Screening of JAK2 Inhibitors from Natural Curcumin and Its Derivatives as Erythropoiesis Stimulant Agents for Thalassemia Therapy: Computer Aided Molecular Design Approaches

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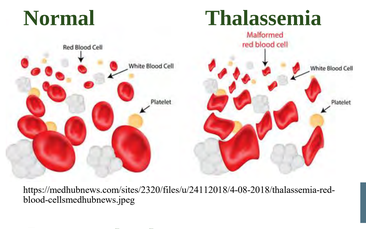
Introduction



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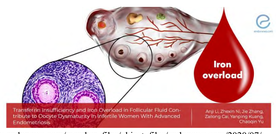
Iron overload



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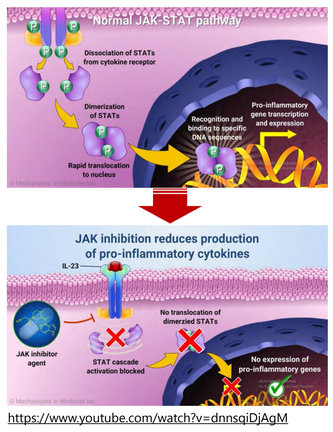


https://www.youtube.com/watch?v=dnnsqiDjAgM

To developed curcumin and its derivatives as JAK2 inhibitors and erythropoiesis stimulant agents

Computer Aided Molecular Design (CAMD)

- Virtual screening
- Biological predictions
- Pharmacokinetic predictions

Janus kinase 2 (JAK2) is an enzyme responsible for regulating erythropoiesis and has been validated as a novel therapeutic process for thalassemia.

Materials and Methods

Curcuminoid analog
European Journal of Medicinal Chemistry 45 (2010) 4446-4457

Erythropoiesis stimulant
PASS prediction

Pharmacokinetic properties (ADMET)
pkCSM

Molecular Docking Calculations
PDB code: 4D0X
Glide XP program

Figure 1 The virtual screening process of natural curcumin and its derivatives to be JAK2 inhibitors

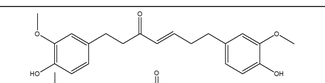
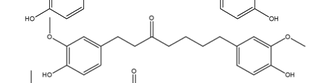
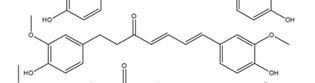
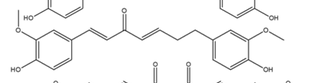
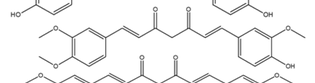
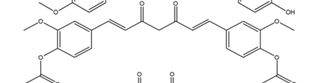
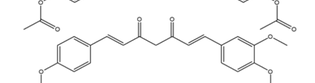
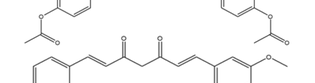
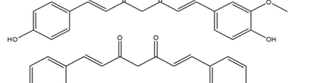
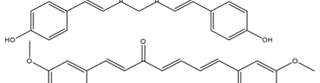
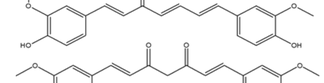
Conclusions

- Eleven curcumin derivatives will be act as JAK2 inhibitors with the high binding affinity in JAK2 binding site docking score ranging from –9.65 to -12.09 kcal/mol.
- H-bond interaction with NH backbone of Leu932 and sigma-pi interaction of aromatic ring on curcumin analog with Leu983 sidechain
- The ADMET predictions suggested that curcumin derivatives 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 based on JAK2 inhibition mechanism.

Results

❑ Biological activity prediction and molecular docking studies

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

Compound	Structures	Erythropoiesis stimulant activity		Docking Score (kcal/mol)
		Pa	Pi	
1		0.307	0.172	-12.086
2		0.332	0.144	-11.364
3		0.273	0.216	-11.326
4		0.273	0.216	-11.001
5		0.334	0.143	-10.634
6		0.298	0.182	-10.618
7		0.274	0.213	-10.510
8		0.267	0.224	-10.449
9		0.523	0.031	-10.084
10		0.279	0.207	-9.948
11		0.353	0.124	-9.650

Curcuminoid analog
European Journal of Medicinal Chemistry 45 (2010) 4446e4457
64 Cpd.

PASS online
Erythropoiesis stimulant
28 Cpd.

pkCSM
Pharmacokinetic properties (ADMET)
11 Cpd.

Glide XP program
Molecular Docking Calculations
PDB code: 4D0X

Figure 2 The virtual screening process of natural curcumin and its derivatives to be JAK2 inhibitors

❑ The pharmacokinetic properties (ADMET) prediction

Table 2 The results of ADMET prediction of hit compounds

Compound	1	2	3	4	5	6	7	8	9	10	11
Caco2 permeability	1.113	1.079	1.135	1.07	1.096	0.915	0.923	1.103	1.084	1.158	1.152
Intestinal absorption (human)	92.9	92.394	92.172	92.37	95.146	89.844	92.74	88.96	92.183	92.523	97.999
Pgp inhibition	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
BBB permeability	-0.314	-0.35	-0.286	-0.285	-0.685	-1.19	-0.973	-0.854	-0.123	-0.259	-0.793
CNS permeability	-2.603	-2.655	-2.486	-2.459	-3.011	-3.162	-3.042	-2.295	-2.322	-2.37	-2.971
CYP2D6 substrate	No	No	No	No	No	No	No	No	No	No	No
CYP3A4 substrate	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
CYP2C19 inhibitior	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CYP2C9 inhibitior	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CYP2D6 inhibitior	No	No	No	No	No	No	No	No	No	No	No
CYP3A4 inhibitior	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total Clearance (ml/min/kg)	0.271	0.364	0.244	0.145	0.149	0.431	0.432	0.145	0.044	0.14	0.188
Renal OCT2 substrate	No	No	No	No	No	No	No	No	No	No	No
AMES toxicity	No	No	No	No	No	No	No	No	Yes	No	No
hERG inhibitor	Yes	Yes	No	Yes	Yes	No	No	No	Yes	No	No
Oral Rat Acute Toxicity (LD_{50})	2	2.003	2.016	2.064	2.155	2.468	2.396	2.288	1.851	2.032	2.233
Hepatotoxicity	No	No	No	No	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

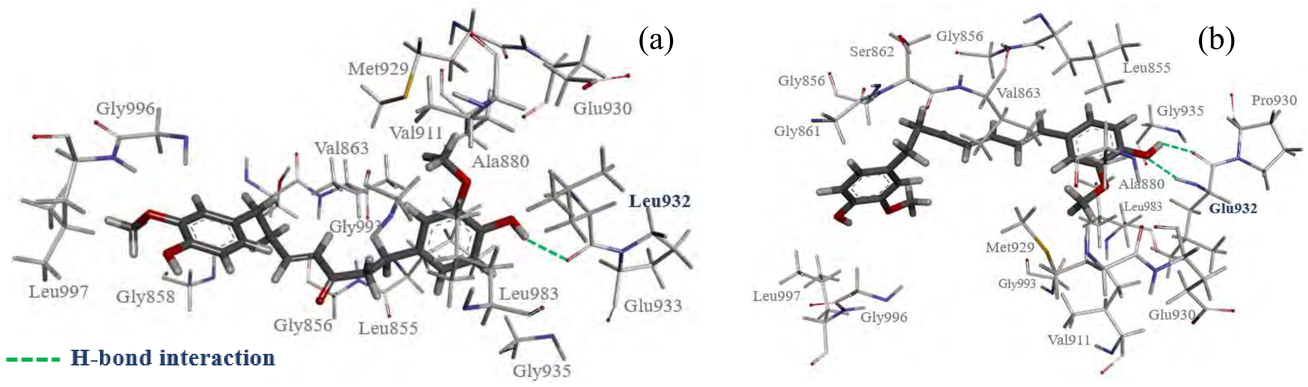


Figure 3 The binding mode of natural curcumin (a) **compound 1** and (b) **compound 2** in JAK2 binding pocket

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