

## In Silico Identification of Tripeptides as Lead Compounds for the Design of KOR Ligands

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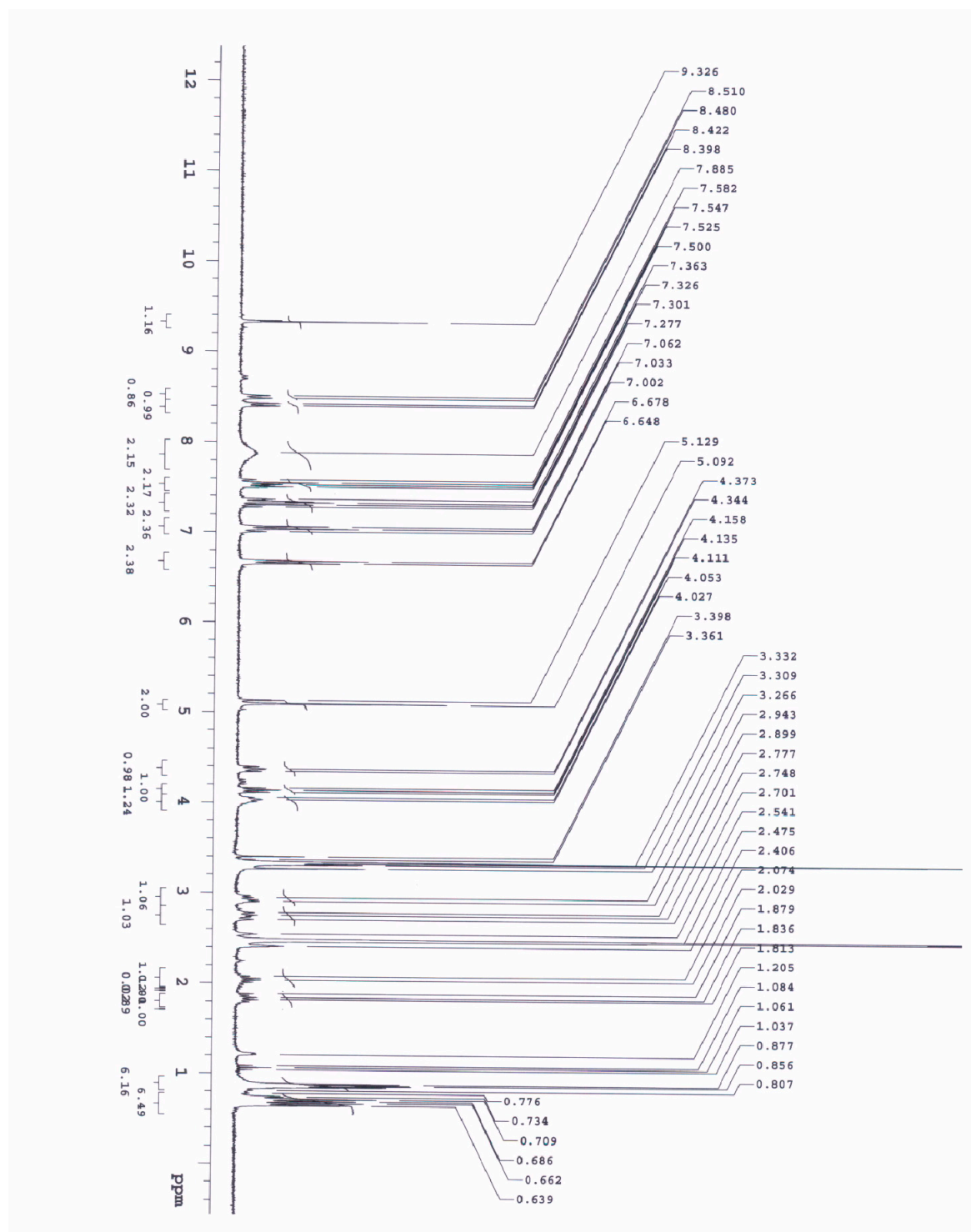
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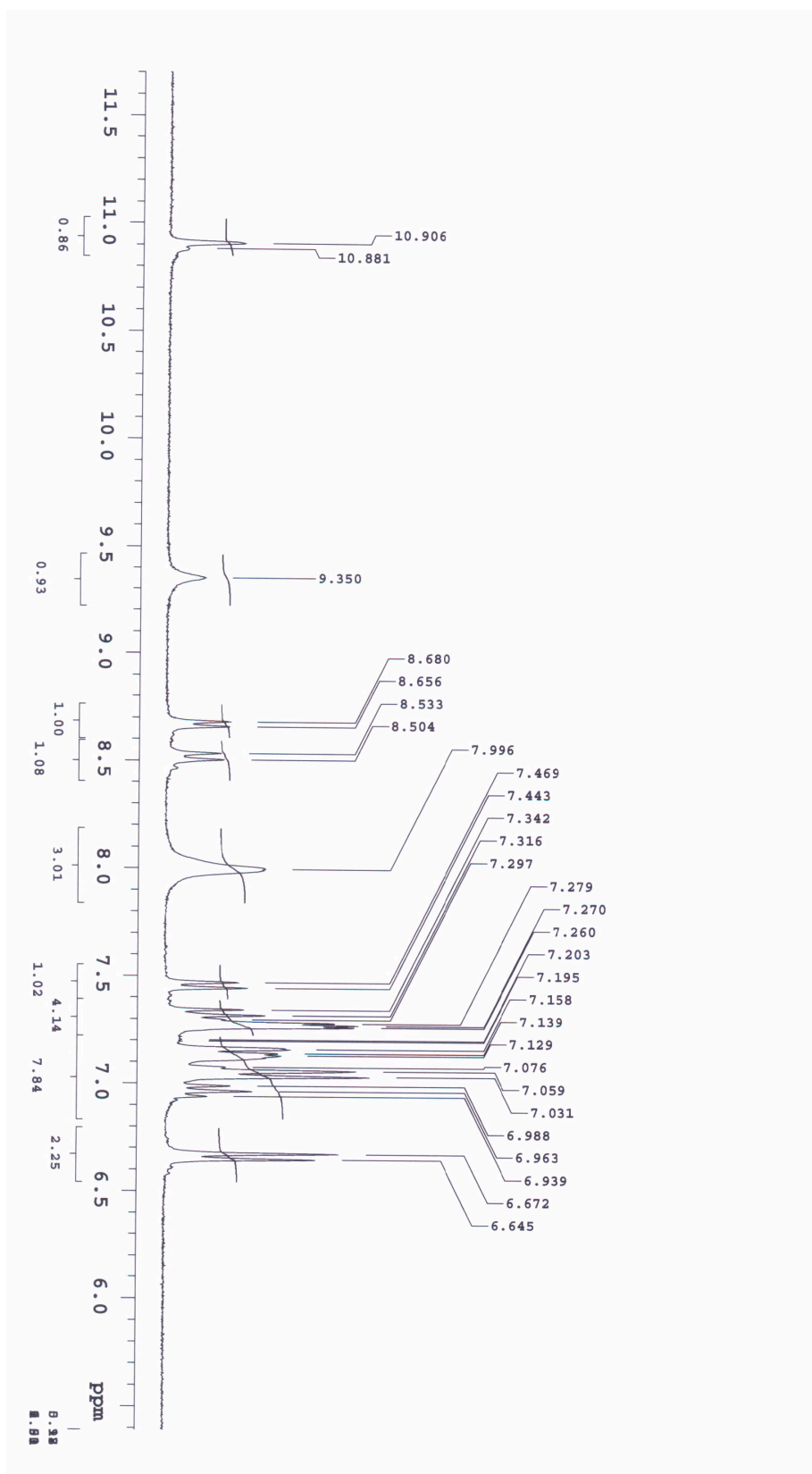
<sup>4</sup> Advanced Pharmaceuticals and Drug Delivery Laboratory, Leslie L. Dan Faculty of Pharmacy, University of Toronto, 27 King's College Circle, Toronto, ON M5S 1A1, Canada; sako.biochem@gmail.com

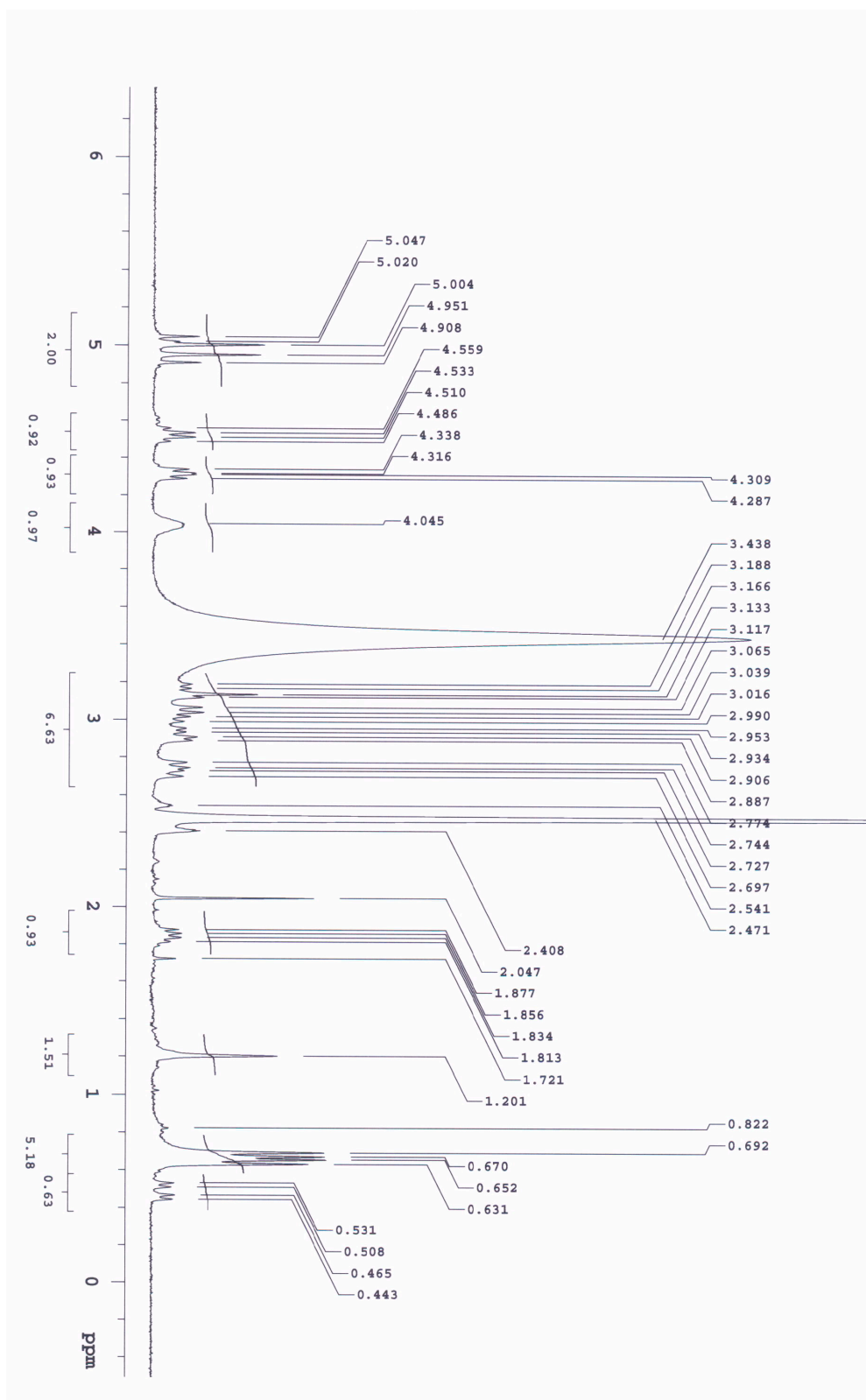
<sup>5</sup> NGN Healthcare, Via Nazionale Torrette, 207, 83013 Mercogliano, Italy; etторе.novellino@unina.it

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Table of Contents	Pages
Figure S1: 1H-NMR of peptide <b>6</b>	2-4
Figure S2: LRMS of peptide <b>5</b>	5
Figure S3: 1H-NMR of peptide <b>11</b>	6-8
Figure S4: LRMS of peptide <b>10</b>	9
Figure S5: ADME prediction for <b>6</b>	10
Figure S6: ADME prediction for <b>11</b>	11





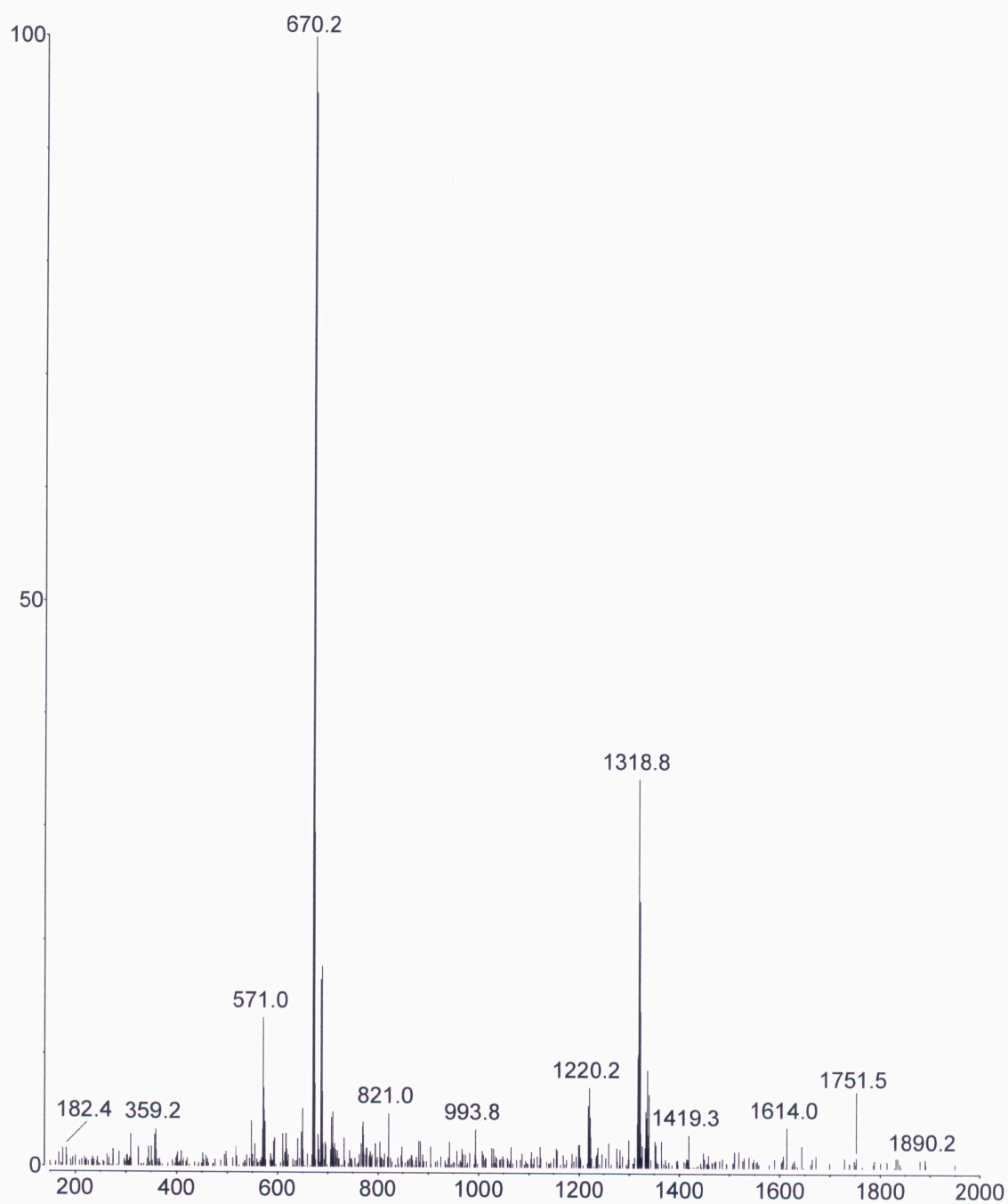


**Figure S1.** <sup>1</sup>H-NMR of peptide 6 in DMSO-d<sub>6</sub>.

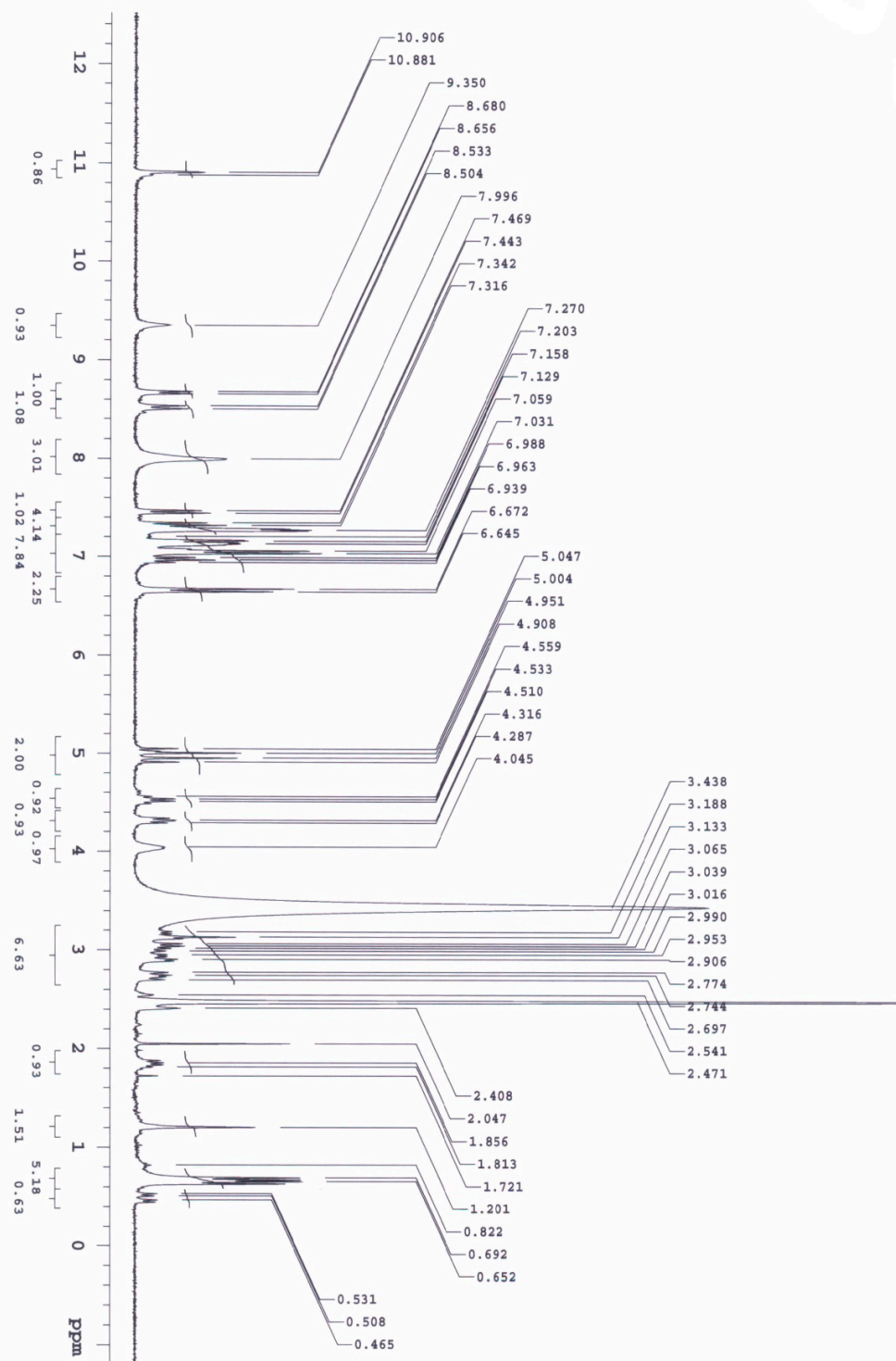
LCQ Instrument Control 12 Feb 2021 07:03 AM

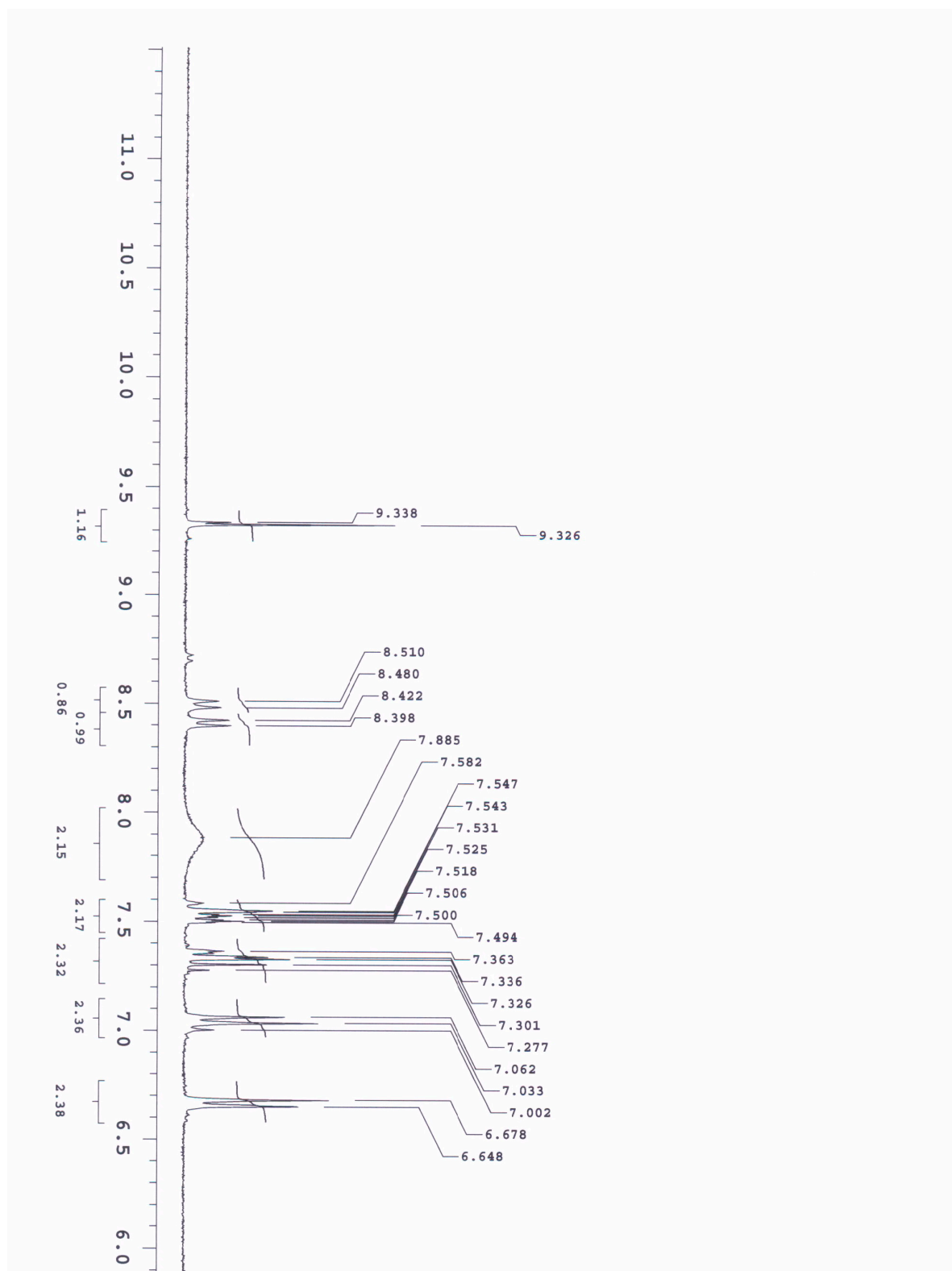
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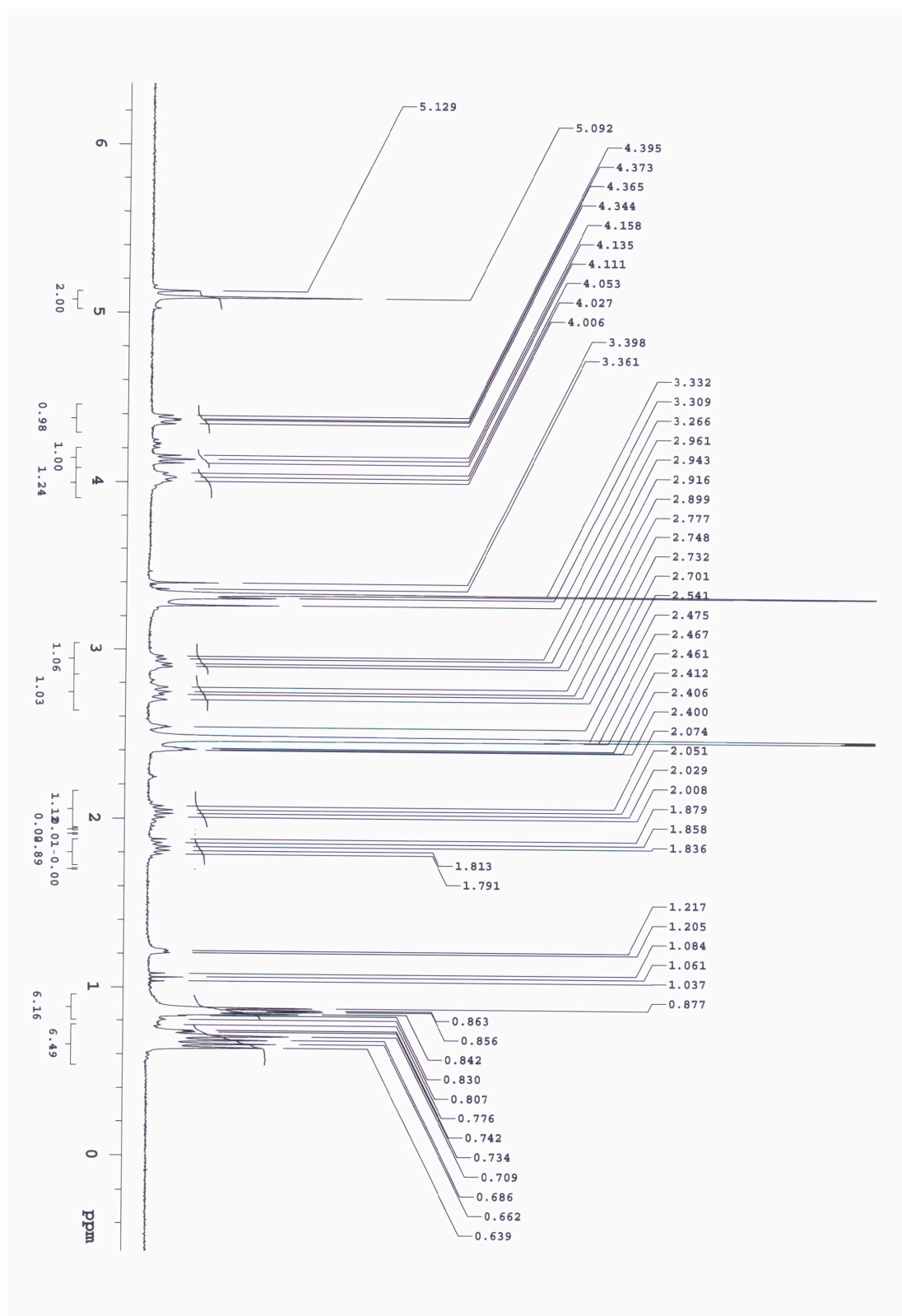
NL: 5.88e+006



**Figure S2.** LRMS of peptide 5.







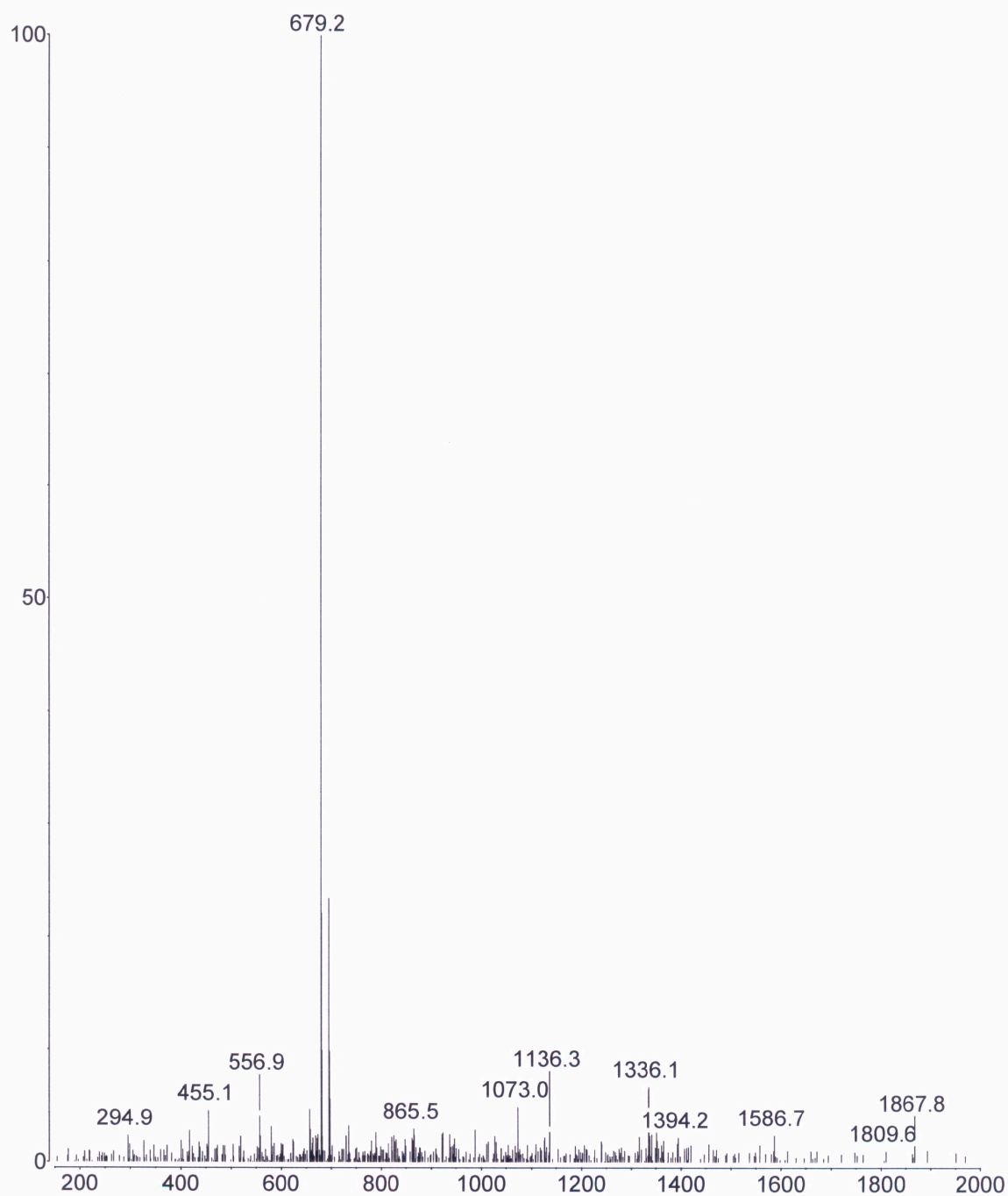
**Figure S3.** <sup>1</sup>H-NMR of peptide **11** in DMSO-d<sub>6</sub>.



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S#: 1115 IT: 47.19 ST: 1.55

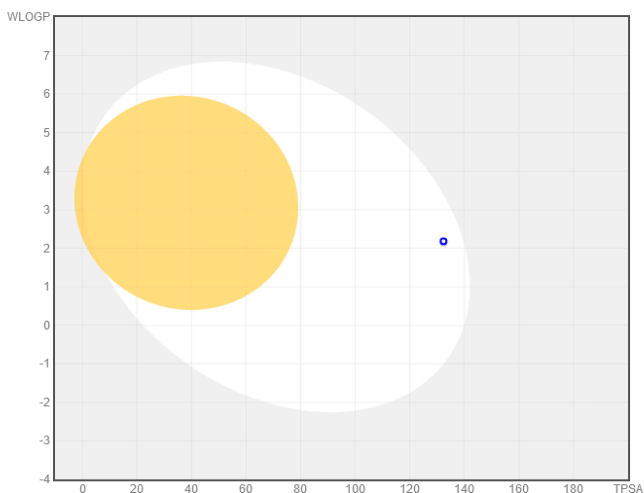
NL: 4.29e+006



**Figure S4. LRMS of peptide 10.**

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Retrieve data: POWERED BY ChemAxon



**Actions**
☐ Show Molecules Name

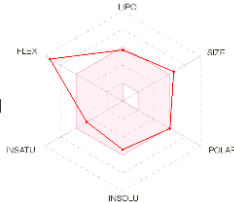
**Legends**

- BBB
- HIA
- PGP+
- PGP---

**Remarks**

None

### Molecule 1



SMILES CC([C@@H](C(=O)N[C@@H](C(=O)OCC1CCCC(C1)Br)C(C)C)NC(=O)[C@@H](Cc1ccc(cc1)O)[NH3+])C

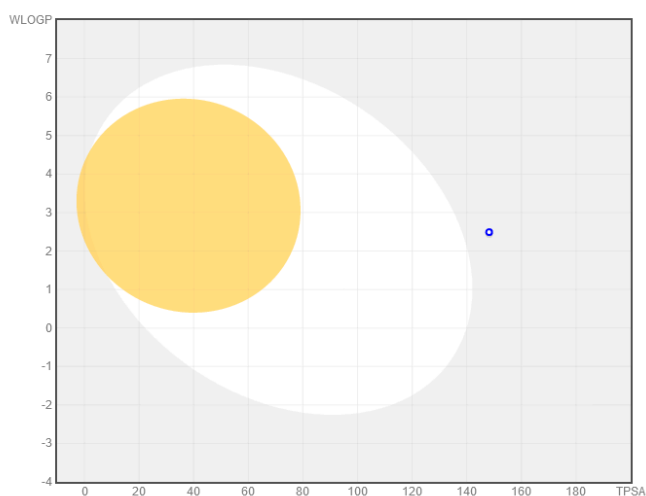
Physicochemical Properties	
Formula	C <sub>26</sub> H <sub>35</sub> BrN <sub>3</sub> O <sub>5</sub>
Molecular weight	549.48 g/mol
Num. heavy atoms	35
Num. arom. heavy atoms	12
Fraction Csp <sup>3</sup>	0.42
Num. rotatable bonds	14
Num. H-bond acceptors	5
Num. H-bond donors	4
Molar Refractivity	139.36
TPSA	132.37 Å <sup>2</sup>
Lipophilicity	
Log P <sub>o/w</sub> (iLOGP)	3.43
Log P <sub>o/w</sub> (XLOGP3)	4.45
Log P <sub>o/w</sub> (WLOGP)	2.18
Log P <sub>o/w</sub> (MLOGP)	-1.28
Log P <sub>o/w</sub> (SILICOS-IT)	4.16
Consensus Log P <sub>o/w</sub>	2.59

Water Solubility	
Log S (ESOL)	-5.38
Solubility	2.29e-03 mg/ml ; 4.17e-06 mol/l
Class	Moderately soluble
Log S (Ali)	-6.95
Solubility	6.18e-05 mg/ml ; 1.13e-07 mol/l
Class	Poorly soluble
Log S (SILICOS-IT)	-6.89
Solubility	7.11e-05 mg/ml ; 1.29e-07 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K <sub>p</sub> (skin permeation)	-6.49 cm/s
Druglikeness	
Lipinski	Yes; 1 violation: MW>500
Ghose	No; 2 violations: MW>480, MR>130
Veber	No; 1 violation: Rotors>10
Egan	No; 1 violation: TPSA>131.6
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5
Synthetic accessibility	4.42

Figure S5. ADME prediction for 6.

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Retrieve data: POWERED BY ChemAxon



**Actions**

☐ Show Molecules Name

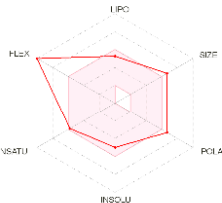
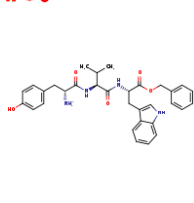
**Legends**

BBB  
HIA  
PGP+  
PGP-

**Remarks**

None

### Molecule 1



SMILES CC([C@@H](C(=O)N[C@@H](C(=O)OCc1ccccc1)Cc1[nH]c2c1cccc2)NC(=O)[C@@H](Cc1ccc(cc1)O)[NH3+])C

#### Physicochemical Properties

Formula	C32H37N4O5
Molecular weight	557.66 g/mol
Num. heavy atoms	41
Num. arom. heavy atoms	21
Fraction Csp3	0.28
Num. rotatable bonds	15
Num. H-bond acceptors	5
Num. H-bond donors	5
Molar Refractivity	158.39
TPSA	148.16 Å²

#### Lipophilicity

Log $P_{ow}$ (ILOGP)	3.18
Log $P_{ow}$ (XLOGP3)	3.68
Log $P_{ow}$ (WLOGP)	2.49
Log $P_{ow}$ (MLOGP)	-1.94
Log $P_{ow}$ (SILICOS-IT)	4.88
Consensus Log $P_{ow}$	2.46

Water Solubility	
Log S (ESOL)	-5.00
Solubility	5.51e-03 mg/ml ; 9.89e-06 mol/l
Class	Moderately soluble
Log S (All)	-6.48
Solubility	1.84e-04 mg/ml ; 3.30e-07 mol/l
Class	Poorly soluble
Log S (SILICOS-IT)	-9.01
Solubility	5.45e-07 mg/ml ; 9.77e-10 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log $K_p$ (skin permeation)	-7.09 cm/s
Druglikeness	
Lipinski	Yes; 1 violation: MW>500
Ghose	No; 3 violations: MW>480, MR>130, #atoms>70
Veber	No; 2 violations: Rotors>10, TPSA>140
Egan	No; 1 violation: TPSA>131.6
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5
Synthetic accessibility	4.77

Figure S6. ADME prediction for 11.