Supplementary Table 1: Activity of key CL-058 analogs as assessed in NG108-cl cells using the clomeleon assay. EC_{50} values offer a relative measure of potency.

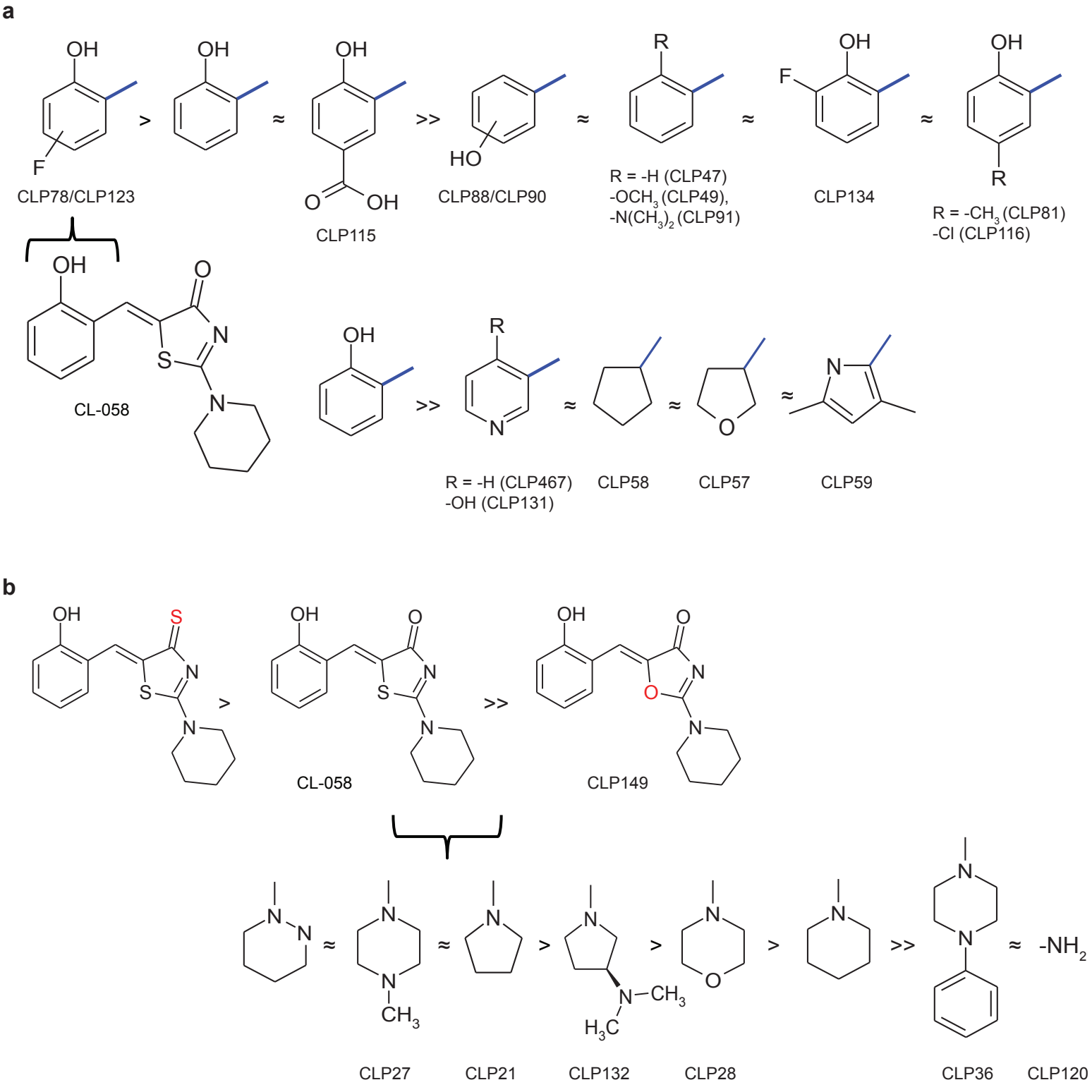
Compound code	Name	EC_{50} (μM)
CL-058	(5Z)-5-[(2-hydroxyphenyl)methylidene]-2-(piperidin-1-yl)-4,5-dihydro-1,3-thiazol-4-one	31.54
CLP78	(5Z)-5-[(5-fluoro-2-hydroxyphenyl)methylidene]-2-(piperidin-1-yl)-4,5-dihydro-1,3-thiazol-4-one	4.304
CLP123	(5Z)-5-[(4-fluoro-2-hydroxyphenyl)methylidene]-2-(piperidin-1-yl)-4,5-dihydro-1,3-thiazol-4-one	2.987
CLP134	(5E)-5-[(3-fluoro-2-hydroxyphenyl)methylidene]-2-(piperidin-1-yl)-4,5-dihydro-1,3-thiazol-4-one	inactive
CLP88	(5Z)-5-[(3-hydroxyphenyl)methylidene]-2-(piperidin-1-yl)-4,5-dihydro-1,3-thiazol-4-one	inactive
CLP90	(5Z)-5-[(4-hydroxyphenyl)methylidene]-2-(piperidin-1-yl)-4,5-dihydro-1,3-thiazol-4-one	inactive
CLP115	4-hydroxy-3-{[(5Z)-4-oxo-2-(piperidin-1-yl)-4,5-dihydro-1,3-thiazol-5-ylidene]methyl}benzoic acid	10.06
CLP47	(5Z)-5-(phenylmethylidene)-2-(piperidin-1-yl)-4,5-dihydro-1,3-thiazol-4-one	inactive
CLP49	(5Z)-5-[(2-methoxyphenyl)methylidene]-2-(piperidin-1-yl)-4,5-dihydro-1,3-thiazol-4-one	inactive
CLP91	(5Z)-5-{[2-(dimethylamino)phenyl]methylidene}-2-(piperidin-1-yl)-4,5-dihydro-1,3-thiazol-4-one	inactive
CLP81	(5Z)-5-[(2-hydroxy-5-methylphenyl)methylidene]-2-(piperidin-1-yl)-4,5-dihydro-1,3-thiazol-4-one	inactive
CLP116	(5Z)-5-[(5-chloro-2-hydroxyphenyl)methylidene]-2-(piperidin-1-yl)-4,5-dihydro-1,3-thiazol-4-one	inactive
CLP131	(5E)-5-[(4-hydroxypyridin-3-yl)methylidene]-2-(piperidin-1-yl)-4,5-dihydro-1,3-thiazol-4-one	inactive
CLP467	(5Z)-2-(piperidin-1-yl)-5-(pyridin-3-ylmethylidene)-4,5-dihydro-1,3-thiazol-4-one	inactive
CLP58	(5Z)-5-(cyclopentylmethylidene)-2-(piperidin-1-yl)-4,5-dihydro-1,3-thiazol-4-one	inactive
CLP57	(5Z)-5-[(2,5-dimethyl-1,3-thiazol-4-yl)methylidene]-2-(piperidin-1-yl)-4,5-dihydro-1,3-thiazol-4-one	inactive
CLP59	(5Z)-5-[(3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-2-(piperidin-1-yl)-4,5-dihydro-1,3-thiazol-4-one	inactive
CLP149	(5Z)-5-[(2-hydroxyphenyl)methylidene]-2-(piperidin-1-yl)-4,5-dihydro-1,3-oxazol-4-one	inactive
CLP27	(5Z)-5-[(2-hydroxyphenyl)methylidene]-2-(4-methylpiperazin-1-yl)-4,5-dihydro-1,3-thiazol-4-one	1.57
CLP21	(5Z)-5-[(2-hydroxyphenyl)methylidene]-2-(pyrrolidin-1-yl)-4,5-dihydro-1,3-thiazol-4-one	2.796
CLP132	(5E)-2-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]-5-[(2-hydroxyphenyl)methylidene]-4,5-dihydro-1,3-thiazol-4-one	1.128
CLP28	(5Z)-5-[(2-hydroxyphenyl)methylidene]-2-(morpholin-4-yl)-4,5-dihydro-1,3-thiazol-4-one	3.605
CLP36	(5Z)-5-[(2-hydroxyphenyl)methylidene]-2-(4-phenylpiperazin-1-yl)-4,5-dihydro-1,3-thiazol-4-one	inactive
CLP120	(5Z)-2-amino-5-[(2-hydroxyphenyl)methylidene]-4,5-dihydro-1,3-thiazol-4-one	inactive
CLP217	(5Z)-2-(1,2-diazinan-1-yl)-5-[(5-fluoro-2-hydroxyphenyl)methylidene]-4,5-dihydro-1,3-thiazol-4-one	0.318
CLP257	(5Z)-2-(1,2-diazinan-1-yl)-5-[(4-fluoro-2-hydroxyphenyl)methylidene]-4,5-dihydro-1,3-thiazol-4-one	0.616
CLP290	2-{[(5Z)-2-(1,2-diazinan-1-yl)-4-oxo-4,5-dihydro-1,3-thiazol-5-ylidene]methyl}-5-fluorophenyl pyrrolidine-1-carboxylate	inactive
CLP355	(5Z)-2-(1,2-diazinan-1-yl)-5-[(4-fluoro-2-hydroxyphenyl)methylidene]-4,5-dihydro-1,3-thiazole-4-thione	0.050
CLP386	6-(2-{[(5Z)-2-(1,2-diazinan-1-yl)-4-oxo-4,5-dihydro-1,3-thiazol-5-ylidene]methyl}-5-fluorophenoxy)-3,4,5-trihydroxyoxane-2-carboxylic acid	Inactive

Supplementary Table 2: CLP257 interactions with classical pharmacological targets: radioligand-receptor binding screen. The receptors tested, their sources, the radioligands used to define the binding sites, and the binding inhibitions induced by 10 μM CLP257 are shown.

Transporter/Receptor/Ion Channel	Source	Assay Conditions (Radioligand, [nM]/ non-specific binding ligand [μM])	% Binding Inhibition at 10μM
A_1 Adenosine	human recombinant (CHO cells)	[^{3}H]DPCPX, 1/DPCPX, 1	<10
A_{2A} Adenosine	human recombinant (HEK-293 cells)	[^{3}H]CGS 21680, 6/NECA, 10	10
A_3 Adenosine	human recombinant (HEK-293 cells)	[^{125}I]AB-MECA, 0.15/IB-MECA, 1	27
α_1 adrenergic	rat cerebral cortex	[^{3}H]prazosin, 0.25/prazosin, 0.5	<10
α_2 adrenergic	rat cerebral cortex	[^{3}H]RX 821002, 0.5/(-)epinephrine, 100	<10
β_1 adrenergic	human recombinant (HEK-293 cells)	[^{3}H](-)CGP 12177, 0.15/alprenolol, 50	<10
β_2 adrenergic	human recombinant (CHO cells)	[^{3}H](-)CGP 12177, 0.3/alprenolol, 50	<10
$Angiotensin_1$	human recombinant (HEK-293 cells)	[^{125}I][Sar1,Ile8]-AT-II, 0.05/angiotensin-II, 10	<10
Benzodiazepine	rat cerebral cortex	[^{3}H]flunitrazepam, 0.4/diazepam, 3	<10
$Bradykinin_2$	human recombinant (CHO cells)	[^{3}H]bradykinin, 0.3/bradykinin, 1	<10
$Cannabinoid_1$	human recombinant (CHO cells)	[^{3}H]CP 55940, 0.5/WIN 55212-2, 10	<10
$Cholecystokinin_A$	human recombinant (CHO cells)	[^{125}I]CCK-8s, 0.08/CCK-8s , 1	10
D_1 dopamine	human recombinant (CHO cells)	[^{3}H]SCH 23390, 0.3/SCH 23390, 1	<10
D_{2S} dopamine	human recombinant (HEK-293 cells)	[^{3}H]methyl-spiperone, 0.3/(+)butaclamol, 10	<10
$Endothelin_A$	human recombinant (CHO cells)	[^{125}I]endothelin-1, 0.03/endothelin-1, 0.1	<10
GABA (non-selective)	rat cerebral cortex	[^{3}H]GABA, 10/GABA, 100	<10
$Galanin_2$	human recombinant (CHO cells)	[^{125}I]galanin, 0.5/galanin, 1	<10
Interleukin 8 receptor beta	human recombinant (HEK-293 cells)	[^{125}I]IL-8, 0.025/IL-8, 0.03	<10
$Corticotropin\ releasing\ factor_1$	human recombinant (HEK-293 cells)	[^{125}I]MIP-1a, 0.01/MIP-1a, 0.1	<10
H_1 histamine	human recombinant (HEK-293 cells)	[^{3}H]pyrilamine, 1/pyrilamine, 1	<10
H_2 histamine	human recombinant (CHO cells)	[^{125}I]APT, 0.075/tiotidine, 100	<10
$melanocortin_4$	human recombinant (CHO cells)	[^{125}I]NDP-a-MSH, 0.05/NDP-a-MSH, 1	<10
$Melatonin_{1A}$	human recombinant (CHO cells)	[^{125}I]2-iodomelatonin, 0.01/melatonin, 1	<10
M_1 muscarinic	human recombinant (CHO cells)	[^{3}H]pirenzepine, 2/atropine, 1	<10
M_2 muscarinic	human recombinant (CHO cells)	[^{3}H]AF-DX 384, 2/atropine, 1	<10
M_3 muscarinic	human recombinant (CHO cells)	[^{3}H]4-DAMP, 0.2/atropine, 1	<10
$Neurkinin_2$	human recombinant (CHO cells)	[^{125}I]NKA, 0.1/[Nleu10]-NKA (4-10), 0.3	<10
$Neurkinin_3$	human recombinant (CHO cells)	[^{3}H]SR 14280, 0.4/SB 222200, 10	<10
Neuropeptide Y_1	SK-N-MC cells (endogenous)	[^{125}I]peptide YY, 0.025/NPY, 1	<10
Neuropeptide Y_2	KAN-TS cells	[^{125}I]peptide YY, 0.015/NPY, 1	<10
$Neurotensin_1$	human recombinant (CHO cells)	[^{125}I]Tyr3-neurotensin, 0.05/neurotensin, 1	<10
δ_2 opioid	human recombinant (CHO cells)	[^{3}H]DADLE, 0.5/naltrexone, 10	13
κ opioid	rat recombinant (CHO cells)	[^{3}H]U 69593, 1/naloxone, 10	11
μ opioid	human recombinant (HEK-293 cells)	[^{3}H]DAMGO, 0.5/naloxone, 10	<10
Nociceptin	human recombinant (HEK-293 cells)	[^{3}H]nociceptin, 0.2/nociceptin, 1	<10
$Thromboxane_{A2}$	human recombinant (HEK-293 cells)	[^{3}H]SQ 29548, 5/U 44069, 10	11
5-HT_{1A} Serotonin	human recombinant (HEK-293 cells)	[^{3}H]8-OH-DPAT, 0.3/8-OH-DPAT, 10	20
5-HT_{1B} Serotonin	rat cerebral cortex	[^{125}I]CYP, 0.1/Serotonin, 10	<10
5-HT_{2A} Serotonin	human recombinant (HEK-293 cells)	[^{3}H]ketanserin, 0.5/ketanserin, 1	17
5-HT_{2B} Serotonin	human recombinant (CHO cells)	[^{125}I](±)DOI, 0.2/(±)DOI, 1	<10
5-HT_3 Serotonin	human recombinant (CHO cells)	[^{3}H]BRL 43694, 0.5/MDL 72222, 10	17
5-HT_{5a} Serotonin	human recombinant (HEK-293 cells)	[^{3}H]LSD, 1.5/Serotonin, 100	<10
5-HT_6 Serotonin	human recombinant (CHO cells)	[^{3}H]LSD, 2/Serotonin, 100	<10
5-HT_7 Serotonin	human recombinant (CHO cells)	[^{3}H]LSD, 2.3/Serotonin, 10	<10
Somatostatin (non-selective)	AtT-20 cells	[^{125}I]Tyr11-somatostatin-14, 0.05/somatostatin-14, 0.3	<10
$Vasoactive\ intestinal\ peptide\ receptor_1$	human recombinant (CHO cells)	[^{125}I]VIP, 0.04/VIP, 1	11
$Vasopressin_{1A}$	human recombinant (CHO cells)	[^{3}H]AVP, 0.3/AVP, 1	<10
Ca^{2+} channel (L, verapamil site)	rat cerebral cortex	[^{3}H]D888, 3/D 600, 10	<10
KV channel	rat cerebral cortex	[^{125}I]a-dendrotoxin, 0.01/a-dendrotoxin, 0.05	<10
SKCa channel	rat cerebral cortex	[^{125}I]apamin, 0.007/apamin, 0.1	<10
Na^+ channel (site 2)	rat cerebral cortex	[^{3}H]batrachotoxinin, 10/veratridine, 300	14
Cl^- channel (GABA-gated)	rat cerebral cortex	[^{35}S]TBPS, 3/picrotoxinin, 20	17
norepinephrine transporter	human recombinant (CHO cells)	[^{3}H]nisoxetine, 1/desipramine, 1	<10
dopamine transporter	human recombinant (CHO cells)	[^{3}H]BTCP, 4/BTCP, 10	<10
5-HT transporter	human recombinant (CHO cells)	[^{3}H]imipramine, 2/imipramine, 10	<10

Supplementary Table 3: Key toxicological results from 7-day repeat dose toxicological study with CLP290 in Sprague-Dawley rats. CLP290 was administered P.O. twice daily at three dose levels (low: 200 mg kg^{-1} day^{-1}, mid: 600 mg kg^{-1} day^{-1}, high: 2000 mg kg^{-1} day^{-1}) and compared to vehicle control. All experiments were done blindly by an independent contract research organization.

Monitored parameters	Findings
clinical condition	Loose and/or pale feces at 600 and 2000 mg kg^{-1} at end of treatment period
body weight	No body weight changes related to treatment with CLP290
food consumption	No changes in food intake related to treatment with CLP290
hematology	Slight decreases in red blood cell count (RBC), hemoglobin concentration (HGB) and hematocrit (HCT) that sometime reached statistical significance in females were observed at the end of the treatment period in the Mid Dose (600 mg kg^{1} day^{-1}) and/or High Dose (2000 mg kg^{1} day^{-1}) males and females. However, considering the modest amplitude of the changes, they were not considered to be toxicologically relevant
coagulation	There were no CLP290 effects on coagulation parameters at any dose level
clinical chemistry	Compared to the control animals, slight changes occasionally reaching statistical significance were observed in the High Dose (2000 mg kg^{1} day^{-1}) males and/or females for a few parameters such as potassium (K), urea (UREA), albumin (ALB), globulin (GLOB) and the corresponding A/G ratio. However, due to the modest amplitude of the changes and/or direction and in the absence of any microscopic correlates, these changes were not considered to be toxicologically relevant. Statistically significant increase in total bilirubin (T-BIL) was also observed in the Low Dose (Group 2, 200 mg kg^{1} day^{-1}) males on Day 8. As this change was not observed at higher dose levels, it was considered to be likely incidental.
urinalysis	There were no CLP290 effects on the urinalysis parameters at any dose level
organ weights	No organ weight changes that were considered to be related to the administration of CLP290. At the end of the treatment period, statistically significant increases in absolute and/or relative liver weights were observed in the High Dose (2000 mg kg^{1} day^{-1}) males and females compared to controls. Nonetheless, due to the modest amplitude of the changes and the absence of any microscopic correlates in the liver, these differences were considered incidental and not toxicologically relevant. Other intergroup differences noted in this study were reflecting expected biological variations in laboratory rats.
pathology and histopathology of heart, kidney, liver and brain	There were no macroscopic findings that were considered to be related to the administration of CLP290. Macroscopic findings observed during this study were considered to be incidental, agonal or within the range of expected spontaneous background change. There were no microscopic findings that were considered to be related to the administration of CLP290. Microscopic changes observed during this study were not considered toxicologically significant as they occurred in controls and treated animals, were of low incidence and severity, or were incidental in this age and strain of laboratory rat.
General conclusions	No Observed Adverse Effect Level (NOAEL) considered to be at 2000 mg kg^{1} day^{-1}. No Observed Effect Level established at 200 mg kg^{1} day^{-1}.



Supplementary Figure 1: **Structure-activity relationship (SAR) of the CL-058 family of compounds.**
a) Impact of modification of the phenol ring. Presence of a hydroxyl group in the ortho position is essential for activity.
b) Substitution of the thiazol central ring to oxazol leads to complete loss of activity, while changing its ketone to a thione increased potency. SAR established the cyclic amine and thiazolidine rings as pharmacophores. The SAR validated the CL058 chemical series for drug optimization.