Pyrrolo[3,2-e][1,4]diazepin-2-one Supported Synthesis

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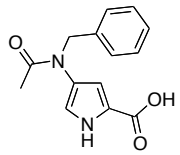
General methods

- Conditions A: C18 column 150 mm × 4.6 mm, 5µm, 5-90% MeOH in H_2O in 20 min. then 90% MeOH for 15 min., 0.1% formic acid (FA), UV: λ = 254 nm.
- Conditions B: C18 column 150 mm × 4.6 mm, 5µm, 5-80% MeOH in H_2O in 20 min. then 90% MeOH for 15 min., 0.1% FA, UV: λ = 254 nm.
- Conditions C: C18 column 150 mm × 4.6 mm, 5µm, 0-90% MeOH in H_2O in 20 min. then 90% MeOH for 15 min., 0.1% FA, UV: λ = 254 nm.

Retention time are expressed in min.

Aminoacylations

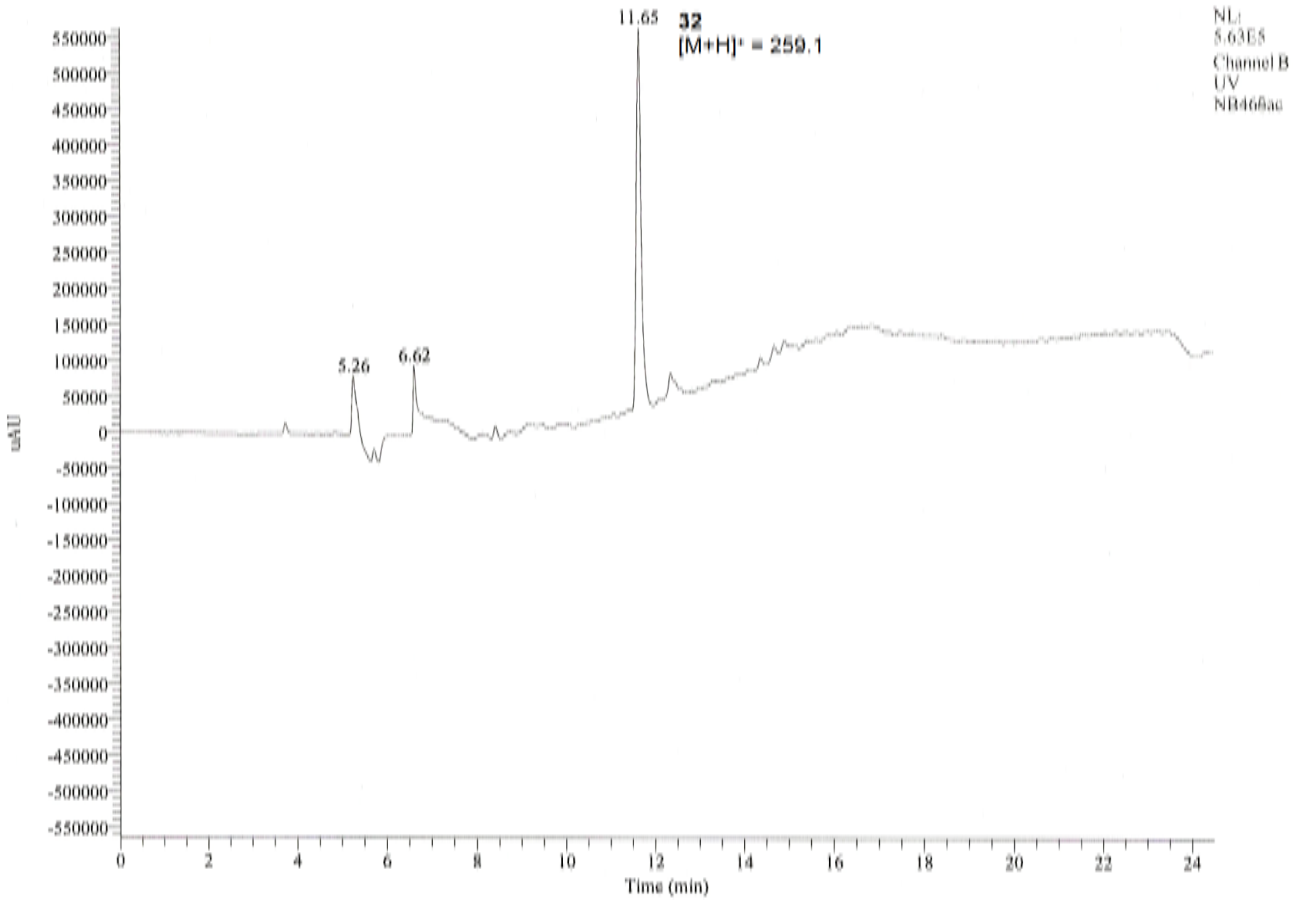
4-(N-Benzylacetamido)-1H-pyrrole-2-carboxylic acid 32



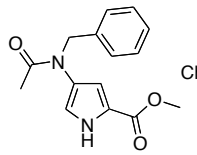
Chemical Formula: $C_{14}H_{14}N_2O_3$
Exact Mass: 258,10

32

Conditions A



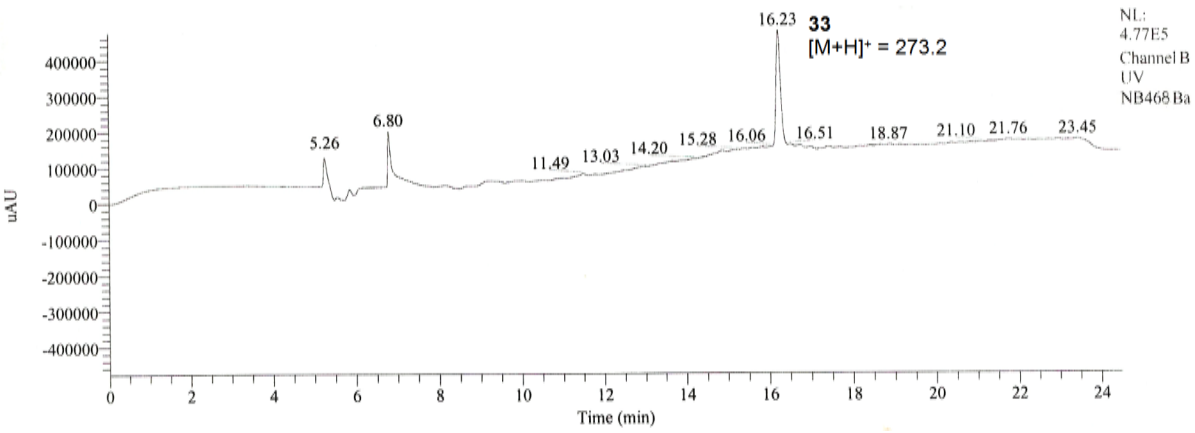
Methyl 4-(N-benzylacetamido)-1H-pyrrole-2-carboxylate 33



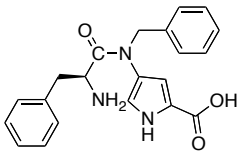
Chemical Formula: $C_{15}H_{16}N_2O_3$
Exact Mass: 272,12

33

Conditions A



(S)-4-(2-Amino-N-benzyl-3-phenylpropanamido)-1H-pyrrole-2-carboxylic acid 30a

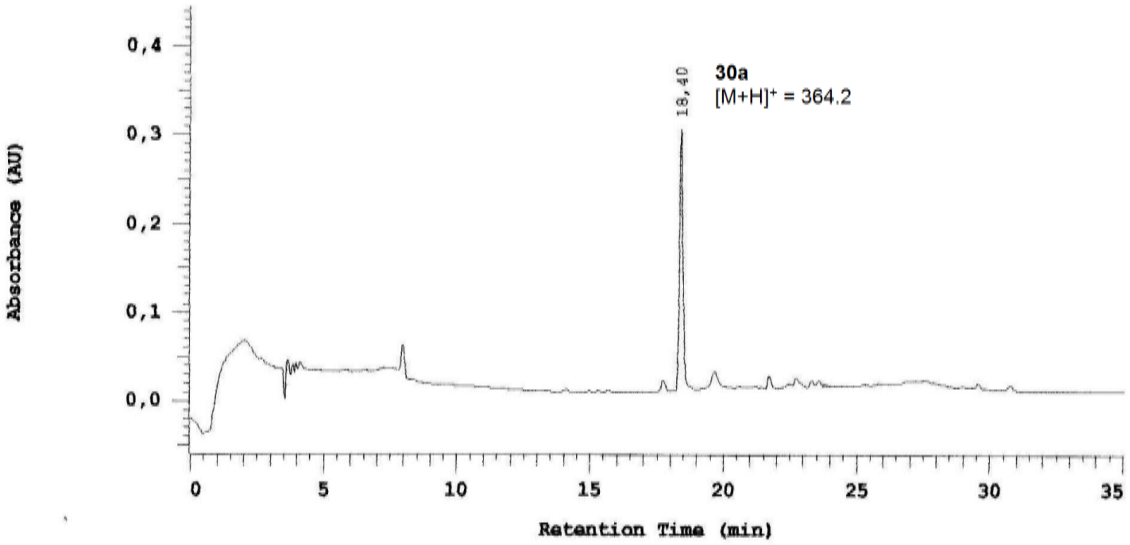


Chemical Formula: $C_{21}H_{21}N_3O_3$
Exact Mass: 363,16

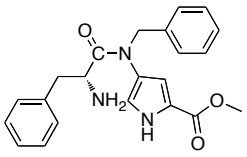
30a

82%
Conditions A

Sample Name: NB481Phe
Sample Description:



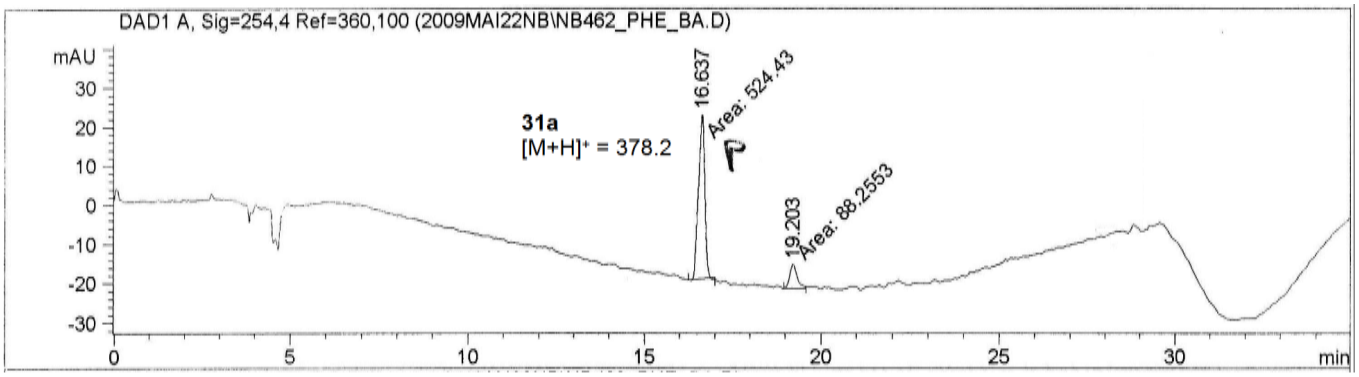
(S)-Methyl 4-(2-amino-N-benzyl-3-phenylpropanamido)-1H-pyrrole-2-carboxylate 31a



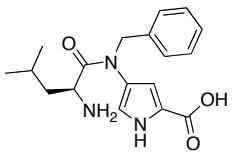
31a

Chemical Formula: $C_{22}H_{23}N_3O_3$
Exact Mass: 377,17

85%



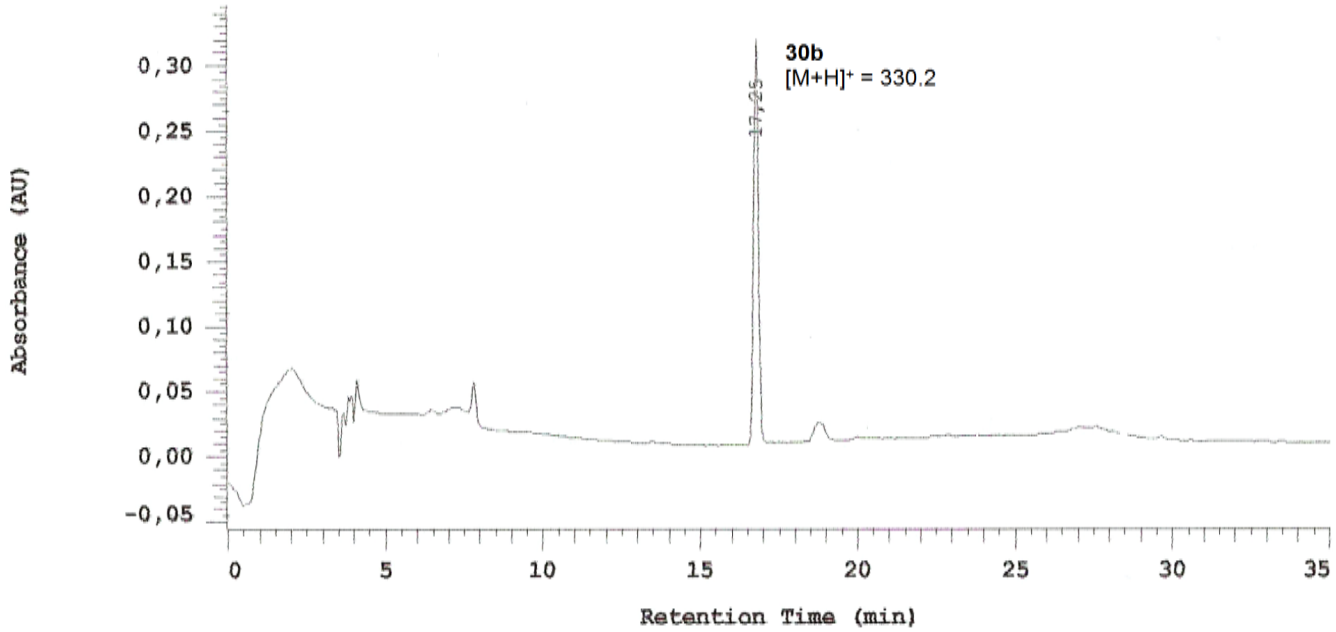
(S)-4-(2-Amino-N-benzyl-4-methylpentanamido)-1H-pyrrole-2-carboxylic acid 30b



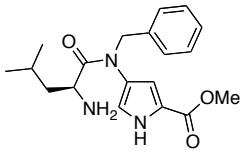
Chemical Formula: $C_{18}H_{23}N_3O_3$
Exact Mass: 329,17

81%

Conditions A



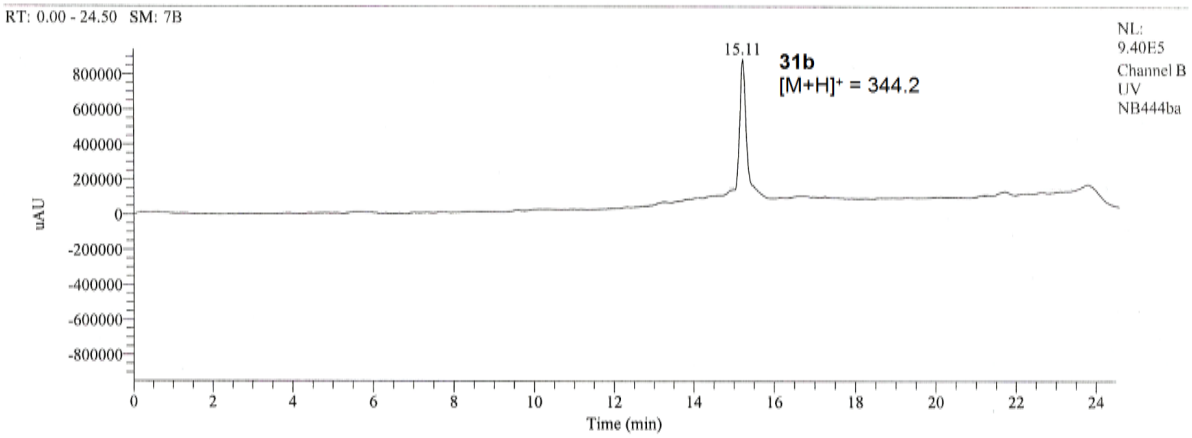
(S)-Methyl 4-(2-amino-N-benzyl-4-methylpentanamido)-1H-pyrrole-2-carboxylate 31b



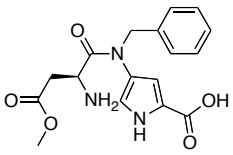
31b

Chemical Formula: $C_{19}H_{25}N_3O_3$
Exact Mass: 343,19

93%
Conditions A



(S)-4-(2-Amino-N-benzyl-4-methoxy-4-oxobutanamido)-1H-pyrrole-2-carboxylic acid 30c

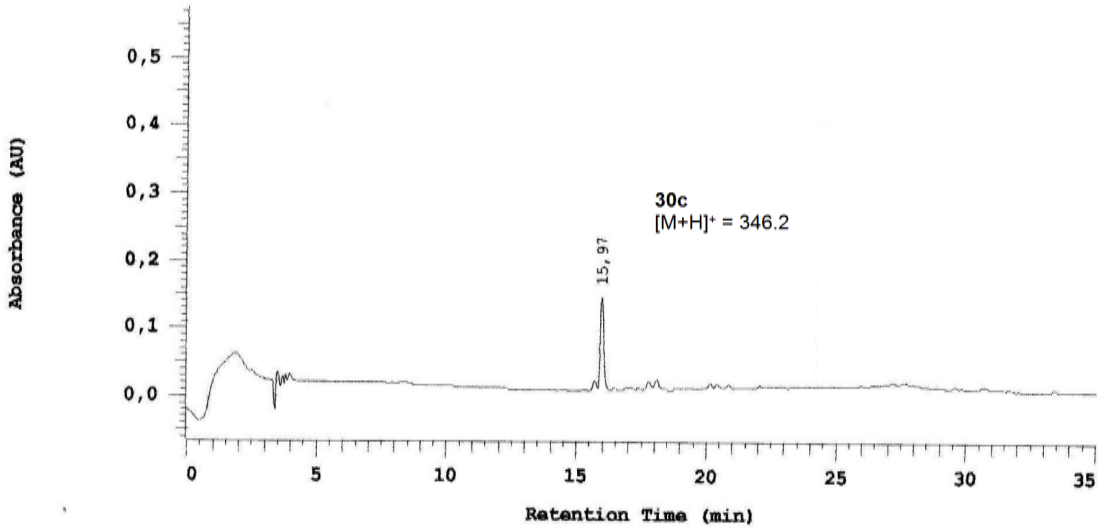


30c

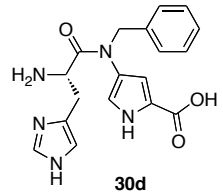
Chemical Formula: $C_{17}H_{19}N_3O_5$
Exact Mass: 345,13

76%
Conditions A

Sample Name: NB481Asp
Sample Description:



(S)-4-(2-Amino-N-benzyl-3-(1H-imidazol-4-yl)propanamido)-1H-pyrrole-2-carboxylic acid 30d

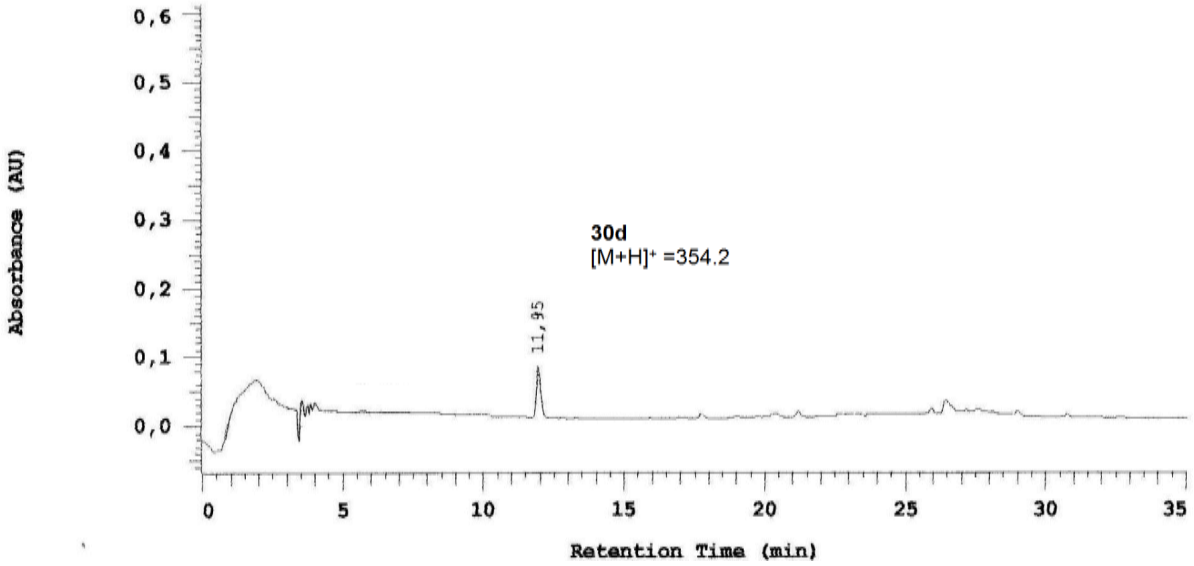


30d

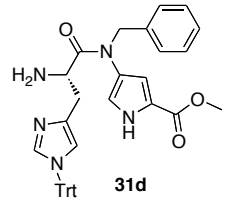
Chemical Formula: $C_{18}H_{19}N_5O_3$
Exact Mass: 353,15

90%
Conditions A

Sample Name: NB481His
Sample Description:



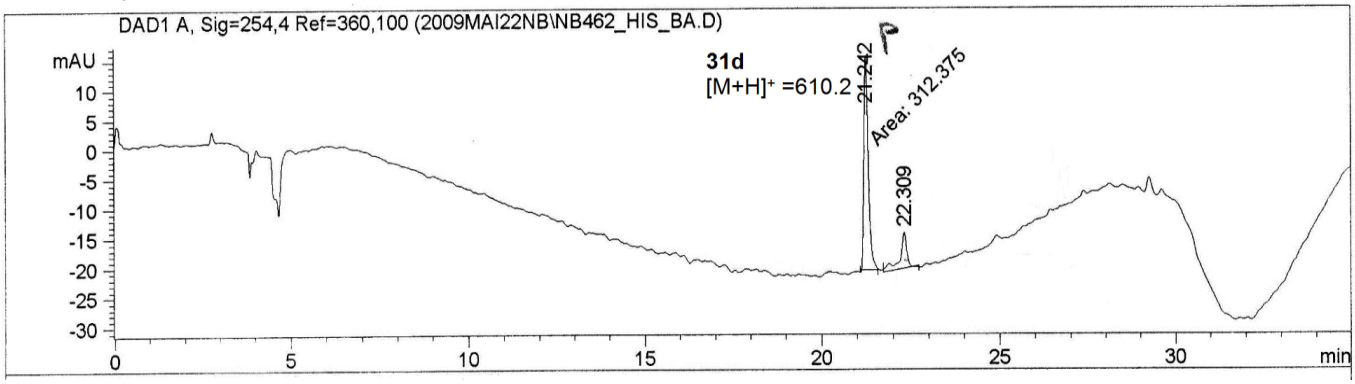
(S)-Methyl 4-(2-amino-N-benzyl-3-(1-trityl-1H-imidazol-4-yl)propanamido)-1H-pyrrole-2-carboxylate 31d



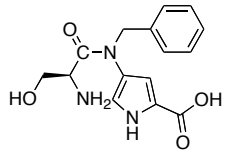
31d

Chemical Formula: $C_{38}H_{35}N_5O_3$
Exact Mass: 609,27

75%



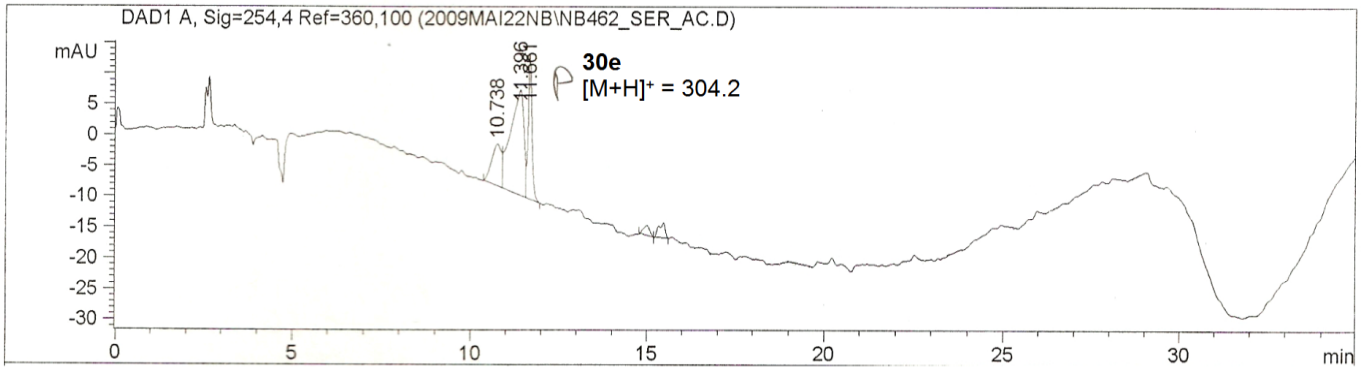
(S)-4-(2-Amino-N-benzyl-3-hydroxypropanamido)-1H-pyrrole-2-carboxylic acid 30e



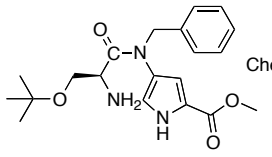
30e

Chemical Formula: $C_{15}H_{17}N_3O_4$
Exact Mass: 303,12

87%



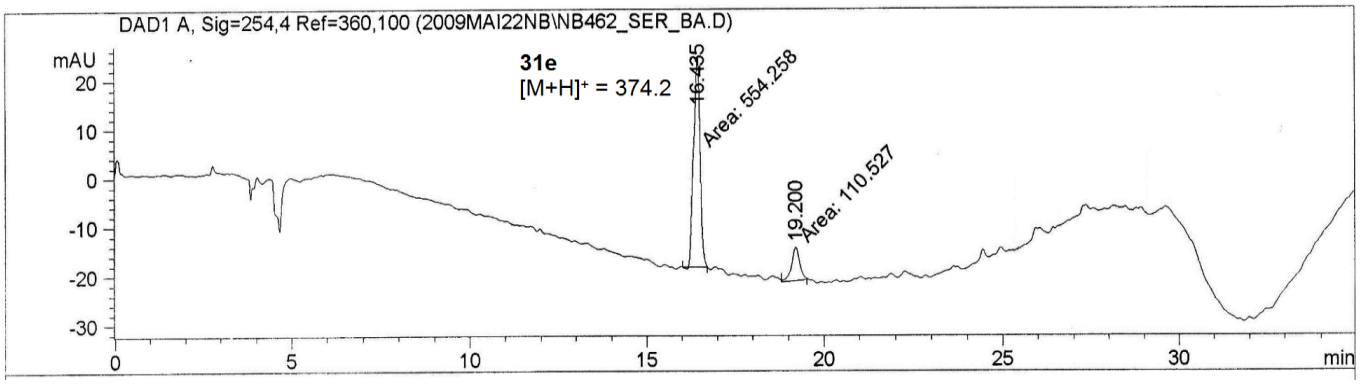
(S)-Methyl 4-(2-amino-N-benzyl-3-(tert-butoxy)propanamido)-1H-pyrrole-2-carboxylate 31e



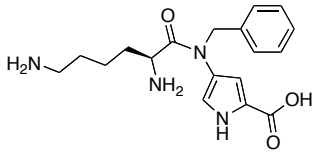
31e

Chemical Formula: $C_{20}H_{27}N_3O_4$
Exact Mass: 373,20

83%



(S)-4-(2,6-Diamino-N-benzylhexanamido)-1H-pyrrole-2-carboxylic acid 30f

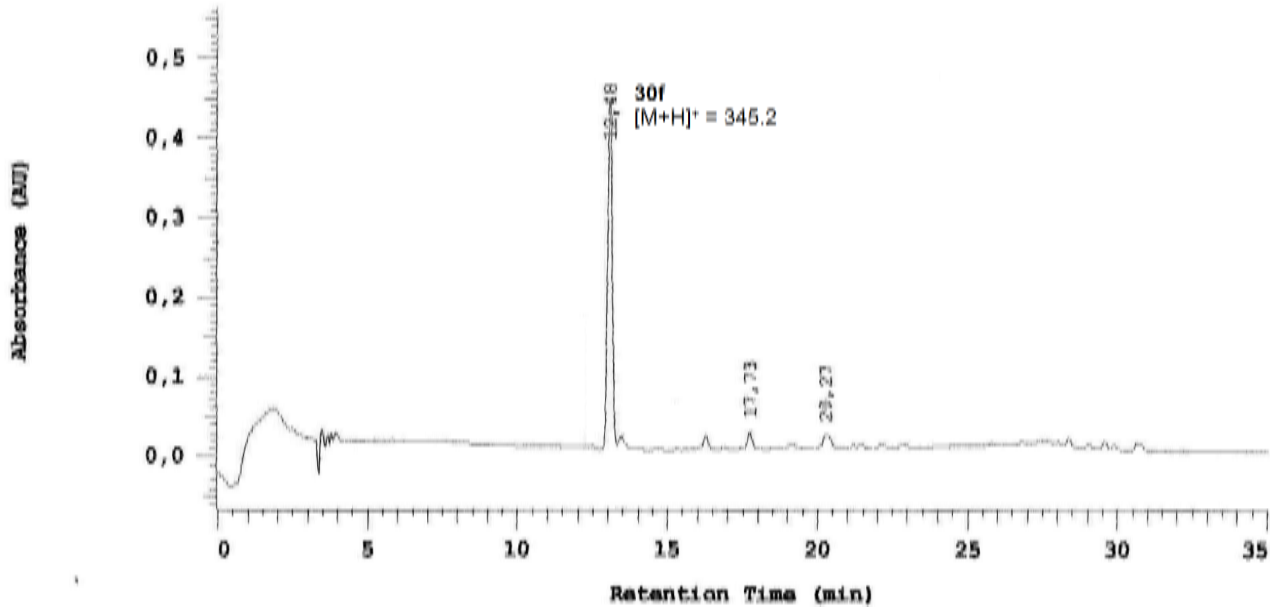


Chemical Formula: $C_{18}H_{24}N_4O_3$
Exact Mass: 344,18

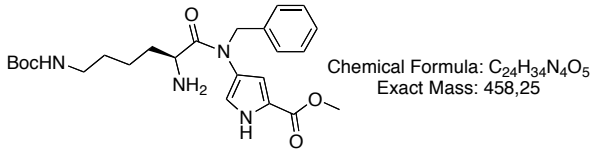
82%
Conditions A

30f

Sample Name: NB481Lys
Sample Description:



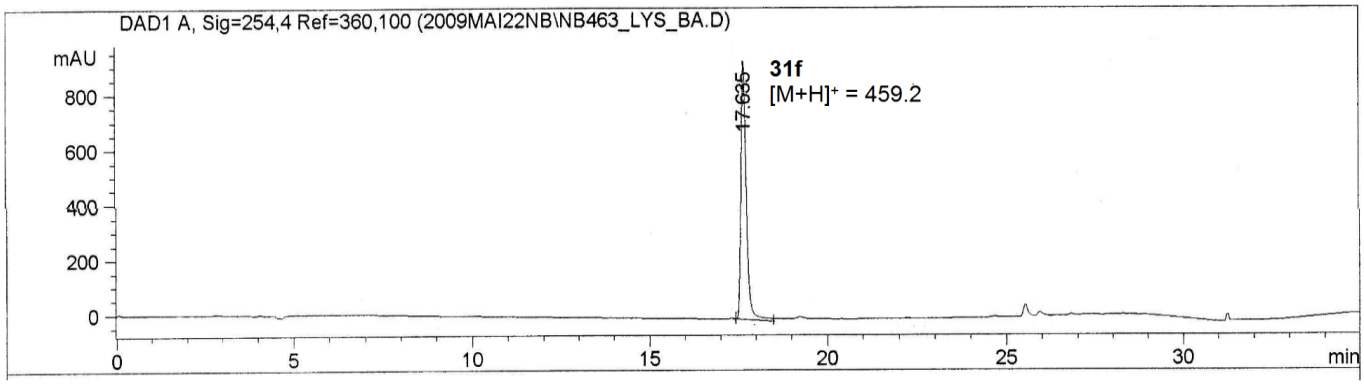
(S)-Methyl 4-(2-amino-N-benzyl-6-((tert-butoxycarbonyl)amino)hexanamido)-1H-pyrrole-2-carboxylate 31f



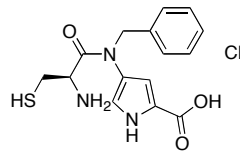
Chemical Formula: $C_{24}H_{34}N_4O_5$
Exact Mass: 458,25

91%

31f



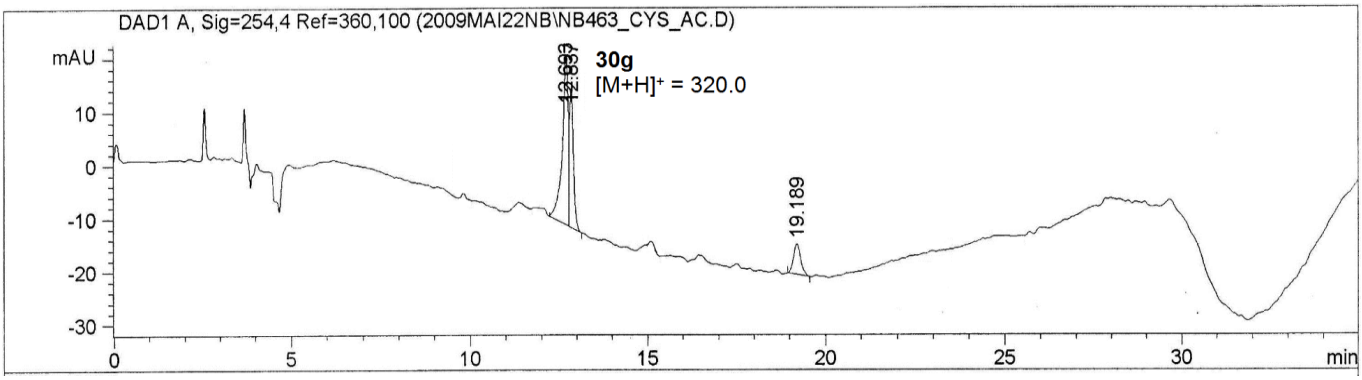
(R)-4-(2-Amino-N-benzyl-3-mercaptopropanamido)-1H-pyrrole-2-carboxylic acid 30g



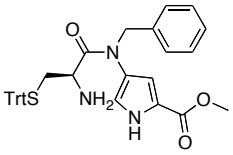
Chemical Formula: $C_{15}H_{17}N_3O_3S$
Exact Mass: 319,10

84%

30g



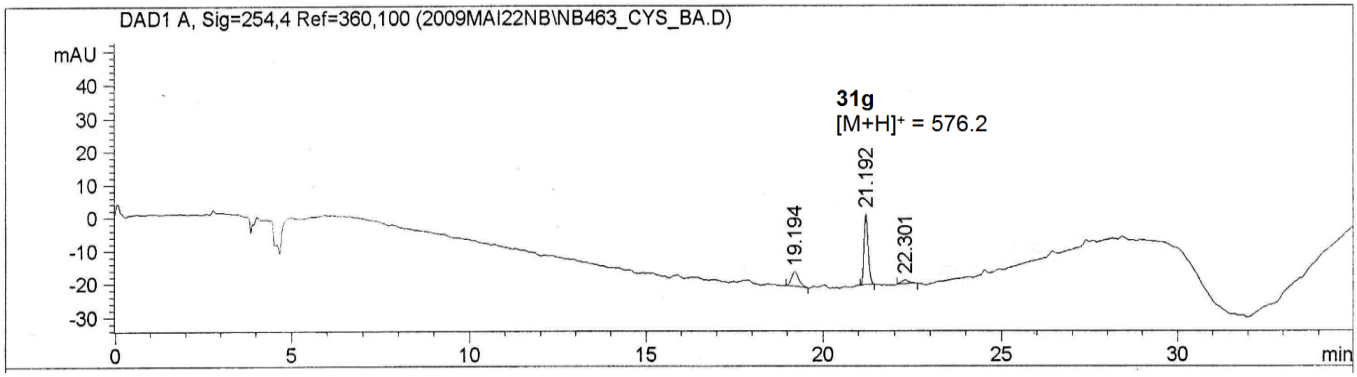
(R)-Methyl 4-(2-amino-N-benzyl-3-(tritylthio)propanamido)-1H-pyrrole-2-carboxylate 31g



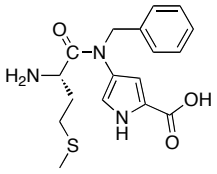
Chemical Formula: $C_{35}H_{33}N_3O_3S$
Exact Mass: 575,22

60%

31g



(S)-4-(2-Amino-N-benzyl-4-(methylthio)butanamido)-1H-pyrrole-2-carboxylic acid 30h

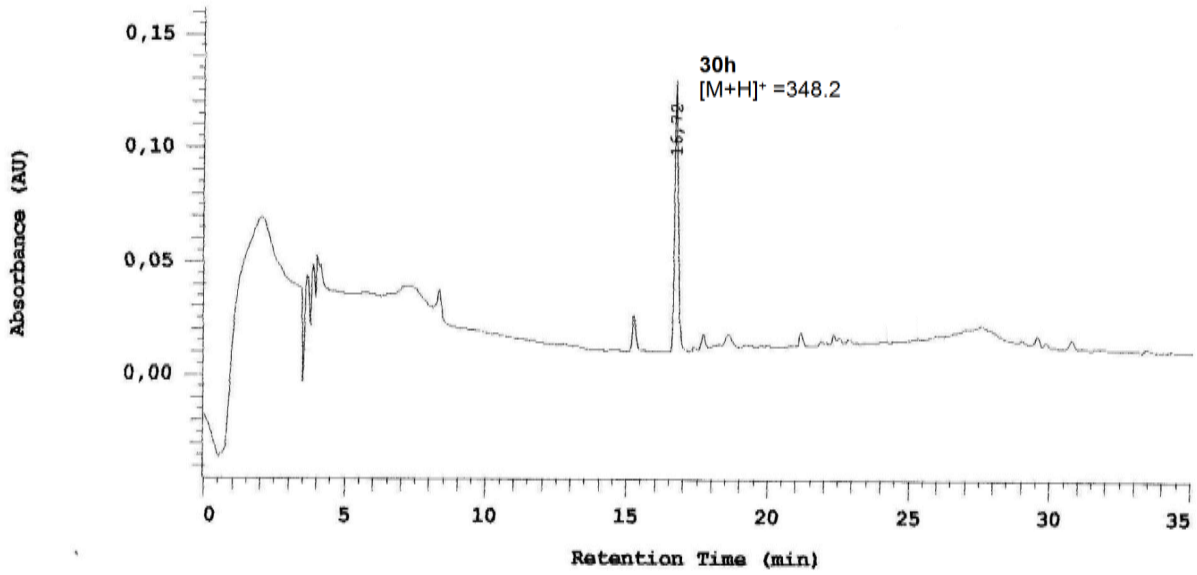


Chemical Formula: $C_{17}H_{21}N_3O_3S$
Exact Mass: 347,13

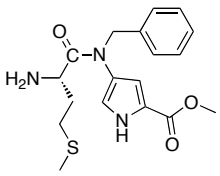
68%
Conditions A

30h

Sample Name: NB481Met
Sample Description:



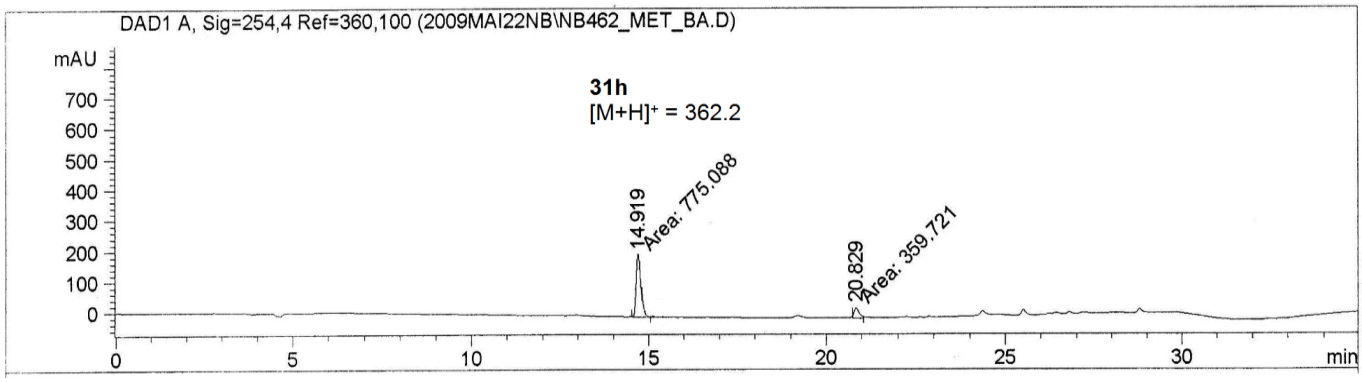
(S)-Methyl 4-(2-amino-N-benzyl-4-(methylthio)butanamido)-1H-pyrrole-2-carboxylate 31h



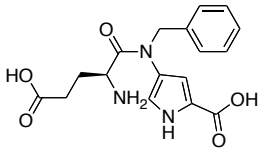
Chemical Formula: $C_{18}H_{23}N_3O_3S$
Exact Mass: 361,15

69%

31h



(S)-4-(2-Amino-N-benzyl-4-carboxybutanamido)-1H-pyrrole-2-carboxylic acid 30i

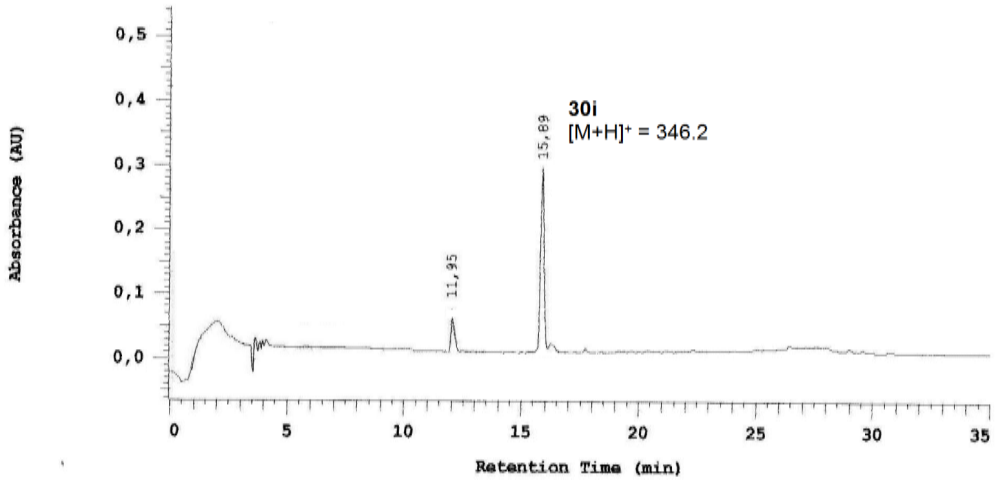


Chemical Formula: $C_{17}H_{19}N_3O_5$
Exact Mass: 345,13

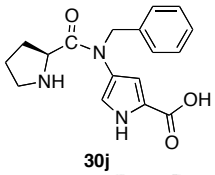
74%
Conditions A

30i

Sample Name: NB481Glu
Sample Description:



(S)-4-(N-Benzylpyrrolidine-2-carboxamido)-1H-pyrrole-2-carboxylic acid 30j

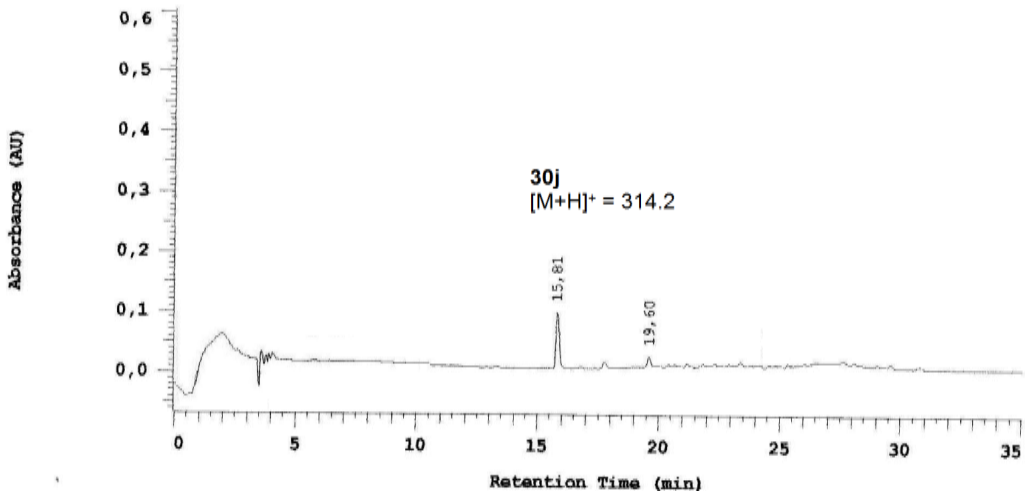


Chemical Formula: $C_{17}H_{19}N_3O_3$
Exact Mass: 313,14

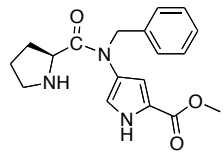
65%
Conditions A

30j

Sample Name: NB481Pro
Sample Description:



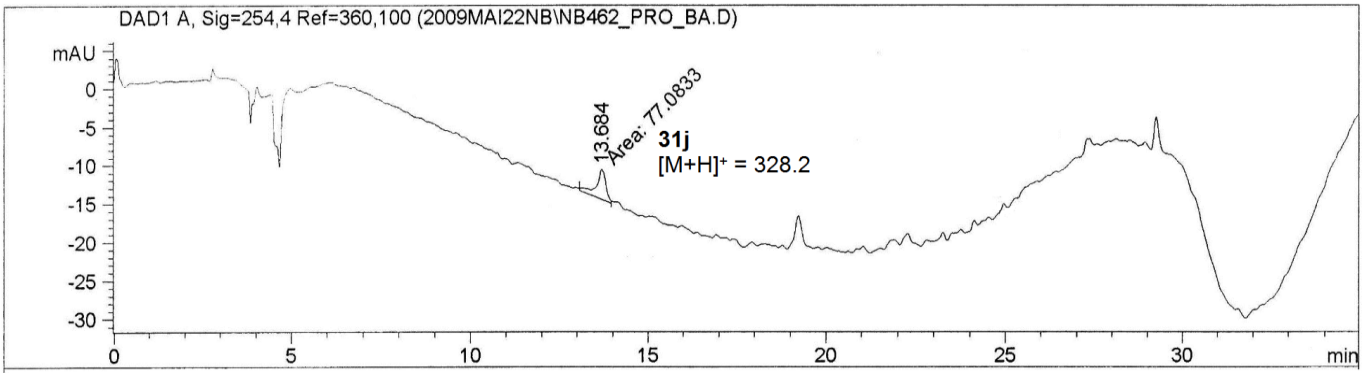
(S)-Methyl 4-(N-benzylpyrrolidine-2-carboxamido)-1H-pyrrole-2-carboxylate 31j



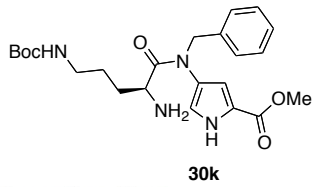
31j

Chemical Formula: $C_{18}H_{21}N_3O_3$
Exact Mass: 327,16

52%



(S)-Methyl 4-(2-amino-N-benzyl-5-((tert-butoxycarbonyl)amino)pentanamido)-1H-pyrrole-2-carboxylate 30k

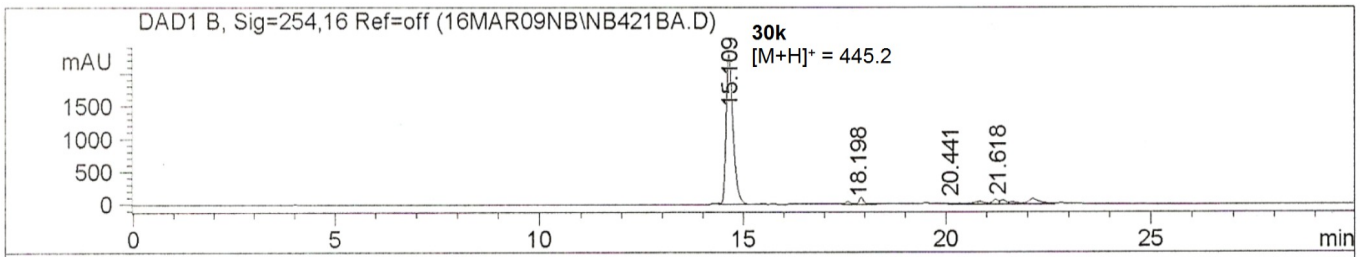


30k

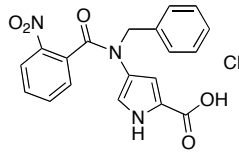
Chemical Formula: $C_{23}H_{32}N_4O_5$
Exact Mass: 444,24

82%

Sample Name NB421ba



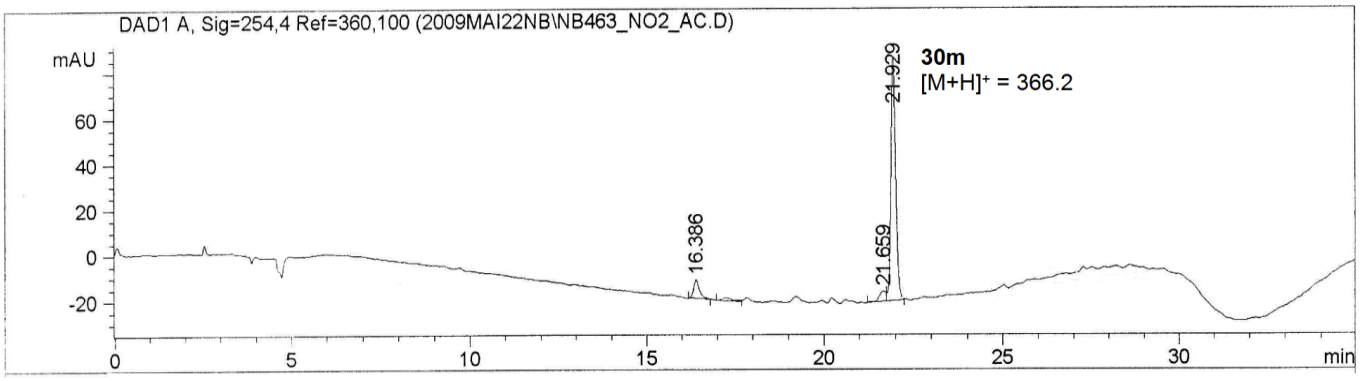
4-(N-Benzyl-2-nitrobenzamido)-1H-pyrrole-2-carboxylic acid 30m



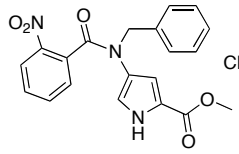
Chemical Formula: $C_{19}H_{15}N_3O_5$
Exact Mass: 365,10

82%

30m



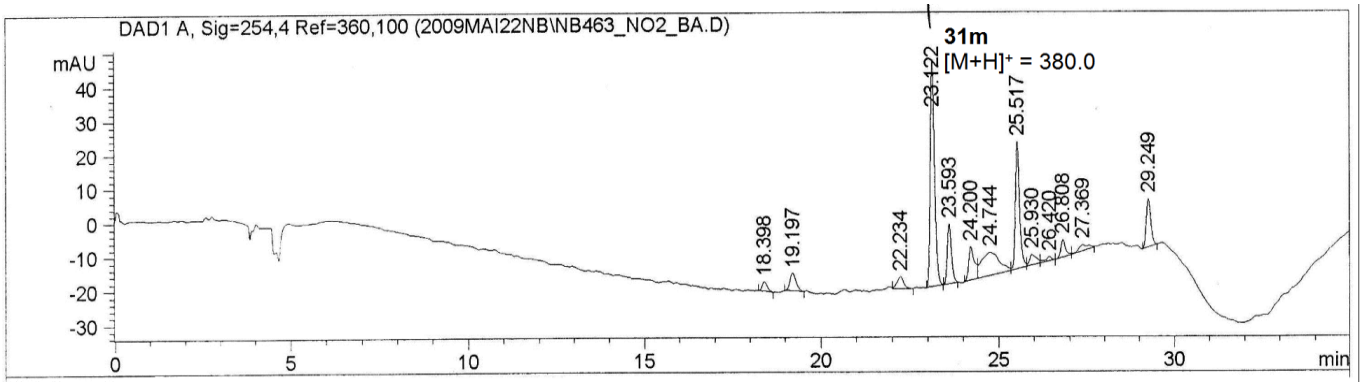
Methyl 4-(N-benzyl-2-nitrobenzamido)-1H-pyrrole-2-carboxylate 31m



Chemical Formula: $C_{20}H_{17}N_3O_5$
Exact Mass: 379,12

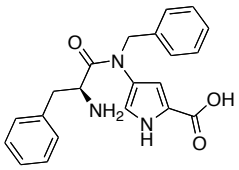
37%

31m



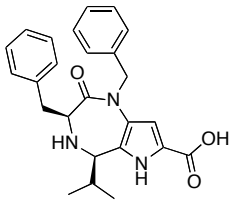
Pictet-Spengler cylizations

On Phe derivative 29a



Chemical Formula: $C_{21}H_{21}N_3O_3$
Exact Mass: 363,16

43a

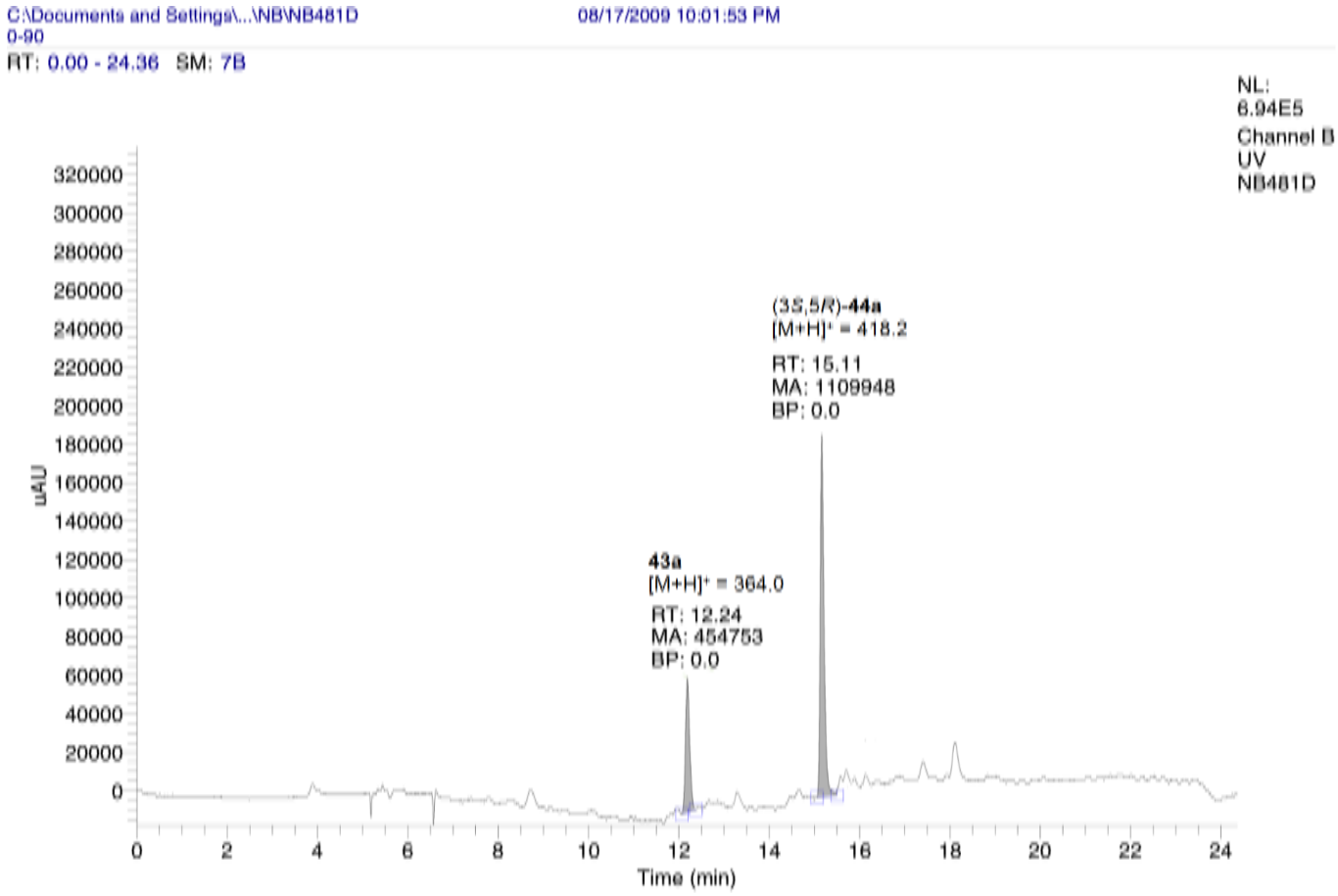


Chemical Formula: $C_{25}H_{27}N_3O_3$
Exact Mass: 417,21

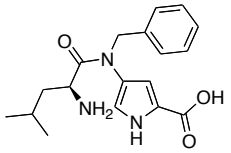
(3*S*,5*R*)-**44a**

Conditions C

43a	(3*S*,5*R*)-**44a**
(R_t; $[M+H]^+$)	(R_t; $[M+H]^+$)
27% (12.2; 364.0)	73% (15.1; 418.2)

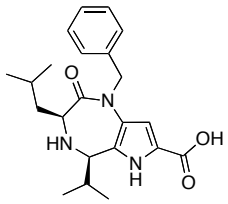


On Leu derivative 29b



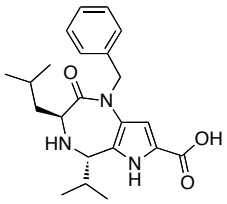
Chemical Formula: $C_{18}H_{23}N_3O_3$
Exact Mass: 329,17

43b



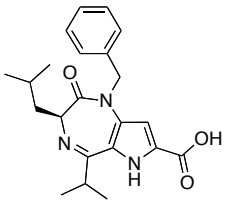
Chemical Formula: $C_{22}H_{29}N_3O_3$
Exact Mass: 383,22

(3*S*,5*R*)-**44b**



Chemical Formula: $C_{22}H_{29}N_3O_3$
Exact Mass: 383,22

(3*S*,5*S*)-**44b**

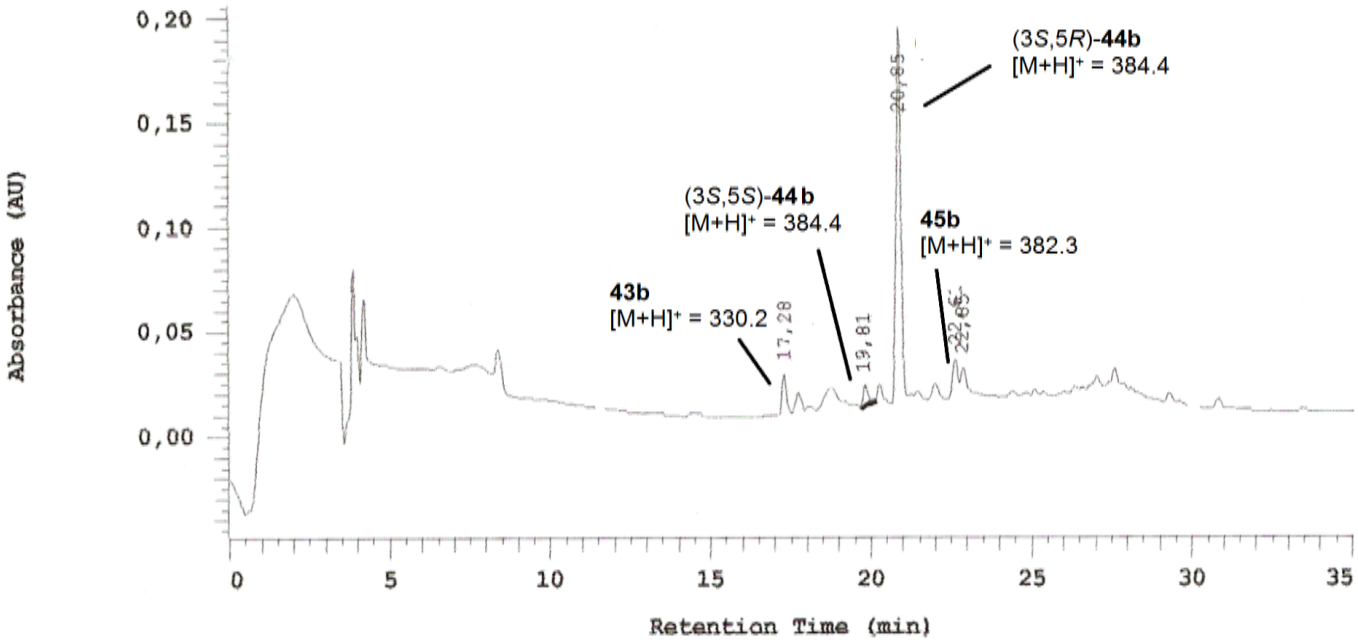


Chemical Formula: $C_{22}H_{27}N_3O_3$
Exact Mass: 381,21

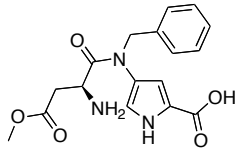
45b

Conditions A

43b	(3*S*,5*R*)-**44b**	(3*S*,5*S*)-**44b**	**45b**
(R_t; $[M+H]^+$)	(R_t; $[M+H]^+$)	(R_t; $[M+H]^+$)	(R_t; $[M+H]^+$)
12% (17.3; 330.2)	72% (20.8; 384.4)	5% (19.8; 384.4)	11% (22.6; 382.3)

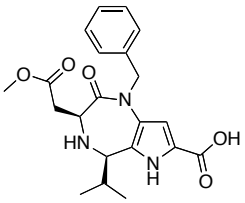


On Asp derivative 29c



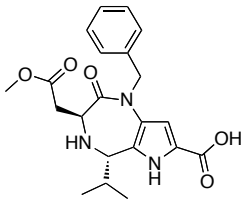
Chemical Formula: $C_{17}H_{19}N_3O_5$
Exact Mass: 345,13

43c



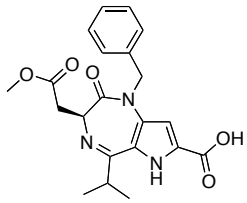
Chemical Formula: $C_{21}H_{25}N_3O_5$
Exact Mass: 399,18

(3*S*,5*R*)-**44c**



Chemical Formula: $C_{21}H_{25}N_3O_5$
Exact Mass: 399,18

(3*S*,5*S*)-**44c**

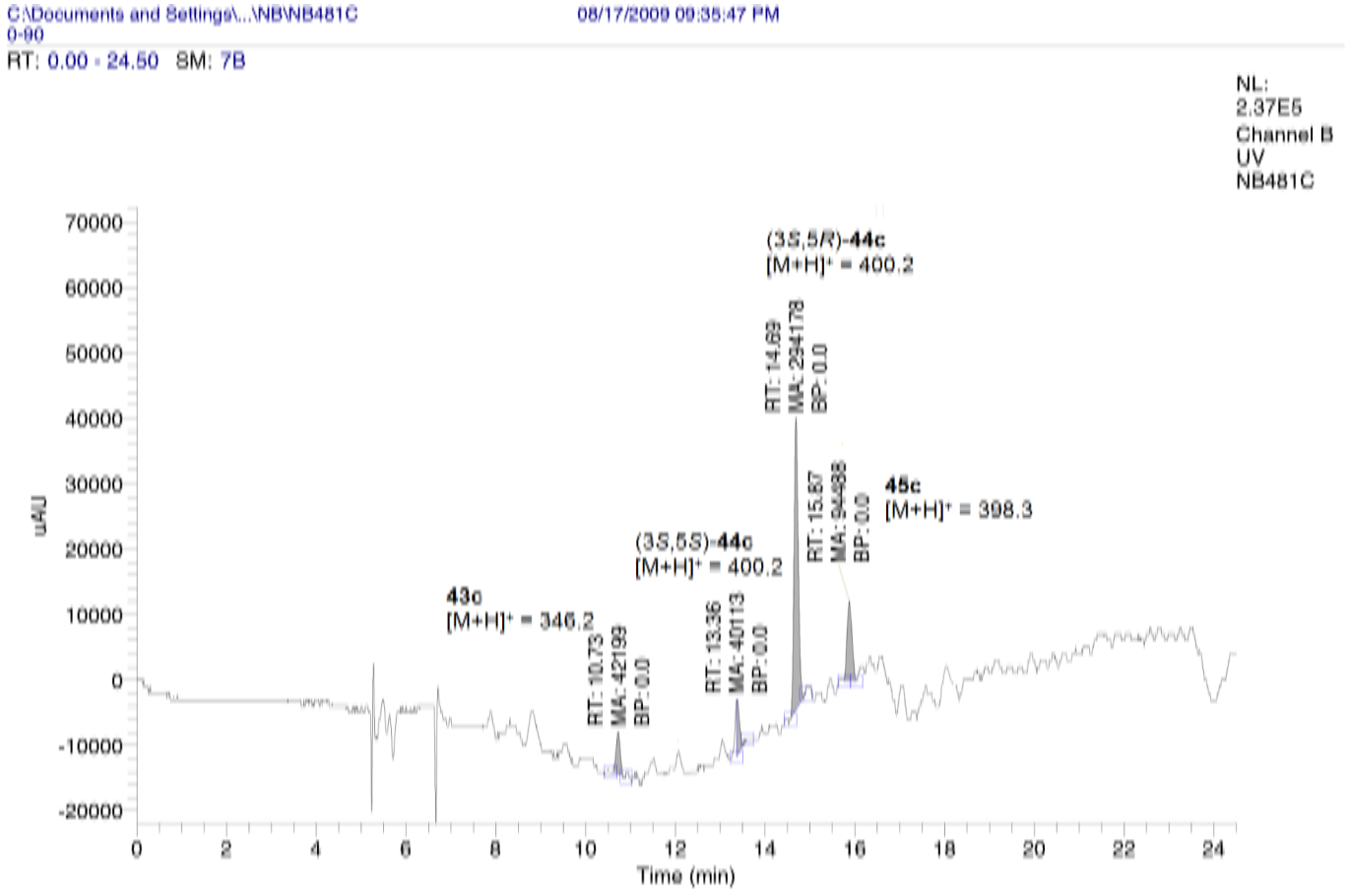


Chemical Formula: $C_{21}H_{23}N_3O_5$
Exact Mass: 397,16

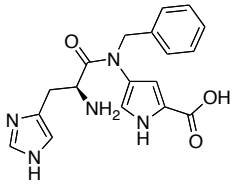
45c

Conditions C

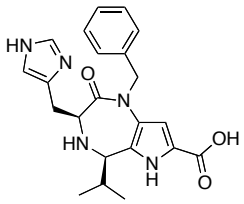
43c	(3*S*,5*R*)-**44c**	(3*S*,5*S*)-**44c**	**45c**
(R_t; $[M+H]^+$)	(R_t; $[M+H]^+$)	(R_t; $[M+H]^+$)	(R_t; $[M+H]^+$)
9% (10.7; 346.2)	63% (14.7; 400.2)	8% (13.4; 400.2)	20% (15.9; 398.3)



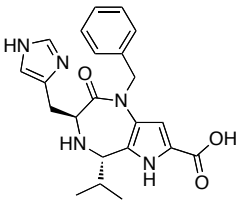
On His derivative 29d



Chemical Formula: $C_{18}H_{19}N_5O_3$
Exact Mass: 353,15
43d



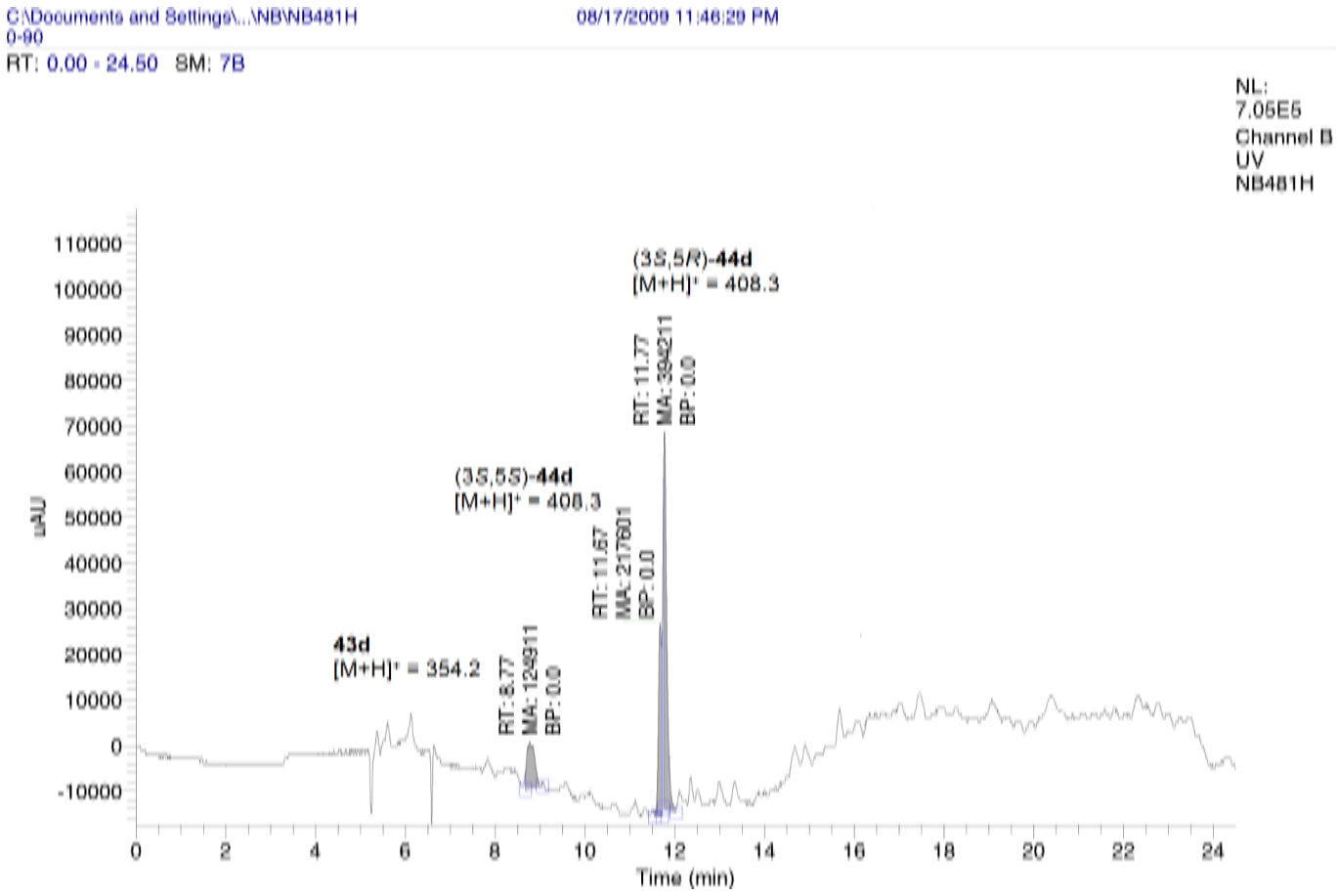
Chemical Formula: $C_{22}H_{25}N_5O_3$
Exact Mass: 407,20
(3*S*,5*R*)-**44d**



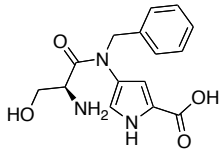
Chemical Formula: $C_{22}H_{25}N_5O_3$
Exact Mass: 407,20
(3*S*,5*S*)-**44d**

Conditions C

43d	(3*S*,5*R*)-**44d**	(3*S*,5*S*)-**44d**
(R_t; $[M+H]^+$)	(R_t; $[M+H]^+$)	(R_t; $[M+H]^+$)
17% (8.8; 354.2)	54% (11.8; 408.3)	29% (11.7; 408.3)

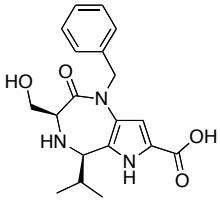


On Ser derivative 29e



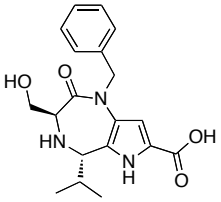
Chemical Formula: $C_{15}H_{17}N_3O_4$
Exact Mass: 303,12

43e



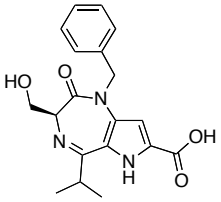
Chemical Formula: $C_{19}H_{23}N_3O_4$
Exact Mass: 357,17

(3*S*,5*R*)-**44e**



Chemical Formula: $C_{19}H_{23}N_3O_4$
Exact Mass: 357,17

(3*S*,5*S*)-**44e**

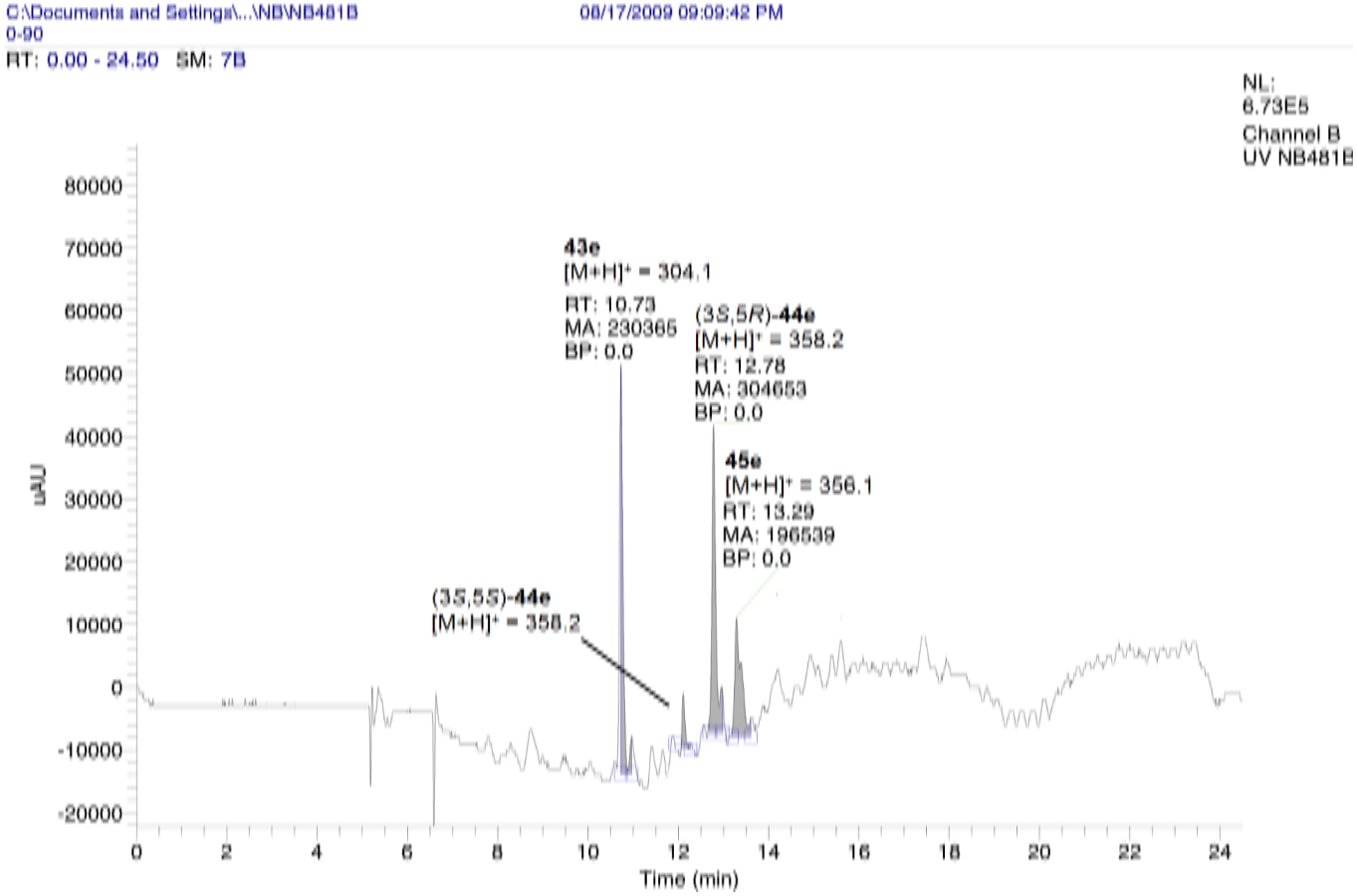


Chemical Formula: $C_{19}H_{21}N_3O_4$
Exact Mass: 355,15

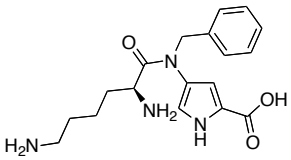
45e

Conditions C

43e	(3*S*,5*R*)-**44e**	(3*S*,5*S*)-**44e**	**45e**
(R_t; $[M+H]^+$)	(R_t; $[M+H]^+$)	(R_t; $[M+H]^+$)	(R_t; $[M+H]^+$)
29% (10.7; 304.1)	38% (12.8; 358.2)	8% (12.2; 358.2)	25% (13.3; 356.1)

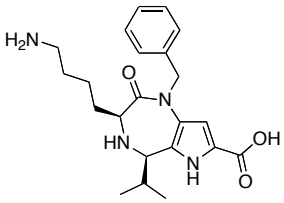


On Lys derivative 29f



Chemical Formula: $C_{18}H_{24}N_4O_3$
Exact Mass: 344,18

43f

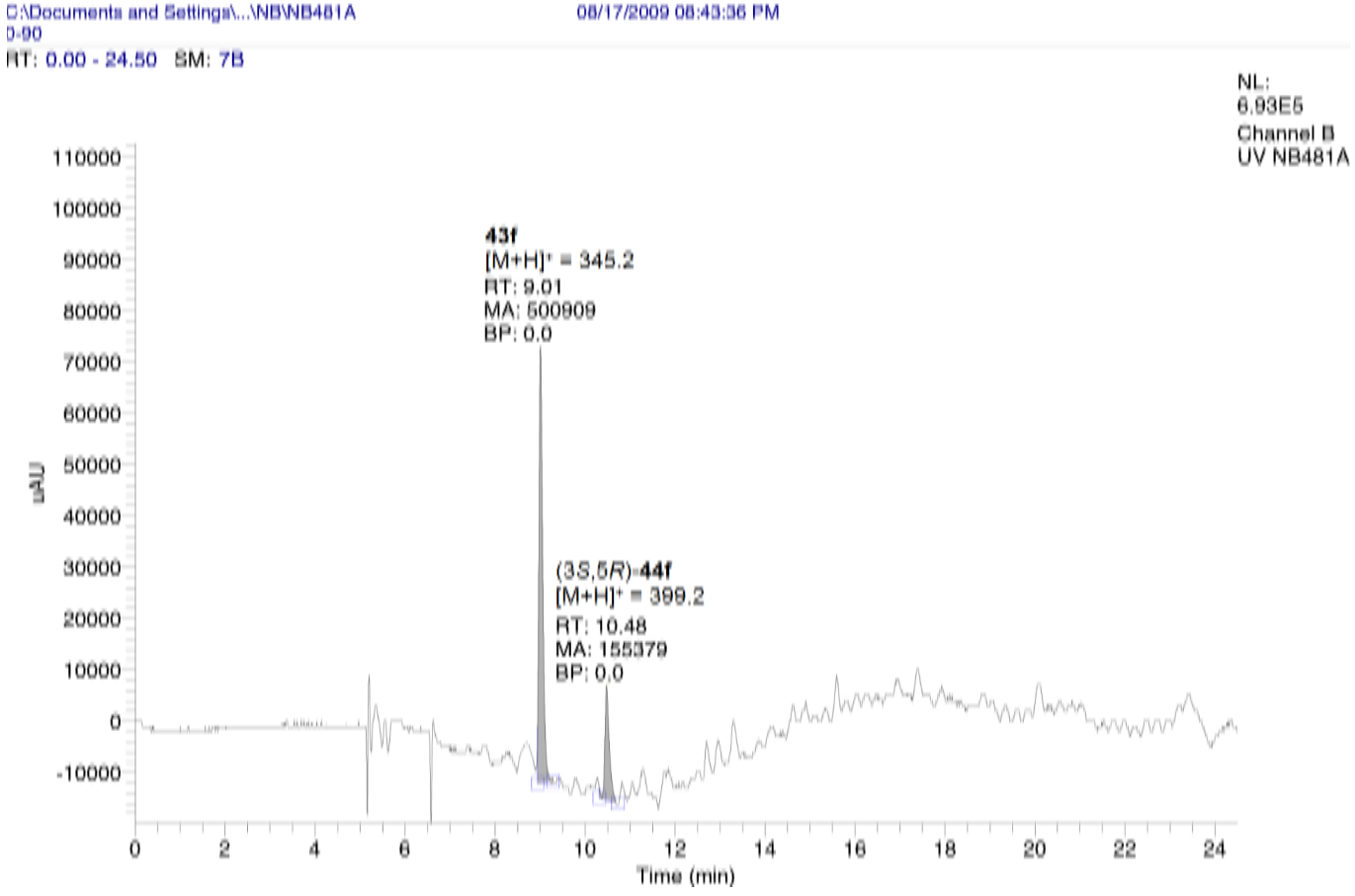


Chemical Formula: $C_{22}H_{30}N_4O_3$
Exact Mass: 398,23

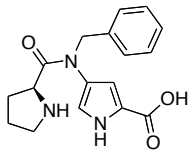
(3*S*,5*R*)-**44f**

Conditions C

43f	(3*S*,5*R*)-**44f**
(R_t; $[M+H]^+$)	(R_t; $[M+H]^+$)
76% (9.0; 345.2)	24% (10.5; 399.2)



On Pro derivative 29j



Chemical Formula: $C_{17}H_{19}N_3O_3$
Exact Mass: 313,14

43j

Conditions C
43j
(R_t; $[M+H]^+$)
78% (11.1; 314.2)

