Supporting Information

An Efficient Method for the Preparation of N-Formamides using Propylphosphonic Anhydride (T3P®)

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1. General

Dry solvents were purchased from chemical suppliers and used without further purification. Analytical thin-layer chromatography (TLC) was performed on commercially available Merck TLC Silica gel 60 F254. Silica gel column chromatography was performed on silica gel 60 (spherical 100-200 µm). IR spectra were recorded on Perkin-Elmer FT/IR-4000 using KBr. $^1$H NMR spectra were recorded on Varian-400 (400 MHz) spectrometer. Chemical shifts of $^1$H NMR spectra were reported relative to tetramethylsilane. $^{13}$C NMR spectra were recorded on Varian-400 (100 MHz) spectrometer. Chemical shifts of $^{13}$C NMR spectra were reported to relative to CDCl₃ (77.16) and DMSO-d₆ (39.5). Splitting patterns were reported as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Experimental Procedure for the Preparation of N-phenyl formamide (2a): To a solution of compound 1a (200 mg, 2.15 mmol) in dichloromethane (5 ml) and HCO$_2$H (118 mg, 2.58 mmol) was added at 0°C then added Et$_3$N (651 mg, 6.45 mmol) and T3P (1.36 g, 4.3 mmol) then reaction mixture was stirred at RT for 10h. The progress of the reaction was monitored by TLC (30% EtOAc/petroleum ether). After completion of the reaction, water (50 ml) was added to the reaction mixture and extracted with di ethyl ether thrice. Combined the organic layers, washed with water, brine and dried over Na$_2$SO$_4$ concentrated u/vacc gave the pure compound 2a (247 mg, 95%) as brown semi solid. IR (KBr, cm$^{-1}$): 3271, 2921, 1683, 1600, 1543, 1440, 1270, 754; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ = 9.7 (bs, 1H); 8.3 (bs, 1H); 7.5 (bs, 2H); 7.2 (t, 2H), 7.0 (t, 1H); MS (EI): m/z 122 (M+1,100).

N-(2-chlorophenyl)formamide (2b): Yield (227 mg, 93%) as White solid, m.p. 80-82 °C. IR (KBr, cm$^{-1}$): 3252, 2901, 2366, 1702, 1665, 1541, 1396, 1299, 1036, 738; $^1$H NMR (400 MHz, DMSO): $\delta$ = 9.43 (bs, 1H); 8.38 (s, 1H); 7.90 (bs, 1H), 7.46-7.44 (d, J=6 Hz, 1H); 7.31-7.28 (t,J=12 Hz, 1H); 7.16-7.13 (t, J=12 Hz, 1H). MS (EI): m/z 156 (M+1,100).

N-(2-methoxyphenyl)formamide (2c): Yield (220 mg, 90%) as pale brown solid. m.p. 83-85 °C, IR (KBr, cm$^{-1}$): 3253, 3221, 2921, 2333, 1662, 1531, 1451, 1384, 1245, 1144, 1028, 738; $^1$H NMR (400 MHz, DMSO): $\delta$ = 9.12 (bs, 1H); 8.36 (s, 1H); 7.90 (bs, 1H), 7.07-7.02 (m, J=6 Hz, 2H); 7.40-6.87 (t, J=11.6 Hz, 1H); 6.90-6.87 (t, J=11.6, 1H); 3.78 (s, 3H). MS (EI): m/z 152 (M+1,100).
N-(3-methoxy-4-methylphenyl)formamide (2d): Yield (224 mg, 93%) as tan colored solid, m.p. 100-102°C; IR (KBr, cm⁻¹): 3453, 2921, 2387, 1725, 1646, 1383, 1294, 1229, 1123, 1031, 774; ¹H NMR (400 MHz, DMSO): δ = 9.66 (bs, 1H); 8.33 (bs, 1H); 7.02 (m, 3H); 3.75 (s, 3H); 2.09 (s, 3H); MS (EI): m/z 166 (M+1,100).

N-(4-methylpyridin-2-yl)formamide (2e): Yield (224 mg, 89%) as brown solid, m.p. 70-72°C; IR (KBr, cm⁻¹): 3445, 2922, 1682, 1617, 1569, 1429, 1383, 1346, 1249, 799; ¹H NMR (400 MHz, DMSO): δ = 10.06 (s, 1H); 8.83 (bs, 1H); 8.10 (s, 1H), 7.25 (bs, 1H); 6.27 (s, 1H), 2.28 (s, 3H); MS (EI): m/z 137 (M+1,100).

N-(isothiazol-4-yl)formamide (2f): Yield (217 mg, 85%) as brown liquid, m.p. 57-59°C; IR (KBr, cm⁻¹), 3226, 3050, 2888, 2228, 1854, 1682, 1547, 1400, 1333, 1214, 1109, 786; ¹H NMR (400 MHz, DMSO): δ = 10.80 (s, 1H); 8.91 (s, 1H), 8.59 (s, 1H), 8.29 (s, 1H), MS (EI): m/z 129 (M+1,100).

N-(2,3-difluorophenyl)formamide (2g): Yield (214 mg, 88%) as white solid, m.p. 92-94°C; IR (KBr, cm⁻¹), 3231, 3181, 3066, 1679, 1619, 1533, 1271, 1201, 1003, 774; ¹H NMR (400 MHz, DMSO): δ = 8.34 (s, 1H); 8.92-8.96 (m, 1H); 6.99-7.16 (m, 3H); MS (EI): m/z 158 (M+1,100).

N-(4-methoxy-2-methylphenyl)formamide (2h): Yield (224 mg, 93%) as Black solid, m.p. 90-92°C; IR (KBr, cm⁻¹): 3472, 3243, 2844, 1657, 1550, 1391, 1288, 1104, 1045, 873, 762; ¹H NMR (400 MHz, DMSO): δ = 9.06 (bs, 1H); 8.21 (s, 1H); 7.41 (bs, 1H), 6.77 (s, 1H); 6.72-6.70 (t, J=6.8, 1H); 3.72 (s, 3H), 2.18 (s, 3H); MS (EI): m/z 166 (M+1,100).
N-(3-fluorophenyl)formamide (2i): Yield (212 mg, 85%) as Pale brown solid, m.p. 71-73°C; IR (KBr, cm⁻¹): 3418, 3221, 2921, 2577, 2066, 1684, 1608, 1488, 1395, 1284, 1139, 1041, 777; ¹H NMR (400 MHz, DMSO): δ = 9.96 (bs, 1H); 8.34 (bs, 1H); 7.48-7.22 (m, 3H); 6.85-6.82 (m, 1H); MS (EI): m/z 140 (M+1,100)

N-(3-(trifluoromethoxy)phenyl)formamide (2j): Yield (203 mg, 88%) as Pale brown solid, m.p. 72-74°C; IR (KBr, cm⁻¹): 3298, 2893, 2478, 2029, 1615, 1554, 1270, 980, 879, 795; ¹H NMR (400 MHz, DMSO): δ = 10.10 (bs, 1H); 8.32 (bs, 1H); 7.39-7.65 (m, 3H); 6.99-7.01 (m, 1H); MS (EI): m/z 204 (M-1,100)

N-(3-(difluoromethoxy)phenyl)formamide (2k): Yield (218 mg, 93%) as Pale brown solid, m.p. 58-60°C; IR (KBr, cm⁻¹): 3266, 2894, 1703, 1673, 1612, 1443, 1383, 1292, 1212, 1035; ¹H NMR (400 MHz, DMSO): δ = 9.94 (bs, 1H); 8.34 (bs, 1H); 7.31-7.41 (m, 3H); 6.90-7.20 (m, 1H); 6.85 (d, J=5.2 Hz, 1H); MS (EI): m/z 188 (M-1,100)

N-(2,4,6-trifluorophenyl)formamide (2l): Yield (211 mg, 89%) as Off white solid, m.p. 112-114°C; IR (KBr, cm⁻¹): 3251, 3060, 2910, 1679, 1442, 1243, 1121, 1042, 873, 694; ¹H NMR (400 MHz, DMSO): δ = 9.46 (bs, 1H); 8.27 (s, 1H); 7.13 (d, J=6.8 Hz, 2H); MS (EI): m/z 176 (M+1,100)
N-(2,5-dimethylphenyl)formamide (2m): Yield (209 mg, 85%) as Off white solid, m.p. 234-236°C, IR (KBr, cm−1): 3248, 2910, 1662, 1533, 1399, 1274, 1191, 1035, 814, 732; 1H NMR (400 MHz, DMSO-d6): δ =9.14(bs, 1H), 8.28(s, 1H), 7.06(d, J=6 Hz, 1H), 6.87(d, J=6 Hz 1H), 2.24(s, 3H), 2.16(s, 3H); MS (EI): m/z 150 (M+1,100).

N-(2-bromo-4,6-difluorophenyl)formamide (2n): Yield (212 mg, 93%) as ash colored solid, m.p. 136-138°C, IR (KBr, cm−1): 3262, 2895, 1703, 1538, 1398, 1209, 1131, 873, 753; 1H NMR (400 MHz, DMSO-d6): δ =9.87(bs, 1H), 8.33(s, 1H), 8.24(bs, 1H), 7.43(t, J=17.2 Hz, 1H), MS (EI): m/z 238 (M,100).

N-(2-iodophenyl)formamide (2o): Yield (201 mg, 89%) as Off White solid, m.p. 92-94°C, IR (KBr, cm−1): 3446, 3225, 1519, 1388, 1276, 1150, 1013, 880, 744; 1H NMR (400 MHz, DMSO-d6): δ =9.14(bs, 1H), 8.35(s, 1H), 7.87(d, J=6.4 Hz 1H), 7.65(bs, 1H), 7.43(t, J=17.2 Hz, 1H), MS (EI): m/z 248 (M+1, 100).

N-(2-(trifluoromethoxy)phenyl)formamide (2p): Yield (173 mg, 75%) as Light green solid, m.p. 58-60°C, IR (KBr, cm−1): 3279, 2917, 1698, 1676, 1607, 1529, 1452, 1252, 1177, 748; 1H NMR (400 MHz, DMSO): δ =9.66(bs, 1H), 8.37(s, 1H), 8.00(bs,1H), 7.32-7.35(m, 2H), 7.21(t, J=11.6 Hz, 1H), 6.94(t, J=5.6 Hz, 1H); MS (EI): m/z 206 (M+1, 100).
N-(pyridin-2-yl)formamide (2q): Yield (202 mg, 78%) as Brown solid, m.p.168-170 °C., IR (KBr, cm−1):3396, 2961, 1681, 1595, 1492, 1388, 1199, 1046, 765; 1H NMR (400 MHz, DMSO): δ =7.89 (d, J=3.2 Hz, 2H), 7.32(t, J=11.2 Hz 2H), 6.45 (t, J=10.4 Hz, 2H); MS (EI): m/z 123 (M+1, 100).

N-(4-(trifluoromethoxy)phenyl)formamide (2r): Yield (208 mg, 90%) as Brown liquid, m.p. 123-125 °C., IR (KBr, cm−1): 3279, 2917, 1676, 1607, 1529, 1452, 1252, 1177, 748; 1H NMR (400 MHz, DMSO): 9.66(bs, 1H), 8.33(bs, 1H), 7.63(bs, 2H), 7.22(d, J=7.6 Hz, 1H); MS (EI): m/z 204 (M-1,100).

N-(4-fluorophenyl)formamide (2s): Yield (230 mg, 92%) as Pale brown slid, m.p. 280-282 °C., IR (KBr, cm−1): 3200, 2924, 2716, 1881, 1740, 1650, 1519, 1328, 1158, 1094, 1038, 829, 597; 1H NMR (400 MHz, DMSO): 9.79 (bs, 1H), 8.27 (bs, 1H), 7.53(bs, 2H), 7.10 (d, J=6.8 Hz, 2H); MS (EI): m/z 140 (M+1,100).

N-(1H-pyrazol-3-yl)formamide (2t): Yield (295 mg, 74%) as brown colored solid, m.p. 181-183 °C.; IR (KBr, cm−1):3396, 2961, 2106, 1687, 1596, 1492, 1388, 1299, 1199, 1046, 765; 1H NMR (400 MHz, DMSO): 12.37 (bs, 1H), 10.5 (bs, 1H), 8.66 (bs, 1H), 7.62 (d, J=9.2 Hz, 1H)), 5.99 (bs, 1H); MS (EI): m/z 112 (M+1,100).

N-(naphthalen-1-yl)formamide (2u): Yield (227 mg, 95%) as light violet solid, m.p. 138-140 °C. ; IR (KBr, cm−1):3225, 2875, 1932, 1656, 1537, 1385, 1286, 1151, 846, 791, 558; 1H NMR (400 MHz, DMSO): δ = 10.01 (bs, 1H); 8.5 (s, 1H); 8.12 (d, J=6 Hz, 1H), 7.92 (t, J=5.6 Hz, 1H); 7.74 (d, J=6.4, 1H); 7.56-7.44 (m, 3H); MS (EI): m/z 172 (M+1,100)
N-(4-methoxyphenyl)formamide(2v): Yield (220 mg, 90%) as Black color solid, m.p. 89-91°C., IR (KBr, cm\(^{-1}\)): 3427, 2923, 2387, 1702, 1608, 1506, 1382, 1250, 1175, 1027, 830. \( ^1 \)H NMR (400 MHz, DMSO): \( \delta = 9.57 \) (bs, 1H); 8.20 (bs, 1H); 7.32 (d, J=10.8 Hz, 2H), 6.87 (d, J=6.8 Hz, 2H); 3.72 (s, 3H). MS (EI): \( m/z \) 152 (M+1,100).

References:

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[Graph of chromatogram with peaks labeled 1 and 2, along with corresponding retention times and areas]
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Instrument ID: ANL-MCL5-LCM

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LCMS REPORT

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MEDICINAL CHEMISTRY LABORATORY - ANALYTICAL RESEARCH
LCMS REPORT

Date of Analysis: 2/10/2017 8:10:08 AM  
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LCMS REPORT

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**Sample Name:** GVR-VK-007-MP-132  
**Instrument ID:** ANL-MCL5-LCMS-001

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- **Column Temperature:** 60°C

![Graph](image)

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*Analysed by:*

P.S. Page 1 of 2
GVR BIOSCIENCES PVT. LTD.
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LCMS REPORT

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Column: ACQUITY UPLC BEH C18 (50mmx2.1mm, 1.7um)
Mobile Phase: B1: 0.1 % FA IN WATER A1: 0.15%FA IN ACN
Gradient: Time (min) /%A1: 0/2, 0.4/2, 2.8/98, 3.4/98, 3.41/2, 3.5/2
Column Flow Rate: 0.6 ml/min
Column Temperature: 60°C

---

**CHART**

**Data File: 215.4 Ref=off (2017/FEB/PRO517024A9513D - 2017/FEB/PRO58LANK-06622017-06.3)**

- Peaks
- RT | Area | Area %
- 1 | 0.93 | 65.449 | 2.793
- 2 | 1.41 | 1.152 | 0.049
- 3 | 1.46 | 21.17.194 | 90.363
- 4 | 1.56 | 141.059 | 6.020
- 5 | 1.69 | 10.141 | 0.774

---

Analysed by:

Page 1 of 2
Date of Analysis: 2/7/2017 9:13:47 AM  Injection Vol: 2.000µL
Acq. Method: RMD-FA-3.5mms  Instrument ID: ANL-MCL5-LCMS-001
Sample Name: GVK-VK-007-NP-120

Column: ACQUITY UPLC BEH C18 (50mmx2.1mm, 1.7µm)
Mobile Phase: B1: 0.1% FA IN WATER A1: 0.1%PA IN ACN
Gradient: Time (min) /%A1: 0/2, 0.4/2, 2.8/98, 3.4/98, 3.41/2, 3.5/2
Column Flow Rate: 0.6 ml/min
Column Temperature: 60°C

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<th>Area %</th>
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Date of Analysis: 2/8/2017 7:18:07 PM
Injection Vol: 0.3000uL
Acq. Method: RMD-FA-3.5mm
Instrument ID: AHL-MC15-LCMS-001
Sample Name: GVK-VK-007-130

RMD-FA-3.5 MIN.M
Column: ACQUITY UPLC BEH C18 (50mmx2.1mm, 1.7um)
Mobile Phase: B: 0.1% FA IN WATER A: 0.1% FA IN ACN
Gradient: Time (min) /%A: 0/2, 0.4/2, 2.8/88, 3.4/98.3.41/2, 3.5/2
Column Flow Rate: 0.6 ml/min
Column Temperature: 60°C

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Analysed by:
Column: ACQUITY UPLC BEH C18 (50mmx2.1mm, 1.7m)
Mobile Phase: B1: 0.1% FA IN WATER A1: 0.1%FA IN ACN
Gradient: Time (min) %A1: 0/2, 0.4/2, 2.8/96, 3.4/98, 3.41/2, 3.5/2
Column Flow Rate: 0.6 ml/min
Column Temperature: 60°C

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Date of Analysis: 2/28/2017  
Injection Vol: 0.300uL 
Sample Name: GVR-MK-009-11 

Column: ACQUITY UPLC BEH C18 (50mmx2.1mm, 1.7um) 
Mobile Phase: B1: 0.1% FA IN WATER  
A1: 0.1% FA IN ACN 
Gradient: Time (min) /%A1: 0/2, 0.4/2, 2.8/98, 3.4/98, 3.41/2, 3.5/2 
Column Flow Rate: 0.6 ml/min 
Column Temperature: 60°C 

<table>
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Date of Analysis: 2/22/2017 2:28:35 AM  
Injection Vol: 0.300uL  
Acq. Method: RND-FA-3.5mms  
Instrument ID: ANL-MCL5-LCMS-001  
Sample Name: GVK-MR-009-7  

Column: ACQUITY UPLC BEH C18 (50mmx2.1mm, 1.7µm)  
Mobile Phase: B1: 0.1% FA IN WATER  
A1: 0.1%FA IN ACN  
Gradient: Time (min)  
B1: 0/2, 0.4/2, 2.0/98, 3.4/98, 3.4/2, 3.5/2  
Column Flow Rate: 0.6 ml/min  
Column Temperature: 60°C  

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<td>4</td>
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<td>0.059</td>
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49

GVR BIOSCIENCES PVT. LTD.  
MEDICINAL CHEMISTRY LABORATORY - ANALYTICAL RESEARCH  
HPLC REPORT  

Date of Analysis: 2/22/2017  
Injection Vol: 0.300uL  
Acq. Method: RND-FA-3.5mins  
Instrument ID: ANL-MC15-ICMS-001  
Sample Name: GVR-RK-009-14  

RND-FA-3.5 MIN.M  
Column: ACQUITY UPLC BEH C18 (50mmx2.1mm, 1.7um)  
Mobile Phase: B1: 0.1% FA IN WATER A1: 0.1%FA IN ACN  
Gradient: Time (min) /%A1: 0/2, 0.4/2, 2.8/98, 3.4/98, 3.41/2, 3.5/2  
Column Flow Rate: 0.6 mL/min  
Column Temperature: 60°C  

---

![Graph](image_url)  

<table>
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Analysed by:  

Page 1 of 2
52

GVK BIOSCIENCES PVT. LTD.
MEDICINAL CHEMISTRY LABORATORY - ANALYTICAL RESEARCH
LCMS REPORT

Vial position : Pl-D-04
Date of Analysis : 2/22/2017 1:04:42 AM  Injection Vol : 0.300uL
Acq. Method : HNE-PR-3.5mins Instrument ID : ANL-MCL5-LCMS-001
Sample Name : GVK-PK-009-6

HNE-FA-3.5 MIN.M
Column: ACQUITY UPLC BEH C18 (50mmx2.1mm, 1.7um)
Mobile Phase: B1: 0.1 % FA IN WATER A1: 0.1%FA IN ACN
Gradient: Time (min) /%A1:  0/2, 0.4/2, 2.8/98,3.4/98,3.41/2,3.5/2
Column Flow Rate: 0.6 mL/min
Column Temperature: 60°C

<table>
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<td>1290.939</td>
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MS Spectrum

[Graph showing a molecular structure with labels 17.9, 20.9, 27.9, 13.1, 17.9, 20.9, 27.9.]

Max: 342.64

2p
UV Chromatogram

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Operator: Thermo Scientific
Instrument Name: UA
Page 1 of 1
Thursday, February 23, 2017, 15:11:40
Vial position: Pl-B-04

Date of Analysis: 2/28/2017  6:12:17 PM  Injection Vol: 0.300uL
Acq. Method: EMD-FA-3.5ms  Instrument ID: AML-MCL5-LCMS-001
Sample Name: GVK-VK-007-MF-143

EMD-FA-3.5 MIN.M
Column: ACQUITY UPLC BEH C18 (50mmx2.1mm, 1.7um)
Mobile Phase: B1: 0.1% FA IN WATER A1: 0.1%FA IN ACN
Gradient: Time (min) /%A1: 0/2, 0.4/2, 2.8/36, 3.4/96, 3.41/2, 3.5/2
Column Flow Rate: 0.6 mL/min
Column Temperature: 60°C

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Vial position : P2-B-01

Date of Analysis : 2/28/2017 11:02:56 PM Injection Vol : 0.300uL

Sample Name : GVR-RX-009-12

RND-FA-3.5 MIN M

Column: ACQUITY UPLC BEH C18 (50mmx2.1mm, 1.7nm)
Mobile Phase: B1: 0.1 % FA IN WATER A1: 0.1%FA IN ACN
Gradient: Time (min) /%A1: 0/2, 0.4/2, 2.8/95, 3.4/95, 3.41/2, 3.5/2
Column Flow Rate: 0.6 mL/min
Column Temperature: 60°C

<table>
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<th>Area %</th>
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<td>0.46</td>
<td>6.429</td>
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**GVR BIOSCIENCES PVT. LTD.**
**MEDICINAL CHEMISTRY LABORATORY - ANALYTICAL RESEARCH**
**LCMS REPORT**

**Vial position:** B1-C-06
**Date of Analysis:** 6/29/2017 3:34:12 AM
**Injection Vol:** 0.300uL
**Acq. Method:** RND-FA-3.5mins
**Instrument ID:** ANL-MCL5-LCMS-001
**Sample Name:** GVR-VK-007-NF-112

**RND-FA-3.5 MIN.M**
**Column:** ACQUITY UPLC BEH C18 (50mmx2.1mm, 1.7um)
**Mobile Phase:** B: 0.1% FA IN WATER A: 0.1% FA IN ACN
**Gradient:** Time (min) /%A: 0/2, 0.4/2, 2.8/98, 3.4/98, 3.41/2, 3.5/2
**Column Flow Rate:** 0.6 ml/min
**Column Temperature:** 60°C

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**Graph with chromatogram and mass spectrum**

**Table:**

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Date of Analysis: 10/6/2017 7:25:59 PM  
Injection Vol: 0.500µL  
Vial position: P1-A-07  
Sample Name: GVK-PHD-VK-61  
Acq. Method: RND-FA-3.5mnms  
Instrument ID: ANL-MOL5-LCMS-001  
Column: ACQUITY UPLC BEH C18 (50mmx2.1mm, 1.7um)  
Mobile Phase: B1: 0.1% FA IN WATER, B2: 0.1%FA IN ACN  
Gradient: Time (min) /%A1: 0/2, 0.2/2, 2.3/98, 3.4/98, 3.41/2, 3.5/2  
Column Flow Rate: 0.6 ml/min  
Column Temperature: 50°C  
*DAD1 A, Sig=215.4 Ref=off (2017/OCT/PRO51719/M4164.D - 2017/OCT/PRO/BLANK-06/02/2017.08.D)  

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