Supporting Information

Towards understanding the structural basis of partial agonism at the dopamine D_3 receptor

Mayako Michino,[§,#] Comfort A. Boateng,[†,#,&] Prashant Donthamsetti,[‡#] Hideaki Yano,[§] Oluyomi M. Bakare,[†] Alessandro Bonifazi,[†] Michael P. Ellenberger,[†] Thomas M. Keck,[†,^] Vivek Kumar,[†] Clare Zhu,[§] Ravi Verma,[§] Jeffrey R. Deschamps,[+] Jonathan A. Javitch,[‡] Amy Hauck Newman[†*] and Lei Shi[§,*]

[§]Computational Chemistry and Molecular Biophysics Unit, Molecular Targets and Medications Discovery Branch, National Institute on Drug Abuse – Intramural Research Program, National Institutes of Health, 333 Cassell Drive, Baltimore, Maryland 21224, United States

[†]Medicinal Chemistry Section, Molecular Targets and Medications Discovery Branch, National Institute on Drug Abuse – Intramural Research Program, National Institutes of Health, 333 Cassell Drive, Baltimore, Maryland 21224, United States

[^]Department of Chemistry & Biochemistry, Department of Biomedical & Translational Sciences College of Science and Mathematics, Rowan University, 201 Mullica Hill Road, Glassboro, New Jersey 08028, United States

[‡]Departments of Psychiatry and Pharmacology, Columbia University College of Physicians and Surgeons, Division of Molecular Therapeutics, New York State Psychiatric Institute, New York, New York 10032, United States

[+]Naval Research Laboratory, Code 6930, 4555 Overlook Avenue, Washington, DC 20375, United States

[&]Department of Basic Pharmaceutical Sciences, Fred Wilson School of Pharmacy, High Point University, One University Parkway, High Point, North Carolina, 27268, United States

[#]Equally Contributing Authors, *Corresponding Authors

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Table S1. MD simulations of D_3R in complex with the full-length compounds and synthons

Ligand	Number of trajectories[a]	Simulation lengths (ns)	Total lengths (ns)
3	2	900, 600	1500
(*R*)-**4**	4	1200, 1200, 300, 300	3000
(*S*)-**4**	6	600, 300, 300, 1500, 1200, 300	4200
(*R*)-**6**	4	900, 600, 900, 300	2700
(*S*)-**6**	7	300, 900, 1200, 1200, 900, 900, 1200	6600
(*R*)-**9**	6	300, 1200, 300, 900, 600, 300	3600
(*S*)-**9**	8	300, 1200, 1200, 300, 150, 1200, 300, 300	4950
10	2	300, 300	600
dopamine	3	180, 300, 300	780
eticlopride	2	360, 300	660
total	36		28590

[a]All simulations were started from a selected frame of a D3R/eticlopride simulation trajectory reported previously,[39] with the bound eticlopride replaced by the indicated ligand; the multiple trajectories for each ligand-bound condition were started from slightly different docked poses of the ligand, with the PP in the OBS and SP in the SBP.

Table S2: Microanalysis Data:

Compound	C	H	N	C	H	N
	Calculated			**Found**		
3	56.58	5.20	10.15	56.49	5.28	10.08
(±)-**4**	56.93	5.35	10.62	56.79	5.69	10.32
(*R*)-**4***						
(*S*)-**4***						
(*R*)-**6**	55.45	6.65	9.24	55.62	6.66	9.05
(*S*)-**6**	55.45	6.65	9.24	55.70	6.60	8.98
(*R*)-**7**	53.99	6.27	9.69	54.24	6.26	9.57
(*S*)-**7**	53.99	6.27	9.69	54.20	6.13	9.54

* Compound (free base) purity was determined by using HPLC and HRMS: (*R*)-**4** *m/z* 473.1503 $(M+H)^+$ and (*S*)-**4** *m/z* 473.1497 $(M+H)^+$

Table S3. Crystal data and structure refinement for (R)-7.

Empirical formula	$C_{13}H_{18}Cl_2N_2O$	
Formula weight	289.19	
Temperature	150(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.4149(3) Å	a= 90°
	b = 11.2516(4) Å	b= 90°
	c = 16.6967(5) Å	g = 90°
Volume	1393.00(9) $Å^3$	
Z	4	
Density (calculated)	1.379 Mg/m^3	
Absorption coefficient	4.109 mm^{-1}	
F(000)	608	
Crystal size	0.445 x 0.161 x 0.084 mm^3	
θ range for data collection	4.739 to 68.870°	
Index ranges	-7<=h<=8, -13<=k<=13, -16<=l<=19	
Reflections collected	7795	
Independent reflections	2356 [R(int) = 0.0212]	
Completeness to θ = 67.679°	97.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7531 and 0.5671	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2356 / 0 / 164	
Goodness-of-fit on F^2	1.037	
Final R indices [I>2σ(I)]	R1 = 0.0197, wR2 = 0.0535	
R indices (all data)	R1 = 0.0200, wR2 = 0.0536	
Absolute structure parameter	0.047(4)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.182 and -0.186 $e.Å^{-3}$	

Table S4. Crystal data and structure refinement for (S)-7.

Empirical formula	$C_{13}H_{18}Cl_2N_2O$	
Formula weight	289.19	
Temperature	150(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.4199(3) Å	a= 90°
	b = 11.2614(5) Å	b= 90°
	c = 16.7031(7) Å	g = 90°
Volume	1395.69(10) $Å^3$	
Z	4	
Density (calculated)	1.376 Mg/m^3	
Absorption coefficient	4.101 mm^{-1}	
F(000)	608	
Crystal size	0.291 x 0.184 x 0.055 mm^3	
θ range for data collection	4.736 to 68.298°	
Index ranges	-8<=h<=8, -13<=k<=12, -18<=l<=20	
Reflections collected	8180	
Independent reflections	2401 [R(int) = 0.0243]	
Completeness to θ = 67.679°	99.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7531 and 0.4985	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2401 / 0 / 168	
Goodness-of-fit on F^2	1.042	
Final R indices [I>2σ(I)]	R1 = 0.0199, wR2 = 0.0571	
R indices (all data)	R1 = 0.0201, wR2 = 0.0573	
Absolute structure parameter	0.047(5)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.151 and -0.151 $e.Å^{-3}$	

Figure S1. Quantitative metrics used by PIA-GPCR. The heatmaps show the average difference of the metric values between the active and inactive states in β2AR (active-state PDBs: 3P0G, 3SN6, 4LDE, 4LDL, 4LDO; inactive-state PDBs: 2RH1, 3D4S, 3NYA, 3NY8, 3NY9) and M2R (active-state PDBs: 4MQS, 4MQT; inactive-state PDB: 3UON). Each cell in the heatmap is colored based on the magnitude of the difference in the metric values measured for the helix sub-segments or binding site residue pair labeled on the X and Y axes. The color is scaled from blue to red, corresponding to the increase and decrease, respectively, of the metric values in the active state compared to the inactive state.

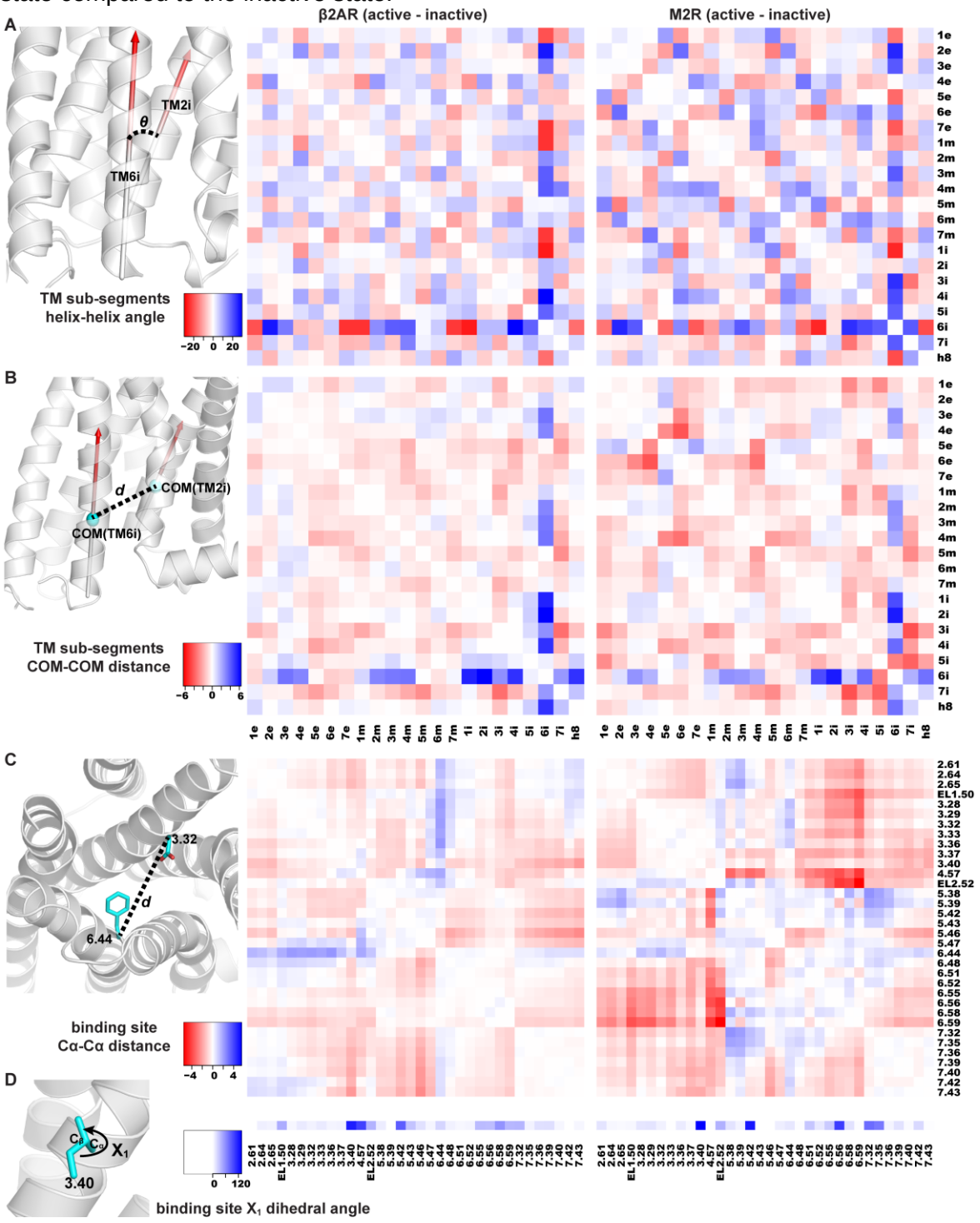

Figure S2. Comparison of the conformations of β1AR bound with partial agonists and antagonists. See Experimental Methods and Figure S1 for the descriptions of the quantitative metrics shown in (A)-(D). The crystal structures of β1AR used in the analysis include those bound with partial agonists (PDBs: 2Y00, 2Y01, 2Y04) and an antagonist (PDBs: 2YCW).

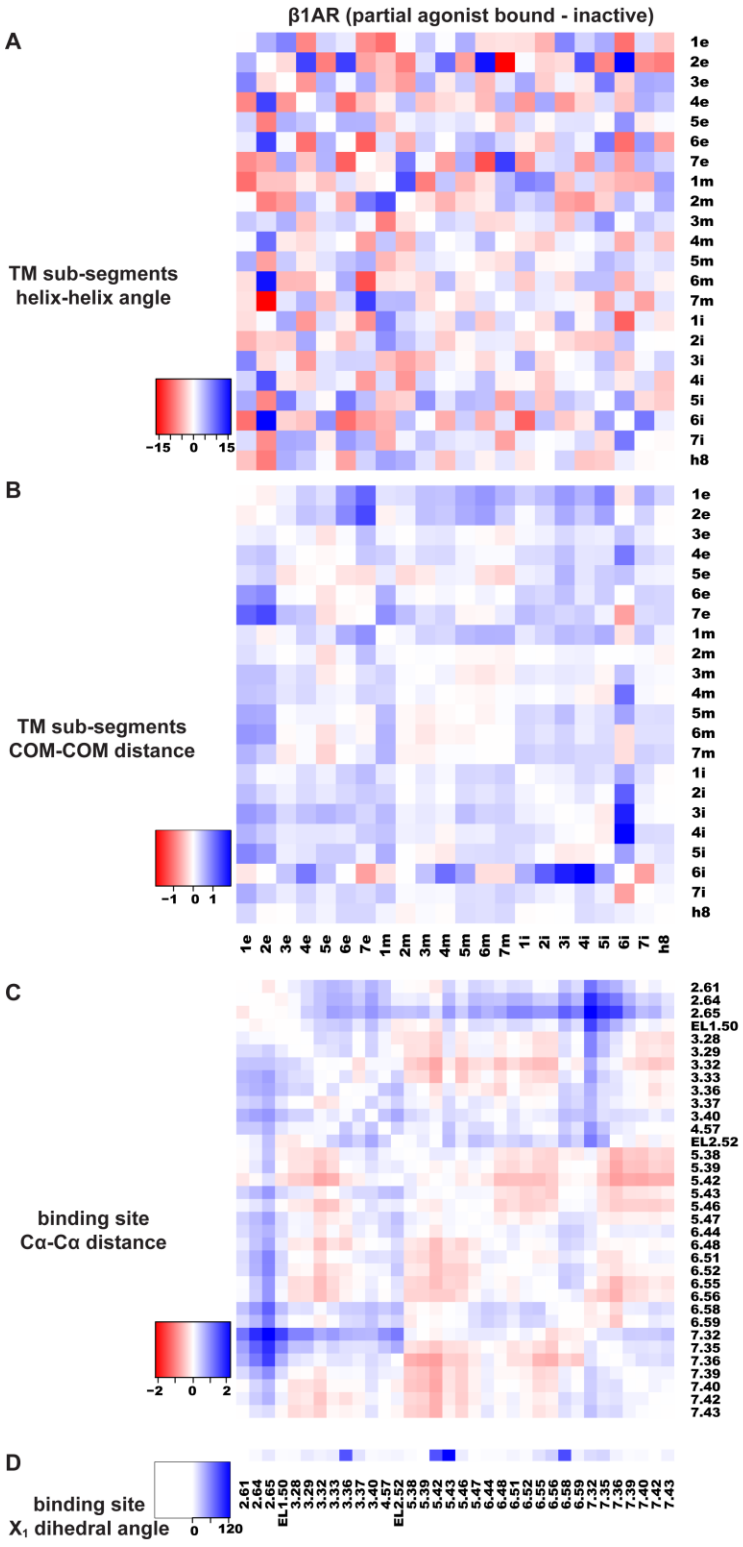

Figure S3. Comparison of the conformations of D_3R bound with dopamine and eticlopride. See Experimental Methods and Figure S1 for the descriptions of the quantitative metrics shown.

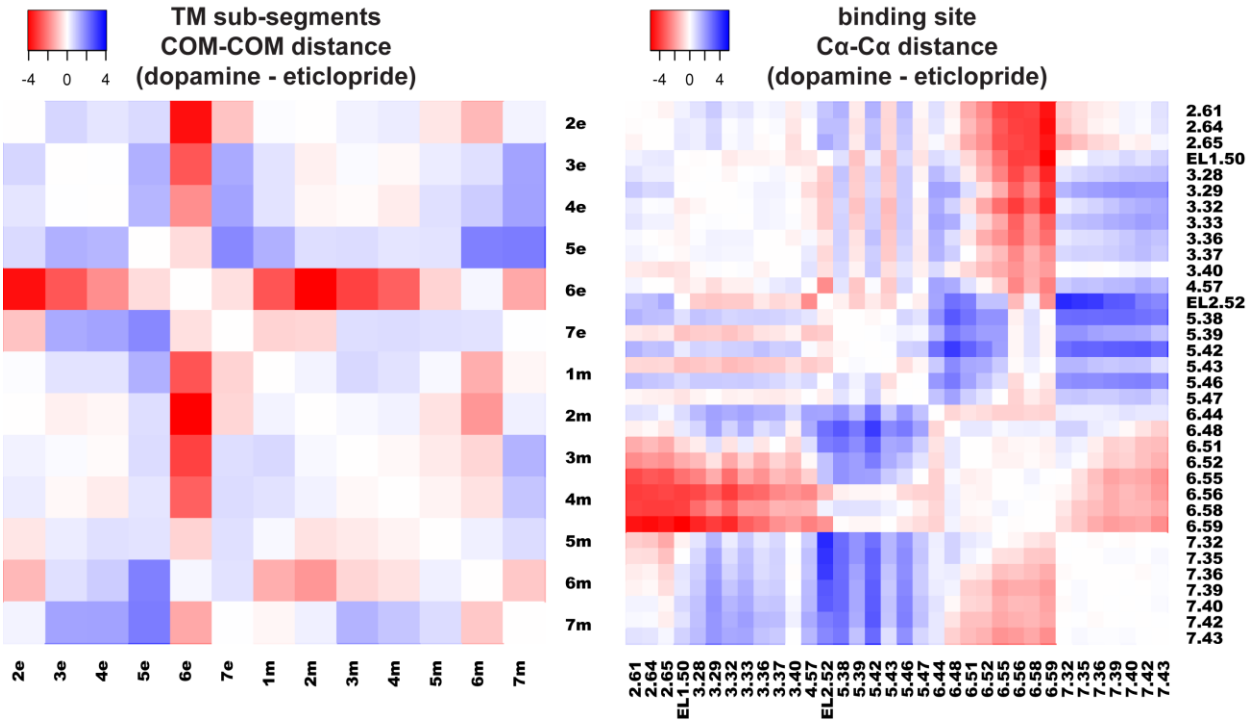

Figure S4. Mass spectrum Analysis of (*R*)-4 in THA using HRMS

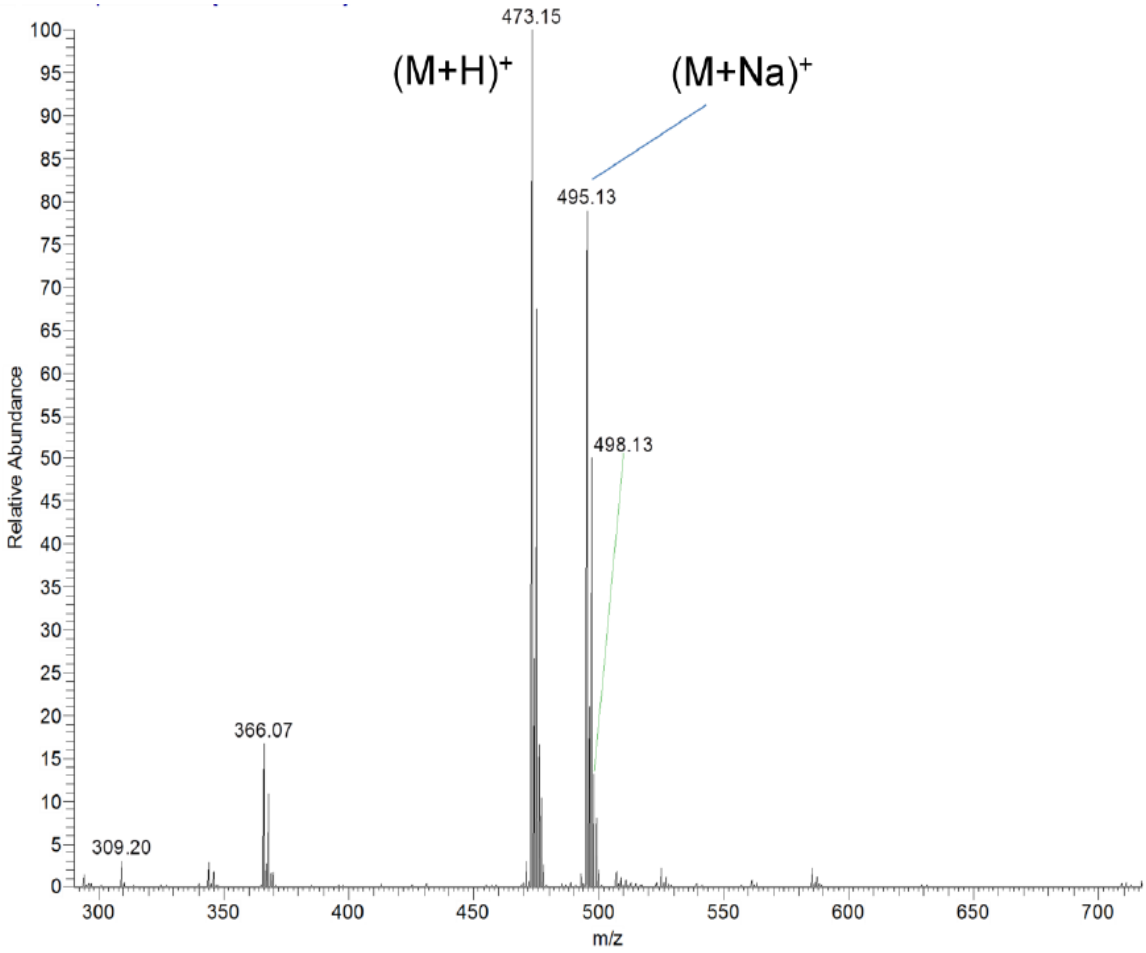

Figure S5. Mass spectrum Analysis of (*S*)-4 in THA using HRMS

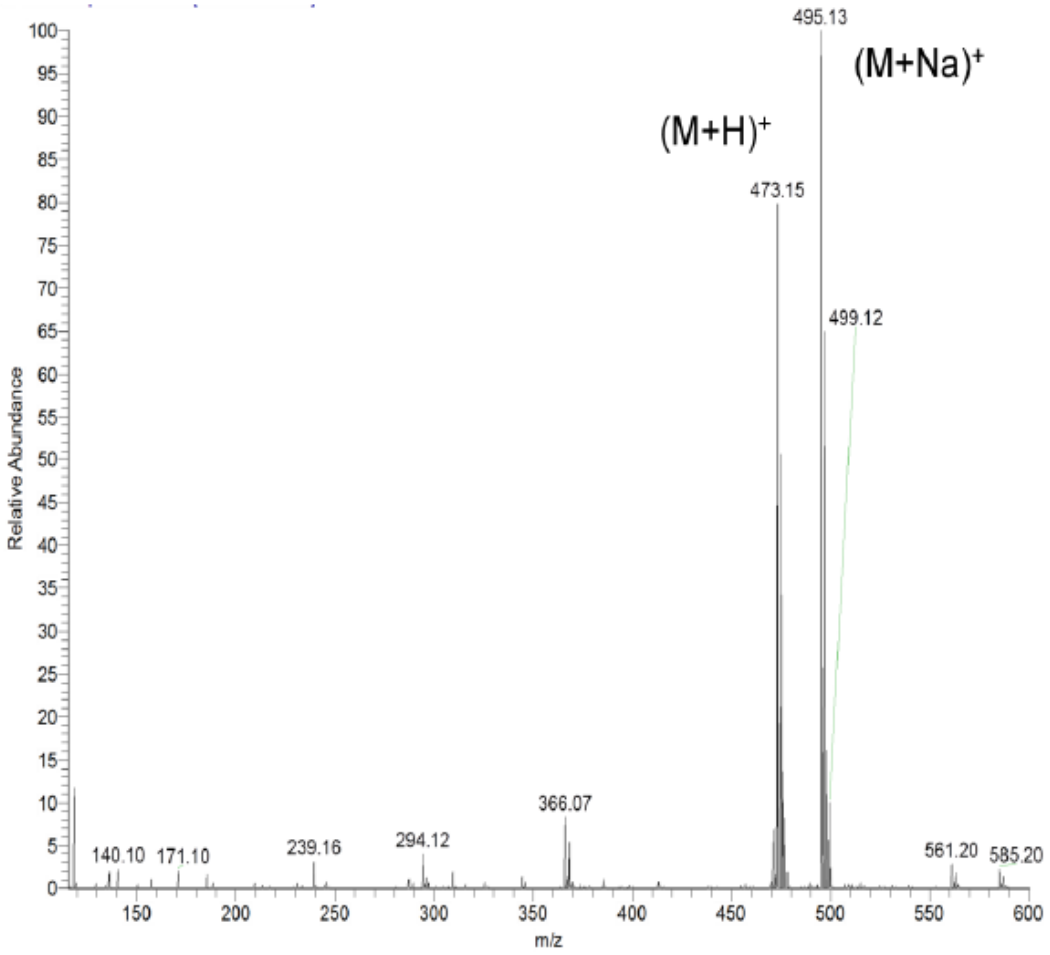

Figure S6. HPLC chromatogram analysis for (±)-4

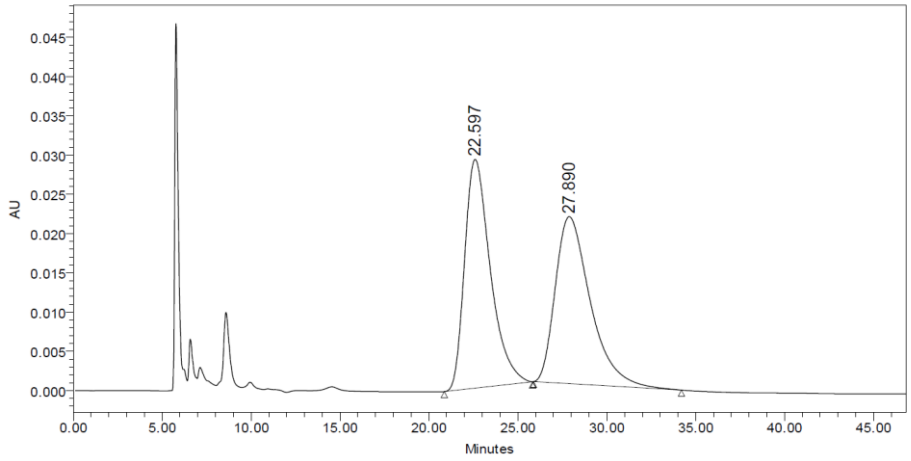

Figure S7. HPLC chromatogram analysis for (*R*)-4

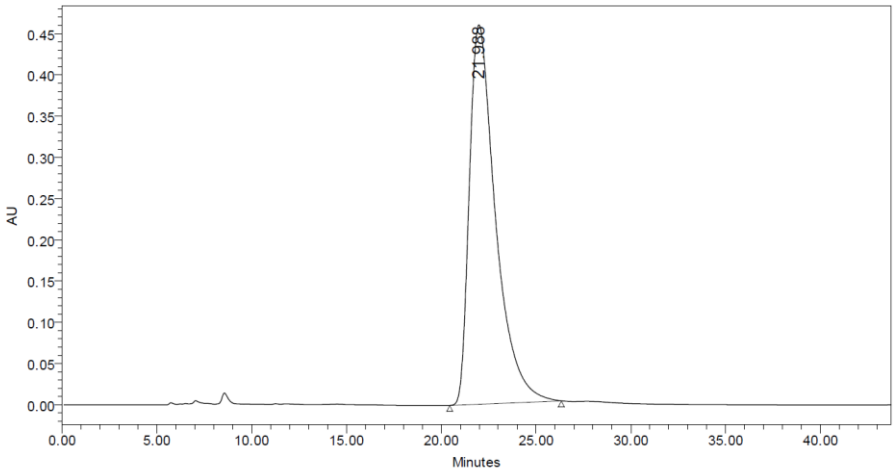

Figure S8. HPLC chromatogram analysis for (*S*)-4

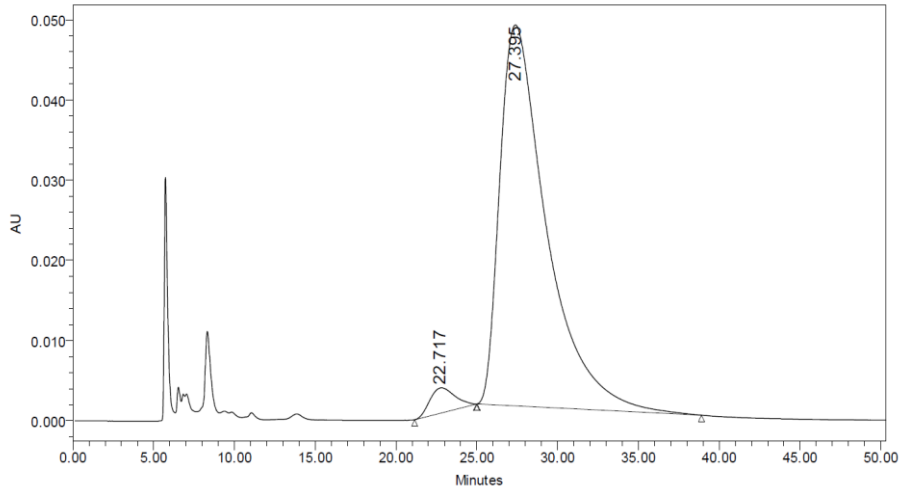

Figure S9. HPLC chromatogram analysis for (±)-7

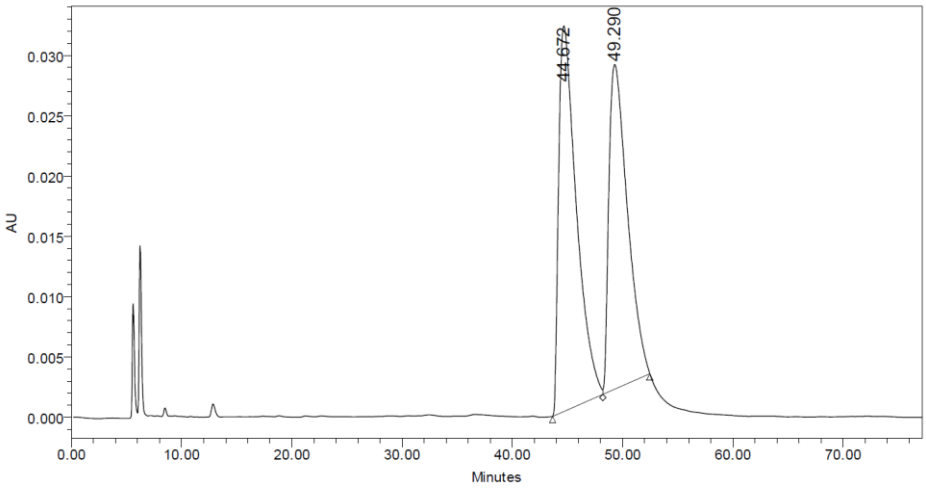

Figure S10. HPLC chromatogram analysis for (*R*)-7

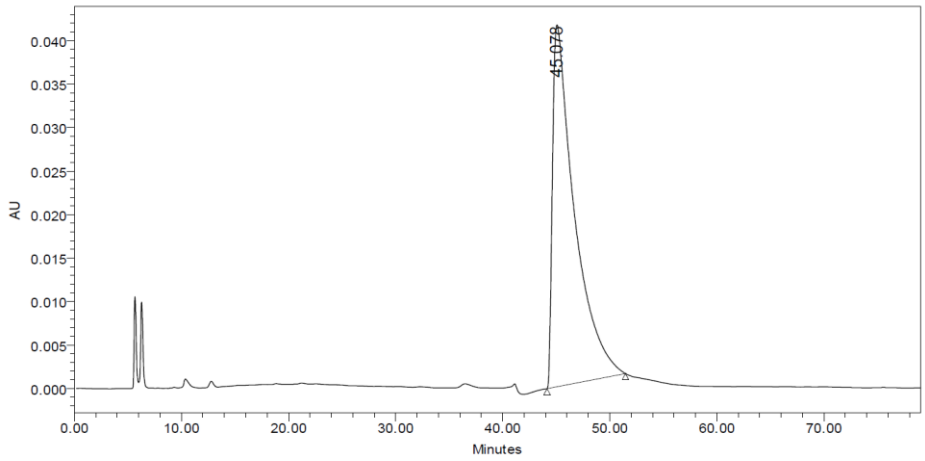

Figure S11. HPLC chromatogram analysis for (*S*)-7

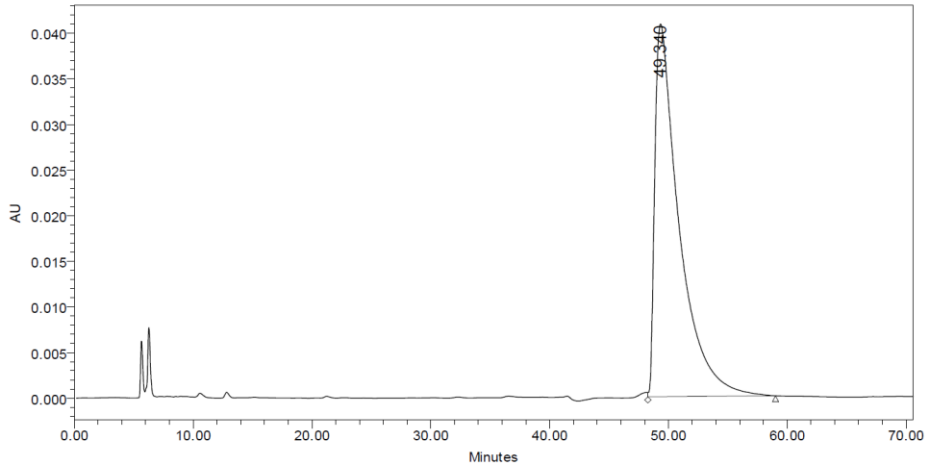

Figure S12. X-ray crystal structure of (*R*)-7. Displacement ellipsoids are at the 50% level.

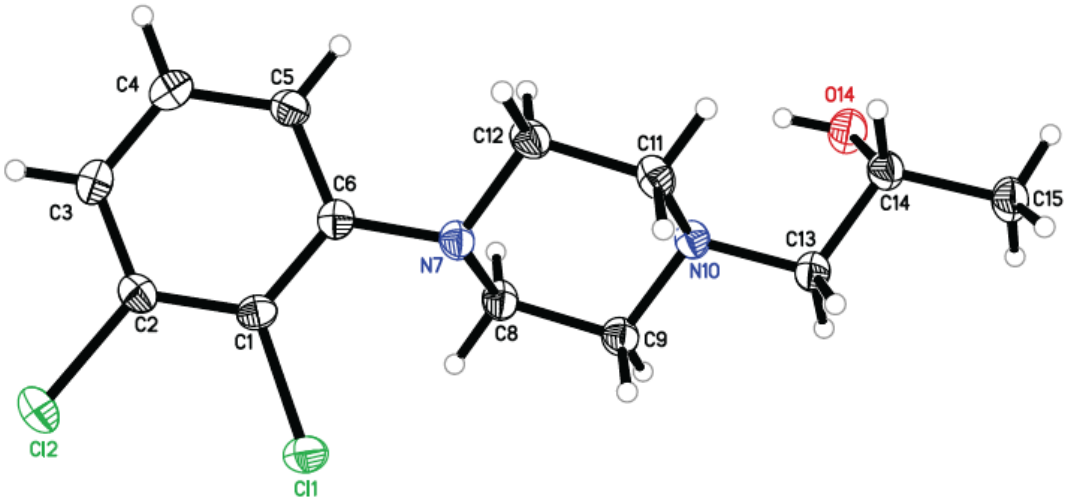

Figure S13. X-ray crystal structure of (*S*)-7. Displacement ellipsoids are at the 50% level.