

Supplementary materials

Synthesis of New Tricyclic 1,2-Thiazine Derivatives with Anti-Inflammatory Activity

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¹H NMR and ¹³C NMR spectra

compound	structure	page	compound	structure	page
5		S2	6d		S6
6a		S3	6e		S7
6b		S4	7		S8
6c		S5			

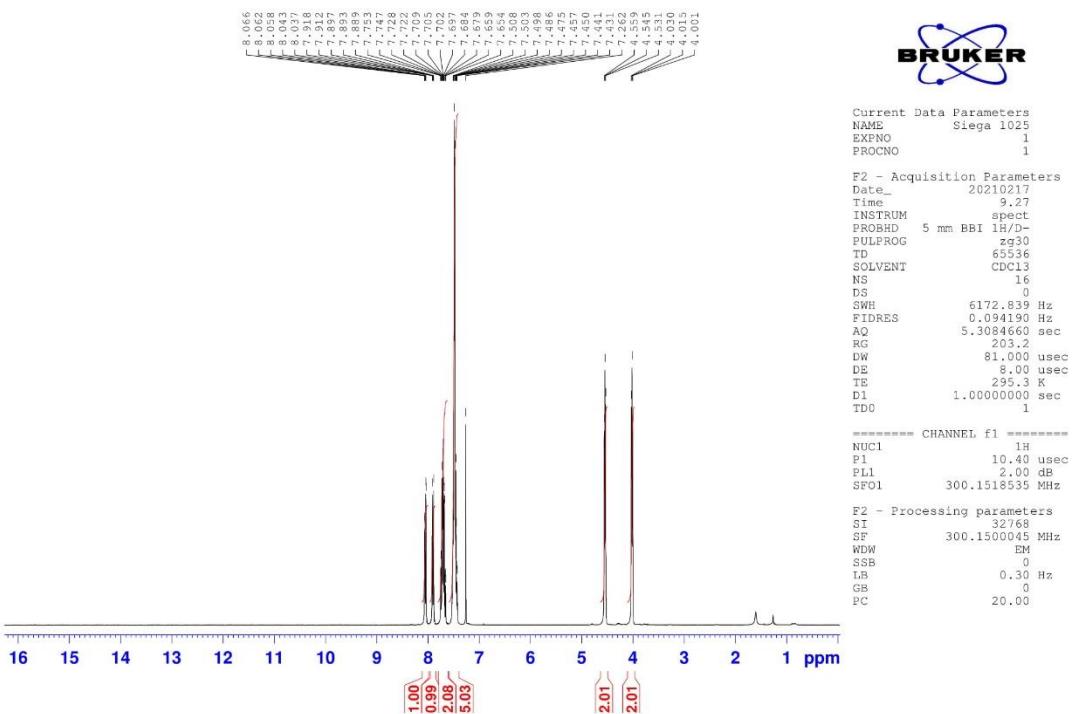


Figure S1. ^1H NMR spectrum of **5** in CDCl_3 .

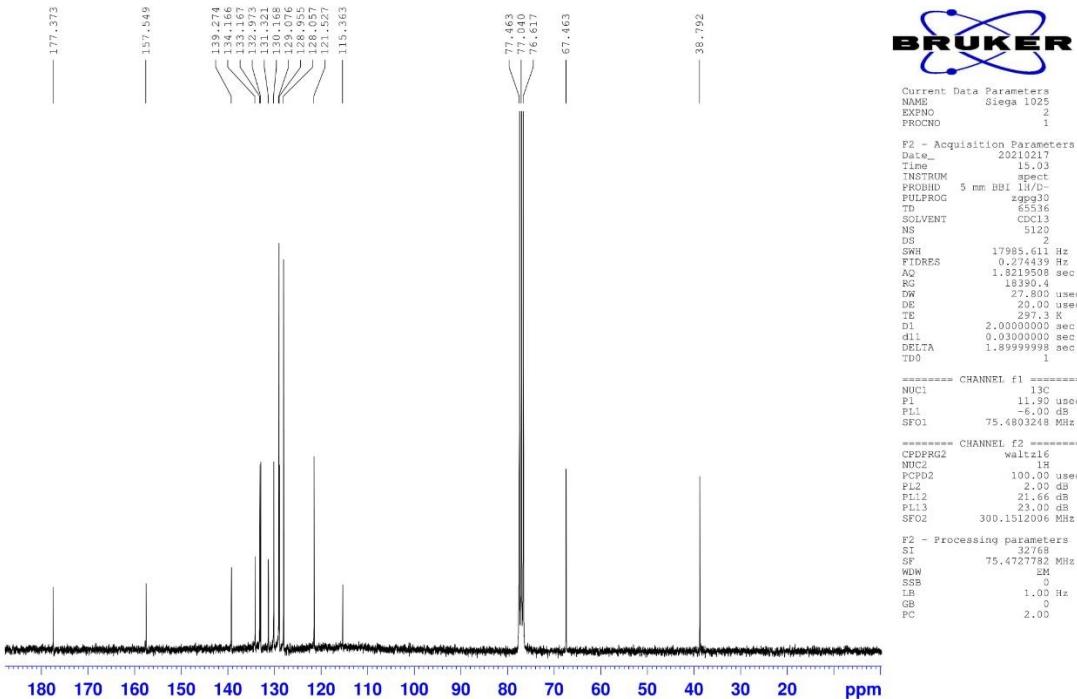


Figure S2. ^{13}C NMR spectrum of **5** in CDCl_3 .

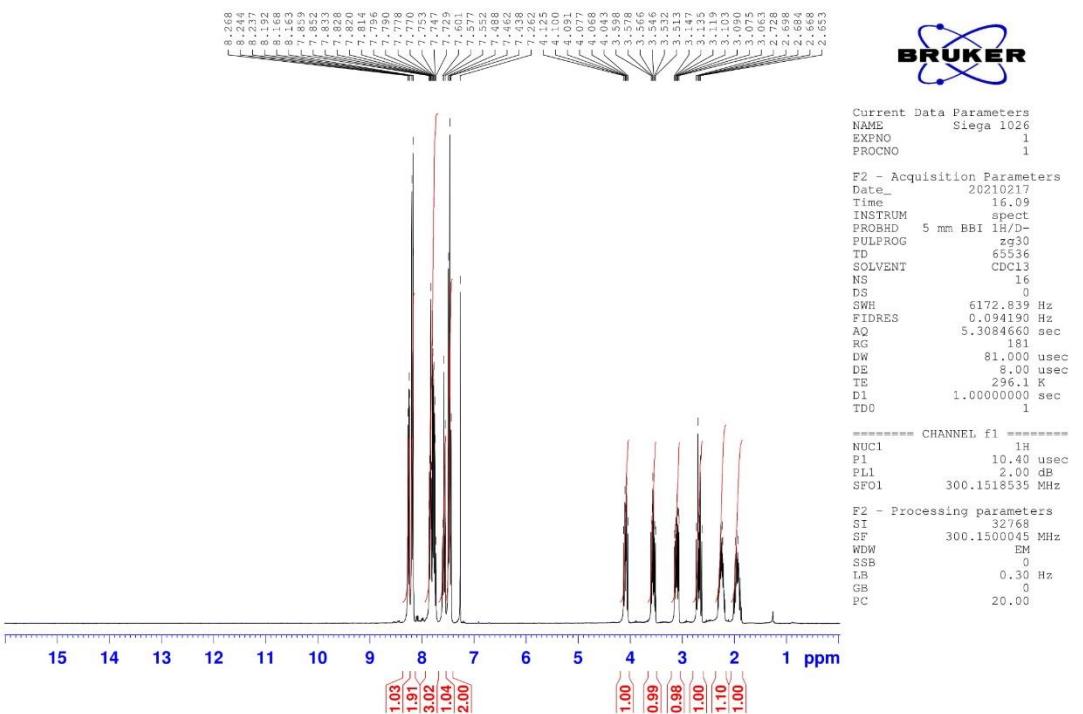


Figure S3. ^1H NMR spectrum of **6a** in CDCl_3 .

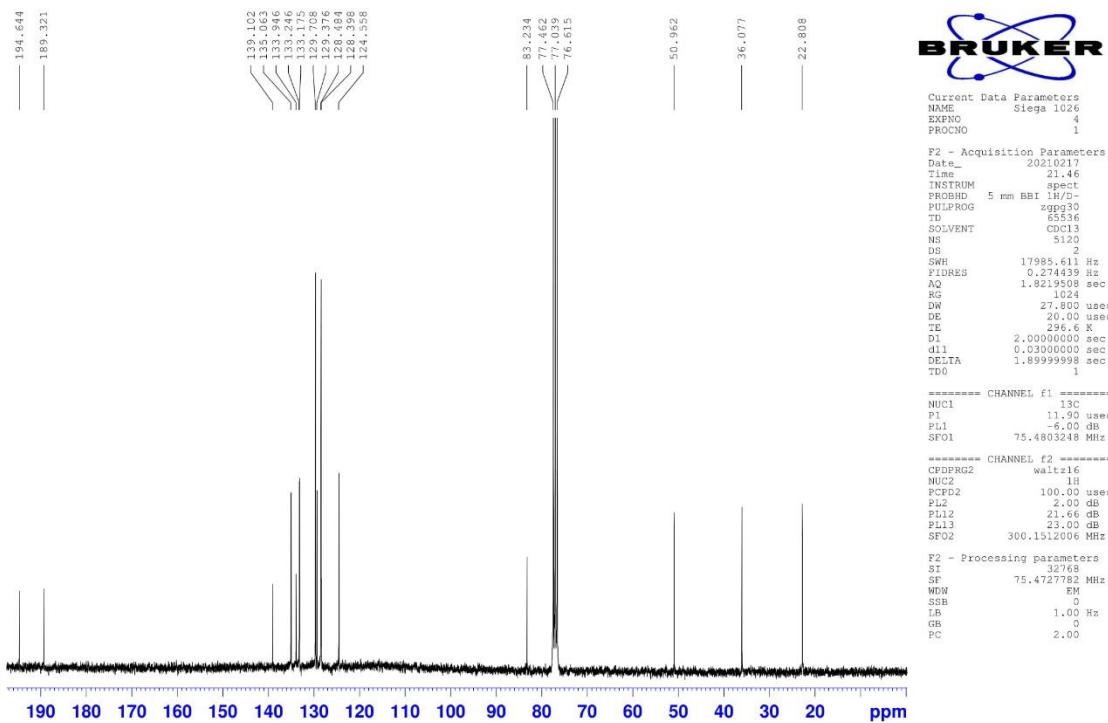


Figure S4. ^{13}C NMR spectrum of **6a** in CDCl_3 .

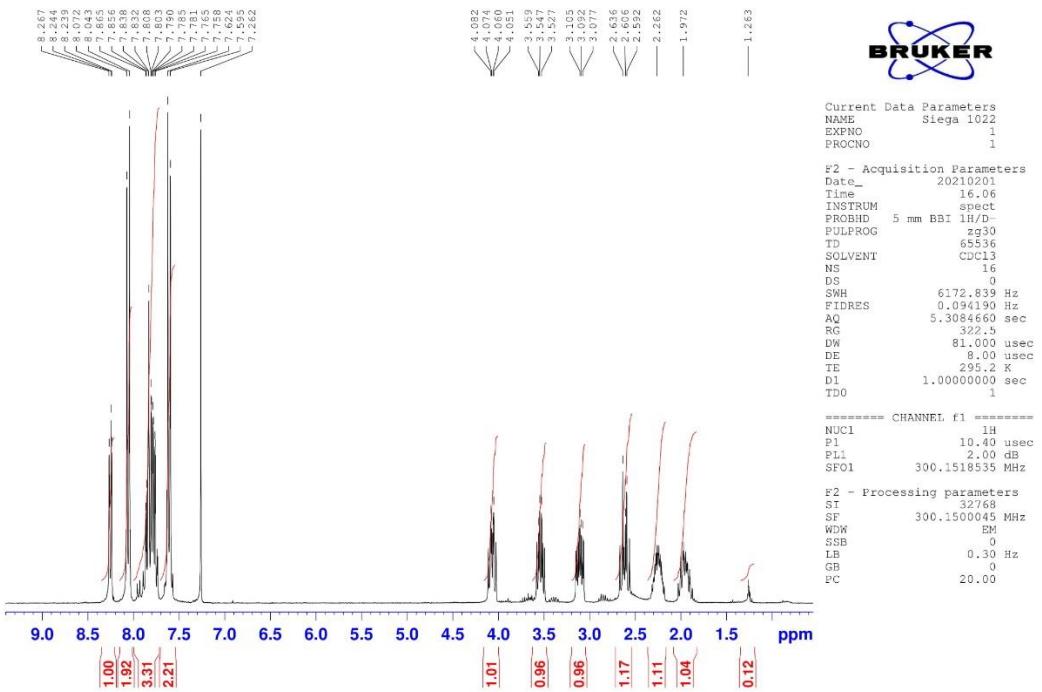


Figure S5. ^1H NMR spectrum of **6b** in CDCl_3 .

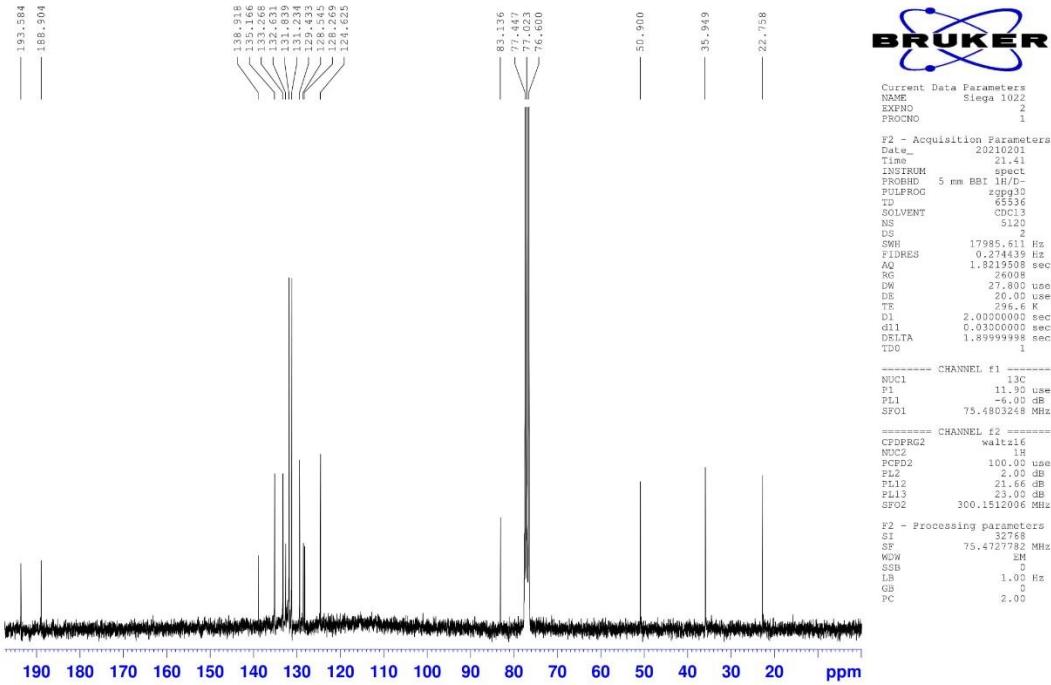


Figure S6. ^{13}C NMR spectrum of **6b** in CDCl_3 .

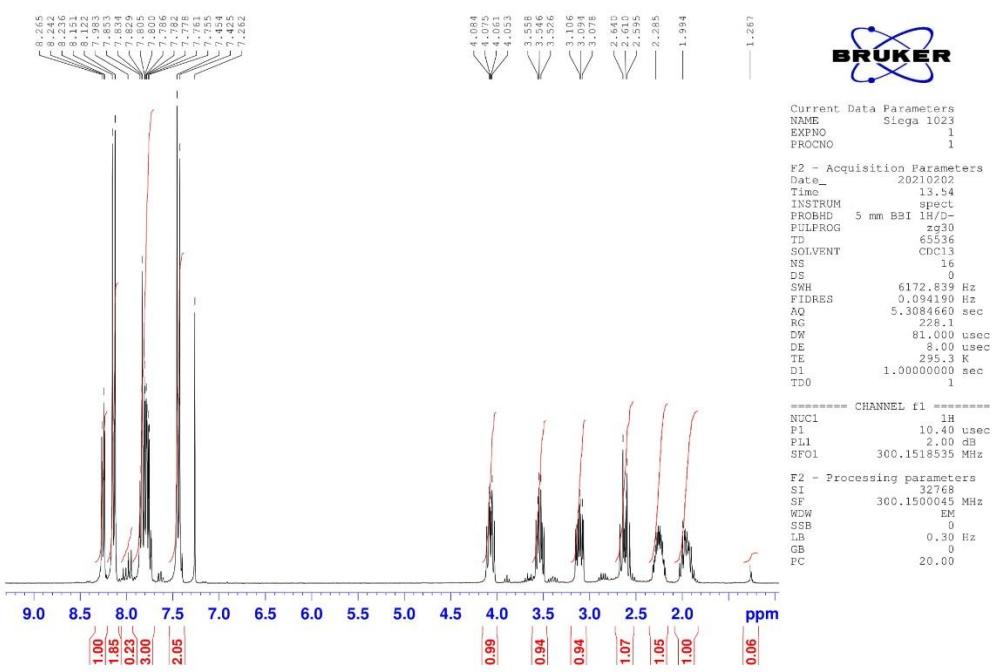


Figure S7. ^1H NMR spectrum of **6c** in CDCl_3 .

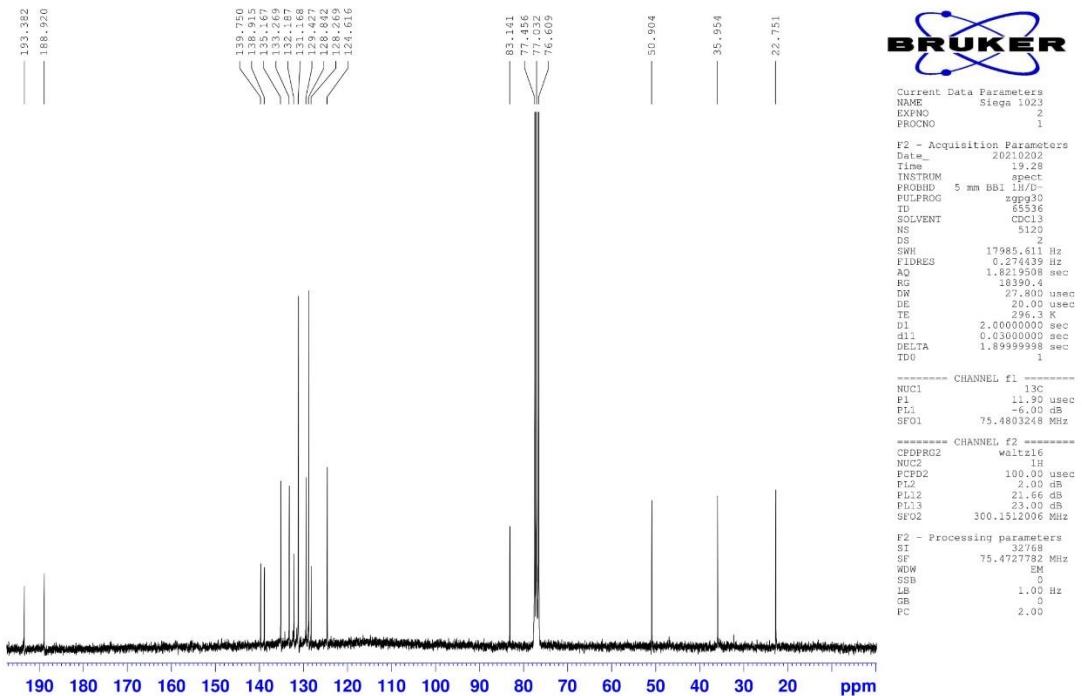


Figure S8. ^{13}C NMR spectrum of **6c** in CDCl_3 .

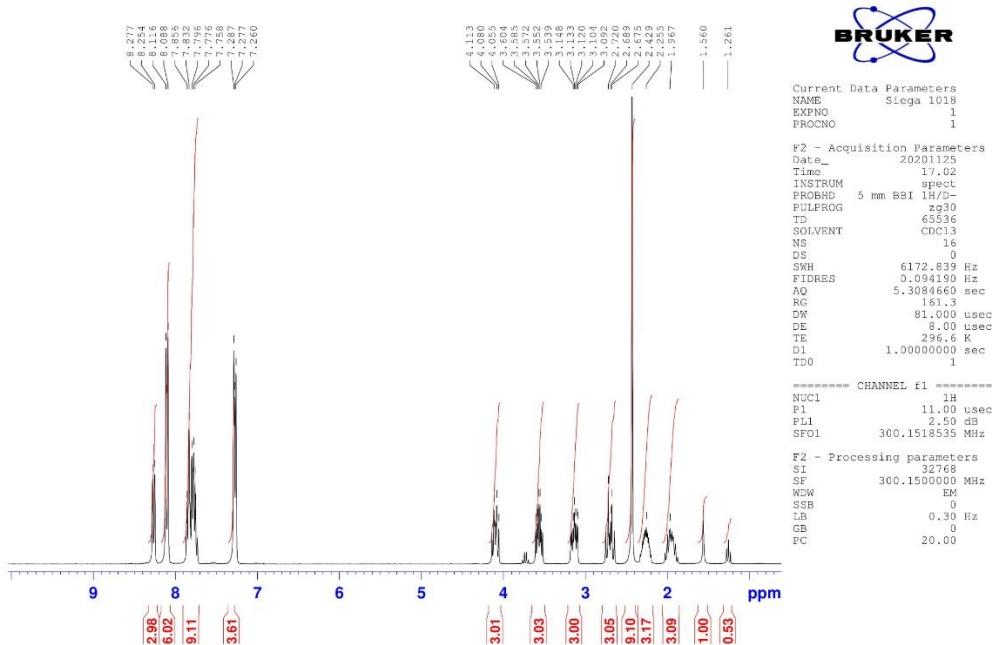


Figure S9. ^1H NMR spectrum of **6d** in CDCl_3 .

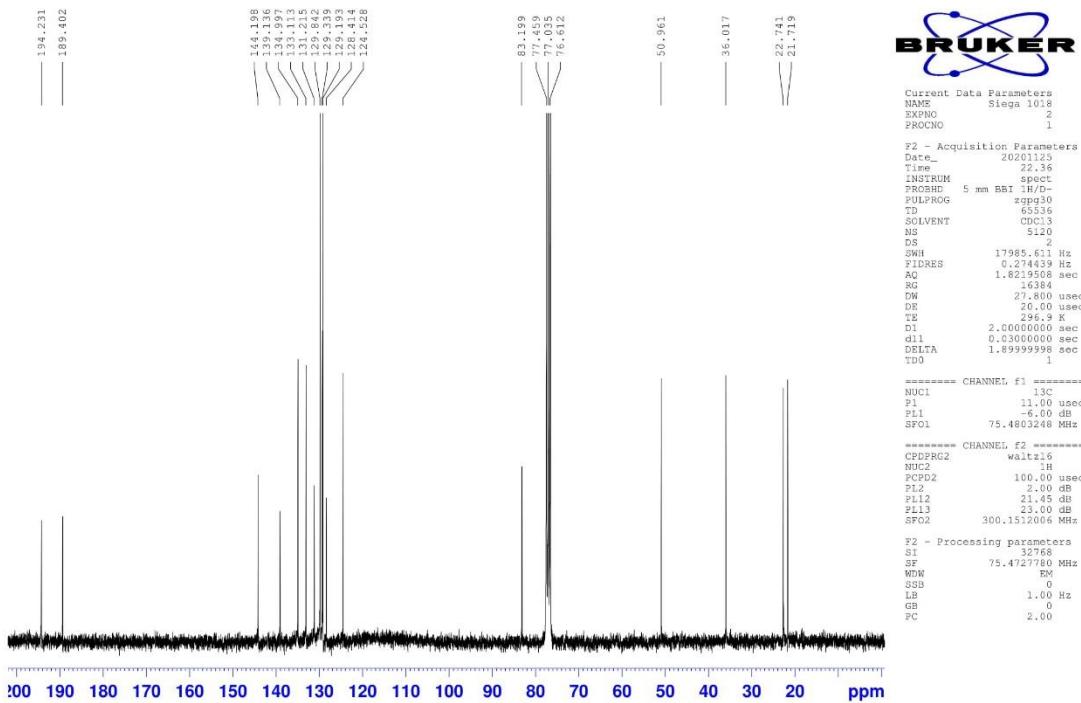


Figure S10. ^{13}C NMR spectrum of **6d** in CDCl_3 .

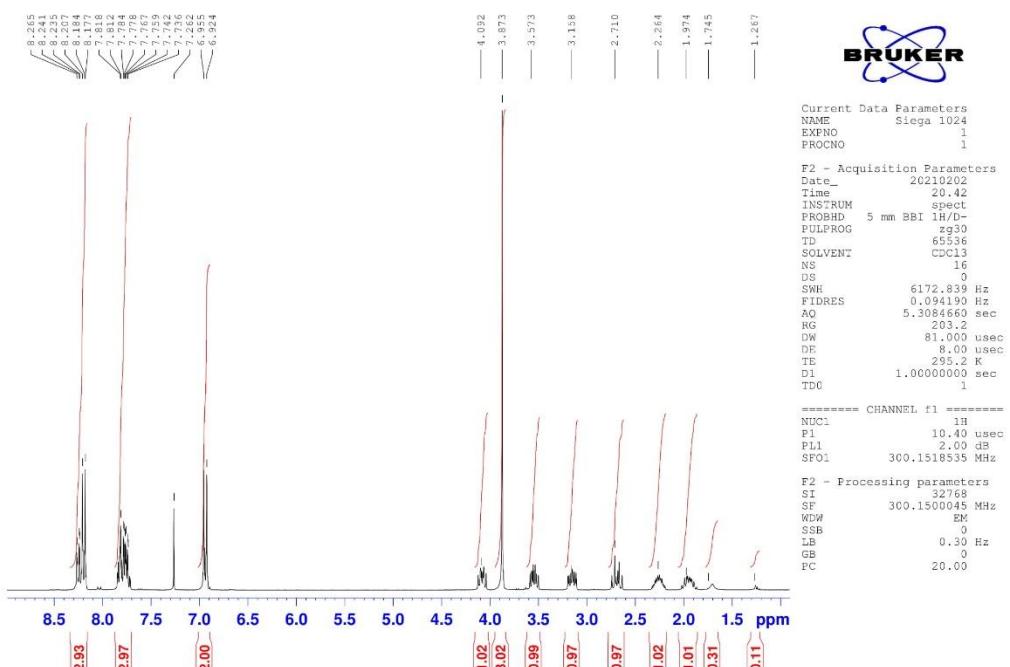


Figure S11. ^1H NMR spectrum of **6e** in CDCl_3 .

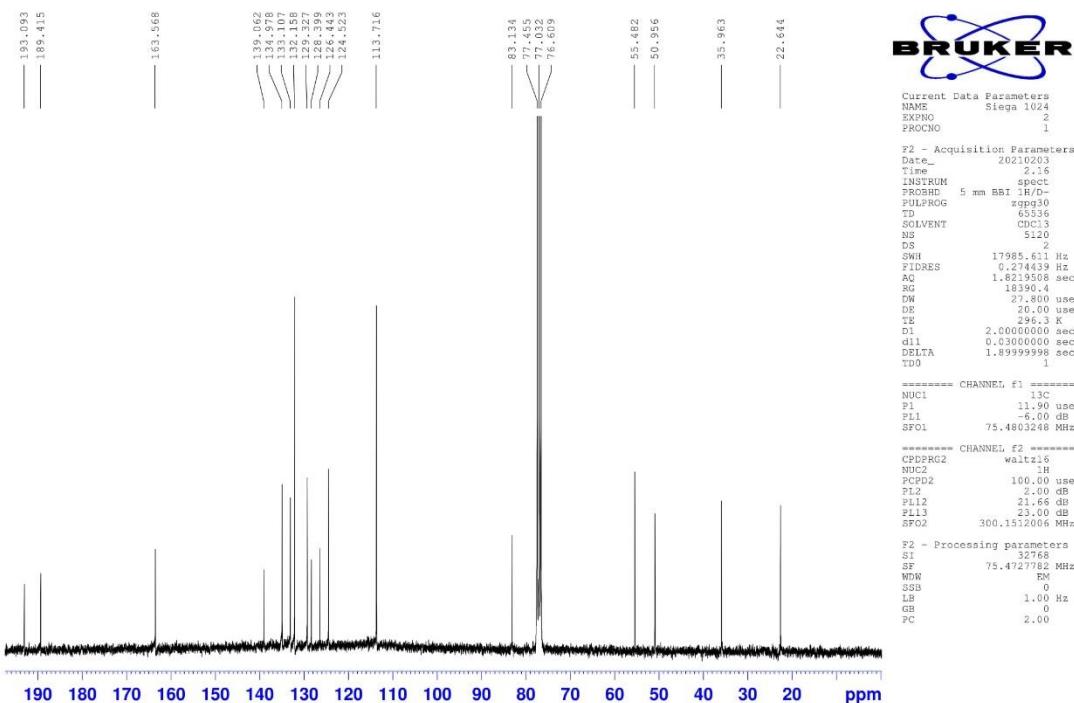


Figure S12. ^{13}C NMR spectrum of **6e** in CDCl_3 .

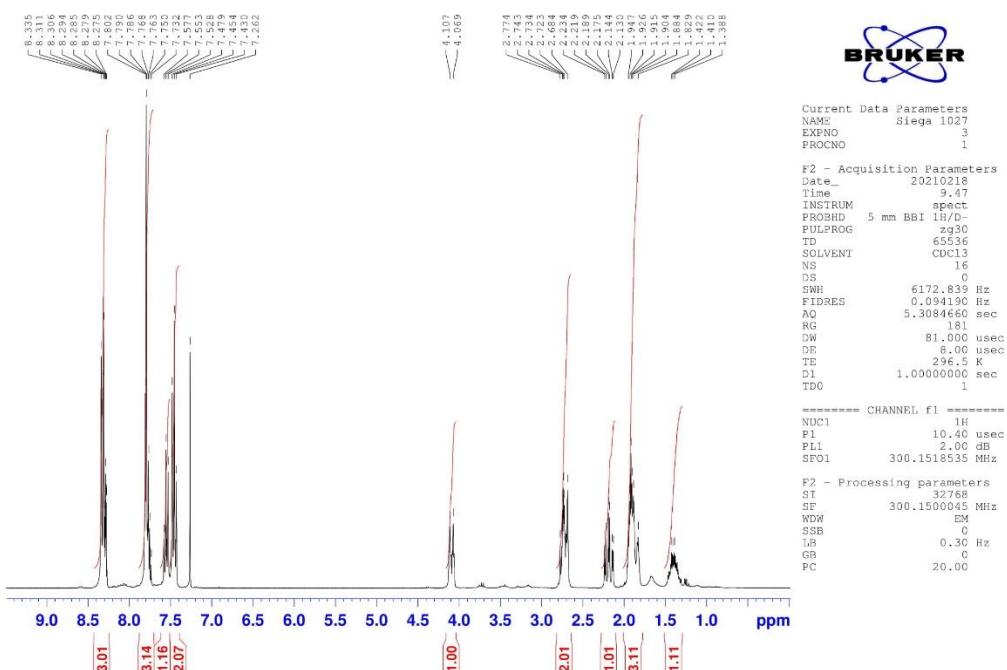


Figure S13. ^1H NMR spectrum of **7** in CDCl_3 .

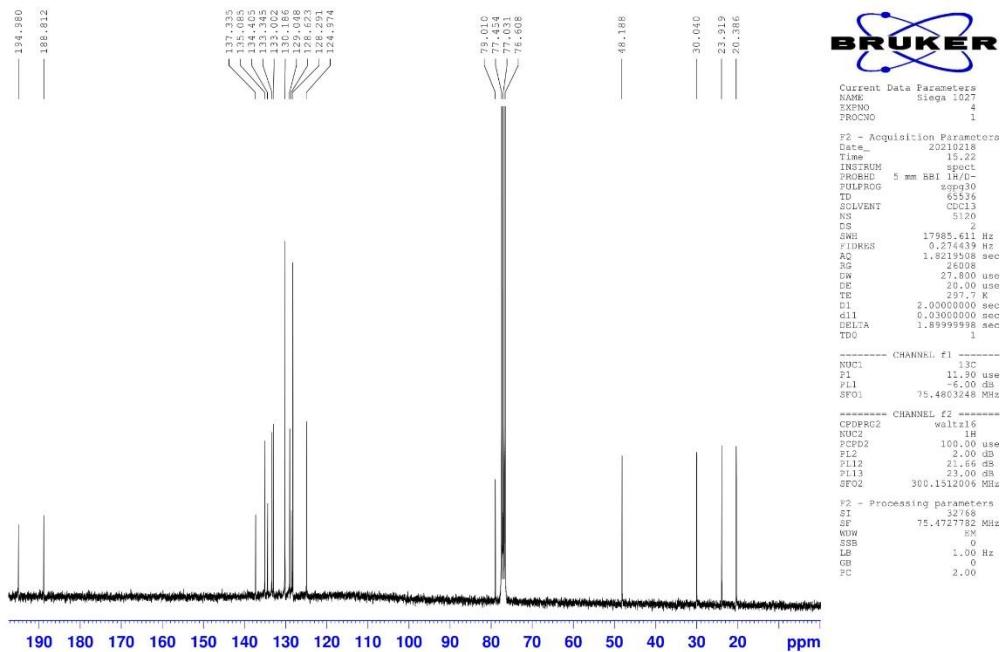


Figure S14. ^{13}C NMR spectrum of **7** in CDCl_3 .

The influence of new 1,2-thiazine derivatives on the thermotropic properties of DPPC model membranes

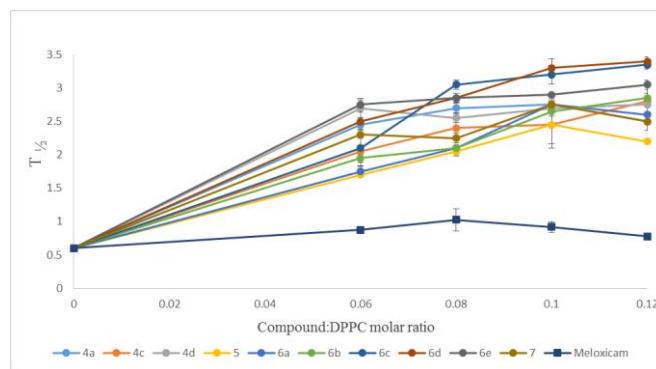


Figure S15. The effect of 1,2-thiazine derivatives in comparison to the meloxicam on the transition half height ($T_{1/2}$) of the main phase transition of DPPC.

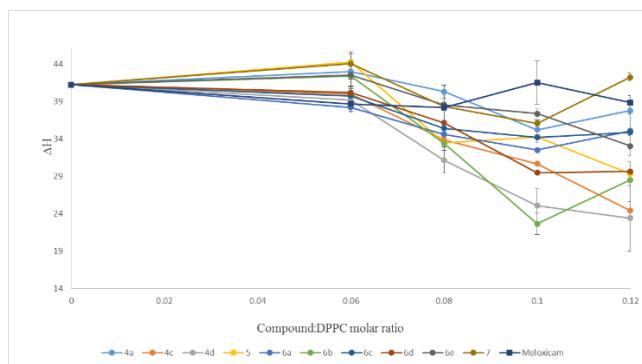


Figure S16. The effect of 1,2-thiazine derivatives in comparison to the meloxicam on the transition enthalpy (ΔH) of the main phase transition of DPPC

Table S1. Values of DPPC phase transition temperatures (T_M) with studied compounds

Compound	DPPC T_M values for different molar ratios of compound studied:lipid ± SD			
	0.06	0.08	0.1	0.12
4a	38,85 ± 0,07	38,4 ± 0,14	37,9 ± 0,14	37,85 ± 0,07
4c	39,35 ± 0,09	39,05 ± 0,07	39,1 ± 0,03	38,75 ± 0,21
4d	39,95 ± 0,04	38,5 ± 0,02	38,05 ± 0,07	38,35 ± 0,20
5	40,15 ± 0,07	39,75 ± 0,08	40 ± 0,02	39,35 ± 0,06
6a	39,95 ± 0,07	39,55 ± 0,07	38,7 ± 0,14	38,65 ± 0,07
6b	40,05 ± 0,08	40,6 ± 0,02	40 ± 0,14	39,25 ± 0,06
6c	39,2 ± 0,06	38,5 ± 0,06	37,6 ± 0,02	37,1 ± 0,13
6d	39 ± 0,00	38,5 ± 0,00	37,25 ± 0,08	37,15 ± 0,06
6e	39,2 ± 0,14	38,9 ± 0,02	38,65 ± 0,07	38,2 ± 0,03
7	39,1 ± 0,06	39,1 ± 0,03	38,5 ± 0,03	38,9 ± 0,13
meloxicam	40,62 ± 0,05	40,69 ± 0,03	40,72 ± 0,04	40,7 ± 0,00

Table S2. Values of DPPC transition half height ($T_{1/2}$) with studied compounds

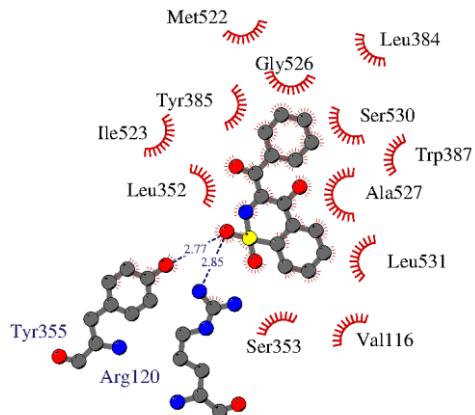
Compound	DPPC $T_{1/2}$ values for different molar ratios of compound studied:lipid \pm SD			
	0.06	0.08	0.1	0.12
4a	2.45 \pm 0.07	2.7 \pm 0.07	2.75 \pm 0.07	2.5 \pm 0.13
4c	2.05 \pm 0.21	2.4 \pm 0.14	2.45 \pm 0.28	2.8 \pm 0.04
4d	2.7 \pm 0.13	2.55 \pm 0.05	2.7 \pm 0.07	2.75 \pm 0.28
5	1.7 \pm 0.03	2.05 \pm 0.07	2.45 \pm 0.35	2.2 \pm 0.04
6a	1.75 \pm 0.06	2.1 \pm 0.00	2.75 \pm 0.07	2.6 \pm 0.14
6b	1.95 \pm 0.07	2.1 \pm 0.03	2.65 \pm 0.07	2.85 \pm 0.07
6c	2.1 \pm 0.14	3.05 \pm 0.07	3.2 \pm 0.14	3.35 \pm 0.07
6d	2.5 \pm 0.00	2.85 \pm 0.07	3.3 \pm 0.02	3.4 \pm 0.00
6e	2.75 \pm 0.06	2.85 \pm 0.05	2.9 \pm 0.00	3.05 \pm 0.07
7	2.3 \pm 0.03	2.25 \pm 0.07	2.75 \pm 0.07	2.5 \pm 0.07
meloxicam	0.87 \pm 0.05	1.02 \pm 0.17	0.92 \pm 0.07	0.77 \pm 0.05

Table S3. Values of DPPC transition enthalpy changes (ΔH) with studied compounds

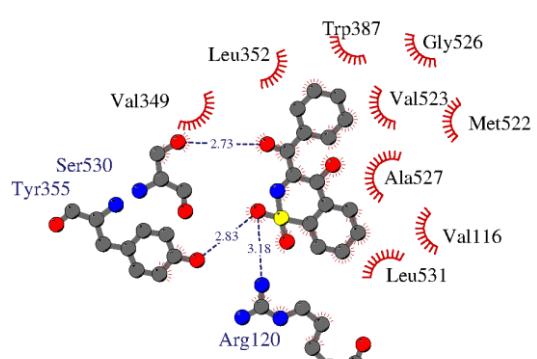
Compound	DPPC ΔH values for different molar ratios of compound studied:lipid \pm SD			
	0.06	0.08	0.1	0.12
4a	42.9 \pm 2.29	40.3 \pm 0.85	35.2 \pm 0.99	37.8 \pm 0.43
4c	40.0 \pm 1.94	33.9 \pm 1.41	30.7 \pm 0.11	24.4 \pm 1.16
4d	39.2 \pm 1.71	31.2 \pm 1.78	25.1 \pm 2.27	23.4 \pm 4.41
5	44.2 \pm 1.43	33.5 \pm 0.09	34.2 \pm 0.79	29.3 \pm 1.61
6a	38.2 \pm 0.20	34.6 \pm 0.27	32.5 \pm 0.12	35.1 \pm 0.18
6b	42.4 \pm 0.06	33.4 \pm 0.52	22.6 \pm 1.43	28.5 \pm 0.81
6c	39.6 \pm 0.81	35.4 \pm 0.01	34.2 \pm 0.29	34.9 \pm 3.09
6d	40.2 \pm 0.12	36.1 \pm 0.60	29.5 \pm 0.19	29.6 \pm 0.31
6e	42.5 \pm 1.51	38.5 \pm 0.53	37.4 \pm 0.43	33.0 \pm 0.51
7	44.0 \pm 2.06	38.3 \pm 1.17	36.1 \pm 0.64	42.2 \pm 1.43
meloxicam	38.7 \pm 0.93	38.2 \pm 2.88	41.5 \pm 2.91	38.8 \pm 0.93

Molecular docking studies

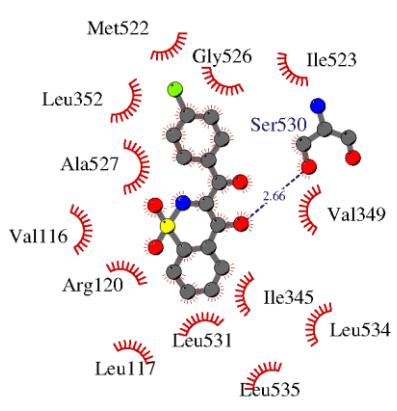
4a - COX-1



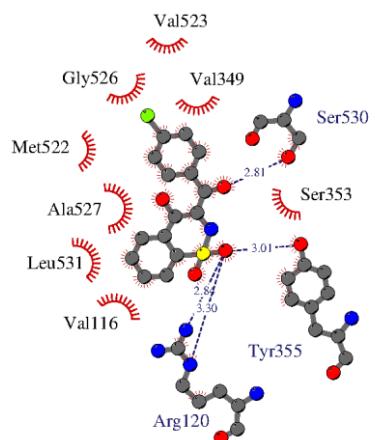
4a - COX-2



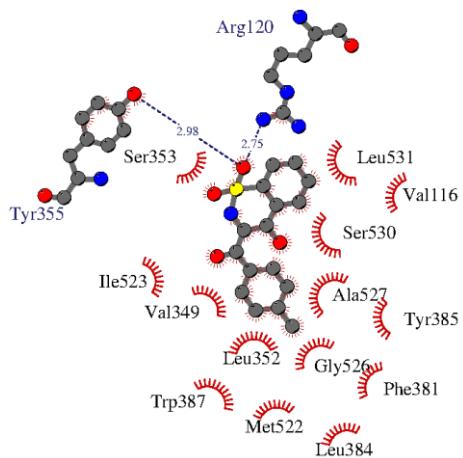
4c - COX-1



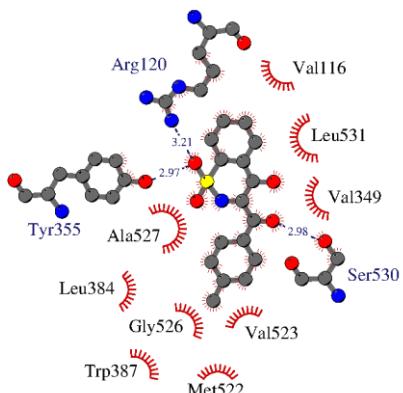
4c - COX-2



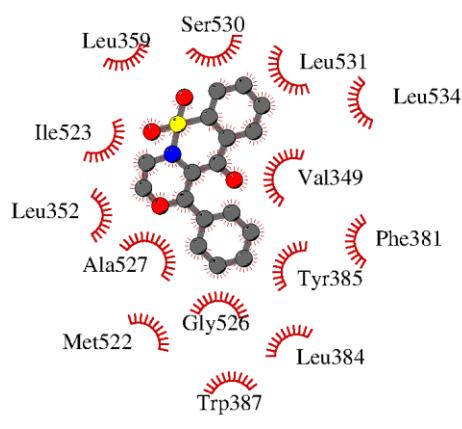
4d - COX-1



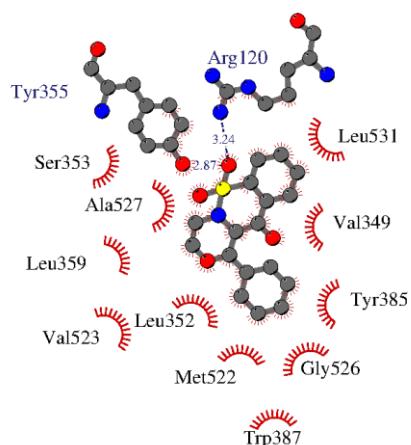
4d - COX-2



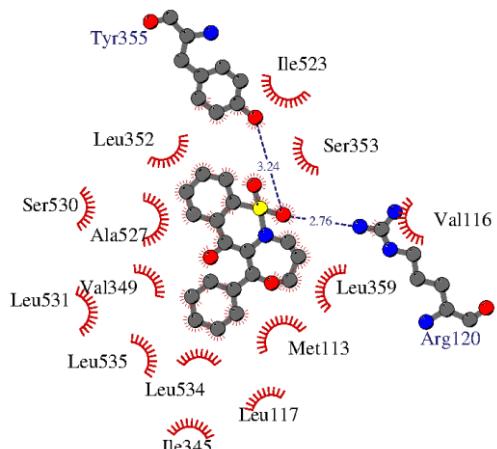
5 - COX-1



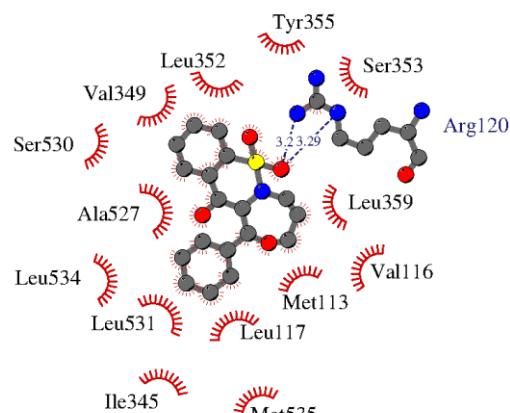
5 - COX-2



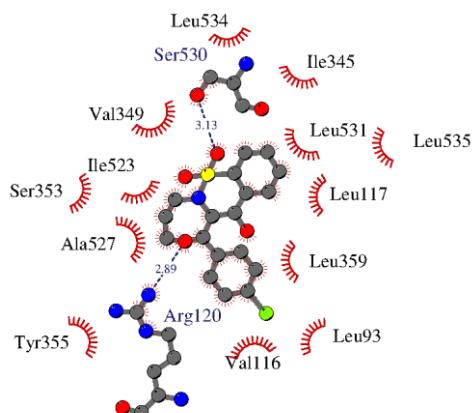
6a - COX-1



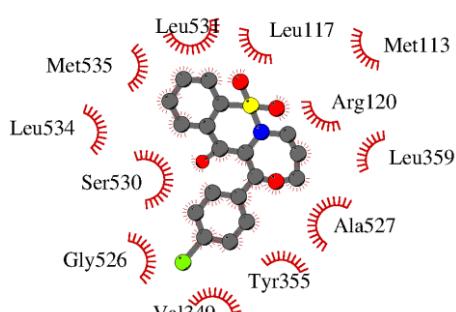
6a - COX-2



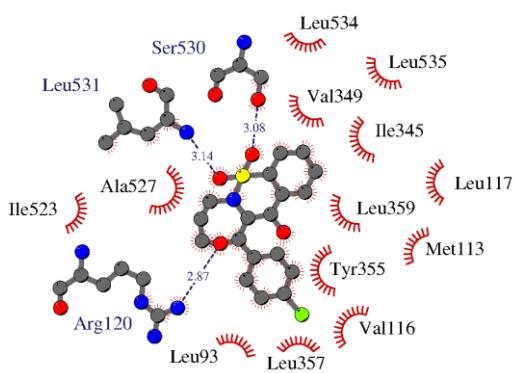
6b - COX-1



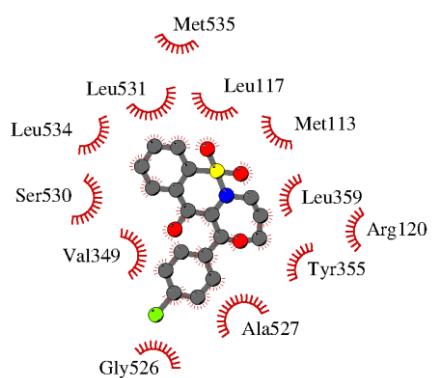
6b - COX-2



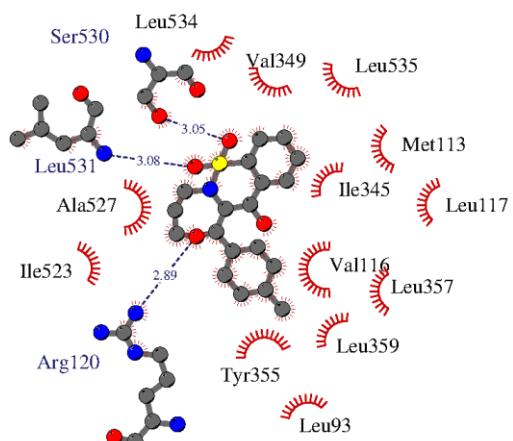
6c - COX-1



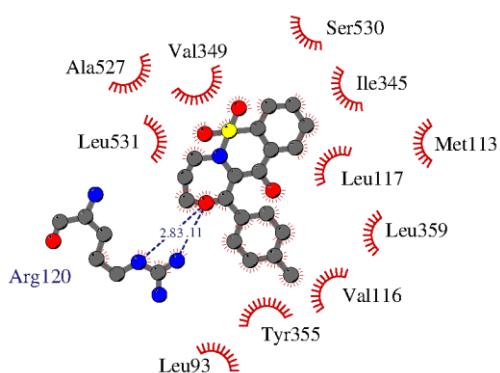
6c - COX-2



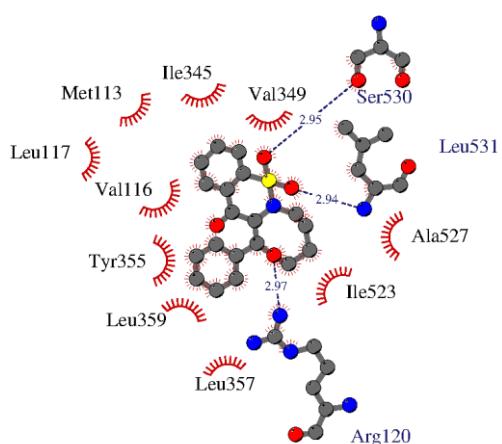
6d - COX-1



6d - COX-2



7 - COX-1



7 - COX-2

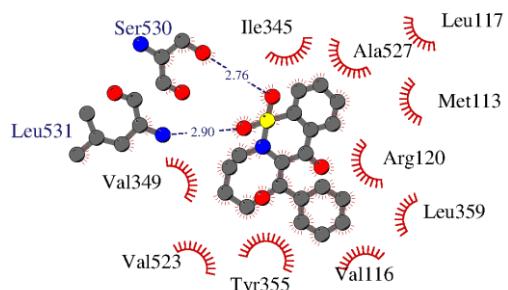


Figure S17. The intermolecular interactions between COX-1 and COX-2 and designed compounds (hydrophobic as red arches and hydrogen bonds as navy blue lines).

Table S4. Free energy of binding and intermolecular interactions of new 1,2-benzothiazine derivatives with COX-1.

Compound	Free energy of binding to COX-1 [kcal/mol]	Hydrogen bonds (distance between electronegative atoms)	Hydrophobic interactions
4a	-8.9	Arg120 (2.85 Å)	Val116, Arg120, Leu352, Ser353, Tyr355, Leu384, Tyr385, Trp387, Met522, Ile523, Gly526, Ala527, Ser530, Leu531
4c	-10.0	Tyr355 (2.77 Å)	Val116, Leu117, Arg120, Ile345, Val349, Leu352, Met522, Ile523, Gly526, Ala527, Ser530, Leu531, Leu534, Leu535
4d	-9.0	Ser530 (2.66 Å)	Val116, Arg120, Val349, Leu352, Ser353, Tyr355, Phe381, Leu384, Tyr385, Trp387, Met522, Ile523, Gly526, Ala527, Ser530, Leu531
5	-9.7	Arg120 (2.75 Å)	Val349, Leu352, Leu359, Phe381, Leu384, Tyr385, Trp387, Met522, Ile523, Gly526, Ala527, Ser530, Leu531, Leu534
6a	-9.4	Tyr355 (2.98 Å)	Met113, Val116, Leu117, Arg120, Leu345, Val349, Leu352, Ser353, Tyr355, Leu359, Ile523, Ala527, Ser530, Leu531, Leu534, Leu535
6b	-9.7	–	Leu93, Val116, Leu117, Arg120, Ile345, Val349, Ser353, Tyr355, Leu359, Ile523, Ala527, Ser530, Leu531, Leu534, Leu535
6c	-9.5	Arg120 (2.76 Å)	Leu93, Met113, Val116, Leu117, Arg120, Ile345, Val349, Tyr355, Leu357, Leu359, Ile523, Ala527, Ser530, Leu531, Leu534, Leu535
6d	-9.3	Tyr355 (3.24 Å)	Leu93, Met113, Val116, Leu117, Arg120, Ile345, Val349, Tyr355, Leu357, Leu359, Ile523, Ala527, Ser530, Leu531, Leu534, Leu535
6e	-8.9	Arg120 (2.89 Å)	Leu93, Met113, Val116, Leu117, Arg120, Ile345, Val349, Tyr355, Leu357, Leu359, Ile523, Ala527, Ser530, Leu531, Leu534, Leu535
7	-8.7	Ser530 (3.13 Å)	Met113, Val116, Leu117, Arg120, Ile345, Val349, Tyr355, Leu357, Leu359, Ala527, Ser530, Leu531

Table S5. Free energy of binding and intermolecular interactions of new 1,2-benzothiazine derivatives with COX-2.

Compound	Free energy of binding		Hydrogen bonds	Hydrophobic interactions
	to COX-2 [kcal/mol]	(distance between electronegative atoms)		
4a	-11.2	Arg120 (3.18 Å) Tyr355 (2.83 Å) Ser530 (2.73 Å)		Val116, Arg120, Val349, Leu352, Tyr355, Trp387, Met522, Val523, Gly526, Ala527, Ser530, Leu531
4c	-12.6	Arg120 (2.84 Å, 3.30 Å) Tyr355 (3.01 Å) Ser530 (2.81 Å)		Val116, Arg120, Val349, Ser353, Tyr355, Met522, Val523, Gly526, Ala527, Ser530, Leu531
4d	-9.4	Arg120 (3.21 Å) Tyr355 (2.97 Å) Ser530 (2.98 Å)		Val116, Arg120, Val349, Tyr355, Leu384, Trp387, Met522, Val523, Gly526, Ala527, Ser530, Leu531
5	-9.8	Arg120 (3.24 Å) Tyr355 (2.87 Å)		Arg120, Val349, Leu352, Ser353, Tyr355, Leu359, Tyr385, Trp387, Met522, Val523, Gly526, Ala527, Leu531
6a	-9.5	Arg120 (3.23 Å, 3.29 Å)		Met113, Val116, Leu117, Arg120, Ile345, Val349, Leu352, Ser353, Tyr355, Leu359, Ala527, Ser530, Leu531, Leu534, Met535
6b	-8.8	—		Met113, Leu117, Arg120, Val349, Tyr355, Leu359, Gly526, Ala527, Ser530, Leu531, Leu534, Met535
6c	-9.2	—		Met113, Leu117, Arg120, Val349, Tyr355, Leu359, Gly526, Ala527, Ser530, Leu531, Leu534, Met535
6d	-9.4	Arg120 (2.83 Å, 3.11 Å)		Leu93, Met113, Val116, Leu117, Arg120, Ile345, Val349, Tyr355, Leu359, Ala527, Ser530, Leu531
6e	-9.6			Ile345, Val349, Leu352, Tyr355, Ser353, Leu359, Tyr385, Trp387, Val523, Gly526, Ala527, Ser530, Leu531, Met535, Leu534,
7	-9.6	Ser530 (2.76 Å) Leu531 (2.90 Å)		Met113, Val116, Leu117, Arg120, Ile345, Val349, Tyr355, Leu359, Val523, Ala527, Ser530, Leu531