Supplementary Information

Design, Synthesis and Activity of a Series of Arylpyrid-3-ylmethanones as Type I Positive Allosteric Modulators of α7 Nicotinic Acetylcholine Receptors

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Table of elemental analyses.

Elemental Analyses						
	Found			**Calculated**		
Compound	*C*	*H*	*N*	*C*	*H*	*N*
7a	69.68	5.65	6.79	69.95	5.87	7.09
7aa	**68.58**	5.12	7.14	**69.10**	5.27	7.33
7b	71.68	5.36	7.84	71.98	5.47	8.00
7c	73.03	5.92	7.29	73.00	6.13	7.40
7d	70.99	6.54	6.36	70.99	6.43	6.62
7e·1/2MeOH	66.88	4.34	5.64	66.73	4.68	5.66
7f	76.84	6.81	7.18	76.98	7.00	7.48
7g	72.84	5.83	7.34	73.00	6.13	7.40
7h·1/2MeOH	71.68	6.03	7.17	71.55	6.39	7.10
7i	76.45	5.77	6.16	76.34	5.72	6.36
7j	65.38	4.76	7.16	65.46	4.71	7.27
7k	71.75	5.36	7.68	71.58	5.15	7.95
7l	63.12	4.27	6.63	63.16	4.34	6.70
7m	76.41	6.41	7.23	76.57	6.69	7.44
7n	76.04	5.39	6.74	76.04	5.44	6.57
7o	69.74	5.80	6.89	70.02	5.88	7.10
7p	68.01	4.78	7.88	68.09	4.86	7.94
7q	68.86	5.20	7.63	68.76	5.22	7.64
7r	69.27	5.68	7.11	69.38	5.56	7.36
7s	69.67	5.58	6.91	69.95	5.87	7.09
7t	64.62	5.30	6.28	64.34	5.16	6.52
7u	73.03	6.11	7.43	73.00	6.13	7.40

7v	69.59	5.40	6.94	69.68	5.59	7.07
7w	69.72	5.39	7.03	69.68	5.59	7.07
7x	69.83	5.34	6.85	69.68	5.59	7.07
7y	76.44	6.55	7.77	76.64	6.71	7.77
7z·MeOH	66.39	5.39	7.03	65.99	5.54	7.00

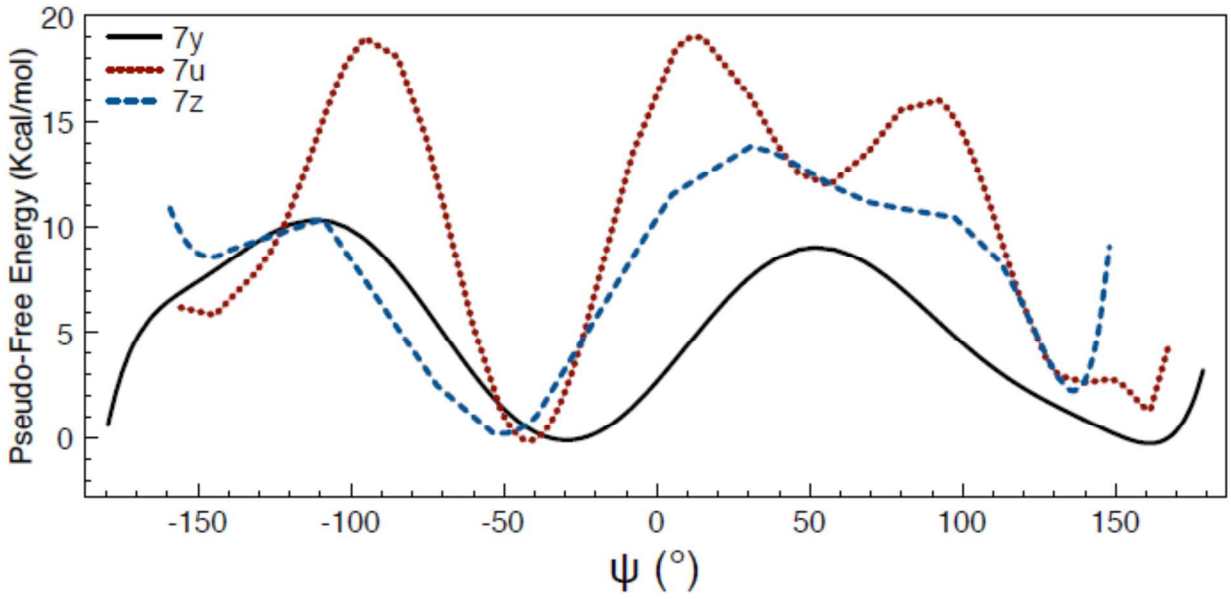
Electrophysiology

95% Confidence intervals for compounds tested in *Xenopus* oocytes expressing human α7 nAChR's. ND is not determined and IA is inactive.

	Potency (μM)			Efficacy (% over control)		
Compound	Lower 95% CI	EC_{50}	Upper 95% CI	Lower 95% CI	Maximum	Upper 95% CI
7a	0.05	**0.14**	0.42	415	**592**	767
7aa	2.3	**4.9**	10.4	273	**468**	662
7b	1.1	**1.9**	3.2	454	**625**	793
7c	-	**ND**	-	19	**37**	55
7d	-	**ND**	-	30	**55**	79
7e		**ND**			**IA**	
7f		**ND**			**IA**	
7g	0.04	**0.13**	0.40	363	**586**	808
7h	0.23	**0.45**	0.90	524	**678**	831
7i	-	**ND**	-	-	**IA**	-
7j	-	**ND**	-	-10	**38**	85
7k	0.09	**0.22**	0.53	230	**305**	381
7l	-	**ND**	-	39	**55**	72
7m	-	**ND**	-	8	**24**	40
7n	-	**ND**	-	20	**28**	37
7o	-	**ND**	-	-19	**42**	126
7p	1.4	**2.5**	4.4	326	**496**	666
7q	0.21	**0.38**	0.67	987	**1220**	1452
7r	0.06	**0.16**	0.41	520	**679**	837
7s	-	**ND**	-	-5	**35**	74
7t	-	**ND**	-	18	**38**	58
7u	-	**ND**	-	80	**130**	180
7v	0.06	**0.14**	0.33	1003	**1300**	1598
7w	0.55	**3.00**	17.00	34	**204**	373
7x	-	**ND**	-	98	**132**	165
7y	0.05	**0.21**	0.77	197	**302**	406
7z	0.48	**0.67**	0.92	1603	**1825**	2048

Adiabatic Potential Energy Calculations. Structural mol2 files were generated using MarvinSketch (Marvin) and all chemical parameters and topology files were generated using SwissParam[1] for use in CHARMM[2]. All structures were solvated in a 20x30x20 Å waterbox and minimized extensively. Constraints were added to mimic hydrogen bonding patterns observed in NMR data. The dihedral angle ψ was defined and constrained to 720 values (per structure) at 0.5° increments and minimized extensively at each point. Finally, the adiabatic potential energy of each point was graphed and fitted to 10th degree polynomials and baselines were subtracted for clarity. The adiabatic potential energy for compounds **7u**, **7y** and **7z** as a function of the dihedral angle (ψ) between the aryl ring of the benzoyl group and the pyridine ring were calculated (see Figure 1). While not a true free energy, this calculation reveals the position of energy barriers in reference to conformational changes while estimating the height and feature of each barrier. The calculation suggests that the three structures do not adopt significantly different dihedral angles with a near equivalent energy minimum at around -50° or 150°. However, the 2-fluorobenzoyl, **7u**, does have a higher energy barrier for free rotation. This suggests that **7u** may lack activity based on a lack of free rotation around the benzoyl due to the large barrier relative to **7y** and **7z**.[3,4]

Figure 1. Calculated adiabatic potential energy for rotation about the dihedral angle (ψ) between the aryl ring of the benzoyl group and the pyridine ring.



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