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Scalable Synthesis of High-Purity (*R, R*)-Dexmethylphenidate Free Base

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Abstract

A practical method for the preparation of high-purity (*R, R*)-dexmethylphenidate free base was developed. The method involves a substitution reaction of 2-chloropyridine and phenylacetonitrile via hydrolysis followed by hydrogenation, configuration inversion, chiral resolution, methyl esterification, and salification to give high-purity dexmethylphenidate hydrochloride. The hydrochloride salt was then neutralized by powder sodium hydroxide overnight to give dexmethylphenidate free base with over 99% purity. This method can be used for the industrial production of the dexmethylphenidate patch API, which could also be further applied for the preparation of other types of amino acid ester free bases.

Keywords: dexmethylphenidate, amino acid ester, free base, high purity

1. Introduction

The dexmethylphenidate hydrochloride slow-release capsule was developed by Novartis Inc. (Har et al., 2000), and it was approved by the US Food and Drug Administration (FDA) in May 2005 for the treatment of attention deficit hyperactivity disorder (ADHD) (Volkmar et al., 2003), which is the most commonly diagnosed behavioral disorder in children. In July of 2010, the FDA approved the methylphenidate patch developed by Shire Plc inc, Inc. It was the first non-oral drug for the treatment of ADHD and provided a more convenient treatment choice for children. The APIs used in the capsule or patch treatments have two major differences, dexmethylphenidate chloride is a chiral, optically pure molecule, where as methylphenidate is the racemic isomer. Furthermore, the hydrochloride salt of dexmethylphenidate is used in the capsule, but it is too hydrophilic to be used in the patch because of the hydrophobic property of skin, for which only the free base could be effective. The main functional groups on both dexmethylphenidate and methylphenidate are amino acid esters (Figure 1). Amino acid esters are not very stable and can be easily hydrolyzed when neutralizing the hydrochloride salt to free base, while there is no publication to report the synthesis method of high purity free base of this kind of compound. Thus, the development of high-purity dexmethylphenidate free base could be deemed as the key step for enabling the entire API development process to meet the safety and quality requirements currently accepted by the International Conference on Harmonization (ICH).

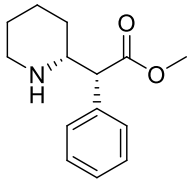


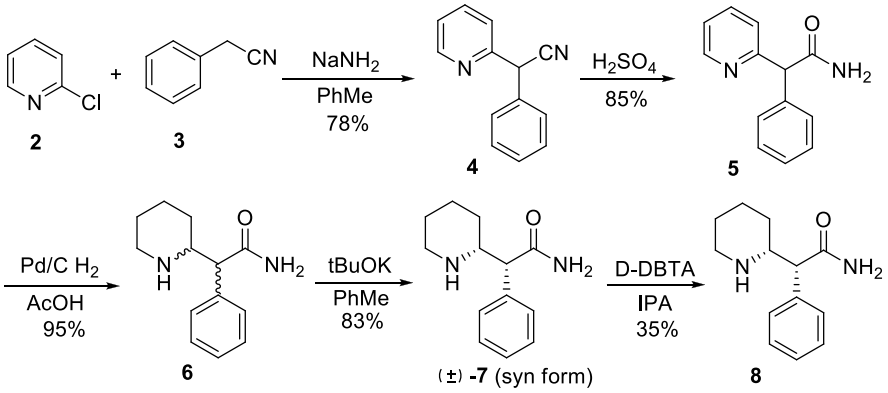
Figure 1. Structure of (*R,R*)-dexmethylphenidate free base (**1**)

As an effective therapeutic molecule, the synthesis of dexmethylphenidate has long attracted the attention (Prashad et al., 2001) of chemists around the world, and different synthetic methods have been invented and reported in the past decades. Of these, scientists from Novartis first invented a synthetic route (Prashad et al., 1999) in which the asymmetric aldol reaction was introduced as the key step; they later further improved (Prashad et al., 1999) upon this route. Following Novartis, additional scientists reported different methods (Gutman et al., 2007 & Davies et al., 1999), such as the use of Evans amide as the key intermediate for the synthetic route by Matsumura (Matsumua et al., 1999 & Matsumura et al., 2000) and coworkers. Moreover, Fox (Fox et al., 2000) and coworkers made an effective improvement on the basis of Matsumura's route by using methylbenzylamine as the key chiral auxiliary. For the

purpose of future API industrialization, a concise method (Axten et al., 1998, Chan et al., 2010, Hu et al., 2000, Kumar et al., 2008, Prashad et al., 2000 & Zhang et al., 2016) was finally confirmed as the synthetic route to dexmethylphenidate. Herein, we report our work towards the convenient and high efficient synthesis of high-purity dexmethylphenidate free base.

2. Results and Discussion

The synthetic route began from the commercially available starting materials 2-chloropyridine (**2**) and phenylacetonitrile (**3**), which were treated with sodium amide to give 2-pyridyl-2-yl-phenylacetonitrile (**4**) in 78% yield. The cyano group on **4** was hydrolyzed by concentrated sulfuric acid to the amide group of intermediate **5** in 85% yield. Owing to the aromatic property of the pyridine ring on compound **5**, which had to be hydrogenated under pressure (above 1.0 mPa) to give 2-pepridyl-2-yl-phenacetamide (**6**) in 95% yield. Compound **6** had two chiral centers with both syn-form and anti-form, the anti-from was converted to the syn-form under the treatment of potassium tert-butoxide in 83% yield to give intermediate **7** with syn-form only. Then, **7** as a racemic mixture was resolved by anhydrous D-dibenzoyl tartaric acid in isopropanol to give the optically pure product **8** in 35% yield with over 99% ee values.



Scheme 1. Synthesis of (R,R)-2-piperidyl-2-yl-phenylacetamide (**8**)

With highly optically pure compound **8** in hand, the condition screening of the methyl esterification reaction was then processed. Concentrated sulfuric acid was used as catalyst, and the reaction was carried out in refluxing methanol for various times. The excess sulfuric acid was neutralized with sodium hydroxide aqueous solution after the reaction was completed to give compound **9** as light yellow oil, which was the crude dexmethylphenidate free base. Different reaction times were investigated to ensure that the conversion of the methyl esterification reaction was as high as possible. The results are listed in Table 1. Approximately half of reactant **8** was converted to **9** after 12 hours (Table 1, entry 1). After 1 d, the conversion increased to 78% (Table 1, entry 2). Two days later, 94.2% of product **9** had been synthesized (Table 1, entry 3). The reaction time was further extended to 3 d, and the conversion reached 96% (Table 1, entry 4). Unfortunately, reactant **8** did not completely disappear after the reaction had been processed for 7 d; at least 1.1% of reactant **8** could not be converted to **9** in this system (Table 1, entries 5–7).

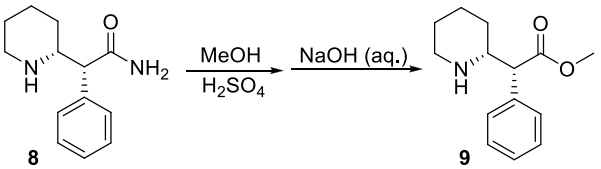


Table 1**.** Condition screening of the methyl esterification reaction

entry	Time (d)	Ratio of 8(%)	Ratio of 9(%)
1	0.5	52	47
2	1	21	78
3	2	5.1	94.2
4	3	3.0	96.0
5	4	1.9	98.0
6	5	1.1	98.4
7	6	1.2	97.6

The results shown in Table 1 indicated that the crude free base product was not qualified for API purity because of the residue of reactant **8**, so a purification procedure was needed. Consequently, concentrated hydrochloride acid was

charged into the ethyl acetate solution of crude product **9**. The dexmethylphenidate hydrochloride salt was precipitated and filtered from the mother solution; then it was recrystallized from deionized water to give a white solid with up to 99.8% purity. Different neutralization methods were tried to obtain a high-purity free base form of dexmethylphenidate.

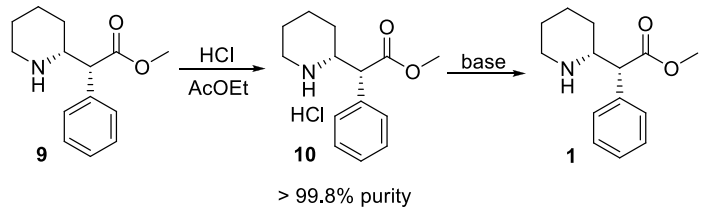


Table 2. Condition screening of the neutralization reaction to free base

entry	Forms of base	Solvent	time	Purity of **1** (%)	Yield(%)
1	10% NaOH (a.q.)	AcOEt/H_2O	10 min	90.7	88
2	10% LiOH (a.q.)	AcOEt/H_2O	10 min	94.2	90
3	$NaOCH_3$	MeOH	10 min	85.0	60
4	tBuOK	Toluene	10 min	76.2	53
5	NaOH (anhydrous solid)	CH_2Cl_2	12 h	99.7	86
6	LiOH (anhydrous solid)	CH_2Cl_2	12 h	99.8	91
7	KOH (anhydrous solid)	CH_2Cl_2	12 h	99.5	88

There are two requirements for high-purity free base, one is that no other impurity is formed or introduced and the second is that the hydrochloride acid must be neutralized completely in the neutralization process. As the piperidine on methylphenidate is a strong organic base, a stronger base is needed to neutralize hydrochloride acid completely from piperidine. Our attempts (Table 2) began with using 10% sodium hydroxide aqueous solution to neutralize hydrochloride acid, the result (Table 2, entry 1) indicated that only 90.7% purity of the product was obtained, and the main by-product (Figure 2) 2-piperdyl-2-yl-phenylacetatic acid (**11**) was identified in this process. Though the purity was improved to 94.2% by using 10% lithium hydroxide aqueous solution, it still remained unattractive (Table 2, entry 2) because the methyl ester group was still easily hydrolyzed in aqueous solution. Anhydrous conditions were introduced using sodium methoxide and potassium tert-butoxide, but the results (Table 2, entries 3 and 4) were less suitable because many unidentified impurities were observed. An alternative method was subsequently developed, anhydrous sodium hydroxide powder and dexmethylphenidate hydrochloride solids were mixed as slurry into dichloromethane under a nitrogen atmosphere and stirred vigorously overnight, followed by filtration of the insoluble solid and concentration of the solution in vacuo. The high-purity methylphenidate free base was successfully prepared using this method in 99.8% purity and 90% yield (Table 2, entry 5). The purity of the free base also up to 99.7% and 99.5% when using the anhydrous solids of lithium hydroxide and potassium hydroxide, respectively (Table 2, entries 6 and 7).

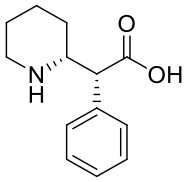


Figure 2. Structure of (*R, R*)-2-piperdyl-2-yl-phenylacetatic acid (**11**)

3. Experimental

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Ultrashield-600 spectrometer with TMS as an internal standard. Chemical shifts (values) and coupling constants (J values) are given in ppm and Hz, respectively. ESI mass spectra were obtained using on an Agilent 6210 TOF spectrometer. Reaction progress and chemical purity were evaluated by HPLC analysis using a Waters symmetry C18 column (5 μm, 250 mm × 4.6 mm) with mobile phases A (MeOH + 0.05% TFA) and B (0.3% TEA), 88:12 v/v, and detection at 230 nm; flow rate: 1.0 mL/min, temperature: 25 ℃. Palladium content was analyzed by Perkin Emler 800 AAS instrument. TLC analysis was conducted using prepared HSGF254 TLC plates. Solvents and reagents were used as received. All the intermediates and products were characterized by 1H & 13C NMR, high resolution ESI mass spectra, HPLC, melting point apparatus and optical rotation apparatus (if needed).

Synthesis of 2-pyridyl-2-yl-phenylacetontrile (4): Sodium amide (3.5 kg, 89.7 mol) was added to toluene (25.0 L) in a

100-L double layer reaction vessel under a nitrogen atmosphere at room temperature. Phenylacetonitrile (**3**, 6.5 kg, 55.6 mol) was added dropwise into the toluene solution over a period of 30 min; the temperature of the solutions was approximately 40 to 50 ℃, then cooled to 15 ℃. Afterwards, 2-chloropyridine (**2**, 6.0 kg, 53.1 mol) was added dropwise into the solution slowly; the reaction temperature temporarily increased to 70 ℃ and decreased to room temperature after 1 h. The reaction was kept at this temperature for 4 h, quenched by dripping water (5.0 L), and then washed by water (5.0 L, three times). Afterwards, approximately 20 L of toluene was distilled out, petroleum ester (5.0 L) was added in one portion, and the solution was cooled to 15 ℃. The product was precipitated and filtered from the mother solution as a light yellow solid (8390.0 g) in 81.5% yield and 99.83% purity, Mp. 84.0 – 86.0 ^{0}C. ^{1}H NMR (600Hz, DMSO-d_6) δ 5.93 (s, 1H), 7.22 – 7.46 (m, 7H), 7.85 – 7.98 (m, 1H), 8.59 (s, 1H). ^{13}C NMR (150Hz, DMSO-d_6) δ 120.2, 122.9, 123.8, 128.6, 129.4, 129.6, 138.4, 150.2, 155.9. HRMS (ESI): Calcd for $[C_{13}H_{10}N_2+H]^+$ 195.0917, $[C_{13}H_{10}N_2+Na]^+$ 217.0736, found: 195.0921, 217.0739.

Synthesis of 2-pyridyl-2-yl-phenylacetyl amide (5): 2-pyridyl-2-yl-phenylacetontrile (**4,** 8000g, 41.2 mol) was added to concentrated sulfuric acid (10.0 L) in a 50-L round bottom reaction vessel and stirred at room temperature. After 24 h, the reaction was quenched by adding water dropwise (10.0 L) and neutralized by 30% sodium hydroxide solution until the pH was 13. Many solids were precipitated and filtered from the solution. The red-colored, crude product was dried by heating in an oven for 6 h and recrystallized from ethanol to give the purified product as a white solid (6720 g) in 77.0% yield and 99.70% purity, Mp. 133.8 – 134.6 ^{0}C. ^{1}H NMR (600Hz, DMSO-d_6) δ 5.12 (s, 1H), 7.23 – 7.46 (m, 8H), 7.75 – 7.95 (m, 2H), 8.59 (s, 1H). ^{13}C NMR (150Hz, DMSO-d_6) δ 59.8, 122.4, 123.5, 127.3, 128.7, 129.1, 137.0, 139.8, 149.2, 160.1, 172.7. HRMS (ESI): Calcd for $[C_{13}H_{12}N_2O+H]^+$, 213.1022, $[C_{13}H_{12}N_2O+Na]^+$ 235.0842 found: 213.1023, 235.0839.

Synthesis of *syn/anti*-2-piperidyl-2-yl-phenylacetyl amide (6): 2-pyridyl-2-yl-phenylacetyl amide (6000.0 g, 28.3 mol) and 10% wet Pd/C catalyst (1500.0 g, 40% dry base) were added into an acetic acid solution (25.0 L) and mixed well in one portion of a 50-L sealed hydrogenation vessel. The vessel was heated to 80 ℃ for 8 h under hydrogen pressure greater than 1.0 mPa. After the reaction was completed, the Pd/C catalyst was filtered, and the acetic acid was removed *in vacuo*. The residue was dissolved in water (10.0 L) and neutralized by 30% sodium hydroxide solution until the pH was 13. The product was precipitated and filtered from the solution and washed by water (10 L, three times) to give a white solid (5860.0 g) in 95% yield with 84.25% *anti*-form and 15.74% *syn*-form, the palladium content is 2 ppm, Mp. 156.0 – 157.5 ^{0}C. ^{1}H NMR (600Hz, DMSO-d_6) δ 0.82 – 0.96 (m, 1H), 0.98 – 1.10 (m, 4H), 1.14 – 1.31 (m, 4H), 1.38 – 1.48 (m, 3H), 1.57 – 1.65 (m, 1H), 1.72 (d, J = 9.0 Hz, 3H), 2.37 (t, J = 10.2 Hz, 2H), 2.47 – 2.54 (m, 2H), 2.66 (d, J = 11.4 Hz, 2H), 2.91 – 2.98 (m, 4H), 3.26 (t, J = 9.6 Hz, 4H), 6.82 – 6.86 (m, 2H), 7.16 – 7.37 (m, 14H), 7.51 – 7.56 (m, 3H). ^{13}C NMR (150Hz, DMSO-d_6) δ 24.6, 24.7, 25.5, 26.3, 26.4, 30.2, 31.0, 46.8, 46.9, 58.1, 58.6, 58.9, 127.1, 127.3, 128.6, 128.7, 128.8, 128.9, 138.9, 139.3, 174.1, 174.5. HRMS (ESI): Calcd for $[C_{13}H_{18}N_2O+H]^+$ 219.1492, found: 219.1493.

Synthesis of *syn*-2-piperidyl-2-yl-phenylacetyl amide (7): *Syn/anti*-2-piperidyl-2-yl-phenylacetyl amide (**6**, 2000.0 g, 9.2 mol) and potassium tert-butoxide (2000.0 g) were added into toluene solution (50.0 L) in a 100-L double layer reaction vessel and mixed well. The solution was heated to 70 ℃ for 16 h, quenched by water, and washed by 6 N hydrochloride acid solutions (1.0 L, twice). The aqueous phase was separated and combined. A 30% sodium hydroxide solution was used to neutralize the solution until the pH value was 13. The product was precipitated, filtered, and dried by heating in an oven for 6 h to give the purified product as a white solid (1710 g) in 85.5% yield and 97.76% purity. Mp. 172.9 – 173.9 ^{0}C. ^{1}H NMR (600Hz, DMSO-d_6) δ 0.82 – 0.88 (m, 1H), 1.09 – 1.16 (m, 2H), 1.22 – 1.28 (m, 1H), 1.45 (d, J = 12.0 Hz, 1H), 1.58 (d, J = 12.6 Hz, 1H), 1.72 – 2.11 (br, 1H), 2.47 – 2.56 (m, 1H), 2.84 – 2.95 (m, 2H), 3.88 (d, J = 10.2 Hz, 1H), 6.82 (s, 1H), 7.15 – 7.45 (m, 5H), 7.53 (s, 1H)..^{13}C NMR (150Hz, DMSO-d_6) δ 24.7, 26.4, 30.2, 46.8, 58.6, 58.9, 127.1, 128.4, 128.9, 139.3, 174.6. HRMS (ESI): Calcd for $[C_{13}H_{18}N_2O+H]^+$ 219.1492, found: 219.1494.

Synthesis of (*R,R*)-2-piperidyl-2-yl-phenylacetyl amide (8): To a 20-L double layer reaction vessel, *syn*-2-piperidyl-2-yl-phenylacetyl amide (**7**, 600.0 g, 2.8 mol) and anhydrous D-dibenzoyl tartaric acid (1002.0 g, 2.8 mol) were added into isopropanol solution (12.0 L) and heated to 60 ℃ until all of the solids were dissolved. Then, the reaction was cooled gradually to 30 ℃. White solids were precipitated, filtered, and transferred into the 6 N hydrochloride acid solution and stirred for 1 h; the precipitates were eliminated, and the solution was neutralized using a 30% sodium hydroxide solution until the pH was 13. The product was precipitated, filtered, and dried by heating in an oven for 6 h to give the purified product as a yellow solid (213.0 g) in 35.5% yield, 99.30% purity, and 99.9% ee values, Mp. 173.1 – 174.0 ^{0}C. ^{1}H NMR (600Hz, DMSO-d_6) δ 0.81 – 0.87 (m, 1H), 1.04 – 1.16 (m, 2H), 1.21 – 1.27 (m, 1H), 1.34 (d, J = 7.2 Hz, 1H), 1.57 (d, J = 12.6 Hz, 1H), 1.83 (s, 1H), 2.39 – 2.51 (m, 2H), 2.93 – 2.96 (m, 2H), 3.33 (d, J = 10.2 Hz, 1H), 6.85 (s, 1H), 7.21 – 7.43 (m, 5H), 7.52 (s, 1H). ^{13}C NMR (150Hz, DMSO-d_6) δ 24.7, 26.0, 26.4, 30.2, 58.6, 58.9, 127.1, 128.6, 128.8, 139.9, 174.5. HRMS (ESI): Calcd for $[C_{13}H_{18}N_2O+H]^+$ 219.1492, found: 219.1495.

Synthesis of (*R,R*)-*O*-methyl-2-piperidyl-2-yl-phenylacetate hydrochloride (10):

(*R,R*)-2-piperidyl-2-yl-phenylacetyl amide (**8**, 200.0 g, 0.92 mol) was added to a methanol solution (500 mL) in a 2-L round bottom flask with four necks. Concentrated sulfuric acid (200 mL) was added dropwise, and the solution was refluxed for 3 d. afterwards, methanol was removed *in vacuo*. The residue was dissolved into a mixture of ethyl acetate (3.0 L) and water (1.0 L), which was neutralized with a 30% sodium hydroxide solution until the pH of the aqueous layer was 13. The top organic layer was separated and concentrated hydrochloride acid (50 mL) was added into the solution and mixed well. The white solid was precipitated, filtered, recrystallized from deionized water (150 mL), and finally dried by heating in an oven for 2 h to give the purified product as a white solid (186.0 g) in 75.5% yield and 99.82% purity. $[\alpha]_D^{20}$ +87.3 (c=1,MeOH), Mp. 222.0 – 223.0, ^{1}H NMR (600Hz, DMSO-d_6) δ 1.24 – 1.26 (m, 1H), 1.35 – 1.41 (m, 2H), 1.52 – 1.68 (m, 3H), 2.95 (s, 1H), 3.25 – 3.28 (m,1H), 3.39 – 3.47 (m,1H), 3.66 (s,3H), 3.78 – 3.84 (m,1H), 4.15(d, *J* = 9.6 Hz,1H), 7.27 – 7.49 (m,5H), 9.02 (br,1H), 9.74 (br,1H). ^{13}C NMR (150Hz, DMSO-d_6) δ 21.8, 21.9, 26.1, 44.9, 53.1, 53.7, 57.2, 128.7, 128.9, 134.7, 171.7. HRMS (ESI): Calcd for $[C_{14}H_{20}N_2OCl - Cl^-]^+$ 234.1489, found: 234.1492.

Synthesis of (*R,R*)-2-piperdyl-2-yl-phenylacetatic acid (11): To a solution of methanol (20.0 mL) (*R,R*)-O-methyl-2-piperidyl-2-yl-phenyl-acetate hydrochloride (**10**, 1.0 g) was added in one portion and 0.1 M sodium hydroxide aqueous solution (10.0 mL) was added dropwise, the reaction was crrried out at room temperature for 3 hours, then 1 N hydrochloride aqueous solution was dripping into until the pH values was up to 2. The white solids were precipitated from the solution and filtered, which was dried by oven at 60 ^{0}C overnight to afford the product as white solid (0.39g, 48% yield) with 99.25% purity, Mp. 220.0 – 221.0 ^{0}C, $[\alpha]_D^{20}$ +22.7 (c=1,H_2O), ^{1}H NMR (600Hz, DMSO-d_6) δ 1.25 – 1.29 (m, 1H), 1.38 – 1.42 (m, 2H), 1.60 – 1.67 (m, 3H), 2.94 – 2.99 (br, 1H), 3.26 (d, *J* = 12.6 Hz, 1H), 3.64 – 3.72 (br, 1H), 4.06 (d, *J* = 9.0 Hz, 1H), 7.21 – 7.46 (m, 5H), 8.56 (s, 1H), 9.69 (s, 1H), 12.75 – 13.65 (br, 1H). ^{13}C NMR (150Hz, DMSO-d_6) δ 21.9, 26.1, 34.4, 45.1, 53.8, 57.2, 128.4, 129.0, 129.4, 135.4, 172.9. HRMS (ESI): Calcd for $[C_{13}H_{17}NO_2+H]^+$ 220.1332, $[C_{13}H_{17}NO_2+Na]^+$ 242.1151, found: 220.1338, 242.1158.

Synthesis of (*R,R*)-*O*-methyl-2-piperidyl-2-yl-phenylacetate free base (1):

(*R,R*)-*O*-methyl-2-piperidyl-2-yl-phenylacetate hydrochloride (**10**, 30.0g, 112.0 mmol) and anhydrous sodium hydroxide solid (4.93 g, 123 mmol) were added into dichloromethane (500 mL) in a 1-L round bottom flask and stirred vigorously under a nitrogen atmosphere. After 12 h, the undissolved solids were filtered, and the organic solution was washed with water (200 mL, twice) and dried with anhydrous magnesium sulfate. The inorganic solid was filtered and the dichloromethane was removed *in vacuo* to give the final free base product as a colorless oil (22.3 g) in 86.1% yield and 99.69% purity, $[\alpha]_D^{20}$ +87.7 (c=1,MeOH), ^{1}H NMR (600Hz, DMSO-d_6) δ 0.82 – 0.88 (m, 1H), 1.07 – 1.14 (m, 1H), 1.15 – 1.27 (m, 2H), 1.38 – 1.43 (m, 1H), 1.59 – 1.61 (m, 1H), 2.46 – 2.51 (m, 1H), 2.92 – 2.99 (m, 1H), 3.01 – 3.03 (m, 1H), 3.34 (d, J = 9.6 Hz, 1H), 3.57 (s, 3H), 7.31 – 7.33 (m, 5H). ^{13}C NMR (150Hz, DMSO-d_6) δ 22.5, 24.6, 28.1, 44.6, 49.9, 52.1, 56.2, 125.7, 126.8, 127.1, 135.1, 171.7. HRMS (ESI): Calcd for $[C_{14}H_{19}N_2O+H]^+$ 234.1489, found: 234.1487.

4. Conclusion

In summary, a new, practical method towards high purity free base of methylphenidate was successfully developed via seven steps starting from simple commercially available materials. This innovative method could also be used for the synthesis of high-purity free base of other amino acid esters.

Acknowledgments

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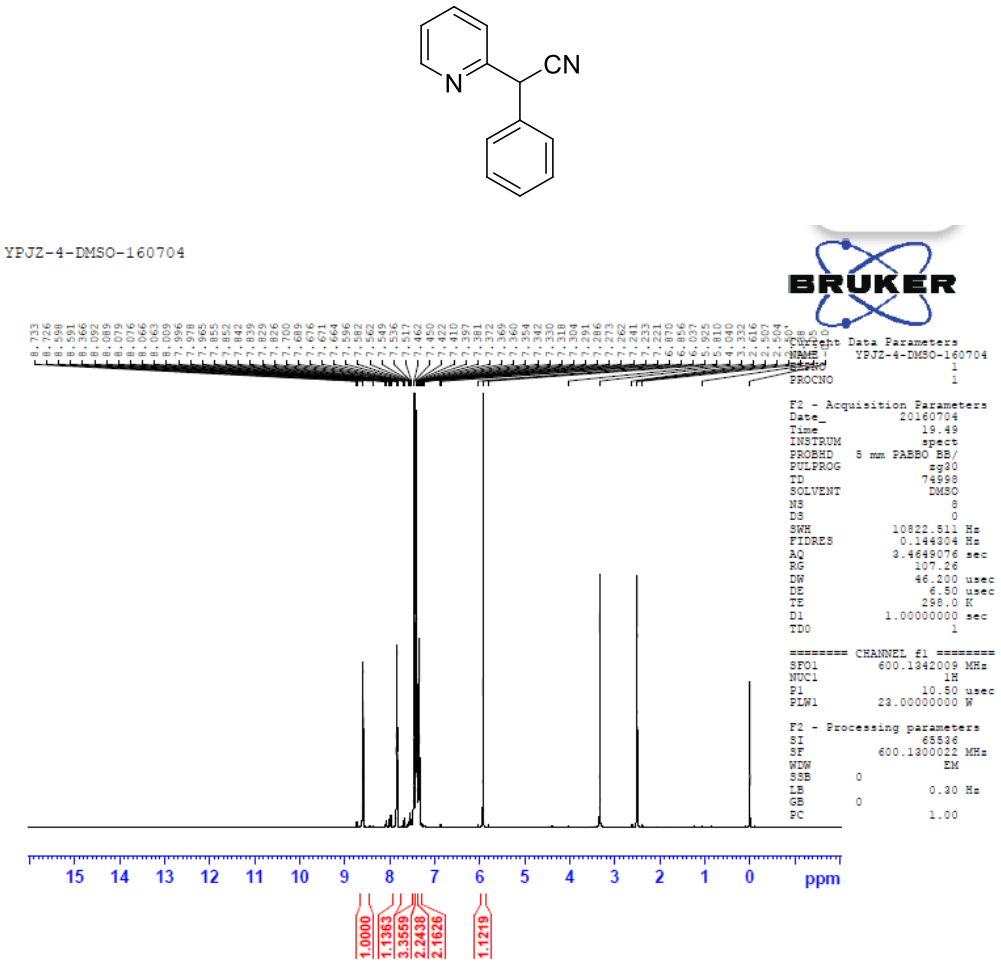
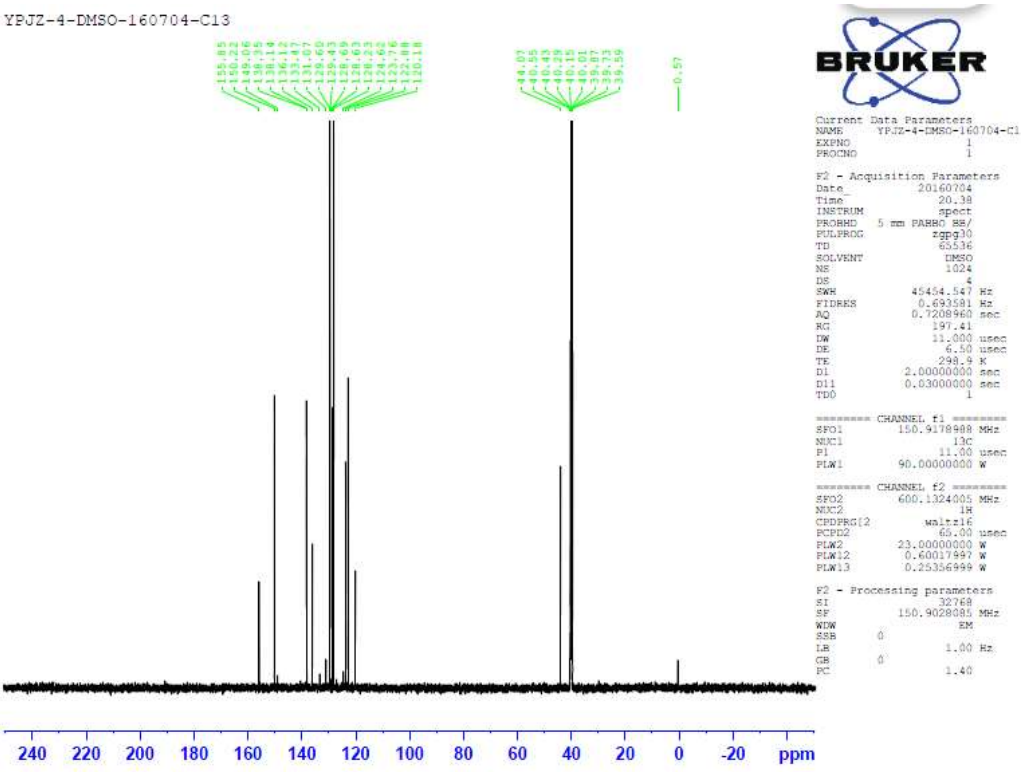
Appendix A

NMR, HRMS and HPLC spectra of 2-pyridyl-2-yl-phenylacetontrile (4)





Qualitative Compound Report

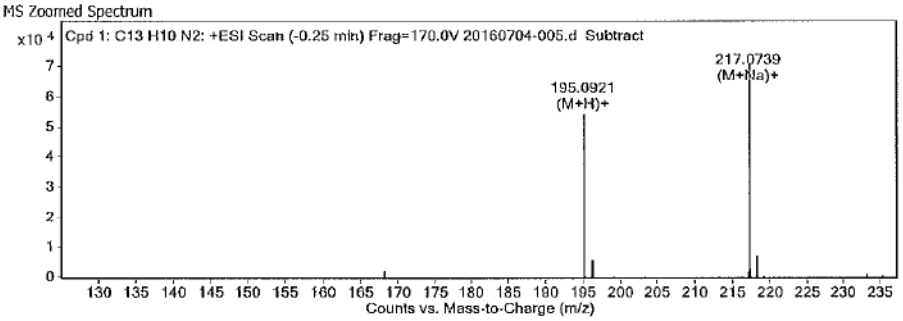
Data File	20160704-005.d	**Sample Name**	YPJZ-4
Sample Type	Sample	**Position**	Vial 64
Instrument Name	Instrument 1	**User Name**	
Acq Method		**IRM Calibration Status**	Success
DA Method	MS.m	**Comment**	N20160704011

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C13 H10 N2	-0.25	194.0847	71407	C13 H10 N2	194.0844	1.69

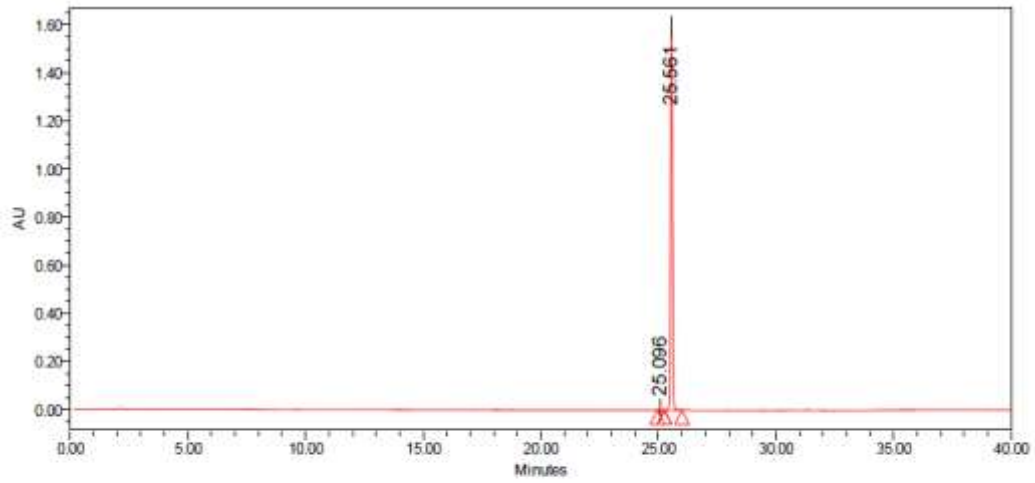
Compound Label	RT	Algorithm	Mass
Cpd 1: C13 H10 N2	-0.25	Find By Formula	194.0847

MS Zoomed Spectrum



MS Spectrum Peak List

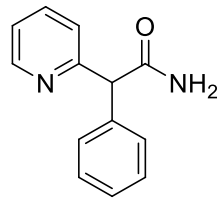
m/z	*Calc m/z*	Diff(ppm)	z	Abund	Formula	Ion
195.0921	195.0917	1.92	1	54458	C13 H11 N2	(M+H)+
217.0739	217.0736	1.41		71407	C13 H10 N2 Na	(M+Na)+

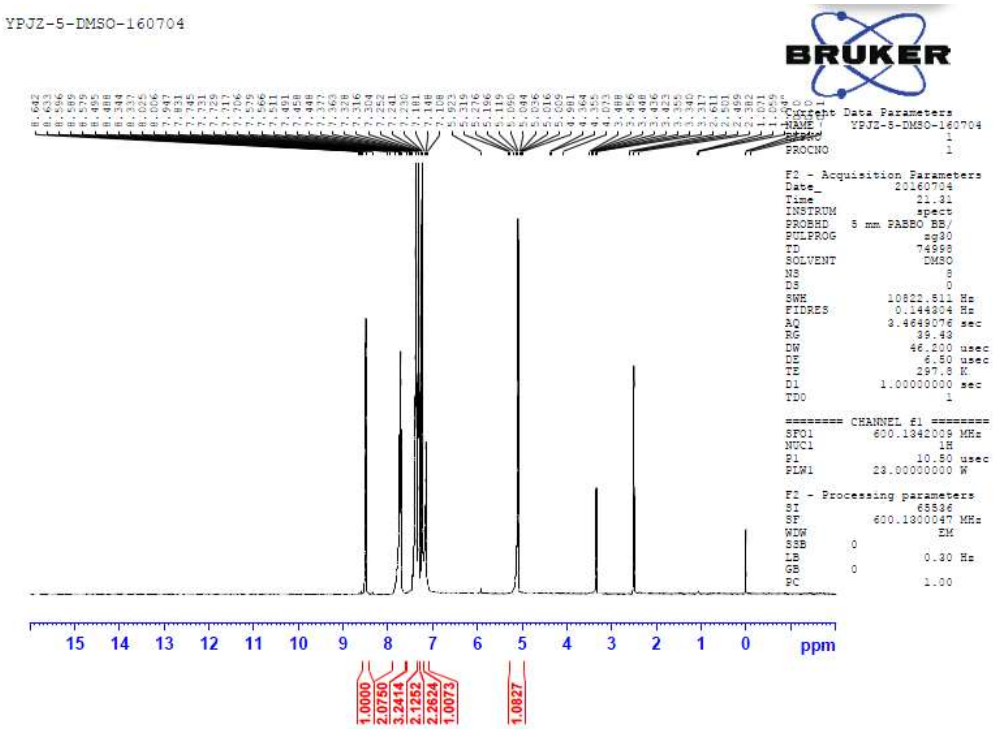


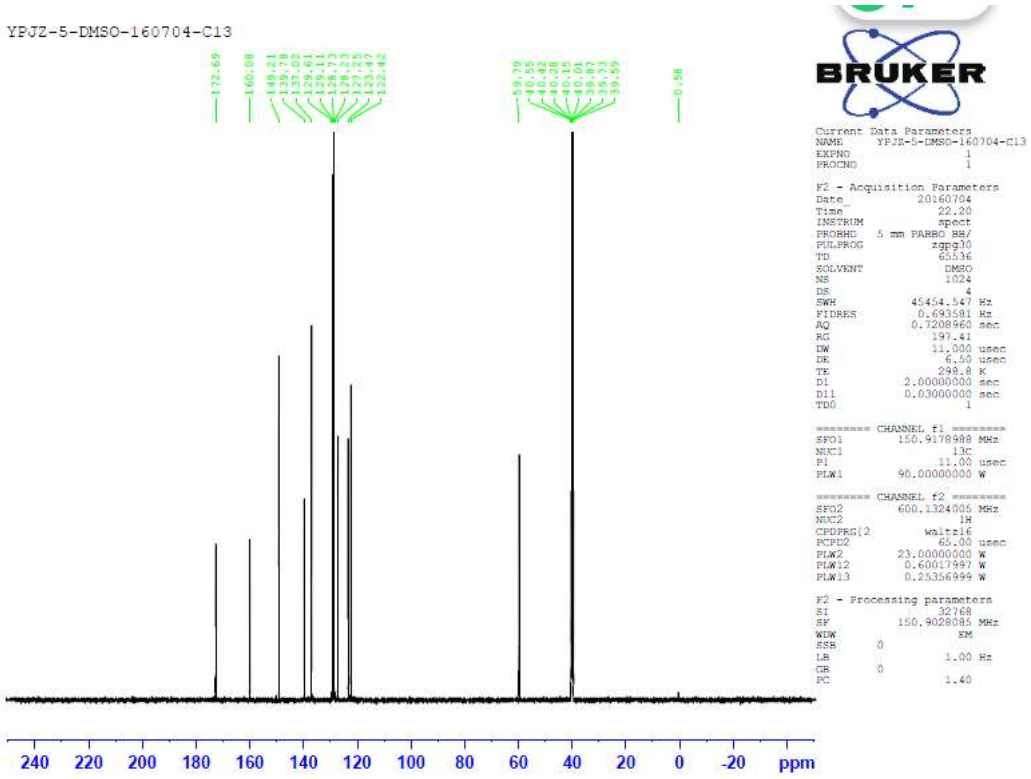
Peak Results

	Name	RT	Area	% Area	Height
1		25.096	14780	0.17	2549
2		25.561	8661812	99.83	1594325

NMR, HRMS and HPLC spectra of 2-pyridyl-2-yl-phenylacetyl amide (5)







Qualitative Compound Report

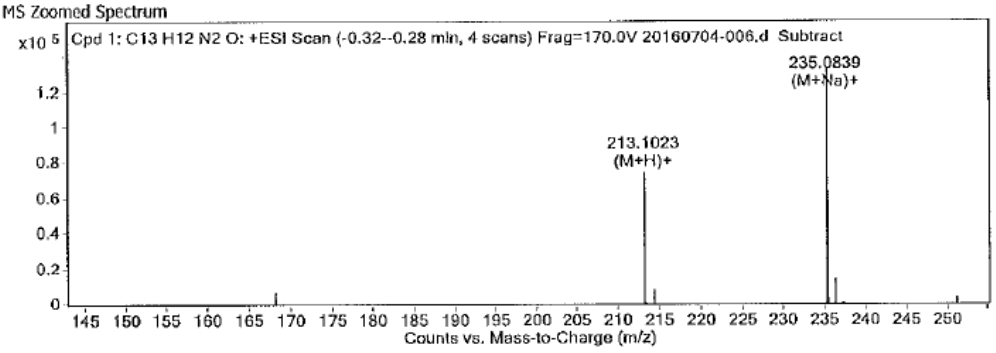
Data File	20160704-006.d	**Sample Name**	YPJZ-5
Sample Type	Sample	**Position**	Vial 65
Instrument Name	Instrument 1	**User Name**	
Acq Method		**IRM Calibration Status**	Success
DA Method	MS.m	**Comment**	N20160704012

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C13 H12 N2 O	-0.28	212.0947	134184	C13 H12 N2 O	212.095	-1.06

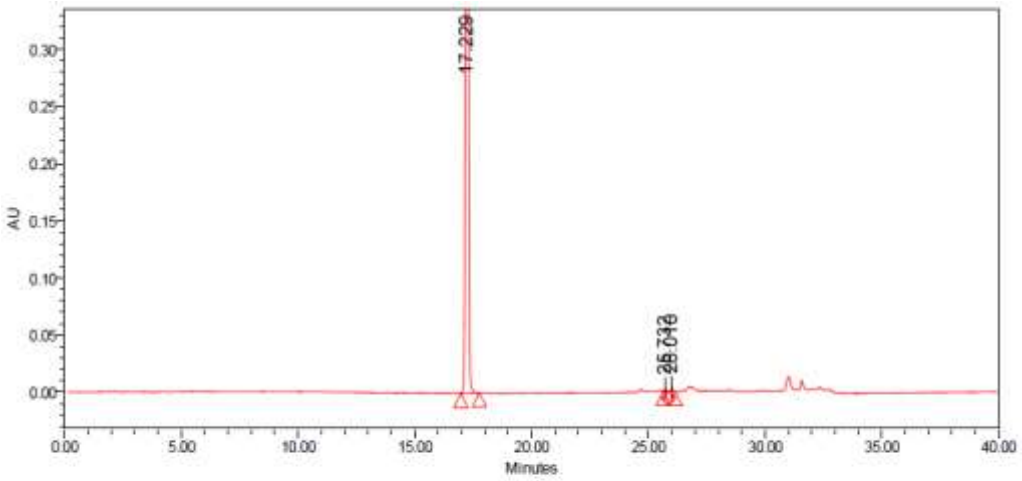
Compound Label	RT	Algorithm	Mass
Cpd 1: C13 H12 N2 O	-0.28	Find By Formula	212.0947

MS Zoomed Spectrum



MS Spectrum Peak List

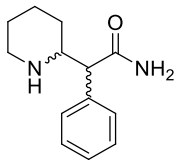
m/z	Calc m/z	Diff(ppm)	z	Abund	Formula	Ion
213.1023	213.1022	0.48	1	74546	C13 H13 N2 O	(M+H)+
235.0839	235.0842	-1.2		134184	C13 H12 N2 Na O	(M+Na)+

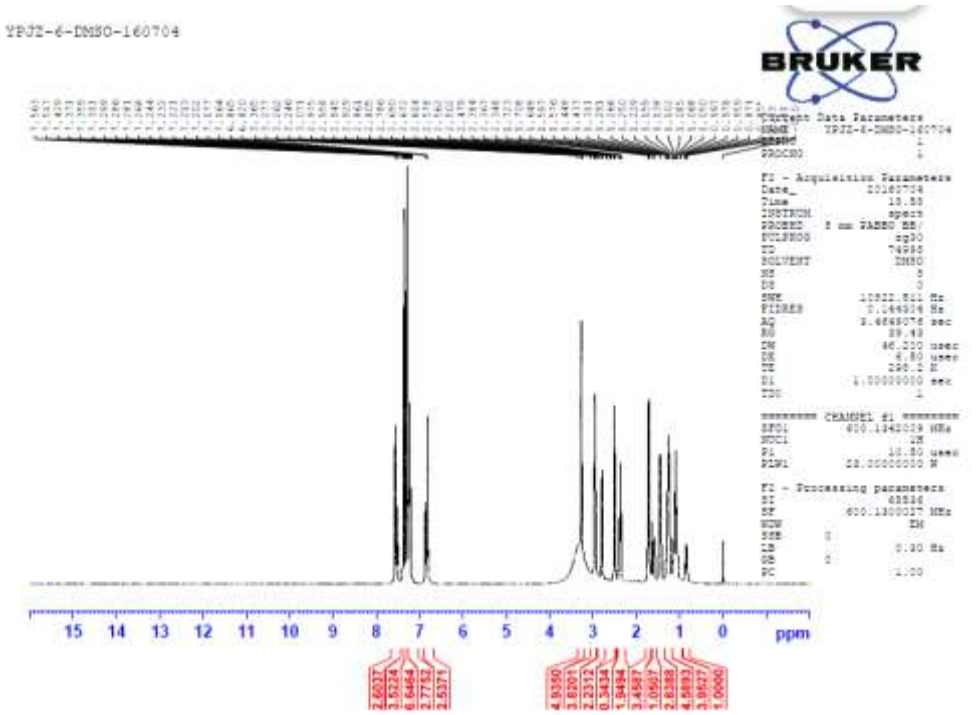


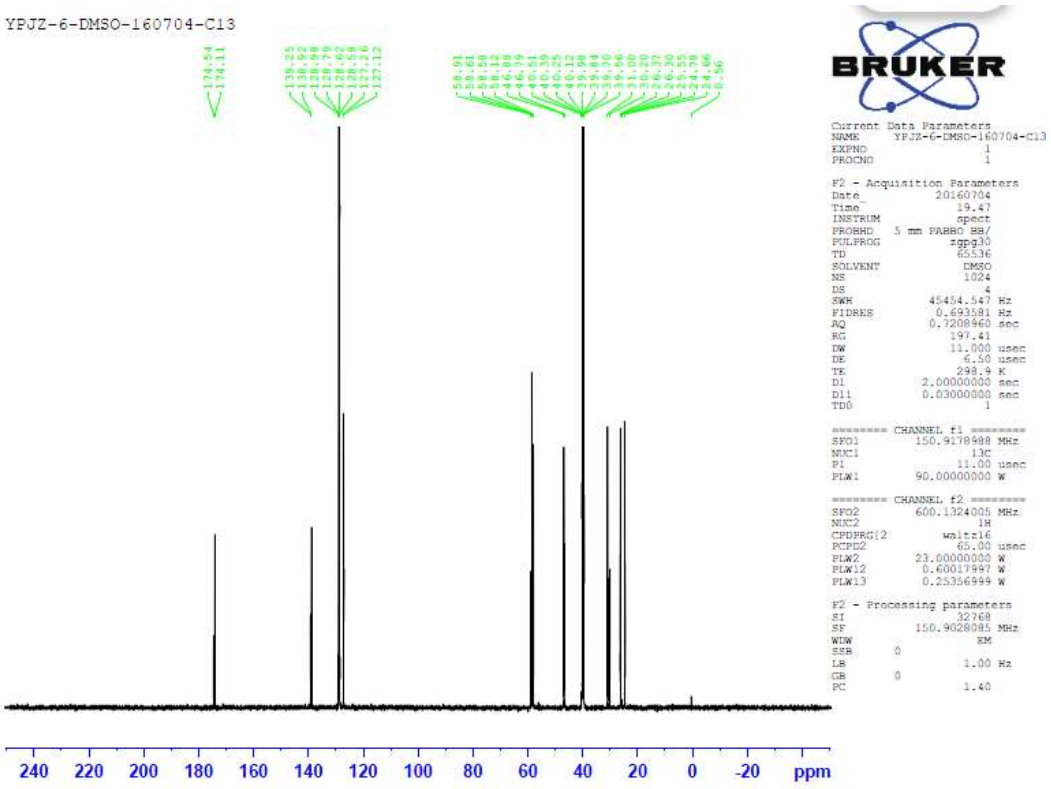
Peak Results

	Name	RT	Area	% Area	Height
1		17.229	9431958	99.70	1523750
2		25.732	9496	0.10	2107
3		26.010	18920	0.20	3546

NMR, HRMS and HPLC spectras *syn/anti*-2-piperidyl-2-yl-phenylacetyl amide (6)







Qualitative Compound Report

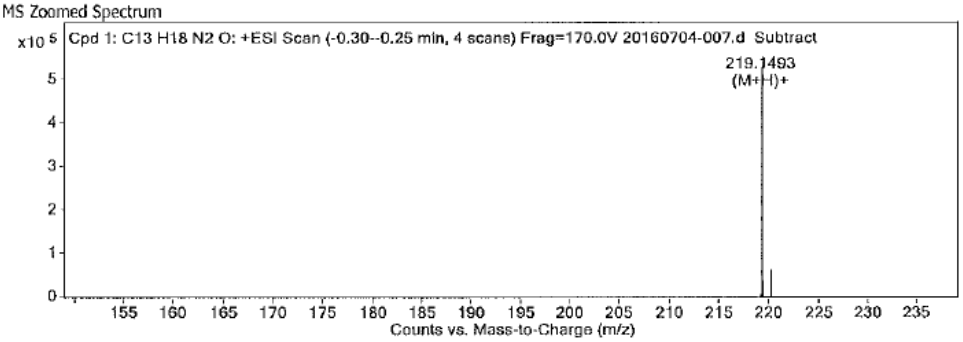
Data File	20160704-007.d	**Sample Name**	YPJZ-6
Sample Type	Sample	**Position**	Vial 66
Instrument Name	Instrument 1	**User Name**	
Acq Method		**IRM Calibration Status**	Success
DA Method	MS.m	**Comment**	N20160704013

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C13 H18 N2 O	-0.25	218.142	530097	C13 H18 N2 O	218.1419	0.45

Compound Label	RT	Algorithm	Mass
Cpd 1: C13 H18 N2 O	-0.25	Find By Formula	218.142

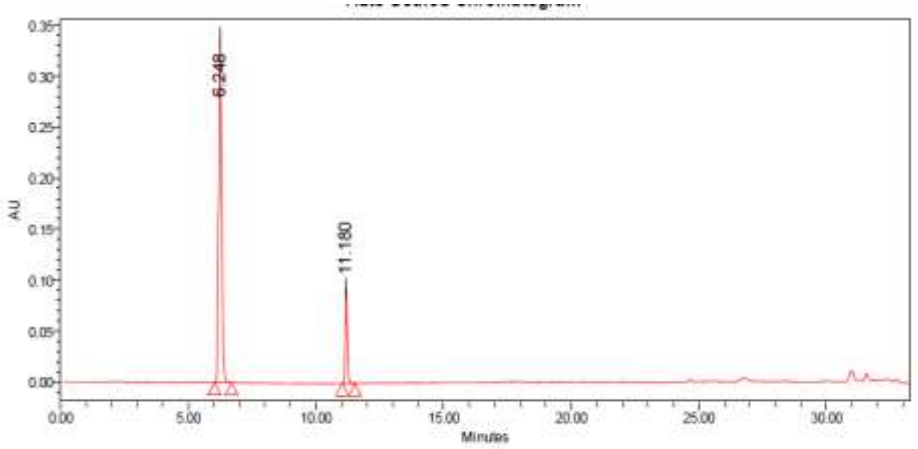
MS Zoomed Spectrum



MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	Abund	Formula	Ion
219.1493	219.1492	0.45	530097	C13 H19 N2 O	(M+H)+

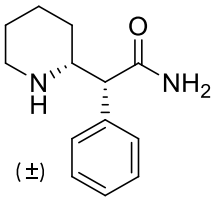
--- End Of Report ---

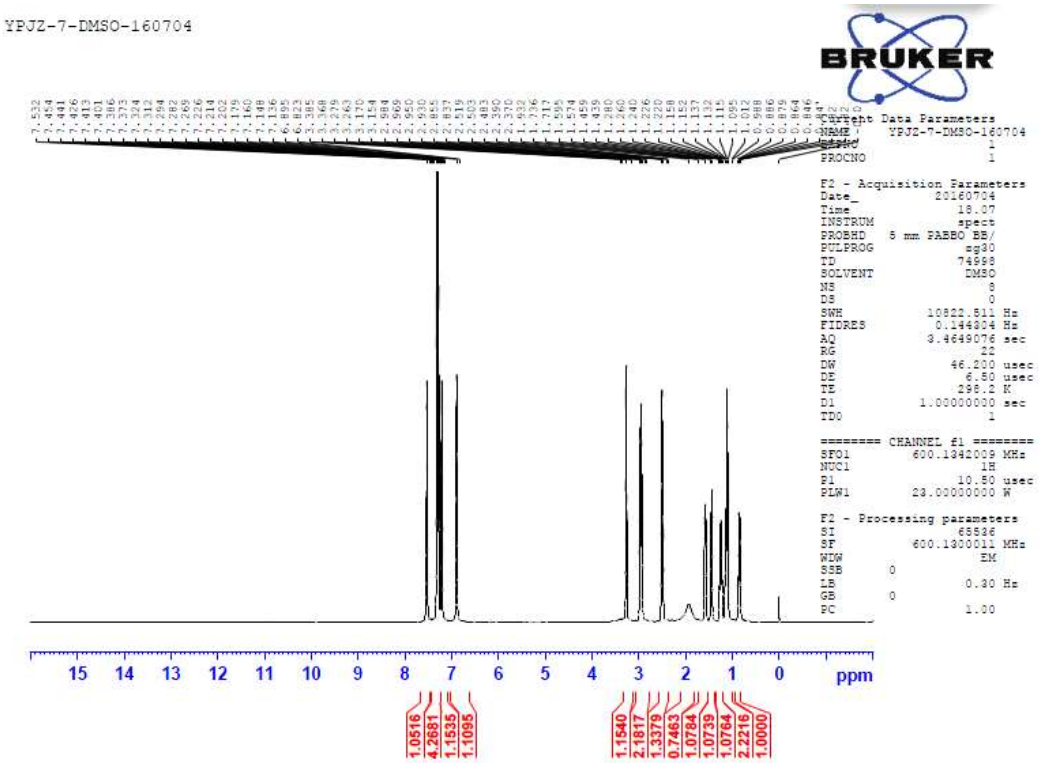


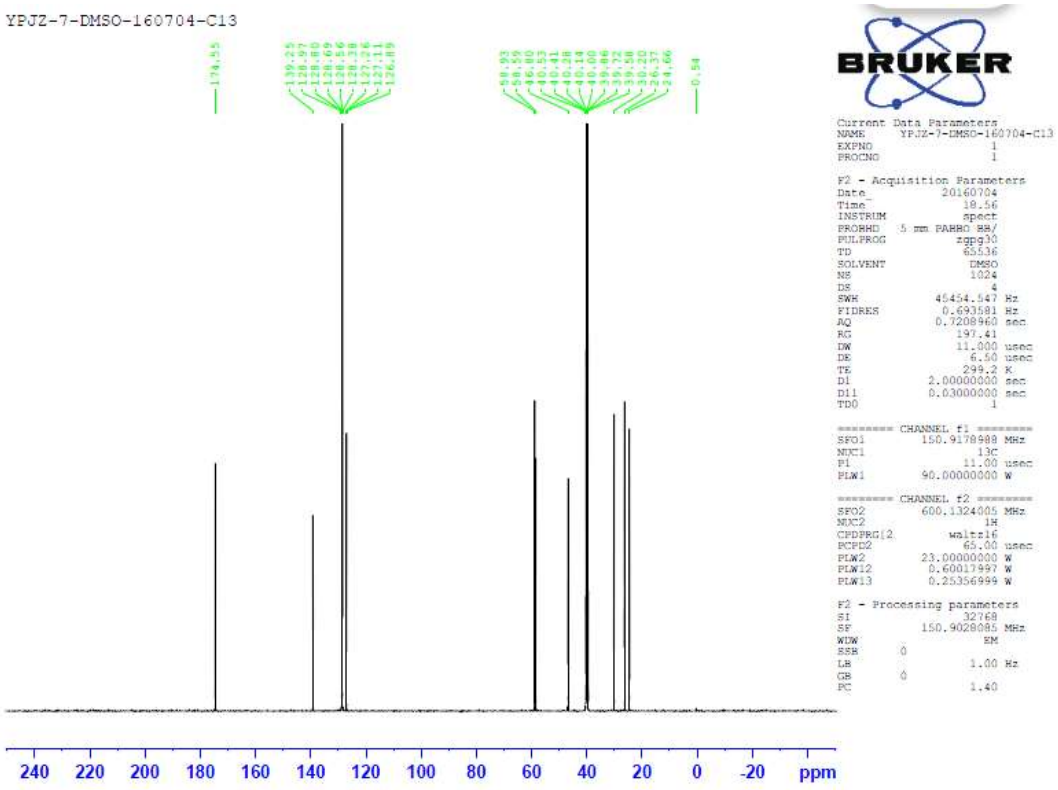
Peak Results

	Name	RT	Area	% Area	Height
1		6.248	2765140	84.26	339271
2		11.180	516352	15.74	93658

NMR, HRMS and HPLC spectra of syn-2-piperidyl-2-yl-phenylacetyl amide (7)







Qualitative Compound Report

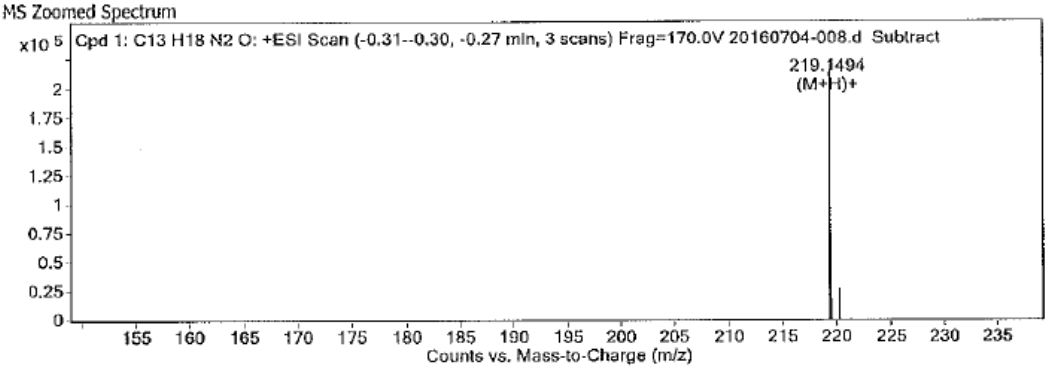
Data File	20160704-008.d	**Sample Name**	YPJZ-7
Sample Type	Sample	**Position**	Vial 67
Instrument Name	Instrument 1	**User Name**	
Acq Method		**IRM Calibration Status**	Success
DA Method	MS.m	**Comment**	N20160704014

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C13 H18 N2 O	-0.28	218.1421	215881	C13 H18 N2 O	218.1419	0.95

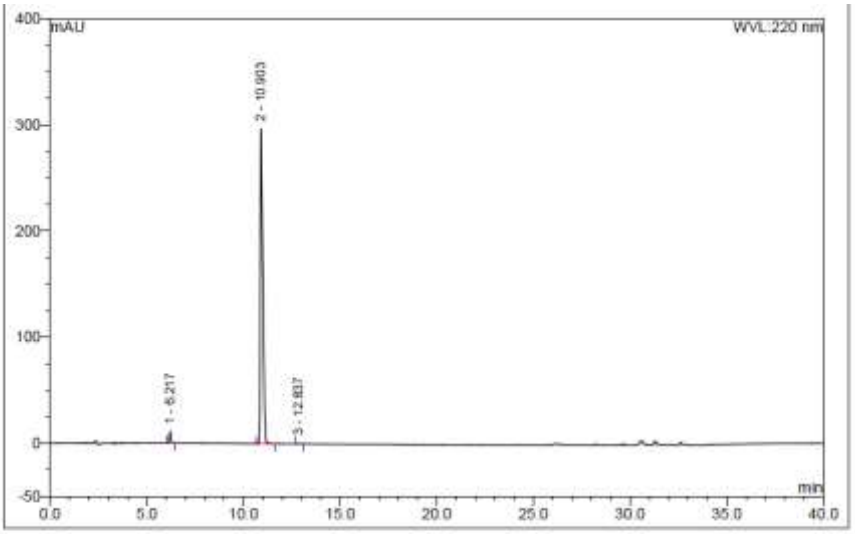
Compound Label	RT	Algorithm	Mass
Cpd 1: C13 H18 N2 O	-0.28	Find By Formula	218.1421

MS Zoomed Spectrum

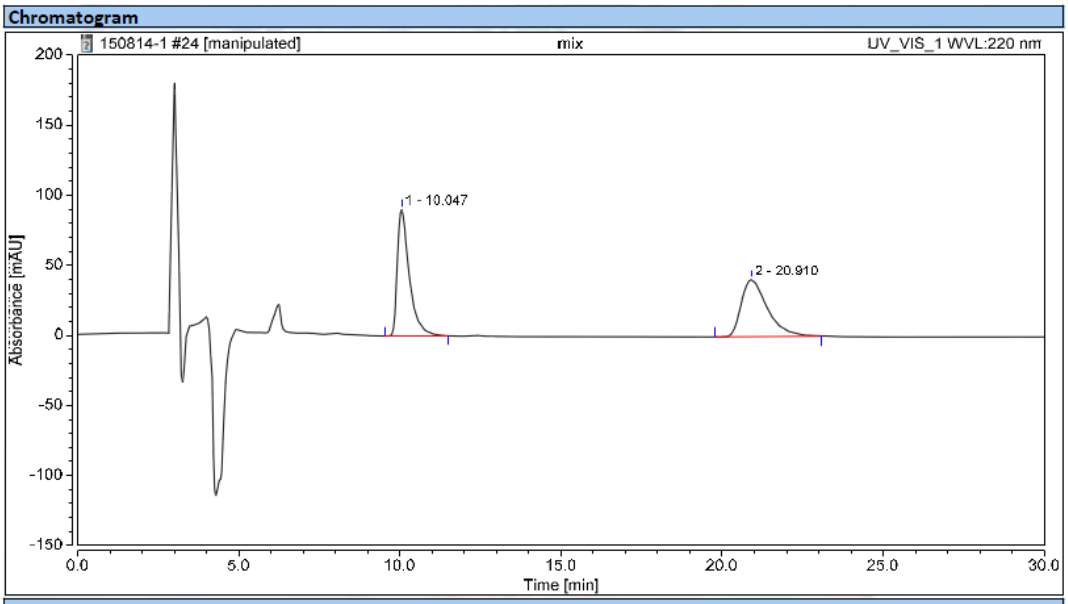


MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	Abund	Formula	Ion
219.1494	219.1492	0.96	215881	C13 H19 N2 O	(M+H)+



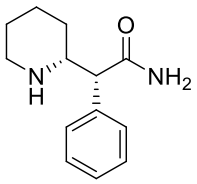
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Resolution	Plates
1	6.22	n.a.	10.8699	0.9576	2.09	24.45	32499
2	10.90	n.a.	296.5871	44.8663	97.76	9.78	31325
3	12.84	n.a.	0.7052	0.0699	0.15	n.a.	117437
Total:			308.162	45.894	100.00	34.236	

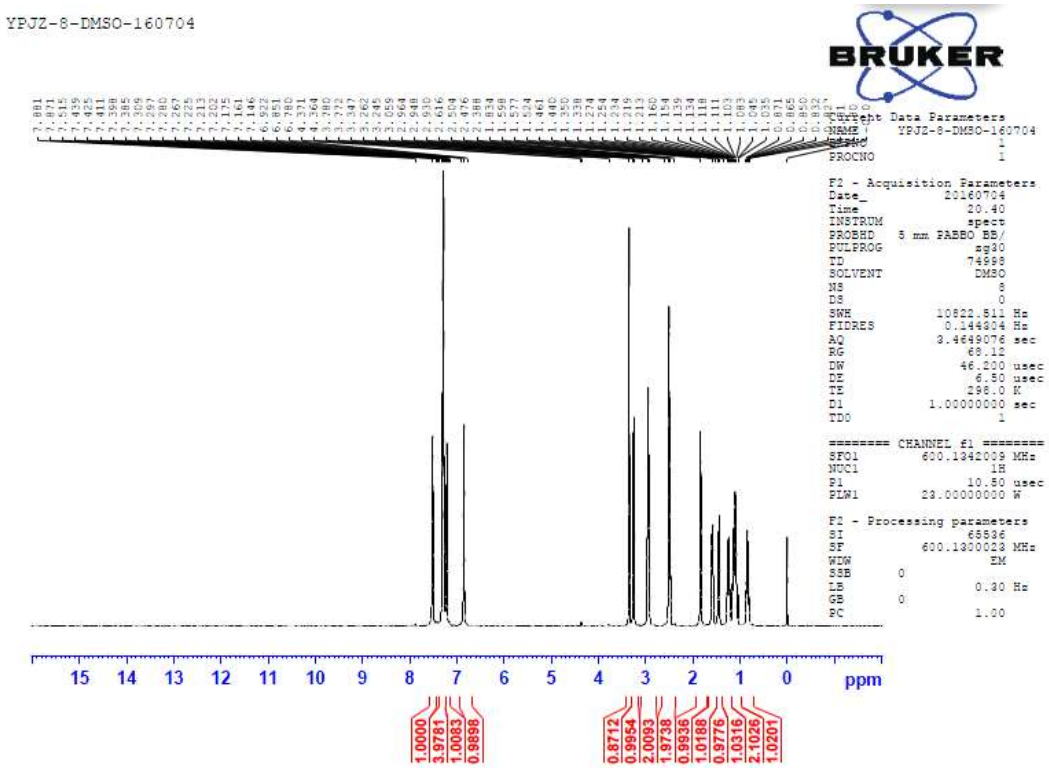


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Resolution (EP)	Plates (EP)
1		10.047	38.785	90.408	50.50	10.55	4023
2		20.910	38.016	40.669	49.50	n.a.	3415
Total:			**76.801**	**131.077**	**100.00**	**10.55**	

NMR, HRMS and HPLC spectra of (R,R)-2-piperidyl-2-yl-phenylacetyl amide (8)




YPJZ-8-DMSO-160704
BRUKER
Current Data Parameters
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PROCNO 1
F2 - Acquisition Parameters
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Time 20.40
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PULPROG zg30
TD 74998
SOLVENT DMSO
NS 8
DS 0
SWH 10822.511 Hz
FIDRES 0.144304 Hz
AQ 3.4649076 sec
RG 68.12
DW 46.200 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 600.1342009 MHz
NUC1 1H
P1 10.50 usec
PLW1 23.00000000 W
F2 - Processing parameters
SI 65536
SF 600.1300023 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.0000 3.9781 1.0083 0.9898
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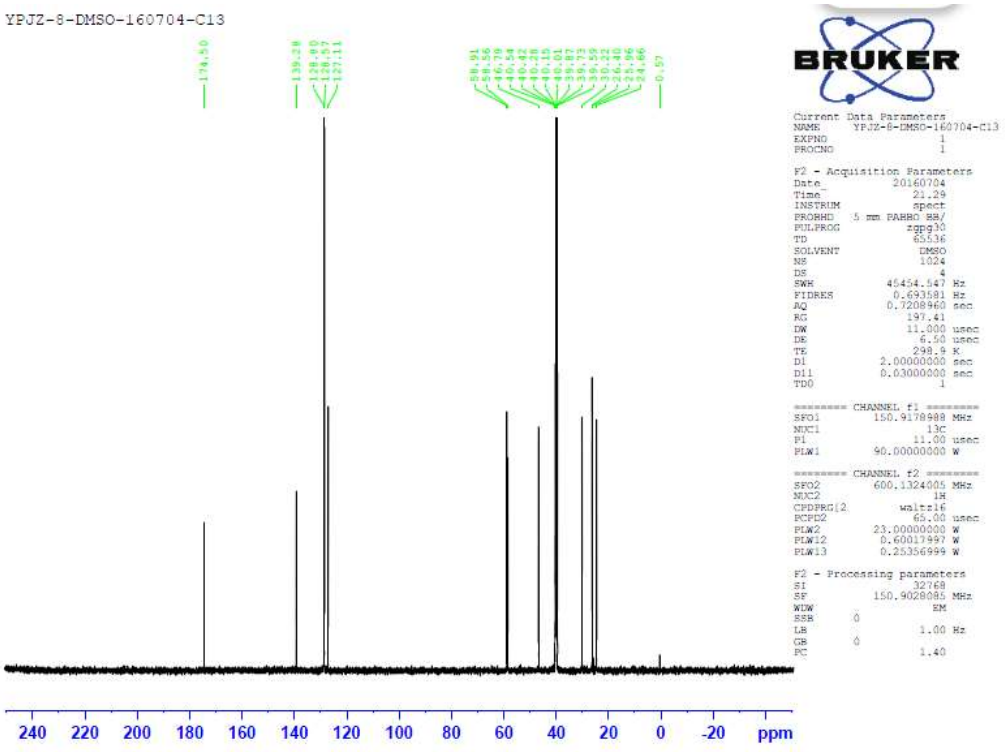
YPJZ-8-DMSO-160704-C13
BRUKER
Current Data Parameters
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EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160704
Time 21.29
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PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1024
DS 4
SWH 45454.547 Hz
FIDRES 0.693581 Hz
AQ 0.7208960 sec
RG 197.41
DW 11.000 usec
DE 6.50 usec
TE 298.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
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SFO1 150.9178988 MHz
NUC1 13C
P1 11.00 usec
PLW1 90.00000000 W
======== CHANNEL f2 ========
SFO2 600.1324005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 65.00 usec
PLW2 23.00000000 W
PLW12 0.60017997 W
PLW13 0.25356999 W
F2 - Processing parameters
SI 32768
SF 150.9028085 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
174.50
139.28
128.80
128.57
127.11
68.91
46.56
46.79
40.54
40.42
40.28
40.15
40.01
39.87
39.73
39.59
30.22
26.40
25.96
24.66
0.57
240 220 200 180 160 140 120 100 80 60 40 20 0 -20 ppm

Qualitative Compound Report

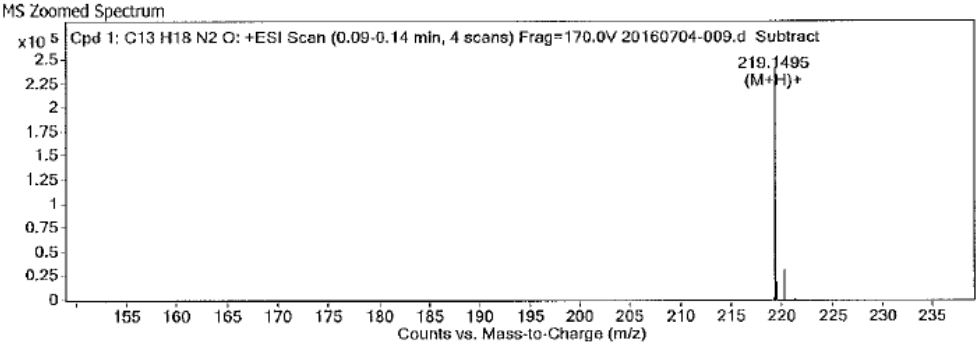
Data File	20160704-009.d	**Sample Name**	YPJZ-8
Sample Type	Sample	**Position**	Vial 68
Instrument Name	Instrument 1	**User Name**	
Acq Method		**IRM Calibration Status**	Success
DA Method	MS.m	**Comment**	N20160704015

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C13 H18 N2 O	0.13	218.1423	243151	C13 H18 N2 O	218.1419	1.56

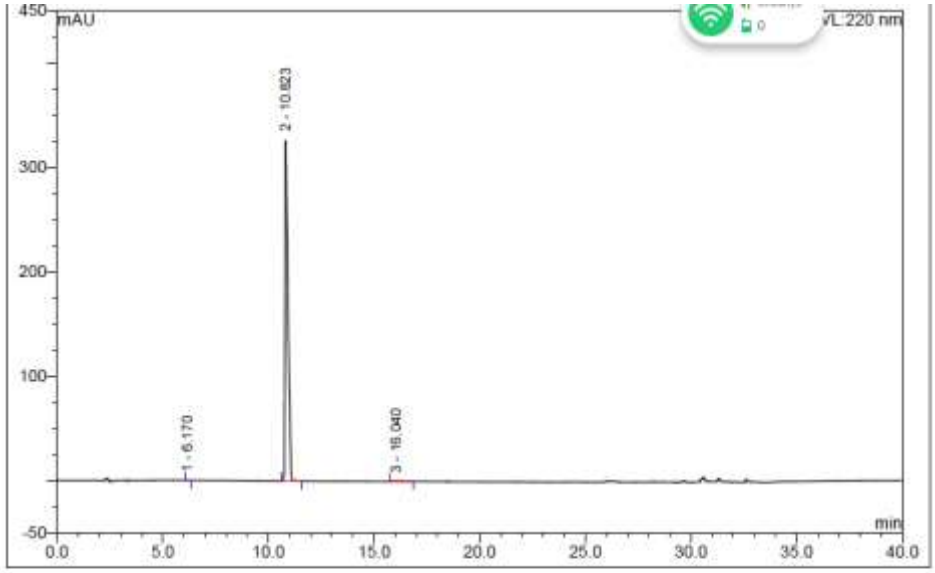
Compound Label	RT	Algorithm	Mass
Cpd 1: C13 H18 N2 O	0.13	Find By Formula	218.1423

MS Zoomed Spectrum

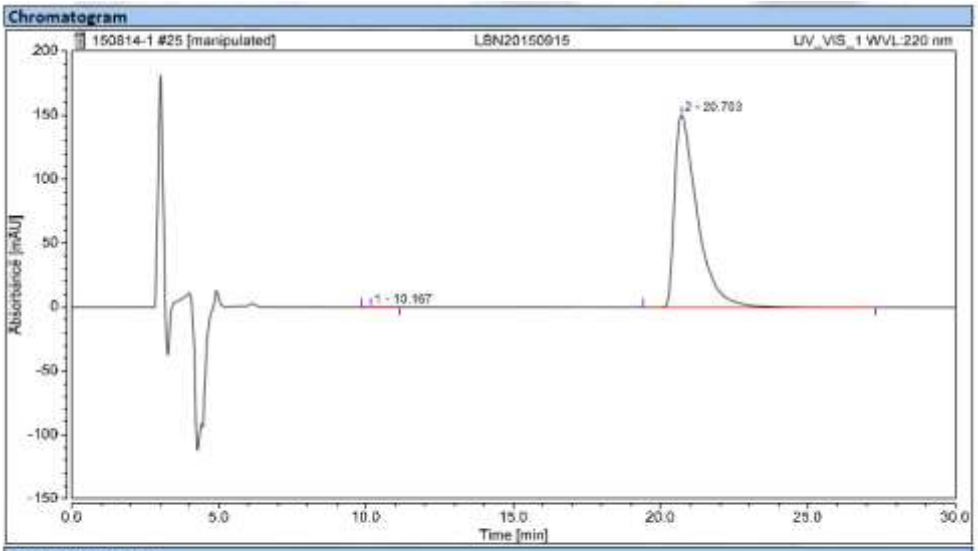


MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	Abund	Formula	Ion
219.1495	219.1492	1.56	243151	C13 H19 N2 O	(M+H)+



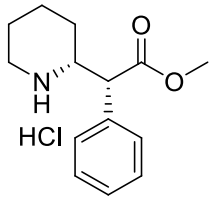
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Resolution	Plates
1	6.17	n.a.	0.2026	0.0192	0.04	23.23	28405
2	10.82	n.a.	326.4462	50.9630	99.30	9.15	28780
3	16.04	n.a.	0.6409	0.3419	0.67	n.a.	5224
Total:			327.290	51.324	100.00	32.387	

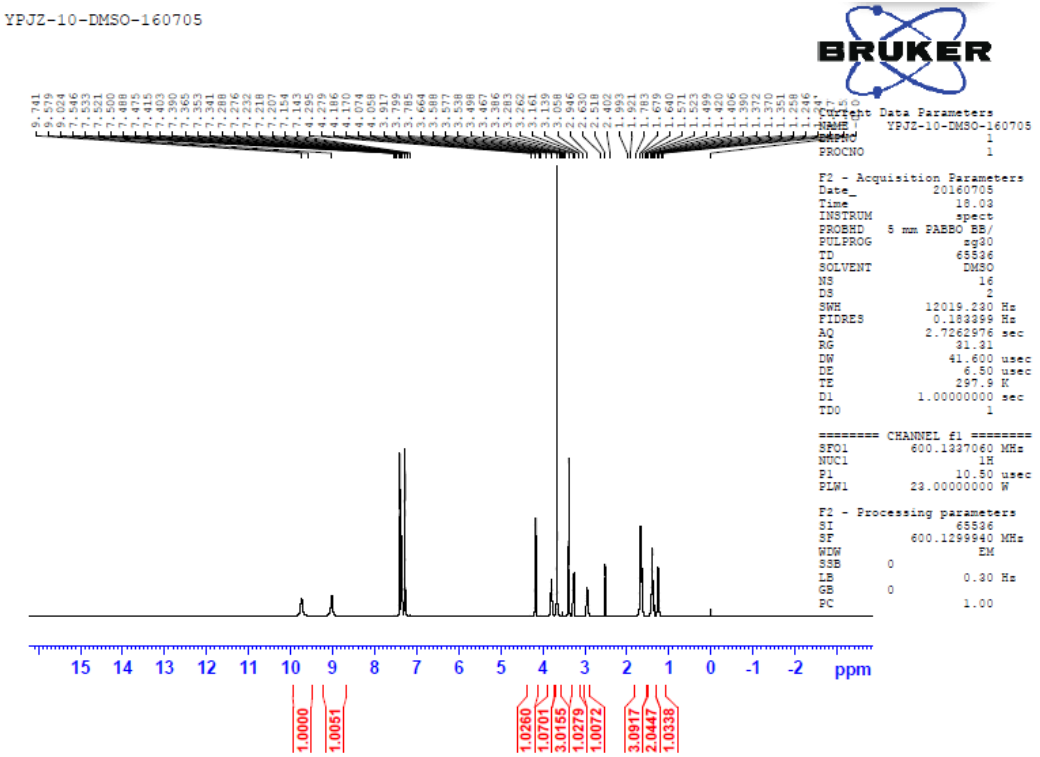


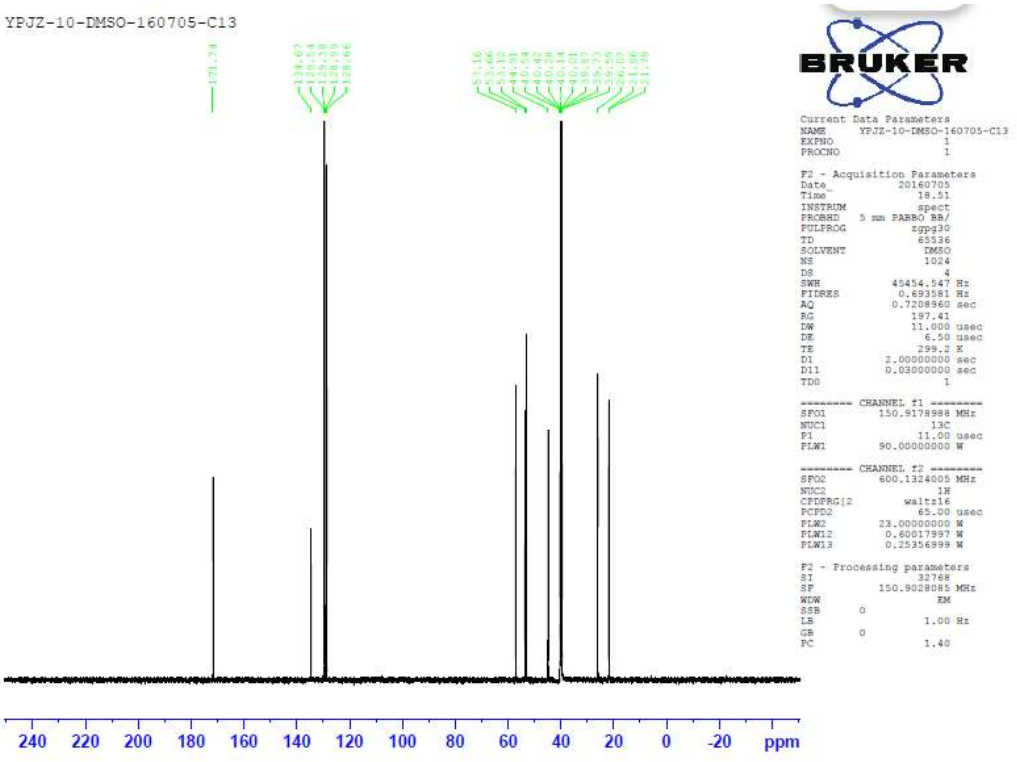
Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Resolution (EP)	Plates (EP)
1		10.167	0.073	0.154	0.05	10.53	3483
2		20.703	133.680	150.529	99.95	n.a.	3954
Total:			133.753	150.683	100.00	10.53	

NMR, HRMS and HPLC spectra of (R,R)-O-methyl-2-piperidyl-2-yl-phenylacetate hydrochloride (10)







Qualitative Compound Report

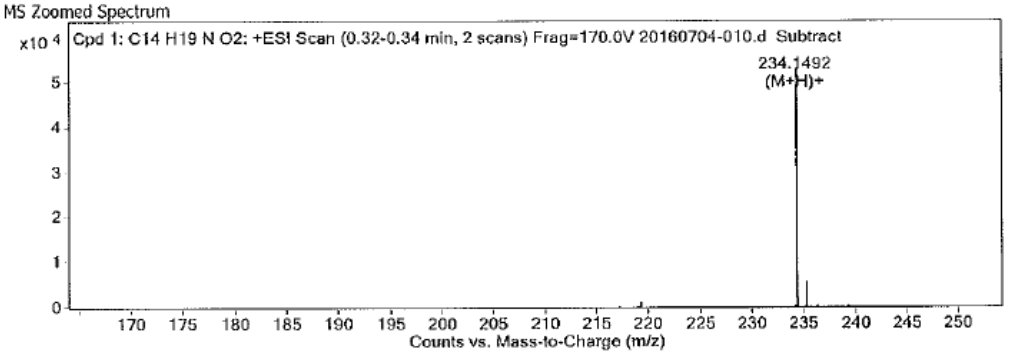
Data File	20160704-010.d	**Sample Name**	YPJZ-10
Sample Type	Sample	**Position**	Vial 69
Instrument Name	Instrument 1	**User Name**	
Acq Method		**IRM Calibration Status**	Success
DA Method	MS.m	**Comment**	N20160704016

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C14 H19 N O2	0.32	233.1419	53275	C14 H19 N O2	233.1416	1.33

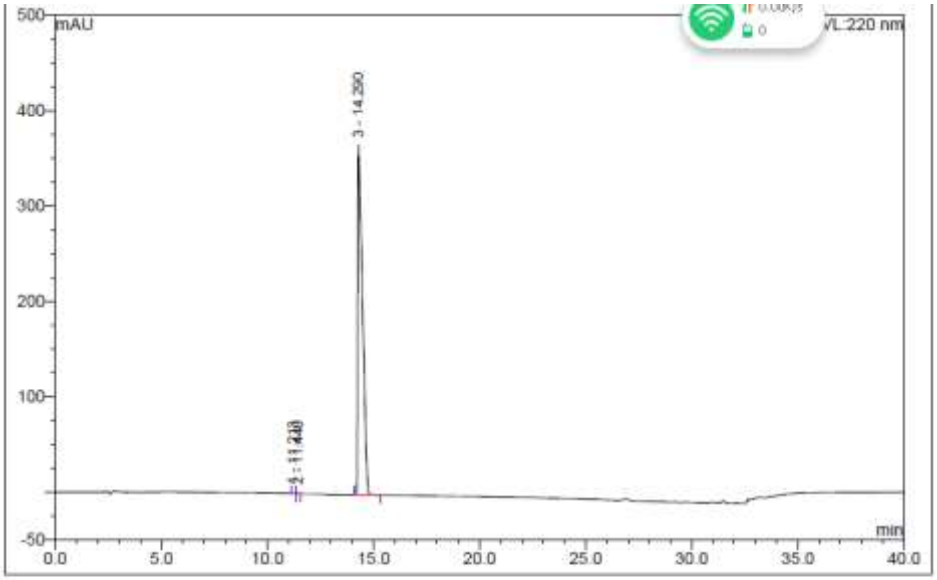
Compound Label	RT	Algorithm	Mass
Cpd 1: C14 H19 N O2	0.32	Find By Formula	233.1419

MS Zoomed Spectrum



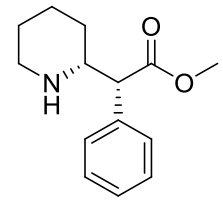
MS Spectrum Peak List

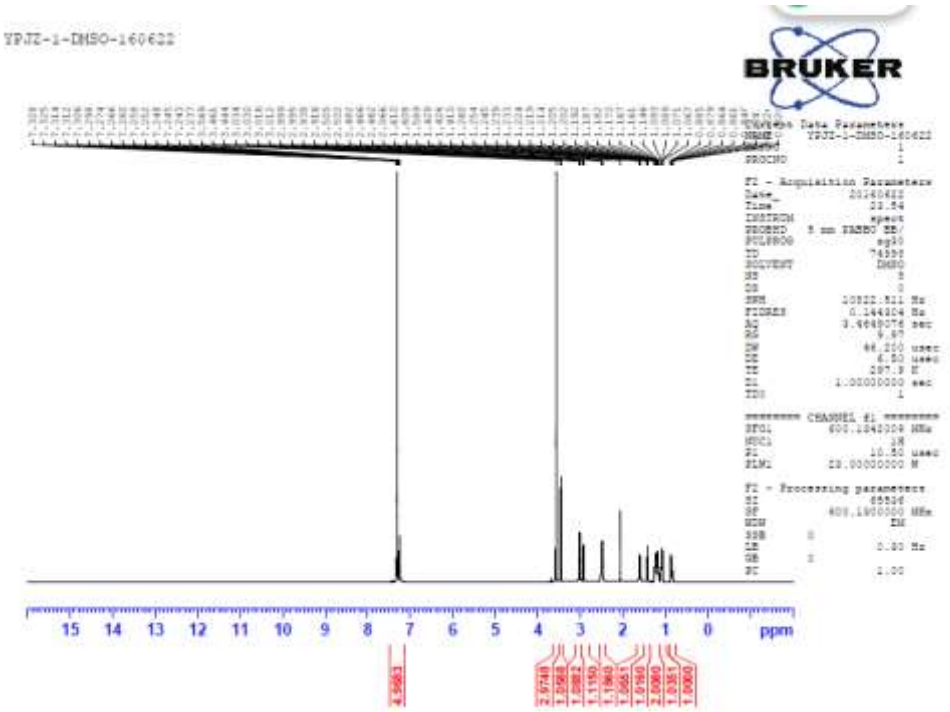
m/z	*Calc m/z*	Diff(ppm)	Abund	Formula	Ion
234.1492	234.1489	1.33	53275	C14 H20 N O2	(M+H)+

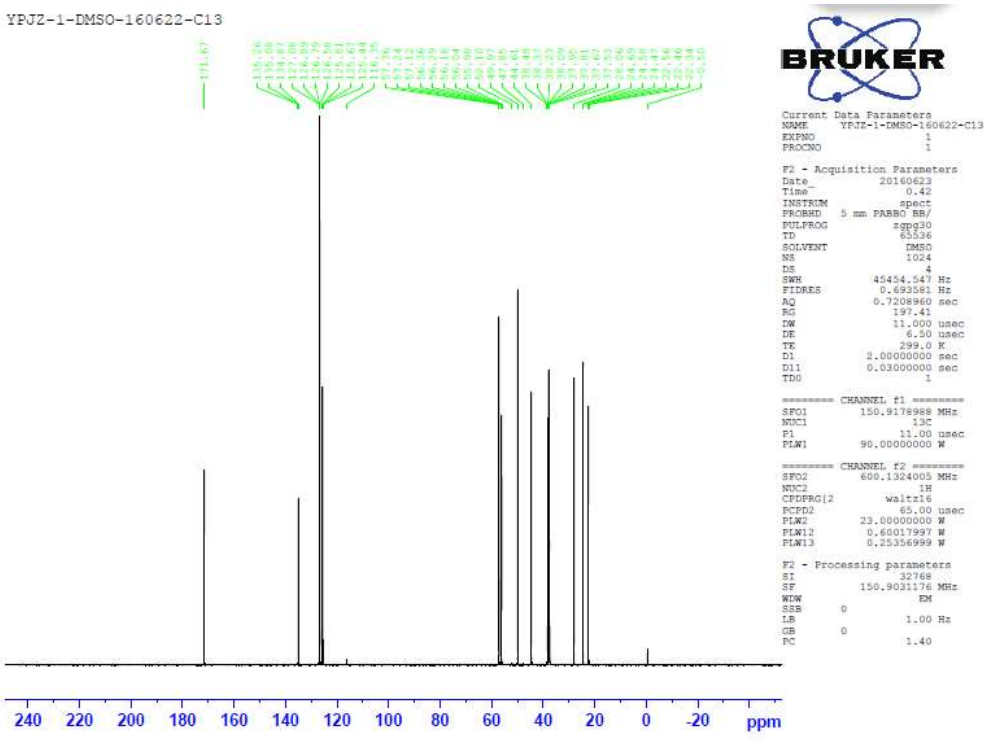


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Resolution	Plates
1	11.21	n.a.	0.9250	0.0774	0.08	1.79	122204
2	11.44	n.a.	1.1640	0.0919	0.10	10.30	133604
3	14.29	n.a.	366.3946	94.3027	99.82	n.a.	17697
Total:			368.484	94.472	100.00	12.093	

NMR, HRMS and HPLC spectra of dexmethylphenidate free base (1)







Qualitative Compound Report

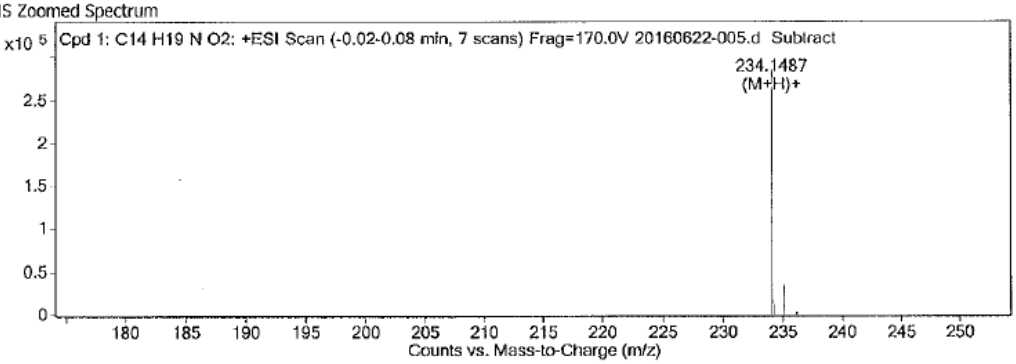
Data File	20160622-005.d	**Sample Name**	YPJZ-1
Sample Type	Sample	**Position**	Vial 7
Instrument Name	Instrument 1	**User Name**	
Acq Method		**IRM Calibration Status**	Success
DA Method	MS.m	**Comment**	N20160622019

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C14 H19 N O2	0.03	233.1414	286354	C14 H19 N O2	233.1416	-0.78

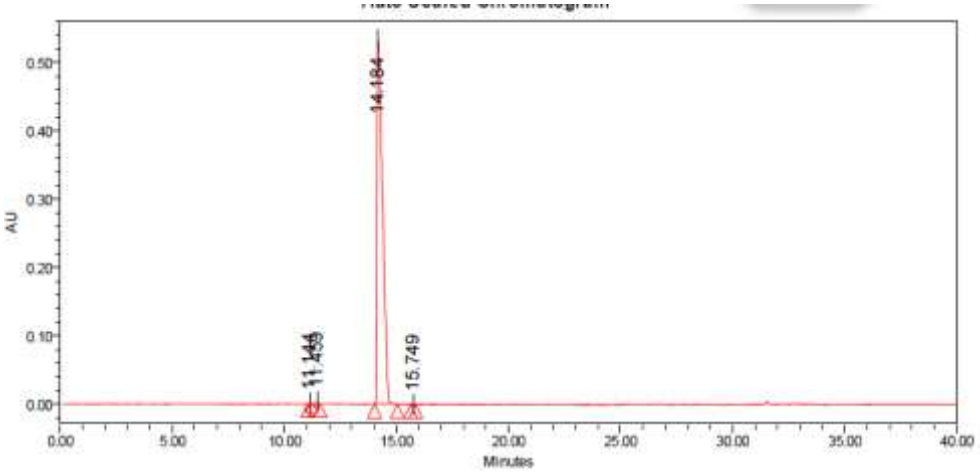
Compound Label	RT	Algorithm	Mass
Cpd 1: C14 H19 N O2	0.03	Find By Formula	233.1414

MS Zoomed Spectrum



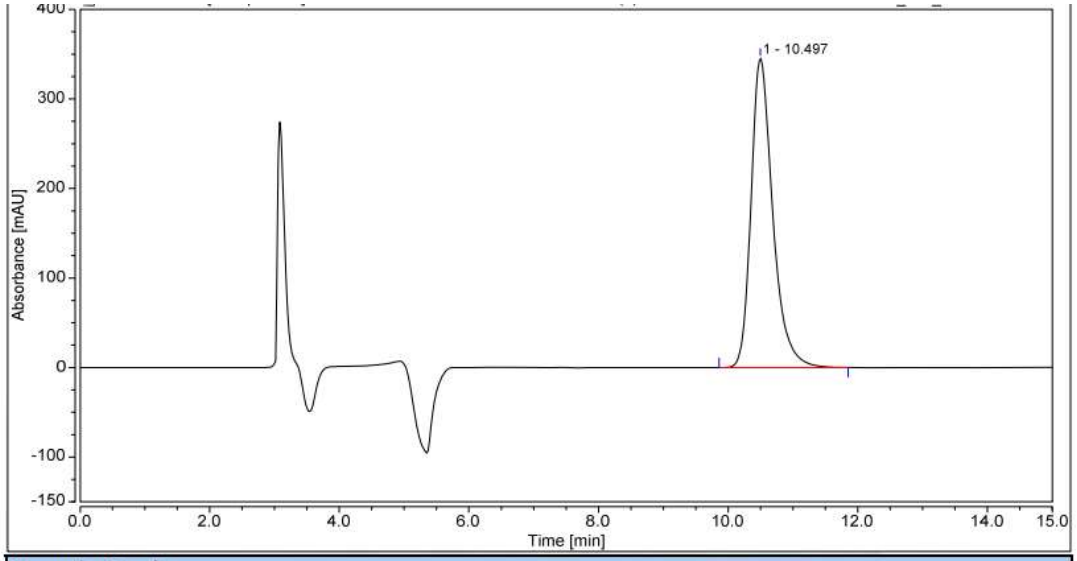
MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	Abund	Formula	Ion
234.1487	234.1489	-0.78	286354	C14 H20 N O2	(M+H)+



Peak Results

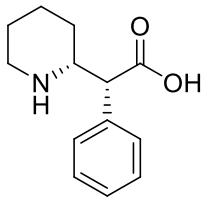
	Name	RT	Area	% Area	Height
1		11.144	4734	0.05	767
2		11.459	20527	0.23	3656
3		14.184	9066470	99.69	533746
4		15.749	3084	0.03	377

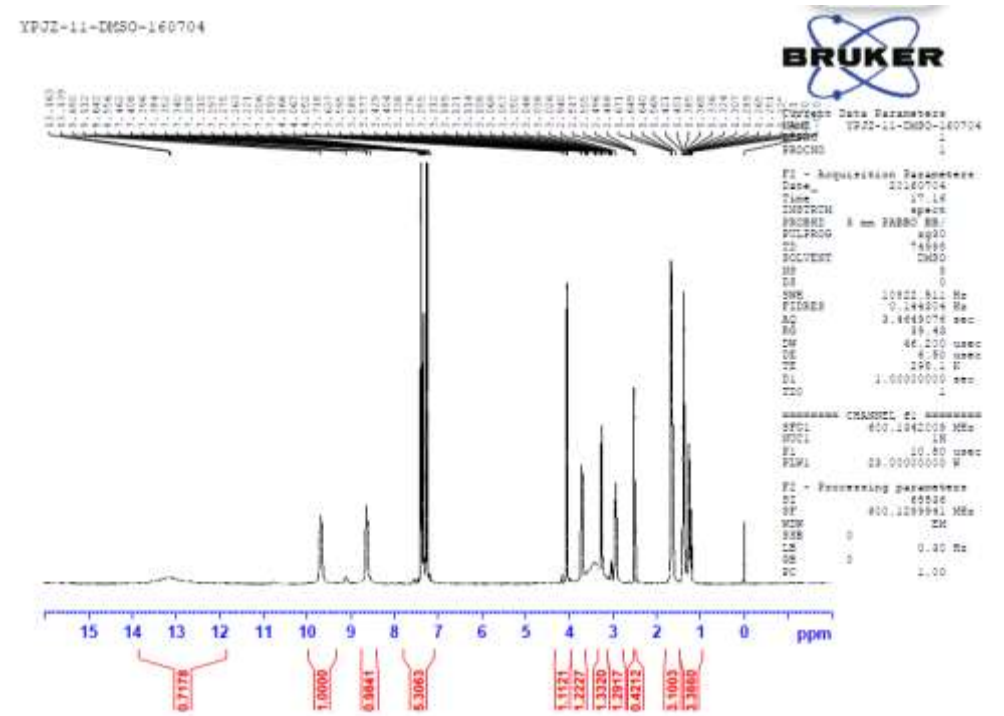


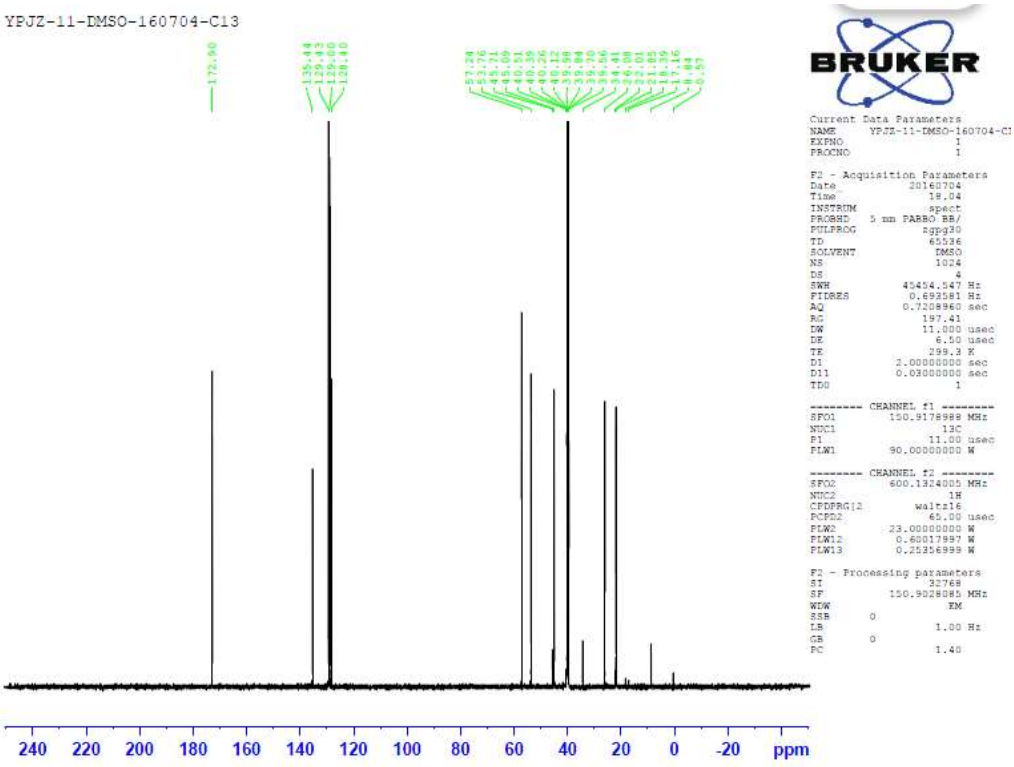
Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Resolution (EP)	Plates (EP)
1		10.497	134.069	345.470	100.00	n.a.	5204

NMR, HRMS and HPLC spectra of (*R*,*R*)-2-piperdyl-2-yl-phenylacetatic acid (11)




YPJZ-11-DMSO-160704
BRUKER
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.7178
1.0000
0.9841
5.3063
1.1121
1.2227
1.3320
1.2917
0.4212
3.1003
3.3880


YPJZ-11-DMSO-160704-C13
BRUKER
240 220 200 180 160 140 120 100 80 60 40 20 0 -20 ppm

Qualitative Compound Report

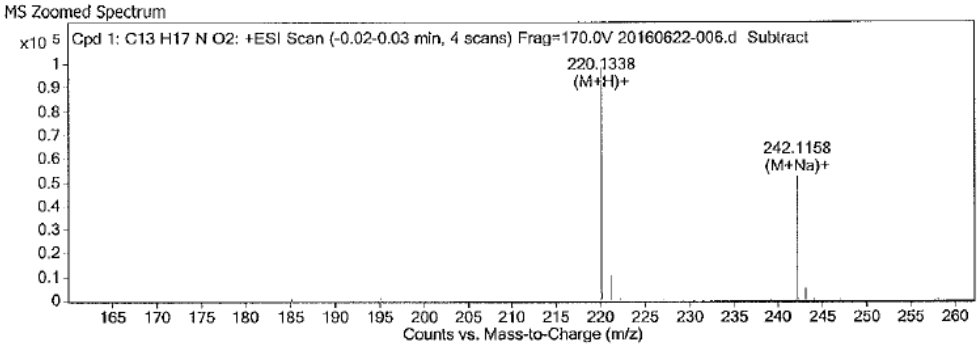
Data File	20160622-006.d	**Sample Name**	YPJZ-11
Sample Type	Sample	**Position**	Vial 8
Instrument Name	Instrument 1	**User Name**	
Acq Method		**IRM Calibration Status**	Success
DA Method	MS.m	**Comment**	N20160622020

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C13 H17 N O2	0.03	219.1265	98729	C13 H17 N O2	219.1259	2.76

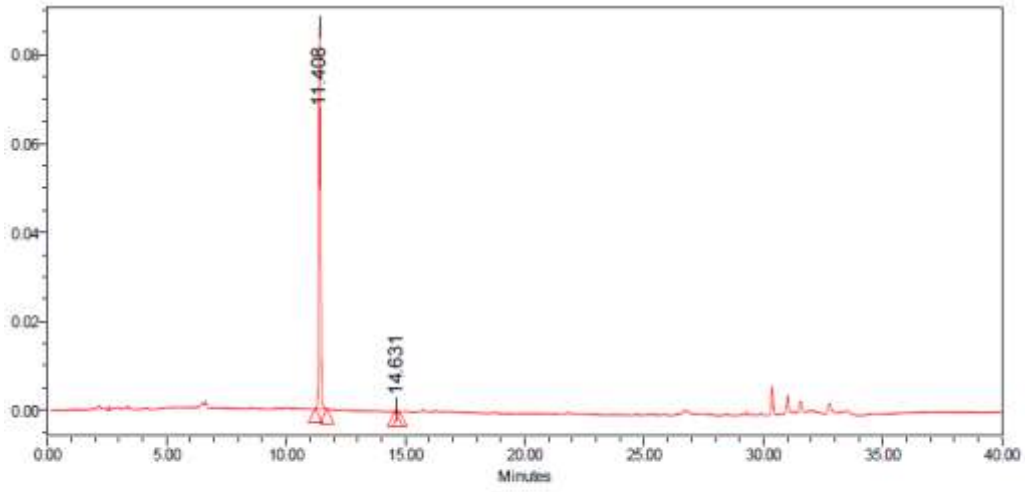
Compound Label	RT	Algorithm	Mass
Cpd 1: C13 H17 N O2	0.03	Find By Formula	219.1265

MS Zoomed Spectrum



MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	z	Abund	Formula	Ion
220.1338	220.1332	2.72		98729	C13 H18 N O2	(M+H)+



Peak Results

	Name	RT	Area	% Area	Height
1		11.408	429622	99.25	85885
2		14.631	3256	0.75	621