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(54) Title: A PROCESS

(57) Abstract

Cis/trans Tilidine base with an enhanced content of the trans isomer is prepared by mixing a substantially pure cis Tilidine base with water under acidic conditions, preferably using phosphoric acid, at pH values between 2 to 6. Alternatively the substantially pure cis Tilidine base is mixed with a solvent, especially diisopropylethylamine or dimethylformamide under basic conditions at pH values of from 8 to 14. The reaction mixtures thus formed are heated to yield isomerised cis/trans Tilidine base with an enhanced content of the trans isomer.

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"A Process"

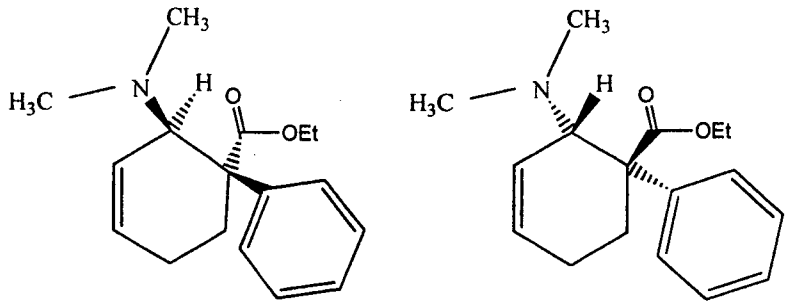
Introduction

The invention relates to a process for isomerisation of Tilidine and derivatives thereof.

Tilidine hydrochloride is a potent therapeutically active analgesic compound which has been used successfully for the treatment of intense and strong pain. It is described in US 3,557,127, DE-C-1518959 and DE-C-1793571.

The compound is a substituted cyclohexanone derivative having the INN chemical name ±-Ethyl-(trans-2-dimethylamine-1-phenyl-3-cyclohexen-trans-1-carboxylate).

Tilidine can exist as either the trans or cis isomer. In this specification trans-tilidine means the racemic mixture of trans-tilidine as shown by the following chemical structures.



RS SR

trans-Tilidine

It has been shown (Liebigs Ann. Chem. 728, 64-87 [1969]) that the reaction of dimethylamine-1, 3-butadien with ethylatropate leads to a cis/trans mixture of Tilidine in a ratio of approximately 80:20.

It is known (Liebigs Ann. Chem. 728, 64-87 [1969]) and accepted that the stereospecific character of Dien (1, 4) – Cyclo addition is dominated by a relative reciprocal orientation of the En – and Dien components before the reaction. This means the constituents of the components introduce specific amounts of electronic density during the reaction. Furthermore, the orientation of the constituents in the Cyclohexene ring is influenced also by that steric factor. Consequently, the cis/trans position in the ring will be directed by their "bulky" constituents.

US 3,557,127 describes methods to rearrange or to separate the cis-isomer to produce the trans-isomer of cyclohexenes. However, such methods are inefficient and uneconomic, especially at a commercial production scale.

US 3 ,679,732 describes a process for partial isomerisation of the cis-isomer in the presence of organic acids such as aliphatic or aromatic monocarboxylic acids, aliphatic or aromatic dicarboxylic acids or anhydrides. The conversion of cis-Tilidine into trans-Tilidine is relatively low and salt impurities are produced.

There is therefore a need for an improved commercially viable process in which the yield of the trans-isomer is maximised and the amount of the cis-isomer present is minimised.

This invention is directed towards providing such a process.

Statements of Invention

According to the invention, there is provided a process for preparing Tilidine comprising:-

mixing a substantially pure cis Tilidine base with either (a) water and an inorganic acid at pH values between 2 and 6, or (b) with a solvent and a base at pH values between 8 and 14; and

heating the reaction mixture thus formed to yield isomerised cis/trans Tilidine base with an enhanced content of the trans isomer.

In one preferred aspect of the invention the process comprises mixing a substantially pure cis Tilidine base with water and an inorganic acid at pH values between 2 and 6, and heating the reaction mixture thus formed to yield isomerised cis/trans Tilidine base with an enhanced content of the trans isomer.

Preferably, the pH is from 3 to 6.

Most preferably the acid is phosphoric acid. This is particularly important as it provides high yield and conversion rate.

Particularly preferred because of improved yield and conversion rate are processes in which the acid, especially phosphoric acid, is added in an amount of from 0.5 to 2.0, most preferably 0.9 to 1.1, and ideally approximately 1:1 molar equivalent to the Tilidine base.

Ideally, the reaction mixture is heated to a temperature of from 90°C to 100°C and kept at this temperature for from 15 to 30 hours.

In a particularly preferred aspect, the invention provides a process comprising mixing cis/trans Tilidine base with water and phosphoric acid, and heating the reaction mixture thus formed to yield isomerised cis/trans Tilidine base with an enhanced content of the trans isomer.

Surprisingly we found that, heating under specific conditions with an acid especially ortho phosphoric acid at pH-values between 2 – 6 (especially 3 – 6) in water as a solvent at 50 – 100°C (especially 95 – 100°C) conversion (cis to trans isomerisation) is achieved in high yields, substantially without side products/impurities.

Preferably, the isomerised Tilidine base has a content of greater than 10% of the trans isomer.

In a preferred embodiment of the invention, isomerised Tilidine base has a content of greater than 60% of the trans isomer.

In one embodiment of the invention the acid comprises a mixture of phosphoric acid and salts thereof.

In one embodiment of the invention, after heating, the reaction mixture is cooled and the cis/trans Tilidine base is extracted by liquid-liquid extraction. Preferably, a solvent such as petroleum ether is added to the solution, the pH is adjusted with a base to 12 – 14, the aqueous layer is separated and the organic layer is evaporated to give the isomerised cis/trans Tilidine base.

According to another aspect of the invention, there is provided a process for preparing Tilidine comprising mixing a substantially pure cis Tilidine base with a solvent and a base at pH values between 8 and 14, and heating the reaction mixture thus formed to yield isomerised cis/trans Tilidine base with an enhanced content of the trans isomer. Preferably, the pH is from 9 to 10.

In one embodiment of the invention, the solvent is diisopropylethylamine. In this case, preferably the reaction mixture is heated to a temperature of from 130°C to 140°C.

In another embodiment of the invention, the solvent is dimethylformamide. In this case, preferably the reaction mixture is heated to a temperature of from 140°C to 150°C.

Preferably, the Tilidine base contains approximately 90 : 10% cis/trans isomers of Tilidine.

In this case isomerised Tilidine base has a content of greater than 10%, ideally greater than 15% of the trans isomer.

Preferably, the solvent is added in a ratio of approximately 1:1 wt:wt equivalent of the Tilidine base.

The invention also provides Tilidine whenever prepared by a process of the invention.

Detailed Description of the Invention

The invention will be more clearly understood from the following description thereof, given by way of example only.

General Isomerisation Procedure

10 g of cis-Tilidine base (36.58 mmole ≥ 97% cis pure by HPLC) are mixed with 30 mls of process water and 4.3 g of phosphoric acid (85%) (37.3mmol). The reaction mixture is heated to reflux at 95 to 100°C and kept for 15 to 30 hours. The solution is then cooled to 40 – 50°C, an extra 30mls of process water are added together with 50 to 60 mls of petroleum ether. The pH is adjusted to 12 – 14 with sodium hydroxide (30%) and the aqueous layer is separated at 40 – 50°C. After washing the organic layer with 20 to 30 mls of process water, the organic layer is evaporated to dryness to give isomerised (cis/trans) Tilidine base.

The yield is 6 to 8 g Tilidine base (yellow oil) with enriched trans-Tilidine.

Example 1

Following the general procedure outlined above, 10 g of pure cis Tilidine base was heated with 0.8 molar amount of phosphoric acid (85%) at pH 5 – 6 in process water at 95 to 100°C for 16 hours to yield 8.8 g of a mixture of 39.5 : 56.8% of cis/trans Tilidine base. The HPLC analysis is given in Fig. 1.

Thus, a high yield and an excellent conversion rate are achieved.

Example 2

Following the general procedure outlined above, 10 g of pure cis Tilidine base was heated with 0.5 molar amount of phosphoric acid (85%) at pH 5 – 6 in process water at 95 to 100°C for 20.5 hours to yield 7.5 g of a mixture of 60.1:37.8% of cis/trans Tilidine base. The HPLC analysis is given in Fig. 2.

Example 3

Following the general procedure outlined above, 10 g of pure cis Tilidine base was heated with 2 molar amount of phosphoric acid (85%) at pH 2 – 3 in process water at 95 to 100°C for 16 hours to yield 7.9 g of a mixture of 73.8:25.7% of cis/trans Tilidine base. The HPLC analysis is given in Fig. 3.

Example 4

Following the general procedure outlined above, 10 g of pure cis Tilidine base was heated with an equimolar amount of phosphoric acid (85%) at pH 3 – 4 in process water at 95 to 100°C for 30 hours to yield 6.4 g of a mixture of 25.1:73.2% of cis/trans Tilidine base. The HPLC analysis is given in Fig. 4.

Example 5

Following the general procedure outlined above, 10 g of pure cis Tilidine base was heated with an equimolar amount of phosphoric acid (85%) at pH 3 – 4 in process water at 95 to 100°C for 7.5 hours to yield 8.5 g of a mixture of 69:31% cis/trans Tilidine base as determined by HPLC analysis.

Example 6

Following the general procedure outlined above, 10 g of pure cis Tilidine base was heated with an equimolar amount of phosphoric acid (85%) at pH 3 – 4 in process water at 95 to 100°C for 18.5 hours to yield 7.0 g of a mixture of 34.3:61.7% of cis/trans Tilidine base as determined by HPLC analysis.

Example 7

Following the general procedure outlined above, 10 g of pure cis Tilidine base was heated with 1.2 molar amount of phosphoric acid (85%) at pH 3 in process water at 95 to 100°C for 15.5 hours to yield 7.5 g of a mixture of 42.5:54.7% of cis/trans Tilidine base as determined by HPLC analysis.

Example 8

Following the general procedure outlined above, 10.8 g of pure cis Tilidine base was heated with an equimolar amount of phosphoric acid (85%) at pH 3 - 4 in process water at 78 to 80°C for 17 hours to yield 9.4 g of a mixture of 86.2:13.5% of cis/trans Tilidine base as determined by HPLC analysis.
The lower reaction temperature leads to a lower conversion.

Example 9

Following the general procedure outlined above, 6.2 g of pure cis Tilidine HCl. 1.5 H_2O was heated at pH 5 - 6 in process water at 95 to 100°C for 20 hours to yield 4.6 g of a mixture of 90.9:8.8% cis/trans Tilidine base as determined by HPLC analysis.
The use of the Tilidine Hydrochloride salt gives less than 10% converion.

Example 10

Following the general procedure outlined above, 10 g of pure cis Tilidine base was heated with an equimolar amount of concentrated H_2SO_4 at pH 1 in process water at 95 to 100°C for more than 16 hours to yield 8.5 g of a mixture of 94.1:4.9% of cis/trans Tilidine base as determined by HPLC.

Example 11

Following the general procedure outlined above, 10 g of pure cis Tilidine base was heated with an equimolar amount of KH_2PO_4 at pH 5 in process water at 95 to 100°C for 21 hours to yield 8.5 g of a mixture of 91.4:8.6% cis/trans Tilidine base as determined by HPLC.

Example 12

Following the general procedure outlined above, 10.1 g of pure cis Tilidine base was heated with an equimolar amount of NaH_2PO_4 at pH 5 - 6 in process water at 95 to 100°C for 18.5 hours to yield 8.6 g of a mixture of 88.9:10.8% cis/trans Tilidine base as determined by HPLC.

We have surprisingly found that the best results in terms of yield and conversion rate with optimum reaction conditions are achieved with 0.5 to 2.0, especially 0.9 to 1.1, ideally approximately 1:1 molar equivalents of phosphoric acid. We have found that other acids provide enhanced yield and/or conversion rates and/or more favourable reaction conditions than prior art processes.

We have also found that, by heating under basic conditions conversion (cis to trans isomerisation) can be achieved in high yields without any side products. The following examples illustrate this aspect of the invention.

Example 13

201g of pure cis Tilidine base (>97% purity by HPLC – see Fig. 5) was dissolved in 201mls of dimethylformamide (DMF) and the mixture thus formed was heated to 140-150°C. This temperature was maintained for 9 hours. The solvent was removed under reduced pressure to afford crude Tilidine base as an oil. The yield

was 170.2g of 73.01:18.3% cis/trans Tilidine-base as determined by HPLC (Fig. 6).

Example 14

137g of pure cis Tilidine base (>97% purity by HPLC – see Fig. 1) was dissolved in 137mls of diisopropylethylamine (Hünig base) and the mixture thus formed was heated to a reflux temperature of 130-140°C. This temperature was maintained for 19 hours. The solvent was removed under reduced pressure to afford crude Tilidine as an oil. The yield was 130g of 79.9:19.5% cis/trans Tilidine-base as determined by HPLC (Fig. 7).

The invention is not limited to the embodiments hereinbefore described which may be varied in detail.

APPENDIX

Data for Fig. 1

Peak Quantitation: AREA Calculation Method: AREA%

No.	RT	Area	Area%	BC	Purity
1	2.61	1987	0.058	BB	0.475
2	2.98	10185	0.298	BB	0.899
3	3.69	2021	0.059	BB	0.671
4	5.16	1938626	56.652	BB	1.000
5	8.03	1346259	39.341	BB	0.999
6	9.89	122924	3.592	BB	0.996
		3422002	100.000		

Data for Fig. 2

Peak Quantitation: AREA Calculation Method: AREA%

No.	RT	Area	Area%	BC	Purity
1	2.63	1879	0.045	BB	0.974
2	2.87	12516	0.300	BB	0.888
3	3.71	4196	0.100	BB	0.993
4	5.22	1576846	37.751	BB	1.000
5	6.83	2350	0.056	BB	0.991
6	7.32	1636	0.039	BB	0.732
7	7.85	2503892	59.945	BV	0.999
8	9.90	73673	1.764	TBB	0.996
		4176988	100.000		

Data for Fig. 3

Peak Quantitation: AREA Calculation Method: AREA%

No.	RT	Area	Area%	BC	Purity
1	2.61	7456	0.131	BB	0.841
2	3.69	7850	0.138	BB	0.997
3	4.71	3251	0.057	BB	0.898
4	5.21	1463439	25.769	BB	1.000
5	6.75	1885	0.033	BB	0.968
6	7.62	4191946	73.814	BB	1.000
7	9.89	3232	0.057	BB	0.690
		5679059	100.000		

Data for Fig. 4

Peak Quantitation: AREA Calculation Method: AREA%

No.	RT	Area	Area%	BC	Purity
1	2.97	15142	0.357	BB	0.989
2	3.69	5455	0.129	BB	0.842
3	4.61	7039	0.166	BB	0.960
4	5.03	3101901	73.133	BB	1.000
5	6.83	7642	0.180	BB	0.936
6	7.36	4447	0.105	BB	0.779
7	8.11	1064949	25.108	BB	1.000
8	9.91	34882	0.822	BB	0.990
		4241457	100.000		

Data for Fig. 5

Peak Quantitation: AREA Calculation Method: AREA%

No.	RT	Area	Area%	BC	Purity
1	6.27	22677	0.327	BB	0.982
2	6.71	148290	2.138	BB	1.000
3	7.41	1259	0.018	BB	0.970
4	9.13	6764288	97.517	BB	1.000
		6936514	100.000		

Data for Fig. 6

No.	RT	Area	Area%	BC	Purity
1	3.43	136319	7.595	BB	0.999
2	4.19	8663	0.483	BB	0.981
3	5.66	4035	0.225	BB	0.978
4	6.45	328326	18.292	BB	1.000
5	9.58	1317547	73.405	BB	1.000
		1794890	100.000		

Data for Fig. 7

No.	RT	Area	Area%	BC	Purity
1	1.91	20432	0.201	BB	0.697
2	2.94	8757	0.086	BB	0.211
3	3.51	4067	0.040	BV	0.879
4	3.71	3544	0.035	VB	0.959
5	3.88	3461	0.034	BB	0.827
6	6.55	1989474	19.574	BB	1.000
7	7.69	828	0.008	BB	0.933
8	8.77	4150	0.041	BB	
9	9.51	8129368	79.981	BB	1.000
		10164081	100.000		

CLAIMS

1. A process for preparing Tilidine comprising: -

mixing a substantially pure cis Tilidine base with either (a) water and an inorganic acid at pH values between 2 and 6, or (b) with a solvent and a base at pH values between 8 and 14; and

heating the reaction mixture thus formed to yield isomerised cis/trans Tilidine base with an enhanced content of the trans isomer.

2. A process as claimed in claim 1 comprising mixing a substantially pure cis Tilidine base with water and an inorganic acid at pH values between 2 and 6, and heating the reaction mixture thus formed to yield isomerised cis/trans Tilidine base with an enhanced content of the trans isomer.

3. A process as claimed in claim 2, wherein the pH is from 3 to 6.

4. A process as claimed in any preceding claim wherein the acid is phosphoric acid.

5. A process as claimed in any of claims 1 to 4 wherein the acid is added in from 0.5 to 2.0 molar equivalents of the Tilidine base.

6. A process as claimed in claim 5 wherein the acid is added in from 0.9 to 1.1 molar equivalents of the Tilidine base.

7. A process as claimed in claim 5 or 6 wherein the acid is added in approximately equimolar equivalent to Tilidine base.

8. A process as claimed in any preceding claim wherein the reaction mixture is heated to a temperature of from 90°C to 100°C and kept at this temperature for a period of from 15 to 30 hours.

9. A process for preparing Tilidine comprising mixing cis/trans Tilidine base with water and phosphoric acid, and heating the reaction mixture thus formed to yield isomerised cis/trans Tilidine base with an enhanced content of the trans isomer.

10. A process as claimed in any preceding claim, wherein isomerised Tilidine base has a content of greater than 10% of the trans isomer.

11. A process as claimed in claim 10 wherein isomerised Tilidine base has a content of greater than 60% of the trans isomer.

12. A process as claimed in any preceding claim, wherein the acid comprises a mixture of phosphoric acid and salts thereof.

13. A process as claimed in any preceding claim, wherein after heating, the reaction mixture is cooled and the cis/trans Tilidine base is extracted by liquid-liquid extraction.

14. A process as claimed in claim 13, wherein a solvent such as petroleum ether is added to the solution, the pH is adjusted with a base to 12 – 14, the aqueous layer is separated and the organic layer is evaporated to give the isomerised cis/trans Tilidine base.

15. A process for preparing Tilidine as defined in claim 2 substantially as hereinbefore described with reference to the examples.

16. Tilidine whenever prepared by a process as claimed in any preceding claim.

17. A process for preparing Tilidine as claimed in claim 1 comprising mixing a substantially pure cis Tilidine base with a solvent and a base at pH values between 8 and 14, and heating the reaction mixture thus formed to yield isomerised cis/trans Tilidine base with an enhanced content of the trans isomer.

18. A process as claimed in claim 17, wherein the pH is from 9 to 10.

19. A process as claimed in claim 17 or 18, wherein the solvent is diisopropylethylamine.

20. A process as claimed in claim 19, wherein the reaction mixture is heated to a temperature of from 130°C to 140°C.

21. A process as claimed in claim 17 or 18, wherein the solvent is dimethylformamide.

22. A process as claimed in claim 21, wherein the reaction mixture is heated to a temperature of from 140°C to 150°C.

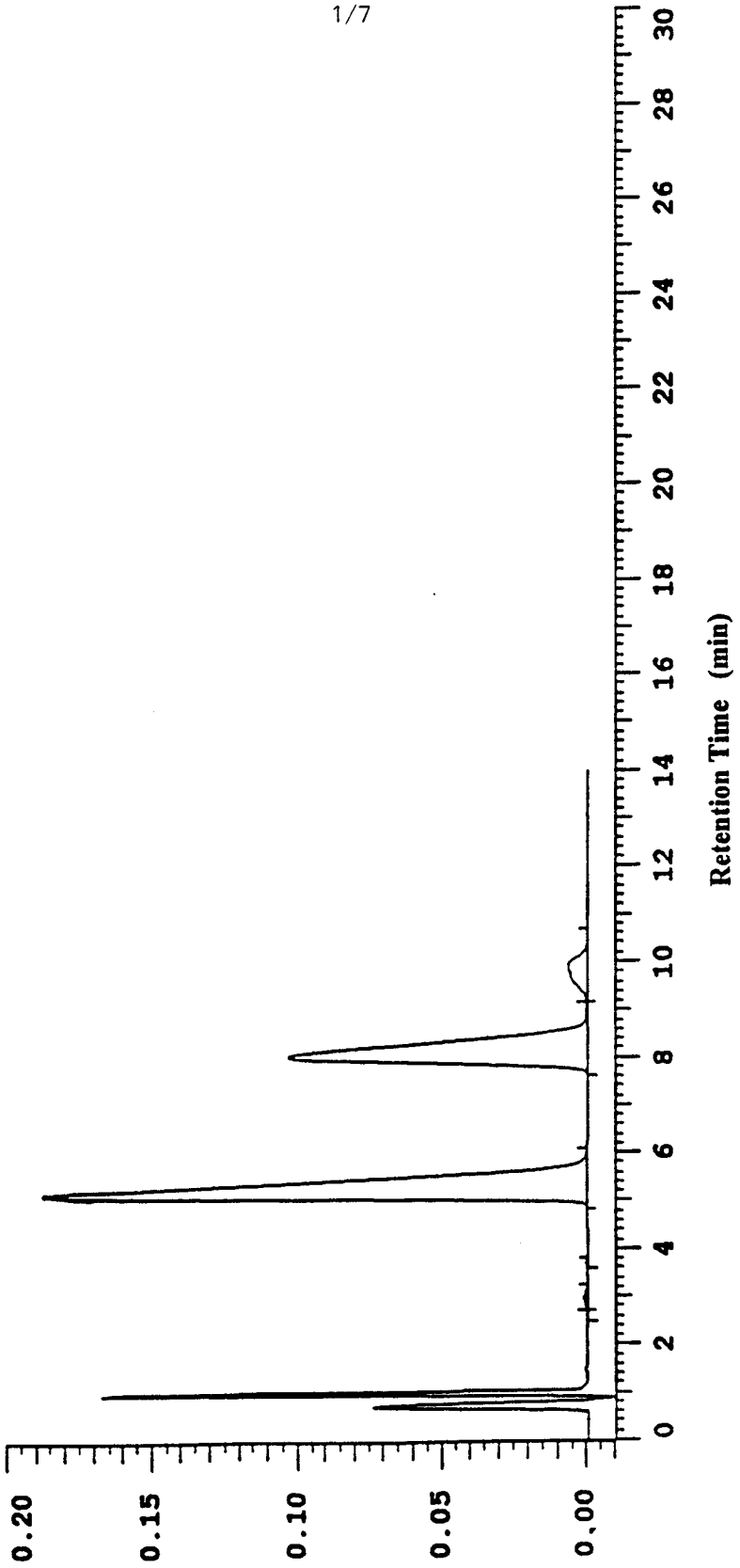
23. A process as claimed in any of claims 17 to 22, wherein the isomerised Tilidine base has a content of greater than 10% of the trans isomer.

24. A process as claimed in any of claims 17 to 23, wherein isomerised Tilidine base has a content of greater than 15% of the trans isomer.

25. A process as claimed in any of claims 17 to 24, wherein the solvent is added in a ratio of approximately 1:1 wt:wt equivalent of the Tilidine base.

26. A process for preparing Tilidine as defined in claim 17 substantially as hereinbefore described with reference to the Examples.

27. Tilidine whenever prepared by a process as claimed in any of claims 17 to 26.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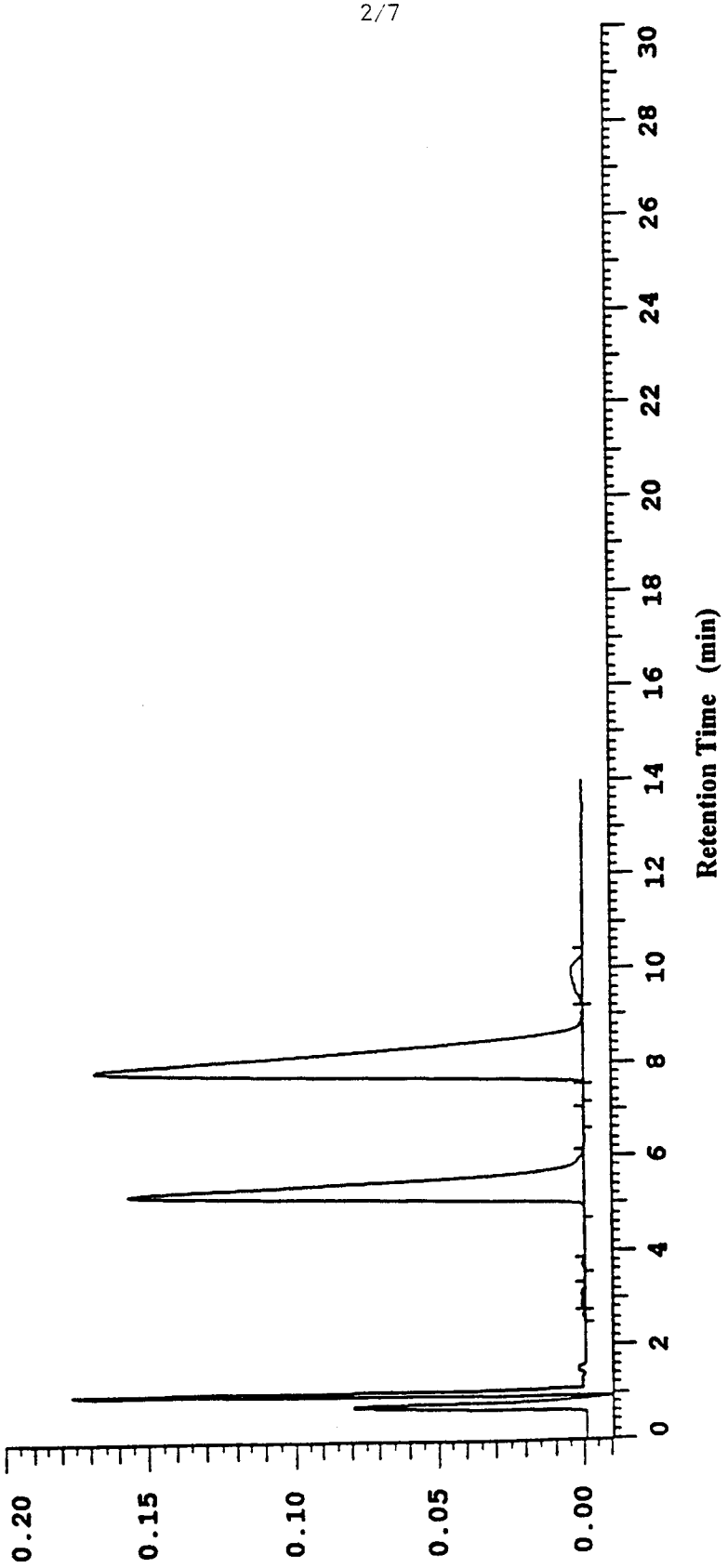
Retention Time (min)

Fig 1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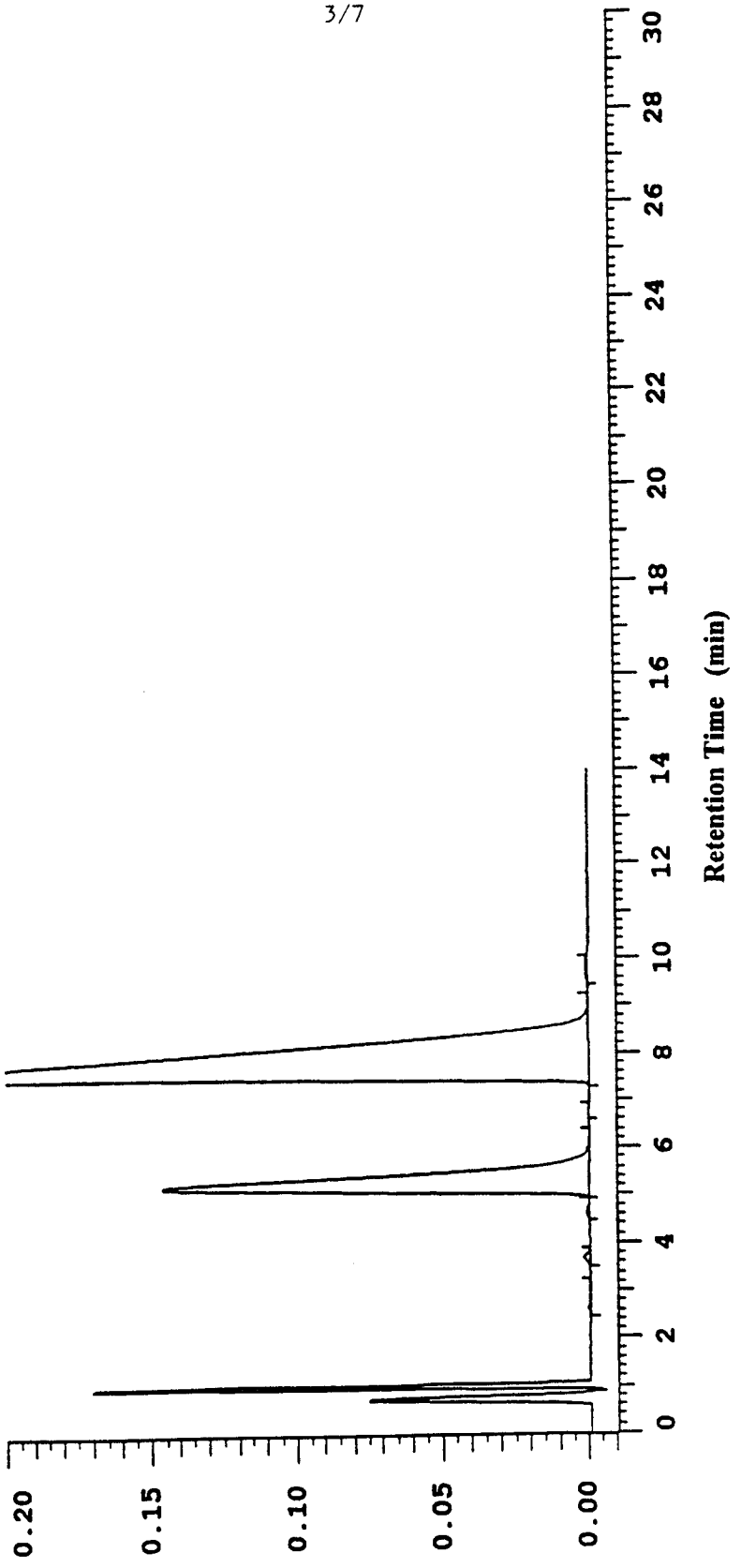
Retention Time (min)

Fig 2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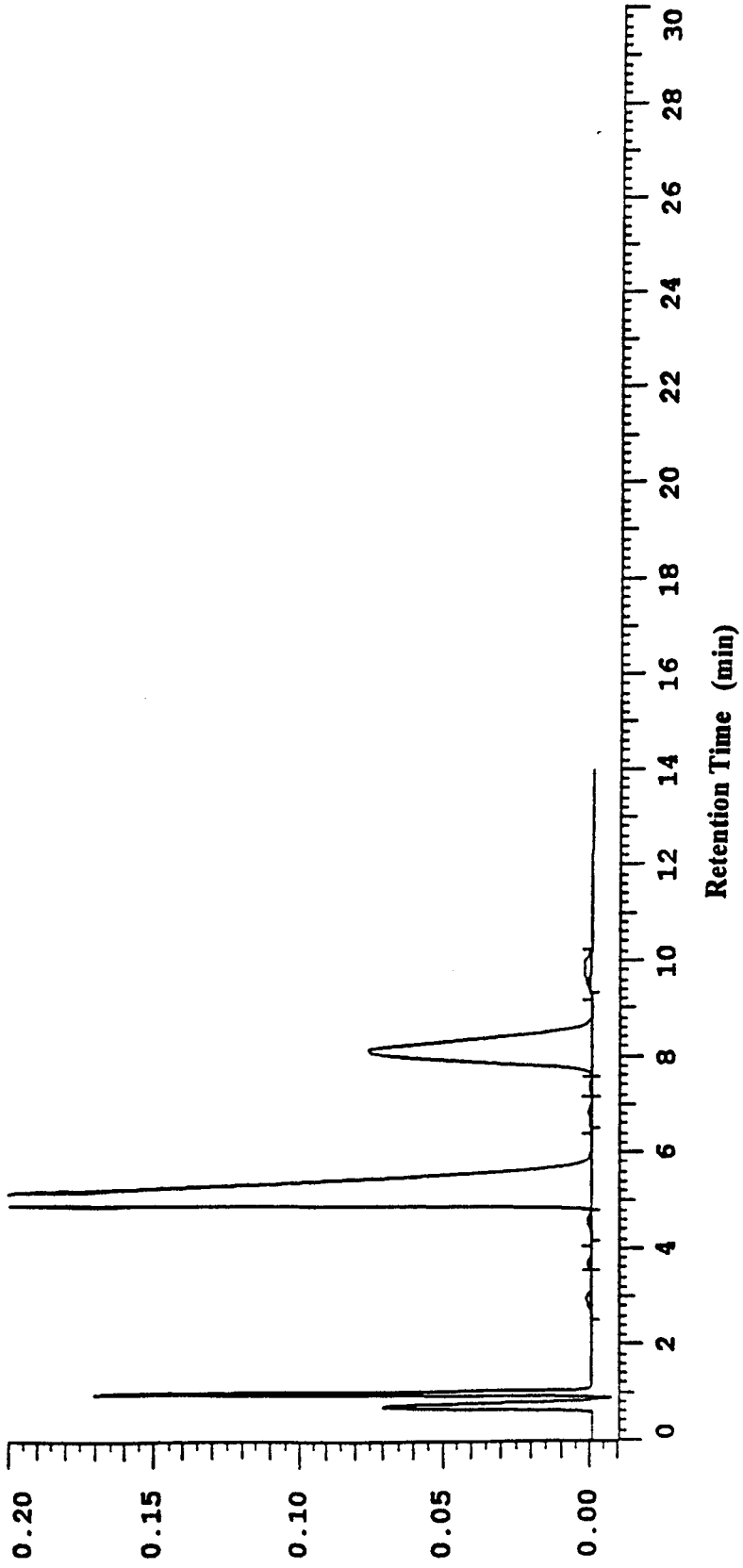
Retention Time (min)

Fig 3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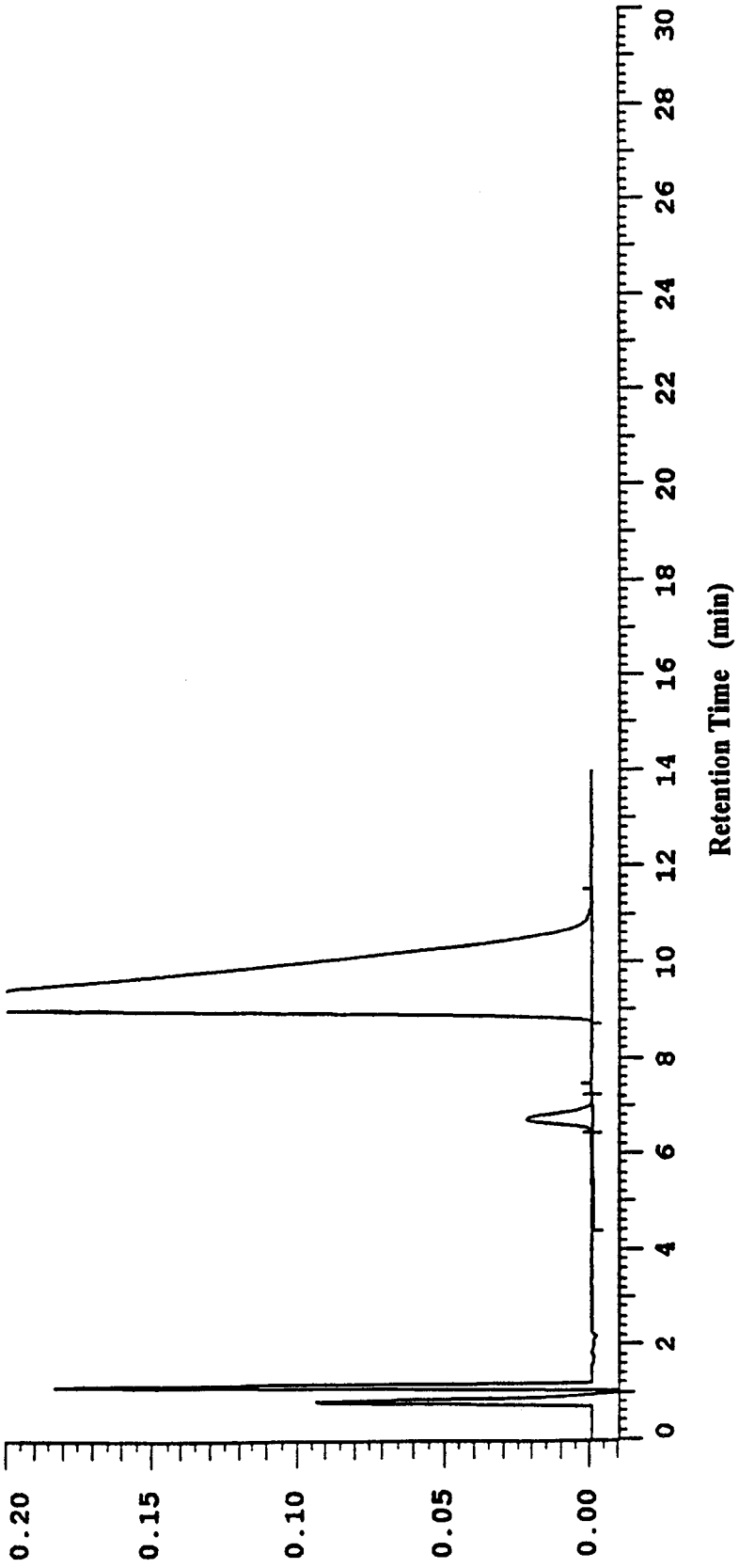
Retention Time (min)

Fig 4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6
8
10
12
14
16
18
20
22
24
26
28
30
Retention Time (min)

Fig 5

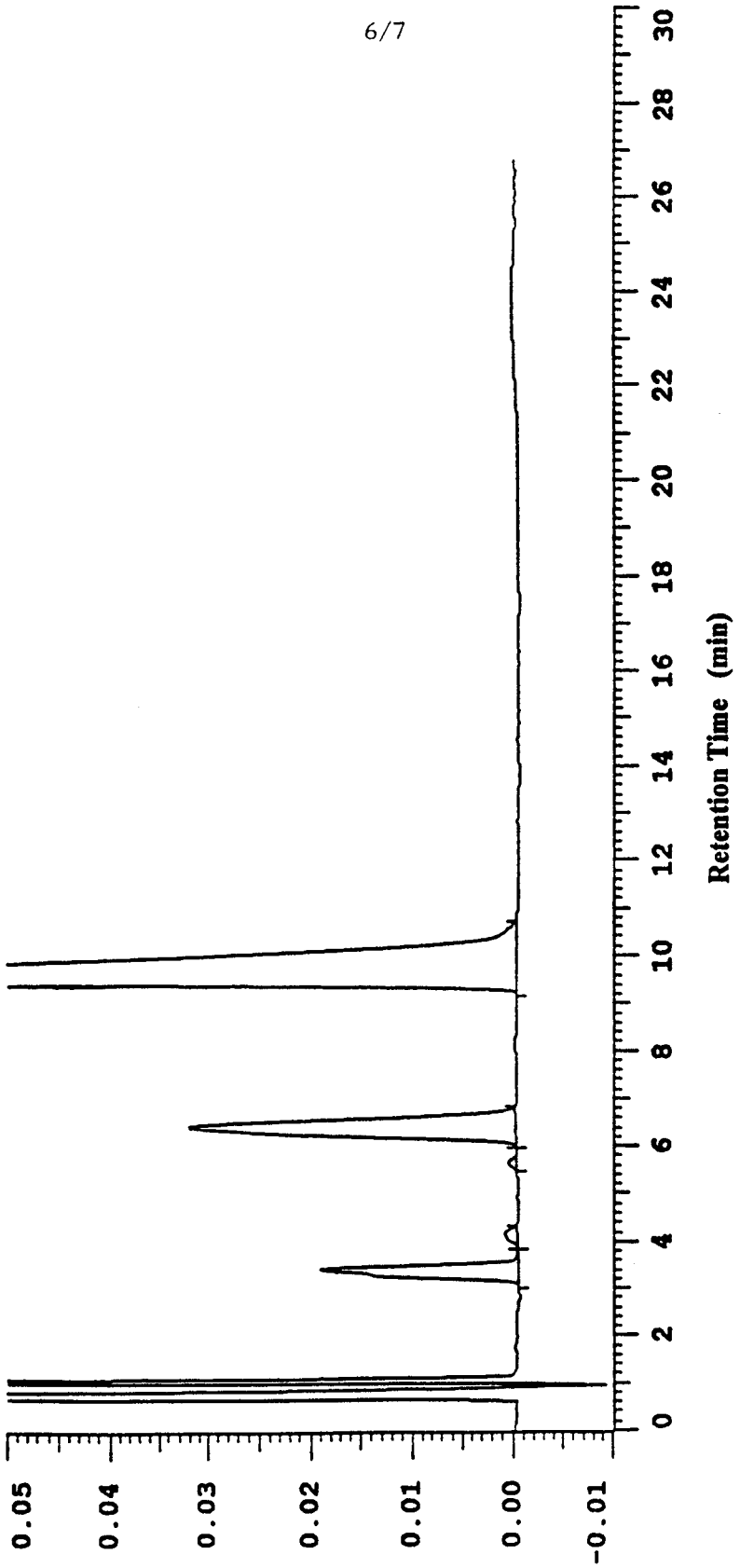
Absorbance (AU)
0.05
0.04
0.03
0.02
0.01
0.00
-0.01
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
Retention Time (min)

Fig 6

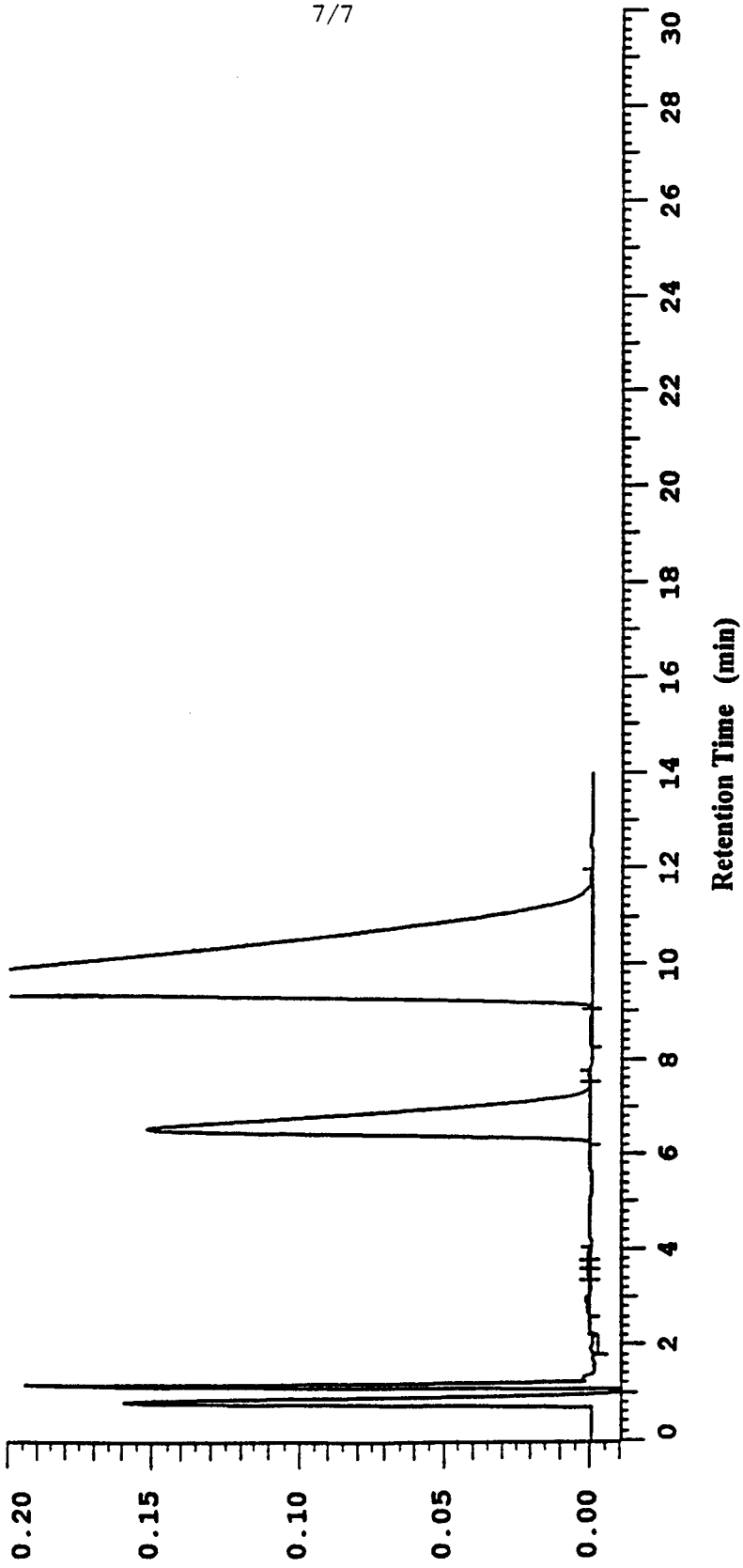
Absorbance (AU)
0.20
0.15
0.10
0.05
0.00
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
Retention Time (min)

Fig 7