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Synthesis of 1-(3-chlorophenethyl)-3-cyclopentylpyrimidine-2,4,6-(1H,3H,5H)-trione (CP8) V.2

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Kang, S.; Cooper, G.; Dunne, S. F.; Dusel, B.; Luan, C.-H.; Surmeier, D. J.; Silverman, R. B. CaV1.3-selective L-type calcium channel antagonists as potential new therapeutics for Parkinson's disease. Nature Communications 2012, 3 (1), 1146. DOI: 10.1038/ncomms2149.

Brimblecombe KR, Connor-Robson N, Bataille CJR, Roberts BM, Gracie C, O'Connor B, Te Water Naude R, Karthik G, Russell AJ, Wade-Martins R, Cragg SJ. Inhibition of striatal dopamine release by the L-type calcium channel inhibitor isradipine co-varies with risk factors for Parkinson's. Eur J Neurosci. 2023 Nov 8. doi: 10.1111/ejn.16180. Epub ahead of print. PMID: 37941514.

Protocol status: Working
We use this protocol and it's working

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Abstract

A structure-activity relationship-based modification of pyrimidine-2,4,6-triones led to 1-(3-chlorophenethyl)-3-cyclopentylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (CP8), a potent and highly selective $Ca_V1.3$ L-type calcium channel antagonist. This protocol is an adaption of **Kang, S., Cooper, G., Dunne, S. et al., 2012**'s method of the synthesis of this chemical.

Guidelines

All solvents and reagents were used as supplied (analytical or HPLC grade) without prior purification. Water was purified by an Elix® UV-10 system. In vacuo refers to the use of a rotary evaporator attached to a diaphragm pump.

Thin layer chromatography was performed on aluminium plates coated with 60 F254 silica.

Plates were visualised using UV light (254 nm) or 1% aq. KMnO4. Flash column chromatography was performed on Kieselgel 60M silica in a glass column.

Nuclear magnetic resonance (NMR) spectra were recorded on Bruker Avance spectrometers (AVIII 400) in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Chemical shifts (d) are reported in parts per million (ppm) referenced to the solvent peak. 1H spectra reported to two decimal places (see **Figure 2**), and 13C spectra reported to one decimal place (see **Figure 3**), and coupling constants (J) are quoted in Hz (reported to one decimal place).

Low-resolution mass spectra were recorded on an Agilent 6120 spectrometer from solutions of MeOH.

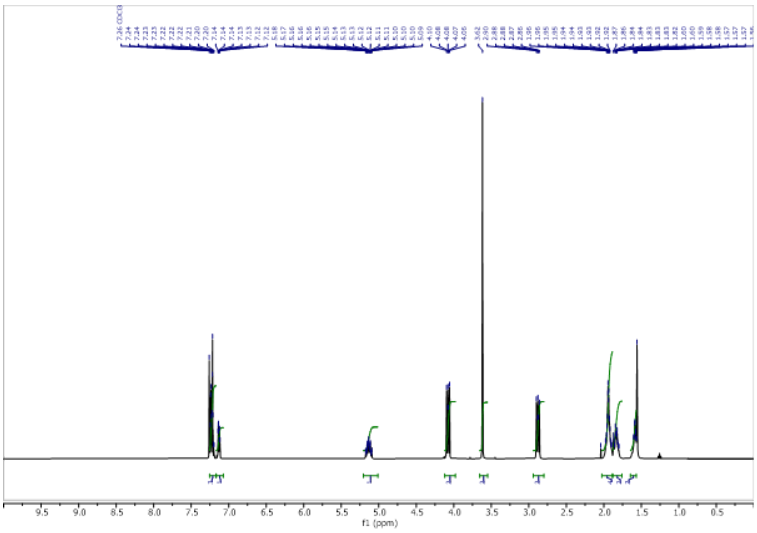

Figure 2 - 1H NMR Spectra

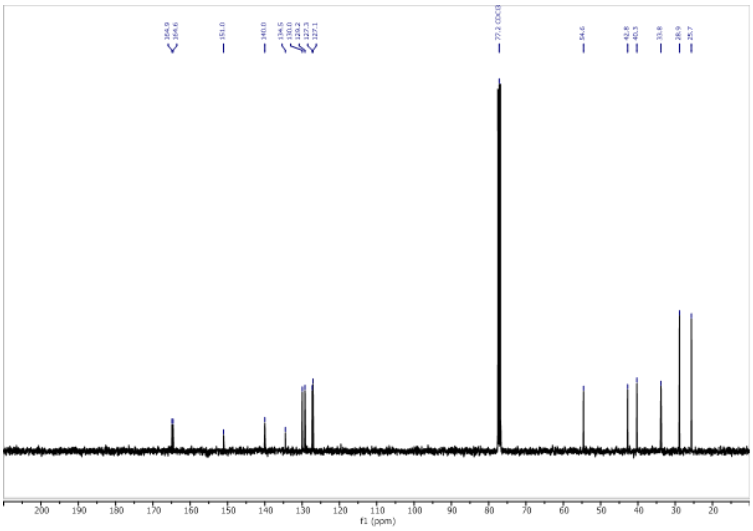

Figure 3 - 13C NMR Spectra

Materials

Equipment:

- Agilent 6120
- Aluminum Plates Coated in F254 Silica
- Bruker Avance spectrometers (AVIII 400)
- Elix UV-10 system

Reagents:

- 2-(3-chlorophenyl)ethylamine (2.58 mmol, 1.0 eq)
- Cyclopentaneisocyanate (2.58 mmol, 1.0 eq)
- Dichloromethane
- Kiesegel 60M Silica
- Malonyl chloride (2.84 mmol, 1.1 eq)

Synthesis of 1-(3-chlorophenethyl)-3-cyclopentylpyrimidine-2,4,6-(1H,3H,5H)-trione (CP8)

1 Add 357 µL 2-(3-chlorophenyl)ethylamine (2.58 mmol, 1.0 eq.) to a solution of 290 mg of Cyclopentaneisocyanate (2.58 mmol, 1.0 eq.) in 10 mL of dichloromethane.

2 Stir at RT for 5 h.

3 Monitor completion with Low-Resolution Mass Spectrometry.

4 Add 276 µL Malonyl chloride (2.84 mmol, 1.1 eq.) dropwise under vigorous stirring over 5 min.

5 Stir mixture for 1 h and concentrate in vacuo.

6 Purify residue by column chromatography on silica gel (EtOAc/pentane, 1:4), product should be a white solid (687 mg, 80%)

Nuclear Magnetic Resonance (NMR) Spectroscopy

7 Check data from NMR spectroscopy is comparable with the literature (**Kang, S., Cooper, G., Dunne, S. et al., 2012**):

^{1}H NMR (400 MHz, CDCl3) δ 7.25 – 7.19 (m, 3H), 7.13 (dt, J = 6.7, 2.1 Hz, 1H), 5.20 – 5.07 (m, 1H), 4.13 – 4.03 (m, 2H), 3.62 (s, 2H), 2.92 – 2.84 (m, 2H), 1.94 (tqd, J = 8.0, 4.9, 2.0 Hz, 4H), 1.89 – 1.79 (m, 2H), 1.61 – 1.57 (m, 2H)

^{13}C NMR (101 MHz, CDCl3) δ 164.9, 164.6, 151.1, 140.0, 134.5, 123.0, 129.2, 127.3, 127.1, 54.6, 42.8, 40.3, 33.8, 28.8, 25.7; LRMS m/z (ESI^{-}) 333.1 [M-H]$^{-}$

Note

The multiplicity of each signal is indicated by: δ (singlet); br. s (broad singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublets); td (triplet of doublets); qt (quartet of triplets); or m (multiplet).

Protocol references

Kang, S.; Cooper, G.; Dunne, S. F.; Dusel, B.; Luan, C.-H.; Surmeier, D. J.; Silverman, R. B. CaV1.3-selective L-type calcium channel antagonists as potential new therapeutics for Parkinson's disease. Nature Communications 2012, 3 (1), 1146. DOI: 10.1038/ncomms2149.