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Structure-Activity Relationship of N,N′-Disubstituted Pyrimidinetriones as $Ca_V1.3$ Calcium Channel-Selective Antagonists for Parkinson's Disease

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Abstract

$Ca_V1.3$ L-type calcium channels (LTCCs) have been a potential target for Parkinson's disease since calcium ion influx through the channel was implicated in the generation of mitochondrial oxidative stress, causing cell death in the dopaminergic neurons. Selective inhibition of $Ca_V1.3$ over other LTCC isoforms, especially $Ca_V1.2$, is critical to minimize potential side effects. We recently identified pyrimidinetriones (PYTs) as a $Ca_V1.3$-selective scaffold; here we report the structure-activity relationship of PYTs with both $Ca_V1.3$ and $Ca_V1.2$ LTCCs. By variation of the substituents on the cyclopentyl and arylalkyl groups of PYT, SAR studies allowed characterization of the $Ca_V1.3$ and $Ca_V1.2$ LTCCs binding sites. The SAR also identified four important moieties that either retain selectivity or enhance binding affinity. Our study represents a significant enhancement of the SAR of PYTs at $Ca_V1.3$ and $Ca_V1.2$ LTCCs and highlights several advances in the lead optimization and diversification of this family of compounds for drug development.

Graphical abstract

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ASSOCIATED CONTENT

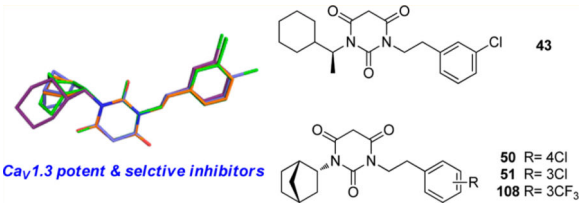
Supporting Information

Spectroscopic and analytical data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.



INTRODUCTION

L-Type calcium channels[1] (LTCCs) are cell membrane proteins activated upon membrane depolarization, selectively modulating calcium ion influx into the cells to initiate diverse intracellular events such as synaptic transmission, secretion, and gene expression. Although these channels are multimeric proteins of five subunits (α_1, α_2, β, γ, δ),[2,3] the α_1 subunit is the major pore-forming subunit, having four different subtypes ($Ca_V1.1$–1.4). $Ca_V1.2$ LTCCs are the major isoform (~90%),[4] expressed in cardiac myocites, smooth muscle, pancreas, and neurons, while $Ca_V1.1$ and $Ca_V1.4$ LTCCs are minor isoforms, restricted to skeletal muscle and retina, respectively.[5] $Ca_V1.3$ LTCCs[6] are expressed similarly as $Ca_V1.2$ LTCCs but are more neuron specific (cerebral cortex, hippocampus, basal ganglia, habenula, and thalamus); they are thought to serve predominantly as modulators in the neuronal system.[7]

Our recent studies[8] showed that Ca_V13 LTCCs are used for rhythmic pacemaking in adult dopaminergic neurons of the substantia nigra pars compacta (SNc).[9,10] The engagement of $Ca_V1.3$ LTCCs during autonomous pacemaking increases with age in animal models of Parkinson's disease (PD),[8] but $Ca_V1.3$ LTCCs seem to be unnecessary for normal functioning of SNc dopaminergic neurons. This reliance of $Ca_V1.3$ LTCCs elevates mitochondrial oxidant stress in SNc dopaminergic neurons, incurring continuous loss of SNc dopaminergic neurons, as demonstrated in a PD model.[11] Antagonization of $Ca_V1.3$ LTCCs could provide a means to diminish cell loss in PD by protecting SNc dopaminergic neurons against toxins, thereby making $Ca_V1.3$ LTCCs an important therapeutic target for PD.[12,13] However, drug candidates must selectively antagonize $Ca_V1.3$ over other ion channels, especially over $Ca_V1.2$ LTCCs, in order to avoid potential cardiovascular side effects.[14]

We have been interested in developing $Ca_V1.3$ selective inhibitors for treating PD; a calcium influx assay was developed using fluorometric imaging plate reader[15] (FLIPR) with a Fluo-8 calcium dye[16] and stably expressed $Ca_V1.3$ and $Ca_V1.2$ LTCCs in HEK293 cells. We tested diverse known $Ca_V1.2$ LTCCs blockers,[17,18] such as isradipine (**1**), verapamil (**2**), and diltiazem (**3**), and synthesized over 100 modified DHPs[19] and various hydropyrimidines[20] (**4**) to obtain $Ca_V1.3$ selective antagonists; however, the best of these compounds have no greater than 2- to 3-fold selectivity for $Ca_V1.3$ over $Ca_V1.2$ LTCCs. More recently, high-throughput screening of molecular libraries identified pyrimidine-2,4,6-trione (PYT) **5** as a potential scaffold for the selective inhibition of $Ca_V1.3$ LTCCs.[21] After SAR-based initial modification of the scaffold, we arrived at *N*-(3-chlorophenethyl)-*N*′-cyclopentylpyrimidine-2,4,6-trione (**6**) as a selective $Ca_V1.3$ LTCC antagonist and *N*-(4-chlorophenethyl)-*N*′-(±)-*endo*-norbornylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**7**) as a potent $Ca_V1.3$ LTCC antagonist among the series of compounds (Figure 1). PYT is a completely

new scaffold as applied to the ion channels, and selective inhibition of $Ca_V1.3$ LTCCs with PYTs is the first approach for the treatment of PD as a potential cure. Herein, we report on our lead optimization efforts to obtain diverse potent and selective compounds.

DESIGN

Our previous study showed that, starting from symmetric N,N′-disubstituted pyrimidine 2,4,6-trione (PYT) **5**, changing a phenethyl group to a cyclopentyl ring led to the discovery of our most selective molecule, **6**, and using an *endo*-norbornyl group led to most potent molecule (7) in this scaffold. We synthesized ∼100 PYT molecules utilizing electronically and/or sterically diverse arylalkyls, alkyls, and three- to seven-membered cycloalkyl rings. All selective compounds in this class share *N*-cycloalkyl and *N*-arylethyl moieties as the side chains. An overlapped visualization of compounds **6** and **7** was used as the starting point for further derivatization to obtain more potent and selective compounds. As shown in Figure 2, molecules **6** and **7** are only different at the cycloalkyl region and the substitution of the aromatic ring. The two extra carbons of the norbornyl ring in **7** or para-chloro substitution on the aromatic ring make **7** 3-fold more potent than **6** toward $Ca_V1.3$ LTCC. It seems that a hydrophobic site is key for selective inhibition of $Ca_V1.3$ over $Ca_V1.2$ LTCCs. On the basis of this analysis, various 2- or 3-alkyl substituted cycloalkyl derivatives, as well as diverse bicycloalkyl derivatives, were prepared to probe the steric demands arising from this hydrophobic binding site. *m*-Chloro and *p*-chlorophenethyl groups were initially chosen as the other side chain to verify the SAR. Since racemic norbornyl derivatives showed good potency for $Ca_V1.3$ LTCCs, we synthesized each enantiomer of the *endo*-norbornyl derivatives to explore the effect of chirality. Diverse ethers and esters were incorporated at the 1, 2, and 3 positions of the cyclopentyl ring to investigate the electronic demands of the cyclopentyl ring region. To explore the steric demands on the ethylene linker of the *N*-phenethyl side chain while maintaining cyclopentyl or *endo*-norbornyl as the other side chain, diverse methyl, *gem*-dimethyl, phenyl, and carbonate moieties were employed on the α- or β-position of the ethylene linker. Similarly, diverse aromatic rings were employed for lead optimization. The moieties used for the construction of the PYT library are shown in Figure 3.

RESULTS AND DISCUSSION

Chemistry

A majority of PYT analogues were synthesized from commercially available amines and isocyanates using the previously established one-pot synthesis of N,N-disubstituted PYTs, which involved the Wöhler[22] urea synthesis and a Biltz and Wittek[23] condensation with activated malonic acid (Scheme 1). Urea formation was accomplished by coupling isocyanates with amines in dichloromethane. If the starting amine was an acid salt, 1 equiv of triethylamine was added to the reaction mixture to initiate urea formation. The addition of malonyl chloride to the urea, performed under dilute conditions (0.02 M in dichloromethane) to avoid intermolecular acylation, provided the condensation products in moderate to high yields. The use of these synthetic approaches permitted the construction of the major library members in sufficient quantities and purity for assay against $Ca_V1.3$ and $Ca_V1.2$ LTCCs.

Commercially unavailable isocyanates and amines were prepared from related ketones, acetonitriles, carboxylic acids, and other amines. Enantiomerically pure (1*S*,2*R*,4*R*)-(−)-*endo*-2-norbornyl isocyanate (**10**) and (1*R*,2*S*,4*S*)-(+)-*endo*-2-nor-bornyl isocyanate (**13**) were prepared via a combination of the Poll[24] and Fukaya[25] procedures (Scheme 2); asymmetric Diels–Alder reactions of cyclopentadiene with an acrylate using (*R*)-pantolactone or (*S*)-2-hydroxy-*N*-methylsuccinimide chiral auxiliary provided chiral carboxylate intermediates. The resulting mixture underwent saponification and catalytic hydrogenation to give enantiomerically pure *endo*-norbornyl carboxylic acids **9** and **12**. Carbonyl azide formation, followed by Curtius rearrangement, provided enantiomerically pure (1*S*,2*R*,4*R*)- or (1*R*,2*S*,4*S*)-*endo*-norbornyl isocyanates (**10, 13**), which were stored in the refrigerator and used for several months without further purification.

Commercially unavailable methyl-substituted phenethylamines (**16a–d**) required for the syntheses were prepared as shown in Scheme 3.[26] Methylation of commercially available phenylacetonitriles (**14a,b**) with iodomethane, using sodium hydride as base, yielded a mixture of mono- and dimethylated acetonitriles (**15a–d**). Reduction of the nitriles with $LiAlH_4$ provided the target phenethylamines (**16a–d**) in high yields.

A majority of alkoxyl or carboxylate substituted cyclopentyl-amines used in these syntheses were easily prepared from the corresponding (*N*-Boc-amino)cyclopentanecarboxylic acids or (*N*-Boc-amino)cyclopentyl alcohols in a two-step process: esterification of the acids/ alcohols with appropriate alcohols/ acids, and Boc deprotection with 50% TFA solution in dichloromethane. Alkyl-substituted cycloalkylamines were synthesized from the corresponding cyclopentanone by reductive amination with a benzylamine (Scheme 4). Especially, *cis*-2-methyl or 2,2-*gem*-dimethylcyclopentyl[27] PYT derivatives were produced by asymmetric reductive amination of a cyclopentanone with a nonracemic α-methylbenzylamine,[28] which occurs specifically from the face opposite[29] that occupied by the adjacent alkyl substituent, to furnish the racemic *cis*-diastereomer in a low yield. This product was then coupled to the isocyanate as before, and the ethylbenzene was removed by treatment with 75% trifluoroacetic acid in dichloromethane. The urea was cyclized with malonyl chloride to furnish the final PYT ring. When the same procedure was applied for the synthesis of 3-alkyl substituted cyclopentyl derivatives, inseparable racemic mixtures were obtained.

Biological Activity

The $Ca_V1.3$ and $Ca_V1.2$ LTCCs assays were carried out with the synthesized PYT molecules using the previously described high-throughput screen with a FLIPR system and Fluo-8 calcium assay kit.[19] Each IC_{50} value, the concentration of test compounds required to inhibit 50% of calcium-dependent fluorescence response in the assay, was determined in triplicate (Tables 1–4). IC_{50} values and associated standard deviations were calculated by curve fitting of the percent inhibition data from the FLIPR assay to a sigmoidal model for a one-site compound target interaction using XLfit. The selectivity of antagonism was defined as the inverse of the ratio of the IC_{50} value with $Ca_V1.2$ LTCCs to that with $Ca_V1.3$ LTCCs. The Z' score of the HTS was >0.6 on the basis of the values from at least a one-half of a

plate of positive and negative controls, and standard deviations associated with the calcium channel FLIPR assay were usually <20%.

To better understand the steric effect of the original *N*-cyclopentyl, *N*-3-chlorophenethyl PYT molecule (**6**) on potency and selectivity, our initial analogue efforts were focused on variations of steric bulkiness at the cyclopentyl moiety by alkyl substitutions on that ring. We used 3-chlorophenethyl and 4-chlorophenethyl moieties as the other side chain to confirm the substitution effect on the aromatic ring. As shown in Table 1, analogues with 1-*cis*-methyl (**19, 20, 24, 25**), 1,1-dimethyl (**21, 22, 26, 27**), 2-methyl (**30, 31**), and 2,2-dimethyl (**32, 33**) substitutions on the cyclopentyl ring had generally 1- to 4-fold increased binding affinity for both $Ca_V1.3$ and $Ca_V1.2$ LTCCs; 1,1-dimethyl-cyclopentyl compound **22** displayed an IC_{50} of 1.7 μM for $Ca_V1.3$ LTCCs. It seems that the binding site preferentially recognizes the stereochemistry of 1,2-cis substituted compounds. The favored 1,2-substitution pattern is also shown when utilizing cyclohexyl as the cycloalkyl chain (**41**). This steric preference was slightly increased with the combination of 4-chlorophenethyl as the other side chain (compounds **20** vs **19, 25** vs **24**, and **22** vs **21**). Alkyl substituted cyclopentyl derivatives had ∼3-fold lower IC_{50} for $Ca_V1.3$ LTCCs, but they also had increased $Ca_V1.2$ binding affinity; their $Ca_V1.3$ selectivities, therefore, were moderate to low. However, it is noteworthy that the 3-methyl- or 3,3-dimethylcyclopentyl derivatives still retained >7-fold selectivity for $Ca_V1.3$ LTCCs. Those compounds having (±)-*trans*-2-methylcyclopentyl (**37, 38**), 3-ethylcyclopentyl (**31, 35**), or 4-methylcyclohexyl (**39–42**) moieties were similar in potency to compound **6** but far less selective. In the bicyclic ring series, a significant potency drop was noted by increasing the bulkiness of the bicyclic rings. It seems the active site that interacts with the cyclopentyl moiety is not big enough to fit bornyl (**53, 54**), *cis*-myrtanyl (**55, 56**), or isopinocamphyl (**57–60**) groups; these bulky molecules have almost no binding to either $Ca_V1.3$ or $Ca_V1.2$ LTCCs. Racemic *endo*-norbornyl compound **7** was the most potent molecule in the previous study.[19] To confirm the stereoactivity relationship, we asymmetrically synthesized each pair of enantiomers (**49** and **50, 51** and **52**, and **107** and **108**) to isolate the more potent and selective enantiomer, as each enantiomer of known chiral LTCC blockers displays different efficacies.[30] Although chiral compounds **50** and **51** displayed excellent selectivity (>48-fold) with good potency (∼2.0 μM) for $Ca_V1.3$ LTCCs, there was only a small stereorelated preference for $Ca_V1.3$ LTCCs with the (1*S*,2*R*,4*R*)-norbornyl moiety; (1*S*,2*R*,4*R*)-norbornyl analogues are 1.1- to 1.8-fold more potent than (1*R*,2*S*,4*S*)-norbornyl analogues for $Ca_V1.3$ LTCCs. Presumably, each *endo*-norbornyl group can freely rotate in the binding site; therefore, they are recognized similarly.

The other interesting molecule resulting from this study is cyclohexylethyl drivative (*S*)-*N*-(3-chlorophenethyl)-*N*-(1-cyclohexylethyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**43**). This compound is slightly more potent (IC_{50} = 4.3 μM) than lead compound **6** and is a moderately selective antagonist for $Ca_V1.3$ LTCCs. In addition to **43**, all three *N*-(1-cyclohexylethyl) derivatives (**44–46**) in this study displayed good selectivity over $Ca_V1.2$, with IC_{50} of 4.3–9.7 μM for $Ca_V1.3$ LTCCs. These compounds have additional carbons between the cycloalkyl and PYT rings that will allow further structural variations on the cyclopentyl side chain.

Another trend that emerges from the SAR of various PYT molecules is the unfavorable effect of polar functionality on the cyclopentyl ring. Previous SAR studies showed that an electron lone pair or charge (hydrophilicity) on the aryl ring limits its binding affinity for both calcium channels. As shown by compounds **65** and **67** in Table 2, charged molecules or even an alcohol derivative (**69**) has no binding affinity for either $Ca_V1.3$ or $Ca_V1.2$ LTCCs, even at 100 μM. A hydrophobic cycloalkyl chain also is favored, and bulky esters or ethers (**63, 66, 68, 74**) do not seriously reduce (1- to 2-fold reduction) binding affinity for both $Ca_V1.2$ and $Ca_V1.3$ LTCCs. It is thought that the hydrophilicity arising from the heteroatoms are counterbalanced by the nonpolar groups, and so the ether bond on the cycloalkyl chain can be utilized as a linker for further modification. The cis-1,2-substitution pattern is also favored when acetoxyl is substituted on the cyclopentyl chain (**71** and **72**), even though it results in 6-fold reduced binding affinity. The favored 3-substitution pattern for selectivity was not observed with the ether or ester substituted derivatives; presumably the binding site in $Ca_V1.2$ LTCCs recognizes hydrophobic functional groups of various inhibitors differently.

When the 3-chlorophenethyl substituent was changed to various fused aromatic rings, such as 1-tetrahydronaphthyl (**77**), 1-indanyl (**78**), and 2-indanyl (**79**), their binding affinity for $Ca_V1.3$ decreased 2-fold while their potency for $Ca_V1.2$ increased (Table 3). Although different lengths of alkyl linkers (**81–84**) were incorporated to adjust the space of this region, it was found that the ethyl linker was best for potency and selectivity. It is not clear whether this region disfavors hydrophilic functionalities, but carboxylate analogues **93–95** did not provide better potency or selectivity for $Ca_V1.3$ LTCCs. Another trend that emerged from the ethyl linker region is the steric preference; methyl- or dimethyl-substituted members or phenyl substituted members (**89, 90, 96–99**) have 1- to 3-fold improved binding affinity for $Ca_V1.3$ LTCCs. However, this modification also results in better interaction with $Ca_V1.2$ LTCCs; the overall selectivity for $Ca_V1.3$ LTCCs was 1- to 5-fold. 3,4- or 3,5-Dichloro and 3,5-bis(trifluoromethyl) substitution on the aromatic ring (**85–87**) led to ∼5-fold improved potency (IC_{50} = 1.2–1.4 μM) for $Ca_V1.3$ LTCCs, but selectivities were moderate.

Previously, $Ca_V1.3$ inhibitory activity was improved with substitution of the cyclopentyl group by the *endo*-norbornyl group; thus, a small series of norbornyl analogues (**100–106**) were prepared to determine optimal arylalkyl moiety (Table 4). The combination of *endo*-norbornyl with β-methyl-4- chlorophenethyl (**100**), α-methyl-4-chlorophenethyl (**101**), β-methyl-3-chlorophenethyl (**102**), β,β-dimethyl-3-chlorophe-nethyl (**103**), 2-(bis-3-(trifluoromethyl)phenyl)ethyl (**104**), 2-(3,5-dichlorophenyl)ethyl (**105**), or 2-(3-(trifluoromethyl)-phenyl)ethyl (**106–108**) led to good $Ca_V1.3$ LTCCs inhibitory activity, with IC_{50} values of 1.8–3.6 μM. Compounds **106–108**, as racemic mixtures or individual enantiomers, gave IC_{50} values of 2–3 μM for $Ca_V1.3$ and ∼40-fold selectivity over $Ca_V1.2$ LTCCs. The (1*S*,2*R*,4*R*)-*endo* analogue (**108**) is slightly more potent than the (1*R*,2*S*,4*S*)-*endo* analogue (**107**), but they are almost the same in their $Ca_V1.3$ LTCCs inhibitory activity and selectivity.

CONCLUSION

Our SAR study of *N*-(3-chlorophenethyl)-*N*'-cyclopentylpyr-imidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**6**) highlights several advancements in lead optimization of the PYT scaffold. One of the trends found from these analogues is that the *endo*-norbornyl moiety provides high selectivity for $Ca_V1.3$ LTCCs with good binding affinity if an appropriate arylalkyl moiety is used as the other side chain. Second, both $Ca_V1.3$ and $Ca_V1.2$ LTCCs have limited space to interact with various steric requirements at the cycloalkyl ring binding site; however, insertion of a one methylene linker between the cycloalkyl and PYT rings retains selectivity. Third, inactive compounds at both $Ca_V1.3$ and $Ca_V1.2$ LTCCs have a charged ion or electron lone pair near the cycloalkyl ring, implying that strong polarity should be avoided for antagonism of $Ca_V1.3$ LTCCs. Fourth, both $Ca_V1.3$ and $Ca_V1.2$ Ca^+ channels preferentially recognize the regiochemistry of 1,2/1,3-substituted cycloalkyl derivatives. The overall SAR of the PYT analogues identified four important series of molecules that either retained selectivity or enhanced binding affinity: The chiral *N*-*endo*-norbornyl analogues **50** ($Ca_V1.3$ IC_{50} = 2.1 ± 0.4 μM, selectivity ≥ 48), **51** ($Ca_V1.3$ IC_{50} = 2.0 ±0.1 μM, selectivity ≥ 50), and **108** ($Ca_V1.3$ IC_{50} = 2.1 ± 0.1 μM, selectivity = 36) have low micromolar activity against $Ca_V1.3$ LTCCs while retaining >36 selectivity. Dimethyl substitution on the cyclopentyl ring (**22**, $Ca_V1.3$ IC50 = 1.7 ± 0.1 μM) or on the arylethyl side chain (**98**, $Ca_V1.3$ IC50 = 2.4 ± 0.2 μM) leads to improved potency for $Ca_V1.3$. Among the studied PYT molecules, 3,4- or 3,5-disubstituted phenethyl derivatives (**85**, $Ca_V1.3$ IC_{50} = 1.4 ± 0.1 μM; **86**, $Ca_V1.3$ IC_{50} = 1.2 ± 0.1 μM) are the most potent inhibitors for $Ca_V1.3$ LTCC. *N*-1-Cyclohexylethyl analogue **43** ($Ca_V1.3$ IC50 = 4.3 ± 0.5 μM, selectivity ≥ 29) is one of the potent and selective molecules; this side chain could be further modified. Our study highlights several advancements in the lead optimization and diversification toward the drug development of PYTs. The superimposition of the energy-minimized structures of selective or potent molecules highlights the overlapping and variable regions (Figure 4); these hotspots are located at or near the cycloalkyl and aromatic rings and should be important for future modifications.

EXPERIMENTAL SECTION

General Methods for Biology

Experimental procedures for the construction and stable transfection of HEK293 cells with $Ca_V1.3$ and $Ca_V1.2$ and procedure for high-throughput screening were previously reported.[17,19] Rat $Ca_V1.3\alpha$ 1D (GenBank code AF370010) containing all alternative splice sites, rat Ca_V β3 (GenBank code M88751), rat Ca_V α2δ-1 (GenBank code 286488), and rabbit $Ca_V1.2\alpha$ 1C (GenBank code P15381) cDNAs were used. Screen Quest Fluo-8 no wash calcium assay kit (ABD Bioquest Inc., Sunnyvale, CA, U.S.) on a FLIPR tetra (Molecular Devices LLC, Sunnyvale, CA, U.S.) were used for the high-throughput assay. HEK293 cell density was 4×10^4 cells/ well and cultured in DMEM with 10% FBS for 4 days.

General Methods for Synthesis and Structure Characterization

Reagents were purchased from Sigma-Aldrich, Alfa-Aesar, TCI America, and Chem-Impex and were used without further purification. Solvents were purified by passage through a solvent column composed of activated alumina and a supported copper redox catalyst. Normal phase flash column chromatography was performed using SuperFlash Si 50 prepacked silica cartridges with an Agilent 971-FP flash purification system. Reaction progress was monitored by thin-layer chromatography (TLC) carried out on SiliCycle silica gel plates (2.5 cm × 7.5 cm, 250 μm thick, 60 F254), visualized by using UV (254 nm) and ninhydrin stain. ^{1}H NMR and ^{13}C NMR spectra were recorded in the indicated solvent on a Bruker Avance-III (500 and 126 MHz for ^{1}H and ^{13}C, respectively) spectrometer. Chemical shifts are given in ppm (δ) relative to the internal standard, and coupling constants (*J*) are in hertz (Hz). MS was performed on a system consisting of an electrospray ionization (ESI) source in a Thermo Finnigan LCQ mass spectrometer. High resolution mass spectra were obtained using an Agilent 6210 LC-TOF spectrometer. Melting points were measured in open capillaries on a Büchi B-540 melting point analyzer. The purity of the compounds was evaluated on an Agilent 1260 reverse phase analytical HPLC system using an Agilent Zorbax Eclipse XDB-C18 (4.6 mm × 50 mm, 5 μm) reverse phase column with UV absorbance and evaporative light scattering detection. Optical rotations were measured using an AA-100 polarimeter. The chiral purity of the compounds was evaluated on a Beckman Gold HPLC system using Daicel CHIRALPAK AD-RH or OD-RH (4.6 mm × 150 mm, 5 μm) reverse phase chiral columns.

General Procedure for PYT Synthesis Using Amine and Isocyanate. Method A

To a solution of an amine (1 mmol) in dry dichloromethane (10 mL), was added an isocyanate (1 mmol), and the mixture was stirred at room temperature for 1–5 h. After dilution with dry dichloromethane (40 mL), malonyl chloride (1.1 mmol) was added dropwise under vigorous stirring at room temperature for 5 min. The resulting pale yellow solution was stirred for an additional 1 h and washed with brine (50 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated at reduced pressure to a small volume. The resultant reaction mixture was purified using a silica gel cartridge (24 g) with an Agilent 971-FP purification system to give analytically pure compounds (20–90% yield).

(1*S*,2*R*,4*R*)-Bicyclo[2.2.1]heptane-2-isocyanate (10)

Precursor **9** was prepared according to Poll[24] and Fukaya.[25] To a solution of ethyl chloroformate (2.04 mL, 21.4 mmol) in hexane (20 mL) was added dropwise a solution of **9** (3.0 g, 21.4 mmol) and triethylamine (3.07 mL, 22 mmol) in hexane (20 mL) at 0 °C. After being stirred for 30 min at the same temperature, the mixture was quickly filtered. The filtrate was dried under vacuum and redissolved in acetone (20 mL). To this solution, a solution of sodium azide (2.2 g, 32 mmol) in water (20 mL) was added dropwise at 0 °C, and stirring continued for 2 h at the same temperature. The mixture was poured into ice–water (50 mL), and the organic materials were extracted with hexane (50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and then heated to reflux for 5 h. After the mixture was cooled to room temperature, the solvent was removed by vacuum evaporation to give a crude product of **10** (2.26g, 75%). The product was used in the next step without

further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (m, 1H), 2.35 (t, *J* = 4.3 Hz, 1H), 2.25 (t, *J* = 4.6 Hz, 1H), 2.12–1.98 (m, 1H), 1.79 (m, 1H), 1.67–1.54 (m, 1H), 1.47 (m, 1H), 1.38–1.29 (m, 3H), 1.05 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 121.20, 55.10, 42.28, 39.32, 37.36, 36.79, 29.54, 21.88. $[\alpha]^{25}_{D}$ (*c* 1, $CHCl_3$) = −1.3.

(1*R*,2*S*,4*S*)-Bicyclo[2.2.1]heptane-2-isocyanate (13)

13 was prepared from **12** following a similar reaction procedure described for **10**, and spectral data were identical to those of **10**. $[\alpha]^{25}_{D}$ (*c* 1, $CHCl_3$) = +1.5.

2-(3-Chlorophenyl)propanenitrile (15a) and 2-(3-Chloro-phenyl)-2-methylpropanenitrile (15b)

To a solution of (3-chlorophenyl)acetonitrile (3.0 g, 20 mmol) in DMF (40 mL) was added NaH (1.6 g, 40 mmol, 60% in oil) portionwise at room temperature. After the mixture was stirred for 15 min, MeI (4.56 g, 32 mmol) was added. The mixture was stirred overnight. The reaction mixture was quenched with saturated NH_4Cl (80 mL), extracted with ethyl acetate (200 mL), dried over $MgSO_4$, and concentrated at reduced pressure. The organic residue was purified by flash column chromatography to give **15a** (0.49 g, 15%) and **15b** (1.61 g, 45%). **15a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.13 (m, 4H), 3.91 (q, *J* = 7.3 Hz, 1H), 1.68 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.90, 135.03, 130.49, 128.40, 127.03, 124.98, 120.97, 30.97, 21.33. MS (ESI): calculated for C_9H_8Cl $[M + H]^+$, 166.04; found, 166.19. **15b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.29 (m, 4H), 1.73 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.41, 130.28, 128.12, 126.13, 125.45, 123.95, 123.49, 37.05, 29.04. MS (ESI): calculated for $C_{10}H_{12}F_3N$ $[M + H]^+$, 204.10; found, 204.24.

2-(3-(Trifluoromethyl)phenyl)propanenitrile (15c) and 2-Methyl-2-(3-(trifluoromethyl)phenyl)propanenitrile (15d)

15c and **15d** were prepared (**15c** = 5%, **15d** = 59% yield) from (3-(trifluoromethyl)phenyl)acetonitrile following a similar reaction procedure described for **15a,b. 15c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.48 (m, 4H), 4.01 (q, *J* = 7.3 Hz, 1H), 1.71 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.01, 131.65 (q, *J* = 32.6 Hz), 130.20, 129.83, 125.12 (d, *J* = 4.0 Hz), 123.72 (q, *J* = 272.5 Hz), 123.64 (q, *J* = 3.9 Hz), 120.81, 31.17, 21.37. MS (ESI): calculated for $C_{10}H_8F_3N$ $[M + H]^+$, 200.07; found, 200.23. **15d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.43 (m, 4H), 1.79 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.48, 131.56 (q, *J* = 32.2 Hz), 129.62, 128.82, 124.87 (d, *J* = 4.3 Hz), 123.79, 123.69 (q, *J* = 277 Hz), 121.82 (d, *J* = 3.8 Hz), 37.20, 29.06. MS (ESI): calculated for $C_{10}H_8F_3N$ $[M + H]^+$, 214.20; found, 214.23.

2-(3-Chlorophenyl)propan-1-amine (16a)

To a solution of **15a** (0.40 g, 2.45 mmol) in THF (25 mL) at 0 °C was added 1.0 M solution of $LiAH_4$ (7.35 mL, 7.35 mmol). After being stirred for 2 h at the same temperature, the mixture was warmed to room temperature, quenched with saturated NH_4Cl (30 mL), and partitioned with ethyl acetate (30 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give **16a** (0.253g, 61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.15 (m, 4H), 3.65 (m, 1H), 2.77 (m, 2H), 1.23 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz,

$CDCl_3$) δ 147.09, 134.97, 130.50, 128.36, 127.00, 124.99, 49.12, 30.92, 21.28. MS (ESI): calculated for $C_9H_{12}ClN$ $[M + H]^+$, 170.07; found, 169.85.

2-(3-Chlorophenyl)-2-methylpropan-1-amine (16b)

16b was prepared (yield 73%) from **15b** following a similar reaction procedure described for **16a**. Pale yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.10 (m, 4H), 2.79 (s, 2H), 1.30 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.42, 134.34, 129.64, 126.63, 126.15, 124.43, 54.47, 39.97, 26.22. MS (ESI): calculated for $C_{10}H_{15}ClN$ $[M + H]^+$, 184.09; found, 183.96.

2-(3-(Trifluoromethyl)phenyl)propan-1-amine (16c)

16c was prepared (yield 61%) from **15c** following a similar reaction procedure described for **16a**. Pale yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66–7.45 (m, 4H), 3.62 (m, 1H), 2.81 (m, 2H), 1.50 (d, J = 6.6 Hz, 3H). MS (ESI): calculated for $C_{10}H_{12}F_3N$ $[M + H]^+$, 204.09; found, 204.43.

2-Methyl-2-(3-(trifluoromethyl)phenyl)propan-1-amine (16d)

16d was prepared (yield 68%) from **15d** following a similar reaction procedure described for **16a**. ^1H NMR (500 MHz, $CDCl_3$) δ 7.71–7.30 (m, 4H), 2.90 (s, 2H), 1.40 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.04, 130.77 (q, J = 32.3 Hz), 129.59, 129.08, 128.85, 123.40 (d, J = 3.9 Hz), 123.15 (m), 122.80 (d, J = 3.7 Hz), 52.91, 38.96, 26.14. MS (ESI): calculated for $C_{11}H_{14}F_3N$ $[M + H]^+$, 218.12; found, 218.23.

(1*S*,2*R*)-2-Methyl-*N*-((*S*)-1-phenylethyl)cyclopentanamine (18a)

A mixture of 2-methylcyclopentanone (0.294 g, 3.0 mmol), (*S*)-1-phenylethanamine (0.774 mL, 6.0 mmol), and a catalytic amount of TsOH in benzene (25 mL) was refluxed overnight. After being cooled to room temperature, the reaction mixture was diluted with 10 mL of absolute EtOH, and sodium cyanoborohydride (569 mg, 9 mmol) was then added to the reaction mixture in three portions over a ∼5 h period. The reaction mixture was quenched with brine (50 mL), partitioned with ethyl acetate (50 mL), dried over $MgSO_4$, and concentrated on reduced pressure. The resulting residue was subjected to silica gel chromatography to purify the major component as **18a** (0.238 g, 36%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.49–7.04 (m, 5H), 3.78 (q, J = 6.6 Hz, 1H), 2.82 (m, 1H), 2.10 (m, 1H), 1.74–1.56 (m, 3H), 1.46–1.35 (m, 1H), 1.33 (d, J = 6.5 Hz, 3H), 1.28 (m, 2H), 0.87 (d, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.29, 128.30, 126.72, 126.67, 59.51, 56.26, 34.02, 31.51, 30.18, 24.99, 20.25, 13.56. MS (ESI): calculated for $C_{14}H_{21}N$ $[M + H]^+$, 204.18; found, 204.14.

(1*R*,2*S*)-2-Methyl-*N*-((*R*)-1-phenylethyl)cyclopentanamine (23a)

23a was prepared (yield 33%) with (*R*)-1-phenylethanamine following a similar reaction procedure described for **18a**. Spectral data were identical to those of **18a**.

(*S*)-2,2-Dimethyl-*N*-((*S*)-1-phenylethyl)cyclopentanamine (18b)

18b was prepared (yield 63%) from (*S*)-1-phenylethanamine and 2,2-dimethylcyclopentanone following a similar reaction procedure described for **18a**. ^1H NMR

(500 MHz, $CDCl_3$) δ 7.49–7.06 (m, 5H), 3.91 (q, *J* = 6.6 Hz, 1H), 2.56 (dd, *J* = 9.6, 7.7 Hz, 1H), 2.44–2.30 (m, 1H), 1.82–1.70 (m, 1H), 1.61–1.54 (m, 1H), 1.48–1.36 (m, 3H), 1.35 (d, *J* = 6.6 Hz, 3H), 1.30–1.19 (m, 1H), 1.05 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.72, 128.29, 126.76, 126.24, 65.58, 57.30, 40.90, 39.96, 31.87, 28.15, 24.36, 21.14, 19.71. MS (ESI): calculated for $C_{15}H_{24}ClN$ $[M + H]^+$, 218.19; found, 218.18.

(*R*)-2,2-Dimethyl-*N*-((*R*)-1-phenylethyl)cyclopentanamine (23b)

23b was prepared (yield 60%) from 2,2-dimethylcyclopenta-none and (*R*)-1-phenylethanamine following a similar reaction procedure described for **18a**. Spectral data were identical to those of **18b**.

3-Methyl-*N*-((*S*)-1-phenylethyl)cyclopentanamine (29a)

Diastereomeric mixture **29a** was prepared (yield 71%) from 3-methylcyclopentanone and (*S*)-1-phenylethanamine following a similar reaction procedure described for **18a**. ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.31 (m, 12H), 7.26–7.12 (m, 4H), 4.07–3.94 (m, 1H), 3.14–2.89 (m, 1H), 2.21–2.05 (m, 1H), 1.91–1.75 (m, 2H), 1.74–1.64 (m, 1H), 1.55 (dd, *J* = 6.8, 2.1 Hz, 3H), 1.41–1.13 (m, 2H), 1.01–0.91 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.56, 128.79, 127.86, 127.24, 56.97, 56.87, 56.63, 56.05, 41.09, 39.99, 33.34, 32.99, 32.50, 32.25, 32.13, 30.96, 29.62, 24.13, 22.64, 20.44. MS (ESI): calculated for $C_{14}H_{21}N$ $[M + H]^+$, 204.18; found, 204.12.

3,3-Dimethyl-*N*-((*S*)-1-phenylethyl)cyclopentanamine (29b)

Diastereomeric mixture **29b** was prepared (yield 75%) from 3,3-dimethylcyclopentanone and (*S*)-1-phenylethanamine following a similar reaction procedure described for **18a**. Major isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.20 (m, 5H), 3.98–3.77 (m, 1H), 2.93–2.78 (m, 1H), 1.95–1.87 (m, 1H), 1.75–1.67 (m, 1H), 1.57–1.54 (m, 3H), 1.47–1.39 (m, 4H), 0.96 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.52, 128.31, 126.76,126.31, 57.28, 46.85, 38.86, 35.29, 29.36, 29.24, 20.72. MS (ESI): calculated for $C_{15}H_{24}ClN$ $[M + H]^+$, 218.19; found, 218.13.

3-Ethyl-*N*-((*S*)-1-phenylethyl)cyclopentanamine (29c)

Diastereomeric mixture **29c** was prepared (yield 74%) from 3-ethyl-cyclopentanone and (*S*)-1-phenylethanamine following a similar reaction procedure described for **18a**. Isomeric mixture: ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.09 (m, 5H), 3.81 (p, *J* = 6.8 Hz, 1H), 3.01–2.82 (m, 1H), 2.20–2.04 (m, 1H), 1.98–1.75 (m, 2H), 1.69–1.57 (m, 1H), 1.52–1.35 (m, 3H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.28–1.19 (m, 2H), 0.89–0.80 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.03, 128.35, 126.77, 126.75, 126.63, 126.59, 56.98, 56.85, 56.57, 56.50, 56.22, 56.20, 56.14, 45.03, 41.09, 40.54, 40.35, 40.07, 39.87, 39.75, 39.65, 38.94, 38.67, 38.58, 34.24, 33.39, 32.79, 31.93, 31.28, 31.16, 30.08, 29.89, 29.36, 29.24, 29.23, 29.21, 29.16, 28.44, 24.70, 24.65, 24.60, 12.87. MS (ESI): calculated for $C_{15}H_{23}N$ $[M + H]^+$, 218.19; found, 218.14.

2,3-Dimethyl-*N*-((*S*)-1-phenylethyl)cyclopentanamine (29d)

Diastereomeric mixture **29d** was prepared (yield 63%) from 2,3-dimethylcyclopentanone and (*S*)-1-phenylethanamine following a similar reaction procedure described for **18a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.14 (m, 5H), 3.82–3.70 (m, 1H), 3.00 (dt, *J* = 7.7, *6.6* Hz, 1H), 1.85–1.78 (m, 1H), 1.73 (m, 1H), 1.69–1.53 (m, 4H), 1.35 (d, *J* = *6.6* Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.62, 128.73, 128.31, 126.72, 58.85, 56.57, 43.21, 40.09, 31.83, 31.14, 24.53, 20.90, 14.02. MS (ESI): calculated for $C_{15}H_{23}N$ $[M + H]^+$, 218.19; found, 218.28.

General Procedure for 19–22, 24–27, and 30–36. (Method B)

To a solution of an *N*-(1-phenylethyl)cyclopentylamine (**18a,b, 23a,b, 29a–d**; 1 mmol) in dry dichloromethane (10 mL) was added an isocyanate (1 mmol), and the mixture was stirred at room temperature for 3 h. The solvent was removed by vacuum distillation, and 95% TFA in water (5 mL) was added to the reaction mixture. After being stirred for 1 h at room temperature, the reaction mixture was concentrated under vacuum, redissolved in toluene, and then dried by vacuum distillation. After the sample was dissolved in dry dichloromethane (40 mL), malonyl chloride (1.1 mmol) was added dropwise under vigorous stirring at room temperature for 5 min. The resulting pale yellow solution was stirred for an additional 1 h and washed with brine (50 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated at reduced pressure to a small volume. The resultant reaction mixture was purified with silica gel (24 g) using an Agilent 971-FP purification system to give analytically pure compounds (50–80% yield).

Spectral Data of the Most Active Compounds. (*S*)-1-(3-Chlorophenethyl)-3-(1-cyclohexylethyl)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (43) and (*R*)-1-(3-Chlorophenethyl)-3-(1-cyclohexylethyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (45)

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.07 (m, 4H), 4.50 (m, 1H), 4.09 (m, 2H), 3.60 (s, 2H), 2.90 (m, 2H), 2.04 (m, 1H), 1.87 (m, 1H), 1.76 (m, 1H), 1.66 (m, 2H), 1.36 (d, *J* = 6.9 Hz, 3H), 1.32–1.06 (m, 4H), 0.86 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.85, 164.64, 150.91, 139.75, 134.27, 129.81, 129.13, 127.21, 126.95, 51.35, 42.50, 39.88, 39.20, 33.57, 30.83, 29.83, 26.07, 25.79, 25.71, 16.29. HRMS (ESI): calculated for $C_{20}H_{25}ClN_2O_3$ $[M – H]^-$, 375.1481; found, 375.1494. **43**, HPLC purity: 99.2%, $[\alpha]^{25}_D$ (*c* 2, $CHCl_3$) = −6.8, chiral HPLC (Daicel AD-RH, 4.6–150 mm, 5 μm; 70% acetonitrile/30% 0.05 M pH 2 phosphate buffer; 0.4 mL/min; 268 nm) t_R = 30.933 min; >99% ee. **45**, HPLC purity: 99.9%, $[\alpha]^{25}_D$ (*c* 2, $CHCl_3$) = +7.0; chiral HPLC (Daicel AD-RH, 4.6–150 mm, 5 μm; 70% acetonitrile/30% 0.05 M pH 2 phosphate buffer; 0.4 mL/min; 268 nm) t_R = 28.017 min; >99% ee.

(*S*)-1-(4-Chlorophenethyl)-3-(1-cyclohexylethyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (44) and (*R*)-1-(4-Chlorophenethyl)-3-(1-cyclohexylethyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (46)

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 4.49 (m, 1H), 4.08 (m, 2H), 3.60 (s, 2H), 2.88 (m, 2H), 2.04 (m, 1H), 1.87 (m, 1H), 1.76 (m, 1H), 1.66 (m, 2H), 1.35 (d, *J* = 6.9 Hz, 3H), 1.31–1.06 (m, 4H), 0.85 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.85, 164.65, 151.06, 136.19, 132.56, 130.37, 128.66, 51.34,

42.56, 39.88, 39.19, 33.27, 30.81, 29.85, 26.06, 25.79, 25.70, 16.28. HRMS (ESI): calculated for $C_{20}H_{25}ClN_2O_3$ $[M-H]^-$, 375.1148; found, 375.1494. **44**, HPLC purity: 97.8%, $[\alpha]^{25}_D$ (*c* 2, $CHCl_3$) = −6.3, chiral HPLC (Daicel AD-RH, 4.6–150 mm, 5 μm; 70% acetonitrile/30% 0.05 M pH 2 phosphate buffer; 0.4 mL/min; 268 nm) t_R = 33.217 min; >99% ee. **46**, HPLC purity: 99.3%, $[\alpha]^{25}_D$ (*c* 2, $CHCl_3$) = +6.5, chiral HPLC (Daicel AD-RH, 4.6–150 mm, 5 μm; 70% acetonitrile/30% 0.05 M pH 2 phosphate buffer; 0.4 mL/min; 268 nm) t_R = 37.199 min; >99% ee.

1-((1*R*,2*S*,4*S*)-Bicyclo[2.2.1]heptan-2-yl)-3-(3-chlorophenethyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (49) and 1-((1*S*,2*R*,4*R*)-Bicyclo[2.2.1]heptan-2-yl)-3-(3-chlorophenethyl)-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (51)

White powder; mp 155–157 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.11 (m, 4H), 4.69–4.56 (m, 1H), 4.18–4.03 (m, 2H), 3.64 (dd, *J* = 9.2, 20.9 Hz, 2H), 2.90 (t, *J* = 7.8 Hz, 2H), 2.66–2.58 (m, 1H), 2.37 (t, *J* = 4.5 Hz, 1H), 2.22 (m, 1H), 1.81 – 1.65 (m, 2H), 1.59–1.50 (m, 1H), 1.47 (m, 1H), 1.45–1.37 (m, 2H), 1.36–1.31 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.90, 164.52, 152.15, 139.84, 134.29, 129.82, 129.09, 127.15, 126.93, 59.65, 42.82, 42.08, 40.90, 37.73, 37.53, 33.66, 29.49, 28.77, 23.86. HRMS (ESI): calculated for $C_{19}H_{21}ClN_2O_3$ $[M-H]^-$, 359.1168; found, 359.1172. **49**, HPLC purity: 99.0%; $[\alpha]^{25}_D$ (*c* 2, $CHCl_3$) = +9.4 chiral HPLC (Daicel OD-RH, 4.6–150 mm, 5 μm; 60% acetonitrile/40% 0.1 M aqueous KPF_6; 0.5 mL/min; 268 nm) t_R = 26.400 min, >99% ee. **51**, HPLC purity: 99.0%; $[\alpha]^{25}_D$ (*c* 2, $CHCl_3$) = −9.1, chiral HPLC (Daicel OD-RH, 4.6–150 mm, 5 μm; 60% acetonitrile/40% 0.1 M aqueous KPF_6; 0.5 mL/min; 268 nm) t_R = 22.867 min, 97.2% ee.

1-((1*R*,2*S*,4*S*)-Bicyclo[2.2.1]heptan-2-yl)-3-(4-chlorophenethyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (50) and 1-((1*S*,2*R*,4*R*)-Bicyclo[2.2.1]heptan-2-yl)-3-(4-chlorophenethyl)-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (52)

White powder; mp 121–123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 4.60 (m, 1H), 4.06 (m, 2H), 3.61 (dd, *J* = 21.1, 10.1 Hz 2H), 2.87 (t, *J* = 7.8 Hz, 2H), 2.58 (t, *J* = 3.8 Hz, 1H), 2.35 (t, *J* = 4.5 Hz, 1H), 2.19 (m, 1H), 1.78–1.61 (m, 2H), 1.58–1.47 (m, 1H), 1.47–1.29 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.90, 164.53, 152.17, 136.27, 132.56, 130.33, 128.68, 59.64, 42.91, 42.06, 40.92, 37.72, 37.54, 33.35, 29.44, 28.76, 23.82. HRMS (ESI): calculated for $C_{19}H_{21}ClN_2O_3$ $[M-H]^-$, 359.1168; found, 359.1183. **50**, HPLC purity: 99.0%; $[\alpha]^{25}_D$ (*c* 2, $CHCl_3$) = +14.5, chiral HPLC (Daicel OD-RH, 4.6–150 mm, 5 μm; 60% acetonitrile/40% 0.1 M aqueous KPF_6; 0.5 mL/min; 268 nm) t_R = 25.367 min, >99% ee. **52**, HPLC purity: 100%; $[\alpha]^{25}_D$ (*c* 2, $CHCl_3$) = −14.7, chiral HPLC (Daicel OD-RH, 4.6–150 mm, 5 μm; 60% acetonitrile/40% 0.1 M aqueous KPF_6; 0.5 mL/min; 268 nm) t_R = 23.367 min, 97.0% ee.

1-Cyclopentyl-3-(3,5-dichlorophenethyl)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (85)

White powder; mp 144–146 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (t, *J* = 1.9 Hz, 1H), 7.16 (d, *J* = 1.9 Hz, 2H), 5.15 (m, 1H), 4.09–4.02 (m, 2H), 3.66 (s, 2H), 2.92–2.80 (m, 2H), 1.95 (m, 4H), 1.85 (m, 2H), 1.66–1.52 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.69, 164.49, 150.85, 141.12, 135.02, 127.49, 127.05, 54.39, 42.36, 40.11, 33.51, 28.72, 25.57.

HRMS (ESI): calculated for $C_{17}H_{18}Cl_2N_2O_3$ $[M - H]^-$, 367.0622; found, 367.0637. HPLC purity: 94.5%.

1-Cyclopentyl-3-(3,4-dichlorophenethyl)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (86)

White powder; mp 131–133 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.32 (m, 2H), 7.12 (d, *J* = 8.2 Hz, 1H), 5.24–5.08 (m, 1H), 4.13–4.03 (m, 2H), 3.66 (s, 2H), 2.93–2.78 (m, 2H), 2.04–1.90 (m, 4H), 1.89–1.79 (m, 2H), 1.67–1.54 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.71, 164.52, 150.87, 138.03, 132.50, 130.91, 130.85, 130.52, 128.40, 54.36, 42.48, 40.12, 33.18, 28.71, 25.56. HRMS (ESI): calculated for $C_{17}H_{18}Cl_2N_2O_3$ $[M - H]^-$, 367.0622; found, 367.0637. HPLC purity: 98.0%.

1-(3,5-Bis(trifluoromethyl)phenethyl)-3-cyclopentylpyrimi-dine-2,4,6(1*H*,3*H*,5*H*)-trione (87)

White powder; mp 163–166 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.73 (s, 2H), 5.27–4.99 (m, 1H), 4.21–4.04 (m, 2H), 3.66 (s, 2H), 3.17–2.93 (m, 2H), 2.00–1.75 (m, 6H), 1.66–1.51 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.57, 164.54, 150.83, 140.26, 131.84 (q, *J* = 33.3 Hz), 129.19 (m), 123.23 (q, *J* = 272.8 Hz), 120.88 (m), 54.38, 42.16, 40.03, 33.66, 28.68, 25.53. HRMS (ESI): calculated for $C_{19}H_{18}F_6N_2O_3$ $[M - H]^-$, 435.1149; found, 435.1169. HPLC purity: 98.5%.

1-((1-(4-Chlorophenyl)cyclopropyl)methyl)-3-cyclopentyl-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (96)

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (s, 4H), 5.00 (p, *J* = 8.7 Hz, 1H), 4.06 (s, 2H), 3.51 (s, 2H), 1.92–1.81 (m, 2H), 1.79–1.66 (m, 4H), 1.59–1.43 (m, 2H), 1.07–0.98 (m, 2H), 0.87–0.78 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.75, 150.82, 140.85, 132.80, 131.52, 128.32, 54.21, 48.83, 40.03, 28.56, 25.49, 25.04, 12.05. HRMS (ESI): calculated for $C_{19}H_{21}ClN_2O_3$ $[M - H]^-$, 359.1168; found, 359.1186. HPLC purity: 96.1%.

1-(2-(3-Chlorophenyl)-2-methylpropyl)-3-cyclopentylpyri-midine-2,4,6(1*H*,3*H*,5*H*)-trione (98)

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.00 (m, 4H), 5.20–4.97 (m, 1H), 4.08 (s, 2H), 3.61 (s, 2H), 1.97–1.73 (m, 6H), 1.61–1.49 (m, 2H), 1.36 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.00, 164.77, 151.22, 148.51, 134.09, 129.42, 126.69, 126.59, 124.55, 54.29, 51.06, 40.22, 40.15, 28.67, 26.94, 25.54. MS (ESI): calculated for $C_{19}H_{23}ClN_2O_3$ $[M - H]^-$, 361.13; found, 361.23. HPLC purity: 99.1%.

1-Cyclopentyl-3-(2-methyl-2-(3-(trifluoromethyl)phenyl)-propyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (99)

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75–7.59 (m, 2H), 7.59–7.39 (m, 2H), 5.08 (p, *J* = 8.7 Hz, 1H), 4.12 (s, 2H), 3.61 (s, 2H), 1.89 (m, 2H), 1.85–1.72 (m, 4H), 1.58–1.48 (m, 1H), 1.42 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.98, 164.66, 151.15, 147.28, 130.37, 129.88, 128.61, 123.32, 123.06, 122.05, 54.27, 51.05, 40.25, 40.09, 28.65, 27.01, 25.51. MS (ESI): calculated for $C_{20}H_{23}F_3N_2O_3$ $[M - H]^-$, 395.16; found, 395.28. HPLC purity: 95.3%.

1-(2-(3-Chlorophenyl)propyl)-3-((±)-*endo*-norbornyl)-pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (102)

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.05 (m, 4H), 4.64–4.49 (m, 1H), 4.11 (m, 1H), 3.97 (m, 1H), 3.67–3.44 (m, 2H), 3.36–3.17 (m, 1H), 2.68–2.45 (m, 1H), 2.37–2.28 (m, 1H), 2.14 (m, 1H), 1.85–1.57 (m, 3H), 1.57–1.49 (m, 1H), 1.46–1.35 (m, 2H), 1.34–1.17 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.89, 165.85, 164.69, 152.33, 152.27, 145.13, 145.08, 134.24, 134.21, 129.74, 129.71, 127.79, 127.09, 125.71, 125.67, 59.62, 59.60, 47.87, 47.77, 47.76, 42.04, 41.96, 40.91, 40.81, 37.87, 37.81, 37.74, 37.70, 37.55, 37.49, 29.69, 29.35, 28.76, 23.83, 23.71, 18.53. MS (ESI): calculated for $C_{20}H_{23}ClN_2O_3$ $[M - H]^-$, 373.13; found, 373.10. HPLC purity: 99.3%.

1-(1-(3-Chlorophenyl)propan-2-yl)-3-((±)-endo-norbornyl)-pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (103)

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.10 (m, 4H), 4.70–4.49 (m, 1H), 4.20–4.02 (m, 2H), 3.73–3.51 (m, 2H), 2.54 (d, *J* = 3.8 Hz, 1H), 2.34 (d, *J* = 4.6 Hz, 1H), 2.13–2.02 (m, 1H), 1.77–1.60 (m, 2H), 1.58–1.48 (m, 1H), 1.48–1.38 (m, 2H), 1.37 (s, 3H), 1.35 (s, 3H), 1.35–1.22 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.87, 165.01, 152.60, 148.54, 134.08, 129.41, 126.68, 126.60, 124.58, 59.72, 51.28, 41.94, 41.00, 40.24, 37.74, 37.52, 29.35, 28.75, 27.03, 26.92, 23.82. MS (ESI): calculated for $C_{21}H_{25}ClN_2O_3$ $[M - H]^-$, 387.15; found, 387.28. HPLC purity: 96.9%.

1-(3,5-Bis(trifluoromethyl)phenethyl-3-((±)-endo-norbornyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (104)

White powder; mp 74–77 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.73 (s, 2H), 4.72–4.57 (m, 1H), 4.22–4.07 (m, 2H), 3.77–3.56 (m, 2H), 3.06 (t, *J* = 7.8 Hz, 2H), 2.61 (d, *J* = 4.1 Hz, 1H), 2.36 (t, *J* = 4.6 Hz, 1H), 2.18 (m, 1H), 1.83–1.63 (m, 2H), 1.60–1.49 (m, 1H), 1.49–1.28 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.76, 164.60, 152.11, 140.31, 131.83 (q, *J* = 33.4 Hz), 129.20 (d, *J* = 3.7 Hz), 123.25 (q, *J* = 272.8 Hz), 120.88 (p, *J* = 3.7 Hz), 59.70, 42.36, 42.09, 40.80, 37.72, 37.52, 33.67, 29.52, 28.74, 23.81. HRMS (ESI): calculated for $C_{21}H_{20}F_6N_2O_3$ $[M - H]^-$, 461.1305; found, 461.1321. HPLC purity: 96.4%.

1-(2(3,5-Dichlorophenyl)ethyl)-3-((±)-endo-norbornyl)-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (105)

White powder; mp 150–151 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (s, 1H), 7.17 (s, 2H), 4.71–4.58 (m, 1H), 4.13–4.01 (m, 2H), 3.65 (dd, *J* = 21.2, 8.7 Hz, 2H), 2.87 (t, *J* = 7.8 Hz, 2H), 2.66–2.58 (m, 1H), 2.42–2.34 (m, 1H), 2.25–2.15 (m, 1H), 1.81–1.66 (m, 2H), 1.61–1.51 (m, 1H), 1.48–1.32 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.85, 164.55, 152.13, 141.15, 135.01, 127.51, 127.05, 59.70, 42.53, 42.11, 40.90, 37.76, 37.55, 33.50, 29.55, 28.80, 23.88. MS (ESI): calculated for $C_{19}H_{20}Cl_2N_2O_3$ $[M - H]^-$, 393.08; found, 393.26. HPLC purity: 98.1%.

1-((±)-exo-Norbornyl)-3-(3-(trifluoromethyl)phenethyl)-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (106), 1-((1*R*,2S,4S)-Bicyclo-[2.2.1]heptan-2-yl)-3-(3-(trifluoromethyl)phenethyl)-

pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (107), and 1-((1*S*,2*R*,4*R*)-Bicyclo[2.2.1]heptan-2-yl)-3-(3-(trifluoromethyl)phenethyl)-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (108)

White powder; mp 65–69 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.26 (m, 4H), 4.59–4.45 (m, 1H), 4.10–3.93 (m, 2H), 3.55 (dd, *J* = 21.0, 12.9 Hz, 2H), 2.89 (t, *J* = 7.8 Hz, 2H), 2.52 (d, *J* = 3.7 Hz, 1H), 2.27 (d, *J* = 4.4 Hz, 1H), 2.11 (m, 1H), 1.71 −1.54 (m, 2H), 1.49–1.41 (m, 1H), 1.40–1.21 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.90, 164.58, 152.17, 138.80, 132.45, 130.84 (q, *J* = 32.0 Hz), 129.05, 125.69 (q, *J* = 3.7 Hz), 124.08 (q, *J* = 272.4 Hz), 123.63 (d, *J* = 4.1 Hz), 59.64, 42.74, 42.09, 40.86, 37.74, 37.54, 33.77, 29.50, 28.77, 23.84. HRMS (ESI): calculated for C20H21F3N2O3 $[M - H]^-$, 393.1432; found, 393.1448. **106**, HPLC purity: 97.9%. **107**, HPLC purity: 96.8%, $[\alpha]^{25}_D$ (*c* 2, $CHCl_3$) = −7.5, chiral HPLC (Daicel OD-RH, 4.6–150 mm, 5 μm; 60% acetonitrile/ 40% 0.1 M aqueous KPF_6; 0.5 mL/min; 268 nm) t_R = 18.800 min, 96.9% ee. **108**, HPLC purity: 99.0%; $[\alpha]^{25}_D$ (*c* 2, $CHCl_3$) = +7.7; chiral HPLC (Daicel OD-RH, 4.6–150 mm, 5 μm; 60% acetonitrile/ 40% 0.1 M aqueous KPF_6; 0.5 mL/min; 268 nm) t_R = 21.583 min; >99% ee.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS USED

LTCC	L-type calcium channel
PD	Parkinson’s disease
PYT	pyrimidinetrione
SNc	substantia nigra pars compacta
FLIPR	fluorometric imaging plate reader
DMEM	Dulbecco’s modified Eagle medium

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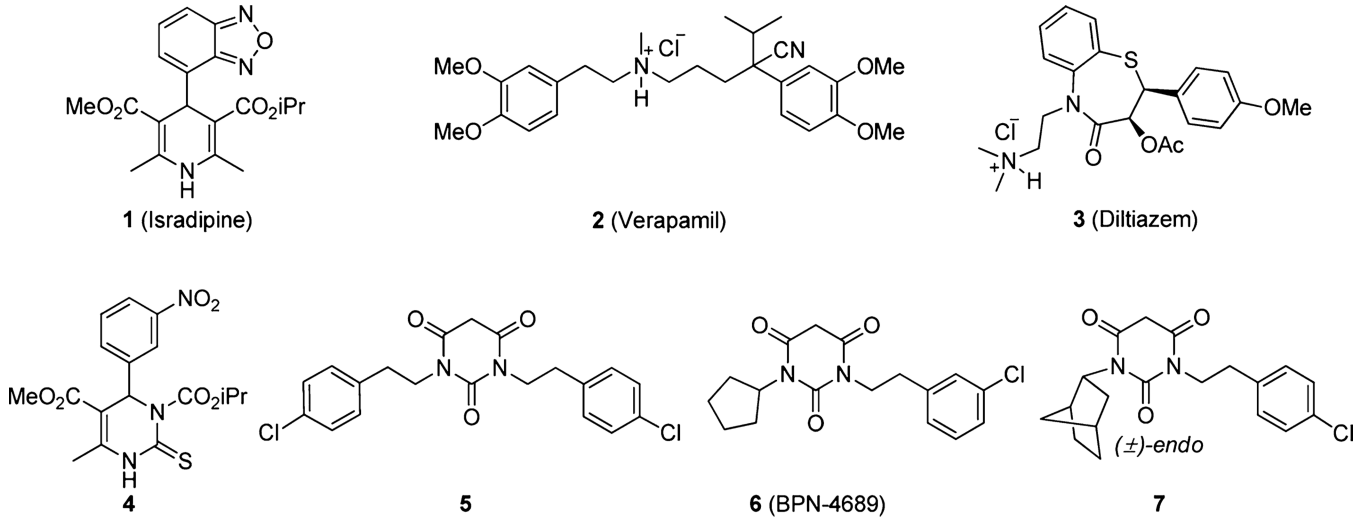


Figure 1.

Example of $Ca_V1.3$ blockers. **1, 2**, and **3** are known nonselective LTCC blockers used for the initial $Ca_V1.3$ study. **4** is a potent and slightly selective molecule. **5** is our initial hit from HTS. **6** is the most selective compound, and **7** is most potent compound in the previous study.

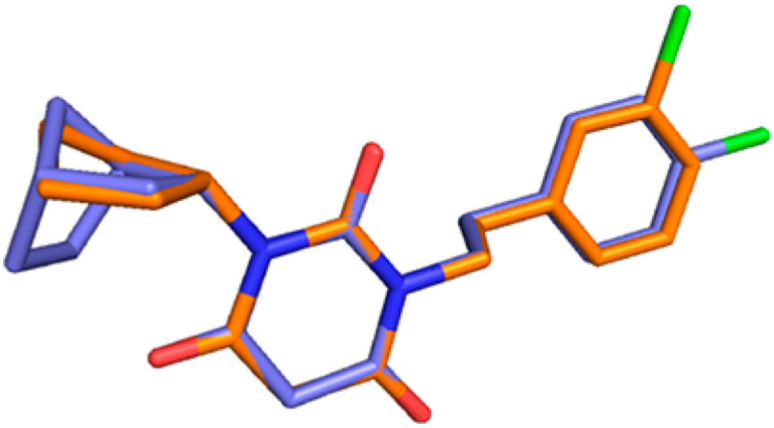


Figure 2.

Overlay of two standard compounds, **6** (orange) and **7** (blue). The figure was generated using Sybyl-X and PyMOL.

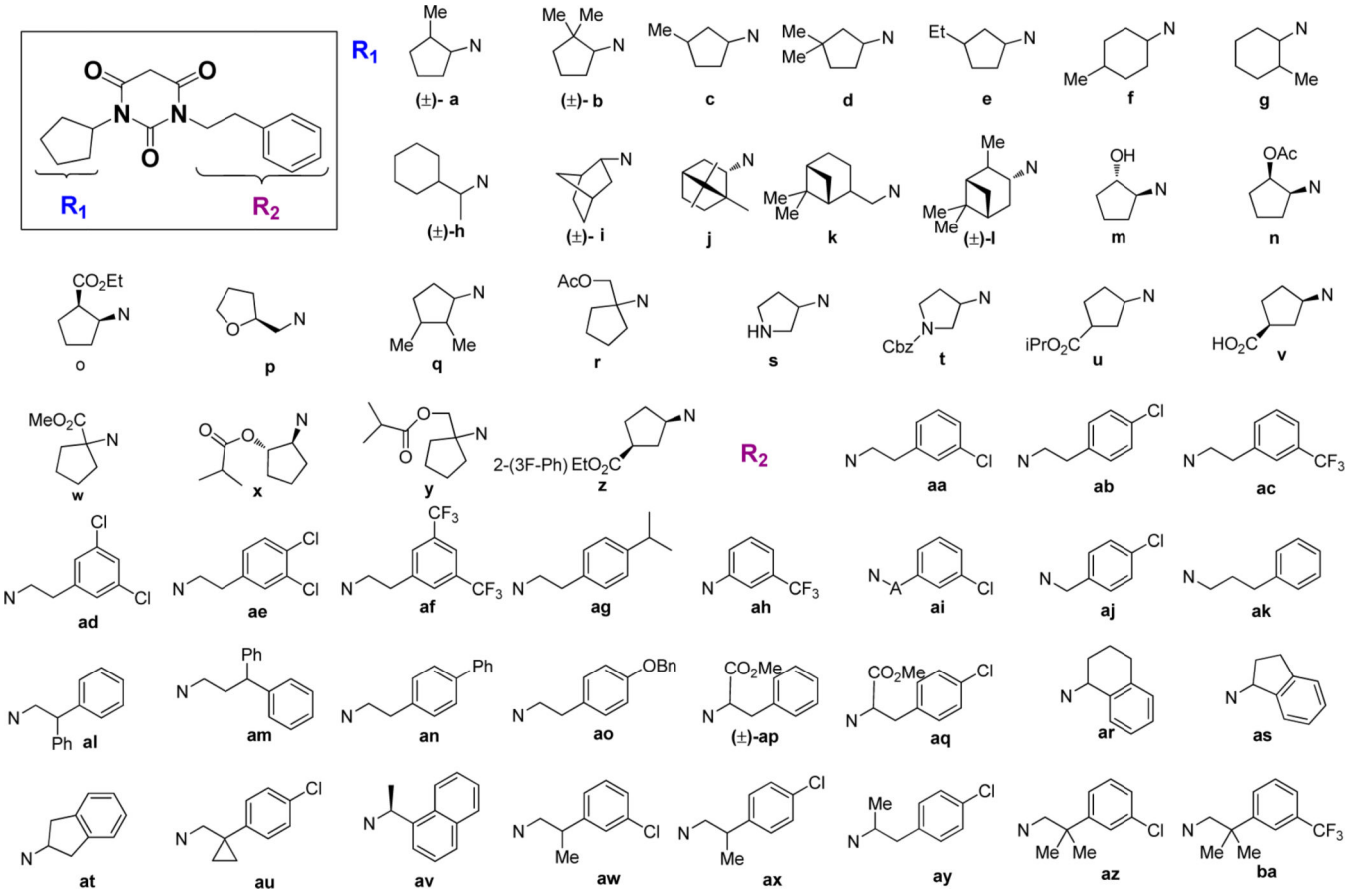


Figure 3.
Diverse *N*-alkyl moieties used for side chains on PYTs.

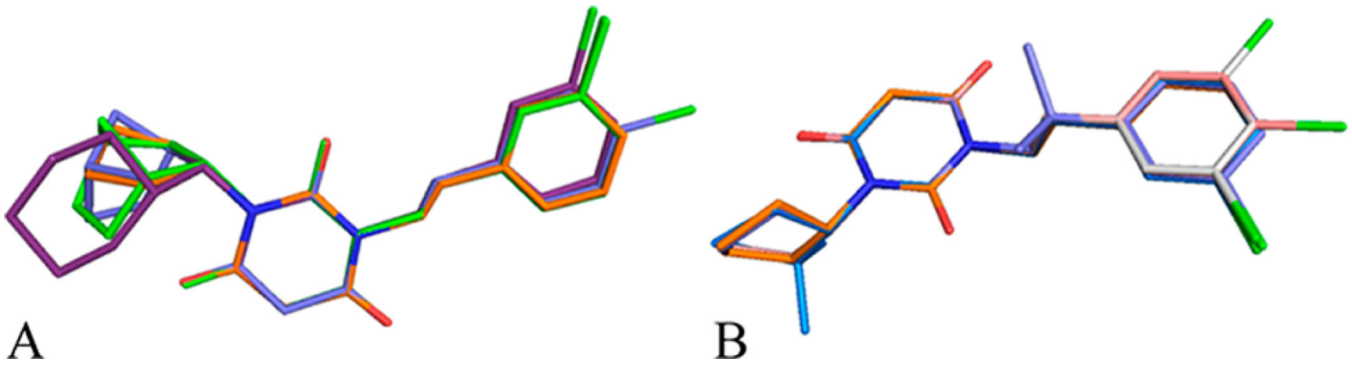
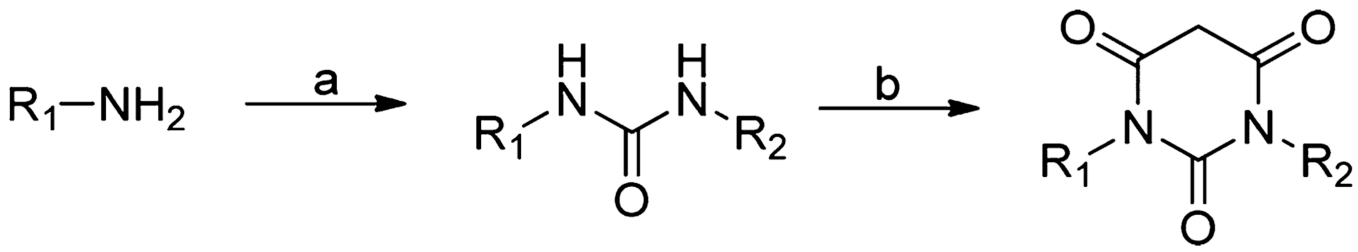


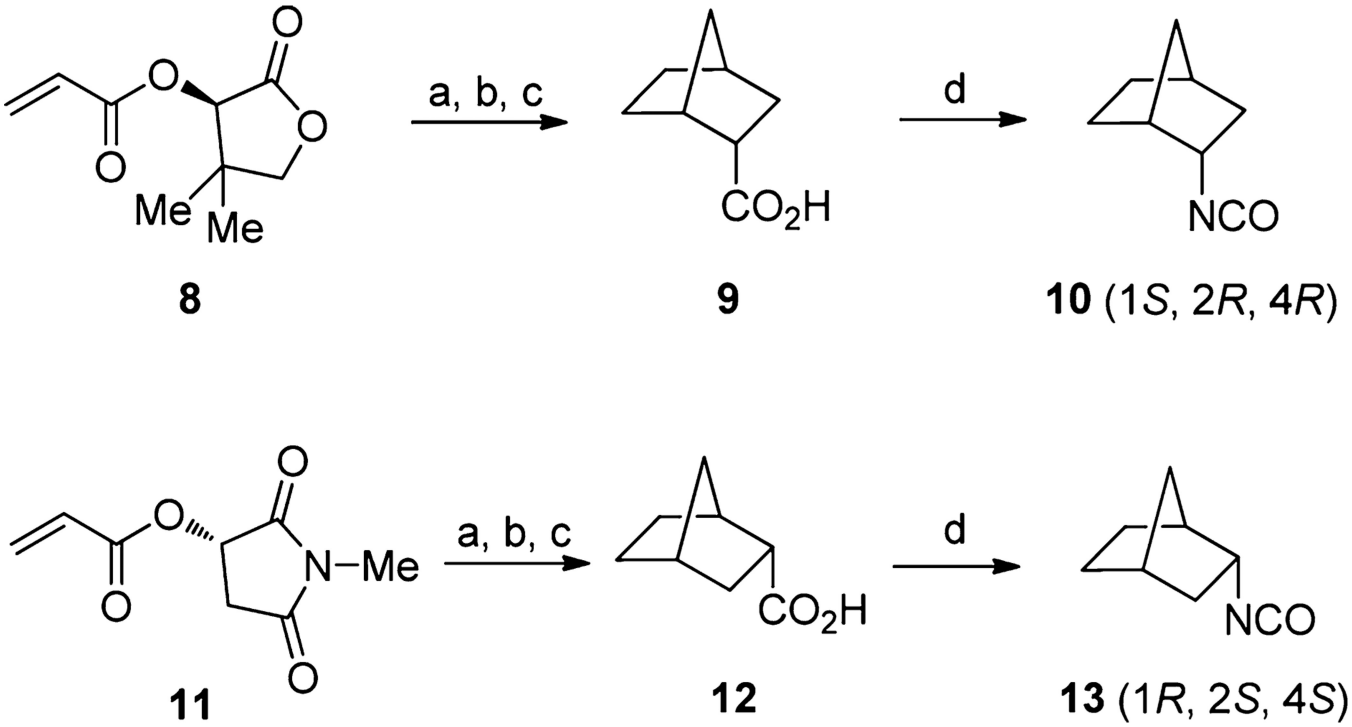
Figure 4.

Overlay of the most interesting molecules: (A) selective compounds **43** (green), **50** (blue), and **51** (puple); (B) potent compounds **22** (skyblue), **85** (pink), **86** (white), and **98** (blue). The picture was generated using Sybyl-X and PyMOL.



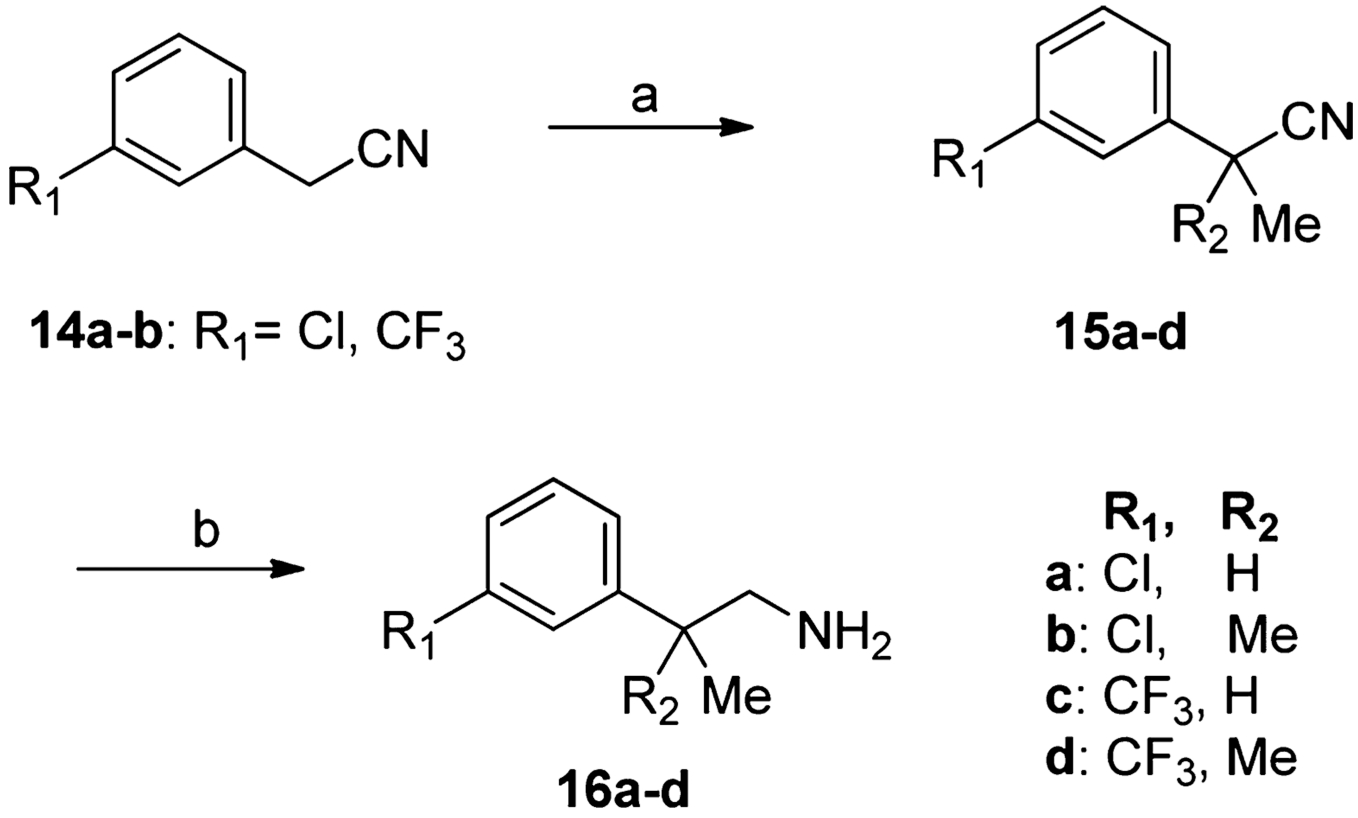
Scheme 1. General Synthetic Process for Assembling the PYT Ringa

[a]Reagents and conditions: (a) isocyanate, CH_2Cl_2 (0.1 M), room temp, 1–5 h; (b) malonyl chloride, CH_2Cl_2 (0.02 M), room temp, 1 h.



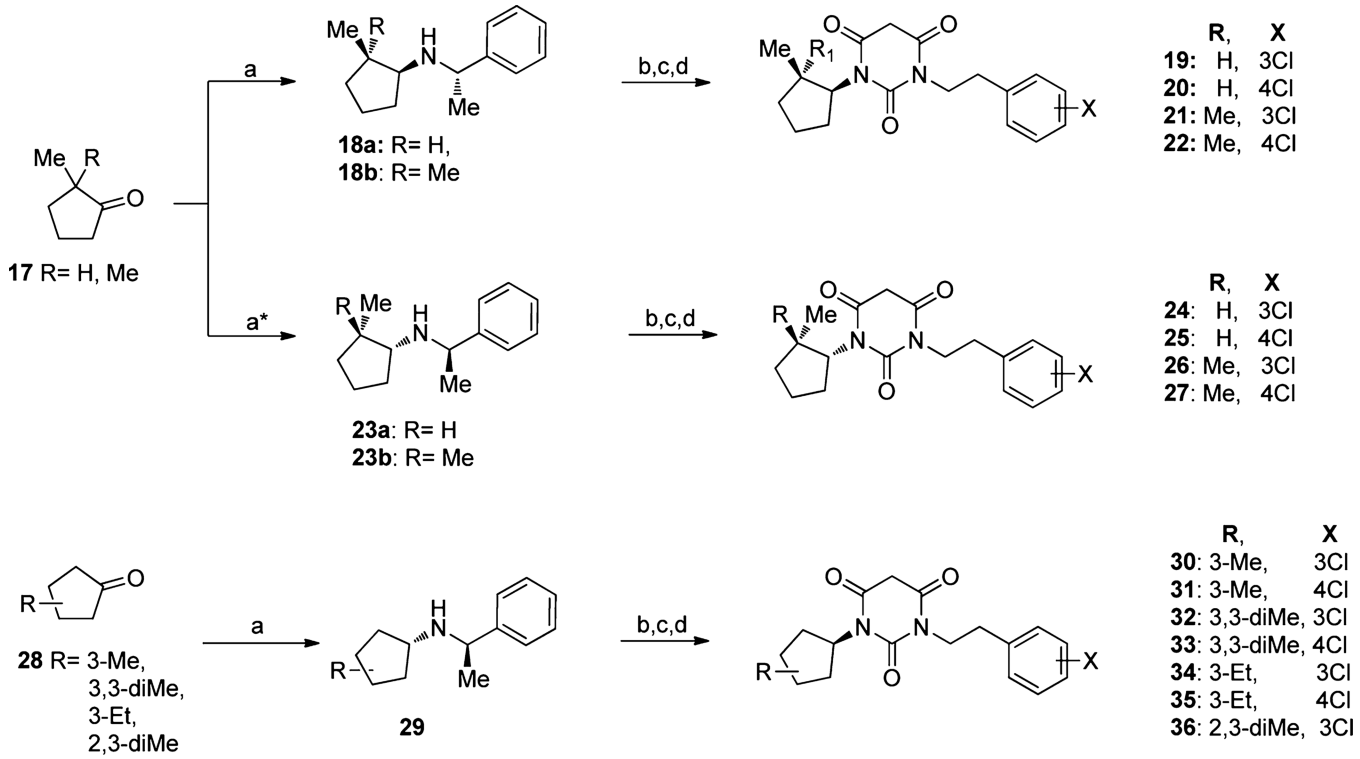
Scheme 2. Asymmetric Syntheses of *endo*-Nornornyl Isocyanates 10 and 13a

[a]Reagents and conditions: See Poll's[22] and Fukaya's[23] procedure. (a) cyclopentadiene, $TiCl_4$; (b) LiOH; (c) 10% Pd/C, H_2; (d) (i) ethyl chloroformate, triethylamine, 0 °C; (ii) NaN_3, acetone-water, 2 h; (iii) hexane, reflux 2 h.



Scheme 3. Synthesis of Methyl-Substituted Phenethylamines 16a–da

[a]Reagents and conditions: (a) NaH, MeI, DMF, room temp, overnight; (b) $LiAlH_4$, THF, 0 °C, 2 h.



Scheme 4. Synthesis of Alkyl Substituted Cycloalkylaminea

[a]Reagents and conditions: (a) (i) (*S*)-α-methylbenzylamine, cat. TsOH, benzene, reflux, overnight; (ii) $NaBH_3CN$, EtOH; *(*R*)-1-phenylethanamine was used under the same conditions; (b) 2-(3-Cl-phenyl)ethyl isocyanate, CH_2Cl_2, room temp; (c) 75% TFA in CH_2Cl_2; (d) malonyl chloride, CH_2Cl_2.

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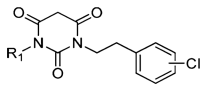
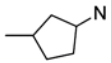
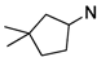
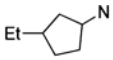
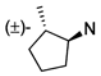
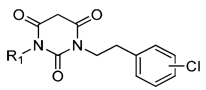
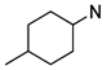
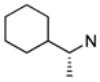
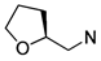
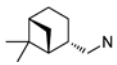
Table 1

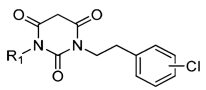
IC_{50} Values and Selectivities of Various Cycloalkyl Analogues



R_1	Compound #	$Ca_v1.3$ IC_{50}(μM)	3-Cl $Ca_v1.2$ IC_{50}(μM)	Selectivity[a]	Compound #	$Ca_v1.3$ IC_{50}(μM)	4-Cl $Ca_v1.2$ IC_{50}(μM)	Selectivity[a]
	**6**	6.3	>100	>100[b]	**7**	5.6 ±1.1	50 ±13	8.9
	**19**	5.5 ±0.6	13 ±2.6	2.3	**20**	3.1 ±0.2	5.1 ±0.5	1.7
	**24**	7.3 ±1.3	9.3 ±2.1	1.3	**25**	2.8 ±0.7	10 ±1.6	3.7
	**21**	2.1 ±0.2	3.5 ±1.1	1.6	**22**	1.7 ±0.1	2.3 ±0.4	1.4
	**26**	2.5 ±0.4	4.7 ±0.5	1.9	**27**	4.7±0.6	4.8 ±0.8	1.0
	**30**	3.7 ±0.1	38 ±3.4	10	**31**	9.8 ±0.8	20.4 ±1.1	2.1
	**32**	5.6 ±0.5	43 ±3.3	7.7	**33**	3.7 ±0.7	26 ±8.9	6.8
	**34**	7.3 ±1.7	15 ±1.5	2.0	**35**	6.7 ±0.7	29 ±10	4.4
	**37**	11 ±3.9	21 ±0.8	1.8	**38**	7.0 ±0.8	23 ±4.4	3.3



R_1	Compound #	$Ca_v1.3$ IC_{50}(μM)	3-Cl $Ca_v1.2$ IC_{50}(μM)	Selectivity[a]	Compound #	$Ca_v1.3$ IC_{50}(μM)	4-Cl $Ca_v1.2$ IC_{50}(μM)	Selectivity[a]
	**39**	35 ±6.8	46 ±0.4	1.3	**40**	11 ±5.4	30 ±4.5	2.7
	**41**	3.7 ±0.8	3.7 ±0.1	1.0	**42**	6.1 ±1.7	8.3 ±0.5	1.4
	**43**	4.3 ±0.5	>100	>29	**44**	8.3 ±0.7	>100	>12
	**45**	9.7 ±1.0	>100	>10	**46**	8.1 ±1.0	>100	>12
	**47**	>100	41 ±11		**48**	>100	>100	
	**49**	3.5 ±0.2	>100	>29	**50**	2.1 ±0.4	100 ±10	48
	**51**	2.0 ±0.1	>100	>50	**52**	1.9 ±0.3	54 ±5.8	11
	**53**	>100	>100		**54**	>100	>100	
	**55**	40 ±2.9	47 ±1.9	1.2	**56**	>100	>100	
	**57**	>100	>100		**58**	18 ±0.1	>100	>6



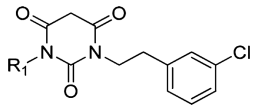
R_1	Compound #	$Ca_v1.3$ IC_{50}(μM)	3-Cl $Ca_v1.2$ IC_{50}(μM)	Selectivity[a]	Compound #	$Ca_v1.3$ IC_{50}(μM)	4-Cl $Ca_v1.2$ IC_{50}(μM)	Selectivity[a]
	**59**	>100	>100		**60**	22 ±4.2	28 ±2.8	1.3

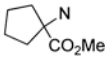
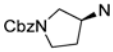
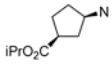
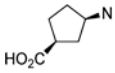
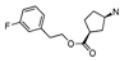
[a] Ratio of the IC_{50} values ($Ca_V1.2/Ca_V1.3$).

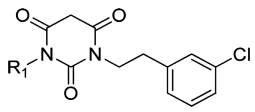
[b] Selectivity was confirmed from the previous study.

Table 2

IC_{50} Values and Selectivity of Various Cycloalkyl Analogues



Compound #	R_1	$Ca_v1.3$ IC_{50}(μM)	$Ca_v1.2$ IC_{50}(μM)	Selectivity
61		32.7 ±11	33.4 ±1.8	1.1
62		39.3 ±6.8	29.1 ±1.3	0.7
63		11.9 ±0.4	10.6 ±1.0	0.9
64		50.3 ±15	33.9 ±0.2	0.7
65		>100	>100	
66		10.4 ±1.3	8.5 ±0.9	0.8
67		>100	>100	
68		9.7 ±0.1	6.7 ±0.1	0.7
69		>100	>100	
70		30.3 ±1.8	34.6 ±4.3	1.1
71		>100	48.1 ±5.3	
72		38.6 ±1.6	23.4 ±0.5	0.6
73		12.0 ±0.9	12.6 ±0.4	1.0



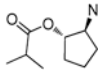
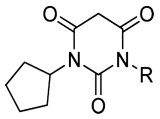
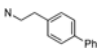
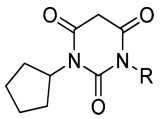
Compound #	R_1	$Ca_v1.3$ IC_{50}(μM)	$Ca_v1.2$ IC_{50}(μM)	Selectivity
74		13.7 ±2.0	12.9 ±0.3	0.9
75		11.7 ±3.2	25.2 ±3.7	2.2
36		3.09 ±0.9	13.2 ±9.7	4.3
76		10.8 ±1.4	10.0 ±0.1	0.9

Table 3

IC_{50} Values and Selectivities of Various Arylalkyl Analogues



Compound	R_1	$Ca_v1.3$ IC_{50}(μM)	$Ca_v1.2$ IC_{50}(μM)	Selectivity
77		19.7 ±1.1	20.0 ±1.0	1.0
78		19.9 ±4.9	24.8 ±0.6	1.2
79		144 ±1.8	16.4 ±0.9	1.1
80		4.6 ±0.4	6.15 ±1.5	1.3
81		>100	>100	
82		43.0 ±10	46.7 ±7.6	1.1
83		17.9 ±1.9	51.7 ±0.7	2.9
84		7.6 ±0.1	21.9 ±1.5	2.9
85		1.4 ±0.4	3.3 ±0.1	2.3
86		1.2 ±0.1	3.4 ±0.6	2.7
87		1.4 ±0.3	2.6 ±0.5	1.8
88		39.0 ±13	57.6 ±5.1	1.5
89		5.2 ±1.1	8.1 ±1.0	1.6
90		4.1 ±1.2	4.7 ±1.1	1.2
91		4.4 ±0.3	5.4 ±0.4	1.2



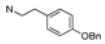
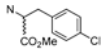
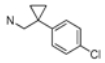
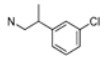
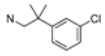
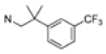
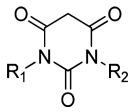
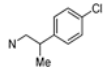
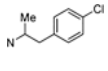
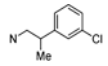
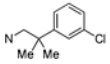
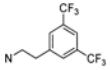
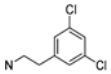
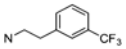
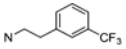
Compound	R_1	$Ca_v1.3$ IC_{50}(μM)	$Ca_v1.2$ IC_{50}(μM)	Selectivity
92		34.1 ±4.9	18.7 ±1.1	0.5
93		>100	>100	
94		55.0 ±1.0	44.3 ±1.7	0.8
95		7.5 ±0.2	13.4 ±1.4	1.8
96		7.3 ±1.0	>100	>26
97		4.2 ±0.3	20.7 ±7.2	5.0
98		2.4 ±0.2	12.6 ±2.6	4.9
99		2.2 ±0.4	4.2 ±0.7	1.9

Table 4

IC_{50} Values and Selectivities of Various Norbornyl Analogues



Compound #	R_1	R_2	$Ca_v1.3$ IC_{50}(μM)	$Ca_v1.2$ IC_{50}(μM)	Selectivity
100			3.4 ±0.2	8.0 ±1.0	2.4
101			3.6 ±0.3	4.1 ±0.6	1.1
102			2.4 ±0.3	5.1 ±1.1	2.1
103			2.3 ±0.4	2.8 ±0.3	1.2
104			1.8 ±0.7	3.8 ±0.4	2.2
105			2.7 ±0.2	4.6 ±1.7	1.7
106			2.4 ±0.2	100 ±6.3	40.8
107			3.0 ±0.5	>100	>33.0

Compound #	R_1	R_2	$Ca_v1.3$ IC_{50}(μM)	$Ca_v1.2$ IC_{50}(μM)	Selectivity
108			2.1 ±0.1	76.6 ±8.0	36.0
109			2.7 ±0.2	3.1 ±0.2	1.2