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Syntheses and analytical characterizations of N-alkyl-arylcyclohexylamines

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Keywords: New psychoactive substances, Research chemicals, Phencyclidine, NMDA receptors, Arylcyclohexylamines

Abstract:
The rise in new psychoactive substances that are available as ‘research chemicals’ (RCs) remains a significant forensic and legislative challenge. A number of arylcyclohexylamines have attracted attention as RCs and continued to be encountered, including 3-MeO-PCP, 3-MeO-PCE and 3-MeO-PCPr. These compounds are commonly perceived as ketamine-like dissociative substances and are believed to act predominantly via antagonism of the N-methyl-D-aspartate (NMDA) receptor. To aid in the identification of newly emerging substances the syntheses of fifteen N-alkyl-arylcyclohexylamines are described. Analytical characterizations were performed via gas chromatography and high performance liquid chromatography coupled to multiple forms of mass spectrometry as well as nuclear magnetic resonance spectroscopy, ultraviolet diode array detection and infrared spectroscopy. The series consisted of the N-alkyl derivatives (N-methyl, N-ethyl, N-propyl) of phenyl-substituted and isomeric 2-, 3- and 4-methoxy phenylcyclohexylamines, as well as the N-alkyl derivatives obtained from a 3-methylphenyl and 2-thienyl moiety. In addition to the presentation of a range of previously unreported data, it was also found that positional isomers of aryl methoxyl-substituted arylcyclohexylamines were readily distinguishable under a variety of analytical conditions.
Syntheses and analytical characterizations of \(N\)-alkyl-arylcyclohexylamines

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Running title: Characterization of \(N\)-alkyl-arylcyclohexylamines

Abstract

The rise in new psychoactive substances that are available as ‘research chemicals’ (RCs) remains a significant forensic and legislative challenge. A number of arylcyclohexylamines have attracted attention as RCs and continued to be encountered, including 3-MeO-PCP, 3-MeO-PCE and 3-MeO-PCPr. These compounds are commonly perceived as ketamine-like dissociative substances and are believed to act predominantly via antagonism of the \(N\)-methyl-D-aspartate (NMDA) receptor. To aid in the identification of newly emerging substances the syntheses of fifteen \(N\)-alkyl-arylcyclohexylamines are described. Analytical characterizations were performed via gas chromatography and high performance liquid chromatography coupled to multiple forms of mass spectrometry as well as nuclear magnetic resonance spectroscopy, ultraviolet diode array detection and infrared spectroscopy. The series consisted of the \(N\)-alkyl derivatives (\(N\)-methyl, \(N\)-ethyl, \(N\)-propyl) of phenyl-substituted and isomeric 2-, 3- and 4-methoxy phenylcyclohexylamines, as well as the \(N\)-alkyl derivatives obtained from a 3-methylphenyl and 2-thienyl moiety. In addition to the presentation of a range of previously unreported data, it was also found that positional isomers of aryl methoxy-substituted arylcyclohexylamines were readily distinguishable under a variety of analytical conditions.
Keywords: New psychoactive substances; ‘research chemicals’; phencyclidine; NMDA receptors; arylcyclohexylamines

Introduction

The non-medical use of dissociative drugs including 1-(1-phenylcyclohexyl)piperidine (PCP), ketamine and their derivatives is a challenge to policy makers, clinicians and forensic investigators charged with their identification. More recent examples of dissociative drugs include ‘research chemicals’ (RCs) such as 3-MeO-PCP, methoxetamine (MXE), diphendine and 2-methoxydiphenidine (2-MXP). In the UK, a range of arylcyclohexylamines were placed under control in 2013 following generic legislation but control status varies across the globe. Within one week of introducing generic control, diphendine was available for purchase in the UK, which added to the existing product catalogues of substances suspected to show dissociative properties in humans. The association of some those newly emerging substances with acute toxicity serves as a reminder that the accurate identification of these substances is essential for the monitoring of new psychoactive substances.

The major pharmacological mechanism that appears to mediate a significant portion of the therapeutically relevant and psychoactive effects of dissociative substances includes uncompetitive antagonism of the N-methyl-D-aspartate (NMDA) receptor. NMDA receptor antagonists exemplify an important pharmacological class that provides promising pharmacological tools. They are used or are being investigated in a number of therapeutic areas including general anesthetics, neuroprotection, management of neuropathic pain and depression. Issues linked with clinical tolerability remain challenging for clinical development of this promising pharmacological class.

Recently a study of the receptor binding profiles of a series of dissociative legal highs included 3-methoxeticyclidine (3-MeO-PC) (3b). Consistent with reports of its potent dissociative effects in humans it showed high affinity for (++)[H]MK-801 labeled NMDA receptors (61 nM). In addition, affinity for the serotonin transporter (115 nM) and lesser affinity at sigma-1 and sigma-2 receptor sites were observed. It is unknown how these additional pharmacological interactions may contribute to the psychoactive properties of 3-MeO-PC and related arylcyclohexylamines and further studies are warranted to explore polypharmacological mechanisms that may be relevant as well.

N-Alkyl-arylcyclohexylamines including PCE, PCPr and PciP were sold on 'street markets' during the 1960-1990s in the United States and PCE in particular enjoyed a large distribution relative to other PCP derivatives. Furthermore, a number of N-alkoxyalkyl secondary amine derivatives were detected in Germany during the 1990s and included PCMEA, PCEEA, PCMPA and PCEPA (Figure 1), respectively. More recently, 3-MeO-PC (3b) and 3-MeO-PCPr (3c) have been sold through Internet based vendors (Figure 1). Several closely related compounds included derivatives of ketamine, such as methoxetamine, 2-MeO-2-
deschloroketamine (‘2-MeO-ketamine’, 2-MK) and N-ethynorketamine (‘N-ethylketamine’, N-EK) (Figure 1) were previously reported.\textsuperscript{\[1,19,21\]} The analytical characterizations of a series of tertiary amine based arylcyclohexylamines including ‘research chemicals’ 3-MeO- and 4-MeO-PCP was previously reported.\textsuperscript{\[4\]} Although a previous publication described the appearance of 3-MeO-PCE,\textsuperscript{\[20\]} detailed information on analytical profiles of the secondary amine N-alkylarylcylohexylamines are lacking.

This study presents the syntheses of 15 N-alkyl-arylcylohexylamines (1a) – (5c) using facile routes that are easily adaptable to forensic laboratories. The series included the N-alkyl derivatives (N-methyl, N-ethyl, N-propyl) of 2-, 3- and 4-MeO-arylcylohexylamine isomers as well as 3-methylphenyl and 2-thienyl compounds (Figure 2A). The comprehensive analytical characterizations included the differentiation between positional isomers of aryl methoxyl-substituted arylcyclohexylamines.

**Experimental**

**Materials**

All starting materials, reagents and solvents used for synthesis (≥ 96%) were obtained from Sigma-Aldrich (St. Louis, USA). Column chromatography was conducted using Merck silica gel, grade 9385 (230-400 mesh, 60 Å). Melting point ranges were obtained using a DigiMelt A160 SRS melting point apparatus (Stanford Research Systems, Sunnyvale, USA) at a ramp rate of 2 °C/min.

**Synthesis procedures**

A representative example is shown for the preparations of (1a) – (1c), where the appropriately substituted Grignard reagent served as the starting point (Figure 2B). NMR data for compounds (1a) – (5c) are provided in Tables 1–6. NMR data of the primary amines are shown as supplementary information.

**Preparation of 1-(thiophen-2-yl)cyclohexan-1-amine (TCA)**

A solution containing the desired Grignard reagent was prepared consisting of 2-bromo thiophene (147 mmol, 24.08 g) in 200 mL dry THF containing freshly crushed Mg (442 mmol, 10.75 g) at room temperature under argon. After stirring for 12 hours at room temperature, cyclohexanone (114 mmol, 11.14 g) was added slowly. The exothermic reaction mixture was then stirred for an additional 24 hours at which point it was quenched with 300 mL distilled water (dH\textsubscript{2}O), titrated to pH 7 with a saturated NH\textsubscript{4}Cl solution and extracted with ethyl acetate (3 x 100 mL). Organic phases were pooled, washed with a saturated sodium bisulfite solution (2 x 150 mL), saline (1 x 150 mL), dried with anhydrous sodium sulfate and concentrated under reduced pressure to give 1-(thiophene-2-yl)cyclohexane-1-ol as an amber oil.

A solution of the crude tertiary alcohol (104 mmol, 18.94 g) in CHCl\textsubscript{3} (50 mL) was added dropwise to a vigorously stirred suspension of NaN\textsubscript{3} (208 mmol, 13.51 g) and
trifluoroacetic acid (312 mmol, 23.86 mL) in CHCl₃ (200 mL) at 0 °C under argon. After addition, the suspension was allowed to recover to room temperature and stir for 24 hours at which point it had set to a solid mass. The reaction mixture was carefully quenched by slow addition to a stirred concentrated aqueous solution of NaHCO₃. Once the evolution of gas was complete, the organic phase was collected, washed with dH₂O and saline, dried with anhydrous sodium sulfate and concentrated under reduced pressure to give the crude azide as a yellow oil. The azide was purified using flash column chromatography on silica gel with hexanes as the mobile phase. Early fractions containing the azide product were pooled and concentrated to produce a light yellow oil (81 mmol, 16.71 g, 77.9% yield).

A solution of the purified azide (81 mmol, 16.71 g) in dry THF (50 mL) was added dropwise over the course of an hour to a vigorously stirred suspension of LiAlH₄ (242 mmol, 9.2 g) in dry THF (200 mL) under argon at 0°C. The reaction mixture was kept at 0 °C for 1 h. It was then quenched by cautious dropwise addition of a 50:50 mixture of THF and ice cold dH₂O (50 mL). A few mL of aqueous KOH were added to ensure a basic pH and ethyl acetate (300 mL) was added and the suspension gravity filtered to remove insoluble inorganic salts. Inorganic salts were washed with ethyl acetate. The organic phase was extracted with aqueous HCl solution (3 x 200 mL), acidic phases pooled, made basic to pH > 12 with KOH pellets and extracted with ethyl acetate (3 x 70 mL). Organic phases were pooled, washed with saline, dried with anhydrous magnesium sulfate, gravity filtered and concentrated under reduced pressure to give a colorless oil. The crude product was purified by flash column chromatography on silica gel eluting with hexanes:ethyl acetate (3:1) containing 0.5 % triethylamine with a gradually increasing ethyl acetate concentration to 50%. Desired fractions were pooled and concentrated under reduced pressure to give 1-(thiophene-2-yl)cyclohexane-1-amine (TCA), a light yellow oil (71 mmol, 12.85 g, 87.7% yield).

The HCl salt of TCA was prepared by dissolving it in ethanol, titrating to pH 1.0 with concentrated HCl, and evaporating under a stream of warm air. Dry acetone (4 Å sieves) was added in 10 mL increments until all residual moisture and HCl was removed. The resulting solid was washed with ethyl acetate (2 x 5 mL), dried, and crystallized by dissolving it in a minimal amount of warm methanol diluted with a 10-fold excess of diethyl ether. The solution was stored at 0 °C overnight. The resulting crystals were collected by decanting the solvent off and then washing with ethyl acetate (2 x 5 mL), followed by drying in an oven at 60 °C. The solids were recrystallized two more times as described to produce white fluffy thin needle-like crystalline solids (m.p. 214.3 – 215.6 °C).

**Preparation of N-methyl-1-(thiophen-2-yl)cyclohexan-1-amine (TCMe) (1a)**

A solution of TCA (7.72 mmol, 1.40 g) and ethyl formate (10 mL) containing 4 Å molecular sieves (1.0 g) were refluxed under an inert atmosphere of argon. As solvent tended to dissipate, additional ethyl formate was added as needed to keep a constant volume. After ~72 h the reaction mixture was quenched by diluting in 400 mL 1N aqueous HCl solution. This solution was extracted with ethyl acetate (3 x 60 mL), organic phases pooled, washed with 2N aqueous HCl solution (2 x 100 mL),
saline (40 mL), dried and concentrated under vacuum to give \(N\text{-}[1\text{(thiophen-2-yl)cyclohexyl}]\text{formamide (N-formyl-TCA)}\) as a white solid (6.69 mmol, 1.40 g, 86.7 % yield). The solid was crystallized from hexanes containing 10% ethyl acetate followed by storage at 0 °C. However, the crude product was sufficient for use in the subsequent reaction.

A solution of dry THF (40 mL) containing \(N\text{-formyl-TCA (6.69 mmol, 1.40 g)}\) was added dropwise to a stirred suspension of LiAlH\(_4\) (21.4 mmol, 0.8117 g) in THF (100 mL) at 0 °C under argon. The stirred reaction mixture was then allowed to warm to room temperature and placed on a mild reflux while maintaining an inert argon atmosphere. Once complete (TLC or GC/MS), the reaction mixture was placed on ice and quenched by dropwise addition of a 50:50 mixture of ice cold THF and dH\(_2\)O with vigorous stirring. The suspension was then diluted with 400 mL ethyl acetate and the inorganic salts removed by gravity filtration. The filtered inorganic material was washed heavily with ethyl acetate, and the washings combined and extracted with aqueous 1N HCl (3 x 200 mL). The pooled aqueous phases were then basified to >pH 12 with KOH pellets and extracted with ethyl acetate (3 x 60 mL). The pooled organic extractions were washed with saline, dried with anhydrous magnesium sulfate and concentrated under reduced pressure to give an amber oil. The crude product was purified using flash column chromatography on silica gel eluting with hexanes:ethyl acetate (4:1) containing 1% triethylamine. Desired fractions were pooled and concentrated yielding colorless TCMe oil (4.92 mmol, 960 mg, 73.5 % yield). HCl salt prepared as described to give a colorless needle-like crystalline solid (148 – 149 °C (phase transition), m.p. 194.8 – 195.9 °C). HR-ESI-MS: observed \[m/z \text{196.11553 (theory [M + H]}^+ : C}_{11}\text{H}_{18}\text{NS}^+ \text{m/z 196.11545).}\]

### Preparation of \(N\text{-ethyl-1\text{(thiophen-2-yl)cyclohexane-1-amine (TCE (1b)})}\)

\(TCA (5.52 \text{ mmol, 1.0 g})\) was dissolved in triethylamine (1 mL) in a beaker and placed on ice. Under a blanket of argon gas, acetyl chloride (11.1 mmol, 0.79 mL) was added dropwise and mixed with a spatula until a waxy white precipitate formed. The solid was suspended in aqueous 2N HCl solution (100 mL) and extracted with ethyl acetate (3 x 75 mL). The pooled organic phases were washed with 2N aqueous HCl solution (2 x 30 mL), dH\(_2\)O (20 mL) and saline (10 mL). The organic solution was dried with anhydrous sodium sulfate and concentrated under reduced pressure to produce \(N\text{-}[1\text{(thiophene-2-yl)cyclohexyl}]\text{acetamide (4.92 mmol, 1.10 g, 89.5 % yield). These crystals were recrystallized from boiling ethyl acetate and stored at 0 °C. The crude product was sufficient in purity for use in the subsequent reaction.}

A solution of \(N\text{-}[1\text{(thiophene-2-yl)cyclohexyl}]\text{acetamide (4.5 mmol, 1.0 g)}\) in dry THF (20 mL) was added dropwise to a stirred suspension of LiAlH\(_4\) (13.4 mmol, 0.51 g) in dry THF (100 mL) on ice under argon. Upon completion of the addition, the reaction mixture was removed from ice and brought to a mild reflux. The reflux was continued and monitored for completion by TLC (~ 4 h). The reaction mixture was quenched with dropwise addition of a 50:50 mixture of ice cold THF and dH\(_2\)O. A few drops of KOH solution were added and the reaction mixture diluted with ethyl acetate (200 mL). The resulting inorganic salts were removed via gravity filtration and washed with ethyl acetate (150 mL). The organic phase was extracted with aqueous 1N HCl...
solution (3 x 75 mL). The pooled aqueous phases were made basic with KOH pellets (pH >12) and extracted with ethyl acetate (3 x 100 mL). The pooled organic fractions were washed with saline (20 mL), dried with anhydrous magnesium sulfate, gravity filtered and concentrated under reduced pressure to produce N-ethyl-1-(thiophene-2-yl)cyclohexane-1-amine (1b) (2.10 mmol, 0.45 g, 46.7 % yield). HCl salt prepared as previously described to give a colorless needle-like crystalline solid (m.p. 193.9 – 195.1 °C; lit: 195–196 °C[22]) HR-ESI-MS: observed m/z 210.13120 (theory [M + H]^+: C_{12}H_{20}NS^+ m/z 210.13110).

Preparation of N-propyl-1-(thiophen-2-yl)cyclohexane-1-amine (TCPPr) (1c)

TCPPr was prepared as described for TCE above in 92% yield from TCA (5.52 mmol, 1.0 g) as a white crystalline solid. Generation of the HCl salt gave a colorless needle-like crystalline solid (116 – 117 °C (phase transition), m.p. 183.8 – 185.5 °C). HR-ESI-MS: observed m/z 224.1465 (theory [M + H]^+: C_{13}H_{22}NS^+ m/z 224.1467).

Preparation of 1-(2-methoxyphenyl)cyclohexan-1-amine (2-MeO-PCA)

2-MeO-PCA was prepared in 54.8% yield from cyclohexanone (26.6 mmol, 2.61 g) and 2-bromoanisole (31.9 mmol, 5.96 g) as described for TCA above. The HCl salt was prepared as described for 3-MeO-PCA to give colorless needles with a melting point of 176.7 – 178.0 °C (lit: 212–215 °C[23]).

Preparation of N-methyl-1-(2-methoxyphenyl)cyclohexan-1-amine (2-MeO-PCMe) (2a)

N-[1-(2-methoxyphenyl)cyclohexyl]formamide (N-formyl-2-MeO-PCA) was prepared as previously described in 67.7 % yield from 2-MeO-PCA (5.21 mmol, 1.07 g) as a white solid. 2-MeO-PCMe was obtained as described in 16.9% yield from N-formyl-2-MeO-PCA (0.86 mmol, 0.20 g), as a colorless oil. The HCl salt was obtained as a white crystalline solid; 107 – 110 °C (phase transition), m.p. 185 – 187 °C. HR-ESI-MS: observed m/z 220.16982 (theory [M + H]^+: C_{14}H_{22}NO^+ m/z 220.16959).

Preparation of N-ethyl-1-(2-methoxyphenyl)cyclohexan-1-amine (2-MeO-PCE) (2b)

N-[1-(2-methoxyphenyl)cyclohexyl]acetamide (N-acetyl-2-MeO-PCA) was prepared as previously described in 93.6 % yield from 2-MeO-PCA (5.50 mmol, 1.13 g) as a white solid. 2-MeO-PCE freebase was prepared as described in 91.2% yield from N-acetyl-2-MeO-PCA (3.92 mmol, 0.97 g) as a colorless oil. The sparkling white crystalline HCl salt gave a m.p. of 194.3 – 195.9 °C. HR-ESI-MS: observed m/z 234.18520 (theory [M + H]^+: C_{15}H_{24}NO^+ m/z 234.18524).

Preparation of N-propyl-1-(2-methoxyphenyl)cyclohexan-1-amine (2-MeO-PCPr) (2c)

N-[1-(2-methoxyphenyl)cyclohexyl]propanamide (N-propionyl-2-MeO-PCA) was prepared as previously described in 88.0 % yield from 2-MeO-PCA (5.41 mmol, 1.11 g) as a white solid. 2-MeO-PCPr was prepared as described in 28.9% yield from N-
propionyl-2-MeO-PCA (1.34 mmol, 0.35 g), as a colorless oil. The HCl salt was a sparkling white crystalline solid (m.p. 213.5 – 214.5 °C). HR-ESI-MS: observed m/z 248.20086 (theory [M + H]^+: C_{16}H_{26}NO^+ m/z 248.20089).

Preparation of 1-(3-methoxyphenyl)cyclohexan-1-amine (3-MeO-PCA)

3-MeO-PCA was prepared in 61.0% yield from cyclohexanone (53.0 mmol, 5.23 g) and 3-bromoanisole (64.0 mmol, 11.97 g). The HCl salt of 3-MeO-PCA was prepared as described previously (m.p. 197.0 – 197.7 °C [4]; lit: 195 – 196 °C [23]).

Preparation of N-methyl-1-(3-methoxyphenyl)cyclohexan-1-amine (3-MeO-PCMe) (3a)

N-[1-(3-methoxyphenyl)cyclohexyl]formamide (N-formyl-3-MeO-PCA) was prepared as previously described in 97.0% yield from 3-MeO-PCA (10.2 mmol, 2.10 g) as a white solid. 3-MeO-PCMe was prepared as described in 79.0% yield from N-formyl-3-MeO-PCA (9.94 mmol, 2.32 g), as colorless oil. The HCl salt of 3-MeO-PCMe (3a) was prepared and recrystallized twice from methanol/diethyl ether at 0 °C to give a colorless, crystalline solid (m.p. 214.5 – 217.0 °C). HR-ESI-MS: observed m/z 220.16948 (theory [M + H]^+: C_{14}H_{22}NO^+ m/z 220.16959).

Preparation of N-ethyl-1-(3-methoxyphenyl)cyclohexan-1-amine (3-MeO-PCE) (3b)

N-[1-(3-methoxyphenyl)cyclohexyl]acetamide (N-acetyl-3-MeO-PCA) was prepared as previously described in 99.1% yield from 3-MeO-PCA (6.33 mmol, 1.30 g) as a deep orange oil. 3-MeO-PCE prepared in 55.3% yield as described from N-acetyl-3-MeO-PCA (1.82 mmol, 0.45 g). HCl salt was prepared to give a white crystalline solid, m.p. 214.0 – 215.5 °C. HR-ESI-MS: observed m/z 234.18519 (theory [M + H]^+: C_{15}H_{24}NO^+ m/z 234.18524).

Preparation of N-propyl-1-(3-methoxyphenyl)cyclohexan-1-amine (3-MeO-PCPr) (3c)

N-[1-(3-methoxyphenyl)cyclohexyl]propanamide (N-propionyl-3-MeO-PCA) was prepared as previously described in 91.0% yield from 3-MeO-PCA (6.33 mmol, 1.30 g) as an orange colored oil. 3-MeO-PCPr prepared as described in 75.5% yield from N-propionyl-3-MeO-PCA (3.82 mmol, 1.0 g) as a colorless oil. HCl salt was prepared as described to give a white crystalline solid, m.p. 181.0 – 183.0 °C. HR-ESI-MS: observed m/z 248.20063 (theory [M + H]^+: C_{16}H_{26}NO^+ m/z 248.20089).

Preparation of 1-(4-methoxyphenyl)cyclohexan-1-amine (4-MeO-PCA)

4-MeO-PCA was prepared as previously described in 49.0% yield from cyclohexanone (41.5 mmol, 4.07 g) and 4-bromoanisole (49.7 mmol, 9.30 g) as colorless oil. HCl salt was prepared to give a thin needle-like crystalline solid, m.p. 251.1 – 252.0 °C (Lit: 233 – 234 °C [23]).
Preparation of N-methyl-1-(4-methoxyphenyl)cyclohexan-1-amine (4-MeO-PCMe) (4a)

N-[1-(4-methoxyphenyl)cyclohexyl]formamide (N-formyl-4-MeO-PCA) was prepared as previously described in 87.0 % yield from 4-MeO-PCA (5.16 mmol, 1.06 g) as a white solid. 4-MeO-PCMe was prepared in 39.5% yield from N-formyl-4-MeO-PCA (3.34 mmol, 0.780 g), as a colorless oil. HCl salt was prepared as described to give a sparkling colorless needle-like solid, m.p. 164.0 – 165.7 °C. HR-ESI-MS: observed m/z 220.1964 (theory [M + H]^+: C_{14}H_{22}NO^+ m/z 220.1696).

Preparation of N-ethyl-1-(4-methoxyphenyl)cyclohexan-1-amine (4-MeO-PCE) (4b)

N-[1-(4-methoxyphenyl)cyclohexyl]acetamide (N-acetyl-4-MeO-PCA) was prepared as previously described in 90.5 % yield from 4-MeO-PCA (6.92 mmol, 1.42 g) as a white solid. 4-MeO-PCE was prepared as described in 50.8% yield from N-acetyl-4-MeO-PCA (2.42 mmol, 0.60 g), as a colorless oil. HCl salt was prepared as described to give a sparkling white crystalline solid, m.p. 189.0 – 191.8 °C. HR-ESI-MS: observed m/z 234.1850 (theory [M + H]^+: C_{15}H_{24}NO^+ m/z 234.1852).

Preparation of N-propyl-1-(4-methoxyphenyl)cyclohexan-1-amine (4-MeO-PCPr) (4c)

N-[1-(4-methoxyphenyl)cyclohexyl]propanamide (N-propyl-4-MeO-PCA) was prepared as previously described in 86.0 % yield from 4-MeO-PCA (6.82 mmol, 1.40 g) as a white solid. 4-MeO-PCPr was prepared as described in 39.4% yield from N-propyl-4-MeO-PCA (2.30 mmol, 0.60 g), as a colorless oil. HCl salt was prepared as described to give a sparkling white crystalline solid, m.p. 184.8 – 186.3 °C. HR-ESI-MS: observed m/z 248.2006 (theory [M + H]^+: C_{16}H_{26}NO^+ m/z 248.2009).

Preparation of 1-(3-methylphenyl)cyclohexan-1-amine (3-Me-PCA)

3-Me-PCA was prepared as described in 70.2% yield from cyclohexanone (25.0 mmol, 2.45 g) and 3-bromotoluene (30.0 mmol, 5.13 g) as colorless oil. HCl salt was prepared to give a white fluffy crystalline solid, m.p. 209 – 212 °C (Lit: 209 – 210 °C[23]).

Preparation of N-methyl-1-(3-methylphenyl)cyclohexan-1-amine (3-Me-PCMe) (5a)

N-[1-(3-methylphenyl)cyclohexyl]formamide (N-formyl-3-Me-PCA) was prepared as previously described in 95.9% yield from 3-Me-PCA (11.1 mmol, 2.1 g) as a light yellow oil. 3-Me-PCMe was prepared as described in 59.0% yield from N-formyl-3-Me-PCA (10.6 mmol, 2.31 g), as a colorless oil. HCl salt was prepared to give fluffy colorless needle-like crystalline solid, m.p. 213.3 – 215.5 °C. HR-ESI-MS: observed m/z 204.1749 (theory [M + H]^+: C_{14}H_{22}N^+ m/z 204.1746).

Preparation of N-ethyl-1-(3-methylphenyl)cyclohexan-1-amine (3-Me-PCE) (5b)


N-[1-(3-methylphenyl)cyclohexyl]acetamide (N-acetyl-3-Me-PCA) was prepared as described in 95.5% yield from 3-Me-PCA (5.28 mmol, 1.0 g) as an orange crystalline solid. 3-Me-PCE prepared as described in 76.4% yield from N-acetyl-3-Me-PCA (6.48 mmol, 1.50 g), as a colorless oil. HCl salt was prepared to give a white crystalline solid, m.p. 234.1 – 235.0 °C (Lit: 236 – 237 °C[24]). HR-ESI-MS: observed m/z 218.19030 (theory [M + H]^+: C_{15}H_{24}N^+ m/z 218.19033).

Preparation of N-propyl-1-(3-methylphenyl)cyclohexan-1-amine (3-Me-PCPr) (5c)

N-[1-(3-methylphenyl)cyclohexyl]propanamide (N-propionyl-3-Me-PCA) was prepared as previously described in 86.5 % yield from 3-Me-PCA (5.28 mmol, 1.0 g) as a white solid. 3-Me-PCPr was prepared as described in 65.0% yield from N-propionyl-3-Me-PCA (5.30 mmol, 1.30 g), as a colorless oil. HCl salt was prepared to give a fluffy white crystalline solid, m.p. 226.0 – 226.8 °C. HR-ESI-MS: observed m/z 232.20588 (theory [M + H]^+: C_{16}H_{26}N^+ m/z 232.20598).

Instrumentation

Nuclear magnetic resonance spectroscopy

$^1$H (400 MHz) and $^{13}$C NMR spectra (100 MHz) were obtained from the hydrochloride salts in CDCl$_3$ solutions (100% and 99.96% D, 0.03% (v/v) TMS) on a Bruker Ultrashield 400 plus spectrometer with a 5 mm BBO S1 (Z gradient plus) probe at 24 °C. Internal chemical shift references were TMS ($\delta = 0.00$ ppm) and solvent ($\delta = 77.0$ ppm).

Gas chromatography ion trap mass spectrometry

Data for all fifteen N-alkyl-arylcyclohexylamines (0.5 mg/mL in methanol) were recorded under full scan electron (EI) and chemical ionization (CI) conditions using HPLC grade methanol as the liquid CI reagent. A Varian 450-GC gas chromatograph coupled to a Varian 220-MS ion trap mass spectrometer and a Varian 8400 autosampler was employed with a Varian CP-1177 injector (275 °C) in split mode (1:50) (Walnut Creek, CA, USA). The Varian MS Data Review function of the Workstation software, version 6.91, was used for data acquisition. Transfer line, manifold and ion trap temperatures were set at 310, 80 and 220 °C, respectively. The carrier gas was helium at a flow rate of 1 mL/min using the EFC constant flow mode. The default settings for CI ionization parameters (0.4 s/scan) were used: CI storage level m/z 19.0; ejection amplitude m/z 15.0; background mass m/z 55; maximum ionization time 2000 µs; maximum reaction time 40 ms; target TIC 5000 counts. An Agilent J&W VF-5ms GC column (30 m × 0.25 mm, 0.25 µm) was employed for separation. The starting temperature was set at 130 °C and held for 1 min. The temperature then increased at 20 °C/min to 280 °C and held constant for 11.50 min to give a total run time of 20.00 min.

Electrospray triple quadrupole mass spectrometry

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Electrospray triple quadrupole tandem mass spectrometry experiments were carried out by direct infusion (10 μL/min at 0.01 mg/mL) of (1a) – (5c) compounds using a Waters Micromass Quattro Premier triple quadrupole MS/MS system (Waters Micromass, Manchester, UK) and the Masslynx version 4.1 software. Optimization of signal intensities were performed in positive MS scan and in product ion scan mode. The optimized source conditions were as follows: capillary 3.12 kV, rf lens 0.1 V, source temperature 100 °C, desolvation temperature 200 °C and the multiplier voltage was 650 V. Nitrogen was used as the cone gas (50 L/h) and desolvation gas (200 L/h) whilst the collision gas was argon (0.3 mL/min flow). The [M + H]+ ion corresponding to all fifteen substances were selected for MS/MS experiments. Product ions were collected over the range m/z 50 and m/z 250. Scan time for each channel was 0.5 s and interscan delay was 0.1 s. The cone voltage and collision energy values were as follows: 10 V and 18 eV for (1a) – (1c); 18 V and 15 eV for all three sets of methoxyphenyl substituted isomers; 15 V and 15 eV for (5a) and (5c) and 15 V and 12 eV for (5b), respectively.

High-resolution electrospray mass spectrometry

Analyses were carried out by characterization using UHPLC-QTOF-MS/MS as described previously.[25,26] Briefly, mobile phases used for UHPLC separation consisted of 100% acetonitrile (1% formic acid) and an aqueous solution of 1% formic acid. The column temperature was set at 40 °C (0.6 mL/min) and data were acquired for 5.5 min. The elution was a 5–70% acetonitrile gradient ramp over 3.5 min, then increased to 95% acetonitrile in 1 min and held for 0.5 min before returning to 5% acetonitrile in 0.5 min. QTOF-MS data were acquired in positive mode scanning from m/z 100 – m/z 1000 with and without auto MS/MS fragmentation. Ionization was achieved with an Agilent JetStream electrospray source and infused internal reference masses. Agilent 6540 QTOF-MS parameters: gas temperature 325 °C, drying gas 10 L/min and sheath gas temperature 400 °C. Internal reference ions at m/z 121.05087 and m/z 922.00979 were used.

High performance liquid chromatography diode array detection

HPLC-DAD analyses[25,26] were carried out on a Dionex 3000 Ultimate system coupled to a UV diode array detector (Thermo Fisher, St Albans, UK), using a Phenomenex Synergi Fusion column (150 mm x 2 mm, 4 μm) that was protected by a 4 mm x 3 mm Phenomenex Synergi Fusion guard column (Phenomenex, Macclesfield, UK). The mobile phases were made from 70% acetonitrile with 25 mM TEAP buffer and an aqueous solution of 25 mM TEAP buffer. Elution was achieved with a gradient that started with 4% acetonitrile and ramped to 70% acetonitrile in 15 min and held for 3 min. The total acquisition time was 18 min at a flow rate of 0.6 mL/min. The diode array detection window was set at 200 nm to 595 nm (collection rate 2 Hz).

Infrared spectroscopy
Infrared (IR) spectra were obtained on a Perkin Elmer Spectrum BX FTIR model (Llantrisant, UK) using a Pike MIRacle ATR system. Data were acquired with the Spectrum v5.01 software (scan range 4000–400 cm\(^{-1}\), resolution 4 cm\(^{-1}\), 16 scans).

Results and discussion

A number of routes exist for the syntheses of arylcyclohexylamines.\[^{[1,27]}\] In the present study, primary amines were synthesized using modified Geneste route (Figure 2B)\[^{[28]}\], similar to the approach taken in previous work on PCP and 1- (1-phenylcyclohexyl)pyrrolidine (PCPy) analogs.\[^{[4]}\] It has been found in practice that the primary amines represent practical intermediates to prepare appropriately substituted secondary and tertiary amines. Secondary amines were synthesized by conversion to the amide, which was found to be high yielding. Subsequent reduction of the amide gave the desired \(N\)-alkyl secondary amines (1a) – (5c) in moderate to good yields.

The syntheses of primary amine intermediates 3-Me-PCA, 2-MeO-PCA, 3-MeO-PCA, 4-MeO-PCA and TCA have been described previously,\[^{[22,23,29,30]}\] and these were based on the implementation of the Geneste route in most cases. A modified imine (sulfinimine) route has been described for 3-MeO-PCA\[^{[31]}\] and a route via an imine stage was employed before for the preparation of secondary amine compounds carrying a 3-methoxyphenyl substituent.\[^{[32]}\] The preparation of secondary amines from primary amine intermediates via alkylation with the appropriate alkyl halide was also reported for TCMe (1a), TCE (1b) and TCPr (1c).\[^{[30,33]}\] The syntheses of the methoxy isomers was described in 1988 using an imine route.\[^{[32]}\]

The characterization of a number of compounds appeared to be unreported in the existing literature, such as 2-MeO-PCE (2b), 2-MeO-PCPr (2c), 3-Me-PCPr (5c), and 4-MeO-PCPr (4c). Likewise, 2-MeO-PCMe (2a) and 4-MeO-PCMe (4a) do not appear in the literature but are apparently available commercially. It was previously suggested\[^{[11]}\] that 3-MeO-PCE (3b), and 3-MeO-PCPr (3c) had not been described in the scientific literature prior to their non-medical use. However, it was noticed that these were in fact described in a 1988 conference proceedings held by researchers at Eli Lilly. Both compounds showed NMDA receptor affinity and \textit{in vivo} activity consistent with NMDA receptor antagonism.\[^{[32]}\]

Chromatography and mass spectrometry

Gas chromatography retention times and ion trap (IT) electron (EI) and chemical ionization (CI) mass spectral data (GC-IT-MS) are summarized in Figures 3 and 4. The proposed mechanism for EI-induced formation of base peak ions, which may have involved the loss of a propyl radical from the cyclohexyl component, was adapted from previously published work and is shown in Figure 5A\[^{[4]}\]. The EI and CI mass spectra recorded for 3-MeO-PCE (3b) (Figure 3H1/H2) were comparable to previously published data\[^{[20]}\] but some differences in relative abundance values were also visible, which might have been associated with the ion trap mass analyzer. For example, under the conditions used, the implementation of GC ion trap EI-MS
frequently resulted in the formation of what appeared to be the protonated molecule instead of the \( M^+ \) ion. In some cases, formation of the \([M + H]^+\) ion formed the base peak similar to what was observed previously during the analysis of methoxetamine (MXE). In the present study, it was noticed that \([M + H]^+\) ions were particularly abundant in the EI-IT-MS spectra of the 2-methoxyphenyl substituted compounds (2a) – (2c) (Figure 3D1, 3E1 and 3F1). Self-ionization was not observed in any EI mass spectra recorded with a quadrupole mass analyzer where \( M^+ \) ions were detectable in appreciable abundance (supplementary information).

When inspecting the EI-IT mass spectra for potential differences between \( N \)-methyl substituted isomers (2a, 3a and 4a), it was observed that an ion at \( m/z \) 189 was particularly abundant in the EI-IT mass spectrum of 4-MeO-PCMe (4a) (Figure 4J1) and that it was absent when using a quadrupole mass analyzer (supplemental data). Figure 5B shows a suggested mechanism that may account for this observation following the neutral loss of formaldehyde (CH\(_2\)O) within the ion trap. The ortho- and meta isomers (2a and 3a) (Figure 3D1 and 3G1) indicated a reduced formation of \( m/z \) 189 which may be explained by the proximity of the 2-OCH\(_3\) group to the terminal methylene radical. Interestingly, the isomers 2-, 3-, and 4-MeO-PC (2b, 3b and 4b) did not display this phenomenon, whereas the three \( N \)-propyl substituted PCPr counterparts (2c, 3c and 4c) formed this ion. Similarly, the most abundant \( m/z \) 189 species was observed in the spectrum of 4-MeO-PCPr (4c) (Figure 4L1), whereas it showed a relatively low abundance under quadrupole conditions (supplementary information). The CI-IT-MS spectra (Figures 3 and 4) yielded the expected \([M + H]^+\) ions and additional formation of an even-electron ion following the loss of the corresponding amine. In this case, the associated ions were formed at \( m/z \) 165 (1a) – (1c), \( m/z \) 189 (2a) – (4c) and \( m/z \) 173 (5a) – (5c), respectively (Figure 5C) and were presumably similar to the species observed under electrospray ionization conditions (see below).

Interestingly, the CI-IT mass spectra recorded for 2-methoxyphenyl substituted substances (2a, 3a and 4a) differed from their isomeric representatives by the relative abundance of the \( m/z \) 189 ion and the corresponding protonated molecules. The meta- and para-substituted compounds appeared to display a decrease in relative abundance of \([M + H]^+\) relative to \( m/z \) 189 in the order of 2-MeO-PCMe (2a) (Figure 3D2) > 3-MeO-PCMe (3a) (Figure 3G2) > 4-MeO-PCMe (4a) (Figure 4J2), respectively. A potential reason for what appeared to be increased stability of 2-MeOPCMe (2a) may have been related to stabilization and increased charge distribution, thus, possibly rendering the protonated molecule more stable (Figure 5D). In addition, all CI-IT mass spectra obtained from the three 2-methoxyphenyl analogs also displayed an ion at \( m/z \) 121 that was either less prominent or absent in the spectra of the meta- and para substituted analogs. Figure 5E depicts an attempt to rationalize its formation, which might require the presence of the 2-methoxyphenyl position.

Representative electrospray ionization (ESI) triple quadrupole (QqQ) tandem mass spectra and ion ratios for the 2-MeO-, 3-MeO-, and 4-MeO-PCE isomers (2b, 3b and 4b) following direct infusion are presented in Figure 6A–C. Collision-induced dissociation (CID) of the product ions gave primarily rise of two product ions at \( m/z \)
189 and m/z 121 that might be suitable for implementing the corresponding ion transitions for screening purposes. In case of 3-MeO-PCE (3b), these two main ions were also observed previously using a triple-quadrupole linear ion trap mass spectrometer. Correspondingly, the remaining ring-substituted PCMe (2a, 3a and 4a) and PCPr isomers (2c, 3c and 4c) also yielded the m/z 189 and m/z 121 ions (supplemental data). Examination of the QqQ spectra in Figure 6A−C also revealed the presence of a product ion at m/z 81 in the spectra of 3-MeO-, and 4-MeO-PCE (3b, 4b) that was absent in the QqQ tandem mass spectrum of 2-MeO-PCE (2b) (Figure 6A). Given that the tandem mass spectra were recorded under identical conditions and collision energies, it was tempting to consider the potential for differentiation between the three PCE isomers based on distinct ion ratios alone. The QqQ tandem mass spectrum of 3-MeO-PCE (3b) showed an increased abundance of the m/z 81 species compared to 4-MeO-PCE (4b) (Figure 6B/6C). Interestingly, the differential formation of m/z 81 was equally observed in the tandem mass spectra of the ring-substituted PCMe (2a, 3a and 4a) and PCPr isomers (2c, 3c and 4c) as well (supplemental data). The ultra high performance liquid chromatography (UHPLC) ESI quadrupole-time-of-flight (Q-TOF) tandem mass spectra for 3-MeO-, and 4-MeO-PCE (2b, 3b) are shown in Figure 6D/7E. Due to extensive in-source CID of the protonated molecule of 4-MeO-PCE (3b) (Figure 6F), a tandem mass spectrum of the m/z 189.12746 base peak was recorded as shown in Figure 6G. As observed in the QqQ tandem mass spectra of the 12 remaining N3alkyl arylcyclohexylamines (supplementary information), formation of the suggested cyclohexen-1-ylium ion at m/z 81 was also frequently detected. The acquisition of high mass accuracy Q-TOF data was considered helpful for the proposal of suggested structural representations associated with m/z 81, m/z 121 and m/z 189, respectively (Figure 7).

Implementation of the HPLC-DAD and UHPLC-Q-TOF-MS methods provided separation of the 2-MeO substituted N-alkyl arylcyclohexylamines (2a−2c) from their 3-MeO-, and 4-MeO counterparts (3a−3c) and (4a−4c), respectively. Co-elution, however, was observed for the latter two groups of meta- and para-substituted methoxyphenyl candidates (Figure 6 and supplementary information). Figure 8 shows the retention times and overlaid diode array spectra (DAD) obtained from PCE isomers (2b), (3b) and (4b), which demonstrated that the availability of full scan ultraviolet information facilitated differentiation between the co-eluting isomers. Similarly, the differentiation between the remaining 3-methoxy and 4-methoxyphenyl isomers (3a/4a) and (3c/4c) was also successful under DAD conditions and the corresponding spectra are shown as supplementary information. The use of HPLC-DAD has been increasingly helpful when applied to a number of investigations that investigated the presence and characterization of ring-substituted isomers.[6,35] In addition, the infrared spectra for all substances have been supplied as supplementary information, which confirmed that the isomeric 2-, 3- and 4-methoxy phenylcyclohexylamines could be differentiated, for example in the form of shifting wavenumbers associated 1,2-, 1,3-, and 1,4-disubstituted benzenes.[36] This was in agreement with shift changes observed with 2-, 3-, and 4-methylphenyl substituted PCP isomers.[37]
Nuclear magnetic resonance spectroscopy

Chemical shifts were assigned using chemical shift position, splitting pattern, $^{13}$C polarization enhancement nurtured during attached nucleus testing (PENDANT) and 2-D techniques (HMQC, HMBC, COSY-90) similar to the approach taken previously for tertiary amine-based PCP and PCPy derivatives. A representative example of an HMQC spectrum for 3-MeO-PCPr (3c) is shown in Figure 9. While some of the present compounds have been described for a range of investigations, limited information appeared available on the analytical properties including detailed NMR analysis. For example, NMR data were reported for thiophene compounds (1a) – (1c) and 3-MeO-PCE (3b) but without chemical shift assignments, which are provided here. The NMR data associated with the primary amine intermediates and a more detailed discussion of the NMR chemical shift behavior is presented in the supplemental section.

Proton chemical shifts

All proton chemical shift values, multiplicities and assignments for arylcyclohexylamines (1a) – (5c) are summarized in Tables 1–3.

Identification of positional isomers is an important requirement of forensic identification. The three positional methoxyphenyl isomers could be readily distinguished by inspecting the downfield aromatic regions of the $^1$H proton spectra. Aromatic multiplicities exhibited $^2$J and $^3$J couplings. The multiplets linked to the para-substituted isomers were readily identified by a characteristic pair of doublets of multiplets that represented the aromatic protons due to additional splitting of the doublets by long-range couplings. The chemical shifts obtained from 2-, and 3-methoxyphenyl isomers were readily distinguishable in all equivalent $N$-alkyl pairs as a reflection of the position on the phenyl ring (Tables 1–3).

Carbon chemical shifts

All chemical shift data are summarized in Tables 4–6.

$^{13}$C chemical shifts were also useful in distinguishing the methoxyphenyl isomers. Due to the symmetry of para-substituted aryl rings, the 4-methoxyphenyl isomers displayed four separate aromatic $^{13}$C chemical shifts; $C_1$, $C_2$–$C_6$, $C_3$–$C_5$, and $C_4$. The 2- and 3-methoxyphenyl counterparts showed six distinct aromatic $^{13}$C chemical shifts. Another distinguishing feature was the $C_1$ chemical shift value. In the spectra of 2- and 4-methoxyphenyl isomers, an upfield shift $>$10 ppm was observed when compared to the meta-substituted series, presumably due to enhanced shielding and electron density from resonance contributions.

Conclusion

Newly emerging psychoactive substances continue to remain a challenge for forensic scientists, clinicians and policy makers. The syntheses and comprehensive analytical
characterizations of 15 N-alkyl-arylcyclohexylamines included a range of 'research chemical' analogues that have not yet been described in detail. It was also demonstrated that positional isomers could be differentiated using analytical techniques typically involved in forensic and clinical casework.

**References**


implementation of Council Decision 2005/387/JHA. Lisbon. 2013. Available at: 


**Figure captions**

**Figure 1.** Phencyclidine (PCP) and other representative arylcyclohexylamine and 1,2-diphenylethylamine examples associated with the recreational ‘research chemicals’ market.

**Figure 2.** A: Fifteen \(N\)-alkyl-arylcylohexylamines subjected to synthesis and analytical characterizations. B: Synthetic routes employed for the preparation of (1a) – (5c)

**Figure 3.** Gas chromatography retention times and ion trap (IT) mass spectra obtained in electron (EI) and chemical ionization (CI) mode.

**Figure 4.** Gas chromatography retention times and ion trap (IT) mass spectra obtained in electron (EI) and chemical ionization (CI) mode.

**Figure 5.** Suggested key ions following mass spectral detection under EI and CI conditions.

**Figure 6.** A-C: Electrospray ionization triple quadrupole mass spectra of three positional \(N\)-ethyl-1-phenylcylohexan-1-amine (PCE) isomers. D-G. Ultra-high performance liquid chromatography quadrupole time of flight tandem mass spectra.
Figure 7. Suggested key ions following mass spectral detection under electrospray ionization conditions.

Figure 8. Ultraviolet full scan spectra of N-ethyl-1-phenylcyclohexan-1-amine (PCE) isomers by high-performance liquid chromatography coupled to diode array detection.

Figure 9. Heteronuclear single quantum coherence spectrum (HSQC) of 3-MeO-PCPr.
Figure 1. Phencyclidine (PCP) and other representative arylcyclohexylamine and 1,2-diphenylethylamine examples associated with the recreational 'research chemicals' market.

118x69mm (300 x 300 DPI)
Figure 2. A: Fifteen N-alkyl-arylcyclohexylamines subjected to synthesis and analytical characterizations. B: Synthetic routes employed for the preparation of (1a) – (5c)

207x225mm (300 x 300 DPI)
EI-IT-MS
4.61 min
A1

CI-IT-MS
(1a)
A2

EI-IT-MS
4.77 min
B1

CI-IT-MS
(1b)
B2

EI-IT-MS
5.25 min
C1

CI-IT-MS
(1c)
C2

EI-IT-MS
5.62 min
D1

CI-IT-MS
(2a)
D2

EI-IT-MS
5.72 min
E1

CI-IT-MS
(2b)
E2

EI-IT-MS
6.15 min
F1

CI-IT-MS
(2c)
F2

EI-IT-MS
6.00 min
G1

CI-IT-MS
(3a)
G2

EI-IT-MS
6.09 min
H1

CI-IT-MS
(3b)
H2
For Peer Review

\[ \text{Chemical Structures} \]

\[ R^1 = 2-, 3-, 4-OCH}_3; R^2 = \text{CH}_3: m/z 176 (2a, 3a, 4a) \]
\[ R^1 = 2-, 3-, 4-OCH}_3; R^2 = \text{C}_2H}_5: m/z 190 (2b, 3b, 4b) \]
\[ R^1 = 2-, 3-, 4-OCH}_3; R^2 = \text{C}_3H}_7: m/z 204 (2c, 3c, 4c) \]

\[ \text{Mass Spectra} \]

\[ m/z 189 \]

\[ \text{Compounds} \]

\[ 2-, 3-, 4\text{-MeO-PCMe} (2a, 3a, 4a) \]
\[ 2-, 3-, 4\text{-MeO-PCE} (2b, 3b, 4b) \]
\[ 2-, 3-, 4\text{-MeO-PCPr} (2c, 3c, 4c) \]
\[ \text{TCE} (1b) \]
\[ \text{TCMe} (1a) \]
\[ \text{3-Me-PCMe} (5a) \]
\[ \text{TCPr} (1c) \]
\[ \text{3-Me-PCE} (5b) \]
\[ \text{3-Me-PCPr} (5c) \]

\[ m/z 121 \]
2-MeO-PCE (2b) 7.68 min
3-MeO-PCE (3b) 7.45 min
4-MeO-PCE (4b) 7.42 min
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

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Table 1. 400 MHz $^1$H NMR spectra of HCl salts in CDCl$_3$.

<table>
<thead>
<tr>
<th>Proton</th>
<th>TCMe (1a)</th>
<th>2-MeO-PCMe (2a)</th>
<th>3-MeO-PCMe (3a)</th>
<th>4-MeO-PCMe (4a)</th>
<th>3-Me-PCMe (5a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_2$</td>
<td>2.59 d (13.0 Hz, 2H$_{eq}$)</td>
<td>2.67 d (12.7 Hz, 2H$_{eq}$)</td>
<td>2.61 d (12.9 Hz, 2H$_{eq}$)</td>
<td>2.62 d (12.8 Hz, 2H$_{eq}$)</td>
<td>2.62 d (13.2 Hz, 2H$_{eq}$)</td>
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<td>$H_2$</td>
<td>1.92–1.73 m (2H$_{ax}$)</td>
<td>1.99–1.80 m (2H$_{ax}$)</td>
<td>2.03–1.76 m (2H$_{ax}$)</td>
<td>1.90–1.75 m (2H$_{ax}$)</td>
<td>1.93–1.77 m (2H$_{ax}$)</td>
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<tr>
<td>$H_3$</td>
<td>1.66–1.54 m (1H$_{eq}$)</td>
<td>1.71–1.56 m (1H$_{eq}$)</td>
<td>1.64–1.45 m (1H$_{eq}$)</td>
<td>1.63–1.52 m (1H$_{eq}$)</td>
<td>1.64–1.45 m (2H)</td>
</tr>
<tr>
<td>$H_1$</td>
<td>6.99 dd (8.0, 1.0 Hz)</td>
<td>6.91 ddd (8.3, 2.5, 1.0 Hz)</td>
<td>6.98 dm (8.9 Hz)</td>
<td>7.34 t (7.8 Hz)</td>
<td>7.18 d (7.8 Hz)</td>
</tr>
<tr>
<td>$H_3$</td>
<td>7.03 td (7.6, 1.2 Hz)</td>
<td>7.22 ddd (7.8, 2.0, 0.9 Hz)</td>
<td>7.64 dm (8.9 Hz)</td>
<td>7.64 dm (8.9 Hz)</td>
<td>7.64 dm (8.9 Hz)</td>
</tr>
<tr>
<td>$H_5$</td>
<td>2.34 s (CH$_3$)</td>
<td>2.32 s (CH$_3$)</td>
<td>2.23 s (CH$_3$)</td>
<td>2.23 s (CH$_3$)</td>
<td>2.23 s (CH$_3$)</td>
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<tr>
<td>$H_6$</td>
<td>9.73 s (NH$_2^+$)</td>
<td>9.30 s (NH$_2^+$)</td>
<td>9.60 s (NH$_2^+$)</td>
<td>9.53 s (NH$_2^+$)</td>
<td>9.58 s (NH$_2^+$)</td>
</tr>
</tbody>
</table>

* b = broad; d = doublet; m = multiplet; s = singlet; triplet; q = quartet; quint = quintet; sex = sextet
Table 2. 400 MHz $^1$H NMR spectra of HCl salts in CDCl$_3$.

<table>
<thead>
<tr>
<th>Proton</th>
<th>TCE (1b)</th>
<th>2-MeO-PCE (2b)</th>
<th>3-MeO-PCE (3b)</th>
<th>4-MeO-PCE (4b)</th>
<th>3-Me-PCE (5b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H$_2$a</td>
<td>2.73 d (13.0 Hz, 2H$_{eq}$)</td>
<td>2.61 d (12.7 Hz, 2H$_{eq}$)</td>
<td>2.77 d (13.0 Hz, 2H$_{eq}$)</td>
<td>2.80 d (12.6 Hz, 2H$_{eq}$)</td>
<td>2.81 d (12.6 Hz, 2H$_{eq}$)</td>
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<tr>
<td></td>
<td>2.39 td (12.5, 3.7 Hz, 2H$_{ax}$)</td>
<td>2.45 td (12.6, 3.9 Hz, 2H$_{ax}$)</td>
<td>2.34 td (13.3, 3.7 Hz, 2H$_{ax}$)</td>
<td>2.33 td (13.1, 3.4 Hz, 2H$_{ax}$)</td>
<td>2.35 td (13.1, 3.6 Hz, 2H$_{ax}$)</td>
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<tr>
<td>H$_3$b</td>
<td>1.86–1.72 m (2H$_{eq}$)</td>
<td>1.94–1.82 m (2H$_{eq}$)</td>
<td>1.88–1.72 m (2H$_{eq}$)</td>
<td>1.89–1.70 m (2H$_{eq}$)</td>
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<td>1.54–1.34 m (2H$_{ax}$)</td>
<td>1.46–1.28 m (2H$_{ax}$)</td>
<td>1.35 qt (12.8, 3.3 Hz, 2H$_{ax}$)</td>
<td>1.29 qt (12.9, 3.4 Hz, 2H$_{ax}$)</td>
<td>1.31 qt (13.0, 3.2 Hz, 2H$_{ax}$)</td>
</tr>
<tr>
<td>H$_4$</td>
<td>1.69–1.53 m (1H$_{eq}$)</td>
<td>1.65–1.57 m (1H$_{eq}$)</td>
<td>1.67–1.56 m (1H$_{eq}$)</td>
<td>1.66–1.54 m (1H$_{eq}$)</td>
<td>1.70–1.54 m (1H$_{eq}$)</td>
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<tr>
<td></td>
<td>1.54–1.34 m (1H$_{ax}$)</td>
<td>1.52 qt (11.7, 4.1 Hz, 1H$_{ax}$)</td>
<td>1.48 qt (12.4, 3.8 Hz, 1H$_{ax}$)</td>
<td>1.48 qt (12.8, 3.8 Hz, 1H$_{ax}$)</td>
<td>1.47 qt (12.4, 3.8 Hz, 1H$_{ax}$)</td>
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<td>H$_1$</td>
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<td>H$_3$</td>
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<td>6.99 dm (8.9 Hz)</td>
<td>7.65 s</td>
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<td>H$_4$</td>
<td>7.39 dd (5.2, 1.1 Hz)</td>
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<td>6.92 ddd (8.1, 2.5, 1.0 Hz)</td>
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<td>7.57 d (7.9 Hz)</td>
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<tr>
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<td>=</td>
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<td>=</td>
<td>7.40–7.35 m</td>
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<td>7.71 dm (8.9 Hz)</td>
<td>7.18 d (7.6 Hz)</td>
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<td>2.69 bs (CH$_3$)</td>
<td>2.69–2.53 m (CH$_3$)</td>
<td>2.68–2.53 m (CH$_3$)</td>
<td>2.67–2.51 m (CH$_3$)</td>
</tr>
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<td>H$_8$</td>
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<td>1.36 t (7.3 Hz, CH$_3$)</td>
<td>1.38 t (7.3 Hz, CH$_3$)</td>
<td>1.29 t (7.3 Hz, CH$_3$)</td>
<td>1.38 t (7.3 Hz, CH$_3$)</td>
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<td>=</td>
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<tr>
<td>H$_c$</td>
<td>=</td>
<td>=</td>
<td>4.01 s (OCH$_3$)</td>
<td>3.91 s (OCH$_3$)</td>
<td>3.83 s (OCH$_3$)</td>
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<td>9.20 bs (NH$_2^+$)</td>
<td>9.53 s (NH$_2^+$)</td>
<td>9.45 s (NH$_2^+$)</td>
<td>9.50 s (NH$_2^+$)</td>
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* b = broad; d = doublet; m = multiplet; s = singlet; triplet; q = quartet; quint = quintet; sex = sextet.
<table>
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<th>Proton</th>
<th>TCPr (1c)</th>
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<th>3-MeO-PCPr (3c)</th>
<th>4-MeO-PCPr (4c)</th>
<th>3-Me-PCPr (5c)</th>
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<td>H₂a</td>
<td>2.73 d (12.7 Hz, 2H&lt;sub&gt;eq&lt;/sub&gt;)</td>
<td>2.65–2.50 m (2H&lt;sub&gt;eq&lt;/sub&gt;)</td>
<td>2.78 d (12.6 Hz, 2H&lt;sub&gt;eq&lt;/sub&gt;)</td>
<td>2.79 d (12.5 Hz, 2H&lt;sub&gt;eq&lt;/sub&gt;)</td>
<td>2.81 d (12.6 Hz, 2H&lt;sub&gt;eq&lt;/sub&gt;)</td>
</tr>
<tr>
<td></td>
<td>2.47–2.32 m (2H&lt;sub&gt;ax&lt;/sub&gt;)</td>
<td>2.45 td (13.0, 3.6 Hz, 2H&lt;sub&gt;ax&lt;/sub&gt;)</td>
<td>2.35 td (13.0, 3.5 Hz, 2H&lt;sub&gt;ax&lt;/sub&gt;)</td>
<td>2.34 td (12.9, 3.5 Hz, 2H&lt;sub&gt;ax&lt;/sub&gt;)</td>
<td>2.35 td (13.0, 3.5 Hz, 2H&lt;sub&gt;ax&lt;/sub&gt;)</td>
</tr>
<tr>
<td>H₃a</td>
<td>1.85–1.74 m (2H&lt;sub&gt;eq&lt;/sub&gt;)</td>
<td>1.93–1.76 m (2H&lt;sub&gt;eq&lt;/sub&gt;)</td>
<td>1.83–1.71 m (2H&lt;sub&gt;eq&lt;/sub&gt;)</td>
<td>1.81–1.69 m (2H&lt;sub&gt;eq&lt;/sub&gt;)</td>
<td>1.82–1.70 m (2H&lt;sub&gt;eq&lt;/sub&gt;)</td>
</tr>
<tr>
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<td>1.53–1.37 m (2H&lt;sub&gt;ax&lt;/sub&gt;)</td>
<td>1.46–1.19 m (2H&lt;sub&gt;ax&lt;/sub&gt;)</td>
<td>1.34 qt (13.0, 3.5 Hz, 2H&lt;sub&gt;ax&lt;/sub&gt;)</td>
<td>1.29 qt (13.2, 3.4 Hz, 2H&lt;sub&gt;ax&lt;/sub&gt;)</td>
<td>1.29 qt (12.7, 3.5 Hz, 2H&lt;sub&gt;ax&lt;/sub&gt;)</td>
</tr>
<tr>
<td>H₄</td>
<td>1.66–1.56 m (1H&lt;sub&gt;eq&lt;/sub&gt;)</td>
<td>1.66–1.57 m (1H&lt;sub&gt;eq&lt;/sub&gt;)</td>
<td>1.70–1.53 m (1H&lt;sub&gt;eq&lt;/sub&gt;)</td>
<td>1.65–1.53 m (1H&lt;sub&gt;eq&lt;/sub&gt;)</td>
<td>1.64–1.54 m (1H&lt;sub&gt;eq&lt;/sub&gt;)</td>
</tr>
<tr>
<td></td>
<td>1.53–1.37 m (1H&lt;sub&gt;ax&lt;/sub&gt;)</td>
<td>1.51 qt (12.3, 3.7 Hz, 1H&lt;sub&gt;ax&lt;/sub&gt;)</td>
<td>1.46 qt (12.5, 3.7 Hz, 1H&lt;sub&gt;ax&lt;/sub&gt;)</td>
<td>1.47 qt (12.6, 3.8 Hz, 1H&lt;sub&gt;ax&lt;/sub&gt;)</td>
<td>1.48 qt (12.8, 3.7 Hz, 1H&lt;sub&gt;ax&lt;/sub&gt;)</td>
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<td>H₁</td>
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<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>H₂</td>
<td>7.48 dd (3.6, 1.4 Hz)</td>
<td>=</td>
<td>7.47 t (2.1 Hz)</td>
<td>7.71 dm (8.9 Hz)</td>
<td>7.66 s</td>
</tr>
<tr>
<td>H₃</td>
<td>7.10 dd (5.1, 3.5 Hz)</td>
<td>7.01 dd (8.8, 1.2 Hz)</td>
<td>=</td>
<td>6.99 dm (8.9 Hz)</td>
<td>=</td>
</tr>
<tr>
<td>H₄</td>
<td>7.39 dd (5.2, 1.2 Hz)</td>
<td>7.45–7.37 m</td>
<td>6.92 ddd (8.0, 2.3, 0.9 Hz)</td>
<td>=</td>
<td>7.56 d (8.0 Hz)</td>
</tr>
<tr>
<td>H₅</td>
<td>7.06 td (7.6, 1.2 Hz)</td>
<td>7.36 t (8.0 Hz)</td>
<td>6.99 dm (8.9 Hz)</td>
<td>7.35 t (7.7 Hz)</td>
<td>=</td>
</tr>
<tr>
<td>H₆</td>
<td>=</td>
<td>7.45–7.37 m</td>
<td>7.32–7.25 m</td>
<td>7.71 dm (8.9 Hz)</td>
<td>7.19 d (7.7 Hz)</td>
</tr>
<tr>
<td>H₇</td>
<td>2.66–2.51 m (CH₃)</td>
<td>2.65–2.50 m (CH₃)</td>
<td>2.50–2.40 m (CH₃)</td>
<td>2.50–2.39 m (CH₃)</td>
<td>2.46–2.40 m (CH₃)</td>
</tr>
<tr>
<td>H₈</td>
<td>1.98–1.83 m (CH₃)</td>
<td>1.93–1.76 m (CH₃)</td>
<td>1.97–1.83 m (CH₃)</td>
<td>1.96–1.81 m (CH₃)</td>
<td>1.96–1.82 m (CH₃)</td>
</tr>
<tr>
<td>H₉</td>
<td>0.84 t (7.5 Hz, CH₃)</td>
<td>0.83 t (7.4 Hz, CH₃)</td>
<td>0.80 t (7.4 Hz, CH₃)</td>
<td>0.79 t (7.4 Hz, CH₃)</td>
<td>0.79 t (7.7 Hz, CH₃)</td>
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<tr>
<td>H₁₀</td>
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<td>3.98 s (OCH₃)</td>
<td>3.91 s (OCH₃)</td>
<td>3.84 s (OCH₃)</td>
<td>2.43 s (CH₃)</td>
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<tr>
<td>NH₂</td>
<td>9.58 s (NH₂⁺)</td>
<td>9.00 bs (NH₂⁺)</td>
<td>9.47 s (NH₂⁺)</td>
<td>9.38 s (NH₂⁺)</td>
<td>9.44 s (NH₂⁺)</td>
</tr>
</tbody>
</table>

* b = broad; d = doublet; m = multiplet; s = singlet; triplet; q = quartet; quint = quintet; sex = sextet.
Table 4. 100 MHz $^{13}$C NMR spectra of HCl salts in CDCl$_3$.

<table>
<thead>
<tr>
<th>Carbon</th>
<th>TCMe (1a)</th>
<th>2-MeO-PCMe (2a)</th>
<th>3-MeO-PCMe (3a)</th>
<th>4-MeO-PCMe (4a)</th>
<th>3-Me-PCMe (5a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C$_1$</td>
<td>61.95</td>
<td>64.08</td>
<td>63.64</td>
<td>63.26</td>
<td>63.49</td>
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<td>C$_{2,6}$</td>
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<td>32.42</td>
<td>33.28</td>
<td>33.21</td>
<td>33.16</td>
</tr>
<tr>
<td>C$_{3,5}$</td>
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<td>22.74</td>
<td>22.03</td>
<td>21.99</td>
<td>22.02</td>
</tr>
<tr>
<td>C$_4$</td>
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<td>25.06</td>
<td>24.96</td>
<td>25.90</td>
<td>25.01</td>
</tr>
<tr>
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<td>123.20</td>
<td>136.91</td>
<td>126.68</td>
<td>135.14</td>
</tr>
<tr>
<td>C$_{2'}$</td>
<td>128.66</td>
<td>157.42</td>
<td>112.93</td>
<td>129.43</td>
<td>128.56</td>
</tr>
<tr>
<td>C$_{3'}$</td>
<td>127.81</td>
<td>111.59</td>
<td>160.48</td>
<td>114.44</td>
<td>139.02</td>
</tr>
<tr>
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<td>130.36</td>
<td>115.14</td>
<td>159.68</td>
<td>124.99</td>
</tr>
<tr>
<td>C$_5'$</td>
<td>–</td>
<td>120.69</td>
<td>129.98</td>
<td>114.44</td>
<td>129.00</td>
</tr>
<tr>
<td>C$_6'$</td>
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<td>130.48</td>
<td>120.09</td>
<td>129.43</td>
<td>129.57</td>
</tr>
<tr>
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<td>26.95</td>
<td>26.10</td>
<td>25.03</td>
<td>26.09</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C$_c$</td>
<td>–</td>
<td>55.65</td>
<td>55.65</td>
<td>55.24</td>
<td>21.61</td>
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</table>
Table 5. 100 MHz $^{13}$C NMR spectra of HCl salts in CDCl$_3$.

<table>
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<tr>
<th>Carbon</th>
<th>TCE (1b)</th>
<th>2-MeO-PCE (2b)</th>
<th>3-MeO-PCE (3b)</th>
<th>4-MeO-PCE (4b)</th>
<th>3-Me-PCE (5b)</th>
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<td>33.33</td>
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<tr>
<td>C$_{3,5}$</td>
<td>22.36</td>
<td>22.76</td>
<td>22.30</td>
<td>22.23</td>
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<td>25.09</td>
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<td>123.96</td>
<td>137.01</td>
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<td>157.06</td>
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<td>128.83</td>
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<td>111.94</td>
<td>160.42</td>
<td>114.43</td>
<td>138.99</td>
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<td>130.50</td>
<td>115.01</td>
<td>159.61</td>
<td>125.31</td>
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<tr>
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<td>–</td>
<td>121.23</td>
<td>129.94</td>
<td>114.43</td>
<td>128.98</td>
</tr>
<tr>
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<td>120.41</td>
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<td>12.07</td>
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<td>12.01</td>
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<td>γ</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
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<td>–</td>
<td>55.57</td>
<td>55.72</td>
<td>55.23</td>
<td>21.66</td>
</tr>
</tbody>
</table>
Table 6. 100 MHz $^{13}$C NMR spectra of HCl salts in CDCl$_3$.

<table>
<thead>
<tr>
<th>Carbon</th>
<th>TCPr (1c)</th>
<th>2-MeO-PCPr (2c)</th>
<th>3-MeO-PCPr (3c)</th>
<th>4-MeO-PCPr (4c)</th>
<th>3-Me-PCPr (5c)</th>
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</thead>
<tbody>
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<td>C$_1$</td>
<td>62.73</td>
<td>64.84</td>
<td>64.42</td>
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<td>22.34</td>
<td>22.22</td>
<td>22.32</td>
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<td>11.45</td>
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<td>55.74</td>
<td>55.22</td>
<td>21.67</td>
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