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Synthesis and biological evaluation of novel T-type Ca^{2+} channel blockers

Hee Kyung Jung,[a] Munikumar Reddy Doddareddy,[a] Joo Hwan Cha,[a] Hyewhon Rhim,[a] Yong Seo Cho,[a] Hun Yeong Koh,[a] Bong Young Jung[b] and Ae Nim Pae[a,*]

[a]*Lifescience Division, Korea Institute of Science and Technology, PO Box 131, Cheongryang, Seoul 130-650, South Korea*
[b]*Department of Chemistry, Korea University, 1-Anamdong, Seoul 136-701, South Korea*

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Abstract—A small molecule library of piperazinylalkylisoxazole derivatives containing about 600 compounds was designed, synthesized and evaluated for blocking effects on T-type Ca^{2+} channel. Several ligands were identified to possess high inhibitory activity against the T-type Ca^{2+} channel. The compound **21** with trifluoromethyl substituents at C_3-position of phenyl group (R^1) and C_2-position of phenyl group (R^2) showed the highest inhibitory activity with IC_{50} value of 1.02 μM, which is comparable to that of mibefradil.

1. Introduction

Calcium is essential for life and is the most common signal transduction element in cells. The calcium penetrates into plasma membrane ion channel on response to membrane depolarization thereby transmitting the signal.[1] The different subtypes of voltage-dependent Ca^{2+} channels have been extensively investigated and classified into two main classes, one that responds to strong depolarization also called as high voltage activated (HVA) and the other, which responds to weak depolarization also called as low voltage activated (LVA). Based on pharmacological studies, HVA Ca^{2+} channels are again divided into L-, N-, P-, Q- and R-types and LVA Ca^{2+} channel is also called as T-type.[2] L-type (long-lived) and T-type (transient) calcium channels both coexist in neurons, heart, vascular smooth muscle and endocrine cells. The rise of concentration of Ca^{2+} is directly connected to cell death or damage and this is the major causative factor in the progressive and delayed death of nerve cells that occurs in cerebral injury and cerebrovascular diseases.[3,4] The Ca^{2+} channel blockers have been used extensively in the treatment of neuropathic pain, hypertension and angina pectoris. Inhibitors of T-type calcium channel have been also reported to play as antiepileptic drugs.[5] Most of these Ca^{2+} channel blockers interacts predominantly or exclusively with the L-type calcium channel. However, these drugs showed some extent feature of unwanted effects such as negative inotropism, atrioventricular blockade or neurohormonal activation.[6] So recently more attention has been paid on the development of active T-type blockers for the reduction of these side effects.

The calcium channel blockers such as flunarizine,[4b] U-92032,[7] nicardipine[8] and mibefradil,[9] (Fig. 1) have been reported as active T-type Ca^{2+} channel blockers. They generally possess diphenylmethylpiperazine or dihydropyridine moieties as the basic skeleton. Mibefradil, the first marketed selective T-type Ca^{2+} channel blocker, which depends on the cell type blocks T-type Ca^{2+} channels 10–30 times more potently than L-type Ca^{2+} channels. It was finally withdrawn due to its pharmacokinetic interactions with other drugs metabolized by cytochromes P-450 3A4 and 2D6 (antihistamines such as astemizole)[10] So there is an urgent need for the development of active T-type Ca^{2+} channel blockers, which are structurally distinct from existing compounds.

To serve this purpose, we designed a new piperazinylalkylisoxazole scaffold (Fig. 2) and developed a small molecule library containing about 600 compounds. We selected a piperazinylalkyl group, based on

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* Corresponding author. Tel.: +82-295-85185; fax: +82-295-85189; e-mail: author@institute.edu

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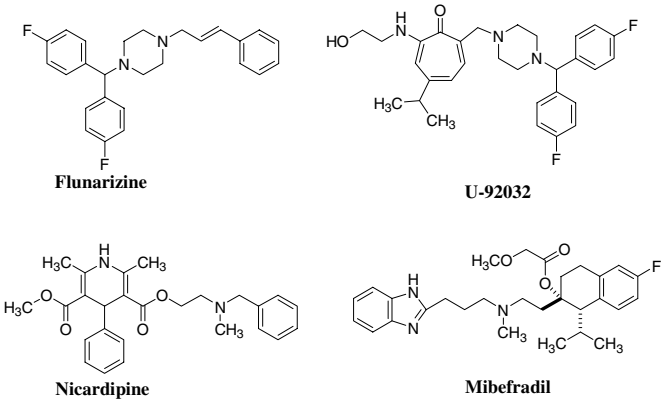
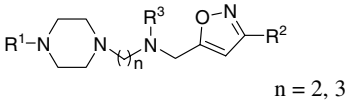


Figure 1. T-type Ca^{2+} calcium channel blockers.



n = 2, 3

8 : R^3 = H
9 : R^3 = Me
10 : R^3 = Et

Figure 2. Piperazinylalkylisoxazole scaffold.

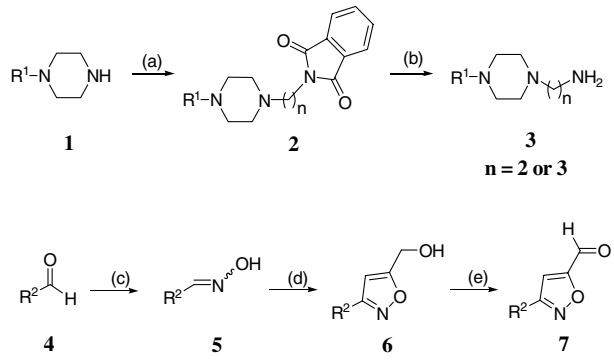
the information available on existing T-type blockers and an isoxazole group as alternative to bioisosteres such as amide,[11] carbonyl,[12] oxygen[13] and heterocycles.[14] A biogenic amine was introduced as a linker between the piperazine group and isoxazole group. Substitutions of R^1 and R^2 on hydrophobic aromatic groups on both sides and length of the alkyl chain ($n = 2$ or 3) gave variation to the library. We designed a synthetic scheme for piperazinylalkylisoxazole library by combination of the substituted phenylpiperazinylalkylamines with the substituted phenylisoxazole aldehydes.

2. Chemistry

The synthetic strategy for obtaining a series of piperazinylalkylisoxazoles was adopted from the solution phase combinatorial synthesis by the reductive amination.[15,16] The preparation of starting materials was outlined in Scheme 1. The phenylalkylpiperazinyl amines were prepared from the commercially available substituted phenylpiperazines **1**. By the reaction of phenylalkylamine **1** using bromoalkylphthalimide and K_2CO_3 in DMF at 80 °C, corresponding piperazinylalkyl phthalimide **2** was obtained after chromatographic purification on silica gel in 50–85% yields.

The treatment of hydrazine on piperazinylphthalimide **2** in ethanol at 70 °C gave phenylethyl(propyl)piperazinyl ethyl (or propyl) amines **3** in 85–99% yield (Scheme 1).

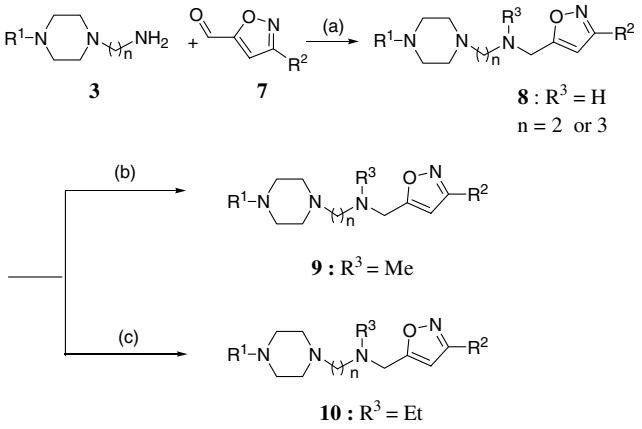
The phenylalkylisoxazole aldehydes **7** for the reductive amination were prepared from the substituted phenyl-



Scheme 1. Reagents and conditions: (a) bromoethylphthalimide (for $n = 2$) or, bromopropylphthalimide (for $n = 3$) K_2CO_3, DMF, 80 °C 2 h, 50–85%; (b) hydrizine, EtOH, 70 °C, 5 h, 85–99%; (c) $NH_2OH{\cdot}HCl$, Na_2CO_3, 60 °C EtOH/H_2O (2/1), 1 h, 90–100%; (d) pyridine (cat.), NCS, 60 °C, THF, 0.5 h, then 3-propynol, Et_3N, 50 °C, rt, 2 h, 60–90%; (e) PCC, silica gel, CH_2Cl_2, 5 h, 50–95%.

aldehydes **4**. Reaction of hydroxylamine·HCl with aldehydes **4** in ethanolic aqueous solution (EtOH/H_2O = 2/1) gave the corresponding oximes **5** in 90–100% yields. The 1,3-dipolar cycloaddition reaction of oximes **5** and 3-propyn-1-ol using NCS (N-chlorosuccinimide) and pyridine provided substituted isoxazolyl methanols **6** in 60–90% yields. The oxidation of alcohols **6** with PCC/SiO_2 in CH_2Cl_2 gave corresponding aldehydes **7** in 50–95% yields (Scheme 1).

The final step of the synthesis was accomplished by the reductive amination[17] of the prepared primary amines **3** with aldehydes **7** using $NaBH(OAc)_3$ as shown in Scheme 2. To a solution of amines **3** and aldehydes **7** in CH_2Cl_2 were added $NaBH(OAc)_3$ (3 equiv) and molecular sieves (four beads). The reaction mixture was stirred for 1 h at room temperature, quenched with saturated sodium bicarbonate solution and extracted with CH_2Cl_2. Subsequent chromatographic purification on silica gel gave the product **8** in 60–90% yields. Tertiary amines **9** and **10** were prepared from the secondary amine **8** by the reductive amination once again. The reaction of compound **8** with formaldehyde and $NaBH(OAc)_3$ in CH_2Cl_2 at room temperature gave the product **9** (R^3 = methyl) in 90% to quantitative yields.



Scheme 2. Reagents and conditions: (a) $NaBH(OAc)_3$ (3 equiv), molecular sieves (four beads), CH_2Cl_2, rt, 1 h, 60–90%; (b) formaldehyde, $NaBH(OAc)_3$ (3 equiv), 4 A molecular sieves, CH_2Cl_2, rt, 1 h, 90%∼quant.; (c) acetaldehyde, $NaBH(OAc)_3$ (3 equiv), molecular sieves, CH_2Cl_2, rt, 1 h, 90%∼quant.

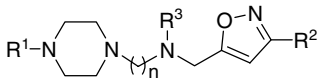
Compound **10** (R^3 = ethyl) was obtained from reductive amination using acetaldehyde. All the prepared compounds were characterized by ^1H NMR, ^{13}C NMR, HPLC, IR and HRMS methods.

3. Results and discussion

The biological activities of the generated phenylpiperazinylalkylisoxazole analogues were evaluated in vitro for the inhibition of T-type Ca^{2+} current as IC_{50} values on HEK 293 cell with stabilized α1G T-type calcium channel.

The activities of 44 selected compounds were shown in Table 1. The activities of this class of compounds for the T-type Ca^{2+} channel inhibition were largely dependent on substitution pattern on phenyl groups of R^1 and R^2. Generally the compounds with shorter chain length ($n = 2$) and with secondary amine group ($R^3 = H$) showed higher activity than their corresponding analogues with longer chain length ($n = 3$) and tertiary amine group (R^3 = methyl or ethyl). Compound **21** with trifluoromethyl groups at 3-position of phenyl group (R^1 = **e**) and at 2-position of phenyl group (R^2 = **m**) showed highest IC_{50} value of 1.02 μM. 2,4-Dimethylphenylpiperazine (R^1 = **f**) analogues showed higher activity (**24** and **25**) than mono methylphenylpiperazine (R^1 = **i**) analogues (**32** and **33**). Compounds **13**, **15** and **41** with less hydrophobic groups like *p*-methoxyphenyl, pyridine and pyrimidine showed lower activity. The cyano group substitution in piperazine ring drastically decreased the activity (**17**). Whereas in case of substitutions on isoxazole side phenyl ring (R^2), 2-methoxy group (R^2 = **l**), 2-trifluoromethyl group[18] (R^2 = **m**), 2, 3-dimethoxy groups (R^2 = **n**) and 2-nitro group (R^2 = **r**), which all act as hydrogen bond acceptors showed good inhibitory activity. From above observations we suggest that hydrogen bond accepting group of the phenyl ring (R^2) at 2-position of isoxazole side is very important for T-type Ca^{2+} channel blocking activity in this class of compounds. Whereas hydrogen bond acceptor group at other positions like that in substituents **k**, **q** and **t** showed lower activity than when it was present in 2-position. Bulkier substituents like *p*-benzyloxy group (R^2 = **t**) decreased the activity (**38**). Compounds with secondary amine group ($R^3 = H$) showed higher activity than their methyl or ethyl analogues with very few exceptions like compounds **26** and **43**. Compounds **51**,

Table 1. IC_{50} values of selected compounds



Compds	*n*	Substituent[b]			IC_{50} (μM[a])
		R^1	R^2	R^3	
11	2	**a**	**l**	H	7.49
12	2	**a**	**m**	H	25.49
13	2	**b**	**l**	H	33.48
14	2	**b**	**m**	H	11.20
15	2	**c**	**l**	H	53.2
16	2	**c**	**l**	H	8.24
17	2	**d**	**l**	H	75.79
18	2	**d**	**m**	H	3.04
19	2	**e**	**k**	H	2.98
20	2	**e**	**l**	H	2.04
21	2	**e**	**m**	H	1.02
22	2	**e**	**n**	H	3.33
23	2	**e**	**r**	H	3.06
24	2	**f**	**l**	H	2.02
25	2	**f**	**m**	H	1.53
26	2	**g**	**l**	H	10.41
27	2	**g**	**m**	H	2.54
28	2	**g**	**r**	H	9.26
29	2	**h**	**k**	H	19.13
30	2	**h**	**l**	H	5.82
31	2	**i**	**k**	H	7.62
32	2	**i**	**l**	H	8.19
33	2	**i**	**m**	H	2.51
34	2	**i**	**n**	H	4.08
35	2	**i**	**o**	H	7.55
36	2	**i**	**q**	H	3.03
37	2	**i**	**r**	H	4.82
38	2	**i**	**t**	H	23.86
39	2	**i**	**p**	H	8.46
40	2	**i**	**s**	H	7.48
41	2	**j**	**l**	H	60.54
42	2	**j**	**m**	H	8.82
43	2	**g**	**l**	Me	4.36
44	2	**h**	**k**	Me	5.49
45	2	**h**	**l**	Me	10.71
46	2	**h**	**m**	Me	4.21
47	2	**j**	**m**	Me	10.56
48	2	**e**	**n**	Et	8.18
49	2	**j**	**m**	Et	18.00
50	2	**j**	**n**	Et	7.01
51	3	**e**	**m**	H	2.71
52	3	**f**	**l**	H	1.55
53	3	**f**	**m**	H	4.17
54	3	**i**	**m**	H	4.75
Mibefradil					0.84

[a] IC_{50} values on HEK 293 cell with stabilized α1G T-type calcium channel.

[b] see Figure 3 for structures.

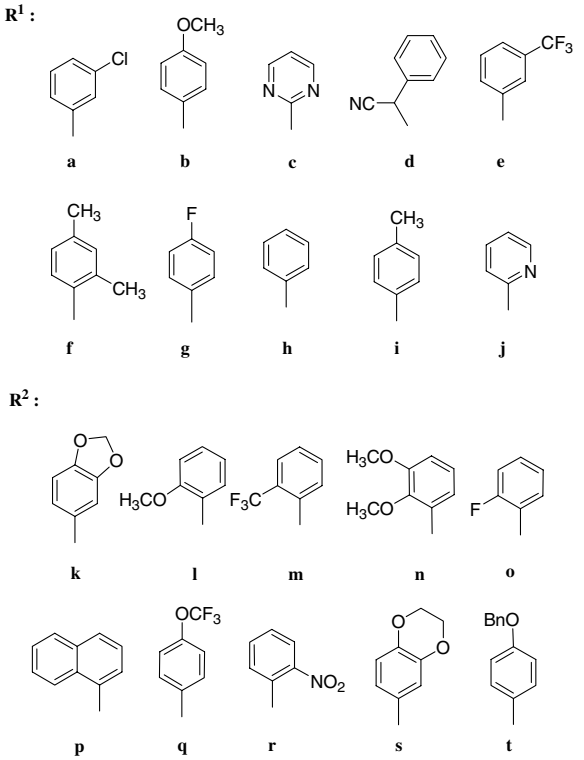


Figure 3. Aromatic substituents R^1; piparazinyl side phenyl ring, R^2; isoxazolyl side phenylring.

53 and **54** with longer chain length ($n = 3$) showed lower activity when compared to the corresponding analogues **21**, **25** and **33** with shorter chain length ($n = 2$). In general, compounds with hydrophobic substituents like 3-trifluoromethyl group ($R^1 =$ **e**) on R^1 and hydrogen bond acceptor groups like methoxy, trifluoromethyl and nitro groups ($R^2 =$ **l**, **m** and **r**) at 2-position of R^2, with shorter chain length ($n = 2$) showed appreciable T-type Ca^{2+} channel blocking activity.

4. Conclusions

A small molecule library of piperazinylalkylisoxazole derivatives containing about 600 compounds was designed, synthesized and evaluated for blocking effects on T-type Ca^{2+} channel. Among them, four compounds (**20**, **21**, **25** and **52**) showed high T-type calcium channel blocking activity.

5. Experimental

All the commercially available reagents were obtained from Aldrich, Fluka, and generally used without further purification. Anhydrous procedures were performed with purified solvents. Reaction was performed under nitrogen atmosphere. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Gemini 300 and Bruker Advance 300 spectrometers. Nuclear magnetic resonance spectra were acquired at 300 (or 200) MHz for ^{1}H, and 75 MHz for ^{13}C NMR. Infrared spectra were obtained on a Perkin Elmer 16FPC FT-IR spectrometer using KBr pellet, $CHCl_3$ or neat. GC/MSD was obtained on a Hewlett Packard 5890. HRMS spectra were obtained on a JMS-700 mass spectrometer (Jeol). Analytical thin layer chromatographies (TLC) were carried out on precoated silica gel plates (Merck Kieselgel 60F254, layer thickness 0.25 mm). Flash column chromatographies were conducted with silica gel grade 230–400 mesh (Merck Kiesegel 60 Art 9385).

5.1. 5-[4-(2-Trifluoromethylphenyl)-piperazin-1-yl-ethylamino methyl]-3-(2-methoxyphenyl)-isoxazole (20)

To a solution of 2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethylamine (50.0 mg, 0.183 mmol) and 3-(2-methoxyphenyl)-isoxazole-5-carbaldehyde (37.5 mg, 0.183 mmol) in CH_2Cl_2 (5 mL) was added $NaBH(OAc)_3$ (154.8 mg, 0.730 mmol) and molecular sieves (four beads) at room temperature. After stirring for 1 h, the reaction mixture was quenched with a saturated sodium bicarbonate solution and extracted with CH_2Cl_2 (5 mL × 3). The collected organic layer was washed with brine, dried over anhydrous $MgSO_4$, evaporated and purified by column chromatography (EtOAc/MeOH = 10:1) to give the product **20** (60.0 mg, 71.2%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (m, 1H), δ 7.44 (m, 2H), δ 7.06 (m, 5H), δ 6.70 (s, 1H), δ 4.03 (s, 2H), δ 3.91 (m, 3H), δ 3.26 (m, 4H), δ 2.84 (m, 2H), δ 2.63 (m, 6H). IR (KBr, cm^{-1}): 2822, 1606, 1450, 1314, 1250, 1162, 1118, 758. ^{13}C NMR (75 MHz, $CDCl_3$): 171.0, 160.9, 157.6, 151.7, 135.0, 131.6, 129.9, 121.3, 119.1, 116.2, 112.6, 111.8, 103.9 57.9, 55.9, 53.3, 49.0, 45.8, 45.4. HRMS (FAB, M+H): Cacld for $C_{24}H_{28}F_3N_4O_2$ 461.2164, found 461.2178.

5.2. 5-[4-(2-Trifluoromethylphenyl)-piperazin-1-yl-ethylamino methyl]-3-(2-trifluoromethylphenyl)-isoxazole (21)

To a solution of 2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl] ethylamine (56.7 mg, 0.207 mmol) and 3-(2-trifluoromethyl-phenyl)-isoxazole-5-carbaldehyde (50.0 mg, 0.207 mmol) in CH_2Cl_2 (5 mL) was added $NaBH(OAc)_3$ (131.8 mg, 0.622 mmol) and molecular sieves (four beads) at room temperature. After stirring for 1 h, the reaction mixture was quenched with a saturated sodium bicarbonate solution and extracted with CH_2Cl_2 (5 mL × 3). The collected organic layer was washed with brine, dried over anhydrous $MgSO_4$, evaporated and purified by column chromatography (EtOAc/MeOH = 10:1) to give the product **21** (92.0 mg, 89.1%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (m, 1H), δ 7.54 (m, 3H), δ 7.24 (m, 1H), δ 6.98 (m, 3H), δ 6.30 (s, 1H), δ 3.95 (s, 2H), δ 3.15 (m, 4H), δ 2.72 (m, 2H), δ 2.50 (m, 6H). IR (KBr, cm^{-1}): 2822, 1450, 1316, 1166, 1124, 768. ^{13}C NMR (75 MHz, $CDCl_3$): 171.9, 161.8, 151.7, 132.3, 132.1, 130.1, 129.9, 129.4, 129.0, 128.8, 126.9, 126.8, 119.1, 116.1, 112.5, 103.8, 57.9, 53.3, 49.0, 45.7, 45.2. HRMS (FAB, M+H): Cacld for $C_{24}H_{25}F_6N_4O$ 499.1933, found 499.1932.

5.3. 5-[4-(2,4-Dimethylphenyl)-piperazin-1-yl-ethylamino methyl]-3-(2-trifluoromethylphenyl)-isoxazole (25)

To a solution of 2-[4-(2,4-dimethyl-phenyl)-piperazin-1-yl]-ethylamine (48.3 mg, 0.207 mmol) and 3-(2-trifluoromethyl-phenyl)-isoxazole-5-carbaldehyde (50.0 mg, 0.207 mmol) in CH_2Cl_2 (5 mL) was added $NaBH(OAc)_3$ (131.8 mg, 0.642 mmol) and molecular sieves (four beads) at room temperature. After stirring for 1 h, the reaction mixture was quenched with a saturated sodium bicarbonate solution and extracted with CH_2Cl_2 (5 mL × 3). The collected organic layer was washed with brine, dried over anhydrous $MgSO_4$, evaporated and purified by column chromatography (EtOAc/MeOH = 10:1) to give the product **25** (88.0 mg, 92.7%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (m, 1H), δ 7.54 (m, 3H), δ 6.87 (m, 3H), δ 6.31 (s, 1H), δ 3.95 (s, 2H), δ 2.75 (m, 6H), δ 2.51 (m, 6H), δ 2.18 (s, 6H). IR (KBr, cm^{-1}): 2938, 2816, 1504, 1456, 1374, 1316, 1176, 1130, 770. ^{13}C NMR (75 MHz, $CDCl_3$): 172.0, 161.8, 149.3, 133.0, 132.9, 132.3, 132.2, 132.1, 130.0, 127.4, 126.9, 126.8, 119.4, 103.8, 58.0, 54.1, 52.1, 45.8, 45.3, 21.1, 18.0. HRMS (FAB, M+H): Cacld for $C_{25}H_{30}F_3N_4O$ 459.2372, found 459.2361.

5.4. 5-[4-(2,4-Dimethylphenyl)-piperazin-1-yl-ethylamino methyl]-3-(2-methoxyphenyl)-isoxazole (52)

To a solution of 3-[4-(2,4-dimethyl-phenyl)-piperazin-1-yl]-propylamine (120.0 mg, 0.485 mmol) and 3-(2-methoxy-phenyl)-isoxazole-5-carbaldehyde (99.6 mg, 0.485 mmol) in CH_2Cl_2 (5 mL) was added $NaBH(OAc)_3$ (308.5 mg, 1.455 mmol) and molecular sieves (four beads) at room temperature. After stirring for 1 h, the reaction mixture was quenched with a saturated sodium bicarbonate solution and extracted with CH_2Cl_2 (5 mL × 3). The collected organic layer was washed with brine, dried over anhydrous $MgSO_4$, evaporated and purified by column chromatography (EtOAc/MeOH = 10:1) to give the product **52** (123.0 mg, 58.5%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (m, 1H), δ 7.42 (m, 1H), δ 6.97 (m, 5H), δ 6.70 (s, 1H), δ 3.99 (s, 2H), δ 3.87 (s, 3H), δ 2.91 (m, 4H), δ 2.79 (m, 2H), δ 2.62 (m, 4H), δ 2.51 (m, 2H), δ 2.28 (m, 6H), δ 1.78 (m, 2H). IR (KBr, cm^{-1}): 2957, 2812, 1604, 1504, 1470, 1376, 1250, 1116, 1024, 756. ^{13}C NMR (75 MHz, $CDCl_3$): 170.8, 160.4, 157.6, 149.3, 133.0, 132.9, 132.1, 131.6, 129.9, 127.4, 121.3, 119.4, 111.8, 104.0, 57.4, 55.9, 54.2, 52.2, 48.6, 45.3, 26.8, 21.1, 18.1. HRMS (FAB, M+H): Cacld for $C_{26}H_{35}N_4O_2$ 435.2760, found 435.2760.

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