

Organocatalyzed enantioselective synthesis of 6-amino-5-cyanodihydropyrano[2,3-c]pyrazoles

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Supplementary Data

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General Information

¹H and ¹³C NMR spectra were recorded on an Advanced Varian-500 (500 MHz) instrument using residual solvent as the standard. TLC was performed with silica gel GF₂₅₄ precoated on aluminium plates (VWR), and spots were visualized with UV and/or iodine vapor. Flash column chromatography was performed on silica-gel (VWR, Fisher). HPLC were recorded on a Shimadzu HPLC system with a Daicel ChiralPak AS column. Unless otherwise indicated, chemicals and solvents used in the reactions and in the synthesis of the catalysts were purchased from Aldrich, Acros, TCI America, Alfa Aesar, or Fisher Scientific, and used as received. THF and ether were distilled from benzophenone and sodium metal. Benzene, toluene, and CH₂Cl₂ were distilled from CaH₂. Unless otherwise specified, all reactions were carried out at ambient temperature in oven-dried glassware.

Representative experimental procedure for the two-component synthesis (12a-k, Table 2): To a stirred solution of 3-methyl-2-pyrazolin-5-one (**10a**, 9.8 mg, 0.10 mmol) and benzylidenemalononitrile (**11a**, 15.4 mg, 0.10 mmol) in anhydrous CH₂Cl₂ (2.0 mL) was added cupreine **2** (1.6 mg, 0.005 mmol). The reaction mixture was then stirred at

room temperature for 27 h. The solvent was then removed under reduced pressure. The crude mixture was subjected to flash column chromatography over silica gel (1:1 hexane/EtOAc) to furnish pure **12a** as a white solid (23.2 mg, 92%). The ee value of this product was determined to be 96% ee.

Except for product **12e**, all the other products obtained in this study are known compounds and have identical spectroscopic properties as those reported ones.²⁻⁶

Representative experimental procedure for the three-component synthesis (Table

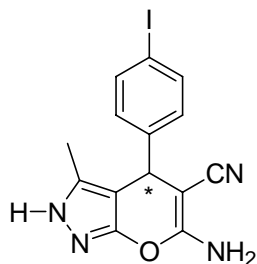
3): To a stirred solution of benzaldehyde (**13a**, 10.6 mg, 0.10 mmol) and malononitrile (**14**, 6.6 mg, 0.10 mmol), 3-methyl-2-pyrazolin-5-one (**10a**, 9.8 mg, 0.1 mmol) in anhydrous CH₂Cl₂ (2.0 mL) was added anhydrous Na₂SO₄ (14.2 mg, 0.10 mmol) and catalyst **2** (1.6 mg, 0.005 mmol). The reaction mixture was then stirred at room temperature for 25 h. After filtration and washing with some additional CH₂Cl₂, the solvent was removed under reduced pressure. The crude mixture was subjected to flash column chromatography over silica gel (1:1 hexane/EtOAc) to furnish **12a** as a white solid (17.4 mg, 69%, 99% ee).

Representative experimental procedure for the four-component synthesis (Table 4):

A mixture of hydrazine hydrate (**15**, 5.0 mg, 0.10 mmol) and ethyl acetoacetate (**16**, 13.0 mg, 0.10 mmol) was stirred at room temperature for 5 minutes. The mixture was then cooled to 0 °C. To this reaction mixture, CH₂Cl₂ (2.0 mL), benzaldehyde (**13a**, 10.6 mg, 0.10 mmol) and malononitrile (**14**, 6.6 mg, 0.10 mmol) was added, which was followed by the addition of anhydrous Na₂SO₄, (28.4 mg, 0.20 mmol) and catalyst **2** (1.6 mg, 0.005 mmol). The mixture was further stirred at the same temperature for 28 h. After filtration and washing with some additional CH₂Cl₂, the solvent was removed under reduced pressure. The crude mixture was subjected to flash column chromatography over silica gel (1:1 hexane/EtOAc) to furnish **12a** as a white solid (10.8 mg, 43%, >99% ee).

NMR data of a new compound:

**6-Amino-5-cyano-4-(4-iodophenyl)-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole
(12e):**



^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 1.79 (s, 3H), 4.59 (s, 1H), 6.70-7.20 (m, 4H), 7.68 (s, 2H), 12.18 (s, 1H) ppm. ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) δ 9.2, 35.3, 56.2, 92.2, 96.6, 120.1, 129.5, 135.3, 136.9, 143.9, 154.2, 160.5 ppm. IR (CHCl_3) ν_{max} 1638, 1595, 1488, 1403 cm^{-1} .

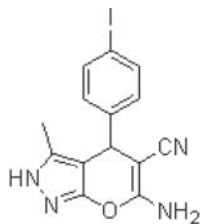
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 Sample directory:
 File: PROTON

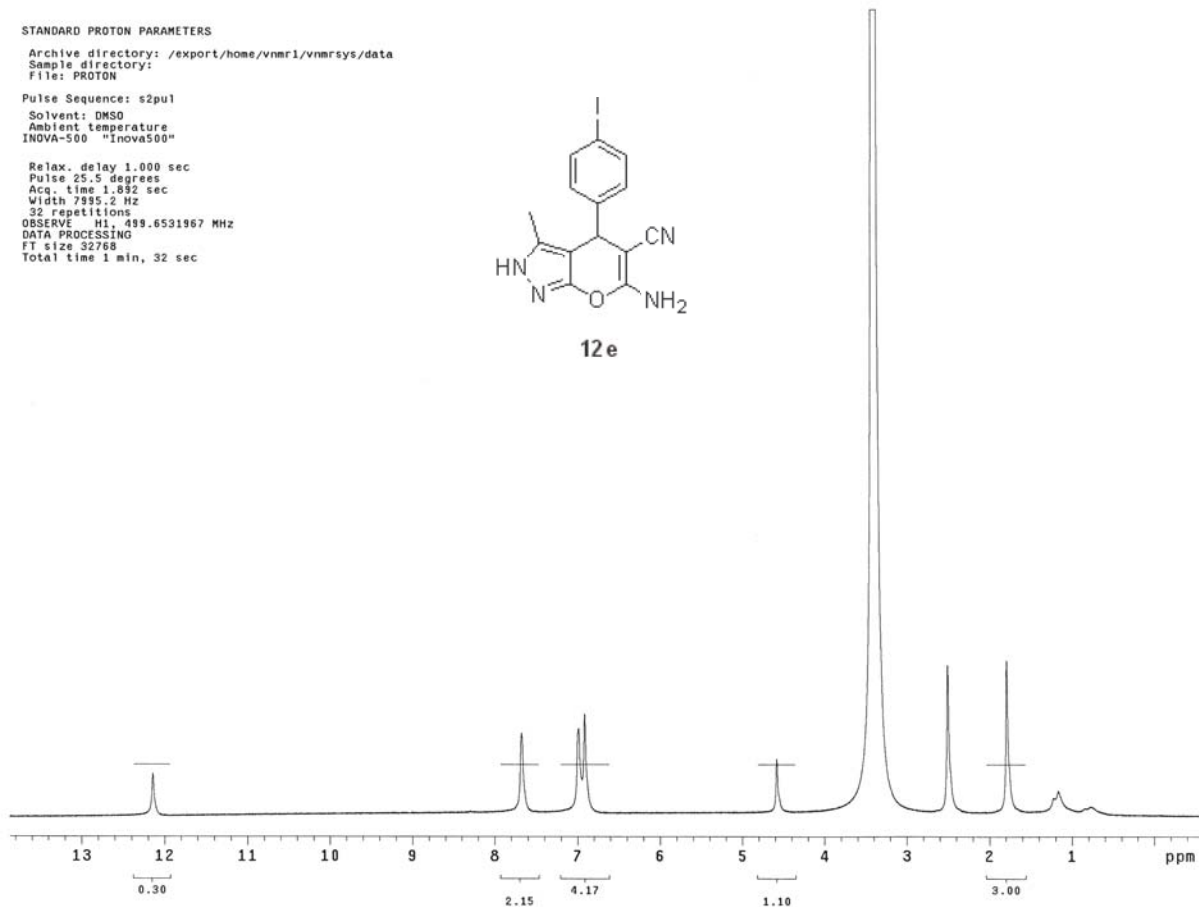
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Solvent: DMSO
 Ambient temperature
 INOVA-500 "Inova500"

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 Pulse 25.5 degrees
 Acq. time 1.892 sec
 Width 7995.2 Hz
 32 repetitions
 OBSERVE H1, 499.6531967 MHz
 DATA PROCESSING
 FT size 32768
 Total time 1 min, 32 sec



12e



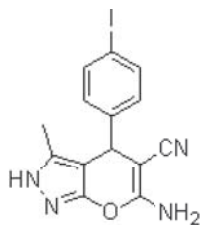
STANDARD CARBON PARAMETERS

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 File: CARBON

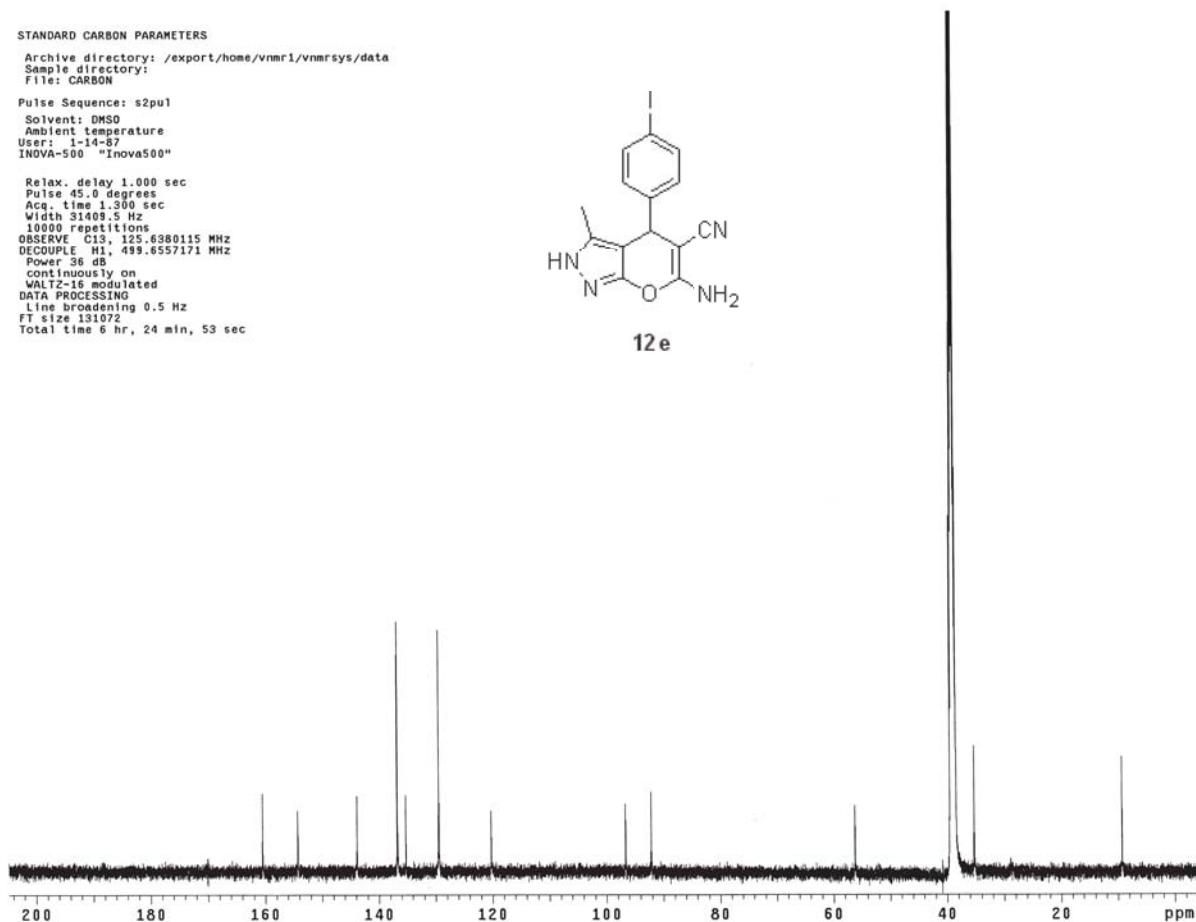
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Solvent: DMSO
 Ambient temperature
 User: 1-14-87
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 DECOUPLE H1, 499.6557171 MHz
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 WALTZ-16 modulated
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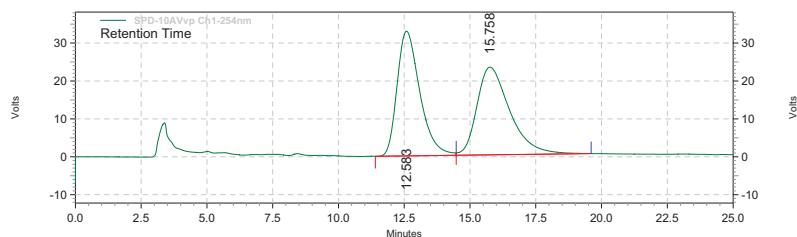


12e



Area % Report

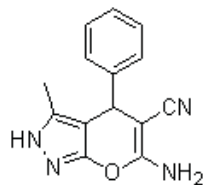
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SPD-10AVvp
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
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15.758	2009902	50.40	23151	41.28

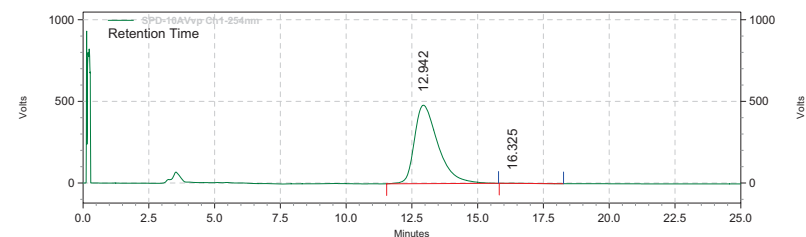
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12 a (racemic)

Area % Report

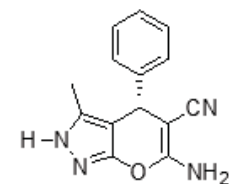
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SPD-10AVvp
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
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16.325	29391	0.10	762	0.16

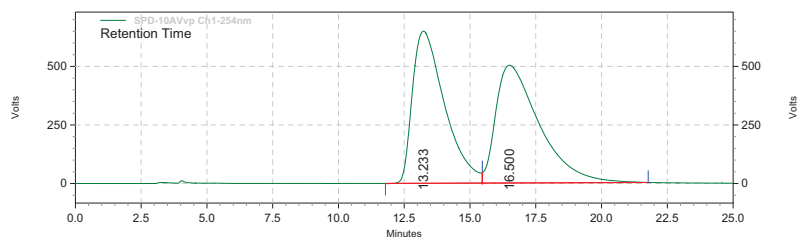
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12 a (>99% ee, entry 7 of Table 4)

Area % Report

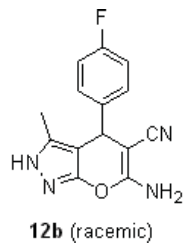
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SPD-10AVvp
Ch1-254nm
Results

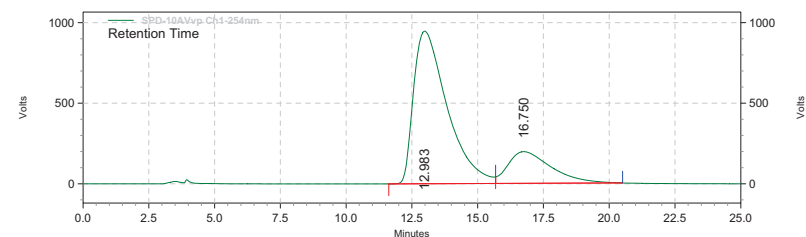
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13.233	55282328	48.89	649150	56.36
16.500	57802446	51.11	502644	43.64

Totals	Area	Area %	Height	Height %
	113084774	100.00	1151794	100.00



Area % Report

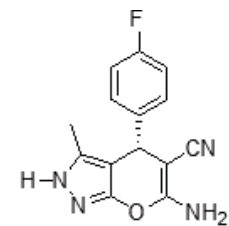
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SPD-10AVvp
Ch1-254nm
Results

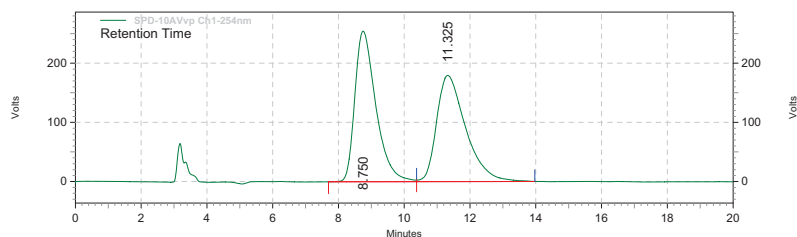
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12.983	84080302	78.93	947186	82.79
16.750	22445182	21.07	196872	17.21

Totals	Area	Area %	Height	Height %
	106525484	100.00	1144058	100.00



Area % Report

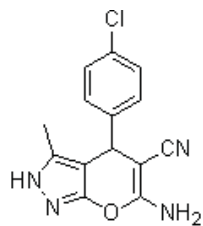
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SPD-10AVvp
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
8.750	11316227	50.67	254674	58.66
11.325	11018985	49.33	179485	41.34

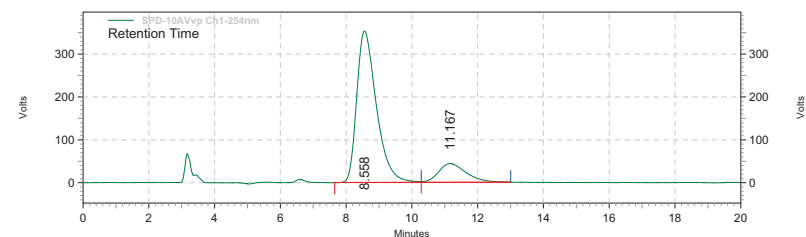
Totals	22335212	100.00	434159	100.00
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12c (racemic)

Area % Report

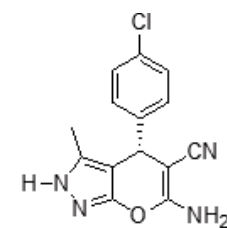
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SPD-10AVvp
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
8.558	14625485	85.21	352982	89.02
11.167	2538032	14.79	43556	10.98

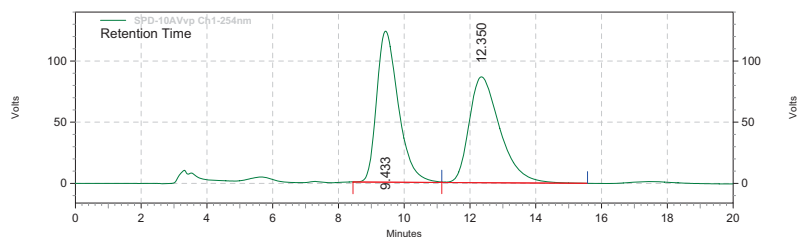
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12c (70% ee, entry 6 of Table 3)

Area % Report

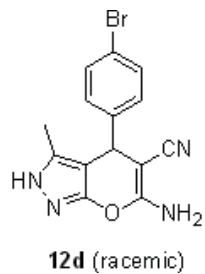
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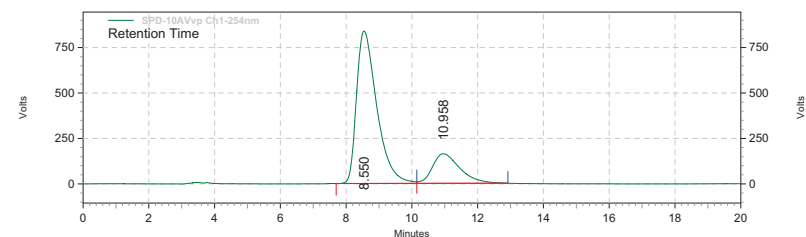
SPD-10AVvp
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
9.433	5645369	50.11	123453	58.79
12.350	5621329	49.89	86534	41.21

Totals	Area	Area %	Height	Height %
	11266698	100.00	209987	100.00

**Area % Report**

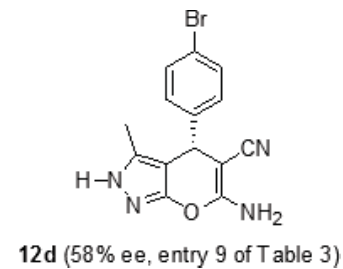
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 Printed: 12/21/2008 1:38:27 PM



SPD-10AVvp
Ch1-254nm
Results

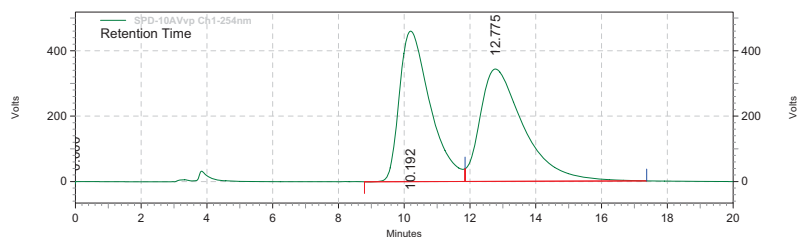
Retention Time	Area	Area %	Height	Height %
8.550	35867009	79.19	838073	83.70
10.958	9422890	20.81	163181	16.30

Totals	Area	Area %	Height	Height %
	45289899	100.00	1001254	100.00



Area % Report

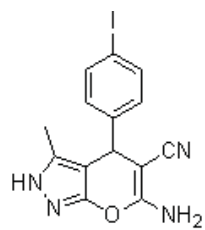
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SPD-10AVvp
 Ch1-254nm
 Results

Retention Time	Area	Area %	Height	Height %
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10.192	29938848	48.68	459920	57.27
12.775	31560936	51.32	343222	42.73

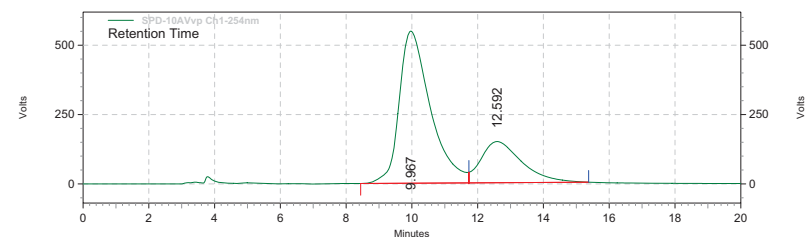
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12e (racemic)

Area % Report

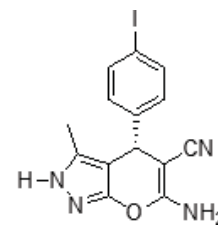
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 Printed: 12/21/2008 1:48:19 PM



SPD-10AVvp
 Ch1-254nm
 Results

Retention Time	Area	Area %	Height	Height %
9.967	36089822	73.88	548082	78.71
12.592	12759267	26.12	148255	21.29

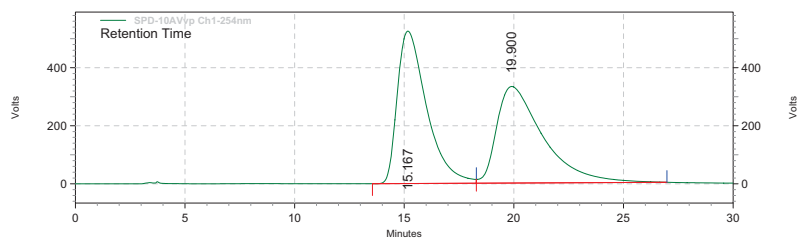
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12e (48% ee, entry 5 of Table 2)

Area % Report

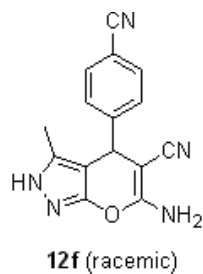
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SPD-10AVvp
Ch1-254nm
Results

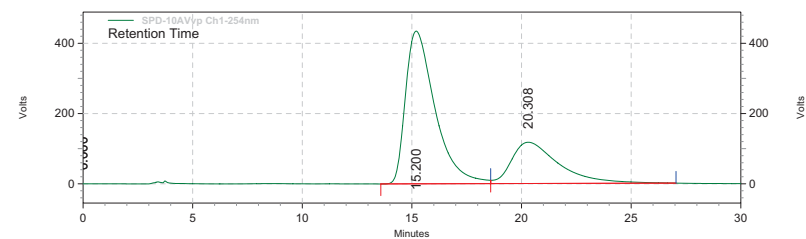
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15.167	48896030	50.03	525003	61.21
19.900	48846572	49.97	332648	38.79

Totals	97742602	100.00	857651	100.00
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Area % Report

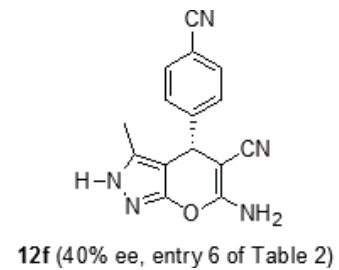
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SPD-10AVvp
Ch1-254nm
Results

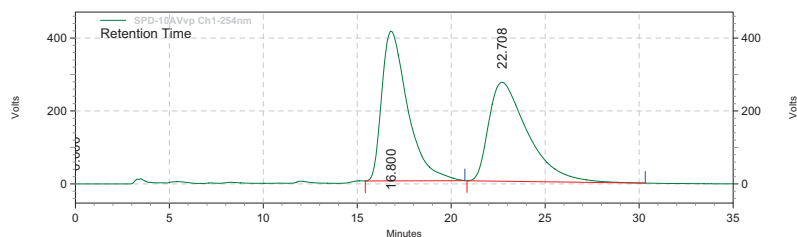
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0.000	0	0.00	0	0.00
15.200	40625451	69.72	434743	78.71
20.308	17646038	30.28	117558	21.29

Totals	58271489	100.00	552301	100.00
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Area % Report

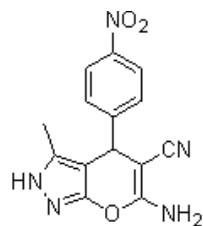
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 Printed: 12/21/2008 2:01:10 PM



SPD-10AVvp
 Ch1-254nm
 Results

Retention Time	Area	Area %	Height	Height %
0.000	0	0.00	0	0.00
16.800	39372627	50.18	410693	60.21
22.708	39083567	49.82	271403	39.79

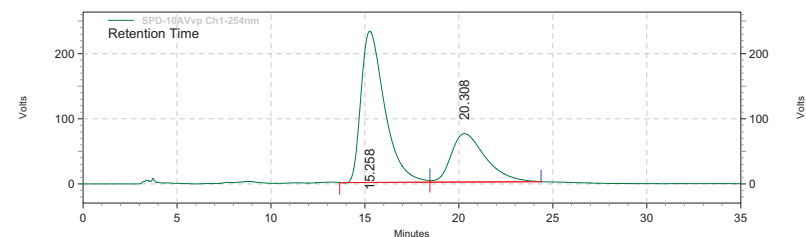
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12g (racemic)

Area % Report

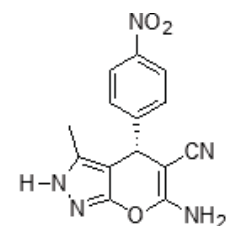
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 Acquired: 11/19/2008 4:33:44 PM
 Printed: 12/21/2008 1:56:53 PM



SPD-10AVvp
 Ch1-254nm
 Results

Retention Time	Area	Area %	Height	Height %
15.258	20328254	68.31	232415	75.75
20.308	9428889	31.69	74406	24.25

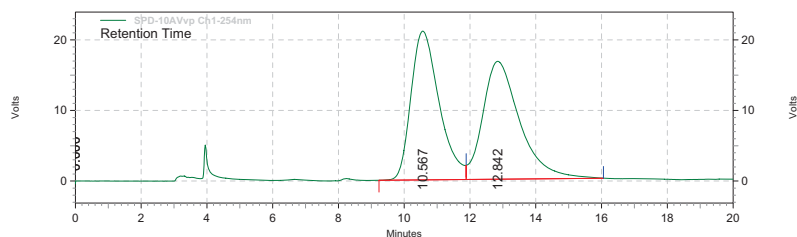
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12g (36% ee, entry 7 of Table 2)

Area % Report

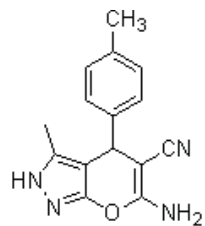
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 Acquired: 11/19/2008 2:43:51 PM
 Printed: 12/21/2008 2:06:21 PM



SPD-10AVvp
 Ch1-254nm
 Results

Retention Time	Area	Area %	Height	Height %
0.000	0	0.00	0	0.00
0.000	0	0.00	0	0.00
10.567	1256699	49.11	21073	55.79
12.842	1302498	50.89	16700	44.21

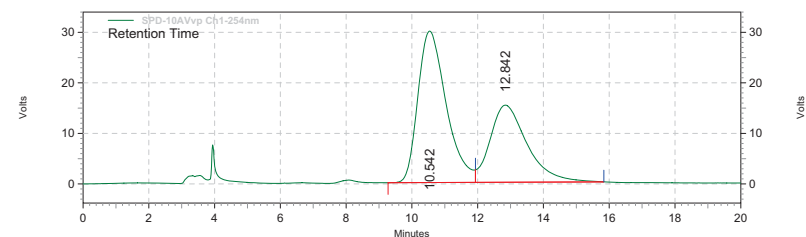
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12h (racemic)

Area % Report

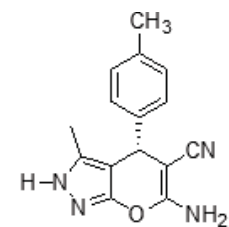
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SPD-10AVvp
 Ch1-254nm
 Results

Retention Time	Area	Area %	Height	Height %
10.542	1791940	60.13	29945	66.26
12.842	1188138	39.87	15251	33.74

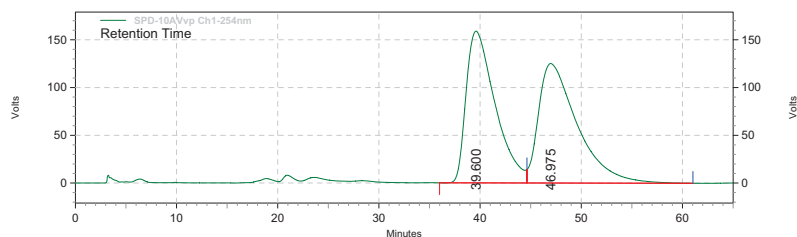
Totals	Area	Area %	Height	Height %
Totals	2980078	100.00	45196	100.00



12h (20% ee, entry 8 of Table 2)

Area % Report

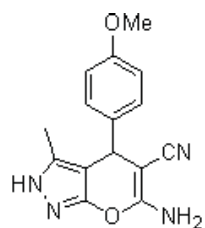
Method Name: C:\EZStart\Projects\Default\Methods\OJ-H.met
 Data: C:\EZStart\Projects\Default\Data\I-SG-10%-1mL-254-142
 User: System
 Acquired: 9/29/2008 3:02:59 PM
 Printed: 12/21/2008 2:13:31 PM



SPD-10AVvp
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
39.600	31695259	48.79	158916	55.94
46.975	33266710	51.21	125153	44.06

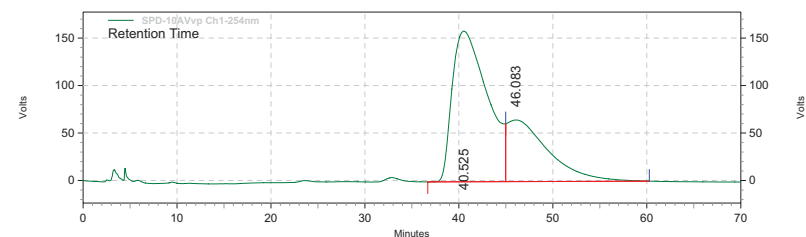
Totals	Area	Area %	Height	Height %
	64961969	100.00	284069	100.00



12i (racemic)

Area % Report

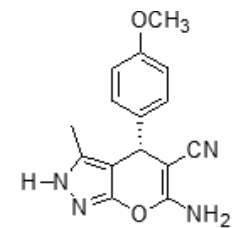
Method Name: C:\EZStart\Projects\Default\Methods\OJ-H.met
 Data: C:\EZStart\Projects\Default\Data\I-SG-207
 User: System
 Acquired: 10/20/2008 10:25:10 AM
 Printed: 12/21/2008 2:09:35 PM



SPD-10AVvp
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
40.525	41345215	67.63	158639	70.96
46.083	19786494	32.37	64920	29.04

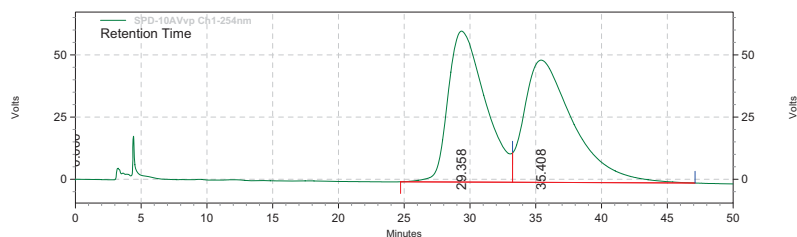
Totals	Area	Area %	Height	Height %
	61131709	100.00	223559	100.00



12i (36% ee, entry 9 of Table 2)

Area % Report

Method Name: C:\EZStart\Projects\Default\Methods\OJ-H.met
 Data: C:\EZStart\Projects\Default\Data\I-SG-235-5%-254-1ml-235-racemic
 User: System
 Acquired: 10/27/2008 10:04:17 AM
 Printed: 12/21/2008 2:27:48 PM



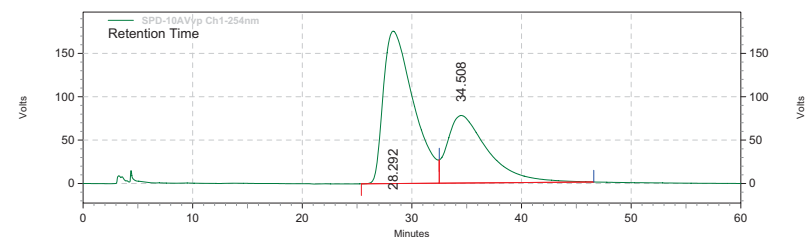
SPD-10AVvp
 Ch1-254nm
 Results

Retention Time	Area	Area %	Height	Height %
0.000	0	0.00	0	0.00
29.358	11942950	48.51	60657	55.24
35.408	12675248	51.49	49148	44.76

Totals	Area	Area %	Height	Height %
	24618198	100.00	109805	100.00

**Area % Report**

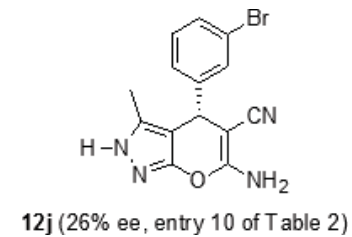
Method Name: C:\EZStart\Projects\Default\Methods\OJ-H.met
 Data: C:\EZStart\Projects\Default\Data\I-SG-235-5%-254-1ml-235-t
 User: System
 Acquired: 10/27/2008 8:52:39 AM
 Printed: 12/21/2008 2:25:09 PM



SPD-10AVvp
 Ch1-254nm
 Results

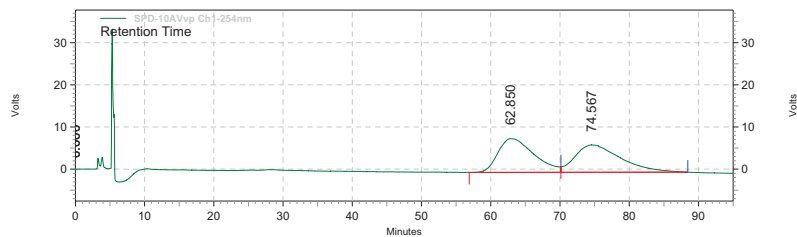
Retention Time	Area	Area %	Height	Height %
28.292	33593143	62.64	175734	69.29
34.508	20036306	37.36	77877	30.71

Totals	Area	Area %	Height	Height %
	53629449	100.00	253611	100.00



Area % Report

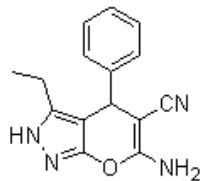
Method Name: C:\EZStart\Projects\Default\Methods\OJ-H.met
 Data: C:\EZStart\Projects\Default\Data\I-SG-254-5%-254-1ml-bl-254-rac
 User: System
 Acquired: 11/3/2008 10:44:27 AM
 Printed: 12/21/2008 2:54:42 PM



SPD-10AVvp
 Ch1-254nm
 Results

Retention Time	Area	Area %	Height	Height %
0.000	0	0.00	0	0.00
0.000	0	0.00	0	0.00
62.850	2880233	49.22	7960	55.11
74.567	2970934	50.78	6484	44.89

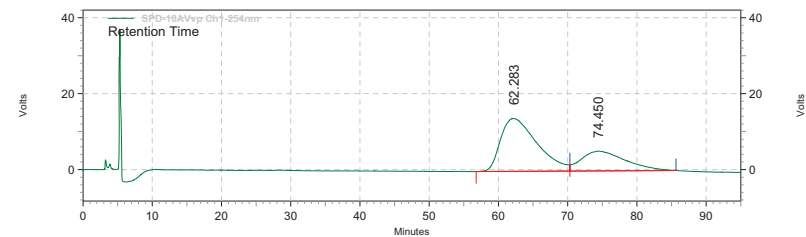
Totals	Area	Area %	Height	Height %
Totals	5851167	100.00	14444	100.00



12k (racemic)

Area % Report

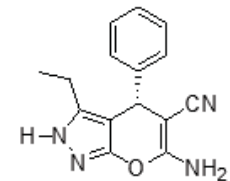
Method Name: C:\EZStart\Projects\Default\Methods\OJ-H.met
 Data: C:\EZStart\Projects\Default\Data\I-SG-257-5%-254-1ml-bl-257-op
 User: System
 Acquired: 11/3/2008 12:29:37 PM
 Printed: 12/21/2008 2:31:36 PM



SPD-10AVvp
 Ch1-254nm
 Results

Retention Time	Area	Area %	Height	Height %
62.283	5097794	68.88	13911	72.64
74.450	2303372	31.12	5240	27.36

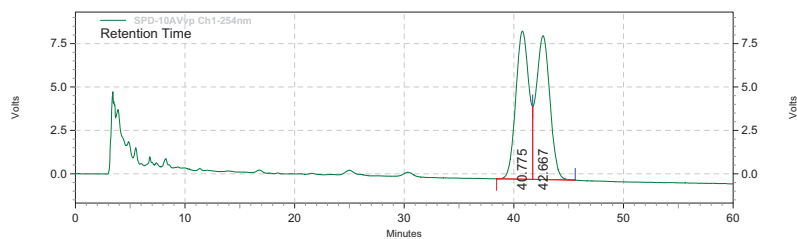
Totals	Area	Area %	Height	Height %
Totals	7401166	100.00	19151	100.00



12k (38% ee, entry 11 of Table 2)

Area % Report

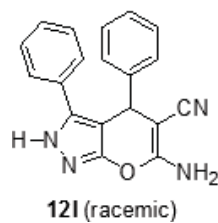
Method Name: C:\EZStart\Projects\Default\Methods\OJ-H.met
 Data: C:\EZStart\Projects\Default\Data\I-SG-518-10%-adh-1ml-254-518
 User: System
 Acquired: 2/19/2009 10:23:46 AM
 Printed: 2/19/2009 4:47:00 PM



SPD-10AVvp
Ch1-254nm
Results

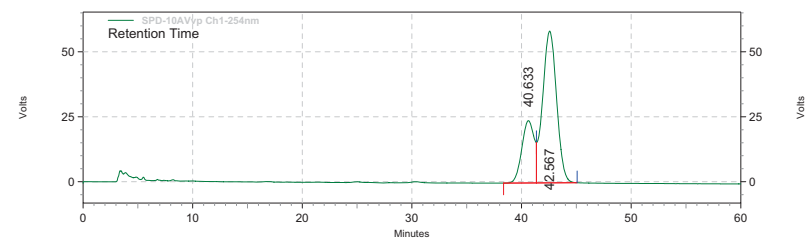
Retention Time	Area	Area %	Height	Height %
40.775	712308	49.69	8529	50.72
42.667	721321	50.31	8286	49.28

Totals	Area	Area %	Height	Height %
	1433629	100.00	16815	100.00



Area % Report

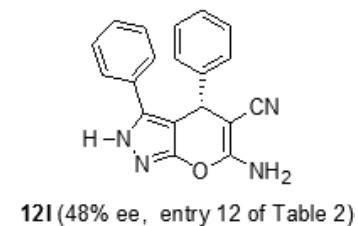
Method Name: C:\EZStart\Projects\Default\Methods\OJ-H.met
 Data: C:\EZStart\Projects\Default\Data\I-SG-518-10%-adh-1ml-254-518-op
 User: System
 Acquired: 2/19/2009 11:28:00 AM
 Printed: 2/19/2009 4:48:22 PM



SPD-10AVvp
Ch1-254nm
Results

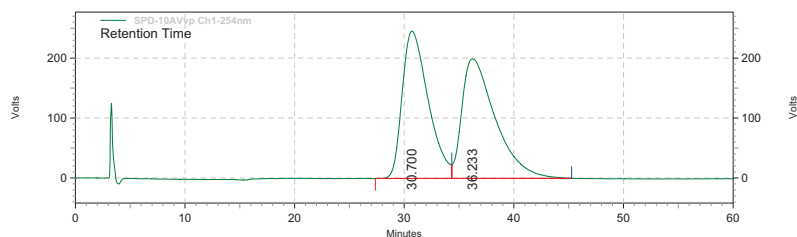
Retention Time	Area	Area %	Height	Height %
40.633	1866353	26.40	23998	29.12
42.567	5202005	73.60	58400	70.88

Totals	Area	Area %	Height	Height %
	7068358	100.00	82398	100.00



Area % Report

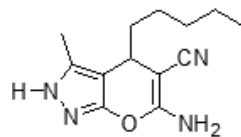
Method Name: C:\EZStart\Projects\Default\Methods\OJ-H.met
 Data: C:\EZStart\Projects\Default\Data\1-SG-AS-254-5%-1ml-179-2nd time
 User: System
 Acquired: 10/12/2008 4:36:26 PM
 Printed: 2/19/2009 4:39:56 PM



SPD-10AVvp
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
30.700	40444851	48.87	245816	55.22
36.233	42318567	51.13	199330	44.78

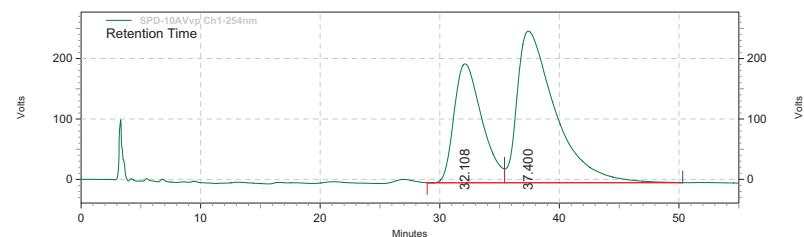
Totals	82763418	100.00	445146	100.00
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12m (racemic)

Area % Report

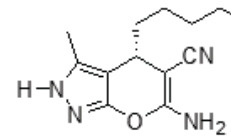
Method Name: C:\EZStart\Projects\Default\Methods\OJ-H.met
 Data: C:\EZStart\Projects\Default\Data\1-SG-AS-254-5%-1ml-178
 User: System
 Acquired: 10/12/2008 2:35:06 PM
 Printed: 2/19/2009 4:42:13 PM



SPD-10AVvp
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
32.108	31857570	36.43	196807	43.95
37.400	55597266	63.57	250964	56.05

Totals	87454836	100.00	447771	100.00
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12m (28% ee, entry 13 of Table 2)