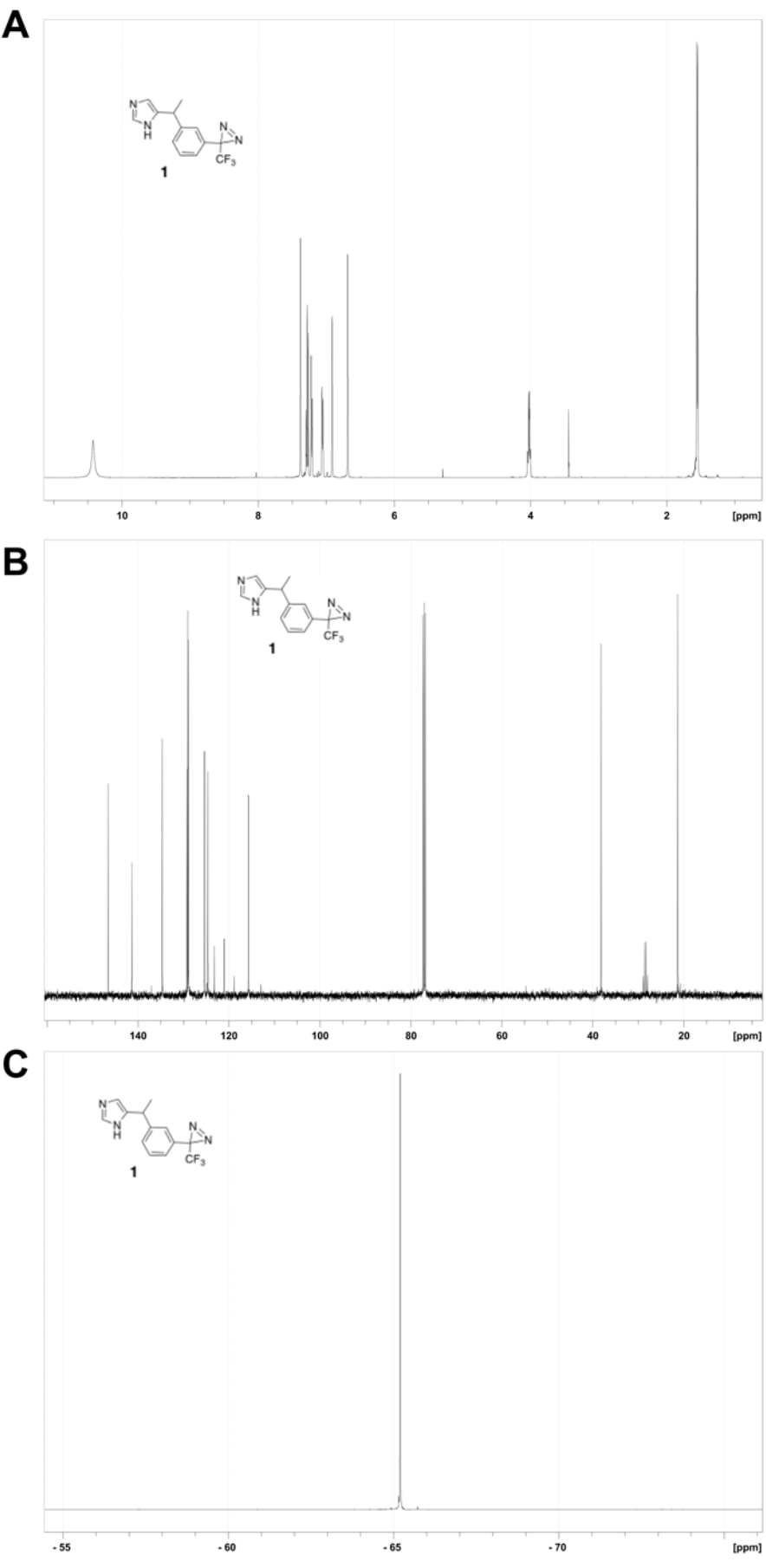
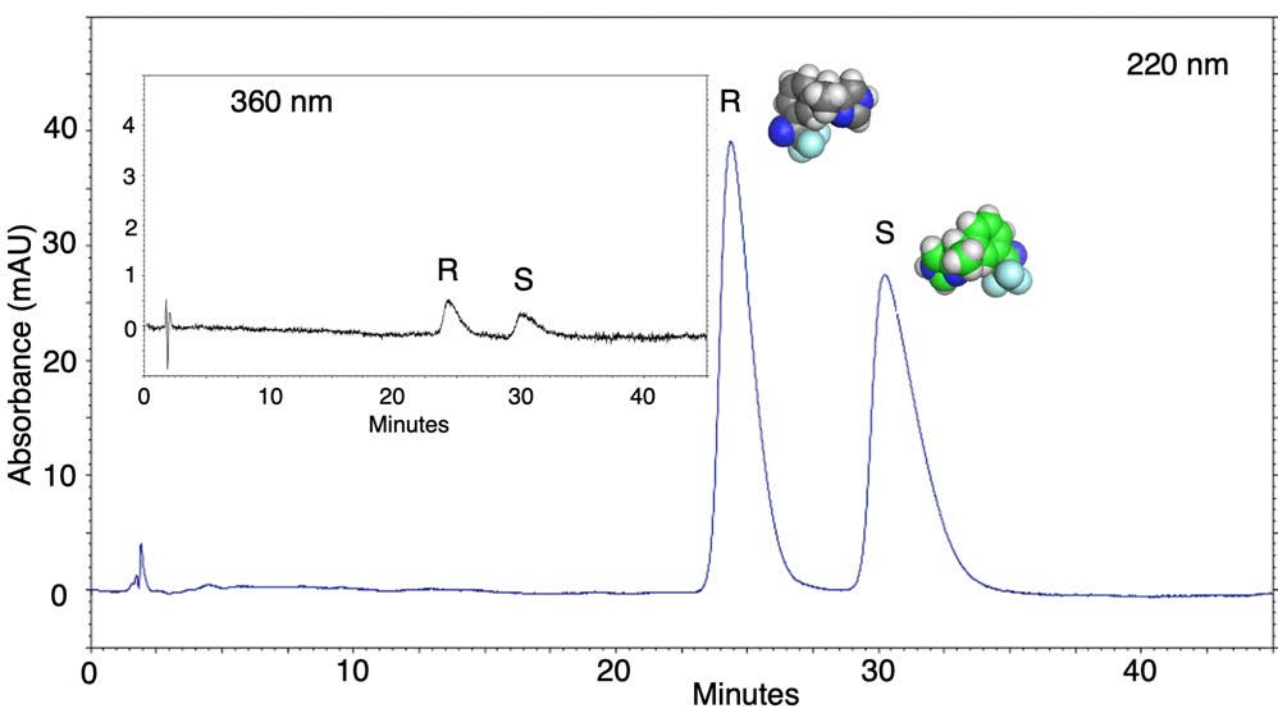
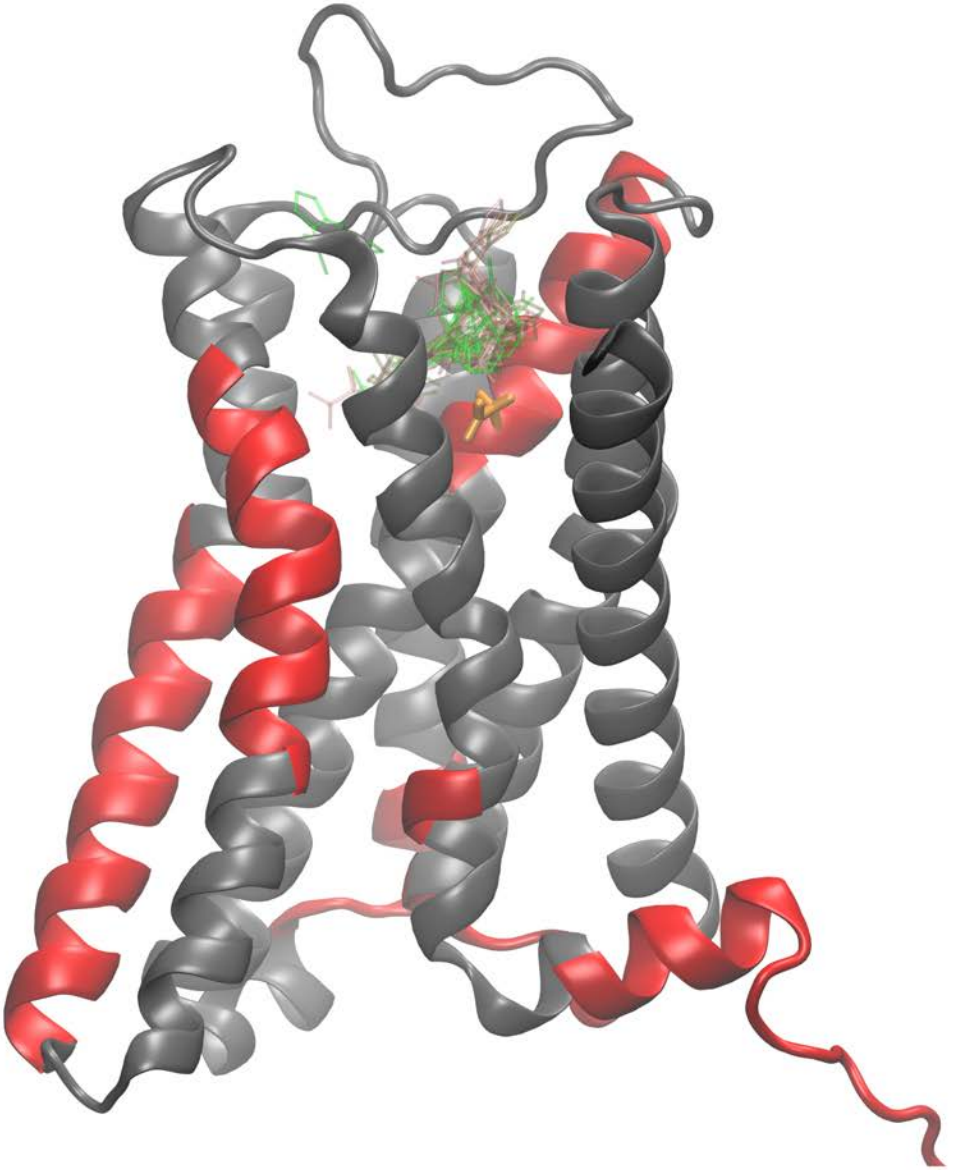


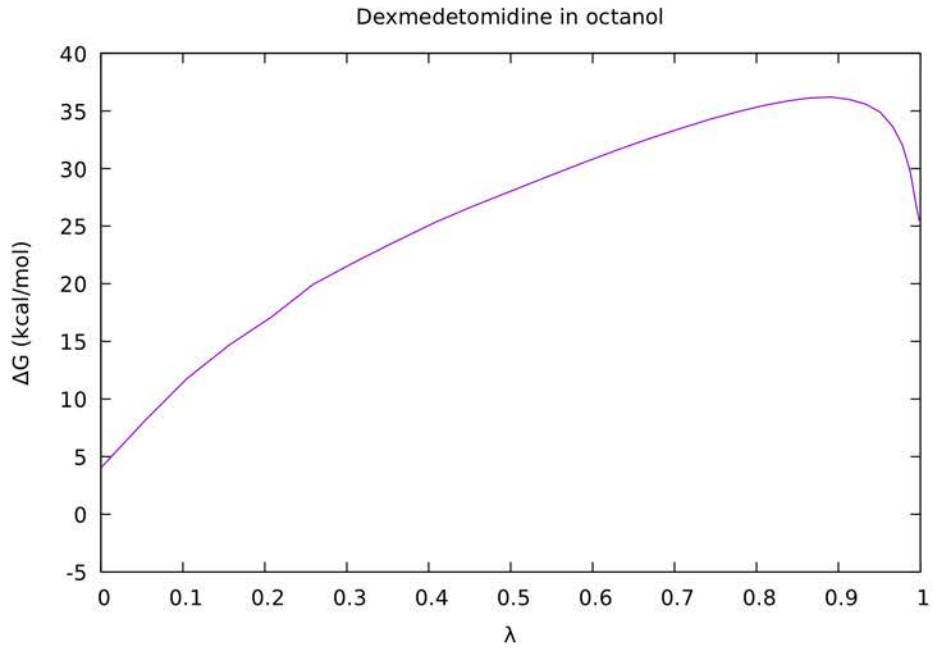
Supplemental Figure 1: Characterization of compound **1**. (**A**) Proton NMR of **1** (500 MHz.) (**B**) 13C NMR of **1** (90 MHz.) (**C**)19F NMR of **1** (340 MHz.)

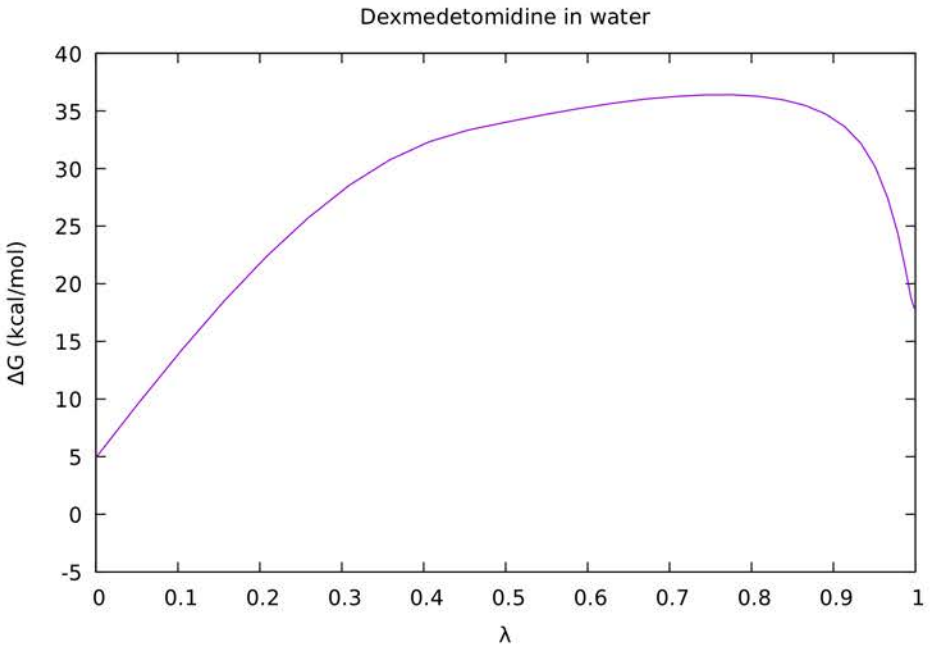


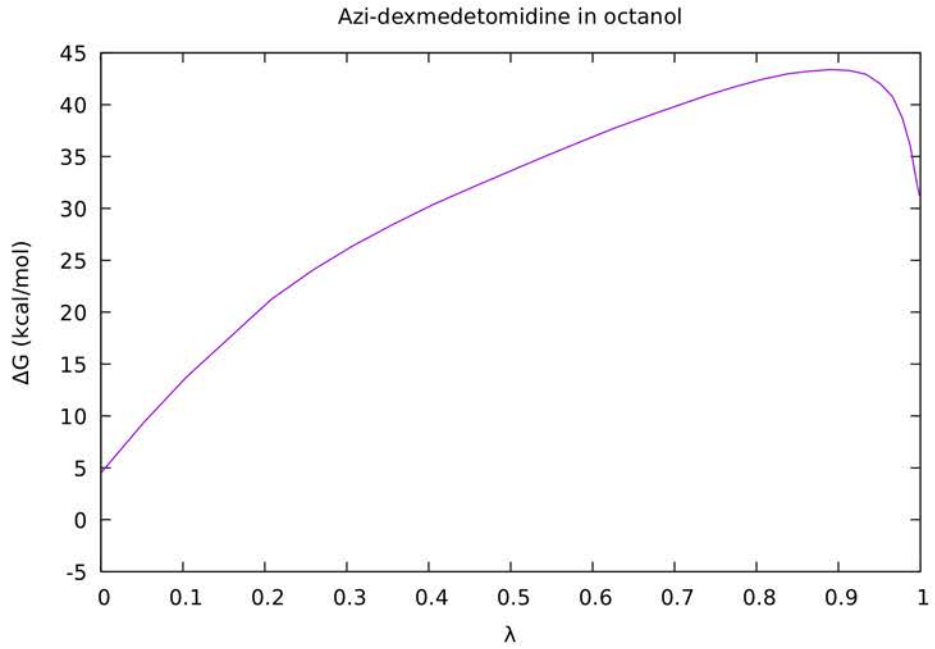
Supplemental Figure 2. HIgh performance liquid chromatography determination of purity and enantiomeric content after azi-medetomidine synthesis. Two clean peaks at 360 (inset) and 220 nm (main frame) absorbance at retention times of 24.4 and 30.2 minutes demonstrate 98% purity and <1% enantiomeric excess. R and S identities are inferred from previously described similar peaks in medetomidine separation.

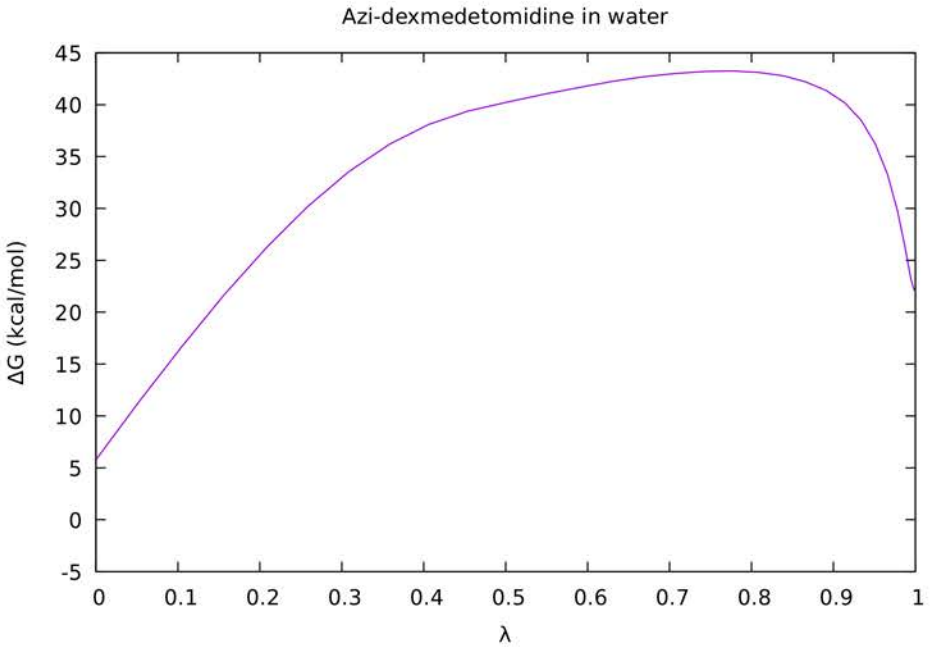


Supplemental Figure 3: Poses identified by docking. Dexmedetomidine is green, azi-dexmedetomidine is pink, azi-levomedetomidine is tan, and D113 sidechain is orange.

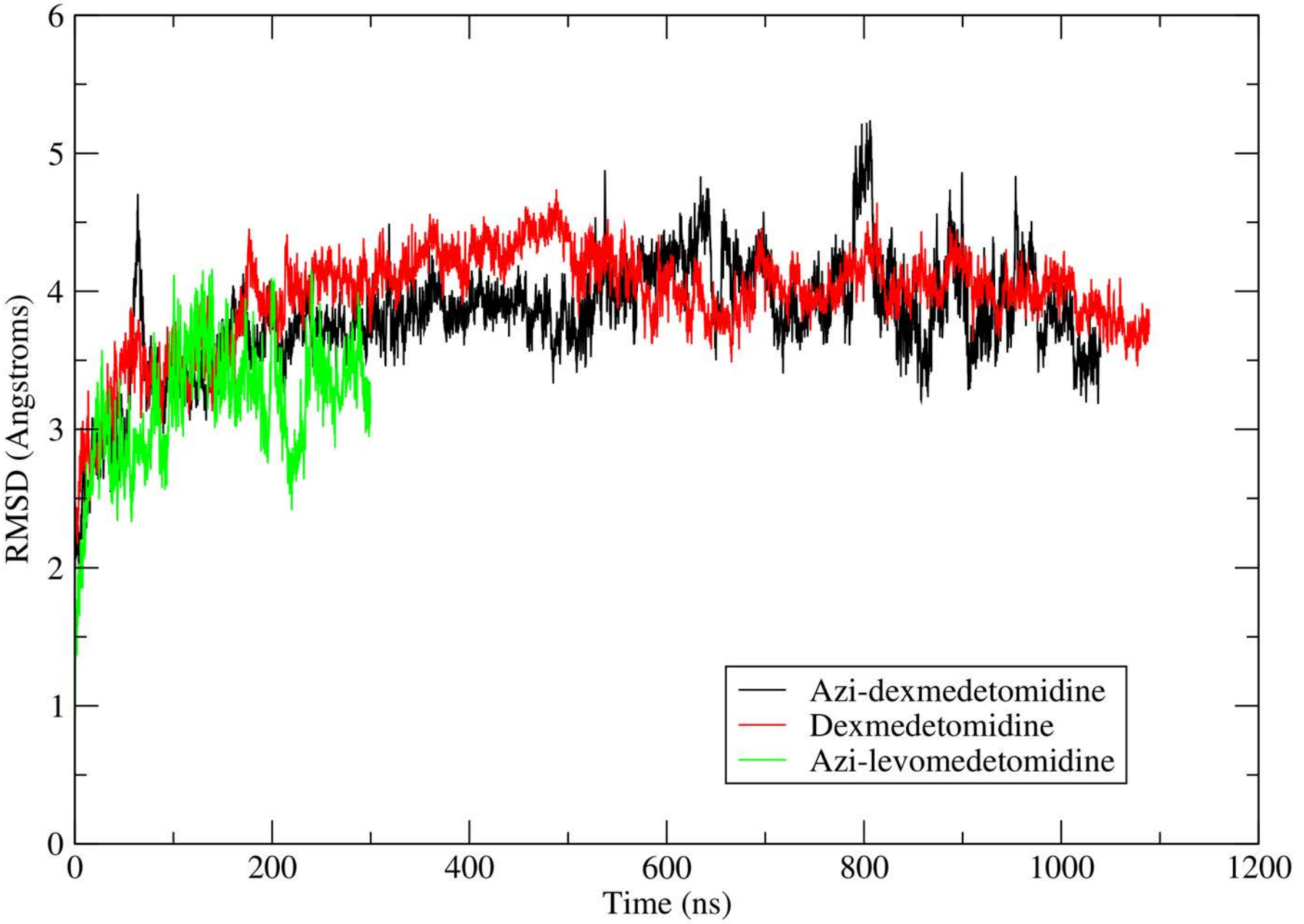








Supplemental Figure 4: Free Energy Curves Used for LogP Calculation.



Supplemental Figure 5: Root-mean-square Deviation of Backbone Atoms of ADRA2A

MKWVTFISLL FLFSSAYSRG VFRR**DAHKSE VAHRFKDLGE ENFKALVLIA FAQYLQQCPF EDHVKLVNEV**
TEFAKTCVAD ESAENCDKSL HTLFGDKLCT VATLRETYGE MADCCAKQEP ERNECFLQHK DDNPNLPRLV
RPEVDVMCTA FHDNEETFLK KYLYEIARRH PYFYAPELLF FAKRYKAAFT ECCQAADKAA CLLPKLDELR
DEGKASSAKQ RLKCASLQKF GERAFKAWAV ARLSQRFPKA EFAEVSKLVT DLTKVHTECC HGDLLECADD
RADLAKYICE NQDSISSKLK ECCEKPLLEK SHCIAEVEND EMPADLPSLA ADFVESKDVC KNYAEAKDVF
LGMFLYEYAR RHPDYSVVLL LRLAKTYETT LEKCCAAADP HECYAKVFDE FKPLVEEPQN LIKQNCELFE
QLGEYKFQNA LLVRYTK**KVP QVSTPTLVEV SRNLGKVGSK** CCKHPEAK**RM PCAEDYLSVV LNQLCVLHEK**
TPVSDRVTKC CTESLVNRRP CFSALEVDET YVPKEFNAET FTFHADICTL SEKERQIK**KQ TALVELVKHK**
PKATKEQLKA VMDDFAAFVE KCCKADDKET CFAEEGKKLV AASQAALGL

Supplemental Table 1: Coverage map for human serum albumin mass spectrometry analysis. Sequence of the purified human serum albumin with high confidence coverage in the mass spectrometry analysis denoted as bold residue codes (representing 93.8% coverage).

MKWVTFISLL FLFSSAYSRG VFRR**DAHKSE VAHRFKDLGE ENFKALVLIA FAQYLQQCPF EDHVKLVNEV**
TEFAKTCVAD ESAENCDKSL HTLFGDKLCT VATLRETYGE MADCCAKQEP ERNECFLQHK DDNPNLPRLV
RPEVDVMCTA FHDNEETFLK KYLYEIARRH PYFYAPELLF FAKRYKAAFT ECCQAADKAA CLLPKLDELR
DEGKASSAKQ RLKCASLQKF GERAFKAWAV ARLSQRFPKA EFAEVSKLVT DLTKVHTECC HGDLLECADD
RADLAKYICE NQDSISSKLK ECCEKPLLEK SHCIAEVEND EMPADLPSLA ADFVESKDVC K**NYAEAKDVF**
LGMFLYEYAR RHPDYSVVLL LRLAKTYETT LEKCCAAADP HECYAKVFDE FKPLVEEPQN LIKQNCELFE
QLGEYKFQNA LLVRYTKKVP QVSTPTLVEV SRNLGKVGSK CCKHPEAK**RM PCAEDYLSVV LNQLCVLHEK**
TPVSDRVTKC CTESLVNRRP CFSALEVDET YVPKEFNAET FTFHADICTL SEKERQIK**KQ TALVELVKHK**
PKATKEQLKA VMDDFAAFVE KCCKADDKET CFAEEGKKLV AASQAALGL

Supplemental Table 2: Coverage map for human serum albumin in the presence of 5 μM *m*Azi-Medetomidine mass spectrometry analysis. Sequence of the purified human serum albumin in the presence of 5 μM mAziMedetomidine with high confidence coverage in the mass spectrometry analysis denoted as bold residue codes (representing 93.6% coverage).

MKWVTFISLL FLFSSAYSRG VFRR**DAHKSE VAHRFKDLGE ENFKALVLIA FAQYLQQCPF EDHVKLVNEV**
TEFAKTCVAD ESAENCDKSL HTLFGDKLCT VATLRETYGE MADCCAKQEP ERNECFLQHK DDNPNLPRLV
RPEVDVMCTA FHDNEETFLK KYLYEIARRH PYFYAPELLF FAKRYKAAFT ECCQAADKAA CLLPKLDELR
DEGKASSAKQ RLKCASLQKF GERAFKAWAV ARLSQRFPKA EFAEVSKLVT DLTKVHTECC HGDLLECADD
RADLAKYICE NQDSISSKLK ECCEKPLLEK SHCIAEVEND EMPADLPSLA ADFVESKDVC KNYAEAKDVF
LGMFLYEYAR RHPDYSVVLL LRLAKTYETT LEKCCAAADP HECYAKVFDE FKPLVEEPQN LIKQNCELFE
QLGEYKFQNA LLVRYTKKVP QVSTPTLVEV SRNLGKVGSK CCKHPEAK**RM PCAEDYLSVV LNQLCVLHEK**
TPVSDRVTKC CTESLVNRRP CFSALEVDET YVPKEFNAET FTFHADICTL SEKERQIK**KQ TALVELVKHK**
PKATKEQLKA VMDDFAAFVE KCCKADDKET CFAEEGKKLV AASQAALGL

Supplemental Table 3: Coverage map for human serum albumin in the presence of 5 μM *m*Azi-Medetomidine mass spectrometry analysis. Sequence of the purified human serum albumin in the presence of 5 μM mAziMedetomidine and 0.5 mM dexmedetomidine with high confidence coverage in the mass spectrometry analysis denoted as bold residue codes (representing 94.3% coverage).

#1	Immonium	b^{+}	b^{2+}	Seq.	y^{+}	y^{2+}	#2
1	86.09643	114.09135	57.54931	L			7
2	72.08078	213.15977	107.08352	V	928.47504	464.74116	6
3	74.06004	314.20745	157.60736	T	829.40662	415.20695	5
4	88.03931	429.23440	215.12084	D	728.35894	364.68311	4
5	86.09643	542.31847	271.66287	L	613.33199	307.16964	3
6	74.06004	895.45358	448.23043	**T-mAziMED**	500.24792	250.62760	2
7				K	147.11281	74.06004	1

Fragment table showing the fragmentation of the 258-LVTDLTK-264 photolabeled peptide of hSA in the presence of 5 μM mAzimedetomidine (mAziMED). Detected identified b (red) and y (blue) ions are colored red and blue, respectively. Residues detected with a modification are noted, and the one modified by mAziMED (T263) additionally noted in bold and underlined.

#1	Immonium	b^{+}	b^{2+}	b^{3+}	Seq.	y^{+}	y^{2+}	y^{3+}	#2
1	60.04439	340.12674	170.56701	114.04710	**S-mAziMED**				9
2	86.09643	453.21081	227.10904	151.74179	L	930.50438	465.75583	310.83964	8
3	110.07127	590.26972	295.63850	197.42809	H	817.42031	409.21379	273.14495	7
4	74.06004	691.31740	346.16234	231.11065	T	680.36140	340.68434	227.45865	6
5	86.09643	804.40147	402.70437	268.80534	L	579.31372	290.16050	193.77609	5
6	120.08078	951.46989	476.23858	317.82815	F	466.22965	233.61846	156.08140	4
7	30.03383	1008.49136	504.74932	336.83530	G	319.16123	160.08425	107.05859	3
8	88.03931	1123.51831	562.26279	375.17762	D	262.13976	131.57352	88.05144	2
9					K	147.11281	74.06004	49.70912	1

Fragment table showing the fragmentation of the 89-**S**LHTLFGDK-97 photolabeled peptide of hSA in the presence of 3 μM mAzimedetomidine (mAziMED). Detected identified b (red) and y (blue) ions are colored red and blue, respectively. Residues detected with a modification are noted, and the one modified by mAziMED (S89) additionally noted in bold and underlined.

#1	Immonium	b^{+}	b^{2+}	b^{3+}	Seq.	y^{+}	y^{2+}	y^{3+}	#2
1	72.08078	100.07570	50.54149	34.03008	V				17
2	120.08078	247.14412	124.07570	83.05289	F	2198.11448	1099.56088	733.37635	16
3	88.03931	362.17107	181.58917	121.39521	D	2051.04606	1026.02667	684.35354	15
4	102.05496	491.21367	246.11047	164.40941	E	1936.01911	968.51320	646.01122	14
5	120.08078	638.28209	319.64468	213.43221	F	1806.97651	903.99190	602.99702	13
6	101.10733	766.37706	383.69217	256.13054	K	1659.90809	830.45769	553.97422	12
7	70.06513	863.42983	432.21855	288.48146	P	1531.81312	766.41020	511.27589	11
8	86.09643	976.51390	488.76059	326.17615	L	1434.76035	717.88382	478.92497	10
9	72.08078	1075.58232	538.29480	359.19896	V	1321.67628	661.34178	441.23028	9
10	102.05496	1204.62492	602.81610	402.21316	E	1222.60786	611.80757	408.20747	8
11	102.05496	1333.66752	667.33740	445.22736	E	1093.56526	547.28627	365.19327	7
12	70.06513	1430.72029	715.86378	477.57828	P	964.52266	482.76497	322.17907	6
13	101.07094	1558.77887	779.89307	520.26447	Q	867.46989	434.23859	289.82815	5
14	87.05529	1672.82180	836.91454	558.27878	N	739.41131	370.20930	247.14196	4
15	86.09643	1785.90587	893.45657	595.97347	L	625.36838	313.18783	209.12765	3
16	86.09643	2151.07737	1076.04232	717.69731	**I-mAziMED**	512.28431	256.64580	171.43296	2
17					K	147.11281	74.06004	49.70912	1

Fragment table showing the fragmentation of the 397-VFDEFKPLVEEPQNL**I**K-413 photolabeled peptide of hSA in the presence of 5 µM mAzimedetomidine (mAziMED). Detected identified b (red) and y (blue) ions are colored red and blue, respectively. Residues detected with a modification are noted, and the one modified by mAziMED (I412) additionally noted in bold and underlined.

#1	Immonium	b^{+}	b^{2+}	b^{3+}	Seq.	y^{+}	y^{2+}	y^{3+}	#2
1	129.11348	157.10840	79.05784	53.04098	R				15
2	110.07127	546.25474	273.63101	182.75643	**H-mAziMED**	1994.98157	997.99443	665.66538	14
3	70.06513	643.30751	322.15739	215.10735	P	1605.83523	803.42125	535.94993	13
4	136.07568	806.37083	403.68905	269.46179	Y	1508.78246	754.89487	503.59900	12
5	120.08078	953.43925	477.22326	318.48460	F	1345.71914	673.36321	449.24456	11
6	136.07568	1116.50257	558.75492	372.83904	Y	1198.65072	599.82900	400.22176	10
7	44.04948	1187.53969	594.27348	396.51808	A	1035.58740	518.29734	345.86732	9
8	70.06513	1284.59246	642.79987	428.86900	P	964.55028	482.77878	322.18828	8
9	102.05496	1413.63506	707.32117	471.88320	E	867.49751	434.25239	289.83735	7
10	86.09643	1526.71913	763.86320	509.57789	L	738.45491	369.73109	246.82315	6
11	86.09643	1639.80320	820.40524	547.27258	L	625.37084	313.18906	209.12846	5
12	120.08078	1786.87162	893.93945	596.29539	F	512.28677	256.64702	171.43377	4
13	120.08078	1933.94004	967.47366	645.31820	F	365.21835	183.11281	122.41097	3
14	44.04948	2004.97716	1002.99222	668.99724	A	218.14993	109.57860	73.38816	2
15					K	147.11281	74.06004	49.70912	1

Fragment table showing the fragmentation of the 169-R**H**PYFYAPELLFFAKRYK-186 photolabeled peptide of hSA in the presence of 5 μM mAzimedetomidine (mAziMED). Detected identified b (red) and y (blue) ions are colored red and blue, respectively. Residues detected with a modification are noted, and the one modified by mAziMED (H170) additionally noted in bold and underlined.

```
9    GNASWNGTEAPGGGARATPYSLQVTLTLVCLAGLLMLLTVFGNVLVIIAVFTSRALKAPQ  68
     GN +W G           PYSL+VT+ L+ L  LLML TVFGNVLVIIAVFTSRALKAPQ
50   GNGTWEG---------GPPYSLEVTMALITLVALLMLFTVFGNVLVIIAVFTSRALKAPQ  100

69   NLFLVSLASADILVATLVIPFSLANEVMGYWYFGKAWCEIYLALDVLFCTSSIVHLCAIS  128
     NLFLVSLASADILVATLVIPFSL+NEVMGYWYFGK WCEIYLALDVLFCTSSIVHLCAIS
101  NLFLVSLASADILVATLVIPFSLSNEVMGYWYFGKVWCEIYLALDVLFCTSSIVHLCAIS  160

129  LDRYWSITQAIEYNLKRTPRRIKAIIITVWVISAVISFPPLISIEKKGGGGGPQPAEPRC  188
     LDRYWSITQAIEYNLKRTPRRIK II  VWVI+AVISFPPLI+IEK+ G    +   P C
161  LDRYWSITQAIEYNLKRTPRRIKCIIFIVWVIAAVISFPPLITIEKESG----KVEMPIC  216

189  EINDQKWYVISSCIGSFFAPCLIMILVYVRIYQIAKRRTRVPPSRRGPDAVAAPPGGTER  248
     +IND+KWY+I S IGSFFAPCLIM+LVY+RIYQIAK RTR+PP +R
217  KINDEKWYIIYSSIGSFFAPCLIMVLVYIRIYQIAKSRTRIPPGKR-------------  262

249  RPNGLGPERSAGPGGAEAEPLPTQLNG--APGEPAPAGPR-DTDALDLEESSSSDHAERP  305
       N      +    G   + LP +LNG  A G     G   + + +D+++SSSS+H E
263  --NNAADVEAKQHNGLTDKDLPVKLNGEKAGGSGGDHGKEAEANGVDMDDSSSSEHQEDN  320

306  PGP--RRPERGPRGKGKARASQVKPGDSLPRRGPGATGIGTPAAGPGEERVGAAKASRWR  363
     P P  ++ ++  RGKGK + SQ+KPGDS+PRR                EER    K SRW+
321  PYPAKKKQDKLSRGKGKTKLSQIKPGDSIPRR-------------EEER--NLKVSRWK  364

364  GRQNREKRFTFVLAVVIGVFVVCWFPFFFTYTLTAV--GCSVPRTLFKFFFWFGYCNSSL  421
     GRQNREKRFTFVLAVVIGVFV+CWFPFFFTYTLTAV   C VP  LFKFFFWFGYCNSSL
365  GRQNREKRFTFVLAVVIGVFVICWFPFFFTYTLTAVCESCYVPVALFKFFFWFGYCNSSL  424

422  NPVIYTIFNHDFRRAFKKILCRGDRKRIV  450
     NPVIYTIFN DFRRAFKKILC+G+RKRIV
425  NPVIYTIFNQDFRRAFKKILCKGERKRIV  453
```

Supplemental Table 8: Alignment of Human and Xenopus Alpha 2a Adrenergic Receptor. Human (top) and Xenopus (bottom) share approximately 66% protein alignment of the alpha 2A adrenergic receptor, with a greater percentage of conserved sequences in the predicted ligand binding region