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Synthesis and Biological Evaluation of 1-Heteroarylmethyl 1,4-Diazepanes Derivatives as Potential T-type Calcium Channel Blockers†

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The synthesis and biological evaluation of 1-heteroarylmethyl 1,4-diazepane derivatives as potential T-type calcium channel blockers is described. In this study, we have identified the compound **21i** exhibiting the most potent T-type calcium channel blocking activity with IC_{50} value of 0.20 μM, which is superior to that of mibefradil.

Key Words : T-type calcium channel blockers, 1,4-Diazepanes, Heteroaromatic compounds, FDSS6000 assay, Patch-clamp assay

Introduction

Calcium ion plays a crucial role in signal transduction pathway in cells. An increase of the calcium ion concentration initiates a wide range of physiological processes, such as muscle contraction, synaptic plasticity, gene expression, and secretion of hormones or neurotransmitters.[1] Voltage-dependent calcium channels (VDCCs) are a class of transmembrane ion channels that allow calcium ion influx into cells by activation at depolarized membrane potentials.[2] They are divided into three main categories based on sequence homology of the pore-forming α1 subunit, voltage gating and pharmacology: $Ca_v1.x$ (L-type); $Ca_v2.x$ (N, P/Q, R-type); and $Ca_v3.x$ (T-type). The T-type or low-voltage activated (LVA) calcium channels regulate the excitability of neuronal cells via unique activation kinetics by a weak depolarization near the resting membrane potential. There are three different genes for the α_1 subunit of T type calcium channels termed α_{1G}, α_{1H}, and α_{1I} respectively with distinct functional and pharmacological profiles. The α_{1H} subtype is widely distributed in both peripheral and central tissues while the α_{1G} and α_{1H} subtypes are primarily expressed in CNS neurons. Recent studies revealed that the T-type calcium channels are involved in many potential therapeutical indications such as hypertension, epilepsy, pain, movement disorders, and cancer.[3] T-type calcium channels are primarily distributed in the thalamus and cortex regions of the brain and play an important role in the generation of neuropathic pain. Therefore, T-type calcium channels may be considered as a novel therapeutic target for treatment of allodynia and hyperalgesia.

Since many researchers investigated the fundamental function of T-type calcium channels in disease states related to CNS disorders, several T-type calcium channel blockers have been reported as described in Fig. 1.[4] Among them, mibefradil (Posicor, Hoffman-La Roche), an anti-hypertensive agent, was initially described as the first selective T-type calcium channel blocker. However, it was withdrawn from the US market in 1998 due to drug-drug interaction with the cytochrome P-450 3A4 enzyme.[5] In fact, it turned out that its effects on cardiovascular function likely resulted from L-type calcium channel blockade. We have recently designed and synthesized potent T-type small molecule inhibitors having good in vitro efficacies. Indeed, we found that homopiperazine derivatives demonstrated good inhibitory activities against T-type calcium channel comparable to that of mibefradil.[6] In connection with this result along with our previous study, we assume that 4 features pharmacophore

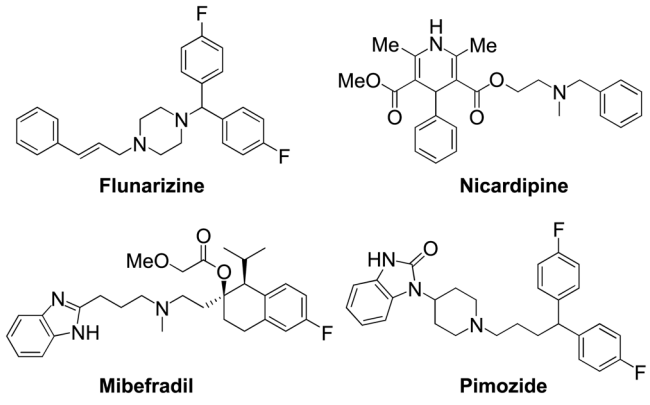


Figure 1. Representative T-type calcium channel blockers.

†This paper is dedicated to Professor Eun Lee on the occasion of his honourable retirement.

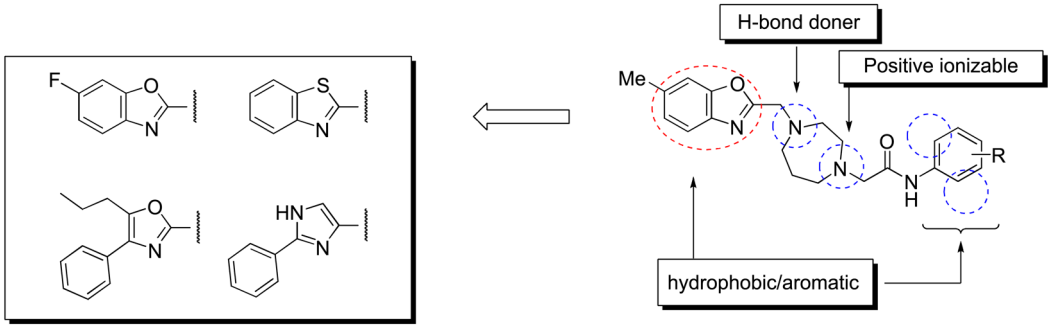
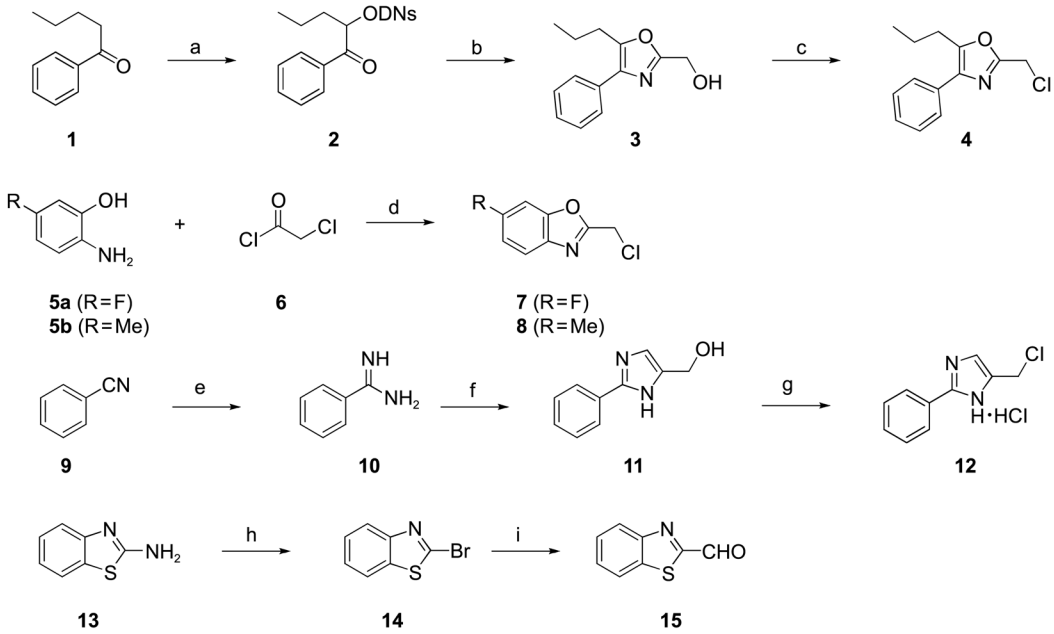


Figure 2. Design of 1-heteroarylmethyl 1,4-diazepanes as T-type calcium channel blockers.



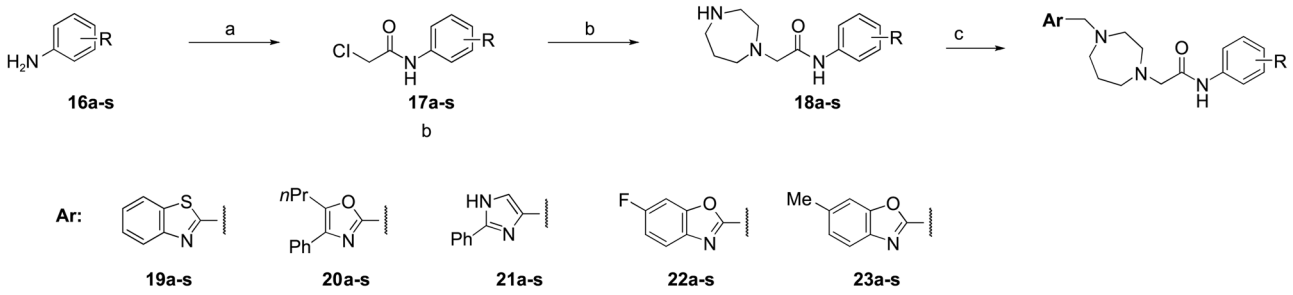
Scheme 1. Reagents and conditions: (a) Ph(I)(OH)ODNs, CH_3CN, reflux, 70%; (b) glycoamide, CH_3CN, reflux, 50%; (c) $SOCl_2$, benzotriazole, 70%; (d) diphenyl ether, 180 °C, 59% (R = Me) or AcOH, μW, 180 °C, 80% (R = F); (e) HMDS, *n*BuLi, Et_2O, 0 °C, 80%; (f) dihydroxyacetone, NH_4Cl, NH_4OH, THF, 80 °C, 70%; (g) $SOCl_2$, CH_2Cl_2, reflux, 95%; (h) $NaNO_2$, CuBr, HBr, CH_3CN, 72%; (i) *n*BuLi, DMF, Et_2O, −78 °C, 70%.

model, which was previously established by CATALYST program,[7] is still effective, but it is necessary to tune the hydrophobic region to increase an inhibitory activity against T-type calcium channel. Thus, we decided to explore the various heteroaromatic component attached to 1,4-diazepane to realize this purpose (Fig. 2). Herein, we describe the optimization of 1,4-diazepanes derivatives as we sought to identify another distinct T-type calcium channel blocker as a potential lead compound.

Results and Discussion

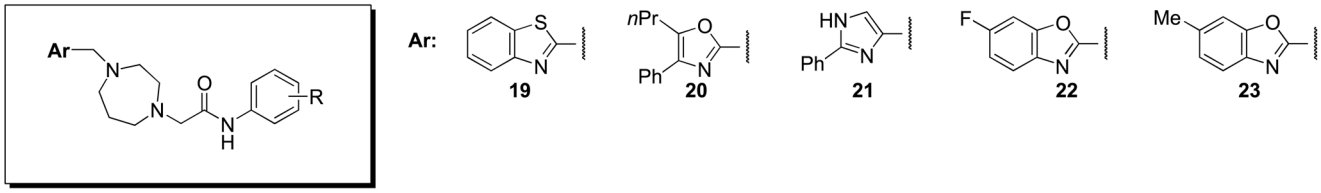
In order to introduce various heteroaromatic ring systems to our target scaffold, we began with synthesis of heteroaromatic compounds having halomethyl or carbonyl groups as activating functional groups (Scheme 1). At first, 2,4,5-trisubstituted oxazole derivative **4** was easily prepared from valerophenone **1** by transformation to hypervalent iodine (III) sulfonate followed by oxazole formation and chlorination.[8] The reaction of chloroacetyl chloride with 2-hydroxy anilines **5a** and **5b** gave 2-chloromethyl benzoxazoles **7** and **8** in 59% and 80% yields respectively. 4-Chloromethyl 2-phenyl-imdidazole **12** was obtained in three step sequences; 1) addition of lithium hexamethylsilazide to benzonitrile **9**, 2) condensation of the corresponding imidamide **10** with dihydroxyketone, and 3) chlorination reaction.[9] We also synthesize benzothiazole **15** in good yield by utilizing the Sandmeyer reaction of 2-aminobenzothiazole and subsequent formylation of the resulting bromobenzothiazole **14**.

With these heteroaromatic compounds in hand, we have achieved the synthesis of a library of 1,4-diazepane derivatives depicted in Scheme 2. A series of chloroacetamides **17a-s** were initially Synthesized by the reaction of anilines **16a-s** with chloroacetyl chloride. S_N2 displacement reaction of **17a-s** with a large excess of 1,4-diazepane afforded the amines **18a-s**. Coupling reactions of these 1,4-diazepane



Scheme 2. Reagents and conditions: (a) chloroacetyl chloride, CH_2Cl_2, 0 to 23 °C, 79~99%; (b) 1,4-diazepane, CH_2Cl_2, 0 °C, 75~85%; (c) iPr$_2$NEt, ArCH$_2$Cl, DMF, 60 °C (in case of **20-23**) or ArCHO, NaBH (OAc)$_3$, MeOH (in case of **19**).

Table 1. *In vitro* T-type calcium channel blocking activity of 1,4-diazepane derivatives using FDSS6000 HTS system[a]



Entry	Code	**R** group	% Inhibition against α_{1G} in HEK293 cell (10 μM)				
			19	**20**	**21**	**22**	**23**
1	**a**	2,6-dimethyl	75.89	56.12	56.00	71.96	66.71
2	**b**	2,4-dimethyl	47.83	33.17	50.80	41.26	56.01
3	**c**	3,4-dimethyl	52.61	31.08	60.11	62.66	70.83
4	**d**	2,6-dimethyl	41.48	64.36	22.29	40.55	47.20
5	**e**	2-F	33.12	58.76	66.51	48.87	48.02
6	**f**	3-F	46.70	55.65	61.72	56.33	61.38
7	**g**	4-F	58.66	61.17	64.25	52.84	62.20
8	**h**	2-Cl	34.35	8.52	52.08	35.95	47.54
9	**i**	3-Cl	38.04	23.32	63.71	53.43	51.99
10	**j**	4-Cl	50.03	22.79	66.15	60.12	59.56
11	**k**	2-CH_3	48.05	44.36	41.68	33.56	46.98
12	**l**	3-CH_3	54.59	38.30	60.72	60.01	78.92
13	**m**	4-CH_3	49.50	44.24	50.92	57.27	63.66
14	**n**	2-OCH_3	40.70	72.08	41.77	42.15	47.54
15	**o**	3-OCH_3	51.86	76.72	59.17	49.78	41.90
16	**p**	4-OCH_3	48.24	75.77	49.50	44.79	46.25
17	**q**	2-CF_3	32.49	72.93	51.91	34.01	32.59
18	**r**	3-CF_3	39.91	31.12	69.16	61.06	74.86
19	**s**	4-CF_3	27.46	12.72	73.93	56.82	32.55
Mibefradil			78.92				

[a] % inhibition value was obtained at 10 μM.

derivatives with the previously prepared heteroaromatic components **4**, **7**, **8**, **12**, and **15** were performed by either *N*-alkylation or reductive amination to afford the desired target compounds **19-23** in good to excellent yields.

Next, biological activity of a library of the synthesized compounds **19-23** comprising heteroaromatic rings and substituted phenyl acetamides was evaluated against HEK293 cells which stably express both T-type calcium channel Cav3.1 with α_{1G} subunit and potassium channel Kir2.1.[10] In order to measure the % inhibition of Ca^{2+} current at certain molar concentration, two assay methods were employed: FDSS6000 assay and patch-clamp assay using a single cell. FDSS6000 assay is developed for high-throughput screening and applied to the whole small molecule library. On the other hand, patch-clamp assay is more accurate and sensitive but manually measures Ca^{2+} current one by one. Therefore, we have first screened the synthesized 95 compounds using FDSS6000 assay as a preliminary assay. Then, we have selected the compounds with % inhibition value of over 50%, which were further

screened by patch-clamp assay to obtain IC_{50} values.

The result of in vitro FDSS6000 assay is demonstrated in Table 1. At first, 49 compounds of 1,4-diazepane derivatives with different heteroaromatic moeities showed over 50% inhibitory activities against T-type calcium channel at the concentration of 10 μM. In particular, the compounds **21a-s**, **22a-s** and **23a-s** having phenylimidazole or benzoxazoles exhibited good inhibitory efficacies (only 6 compounds inhibition values are less than 40%) regardless of R groups on the phenylacetamide, which indicated that the electronic natures of R groups in the compounds **21a-s**, **22a-s**, and **23a-s** are not significantly important to affect the T-type calcium channel blockade. On the other hand, biological activities of the compounds **19a-s** are relatively lower than other series of 1,4-diazepane analogues. In case of the compounds **20a-s**, the % inhibition values varied from 12% to 76% depending on R groups. Overall, the effects of the individual heteroaromatic rings on the inhibition of T-type calcium current were not significantly different. However, we found that the phenylimidazole analogues **21e-j** and **21q-s** were more potent than the others comparing the inhibition values of the compounds having the electron withdrawing R groups such as F, Cl and CF_3 (entries 5-10, and 17-19), whereas methylbenzoxazoles or phenyloxazoles showed better channel blocking activities when R groups are the electron donating substituents. In addition, most of the compounds containing the 2-substituted R groups gave lower efficacies compared to those of the 3- or 4-substituted ones, which suggested that steric interaction at the 2-position on the terminal phenyl moiety presumably disturbed aromatic liphophilic interaction between the 2-substitued phenyl derivatives and calcium channel.

According to the preliminary FDSS6000 assay results, the compounds with high % inhibition values (> 50%) were selected and further evaluated against T-type calcium channel to obtain IC_{50} values using patch-clamp assay method. The results are shown in Table 2. The selected 42 compounds show moderate to potent T-type calcium current blocking activity with IC_{50} values from 0.20 to 7.69 μM. Several structure-activity relationships (SAR) were identified from this study. At first, considering biological activities of the compounds showing high efficacies (IC_{50} < 1 μM), a series of 1,4-diazepanes **21** attached to phenylimidazoles were more potent than other series of the compounds. In this series, the SAR was well correlated to the position and nature of subtitituents (entries 14-26). In fact, the T-type calcium channel blocking activities are intensified when the electron withdrawing groups such as F, Cl, and CF_3 are located at the 3- or 4-position of phenyl group (entries 17-18, 20-21, and 25-26). In particular, we observed the highest inhibitory activity with IC_{50} value of 0.20 μM in case of the 1,4-diazepane derivative **21i** containing 3-chloro substituted phenylacetamide. We also found that the benzothiazole analogue **19g** and oxazole analogue **20f** showed the high T-type calcium channel blocking activities within each series. This result is consistent with the fact that the electron-withdrawing groups at the 3- or 4-position of the phenyl ring are significantly important to increase the inhibitory potency. On the other hand, all the selected benzoxazoles except the compound **22r** exhibited IC_{50} values higher than 1 μM, which

Table 2. Inhibitory activities of the selected compounds against T-type calcium channel

Entry	Compound	T-type (α_{1G}) IC_{50}, μM[a]	Entry	Compound	T-type (α_{1G}) IC_{50}, μM[a]
1	**19a**	6.38 ± 2.31	23	**21o**	0.98 ± 0.07
2	**19c**	1.03 ± 0.04	24	**21q**	1.04 ± 0.08
3	**19g**	0.59 ± 0.08	25	**21r**	0.34 ± 0.01
4	**19o**	0.72 ± 0.04	26	**21s**	0.42 ± 0.05
5	**20a**	2.27 ± 1.07	27	**22a**	2.47 ± 0.64
6	**20d**	3.23 ± 0.79	28	**22c**	2.20 ± 0.09
7	**20e**	0.98 ± 0.32	29	**22f**	4.01 ± 0.48
8	**20f**	0.60 ± 0.32	30	**22g**	1.38 ± 0.04
9	**20g**	3.20 ± 1.90	31	**22i**	2.08 ± 0.10
10	**20n**	7.33 ± 2.09	32	**22j**	2.66 ± 0.29
11	**20o**	1.43 ± 1.13	33	**22l**	2.29 ± 0.09
12	**20p**	4.93 ± 0.99	34	**22m**	4.51 ± 0.06
13	**21a**	2.53 ± 0.17	35	**22r**	0.81 ± 0.11
14	**21b**	1.33 ± 0.24	36	**22s**	1.36 ± 0.55
15	**21c**	0.66 ± 0.04	37	**23a**	7.69 ± 0.42
16	**21e**	2.42 ± 0.13	38	**23b**	3.40 ± 0.50
17	**21f**	0.55 ± 0.08	39	**23c**	1.44 ± 0.45
18	**21g**	1.26 ± 0.09	40	**23f**	7.33 ± 0.55
19	**21h**	1.26 ± 0.15	41	**23g**	4.33 ± 0.24
20	**21i**	0.20 ± 0.04	42	**23l**	4.34 ± 0.76
21	**21j**	0.82 ± 0.06	43	Mibefradil	1.34 ± 0.49
22	**21m**	2.25 ± 0.06			

[a]IC_{50} value (± SD) was obtained from a dose-response curve.

imply that the benzoxazole group is not acceptable pharmacophore to improve the inhibitory effect against T-type calcium channel (entries 27-42).

Conclusion

In summary, a new series of 1,4-diazepane derivatives having various heteroaryl rings were synthesized and biologically evaluated to develop novel effective T-type calcium channel blockers. We have synthesized a library of 95 new compounds, which were preliminarily screened by FDSS6000 HTS system. In this event, we found that the compounds having phenylimidazole moiety show relatively higher inhibitory activities against T-type calcium channel compared to other series of the compounds. Moreover, patch-clamp assay of the compounds with % inhibition values higher than 50% turned out that not only the heteroaromatic ring system but also the characteristics of the substituent on phenylacetamide unit have a significant influence on T-type calcium channel blocking activity. At last, we have identified **21i** exhibiting the most potent T-type calcium channel blocking activity, which is superior to that of mibefradil. Further evaluations of the lead compound **21i** regarding selectivity, pharmacokinetics and neuronal analgesic effect is currently in progress.

Experimental Section

1-Oxo-1-phenylpentan-2-yl 2,4-dinitrobenzenesulfonate (2). HDNIB ([Hydroxy-(2,4-dinitrobenzenesulfonyloxy)iodo] benzene, 6.9 g, 14.8 mmol), prepared from the reaction of iodobenzene diacetate and dinitrobenzenesulfonic acid in CH_3CN, and valerophenone **1** (2.1 mL, 11.2 mmol) was dissolved in CH_3CN (50 ml) and the reaction mixture was irradiated at 60 °C for 5 min via microwave (50 W). The mixture was poured into waster (70 mL) and extracted with EtOAc (3 × 60 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (hexane:EtOAc = 5:1) to give 1-oxo-1-phenylpentan-2-yl 2,4-dinitrobenzenesulfonate (2.6 g, 57%) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.64 ~ 8.54 (m, 2H), 8.37 (d, J = 8.7 Hz, 1H), 7.87 ~ 7.84 (m, 2H), 7.68 ~ 7.49 (m, 3H), 6.21 ~ 6.17 (m, 1H), 2.02 ~ 1.95 (m, 2H), 1.60-1.54 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H).

(4-Phenyl-5-propyloxazol-2-yl)methanol (3). The mixture of 1-oxo-1-phenylpentan-2-yl 2,4-dinitrobenzenesulfonate (1.6 g, 3.92 mmol) and glycoamide (0.89 g, 1.18 mmol) in CH_3CN (50 mL) was stirred at 85 °C for 20 h. The reaction was quenched with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane: EtOAc = 4:1) to afford (4-phenyl-5-propyloxazol-2-yl) methanol **3** (579 mg , 68%) as a oil . ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 ~ 7.61 (m, 2H), 7.44 ~ 7.30 (m, 3H), 4.75 (s, 2H), 2.84 (t, J = 7.7 Hz, 2H), 2.60 (bs, 1H), 1.76 (sextet, J = 7.5 Hz, 2H), 1.00 (t, J = 7.4 Hz, 3H).

2-(Chloromethyl)-4-phenyl-5-propyloxazole (4). The mixture of (4-phenyl-5- propyloxazol-2-yl)methanol (1.0 g, 4.60 mmol), thionyl chloride (0.42 mL, 5.80 mmol), and benzotriazole (0.51 mL, 5.80 mmol) was stirred at room temperature for 2 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:EtOAc = 4:1) to give 2-(chloro-methyl)-4-phenyl-5-propyloxazole **4** (716 mg, 66%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 ~ 7.61 (m, 2H), 7.44 ~ 7.32 (m, 3H), 4.63 (s, 2H), 2.87 (t, J = 7.6 Hz, 2H), 1.78 (sextet, J = 7.5 Hz, 2H), 1.01 (t, J = 7.4 Hz, 3H).

2-(Chloromethyl)-6-fluorobenzo[*d*]oxazole (7). 2-Amino-5-fluorophenol **5a** (500 mg, 3.93 mmol), prepared from reduction of 5-fluoro-2nitrophenol by H_2 and Pd/C, was taken in AcOH (2 mL) in a sealed tube and chloroacetyl chloride (666 mg, 5.89 mmol) was added. The reaction mixture was microwave-irradiated at 180 °C, 300 W for 10 min. The reaction mixture was cooled to rt and diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ solution. The organic layer was washed with H_2O (2 × 10 mL), dried over $MgSO_4$, filtered and concentrated. 2-(Chloromethyl)-6-fluorobenzo[*d*]oxazole **7** (580 mg, 80%) was obtained by flash column chromatography on silica gel (hexane:EtOAc = 4:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (dd, 1H, J = 8.8 Hz), 7.30 (dd, 1H, J = 8.0 Hz), 7.15 (dt, 1H, J = 8.8 Hz), 4.74 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.3, 161.3, 159.8, 137.1, 121.0, 113.1, 99.1, 36.2.

2-(Chloromethyl)-6-methylbenzo[*d*]oxazole (8). Following the similar procedure used for the synthesis of 7, the reaction of 2-amino-5-methylphenol (0.8 g, 6.50 mmol) and chloroacetyl chloride (1.04 ml, 13.0 mmol) in diphenyl ether (1.0 g) at 180 °C for 1 h (without microwave-irradiation) gave the title compound **8** (0.70 g, 59%) after purified by column chromatography on silica gel (hexane/EtOAc = 9:1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60 (d, 1H, J = 8.2 Hz), 7.35 (bs, 1H), 7.18 (dd, 1H, J = 8.1, 0.9 Hz, 1H), 4.74 (s, 2H), 2.49 (s, 3H).

Benzimidamide (10). To a solution of 1.1.1.3.3.3-hexamethyldisilane **9** (12 mL, 58.2 mmol) in diethyl ether (100 mL) at 0 °C was added *n*-BuLi (24.2 mL, 2.5 M in hexane, 60.5 mmol). After 10 min, benzonitrile (2.50 g, 24.0 mmol) was added and the reaction mixture was stirred for 1 h and quenched with 1N HCl (120 ml). The solution was washed with H_2O and 6N NaOH (pH > 10), and then extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give the title compound **10** (1.45 g, 50%), which was used for the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (q, 2H, J = 1.38 Hz), 7.49 ~ 7.41 (m, 3H), 4.92 (s, 3H).

(2-Phenyl-1*H*-imidazol-5-yl)methanol (11). An ammonia solution (8 mL) of benzimidamide (0.7 g, 5.83 mmol), 1.3-dihydroxy acetone dimer (1.05 g, 5.83 mmol), and ammonium chloride (1 g) in THF (2 mL) was stirred at 80

°C for 45 min. After completion of the reaction, 1N HCl was added until pH value is 8.6. The mixture was further diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residual oil was purified by column chromatography on silica gel (EtOAc:MeOH = 10:1) to give the title compound (360 mg , 36%) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85~7.83 (m, 2H), 7.44~7.35 (m, 3H), 7.09 (s, 1H), 5.17 (s, 1H), 4.62 (s, 2H).

5-(Chloromethyl)-2-phenyl-1*H*-imidazole hydrochloride (12). To a solution of (2-phenyl-1*H*-imidazol-5-yl)methanol (360 mg, 2.07 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added thionyl chloride (0.45 ml, 6.20 mmol). The reaction mixture was at 45 °C for 90 min and quenched with water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give the title compound (448 mg, 95%), which was used for the next alkylation step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.96 ~ 7.93 (m, 2H), 7.74 ~ 7.66 (m, 4H), 4.87 (s, 2H).

2-Bromobenzothiazole (14). To a solution of 2-aminobenzothiazole **13** (100 mg, 0.67 mmol), sodium nitrite (69 mg, 1.00 mmol), and CuBr (143 mg, 1.00 mmol) in CH_3CN (5 mL) was slowly added hydrobromic acid (133 mL, 0.67 mmol, 30% in acetic acid). The reaction mixture was stirred at room temperature for 3 h and quenched with 5% NaOH solution (20 mL). The solution was extracted with CH_2Cl_2 (3 × 20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude oil was purified by column chromatography on silica gel (hexane/EtOAc = 10:1) to give 2-bromobenzothiazole **14** (103 mg, 72%) as pinkish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (dd, 1H, *J* = 8.0, 0.3 Hz), 7.76 (d, 1H, *J* = 8.0 Hz), 7.46 ~ 7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.3, 138.9, 137.3, 126.6, 125.8, 122.8, 120.9.

Benzo[*d*]thiazole-2-carbaldehyde (15). To a solution of 2-bromobenzothiazole **14** (84.5 mg, 0.40 mmol) in anhydrous Et_2O (4 mL) cooled at −78 °C was added *n*-BuLi (296 μL, 1.6 M in hexane). The resulting solution was stirred at −78 °C for 45 min. After DMF (61 μL, 0.79 mmol) was added, the reaction mixture was stirred at −78 °C for 30 min and then slowly warmed to 25 °C over 2 h. The solution was quenched with water (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine, dried over MgSO4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 20:1) to give the aldehyde **15** (45.3 mg, 70%) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.02 (s, 1H), 8.23 (dd, 1H, *J* = 8.0, 0.9 Hz), 7.99 (dd, 1H, *J* = 8.0, 1.3 Hz), 7.62 ~ 7.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 185.5, 165.3, 153.5, 136.4, 128.4, 127.4, 125.8, 122.7.

General Procedure for Coupling Reaction (the Compounds 19a-s). To a solution of benzothazole-2-carbaldehyde **15** (0.15 mmol) and 1,4 diazepane derivative **18** (0.20 mmol) in CH_2Cl_2 (5 mL) cooled to 0 °C was added $NaBH(OAc)_3$ (0.45 mmol). The reaction mixture was stirred until no starting material was detected by TLC and then quenched with water. The solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 1:1) to afford the compound **19**.

2-(4-(Benzo[*d*]thiazol-2-ylmethyl)-1,4-diazepan-1-yl)-*N*-(2,6-dimethylphenyl)acetamide (19a). The title compound (55 mg, 74%) was obtained from the reaction of **15** (30 mg, 0.18 mmol), **18a** (62 mg, 0.24 mmol) and $NaBH(OAc)_3$ (117 mg, 0.55 mmol) in CH_2Cl_2 (5 mL). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.81 (br s, 1H), 7.96 (d, 1H, *J* = 8.1 Hz), 7.83 (d, 1H, *J* = 7.9 Hz), 7.45 (dd, 1H, *J* = 7.7, 7.5 Hz), 7.36 (dd, 1H, *J* = 7.8, 7.3 Hz), 7.12~7.07 (m, 3H), 4.11 (s, 2H), 3.39 (s, 2H), 3.02~2.91 (m, 8H), 2.24 (s, 6H), 1.94 (quint, 2H, *J* = 5.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.5, 169.3, 153.3, 135.3, 135.1, 133.8, 128.3, 127.2, 125.9, 124.9, 122.8, 121.8, 61.9, 60.8, 57.1, 55.9, 55.2, 54.9, 28.4, 18.7.

2-(4-(Benzo[*d*]thiazol-2-ylmethyl)-1,4-diazepan-1-yl)-*N*-(3,4-dimethylphenyl)acetamide (19c). The title compound (35 mg, 75%) was obtained from the reaction of **15** (20 mg, 0.12 mmol), **18c** (42 mg, 0.16 mmol) and $NaBH(OAc)_3$ (78 mg, 0.37 mmol) in CH_2Cl_2 (5 mL). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.18 (br s, 1H), 7.96 (d, 1H, *J* = 8.1 Hz), 7.87 (d, 1H, *J* = 7.5 Hz), 7.46~7.09 (m, 4H), 7.08 (d, 1H, *J* = 8.1 Hz), 4.12 (s, 2H), 3.30 (s, 2H), 2.96~2.89 (m, 8H), 2.25 (s, 3H), 2.22 (s, 3H), 1.92 (quint, 2H, *J* = 5.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.5, 168.8, 153.3, 137.3, 135.4, 135.3, 132.5, 125.9, 124.9, 122.8, 121.8, 120.7, 116.9, 62.2, 60.8, 56.6, 56.1, 54.91, 54.86, 28.4, 19.9, 19.2.

2-(4-(Benzo[*d*]thiazol-2-ylmethyl)-1,4-diazepan-1-yl)-*N*-(4-fluorophenyl)acetamide (19g). The title compound (45 mg, 91%) was obtained from the reaction of **15** (20 mg, 0.12 mmol), **18g** (40 mg, 0.16 mmol) and $NaBH(OAc)_3$ (78 mg, 0.37 mmol) in CH_2Cl_2 (5 mL). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.30 (br s, 1H), 7.96 (d, 1H, *J* = 8.1 Hz), 7.87 (d, 1H, *J* = 7.9 Hz), 7.57~7.53 (m, 2H), 7.46 (ddd, 1H, *J* = 8.2, 8.2, 1.0 Hz), 7.37 (ddd, 1H, *J* = 8.0, 8.0, 0.9 Hz), 7.01 (dd, 2H, *J* = 8.7, 8.7 Hz), 4.13 (s, 2H), 3.31 (s, 2H), 2.96~2.91 (m, 8H), 1.92 (quint, 2H, *J* = 5.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.2, 169.0, 159.2 ($^1J_{C\text{-}F}$ = 242 Hz), 153.3, 135.3, 133.8, 125.9, 125.0, 122.8, 121.8, 121.0 ($^3J_{C\text{-}F}$ = 7.7 Hz), 115.7 ($^2J_{C\text{-}F}$ = 22.4 Hz), 62.0, 60.8, 56.6, 55.9, 54.9, 54.9, 28.4.

2-(4-(Benzo[*d*]thiazol-2-ylmethyl)-1,4-diazepan-1-yl)-*N*-(4-methoxyphenyl)acetamide (19o). The title compound (63 mg, 93%) was obtained from the reaction of **15** (25 mg, 0.15 mmol), **18o** (52 mg, 0.20 mmol) and $NaBH(OAc)_3$ (97 mg, 0.46 mmol) in CH_2Cl_2 (5 mL). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.30 (br s, 1H), 7.96 (d, 1H, *J* = 8.1 Hz), 7.87 (d, 1H, *J* = 7.9 Hz), 7.48~7.35 (m, 3H), 7.22 (dd, 1H, *J* = 8.1, 8.1 Hz), 7.05 (dd, 1H, *J* = 8.0, 1.1 Hz), 6.67 (dd, 1H, *J* = 8.2, 2.4 Hz), 4.13 (s, 2H) 3.81 (s, 3H), 3.31 (s, 2H), 2.98~2.90 (m, 8H), 1.92 (quint, 2H, *J* = 5.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4, 169.0, 160.2, 153.3, 138.9, 135.3, 129.7, 125.9, 122.8, 121.8, 111.5, 110.0, 105.1, 62.2, 60.8, 56.6, 56.1, 55.3, 54.92, 54.87, 28.4.

General Procedure for Coupling Reaction (the compounds 20-23). 1,4-Diazepane derivative **18** (0.11 mmol) was added to a solution of heteroaromatic compound (0.1 mmol) in DMF (6 mL) containing DIPEA (0.2 mmol). The reaction mixture was stirred at 70 °C for 5 h. The reaction progress was monitored by TLC. After the consumption of heteroaromatic compound, the reaction was quenched by using saturated $NaHCO_3$ solution. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with H_2O (3 × 10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (MeOH/EtOAc=1:1) to afford the corresponding product.

***N*-(2,6-Diethylphenyl)-2-(4-((4-phenyl-5-propyloxazol-2-yl)methyl)-1,4-diazepan-1-yl)acetamide (20a).** The title compound (103 mg, 83%) was obtained from the reaction of **4** (60 mg, 0.254 mmol) and **18a** (96 mg, 0.33 mmol) in DMF (8 mL) in the presence of DIPEA (66 mg, 0.509 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.77 (br s, 1H), 7.63 (d, 2H, *J* = 8.2 Hz), 7.42 (t, 2H, *J* = 1.6 Hz), 7.39~7.19 (m, 2H), 7.12 (d, 2H, *J* = 7.6 Hz), 3.87 (s, 2H), 3.34 (s, 2H), 2.9 (m, 8H), 2.83 (t, 2H, *J* = 7.6 Hz), 2.57 (q, 4H, *J* = 7.6 Hz), 1.9 (quintet, 2H, *J* = 6.0 Hz), 1.73 (q, 2H, *J* = 7.2 Hz), 1.18 (t, 6H, *J* = 7.6 Hz), 0.97 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.0, 159.5, 148.3, 141.1, 134.3, 132.5, 132.3, 128.5, 127.8, 127.3, 126.8, 126.4, 62.2, 56.8, 55.5, 54.9, 54.8, 53.9, 28.0, 27.8, 25.0, 21.5, 14.5, 13.8.

***N*-(2,6-Dimethylphenyl)-2-(4-((4-phenyl-5-propyloxazol-2-yl) methyl)-1,4-diazepan-1-yl)acetamide (20d).** The title compound (80 mg, 68%) was obtained from the reaction of **4** (60 mg, 0.254 mmol) and **18d** (86 mg, 0.33 mmol) in DMF (8 mL) in the presence of DIPEA (66 mg, 0.509 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.76 (bs, 1H), 7.62 (d, 2H, *J* = 7.4 Hz), 7.40 (t, 2H, *J* = 8.0 Hz), 7.31 (d, 1H, *J* = 7.2 Hz), 7.09 (m, 3H), 3.87 (s, 2H), 3.34 (s, 2H), 2.96~2.89 (m, 8H), 2.83 (t, 3H, *J* = 7.6 Hz), 2.2 (s, 6H), 1.91 (quintet, 2H, *J* = 6.0 Hz), 1.74 (q, 2H, *J* = 7.4 Hz), 0.98 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3, 159.5, 148.3, 135.0, 134.3, 133.7, 132.3, 128.5, 128.2, 127.3, 127.1, 126.8, 62.2, 56.6, 55.4, 54.9, 54.8, 53.9, 28.0, 27.8, 21.5, 18.6, 13.8.

***N*-(2-Fluorophenyl)-2-(4-((4-phenyl-5-propyloxazol-2-yl)methyl)-1,4-diazepan-1-yl)acetamide (20e).** The title compound (98 mg, 80%) was obtained from the reaction of **4** (60 mg, 0.254 mmol) and **18e** (83 mg, 0.33 mmol) in DMF (8 mL) in the presence of DIPEA (66 mg, 0.509 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.65 (bs, 1H), 8.89 (t, 1H, *J* = 7.6 Hz), 7.64 (d, 2H, *J* = 8.4 Hz), 7.4 (t, 2H, *J* = 7.6 Hz), 7.3 (d, 1H, *J* = 7.2 Hz), 7.11~7.01 (m, 3H), 3.88 (s, 2H), 3.3 (s, 2H), 2.95~2.83 (m, 10H), 1.92 (quintet, 2H, *J* = 5.8 Hz), 1.76 (q, 2H, *J* = 7.4 Hz), 0.99 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3, 159.5, 153.6, 151.2, 148.3, 134.3, 132.3, 127.2, 126.8, 126.3, 126.1, 124.3, 129.1, 114.8, 62.8, 56.5, 56.3, 55.4, 55.0, 53.6, 28.3, 27.8, 21.5, 13.8.

***N*-(3-Fluorophenyl)-2-(4-((4-phenyl-5-propyloxazol-2-yl)methyl)-1,4-diazepan-1-yl)acetamide (20f).** The title compound (70 mg, 65%) was obtained from the reaction of **4** (60 mg, 0.254 mmol) and **18f** (83 mg, 0.33 mmol) in DMF (8 mL) in the presence of DIPEA (66 mg, 0.509 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.39 (bs, 1H), 7.64 (d, 2H, *J* = 7.2 Hz), 7.54 (d, 1H, *J* = 8.4 Hz), 7.41 (t ,2H, *J* = 7.6 Hz), 7.3~7.17 (m, 3H), 6.77 (d ,1H, *J* = 6.0 Hz), 3.89 (s, 2H), 3.27 (s, 2H), 2.94~2.83 (m, 10H), 1.91 (quintet, 2H, *J* = 6.0 Hz), 1.75 (q, 2H, *J* = 7.6 Hz), 0.99 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3, 164.2, 159.4, 148.3, 139.2, 134.4, 132.2, 130.1, 128.6, 127.3, 126.8, 114.5, 110.8, 106.9, 62.4, 56.0, 55.1, 54.9, 54.8, 54.0, 28.1, 27.8, 21.5, 13.8.

***N*-(4-Fluorophenyl)-2-(4-((4-phenyl-5-propyloxazol-2-yl)methyl)-1,4-diazepan-1-yl)acetamide (20g).** The title compound (60 mg, 52%) was obtained from the reaction of **4** (60 mg, 0.254 mmol) and **18g** (83 mg, 0.33 mmol) in DMF (8 mL) in the presence of DIPEA (66 mg, 0.509 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.3 (bs, 1H), 7.65 (d, 2H, *J* = 8.4 Hz), 7.53 (q, 2H, *J* = 4.4 Hz), 7.42 (t, 2H, *J* = 7.0 Hz), 7.32 (d, 1H, *J* = 7.6 Hz), 6.96 (t, 2H, *J* = 8.8 Hz), 3.9 (s, 2H), 3.27 (s, 2H), 2.94~2.83 (m, 10H), 1.90 (quintet, 2H, *J* = 4.0 Hz), 1.75 (q, 2H, *J* = 7.6 Hz), 0.99 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.0, 160.4, 159.3, 158.0, 148.3, 134.4, 133.7, 132.2, 128.6, 127.3, 126.8, 121.0, 115.7, 115.4, 62.3, 56.0, 55.1, 54.9, 54.8, 53.9, 28.1, 27.8, 21.5, 13.8.

***N*-(2-Methoxyphenyl)-2-(4-((4-phenyl-5-propyloxazol-2-yl)methyl)-1,4-diazepan-1-yl)acetamide (20n).** The title compound (60 mg, 51%) was obtained from the reaction of **4** (60 mg, 0.254 mmol) and **18n** (87 mg, 0.33 mmol) in DMF (8 mL) in the presence of DIPEA (66 mg, 0.509 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.82 (bs, 1H), 8.4 (d, 1H, *J* = 8.0 Hz), 7.64 (d, 2H, *J* = 7.2 Hz), 7.41 (t, 2H, *J* = 7.6 Hz), 7.30 (m, 1H), 7.04~6.96 (m, 2H), 6.87 (d, 1H, *J* = 8.0 Hz), 3.89 (s, 2H), 3.85(s,3H), 3.28 (s, 2H), 2.98~2.83 (m, 10H), 1.93 (quintet, 2H, *J* = 6.0 Hz), 1.76 (q, 2H, *J* = 7.4 Hz), 0.99 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 168.9, 159.5, 148.3, 148.2, 134.4, 132.3, 128.5, 127.4, 127.3, 126.8, 123.6, 121.0, 119.5, 109.9, 63.4, 56.4, 55.8, 55.6, 55.3, 54.6, 53.5, 27.8, 27.7, 21.6, 13.8.

***N*-(3-Methoxyphenyl)-2-(4-((4-phenyl-5-propyloxazol-2-yl)methyl)-1,4-diazepan-1-yl)acetamide (20o).** The title compound (62 mg, 53%) was obtained from the reaction of **4** (60 mg, 0.254 mmol) and homopiperazine derivative (87 mg, 0.33 mmol) in DMF (8 mL) in the presence of DIPEA (66 mg, 0.509 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.29 (bs, 1H), 7.64 (d, 2H, *J* = 8.0 Hz), 7.41 (m, 3H), 7.31 (d ,1H, *J* = 7.6 Hz), 7.16 (t, 1H, *J* = 8.0 Hz), 7.01 (d, 1H, *J* = 1.2 Hz), 6.60 (d ,1H, *J* = 2.0 Hz), 3.89 (s, 2H), 3.80 (s, 3H), 3.26 (s, 3H), 2.94~2.83 (m, 10H), 1.91 (quintet, 2H, *J* = 5.6 Hz), 1.76 (q, 2H, *J* = 7.4 Hz), 0.99 (t, 3H, *J* = 7.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.1, 160.2, 159.3, 148.3, 138.9, 134.4, 132.2, 129.6, 128.6, 127.3, 126.8, 111.5, 109.9, 105.0, 62.5, 56.0, 55.3, 55.0, 54.9, 54.8, 53.9, 28.0, 27.8, 21.5, 13.8.

***N*-(4-Methoxyphenyl)-2-(4-((4-phenyl-5-propyloxazol-2-yl)methyl)-1,4-diazepan-1-yl)acetamide (20p).** The title compound (55 mg, 47%) was obtained from the reaction of **4** (60 mg, 0.254 mmol) and **18p** (96 mg, 0.33 mmol) in DMF (8 mL) in the presence of DIPEA (66 mg, 0.509 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.18 (bs, 1H), 7.64

(d, 2H, *J* = 7.6 Hz), 7.48~7.39 (m, 4H), 7.31 (d, 1H, *J* = 7.2 Hz), 6.82 (d, 2H, *J* = 6.8 Hz), 3.9 (s, 2H), 3.77 (s, 3H), 3.26 (s, 2H), 2.94~2.83 (m, 10H), 1.91 (quintet, 2H, *J* = 5.6 Hz), 1.76 (q, 2H, *J* = 7.4 Hz), 0.99 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.7, 159.3, 156.2, 148.3, 134.4, 132.2, 130.9, 128.6, 127.3, 126.8, 120.9, 114.1, 62.3, 56.01, 55.4, 55.0, 54.7, 53.9, 28.0, 27.86, 21.5, 13.8.

***N*-(2,6-Diethylphenyl)-2-(4-((2-phenyl-1*H*-imidazol-5-yl)methyl)-1,4-diazepan-1-yl)acetamide (21a).** The title compound (73 mg, 94%) was obtained from the reaction of **12** (40 mg, 0.174 mmol) and **18a** (56 mg, 0.192 mmol) in DMF (8 mL) in the presence of DIPEA (45 mg, 0.349 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.0 (bs, 1H), 8.79 (bs, 1H), 7.83 (d, 2H, *J* = 7.6 Hz), 7.39~7.33 (m, 3H), 7.23~7.20 (m, 1H), 7.13 (d, 2H, *J* = 7.6 Hz), 7.0~6.9 (m, 1H), 4.13 (s, 2H), 3.34 (s, 2H), 2.94~2.78 (m, 8H), 2.60 (q, 4H, *J* = 7.6 Hz), 1.88 (quintet, 2H, *J* = 3.2 Hz), 1.20 (t, 6H, *J* = 7.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.0, 141.1, 132.5, 130.2, 128.8, 128.5, 127.8, 126.4, 125.0, 62.3, 56.5, 55.5, 55.1, 54.2, 27.9, 25.0, 14.5.

***N*-(2,4-Dimethylphenyl)-2-(4-((2-phenyl-1*H*-imidazol-5-yl)methyl)-1,4-diazepan-1-yl)acetamide (21b).** The title compound (60 mg, 82%) was obtained from the reaction of **12** (40 mg, 0.174 mmol) and **18b** (50 mg, 0.192 mmol) in DMF (8 mL) in the presence of DIPEA (45 mg, 0.349 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.20 (bs, 1H), 7.90 (d, 2H, *J* = 6.8 Hz), 7.72 (d, 1H, *J* = 8.0 Hz), 7.40~7.32 (m, 3H), 7.10 (s, 1H), 6.99~6.96 (m, 2H), 3.88 (s, 2H), 3.30 (s, 2H), 2.96~2.86 (m, 8H), 2.26 (s, 3H), 2.21 (s, 3H), 1.98 (quintet, 2H, *J* = 5.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.6, 147.3, 134.7, 132.9, 131.1, 130.0, 128.8, 128.7, 127.3, 125.3, 122.6, 62.9, 60.4, 55.4, 54.5, 54.0, 53.3, 26.7, 20.8, 17.9.

***N*-(3,4-Dimethylphenyl)-2-(4-((2-phenyl-1*H*-imidazol-5-yl)methyl)-1,4-diazepan-1-yl)acetamide (21c).** The title compound (55 mg, 75%) was obtained from the reaction of **12** (40 mg, 0.174 mmol) and **18c** (50 mg, 0.192 mmol) in DMF (8 mL) in the presence of DIPEA (45 mg, 0.349 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.21 (bs, 1H), 7.83 (d, 2H, *J* = 7.2 Hz), 7.41~7.27 (m, 5H), 7.06~6.99 (m, 2H), 3.73 (s, 2H), 3.34 (s, 2H), 2.86~2.81 (m, 8H), 2.24 (s, 3H), 2.22 (s, 3H), 1.88 (quintet, 2H, *J* = 5.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.0, 137.3, 135.3, 130.2, 130.0, 128.8, 128.6, 128.2, 125.0, 120.7, 116.9, 62.5, 61.9, 56.6, 55.2, 55.0, 54.2, 27.8, 19.9, 19.2.

***N*-(2-Fluorophenyl)-2-(4-((2-phenyl-1*H*-imidazol-5-yl)methyl)-1,4-diazepan-1-yl)acetamide (21e).** The title compound (70 mg, 98%) was obtained from the reaction of **12** (40 mg, 0.174 mmol) and **18e** (48 mg, 0.192 mmol) in DMF (8 mL) in the presence of DIPEA (45 mg, 0.349 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.69 (bs, 1H), 8.40 (t, 1H, *J* = 8.0 Hz), 7.87 (d, 2H, *J* = 7.6 Hz), 7.35~7.30 (m, 3H), 7.14~7.02 (m, 3H), 6.98 (s, 1H), 3.68 (s, 2H), 3.26 (s, 2H), 2.83~2.77 (m, 8H), 1.86 (quintet, 2H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.4, 153.6, 151.2, 146.7, 130.3, 128.8, 128.4, 126.2, 125.1, 124.6, 124.2, 121.1, 114.9, 62.9, 56.3, 55.6, 55.1, 53.8, 28.0.

***N*-(3-Fluorophenyl)-2-(4-((2-phenyl-1*H*-imidazol-5-yl)methyl)-1,4-diazepan-1-yl)acetamide (21f).** The title compound (40 mg, 56%) was obtained from the reaction of **12** (40 mg, 0.174 mmol) and **18f** (48 mg, 0.192 mmol) in DMF (8 mL) in the presence of DIPEA (45 mg, 0.349 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.43 (bs, 1H), 7.86 (dd, 2H, *J* = 6.6 Hz), 7.59~7.55 (m, 1H), 7.42~7.31 (m, 3H), 7.22 (m, 2H), 6.99 (s, 1H), 6.82~6.76 (m, 1H), 3.47 (s, 2H), 3.26 (s, 2H), 2.85~2.80 (m, 8H), 1.88 (quintet, 2H, *J* = 5.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.6, 164.6, 161.1, 139.2, 130.2, 130.1, 130.0, 128.8, 128.6, 125.0, 114.6, 110.9, 110.6, 107.0, 106.7, 62.5, 60.4, 56.0, 55.1, 54.2, 28.1.

***N*-(4-Fluorophenyl)-2-(4-((2-phenyl-1*H*-imidazol-5-yl)methyl)-1,4-diazepan-1-yl)acetamide (21g).** The title compound (30 mg, 42%) was obtained from the reaction of **12** (40 mg, 0.174 mmol) and **18g** (48 mg, 0.192 mmol) in DMF (8 mL) in the presence of DIPEA (45 mg, 0.349 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.35 (bs, 1H), 7.86 (t, 2H, *J* = 7.2 Hz), 7.57 (dd, 2H, *J* = 8.7 Hz), 7.42~7.32 (m, 3H), 6.98~6.94 (m, 3H), 3.71 (s, 2H), 3.26 (s, 2H), 2.85~2.78 (m, 8H), 1.89 (quintet, 2H, *J* = 5.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.1, 133.8, 130.2, 128.8, 128.6, 125.0, 121.1, 121.0, 115.7, 115.4, 62.5, 60.4, 55.9, 55.2, 55.0, 54.2, 28.2.

***N*-(2-Chlorophenyl)-2-(4-((2-phenyl-1*H*-imidazol-5-yl)methyl)-1,4-diazepan-1-yl)acetamide (21h).** The title compound (69 mg, 93%) was obtained from the reaction of **12** (40 mg, 0.174 mmol) and **18h** (51 mg, 0.192 mmol) in DMF (8 mL) in the presence of DIPEA (45 mg, 0.349 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.97 (bs, 1H), 8.47 (dd, 1H, *J* = 8.0 Hz), 7.86 (d, 2H, *J* = 7.6 Hz), 7.36~7.23 (m, 5H), 7.04 (dt, 1H, *J* = 7.8 Hz), 6.97 (s, 1H), 3.69 (s, 2H), 3.26 (s, 2H), 2.85~2.79 (m, 8H), 1.89 (quintet, 2H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.4, 146.8, 134.5, 130.3, 129.1, 128.8, 128.4, 127.7, 125.2, 124.5, 122.6, 120.9, 63.1, 56.2, 55.3, 53.7, 27.5.

***N*-(3-Chlorophenyl)-2-(4-((2-phenyl-1*H*-imidazol-5-yl)methyl)-1,4-diazepan-1-yl)acetamide (21i).** The title compound (60 mg, 81%) was obtained from the reaction of **12** (40 mg, 0.174 mmol) and **18i** (51 mg, 0.192 mmol) in DMF (8 mL) in the presence of DIPEA (45 mg, 0.349 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.38 (bs, 1H), 7.85~7.83 (m, 2H), 7.71 (t, 2H, *J* = 2.0 Hz), 7.44~7.31 (m, 4H), 7.22 (t, 1H, *J* = 8.4 Hz), 7.07 (d, 1H, *J* = 8.0 Hz), 6.99 (s, 1H), 3.72 (s, 2H), 3.29 (s, 2H), 2.88~2.80 (m, 8H), 1.87 (quintet, 2H, *J* = 3.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3, 138.8, 134.6, 130.2, 130.0, 128.9, 128.6, 125.0, 124.2, 119.4, 117.4, 100.8, 62.5, 55.9, 55.0, 54.2, 28.0.

***N*-(4-Chlorophenyl)-2-(4-((2-phenyl-1*H*-imidazol-5-yl)methyl)-1,4-diazepan-1-yl)acetamide (21j).** The title compound (55 mg, 74%) was obtained from the reaction of **12** (40 mg, 0.174 mmol) and **18j** (51 mg, 0.192 mmol) in DMF (8 mL) in the presence of DIPEA (45 mg, 0.349 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.36 (bs, 1H), 7.85 (dd, 2H, *J* = 8.0 Hz), 7.54~7.50 (m, 2H), , 7.39~7.32 (m, 3H), 7.23 (d, 2H, *J* = 8.4 Hz), 6.97 (s, 1H), 3.70 (s, 2H), 3.23 (s, 2H), 2.88~2.77 (m, 8H), 1.85 (quintet, 2H, *J* = 6.0 Hz);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3, 136.2, 130.2, 129.0, 128.8, 128.6, 125.1, 120.6, 62.4, 55.9, 55.0, 54.2, 28.0.

2-(4-((2-Phenyl-1*H*-imidazol-5-yl)methyl)-1,4-diazepan-1-yl)-*N*-*p*-tolylacetamide (21m). The title compound (40 mg, 66%) was obtained from the reaction of **12** (40 mg, 0.174 mmol) and **18m** (47 mg, 0.192 mmol) in DMF (8 mL) in the presence of DIPEA (45 mg, 0.349 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.24 (bs, 1H), 7.85 (d, 2H, *J* = 7.2 Hz), 7.46 (d, 2H, *J* = 8.0 Hz), 7.39~7.30 (m, 3H), 7.10 (d, 2H, *J* = 8.0 Hz), 6.97 (s, 1H), 3.70 (s, 2H), 3.23 (s, 2H), 2.88~2.78 (m, 8H), 2.30 (s, 3H), 1.86 (quintet, 2H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.0, 135.0, 133.8, 130.3, 129.5, 128.8, 128.5, 125.1, 119.4, 62.5, 55.9, 55.2, 55.0, 54.2, 28.0, 20.8.

***N*-(3-Methoxyphenyl)-2-(4-((2-phenyl-1*H*-imidazol-5-yl)methyl)-1,4-diazepan-1-yl) acetamide (21o).** The title compound (45 mg, 61%) was obtained from the reaction of **12** (40 mg, 0.174 mmol) and **18o** (51 mg, 0.192 mmol) in DMF (8 mL) in the presence of DIPEA (45 mg, 0.349 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.33 (bs, 1H), 7.87 (d, 2H, *J* = 6.9 Hz), 7.38~7.30 (m, 4H), 7.21 (t, 1H, *J* = 8.1 Hz), 6.98 (s, 1H), 6.67 (dd, 1H, *J* = 8.1 Hz), 3.79 (s, 3H), 3.70 (s, 2H), 3.23 (s, 2H), 2.83~2.77 (m, 8H), 1.84 (quintet, 2H, *J* = 5.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3, 160.2, 146.7, 138.8, 130.3, 129.7, 128.8, 128.5, 125.1, 116.6, 109.9, 105.3, 62.5, 55.9, 55.3, 55.1, 55.0, 54.2, 28.0.

2-(4-((2-Phenyl-1*H*-imidazol-5-yl)methyl)-1,4-diazepan-1-yl)-*N*-(2-(trifluoromethyl) phenyl)acetamide (21q). The title compound (54 mg, 68%) was obtained from the reaction of **12** (40 mg, 0.174 mmol) and **18q** (58 mg, 0.192 mmol) in DMF (8 mL) in the presence of DIPEA (45 mg, 0.349 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.95 (bs, 1H), 8.43 (d, 1H, *J* = 8.4 Hz), 7.86 (dd, 2H, *J* = 8.8 Hz), 7.61 (d, 1H, *J* = 8.0 Hz), 7.56 (t, 1H, *J* = 8.0 Hz), 7.38~7.30 (m, 3H), 7.20 (t, 1H, *J* = 7.6 Hz), 6.98 (s, 1H), 3.68 (s, 2H), 3.26 (s, 2H), 2.86~2.78 (m, 8H), 1.87 (quintet, 2H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.8, 146.7, 135.4, 133.0, 130.4, 128.8, 128.5, 126.0, 125.5, 125.1, 123.8, 122.7, 62.6, 56.4, 55.3, 54.4, 54.0, 27.2.

2-(4-((2-Phenyl-1*H*-imidazol-5-yl)methyl)-1,4-diazepan-1-yl)-*N*-(3-(trifluoromethyl) phenyl)acetamide (21r). The title compound (70 mg, 88%) was obtained from the reaction of **12** (40 mg, 0.174 mmol) and **18r** (58 mg, 0.192 mmol) in DMF (8 mL) in the presence of DIPEA (45 mg, 0.349 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.50 (bs, 1H), 7.90 (s, 1H), 7.86 (d, 2H, *J* = 7.2 Hz), 7.76 (d, 1H, *J* = 7.6 Hz), 7.40~7.29 (m, 5H), 6.97 (s, 1H), 3.70 (s, 2H), 3.25 (s, 2H), 2.83~2.76 (m, 8H), 1.85 (quintet, 2H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.6, 146.7, 138.2, 131.5, 131.2, 130.2, 129.5, 128.8, 128.5, 125.1,122.4, 120.6, 116.0, 62.3, 56.0, 55.0, 54.9, 54.2, 28.0.

2-(4-((2-Phenyl-1*H*-imidazol-5-yl)methyl)-1,4-diazepan-1-yl)-*N*-(4-(trifluoromethyl) phenyl)acetamide (21s). The title compound (60 mg, 75%) was obtained from the reaction of **12** (40 mg, 0.174 mmol) and **18s** (58 mg, 0.192 mmol) in DMF (8 mL) in the presence of DIPEA (45 mg, 0.349 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.56 (bs, 1H), 7.86 (d, 2H, *J* = 7.6 Hz), 7.70 (d, 2H, *J* = 8.4 Hz), 7.50 (d, 1H, *J* = 8.0 Hz), 7.38~7.28 (m, 4H), 6.97 (s, 1H), 3.70 (s, 2H), 3.21 (s, 2H), 2.87~2.75 (m, 8H), 1.86 (quintet, 2H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.7, 146.8, 140.6, 132.6, 128.8, 128.6, 126.2, 125.4, 125.1, 122.7, 119.0, 62.5, 55.9, 55.4, 55.0, 54.2, 28.1.

***N*-(2,6-Diethylphenyl)-2-(4-((6-fluorobenzo[*d*]oxazol-2-yl)methyl)-1,4-diazepan-1-yl)acetamide (22a).** The title compound (66 mg, 44%) was obtained from the reaction of **7** (70 mg, 0.38 mmol) and **18a** (100 mg, 0.345 mmol) in DMF (8 mL) in the presence of DIPEA (89 mg, 0.69 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.76 (bs, 1H), 7.61 (dd, 1H, *J* = 8.8 Hz), 7.20 (d, 2H, *J* = 6.4 Hz), 7.14~7.07 (m, 3H), 4.02 (s, 2H), 3.36 (s, 2H), 2.97~2.89 (m, 8H), 2.57 (q, 4H, *J* = 7.6 Hz), 1.93 (quintet, 2H, *J* = 5.8 Hz), 1.17 (t, 6H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9, 164.3, 161.8, 159.3, 141.1, 137.1, 132.5, 127.8, 126.4, 120.3, 112.5, 98.8, 62.2, 56.6, 55.4, 55.2, 55.1, 54.1, 28.0, 25.0, 14.5.

***N*-(3,4-Dimethylphenyl)-2-(4-((6-fluorobenzo[*d*]oxazol-2-yl) methyl)-1,4-diazepan-1-yl)acetamide (22c).** The title compound (135 mg, 86%) was obtained from the reaction of **7** (78 mg, 0.42 mmol) and **18c** (100 mg, 0.382 mmol) in DMF (8 mL) in the presence of DIPEA (99 mg, 0.765 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.09 (bs, 1H), 7.65 (dd, 1H, *J* = 8.8 Hz), 7.34 (s, 1H), 7.27~7.24 (m, 3H), 7.12~7.05 (m, 2H), 4.04 (s, 2H), 3.26 (s, 2H), 2.98~2.86 (m, 8H), 2.24 (s, 3H), 2.22 (s, 3H), 1.91 (quintet, 2H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.7, 164.3, 161.8, 159.4, 137.3, 137.2, 135.3, 132.4, 129.9, 120.6, 120.3, 116.8, 112.5, 98.9, 62.3, 60.4, 56.0, 55.2, 55.0, 54.0, 28.0, 19.9, 19.2.

2-(4-((6-Fluorobenzo[*d*]oxazol-2-yl)methyl)-1,4-diazepan-1-yl)-*N*-(3-fluorophenyl) acetamide (22f). The title compound (72 mg, 45%) was obtained from the reaction of **7** (81 mg, 0.438 mmol) and **18f** (100 mg, 0.398 mmol) in DMF (8 mL) in the presence of DIPEA (103 mg, 0.796 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.32 (bs, 1H), 7.64 (dd, 1H, *J* = 4.8 Hz), 7.54 (dt, 1H, *J* = 2.4 Hz), 7.25~7.14 (m, 3H), 7.10~7.05 (m, 1H), 6.80~6.75 (m, 1H), 4.03 (s, 2H), 3.26 (s, 2H), 2.97~2.85 (m, 8H), 1.91 (quintet, 2H, *J* = 5.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.1, 164.3, 164.2, 161.8, 159.4, 139.2, 137.2, 130.1, 120.3, 114.5, 112.5, 110.9, 106.8, 98.8, 62.2, 56.0, 55.2, 55.1, 55.0, 54.0, 28.1.

2-(4-((6-Fluorobenzo[*d*]oxazol-2-yl)methyl)-1,4-diazepan-1-yl)-*N*-(4-fluorophenyl) acetamide (22g). The title compound (130 mg, 82%) was obtained from the reaction of **7** (81 mg, 0.438 mmol) and **18g** (100 mg, 0.398 mmol) in DMF (8 mL) in the presence of DIPEA (103 mg, 0.796 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.21 (bs, 1H), 7.64 (dd, 1H, *J* = 4.8 Hz), 7.51 (dd, 2H, *J* = 4.8 Hz), 7.25 (dd, 1H, *J* = 5.6 Hz), 7.1~7.05 (m, 1H), 7.0~6.96 (m, 2H), 4.03 (s, 2H), 3.25 (s, 2H), 2.95~2.85 (m, 8H), 1.96 (quintet, 2H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.9, 164.3, 161.8, 160.4, 159.4, 157.9, 137.2, 133.7, 120.9, 120.3, 115.7, 112.5, 98.8, 62.1, 56.0, 55.2, 55.1, 55.0, 54.0, 28.0.

***N*-(3-Chlorophenyl)-2-(4-((6-fluorobenzo[*d*]oxazol-2-yl)methyl)-1,4-diazepan-1-yl)acetamide (22i).** The title compound (113 mg, 73%) was obtained from the reaction of

7 (76 mg, 0.41 mmol) and **18i** (100 mg, 0.373 mmol) in DMF (8 mL) in the presence of DIPEA (97 mg, 0.746 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.27 (bs, 1H), 7.67 (t, 1H, *J* = 2.0 Hz), 7.65 (dd, 1H, *J* = 5.2 Hz), 7.47~7.37 (m, 1H), 7.25~7.20 (m, 2H), 7.10~7.04 (m, 2H), 4.03 (s, 2H), 3.26 (s, 2H), 2.97~2.85 (m, 8H), 1.91 (quintet, 2H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.1, 164.3, 161.3, 159.4, 138.7, 137.2, 134.6, 130.0, 124.1, 120.3, 119.3, 117.2, 112.5, 98.9, 62.2, 56.0, 55.2, 55.06, 55.01, 54.0, 28.0.

***N*-(4-Chlorophenyl)-2-(4-((6-fluorobenzo[*d*]oxazol-2-yl) methyl)-1,4-diazepan-1-yl)acetamide (22j).** The title compound (55 mg, 35%) was obtained from the reaction of **7** (76 mg, 0.41 mmol) and **18j** (100 mg, 0.373 mmol) in DMF (8 mL) in the presence of DIPEA (97 mg, 0.746 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.27 (bs, 1H), 7.65 (dd, 1H, *J* = 4.8 Hz), 7.52~7.48 (m, 2H), 7.28~7.24 (m, 3H), 7.12~7.07 (m, 1H), 4.04 (s, 2H), 3.26 (s, 2H), 2.98~2.86 (m, 8H), 1.92 (quintet, 2H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.0, 164.3, 161.8, 159.4, 137.2, 136.2, 129.0, 120.5, 120.3, 120.2, 112.5, 98.9, 62.2, 56.0, 55.2, 55.1, 55.0, 54.0, 28.0.

2-(4-((6-Fluorobenzo[*d*]oxazol-2-yl)methyl)-1,4-diazepan-1-yl)-*N*-*m*-tolylacetamide (22l). The title compound (83 mg, 52%) was obtained from the reaction of **7** (83 mg, 0.44 mmol) and **18l** (100 mg, 0.4 mmol) in DMF (8 mL) in the presence of DIPEA (104 mg, 0.8 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.17 (bs, 1H), 7.64 (dd, 1H, *J* = 5.2 Hz), 7.40 (s, 1H), 7.32 (d, 1H, *J* = 8.0 Hz), 7.25 (dd, 1H, *J* = 8.0 Hz), 7.19 (t, 1H, *J* = 8.0 Hz), 7.10 (m, 1H), 6.91 (d, 1H, *J* = 7.6 Hz), 4.03 (s, 2H), 3.29 (s, 2H), 2.97~2.85 (m, 8H), 2.40 (s, 3H), 1.92 (quintet, 2H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8, 164.3, 161.8, 159.4, 138.9, 137.5, 135.2, 128.8, 124.9, 120.3, 119.9, 116.4, 112.5, 98.8, 62.3, 56.0, 56.2, 55.1, 54.9, 54.0, 28.0, 21.4.

2-(4-((6-Fluorobenzo[*d*]oxazol-2-yl)methyl)-1,4-diazepan-1-yl)-*N*-*p*-tolylacetamide (22m). The title compound (94 mg, 59%) was obtained from the reaction of **7** (83 mg, 0.44 mmol) and **18m** (100 mg, 0.4 mmol) in DMF (8 mL) in the presence of DIPEA (104 mg, 0.8 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.15 (bs, 1H), 7.64 (dd, 1H, *J* = 4.8 Hz), 7.43 (d, 2H, *J* = 8.0 Hz), 7.25 (dd, 1H, *J* = 8.0 Hz), 7.10~7.05 (m, 3H), 4.03 (s, 2H), 3.24 (s, 2H), 2.97~2.85 (m, 8H), 2.29 (s, 3H), 1.91 (quintet, 2H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.7, 164.4, 161.8, 159.3, 137.2, 135.1, 133.6, 129.4, 120.3, 119.3, 112.5, 98.8, 62.3, 56.0, 55.2, 54.9, 54.0, 28.0, 20.8.

2-(4-((6-Fluorobenzo[*d*]oxazol-2-yl)methyl)-1,4-diazepan-1-yl)-*N*-(3-(trifluoromethyl) phenyl)acetamide (22r). The title compound (50 mg, 34%) was obtained from the reaction of **7** (68 mg, 0.365 mmol) and **18r** (100 mg, 0.331 mmol) in DMF (8 mL) in the presence of DIPEA (85 mg, 0.663 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.41 (bs, 1H), 7.85 (s, 1H), 7.69 (d, 1H, *J* = 8.0 Hz), 7.65 (dd, 1H, *J* = 8.4 Hz), 7.39 (t, 1H, *J* = 8.0 Hz), 7.35 (d, 1H, *J* = 8.0 Hz), 7.25 (dd, 1H, *J* = 5.6 Hz), 7.11~7.06 (m, 1H), 4.04 (s, 2H), 3.29 (s, 2H), 2.98~2.87 (m, 8H), 1.94 (quintet, 2H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.3, 164.6, 161.8, 159.4, 138.1, 137.2, 131.5, 129.5, 122.5, 120.6, 120.3, 116.0, 112.5, 112.3, 98.8, 62.1, 56.0, 55.2, 55.0, 54.9, 54.1, 28.0.

2-(4-((6-Fluorobenzo[*d*]oxazol-2-yl)methyl)-1,4-diazepan-1-yl)-*N*-(4-(trifluoromethyl) phenyl)acetamide (22s). The title compound (100 mg, 67%) was obtained from the reaction of **7** (68 mg, 0.365 mmol) and **18s** (100 mg, 0.331 mmol) in DMF (8 mL) in the presence of DIPEA (85 mg, 0.663 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.45 (bs, 1H), 7.68~7.62 (m, 3H), 7.56 (d, 2H, *J* = 8.8 Hz), 7.26 (dd, 1H, *J* = 8.0 Hz), 7.12~7.07 (m, 1H), 4.05 (s, 2H), 3.29 (s, 2H), 2.99~2.87 (m, 8H), 1.93 (quintet, 2H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.4, 164.2, 161.8, 159.4, 140.6, 137.2, 126.3, 125.7, 120.3, 118.9, 112.5, 98.9, 62.2, 56.0, 55.2, 55.0, 55.0, 54.0, 28.0.

***N*-(2,6-Diethylphenyl)-2-(4-((6-methylbenzo[*d*]oxazol-2-yl)methyl)-1,4-diazepan-1-yl)acetamide (23a).** The title compound (59 mg, 49%) was obtained from the reaction of **8** (50 mg, 0.28 mmol) and **18a** (96 mg, 0.33 mmol) in DMF (8 mL) in the presence of DIPEA (96 μL, 0.55 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.76 (bs, 1H), 7.55 (d, 1H, *J* = 8.1 Hz), 7.29-7.11 (m, 6H), 4.01 (s, 2H), 3.25 (s, 2H), 2.97-2.92 (m, 8H), 2.56 (q, 4H, *J* = 7.6 Hz), 2.48 (s, 3H), 1.92 (quintet, 2H, *J* = 5.7 Hz), 1.17 (t, 6H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.1, 163.3, 151.3, 141.3, 138.8, 135.6, 132.7, 127.9, 126.5, 125.7, 119.5, 111.0, 62.3, 56.8, 55.6, 55.5, 55.2, 54.2, 28.1, 25.1, 21.8, 14.6.

***N*-(2,4-Dimethylphenyl)-2-(4-((6-methylbenzo[*d*]oxazol-2-yl)methyl)-1,4-diazepan-1-yl)acetamide (23b).** The title compound (79 mg, 58%) was obtained from the reaction of **8** (61 mg, 0.34 mmol) and **18b** (114 mg, 0.44 mmol) in DMF (8 mL) in the presence of DIPEA (129 μL, 0.67 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.20 (bs, 1H), 7.93 (d, 1H, *J* = 8.2 Hz), 7.56 (d, 1H, *J* = 8.1 Hz), 7.30 (bs, 1H), 7.14 (d, 1H, *J* = 8.1 Hz), 7.01 (d, 1H, *J* = 8.3 Hz), 6.96 (s, 1H), 4.00 (s, 2H), 3.28 (s, 2H), 2.96-2.87 (m, 8H), 2.48 (s, 3H), 2.27 (s, 3H), 2.18 (s, 3H), 1.90 (quintet, 2H, *J* = 5.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.2, 163.2, 151.2, 138.7, 135.1, 133.8, 133.3, 131.0, 127.4, 125.6, 121.3, 119.4, 110.9, 62.9, 56.5, 55.4, 54.0, 28.1, 21.8, 20.9, 17.8.

***N*-(3,4-dimethylphenyl)-2-(4-((6-methylbenzo[*d*]oxazol-2-yl)methyl)-1,4-diazepan-1-yl)acetamide(23c).** The title compound (66 mg, 48%) was obtained from the reaction of **8** (61 mg, 0.34 mmol) and **18c** (114 mg, 0.44 mmol) in DMF (8 mL) in the presence of DIPEA (120 μL, 0.67 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.18 (bs, 1H), 7.58 (d, 1H, *J* = 8.1 Hz), 7.36-7.26 (m, 3H), 7.15 (dd, 1H, *J* = 8.1, 0.9 Hz), 7.05 (d, 1H, *J* = 8.1 Hz), 4.04 (s, 2H), 3.28 (s, 2H), 2.98-2.88 (m, 8H), 2.49 (s, 3H), 2.22 (s, 3H), 2.19 (s, 3H), 1.92 (quintet, 1H, *J* = 5.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.2, 151.3, 138.8, 137.4, 135.7, 135.5, 132.6, 130.1, 125.7, 120.8, 119.5, 117.0, 111.0, 62.5, 56.1, 55.4, 55.1, 54.1, 28.0, 21.8, 20.0, 19.3.

***N*-(3-Fluorophenyl)-2-(4-((6-methylbenzo[*d*]oxazol-2-yl)methyl)-1,4-diazepan-1-yl)acetamide (23f).** The title compound (64 mg, 48%) was obtained from the reaction of **8** (61 mg, 0.34 mmol) and **18f** (110 mg, 0.44 mmol) in DMF (8 mL) in the presence of DIPEA (120 μL, 0.67 mmol). ^{1}H

NMR ($CDCl_3$, 400 MHz) δ 9.29 (bs, 1H), 7.52-7.47 (m, 2H), 7.20-7.07 (m, 3H), 6.72-6.71 (m, 1H), 3.97 (s, 2H), 3.20 (s, 2H), 2.94-2.73 (m, 8H), 2.41 (s, 3H), 1.83 (quintet, 2H, J = 5.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.2, 164.3, 163.1, 151.2, 139.3, 139.2, 138.8, 135.6, 130.2, 130.1, 125.7, 119.4, 114.6, 110.9, 110.7, 107.0, 106.7, 62.4, 56.1, 55.4, 55.2, 55.1, 54.1, 28.2, 21.8.

***N*-(4-Fluorophenyl)-2-(4-((6-methylbenzo[*d*]oxazol-2-yl) methyl)-1,4-diazepan-1-yl) acetamide (23g).** The title compound (115 mg, 87%) was obtained from the reaction of **8** (61 mg, 0.34 mmol) and **18g** (110 mg, 0.44 mmol) in DMF (8 mL) in the presence of DIPEA (120 μL, 0.67 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.25 (bs, 1H), 7.57 (d, 1H, J = 8.1 Hz), 7.51-7.47 (m, 2H), 7.31 (s, 1H), 7.14 (dd, 1H, J = 8.1, 0.6 Hz), 7.00-6.94 (m, 2H), 4.03 (s, 2H), 3.25 (s, 2H), 2.97-2.84 (m, 8H), 2.48 (s, 3H), 1.89 (quintet, 2H, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.0, 163.1, 160.9, 157.7, 152.9, 151.2, 138.8, 135.6, 133.8, 125.7, 121.0, 120.9, 119.4, 115.8, 115.5, 110.9, 62.3, 56.1, 55.4, 55.2, 55.1, 54.1, 28.2, 21.8.

2-(4-((6-Methylbenzo[*d*]oxazol-2-yl)methyl)-1,4-diazepan-1-yl)-*N*-*p*-tolylacetamide (23l). The title compound (111 mg, 84%) was obtained from the reaction of **8** (61 mg, 0.34 mmol) and **18l** (108 mg, 0.44 mmol) in DMF (8 mL) in the presence of DIPEA (120 μL, 0.67 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.17 (bs, 1H), 7.57 (dd, 1H, J_1 = 8.1 Hz, J_2 = 3.4 Hz), 7.42 (d, 1H, J = 8.4 Hz), 7.32 (s, 1H), 7.16-7.08 (m, 3H), 4.02 (s, 2H), 3.24 (s, 2H), 2.97-2.83 (m, 8H), 2.47 (s, 3H), 2.30 (s, 3H), 1.89 (quintet, 2H, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8, 163.2, 151.2, 138.8, 135.6, 135.2, 133.7, 129.5, 125.7, 119.4, 119.3, 110.9, 62.5, 56.1, 55.4, 55.3, 55.1, 54.1, 28.1, 21.8, 21.0.

Experimental Procedure for FDSS6000 Assay. HEK293 cells which stably express both α_{1G} and Kir2.1 subunits were grown in Dulbecco's modified Eagle's medium supplemented with 10% (v/v) fetal bovine serum, penicillin (100 U/mL), streptomycin (100 μg/mL), geneticin (500 μg/mL), and puromycin (1 μg/mL) at 37 °C in a humid atmosphere of 5% CO_2 and 95% air. Cells were seeded into 96-well black wall clear bottom plates at a density of 4×10^4 cells/well and were used the next day for high-throughput screening (HTS) FDSS6000 assay. For FDSS6000 assay, cells were incubated for 60 min at room temperature with 5 μM fluo3/AM and 0.001% Pluronic F-127 in a Hepes-buffered solution composed of (in mM): 115 NaCl, 5.4 KCl, 0.8 $MgCl_2$, 1.8 $CaCl_2$, 20 Hepes, and 13.8 glucose (pH 7.4). During the fluorescence-based FDSS6000 assay, α_{1G} T-type Ca^{2+} channels were activated using high concentration of KCl (70 mM) in 10 mM $CaCl_2$ contained Hepes-buffered solution and the increase in $[Ca^{2+}]_i$ by KCl-induced depolarization was detected. During the whole procedure, cells were washed using the BIO-TEK 96-well washer. All data were collected and analyzed using FDSS6000 and related software (Hamamatsu, Japan).

Experimental Procedure for Patch-clamp (Electrophysiological Recording).[11] For the recordings of α_{1G} T-type Ca^{2+} currents, the standard whole-cell patch-clamp method was utilized. Briefly, borosilicate glass electrodes with a resistance of 3-4 MX were pulled and filled with the internal solution contained (in mM): 130 KCl, 11 EGTA, 5 Mg-ATP, and 10 Hepes (pH 7.4). The external solution contained (in mM): 140 NaCl, 2 $CaCl_2$, 10 Hepes, and 10 glucose (pH 7.4). α_{1G} T-type Ca^{2+} currents were evoked every 15 s by a 50 ms depolarizing voltage step from −100 mV to −30 mV. The molar concentrations of test compounds required to produce 50% inhibition of peak currents (IC_{50}) were determined from fitting raw data into dose-response curves. The current recordings were obtained using an EPC-9 amplifier and Pulse/Pulsefit software program (HEKA, Germany).

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