

## SUPPORTING INFORMATION

### Research developments in the syntheses, anti-inflammatory activities and structure-activity relationships of pyrimidines

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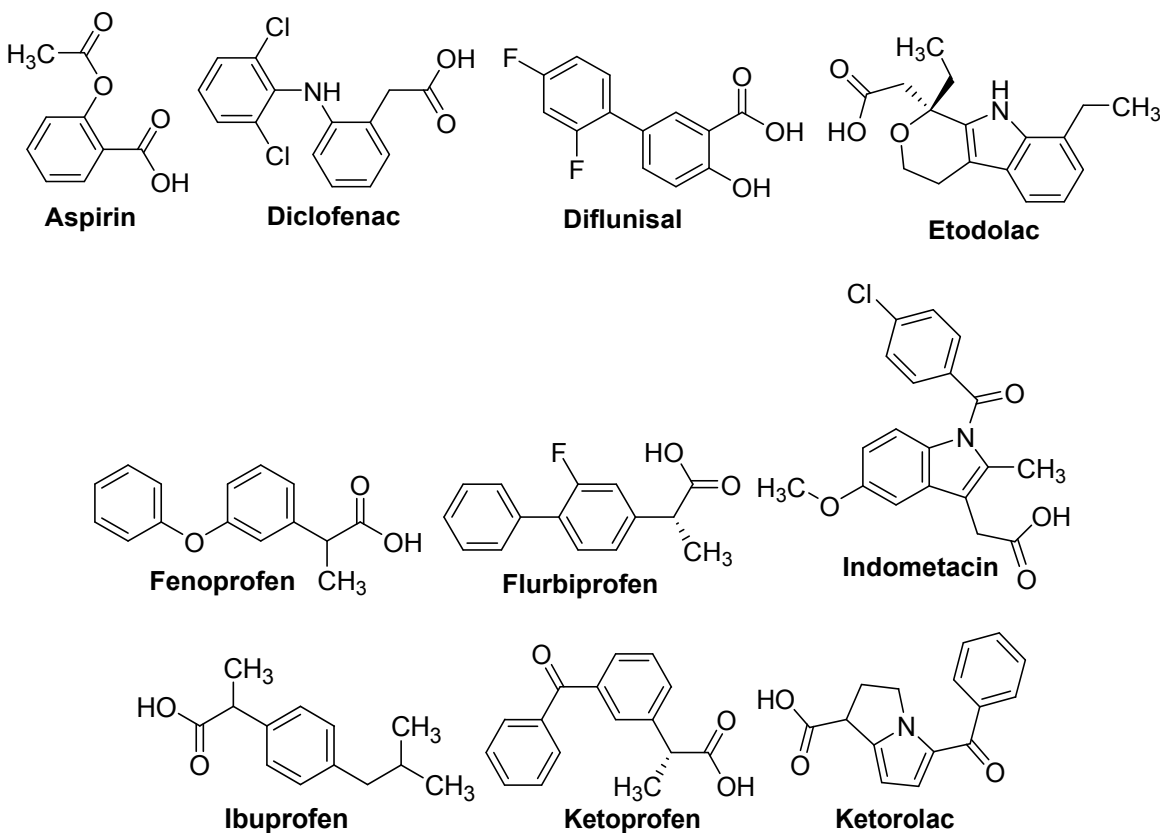
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#### Figures SI:



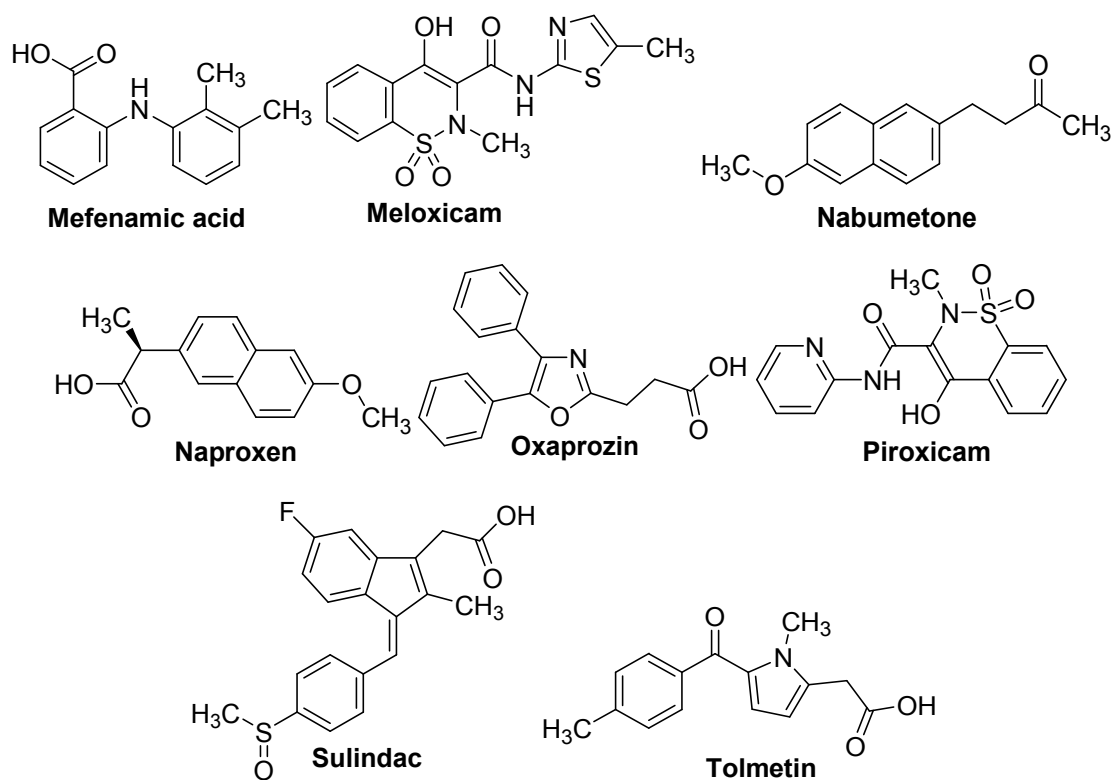


Figure SI-1: Chemical structures of selected FDA-approved NSAIDs

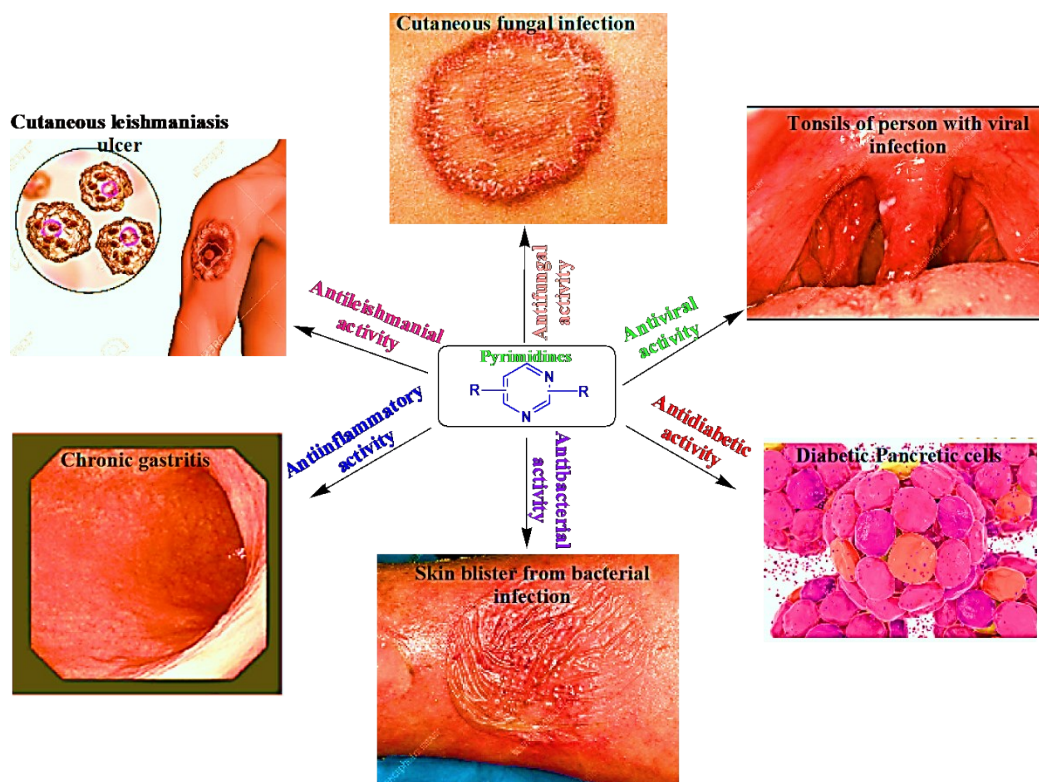


Figure SI-2: Pharmacological activities of pyrimidines

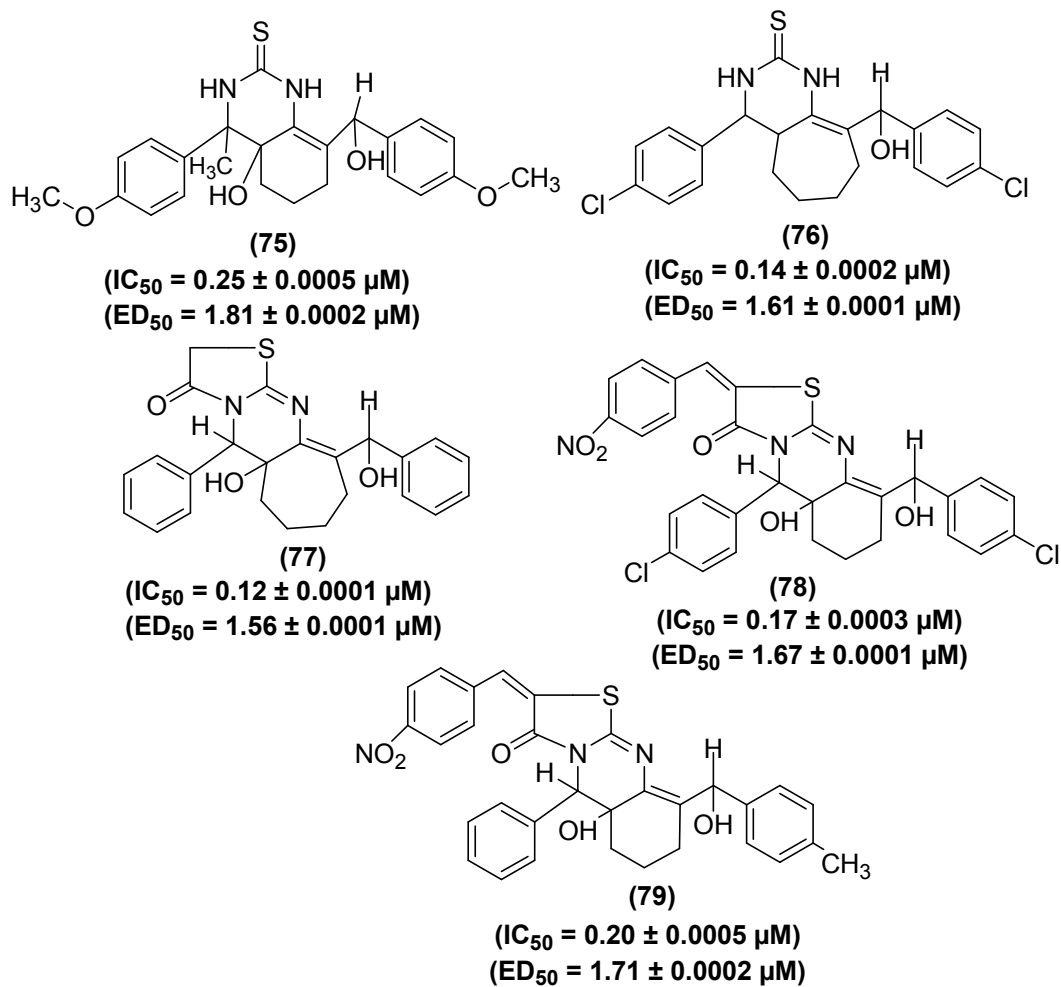
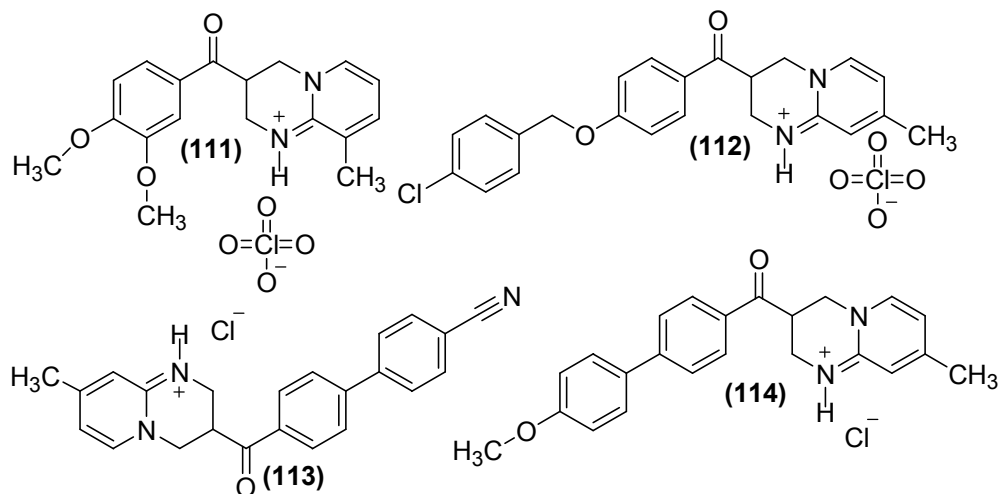
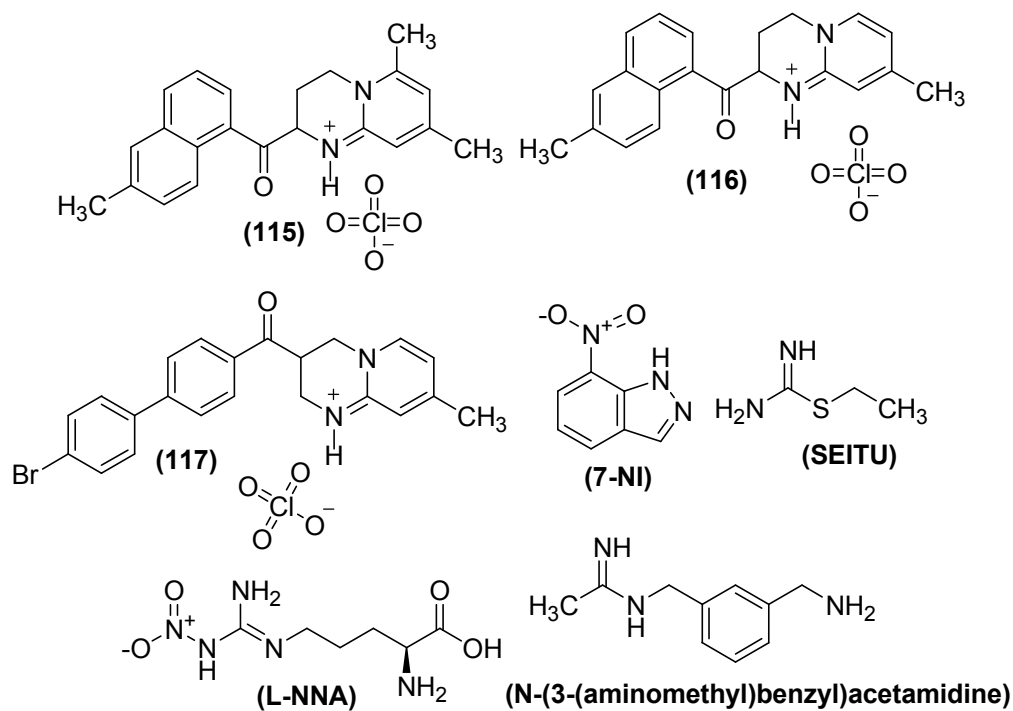
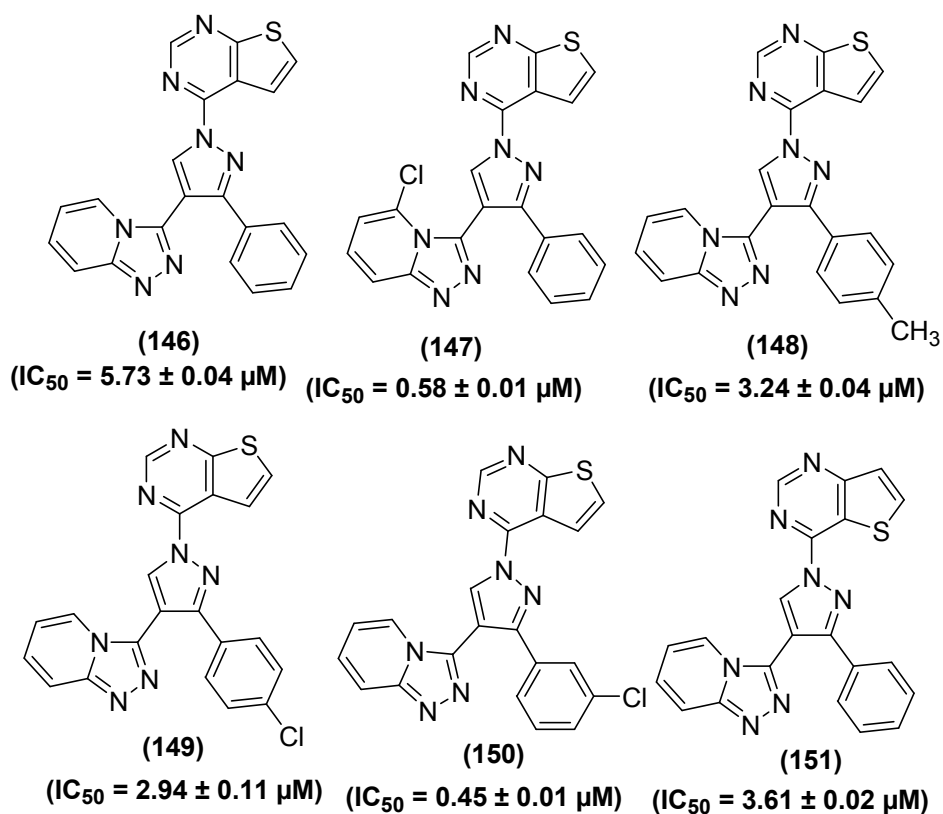


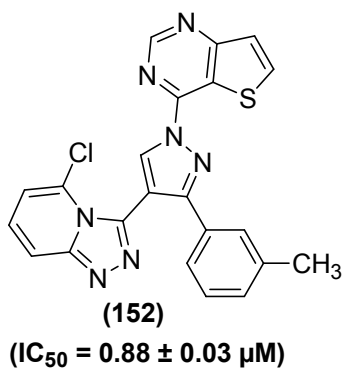
Figure SI-3: Chemical structures of selected thiopyrimidines (75-79)



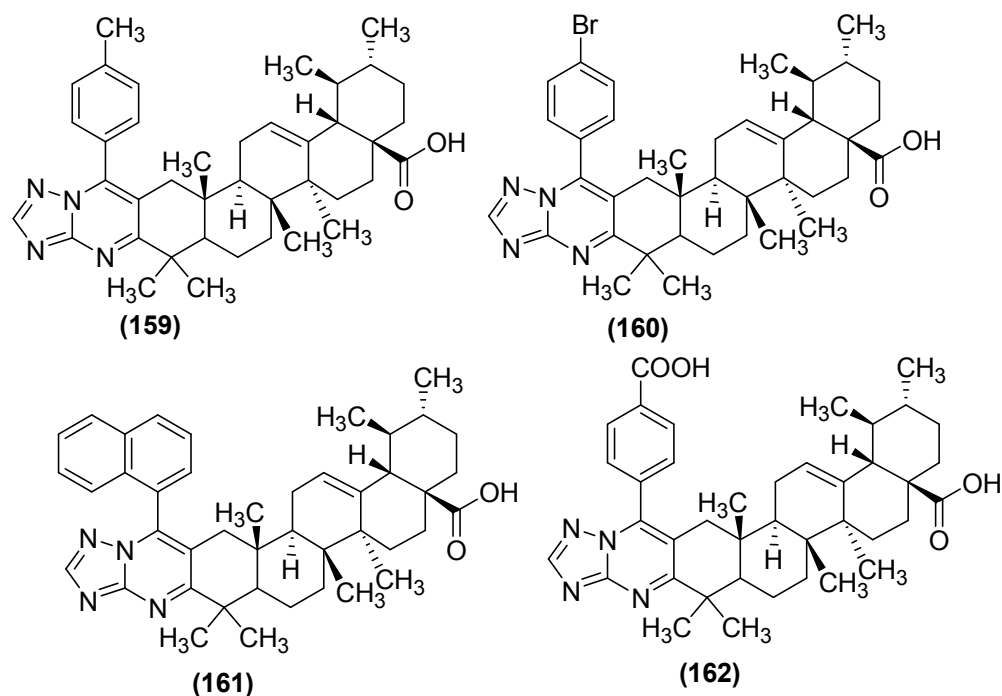


**Figure SI-4:** Chemical structures of selected pyrido[1,2-*a*]pyrimidines (111-117), and known inhibitors of NOS, *N*-(3-(aminomethyl)benzyl)acetamide, SEITU, 7-NI and L-NNA





**Figure SI-5:** Chemical structures of selected thienopyrimidine derivatives (**146-152**)

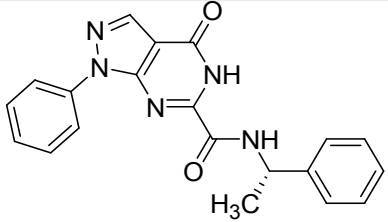
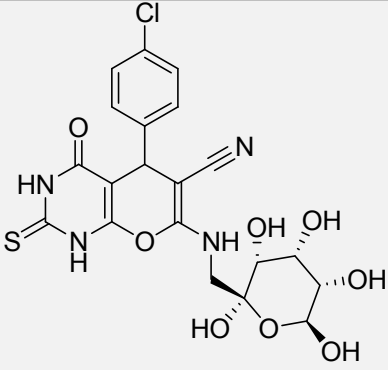
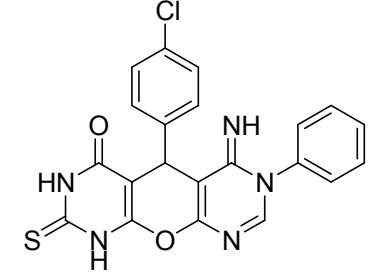
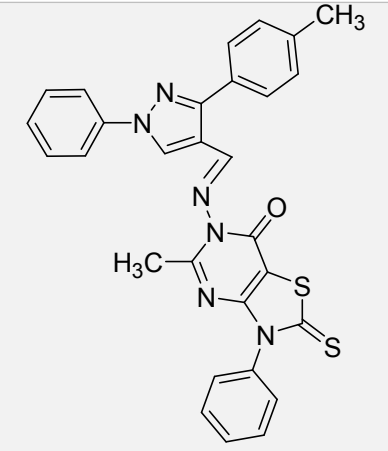
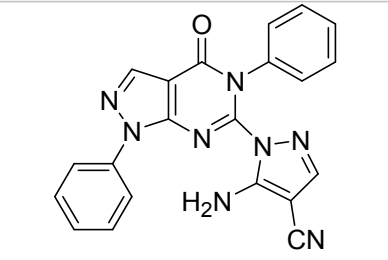


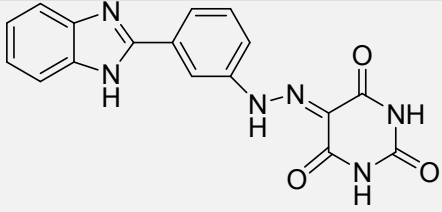
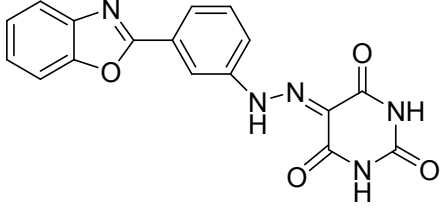
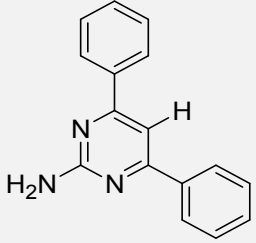
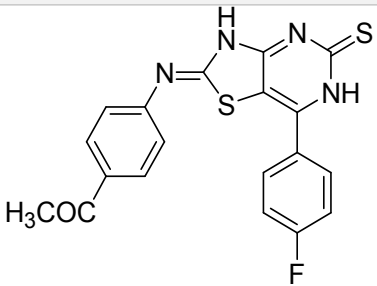
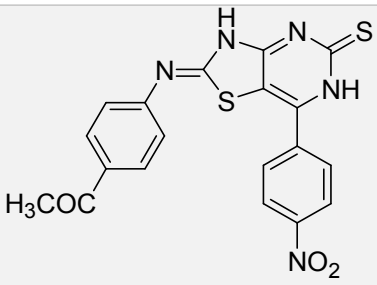
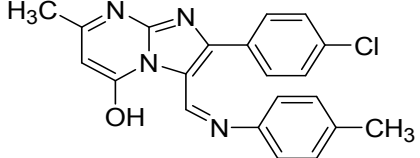
**Figure SI-6:** Chemical Structures of selected ursolic acid-based 1,2,4-triazolo[1,5-*a*]pyrimidines (**159-162**)

**Tables SI:**

**Table SI-1:** Chemical structures, IC<sub>50</sub> values, and target (COX-1/COX-2 enzyme) of the most potent pyrimidines

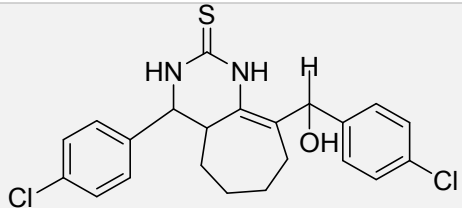
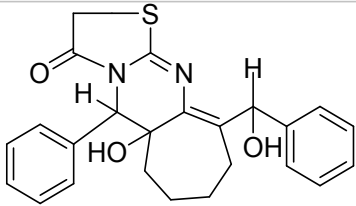
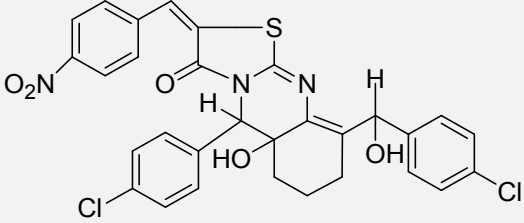
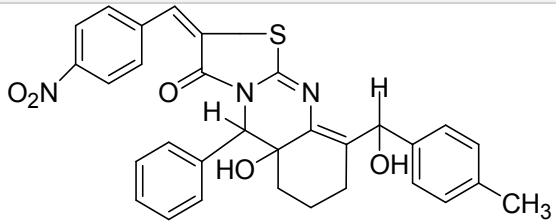
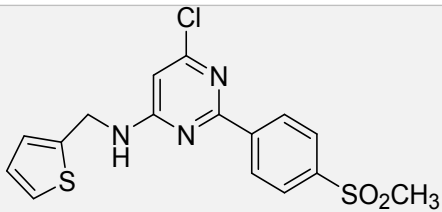
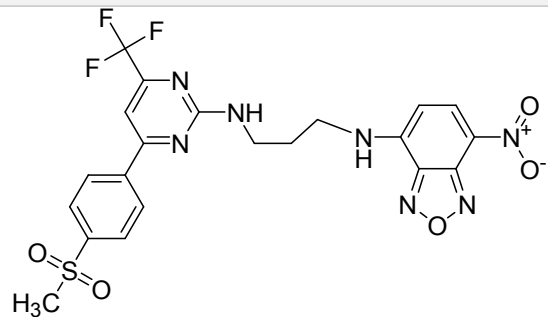
Comp. No.	Chemical structure	IC <sub>50</sub> (μM)	Target (COX-1 or COX-2)	Ref. No.
3b		19.45 ± 0.07	COX-1	75

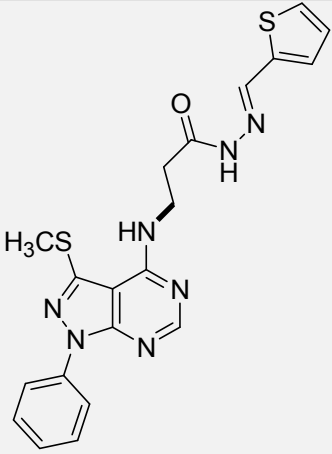
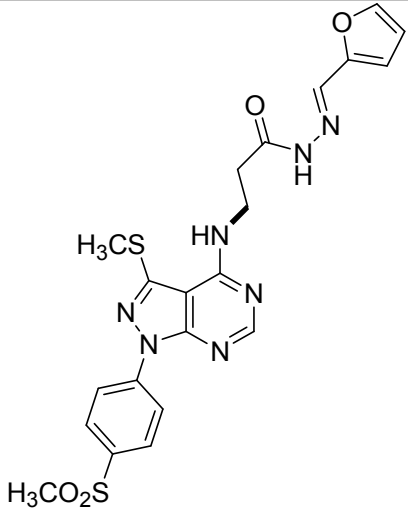
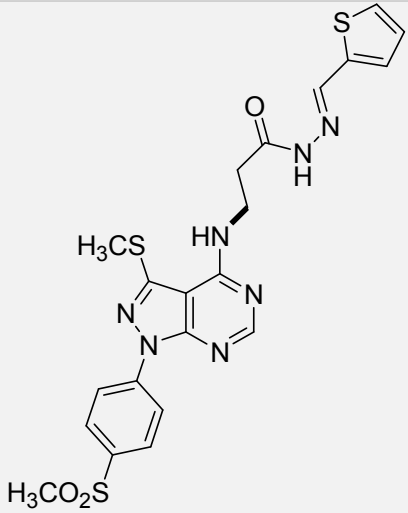
4d		23.8 ± 0.20	COX-2	75
5		0.04 ± 0.09	COX-2	76
6		0.04 ± 0.02	COX-2	76
7		0.36	COX-2	77
10		2.74 and 0.22	COX-1 and COX-2	78

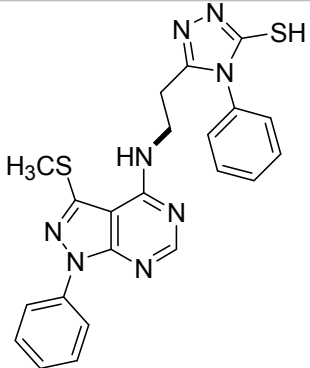
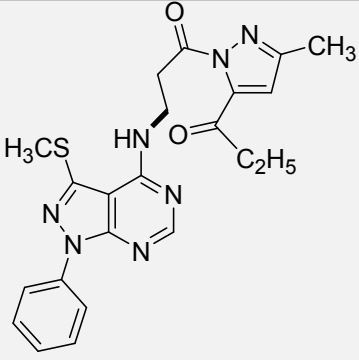
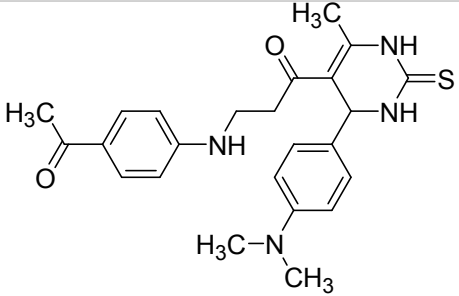
24a		2.76	COX-1	81
24b		1.92	COX-1	81
32		0.003	COX-2	83
48e		0.92	COX-2	85
48g		0.87	COX-2	85
49		13	COX-2	86

69		0.56	COX-2	91
71		0.104	COX-2	92
72		0.114	COX-2	92
73		0.057	COX-2	92
74		0.012	COX-2	93
75		0.25 ± 0.0005	COX-2	94

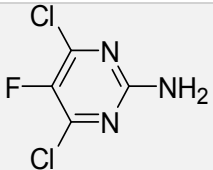


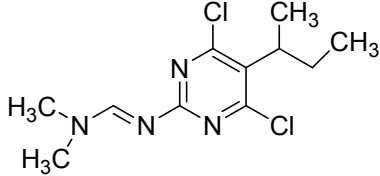
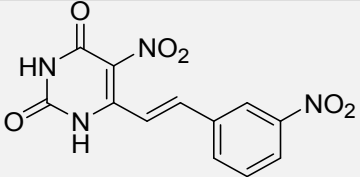
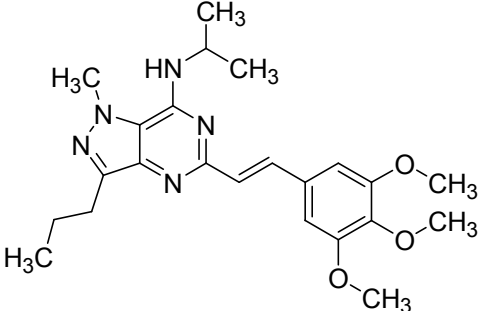
76		$0.14 \pm 0.0002$	COX-2	94
77		$0.12 \pm 0.0001$	COX-2	94
78		$0.17 \pm 0.0003$	COX-2	94
79		$0.20 \pm 0.0005$	COX-2	94
80		0.0012	COX-2	95
93		1.8	COX-2	100

96		0.11	COX-2	103
97		0.10	COX-2	103
98		0.10	COX-2	103

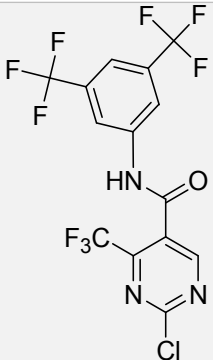
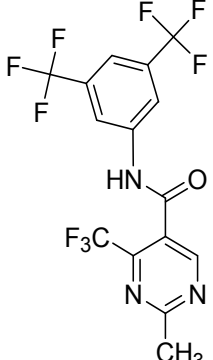
99		0.10	COX-2	103
100		0.10	COX-2	103
106		0.046	COX-2	106

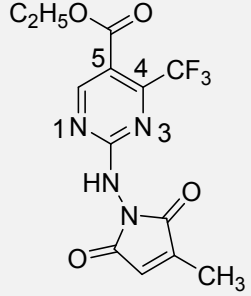
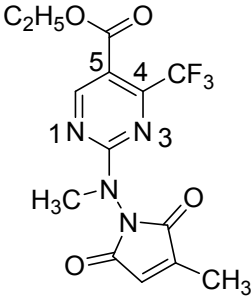
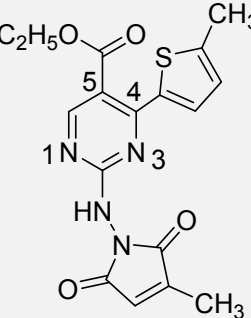
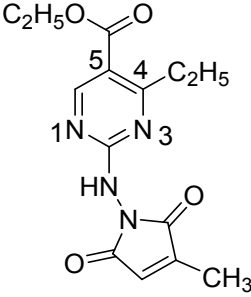

**Table SI-2:** Chemical structures, IC<sub>50</sub> values, and target inflammatory mediator (NO) of the most potent pyrimidines

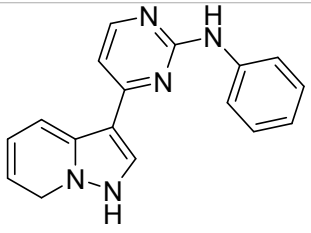
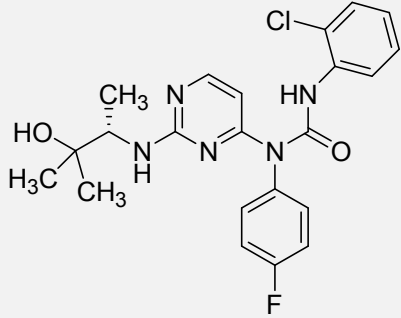
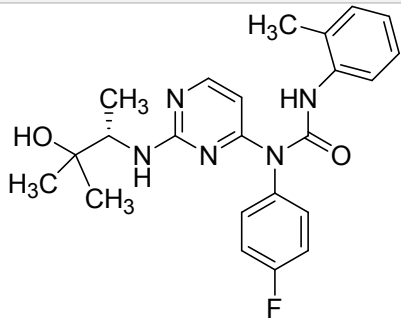
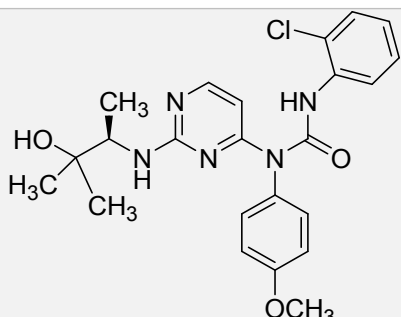
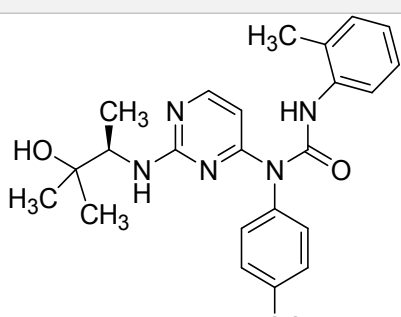
Comp. No.	Chemical structure	IC <sub>50</sub> (μM)	Target inflammatory mediators	Ref. No.
118		2	NO	113

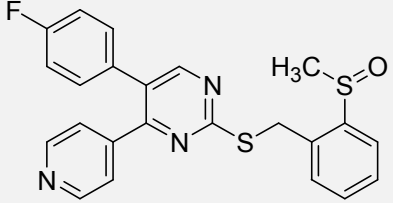
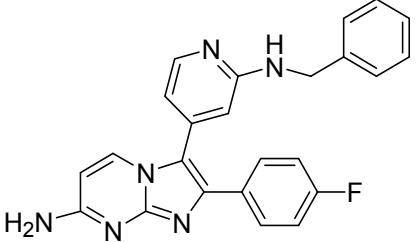
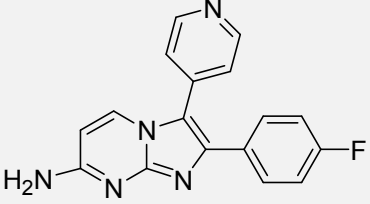
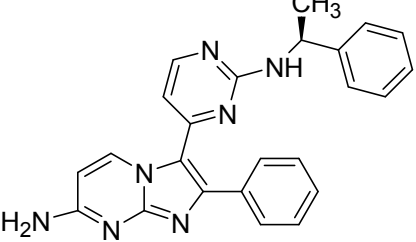
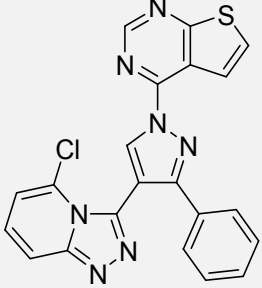
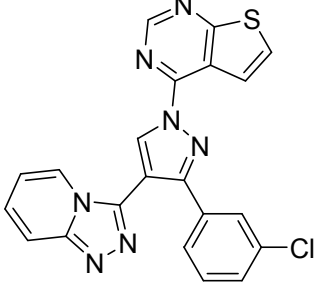
119		2.57	NO	114
121		8.6 and 6.2	NO and iNOS	116
125		3.17 and 1.12	NO and iNOS	118

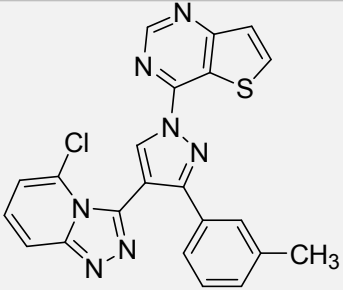
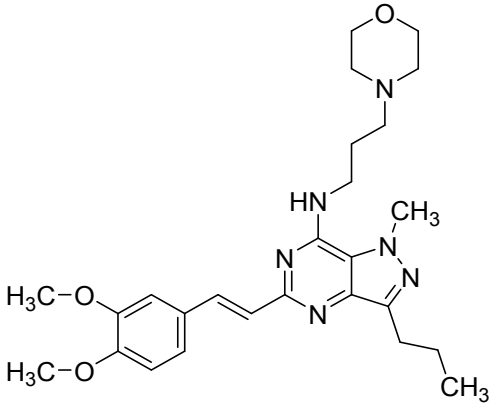
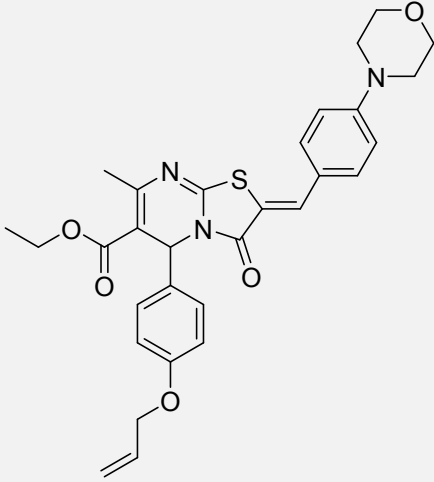
**Table SI-3:** Chemical structures, IC<sub>50</sub> values, and targets (NF-κB and cytokines) of the most potent pyrimidines

Comp. No.	Chemical structure	IC <sub>50</sub> (μM)	Target (NF-κB/cytokines)	Ref. No.
128		0.05	NF-κB	127
129		0.05	NF-κB	127

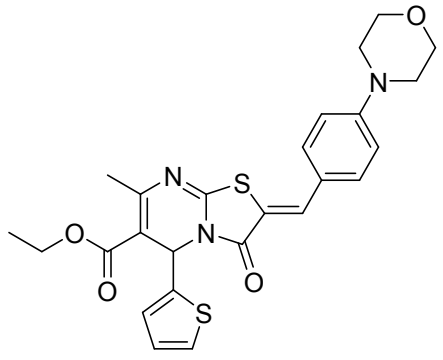
130		2	AP-1 and NF-κB	128
131		0.3	AP-1 and NF-κB	128
132		0.045	AP-1 and NF-κB	128
133		0.4	AP-1 and NF-κB	128
134		0.035	AP-1 and NF-κB	128

135		0.6 ± 0.05	NF-κB	129
136		0.122	TNF-α	130
137		0.176	TNF-α	130
138		0.092	TNF-α	130
139		0.135	TNF-α	130

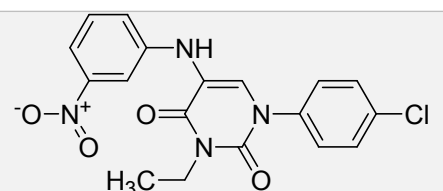
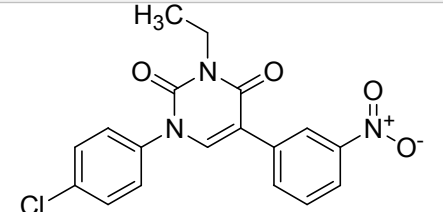
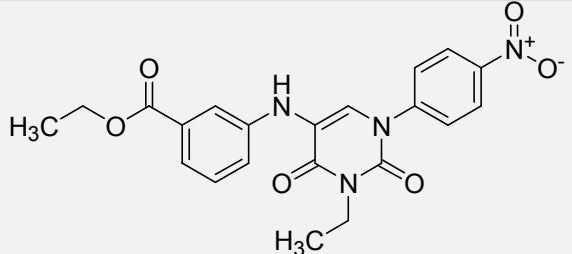
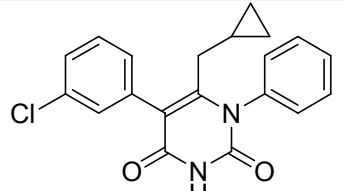
140		3.2 and 2.3	TNF- $\alpha$ and IL-1 $\beta$	131
141		0.006	MAPK and TNF- $\alpha$	132
142		0.040 and 0.570	TNF- $\alpha$ and MAPK	132
144		0.0006 and 0.008	TNF- $\alpha$ and MAPK	132
147		0.58 $\pm$ 0.01	STAT3, IL-6	134
150		0.45 $\pm$ 0.01	STAT3, IL-6	134

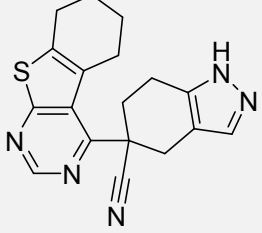
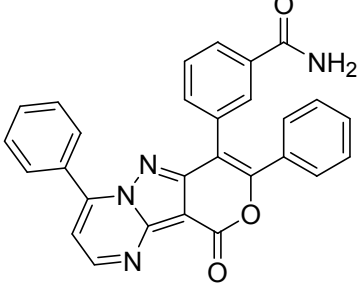
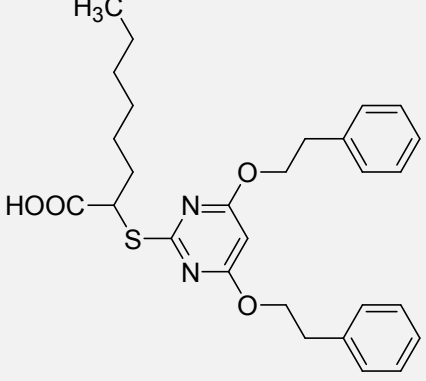
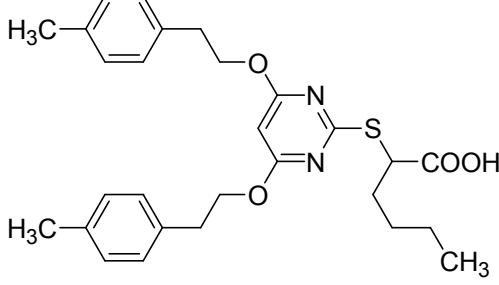
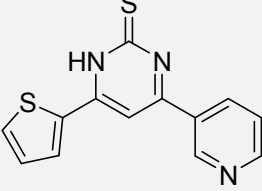
152		0.88 ± 0.03	STAT3, IL-6	134
153		5.63, 4.38	TNF- $\alpha$ , IL-6	135
157		0.60 and 1.16	IL-6 and TNF- $\alpha$	137



158		0.56 and 0.89	IL-6 and TNF- $\alpha$	137
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**Table SI-4:** Chemical structures, IC<sub>50</sub> values, and targets (PDE4 and LOX enzymes) of the most potent pyrimidines

Comp. No.	Chemical structure	IC <sub>50</sub> ( $\mu$ M)	Target Enzyme (PDE4/LOX)	Ref. No.
169		6.54 $\pm$ 1.38	PDE4	148
170		0.62 $\pm$ 9.92	PDE4	148
171		(5.72 $\pm$ 0.80	PDE4	148
172		4.87 $\pm$ 1.37	PDE4	148

173		$2.0 \pm 0.41$ and $3.14 \pm 1.02$	PDE4B and PDE4D	149
174		$1.33 \pm 0.64$ and $2.84 \pm 0.64$	PDE4B and PDE4D	150
184		0.4 and 2.8	5-LOX	157
185		0.5 and 3.1	5-LOX	157
190		4.91	5-LOX	160

191	 <chem>Nc1nc2ccccc2n1</chem>	6.98	5-LOX	160
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