

Supporting Information

Discovery and Synthesis of HIV Integrase Inhibitors: Dihydroxypyrimidine-4-carboxamides as Novel Potent and Selective Agents

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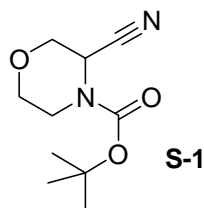
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Experimental details and data for nitriles and amidoximes.

Nitriles and amidoximes, used as starting materials for the synthesis of pyrimidines, were either commercially available or synthesized following literature procedures or as described hereafter.

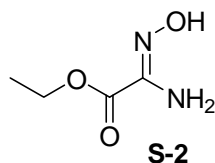
A general method for the synthesis of nitriles involves the conversion of the corresponding carboxylic acids into the primary amides followed by dehydration. This procedure is exemplified by the synthesis of **tert-butyl-3-cyanomorpholine-4-carboxylate (S-1)**, used in the synthesis of inhibitor **31**.



Step 1: to a stirred solution of 4-(*tert*-butoxycarbonyl)morpholine-3-carboxylic acid (1 eq.), pyridine (0.6 eq.) and di-*tert*-butyl dicarbonate (1.3 eq) in dioxane (0.2 M), NH_4HCO_3 (1.26 eq.) was added and the mixture was stirred at room temperature for 20 hours. Mixture was concentrated, taken up in EtOAc and washed with water and brine. Organics were dried over Na_2SO_4 and evaporated giving *tert*-butyl 3-(aminocarbonyl)morpholine 4-carboxylate as an oil which crystallized at room temperature (90% yield). ^1H NMR (DMSO- d_6 , 300 MHz) δ 7.35 (bs, 1 H), 7.06 (bs, 1 H), 4.15 (bs, 2 H), 3.76 (bs, 1 H), 3.57-3.51 (m, 2 H), 3.28 (m, 1 H), 3.18 (m, 1 H), 1.36 (s, 9 H); MS m/z 231 ($\text{M}+\text{H}$) $^+$. Step 2: the compound from above was taken in dichloromethane (0.2 M) and treated with 2.1 eq. of triethylamine. The solution was cooled to 0°C and trifluoroacetic anhydride (1.1 eq.) was added dropwise under nitrogen. After 3.5 hours stirring at room temperature, volatiles were removed in vacuo, residues was taken in EtOAc and washed with brine. The organic layer was dried over Na_2SO_4 , filtered and evaporated yielding title compound **S-1** as a brown solid (85% yield). ^1H NMR (DMSO- d_6 , 400 MHz) δ 5.04 (d, $J = 2.7$ Hz, 1 H), 3.96 (d, $J = 12.2$ Hz, 1 H), 3.86 (dd, $J = 11.5, 2.6$ Hz, 1 H), 3.69 (d, $J = 12.4$ Hz, 1 H), 3.56 (dd, $J = 12.2, 3.2$ Hz, 1 H), 3.40 (td, $J = 11.9, 2.89$ Hz, 1 H), 2.97 (m, 1 H), 1.43 (s, 9 H); MS m/z 213 ($\text{M}+\text{H}$) $^+$.

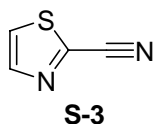
Methods followed for the preparation of starting materials follow.

Ethyl amino(hydroxymino)ethanoate (S-2), used in the synthesis of inhibitor **10**



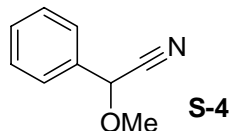
Ref.: Branco, P.S.; Prabhakar, S.; Lobo, A. M.; Williams, D. J. Reaction of hydroxylamines with ethyl cyanofornate. Preparation of aminonitrones and their synthetic applications. *Tetrahedron* **1992**, *48*, 6335-6360.

1,3-Thiazole-2-carbonitrile (S-3, used in the synthesis of inhibitor 15)



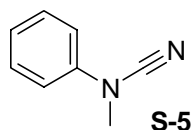
Ref.: Henry, D. W. Chemotherapeutic nitroheterocycles. Derivatives of 5-nitrothiazole-2-carboxaldehyde and 5-nitrothiazole-2-carboxylic acid. *J. Med. Chem.* **1969**, *12*, 303-306.

Methoxy-phenyl-acetonitrile (S-4, used in the synthesis of inhibitor 17).



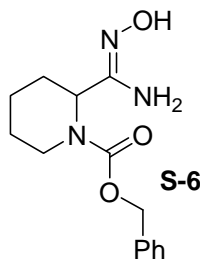
Step 1: benzaldehyde (5.0g, 47.11 mmol) was stirred with a suspension of the K-10/trimethylorthoformate reagent (15g) in hexane (30 ml) for 1 hour, then the suspension was filtered. The filtrate was washed with a saturated solution of NaHCO₃ twice, dried (Na₂SO₄), filtered and concentrated under vacuum to give (dimethoxymethyl)benzene, that was submitted to the next step without further purification, g 6.82 (95% yield). ¹H NMR (CDCl₃, 400 MHz) δ 7.47-7.31 (m, 5 H), 5.40 (s, 1 H), 3.34 (s, 6 H). Step 2: cyanotrimethylsilane (1.3 ml, 9.86 mmol) was added to the acetal from step 1 (1.5 g, 9.86 mmol) in dichloromethane (15 ml), followed by SnCl₂ (0.123 g, 0.65 mmol). The reaction was stirred at room temperature for 6 hours and then it was diluted with dichloromethane and a saturated solution of NaHCO₃. The aqueous phase was extracted with dichloromethane three times and the organic phase was dried (NaHCO₃), filtered and concentrated under vacuum to give methoxy-phenyl-acetonitrile, 1.45 g (quantitative yield). ¹H NMR (CDCl₃, 400 MHz) δ 7.51-7.40 (m, 5 H), 5.21 (s, 1 H), 3.54 (s, 3 H).

Methyl(phenyl)cyanamide (S-5, used in the synthesis of inhibitor 20).



Ref.: Bakunov, S. A.; Rukavishnikov, A. V.; Tkachev, A. V. Modification of the Thiemann rearrangement: one-pot synthesis of N,N-disubstituted cyanamides from amidoximes. *Synthesis*, **2000**, *8*, 1148-1159.

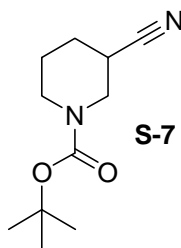
Benzyl 2-[amino(hydroxyimino)methyl]piperidine-1-carboxylate (S-6, used in the synthesis of inhibitors **24**, **27-29**).



Step 1: to a stirred solution (about 0.08 M) of piperidine-2-carboxylic acid (1 eq) and sodium carbonate (1.5 eq) in water cooled in an ice bath, benzylchloroformate (1.2 eq) was added dropwise with vigorous stirring. The mixture was stirred overnight at room temperature. The basic aqueous mixture was extracted two times with Et₂O. The separated alkaline layer was acidified with 1 N HCl to pH 1 and extracted with AcOEt. The extract was washed with brine, dried (Na₂SO₄), filtered and concentrated to 1-[(benzyloxy)carbonyl]piperidine-2-carboxylic acid, obtained as a white solid (100% yield). ¹H NMR (CDCl₃, 400 MHz) δ 7.38-7.33 (m, 5 H), 5.22-5.17 (m, 2 H), 5.02-4.92 (m, 1 H), 4.06 (d, *J* = 12.6 Hz, 1 H), 3.06 (dt, *J* = 32 Hz, 12.6 Hz, 1 H), 2.28 (t, *J* = 13.0 Hz, 1 H), 1.74-1.65 (m, 3 H), 1.47-1.30 (m, 2 H). Step 2: 1-[(benzyloxy)carbonyl]piperidine-2-carboxylic acid from previous step was charged in a flask and NH₃ was added (2.5 eq) as a 0.5 M solution in dioxane. To the stirred solution were added 1.3 eq of EDCI and 1.3 eq of HOBT, and the reaction mixture was stirred overnight at room temperature. After evaporation of dioxane, the residue was poured into AcOEt and washed with HCl 1 N, saturated NaHCO₃ and brine. The organic extract was dried (Na₂SO₄), filtered and concentrated to benzyl 2-(aminocarbonyl)piperidine-1-carboxylate, obtained as a white solid (87% yield). ¹H NMR (DMSO-d₆, 400 MHz) δ 7.36 (bs, 5 H), 7.05 (bs, 2 H), 5.06 (bs, 2 H), 4.57 (d, *J* = 4.2 Hz, 1 H), 3.89 (d, *J* = 13.1 Hz, 1 H), 3.15-2.93 (m, 1 H), 2.07 (m, 1 H), 1.33-1.28 (m, 3 H), 1.32-1.92 (m, 2 H). Step 3: to a stirred solution of benzyl 2-(aminocarbonyl)piperidine-1-carboxylate from above, and triethylamine (3 eq) in CH₂Cl₂, 1.5 eq of trifluoroacetic anhydride were added dropwise with an external cooling. Reaction mixture was stirred at room temperature for 1 h. The solution was partitioned between dichloromethane and HCl 1 N, the organic phase was washed with brine, dried (Na₂SO₄), filtered and concentrated to an oily residue containing the crude nitrile. Formation of the corresponding amidoxime was accomplished by refluxing

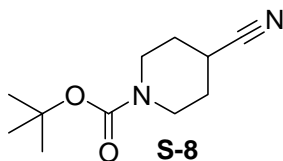
this residue in absolute ethanol in the presence of 3 eq of triethylamine and 1.5 eq of hydroxylamine hydrochloride. After 3 h the reaction mixture was allowed to cool to room temperature and concentrated, and the residue triturated with water and dried to obtain the benzyl 2-[(Z)-amino(hydroxyimino)methyl]piperidine-1-carboxylate (about 54% yield). ¹H NMR (DMSO-d₆, 400 MHz) δ 9.17 (s, 1 H), 7.37-7.28 (bs, 5 H), 5.26 (bs, 2 H), 5.10-5.00 (m, 2 H), 4.72 (bs, 1 H), 3.87 (d, *J* = 16.0 Hz, 1 H), 3.10 – 2.98 (m, 1 H), 2.49-2.48 (m, 1 H), 1.58 – 1.28 (m, 5 H).

***tert*-Butyl-3-cyanopiperidine-1-carboxylate (S-7, used in the synthesis of inhibitor 25).**



As for the procedure used in the preparation of **S-1**, replacing in step 1 4-(*tert*-butoxycarbonyl)morpholine-3-carboxylic acid with 1-(*tert*-butoxycarbonyl)piperidine-3-carboxylic acid. Spectral data matches literature data.¹

***tert*-Butyl-4-cyanopiperidine-1-carboxylate (S-8, used in the synthesis of inhibitor 26).**

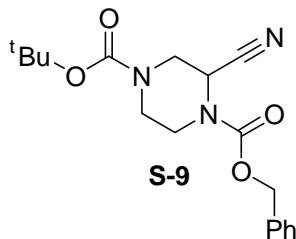


As for the procedure used in the preparation of **S-1**, replacing in step 1 4-(*tert*-butoxycarbonyl)morpholine-3-carboxylic acid with 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid. Spectral data matches literature data.²

1-Benzyl 4-*tert*-butyl 2-cyanopiperazine-1,4-dicarboxylate (S-9, used in the synthesis of inhibitor 30).

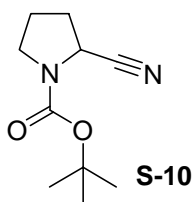
¹ Nakajima, N.; Saito, M.; Ubukata, M. Activated dimethyl sulfoxide dehydration of amide and its application to one pot preparation of benzyl-type perfluoroimidates.

² Ref.: Orjales, A.; Mosquera, R.; Toledo, A.; Pumar, C. M.; García, N.; Cortizo, L.; Labeaga, L.; Inneráriti, A. Syntheses and binding studies of new [(aryl)(aryloxy)methyl]piperidine derivatives and related compounds as potential antidepressant drugs with high affinity for serotonin(5-HT) and norepinefrine (NE) transporters. *J. Med. Chem.* **2003**, *46*, 5512-5532.



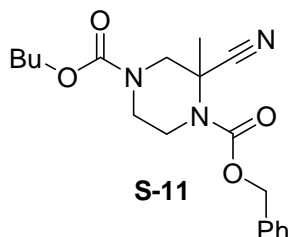
As for the procedure used in the preparation of **S-1**, replacing in step 1 4-(*tert*-butoxycarbonyl)morpholine-3-carboxylic acid with 1-[(benzyloxy)carbonyl]-4-(*tert*-butoxycarbonyl)piperazine-2-carboxylic acid.³ MS m/z 346 (M+H)⁺.

***tert*-Butyl-2-cyanopyrrolidine-1-carboxylate (S-10)**, used in the synthesis of inhibitor **32**).



As for the procedure used in the preparation of **S-1**, replacing in step 1 4-(*tert*-butoxycarbonyl)morpholine-3-carboxylic acid with 1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid. Spectral data matches literature data.⁴

1-Benzyl-4-*tert*-butyl-2-cyano-2-methylpiperazine-1,4-dicarboxylate (S-11), used in the synthesis of inhibitor **54**).



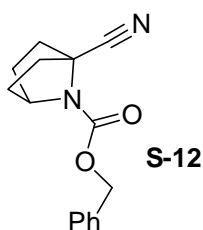
Step 1: to a cooled (-75 °C) solution of 2 M LDA in heptane/THF (1.5 eq) in THF, a solution of 1-[(benzyloxy)carbonyl]-4-(*tert*-butoxycarbonyl)piperazine-2-carboxylic acid in THF was added dropwise, while keeping temperature at -75 °C. After 1 hour stirring, MeI (1.2 eq) was added and the mixture was stirred for additional 2 hours at -75 °C. Reaction mixture was then left warming at room temperature, evaporated, diluted with EtOAc, washed with NaHCO₃ss, brine, and dried over Na₂SO₄. Crude 1-

³ Bigge, C. F.; Hays, S. J.; Novak, P. M.; Drummond, J. T.; Johnson, G.; Bobovski, T. P. New preparations of the N-methyl-D-aspartate receptor antagonist, 4-(3-phosphonopropyl)-2-piperazinecarboxylic acid (CPP). *Tetr. Lett.* **1989**, 30, 5193-5196.

⁴ Shono, T.; Terauchi, J.; Kitajima, K.; Takeshima, Y.; Matsumura, Y. Electroorganic chemistry 139. Electroreductive decyanation of nitriles and its application to synthesis of α -alkylamines. *Tetrahedron*, **1992**, 48, 8253-8262.

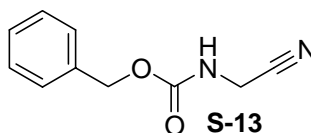
[(benzyloxy)carbonyl]-4-(*tert*-butoxycarbonyl)-2-methylpiperazine-2-carboxylic acid was directly used in the next step. MS m/z 379 (M+H)⁺. Step 2: compound from previous step was subjected to amide formation and dehydration, using the same procedure described for the synthesis of **S-1**. 1-Benzyl-4-*tert*-butyl-2-cyano-2-methylpiperazine-1,4-dicarboxylate **S-11** was purified by flash chromatography on silica gel eluting with petroleum ether/ethyl acetate 85:15 v/v. ¹H NMR (DMSO-*d*₆, 300 MHz, 340 K) δ 7.45-7.30 (m, 5 H), 5.19 (d, *J* = 13 Hz, 2 H), 4.05 (d, *J* = 14 Hz, 1 H), 3.87-3.78 (m, 1 H), 3.66 (d, *J* = 14 Hz, 1 H), 3.62-3.35 (m, 3 H), 1.66 (s, 3 H), 1.45 (s, 9 H); MS m/z 360 (M+H)⁺.

Benzyl 1-cyano-7-azabicyclo[2.2.1]heptane-7-carboxylate (S-12, used in the synthesis of inhibitor **58**).



The procedure to prepare compound **S-12** was identical to the procedure used in the preparation of **S-1**, replacing in step 1 4-(*tert*-butoxycarbonyl)morpholine-3-carboxylic acid with 7-[(benzyloxy)carbonyl]-7-azabicyclo[2.2.1]heptane-1-carboxylic (prepared from 7-benzyl 1-*tert*-butyl 7-azabicyclo[2.2.1]heptane-1,7-dicarboxylate⁵). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 7.42-7.30 (m, 5 H), 5.14 (s, 2 H), 4.32 (t, *J* = 5.0 z, 1 H), 2.2-1.98 (m, 4 H), 1.90-1.70 (m, 2 H), 1.62-1.45 (m, 2 H); MS m/z 257 (M+H)⁺.

Benzyl (cyanomethyl)carbamate (S-13, used in the synthesis of inhibitor **35**)

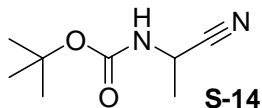


As for the procedure used in the preparation of **S-1**, replacing in step 1 4-(*tert*-butoxycarbonyl)morpholine-3-carboxylic acid with {[(benzyloxy)carbonyl]amino}acetic acid. Spectral data matches literature data.⁶

***tert*-Butyl-(1-cyanoethyl)carbamate (S-14**, used in the synthesis of inhibitor **37**).

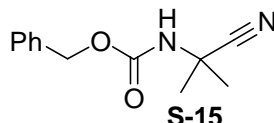
⁵ Campbell, J. A.; Rapoport, H. Chiroselective syntheses of conformationally constrained 7-azabicycloheptane aminoacids by transannular alkylation. *J. Org. Chem.* **1996**, *61*, 6313-6325.

⁶ Schmidt, U., Utz, R.; Lieberknecht, A.; Griesser, H.; Potzulli, B.; Wagner, K.; Fisher, P. Amino acids and peptides; 59. Synthesis of biologically active cyclopeptides; 9. Synthesis of 16 isomers of Dolastatin 3; I. Synthesis of the 2-(1-aminoalkyl)thiazole-4-carboxylic acids. *Synthesis*, **1987**, *3*, 233-236



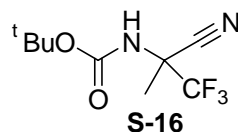
As for the procedure used in the preparation of **S-1**, replacing in step 1 4-(*tert*-butoxycarbonyl)morpholine-3-carboxylic acid with 2-[(*tert*-butoxycarbonyl)amino]propanoic acid. Spectral data matches literature data.⁷

Benzyl 1-cyano-1-methylethylcarbamate (S-15), used in the synthesis of inhibitors **38-40**).



To a suspension of 2-amino-2-methylpropanenitrile⁸ in water an equimolar amount of Na₂CO₃ and a slight excess (1.1 eq) of benzyl chloroformate were added, with an external cooling (ice bath). Reaction mixture was stirred over night at room temperature, extracted in ethyl acetate and the organic phase was washed with NaHCO₃ss, dried (Na₂SO₄), filtered and concentrated. Product was obtained as a white solid upon trituration with Et₂O (99% yield). ¹H NMR (CDCl₃, 300 MHz) δ 7.48-7.33 (bs, 5 H), 5.15 (s, 2 H), 4.98 (bs, 2 H), 1.68 (s, 6 H); ¹³C NMR (CDCl₃, 60 MHz) δ 153.33, 130.81, 127.81, 127.63, 127.55, 120.64, 66.56, 46.19, 26.67; MS *m/z* 219 (M+H)⁺.

***tert*-Butyl (1-cyano-2,2,2-trifluoro-1-methylethyl)carbamate (S-16)**, used in the synthesis of inhibitor **41**).



To a cooled (-78 °C) solution of methyl 2-[(*tert*-butoxycarbonyl)imino]-3,3,3-trifluoropropanoate⁹ in anhydrous diethyl ether, 1.05 eq. of MeMgCl (3M solution in Et₂O) were added dropwise. Reaction mixture was stirred 1 hour at 78 °C and 2 hours at room temperature. The reaction was quenched with 1 N HCl and extracted in Et₂O. The organic layer was washed with brine, dried over Na₂SO₄, filtered and evaporated yielding methyl 2-[(*tert*-butoxycarbonyl)amino]-3,3,3-trifluoro-2-methylpropanoate as an orange oil. After hydrolysis of the methyl ester (1N NaOH, methanol, reflux, 1 h), the acid was carried

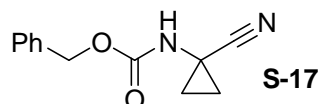
⁷ Kohrt, A.; Hartke, K. Dithio and thiono esters, 53. Synthesis of N-protected α-amino dithioesters from α-amino nitriles and α-amino acids. *Liebigs Ann. Chem.* **1992**, 6, 595-606.

⁸ *Organic Synthesis* Coll. Vol. II, page 29

⁹ Dessipri, E; Tirrel, D. A. Trifluoroalanine *N*-carboxy anhydride: a reactive intermediate for the synthesis of low surface energy polypeptides. *Macromolecules*, **1994**, 27, 5463-5470

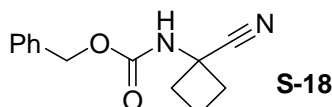
through the synthesis of the nitrile following the same procedure used in the preparation of **S-1**. ^1H NMR (DMSO- d_6 , 300 MHz) δ 8.40 (bs, 1 H), 1.81 (s, 3 H), 1.46 (s, 9 H); ^{19}F NMR (DMSO- d_6 , 376 MHz) δ -79.50; MS m/z 239 (M+H) $^+$.

Benzyl-(1-cyanocyclopropyl)carbamate (S-17), used in the synthesis of inhibitor **42**).



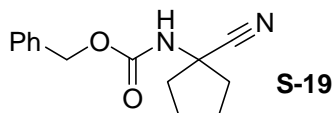
As for the procedure used in the preparation of **S-1**, replacing in step 1 4-(*tert*-butoxycarbonyl)morpholine-3-carboxylic acid with 1-[[[(benzyloxy)carbonyl]amino]cyclopropanecarboxylic acid. ^1H NMR (CDCl $_3$, 300 MHz) δ 7.32 (bs, 5 H), 5.28 (bs, 1 H), 5.20-5.08 (m, 2 H), 1.51-1.43 (m, 2 H), 1.29-1.21 (m, 2 H); MS m/z 217 (M+H) $^+$.

Benzyl-(1-cyanocyclobutyl)carbamate (S-18), used in the synthesis of inhibitor **43**).



1-cyanocyclobutanaminium chloride was prepared from cyclobutanone following a literature procedure.¹⁰ The crude compound was dissolved in water and treated with 2.0 eq of Na $_2$ CO $_3$. Reaction mixture was cooled at 0 °C and 1.1 equivalents of benzyl chloroformate were added dropwise. The reaction was left over night at room temperature and then extracted in ethyl acetate. The organic layer was washed with NaHCO $_3$ ss and brine, dried over anhydrous sodium sulfate, filtered and concentrated. Product **S-18** was obtained in quantitative yield upon trituration with diethyl ether. ^1H NMR (CDCl $_3$, 400 MHz) δ 7.35 (bs, 5 H), 5.98 (bs, 1 H), 5.13-5.08 (m, 1 H), 4.67-4.66 (m, 1 H), 2.65-2.63 (m, 2 H), 2.37-2.30 (m, 2 H), 2.12-2.00 (m, 2 H); ^{13}C NMR (CDCl $_3$, 75 MHz) δ 127.24, 126.76, 126.75, 126.71, 126.66, 93.50, 69.47, 51.11, 47.79, 35.30, 15.07; MS m/z 231 (M+H) $^+$.

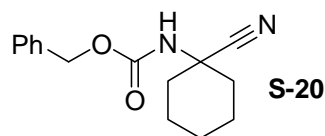
Benzyl-(1-cyanocyclopentyl)carbamate (S-19), used in the synthesis of inhibitor **44**).



As for the procedure used in the preparation of **S-1**, replacing in step 1 4-(*tert*-butoxycarbonyl)morpholine-3-carboxylic acid with 1-[[[(benzyloxy)carbonyl]amino]cyclopentanecarboxylic acid. MS m/z 245 (M+H) $^+$.

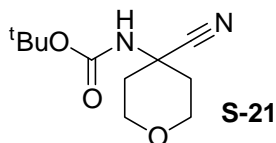
¹⁰ Mai, K.; Patil, G. Facile synthesis of α -aminonitriles. *Tetrahedron Lett.* **1984**, 25, 4583-4586

Benzyl-(1-cyanocyclohexyl)carbamate (S-20, used in the synthesis of inhibitor 45).



As for the procedure used in the preparation of **S-1**, replacing in step 1 4-(*tert*-butoxycarbonyl)morpholine-3-carboxylic acid with 1-[(benzyloxy)carbonyl]amino}cyclohexanecarboxylic acid. MS m/z 259 (M+H)⁺.

***tert*-Butyl 4-cyanotetrahydro-2*H*-pyran-4-yl-carbamate (S-21, used in the synthesis of inhibitor 46).**



As for the procedure used in the preparation of **S-1**, replacing in step 1 4-(*tert*-butoxycarbonyl)morpholine-3-carboxylic acid with 4-[(*tert*-butoxycarbonyl)amino]tetrahydro-2*H*-pyran-4-carboxylic acid. ¹H NMR (CDCl₃, 300 MHz) δ 4.71 (bs, 1 H), 3.96 (t, $J = 3.5$ Hz, 1 H), 3.93 (t, $J = 4.1$ Hz, 1 H), 3.79-3.76 (m, 2 H), 2.37-2.34 (m, 2 H), 1.89-1.82 (m, 2 H), 1.50 (s, 7 H), 1.47 (s, 2 H); MS m/z 227 (M+H)⁺.

HPLC analysis of the final compounds.

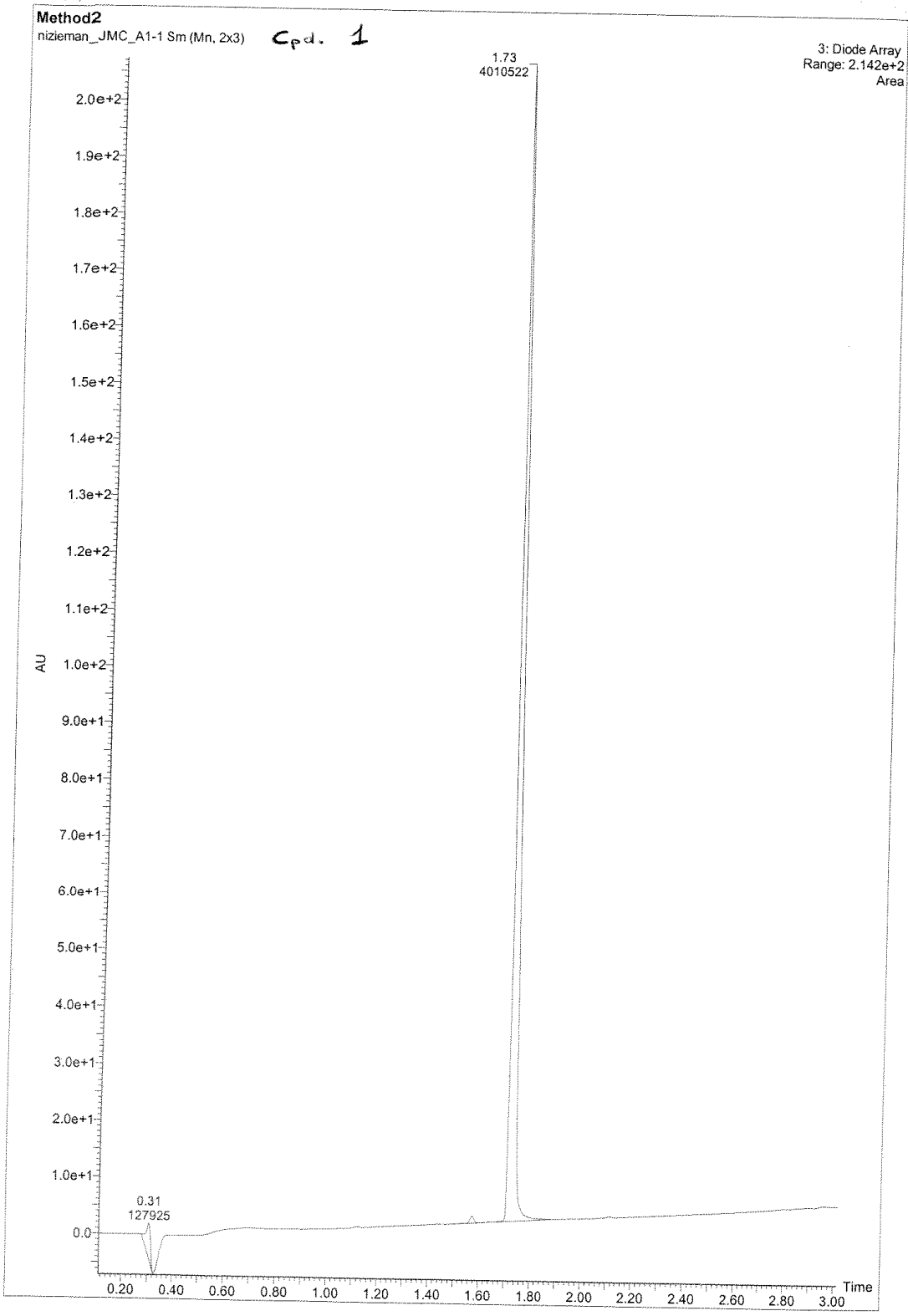
The stationary phases used were: Acquity UPLC™ BEH C18 1.7 μm, 2.1 * 50 mm (column A); Gemini 5 μm C18 110A, 50 * 4.60 mm (column B). Mobile phase comprised a linear gradient of binary mixtures of H₂O containing 0.1% formic acid (solvent A) and MeCN containing 0.1% formic acid (solvent B) or H₂O containing 0.1% TFA (solvent C) and MeCN containing 0.1% TFA (solvent D).

Cpd No (Table)	Retention Time 1 ^a	Retention Time 2 ^b	Retention Time 3 ^c	Retention Time 4 ^c
1 (1)	1.73	2.25		
2	1.71		5.05	
3 (1)	1.81	2.42		1.60
4 (1)	0.97	1.14		0.91
5 (1)	1.78			1.54
6 (1)	1.85			1.50
7 (1)	2.07	2.45		1.82
8 (1)	1.83	2.45		1.62
9 (1,2)	1.74		5.02	1.40
10 (2)	1.23	1.67		
11 (2)	1.33		4.05	
12 (2)	1.60	2.24		
13 (2)	1.80		5.12	1.46
14 (2)	1.81			1.57
15 (2)	1.54	2.16		
16 (2)	1.61	2.26		
17 (3)	1.75	2.48		
18 (3)	1.61	2.28		
19 (3)	1.15	1.55		
20 (3)			5.12	
21 (3)	1.11	1.53		
22 (3)	1.42	2.03		
23 (3)	1.20	1.68		

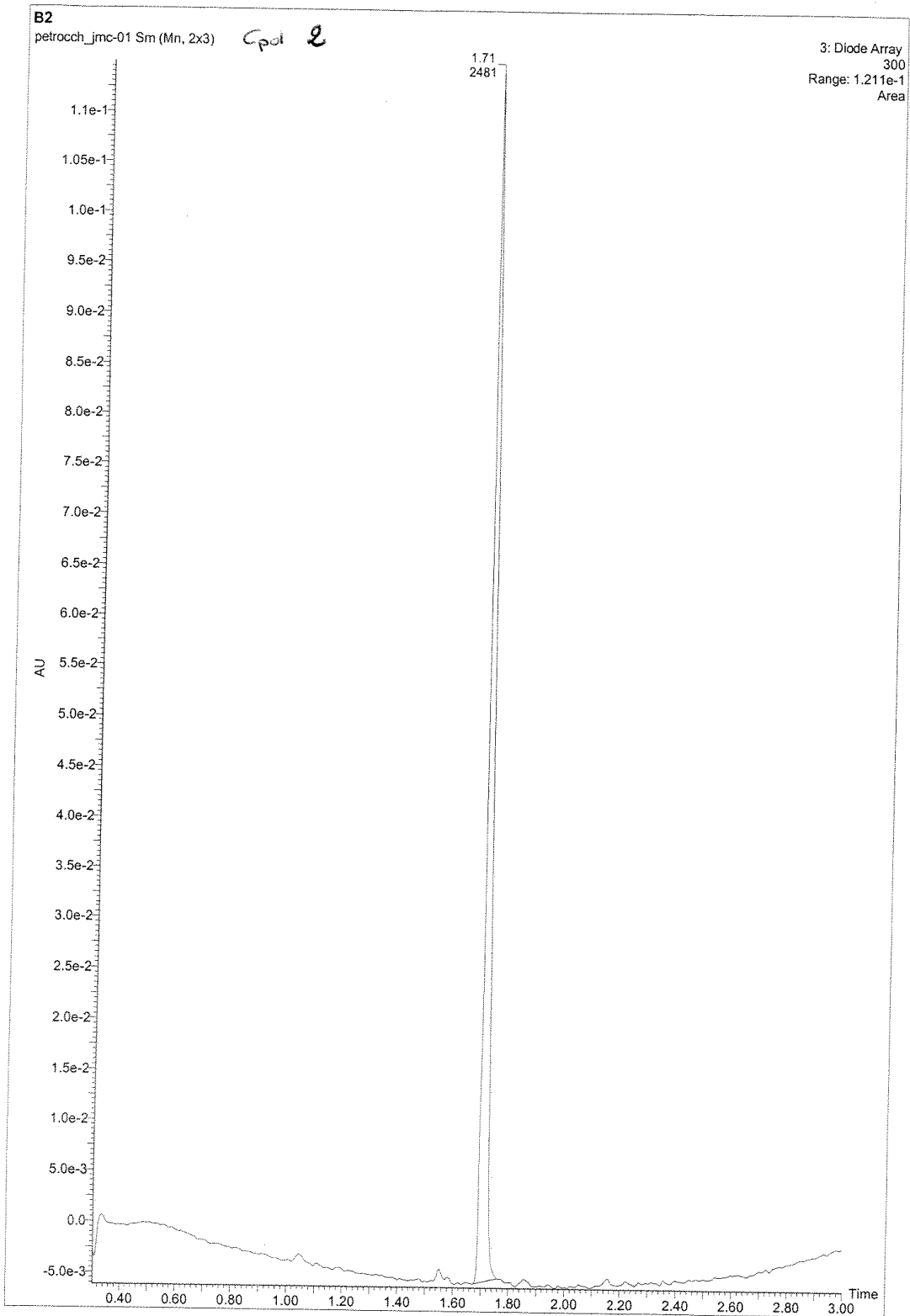
24 (5)	0.95	1.30		
25 (5)	0.98	1.33		
26 (5)	0.95	1.30		
27 (5)	1.03		3.35	
28 (5)	1.01	1.38		
29 (5)	1.16	1.61		
30 (5)	0.96	1.31		
31 (5)	0.99	1.26	3.24	
32 (5)	0.95	1.28		
33 (5)	1.01	1.11		1.36
34 (5)	0.97	1.33		
35 (6)	0.80	1.11	3.14	
36 (6)	1.18	1.61		
37 (6)	1.00		3.20	
38 (6)	1.00		3.24	
39 (6)	0.99	1.34		
40 (6)	1.60	2.24		
41 (6)	1.97			1.73
42 (6)	1.06	1.48		
43 (6)	1.07	1.46		
44 (6)	1.11	1.56		
45 (6)	1.20		3.14	1.05
46 (6)	1.09	1.52		

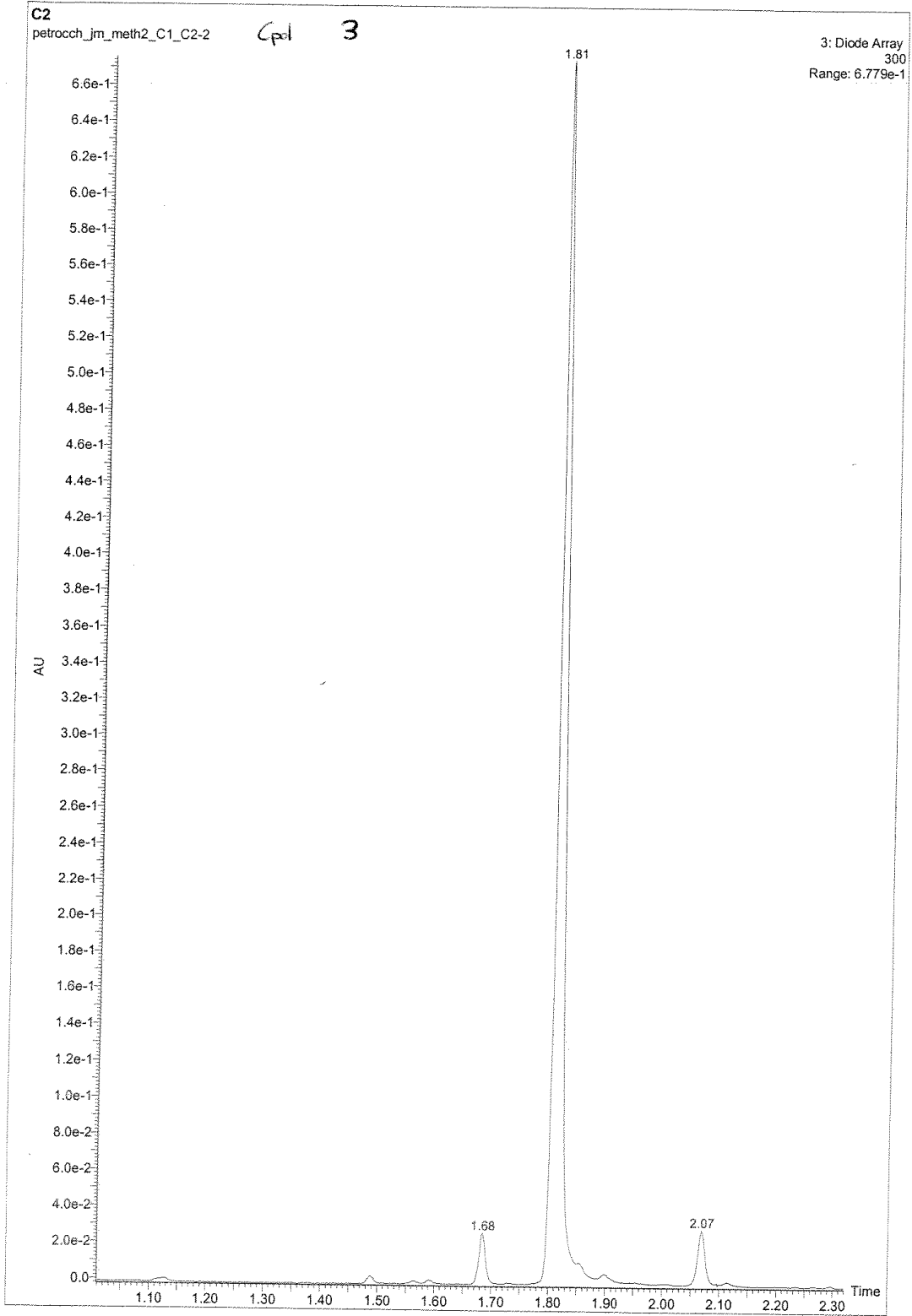
^a Column A; flow 0.5 mL/min; 10 % solvent B (0.1 min) to 100% solvent B over 2.6 min and then isocratic. ^b Column A; flow 0.5 mL/min; 5% solvent B (0.1 min) to 50% solvent B over 2.1 min and then isocratic. ^c Column B; flow 1.0 mL/min; 10% solvent D (0.1 min) to 100% solvent D over 7.5 min and then isocratic. ^d Column A; flow 0.5 mL/min; 10 % solvent B (0.1 min) to 100% solvent B over 2.1 min and then isocratic.

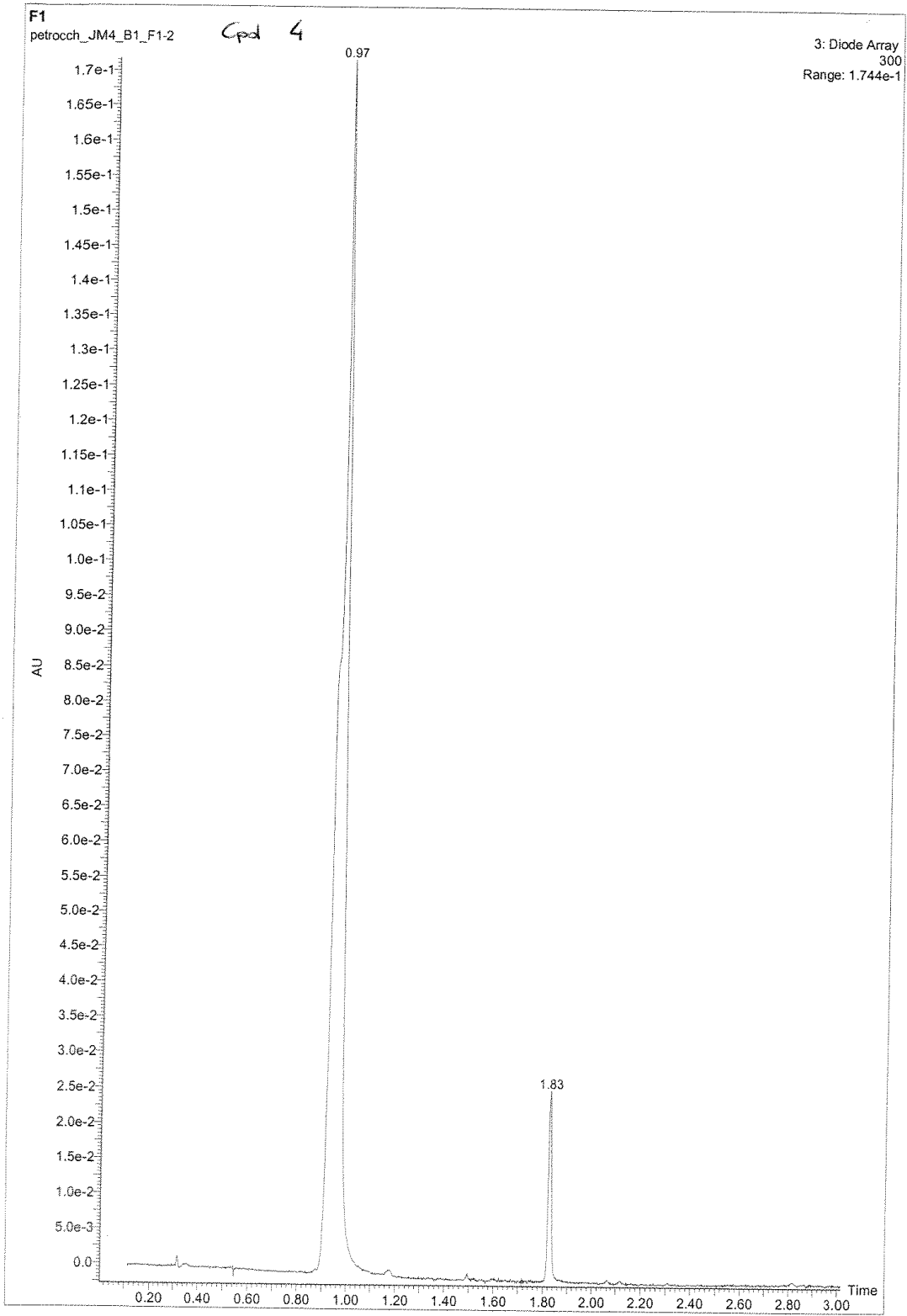
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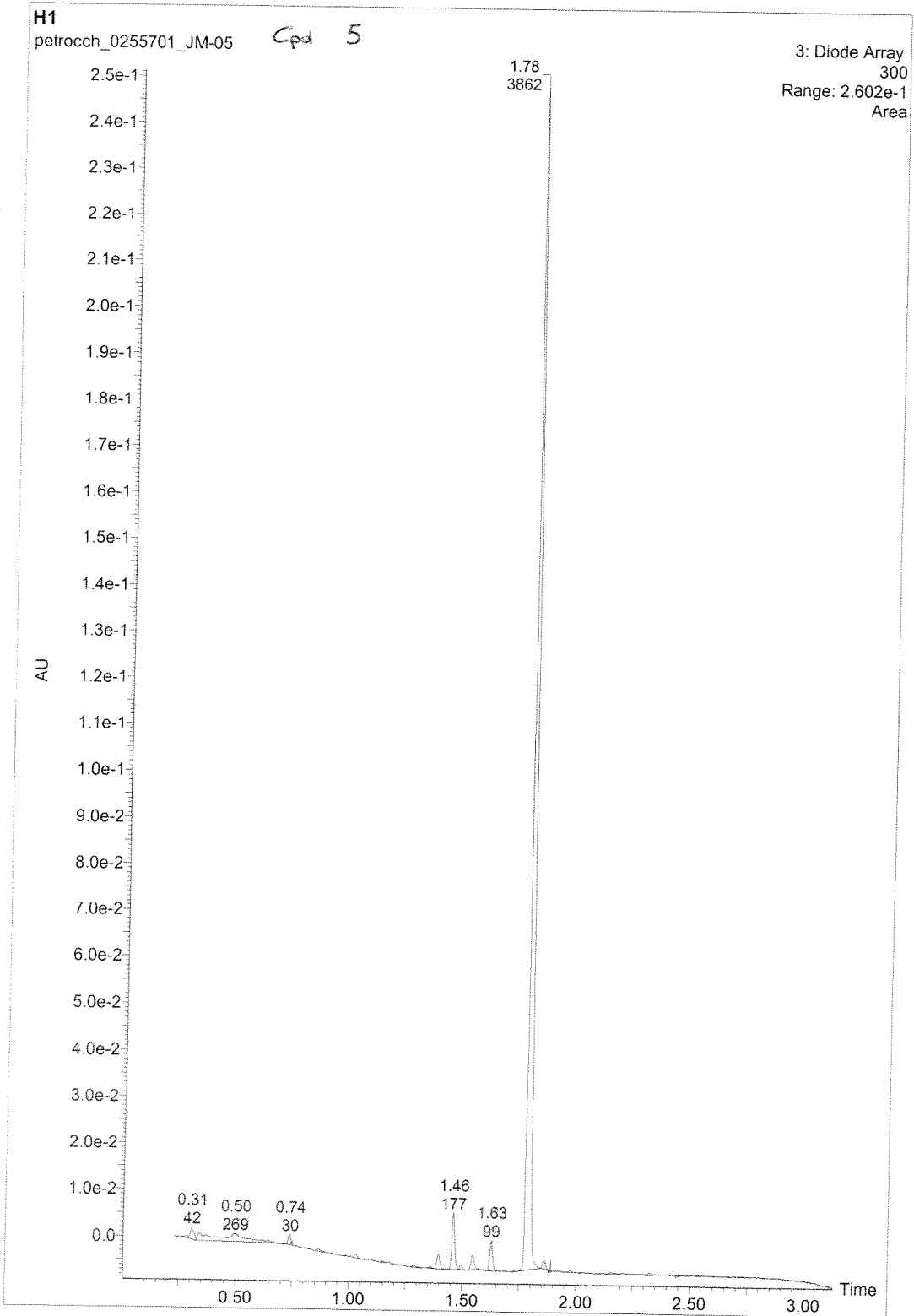


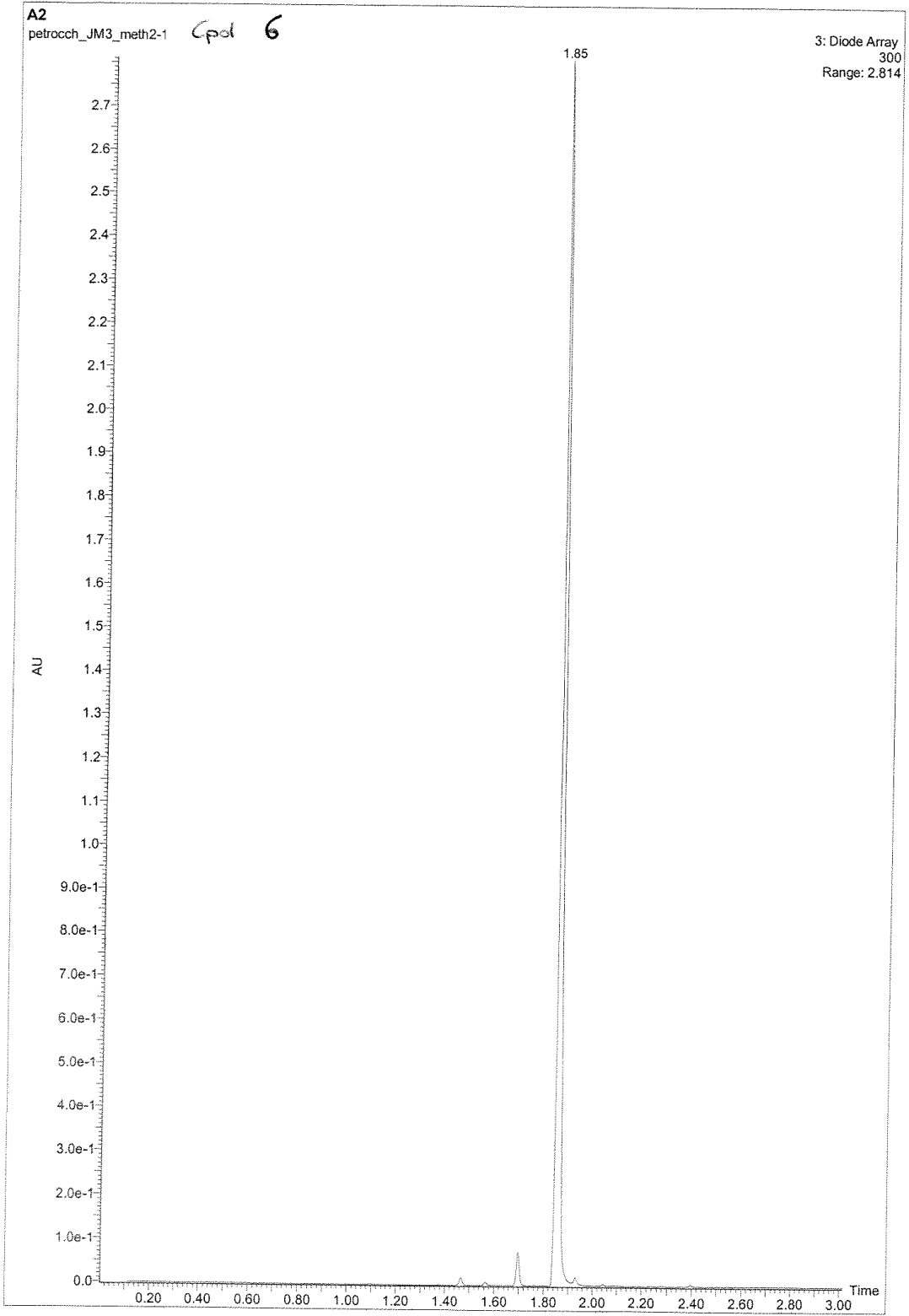
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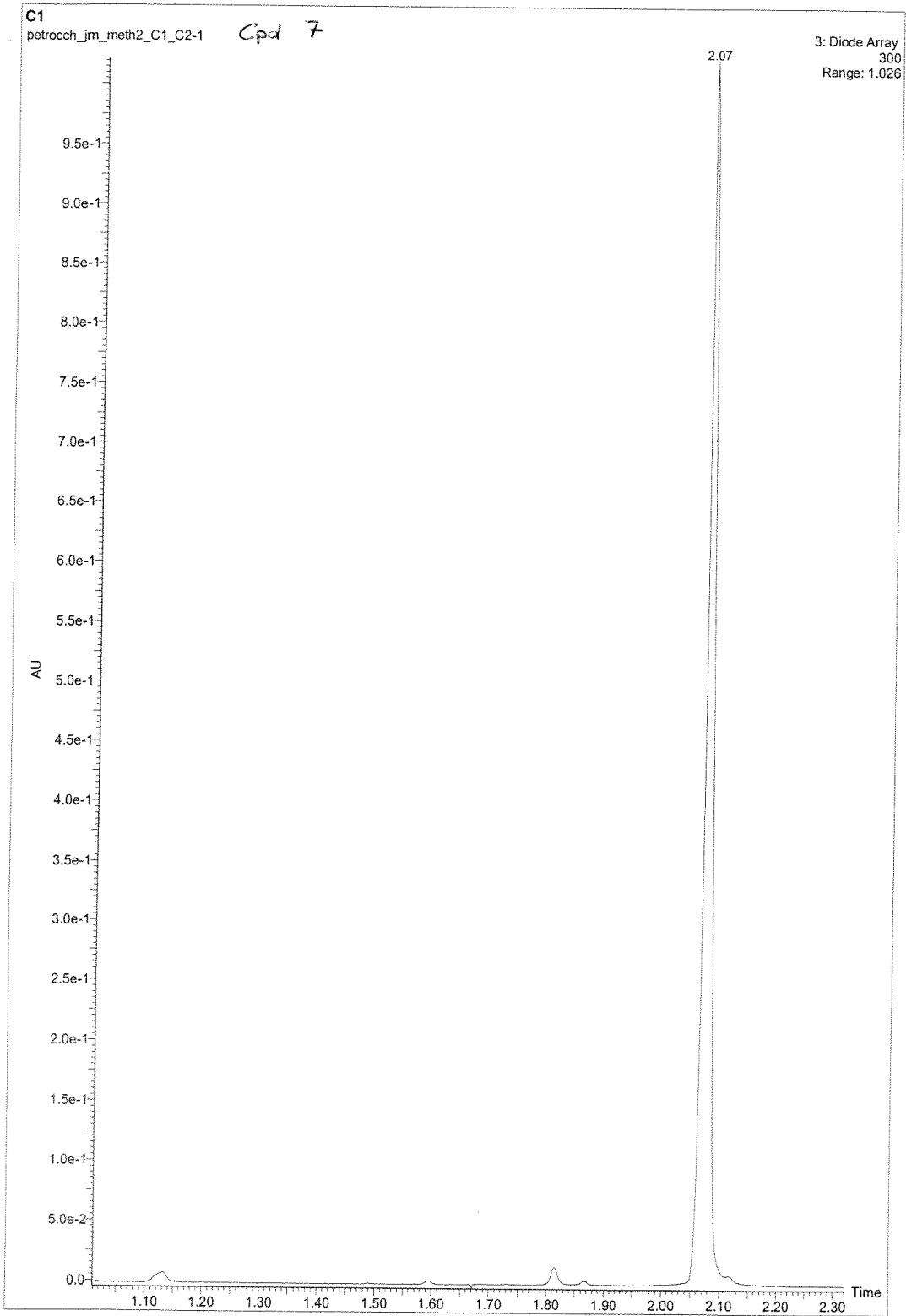


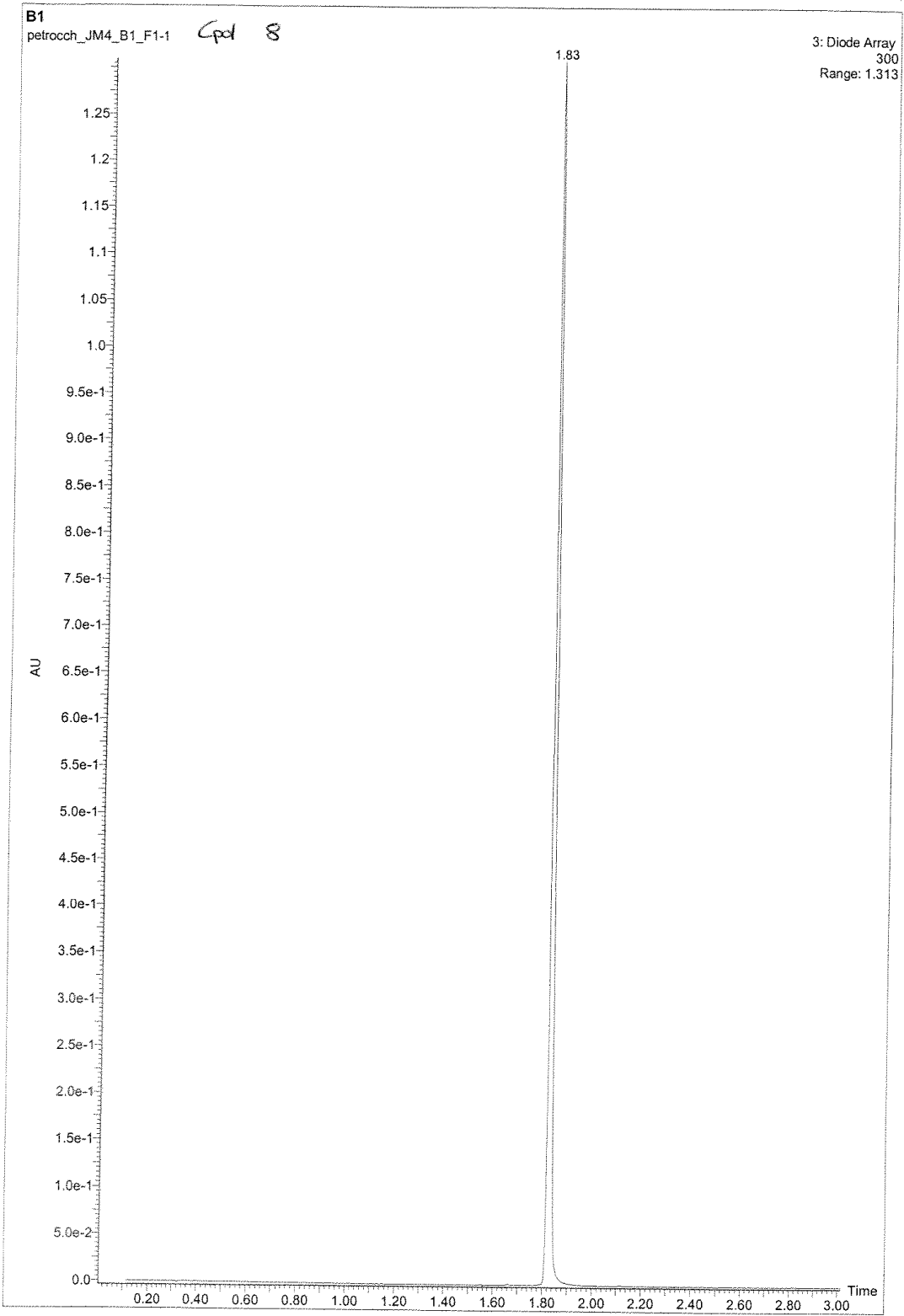


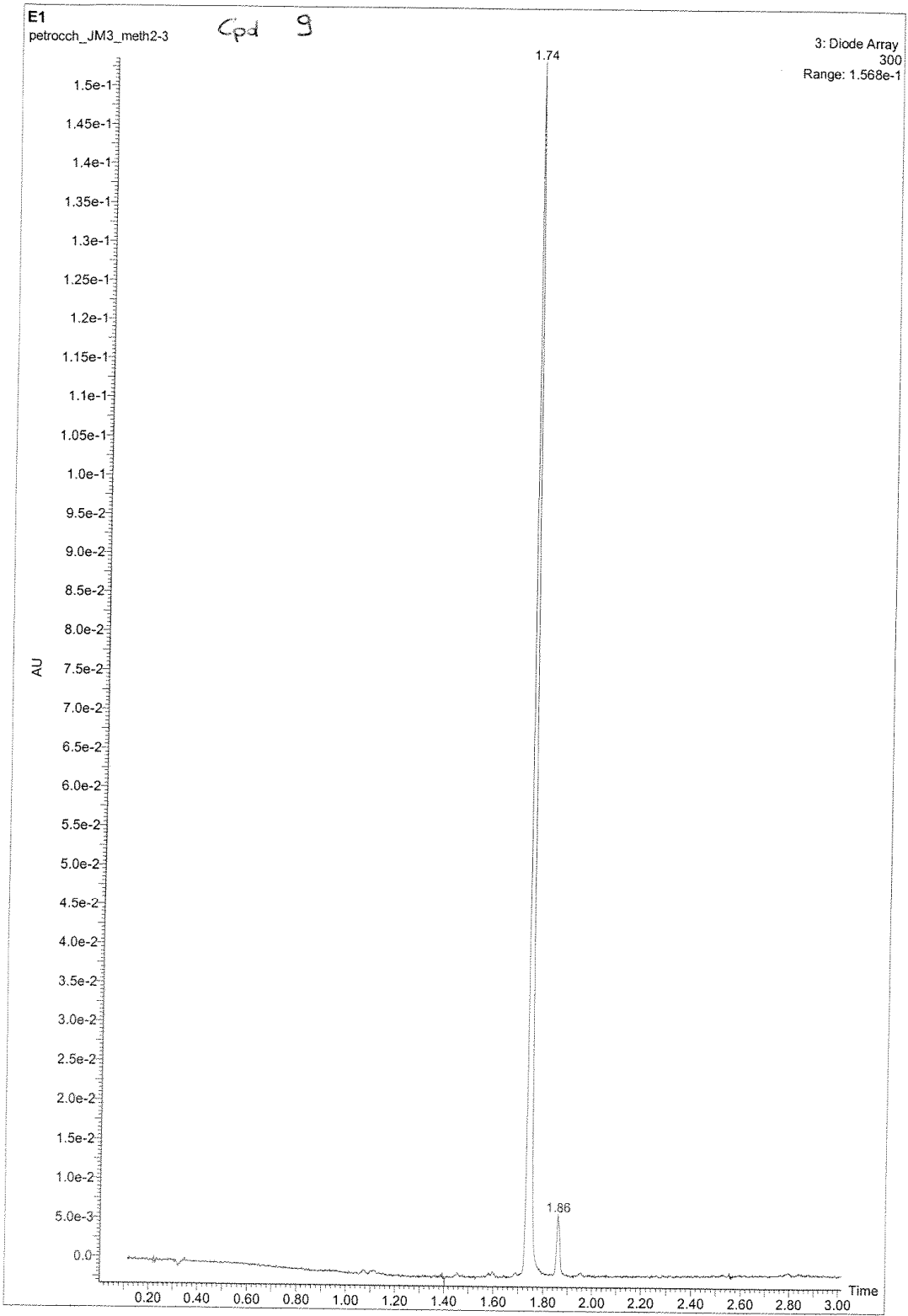


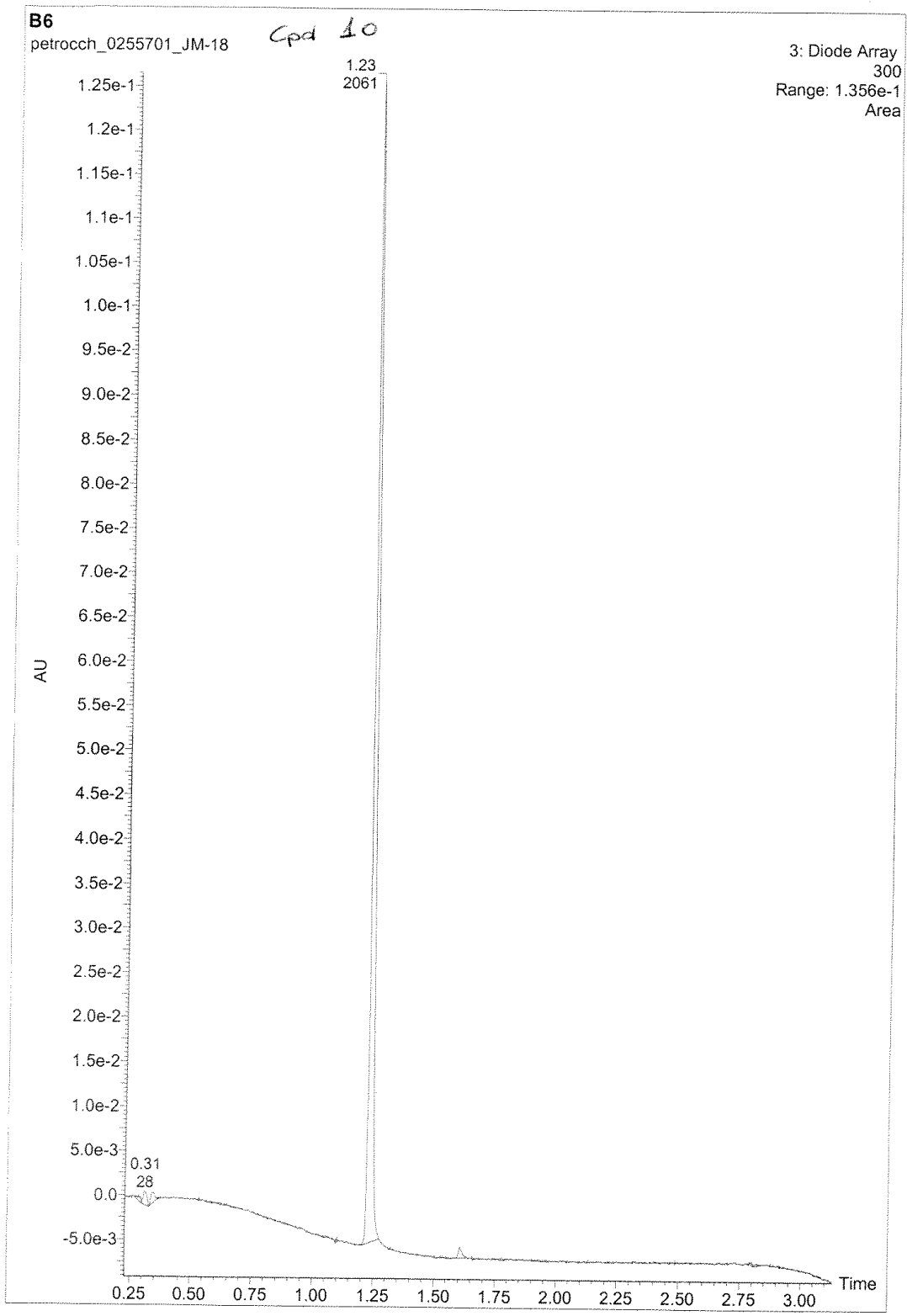


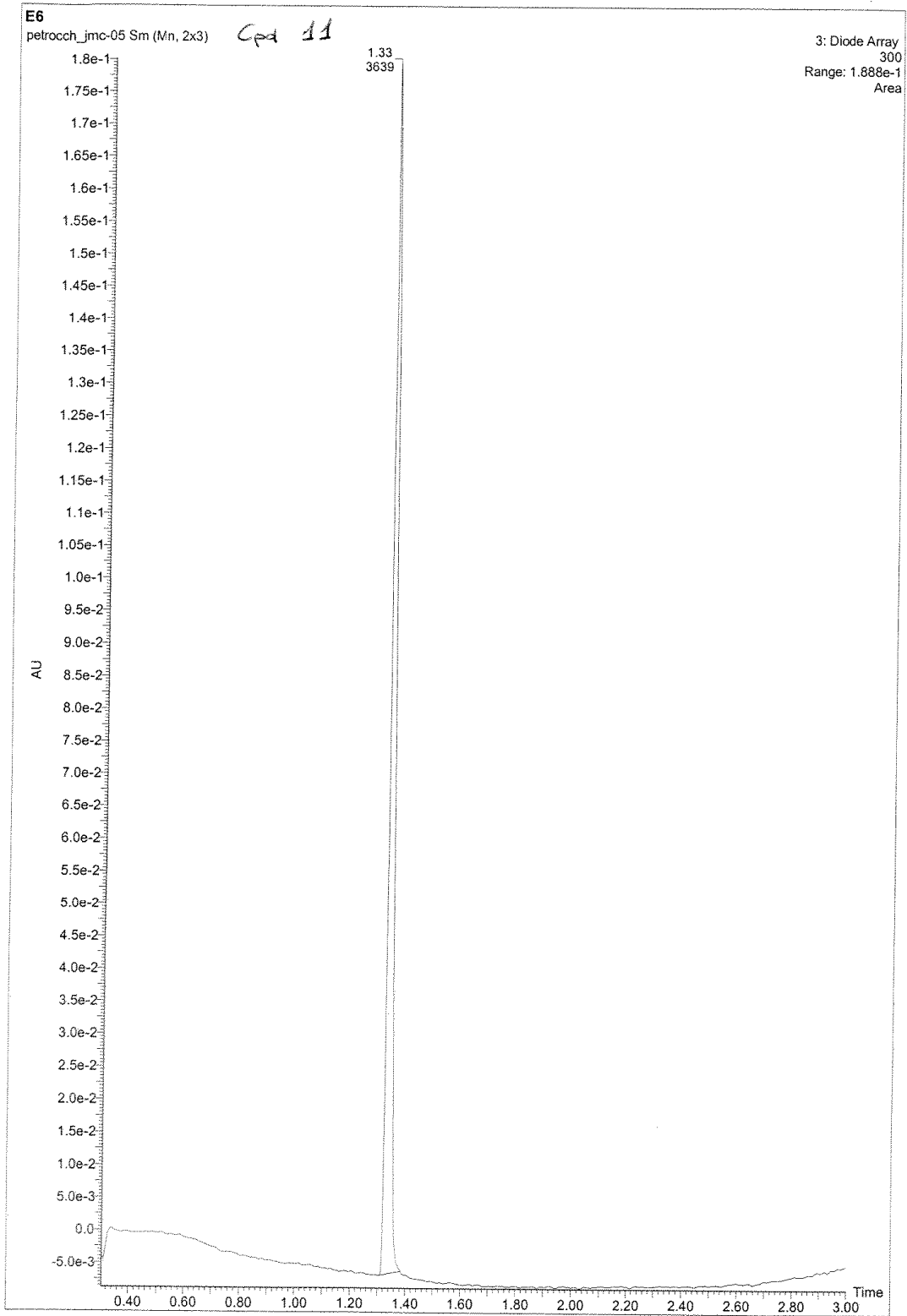


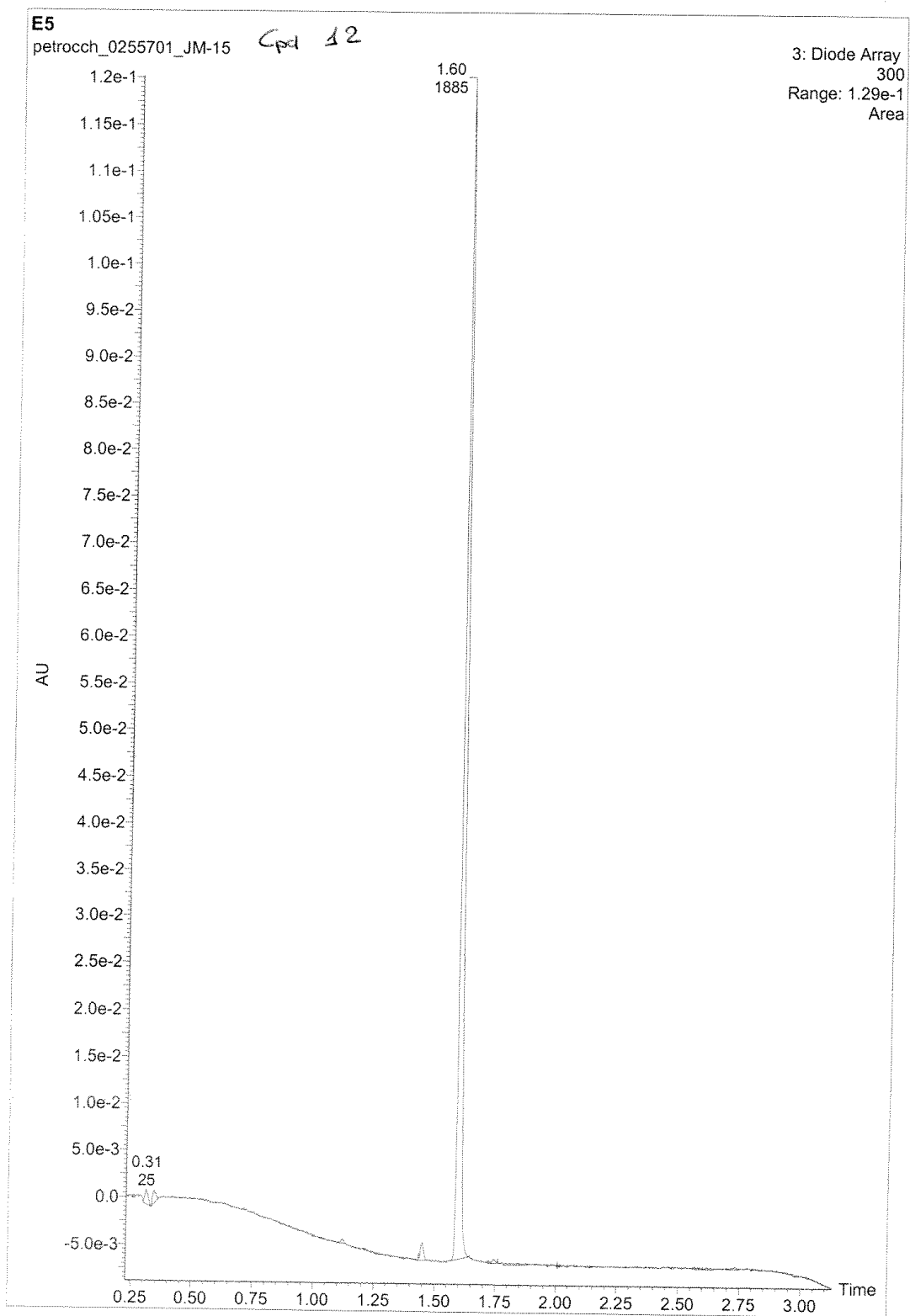


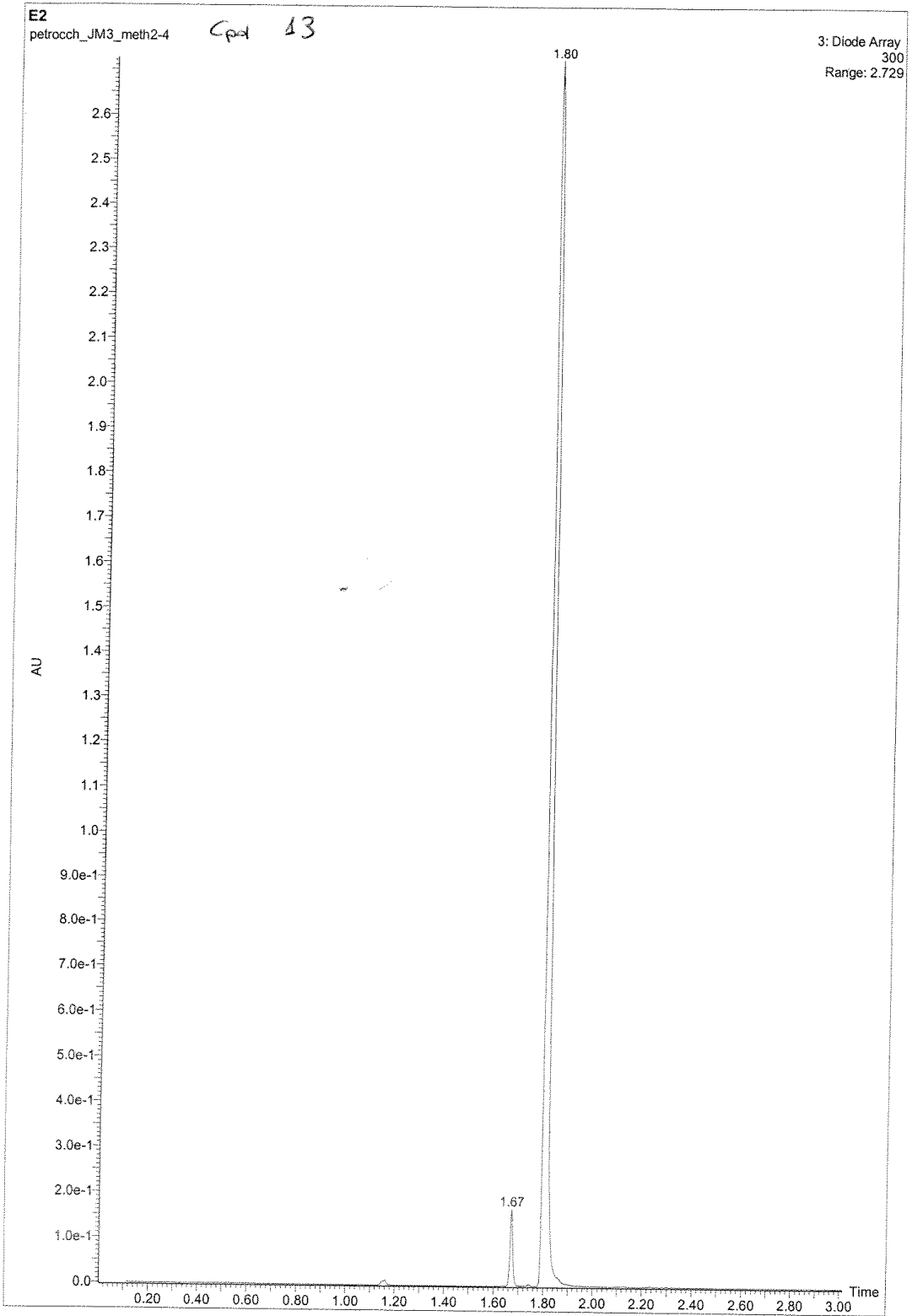


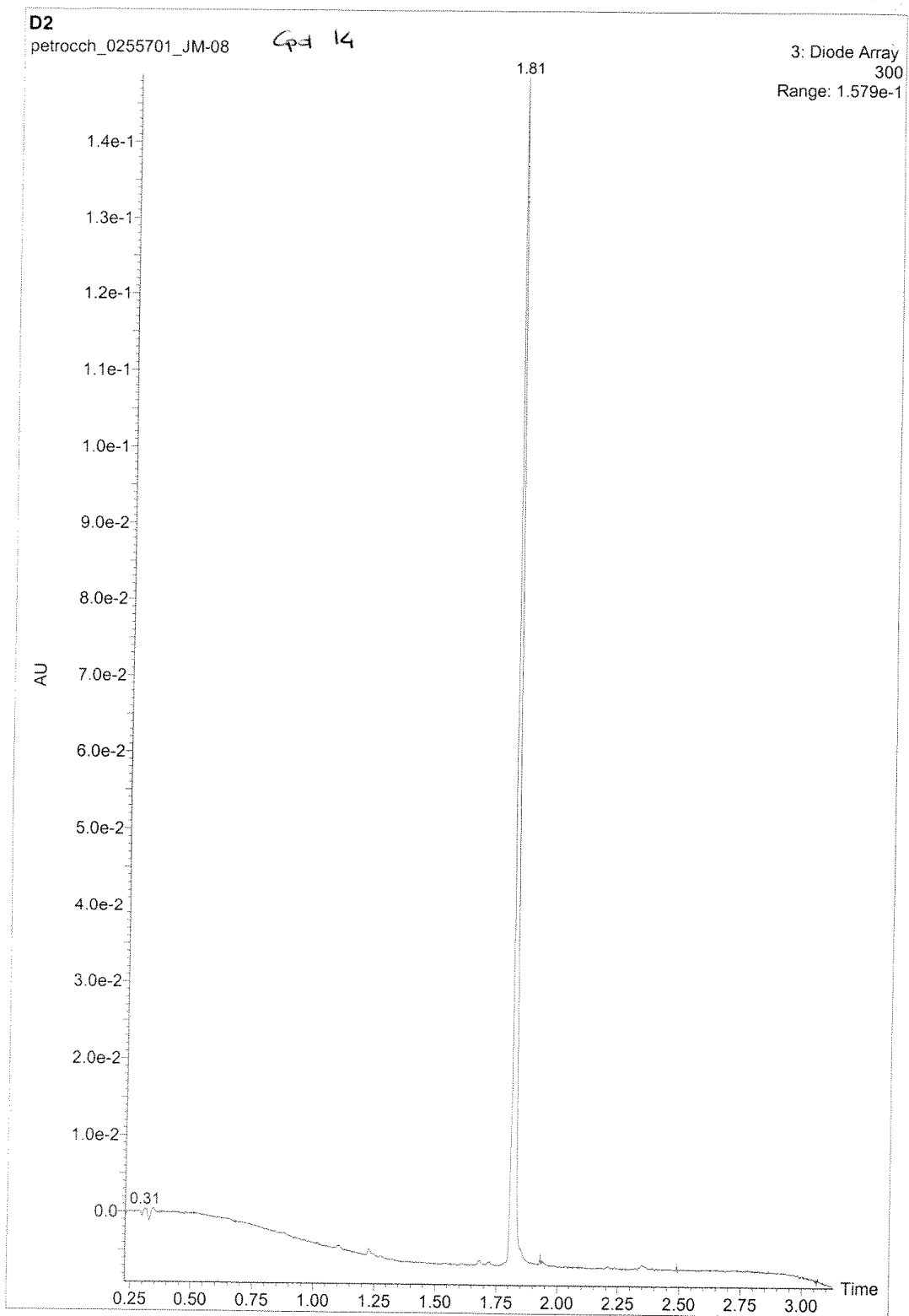


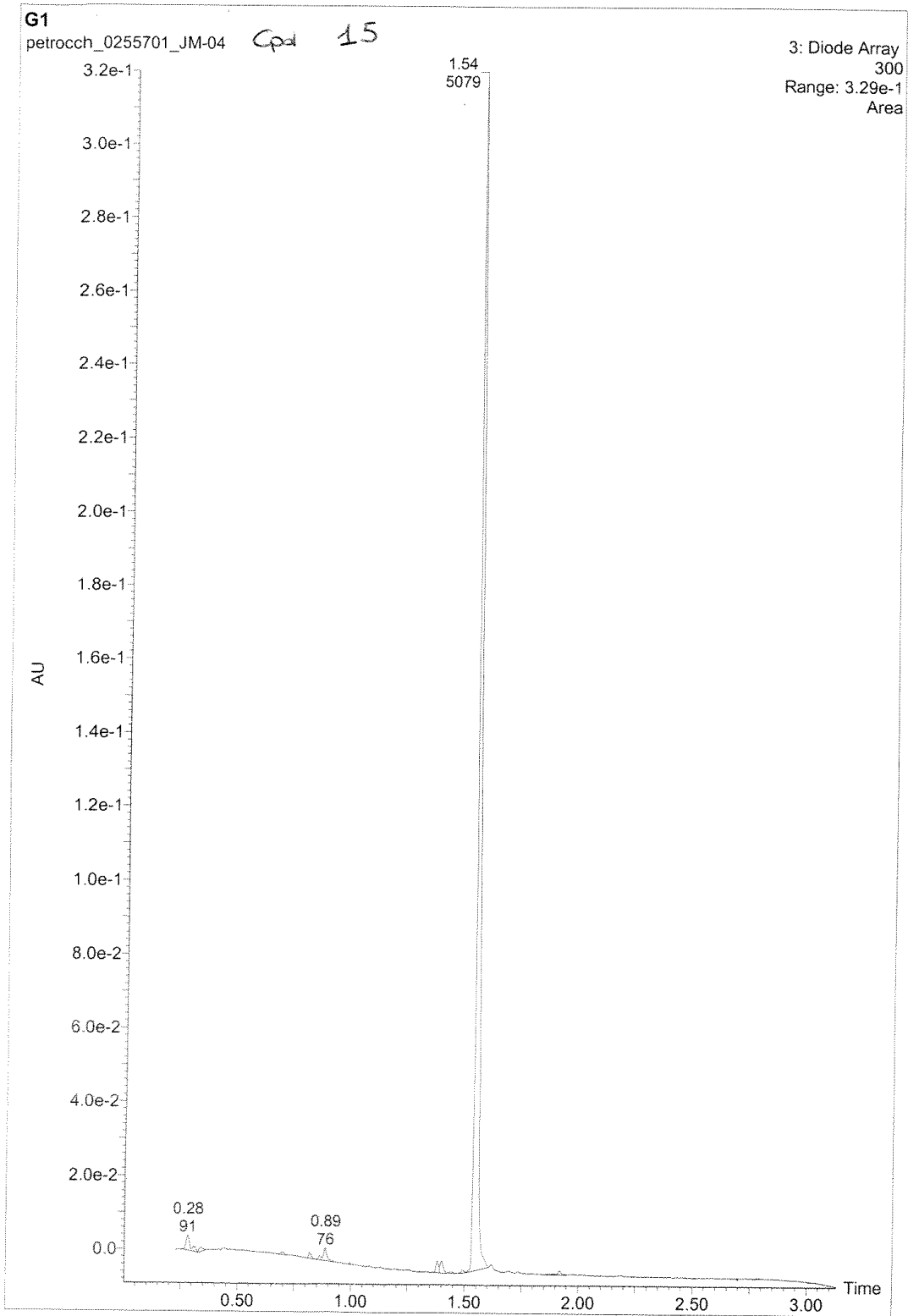


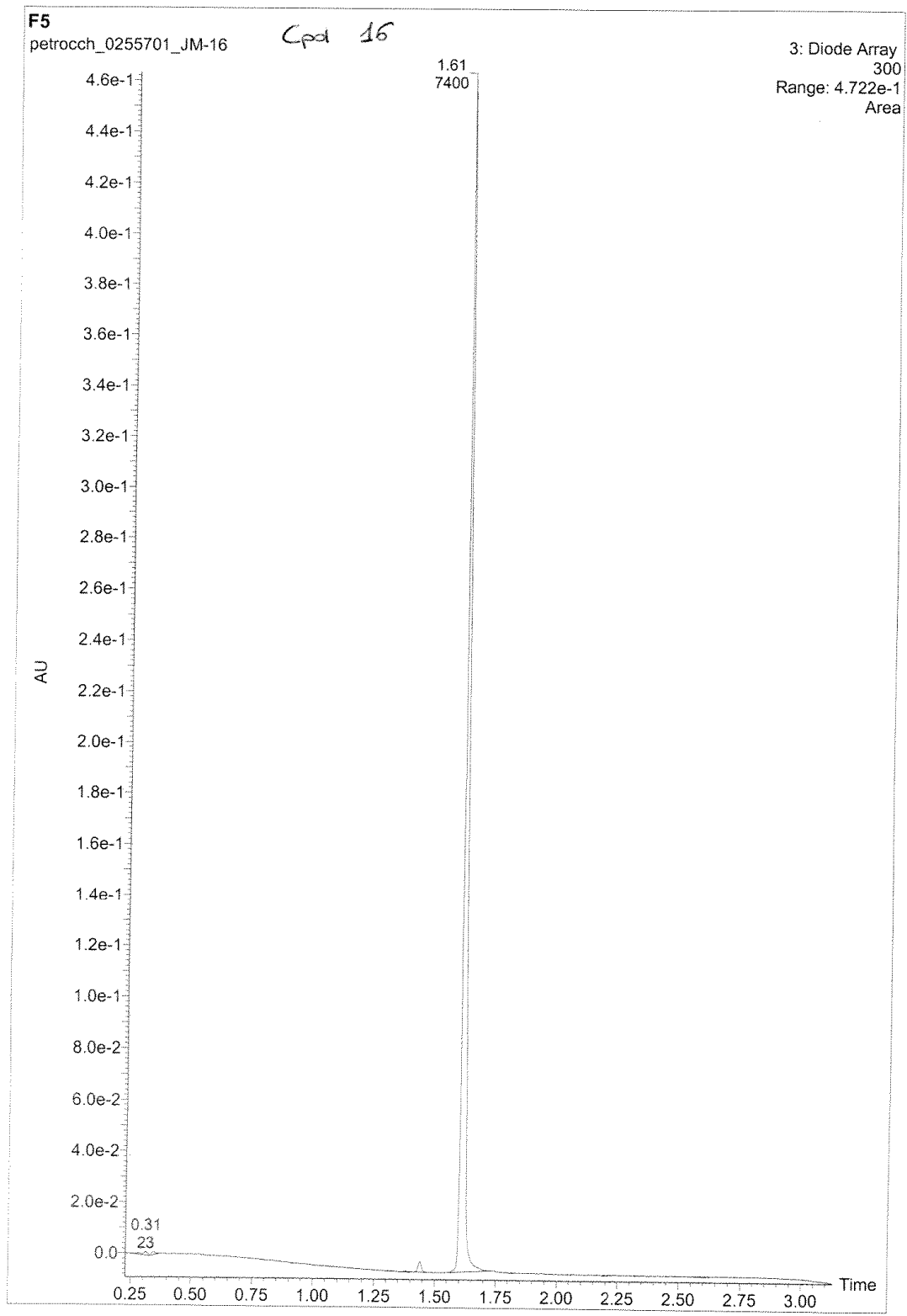


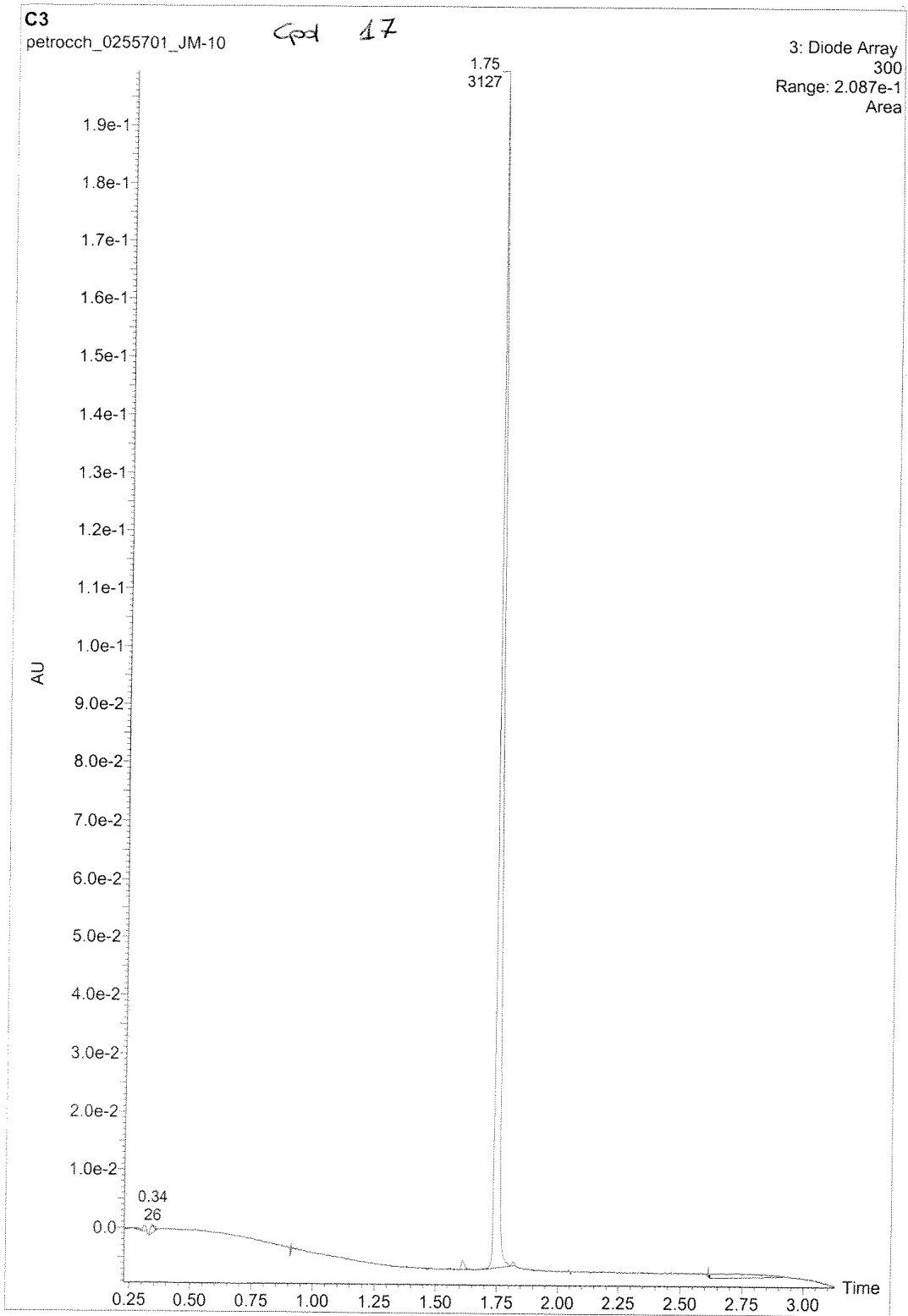


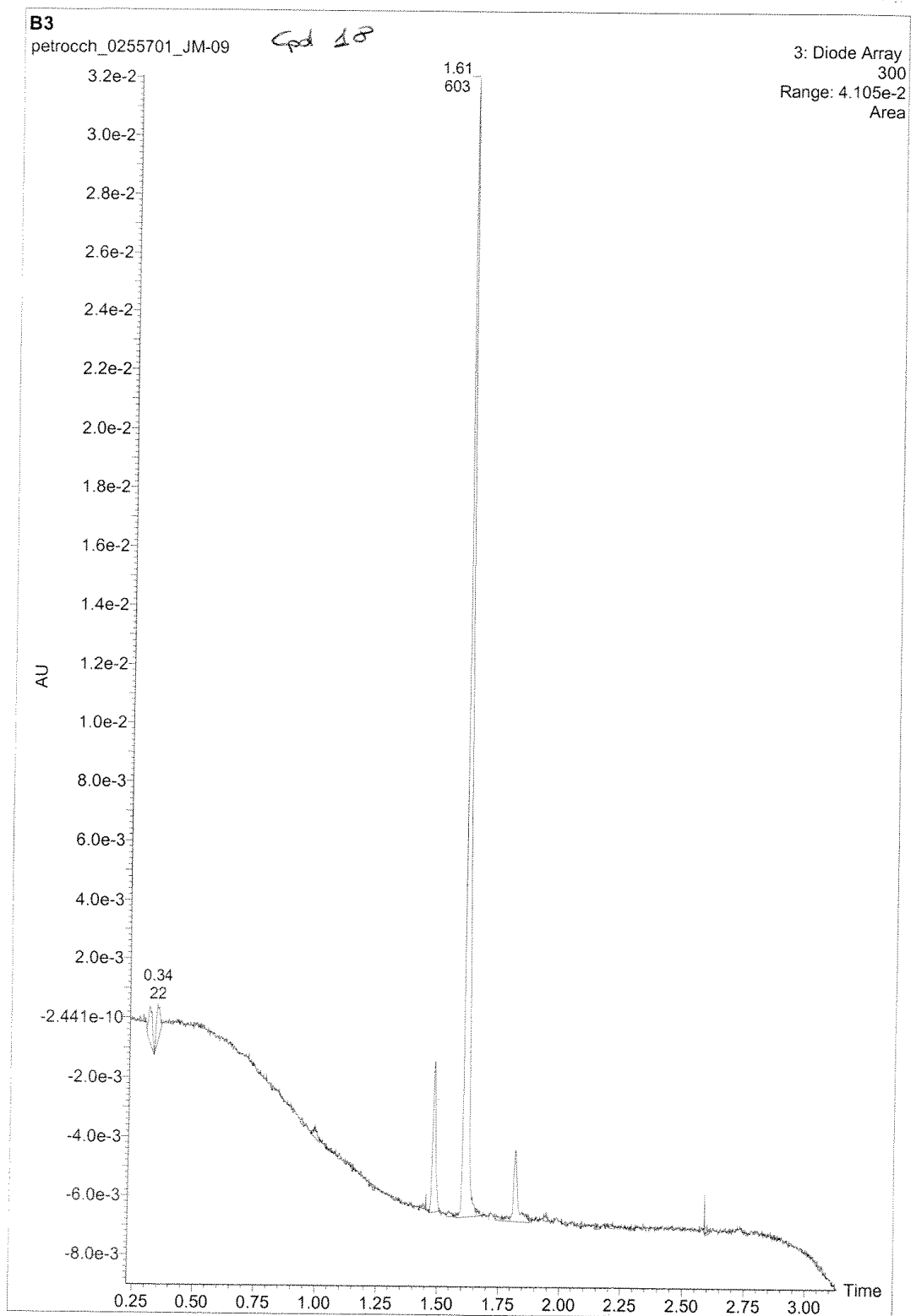


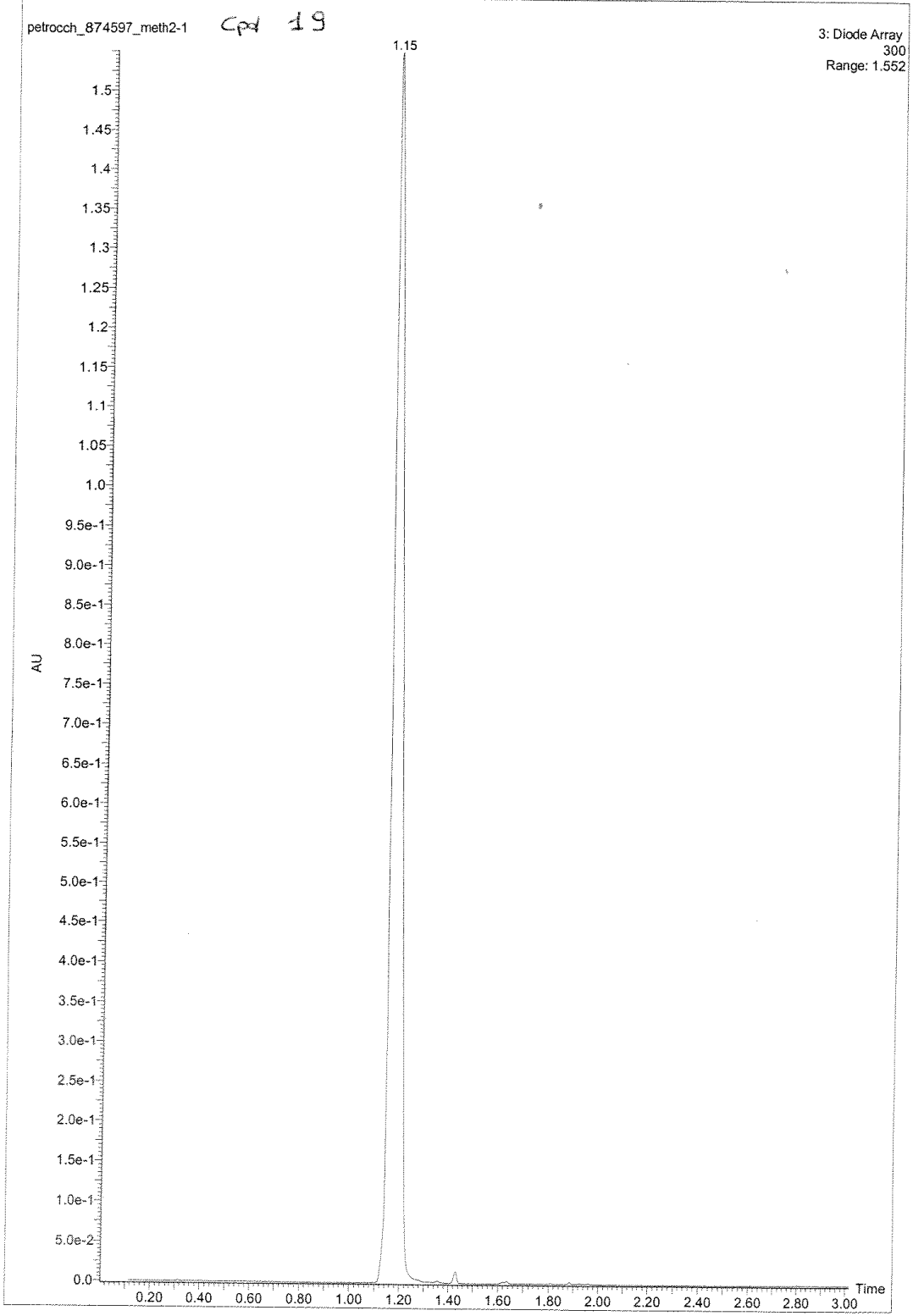


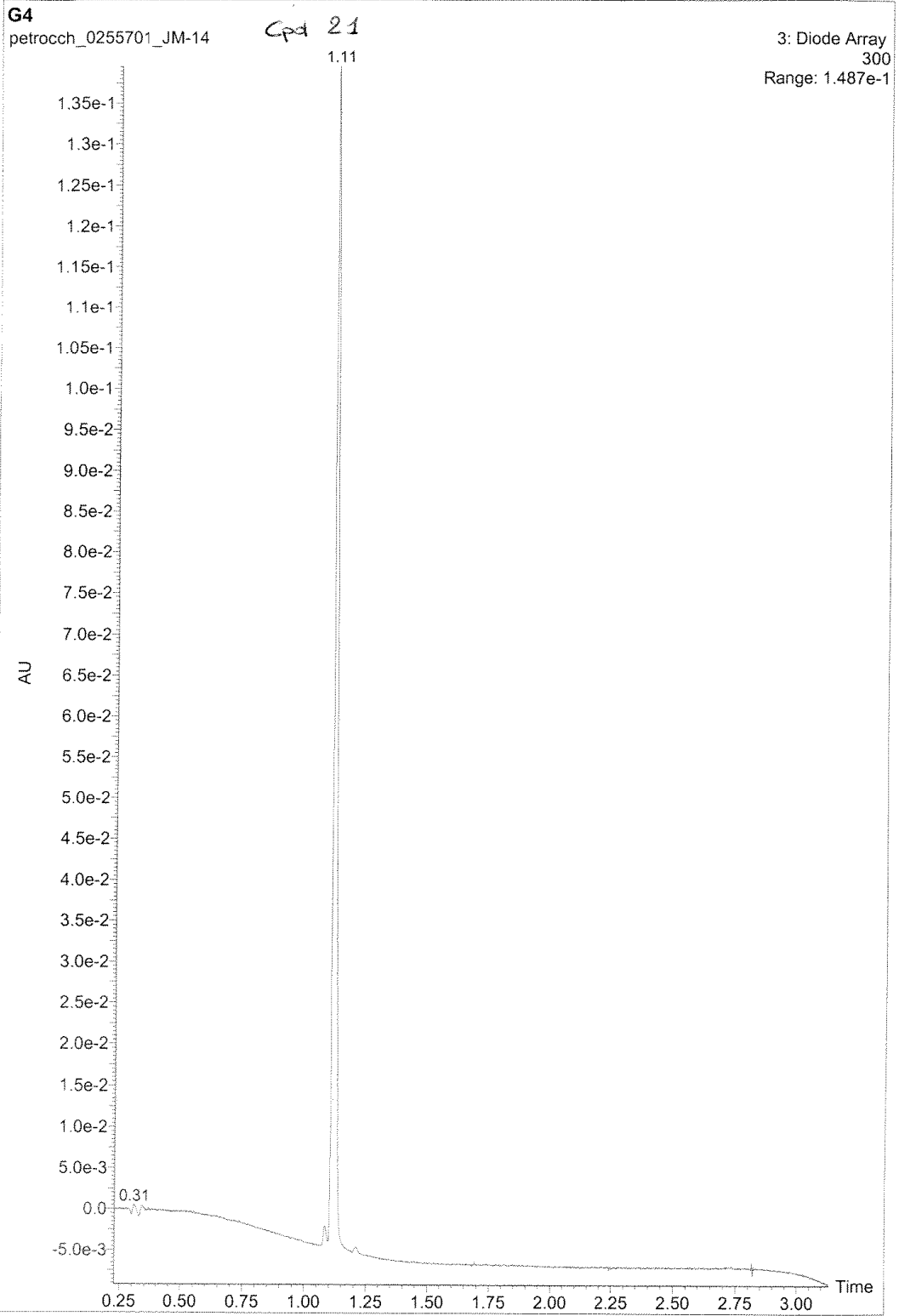


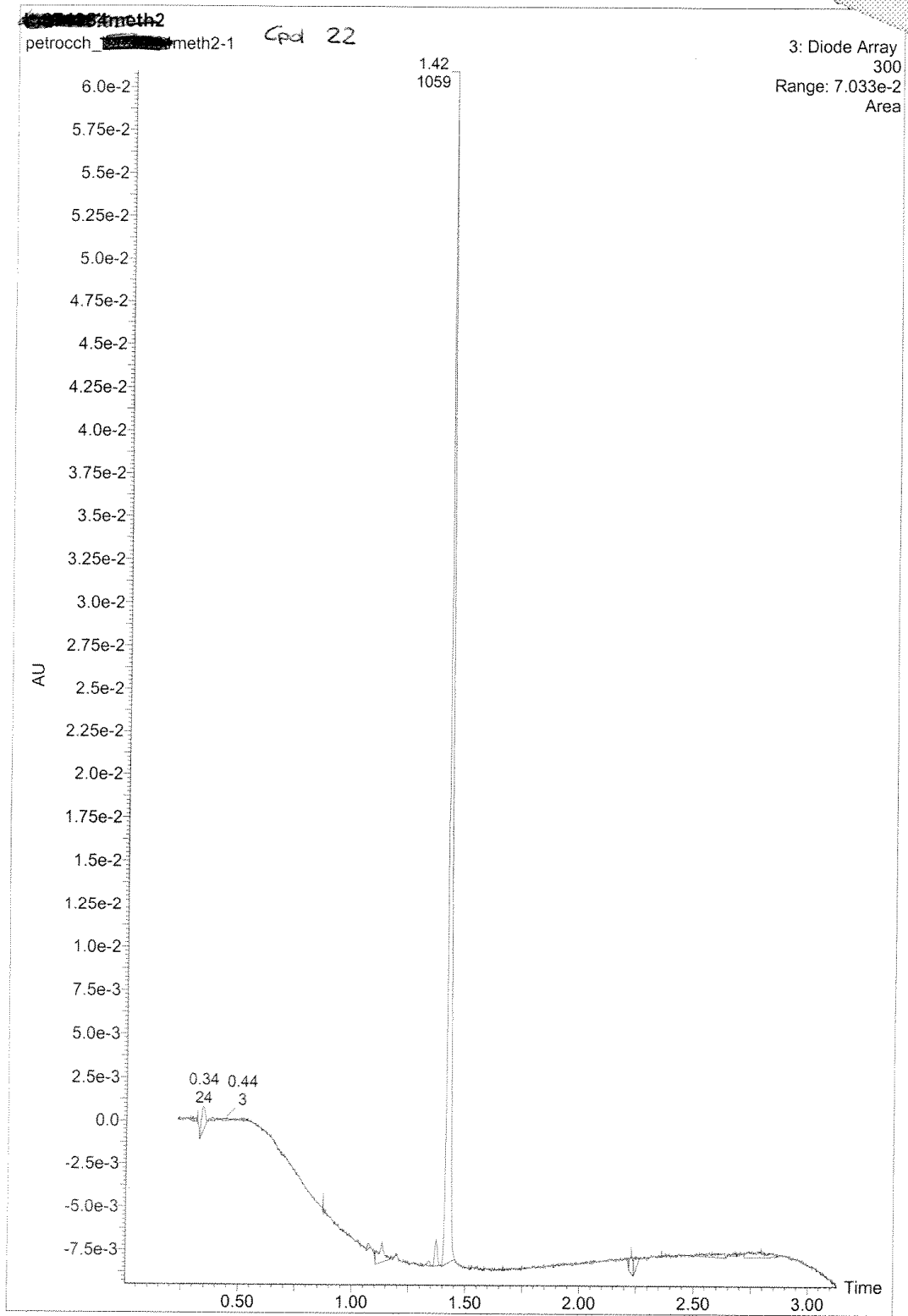


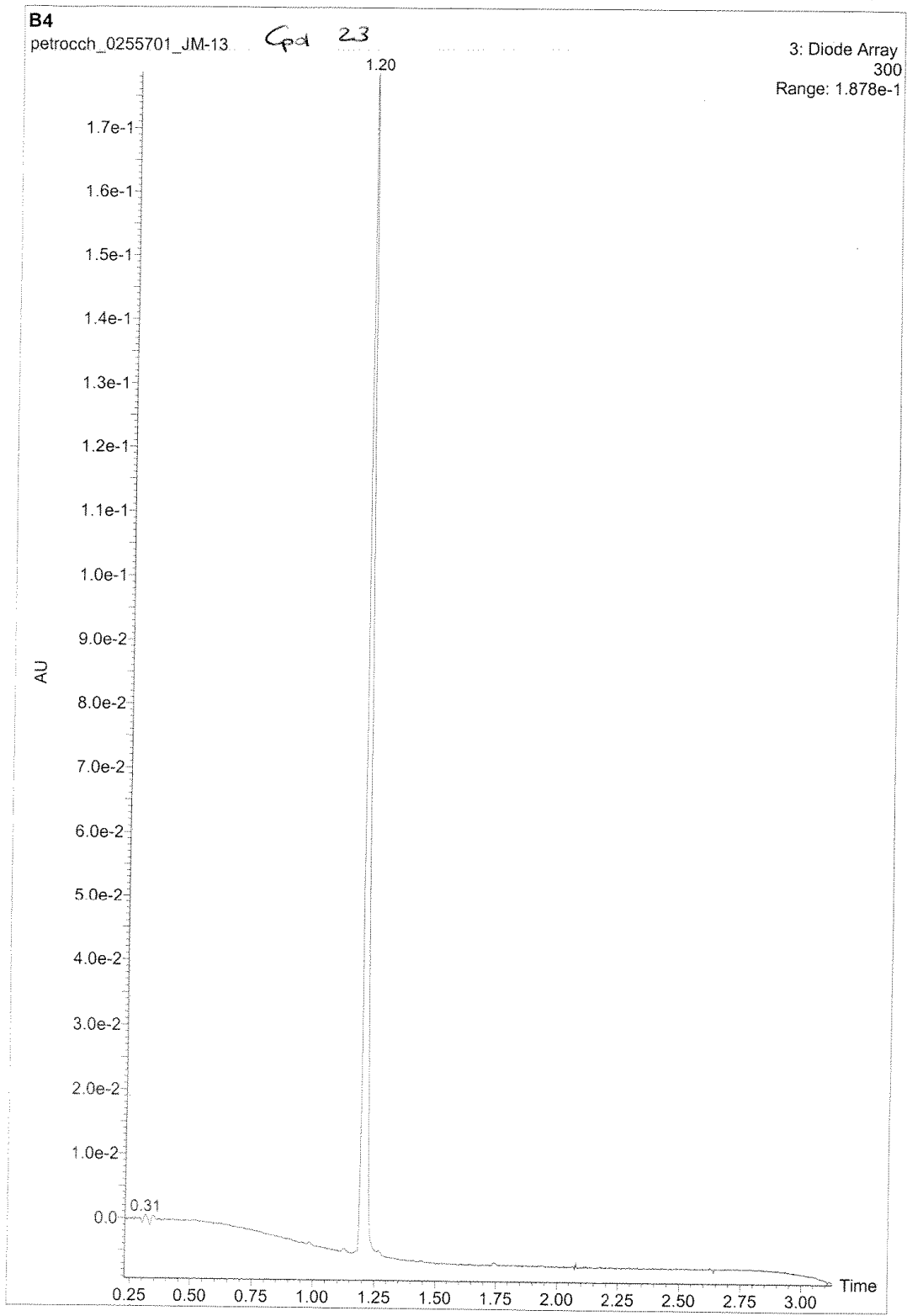


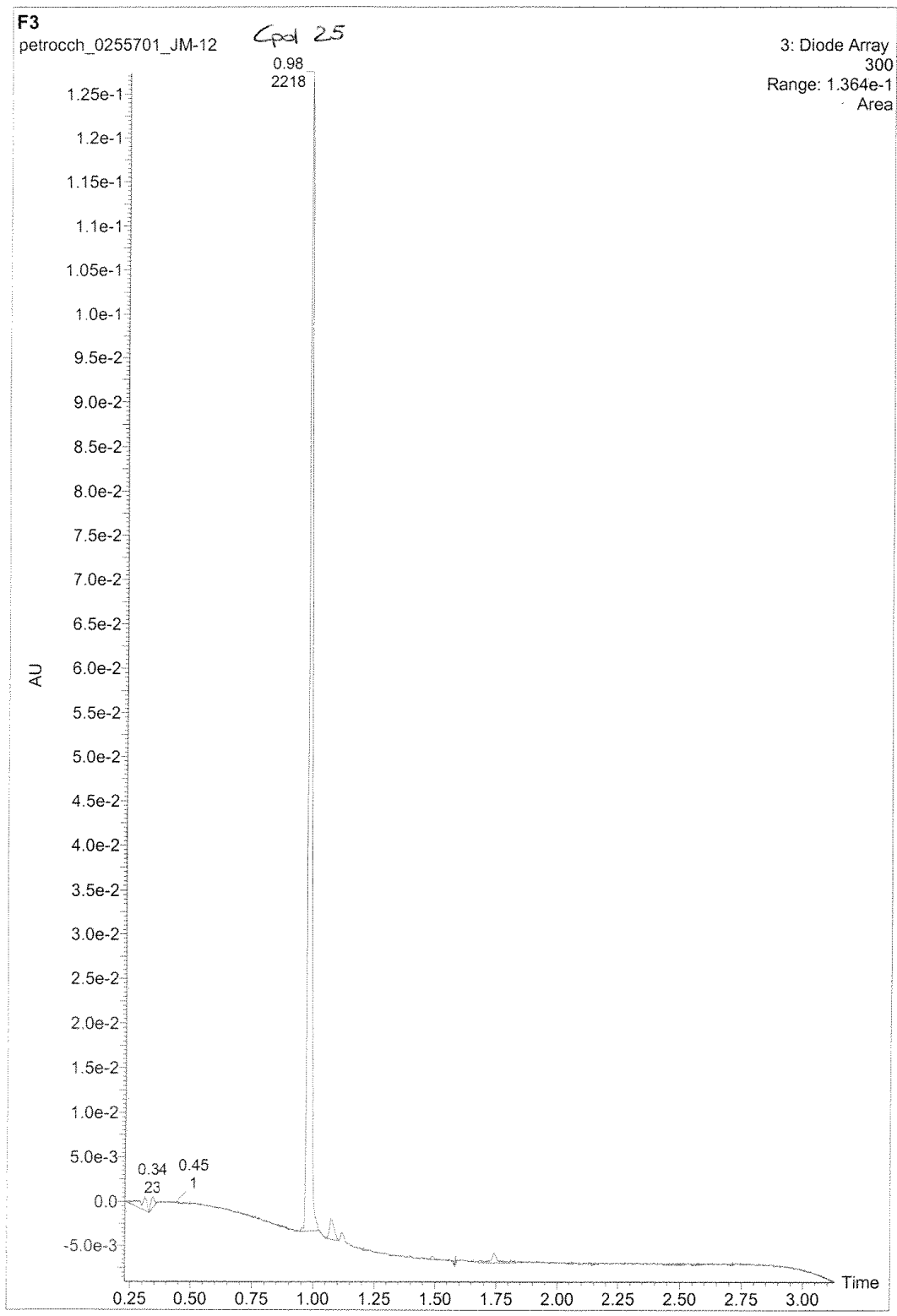


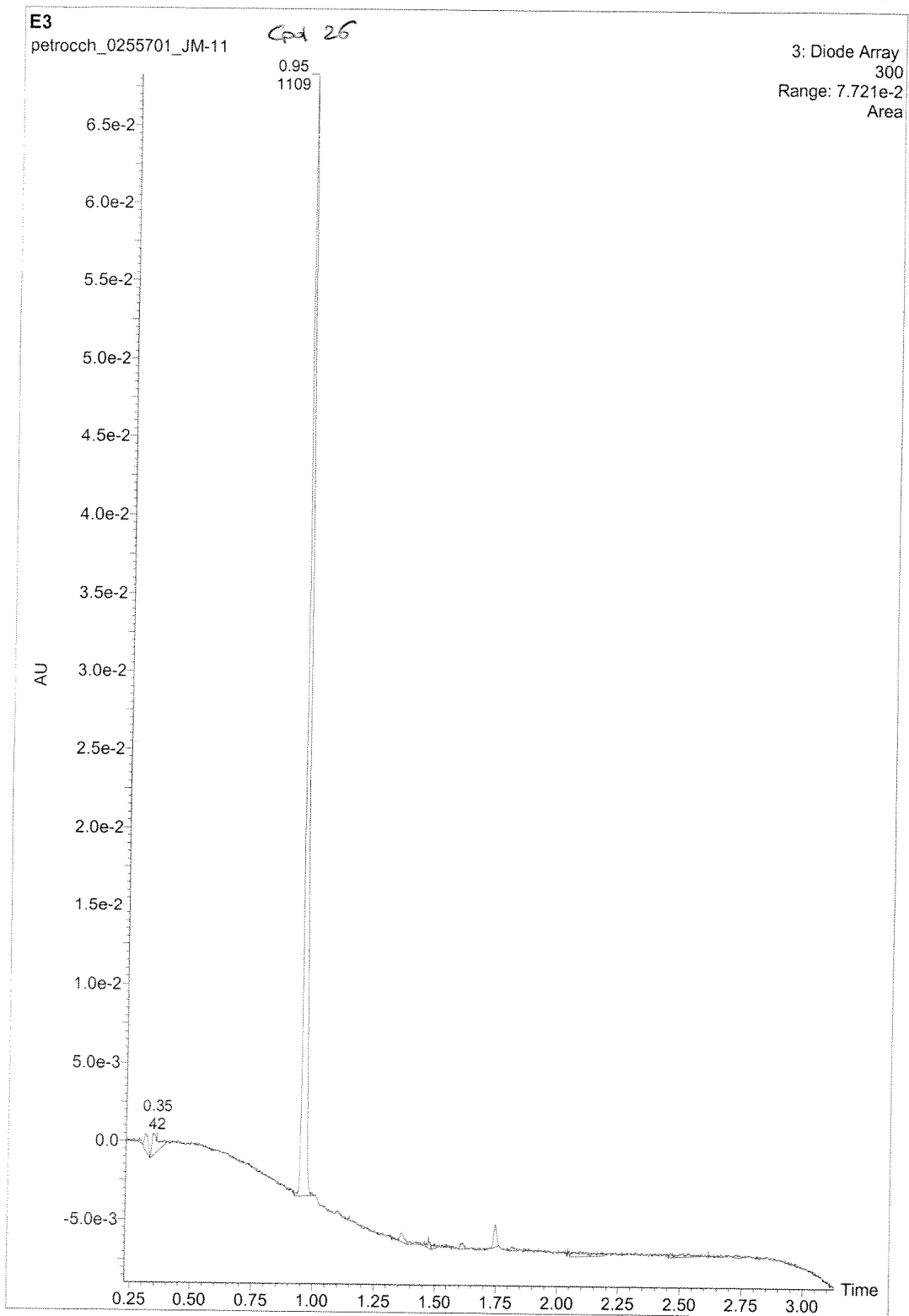


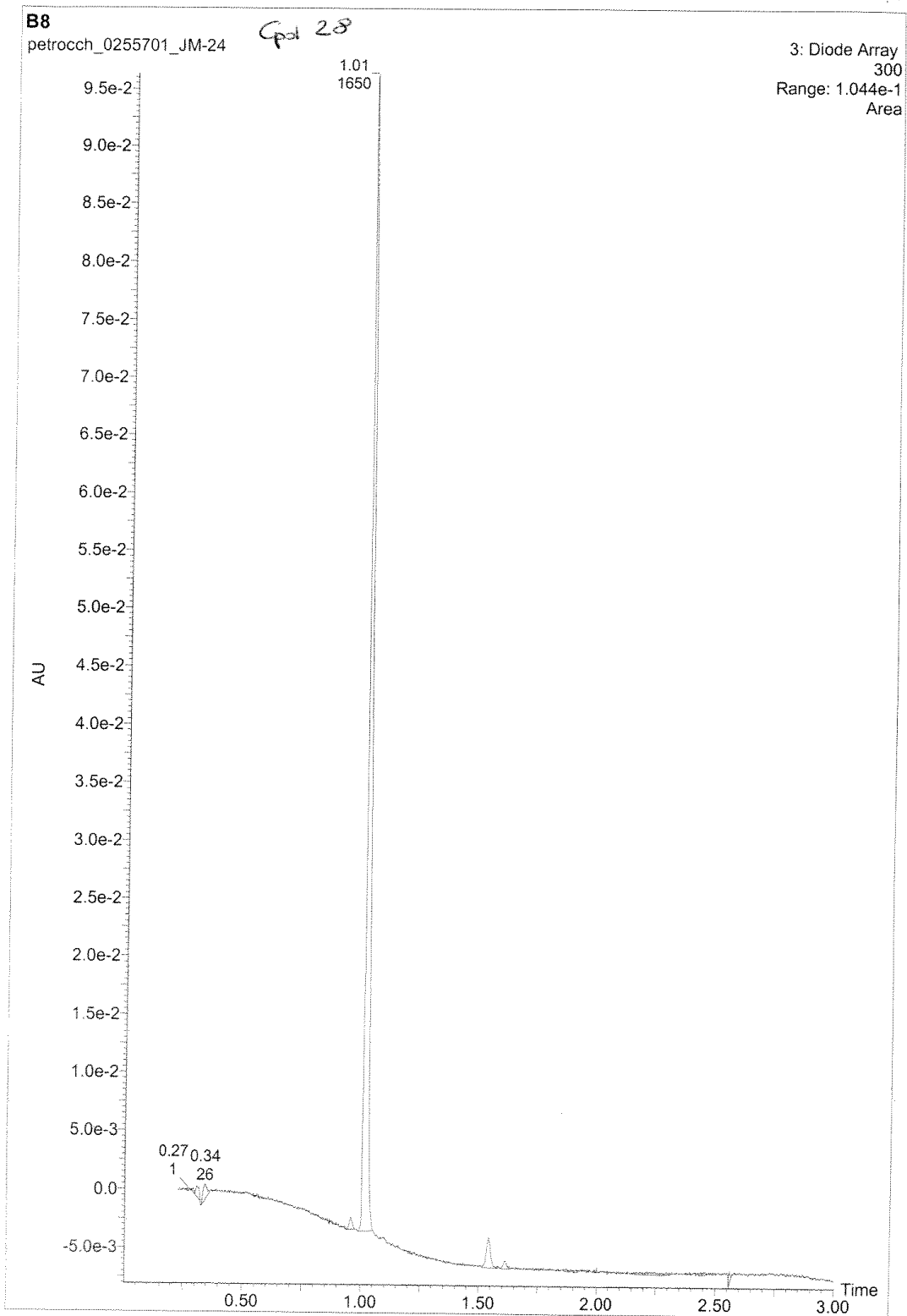


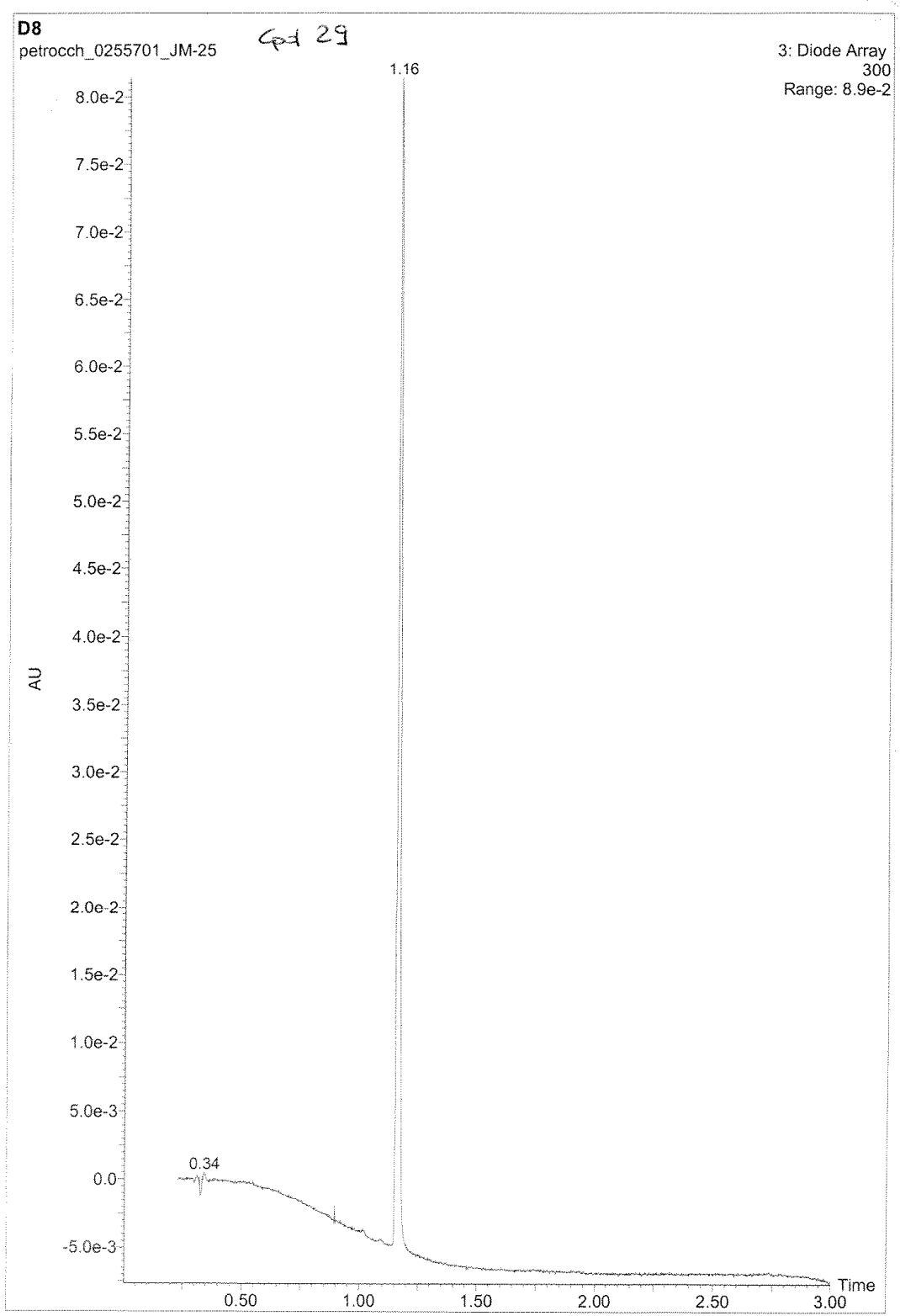


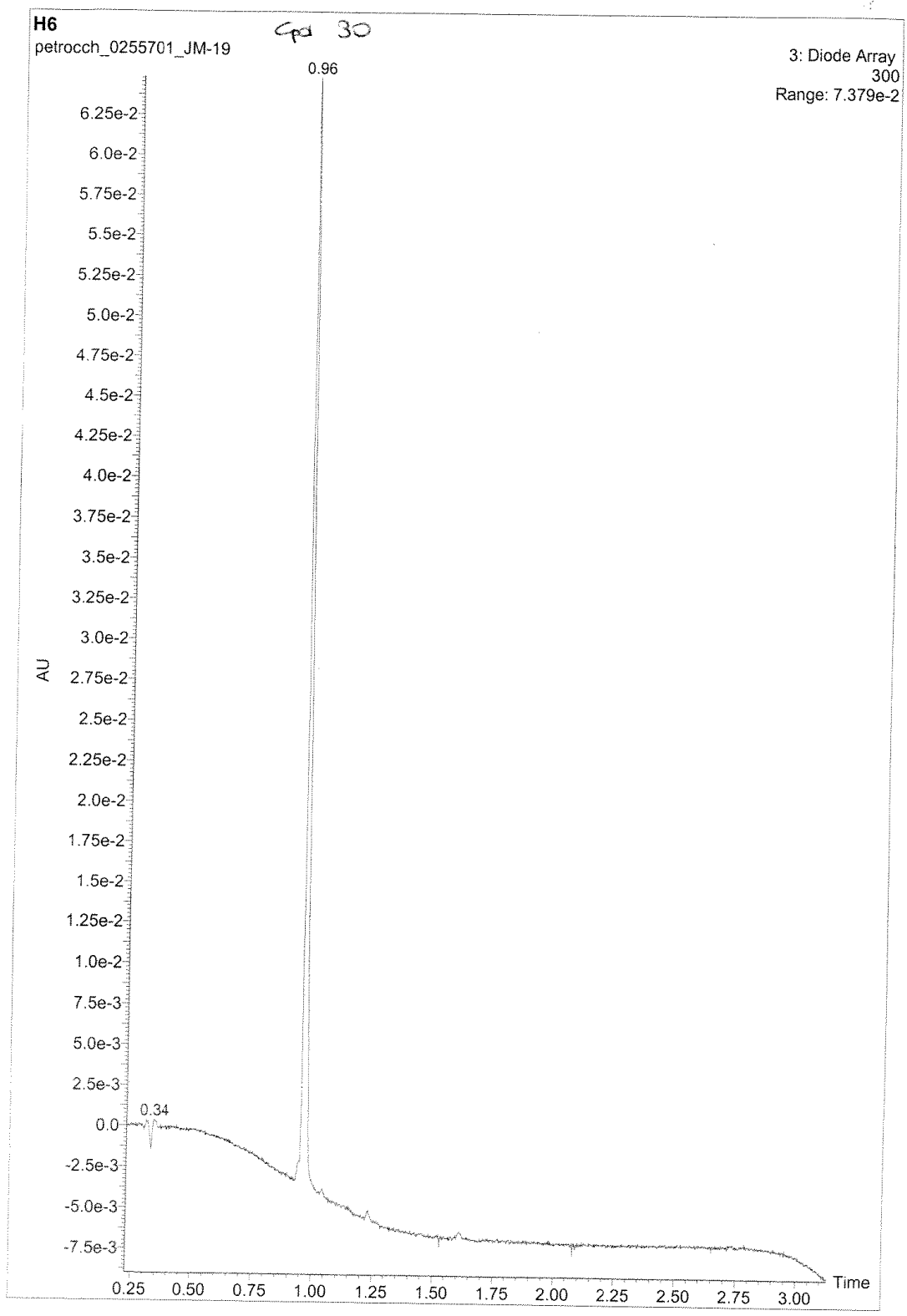


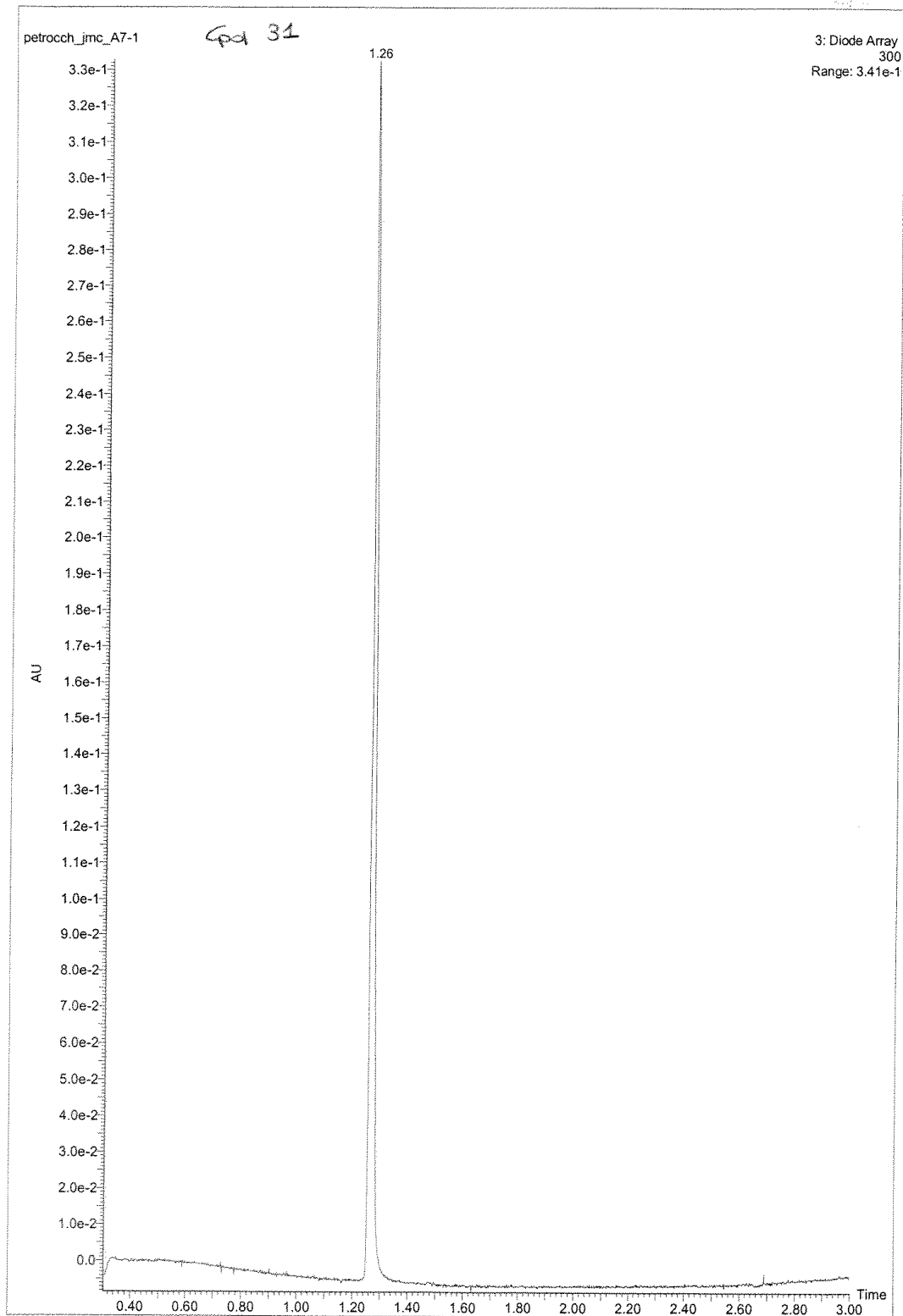


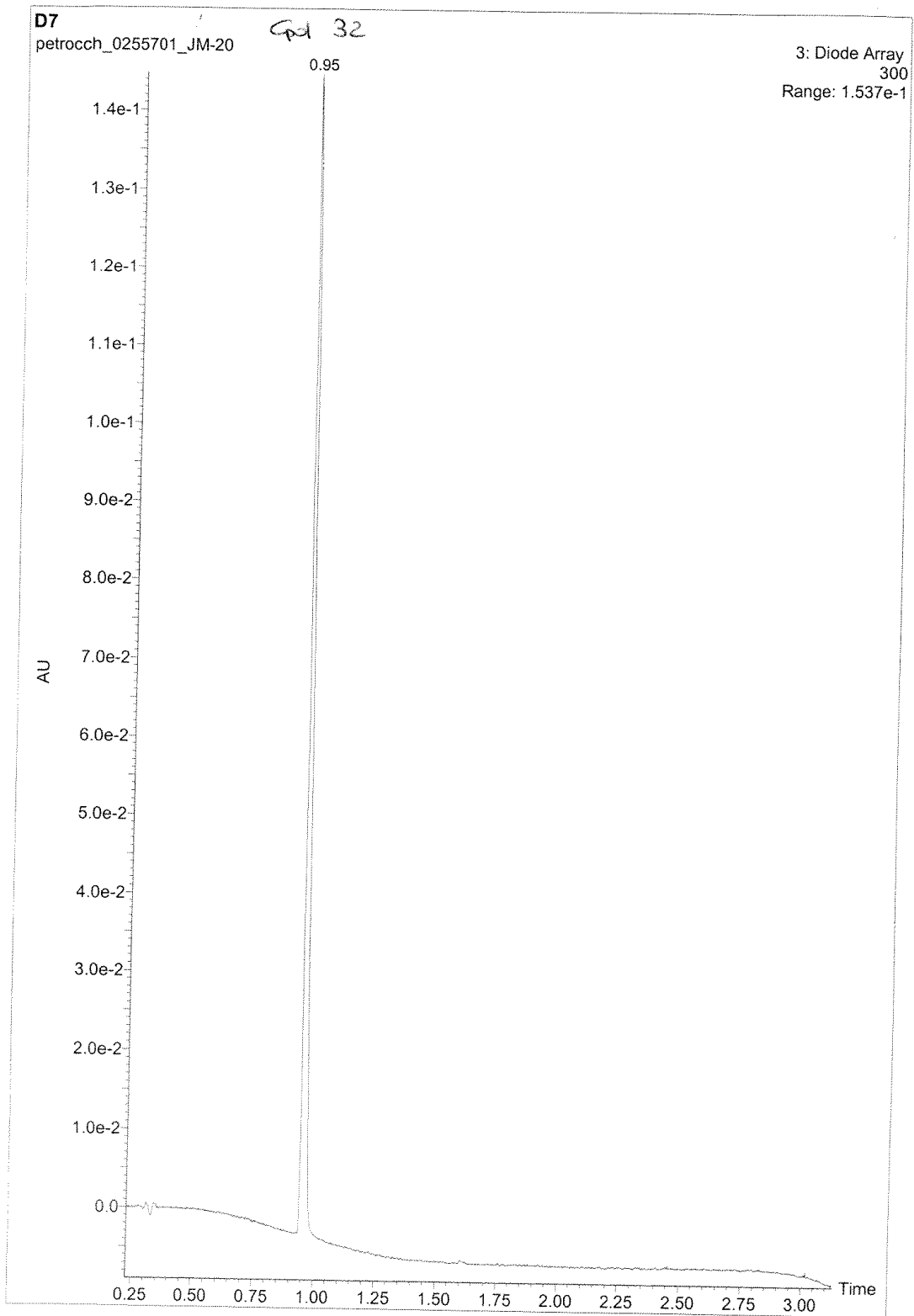


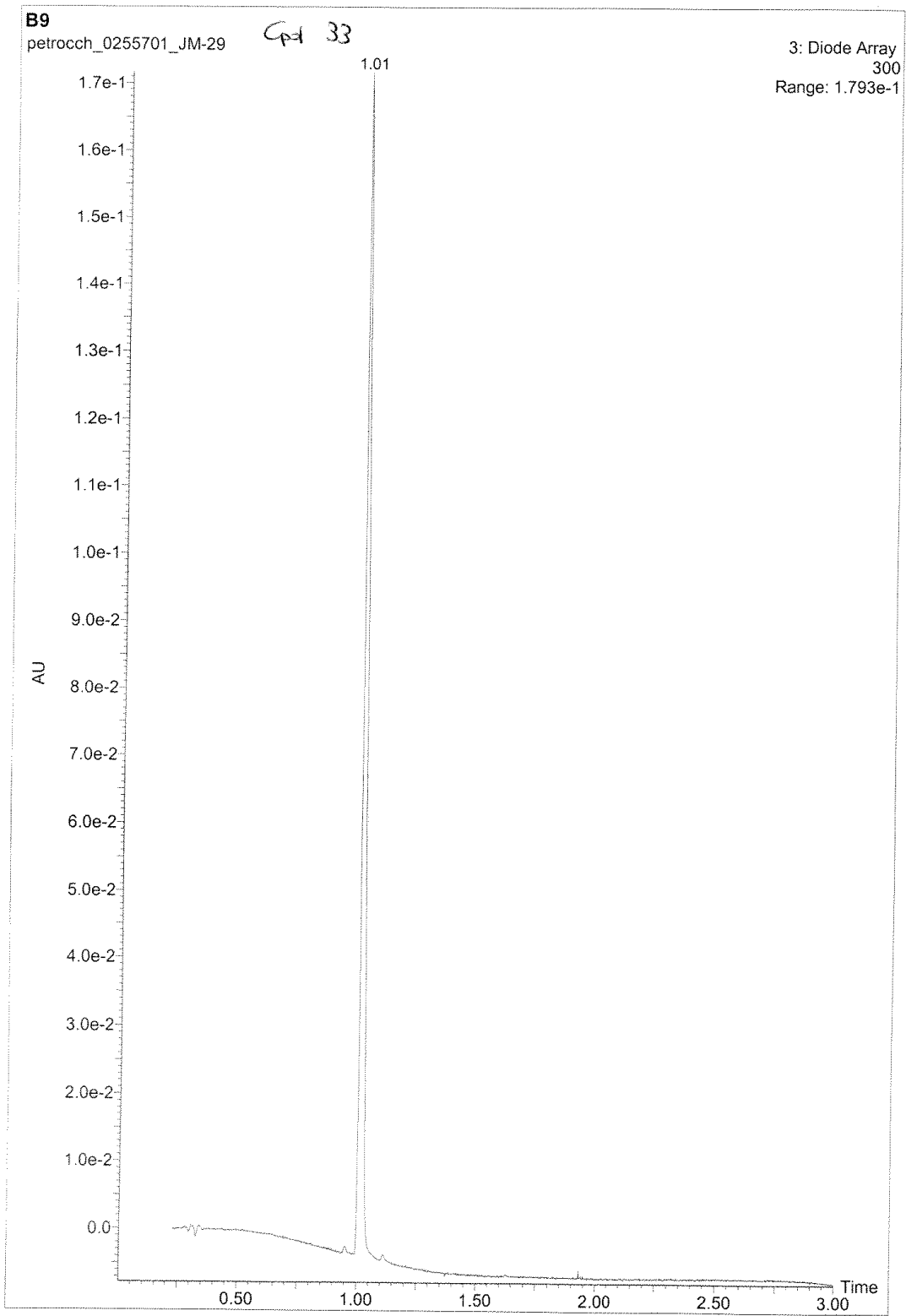


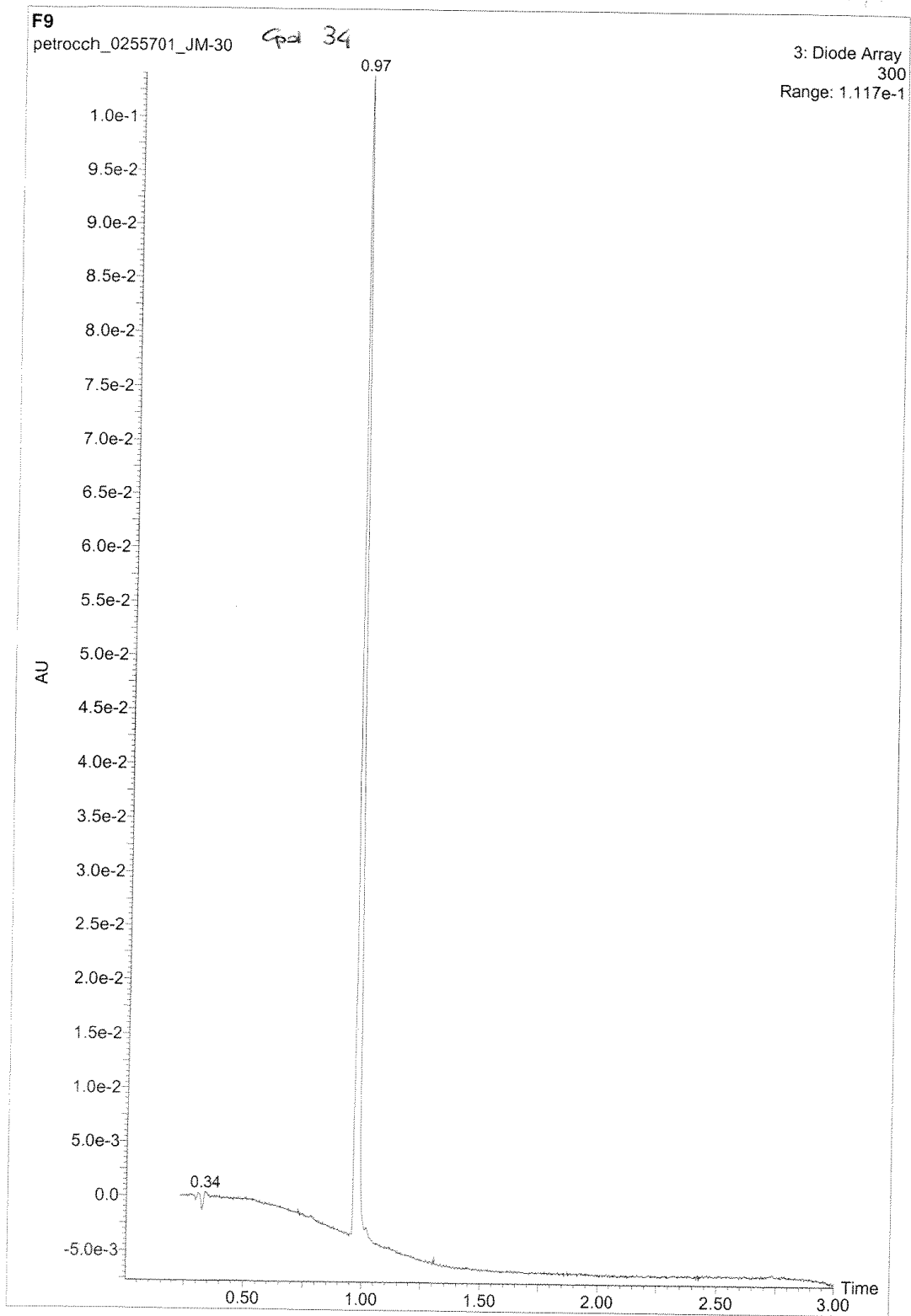




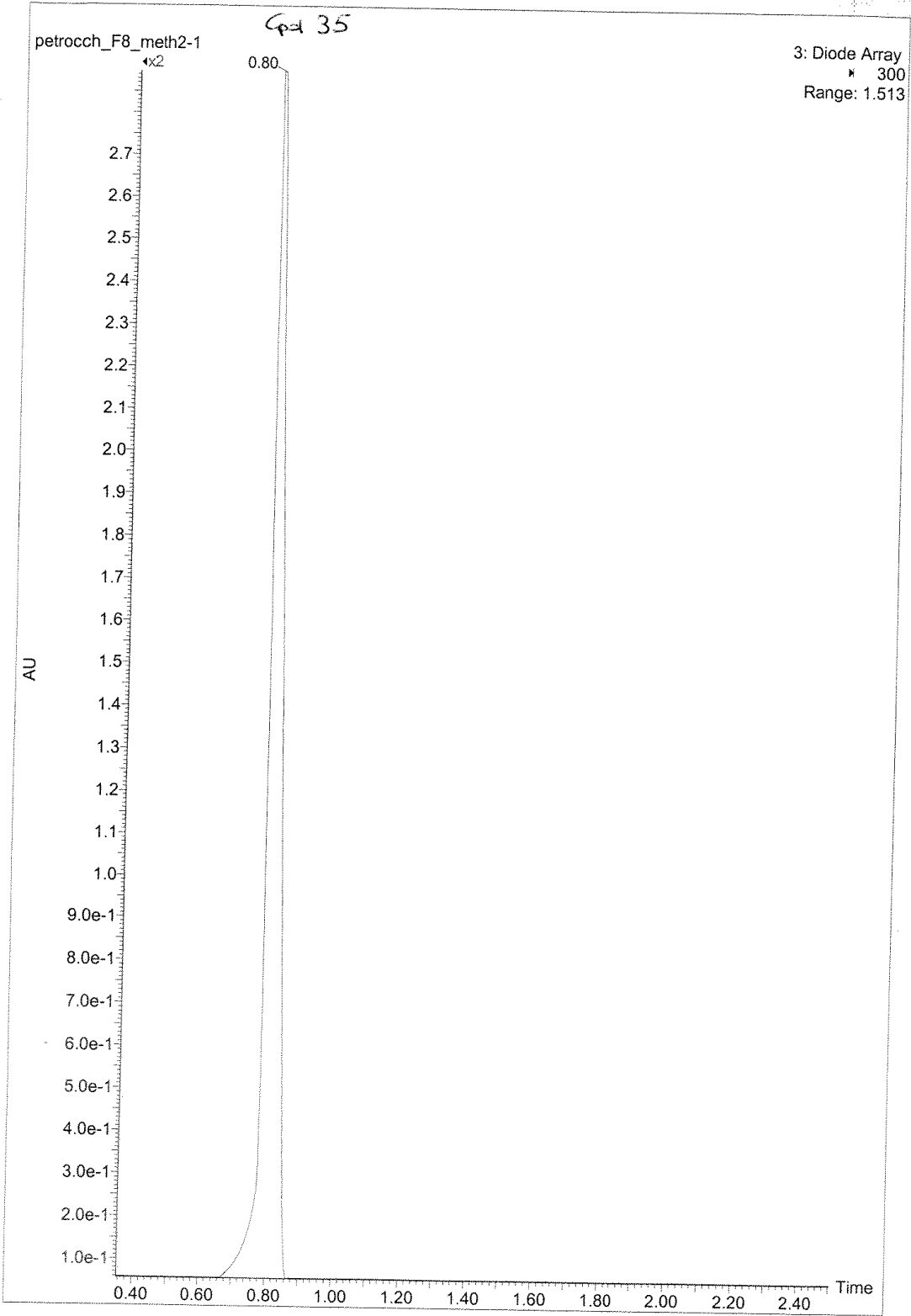


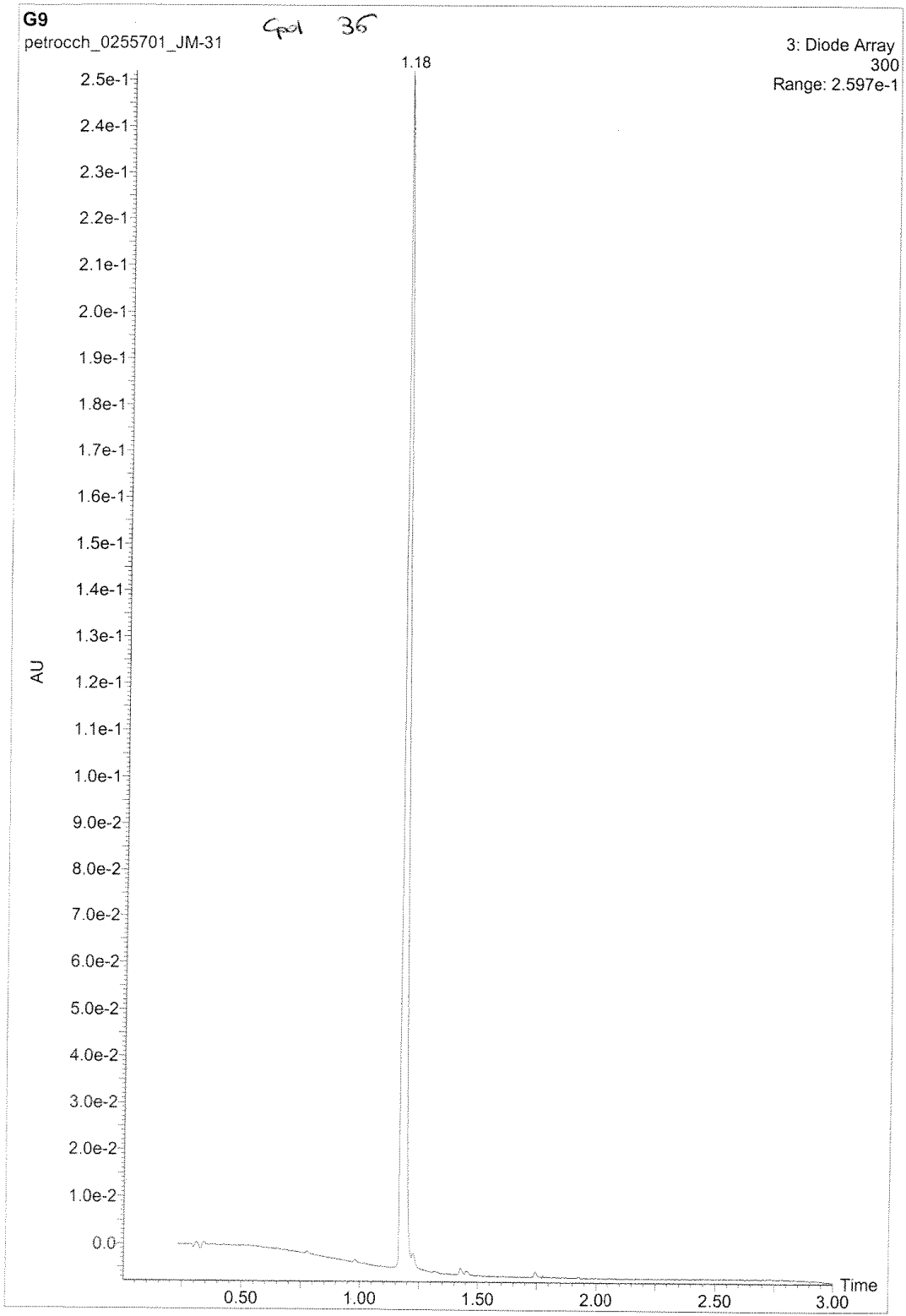


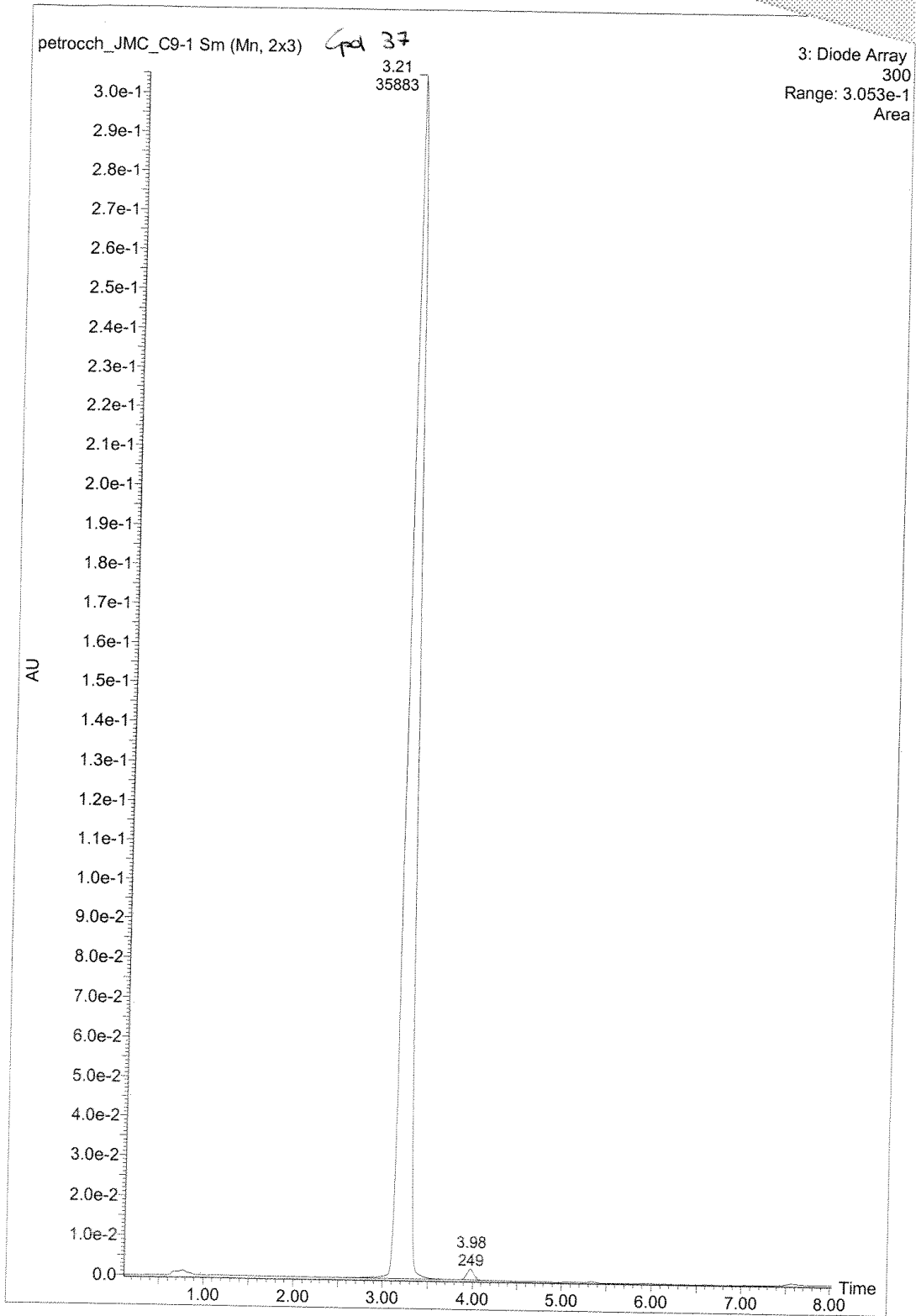


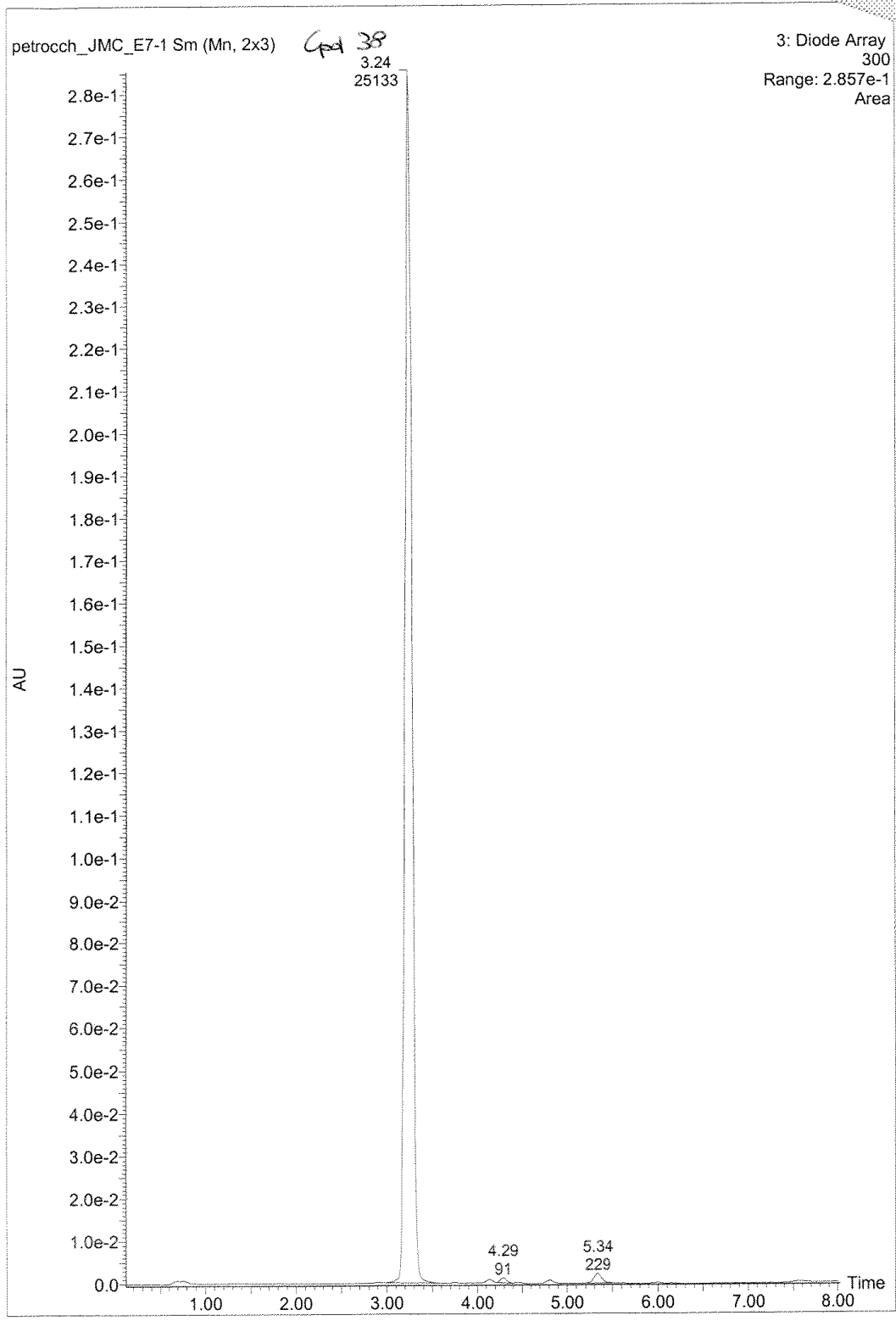


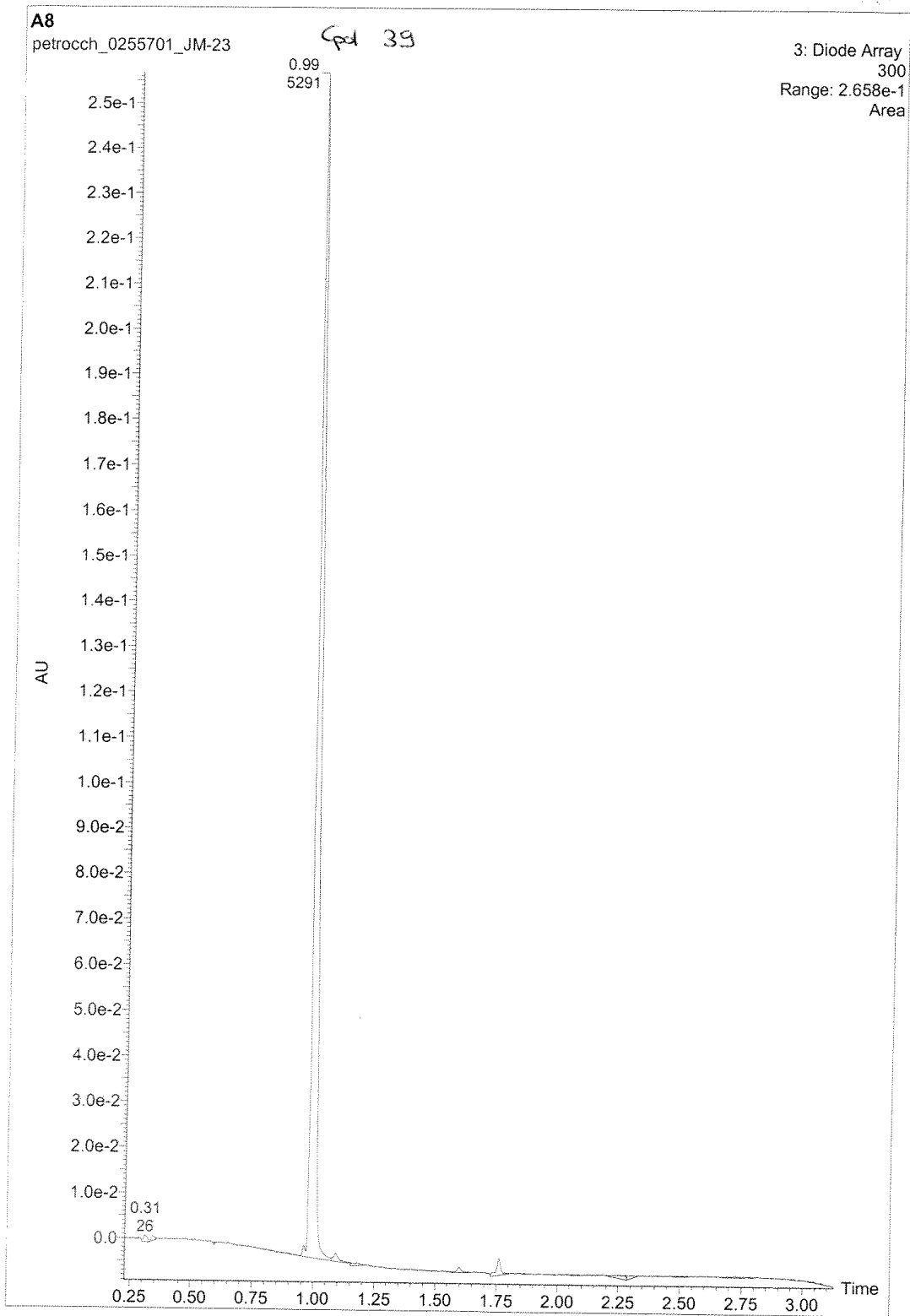
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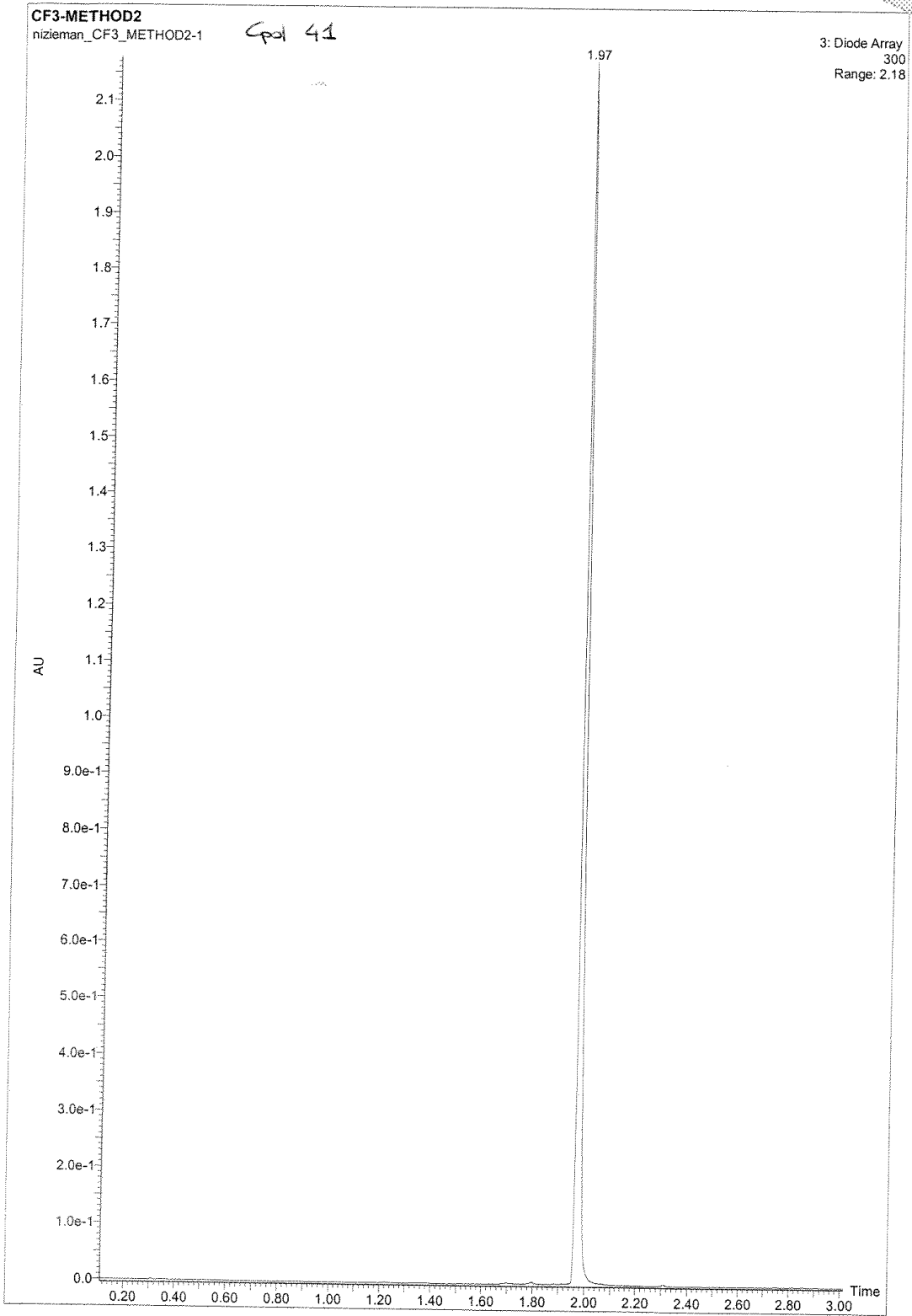


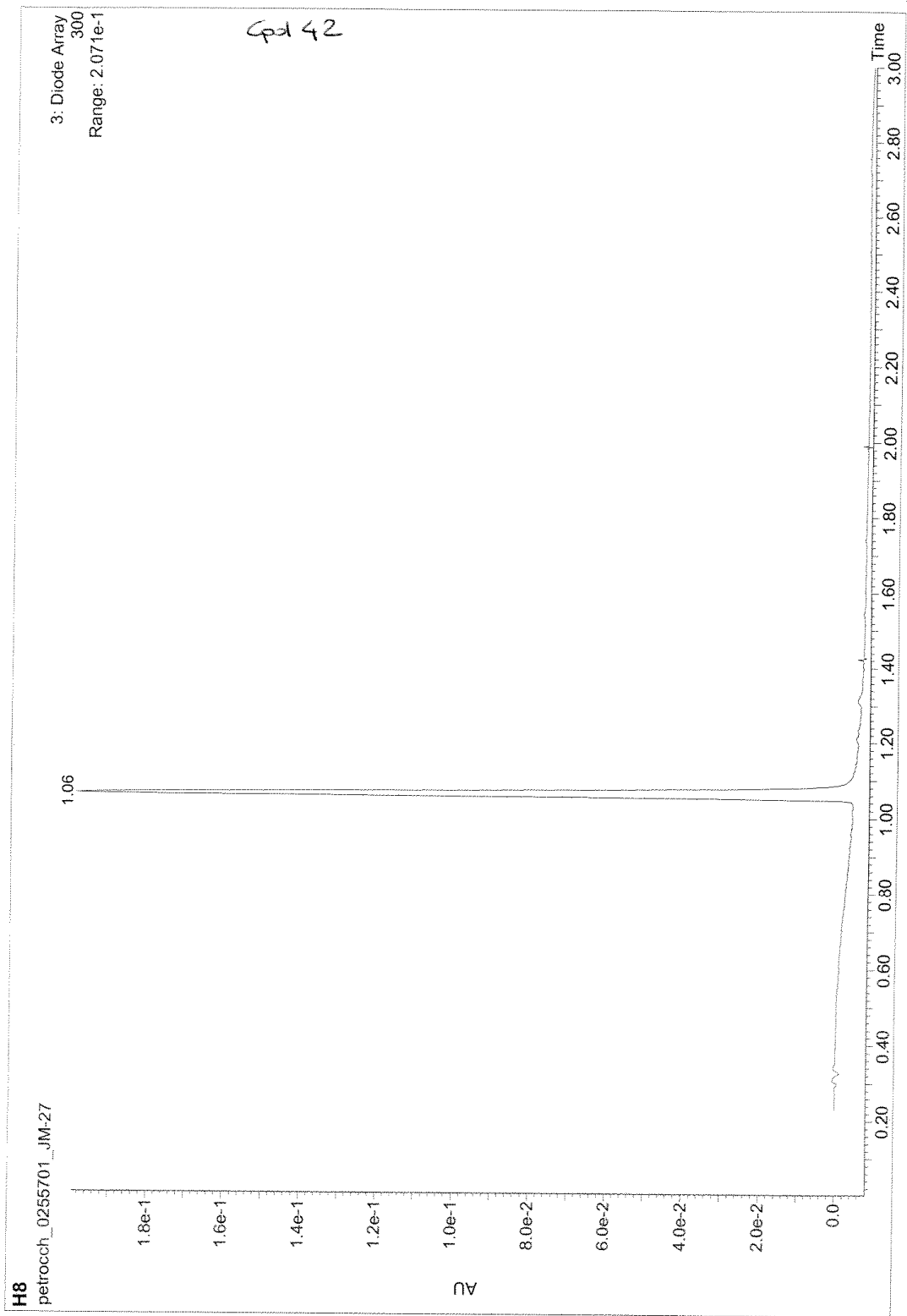


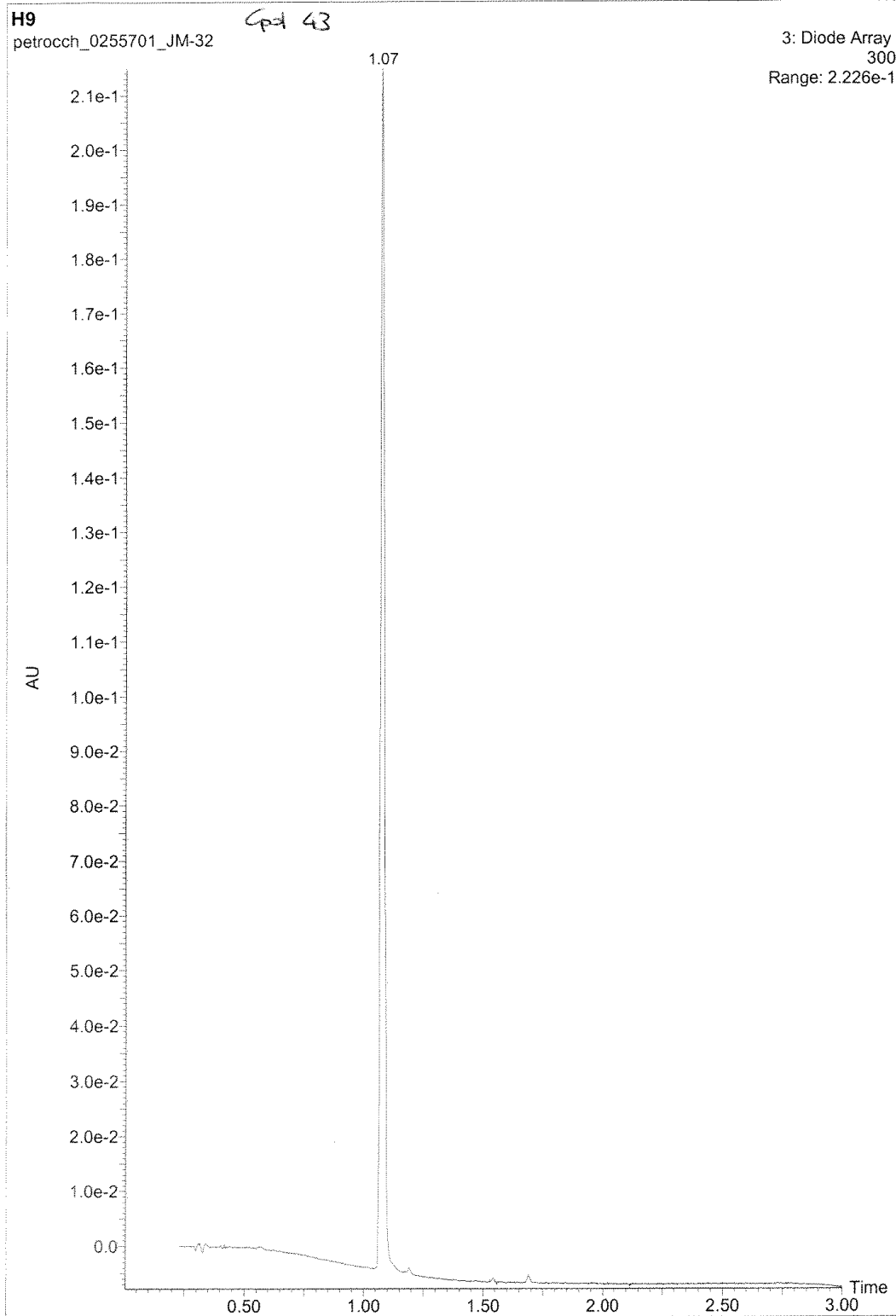












A9

petrocch_0255701_JM-28

Cpd 44

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Range: 1.175e-1

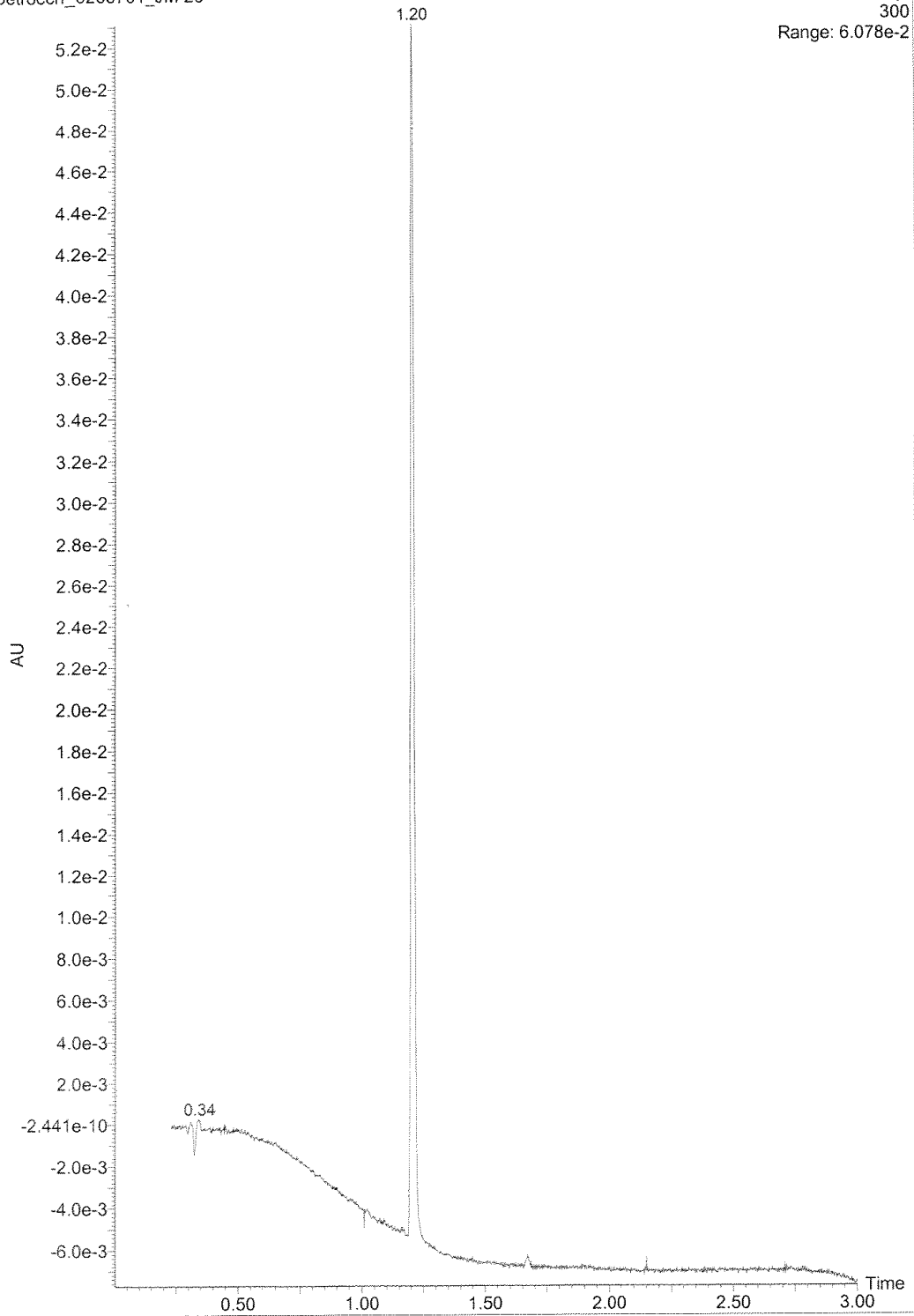


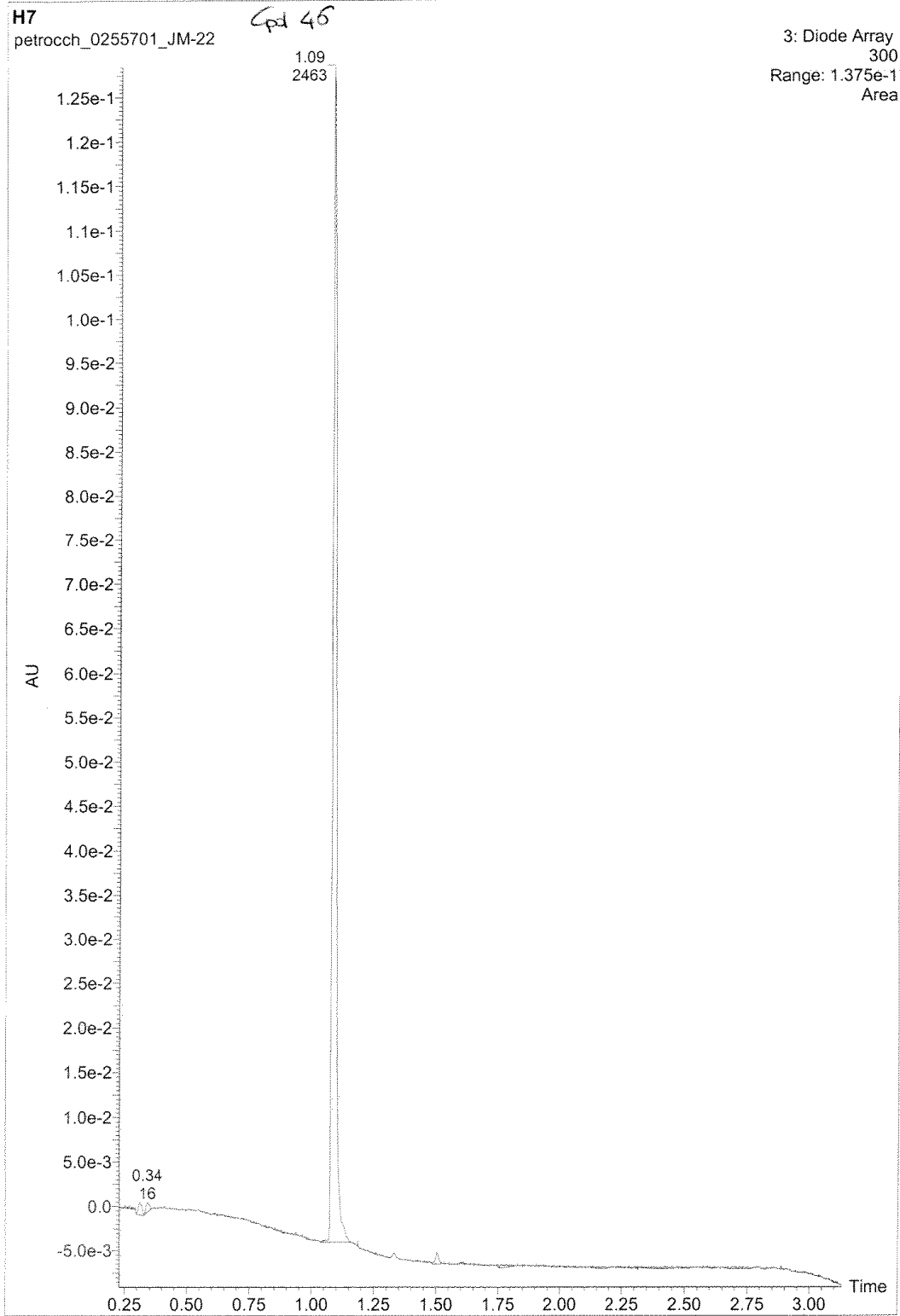
E8

petrocch_0255701_JM-26

Cpd 45

3: Diode Array
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Range: 6.078e-2





Metabolic stability of 38 in liver microsomes, in the presence of UDPGA

