Palladium-Catalyzed $\alpha$-Arylation of Cyclic $\beta$-Dicarboxyl Compounds for the Synthesis of CaV1.3 Inhibitors

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ABSTRACT: Cyclic $\alpha$-aryl $\beta$-dicarboxyl derivatives are important scaffolds in medicinal chemistry. Palladium-catalyzed coupling reactions of haloarenes were conducted with diverse five- to seven-membered cyclic $\beta$-dicarboxyl derivatives including barbiturate, pyrazolidine-3,5-dione, and 1,4-diazepane-5,7-dione. The coupling reactions of various para- or meta-substituted aryl halides occurred efficiently when Pd($t$-Bu$_3$P)$_2$, Xphos, and Cs$_2$CO$_3$ were used under 1,4-dioxane reflux conditions. Although the couplings of ortho-substituted aryl halides with pyrazolidine-3,5-dione and 1,4-diazepane-5,7-dione were moderate, the coupling with barbiturate was limited. Using the optimized reaction conditions, we synthesized several 5-aryl barbiturates as new scaffolds of CaV1.3 Ca$^{2+}$ channel inhibitors. Among the synthesized molecules, 14e was the most potent CaV1.3 inhibitor with an IC$_{50}$ of 1.42 $\mu$M.

INTRODUCTION

Cyclic $\alpha$-aryl $\beta$-dicarboxyl derivatives are important scaffolds in medicinal chemistry that have been widely applied to the development of biologically active compounds. The most common cyclic $\alpha$-aryl $\beta$-dicarboxyl derivative is 5-arylbarbiturate, a six-membered ring system. Phenobarbital, 5-phenyl-5-ethyl barbituric acid (Figure 1, 1), is an allosteric modulator of the GABAA receptor$^1$ in the central nervous system and is widely prescribed to treat seizures. Various substructures of 5-aryl barbiturates have been widely applied in the development of biologically active compounds by targeting gelatinase,$^2$ matrix metalloproteinases (MMPs),$^3,4$ and the tumor necrosis factor $\alpha$ converting enzyme (TACE).$^5$ Another six-membered $\alpha$-aryl $\beta$-dicarboxyl ring is 2-arylcyclohexane-1,3-dione. This ring system has been used in the development of isocitrate dehydrogenase 1 (IDH1) inhibitors.$^6$ Seven-membered $\alpha$-aryl $\beta$-dicarboxyl rings, such as 6-aryl-1,4-diazepane-5,7-dione, have also been widely used in the development of human immunodeficiency virus (HIV) capsid assembly inhibitors$^7$ and alpha7 nicotinic acetylcholine receptor modulators (2).$^8$ The five-membered $\alpha$-aryl $\beta$-dicarboxyl rings, 4-aryloxazolidine-3,5-dione$^9$ and 2-aryl-1,3-dione pinoxaden (3),$^{10}$ have been used as aldose reductase inhibitors and yeast carboxyl transferase inhibitors, respectively.

L-Type calcium channels (LTCCs) with a CaV1.3 pore-forming subunit mediate activity-dependent calcium influx into neuronal cells, initiating a diverse set of intracellular events. In particular, CaV1.3 channels are robustly expressed in dopaminergic neurons in the substantia nigra pars compacta (SNpc), where they elevate mitochondrial oxidative stress.$^{11}$ This stress has been hypothesized to contribute to loss of these neurons in Parkinson’s disease (PD).$^{12}$ Thus, selective inhibitors of these channels may slow down disease progression.$^{13}$ Currently, we are exploring the potential value
of C-aryl barbiturate derivatives (4) as negative allosteric modulators of CaV1.3 channels.14,15

The 5-aryl barbiturates are conventionally synthesized via the condensation of 2-aryl malonates with ureas. The 2-aryl malonates can be prepared using α-carbonylation of aryl acetate esters16 or cross-couplings of malonates with haloarenes using palladium17 or copper18 catalysts (Scheme 1A). However, the α-carbonylation of aryl acetate esters in the 2-aryl malonate synthesis has been limited because of the lack of commercial availability of aryl acetates. Meanwhile, the cross-coupling of malonates with haloarenes has narrow compatibility with electron-deficient aryl groups owing to side reactions.19 In addition, all of these methods perform aryl diversification at an early stage of library construction. Our attempts to develop 5-aryl barbiturates as negative allosteric modulators of LTCC CaV1.3 by adapting conventional syntheses of aryl malonates followed by condensation with ureas are less efficient for a ligand-based drug discovery campaign because incorporation of early-stage diversification approaches requires tedious repetitive synthesis of intermediates.

Alternatively, direct arylation of barbiturate has been achieved using rhodium(II)-catalyzed C–H functionalization with arenes.19 Although the reaction facilitates the synthesis of various 5-aryl barbiturates from commercial arenes, the reaction requires additional synthesis of diazo-barbiturate intermediates individually and the separation of aryl regioisomers.19 We thought that 5-arylbarbiturates could be easily synthesized from barbiturate and a haloarene by applying Hartwig’s approach17 using palladium-catalyzed cross-coupling for the aryl malonate synthesis. However, to the best of our knowledge, no studies have yet reported a palladium-catalyzed coupling reaction between barbiturate and a haloarene. In this study, we explored the palladium-catalyzed coupling reactions of various haloarenes with barbiturates and extended the coupling reaction to five- and seven-membered α-aryl β-dicarbonyl rings. Using optimized reaction conditions, we ultimately synthesized specifically designed 5-aryl barbiturates

Scheme 1. Diverse Methods for 5-Aryl Barbiturate Synthesis

A Conventional method

B Ref. 19

C Current work
and tested the inhibitory activity toward CaV1.3 and CaV1.2 L-type calcium channels (LTCC).

### RESULTS AND DISCUSSION

We prepared each of the five-, six-, and seven-membered cyclic β-dicarbonyl compounds used to evaluate the palladium-catalyzed α-arylation using the synthetic process shown in Scheme 2. 1,3-Diphenethylbarbiturate (5) was synthesized via a two-step reaction: urea formation from phenethylamine with phenethylisocyanate followed by condensation with malonyl dichloride. To prepare the five-membered cyclic β-dicarbonyl compound (6), we converted commercially available 1,2-di(benzylidene)hydrazine to 1,2-dibenzylhydrazine via palladium-catalyzed reduction under a hydrogen atmosphere. This crude 1,2-dibenzylhydrazine was condensed with malonyl chloride without further purification to produce the requisite pyrazolidine-3,5-dione (6).

#### Table 1. Screen of Coupling Conditions

| #  | X   | catalyst     | ligand | base  | solvent | time (h) | % conversion |
|----|-----|--------------|--------|-------|---------|----------|--------------|
| 1  | I   | Pd(dba)3     | Xphos  | NaH   | THF     | 6        | 14           |
| 2  | I   | Pd(t-Bu3P)2 | Xphos  | Cs2CO3| THF     | 24       | 34           |
| 3  | I   | Pd(t-Bu3P)2 | Xphos  | Cs2CO3| 1,4-dioxane | 0.5 | 99           |
| 4  | I   | Pd(PPh3)4   | Xphos  | Cs2CO3| 1,4-dioxane | 0.5 | 98           |
| 5  | I   | Pd(dba)3     | Xphos  | Cs2CO3| 1,4-dioxane | 0.5 | 94           |
| 6  | I   | Pd(t-Bu3P)2 | (tBu)3P| Cs2CO3| 1,4-dioxane | 18  | 74           |
| 7  | I   | Pd(t-Bu3P)2 | t-BuMePhos | Cs2CO3| 1,4-dioxane | 18  | 59           |
| 8  | I   | Pd(t-Bu3P)2 | RuPhos | Cs2CO3| 1,4-dioxane | 12  | 97           |
| 9  | I   | Pd(t-Bu3P)2 | BINAP  | Cs2CO3| 1,4-dioxane | 24  |              |
| 10 | I   | Pd(t-Bu3P)2 | Xphos  | K2CO3 | 1,4-dioxane | 1   | 97           |
| 11 | I   | Pd(t-Bu3P)2 | Xphos  | tBuOK | 1,4-dioxane | 1   | 86           |
| 12 | I   | Pd(t-Bu3P)2 | Xphos  | TEA   | 1,4-dioxane | 24  |              |
| 13 | I   | Pd(t-Bu3P)2 | Xphos  | Cs2CO3| DMF     | 6       | 27           |
| 14 | I   | Pd(t-Bu3P)2 | Xphos  | Cs2CO3| toluene | 6       | 26           |
| 15 | I   | Pd(t-Bu3P)2 | Xphos  | Cs2CO3| AcCN    | 6       | 3            |
| 16 | I   | Pd(t-Bu3P)2 | Xphos  | Cs2CO3| tBuOH   | 24      |              |
| 17 | I   | Pd(t-Bu3P)2 | Xphos  | Cs2CO3| Et2O    | 24      |              |
| 18 | I   | Pd(t-Bu3P)2 | Xphos  | Cs2CO3| Bu3O    | 2       | 97           |
| 19 | I   | Pd(t-Bu3P)2 | Xphos  | Cs2CO3| MeTHF   | 8       | 64           |
| 20 | I   | Pd(t-Bu3P)2 | Xphos  | Cs2CO3| CPME    | 0.5     | 95           |
| 21 | Br  | Pd(t-Bu3P)2 | Xphos  | Cs2CO3| 1,4-dioxane | 0.5 | 98           |
| 22 | Cl  | Pd(t-Bu3P)2 | Xphos  | Cs2CO3| 1,4-dioxane | 0.5 | 99           |

*Reaction conditions: aryl halide 1.2 equiv, catalyst 0.05 equiv, ligand 0.10 equiv, base 3 equiv, reflux. 1,2-methyltetrahydrofuran. Cyclopentyl methyl ether.*
Table 2. Synthesis of 5-Aryl Barbiturates 10a–o

| #   | R      | time (h) | yield (%) |
|-----|--------|----------|-----------|
| 10a | m-NO₂  | 0.5      | 85        |
| 10b | p-NO₂  | 0.5      | 88        |
| 10c | o-NO₂  | 0.5      | trace     |
| 10d | m-CN   | 0.5      | 80        |
| 10e | p-CN   | 0.5      | 77        |
| 10f | m-CF₃  | 0.5      | 89        |
| 10g | p-CF₃  | 0.5      | 86        |
| 10h | (m) -CO₂Me | 0.5 | 93 |
| 10i | (p) -CO₂Me | 0.5 | 95 |
| 10j | H      | 0.5      | 73        |
| 10k | m-Me   | 0.5      | 73        |
| 10l | p-Me   | 0.5      | 79        |
| 10m | m-OMe  | 0.5      | 73        |
| 10n | p-OMe  | 0.5      | 73        |
| 10o | o-OMe  | 18       | trace     |

*Reaction condition: arylhalide 1.2 equiv; Pd(t-Bu₂P)₂ 0.05 equiv; Xphos 0.10 eq; Cs₂CO₃ 3 equiv; reflux.*

one of the amines of N₁,N₂-dibenzylethane-1,2-diamine (7) and acylated the other amine with methyl malonyl chloride. Then, the Boc-protecting group was removed with HCl to form intermediate 8. We completed the synthesis of 9 via microwave-assisted TsOH-catalyzed cyclization of 8 (Scheme 2C).

Although Hartwig’s research group has found malonate arylation with palladium to be efficient when using Pd(dba)₃, a bulky phosphine ligand P(tBu)₃, and NaH with refluxing in THF for 1–14 h,17 the effectiveness of these reaction conditions in the synthesis of α-aryl barbiturate using 1-iodo-3-nitrobenzene and N,N’-disubstituted barbiturate was limited (Table 1, #1–2); the starting material disappeared with only 14–34% conversion to the product. Since barbiturate is more acidic than malonate, it is a weaker nucleophile, and thus, it is estimated that different reaction conditions are required. We achieved improved conversion to the product when we used Cs₂CO₃ as the base in refluxing (101 °C) 1,4-dioxane (Table 1, #3). We decided that the reaction termination point would be when less than 3% of the starting material remained or when no percent change of the product occurred even after an additional 30 min reaction time via LC/MS analysis of the reaction mixture. The initial modification of the α-aryl barbiturates confirmed that the use of diverse palladium catalysts in combination with various phosphine ligands was effective (Table 1, #3–8). As shown in Table 1 #3–5, when 1-iodo-3-nitrobenzene was coupled with the barbiturate, use of Pd(t-Bu₂P)₂, Pd(PPh₃)₄, or Pd(dba)₃ allowed arylation in high conversion within 30 min. When we fixed Pd(t-Bu₂P)₂ as the catalyst, Xphos was superior to RuPhos, (tBu)₂P, t-BuMePhos, or BINAP as the ligand (Table 1, #5–9). Although RuPhos provided the highest yield (Table 1, #8), this reaction proved much slower, requiring 12 h for full conversion. After fixing the catalyst and ligand as Pd(t-Bu₂P)₂ and Xphos, we analyzed the reactions using Cs₂CO₃, K₂CO₃, tBuOK, and triethylamine (Table 1 #9–11). Reactions with Cs₂CO₃ in refluxing dioxane produced the fastest reaction rates, providing completely converted 5-arylbarbiturate within 30 min. Although we regarded K₂CO₃ and tBuOK as suitable bases, reactions with them were a little slower. We also evaluated the optimal solvent to use with Pd(t-Bu₂P)₂, Xphos, and Cs₂CO₃. In this case, 1,4-dioxane (Table 1, #3) proved superior to DMF, toluene, THF, AcCN, or tBuOH as the solvent (Table 1, #13–16). Reactions with DMF, toluene, THF, and AcCN were much slower, and the reaction in tBuOH failed to produce the target product. Among various ethers such as ethyl ether, butyl ether, 2-methyltetrahydrofuran (MeTHF), and cyclopentyl methyl ether (CPME), high-boiling-point solvents CPME and butyl ether displayed similar % conversion to dioxane, but low-boiling-point solvents ethyl ether and MeTHF were inferior to 1,4-dioxane (Table 1, #17–20). For the remainder of these initial studies, we fixed the reaction with Pd(t-Bu₂P)₂, Xphos, and Cs₂CO₃ in dioxane as the standard reaction conditions. Even when these optimized reaction conditions were used with 3-nitro-bromobenzene and 3-nitro-chlorobenzene in the coupling with 5, the reaction was finished within 30 min (Table 1, #21–22).

Coulping of Aryl Iodides with Barbiturates. After evaluating the optimized reaction conditions, we further explored the scope of the barbiturate and substituted aryl iodide coupling reaction. In particular, as shown in Table 2, we examined the electron-withdrawing or -donating effect at the α-, m-, or p- position of the aryl ring. The reactions of meta- and para-substrates, which have diverse electron densities, occurred well with the optimized conditions, giving over 75% purified yields with only a 30 min reaction time. Electron-rich methoxyl (10m–n) and methyl (10k–l) substituents, as well as electron-poor nitro (10a–b), nitrile (10d–e), trifluoromethyl (10f–g), and ester (10h–i) substituents generated excellent yields of the coupled product. However, we observed almost no conversion when ortho-substrates (10c, 10o) were used with the barbiturate. Although various ligands, bases, and
Table 3. Syntheses of 14a−g and 15a−g

solvents were tested again with ortho-substituted phenyl iodoide, we could not find appropriate reaction conditions. The lack of ortho-position reactivity differed somewhat from the reactivity with malonate. Presumably, steric hindrance caused by the 1,3-dicarbonyl of the pyrimidinetrione ring and the ortho-substituents of the palladium complex at the transition state limited the reaction relative to the reaction with the freely rotatable 1,3-dicarbonyl in malonate.

We coupled a series of o-, m-, and p-substituted electron-rich and electron-poor aryl iodides with a five-membered 1,3-dicarbonyl ring, the pyrazolidine-3,5-dione at the transition state limited the reaction relative to the reaction with the freely rotatable 1,3-dicarbonyl in malonate.

As demonstrated, we synthesized specifically designed 5-aryl N,N′-disubstituted barbiturates as potential CaV1.3 inhibitors. The intermediate N,N′-disubstituted barbiturates (13a−g) were synthesized from commercially available amines and isocyanates in

Table 3. Syntheses of 14a−g and 15a−g

| #  | R      | time (h) | yield (%) | #  | R      | time (h) | yield (%) |
|----|--------|----------|-----------|----|--------|----------|-----------|
| 11a| m-NO2  | 0.25     | 76        | 12a| m-NO2  | 0.5      | 79        |
| 11b| p-NO2  | 0.25     | 86        | 12b| p-NO2  | 0.5      | 66        |
| 11c| o-NO2  | 20       | 28        | 12c| o-NO2  | 20       | 43        |
| 11d| H      | 0.25     | 60        | 12d| H      | 0.75     | 91        |
| 11e| m-OMe  | 0.25     | 69        | 12e| m-OMe  | 0.5      | 86        |
| 11f| p-OMe  | 0.25     | 64        | 12f| p-OMe  | 0.5      | 89        |
| 11g| o-OMe  | 20       | 27        | 12g| o-OMe  | 20       | 69        |

Scheme 3. Synthesis of Diverse 5-Arylic Barbiturates

&Reaction condition: (a) amine and isocyanate, dichloromethane, rt, 5 h; (b) malonyl dichloride, dichloromethane, rt, 3 h; (c) aryl halide (1.2 equiv), Pd(t-Bu3P)2 (0.05 equiv), Xphos (0.1 equiv), refluxing dioxane; Cs2CO3 (3 equiv), reflux 30 min.

Also underwent arylation, although the yields were moderate (~27%). Additionally, we applied the coupling reactions of the same aryl iodides with a seven-membered ring system, 1,3-dicarbonyl 1,4-diazepane-5,7-dione, to explore the ring size dependency. The coupling reactions of 1,3-dicarbonyls in a seven-membered ring were similar to or slightly slower than the reactions of 1,3-dicarbonyls in a six-membered ring, and ortho-substituted aryl iodides underwent the coupling reaction with improved yields. The o-nitrophenyl substituent (12c) and o-methoxyl substituent yields were 43 and 69%, respectively.
dichloromethane followed by condensation with malonyl chloride (Scheme 3) using the previously established one-pot synthesis of N,N′-disubstituted barbiturates. The addition of malonyl chloride was performed at dilute conditions (0.02 M in dichloromethane) to avoid intermolecular acylation. Finally, the palladium-catalyzed coupling reaction of 13a–g with 1-iodo-3-nitrobenzene or 1-iodo-3-(trifluoromethyl)-benzene generated good yields of N-(4-((3-chlorophenyl)-butyl)-N′-cyclopend-5,7-dione proceeds endothermically. We used Cs2CO3 in refluxing with DCM (50 mL) or CDCl3. HRMS was performed on a system consisting of an electrospray ionization (ESI) source in an Agilent 6230B time-of-flight (TOF) liquid chromatography-mass spectrometer. The purity of the compounds was evaluated on a Shimadzu reverse-phase analytical LCMS system (column: Kintex C18, 2.6 μm, 100 mm × 2.1 mm). Puriﬁcations of all compounds that were subjected to the biological assay were >95%, strongly at 10 μM. The compound IC50 values ranged from 1 to 4 μM for CaV1.3 LTCCs and 2–5 μM for CaV1.2 LTCCs. Among the evaluated compounds, 14e was the most potent inhibitor of CaV1.3 LTCCs with an IC50 of 1.42 μM.

In summary, the palladium-catalyzed coupling reaction of cyclic β-dicarbonyl derivative such as pyrimidine-2,4,6-(1H,3H,5H)-trione, pyrazolidine-3,5-dione, and 1,4-diazepane-5,7-dione proceeds efﬁciently with various para- and meta-substituted aryl halides. Use of Xphos, Pd(t-Bu3P)2, and Cs2CO3 in reﬂuxing 1,4-dioxane generated high product yields with short reaction times. However, the yield of ﬁve- and seven-membered cyclic β-dicarbonyl compounds with ortho-substituted aryl halides was moderate, and the yield of six-membered cyclic β-dicarbonyl compounds with ortho-substituted aryl halides was low. Using the optimized reaction conditions, we synthesized 5-aryl barbiturates as a new scaffold for CaV1.3 LTCC inhibitors. Among the synthesized compounds, 14e was the most potent inhibitor of CaV1.3 LTCCs with an IC50 value of 1.42 μM. The method developed will be used in further syntheses of medicinally important compounds.

### EXPERIMENTAL SECTION

#### General Synthesis Information

All starting reagents were purchased from Enamine, Sigma-Aldrich, and TCI and were used without extra puriﬁcations. A Biotage 356007 synthesizer was used for microwave-assisted reactions. TLC analysis was carried out using Merck precoated silica gel plates with the ﬂuorescent indicator P254 and visualized under UV light (254, 365 nm) or by staining with ninhydrin or p-anisaldehyde. Silica gel ﬂash chromatography was performed with MPLC (Combi-Flash NextGen 300+) to obtain the compounds. The reaction monitoring was performed on a system consisting of an electrospray ionization (ESI) source in a Shimadzu reverse-phase analytical LC/MS (liquid chromatography-mass spectrometer) system (column: Kintex C18, 2.6 μm, 100 mm × 2.1 mm). 1H and 13C NMR spectra were recorded using a Bruker AVANCE III HD (400 and 100 MHz for 1H and 13C, respectively) spectrometer. At the chemical shift reports, δ values were calculated in parts per million downﬁeld from TMS (δ = 0.0) as the internal standard in DMSO-d6 or CDCl3. HRMS was performed on a system consisting of an electrospray ionization (ESI) source in an Agilent 6230B time-of-ﬂight (TOF) liquid chromatography-mass spectrometer. The purity of the compounds was evaluated on a Shimadzu reverse-phase analytical LCMS system (column: Kintex C18, 2.6 μm, 100 mm × 2.1 mm). Purities of all compounds that were subjected to the biological assay were >95%.

**Table 4. Synthetic Yields of 5-Aryl Barbiturates and IC50 of CaV1.3 Inhibition**

| #     | yield (%) | % Inhibition (10 μM) | IC50 (μM) |
|-------|-----------|----------------------|-----------|
| 14a   | 63        | 76.9                 | 72.7      | 3.78 | 3.72 |
| 14b   | 66        | 95.6                 | 98.8      | 2.31 |
| 14c   | 65        | 97.3                 | 99.2      | 4.10 |
| 14d   | 59        | 93.1                 | 81.2      | 2.80 | 4.53 |
| 14e   | 60        | 93.8                 | 96.1      | 1.42 | 2.41 |
| 14f   | 58        | 79.8                 | 100.0     |     |
| 14g   | 57        | 82.8                 | 88.2      |     |

#### REFERENCES

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(benzylamino)ethyl)carbamate. 1H NMR (400 MHz, DMSO-d6) δ 7.37–7.08 (m, 10H), 4.39 (s, 2H), 3.65 (s, 2H), 3.27–3.06 (m, 2H), 2.59 (t, J = 8.8 Hz, 2H), 2.15–2.01 (m, 1H), 1.36 (s, 9H).

Methyl 3-(Benzyl(2-(benzylamino)ethyl)amino)-3-oxopropanoate (8). Methyl malonyl chloride (30 mmol) was added dropwise into a stirred solution of t-butyl benzyl(2-(benzylamino)ethyl)carbamate (14.7 mmol) in THF (50 mL) under a N2 atmosphere. After stirring for 2 h, the solvent was removed by rotary evaporation. Then, 20 mL of 4M HCl solution was added to the residue, and the reaction mixture was stirred for 3 h. After adding deionized water (50 mL), the organic material was extracted with DCM (50 mL × 3 mL). The combined organic layer was dried over MgSO4, filtered, and dried in vacuo. The residue was purified by column chromatography on silica gel with dichloromethane/methanol as the eluent to give the title compound.1H NMR (400 MHz, CDCl3) δ 7.68–7.57 (m, 1H), 7.38 (s, 2H), 7.36 (s, 2H), 4.58 (s, 1H), 4.32 (m, 2H), 3.74 (t, J = 5.7 Hz, 2H), 3.68 (s, 1H), 3.65 (s, 1H), 3.62 (s, 2H), 3.07 (t, J = 5.7 Hz, 2H); 13C NMR (100 MHz, CDCl3) δ 169.88, 168.14, 135.23, 130.56, 130.31, 129.43, 129.12, 129.08, 128.17, 126.77, 52.94, 52.36, 50.71, 43.97, 42.46, 41.08.

1,4-Dibenzyl-1,4-diazepane-5,7-dione (9). 1,4-Dibenzyl-1,4-diazepane-5,7-dione (3 mmol) and p-toluene sulfonic acid (0.6 mmol) were dissolved in anhydrous DMF (4 mL) under a N2 atmosphere. The reaction mixture was stirred for 1 h at 180 °C under microwave irradiation. After completion of the reaction as confirmed by LC/MS monitoring, the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel with dichloromethane/methanol as the eluent to give the slightly impure title compound. The mixture was purified by recrystallization using dichloromethane and diethyl ether. The three-step yield was 23%.1H NMR (400 MHz, CDCl3) δ 7.35–7.22 (m, 7H), 7.25–7.15 (m, 3H), 4.58 (s, 4H), 3.88 (s, 2H), 3.37 (s, 4H); 13C NMR (100 MHz, CDCl3) δ 165.59, 136.56, 128.78, 128.15, 127.77, 50.74, 46.92, 46.15; HRMS (ESI, m/z) calcd for C19H18N2O2 [M + H]+ 309.1389; found 309.1389.

General Procedure I for the Pd-Catalyzed Arylation. 1,3-Diphenethylpyrimidine-2,4,6-(1H,3H,5H)-trione (0.5 mmol), iodobenzene (0.6 mmol), Pd(d-Bu3P)2 (0.05 equiv), Xphos (0.10 equiv), and Cs2CO3 (1.5 mmol) were dissolved in 4 mL of anhydrous 1,4-dioxane under a N2 atmosphere. The reaction mixture was refluxed for 0.5–24 h. After completion of the reaction, as confirmed by LC/MS, the reaction mixture was cooled to room temperature and the solvent was removed under vacuum. The residue was mixed with DCM (25 mL) and 5% Na2CO3 (25 mL) and stirred for 5 min. The aqueous layer was collected and rinsed with DCM (25 mL). After an aqueous HCl solution (1 N, 25 mL) was added to the remaining aqueous layer to adjust to pH 4–5, the organic material was extracted with CH2Cl2 (2 mL × 50 mL). The combined organic layer was dried over MgSO4, and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel with hexane/EA to give the target product. 1,3-Diphenethyl-5-(3-(trifluoromethyl)phenyl)pyrimidine-2,4,6-(1H,3H,5H)-trione (10a). General Procedure I was followed using 3-iodobenzene to give the title compound. Yield 71%; 1H NMR (400 MHz, CDCl3) δ 7.76 (d, J = 7.8 Hz, 1H), 7.47–7.38 (m, 2H), 7.32–7.16 (m, 10H), 7.11–7.07 (m, 1H), 4.58 (s, 1H), 4.32–4.02 (m, 4H), 2.91 (t, J = 7.6 Hz, 4H); 13C NMR (100 MHz, CDCl3) δ 166.14, 165.01, 137.44, 137.01, 130.81 (q, J = 134.6 Hz), 130.45, 129.08, 128.66, 128.97, 118.07, 113.36, 54.69, 43.29, 33.83, 29.74; HRMS (ESI, m/z) calcd for C26H24F2N3O3 [M + H]+ 438.1812; found 438.1815.

1,3-Diphenethyl-5-(3-(trifluoromethyl)phenyl)pyrimidine-2,4,6-(1H,3H,5H)-trione (10b). General Procedure I was followed using 4-iodobenzene to give the title compound. Yield 80%; 1H NMR (400 MHz, CDCl3) δ 7.65 (dd, J = 8.4 Hz, 2H), 7.32–7.14 (m, 10H), 6.99 (d, J = 8.4 Hz, 2H), 4.55 (s, 1H), 4.30–4.02 (m, 4H), 2.92 (t, J = 7.5 Hz, 4H); 13C NMR (100 MHz, CDCl3) δ 166.79, 160.15, 150.90, 137.69, 134.76, 130.45, 129.04, 128.61, 126.78, 119.60, 114.23, 114.09, 55.61, 55.33, 43.38, 34.00; HRMS (ESI, m/z) calcd for C26H24F2N3O3 [M + H]+ 438.1812; found 438.1816.
General Procedure II for the Synthesis of 11a–g and 12a–g. A cyclic β-dicarbonyl compound (0.7 mmol), iodobenzene (0.84 mmol), Pd(o-Bu)3P2 (0.05 equiv), Xphos (0.1 equiv), and Cs2CO3 (3 equiv) were dissolved in 4 mL of anhydrous 1,4-dioxane under a N2 atmosphere. The reaction mixture was refluxed until the reaction was complete by LC/MS monitoring. The reaction mixture was cooled down to room temperature, passed through a Celite pad, and then dried in vacuo. The residue was purified by column chromatography on silica gel with dichloromethane/MeOH as the eluent to give the target product.

1,2-Dibenzy1-(4-3-nitrophenyl)pyrazolidine-3,5-dione (11a). General Procedure II was followed using 1-iodo-3-nitrobenzene to give the title compound. Yield 76%; 1H NMR (400 MHz, CDCl3) δ 9.01 (t, J = 2.0 Hz, 1H), 8.46 (d, J = 7.9 Hz, 1H), 7.86–7.79 (m, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 7.4 Hz, 6H), 7.14 (dd, J = 7.4, 2.1 Hz, 4H), 4.76 (s, 4H), 1.61 (d, J = 15.4 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ 169.92, 149.58, 138.00, 137.93, 131.65, 129.52, 129.39, 128.78, 128.47, 120.14, 118.47, 87.07, 49.85, 48.67, 30.31; HRMS (ESI, m/z) calcd for C23H20N3O4 [M + H]+ 402.1448; found 402.1442.

1,2-Dibenzy1-(4-4-nitrophenyl)pyrazolidine-3,5-dione (11b). General Procedure II was followed using 1-iodo-4-nitrobenzene to give the title compound. Yield 86%; 1H NMR (400 MHz, DMSO-d6) δ 8.52–8.44 (m, 2H), 8.03–7.94 (m, 2H), 7.29–7.15 (m, 10H), 4.60 (s, 4H), 3.39 (s, 1H); 13C NMR (100 MHz, DMSO-d6) δ 169.93, 146.24, 139.89, 138.03, 128.62, 128.52, 127.45, 123.94, 121.60, 86.32, 47.43; HRMS (ESI, m/z) calcd for C23H20N3O4 [M + H]+ 402.1448; found 402.1447.

1,2-Dibenzy1-(4-2-phenyl)pyrazolidine-3,5-dione (11c). General Procedure II was followed using 1-iodo-2-nitrobenzene to give the title compound. Yield 28%; 1H NMR (400 MHz, CDCl3) δ 8.27 (dd, J = 8.2, 1.4 Hz, 1H), 7.71 (td, J = 7.5, 1.4 Hz, 1H), 7.60 (ddd, J = 8.1, 7.5, 1.5 Hz, 4H), 7.45 (d, J = 7.5 Hz, 1H), 7.36–7.27 (m, 6H), 7.16–7.07 (m, 4H), 4.98 (d, J = 16.2 Hz, 2H), 4.83 (s, 1H), 4.64 (d, J = 16.2 Hz, 2H); 13C NMR (100 MHz, DMSO-d6) δ 169.52, 148.21, 139.14, 137.96, 128.93, 129.82, 128.81, 127.46, 116.78, 115.71, 49.08, 47.62; HRMS (ESI, m/z) calcd for C23H20N3O4 [M + H]+ 402.1448; found 402.1444.

1,2-Dibenzy1-(4-phenyl)pyrazolidine-3,5-dione (11d). General Procedure II was followed using iodobenzene to give the title compound. Yield 60%; 1H NMR (400 MHz, CDCl3) δ 7.38–7.26 (m, 10H), 7.25–7.20 (m, 4H), 5.35 (s, 1H), 4.73 (d, J = 14.6 Hz, 2H), 4.57 (d, J = 14.6 Hz, 2H), 3.40–3.28 (m, 2H), 3.22–3.10 (m, 2H); 13C NMR (100 MHz, CDCl3) δ 167.27, 136.64, 134.85, 128.94, 128.77, 127.28, 127.79, 127.48, 126.95, 62.67, 51.34, 46.23; HRMS (ESI, m/z) calcd for C23H20N3O4 [M + H]+ 357.1598; found 357.1593.

1,2-Dibenzy1-(4-3-methoxyphenyl)pyrazolidine-3,5-dione (11e). General Procedure II was followed using 1-iodo-3-methoxybenzene to give the title compound. Yield 69%; 1H NMR (400 MHz, CDCl3) δ 7.34–7.27 (m, 1H), 7.34–7.17 (m, 10H), 7.01–6.93 (m, 2H), 6.89–6.80 (m, 2H), 4.50 (s, 1H), 4.31–3.98 (m, 4H), 2.98–2.77 (m, 4H); 13C NMR (100 MHz, CDCl3) δ 167.19, 159.75, 150.95, 137.70, 129.05, 128.99, 128.60, 126.76, 125.57, 114.80, 55.36, 54.88, 43.26, 33.97; HRMS (ESI, m/z) calcd for C23H20N3O4 [M + H]+ 443.1965; found 443.1969.
1,4-Dibenzyl-6-(3-methoxyphenyl)-1,4-diazepane-5,7-dione (12e). General procedure II was followed using 1-iodo-3-methoxybenzene to give the title compound. Yield 86%; 1H NMR (400 MHz, CDCl$_3$) δ 7.34–7.18 (m, 1H), 6.91–6.85 (m, 1H), 6.84–6.79 (m, 2H), 5.32 (s, 1H), 4.83–4.46 (m, 4H), 3.73 (s, 3H), 3.43–3.31 (m, 2H), 3.18–3.06 (m, 2H); 13C NMR (100 MHz, CDCl$_3$) δ 167.20, 160.13, 136.67, 136.36, 130.00, 128.77, 128.27, 127.79, 118.80, 113.49, 111.83, 63.10, 55.22, 51.32, 46.18; HRMS (ESI, m/z) calcd for C$_{26}$H$_{27}$N$_2$O$_3$ [M + H]$^+$ 415.2016; found 415.2017.

1,4-Dibenzyl-6-(4-methoxyphenyl)-1,4-diazepane-5,7-dione (12f). General procedure II was followed using 1-iodo-4-methoxybenzene to give the title compound. Yield 91%; 1H NMR (400 MHz, CDCl$_3$) δ 7.32–7.26 (m, 6H), 7.25–7.19 (m, 6H), 6.92–6.84 (m, 2H), 5.28 (d, J = 1.0 Hz, 4H), 4.71 (d, J = 14.6 Hz, 2H), 4.56 (d, J = 14.6 Hz, 2H), 3.80 (s, 3H), 3.41–3.30 (m, 2H); 13C NMR (100 MHz, CDCl$_3$) δ 167.50, 158.89, 136.70, 128.38, 128.25, 127.77, 127.64, 114.25, 61.50, 55.52, 51.35, 46.60; HRMS (ESI, m/z) calcd for C$_{26}$H$_{27}$N$_2$O$_3$ [M + H]$^+$ 415.2016; found 415.2016.

**General Procedure III.** 3-Chlorophenethyl isocyanate (1.0 mmol) and arylamine (1.0 mmol) were dissolved in DCM (2 mL) and stirred for 5 h. The reaction was followed by TLC monitoring. The suspension was filtered to obtain a solid product (urea). The solid was washed with ether and dried in the oven. Without any other separation process, the next reaction was carried out in situ. The previous crude mixture was dissolved in DCM, and malononitrile chloride was added (1.5 equiv). The mixture was stirred for 5 h. The reaction was followed by TLC monitoring, and then, the solvent was removed under vacuum. The residue was purified by silica gel flash chromatography (EA/Hex) to give 13a–g.

1-(4-(3-Chlorophenyl)butyl)-3-cyclopentylpyrimidine-2,4,6-(1H,3H,5H)-trione (13a). General procedure III was followed using cyclopentyl isocyanate and 4-(3-chlorophenyl)butylamine to give the title compound. Yield 44%; 1H NMR (400 MHz, CDCl$_3$) δ 7.28–7.12 (m, 12H), 7.05 (d, J = 7.2, 1.7 Hz, 1H), 5.15 (m, 1H), 3.92–3.84 (m, 2H), 3.63 (s, 2H), 2.67–2.59 (m, 2H), 2.04–1.87 (m, 4H), 1.90–1.80 (m, 2H), 1.69–1.55 (m, 4H), 1.33–1.23 (m, 2H); 13C NMR (100 MHz, CDCl$_3$) δ 158.57, 144.46, 140.82, 134.20, 130.20, 129.82, 128.60, 128.16, 124.19, 40.25, 35.40, 35.04, 33.79, 30.09, 28.66, 23.78; HRMS (ESI) calcd for C$_{26}$H$_{27}$N$_2$O$_3$ [M + H]$^+$ 363.1470; found 363.1473.

1-(3-Chlorophenethyl)-3-(3-(4-chlorophenyl)propyl)pyrimidine-2,4,6-(1H,3H,5H)-trione (13b). General procedure III was followed using 3-(4-chlorophenyl)propylamine to give the title compound. Yield 85%; 1H NMR (400 MHz, CDCl$_3$) δ 7.33–7.11 (m, 6H), 7.15–7.09 (m, 2H), 4.17–3.99 (m, 2H), 3.98–3.86 (m, 2H), 3.58 (s, 2H), 2.91–2.81 (m, 2H), 2.73–2.59 (m, 2H), 2.02–1.85 (m, 2H); 13C NMR (100 MHz, CDCl$_3$) δ 164.34, 164.21, 151.09, 139.69, 139.31, 131.81,
procedure III was followed using 3-(4-tri-141.48, 133.48, 130.76, 130.74, 130.69, 128.99, 128.61, 127.91, pyrimidine-2,4,6(1H,3H,5H)-trione (CFl (found 433.1079.

General procedure III was followed using 3-(3-chlorophenethyl)-3-(3-(4-chlorophenyl)propyl)-pyrimidine-2,4,6(1H,3H,5H)-trione (13c). General procedure III was followed using 3-(3-chlorophenethyl)-3-(3-(4-chlorophenyl)-5-(3-fluoromethyl)phenyl)pyrimidine-2,4,6(1H,3H,5H)-trione (14a). General procedure I was followed to give the title compound. Yield 63%;\(^\text{1}^H\) NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.89 (s, 1H), 8.39 (d, J = 8.0 Hz, 1H), 7.78−7.65 (m, 1H), 7.36−7.15 (m, 4H), 5.53 (m, 1H), 3.81 (m, 2H), 2.73−2.55 (m, 3H), 2.06 (m, 2H), 1.84 (m, 2H), 1.70−1.41 (m, 8H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 162.30, 161.93, 151.90, 147.20, 154.45, 142.12, 136.00, 133.31, 130.47, 128.70, 126.60, 127.40, 126.07, 126.67, 116.38, 86.69, 51.08, 34.93, 29.04, 28.87, 28.25, 25.94, 25.90; HRMS (ESI) calcld for C\(_{29}\)H\(_{24}\)ClF\(_6\)N\(_2\)O\(_3\) [M + H]^+ 484.1634; found 483.1639.

1-(3-Chlorophenethyl)-3-(3-(3-trifluoromethyl)phenyl)propyl)-pyrimidine-2,4,6(1H,3H,5H)-trione (14b). General procedure I was followed to give the title compound. Yield 66%;\(^\text{1}^H\) NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.28 (d, J = 2.0 Hz, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.37−7.12 (m, 11H), 4.06−3.92 (m, 2H), 3.88−3.72 (m, 2H), 2.87−2.73 (m, 2H), 2.57 (t, J = 7.7 Hz, 2H), 1.78 (m, 2H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 161.88, 161.74, 152.24, 147.42, 141.40, 140.91, 133.39, 133.33, 130.66, 130.58, 128.93, 128.58, 127.84, 127.39 (q, J = 30.8 Hz), 127.10, 126.44, 125.93 (q, J = 3.2 Hz), 125.63 (q, J = 269.8 Hz), 118.26 (q, J = 4.8 Hz), 86.79, 49.07, 41.20, 34.42, 32.57, 30.09; HRMS (ESI) calcld for C\(_{28}\)H\(_{24}\)ClF\(_3\)N\(_2\)O\(_3\) [M + H]^+ 536.1111, found 536.1108.

1-(3-Chlorophenethyl)-3-(3-(4-chlorophenyl)propyl)-5-(3-fluoromethyl)pyrimidine-2,4,6(1H,3H,5H)-trione (14c). General procedure I was followed to give the title compound. Yield 65%;\(^\text{1}^H\) NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.27 (s, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.50−6.99 (m, 11H), 4.08−3.95 (m, 2H), 3.89−3.74 (m, 2H), 2.89−2.76 (m, 2H), 2.59 (t, J = 7.7 Hz, 2H), 1.85−1.74 (m, 2H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 161.86, 161.72, 152.22, 145.03, 142.74, 140.84, 133.43, 133.32, 130.57, 130.50, 128.94, 128.67, 128.55, 127.85, 127.44, 127.42 (q, J = 28.5 Hz), 127.12, 126.43, 126.11, 125.98 (q, J = 3.7 Hz), 125.63 (q, J = 271.0 Hz), 118.31 (q, J = 4.0 Hz), 86.86, 49.07, 41.22, 34.41, 32.85, 29.98; HRMS (ESI) calcld for C\(_{29}\)H\(_{24}\)ClF\(_3\)N\(_2\)O\(_3\) [M + H]^+ 563.1111, found 563.1108.

1-(3-Chlorophenethyl)-3-(3-(4-(trifluoromethyl)phenyl)propyl)-5-(3-fluoromethyl)pyrimidine-2,4,6(1H,3H,5H)-trione (14d). General procedure I was followed to give the title compound. Yield 59%;\(^\text{1}^H\) NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.29 (d, J = 2.0 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.36−7.10 (m, 6H), 4.05−3.96 (m, 2H), 3.89−3.79 (m, 2H), 3.18 (s, 1H), 2.87−2.75 (m, 2H), 2.69 (t, J = 7.7 Hz, 2H), 1.85 (b, J = 6.7 Hz, 2H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 161.89, 161.75, 152.26, 147.39, 142.74, 140.90, 133.41, 133.33, 130.56, 129.49, 128.93, 127.84, 127.42 (q, J = 30.2 Hz), 127.10, 126.94 (q, J = 31.3 Hz), 126.44, 125.96 (q, J = 4.0 Hz), 125.61 (q, J = 271.2 Hz), 125.49 (q, J = 3.8 Hz), 124.96 (q, J = 269.4 Hz), 118.28 (q, J = 4.5 Hz), 86.81, 49.06, 41.21, 34.42, 33.07, 29.84; HRMS (ESI) calcld for C\(_{29}\)H\(_{24}\)ClF\(_3\)N\(_2\)O\(_3\) [M + H]^+ 597.1374; found 597.1378.

1-(3-Chlorophenethyl)-3-(3-(4-trifluoromethyl)butyl)-5-(3-fluoromethyl)pyrimidine-2,4,6(1H,3H,5H)-trione (14e). General procedure I was followed to give the title compound. Yield 60%;\(^\text{1}^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.64−7.60 (m, 1H), 7.52−7.42 (m, 2H), 7.27−7.25 (m, 1H), 7.25−4.26, 4.108, 40.66, 34.94, 33.45, 28.20, 27.37; HRMS (ESI, m/z) calcld for C\(_{29}\)H\(_{26}\)ClF\(_{5}\)N\(_2\)O\(_3\) [M + H]^+ 467.1344; found 467.1345.

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7.22 (m, 2H), 7.20–7.17 (m, 3H), 7.12–7.04 (m, 3H), 4.67 (s, 1H), 4.27–4.06 (m, 2H), 4.00–3.84 (m, 2H), 2.98–2.84 (m, 2H), 2.61 (t, J = 6.9 Hz, 2H), 1.65–1.56 (m, 4H); 13C NMR (100 MHz, CDCl3) δ 166.11, 160.10, 150.62, 140.20, 139.41, 134.33, 134.08, 131.73 (q, J = 32.4 Hz), 131.64, 131.27, 129.90, 129.86, 129.73, 129.10, 128.48, 127.15, 127.07, 125.75 (q, J = 3.6 Hz), 125.26 (q, J = 3.7 Hz), 123.59 (q, J = 273.7 Hz), 55.13, 43.01, 42.23, 34.65, 33.53, 28.40, 27.40; HRMS (ESI, [M + H]+) calcd for C29H26Cl2F3N2O3 [M + H]+ 577.1267; found 577.1269.

1-(3-Chlorophenethyl)-3-(4-(3-chlorophenyl)butyl)-5-(3-(trifluoromethyl) phenyl) pyrimidin-2,4,6(1H,3H,5H)-trione (14f). General procedure I was followed to give the title compound. Yield 58%; 1H NMR (400 MHz, CDCl3) δ 7.63 (d, J = 7.8 Hz, 1H), 7.48 (dd, J = 15.6, 7.8 Hz, 2H), 7.26 (d, J = 7.0 Hz, 1H), 7.22–7.12 (m, 6H), 7.12–7.05 (m, 1H), 7.06–6.99 (m, 1H), 4.67 (s, 1H), 4.27–4.05 (m, 2H), 4.02–3.84 (m, 2H), 2.91 (t, J = 7.6 Hz, 2H), 2.61 (t, J = 6.9 Hz, 2H), 1.71–1.53 (m, 4H); 13C NMR (100 MHz, CDCl3) δ 166.12, 166.11, 150.63, 145.82, 139.42, 134.33, 134.12, 134.08, 131.73 (q, J = 33.3 Hz), 131.23, 129.91, 129.86, 129.65, 129.11, 128.54, 127.16, 127.07, 126.60, 126.14, 125.75 (q, J = 3.3 Hz), 125.32 (q, J = 3.8 Hz), 123.59 (q, J = 273.7 Hz), 55.13, 43.02, 42.15, 35.13, 33.53, 28.20, 27.44; HRMS (ESI, [M + m/z] calcd for C29H26ClF3N2O3 [M + H]+ 577.1267; found 577.1269.

1-(3-Chlorophenethyl)-5-(3-(3-(trifluoromethyl)phenoxy)butyl)pyrimidin-2,4,6(1H,3H,5H)-trione (14g). General procedure I was followed to give the title compound. Yield 57%; 1H NMR (400 MHz, CDCl3) δ 7.64–7.59 (m, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.51–7.42 (m, 2H), 7.30–7.23 (m, 3H), 7.22–7.15 (m, 3H), 7.08 (ddd, J = 5.8, 4.2, 2.2 Hz, 1H), 4.67 (s, 1H), 4.28–4.06 (m, 2H), 4.03–3.85 (m, 2H), 2.97–2.85 (m, 2H), 2.75–2.65 (m, 2H), 1.68–1.57 (m, 4H); 13C NMR (100 MHz, CDCl3) δ 166.14, 166.09, 150.63, 145.86, 139.40, 134.33, 134.07, 131.74 (q, J = 32.8 Hz), 131.29, 129.90, 129.86, 129.10, 128.68, 128.34 (q, J = 32.3 Hz), 127.15, 127.07, 125.76 (q, J = 3.6 Hz), 125.32 (q, J = 3.8 Hz), 125.21 (q, J = 3.8 Hz), 124.31 (q, J = 268.6 Hz), 123.57 (q, J = 272.5 Hz), 55.13, 43.02, 42.15, 35.13, 33.53, 28.20, 27.44; HRMS (ESI, [M + m/z] calcd for C29H26ClF3N2O3 [M + H]+ 577.1261; found 577.1256.

Cell Culture. HEK293 cells stably expressing CaV1.3 or CaV1.2 were constructed as described previously.13,14,22 Additionally, the two cell lines were stably transfected with KCNJ2 (Kir2.1). Cells were grown in DMEM with 10% FBS solution and penicillin/streptomycin at 37 °C in 5% CO2. The day before patch-clamp recording, cultures were moved to a 28 °C incubator to facilitate the automated electrophysiology procedure.

Automated Electrophysiology. Automated patch-clamp recordings were performed at room temperature using the Syncropatch 768 PE platform (Nanion Technologies) as previously described.23 Eight-hole, 384-well recording chips with medium resistance (2–4 MΩ) were used in this study. The external solution contained (in mM) 120 NaCl, 20 CsCl, 10 BaCl2, 1 MgCl2, 15 HEPES, and 5 glucose (pH 7.4). The composition of the internal solution was (in mM) 80 CsF, 50 NMDG, 10 HEPES, 5 BAPTA, 10 phosphocreatine, 2 MgATP, 0.5 NaGTP, and 0.1 leupeptin, (pH 7.2–7.3). Whole-cell currents were recorded in a whole-cell configuration at 0 mV, 250 ms after the start of the voltage pulse from a holding potential of −60 mV before and after addition of various concentrations of compounds or vehicle. Whole-cell currents were not leak subtracted. The contribution of background currents was determined by recording whole-cell currents at the end of the experiment after addition of CdCl2 (5 mM). Only CdCl2-sensitive currents were used for analysis.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c00889.

1H and 13C NMR spectra of 10a−n, 11a−g, 12a−g, and 14a−g (PDF)

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Notes
The authors declare no competing financial interest.

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ABBREVIATIONS USED
LTCCs: L-type calcium channel; GABA: γ-aminobutyric acid; MMP: matrix metalloproteinase; TNF-α: tumor necrosis factor α; TACE: TNF-α converting enzyme; IDH1: isocitrate dehydrogenase; MMP:matrix metalloproteinase; TNF-α:tumor necrosis factor α; TACE:TNF-α converting enzyme; IDH1:isocitrate dehy-
dorgenase 1; HIV:human immunodeficiency virus; SNc: substantia nigra pars compacta; PD:Parkinson’s disease

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