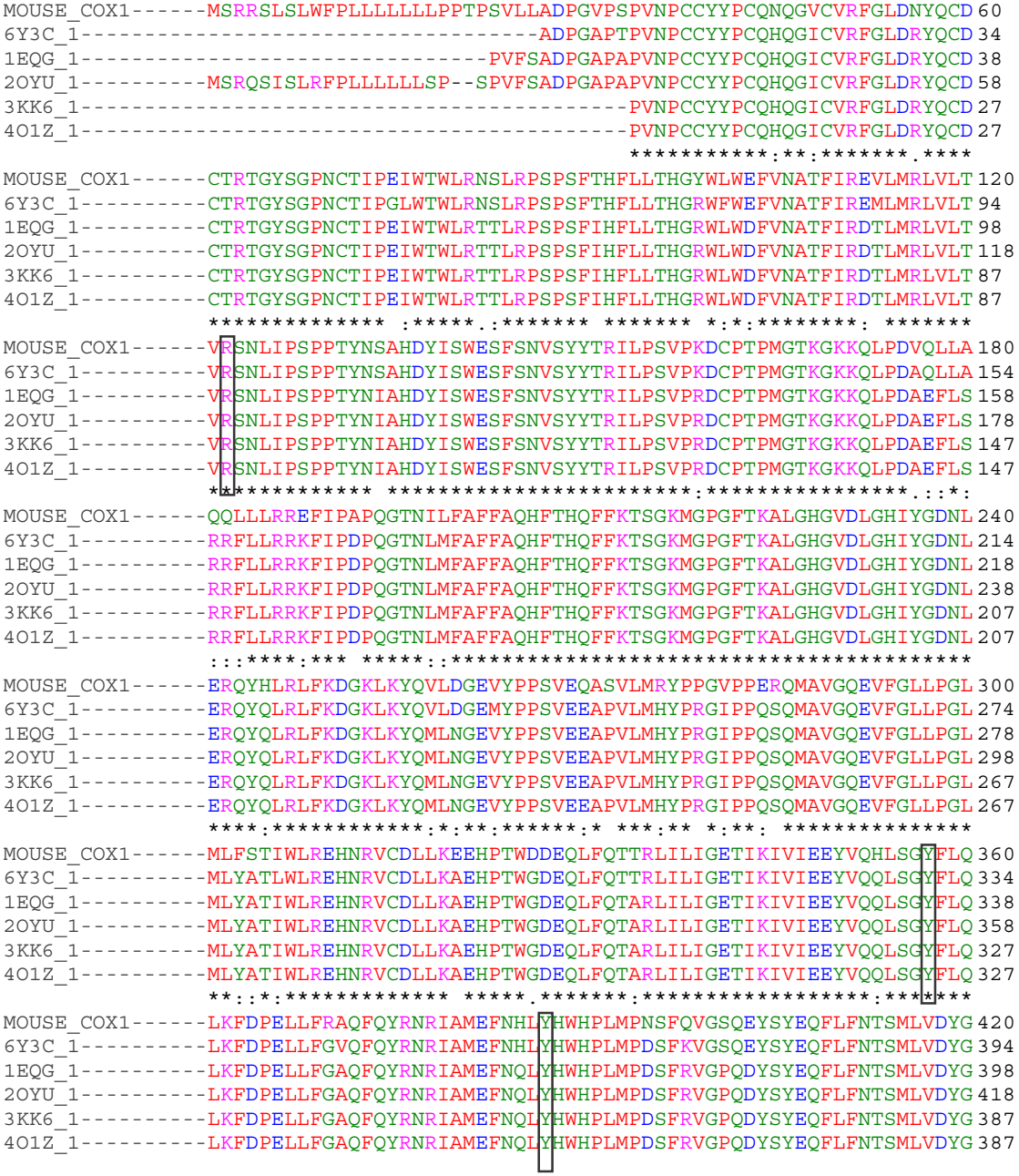
Supporting Information

For

A computational method for the binding mode prediction of COX-1 and COX-2 inhibitors: analyzing the union of coxibs, oxicams, propionic and acetic acids.

Estefany Bello -Vargas [1], Mario Alberto Leyva-Peralta [2], Zeferino Gómez-Sandoval [3], Mario Ordóñez[1], Rodrigo Said Razo-Hernández[4].

Secuencial analysis



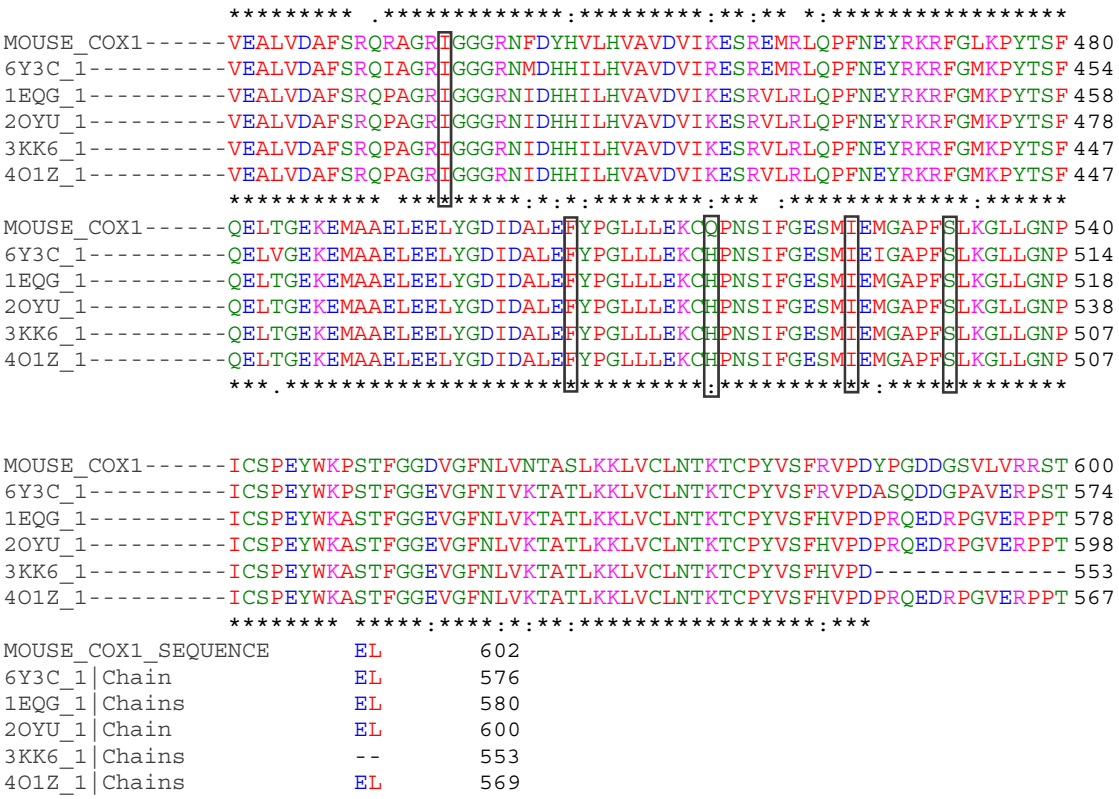
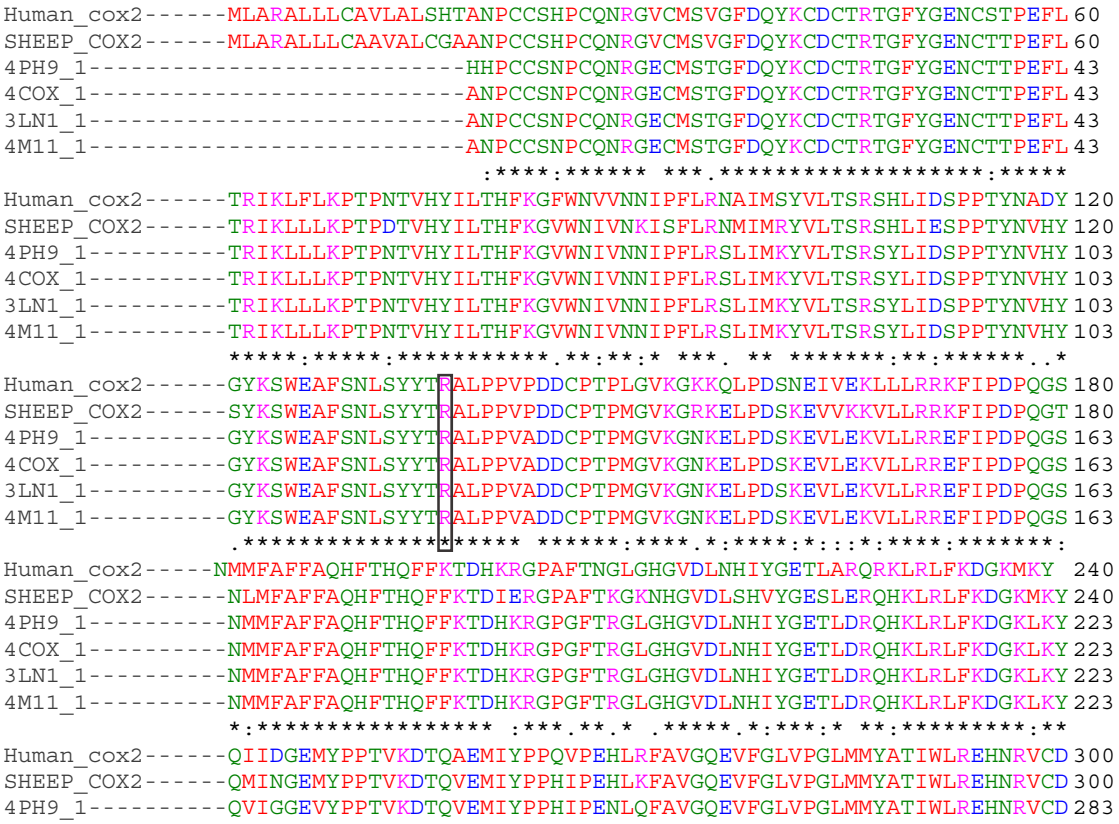


Figure S1. Comparative sequence analysis for COX-1. The aminoacid residues inside box line black



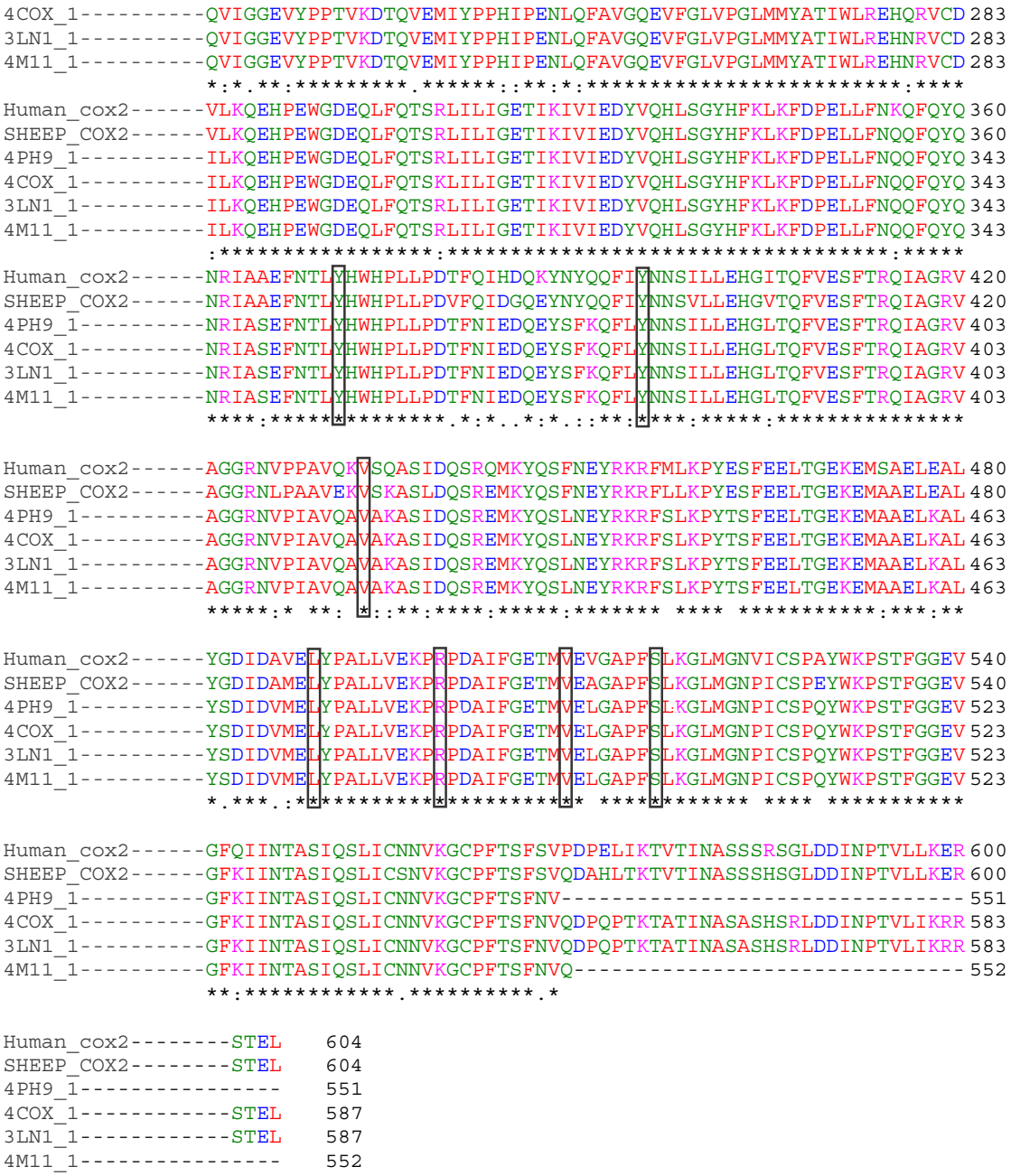


Figure S2. Comparative sequence analysis for COX-2. The aminoacid residues inside box line black

Results docking molecular

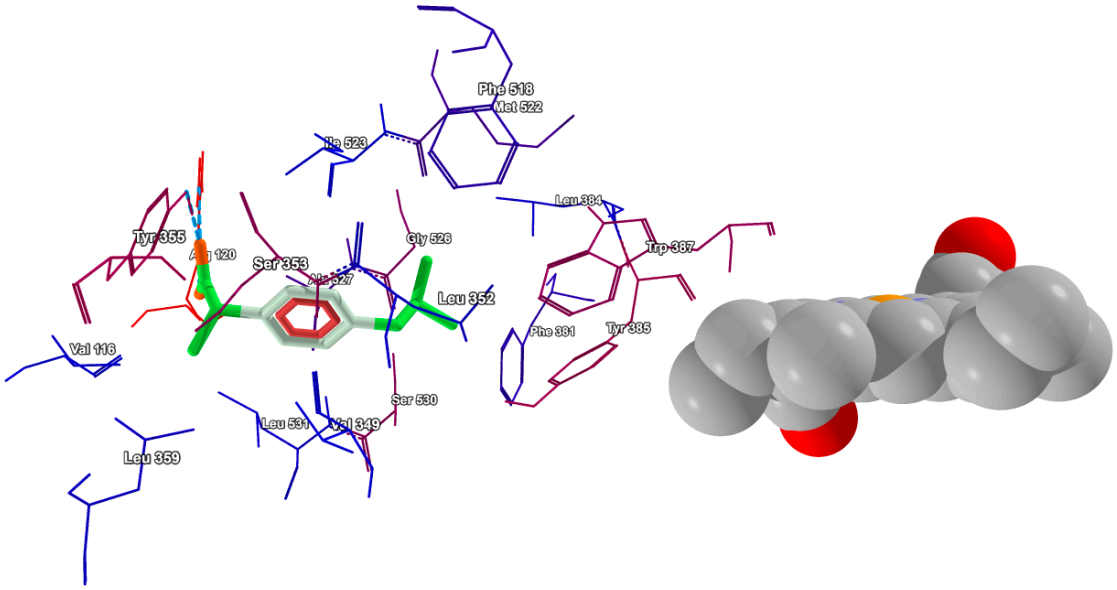


Figure S3. Binding mode of Ibuprofen in 1EQG crystal (COX-1).

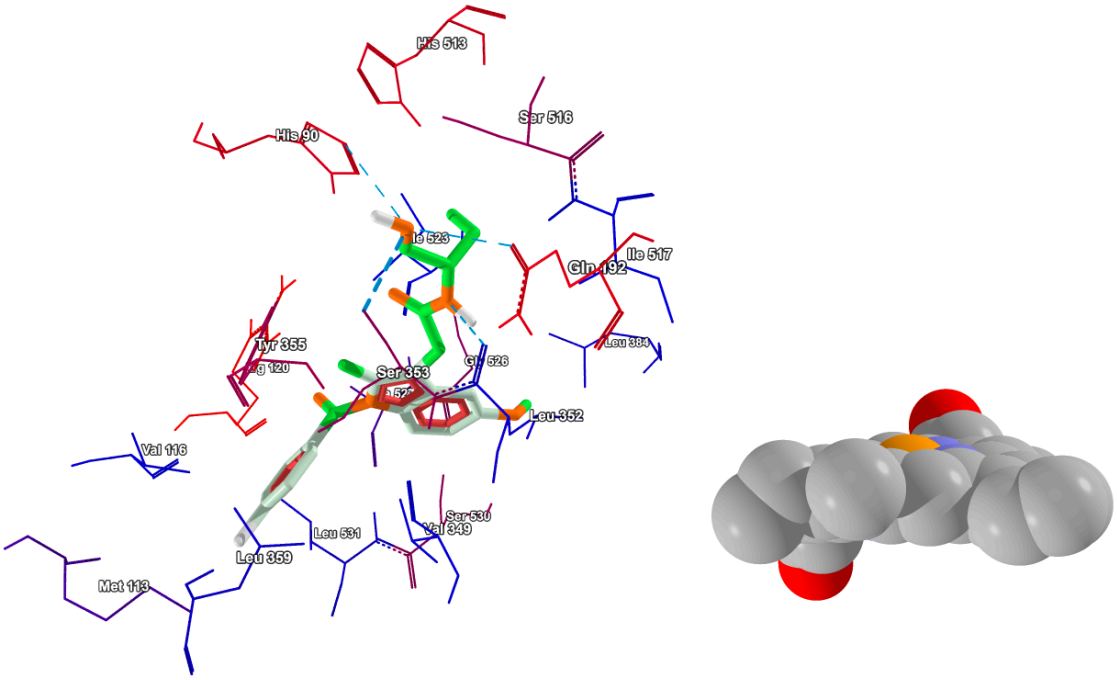


Figure S4. Binding mode of Ibuprofen in 2OYU crystal (COX-1).

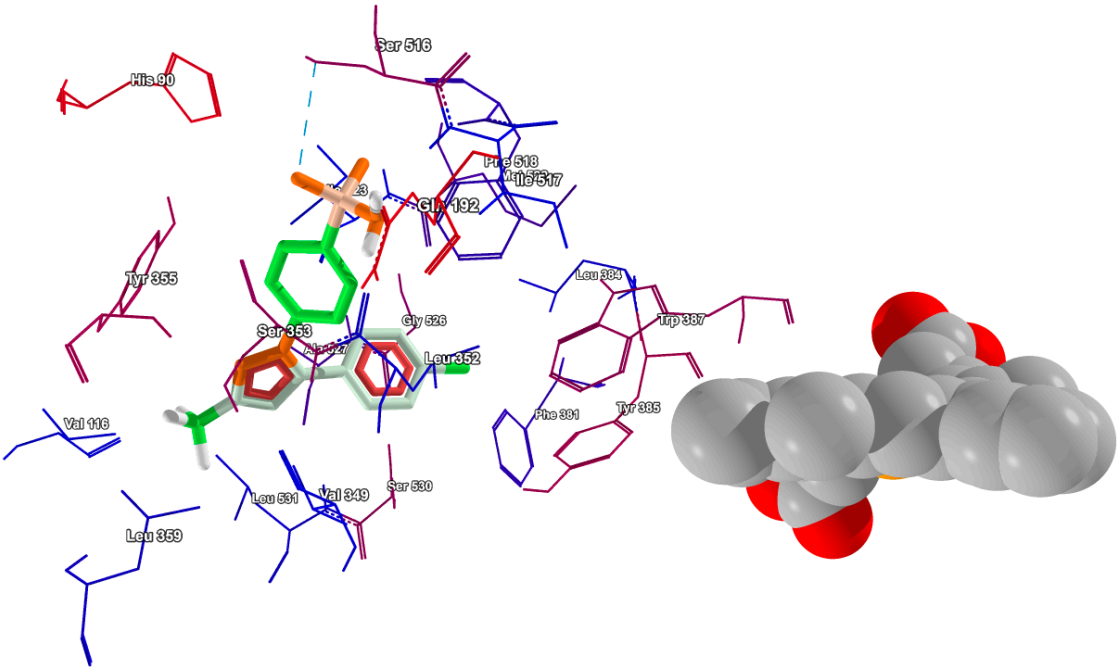


Figure S5. Binding mode of Ibuprofen in 3KK6 crystal (COX-1).

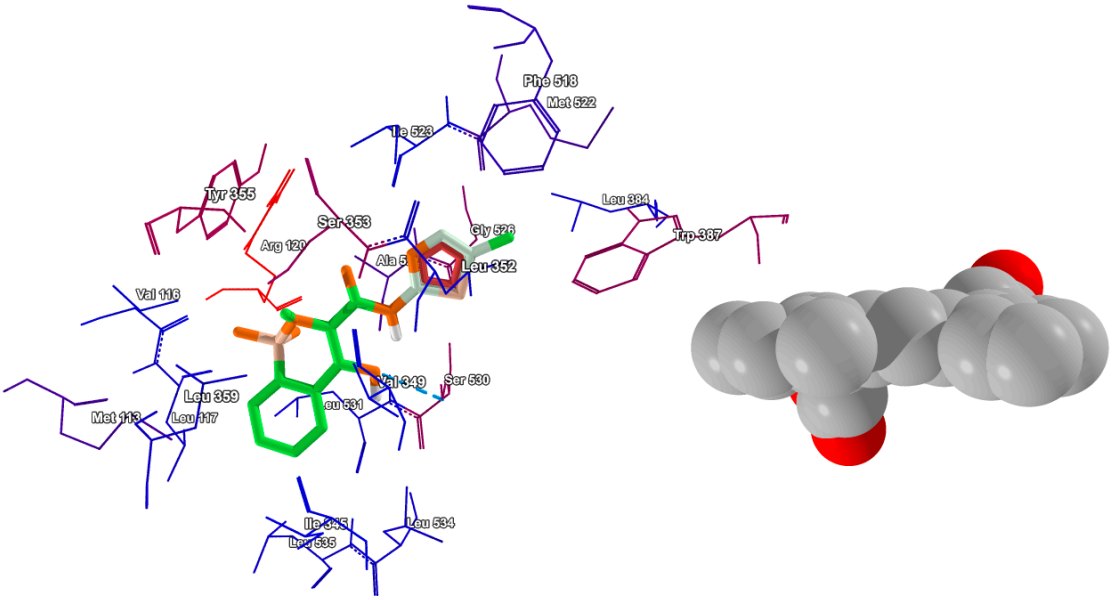


Figure S6. Binding mode of Ibuprofen in 4O1Z crystal (COX-1).

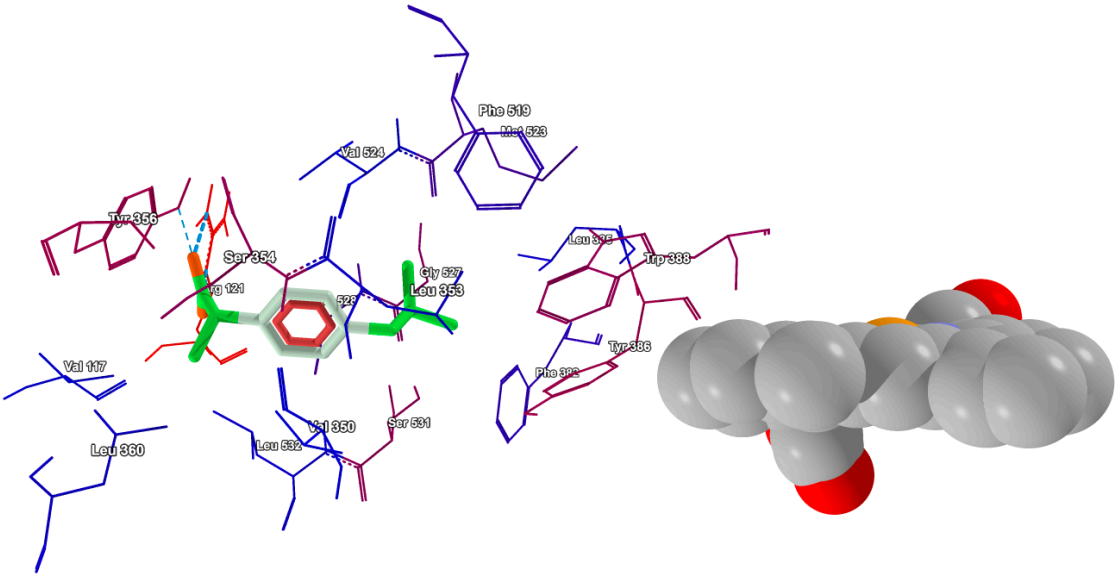


Figure S7. Binding mode of Ibuprofen in 4PH9 crystal (COX-2).

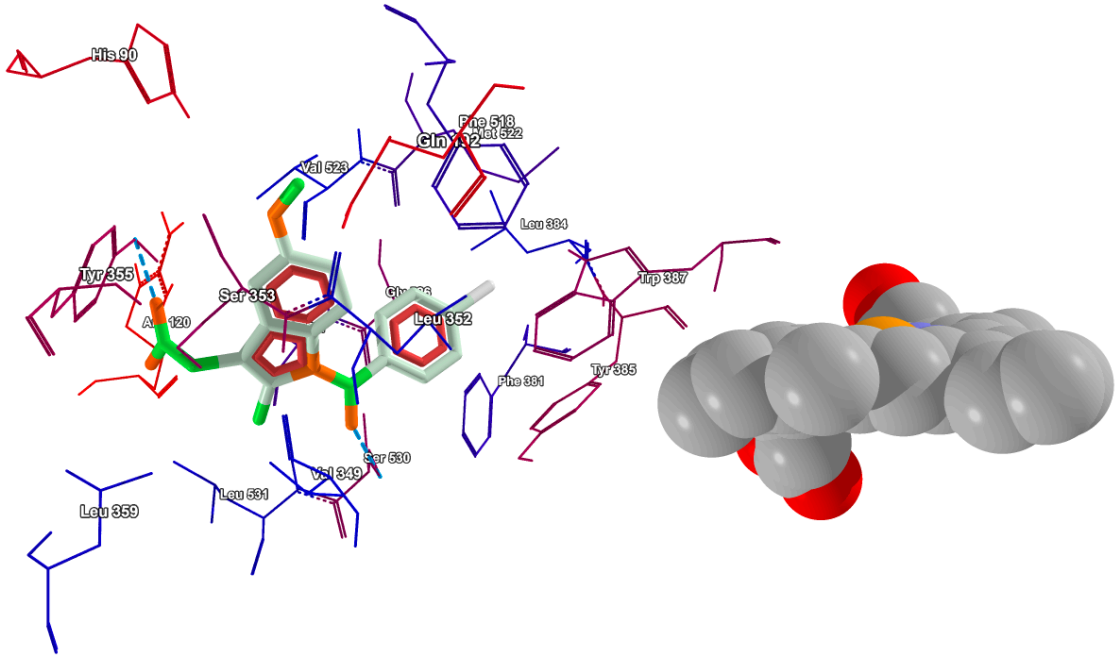


Figure S8. Binding mode of Indomethacin in 4COXcrystal (COX-2).

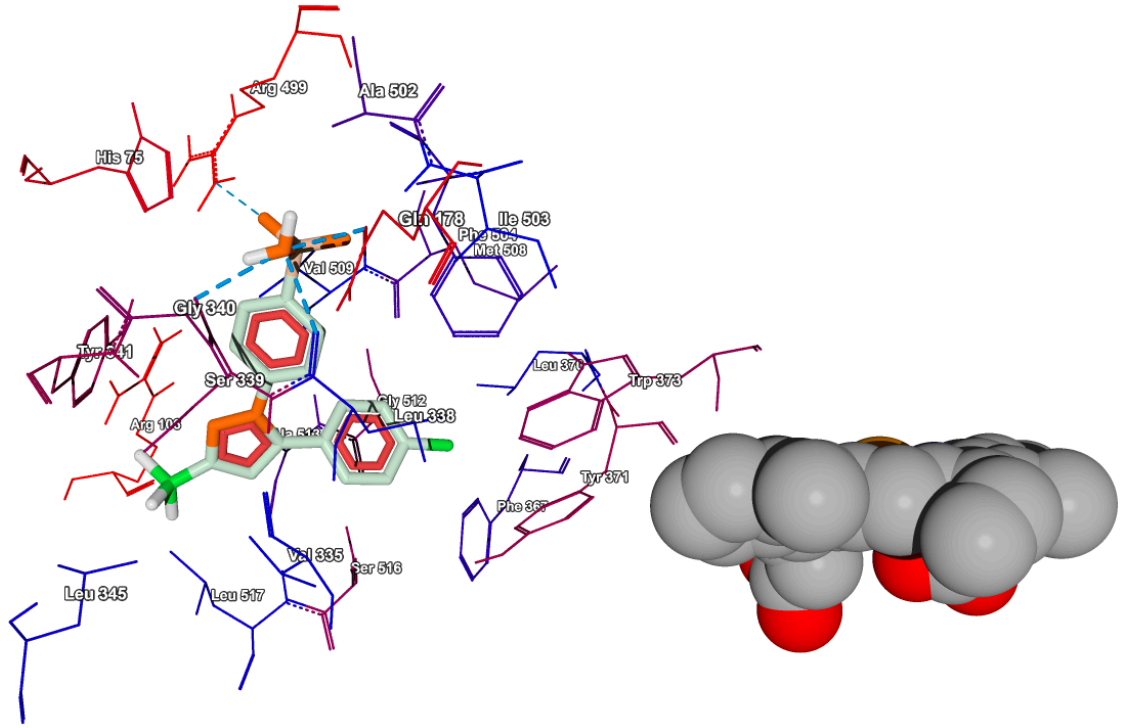


Figure S9. Binding mode of Celecoxib in 3LN1 crystal (COX-2).

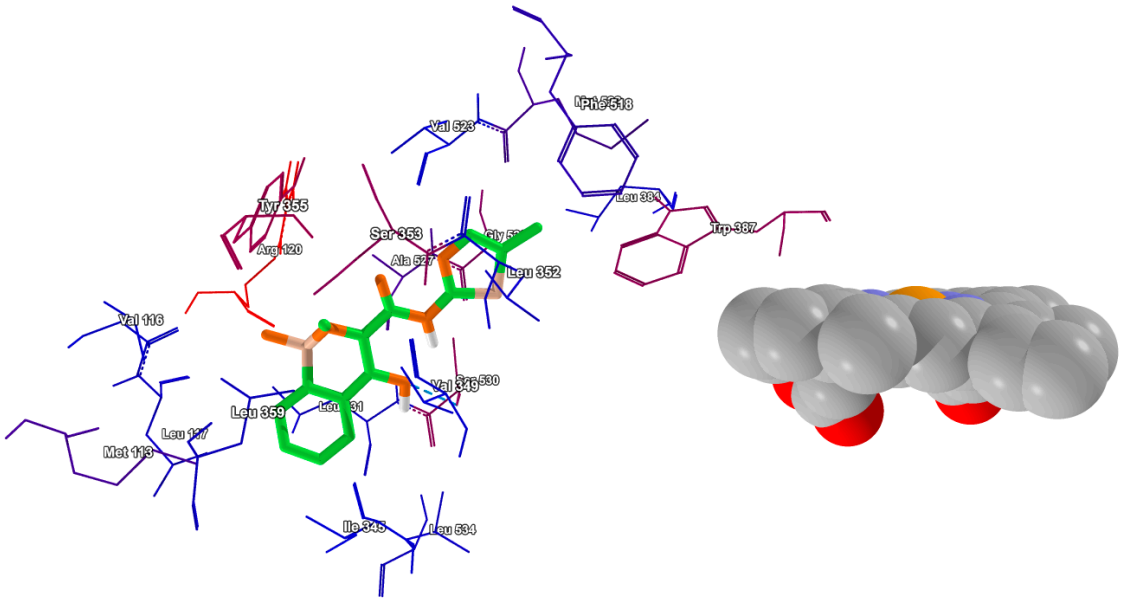


Figure S10. Binding mode of Meloxicam in 4M11 crystal (COX-2).

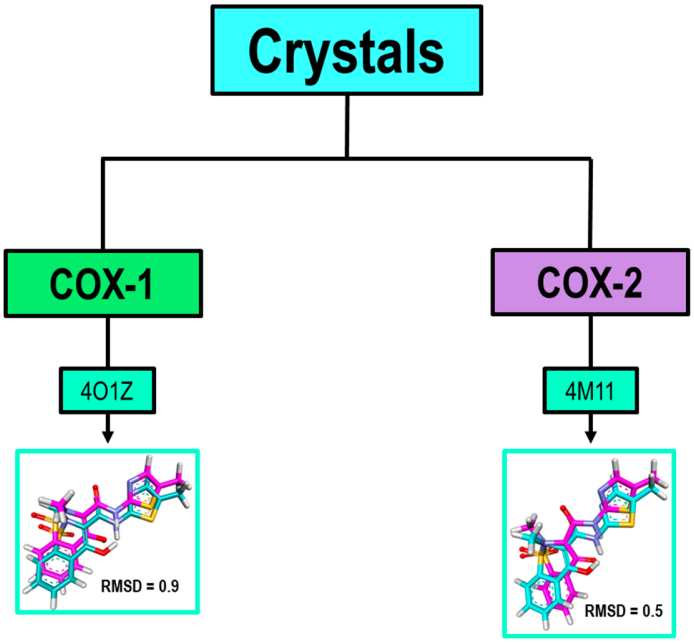
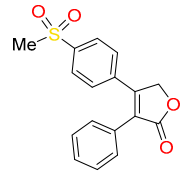
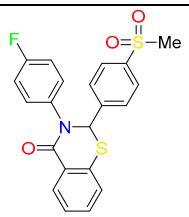
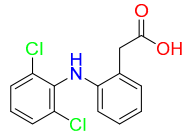
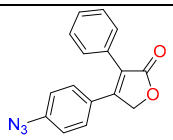
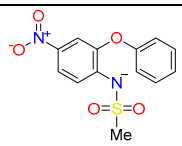
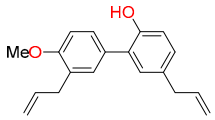
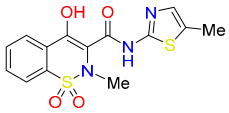
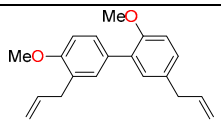
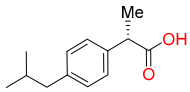
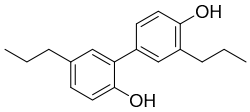
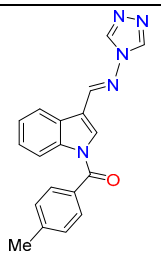
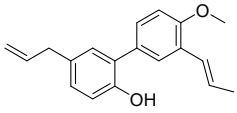
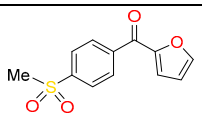
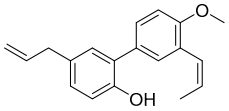
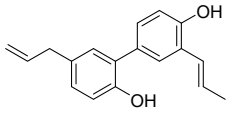


Figure S11. RMSD values obtained of structural validation of computational model with **Meloxicam** (Magenta) presented a parallel orientation of the nitrogen atom of the thiazole ring to the carbonyl of the amide original pose and color pose obtained in the molecule after experiment as show: Meloxicam (cyan).

Anti-inflammatory compound

Table S1. IC_{50} Values of NSAIDs and anti-inflammatory compounds.

Compounds	IC_{50} values (μM)		Compounds	IC_{50} values (μM)	
	COX-1	COX-2		COX-1	COX-2
MW: 244.27	0.59	3.1	MW: 263.13-	1.8	2.1
MW: 381.08	50	0.28	MW: 271.07	78.7 ± 3.60	0.3 ± 0.04
MW: 357.08	0.13	5.7	MW: 349.08	1.92 ± 0.9	8.21 ± 1.6

 MW: 314.06	100	0.39	 MW: 413.06	12.95	0.05
 MW: 295.02	18.79	1.24	 MW: 277.09	159.72	0.196
 MW: 307.04	9.2	0.52	 MW: 280.15	0.1	0.06
 MW: 353.05	19.4	1.37	 MW: 294.16	11.4	7.7
 MW: 206.13	2.9	1.1	 MW: 270.16	0.8	2.1
 MW: 329.13 **30**	7.89	0.98	 MW: 280.15	0.7	0.2
 MW: 250.03	15.1 ± 0.94	19.2 ± 1.80	 MW: 280.15	2.8	0.9
 MW: 266.13	0.6	2.7			

Interaction energy values (Kcal/mol) of COXs inhibitors

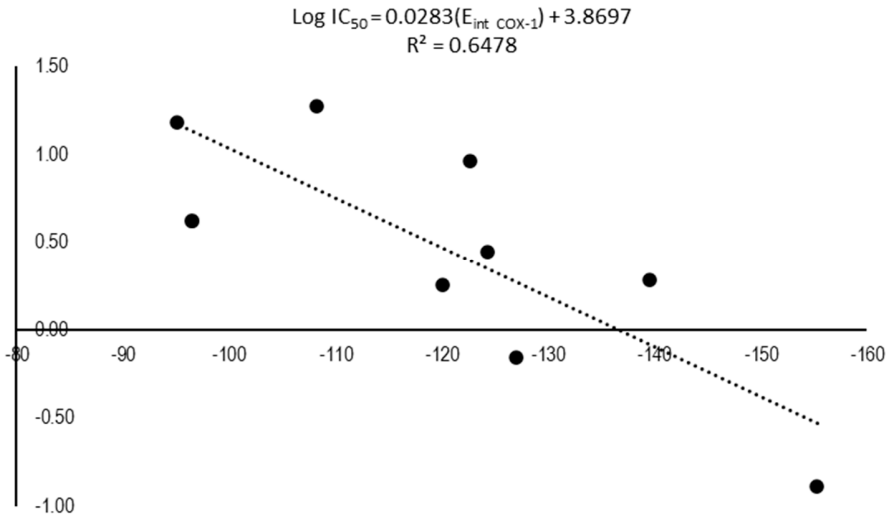


Figure S12.

Table S2. Interaction energy values (Kcal/mol) of COX-1 inhibitors that were coupled to the 1EQG crystal. Log $IC_{50\,exp}$, Log $IC_{50\,calc}$ and delta error (Δ error) values as show.

Compounds	Energy	Log $IC_{50\,exp}$	Log $IC_{50\,calc}$	Δ error
Ibuprofen[1]	-96.57	0.61	1.14	0.53
13	-120.03	0.26	0.47	0.21
19	-127.04	-0.15	0.27	0.12
20	-124.25	0.45	0.35	-0.1
29	-139.49	0.28	-0.08	-0.36
34	-95.09	1.18	1.18	0
Diclofenac	-108.23	1.27	0.81	-0.46
Indomethacine	-155.27	-0.89	-0.52	-1.41
Nimesulide	-122.59	0.96	0.40	-0.56

[1] Ligand corresponding to the crystal.

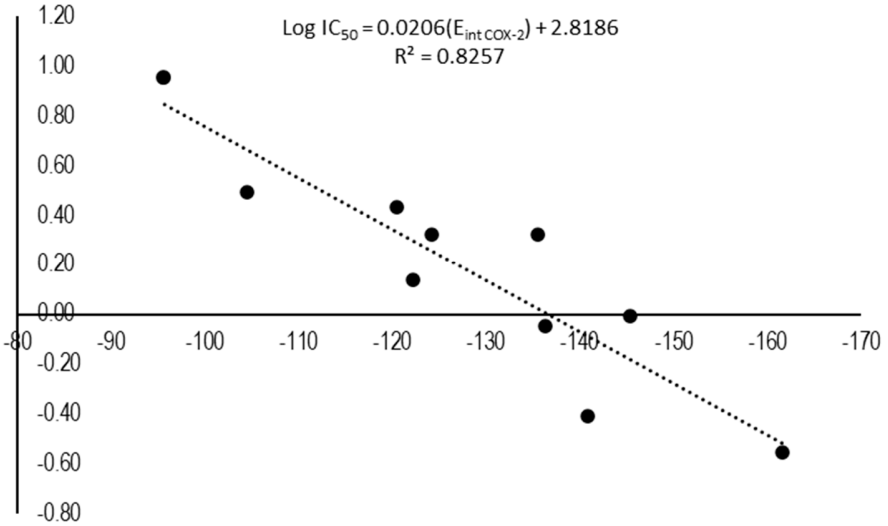


Figure S13.

Table S3. Interaction energy values (Kcal/mol) of COX-2 inhibitors that were coupled to the 4PH9 crystal. Log $IC_{50\ exp}$, Log $IC_{50\ calc}$ and delta error (Δ error) values as show.

Compounds	Energy	Log $IC_{50\ exp}$	Log $IC_{50\ calc}$	Δ error
Ibuprofen[1]	-95.66	0.95	0.85	-0.1
13	-135.53	0.32	0.03	-0.29
16	-124.25	0.32	0.26	-0.06
20	-136.32	-0.05	0.01	0.06
21	-120.5	0.43	0.34	-0.09
30	-145.4	-0.01	-0.18	-0.17
Celecoxib	-161.57	-0.55	-0.51	0.04
Flurbiprofen	-104.45	0.49	0.67	0.18
Meloxicam	-122.27	0.14	0.30	0.16

[1] Ligand corresponding to the crystal.

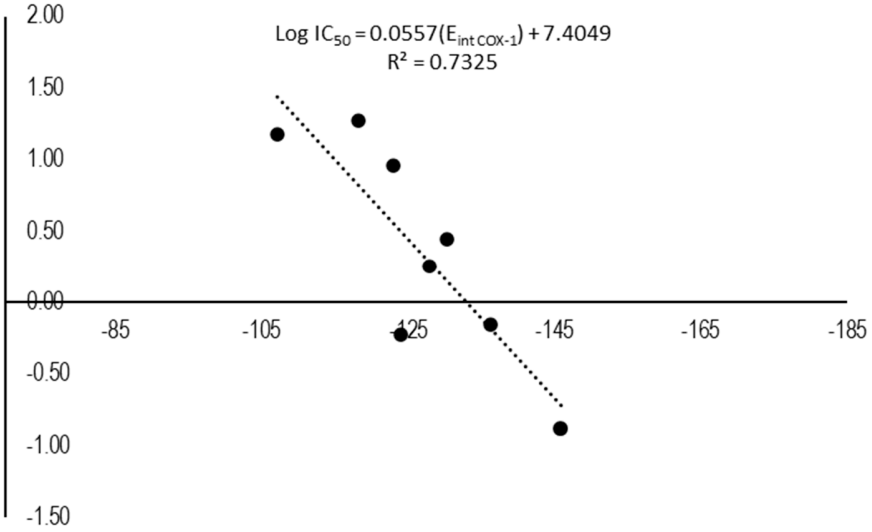


Figure S14.

Table S4. Interaction energy values (Kcal/mol) of COX-1 inhibitors that were coupled to the 2OYU crystal. Log $IC_{50\ exp}$, Log $IC_{50\ calc}$ and delta error (Δerror) values as show.

Compounds	Energy	Log $IC_{50\ exp}$	Log $IC_{50\ calc}$	Δ error
Indomethacin[1]	-145.91	-0.89	-0.72	0.17
13	-127.84	0.26	0.28	0.02
19	-136.29	-0.15	-0.19	-0.04
20	-130.2	0.45	0.15	-0.3
21	-123.93	-0.22	0.50	0.72
34	-107.02	1.18	1.44	0.26
Diclofenac	-118.2	1.27	0.82	-0.45
Nimesulide	-122.99	0.96	0.55	-0.41

[1] Ligand corresponding to the crystal.

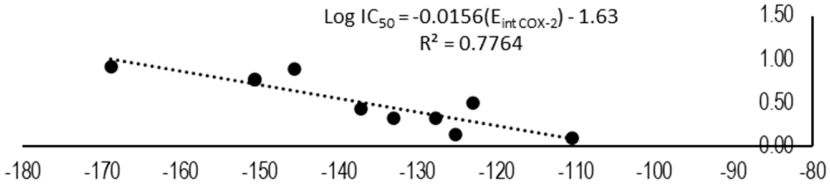


Figure S15.

Table S5. Interaction energy values (Kcal/mol) of COX-2 inhibitors that were coupled to the 4COX crystal. Log $IC_{50\ exp}$, Log $IC_{50\ calc}$ and delta error (Δ error) values as show.

Compounds	Energy	Log $IC_{50\ exp}$	Log $IC_{50\ calc}$	Δ error
Indomethacin[1]	-150.6	0.76	0.72	-0.04
13	-127.7	2.1	2.0	-0.1
15	-145.69	0.89	0.64	-0.25
16	-133.07	0.32	0.45	0.13
21	-137.15	0.43	0.51	0.08
29	-168.87	0.91	1.00	0.09
Diclofenac	-110.47	0.09	0.09	0
Flurbiprofen	-123.05	0.49	0.29	-0.2

[1] Ligand corresponding to the crystal.

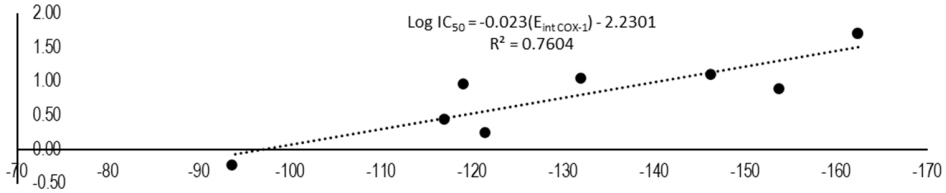


Figure S16.

Table S6. Interaction energy values (Kcal/mol) of COX-1 inhibitors that were coupled to the 3KK6 crystal. Log $IC_{50\ exp}$, Log $IC_{50\ calc}$ and delta error (Δ error) values as show.

Compounds	Energy	Log $IC_{50\ exp}$	Log $IC_{50\ calc}$	Δ error
Celecoxib[1]	-162.39	1.70	1.51	-0.19
13	-121.38	0.26	0.56	0.3
15	-131.88	1.06	0.80	-0.26
20	-116.91	0.45	0.46	0.01
26	-146.17	1.11	1.13	0.02
30	-153.73	0.90	1.31	0.41
Flurbiprofen	-93.58	-0.23	-0.08	0.15
Nimesulide	-119.00	0.96	0.51	-0.45

[1] Ligand corresponding to the crystal.

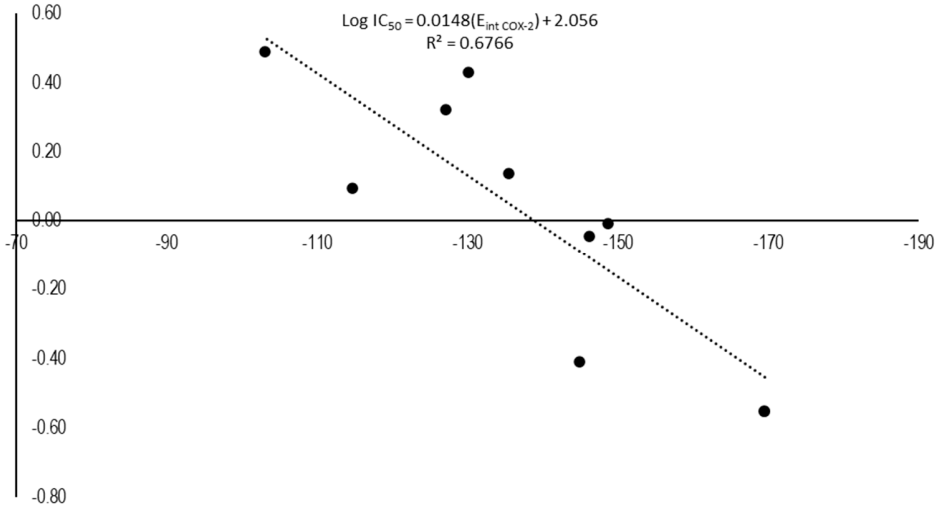


Figure S17.

Table S7. Interaction energy values (Kcal/mol) of COX-2 inhibitors that were coupled to the 3LN1 crystal. Log $IC_{50\,exp}$, Log IC_{50} calc and delta error (Δ error) values as show.

Compounds	Energy	Log $IC_{50\,exp}$	Log $IC_{50\,calc}$	Δ error
Celecoxib[1]	-169.55	-0.55	-0.45	0.1
16	-127.07	0.32	0.18	-0.14
20	-146.17	-0.05	-0.11	-0.06
21	-130.13	0.43	0.13	0.3
30	-148.72	-0.01	-0.15	-0.14
Diclofenac	-114.72	0.09	0.36	0.27
Flurbiprofen	-103.01	0.49	0.53	0.04
Meloxicam	-135.43	0.14	0.05	-0.09
Rofecoxib	-144.84	-0.41	-0.09	0.32

[1] Ligand corresponding to the crystal.

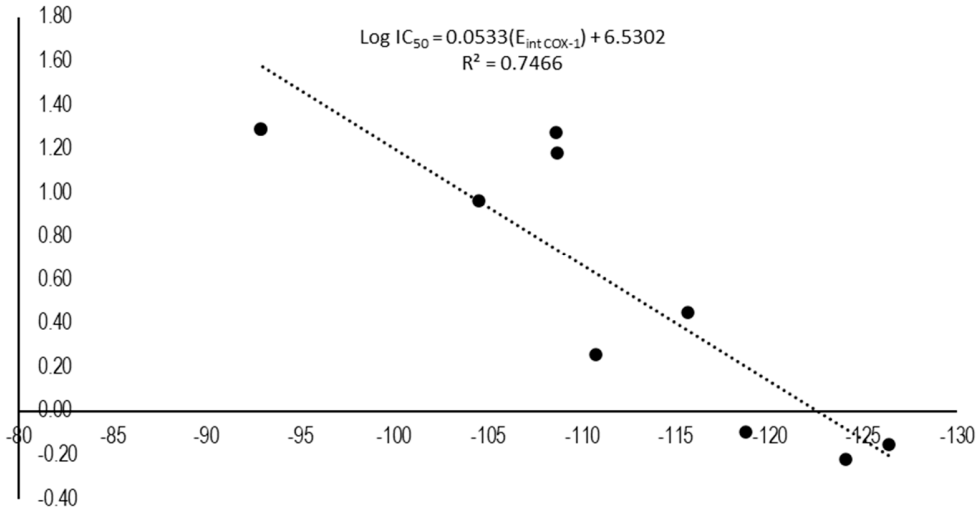


Figure S18.

Table S8. Interaction energy values (Kcal/mol) of COX-1 inhibitors that were coupled to the 4O1Z crystal. Log IC $_{50\,exp}$, Log IC$_{50\,calc}$ and delta error (Δerror) values as show.

Compounds	Energy	Log IC$_{50\,exp}$	Log IC$_{50\,calc}$	Δ error
Meloxicam[1]	-92.91	0.96	1.58	0.62
13	-110.750	0.26	0.63	0.37
16	-118.69	-0.10	0.20	0.3
19	-126.32	-0.15	-0.20	-0.05
20	-115.64	0.45	0.37	-0.08
21	-124.05	-0.22	-0.08	0.14
34	-108.68	1.18	0.74	-0.44
Diclofenac	-108.64	1.27	0.74	-0.53
Nimesulide	-104.48	0.96	0.96	0

[1] Ligand corresponding to the crystal.

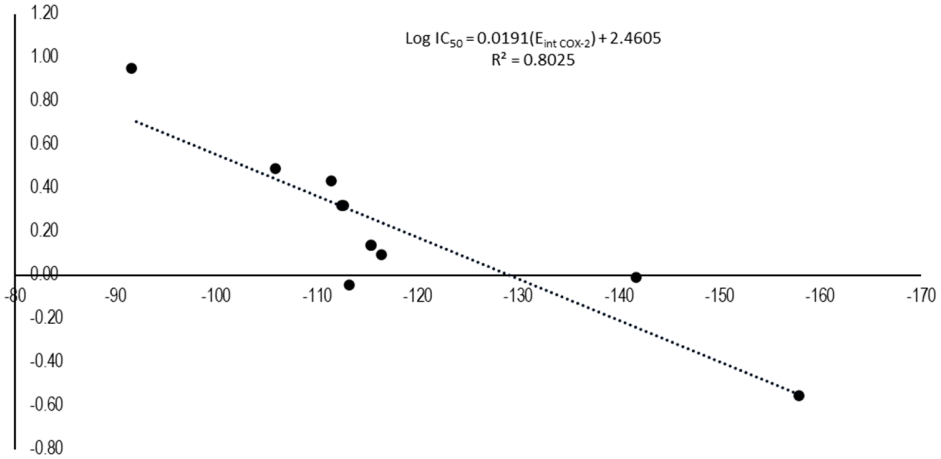


Figure S19.

Table S9. Interaction energy values (Kcal/mol) of COX-2 inhibitors that were coupled to the **4M11** crystal. Log IC$_{50\,exp}$, Log IC$_{50\,calc}$ and delta error (Δ error) values as show.

Compounds	Energy	Log IC$_{50\,exp}$	Log IC$_{50\,calc}$	Δ error
Meloxicam[1]	-115.40	0.14	0.26	0.12
13	-112.49	0.32	0.31	-0.01
16	-112.64	0.32	0.31	-0.01
20	-113.17	-0.05	0.30	0.35
21	-111.41	0.43	0.33	-0.1
30	-141.68	-0.01	-0.25	-0.24
Celecoxib	-157.82	-0.55	-0.55	0
Diclofenac	-116.44	0.09	0.24	0.15
Flurbiprofen	-105.91	0.49	0.44	-0.05
Ibuprofen	-91.59	0.95	0.71	-0.24

[1] Ligand corresponding to the crystal.

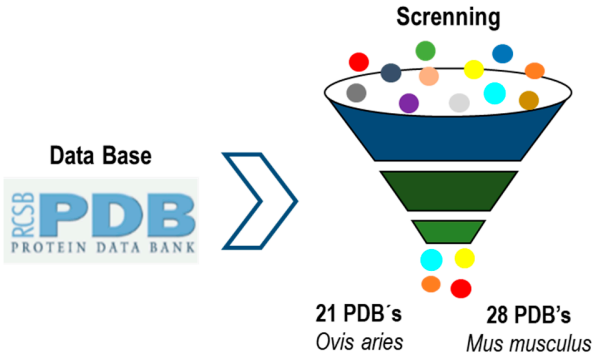


Figure S20. Search of crystals from COX-1 and COX-2.

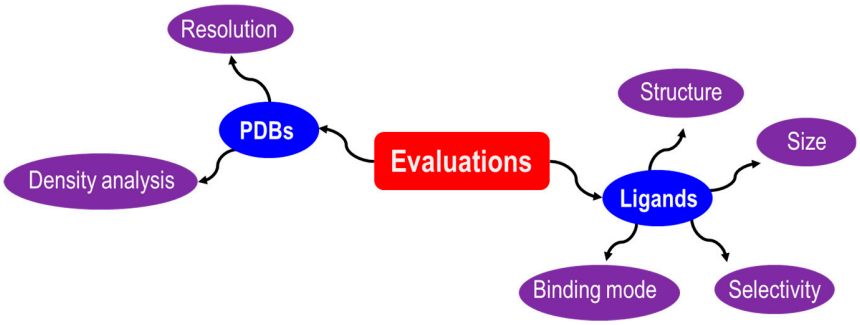


Figure S21. Analysis of crystals COXs with respect PDB and Ligands.

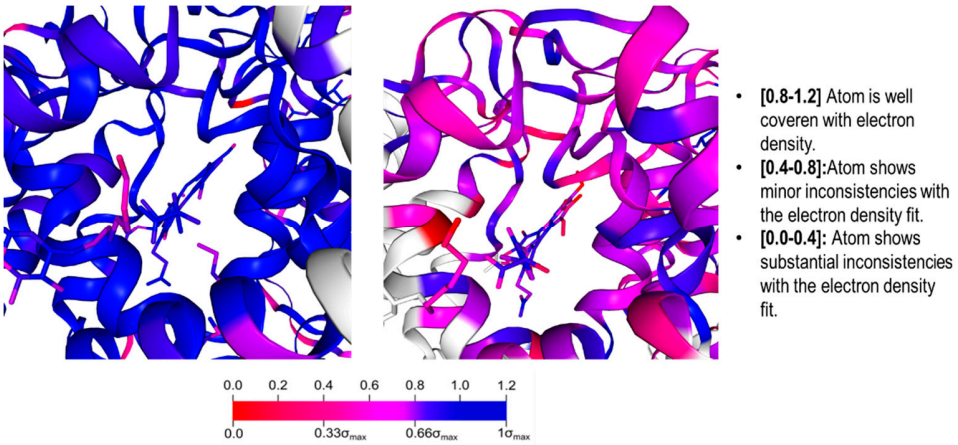


Figure S22. Examples of analysis about active site in crystals of COX-1 with EDIA. a) Ibuprofen (4PH9) with resolution of 2.6 Å, b) Flurbiprofen (3N8Z) with resolution of 2.9 Å.

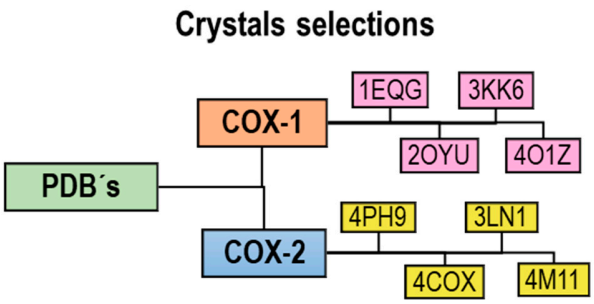


Figure S23. Final selection of crystals from computational model.

Table S10. Crystals and their flexible residues shown in the flexible docking.

PDBs	Flexible residues
1EQG (COX-1)	Phe381, Phe518, Ser353, Ser530, Trp387, Tyr355, Val116, Val349, Arg120, Ile523, Leu 352 Leu359, Leu531, Met522.
4PH9 (COX-2)	Phe519, Ser354, Ser531, Trp388, Tyr356, Tyr386, Val117, Val350, Val524, Arg121, Leu353, Leu360, Leu532, Met523.
2OYU (COX-1)	Leu531, Leu359, Leu352, Ile523, Ile517, Arg120, Val349, Tyr355, Gln192, Ser530, Ser516, Ser353.
4COX (COX-2)	Phe381, Phe518, Ser353, Ser530, Trp387, Tyr355, Tyr385, Val349, Val523, Arg120, Leu352, Leu384, Leu531, Met522.
3KK6 (COX-1)	His90, Phe381, Phe518, Ser353, Ser516, Ser530, Trp387, Gln192, Tyr355, Val116, Val349, Ile517, Ile523, Leu352, Leu359, Leu531, Met522.
3LN1 (COX-2)	His75, Phe367, Phe504, Ser339, Ser516, Trp373, Gln178, Tyr341, Tyr371, Val335, Val509, Arg499, Leu338, Leu345, Leu370, Leu517.
4O1Z (COX-1)	Ser353, Ser530, Trp387, Tyr355, Val116, Val349, Arg120, Ile345, Ile523, Leu117, Leu352, Leu359, Leu384, Leu531, Leu534, Leu535, Met113, Met522.
4M11 (COX-2)	Phe518, Ser530, Trp387, Tyr355, Val349, Val523, Arg120, Ile345, Leu117, Leu352, Leu359, Leu531, Leu534, Met113, Met522.