# Design and Molecular Simulation of 5-Hydroxy-7-Methoxyflavanone Derivatives Derived from Extraction for Potential Anti-Inflammatory Agents

**Narisa Oadkhong**[1], Nathaporn Cheechana[1,2] and Puttinan Meepowpan[1,3,4*]

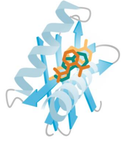
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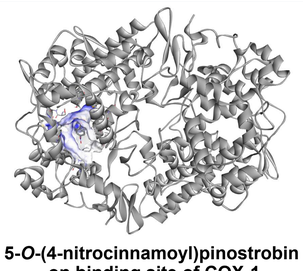
## ABSTRACT



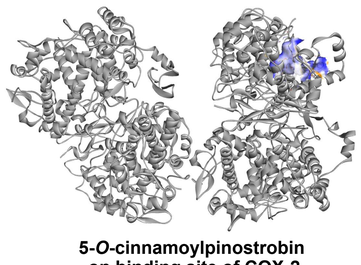

Crude extract from *Boesenbergia rotunda*

*In silico* Molecular Docking





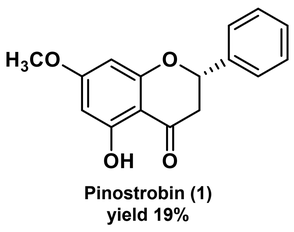
5-*O*-(4-nitrocinnamoyl)pinostrobin on binding site of COX-1



5-*O*-cinnamoylpinostrobin on binding site of COX-2

Structural modification

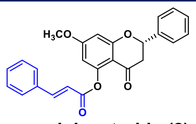




Pinostrobin (1) yield 19%

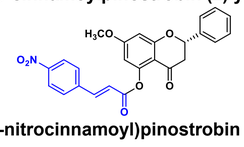
Synthesis

Steglich Esterification



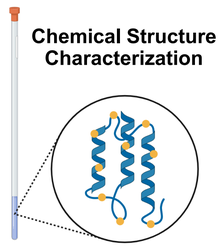
5-*O*-cinnamoylpinostrobin (2) yield 82%

Esterification of Acyl chloride



5-*O*-(4-nitrocinnamoyl)pinostrobin (3) yield 57%

Chemical Structure Characterization




## INTRODUCTION

### Inflammation

Physiological stimulus → Cyclooxygenase-1 (COX-1) Constitutive → Stomach, Intestine, Kidney, Platelet

NSAIDS



Inflammatory stimulus → Cyclooxygenase-2 (COX-2) Inducible → Inflammatory site: Macrophages, Synoviocytes

### Natural Product



*Boesenbergia rotunda* (fingerroot)

Pinostrobin

- Anti-inflammatory
- Anti-cancer
- Anti-oxidant
- Anti-viral

## METHODOLOGY

### Extraction, Isolation, Purification and Identification



6.6 kg of dry *B. rotunda*



Extraction with Acetone for 72 h (3 times) and filtration.



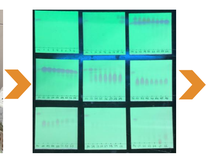
Evaporation



Crude extract

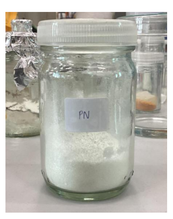


Separation by column chromatography

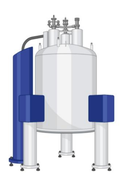


Monitoring by Thin Layer Chromatography (TLC)

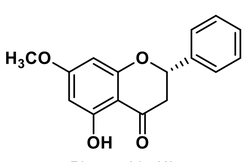
Recrystallization and filtration



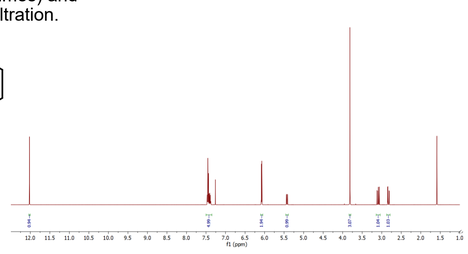
Pinostrobin 33.86 g (yield 19%)



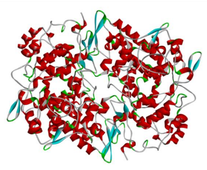
Structural identification by Nuclear Magnetic Resonance (NMR)



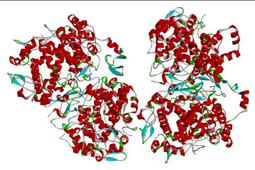
Pinostrobin (**1**)



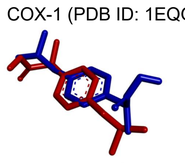
### *In silico* Molecular Docking



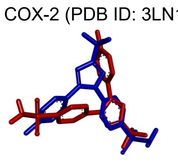
COX-1 (PDB ID: 1EQG)



COX-2 (PDB ID: 3LN1)



Ibuprofen
RMSD = 1.791 Å



Celecoxib
RMSD = 1.327 Å

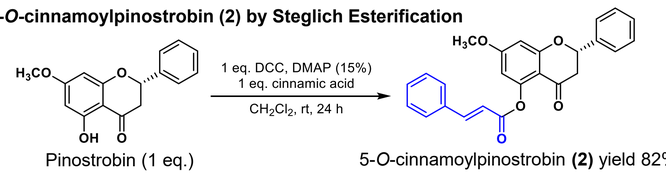
Co-crystallization ligand
Docked ligand

**Table 1** Grid Box Parameters for Molecular Docking of COX-1 and COX-2

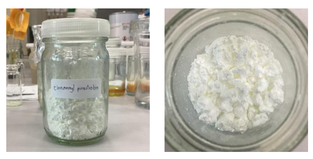
| Parameter | Protein | |
|---|---|---|
| | 1EQG | 3LN1 |
| Center X | 26.642 | 30.597 |
| Center Y | 33.105 | -22.559 |
| Center Z | 200.251 | -15.758 |
| Size X | 18 | 28 |
| Size Y | 18 | 16 |
| Size Z | 24 | 24 |

### Synthesis of Pinostrobin derivatives

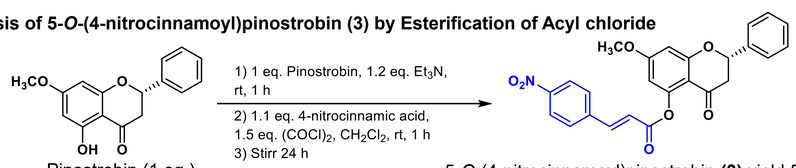
**1. Synthesis of 5-*O*-cinnamoylpinostrobin (2) by Steglich Esterification**



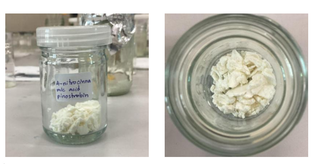

Pinostrobin (1 eq.) → 5-*O*-cinnamoylpinostrobin (**2**) yield 82%



**2. Synthesis of 5-*O*-(4-nitrocinnamoyl)pinostrobin (3) by Esterification of Acyl chloride**




Pinostrobin (1 eq.) → 5-*O*-(4-nitrocinnamoyl)pinostrobin (**3**) yield 57%



## RESULTS

### Binding Energy

**Table 2** Predicted binding affinities of Pinostrobin derivatives on COX-1

| Derivatives | Affinity (kcal/mol) | Hydrogen bond | Electrostatic | Non-polar |
|---|---|---|---|---|
| Pinostrobin (**1**) | -8.0 | - | - | Val116, Val349, Leu352, Ser353, Try355, Tyr385, Phe381, Ala527, Ser530 |
| 5-*O*-cinnamoylpinostrobin (**2**) | -8.9 | Tyr355 | Arg120, Met522 | Val116, Val349, Leu352, Try355, Tyr385, Trp387, Ile523, Ala527 |
| 5-*O*-(4-nitrocinnamoyl)pinostrobin (**3**) | -9.0 | Tyr355 | Arg120, Met522 | Val116, Val349, Leu352, Try355, Tyr385, Trp387, Ile523, Ala527 |
| Ibuprofen | -7.6 | Arg120, Tyr355 | - | Arg120, Val349, Tyr385, Trp387, Ala527 |

**Table 3** Predicted binding affinities of Pinostrobin derivatives on COX-2

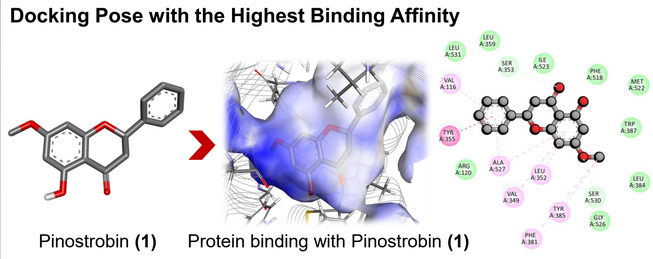
| Derivatives | Affinity (kcal/mol) | Hydrogen bond | Electrostatic | Non-polar |
|---|---|---|---|---|
| Pinostrobin (**1**) | -9.3 | Tyr371 | - | Val335, Leu338, Phe367, Leu370, Tyr371, Trp373, Ala502, Val509, Ala513 |
| 5-*O*-cinnamoylpinostrobin (**2**) | -9.1 | - | - | His75, Leu78, Val102, Val335, Ser339, Tyr341, Tyr371, Trp373, Val509, Ala513 |
| 5-*O*-(4-nitrocinnamoyl)pinostrobin (**3**) | -8.3 | - | - | His75, Leu78, Val102, Val335, Ser339, Tyr341, Tyr371, Trp373, Val509, Ala513 |
| Celecoxib | -12.4 | Gln178, Leu338, Arg499, Phe504 | - | Val335, Ser339, Tyr341, Leu345, Leu370, Tyr371, Trp373, Val509, Gly512, Ala513 |

## RESULTS

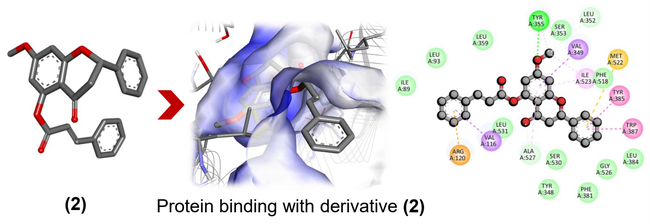
### *In silico* Molecular Docking approach

#### COX-1

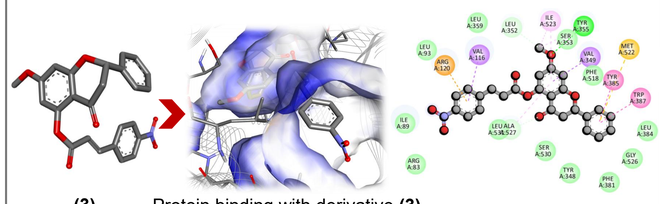
**Docking Pose with the Highest Binding Affinity**



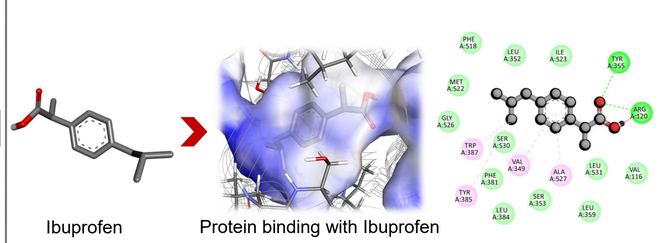
Pinostrobin (**1**) — Protein binding with Pinostrobin (**1**)



(**2**) — Protein binding with derivative (**2**)



(**3**) — Protein binding with derivative (**3**)



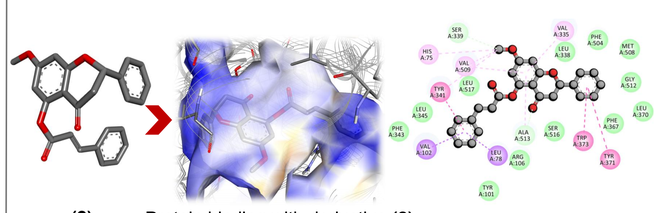
Ibuprofen — Protein binding with Ibuprofen

#### COX-2

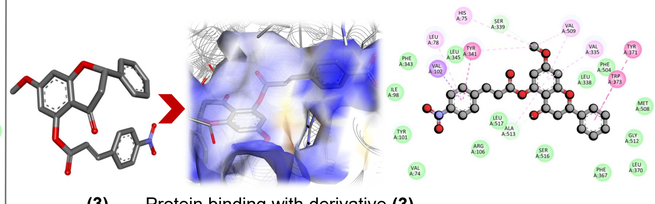
**Docking Pose with the Highest Binding Affinity**



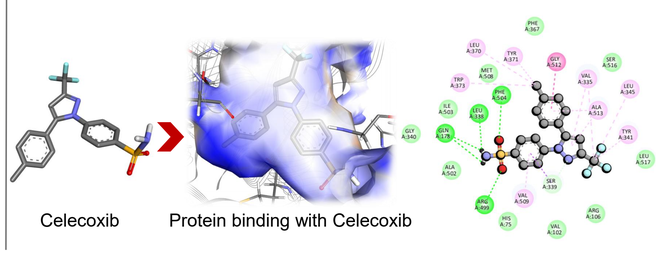
Pinostrobin (**1**) — Protein binding with Pinostrobin (**1**)



(**2**) — Protein binding with derivative (**2**)



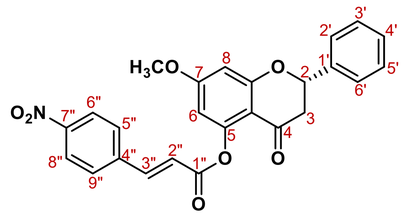
(**3**) — Protein binding with derivative (**3**)

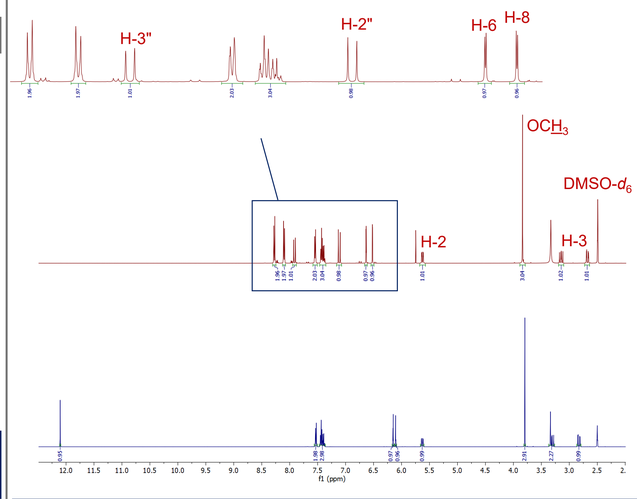


Celecoxib — Protein binding with Celecoxib

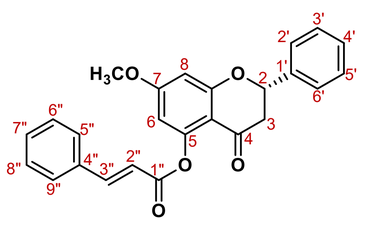
### Structural Characterization of Synthesized Derivatives

**$^1$H-NMR (500 MHz, DMSO-$d_6$) of derivative (3)**






**$^1$H-NMR (500 MHz, $CDCl_3$) of derivative (2)**






## CONCLUSION

5-Hydroxy-7-methoxyflavanone, or pinostrobin, is a bioactive compound extracted from *Boesenbergia rotunda* (fingerroot) with yields of 19%. It was structurally designed and subjected to computational molecular simulations (*In silico* Molecular Docking) to study its binding affinity toward target proteins. The compounds that exhibited the best binding affinities to the cyclooxygenase enzymes (COX-1 and COX-2), which are involved in inflammation, were 5-*O*-cinnamoylpinostrobin and 5-*O*-(4-nitrocinnamoyl)pinostrobin, with binding energies of −9.0 and −9.1 kcal/mol, respectively.

Subsequently, structural modification of pinostrobin derivatives was carried out via an esterification reaction, yielding two derivatives: 5-*O*-cinnamoylpinostrobin and 5-*O*-(4-nitrocinnamoyl)pinostrobin, with yields of 82% and 57%, respectively. The results of this study preliminarily indicate that pinostrobin derivatives have potential for further development as anti-inflammatory agents.

## REFERENCES

[1] Utama, K., Khamto, N., Janthong, A., Thiraphatchotiphum, C., Roytrakul, S., Kantapan, J., Meepowpan, P., & Sangthong, P. (2025). Discovery of cinnamoyl–flavonoid hybrid derivatives as inhibitors of SARS-CoV-2 Mpro and anti-inflammatory agents: Experimental and in silico insights into their efficacy against lipopolysaccharide- induced lung injury. *European Journal of Pharmacology*, *998, 177636.* https://doi.org/10.1016/j.ejphar.2025.177636

[2] Vale, J. A. do, Rodrigues, M. P., Lima, Â. M. A., Santiago, S. S., Lima, G. D. de A., Almeida, A. A., Oliveira, L. L. de, Bressan, G. C., Teixeira, R. R., & Machado-Neves, M. (2022). Synthesis of cinnamic acid ester derivatives with antiproliferative and antimetastatic activities on murine melanoma cells. *Biomedicine and Pharmacotherapy*, *148,* 112689. https://doi.org/10.1016/j.biopha.2022.112689

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ORGANIC SYNTHESIS RESEARCH LABORATORY CHIANG MAI UNIVERSITY