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Designing of promising Tromethamine-Diflunisal-Pyrrole combinations based on COX binding, drug-properties and safety

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Supplementary Data

Suppl. Table 1 — Surrounding COX-1 residue that had shown interactions with the structures in the docked complexes

No.	Hydrogen bond -forming residues of COX-1	Residues of COX-1 showing hydrophobic interaction
DF	Gly225,Asn375, Val228,Asn537	Gly225,Asn375,Val228,Asn537,Gly536,His226,Gly227,Pro538,Asp229,Ile337
DF2	Arg120	Ser530,Ile523,Val349,Leu531,Ala527,Leu352,Tyr355,Ser353, Leu359,Val116
DF5	Asn375	Asn375,gly225,Gly227,Gly536,Val228, Arg374,Pro538,Asp229,Ile337,Asn537,Tyr544,Ile539,Leu334
DF6	Asn375,Val228	Asn375,Val228,Ile337,Arg333,Leu334,Tyr544,Ile539,Gly536, Asn537,Gly225,His226,Gly227,G374,Pro538
DF7	Gln351,Ser353, His90,Pro514	Gln351,Ser353,His90,Pro514,Gln350,Gly354,Gln192,Asn515, Gln350,Gly354
DF9	Asp584,Arg581, Gln192	Asp584,Arg581,Gln192,Gly193,Pro191,Pro514,Asn515,Gln350,Gly354
DF10	Asn375	Asn375,Leu334,Tyr544,Ile539,Asp229,Pro538,Ile337,Gly227, Gly536,Val228,537,Arg374,Gly225
DF11	Val228,Asn375	Val228,Asn375,Arg333,Gly227,Gly225,Pro538,His226,Arg374, Gly536,Ile337,Tyr544,Ile539,Asn537,Leu334
DF12	Asp135,Gly45, Arg469	Asp135,Gly45,Arg469,Cys47,Ser154, Tyr39,Cys36,Pro156,Pro153,Gln461,Ile46
DF14	Tyr335,Gln350	Gln350,Gln358,Gly354,Gln351,Ser579,Glu347,Phe580,Arg581
DF15	Gly354,His90	Tyr355,Phe356,Thr94,Gln192,Asn515,His95,Pro514,Ser516
DF16	Gly536,Val228, Asn375	Gly536,Val228,Asn375,Gly227,Arg374,Asn537,Leu334,His226,Gly225,Pro538Ile539,Tyr544,Asp229,Arg333
DF17	Arg120	Tyr64,Arg83,Arg469,Gln44,Gly471,Phe470,Leu123,Val119
DF19	Arg120	Val116, Leu93, Leu112,Trp100,Tyr355,Leu359,Arg120
DF20	Asp135,Lys157	Asp135,Lys157,Tyr39,Pro153,Cys36,Cys47,Gln461,Pro156, Arg459,Ser154
DF21	Gln351,Gln350, Tyr355	Tyr355,Gln350,Phe356,Pro514,Ser516,His90,Thr94,Ser353, Asn515,Gln192,Gly354
DF22	Gln350,Gln351, Phe356,Gly354, Asn515	Gln350,Phe356,Gly354,Asn515,Asn104,Gln358,Tyr355,Arg97, Gln192,Thr94
DF24	Asp584,Arg581, Gln192	Asp584,Arg581,Gln192,Gly193,Pro191,Pro514,Asn515,Gln350,Gly354
DF27	Tyr355,Gln350	Tyr355,Gln350,Asn515,Thr94,Pro191,Gln192,Ser353,Gly354, Pro514,Ser516,Gln351,Arg581,Phe356
DF29	Glu524	Glu524,Pro86,Arg120,Arg83,Thr89,Leu112,Trp100,Leu93, Val116,Leu359,Tyr355

Suppl. Table 2 — Surrounding COX-2 residues showing interactions with the structures in the docked complexes

No	Hydrogen bond -forming residues of COX-2	Residues of COX-2 showing hydrophobic interaction
DF	Asn43,Lys468 Gln42	Asn43,Lys468,Gln42,Arg469,His39,Cys41,Arg44,Gln461,Gly45,Leu152, Pro153
DF1	Tyr385, Met522	Tyr385,Met522,Leu384,Gly526,Trp387,Ser530,Leu352,Val349, Tyr355,Ser353,Ala527,Leu531
DF2	Tyr385	Tyr385,Phe381,Gly526,Trp387,Ser530,Tyr348,Val523,Leu531,Leu352, Ala527,Val349,Tyr355,Ser353
DF3	Asn43,Glu465 Cys41	Asn43,Glu465,Cys41,Arg469,Lys468, Leu152,Gly45,Arg44,Pro153,Tyr130,His39,Cys47
DF5	Lys459, Asp157	Lys459,Asp157,Pro153,Cys36,His39,Pro156,Gly135,Asp133,Tyr136, Pro154
DF7	Pro154,Cys47, His39	Pro154,Cys47,His39,Asn34,Cys36,Gly135,Pro156,Val46,Pro153
DF12	Tyr115	Arg120,Val116,Leu93,Val89,Ile112,Trp100
DF14	Pro154,Ser49	Pro154,Ser49,Pro156,Asn34,Gly135,Cys36,His39,Met48,Cys47,Pro153, Gln461
DF19	Tyr385	Trp387,Ser530,Phe381,Phe205,Tyr348,Val344,Val349,Ala527,Leu531, Tyr355,Met522,Gly526,Phe518,Leu352,Val523,Tyr385
DF24	His39,Cys47	His39,Cys47,Cys36,Gln461,Pro156,Pro153,Val155,Asp157,Pro154,Gly135,Tyr136
DF25	His39,Gln461, Cys47,Cys41	His39,Gln461,Cys47,Cys41,Asp133,Pro154,Asn134,Pro156,Gly135, Pro153,Val46,Leu152,Cys36,Arg44,Gln42,Gly45
DF26	His39,Arg44, Cys47,Gly135, Asn34	His39,Arg44,Cys47,Gly135,Asn34,Leu152,Gln461,Cys41,Glu465,Gly45, Pro156,Pro153,Cys36,Tyr130
DF27	Glu465,Cys41	Glu465,Cys41,Tyr136,Pro156,Gly135,Pro153,Cys47,Pro154,Cys36,His39, Gln461,Leu152,Lys468,Gly45

Suppl. Table 3 — Oral activity of the studied structural combinations

No.	Mass (g/mol)	Number of Hydrogen Acceptors	Log P	Molar Refractivity	Number of Hydrogen donors
Diflunisal	250.20	5	3.04	60.78	2
Difluinsal ion	249.19	5	1.7	58.83	1
DF3	353.32	7	1.17	84.76	5
DF5/DF10	315.27	5	4.03	80.56	3
DF6/DF11	315.27	5	4.03	80.56	3
DF7/DF12	315.27	5	4.03	80.56	3
DF9/DF14	315.27	5	4.03	80.56	3
DF15	314.26	5	2.70	78.62	2
DF16	314.26	5	2.70	78.62	2
DF17	314.26	5	2.70	78.62	2
DF19	314.26	5	2.70	78.62	2
DF20	418.39	7	2.17	104.54	6
DF21	418.39	7	2.17	104.54	6
DF22	418.39	7	2.17	104.54	6
DF24	418.39	7	2.17	104.54	6
DF25	418.39	8	2.87	104.37	5
DF26	418.39	8	2.87	104.37	5
DF27	418.39	8	2.87	104.37	5
DF29	418.39	8	2.87	104.37	5

Suppl. Table 4 — Median lethal dose of studied structurally modified Diflunisal structures

Compound No.	Rat oral LD_{50}* (mg/kg)	Toxicity class	Prediction accuracy
Diflunisal	392	4	100
Diflunisal ion	392	4	100
DF3	1900	4	68.07
DF4	392	4	68.07
DF5/ DF10	392	4	68.07
DF6/ DF11	392	4	67.38
DF7/ DF12	392	4	68.07
DF8/ DF13	392	4	67.38
DF9/ DF14	392	4	67.38
DF15	392	4	68.07
DF16	392	4	67.38
DF17	392	4	68.07
DF18	392	4	67.38
DF19	392	4	67.38
DF20	200	3	67.38
DF21	200	3	67.38
DF22	200	3	67.38
DF23	200	3	54.26
DF24	200	3	67.38
DF25	495	4	67.38
DF26	495	4	54.26
DF27	495	4	67.38
DF28	1000	4	54.26
DF29	495	4	67.38