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Morpholin-2-one derivatives as novel selective T-type Ca^{2+} channel blockers

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Abstract—Morpholin-2-one-5-carboxamide derivatives were prepared by using the one-pot Ugi multicomponent reaction and evaluated for blocking effects on T- and N-type Ca^{2+} channels. Among them, compound **5i** produced the highest potency ($IC_{50} = 0.45 \pm 0.02$ μM), while compounds **5d**, **5f**, **5k**, **5n**, **5o**, and **6m** produced relatively high potency as well as selectivity on T-type Ca^{2+} channels. These novel scaffolds showed potent and selective T-type Ca^{2+} channel blocking activities.

Voltage-dependent Ca^{2+} channels (VDCC) are the primary route for translating electrical signals into biochemical events underlying key processes such as enzyme activity, neurotransmitter release, neuronal excitability, neurite outgrowth, and gene transcription.[1] Ca^{2+} channels have been subdivided into two major classes based on electrophysiological and pharmacological properties: high voltage-activated (HVA), which are further divided into L-, N-, P-, Q-, and R-subtypes, and low voltage-activated (LVA) or transient (T-type) Ca^{2+} channels.[2–4] HVA Ca^{2+} channels are activated by a relatively strong membrane depolarization and are important for contraction, secretion, neurotransmitter release, and gene expression. LVA or T-type Ca^{2+} channels are activated by a small membrane depolarization and play a crucial role in excitability of both central and peripheral neurons.[5–7] Furthermore, many reports have suggested that T-type Ca^{2+} channels are implicated in pathogenesis of epilepsy and neuropathic pain.[8–13] Targets of anti-epileptic drugs include neuronal voltage-dependent Na^+ channels,[14] γ-aminobutyric acid (GABA) receptors,[15] VDCC, especially T-type Ca^{2+} channels,[16] and *N*-methyl-D-aspartate (NMDA) receptors. Recent evidence has also led to the application of ligands competing with glutamate binding on α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) and kainic acid (KA) receptors to minimize symptoms of epilepsy.[17]

Mibefradil was first introduced as a new class of selective T-type Ca^{2+} channel blockers.[18] However, it is currently regarded as a non-selective and broad-spectrum ion channel blocker having activities on HVA Ca^{2+}, Na^+, K^+, and Cl^- channels and finally withdrawn due to its pharmacokinetic interactions with other drugs metabolized by cytochromes P450, 3A4 and 2D6.[19] Ethosuximide, an anti-epileptic drug, and Kurtoxin, a peptide isolated from a venomous scorpion, were also reported to inhibit T-type Ca^{2+} channels. Recently, certain derivatives of 3,4-dihydroquinazoline[20] and piperazinyl alkylisoxazole[21] have been shown to be potent and selective blockers of T-type Ca^{2+} channels. However, no selective T-type Ca^{2+} channel blocker has been reported with results from pharmacokinetic and in vivo studies. Therefore, the investigation of new T-type Ca^{2+} channel blockers is still needed to understand defined physiological roles of the channels and to develop clinically applicable drug targets for epilepsy and neuropathic pain.

Herein, we described the synthesis of morpholin-2-one derivatives and assayed them against T-type Ca^{2+}

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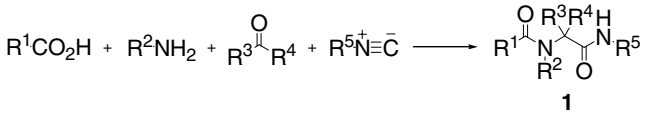
channels using two-microelectrode voltage-clamp techniques in *Xenopus* oocytes and whole-cell patch-clamp techniques in HEK293 cells according to the previous studies.[22,23] With the aim of creating various chemical scaffolds, we selected the multicomponent reaction, in which three or more reactants combine in the one-pot procedure to give a single final product. The multicomponent reaction with varying each component provides a powerful tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles. The multicomponent reactions containing isocyanides provide by far the most versatile reactions in terms of scaffolds and number of accessible compounds.[24] Especially, the Ugi four-component condensation reaction, which combines a carboxylic acid, an amine, a carbonyl compound, and an isocyanide to afford an α-amino amide **1**, has come into widespread use for generating large collections of molecules in combinatorial synthesis (Scheme 1).

In the course of our study to expand the structural diversity accessible through isocyanide chemistry, we reported the useful synthesis of α-aminobutyrolactones,[25a] α-aminovalerolactones,[25b] 2,5-diketopiperazines,[25c] and morpholin-2-ones,[26] using functionalized compounds as components of multicomponent condensation reactions. To test T-type Ca^{2+} channel activities, some compounds of those scaffolds were preliminarily screened against $Ca_V3.2$ T-type Ca^{2+} channels expressed in *Xenopus* oocytes.

Among them, morpholin-2-one derivatives are found to have T-type Ca^{2+} channel blocking activities and totally different scaffolds from the reported ones in the previous studies (Fig. 1).[20,21] We, therefore, developed a morpholin-2-one chemical library using various α-amino acids and isocyanides to optimize structure–activity relationship for the T-type Ca^{2+} channel.

The morpholin-2-one library was prepared by using the well-known one-pot Ugi five-center-three-component reaction as illustrated in Scheme 2.[26,27] The reaction of the commercially available glycolaldehyde dimer **2** with various α-amino acids **3** and isocyanides **4** provided 3-substituted morpholin-2-one-5-carboxamide derivatives **5** and **6** in moderately good yield as shown in Table 1. The diastereoselectivities were 5.9–1.6:1 by ^1H NMR spectroscopy, where each diastereomer was separated by column chromatography on silica gel. The relative stereochemistry of the products was analogous to that of **6a** which was confirmed by X-ray crystallography.[26]

As preliminary assays, the activities of the synthetic morpholin-2-one analogues (100 μM) with the reference compound mibefradil were determined against $Ca_V3.2$ channels expressed in *Xenopus* oocytes using a two-



Scheme 1. The Ugi four-component condensation reaction.

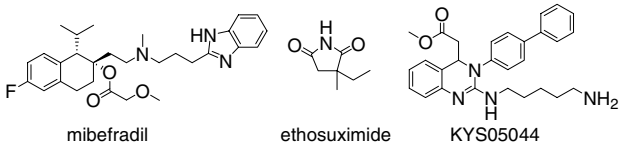
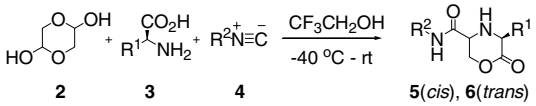


Figure 1. Chemical structures of known T-type Ca^{2+} channel blockers.



Scheme 2. One-pot synthesis of morpholin-2-one-5-carboxamide derivatives.

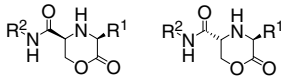
electrode voltage clamp method[22] and are summarized in Table 1.

Morpholin-2-one derivatives prepared from *tert*-butyl isocyanide and tosylmethyl isocyanide gave poor Ca^{2+} channel blocking activities (Entry 1 and 2). Irrespective of α-amino acid components, benzyl and cyclohexyl amides inhibited T-type Ca^{2+} channels by more than 50%. Usually, 3,5-*cis* adducts produced higher activity than their *trans* analogues. Morpholin-2-one derivatives prepared from α-methylbenzyl isocyanide gave also good activities, but in the case of **6l** and **6m**, *trans* compounds showed better activities.

The compounds showing more than ~45% inhibition were re-evaluated for the blocking effects on $Ca_V3.1$ channels expressed in HEK293 cells at the concentration of 10 μM by whole-cell patch-clamp methods.[23] The molar concentrations (IC_{50}) of test compounds required to produce 50% inhibition on $Ca_V3.1$ channels were determined from fitting raw data into dose–response curves.

The summarized results are shown in Table 2. The inhibitory activities of the selected compounds ranged from 63.4% to 86.2% at the concentration of 10 μM. With regard to IC_{50} values, all compounds showed relatively potent activities (IC_{50} values from 0.45 ± 0.02 to 2.75 ± 0.35) when compared with mibefradil ($IC_{50} = 1.34 \pm 0.49$ μM). Among them, compound **5i**, prepared from 4-chloro-L-phenylalanine and benzyl isocyanide, showed the highest potency ($IC_{50} = 0.45 \pm 0.02$ μM). The effects of alkyl substitute R^1 were not crucial for the inhibitory activities. In addition, these compounds were also examined using $Ca_V2.2$ N-type Ca^{2+} channels expressed in HEK293 cells according to the previous study.[20a] The blocking activities of these compounds against N-type Ca^{2+} channels are also summarized in Table 2. Under our assay condition, mibefradil showed lower selectivity for T-type Ca^{2+} channels (T/N ratio = 1.6) as known before.[28] All compounds were more selective for T-type channels compared with N-type channels (T/N ratios from 2.5 to 37.3). However, compound **5i**, the most potent compound in this study, showed the lowest selectivity (T/N ratio = 2.5). Taking into consideration that the spontaneous current run-down in electrophysiological experiments is typically

Table 1. In vitro Ca^{2+} channel blocking effects of morpholin-2-one derivatives



5 (*cis*) **6** (*trans*)

Entry	Compound	R^1	R^2	Yield[a] (%)	dr[b] (**5**:**6**)	*Xenopus* oocyte (T-type: $Ca_V3.2$) % inhibition (100 μM)	
						5	**6**
1	**5a/6a**	$PhCH_2$–	$(CH_3)_3C$–	90	1:2.4	43.0	42.0
2	**5b/6b**	$PhCH_2$–	$TosCH_2$–	37	1:3.7	13.0	25.0
3	**5c/6c**	$(CH_3)_2CH$–	$PhCH_2$–	56	1:2.9	82.0	—
4	**5d/6d**	$CH_3CH_2CH(CH_3)$–	$PhCH_2$–	67	1:5.3	70.0	—
5	**5e/6e**	$CH_3SCH_2CH_2$–	$PhCH_2$–	44	1:1.6	74.0	—
6	**5f/6f**	$PhCH_2$–	$PhCH_2$–	70	1:1.5	87.0	5.0
7	**5g/6g**	$PhCH_2$–	Cyclohexyl	53	1:5.4	76.0	30.3
8	**5h/6h**	*p*-$FC_6H_4CH_2$–	$PhCH_2$–	94	1:3.9	70.9	12.3
9	**5i/6i**	*p*-$ClC_6H_4CH_2$–	$PhCH_2$–	74	1:2.5	73.5	19.1
10	**5j/6j**	*p*-$NO_2C_6H_4CH_2$–	$PhCH_2$–	35	1:2.9	74.8	6.5
11	**5k/6k**	*p*-$MeOC_6H_4CH_2$–	$PhCH_2$–	71	1:3.2	54.6	16.2
12	**5l/6l**	*p*-$FC_6H_4CH_2$–	$PhCH(CH_3)$–[c]	32	1:3.5	35.6	83.6
13	**5m/6m**	*p*-$ClC_6H_4CH_2$–	$PhCH(CH_3)$–	34	1:4.2	48.4	73.3
14	**5n/6n**	*p*-$NO_2C_6H_4CH_2$–	$PhCH(CH_3)$–	30	1:5.9	60.8	25.2
15	**5o/6o**	*p*-$HOC_6H_4CH_2$–	$PhCH(CH_3)$–	47	1:4.6	45.8	27.6
16	Mibefradil	—	—	—	—	86.0	

[a] Isolated yield.
[b] Diastereomeric ratios were determined by ^1H NMR spectroscopy.
[c] $PhCH(CH_3)$:(*S*)-(−)-α-methylbenzyl.

Table 2. The inhibitory activities and selectivity data for selected compounds

Compound	HEK293 cell (T-type: $Ca_V3.1$)		HEK293 cell (N-type: $Ca_V2.2$) % inhibition[b] (10 μM)	Selectivity (T/N type)
	% Inhibition (10 μM)	IC_{50}[a] (μM)		
5c	78.8 ± 0.8	0.99 ± 0.44	25.3 ± 0.9	3.1
5d	**63.4 ± 7.3**	**1.22 ± 0.08**	**1.7 ± 0.9**	**37.3**
5e	75.1 ± 1.2	1.86 ± 0.19	15.4 ± 1.4	4.9
5f	**78.9 ± 2.8**	**1.01 ± 0.06**	**4.8 ± 1.1**	**16.4**
5g	73.6 ± 3.3	2.18 ± 0.62	9.4 ± 1.2	7.8
5h	77.6 ± 3.2	2.75 ± 0.35	7.1 ± 2.2	10.9
5i	**83.6 ± 0.7**	**0.45 ± 0.02**	33.7 ± 1.7	2.5
5j	86.2 ± 3.3	1.13 ± 0.21	7.6 ± 1.6	11.3
5k	**74.0 ± 1.5**	**2.04 ± 0.43**	**2.5 ± 2.2**	**29.6**
6l	80.8 ± 1.2	1.48 ± 0.26	11.3 ± 0.5	7.2
5m	64.0 ± 2.5	1.61 ± 0.37	10.9 ± 0.9	5.9
6m	**79.0 ± 1.5**	**1.33 ± 0.36**	**4.0 ± 0.4**	**19.8**
5n	**80.2 ± 2.5**	**2.13 ± 0.17**	**4.0 ± 0.8**	**20.1**
5o	**77.0 ± 1.0**	**1.39 ± 0.42**	**4.7 ± 1.2**	**16.4**
Mibefradil	89.8 ± 3.3	1.34 ± 0.49	57.4 ± 1.3	1.6

[a] IC_{50} value was determined from the dose–response curve.
[b] % inhibition value (±SE) was obtained by repeated procedures ($n \geqslant 4$).

<5%, inhibitions of >5% may reflect a true drug effect. In this regard, compounds **5d**, **5f**, **5k**, **5n**, **5o**, and **6m** produced relatively potent activities on T-type channels (IC_{50} values from 1.01 ± 0.06 to 2.13 ± 0.17), while they produced <5% inhibition on N-type channels. Their T/N ratios showing in vitro efficacy profile ranged from 16.4 to 37.3, suggesting relatively selective effects on T-type channels.

Based on the hypothetical 3D pharmacophore model developed for T-type Ca^{2+} channel,[29] the morpholin-2-one derivatives were also applied to explain their high inhibitory activities. Compound **5i**, where R^1 and R^2 are *p*-chlorobenzyl and benzyl group, respectively, was selected representatively and mapped to the five-feature 3D pharmacophore model. As shown in Figure 2, compound **5i** was well satisfied with essential five-feature

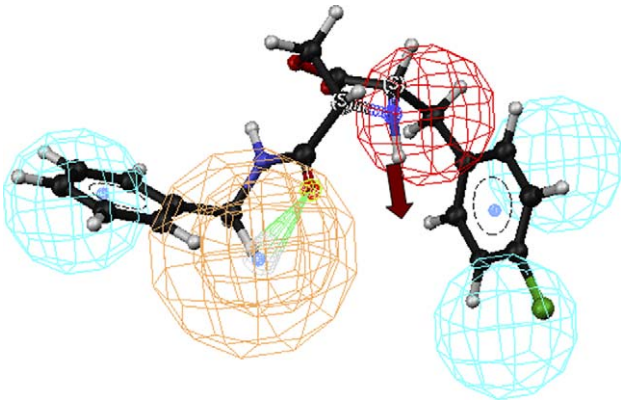


Figure 2. The mapping of compound **5i** to five-feature pharmacophore model. Arrow shows the direction of positive ionizable N of morpholine moiety.

pharmacophores. In case of *trans* compounds **6l** and **6m** which showed good inhibition, the best fit compound's mapping was reversed as shown in Figure 3. Even though *cis* isomers **5l** and **5m** showed similar mapping (Fig. 4), the positive ionizable nitrogen of the morpholine moiety is in opposite side when compared to that of **5i**, **6l**, and **6m**. The direction of the morpholine N is also indicated in the Figures 2–4, which may play important role in binding when we consider the three-dimensional shape of the binding site. This may be the reason for the poor inhibitory values of the *cis* analogues (**5l** and **5m**). Whereas other *trans* compounds **6n** and **6o** (which are similar to **6l** and **6m**) showed poor inhibition due to the fact that they contained nitro group and hydroxyl group, respectively, in place of hydrophobic region where **6l** and **6m** contained highly hydrophobic halide atom.

In conclusion, we have explored morpholin-2-one-5-carboxamide derivatives as a novel class of T-type Ca^{2+} channel blockers and found that these novel scaffolds showed potent and selective T-type Ca^{2+} channel blocking activities. Further studies on understanding of structure–activity relationship and developing T-type Ca^{2+} channel drugs are under progress based on the results of morpholin-2-one derivatives.

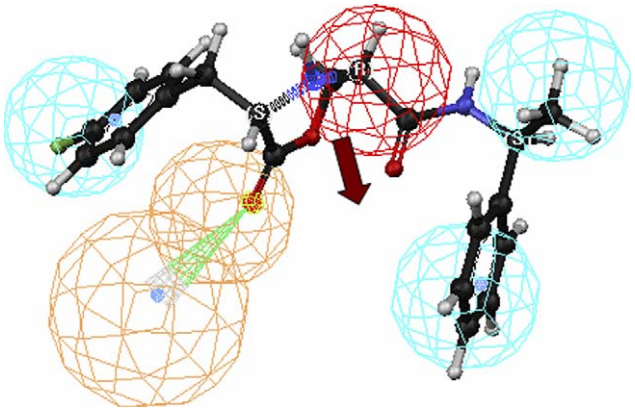


Figure 3. The mapping of compound **6l** to five-feature pharmacophore model. Arrow shows the direction of positive ionizable N of morpholine moiety.

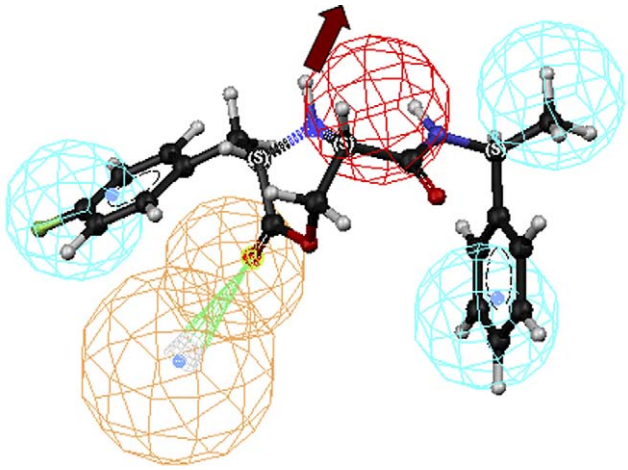


Figure 4. The mapping of compound **5l** to five-feature pharmacophore model. Arrow shows the direction of positive ionizable N of morpholine moiety.

Acknowledgments

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27. A typical procedure; The solution of glycolaldehyde dimer (35.2 mg, 0.293 mmol) and benzyl isocyanide (85.6 μL, 0.703 mmol) in CF_3CH_2OH (8 mL) was added slowly to a suspension of 4-chloro-L-phenylalanine (117 mg, 0.586 mmol) in CF_3CH_2OH (10 mL) at −40 °C under nitrogen. The mixture was allowed to reach room temperature. After stirring for 24 h, the reaction mixture was concentrated under reduced pressure. H_2O (5 mL) and EtOAc (10 mL) were added to the residue, and the resulting aqueous solution was extracted with EtOAc (4×10 mL). The combined organic extracts were washed with brine (10 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel with a mixture of hexane and ethyl acetate (1:1) to give **5i** (44.5 mg, 21%) and **6i** (111.1 mg, 53%).Compound **5i**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.13 (m, 10H), 4.70 (ABX, J_{AB} = 11.7 Hz, J_{AX} = 3.9 Hz, 1H), 4.55 (ABX, J_{AB} = 11.7 Hz, J_{BX} = 4.8 Hz, 1H), 4.41, 4.37 (ABX, J_{AB} = 14.3 Hz, J_{AX} = 4.4 Hz, J_{BX} = 4.5 Hz, 2H), 3.96–3.94 (m, 1H), 3.8–3.77 (m, 1H), 3.24 (ABX, J_{AB} = 14.1 Hz, J_{AX} = 4.1 Hz, 1H), 4.55 (ABX, J_{AB} = 14.1 Hz, J_{BX} = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 169.9, 137.6, 134.9, 133.2, 130.8, 129.0, 128.8, 127.6, 127.4, 67.9, 54.6, 54.1, 43.3, 37.2.Compound **6i**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.25 (m, 4H), 7.16–7.09 (m, 6H), 4.79 (dd, J = 12.3, 7.3 Hz, 1H), 4.28–4.19 (m, 3H), 3.86 (dd, J = 10.3, 7.5 Hz, 1H), 3.53–3.51 (m, 1H), 3.28 (ABX, J_{AB} = 14.5 Hz, J_{AX} = 4.1 Hz, 1H), 2.76 (ABX, J_{AB} = 14.5 Hz, J_{BX} = 9.2 Hz, 1H), 1.89 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 169.7, 137.9, 135.7, 133.3, 130.9, 129.3, 129.2, 128.2, 128.1, 66.7, 54.2, 53.4, 43.5, 35.7.
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