

Supporting Information

***N*-(3-Fluoro-4-(4-(2-methoxy or 2,3-dichlorophenyl) piperazine-1-yl)-butyl)-aryl carboxamides as Selective Dopamine D3 Receptor Ligands: Critical Role of the Carboxamide Linker for D3 Receptor Selectivity**

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Table S1: Microanalysis Data:

Compd	C	H	N	C	H	N
	Calculated			Found		
8a	62.02	6.10	9.98	62.02	5.94	9.97
8b	62.28	5.43	11.17	61.99	5.38	11.08
8c	59.53	5.96	8.01	59.71	5.76	8.04
8d	59.03	5.26	8.98	59.04	4.98	8.78
8e	64.64	6.73	9.05	64.63	6.49	9.01
8f	52.23	4.97	7.03	52.17	4.66	6.99
8g	67.19	6.93	13.06	67.05	6.86	13.01
8h	54.26	4.92	10.12	54.07	4.97	10.06
8i	73.55	6.81	8.87	73.60	6.80	8.76
8j	59.81	5.02	6.97	59.54	4.95	6.91
8k	58.74	5.69	7.90	58.67	5.52	7.94
8l	52.64	4.59	7.37	52.39	4.52	7.25
8m	57.64	6.27	9.96	57.61	6.08	9.87
8n	52.71	5.10	9.46	52.86	4.99	9.47
8o	56.55	5.10	7.33	56.89	4.91	7.28
13a	56.52	6.73	6.38	56.77	6.51	6.45
13b	53.73	5.56	6.27	53.48	5.60	6.28
13c	62.65	6.77	6.00	62.76	6.53	6.04
13d	59.07	5.95	5.90	59.04	5.89	5.90
13e	61.57	7.05	6.53	61.70	6.95	6.41
13f	54.47	5.82	5.78	54.40	5.60	5.62
14a	55.62	5.34	6.08	55.66	5.16	6.03
14b	56.64	5.05	6.19	56.87	5.00	6.29
15a	55.94	5.55	5.93	55.97	5.47	5.86
15b	55.43	5.43	5.88	55.36	5.24	5.83

Table S2. Amino Acid Sequence Transition Points for the Chimeric Receptor Proteins

	<u>D3</u>	<u>D2</u>	
Chimera A	MAVLKERALQ	–	<i>TTTNYLIVSL</i>
Chimera B	DVFTLDVMM	–	<i>CTASILNLCA</i>
Chimera C	NLCAISIDRY	–	<i>TAVAMPMLYN</i>
Chimera D	WVLAFAVSCP	–	<i>LLFGLNNADQ</i>
Chimera E	YLPFGVTVLV	–	<i>YIKIYIVLRR</i>
Chimera F	AFIVCWLPFF	–	<i>ITHILNIHCD</i>
	<u>D2</u>	<u>D3 E2 loop</u>	<u>D2</u>
Chimera D2/D3 E2 loop	<i>FTISCYLLFG</i>	–	FNTTGDPTVCSISN – <i>PAFVVYSSIV</i>
	<u>D3</u>	<u>D2 E2 loop</u>	<u>D3</u>
Chimera D2/D2 E2 loop	FAVSCPLLEFG	–	<i>LNNADQNECIAN</i> – PDFVIYSSV

The transition points for the amino acid sequence of the chimeric receptor proteins are shown using the single letter amino acid code. Designated transition points correspond to the changes in the DNA sequence for the human D2 and D3 dopamine receptor genes. The corresponding D2 receptor amino acid sequence is shown in italics, while the D3 amino acid sequence is not italicized.

Table S3. Amino Acid Sequence of Wild type and Chimeric Human D3/D2 Dopamine Receptors

D2 Sequence

D3 Sequence

Human D2 Dopamine Receptor

MDPLNLSWYDDDLERQNWSRPFNGSDGKA
 DRPHYNYYATLLTLLIAVIVFGNVLVCM AVSREKALQTTT
 NYLIVSLAVADLLVATLVMPWVVYLEVVG EWKFSRIHCDI
 FVTLDVMMCTASILNLCAISIDRYTAVAMPMLYNTRYSSK
 RRVTVMISIVWVLSFTISCP LLFGLNNADQNECIANPAF
 VVYSSIVSFYVPFIVTLLVYIKIYIVLRRRRKR VNTKRSS
 RAFRAHLRAPLKGNCTHPEDMKLCTVIMKSN GSFVNRRR
 VEARRAQELEMELSSSTSPPERTRYSPIPPSHHQLTLPD
 PSHHGLHSTPDSPAKPEKNGHAKDHPKIAKIFEIQTMPNG
 KTRTSLKTMSSRRKLSQQKEKKATQMLAIVLGVFIICWLPF
 FITHILNIHCD CNIPPVLYSAFTWLG YVNSAVNPIIYTTF
 NIEFRKAFLKILHC

MASLSQLSSHLNYTCGAENSTGASQARPHAYYALSICALI
LAIVFGNGLVCM AVLKERALQTTTNYLIVSLAVADLLVAT
LVMPWVVYLEVVG EWKFSRIHCDIFVTL DVMMCTASILNL
CAISIDRYTAVAMPMLYNTRYSSKRRVTVMISIVVLSFTI
SCPLL FGLNNADQNECIANPAFVVYSSIVSFYVPFIVTLLV
YIKIYIVLRRRRKR VNTKRSSRAFRAHLRAPLKGNC THPE
DMKLCTVIMKSN GSFVNRRRVEAARRAQELEM EMLSSTS
PPERTRYSP IPPSHHQLTLPDP SHHGLHSTPD SPAKPEKNG
HAKDHPKIAKIFE IQTMPNGKTRTSLKTMSRRKLSQQKEK
KATQMLAIVLGVFI ICWLPFFITHILNIHCDCNIPPVLYSAF
TWLGYVNSAVNPIIYTTFNIEFRK AFLKILHC

Chimera B (rtan12)

MASLSQLSSHLNYTCGAENSTGASQA
RPHAYYALSICALILAIVFGNGLVCM AVLKERALQTTTNY
LVVSLAVADLLVATLVMPWVVYLEVTGGVWNFSRICCDV
FVTL DVMMCTASILNLCAISIDRYTAVAMPMLYNTRYSSKR
RVTVMISIVVLSFTI SCPLL FGLNNADQNECIANPAFV
VYSSIVSFYVPFIVTLLVYIKIYIVLRRRRKR VNTKRSSR
AFRAHLRAPLKGNC THPE DMKLCTVIMKSN GSFVNRRRV
EARRAQELEM EMLSSTSPPERTRYSP IPPSHHQLTLPDP
SHHGLHSTPD SPAKPEKNGHAKDHPKIAKIFE IQTMPNGK
TRTSLKTMSRRKLSQQKEKKATQMLAIVLGVFI ICWLPFF
ITHILNIHCDCNIPPVLYSAFTW LGYVNSAVNPIIYTTFNIE
FRK AFLKILHC

Chimera C (rtan11)

MASLSQLSSHLNYTCGAENSTGASQARPHAYYALSICALI
LAIVFGNGLVCM AVLKERALQTTTNYLVVSLAVADLLVAT
LVMPWVVYLEVTGGVWNFSRICCDV FVTL DVMMCTASILN
LCAISIDRYTAVAMPMLYNTRYSSKRRVTVMISIVVLSFTI
ISCP LL FGLNNADQNECIANPAFVVYSSIVSFYVPFIVTLL
VYIKIYIVLRRRRKR VNTKRSSRAFRAHLRAPLKGNC THP
EDMKLCTVIMKSN GSFVNRRRVEAARRAQELEM EMLSST
SPPERTRYSP IPPSHHQLTLPDP SHHGLHSTPD SPAKPEKN
GHAKDHPKIAKIFE IQTMPNGKTRTSLKTMSRRKLSQQKE
KKATQMLAIVLGVFI ICWLPFFITHILNIHCDCNIPPVLYS
AFTW LGYVNSAVNPIIYTTFNIEFRK AFLKILHC

Chimera D (TMS4)

MASLSQLSSHLNYTCGAENSTGASQA
RPHAYYALSICALILAIVFGNGLVCM AVLKERALQTTTNY
LVVSLAVADLLVATLVMPWVVYLEVTGGVWNFSRICCDV
VTL DVMMCTASILNLCAISIDRYTAVVMPVHYQHGTGQSS
CRRVALMITAVWVLAFAVSCPLL FGLNNADQNECIANPA
FVVYSSIVSFYVPFIVTLLVYIKIYIVLRRRRKR VNTKRS
SRAFRAHLRAPLKGNC THPE DMKLCTVIMKSN GSFVNRR
RVEAARRAQELEM EMLSSTSPPERTRYSP IPPSHHQLTLP
DP SHHGLHSTPD SPAKPEKNGHAKDHPKIAKIFE IQTMPN
GKTRTSLKTMSRRKLSQQKEKKATQMLAIVLGVFI ICWLP
FFITHILNIHCDCNIPPVLYSAFTW LGYVNSAVNPIIYTT
FNIEFRK AFLKILHC

Chimera E (TMS5)

MASLSQLSSHLNYTCGAENSTGASQA
RPHAYYALSICALILAIVFGNGLVCM AVLKERALQTTTNY
LVVSLAVADLLVATLVMPWVVYLEVTGGVWNFSRICCDVF
VTLDVMMCTASILNLC A ISIDRYTAVVMPVHYQHGTGQSS
CRRVALMITAVWVLAFAVSCPLLFGFNTTGDPTVCSISNP
DFVIYSSVVSFYLPFGVTVLVYIKIYIVLRRRRKR VNTKR
SSRAFRAHLRAPLKGNCTHPEDMKLCTVIMKSNGSFPVNR
RRVEAARRAQELEMELSSSTSPPERTRYSPIPPSHHQLTL
PDP SHHGLHSTPDSPAKPEKNGHAKDHPKIAKIFEIQTMP
NGKTRTSLKTMSRRKLSQQKEKKATQMLAIIVLGVFIICWL
PFFITHILNIHCDCNIPPVLYSAFTWLG YVNSAVNPIIYT
TFNIEFRKAFLKILHC

Chimera F (rtan7)

MASLSQLSSHLNYTCGAENSTGASQA
RPHAYYALSICALILAIVFGNGLVCM AVLKERALQTTTNY
LVVSLAVADLLVATLVMPWVVYLEVTGGVWNFSRICCDV
FVTLDVMMCTASILNLC A ISIDRYTAVVMPVHYQHGTGQS
SCRRVALMITAVWVLAFAVSCPLLFGFNTTGDPTVCSISNP
DFVIYSSVVSFYLPFGVTVLVYARIYVVLKQRRRKRILTR
QNSQCNSVRPGFPQQTLSPDPAHLELKRYYSICQDTALGG
PGFQERGGELKREEKTRNSLSPTIAPKLSLEVRKLSNGRL
STSLKLGPLQPRGVPLREKKATQMVAIVLGA FIVCWL PFFI
THILNIHCDCNIPPVLYSAFTWLG YVNSAVNPIIYTTFN
IEFRKAFLKILHC

Chimera G (D2(D3loop))

MDPLNLSWYDDDLERQNW SRPFNGSDGKA
DRPHYNYATLLTLLIAVIVFGNVLVCM AVSREKALQTTT
NYLIVSLAVADLLVATLVMPWVVYLEVVGEWKFSRIHCDI
FVTLDVMMCTASILNLC A ISIDRYTAVAMPMLYNTRYSSK
RRVTVMISIVWVLSFTISCPLLFGFNTTGDPTVCSISNPAF
VYSSIVSFYVPFIVTLLVYIKIYIVLRRRRKR VNTKRSS
RAFRAHLRAPLKGNCTHPEDMKLCTVIMKSNGSFPVNR RR
VEAARRAQELEMELSSSTSPPERTRYSPIPPSHHQLTL PD
PSHHGLHSTPDSPAKPEKNGHAKDHPKIAKIFEIQTMPNG
KTRTSLKTMSRRKLSQQKEKKATQMLAIIVLGVFIICWLPF
FITHILNIHCDCNIPPVLYSAFTWLG YVNSAVNPIIYTTF
NIEFRKAFLKILHC

Chimera H (D3(D2loop))

MASLSQLSSHLNYTCGAENSTGASQARPHAYYALSICALI
LAIVFGNGLVCM AVLKERALQTTTNYLVVSLAVADLLVAT
LVMPWVVYLEVTGGVWNFSRICCDVFVTLDVMMCTASILN
LCAISIDRYTAVVMPVHYQHGTGQSSCRRVALMITAVWVLA
FAVSCPLLFG LNNADQNECIIANP DFVIYSSVVSFYLPFG
VTVLVYARIYVVLKQRRRKRILTRQNSQCNSVRPGFPQQT
LSPDPAHLELKRYYSICQDTALGGPGFQERGGELKREEK
RNSLSPTIAPKLSLEVRKLSNGRLSTSLKLGPLQPRGVPLR
EKKATQMVAIVLGA FIVCWL PFFLTHVLNTHCQTCHVSPE
LYSATTWLG YVNSALNPVIYTTFNIEFRKAFLKILSC

MASLSQLSSHLYNYTCGAENSTGASQARPHAYYALSICALI
LAIVFGNGLVCM AVLKERALQTTTNYLVVSLAVADLLVAT
LVMPWVVYLEVTGGVWNFSRICCDVFTLDVMMCTASILN
LCAISIDRYTAVVMPVHYQHGTGQSSCRRVALMITAVWVL
FAVSCPLLFGFNTTGDPTVCSISNPDFVIYSSVVSFYLPFG
VTVLVYARIYVVLKQRRRKRIILTRQNSQCNSVRPGFPQQT
LSPDPAHLELKRYYSICQDTALGGPGFQERGGELKREEKT
RNSLSPTIAPKLSLEVRKLSNGRLSTSLKLGPLQPRGVPLR
EKKATQMVAIVLGAFIVCWLPFFLTHVLNTHCQTCHVSPE
LYSATTWLG YVNSALNPVIYTTFNIEFRKAFLKILSC