**Biased ligands of class A G protein-coupled receptors over the past 20 years**

Jixia Wang a,b, Fangfang Xu b, Yanfang Liu a,b, Han Zhou a,b, Wenjie Yuan b, Fan Liu a, Ye Fang a,\*, Xinmiao Liang a,b,\*

a Key Laboratory of Phytochemistry and Natural Medicines, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China

b Jiangxi Provincial Key Laboratory for Pharmacodynamic Material Basis of Traditional Chinese Medicine, Ganjiang Chinese Medicine Innovation Center, Nanchang 330000, China

\* Corresponding authors: Ye Fang, Xinmiao Liang

Tel.: +86 411 84379519; fax: +86 411 84379539.

E-mail addresses: fangye@dicp.ac.cn, liangxm@dicp.ac.cn

**Table S1** Class A GPCR biased ligands.

| No. | Receptor family | Target | Name in main text | Ligand | Biased signaling | Reference |
| --- | --- | --- | --- | --- | --- | --- |
|  | 5-Hydroxytryptamine | 5HT1A | 5-HT1A | compound 1 | G protein | [1] |
|  | 5-Hydroxytryptamine | 5HT1A | 5-HT1A | compound 2 | G protein | [1] |
|  | 5-Hydroxytryptamine | 5HT1A | 5-HT1A | compound 4 | G protein | [1] |
|  | 5-Hydroxytryptamine | 5HT1A | 5-HT1A | NLX-101 (F15599) | pERK1/2 over β-arrestin recruitment or Ca2+ mobilization | [2, 3] |
|  | 5-Hydroxytryptamine | 5HT1A | 5-HT1A | NLX-112 (befiradol) | pERK1/2 over β-arrestin recruitment or Ca2+ mobilization | [4, 5] |
|  | 5-Hydroxytryptamine | 5HT1A | 5-HT1A | NLX-260 (Compound 44) | pERK1/2 over cAMP inhibition, β-arrestin recruitment and Ca2+ mobilization | [3] |
|  | 5-Hydroxytryptamine | 5HT1A | 5-HT1A | NLX-249 (Compound 56) | β-arrestin recruitment over pERK1/2, cAMP inhibition and Ca2+ mobilization | [3] |
|  | 5-Hydroxytryptamine | 5HT1A | 5-HT1A | compound 14 | pERK1/2 over cAMP inhibition | [6] |
|  | 5-Hydroxytryptamine | 5HT1A | 5-HT1A | NLX-204 (compound 17) | pERK1/2 over cAMP inhibition, β-arrestin recruitment and Ca2+ mobilization | [6] |
|  | 5-Hydroxytryptamine | 5HT1A | 5-HT1A | compound 27 | pERK1/2 over cAMP inhibition or β-arrestin recruitment | [6] |
|  | 5-Hydroxytryptamine | 5HT1A | 5-HT1A | 8-Oh-DPAT | β-arrestin | [6] |
|  | 5-Hydroxytryptamine | 5HT1B | / | 3-T1AM | cAMP inhibition over PLC activation | [7] |
|  | 5-Hydroxytryptamine | 5HT2A | 5-HT2A | 25H-NBF | β-arrestin | [8] |
|  | 5-Hydroxytryptamine | 5HT2A | 5-HT2A | 25H-NBMD | β-arrestin | [8] |
|  | 5-Hydroxytryptamine | 5HT2A | 5-HT2A | 25H-NBOH | β-arrestin | [8] |
|  | 5-Hydroxytryptamine | 5HT2A | 5-HT2A | 25H-NBOMe | β-arrestin | [8] |
|  | 5-Hydroxytryptamine | 5HT2A | 5-HT2A | 4a | β-arrestin | [9] |
|  | 5-Hydroxytryptamine | 5HT2A | 5-HT2A | 4b | β-arrestin | [9] |
|  | 5-Hydroxytryptamine | 5HT2A | 5-HT2A | 6e | β-arrestin | [9] |
|  | 5-Hydroxytryptamine | 5HT2A | 5-HT2A | 6f | β-arrestin | [9] |
|  | 5-Hydroxytryptamine | 5HT2A | 5-HT2A | altanserin | Gi1 over Gq | [10] |
|  | 5-Hydroxytryptamine | 5HT2A | 5-HT2A | pimavanserin | Gi1 over Gq | [10] |
|  | 5-Hydroxytryptamine | 5HT2A | 5-HT2A | *(R)*-69 | Gq protein | [11] |
|  | 5-Hydroxytryptamine | 5HT2A | 5-HT2A | *(R)*-70 | Gq protein | [11] |
|  | 5-Hydroxytryptamine | 5HT2B | 5-HT2B | ergotamine | β-arrestin | [12] |
|  | 5-Hydroxytryptamine | 5HT2B | 5-HT2B | lysergic acid diethylamide | β-arrestin | [12] |
|  | 5-Hydroxytryptamine | 5HT2C | 5-HT2C | (*R*)-asimilobine | Gq protein | [13] |
|  | 5-Hydroxytryptamine | 5HT2C | 5-HT2C | 11b | Gq protein | [14] |
|  | 5-Hydroxytryptamine | 5HT2C | 5-HT2C | 11f | Gq protein | [14] |
|  | 5-Hydroxytryptamine | 5HT2C | 5-HT2C | compound (+)-7e | Gq protein | [15] |
|  | 5-Hydroxytryptamine | 5HT2C | 5-HT2C | compound (+)-15a | Gq protein | [16] |
|  | 5-Hydroxytryptamine | 5HT2C | 5-HT2C | compound (+)-19 | Gq protein | [16] |
|  | 5-Hydroxytryptamine | 5HT2C | 5-HT2C | aripiprazole | G protein | [17] |
|  | 5-Hydroxytryptamine | 5HT2C | 5-HT2C | lorcaserin | G protein | [17] |
|  | 5-Hydroxytryptamine | 5HT2C | 5-HT2C | MBP | G protein | [17] |
|  | 5-Hydroxytryptamine | 5HT4R | / | RS 67333 | Gs over Gq | [18] |
|  | 5-Hydroxytryptamine | 5HT4R | / | prucalopride | Gs over Gq | [18] |
|  | 5-Hydroxytryptamine | 5HT7R | 5-HT7 | 1g | β-arrestin | [19] |
|  | 5-Hydroxytryptamine | 5HT7R | 5-HT7 | 2b | G protein | [20] |
|  | 5-Hydroxytryptamine | 5HT7R | 5-HT7 | serodolin | β-arrestin | [21] |
|  | 5-Hydroxytryptamine | 5HT7R | 5-HT7 | 3c | G protein | [22] |
|  | 5-Hydroxytryptamine | 5HT7R | 5-HT7 | 3f | G protein | [22] |
|  | 5-Hydroxytryptamine | 5HT7R | 5-HT7 | 3i | G protein | [22] |
|  | 5-Hydroxytryptamine | 5HT7R | 5-HT7 | 3p | G protein | [22] |
|  | Acetylcholine (muscarinic) | ACM1 | M1 | TBPB | G protein | [23] |
|  | Acetylcholine (muscarinic) | ACM1 | M1 | AC-260584 | G protein | [23] |
|  | Acetylcholine (muscarinic) | ACM1 | M1 | VU0357017 | G protein | [24] |
|  | Acetylcholine (muscarinic) | ACM1 | M1 | VU0364572 | G protein | [24] |
|  | Acetylcholine (muscarinic) | ACM2 | M2 | Iper-6-naph | Gi protein | [25] |
|  | Acetylcholine (muscarinic) | ACM2 | M2 | Iper-6-phth | Gi protein | [25] |
|  | Acetylcholine (muscarinic) | ACM2 | M2 | McN-A-343 | G15 over Gi | [26] |
|  | Acetylcholine (muscarinic) | ACM2 | M2 | 6A | Gi over Gq | [27] |
|  | Acetylcholine (muscarinic) | ACM2 | M2 | 7A | Gi over Gq | [27] |
|  | Acetylcholine (muscarinic) | ACM3 | M3 | PD 102807 | β-arrestin | [28] |
|  | Acetylcholine (muscarinic) | ACM4 | M4 | xanomeline | Gi2 over pERK1/2 and Ca2+ mobilization | [29] |
|  | Acetylcholine (muscarinic) | ACM4 | M4 | 6A | Gi over Gq | [27] |
|  | Acetylcholine (muscarinic) | ACM4 | M4 | 7A | Gi over Gq | [27] |
|  | Acetylcholine (muscarinic) | ACM5 | M5 | 7A | Gi over Gq | [27] |
|  | Adrenoceptors | ADA1A | α1A | oxymetazoline | extracellular acidification rate over Ca2+ mobilization and cAMP production | [30] |
|  | Adrenoceptors | ADA1A | α1A | phenylephrine | extracellular acidification rate over Ca2+ mobilization and cAMP production | [30] |
|  | Adrenoceptors | ADA1A | α1A | cirazoline | cAMP production and Ca2+ mobilization | [30] |
|  | Adrenoceptors | ADA1A | α1A | A61603 | cAMP production and Ca2+ mobilization | [30] |
|  | Adrenoceptors | ADA2C | α2C | clonidine | β-arrestin recruitment over cAMP inhibition, Ca2+ mobilization or receptor internalization | [31] |
|  | Adrenoceptors | ADA2C | α2C | UK14,304 (brimonidine) | β-arrestin recruitment over cAMP inhibition, Ca2+ mobilization or receptor internalization | [31] |
|  | Adrenoceptors | ADA2C | α2C | guanabenz | β-arrestin recruitment over cAMP inhibition, Ca2+ mobilization or receptor internalization | [31] |
|  | Adrenoceptors | ADA2C | α2C | moxonidine | β-arrestin recruitment over cAMP inhibition, Ca2+ mobilization or receptor internalization | [31] |
|  | Adrenoceptors | ADA2C | α2C | phenylephrine | β-arrestin recruitment over cAMP inhibition, Ca2+ mobilization or receptor internalization | [31] |
|  | Adrenoceptors | ADRB1 | β1 | metoprolol | β-arrestin | [32] |
|  | Adrenoceptors | ADRB1 | β1 | nebivolol | β-arrestin | [33] |
|  | Adrenoceptors | ADRB1 | β1 | bucindolol | β-arrestin | [34, 35] |
|  | Adrenoceptors | ADRB1 | β1 | alprenolol | β-arrestin | [36] |
|  | Adrenoceptors | ADRB1 | β1 | STD-101-D1 | G protein | [37] |
|  | Adrenoceptors | ADRB1 | β1 | xamoterol | G protein | [37, 38] |
|  | Adrenoceptors | ADRB2 | β2 | formoterol | β-arrestin | [39] |
|  | Adrenoceptors | ADRB2 | β2 | dichloroisoproterenol | β-arrestin | [39] |
|  | Adrenoceptors | ADRB2 | β2 | salmeterol | β-arrestin | [39] |
|  | Adrenoceptors | ADRB2 | β2 | pindolol | β-arrestin | [39] |
|  | Adrenoceptors | ADRB2 | β2 | isoetharine | β-arrestin | [40] |
|  | Adrenoceptors | ADRB2 | β2 | N-cyclopentylbutanephrine | β-arrestin | [40] |
|  | Adrenoceptors | ADRB2 | β2 | ethylnorepinephrine | β-arrestin | [40] |
|  | Adrenoceptors | ADRB2 | β2 | ICL3-9 | Gs protein | [41] |
|  | Adrenoceptors | ADRB2 | β2 | ICL3-4 | β-arrestin | [41] |
|  | Adrenoceptors | ADRB2 | β2 | *(R,R)*-fenoterol | Gs over Gi | [42] |
|  | Adrenoceptors | ADRB2 | β2 | *(S,R)*-4'-methoxyfenoterol | Gs protein | [43] |
|  | Adrenoceptors | ADRB2 | β2 | *(R,S')*-4'-methoxy-1-naphthyl-fenoterol | Gs protein | [44] |
|  | Adrenoceptors | ADRB2 | β2 | *(S,S')*-4'-methoxy-1-naphthyl-fenoterol | Gs protein | [44] |
|  | Adrenoceptors | ADRB2 | β2 | ICL1-9 | β-arrestin | [45] |
|  | Adrenoceptors | ADRB2 | β2 | carmoterol | β-arrestin | [46] |
|  | Adrenoceptors | ADRB2 | β2 | L2 | β-arrestin | [47] |
|  | Adrenoceptors | ADRB2 | β2 | L4 | β-arrestin | [47] |
|  | Adrenoceptors | ADRB2 | β2 | L12 | β-arrestin | [47] |
|  | Adrenoceptors | ADRB2 | β2 | ractopamine | Gs protein | [48] |
|  | Adrenoceptors | ADRB2 | β2 | dobutamine | Gs protein | [48] |
|  | Adrenoceptors | ADRB2 | β2 | higenamine | Gs protein | [48] |
|  | Adrenoceptors | ADRB2 | β2 | C1-S | Gs protein | [49] |
|  | Adrenoceptors | ADRB2 | β2 | carvedilol | β-arrestin | [50] |
|  | Adrenoceptors | ADRB2 | β2 | propranolol | β-arrestin | [51] |
|  | Adrenoceptors | ADRB2 | β2 | ICI-118,551 | β-arrestin | [51] |
|  | Dopamine | DRD1 | D1 | apomorphine | G protein | [52] |
|  | Dopamine | DRD1 | D1 | SKF83959 | G protein | [52] |
|  | Dopamine | DRD1 | D1 | SKF38393 | G protein | [52] |
|  | Dopamine | DRD1 | D1 | SKF82957 | G protein | [52] |
|  | Dopamine | DRD1 | D1 | SKF77434 | G protein | [52] |
|  | Dopamine | DRD1 | D1 | SKF75670 | G protein | [52] |
|  | Dopamine | DRD1 | D1 | compound 10 | G protein | [53] |
|  | Dopamine | DRD1 | D1 | compound 35 | Gs protein | [53] |
|  | Dopamine | DRD1 | D1 | PF-06649751 (CVL-751, tavapandon) | G protein | [54] |
|  | Dopamine | DRD1 | D1 | PF-8294 | Gs protein | [55] |
|  | Dopamine | DRD1 | D1 | PF-6142 | Gs protein | [55] |
|  | Dopamine | DRD1 | D1 | PF-1119 | Gs protein | [55] |
|  | Dopamine | DRD1 | D1 | PF-2334 | Gs protein | [55] |
|  | Dopamine | DRD2 | D2 | UNC9975 | β-arrestin | [56] |
|  | Dopamine | DRD2 | D2 | UNC0006 | β-arrestin | [56] |
|  | Dopamine | DRD2 | D2 | UNC9994 | β-arrestin | [56] |
|  | Dopamine | DRD2 | D2 | compound 7 | β-arrestin | [57] |
|  | Dopamine | DRD2 | D2 | MLS1547 | G protein | [58] |
|  | Dopamine | DRD2 | D2 | *(S)*-1 | Go over Gi | [59] |
|  | Dopamine | DRD2 | D2 | *(S)*-2 | Go over Gi | [59] |
|  | Dopamine | DRD2 | D2 | *(R)*-4 | β-arrestin | [59] |
|  | Dopamine | DRD2 | D2 | compound 1 | G protein | [60] |
|  | Dopamine | DRD2 | D2 | benzoxazinone 9d | β-arrestin | [61] |
|  | Dopamine | DRD2 | D2 | 13b | β-arrestin | [62] |
|  | Dopamine | DRD2 | D2 | pramipexole | β-arrestin | [62] |
|  | Dopamine | DRD2 | D2 | quinpirole | β-arrestin | [62] |
|  | Dopamine | DRD2 | D2 | ropinirole | β-arrestin | [62] |
|  | Dopamine | DRD2 | D2 | 16c | G protein | [63] |
|  | Dopamine | DRD2 | D2 | 11 | Go protein | [64] |
|  | Dopamine | DRD2 | D2 | 19 | Go protein | [64] |
|  | Dopamine | DRD2 | D2 | compound 19 | G protein | [65] |
|  | Dopamine | DRD2 | D2 | MS1768 | G protein | [66] |
|  | Dopamine | DRD2 | D2 | 36 | G protein | [66] |
|  | Dopamine | DRD2 | D2 | 39 | G protein | [66] |
|  | Dopamine | DRD2 | D2 | 40 | G protein | [66] |
|  | Dopamine | DRD2 | D2 | 42 | G protein | [66] |
|  | Dopamine | DRD2 | D2 | carbaldoxime 8b | Go protein | [67] |
|  | Dopamine | DRD2 | D2 | aripiprazole | Go protein | [67] |
|  | Dopamine | DRD2 | D2 | cariprazine | G protein | [68] |
|  | Dopamine | DRD2 | D2 | 32 | G protein | [68] |
|  | Dopamine | DRD2 | D2 | 10 | cAMP inhibition over pERK1/2 | [69] |
|  | Dopamine | DRD2 | D2 | 36 | cAMP inhibition over pERK1/2 | [70] |
|  | Dopamine | DRD3 | D3 | SK609 | G protein | [71] |
|  | Dopamine | DRD3 | D3 | SK608 | G protein | [71] |
|  | Histamine | HRH4 | H4 | JNJ7777120 | β-arrestin | [72, 73] |
|  | Histamine | HRH4 | H4 | 47 indolecarboxamides | β-arrestin | [74] |
|  | Histamine | HRH4 | H4 | VUF5228 | β-arrestin | [75] |
|  | Histamine | HRH4 | H4 | VUF10214 | β-arrestin | [75] |
|  | Histamine | HRH4 | H4 | VUF5223 | β-arrestin | [75] |
|  | Histamine | HRH4 | H4 | VUF10056 | β-arrestin | [75] |
|  | Histamine | HRH4 | H4 | VUF6002 | β-arrestin | [75] |
|  | Histamine | HRH4 | H4 | VUF11273 | β-arrestin | [75] |
|  | Histamine | HRH4 | H4 | VUF11012 | β-arrestin | [75] |
|  | Histamine | HRH4 | H4 | VUF5222 | Gi protein | [75] |
|  | Histamine | HRH4 | H4 | VUF10778 | Gi protein | [75] |
|  | Histamine | HRH4 | H4 | VUF10185 | Gi protein | [75] |
|  | Histamine | HRH4 | H4 | VUF10192 | Gi protein | [75] |
|  | Histamine | HRH4 | H4 | UR-PI376 | Gi protein | [75] |
|  | Histamine | HRH4 | H4 | VUF10306 | Gi protein | [75] |
|  | Histamine | HRH4 | H4 | VUF4656 | Gi protein | [75] |
|  | Histamine | HRH4 | H4 | clozapine | Gi protein | [75] |
|  | Trace amine | TAAR1 | TAAR1 | ZH8651 | Gs and Gq protein | [76] |
|  | Trace amine | TAAR1 | TAAR1 | ZH8659 | Gq protein | [76] |
|  | Trace amine | TAAR1 | TAAR1 | ZH8667 | Gs protein | [76] |
|  | Trace amine | TAAR1 | TAAR1 | SEP-363856 | Gs protein | [76] |
|  | Trace amine | TAAR1 | TAAR1 | β-phenylethylamine | Gs protein | [76] |
|  | Trace amine | TAAR1 | TAAR1 | 3-iodothyronamine | Gs protein | [76] |
|  | Trace amine | TAAR1 | TAAR1 | cyclohexylamine | Gq protein | [76] |
|  | Angiotensin | AGTR1 | TAAR1 | TRV120023 | β-arrestin | [77] |
|  | Angiotensin | AGTR1 | AT1R | TRV120027 | β-arrestin | [77-79] |
|  | Angiotensin | AGTR1 | AT1R | TRV120055 | Gq protein | [80] |
|  | Angiotensin | AGTR1 | AT1R | [Sar1, Ile4, Ile8]-angiotensin II | β-arrestin | [81, 82] |
|  | Angiotensin | AGTR1 | AT1R | Ang-(1-7) | β-arrestin | [83] |
|  | Angiotensin | AGTR1 | AT1R | SIII | G12 protein | [84] |
|  | Apelin | APJ | APJ | ML233 | β-arrestin | [85] |
|  | Apelin | APJ | APJ | compound 1 | G protein | [86] |
|  | Apelin | APJ | APJ | compound 4 | G protein | [86] |
|  | Apelin | APJ | APJ | compound 11 | G protein | [86] |
|  | Apelin | APJ | APJ | compound 15 | G protein | [86] |
|  | Apelin | APJ | APJ | 29 | Ca2+ mobilization over β-arrestin recruitment | [87] |
|  | Apelin | APJ | APJ | K16P | Gi protein | [88] |
|  | Apelin | APJ | APJ | Apelin-36-L28A | G protein | [89] |
|  | Apelin | APJ | APJ | Apelin-36-L28C(30kDa-PEG) | G protein | [89] |
|  | Apelin | APJ | APJ | MM07 | G protein | [90] |
|  | Apelin | APJ | APJ | CMF-019 | G protein | [91] |
|  | Apelin | APJ | APJ | SBI-’569 | β-arrestin | [92] |
|  | Apelin | APJ | APJ | SBI-’681 | β-arrestin | [92] |
|  | Apelin | APJ | APJ | SBI-’547 | Gi protein | [92] |
|  | Apelin | APJ | APJ | SBI-’612 | Gi protein | [92] |
|  | Apelin | APJ | APJ | (-)-epicatechin | β-arrestin | [93] |
|  | Apelin | APJ | APJ | WN353 | G protein | [94] |
|  | Apelin | APJ | APJ | WN561 | G protein | [94] |
|  | Complement | C3AR | / | EP141 | G protein | [95] |
|  | Complement | C5AR1 | C5aR1 | BM213 | G protein | [96, 97] |
|  | Endothelin | EDNRA | ETA | ET-2 | G protein | [98] |
|  | Endothelin | EDNRA | ETA | ET-3 | G protein | [98] |
|  | Formylpeptide | FPR2 | / | F2Pal10 | G protein | [99] |
|  | Ghrelin | GHSR | GHSR | YIL781 | G protein | [100] |
|  | Ghrelin | GHSR | GHSR | Abb13d | G protein | [100] |
|  | Ghrelin | GHSR | GHSR | N8279 (NCATS-SM8864) | Gq protein | [101] |
|  | Melanocortin | MC4R | MC4R | CJL-5-58 | G protein | [102] |
|  | Melanocortin | MC4R | MC4R | SHU9119 | pERK1/2 over cAMP production | [103] |
|  | Melanocortin | MC4R | MC4R | MBP10 | pERK1/2 over cAMP production | [103] |
|  | Melanocortin | MC4R | MC4R | BMS- 470539 | pERK1/2 over cAMP production | [104] |
|  | Melanocortin | MC4R | MC4R | [D-Trp 8 ]-γMSH | pERK1/2 over cAMP production | [104] |
|  | Melanocortin | MC4R | MC4R | setmelanotide | Gq protein | [105] |
|  | Melanocortin | MC4R | MC4R | Agouti-related peptide | Gi, Kir7.1, ERK1/2 and Akt over Gs | [106] |
|  | Neuropeptide S | NPSR1 | NPSR | hNPS-(1-10) | Gq over Gs | [107] |
|  | Neuropeptide S | NPSR1 | NPSR | analog 4 (RTI-263, SerPheLysAsn-NH2) | Gq over Gs | [108] |
|  | Neuropeptide Y | NPY1R | / | G(34)-NPY | G protein | [109] |
|  | Neurotensin | NTR1 | NTR1 | SBI-553 | β-arrestin | [110] |
|  | Neurotensin | NTR1 | NTR1 | ML314 | β-arrestin | [111] |
|  | Opioid | OPRD | DOR | mitragynine | Gi protein | [112] |
|  | Opioid | OPRD | DOR | 7-hydroxymitragynine | Gi protein | [112] |
|  | Opioid | OPRD | DOR | speciogynine | Gi protein | [112] |
|  | Opioid | OPRD | DOR | paynantheine | Gi protein | [112] |
|  | Opioid | OPRD | DOR | PN6047 | G protein | [113] |
|  | Opioid | OPRD | DOR | TAN-67 | G protein | [114] |
|  | Opioid | OPRD | DOR | TRV250 | Gi protein | [115] |
|  | Opioid | OPRD | DOR | rubiscolin-5 | G protein | [116] |
|  | Opioid | OPRD | DOR | rubiscolin-6 | G protein | [116] |
|  | Opioid | OPRD | DOR | BMS 986187 | G protein | [117] |
|  | Opioid | OPRD | DOR | UFP-512 | G protein | [118] |
|  | Opioid | OPRD | DOR | BAM 18 | β-arrestin | [119] |
|  | Opioid | OPRD | DOR | BAM 12 | G protein | [119] |
|  | Opioid | OPRK | KOR | mitragynine | Gi protein | [112] |
|  | Opioid | OPRK | KOR | 7-hydroxymitragynine | Gi protein | [112] |
|  | Opioid | OPRK | KOR | speciogynine | Gi protein | [112] |
|  | Opioid | OPRK | KOR | paynantheine | Gi protein | [112] |
|  | Opioid | OPRK | KOR | 6'-GNTI | G protein | [120] |
|  | Opioid | OPRK | KOR | RB-64 | Gi protein | [121] |
|  | Opioid | OPRK | KOR | triazole 1.1 | G protein | [122, 123] |
|  | Opioid | OPRK | KOR | HS666 | G protein | [124] |
|  | Opioid | OPRK | KOR | collybolide | Gi protein | [125] |
|  | Opioid | OPRK | KOR | compound 2.1 | G protein | [123] |
|  | Opioid | OPRK | KOR | noribogaine | G protein | [126] |
|  | Opioid | OPRK | KOR | compound 81 | G protein | [127] |
|  | Opioid | OPRK | KOR | LOR17 | G protein | [128] |
|  | Opioid | OPRK | KOR | nalfurafine | G protein | [129, 130] |
|  | Opioid | OPRK | KOR | WMS-X600 | β-arrestin | [129] |
|  | Opioid | OPRK | KOR | compound 2.3 | G protein | [131] |
|  | Opioid | OPRK | KOR | U62066 | G protein | [132] |
|  | Opioid | OPRK | KOR | ICI-199,441 | G protein | [133] |
|  | Opioid | OPRK | KOR | etorphine | G protein | [133] |
|  | Opioid | OPRK | KOR | levorphanol | G protein | [133] |
|  | Opioid | OPRK | KOR | nalbuphine | β-arrestin | [133] |
|  | Opioid | OPRK | KOR | tifluadom | β-arrestin | [133] |
|  | Opioid | OPRM | MOR | PZM21 | Gi protein | [134] |
|  | Opioid | OPRM | MOR | TRV130 (oliceridine) | Gi protein | [135, 136] |
|  | Opioid | OPRM | MOR | SHR9352 | G protein | [137] |
|  | Opioid | OPRM | MOR | TRV734 | Gi protein | [138, 139] |
|  | Opioid | OPRM | MOR | buprenorphine | G protein | [140] |
|  | Opioid | OPRM | MOR | C5 guano | G protein | [141] |
|  | Opioid | OPRM | MOR | C6 guano | G protein | [141] |
|  | Opioid | OPRM | MOR | SR-17018 | G protein | [142] |
|  | Opioid | OPRM | MOR | SR-14968 | G protein | [142, 143] |
|  | Opioid | OPRM | MOR | fentanyl | β-arrestin | [142] |
|  | Opioid | OPRM | MOR | SR-11501 | β-arrestin | [142] |
|  | Opioid | OPRM | MOR | SR-15098 | G protein | [142] |
|  | Opioid | OPRM | MOR | SR-15099 | G protein | [142] |
|  | Opioid | OPRM | MOR | LPM3480392 | Gi protein | [144] |
|  | Opioid | OPRM | MOR | compound 44 | G protein | [145] |
|  | Opioid | OPRM | MOR | NAP | G protein | [146] |
|  | Opioid | OPRM | MOR | morphine | Gi protein | [147] |
|  | Opioid | OPRM | MOR | mitragynine | Gi protein | [148] |
|  | Opioid | OPRM | MOR | 7-hydroxymitragynine | Gi protein | [148] |
|  | Opioid | OPRM | MOR | speciogynine | Gi protein | [112] |
|  | Opioid | OPRM | MOR | paynantheine | Gi protein | [112] |
|  | Opioid | OPRM | MOR | CYX-6 | G protein | [149] |
|  | Opioid | OPRM | MOR | mitragynine pseudoindoxyl | Gi protein | [150] |
|  | Opioid | OPRM | MOR | levorphanol | Gi protein | [151] |
|  | Opioid | OPRM | MOR | herkinorin | G protein | [152] |
|  | Opioid | OPRM | MOR | kurkinorin | G protein | [153] |
|  | Opioid | OPRM | MOR | endomorphin-1 | G protein | [154] |
|  | Opioid | OPRM | MOR | endomorphin-2 | G protein | [154] |
|  | Opioid | OPRM | MOR | Met-Enkephalin-Rf | G protein | [154] |
|  | Opioid | OPRM | MOR | loperamide | G protein | [154] |
|  | Opioid | OPRM | MOR | a-neoendorphin | G protein | [154] |
|  | Opioid | OPRM | MOR | corydine | Gi protein | [155] |
|  | Opioid | OPRM | MOR | corydaline | Gi protein | [155] |
|  | Opioid | OPRM | MOR | Dmt-c[D-Lys- Phe-Asp] NH2 (C33) | β-arrestin | [156] |
|  | Opioid | OPRM | MOR | Dmt-c[D-Lys-Phe-p-CF3-Phe-Asp]NH2 (F-81) | G protein | [156] |
|  | Opioid | OPRM | MOR | Tyr-c[D-Lys-Phe-Tyr-Gly] (Compound 1) | G protein | [157] |
|  | Opioid | OPRM | MOR | desmetramadol | G protein | [158] |
|  | Opioid | OPRM | MOR | bilorphin | G protein | [159] |
|  | Opioid | OPRM | MOR | carfentanil | β-arrestin | [160] |
|  | Opioid | OPRX | NOP | MCOPPB | G protein | [161] |
|  | Opioid | OPRX | NOP | NNC 63-0532 | G protein | [161] |
|  | Opioid | OPRX | NOP | buprenorphine | Gi protein | [161] |
|  | Opioid | OPRX | NOP | RTI-819 | G protein | [161] |
|  | Opioid | OPRX | NOP | RTI-856 | G protein | [161] |
|  | Opioid | OPRX | NOP | Ro 65-6570 | G protein | [162] |
|  | Opioid | OPRX | NOP | cebranopadol | G protein | [163] |
|  | Opioid | OPRX | NOP | BPR1M97 | G protein | [164] |
|  | Proteinase-activated | PAR2 | PAR2 | SLAAAA-amide | pERK1/2 over Ca2+ mobilization | [165] |
|  | Proteinase-activated | PAR2 | PAR2 | GB88 | Gi protein, G12/13 protein and pERK1/2 over Gq protein | [166] |
|  | Proteinase-activated | PAR2 | PAR2 | cathepsin S | Gs protein | [167] |
|  | Relaxin family | RXFP1 | RXFP1 | ML290 | cGMP and cAMP accumulation over pERK1/2 | [168] |
|  | Relaxin family | RL3R1 | / | H2 Relaxin | activator protein (AP)-1 over pERK1/2 and cAMP inhibition | [169] |
|  | Tachykinin | NK1R | / | SP6-11 | Gq over Gs | [170] |
|  | Urotensin | UR2R | / | [Orn8]UII | G protein | [171] |
|  | Urotensin | UR2R | / | [Orn5]URP | G protein | [171] |
|  | Urotensin | UR2R | / | urantide | G protein | [171] |
|  | Vasopressin/oxytocin | V2R | / | MCF14 | Gs protein | [172] |
|  | Vasopressin/oxytocin | V2R | / | SR121463 | β-arrestin | [172] |
|  | Vasopressin/oxytocin | V2R | / | I8-arachnotocin | G protein | [173] |
|  | Vasopressin/oxytocin | OXYR | OXYR | atosiban | Gi over Gq | [174] |
|  | Chemokine | CCR1 | / | CCL15 (28–92) | Gi protein | [175] |
|  | Chemokine | CCR1 | / | CCL15 (29–92) | Gi protein | [175] |
|  | Chemokine | CCR1 | / | CCL15 (30–92) | Gi protein | [175] |
|  | Chemokine | CCR1 | / | CCL15 (31–92) | Gi protein | [175] |
|  | Chemokine | CCR1 | / | CCL15 (26–92) | β-arrestin | [175] |
|  | Chemokine | CCR5 | / | J113863 | Gi over Goa and Ca2+ mobilization | [176] |
|  | Chemokine | CCR5 | / | 5P12-RANTES | Gi over Gq | [177] |
|  | Chemokine | CCR5 | / | 5P14-RANTES | Gi over Gq | [177] |
|  | Chemokine | CCR5 | / | 6P4-RANTES | Gq over Gi | [177] |
|  | Chemokine | CCR5 | / | PSC-RANTES | Gq over Gi | [177] |
|  | Chemokine | CXCR2 | / | CXCL1-3 | G protein | [178] |
|  | Chemokine | CXCR2 | / | CXCL5-7 | G protein | [178] |
|  | Chemokine | CXCR3 | / | CXCL9 | G protein | [179] |
|  | Chemokine | CXCR3 | / | CXCL11 | β-arrestin | [180] |
|  | Chemokine | CXCR3 | / | VUF10661 | β-arrestin | [180] |
|  | Chemokine | CXCR3 | / | VUF11418 | G protein | [180] |
|  | Chemokine | CXCR3 | / | FAUC1036 | β-arrestin | [181] |
|  | Chemokine | CXCR3 | / | FAUC1104 | G protein | [181] |
|  | Chemokine | CXCR4 | / | ATI-2341 | Gi protein | [182] |
|  | Free fatty acid | FFAR4 | FFA4 | eicosapentaenoic acid | Gs over Gi or Gq | [183] |
|  | Free fatty acid | FFAR4 | FFA4 | TUG891 | Gq over Gi | [183] |
|  | Free fatty acid | FFAR4 | FFA4 | compound 25 | β-arrestin | [184] |
|  | Free fatty acid | FFAR4 | FFA4 | compound 50 | β-arrestin | [184] |
|  | Lysophospholipid | S1PR1 | S1PR1 | HDL-bound S1P | MAPK and β-arrestin recruitment over cAMP inhibition | [185] |
|  | Lysophospholipid | S1PR1 | S1PR1 | FTY720-P | β-arrestin | [186] |
|  | Lysophospholipid | S1PR1 | S1PR1 | BMS-986104 | G protein | [187] |
|  | Lysophospholipid | S1PR3 | S1PR3 | ALESIA | G12 protein | [188] |
|  | Cannabinoid | CNR1 | CB1 | CP 55,940 | β-arrestin | [189] |
|  | Cannabinoid | CNR1 | CB1 | Δ9-tetrahydrocannabinol | β-arrestin | [189, 190] |
|  | Cannabinoid | CNR1 | CB1 | 2-arachidonoylglycerol | G protein | [189] |
|  | Cannabinoid | CNR1 | CB1 | anandamide | G protein | [189] |
|  | Cannabinoid | CNR1 | CB1 | ICAM-b | β-arrestin | [191] |
|  | Cannabinoid | CNR1 | CB1 | compound 7d | β-arrestin | [192] |
|  | Cannabinoid | CNR1 | CB1 | compound 8d | β-arrestin | [192] |
|  | Cannabinoid | CNR1 | CB1 | EG-018 | G protein | [193] |
|  | Cannabinoid | CNR1 | CB1 | CB-02 | Gi protein | [194] |
|  | Cannabinoid | CNR1 | CB1 | CB-05 | Gi protein | [194] |
|  | Cannabinoid | CNR1 | CB1 | (+)-(R,S)-14 | Gi protein | [195] |
|  | Cannabinoid | CNR2 | CB2 | UR144 | β-arrestin | [196] |
|  | Cannabinoid | CNR2 | CB2 | STS135 | β-arrestin | [196] |
|  | Cannabinoid | CNR2 | CB2 | AM-1248 | β-arrestin | [196] |
|  | Cannabinoid | CNR2 | CB2 | 4-O-methylhonokiol | β-arrestin | [196] |
|  | Cannabinoid | CNR2 | CB2 | THC | G protein | [196] |
|  | Cannabinoid | CNR2 | CB2 | JWH133 | G protein | [196] |
|  | Cannabinoid | CNR2 | CB2 | WIN-55212 | G protein | [196] |
|  | Cannabinoid | CNR2 | CB2 | KM233 | G protein | [196] |
|  | Cannabinoid | CNR2 | CB2 | HU308 | G protein | [196] |
|  | Cannabinoid | CNR2 | CB2 | AM1241 | G protein | [196] |
|  | Cannabinoid | CNR2 | CB2 | JWH015 | G protein | [196] |
|  | Cannabinoid | CNR2 | CB2 | MAM2201 | G protein | [196] |
|  | Cannabinoid | CNR2 | CB2 | AM2232 | G protein | [196] |
|  | Cannabinoid | CNR2 | CB2 | SRE601 | G protein | [196] |
|  | Cannabinoid | CNR2 | CB2 | 2-arachidonoyl glycerol | G protein | [196] |
|  | Cannabinoid | CNR2 | CB2 | Meth-anandamide | G protein | [196] |
|  | Cannabinoid | CNR2 | CB2 | 14 | internalisation over cAMP and pERK1/2 | [197] |
|  | Cannabinoid | CNR2 | CB2 | 15 | internalisation over cAMP and pERK1/2 | [197] |
|  | Cannabinoid | CNR2 | CB2 | 7 | pERK1/2 over cAMP and internalisation | [197] |
|  | Prostanoid | PE2R2 | / | 18a | G protein | [198] |
|  | Prostanoid | PE2R4 | / | PGE2 | Gs over Gi and β-arrestin | [199] |
|  | Prostanoid | PE2R4 | / | PGE1 alcohol | Gi1 and β-arrestin over Gs | [199] |
|  | Adenosine | AA1R | A1R | VCP746 | Gi protein over pERK1/2 | [200] |
|  | Adenosine | AA1R | A1R | 6 | cAMP inhibition over Ca2+ mobilization | [201] |
|  | Adenosine | AA1R | A1R | 16 | Ca2+ mobilization over cAMP inhibition | [201] |
|  | Adenosine | AA1R | A1R | capadenoson | cAMP inhibition over pERK1/2 and Ca2+ mobilization | [202] |
|  | Adenosine | AA1R | A1R | 8h | cAMP accumulation over pERK1/2 | [203] |
|  | Adenosine | AA1R | A1R | LUF5589 | G protein | [204] |
|  | Adenosine | AA1R | A1R | BnOCPA | Gob protein | [205] |
|  | Bile acid | GPBAR | GPBAR | R399 | β-arrestin | [206] |
|  | Bile acid | GPBAR | GPBAR | INT-777 | Gs protein | [206] |
|  | Hydroxycarboxylic acid | HCAR2 | HCAR2 | compound 9n | Gi protein | [207] |
|  | Hydroxycarboxylic acid | HCAR2 | HCAR2 | MK-0354 | G protein | [208, 209] |
|  | Hydroxycarboxylic acid | HCAR2 | HCAR2 | MK6892 | G protein | [210] |
|  | Hydroxycarboxylic acid | HCAR2 | HCAR2 | monomethyl fumarate | G protein | [210] |
|  | Class A Orphans | GPR84 | / | DL-175 | G protein | [211] |
|  | Class A Orphans | GPR84 | / | OX04528 | G protein | [212] |
|  | Class A Orphans | GPR84 | / | OX04529 | G protein | [212] |
|  | Class A Orphans | MRGX2 | / | AG-30/5C | G protein | [213] |
|  | Class A Orphans | MRGX2 | / | icatibant | G protein | [213] |

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