

MOUSE_COX1-----MSRRSLSWFPLLLLLLLPPTPSVILLADGVPSPVNPCYYPCQNQGVCVRFGLDNYQCD 60
6Y3C_1-----ADPGAPTPVNPCYYPCQHGGICVRFGLDRYQCD 34
1EQG_1-----PVFSADPGAPAPVNPCYYPCQHGGICVRFGLDRYQCD 38
2OYU_1-----MSRQSISLRFPLLLLLLSP--SPVFSADPGAPAPVNPCYYPCQHGGICVRFGLDRYQCD 58
3KK6_1-----PVNPCCYYPCQHGGICVRFGLDRYQCD 27
4O1Z_1-----PVNPCCYYPCQHGGICVRFGLDRYQCD 27

*****;*:*****.***
MOUSE_COX1-----CTRTGYSGPNCTIPEIWTLWRNSLRPSPSFTHFLLTHGYWLWFEVFNATFIREVLMLRLVLT 120
6Y3C_1-----CTRTGYSGPNCTIPGLWTWLRNSLRPSPSFTHFLLTHGRWFWEVFNATFIREMLMLRLVLT 94
1EQG_1-----CTRTGYSGPNCTIPEIWTWLRNTRLRPSPSFIHFLLLTHGRWLWDFVNATFIRDITLMRLVLT 98
2OYU_1-----CTRTGYSGPNCTIPEIWTWLRRTLRLRPSPSFIHFLLLTHGRWLWDFVNATFIRDITLMRLVLT 118
3KK6_1-----CTRTGYSGPNCTIPEIWTWLRRTLRLRPSPSFIHFLLLTHGRWLWDFVNATFIRDITLMRLVLT 87
4O1Z_1-----CTRTGYSGPNCTIPEIWTWLRRTLRLRPSPSFIHFLLLTHGRWLWDFVNATFIRDITLMRLVLT 87

*****;*****.***** *;*:*****.*****
MOUSE_COX1-----VRSNLIPSPTYNSAHDYISWESFSNVSYTIRILPSVPKDCPTPMGTGKGKQLPDVQLLA 180
6Y3C_1-----VRSNLIPSPTYNSAHDYISWESFSNVSYTIRILPSVPKDCPTPMGTGKGKQLPDAQLLA 154
1EQG_1-----VRSNLIPSPTYNIAHDYISWESFSNVSYTIRILPSVPRDCPTPMGTGKGKQLPDAEFLS 158
2OYU_1-----VRSNLIPSPTYNIAHDYISWESFSNVSYTIRILPSVPRDCPTPMGTGKGKQLPDAEFLS 178
3KK6_1-----VRSNLIPSPTYNIAHDYISWESFSNVSYTIRILPSVPRDCPTPMGTGKGKQLPDAEFLS 147
4O1Z_1-----VRSNLIPSPTYNIAHDYISWESFSNVSYTIRILPSVPRDCPTPMGTGKGKQLPDAEFLS 147

***** *****;*****.*****
MOUSE_COX1-----QQLLLRREFIPAPQGTNILFAFFAQHFTHQFFKTSGKMGPGFTKALGHGVDLGHIYGDNL 240
6Y3C_1-----RRFLLRRKFIPDPQGTNLMFAFFAQHFTHQFFKTSGKMGPGFTKALGHGVDLGHIYGDNL 214
1EQG_1-----RRFLLRRKFIPDPQGTNLMFAFFAQHFTHQFFKTSGKMGPGFTKALGHGVDLGHIYGDNL 218
2OYU_1-----RRFLLRRKFIPDPQGTNLMFAFFAQHFTHQFFKTSGKMGPGFTKALGHGVDLGHIYGDNL 208
3KK6_1-----RRFLLRRKFIPDPQGTNLMFAFFAQHFTHQFFKTSGKMGPGFTKALGHGVDLGHIYGDNL 237
4O1Z_1-----RRFLLRRKFIPDPQGTNLMFAFFAQHFTHQFFKTSGKMGPGFTKALGHGVDLGHIYGDNL 207

:::****:* ** *:*****
MOUSE_COX1-----ERQYHLRLFKDGKLKYQVLDGEVYPSPVEQASVLMRYPPGVPPERQMAGVQEVEFGLLPGL 300
6Y3C_1-----ERQYQLRLFKDGKLKYQVLDGEMYPPSVEEAPVLMHYPRGIIPPQSQMAVGQEVEFGLLPGL 274
1EQG_1-----ERQYQLRLFKDGKLKYQMLNGEVYPPSVEEAPVLMHYPRGIIPPQSQMAVGQEVEFGLLPGL 278
2OYU_1-----ERQYQLRLFKDGKLKYQMLNGEVYPPSVEEAPVLMHYPRGIIPPQSQMAVGQEVEFGLLPGL 298
3KK6_1-----ERQYQLRLFKDGKLKYQMLNGEVYPPSVEEAPVLMHYPRGIIPPQSQMAVGQEVEFGLLPGL 267
4O1Z_1-----ERQYQLRLFKDGKLKYQMLNGEVYPPSVEEAPVLMHYPRGIIPPQSQMAVGQEVEFGLLPGL 267

*****;*:*****;* ** *:*****
MOUSE_COX1-----MLFSTIWLREHNRVCDLLKEEHPTWDEQLFQTARLILIGETIKIVIEEYVQQLSGYFLQ 360
6Y3C_1-----MLYATLWLREHNRVCDLLKAHEHPTWGDEQLFQTARLILIGETIKIVIEEYVQQLSGYFLQ 334
1EQG_1-----MLYATIWLREHNRVCDLLKAHEHPTWGDEQLFQTARLILIGETIKIVIEEYVQQLSGYFLQ 338
2OYU_1-----MLYATIWLREHNRVCDLLKAHEHPTWGDEQLFQTARLILIGETIKIVIEEYVQQLSGYFLQ 358
3KK6_1-----MLYATIWLREHNRVCDLLKAHEHPTWGDEQLFQTARLILIGETIKIVIEEYVQQLSGYFLQ 327
4O1Z_1-----MLYATIWLREHNRVCDLLKAHEHPTWGDEQLFQTARLILIGETIKIVIEEYVQQLSGYFLQ 327

,:*:*** *****.*****
MOUSE_COX1-----LKFDPELLFRAQFYQRNRRIAMEFNHLYHHWPLMPNSFQVGSQYESYEQLFNNTSMMLVDYG 420
6Y3C_1-----LKFDPELLFGVFQFYQRNRRIAMEFNHLYHHWPLMPDSFKVGSQYESYEQLFNNTSMMLVDYG 394
1EQG_1-----LKFDPELLFGAQFYQRNRRIAMFNQLYHHWPLMPDSFRVGPQDYSYEQLFNNTSMMLVDYG 398
2OYU_1-----LKFDPELLFGAQFYQRNRRIAMFNQLYHHWPLMPDSFRVGPQDYSYEQLFNNTSMMLVDYG 418
3KK6_1-----LKFDPELLFGAQFYQRNRRIAMFNQLYHHWPLMPDSFRVGPQDYSYEQLFNNTSMMLVDYG 387
4O1Z_1-----LKFDPELLFGAOFQYRNRIAMEFNQLYHHWPLMPDSFRVGPQDYSYEQLFNNTSMMLVDYG 387

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***** .*****:*****:*.** *:*****
MOUSE_COX1-----VEALVDAFSRQAGRIIGGRNFDYHVLHVAVDVIKESREMRLQPPFNEYRKRFGKLPYTSF 480
6Y3C_1-----VEALVDAFSRQIAGRIIGGRNMDHHILHVAVDVIREMRLQPPFNEYRKRFGMKPYTSF 454
1EQG_1-----VEALVDAFSRQAGRIIGGRNIDHHILHVAVDVIKESRVLRLQPPFNEYRKRFGMKPYTSF 458
2OYU_1-----VEALVDAFSRQAGRIIGGRNIDHHILHVAVDVIKESRVLRLQPPFNEYRKRFGMKPYTSF 478
3KK6_1-----VEALVDAFSRQAGRIIGGRNIDHHILHVAVDVIKESRVLRLQPPFNEYRKRFGMKPYTSF 447
4O1Z_1-----VEALVDAFSRQAGRIIGGRNIDHHILHVAVDVIKESRVLRLQPPFNEYRKRFGMKPYTSF 447
***** *****:*.**:*****:*** :*****:*****
MOUSE_COX1-----QELTGEKEMAAELEEYGDIDALEFYPGLLLEKCHPNSIFGESMIEMGAPFSLKGLLGNP 540
6Y3C_1-----QELVGEKEMAAELEEYGDIDALEFYPGLLLEKCHPNSIFGESMIEMGAPFSLKGLLGNP 514
1EQG_1-----QELTGEKEMAAELEEYGDIDALEFYPGLLLEKCHPNSIFGESMIEMGAPFSLKGLLGNP 518
2OYU_1-----QELTGEKEMAAELEEYGDIDALEFYPGLLLEKCHPNSIFGESMIEMGAPFSLKGLLGNP 538
3KK6_1-----QELTGEKEMAAELEEYGDIDALEFYPGLLLEKCHPNSIFGESMIEMGAPFSLKGLLGNP 507
4O1Z_1-----QELTGEKEMAAELEEYGDIDALEFYPGLLLEKCHPNSIFGESMIEMGAPFSLKGLLGNP 507
***.*****:*****:*****:*****:*****
MOUSE_COX1-----ICSPYWKPSTFGGVDGFNLVNTASLKKLVCLNTKTCPVVSFRVPDYPGDDGSVLVRST 600
6Y3C_1-----ICSPYWKPSTFGGEVGFNIVKTATLKKLVCLNTKTCPVVSFRVPDASQDDGPAVERPST 574
1EQG_1-----ICSPYWKASTFGGEVGFNLVKATLKKLVCLNTKTCPVVSFHVDPDRQEDRPGVERPPT 578
2OYU_1-----ICSPYWKASTFGGEVGFNLVKATLKKLVCLNTKTCPVVSFHVDPDRQEDRPGVERPPT 598
3KK6_1-----ICSPYWKASTFGGEVGFNLVKATLKKLVCLNTKTCPVVSFHVDP----- 553
4O1Z_1-----ICSPYWKASTFGGEVGFNLVKATLKKLVCLNTKTCPVVSFHVDPDRQEDRPGVERPPT 567
***** *****:*****:*.**:*****:*****:***
MOUSE_COX1_SEQUENCE      EL      602
6Y3C_1|Chain              EL      576
1EQG_1|Chains             EL      580
2OYU_1|Chain              EL      600
3KK6_1|Chains             --      553
4O1Z_1|Chains             EL      569

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

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Human_cox2-----MLARALLLCAVLALSHTANPCCSHPCQNRGVCMSVGFDDQYKCDCTRTGFYGENCTTPEFL 60
SHEEP_COX2-----MLARALLLCAVALCGAANPCCSHPCQNRGVCMSVGFDDQYKCDCTRTGFYGENCTTPEFL 60
4PH9_1-----HHPCCSNPCQNRGECMSTGFDQYKCDCTRTGFYGENCTTPEFL 43
4COX_1-----ANPCCSNPCQNRGECMSTGFDQYKCDCTRTGFYGENCTTPEFL 43
3LN1_1-----ANPCCSNPCQNRGECMSTGFDQYKCDCTRTGFYGENCTTPEFL 43
4M11_1-----ANPCCSNPCQNRGECMSTGFDQYKCDCTRTGFYGENCTTPEFL 43
:****:***** ***.*****:*****:*****
Human_cox2-----TRIKLFLKPTPNTVHYILTHFKGFVNIVNNIPFLRNAIMSYVLTSRSHLIDSPPTYNADY 120
SHEEP_COX2-----TRIKLLLKPTPDVHYILTHFKGVNIVNNKISFLRMIMRYVLTSRSHLIESPPTYNVHY 120
4PH9_1-----TRIKLLLKPTPNTVHYILTHFKGVNIVNNIPFLRLIMKYVLTSRSYLIDSPPTYNVHY 103
4COX_1-----TRIKLLLKPTPNTVHYILTHFKGVNIVNNIPFLRLIMKYVLTSRSYLIDSPPTYNVHY 103
3LN1_1-----TRIKLLLKPTPNTVHYILTHFKGVNIVNNIPFLRLIMKYVLTSRSYLIDSPPTYNVHY 103
4M11_1-----TRIKLLLKPTPNTVHYILTHFKGVNIVNNIPFLRLIMKYVLTSRSYLIDSPPTYNVHY 103
*****:*****:*****:*****:*****:*****:*****
Human_cox2-----GYKSWEAFSNLSYYTRALPPVDDCPTPLGVKGGKQLPDSNEIVEKLLLRKFIPDPQGS 180
SHEEP_COX2-----SYKSWEAFSNLSYYTRALPPVDDCPTPMGVKGRKELPDSKEVVKKVLLRRKFIPDPQGT 180
4PH9_1-----GYKSWEAFSNLSYYTRALPPVDDCPTPMGVKGNKELPDSKEVLEKVLRLRREFIPDPQGS 163
4COX_1-----GYKSWEAFSNLSYYTRALPPVDDCPTPMGVKGNKELPDSKEVLEKVLRLRREFIPDPQGS 163
3LN1_1-----GYKSWEAFSNLSYYTRALPPVDDCPTPMGVKGNKELPDSKEVLEKVLRLRREFIPDPQGS 163
4M11_1-----GYKSWEAFSNLSYYTRALPPVDDCPTPMGVKGNKELPDSKEVLEKVLRLRREFIPDPQGS 163
*****:*****:*****:*****:*****:*****:*****
Human_cox2-----NMMFAFFAQHFTHQFFKTDHKGPAFTNGLGHGVLDLNIYGETLARQKRLRLFKDGKMKY 240
SHEEP_COX2-----NLMFAFFAQHFTHQFFKTDIERGPAFTKGKNHGVLDLSHVYGESLERQHKLRLFKDGKMKY 240
4PH9_1-----NMMFAFFAQHFTHQFFKTDHKGPGFTRGLGHGVLDLNIYGETLDRQHKLRLFKDGKMKY 223
4COX_1-----NMMFAFFAQHFTHQFFKTDHKGPGFTRGLGHGVLDLNIYGETLDRQHKLRLFKDGKMKY 223
3LN1_1-----NMMFAFFAQHFTHQFFKTDHKGPGFTRGLGHGVLDLNIYGETLDRQHKLRLFKDGKMKY 223
4M11_1-----NMMFAFFAQHFTHQFFKTDHKGPGFTRGLGHGVLDLNIYGETLDRQHKLRLFKDGKMKY 223
*:*****:*****:*****:*****:*****:*****:*****
Human_cox2-----QIIDGEMYPPPTVKDTQAEIYPPQVPEHLRFVAVGQEVFGLVPGLMMYATIWLREHNRVCD 300
SHEEP_COX2-----QMINGEMYPPPTVKDTQVEIYPPHIPHLKFAVGQEVFGLVPGLMMYATIWLREHNRVCD 300
4PH9_1-----QVIGGEVYPPPTVKDTQVEIYPPHIPENLQFAVGQEVFGLVPGLMMYATIWLREHNRVCD 283

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4COX_1-----QVIGGEVYPPTVKDTQVEMIYPPHIPENLQFAVGQEVFGLVPGLMYATIWLREHQRVCD 283
3LN1_1-----QVIGGEVYPPTVKDTQVEMIYPPHIPENLQFAVGQEVFGLVPGLMYATIWLREHNRVCD 283
4M11_1-----QVIGGEVYPPTVKDTQVEMIYPPHIPENLQFAVGQEVFGLVPGLMYATIWLREHNRVCD 283
               *:.*.*:*****.*****:.*.*:*****:*****:*****
Human_cox2----VLKQEHPEWGDEQLFQTSRLILIGETIKIVIEDYVQHLSGYHFKLKFDPPELLFNKQFQYQ 360
SHEEP_COX2----VLKQEHPEWGDEQLFQTSRLILIGETIKIVIEDYVQHLSGYHFKLKFDPPELLFNKQFQYQ 360
4PH9_1-----ILKQEHPEWGDEQLFQTSRLILIGETIKIVIEDYVQHLSGYHFKLKFDPPELLFNKQFQYQ 343
4COX_1-----ILKQEHPEWGDEQLFQTSRLILIGETIKIVIEDYVQHLSGYHFKLKFDPPELLFNKQFQYQ 343
3LN1_1-----ILKQEHPEWGDEQLFQTSRLILIGETIKIVIEDYVQHLSGYHFKLKFDPPELLFNKQFQYQ 343
4M11_1-----ILKQEHPEWGDEQLFQTSRLILIGETIKIVIEDYVQHLSGYHFKLKFDPPELLFNKQFQYQ 343
               :*****:*****:*****:*****:*****:*****:*****
Human_cox2----NRIAAEFNTLYHWHPLLPDFTQIHDQKYNYYQFIYNNSILLEHGITQFVESFTRQIAGRV 420
SHEEP_COX2----NRIAAEFNTLYHWHPLLPDVFQIDGQENYQFIYNNSVLEHGVTFVESFTRQIAGRV 420
4PH9_1-----NRIASEFNTLYHWHPLLPDFTFNIEDQEYSFKQFLYNNSILLEHGLTQFVESFTRQIAGRV 403
4COX_1-----NRIASEFNTLYHWHPLLPDFTFNIEDQEYSFKQFLYNNSILLEHGLTQFVESFTRQIAGRV 403
3LN1_1-----NRIASEFNTLYHWHPLLPDFTFNIEDQEYSFKQFLYNNSILLEHGLTQFVESFTRQIAGRV 403
4M11_1-----NRIASEFNTLYHWHPLLPDFTFNIEDQEYSFKQFLYNNSILLEHGLTQFVESFTRQIAGRV 403
               *****:.*.*:.*.*:.*.*:.*.*:*****:*****
Human_cox2----AGGRNVPPAVQKVSQASIDQSRQMKYQSFNEYRKRFLKPYESFEELTGEKEMSAEELAL 480
SHEEP_COX2----AGGRNLPAAVEKVSQASLDQSRQMKYQSFNEYRKRFLKPYESFEELTGEKEMAAELAL 480
4PH9_1-----AGGRNVPIAVQAVAKASIDQSRQMKYQSLNEYRKRFSLKPYTSFEELTGEKEMAAELKAL 463
4COX_1-----AGGRNVPIAVQAVAKASIDQSRQMKYQSLNEYRKRFSLKPYTSFEELTGEKEMAAELKAL 463
3LN1_1-----AGGRNVPIAVQAVAKASIDQSRQMKYQSLNEYRKRFSLKPYTSFEELTGEKEMAAELKAL 463
4M11_1-----AGGRNVPIAVQAVAKASIDQSRQMKYQSLNEYRKRFSLKPYTSFEELTGEKEMAAELKAL 463
               *****:.*.*:.*.*:.*.*:.*.*:*****:*****
Human_cox2----YGDIDAVELYPALLVEKPRPDALFGETMVELGAPFSLKGLMGNVICSPAYWKPSTFGGEV 540
SHEEP_COX2----YGDIDAMELYPALLVEKPRPDALFGETMVEAGAPFSLKGLMGNPICSPYWKPSTFGGEV 540
4PH9_1-----YSDIDVMELYPALLVEKPRPDALFGETMVELGAPFSLKGLMGNPICSPQYWKPSTFGGEV 523
4COX_1-----YSDIDVMELYPALLVEKPRPDALFGETMVELGAPFSLKGLMGNPICSPQYWKPSTFGGEV 523
3LN1_1-----YSDIDVMELYPALLVEKPRPDALFGETMVELGAPFSLKGLMGNPICSPQYWKPSTFGGEV 523
4M11_1-----YSDIDVMELYPALLVEKPRPDALFGETMVELGAPFSLKGLMGNPICSPQYWKPSTFGGEV 523
               *.***:.*.*:.*.*:.*.*:.*.*:*****:*****
Human_cox2----GFKIINTASIQSLICNNVKGCPFTSFVSDPELIKTVTINASSSRSGLDLDINPTVLLKER 600
SHEEP_COX2----GFKIINTASIQSLICNNVKGCPFTSFVSDAHLTKTVTINASSSHSGLDLDINPTVLLKER 600
4PH9_1-----GFKIINTASIQSLICNNVKGCPFTSFNV----- 551
4COX_1-----GFKIINTASIQSLICNNVKGCPFTSFNVQDPQPTKTATINASASHSRLLDINPTVLIKRR 583
3LN1_1-----GFKIINTASIQSLICNNVKGCPFTSFNVQDPQPTKTATINASASHSRLLDINPTVLIKRR 583
4M11_1-----GFKIINTASIQSLICNNVKGCPFTSFNVQ----- 552
               **:*****.*****.*
Human_cox2-----STEL 604
SHEEP_COX2-----STEL 604
4PH9_1----- 551
4COX_1-----STEL 587
3LN1_1-----STEL 587
4M11_1----- 552

```

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

Results docking molecular

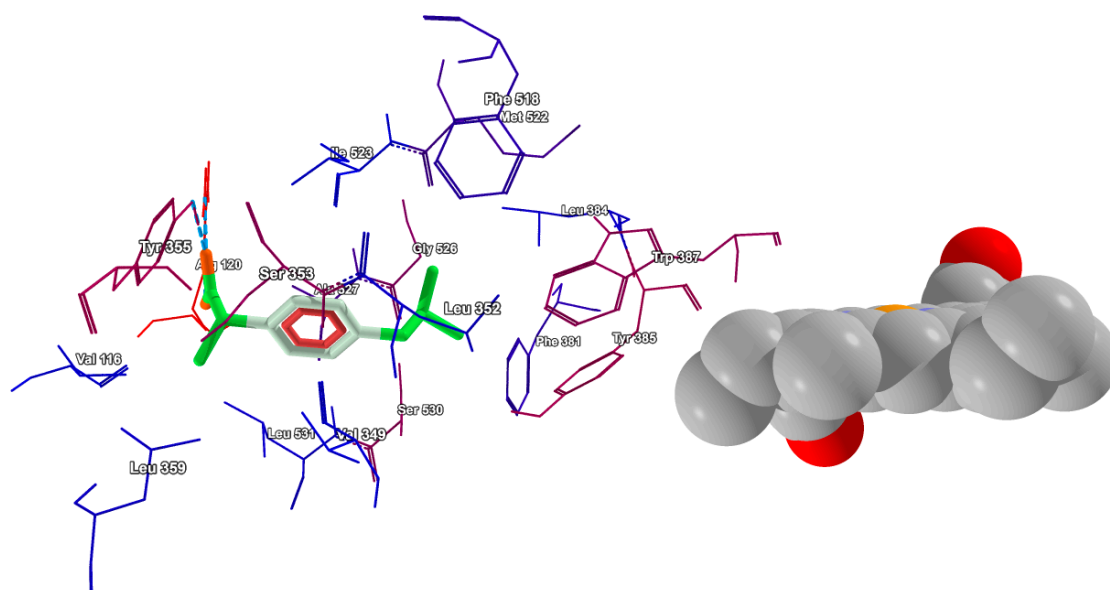


Figure S3. Binding mode of Ibuprofen in 1EQG crystal (COX-1).

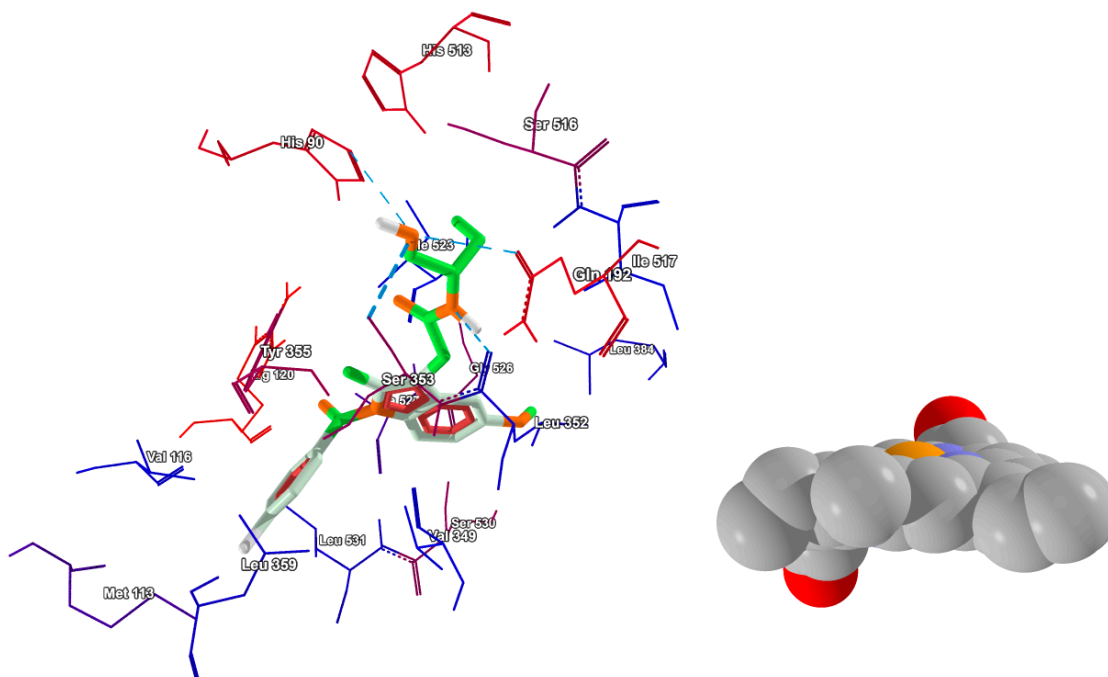


Figure S4. Binding mode of Ibuprofen in 2OYU crystal (COX-1).

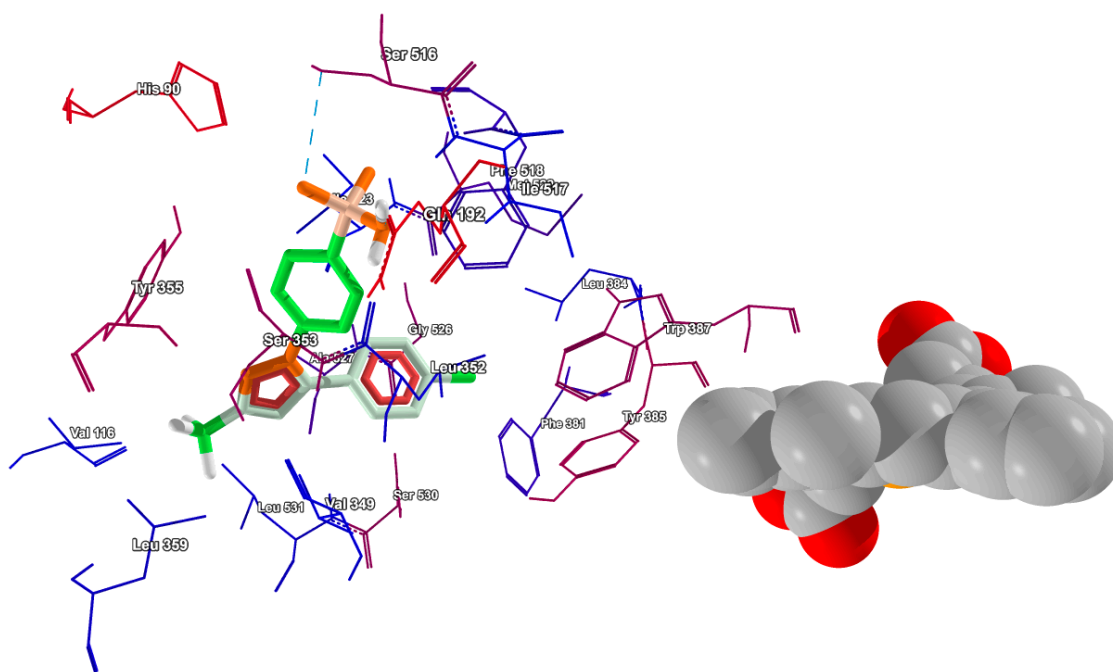


Figure S5. Binding mode of Ibuprofen in 3KK6 crystal (COX-1).

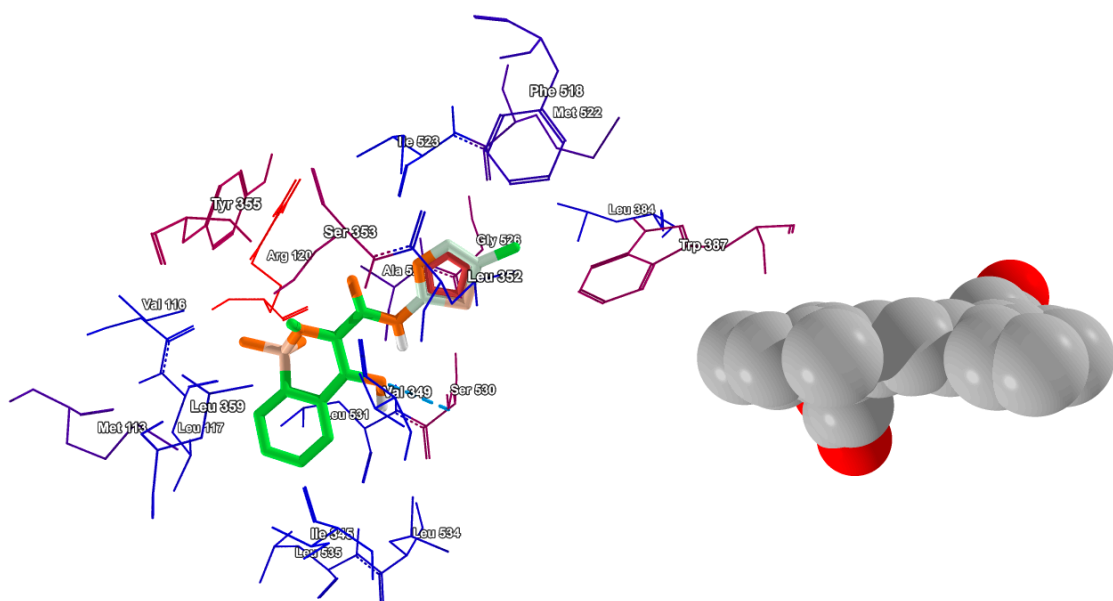


Figure S6. Binding mode of Ibuprofen in 4O1Z crystal (COX-1).

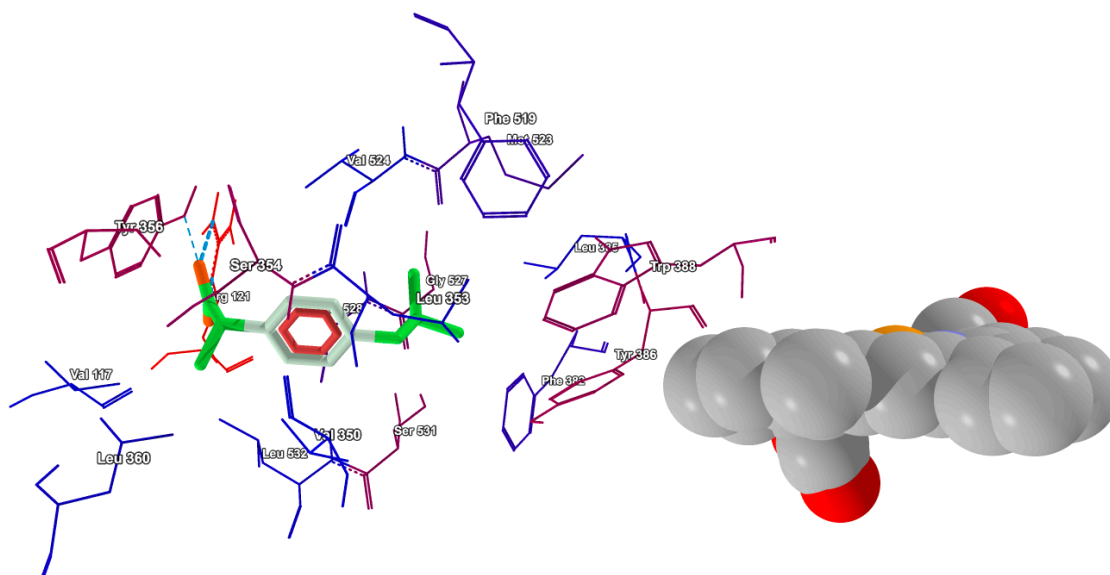


Figure S7. Binding mode of Ibuprofen in 4PH9 crystal (COX-2).

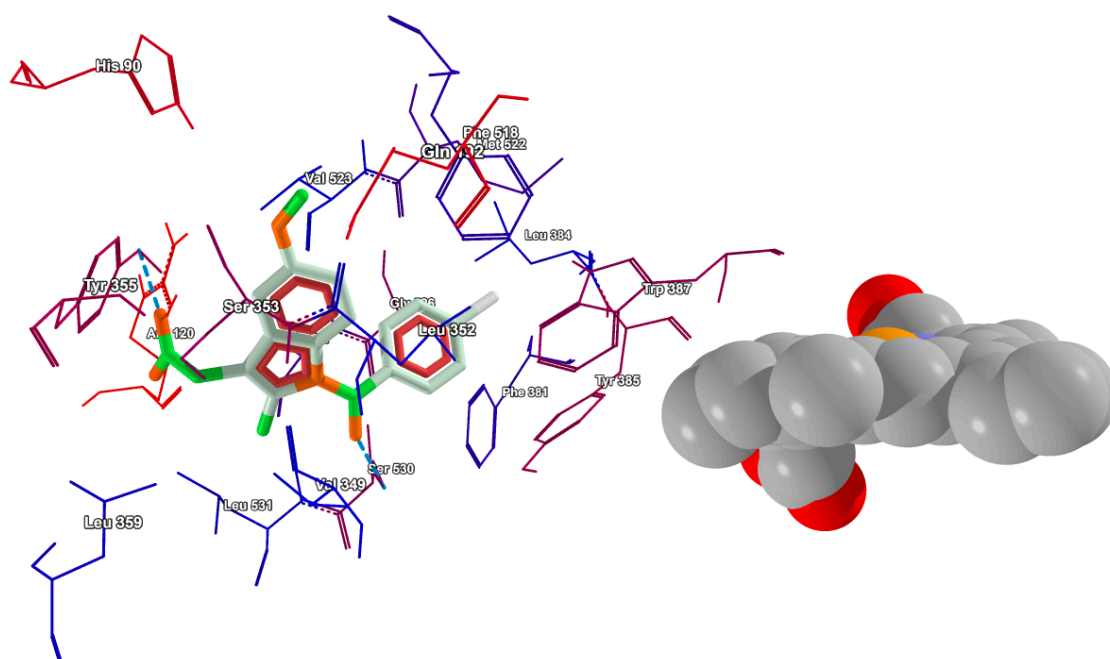


Figure S8. Binding mode of Indomethacin in 4COXcrystal (COX-2).

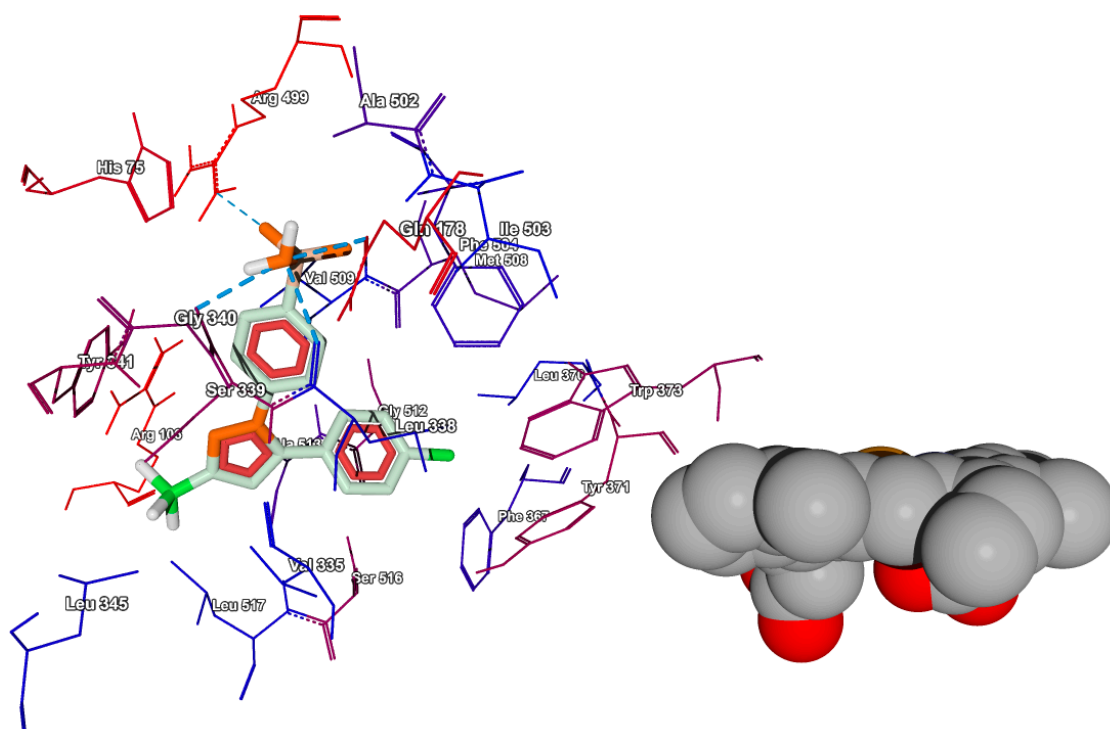


Figure S9. Binding mode of Celecoxib in 3LN1 crystal (COX-2).

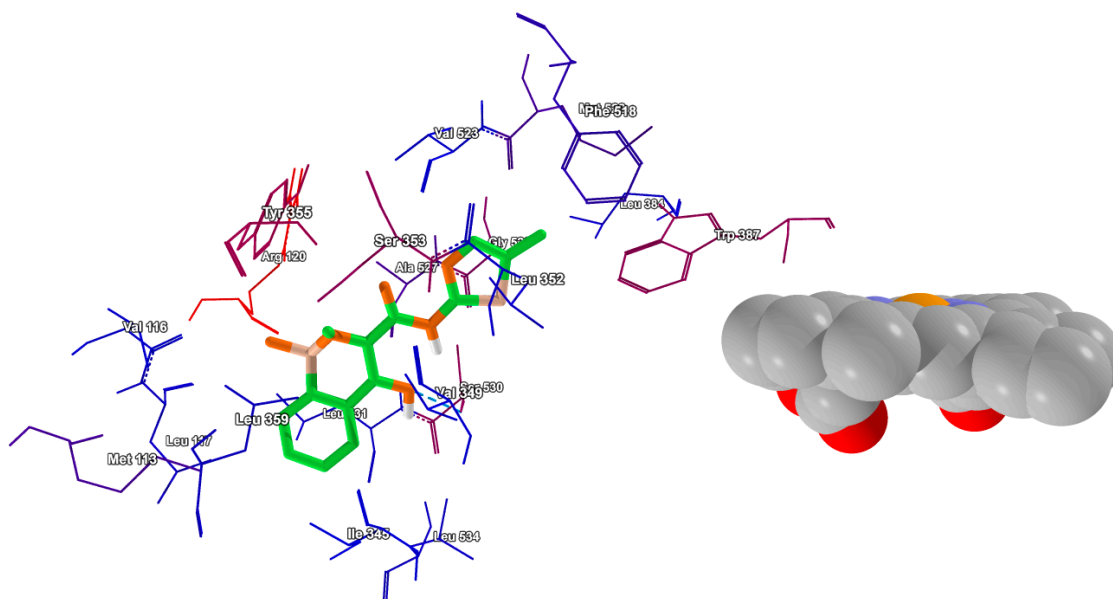


Figure S10. Binding mode of Meloxicam in 4M11 crystal (COX-2).

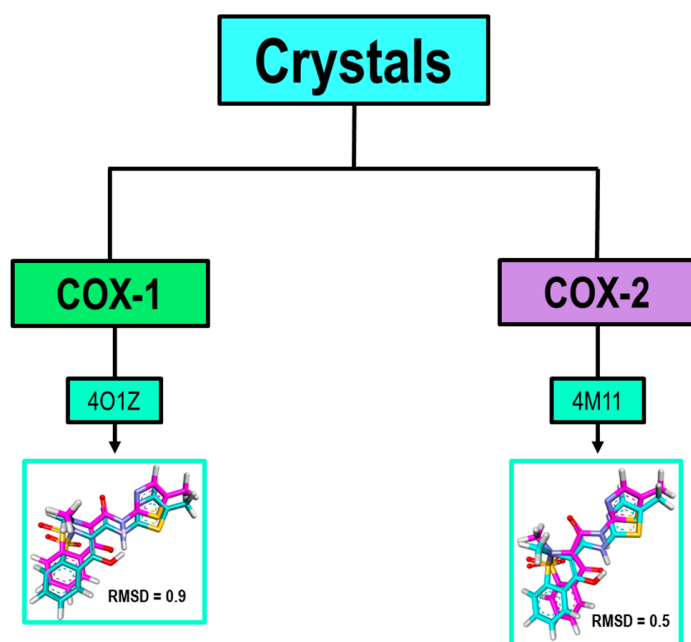
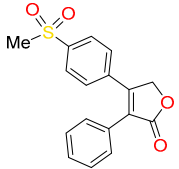
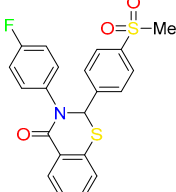
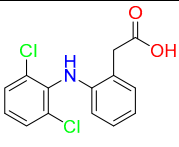
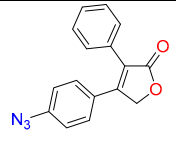
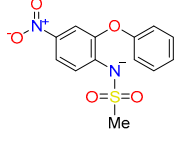
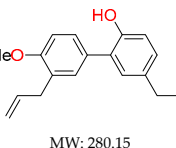
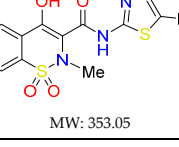
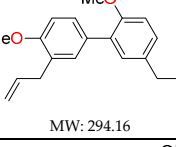
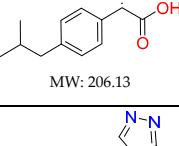
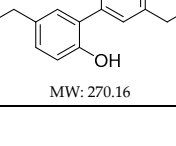
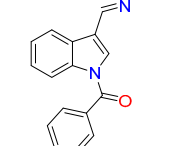
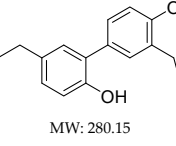
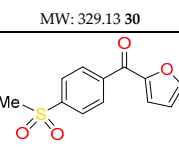
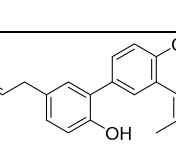
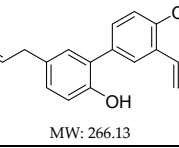


Figure S11. RMSD values obtained of structural validation of computational model with **Meloxicam** (Magenta) presented a parallel orientation of the nitrogen atom of the thiazole ring to the carbonyl of the amide original pose and color pose obtained in the molecule after experiment as show: Meloxicam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

Anti-inflammatory compound

Table S1. IC₅₀ 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

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

Interaction energy values (Kcal/mol) of COXs inhibitors

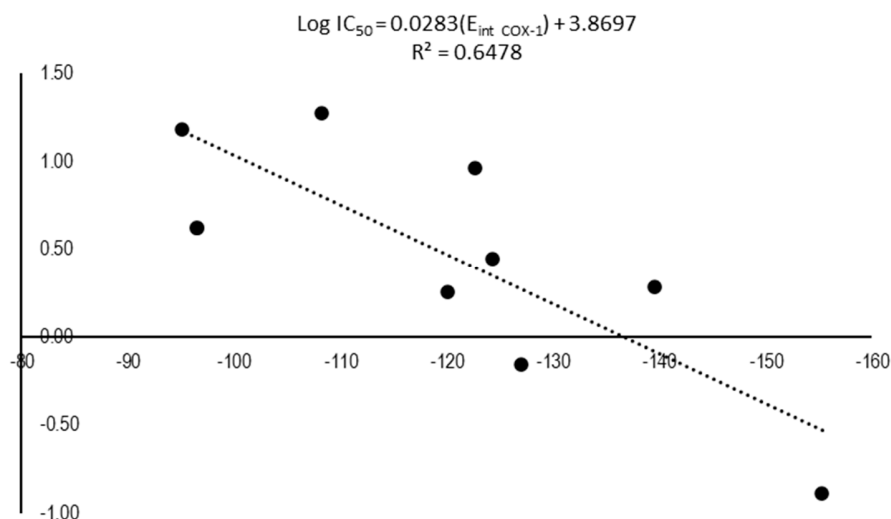


Figure S12.

Table S2. Interaction energy values (Kcal/mol) of COX-1 inhibitors that were coupled to the 1EQG crystal. Log IC₅₀ exp, Log IC₅₀ 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.

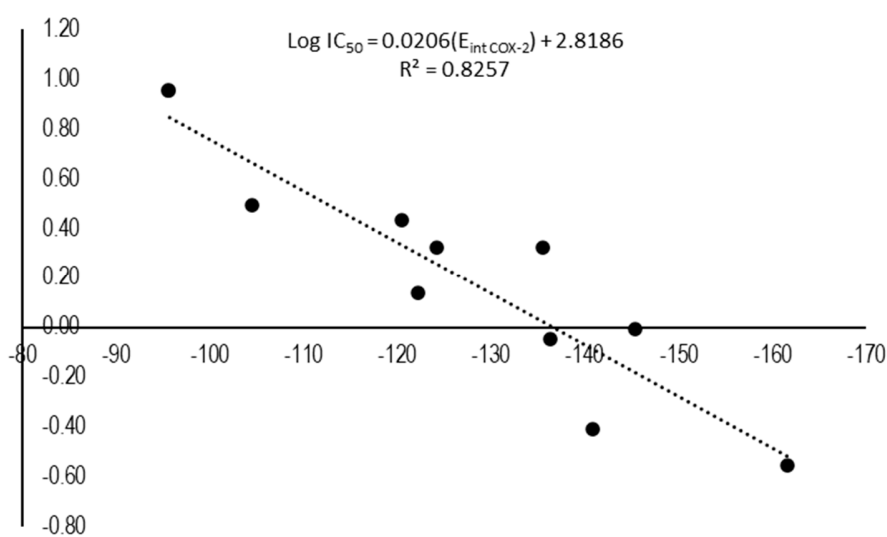


Figure S13.

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.

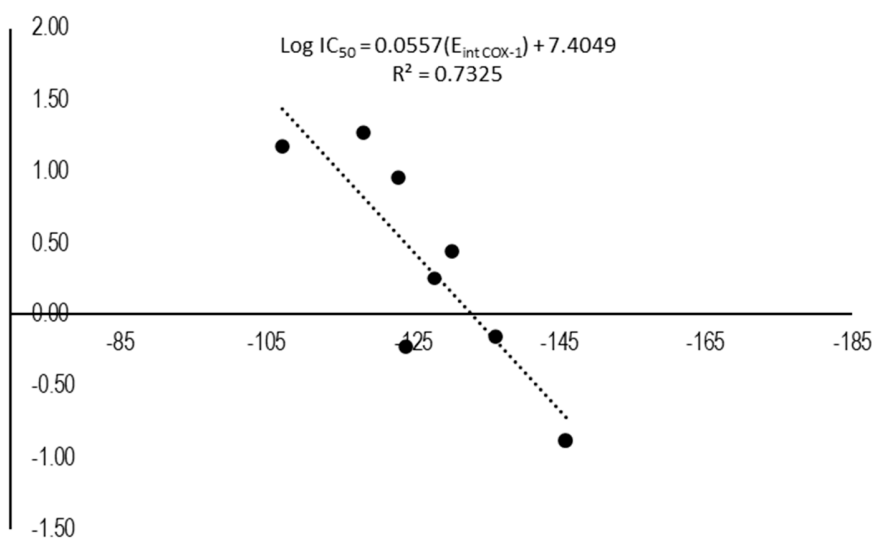


Figure S14.

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.

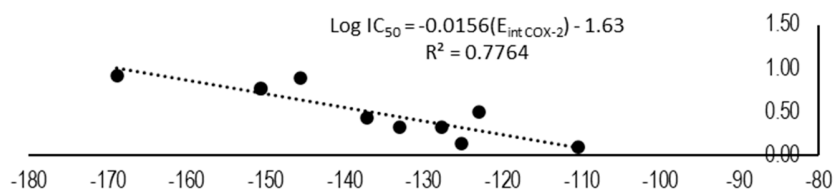


Figure S15.

Table S5. Interaction energy values (Kcal/mol) of COX-2 inhibitors that were coupled to the 4COX crystal. Log IC₅₀ exp, Log IC₅₀ 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.

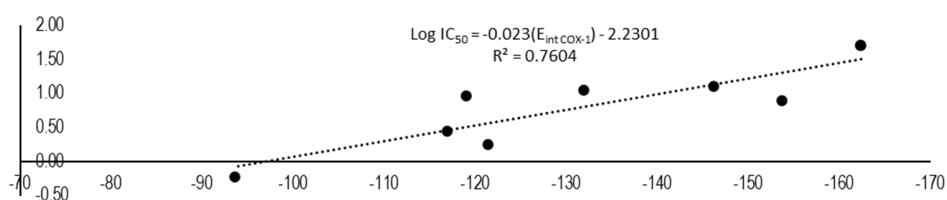


Figure S16.

Table S6. Interaction energy values (Kcal/mol) of COX-1 inhibitors that were coupled to the 3KK6 crystal. Log IC₅₀ exp, Log IC₅₀ 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.

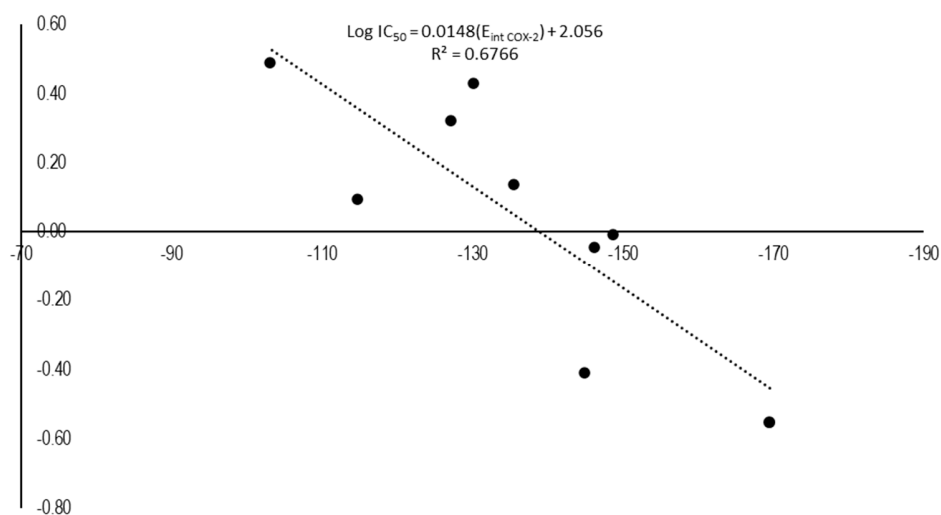


Figure S17.

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.

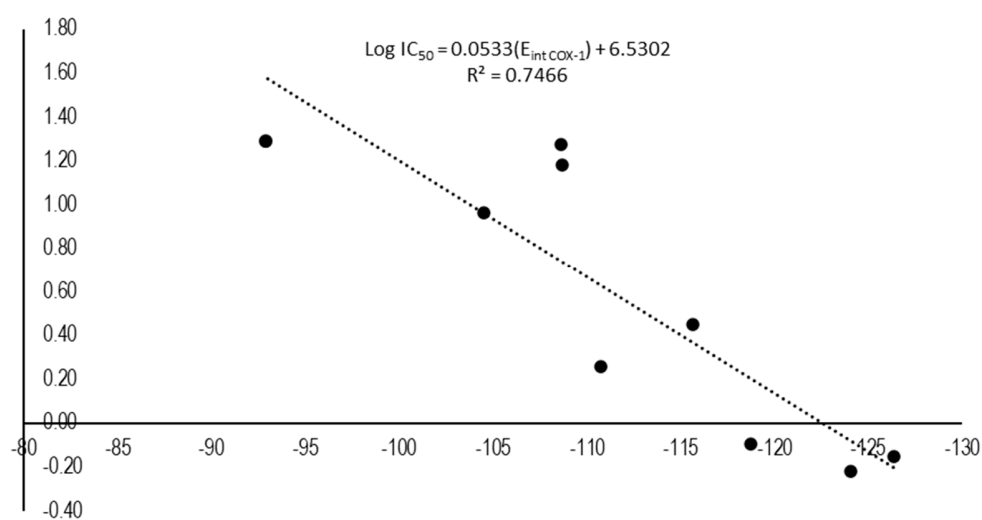


Figure S18.

Table S8. Interaction energy values (Kcal/mol) of COX-1 inhibitors that were coupled to the 4O1Z crystal. Log IC₅₀ exp, Log IC₅₀ 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.

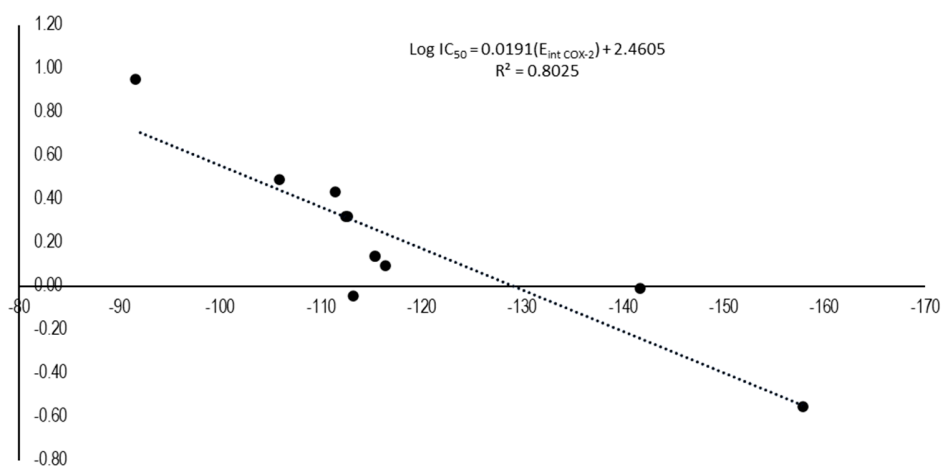


Figure S19.

Table S9. Interaction energy values (Kcal/mol) of COX-2 inhibitors that were coupled to the 4M11 crystal. Log IC₅₀ exp, Log IC₅₀ 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.

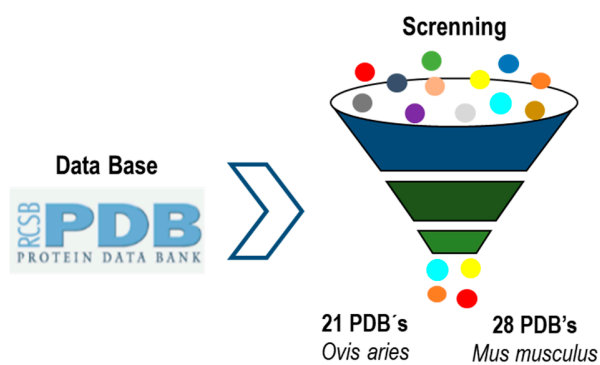


Figure S20. Search of crystals from COX-1 and COX-2.

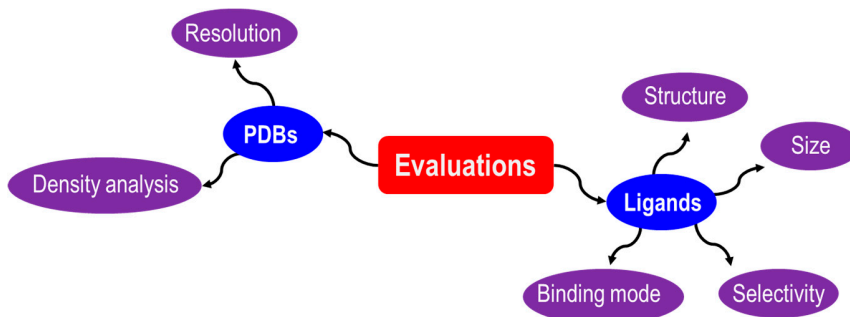


Figure S21. Analysis of crystals COXs with respect PDB and Ligands.

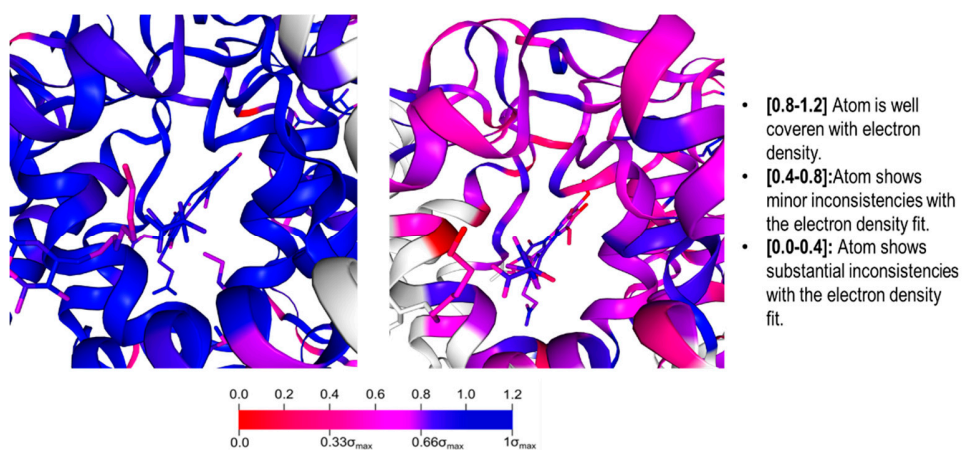


Figure S22. Examples of analysis about active site in crystals of COX-1 with EDIA. a) Ibuprofen (4PH9) with resolution of 2.6 Å, b) Flurbiprofen (3N8Z) with resolution of 2.9 Å.

Crystals selections

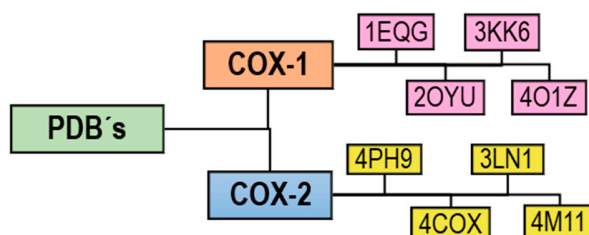


Figure S23. Final selection of crystals from computational model.

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.