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McLaughlin, G, Morris, N, Kavanagh, PV, Power, JD, Dowling, G, Twamley, B, O'Brien, J, Hessman, G, Murphy, B, Walther, D, Partilla, JS, Baumann, MH and Brandt, SD

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Analytical characterization and pharmacological evaluation of the new psychoactive substance 4-fluoromethylphenidate (4F-MPH) and differentiation between (\pm) -*threo*- and (\pm) -*erythro*- diastereomers.

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Methylphenidate



4-Fluoromethylphenidate

Table of contents

- 1. Examples of powdered 4F-MPH and tablet products.
- 2. TLC analysis of vendor sample containing both (±)-*threo* and (±)-*erythro*racemates of 4F-MPH, followed by LC-MS analysis of the isolated bands.
- 3. Preparation of 4F-MPH tablets for GC-MS/LC-MS analysis
- 4. GC-induced thermal degradation of 4-fluoromethylphenidate isomers (4F-MPH) to methyl 4-fluorophenyl acetate (7.26 min).
- 5. EI-MS data obtained for vendor samples 1-3.
- 6. ESI-MS data obtained for vendor samples 1-3.
- ¹³C NMR spectra obtained for the isolated (±)-*erythro* and (±)-*threo* racemates of 4F-MPH (HCl salt in DMSO-d₆).
- 8. ¹H and¹³C NMR spectra obtained for the isolated (±)-*erythro* and (±)-*threo* racemates of 4F-MPH (Free Base in CDCl₃)
- 9. ¹³C and ¹H NMR spectra obtained for one of the powdered 4F-MPH products identified as mixed (±)-*erythro* and (±)-*threo* racemates (HCl salt in DMSO-d₆).
- 10. ¹³C and ¹H NMR spectra obtained for one of the powdered 4F-MPH products identified as the (±)-*threo* racemate (HCl salt in DMSO-d₆)
- 11. Two-dimensional NMR experiments
 - Heteronuclear single quantum coherence spectroscopy (HSQC)
 - Heteronuclear Multiple Bond Correlation (HMBC)
- 12. IR spectra for isolated (±)-*threo*-racemate, isolated (±)-*erythro*-racemate, and vendor samples 1-3
- 13. Additional x-ray crystal data for isolated (±)-*threo* and (±)-*erythro* racemates of 4F-MPH
- 14. High Resolution Mass Spectrometry data obtained for isolated (±)-*threo*-racemate, isolated (±)-*erythro*-racemate, and vendor samples

1. Examples of powdered 4F-MPH and tablet products













2. TLC analysis of vendor sample containing both (\pm) -*threo*- and (\pm) -*erythro*-racemates of 4F-MPH, followed by LC-MS analysis of the isolated bands.



3. Preparation of 4F-MPH tablets for GC-MS/LC-MS analysis

For analysis of the 4F-MPH tablets by gas chromatography mass spectrometry (GC-MS), the tablet was crushed using a mortar and pestle and 10 mg was added to 1 mL of methanol. This solution was added to a Corning[®] Costar[®] Spin-X[®] centrifuge tube filter (cellulose acetate membrane, 0.45 μ m) (Corning Inc, United States) and centrifuged at 2500 rpm for 3 minutes. Furthermore, 100 μ L of this filtered solution was added to 900 μ L methanol in a GC vial.

For analysis of the 4F-MPH tablets by liquid chromatography mass spectrometry (LC-MS), the tablet was crushed using a mortar and pestle and 10 mg was added to 1 mL of acetonitrile/water (1:1) with 0.1% formic acid. This solution was added to a Corning[®] Costar[®] Spin-X[®] centrifuge tube filter (cellulose acetate membrane, 0.45 μ m) (Corning Inc, United States) and centrifuged at 2500 rpm for 3 minutes. Furthermore, 20 μ L of this filtered solution was added to 980 μ L acetonitrile/water (1:1) with 0.1% formic acid in a LC vial.

4. GC-induced thermal degradation of 4-fluoromethylphenidate isomers (4F-MPH) to methyl 4-fluorophenyl acetate (7.26 min)



5. EI-MS data obtained for vendor samples 1-3

Vendor 1: both (±)-*threo*- and (±)-*erythro* racemates of 4F-MPH (Powder)











6. LC-ESI-MS of vendor samples 1-3

Vendor 1: both (±)-threo- and (±)-erythro racemates of 4F-MPH (Powder)









/Users/gavinmc...rs/PVK000015.D/ Injection 1 Function 1 (D_Vendor2_4FMPH) MS + spectrum 9.71





Vendor 3: (±)-threo-racemate of 4F-MPH (Tablet)

7. ¹³C NMR spectra obtained for the isolated (±)-*erythro*- and (±)-*threo*- racemates of 4F-MPH (HCl salt in DMSO- d_6).



8. ¹H and ¹³C NMR spectra obtained for the isolated (±)-*erythro*- and (±)-*threo* racemates of 4F-MPH (Free Base in CDCl₃)





¹³C and ¹H NMR spectra obtained for one of the powdered 4F-MPH products identified as mixed (±)-*erythro*- and (±)-*threo*- racemates (HCI salt in DMSO-d₆)



10. ¹³C and ¹H NMR spectra obtained for one of the powdered 4F-MPH products identified as the (±)-*threo*- racemate (HCl salt in DMSO-d₆)



- 11. Two-dimensional NMR experiments
- Heteronuclear single quantum coherence spectroscopy (HSQC)
- (±)-threo-4F-MPH racemate (HCl salt in DMSO)



(±)-erythro-4F-MPH racemate (HCl salt in DMSO)



4F-MPH vendor product identified as (\pm) -threo- and (\pm) -erythro-4F-MPH racemates (HCl salt in DMSO)



4F-MPH vendor product identified as (±)-*threo*-4F-MPH racemate (HCl salt in DMSO)



Heteronuclear Multiple Bond Correlation (HMBC)

(±)-threo-4F-MPH racemate (HCl salt in DMSO)



(±)-erythro-4F-MPH racemate (HCl salt in DMSO)



4F-MPH vendor product identified as (\pm) -threo- and (\pm) -erythro-4F-MPH racemates (HCl salt in DMSO)



4F-MPH vendor product identified as (±)-*threo*-4F-MPH racemate (HCl salt in DMSO)











13. X-ray crystallography supporting information



Left: *eythro* salt hydrogen bonded dimer with hydrogen atoms omitted for clarity. The cell is shown. Only atoms involved in H-bonding interactions are labelled. Right: *threo* salt hydrogen bonding network extending parallel to the b-axis

14. High resolution mass spectrometry data obtained for isolated (\pm) -threoracemate, isolated (\pm) -erythro-racemate, and vendor samples





SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

Bruker Compass Da	taAnalysis 4.1	printed:	06/07/2016 15:10:50	Page 1 of 1
Analysis Name	D:\Data\GML_Erythro_4FMPH_RA6_01_	4048.d		

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 Bruker Open Access LC-MS - Formula Identification Report

 Sample-ID
 Station

 Submitter
 Supervisor

 Analysis Name
 GML_Threo_4FMPH_RA7_01_4049.d

Analysis Name GML_Threo_4FMPH_RA7_01_4049.d Sample Description



SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

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 printed:
 06/07/2016 15:14:04
 Page 1 of 1

 Analysis Name
 D:\Data\GML_Threo_4FMPH_RA7_01_4049.d

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 Bruker Open Access LC-MS - Formula Identification Report

 Sample-ID
 Station

 Submitter
 Supervisor

Supervisor Acquisition Date 06/07/2016 15:10:46

Analysis Name GML_Vendor_1_RA8_01_4050.d Sample Description



SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

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Page 1 of 1

Trinity College Dublin Bruker Open Access LC-MS - Formula Identification Report Sample-ID Station Submitter Supervisor Analysis Name GML_Vendor_2_RB1_01_4051.d

Acquisition Date 06/07/2016 15:14:03

Sample Description



SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

Bruker Compass DataAnalysis 4.1 printed: 06/07/2016 15:21:11 Page 1 of 1 Analysis Name D:\Data\GML_Vendor_2_RB1_01_4051.d

Trinity College Dublin Bruker Open Access LC-MS - Formula Identification Report Sample-ID Station Submitter Supervisor

Analysis Name GML_Vendor_3_Tablet_RB2_01_4052.d Sample Description

Acquisition Date 06/07/2016 15:17:21



SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

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