

Identification of Novel JAK2 Inhibitors as Erythropoiesis Stimulant Agents for Thalassemia Therapy

Sirintip Sangsawang¹, Siripen Modmung¹, Bandit Khamsri¹, Somjintana Taweapanich¹, Chan Inntam¹, Jidapa Sangswan², Pharit Kamsri³, Auradee Punkvang³, Khomson Suttisintong⁴, Kanjana Pangjit⁵, Noriyuki Kurita⁶ and Pornpan Pungpo^{1*}

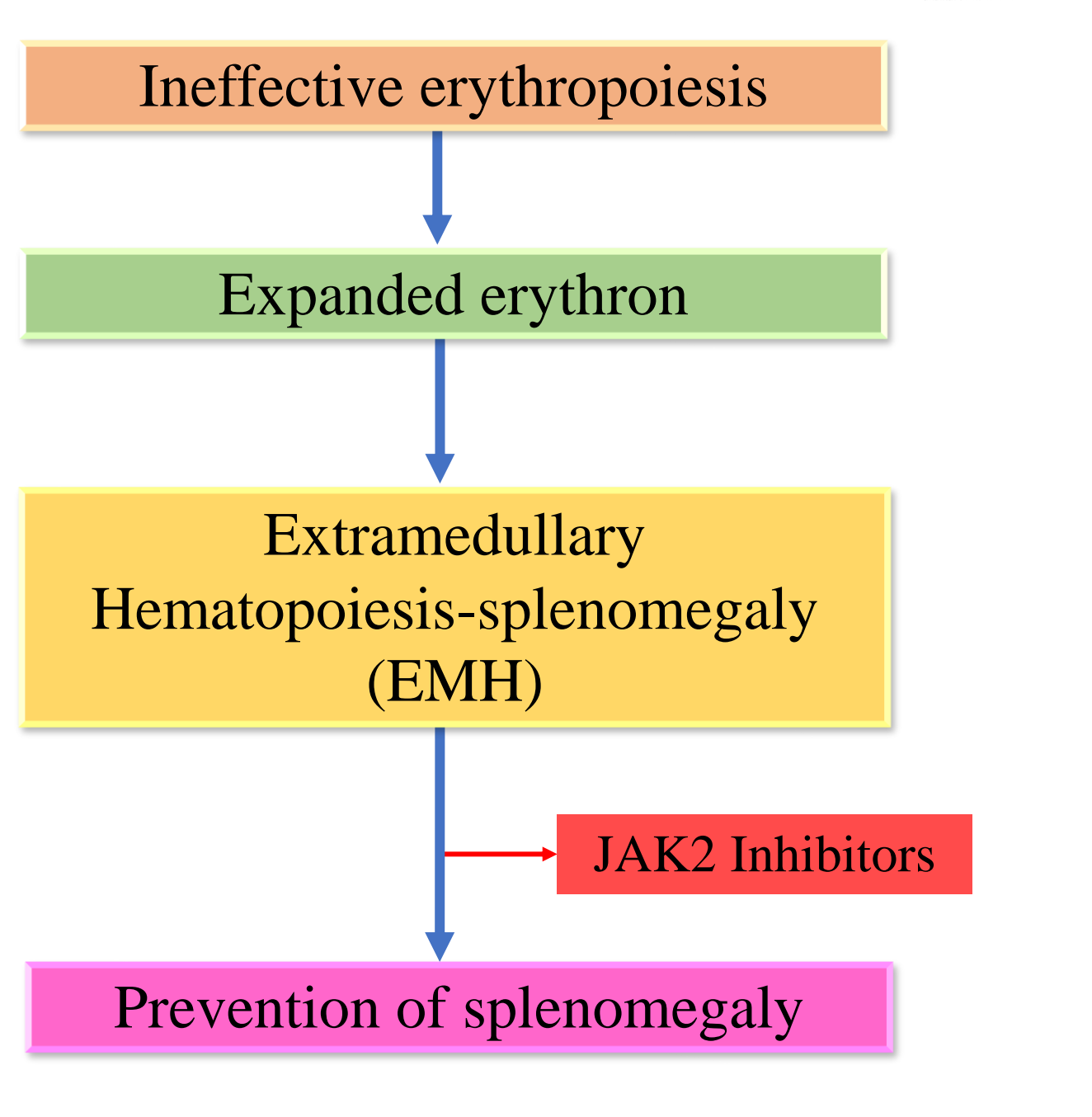
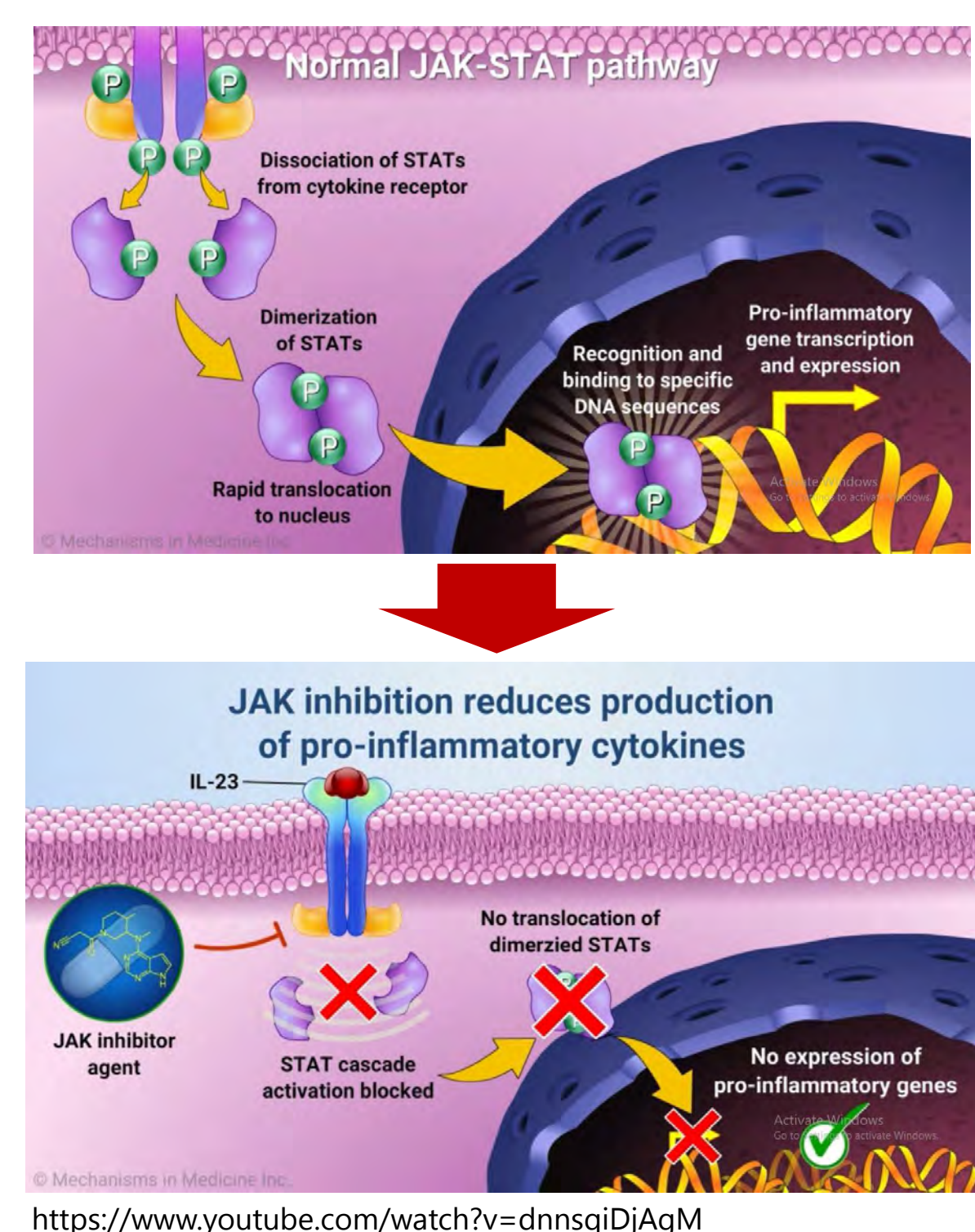
¹ Department of Chemistry, Faculty of Science, Ubon Ratchathani University, Ubon Ratchathani 34190, Thailand
² Department of Biological Science, Faculty of Science, Ubon Ratchathani University, Ubon Ratchathani 34190, Thailand
³ Division of Chemistry, Faculty of Science, Nakhon Phanom University, Nakhon Phanom 48000, Thailand
⁴ National Nanotechnology Center, NSTDA, 111 Thailand Science Park, Klong Luang, Pathum Thani, Thailand
⁵ College of Medicine and Public Health, Ubon Ratchathani University, Warin Chamrap, Ubon Ratchathani, 34190, Thailand
⁶ Department of Computer Science and Engineering, Toyohashi University of Technology, Toyohashi 441-8580, Japan

*Email: pornpan_ubu@yahoo.com



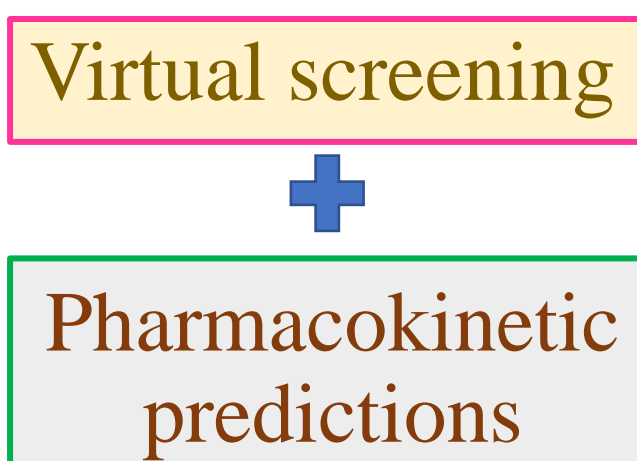
Introduction

Janus kinase 2 (JAK2) is an enzyme responsible for regulating erythropoiesis



The key target for developing inhibitors in the new pathway therapeutic option for thalassemia

Computer Aided Molecular Design (CAMD)



Results

Biological activity prediction and molecular docking studies

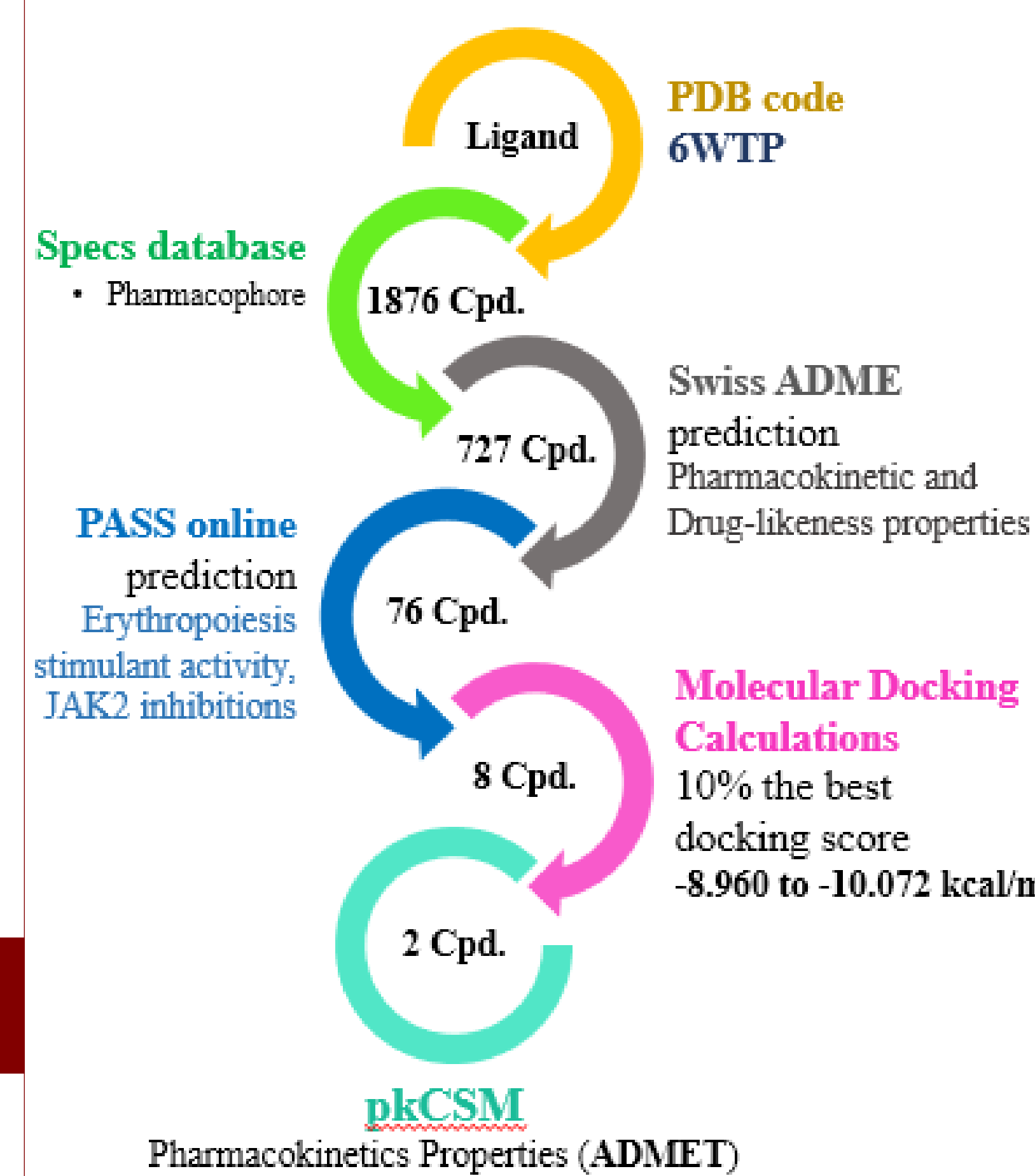


Table 1 The results of the erythropoiesis stimulant activity and JAK2 inhibition using PASS online prediction and the docking score from molecular docking calculations

Specs ID	Erythropoiesis stimulant activity		JAK2 Inhibitors		Docking score (kcal/mol)
	Pa	Pi	Pa	Pi	
AN-979/41713534	0.369	0.111	0.196	0.077	-10.072
AE-848/36435006	0.379	0.104	0.180	0.087	-9.907
AK-968/15255921	0.259	0.237	0.192	0.080	-9.902
AO-854/43444295	0.331	0.145	0.184	0.085	-9.424
AN-652/41971735	0.396	0.091	0.190	0.081	-9.420
AN-648/15101115	0.367	0.113	0.423	0.005	-9.335
AO-548/11107986	0.541	0.025	0.208	0.068	-9.320
AT-417/43484991	0.320	0.157	0.371	0.008	-8.960

Figure 2 The virtual screening process of JAK2 inhibition from specs database

The pharmacokinetic properties (ADMET) prediction

Table 2 The results of ADMET prediction of selected compounds

Specs ID	Caco2	Intestinal absorption (human)	Pgp inhibitor	BBB	CNS	CYP2D6 substrate	CYP3A4 substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Total Clearance	Renal OCT2 substrate	AMES toxicity	hERG toxicity	Oral Rat Acute Toxicity (LD50)	Hepato toxicity
AN-979/41713534	1.249	91.680	Yes	-0.332	-2.273	No	Yes	No	Yes	Yes	No	Yes	-0.082	No	No	Yes	2.256	Yes
AN-648/15101115	1.137	94.696	Yes	-0.551	-2.352	No	Yes	Yes	Yes	No	No	Yes	-0.095	No	No	Yes	3.239	Yes

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

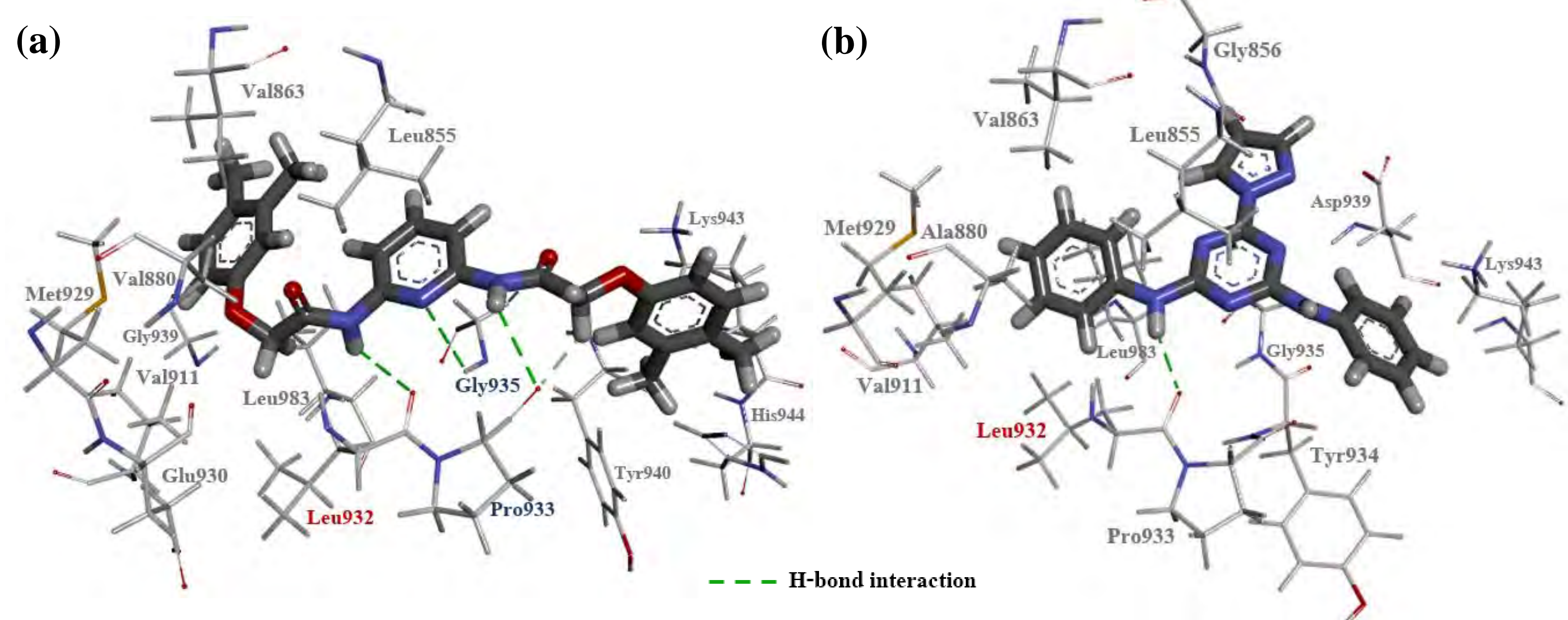


Figure 3 The binding mode of (a) AN-979/41713534 and (b) AN-648/15101115 in JAK2 binding pocket

Materials and Methods

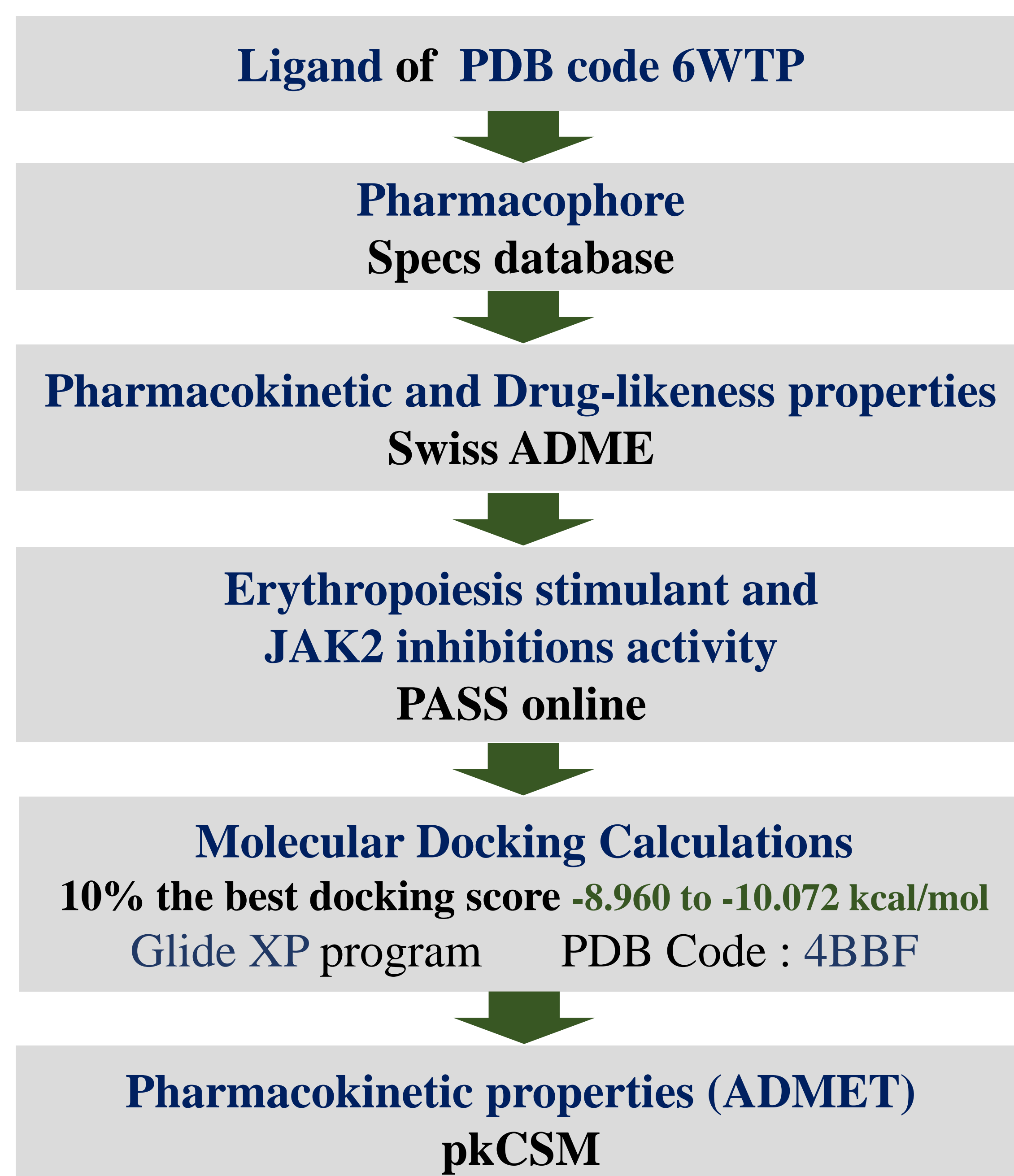


Figure 1 The virtual screening process to be JAK2 inhibitors

Conclusions

- Based on pharmacokinetic properties prediction, two promising compounds, AN-979/41713534 and AN-648/15101115 were obtained
- The binding mode and binding interactions in the ATP binding site of JAK2, the hydrogen bond interactions with Leu932 backbone in the ATP binding site of JAK2 are key interaction for binding of new finding compounds
- The Caco2 permeability of these two compounds was high.
- The BBB and CNS permeability values suggested that the selected compounds were poorly distributed to the brain and unable to penetrate the CNS
- The finding compounds were proposed as novel and potential JAK2 inhibitors as ESA for thalassemia therapy

Acknowledgments

- National Science, Research and Innovation Fund (NSRF)
- Faculty of Science, Ubon Ratchathani University
- Ubon Ratchathani University
- Nakhon Phanom University
- National Electronics and Computer Technology Center (NECTEC)