Proposal of JAK2 Inhibitors from Natural Chalcone Derivatives as Erythropoiesis Stimulant Agents for Thalassemia Therapy: Biological Predictions, Molecular Docking and Pharmacokinetic Predictions

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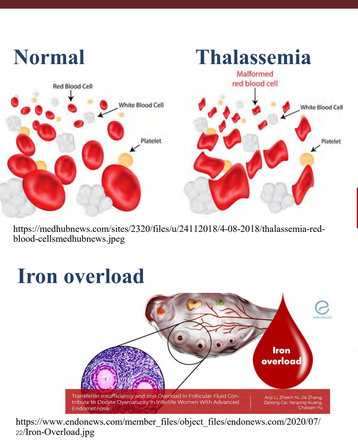
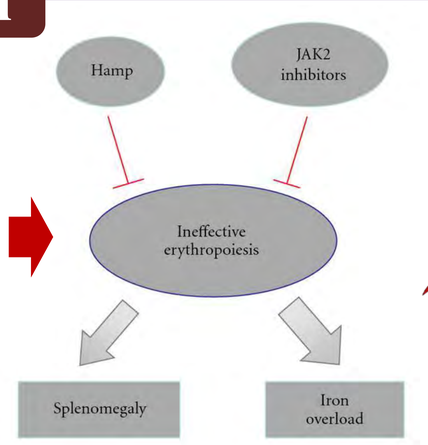
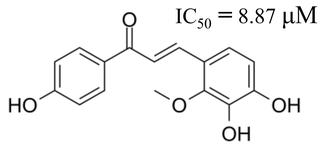
Introduction





Licochalcone B

JAK2 Inhibitor



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Computer Aided Molecular Design (CAMD)

- Virtual screening
- Biological predictions
- Pharmacokinetic predictions

The **ineffective erythropoiesis** inhibition by JAK2 inhibitors has been developed as novel **thalassemia therapy.**

Materials and Methods

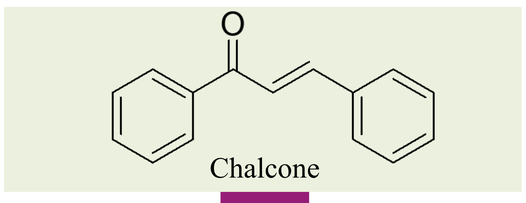


Figure 1 General structure of chalcone

Similarity Search
Super Natural II database

→ **PAINS**
SwissADME

→ **Drug-likeness**
(Lipinski's rule of five)
SwissADME

→ **Erythropoiesis stimulant**
JAK2 inhibitions activity
PASS online

→ **Pharmacokinetic Properties (ADMET)**
pkCSM

→ **Molecular Docking Calculation**
Glide XP program
PDB code: 4D0X

Figure 2 The virtual screening process of natural chalcone to be JAK2 inhibitors

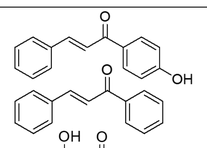
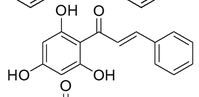
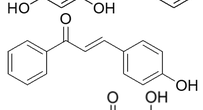
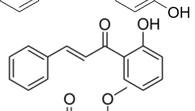
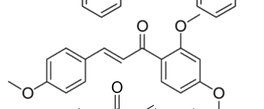
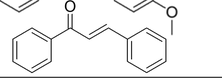
Conclusions

- Seven natural chalcone derivatives were identified as JAK2 inhibitors with erythropoiesis simulating agent property.
- These finding compounds were strongly bound with JAK2 binding site docking score ranging from -8.27 to -7.23 kcal/mol.
- The main interaction of chalcone derivative is H-bond interactions between an oxygen atom of meta-substitution on chalcone analog with NH backbone of Leu932.
- The pharmacokinetic properties predictions demonstrated that collected compounds were suitable for acting as drug.
- These finding results aid to collect the potential compounds for biological assay evaluations and development as novel drug for thalassemia therapy.

Results

❑ Biological activity prediction and molecular docking studies

Table 1 The results of the erythropoiesis stimulant activity and JAK2 inhibition using PASS online prediction and the docking score from molecular docking calculations

Name	Structures	Erythropoiesis stimulant activity		JAK2 Inhibitors		Docking Score (kcal/mol)
		Pa	Pi	Pa	Pi	
4'-hydroxychalcone (1)		0.554	0.022	0.230	0.051	-8.265
Trans-chalcone (2)		0.599	0.013	0.253	0.036	-8.243
Pinocembrin Chalcone (3)		0.528	0.029	0.219	0.059	-8.140
4-hydroxychalcone (4)		0.554	0.022	0.230	0.051	-8.144
2'-hydroxychalcone (5)		0.554	0.022	0.226	0.053	-8.082
Metochalcone (6)		0.367	0.113	0.219	0.059	-8.057
Chalcone (7)		0.599	0.013	0.253	0036	-7.331

Pa : probability to be active
Pi : probability to be inactive

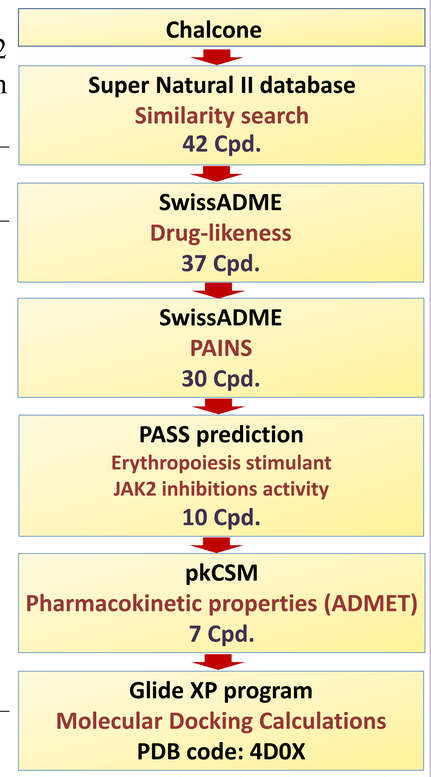


Figure 3 The virtual screening process of natural chalcone to be JAK2 inhibitors

❑ The pharmacokinetic properties (ADMET) prediction

Table 2 The results of ADMET prediction of selected compounds

Compound	1	2	3	4	5	6	7
Caco2 permeability	1.632	1.708	0.952	1.426	1.678	1.386	1.335
Intestinal absorption (human)	94.046	95.266	91.209	92.021	93.686	94.804	94.977
Pgp inhibition	No	No	No	No	No	No	No
BBB permeability	0.165	0.575	-0.716	0.181	0.153	0.226	0.56
CNS permeability	-1.605	-1.242	-2.279	-1.549	-1.249	-1.416	-1.243
CYP2D6 substrate	No	No	No	No	No	No	No
CYP3A4 substrate	Yes	Yes	No	Yes	Yes	Yes	Yes
CYP2C19 inhibitior	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CYP2C9 inhibitior	No	Yes	Yes	No	No	Yes	Yes
CYP2D6 inhibitior	No	No	No	No	No	No	No
CYP3A4 inhibitior	No	No	No	No	No	Yes	No
Total Clearance (ml/min/kg)	0.149	0.175	0.168	0.183	0.077	0.298	0.223
Renal OCT2 substrate	No	No	No	No	Yes	No	No
AMES toxicity	No	No	No	No	No	Yes	No
hERG inhibitor	No	No	No	No	No	No	No
Oral Rat Acute Toxicity (LD_{50})	2.129	1.929	2.228	1.998	2.041	2.154	1.843
Hepatotoxicity	No	No	No	No	No	No	No

Caco2 > 0.90
high Caco2 permeability

Intestinal absorption (human) < 30%
is considered to be poorly adsorbed

BBB > 0.3
can readily cross the blood-brain
BBB < -1
poorly distributed to the brain

CNS > -2
can penetrate the Central Nervous System (CNS)
CNS < -3
unable to penetrate the CNS

❑ The binding mode and binding interactions of active compounds in JAK2 binding pocket

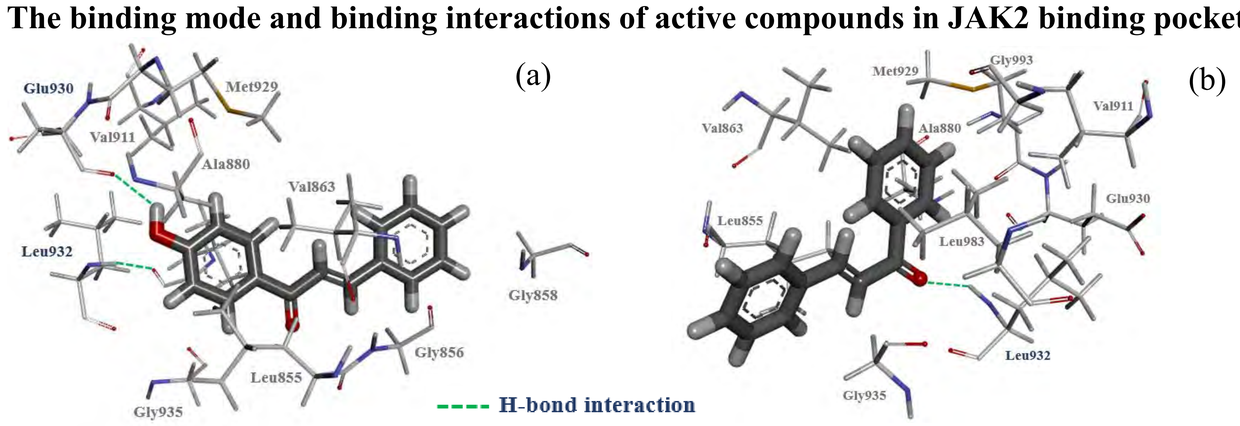


Figure 4 The binding mode of natural chalcone (a) **4'-hydroxychalcone (1)** and (b) **Trans-chalcone (2)** in JAK2 binding pocket

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