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Novel Dihydropyrazine Analogues as NPY Antagonists

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Abstract—The dihydropyridine **1** is currently one of the lead compounds in the neuropeptide-Y_1 (NPY-Y_1) receptor antagonist program. Compound **1** is a selective, high affinity ligand at the NPY-Y_1 receptors ($IC_{50}=4.2$ nM) in SK-N-MC cells. To further expand the SAR study surrounding this dihydropyridine core structure we succeeded in synthesizing an analogous series of dihydropyrazine derivatives **2**. This structural modification yielded compounds substantially different from the parent molecules in terms of molecular polarization and electron distribution while the overall molecular structure was generally preserved. This altered property should therefore provide us with additional SAR information on the optimal binding requirement with NPY receptors.

One of the fastest growing public health concerns in most western societies is the increasing number of overweight citizens.[1] The cause of obesity is largely believed to be multifactorial. This metabolic disorder is in part behavioral, environmental, and has also a significant genetic linkage. While the etiology of obesity is still unknown its progression is closely associated with the unbalance between food intake and net energy expenditure.[1] Neuropeptide Y (NPY), a 36 amino acid peptide that is widely distributed in the central and peripheral nervous systems, is implicated in a variety of biological functions including feeding behaviors.

Antagonists of NPY receptors (and its subtypes) have long been a pharmaceutical targets aimed as a potential treatment of obesity.[2a,2b] Our continuing research in this area has resulted in several novel series of potent NPY antagonists, especially antagonists at the Y_1 receptor subtype which included the dihydropyridine (DHP) derivative **1**.[3] In an effort to further identify the key structural elements and to define the pharmacological prerequisite of potent and selective NPY inhibitors, an analogous series of dihydropyrazine compounds was prepared and screened for their Y_1 receptor activity in human neuroblastoma (SK-N-MC) cells (Fig. 1).[4]

While many 1,4-dihydropyrazine-3,5-dicarboxyl esters are known in the literature, there is only a handful of published articles on using dihydropyrazines as a surrogate of dihydropyridine in the study of biologically active compounds.[5,6] In the present study, the core DHP structure of the lead series (**1**) was replaced with a 1,4-dihydro-4-phenyl-2,6-dimethyl-3,5-pyrazine (DHPZ) ring. The desired 2,6-dimethyl substituted pyrazine is unknown. The procedure of Chorvat and Rorig for the 2,6-*unsubstitued* pyrazine was attempted with suitable modifications to accommodate the two methyl groups, however the result was unacceptable.[6] To overcome this obstacle, a modified synthetic approach which ultilized 2-diazo acetoacetate as the alkylating agent was investigated,[7] and was found to be very practical for the preparation of this class of novel 2,6-disubstituted dihydropyrazine system. The key reaction (Scheme 1) is a rhodium catalyzed *N*-alkylation of a nitro aniline derivative with diazo acetoacetate. In this method, the aniline group of 3-nitroaniline (**3a**), and 4-fluoro-3-nitroaniline (**3b**) were smoothly alkylated by the diazo compound in the presence of catalytic amount (0.2–0.4 mol%) of rhodium acetate dimer to give the bis-alkylated anilines (**4a** and **4b**). It is interesting to point out that the X-ray crystallographic structure of **4a** adopts a classical propeller shape in which two of the three propeller blades are formed by the rigid enol H-bonded six-membered acetoacetate rings.[8]

This bis-alkylated aniline was then cyclized with ammonium acetate in warm *tert*-butanol. Isopropanol

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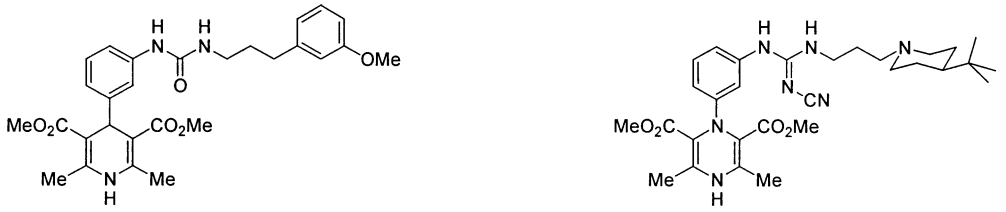
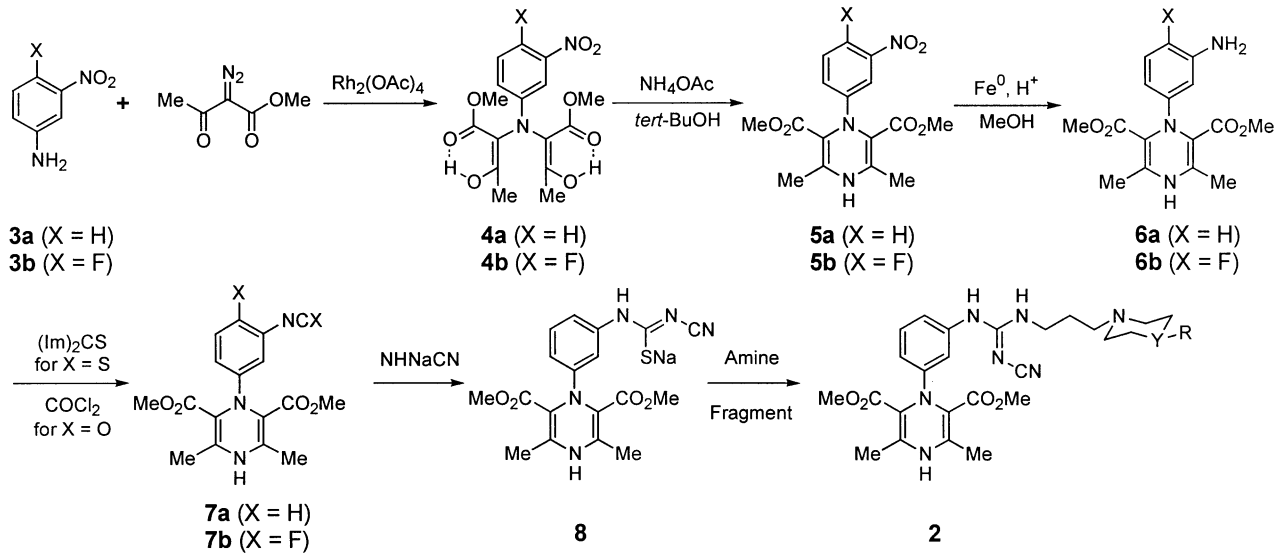


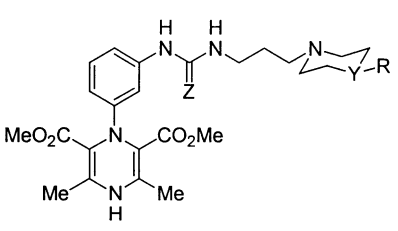
Figure 1.



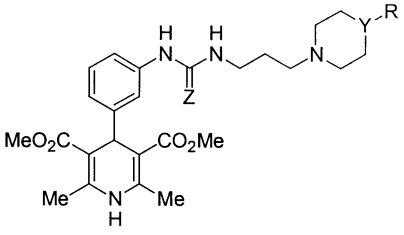
Scheme 1.

was found to be undesirable for such transformation due to the facile ester exchange of the methyl group to isopropyl group thus complicating the final purification step. However *tert*-butanol solvent neatly circumvented this side reaction. The nitro group in **5a** was reduced by iron powder in the presence of acid and the aniline **6a** was converted into the thioisocyanate using thiocarbonyl diimidazole in DMF, the desired product was isolated by crystallization. Conversion of **7a** to the final cyanoguanidine targets (**2a** and **2b**) was accomplished by a two step procedure of Tilley and Ramuz.[9] The amines used in the second step were chosen to give products that are analogous to the products previously prepared in the dihydropyridine series. Likewise the urea and thiourea

Table 1. NPY Binding affinities of dihydropyrazine derivatives (**2a**–**2g**)



Dihydropyrazine analogues of 2a-2g



Dihydropyridine Analogues

Compd	Z	Y	R	Y_1 (nM)[a]	Y_1 (nM)[a]
2a	N–CN	CH	Ph	268	5.4
2b	N–CN	CH	*tert*-Bu	231	<1.0
2c	S	CH	*tert*-Bu	>1000	[b]
2d	S	CH	3-MeOPh	945	12.8
2e	S	N	*cyclo*-Hex	>1000	132
2f	O	CH	3-MeOPh	554	4.2
2g	O	N	*cyclo*-Hex	434	176

[a]^{125}I-PYY binding in SK-N-MC cell membranes (IC_{50}).
[b]The corresponding dihydropyridine analogue is unavailable for comparison.

analogues were prepared from the corresponding isocyanate and thioisocyanate precursors. The preparation of some of these compounds were described elsewhere.[3,10]

At first, it was thought that replacing the DHP ring with a DHPZ would allow us to explore the SAR surrounding the DHP ring system. Such modification could also render the molecule more resistent toward oxidative metabolism to give the biologically inactive pyridine derivative. All the targets in this series were screened in the standard ^{125}I-PYY binding in intact human neuroblastoma (SK-N-MC)[4] cells and the results are shown in Table 1. For the purposes of comparison, the corresponding dihydropyridine (DHP) analogues are also shown on the right hand panel. As it can be seen from the table, dihydropyridine parent compounds show consistently higher binding affinities in the identical assay. Our results echoed that of Chorvat and Rorig in which DHPZ analogues of nifedipine-like compounds failed to show calcium antagonism and vasodilation activity.[6] The failure is believed to be attributed to the *near* sp^2 nitrogen at the 4-position of DHPZ in which the 4-phenyl appendage projects into a space less directly above the DHPZ core. Equally important is the fact that the dihedral angles of the 4-phenyl ring with respect to either DHP or DHPZ are substantially different. This result strongly suggests that the drug–receptor interaction is mainly dictated by the simultaneous recognition of the 4-aryl ring fragment and the DHP moiety. Unfortunately DHPZ is too conformationally restricted to be efficiently recognized for high affinity binding.

Acknowledgements

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10. Experimental details: **4a** and **4b**: A mixture of 3-nitroaniline (3.6 mmol), rhodium acetate dimer (0.0086 mmol) and 10 mL of dry benzene was warmed to reflux. To this was added a solution of methyl α-acetyl-α-diazoacetate[7] (13.0 mmol) in benzene (10 mL) dropwise over a period of 2 h. The resulting mixture was refluxed until all the diazoacetate was consumed. After cooling to room temperature, the volatiles were removed in vacuo and the residue was filtered over silica gel, eluted with 20% v/v ethyl acetate in hexanes. The crude material obtained from the filtration was subjected to further crystallization to give **4a** as orange crystals (0.95 mmol, 26.3%): mp 146–147 °C; ^{1}H NMR ($CDCl_3$) δ 12.76 (s, 1H), 12.73 (s, 1H), 7.56 (dd, 1H, J = 8.2, 2.0 Hz), 7.41 (t, 1H, J = 2.2 Hz), 7.31 (t, 1H, J = 8.2 Hz), 6.92 (dd, 1H, J = 8.2, 2.4 Hz), 3.74 (s, 6H), and 1.84 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 177.1, 172.4, 149.9, 130.2, 120.0, 113.3, 108.3, 52.0, and 19.6. Anal. calcd for $C_{16}H_{18}N_2O_8$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.31; H, 4.95; N, 7.65. Likewise **4b** was prepared from 4-fluoro-3-nitroaniline (ref 3 or commercially available now) as orange crystals (yield not determined): mp 161–163 °C; ^{1}H NMR ($CDCl_3$) δ 12.73 (s, 2H), 7.19 (dd, 1H, J = 5.9, 3.2 Hz), 7.10 (t, 1H, J = 9.5 Hz), 6.86 (dt, 1H, J_d = 9.2 Hz, J_t = 3.6 Hz), 3.75 (s, 6H), and 1.87 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 177.1, 172.3, 150.0, 146.6, 145.6, 120.0 (d, J_F = 7.1 Hz), 119.3 (d, J_F = 22.2 Hz), 109.7, 107.1, 52.0, and 19.6. Anal. calcd for $C_{16}H_{17}FN_2O_8$: C, 50.00; H, 4.46; N, 7.29. Found: C, 50.21; H, 4.56; N, 7.28.

5a and **5b**: **4a** (3.1 mmol) was refluxed with ammonium acetate (290 mg) in *tert*-butanol (30 mL) and the reaction was completed in less than 0.5 h. After chromatography (silica gel, 40% v/v ethyl acetate in hexanes), 750 mg product was isolated as orange foam (69%); ^{1}H NMR ($CDCl_3$) δ 7.66 (dd, 1H, J = 8.2, 1.4 Hz), 7.47 (t, 1H, J = 2.3 Hz), 7.26 (t, 1H, J = 8.2 Hz), 6.95 (dd, 1H, J = 8.2, 2.5 Hz), 6.21 (s, 1H), 3.78 (s, 6H), and 2.45 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.6, 151.5, 149.5, 148.9, 129.3, 119.1, 114.6, 108.6, 108.1, 52.0, and 18.1. Anal. calcd for $C_{16}H_{17}N_3O_6 \cdot 0.25H_2O$: C, 54.62; H, 5.01; N, 11.94. Found: C, 54.83; H, 5.22; N, 11.39. Likewise **5b** was prepared from **4b**, and the material was isolated as an orange foam (50%); ^{1}H NMR ($CDCl_3$) δ 7.19 (dd, 1H, J = 5.9, 3.2 Hz), 7.10 (t, 1H, J = 9.5 Hz), 6.86 (dt, 1H, J_d = 9.2 Hz, J_t = 3.6 Hz), 3.75 (s, 6H), and 1.87 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.5, 151.2, 149.7, 148.0, 147.1, 120.0 (d, J_F = 7.1 Hz), 118.2 (d, J_F = 22.2 Hz), 109.9, 108.7, 52.0, and 18.1. Anal. calcd for $C_{16}H_{16}FN_3O_6 \cdot 0.35EtOAc \cdot 0.67H_2O$: C, 51.20; H, 4.97; N, 10.29. Found: C, 51.19; H, 4.69; N, 10.29.

6a: **5a** (219 mg, 0.63 mmol) was dissolved in 30 mL methanol containing 3 mL of water in a flask equipped with a mechanical stirrer. Iron powder (300 mg) was added, followed by one drop of 37% hydrochloric acid. The whole mixture was refluxed gently with mechanical stirring for 3.5 h. Usual extractive work up furnished **5a** as yellow solid (176 mg, 88%): mp 212–213 °C; ^{1}H NMR ($CDCl_3$) δ 6.91 (t, 1H, J = 8.0 Hz), 6.20 (dd, 1H, J = 7.8, 2.0 Hz), 6.11 (dd, 1H, J = 8.2, 2.3 Hz), 6.00 (t, 1H, J = 2.2 Hz), 5.93 (s, 1H), 3.77 (s, 6H), and 2.38 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 166.8, 152.0, 148.5, 146.9, 129.6, 109.5, 107.8, 104.2, 100.3, 51.8, and 17.9. Anal. calcd for $C_{16}H_{19}N_3O_4$: C, 60.56; H, 6.04; N, 13.24. Found: C, 60.05; H, 6.14; N, 12.66.

7a: **6a** (3.8 mmol) in 16 mL of DMF was slowly added into a DMF solution (20 mL) of 1,1′-thiocarbonyldiimidazole (5.2 mmol) and the reaction went to completion in 0.5 h. After DMF was removed in vacuo, the residue was purified by chromatography on silica gel eluted with 50% v/v ethyl acetate in hexanes to give a yellow powder (1.19 g, 87%); ^{1}H NMR ($CDCl_3$) δ 7.09 (t, 1H, J = 8.1 Hz), 6.73 (dd, 1H, J = 7.8, 1.9 Hz), 6.59 (dd, 1H, J = 8.3, 2.4 Hz), 6.47 (t, 1H, J = 2.1 Hz), 6.06 (s, 1H), 3.79 (s, 6H), and 2.43 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 166.0, 151.7, 149.1, 131.3, 129.6, 117.7, 112.6, 110.3, 108.9, 52.0, and 18.1. Anal. calcd for $C_{17}H_{17}N_3O_4S \cdot 0.2H_2O$: C, 56.25; H, 4.83; N, 11.58. Found: C, 56.28; H, 4.96; N, 11.11.

2a: **7a** (144 mg, 0.40 mmol) was added into sodium cyanamide (28 mg, 0.44 mmol) in 3 mL of EtOH and the mixture was stirred for 20 min. EtOH was then removed in vacuo and the resultant foam-like material was mixed 4-phenyl-piperidine-1-propan-amine[3] (105 mg, 0.48 mmol) in 5 mL of THF. The mixture was cooled down to 0 °C and $HgCl_2$ (109 mg) was added. The reaction was completed in 15 min. After filtration and extraction, the organic layer was concentrated and purified by chromatography (silica gel, eluted with 10% v/v MeOH in CH_2Cl_2), **6a** was isolated as a yellow foam (175 mg, 75%); ^{1}H NMR ($CDCl_3$) δ 7.05–7.35 (m, 6H), 6.75 (br, 1H), 6.65 (d, 1H, J = 7.5 Hz), 6.58 (d, 1H, J = 8.3 Hz), 6.53 (br, 1H), 5.98 (br, 1H), 3.72 (s, 6H), 3.38 (m, 2H), 2.97 (m, 2H), 2.30–2.55 (m, 3H), 2.39 (s, 6H), 2.03 (m, 2H), 1.65–1.80 (m, 4H), 1.40–1.60 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 166.2, 152.6, 149.4, 129.9, 128.5, 126.9, 126.3, 118.3, 116.3, 112.5, 110.4, 108.7, 54.1, 51.8, 42.4, 41.0, 32.7, 29.8, 25.6, and 17.9. Anal. calcd for $C_{32}H_{39}N_7O_4 \cdot 0.7CH_2Cl_2 \cdot 0.24H_2O$: C, 60.48; H, 6.34; N, 15.10. Found: C, 60.59; H, 6.71; N, 14.45.

2b: Likewise **2b** was prepared from **6a** (116 mg, 0.32 mmol) and 4-*tert*-butyl-piperidine-1-propanamine[3] (77 mg, 0.39 mmol). The desired product was isolated as a yellow foam-like material (130 mg, 72%); ^{1}H NMR ($CDCl_3$) δ 7.41 (br, 1H), 7.10 (t, 1H, J = 8.0 Hz), 6.60 (d, 2H, J = 7.6 Hz), 6.54 (br, 1H), 5.70 (br, 1H), 3.76 (s, 6H), 3.31 (m, 2H), 3.06 (m, 2H), 2.51 (m, 2H), 2.42 (m, 6H), 2.07 (m, 2H), 1.79 (m, 2H), 1.62 (m, 2H), 1.15–1.40 (m, 2H), 1.00 (m, 1H), and 0.80 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 166.3, 149.8, 129.9, 118.1, 116.4, 110.5, 108.5, 54.2, 51.9, 45.9, 40.1, 32.1, 27.3, 25.6, and 17.8. Anal. calcd for $C_{30}H_{43}N_7O_4 \cdot 0.4CH_2Cl_2 \cdot 0.4H_2O$: C, 60.16; H, 7.41; N, 16.16. Found: C, 60.36; H, 7.54; N, 16.19.

2c: **7a** (25 mg, 0.069 mmol) was refluxed with 4-*tert*-butyl-piperidine-1-propanamine[3] (16 mg, 0.081 mmol) in 2 mL of benzene for 30 min. Chromatographic purification (silica gel, eluted with 10% v/v MeOH in CH_2Cl_2) of the resultant residue after concentration in vacuo gave **2c** as a yellow powder (64%); ^{1}H NMR ($CDCl_3$) δ 8.20 (br, 1H), 7.98 (br, 1H), 7.05 (t, 1H, J = 8.1 Hz), 6.79 (br, 1H), 6.66 (d, 1H, J = 8.0 Hz), 6.50–6.60 (m, 2H), 3.70 (s, 6H), 3.55 (m, 2H), 3.28 (m, 2H), 2.72 (m, 2H), 2.30–2.55 (m, 2H), 2.37 (s, 6H), 1.86 (m, 2H), 1.50–1.80 (m, 2H), 0.95–1.25 (m, 1H), and 0.79 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 180.9, 166.3, 152.8, 150.1, 129.9, 116.3, 112.7, 109.9, 108.5, 53.9, 51.8, 44.9, 42.1, 32.1, 29.8, 27.2, 24.7, 24.5, and 17.8. MS matched for $C_{29}H_{43}N_5O_4S$.

2d: **7a** (500 mg, 1.4 mmol) was refluxed with 4-(3-methoxy-phenyl)-piperidine-1-propanamine[3] (380 mg, 1.5 mmol) in 8 mL of benzene for 2 h. Chromatographic purification (silica gel, 100% CH_2Cl_2 first, followed by 10% v/v MeOH in CH_2Cl_2) of the residue after concentration in vacuo gave **2d** as a yellow foam (807 mg, 95%); ^{1}H NMR ($CDCl_3$) δ 7.61 (br, 1H), 7.20 (t, 1H, J = 7.9 Hz), 7.12 (t, 1H, J = 8.1 Hz), 6.88 (br, 1H), 6.60 (m, 3H), 6.57 (dd, 1H, J = 8.3, 2.1 Hz), 6.47 (br, 1H), 3.78 (s, 3H), 3.73 (s, 6H), 3.60–3.80 (m, 2H), 2.94 (m, 2H), 2.37 (s, 6H), 2.25–2.50 (m, 3H), 2.03 (m, 2H), 1.60–1.85 (m, 4H), 1.40–1.60 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 166.0, 159.6, 152.5, 149.2, 147.7, 130.2, 129.5, 119.5, 115.8, 113.1, 112.2, 111.1, 109.7, 108.8, 63.6, 55.2, 54.2, 51.8, 42.5, 32.8, 25.4, and 18.0. Anal. calcd for $C_{32}H_{41}N_5O_5S$ $0.64CH_2Cl_2 \cdot 1.31H_2O$: C, 57.17; H, 6.60; N, 10.21. Found: C, 57.07; H, 6.19; N, 10.22.

2e: **7a** (500 mg, 1.4 mmol) was refluxed with 4-cyclohexyl-1-piperazine-1-propanamine[3] (345 mg, 1.5 mmol) in 8 mL of benzene for 2 h. Chromatographic purification (silica gel, 100% CH_2Cl_2 first, followed by 10% v/v MeOH in CH_2Cl_2) of the residue after concentration in vacuo gave **2e** as a yellow foam (752 mg, 92%); ^{1}H NMR ($CDCl_3$) δ 7.63 (br, 1H), 7.11 (t, 1H, J = 8.0 Hz), 6.85 (br, 1H), 6.72 (br, 1H), 6.60 (d, 1H, J = 8.2 Hz), 6.56 (dd, 1H, J = 8.3, 2.2 Hz), 6.45 (br, 1H), 3.75 (s, 6H), 3.65 (m, 2H), 2.40 (s, 6H), 2.31 (t, 2H, J = 6.6 Hz), 2.20–2.60 (m, 8H), 2.16 (m, 1H), 1.50–1.95 (m, 7H), 1.00–1.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 165.9, 152.5, 149.2, 130.1, 112.0, 108.8, 63.6, 53.2, 51.9, 48.7, 29.0, 26.2, 25.8, 25.3, and 18.0. Anal. calcd for $C_{30}H_{44}N_6O_4S$ $0.58H_2O$: C, 60.54; H, 7.65; N, 14.12. Found: C, 60.53; H, 7.64; N, 13.57.

2f: **6a** (150 mg, 0.47 mmol) was slowly added into a mixture of 1,1′-carbonyldiimidazole (117 mg, 0.72 mmol) and triethyl-amine (145 mg, 1.44 mmol) in 5 mL of DMF and the reaction mixture was stirred for 60 min. 4-(3-Methoxyphenyl)-piperidine-1-propanamine[3] (176 mg, 0.69 mmol) was added into the reaction mixture, and the reaction was stirred at room temperature for 30 min. DMF was removed in vacuo and the residue was purified by chromatography (silica gel, 10% v/v MeOH in CH_2Cl_2 first, followed by 2 M ammonia in MeOH) to give **2f** as an orange foam (200 mg, 72%); ^{1}H NMR ($CDCl_3$) δ 7.55 (br, 1H), 7.35 (br, 1H), 7.20 (t, 1H, J = 7.6 Hz), 6.92 (t, 1H, J = 8.1 Hz), 6.60–6.80 (m, 4H), 6.54 (d, 1H, J = 7.6 Hz), 6.32 (dd, 1H, J = 8.2, 2.0 Hz), 5.99 (br, 1H), 3.77 (s, 3H), 3.71 (s, 6H), 3.16 (m, 2H), 3.03 (m, 2H), 2.46 (m, 3H), 2.29 (s, 6H), 1.95–2.20 (m, 2H), 1.60–1.90 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 166.6, 159.7, 156.8, 151.9, 149.7, 147.4, 139.4, 129.5, 129.2, 119.3, 112.9, 111.4, 108.9, 108.5, 106.1, 56.0, 55.2, 54.1, 51.7, 42.2, 38.6, 32.8, 26.8, and 17.6. Anal. calcd for $C_{32}H_{41}N_5O_6 \cdot 0.27CH_2Cl_2 \cdot 0.51H_2O$: C, 62.13; H, 6.88; N, 11.23. Found: C, 62.04; H, 7.06; N, 11.08.

2g: Likewise **2g** was prepared from **6a** (150 mg, 0.47 mmol) and 4-cyclohexyl-1-piperazine-1-propanamine[3] (160 mg, 0.70 mmol). The desired product was isolated as an orange foam (210 mg, 78%); ^{1}H NMR ($CDCl_3$) δ 7.20 (br, 1H), 7.00 (t, 1H, J = 8.0 Hz), 6.87 (br, 1H), 6.68 (d, 1H, J = 7.7 Hz), 6.59 (m, 1H), 6.39 (dd, 1H, J = 8.1, 2.3 Hz), 3.75 (s, 6H), 3.19 (m, 2H), 2.36 (s, 6H), 2.29–2.70 (m, 10H), 2.21 (m, 1H), 1.50–1.95 (m, 7H), 0.95–1.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 159.2, 108.8, 63.5, 56.4, 53.6, 49.0, 39.8, 29.0, 26.7, 26.3, 25.9, and 17.8. Anal. calcd for $C_{30}H_{44}N_6O_5$ $0.02CH_2Cl_2 \cdot 0.73H_2O$: C, 61.79; H, 7.86; N, 14.40. Found: C, 61.57; H, 8.39; N, 14.73.