.1, 55.8, 59.5, 91.8, 122.3, 123.0, 127.6, 128.9, 129.3, 131.6, 132.8, 133.1, 137.0, 137.6, 143.5, 143.6, 146.9, 147.4, 168.8. HRMS for $C_{29}H_{32}IN_2O_3$ (MH^+) Calcd 583.1458. Found 583.1466. Elemental analysis for $C_{29}H_{32}IN_2O_3 \cdot 2HCl$: C, 56.82; H, 5.36; N, 6.21. Found C, 54.73; H, 5.55; N, 5.79.

(*R*)-1-(4-Iodophenyl)-ethylamine: To a solution of (*R*)-α-methylbenzylamine (7.0 g, 57.8 mmol, 1 equiv)/10 mL DCE was added trifluoroacetic anhydride (10 mL, 1.22 equiv) in 10 mL DCE below 30 °C. The mixture was stirred for 1.5 h and then cooled to 0 °C. Iodine (7.0 g, 0.48 equiv) was added followed by addition of bis(trifluoroacetoxy)iodobenzene (12.6 g, 0.5 equiv). The mixture was stirred for overnight and quenched by 10% sodium sulfite (130 mL). DCM (130 mL) was added and the organic layer was washed with saturated sodium bicarbonate. After drying over sodium carbonate and removal of DCM, the solid was dissolved in 50 mL ether by heating followed by addition of 150 mL hexane. White solids were precipitated out and the mixture was further stirred for 2 h. Filtration afforded white crystals, which were washed with hexane 30 mL × 2 and air dried. Desired product (9.2 g) was obtained in 46% yield. ^{1}H NMR ($CDCl_3$): δ 1.6 (d, 3H, J = 7.3 Hz), 5.08 (m, 1H), 6.40 (br s, 1H), 7.05 (d, 2H, J = 8.3 Hz), 7.70 (d, 2H, J = 8.3 Hz). The amide (1 g, 2.91 mmol, 1 equiv) was dissolved in 35 mL MeOH, 10 mL water, and 6 mL 2 N NaOH. The solution was stirred overnight, the solvent was removed and extraction with DCM several times provided the desired product as colorless oil (0.69 g, 96% yield). ^{1}H NMR ($CDCl_3$): δ 1.22 (d, 3H, J = 6.5 Hz), 1.40 (s, 2H), 3.98 (q, 1H, J = 6.6 Hz), 7.00 (d, 2H, J = 8.3 Hz), 7.58 (d, 2H, J = 8.3 Hz). ^{13}C NMR ($CDCl_3$): δ 27.12, 51.98, 93.09, 128.92, 138.36, 148.38. HRMS for $C_8H_{11}IN$ (MH^+) Calcd 247.9936. Found 247.9936. Elemental analysis: calcd C, 38.89; H, 4.08; N, 5.67. Found C, 39.01; H, 3.99; N, 5.61. Optical rotation: $[\alpha]_D$ +15.1 (*c* 1.4, MeOH).

(*R*)-1-(4-Iodophenyl)-propylamine: ^{1}H NMR ($CDCl_3$): δ 0.82 (d, 3H, J = 7.3 Hz), 1.46 (s, 2H), 1.60 (m, 2H), 3.78 (t, 1H, J = 6.7 Hz), 7.05 (d, 2H, J = 8.3 Hz), 7.60 (d, 2H, J = 8.3 Hz). ^{13}C NMR ($CDCl_3$): δ 12.14, 33.60, 58.46, 93.10, 129.56, 138.35, 146.99. HRMS for $C_9H_{13}IN$ (MH^+) Calcd 262.0093. Found 262.0092. Elemental analysis: calcd: C, 41.40; H, 4.63; N, 5.36. Found: C, 41.69; H, 4.16; N, 4.60.

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