*Supplementary Files:*

# Probing Multi-Target Action of Phlorotannins as New Monoamine Oxidase Inhibitors and Dopaminergic Receptor Modulators with Potential for the Treatment of Neuronal Disorders

**Su Hui Seong [1], Pradeep Paudel [1], Jeong-Wook Choi [1], Dong Hyun Ahn [2], Taek-Jeong Nam [1], Hyun Ah Jung [3,*], and Jae Sue Choi [1,*]**

[1] Department of Food and Life Science, Pukyong National University, Busan 48513, Korea; seongsuhui@naver.com (S.H.S.), phr.paudel@gmail.com (P.P.), wook8309@naver.com (J.W.C.), namtj@pknu.ac.kr (T.J.N.)

[2] Department of Food Science and Technology, Pukyong National University, Busan 48513, Korea; dhahn@pknu.ac.kr (D.H.A.)

[3] Department of Food Science and Human Nutrition, Chonbuk National University, Jeonju 54896, Korea

* Correspondence: jungha@jbnu.ac.kr (H.A.J.); choijs@pknu.ac.kr (J.S.C.); Tel.: +82-63-270-4882 (H.A.J.); +82-51-629-5845 (J.S.C.)

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**Table S1.** Binding sites and docking score of compounds in human $D_1R$ built by homology modeling.

| Compounds | B-energy (kcal/mol) | No. of H-bonds | H-bond interaction residues | Other interacting residues |
|---|---|---|---|---|
| Dopamine [a] (Agonist) | –5.39 | 5 | Asp103 (two salt bridges), Ser202, Ser199, Ser198 (O-H bond) | Phe288 (π-cation), Phe289 (π-π T-shaped), Ile104 (π-alkyl) |
| SCH 23390 [a] (Antagonist) | –6.86 | 2 | Asp103, Ser107 (O-H bond), | Asn292 (two C-H bonds), Ile104, Leu190 (π-sigma), Phe288 (π-π T-shaped), Phe289, Val100 (π-alkyl) |
| Phloroglucinol | –3.52 | 2 | Ser107, Ser199 (O-H bond) | Ile104 (π-sigma), Ser202 (π-OH bond) |
| Dieckol | –7.29 | 2 | Tyr194, Asp103 (O-H bond) | Ile154, Leu190, Ile201 (π-sigma), Ser198 (π-Lone pair), Phe288 (π-π T-shaped), Ile104, Ile154, Pro158, Ile201 (π-Alkyl) |
| PFF-A | –4.11 | 5 | Lys81, Tyr194, Ala195, Asp103, Asp314 (O-H bond) | Lys81 (π-cation), Ser188 (π-OH bond), Val317 (π-sigma), Phe288 (π-π T-shaped), Ile104, Leu190, Cys186 (π-alkyl) |

[a] Dopamine and SCH 23390 were used as positive ligands.

**Table S2.** Binding sites and docking score of compounds in human $D_3R$.

| Compounds | B-energy (kcal/mol) | No. of H-bonds | H-bond interaction residues | Other interacting residues |
|---|---|---|---|---|
| Dopamine [a] (Agonist) | –5.84 | 5 | Asp110 (two salt bridges), Val111, Thr115, Ser196 (O-H bond) | Val111 and Cys114 (alkyl), Phe346 (π-alkyl) |
| Eticlopride [a] (Antagonist) | –8.50 [b] | 2 | Asp110 (salt bridge, O-H bond) | Val111, Cys114, Val189 (alkyl), Phe346, His349, Ile183 (π-alkyl), Phe345 (π-π T-shaped) |
| Phloroglucinol | –3.98 | 2 | Cys181 and Asp110 (O-H bond) | Ile183 and Val107 (π-alkyl) |
| Dieckol | –9.78 | 4 | Ser192, Cys181, Val86, Val189 (O-H bond) | Asp110 (π anion), His349 (π-lone pair), Phe345 (π-π stacked), Tyr365 (π-π T-shaped), Leu89, Val180, Val111, Cys114, Val189 (π-alkyl), Val111, Ser182 (C-H bond) |
| PFF-A | –9.17 | 5 | Ile183, Tyr373, Tyr365, Asp110, Val189 (O-H bond) | Asp110 (π-anion), Cys114 (π-sulfur), Phe346 (π-π stacked), Val86, Ile183, Val189 (π-alkyl), Ser192 (C-O bond) |

[a] Dopamine and eticlopride were used as positive ligands. [b] RMSD value: 0.48 Å

**Table S3.** Binding sites and docking score of compounds in human $D_4R$.

| Compounds | B-energy (kcal/mol) | No. of H-bonds | H-bond interaction residues | Other interacting residues |
|---|---|---|---|---|
| Dopamine [a] (Agonist) | –5.68 | 3 | Asp115 (salt bridge), Ser196 (O-H bond) | Cys119 (π-alkyl), Val116 (π-sigma), Phe410 (π-π T shaped) |
| Clozapine [a] (Antagonist) | –9.49 | 1 | Asp115 (salt bridge) | Arg186, Leu187, Val193, Val116, Cys119 (alkyl), Phe411, His414, Val193, Val116 (π-alkyl), Phe410, His414 (π-π T-shaped), Leu187 (π-sigma), Cys185 (C-O bond) |
| Phloroglucinol | –4.21 | 4 | Ser94, Leu90, Val87, Tyr438 (O-H bond) | Leu90 (amide-π stacked), Leu111 (π-alkyl), Phe91 (van der Waals) |
| Dieckol | –9.91 | 7 | Cys185, His414, Ser197, Leu187, Asp115, Tyr438 (O-H bond) | His414 (π-cation), Glu95, Asp115 (π-anion), Leu188, Val193, Thr434 (π-sigma), Met112 (Pi-sulfur), His414 (π-π T-shaped), Cys185, Leu187, Val193, Arg186 (π-alkyl) |
| PFF-A | –10.4 | 8 | Ser94, Arg186, Ser197, Leu187, Asp115, Cys185, Tyr438 (O-H bond) | His414 (π-cation), Cys185 (π-lone pair), His414 (π-π T-shaped), Arg186, Leu187, Met112, Cys185, Val193, Leu111 (π-alkyl) |

[a] Dopamine and clozapine were used as positive ligands.

**Table S4.**

| Assay | Receptors (Gene name) | Source | Stimulus | Incubation | Measured Component | Detection Method |
|---|---|---|---|---|---|---|
| Agonist effect | $D_1$ (*h*) (DRD1) | Human recombinant (CHO cells) | None (control: 10 μM dopamine) | 30 min RT | cAMP | HTRF |
| Antagonist effect | | | Dopamine (300 nM) | 30 min RT | cAMP | HTRF |
| Agonist effect | $D_3$ (*h*) (DRD3) | Human recombinant (CHO cells) | None (control: 300 nM dopamine) | 30 min 37 °C | cAMP | HTRF |
| Antagonist effect | | | Dopamine (10 nM) | 30 min 37 °C | cAMP | HTRF |
| Agonist effect | $D_4$ (*h*) (DRD4) | Human recombinant (CHO cells) | None (control: 10 μM dopamine) | 10 min 37 °C | cAMP | HTRF |
| Antagonist effect | | | Dopamine (100 nM) | 10 min 37 °C | cAMP | HTRF |
| Agonist effect | $M_5$ (*h*) (CHRM5) | Human recombinant (RBL cells) | None (control: 0.624 μM ACh) | RT | Intracellular $[Ca^{2+}]$ | Fluorimetry |
| Antagonist effect | | | ACh (10 nM) | RT | Intracellular $[Ca^{2+}]$ | Fluorimetry |
| Agonist effect | $NK_1$ (*h*) (TACR1) | Human endogenous (U373MG cells) | None (control: 30 nM [$Sar^9$, $Met(O_2)^{11}$]-SP) | RT | Intracellular $[Ca^{2+}]$ | Fluorimetry |
| Antagonist effect | | | [$Sar^9$, $Met(O_2)^{11}$]-SP (1 nM) | RT | Intracellular $[Ca^{2+}]$ | Fluorimetry |
| Agonist effect | $V_{1a}$ (*h*) (AVPR1A) | Human recombinant (CHO cells) | None (control: 1 μM AVP) | RT | Intracellular $[Ca^{2+}]$ | Fluorimetry |
| Antagonist | | | AVP (10 nM) | RT | Intracellular | Fluorimetry |

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|---|---|---|---|---|---|---|
| effect | | | | | $[Ca^{2+}]$ | |
| Agonist effect | 5-$HT_{1A}$ (*h*) (HTR1A) | Human recombinant (BA/F3 cells) | None (control: 2.5 μM serotonin) | RT | Intracellular $[Ca^{2+}]$ | Fluorimetry |
| Antagonist effect | | | Serotonin (30 nM) | RT | Intracellular $[Ca^{2+}]$ | Fluorimetry |

HTRF: Homogeneous time resolved fluorescence