

Supporting Information

Synthesis and in Vivo Evaluation of Phenethyl Piperazine Amides: Selective 5-Hydroxytryptamine_{2A} Receptor Antagonists for the Treatment of Insomnia

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Table of Contents

Table of Contents.....	S1
In-vitro profiling data of 14	S2-6
In-vitro profiling data of 27	S2-6
DSC graph of 14	S7
DSC graph of 27	S7
PXRD of 27	S8

In-vitro profiling of **14** and **27** against a panel of receptors was performed at Cerep. Table 1-1 is the result.

Table 1 - 1

Summary Results

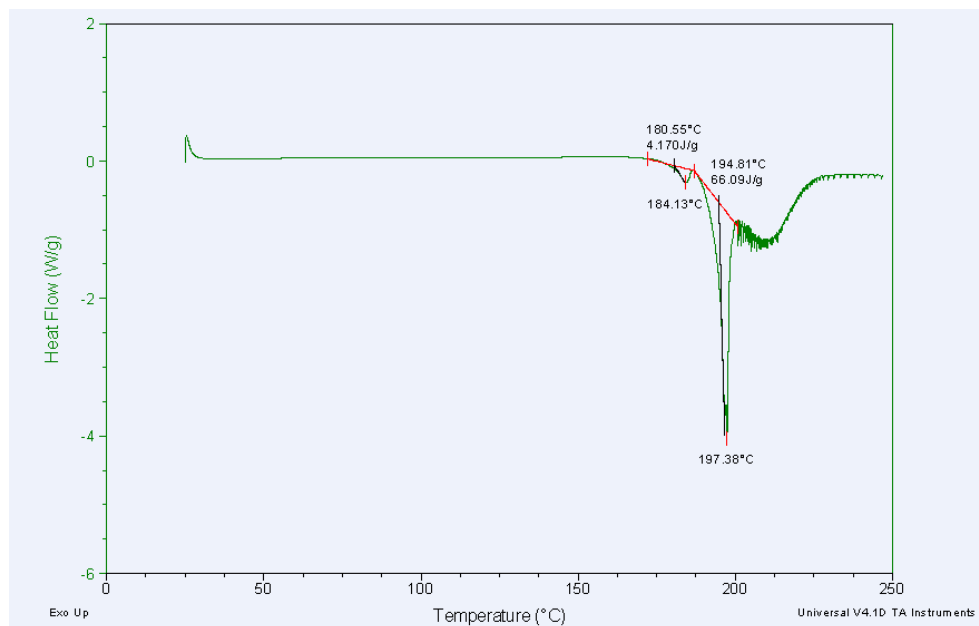
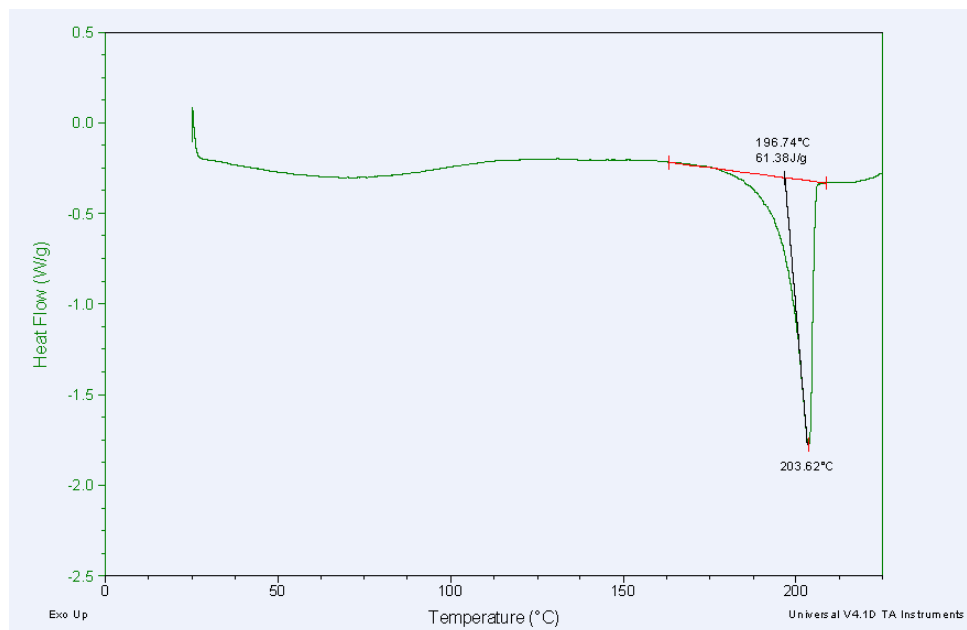
Assay Cerep Compound I.D.	Client Compound I.D.	Test Concentration (M)	% Inhibition of Control Specific Binding
A₁ (h)			
952073-1	27	1.0E-06	-2
952073-2	14	1.0E-06	4
A_{2A} (h)			
952073-1	27	1.0E-06	-3
952073-2	14	1.0E-06	-1
A₃ (h)			
952073-1	27	1.0E-06	-6
952073-2	14	1.0E-06	-21
α₁ (non-selective)			
952073-1	27	1.0E-06	0
952073-2	14	1.0E-06	-4
α₂ (non-selective)			
952073-1	27	1.0E-06	8
952073-2	14	1.0E-06	5
β₁ (h)			
952073-1	27	1.0E-06	8
952073-2	14	1.0E-06	2
β₂ (h)			
952073-1	27	1.0E-06	-4
952073-2	14	1.0E-06	7
AT₁ (h)			
952073-1	27	1.0E-06	-15
952073-2	14	1.0E-06	3
AT₂ (h)			
952073-1	27	1.0E-06	5
952073-2	14	1.0E-06	2
BZD (central)			
952073-1	27	1.0E-06	-1
952073-2	14	1.0E-06	6
BZD (peripheral)			
952073-1	27	1.0E-06	9
952073-2	14	1.0E-06	-1
BB (non-selective)			
952073-1	27	1.0E-06	-20
952073-2	14	1.0E-06	-11
B₂ (h)			
952073-1	27	1.0E-06	7
952073-2	14	1.0E-06	-5
CGRP (h)			
952073-1	27	1.0E-06	-11
952073-2	14	1.0E-06	22

Assay Cerep Compound I.D.	Client Compound I.D.	Test Concentration (M)	% Inhibition of Control Specific Binding
CB₁ (h)			
952073-1	27	1.0E-06	-4
952073-2	14	1.0E-06	-5
CCK_A (h) (CCK₁)			
952073-1	27	1.0E-06	-19
952073-2	14	1.0E-06	0
CCK_B (h) (CCK₂)			
952073-1	27	1.0E-06	-13
952073-2	14	1.0E-06	11
D₁ (h)			
952073-1	27	1.0E-06	22
952073-2	14	1.0E-06	-8
D_{2S} (h)			
952073-1	27	1.0E-06	15
952073-2	14	1.0E-06	5
D₃ (h)			
952073-1	27	1.0E-06	1
952073-2	14	1.0E-06	7
D_{4.4} (h)			
952073-1	27	1.0E-06	5
952073-2	14	1.0E-06	7
D₅ (h)			
952073-1	27	1.0E-06	5
952073-2	14	1.0E-06	10
ET_A (h)			
952073-1	27	1.0E-06	6
952073-2	14	1.0E-06	2
ET_B (h)			
952073-1	27	1.0E-06	6
952073-2	14	1.0E-06	7
GABA (non-selective)			
952073-1	27	1.0E-06	-9
952073-2	14	1.0E-06	9
GAL1 (h)			
952073-1	27	1.0E-06	-10
952073-2	14	1.0E-06	-9
GAL2 (h)			
952073-1	27	1.0E-06	-1
952073-2	14	1.0E-06	3
PDGF			
952073-1	27	1.0E-06	-2
952073-2	14	1.0E-06	1
CXCR2 (h) (IL-8B)			
952073-1	27	1.0E-06	11
952073-2	14	1.0E-06	9
TNF-α (h)			

Assay Cerep Compound I.D.	Client Compound I.D.	Test Concentration (M)	% Inhibition of Control Specific Binding
952073-1	27	1.0E-06	7
952073-2	14	1.0E-06	-1
CCR1 (<i>h</i>)			
952073-1	27	1.0E-06	1
952073-2	14	1.0E-06	2
H ₁ (<i>h</i>)			
952073-1	27	1.0E-06	5
952073-2	14	1.0E-06	5
H ₂ (<i>h</i>)			
952073-1	27	1.0E-06	-1
952073-2	14	1.0E-06	3
MC ₄ (<i>h</i>)			
952073-1	27	1.0E-06	-1
952073-2	14	1.0E-06	2
MT ₁ (<i>h</i>)			
952073-1	27	1.0E-06	8
952073-2	14	1.0E-06	9
M ₁ (<i>h</i>)			
952073-1	27	1.0E-06	0
952073-2	14	1.0E-06	12
M ₂ (<i>h</i>)			
952073-1	27	1.0E-06	-3
952073-2	14	1.0E-06	-6
M ₃ (<i>h</i>)			
952073-1	27	1.0E-06	-1
952073-2	14	1.0E-06	-9
M ₄ (<i>h</i>)			
952073-1	27	1.0E-06	-1
952073-2	14	1.0E-06	-1
M ₅ (<i>h</i>)			
952073-1	27	1.0E-06	-1
952073-2	14	1.0E-06	-2
NK ₁ (<i>h</i>)			
952073-1	27	1.0E-06	-1
952073-2	14	1.0E-06	2
NK ₂ (<i>h</i>)			
952073-1	27	1.0E-06	-14
952073-2	14	1.0E-06	5
NK ₃ (<i>h</i>)			
952073-1	27	1.0E-06	-4
952073-2	14	1.0E-06	5
Y ₁ (<i>h</i>)			
952073-1	27	1.0E-06	-1
952073-2	14	1.0E-06	-1
Y ₂ (<i>h</i>)			
952073-1	27	1.0E-06	0
952073-2	14	1.0E-06	-1

Assay Cerep Compound I.D.	Client Compound I.D.	Test Concentration (M)	% Inhibition of Control Specific Binding
NT ₁ (<i>h</i>) (NTS1)			
952073-1	27	1.0E-06	-15
952073-2	14	1.0E-06	-5
δ ₂ (<i>h</i>) (DOP)			
952073-1	27	1.0E-06	-2
952073-2	14	1.0E-06	17
κ (KOP)			
952073-1	27	1.0E-06	4
952073-2	14	1.0E-06	12
μ (<i>h</i>) (MOP) (agonist site)			
952073-1	27	1.0E-06	7
952073-2	14	1.0E-06	-1
ORL1 (<i>h</i>) (NOP)			
952073-1	27	1.0E-06	-6
952073-2	14	1.0E-06	-6
PACAP (PAC ₁) (<i>h</i>)			
952073-1	27	1.0E-06	-4
952073-2	14	1.0E-06	-6
PCP			
952073-1	27	1.0E-06	-12
952073-2	14	1.0E-06	4
TXA ₂ /PGH ₂ (<i>h</i>) (TP)			
952073-1	27	1.0E-06	-5
952073-2	14	1.0E-06	5
P2X			
952073-1	27	1.0E-06	-6
952073-2	14	1.0E-06	3
P2Y			
952073-1	27	1.0E-06	7
952073-2	14	1.0E-06	-1
5-HT _{1A} (<i>h</i>)			
952073-1	27	1.0E-06	39
952073-2	14	1.0E-06	10
5-HT _{1B}			
952073-1	27	1.0E-06	-2
952073-2	14	1.0E-06	7
5-HT _{2A} (<i>h</i>)			
952073-1	27	1.0E-06	103
952073-2	14	1.0E-06	100
5-HT _{2C} (<i>h</i>)			
952073-1	27	1.0E-06	42
952073-2	14	1.0E-06	48
5-HT ₃ (<i>h</i>)			
952073-1	27	1.0E-06	3
952073-2	14	1.0E-06	8
5-HT _{5A} (<i>h</i>)			
952073-1	27	1.0E-06	-3

Assay Cerep Compound I.D.	Client Compound I.D.	Test Concentration (M)	% Inhibition of Control Specific Binding
952073-2	14	1.0E-06	-8
5-HT ₆ (<i>h</i>)			
952073-1	27	1.0E-06	7
952073-2	14	1.0E-06	-11
5-HT ₇ (<i>h</i>)			
952073-1	27	1.0E-06	42
952073-2	14	1.0E-06	38
σ (non-selective)			
952073-1	27	1.0E-06	0
952073-2	14	1.0E-06	3
sst (non-selective)			
952073-1	27	1.0E-06	-9
952073-2	14	1.0E-06	-6
VIP ₁ (<i>h</i>) (VPAC ₁)			
952073-1	27	1.0E-06	9
952073-2	14	1.0E-06	-2
V _{1a} (<i>h</i>)			
952073-1	27	1.0E-06	12
952073-2	14	1.0E-06	0
Ca ²⁺ channel (L, verapamil site) (phenylalkylamines)			
952073-1	27	1.0E-06	29
952073-2	14	1.0E-06	30
K ⁺ _v channel			
952073-1	27	1.0E-06	-11
952073-2	14	1.0E-06	-5
SK ⁺ _{Ca} channel			
952073-1	27	1.0E-06	-17
952073-2	14	1.0E-06	7
Na ⁺ channel (site 2)			
952073-1	27	1.0E-06	18
952073-2	14	1.0E-06	17
Cl ⁻ channel			
952073-1	27	1.0E-06	1
952073-2	14	1.0E-06	-20
NE transporter (<i>h</i>)			
952073-1	27	1.0E-06	4
952073-2	14	1.0E-06	-1
DA transporter (<i>h</i>)			
952073-1	27	1.0E-06	10
952073-2	14	1.0E-06	7
5-HT transporter (<i>h</i>)			
952073-1	27	1.0E-06	-5
952073-2	14	1.0E-06	-12

DSC graph of **14** (oxalate salt):DSC graph of **27** (HCl salt):

PXRD of **27** (HCl salt):

