

**Molecular modeling studies of pyrrolo[2,3-d]pyrimidin-4-amine derivatives as JAK1 inhibitors based on 3D-QSAR, molecular docking, molecular dynamics (MD) and MM-PBSA calculations.**

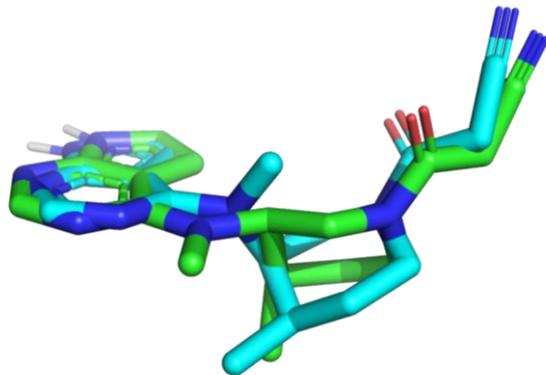
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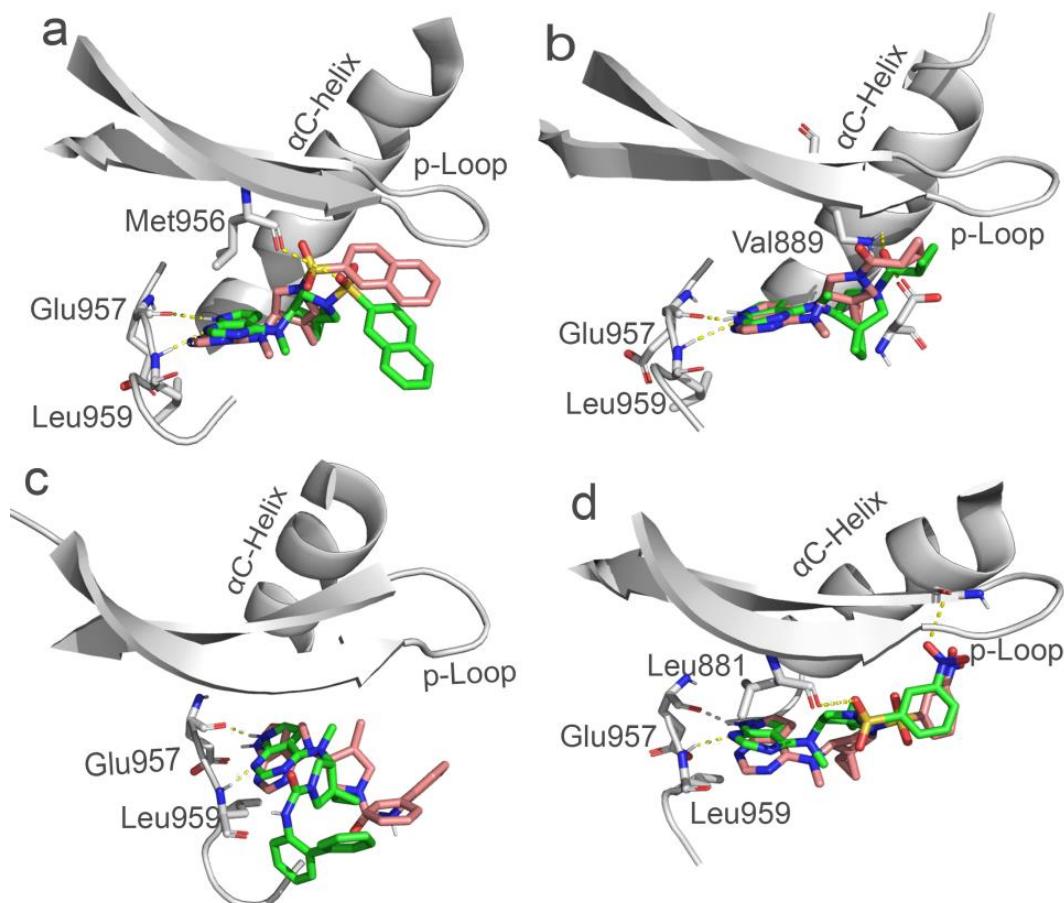
<sup>b</sup> *Department of Cellular Molecular Medicine, College of Medicine, Chosun University, Gwangju 501-759, Republic of Korea*

## Supplementary Material

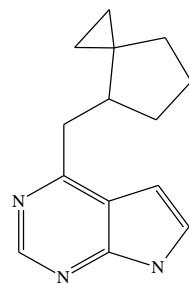
**Figure S1:** The crystal structure pose of **CP-690550** (PDB 3EYG) overlapped with the docked pose inside JAK1



**Figure S2.** Comparison of the binding poses of the compounds **03**, **13**, **36** and **49** before (salmon) and after (green) the Molecular Dynamics simulations. a) Binding pose of compound **03** with JAK1 b) Binding pose of compound **13** with JAK1. (c) Binding pose of compound **36** with JAK1. (d) Binding pose of compound **49** with JAK1.



**Figure S3.** The common substructure used for the alignment of the dataset compounds.



**Figure S4.** Scatter plot for the receptor-based CoMFA model and the ligand-based CoMFA model. (a) Receptor-based CoMFA model for JAK1 (b) Ligand-based CoMFA model for JAK1. The values on x-axis and y-axis represent the predicted  $\text{pIC}_{50}$  value and the experimental/actual  $\text{pIC}_{50}$  values respectively.

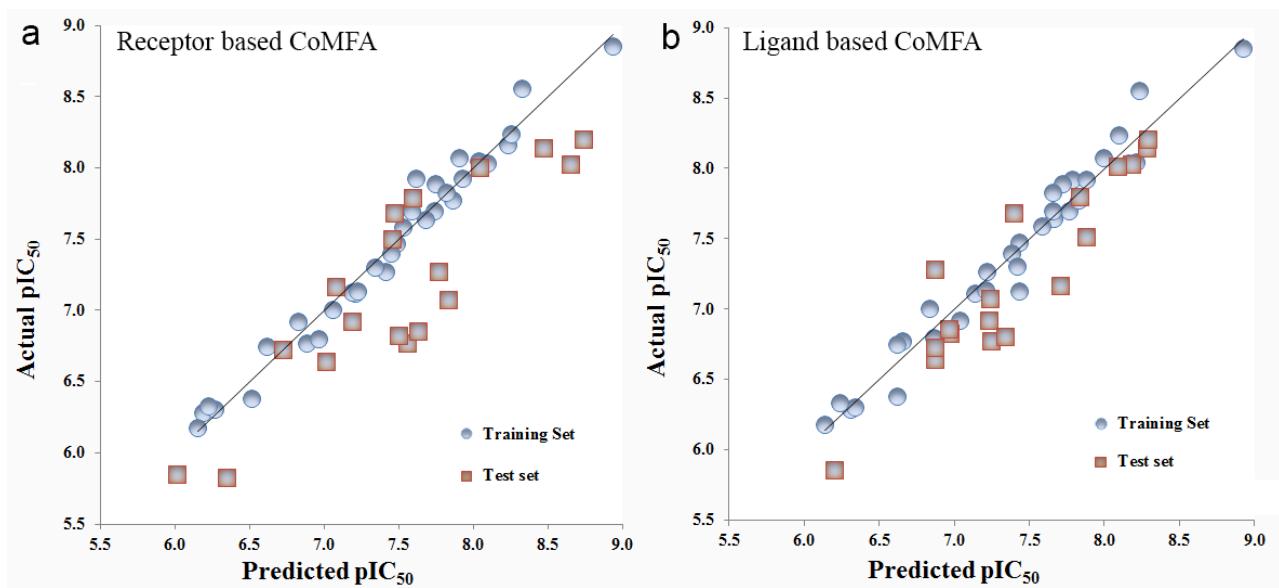
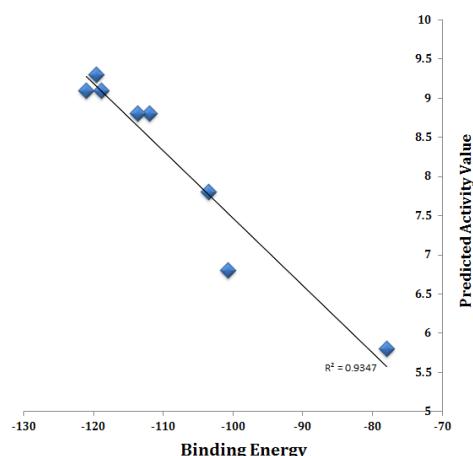
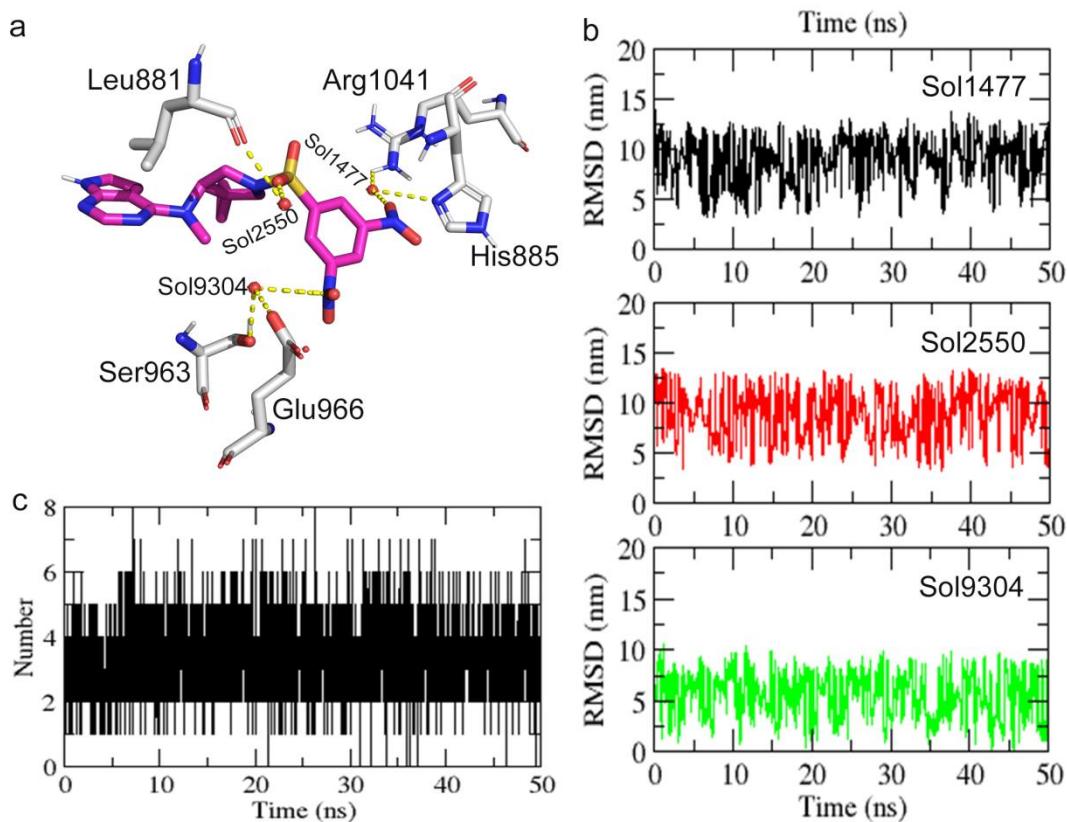


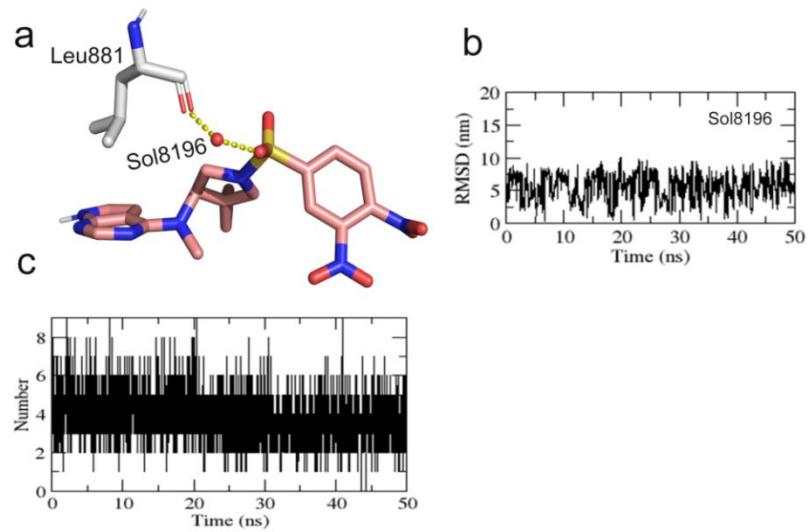
Figure S5. The scatter plot of the predicted activity value and the binding energy value for compound **03, 13, 36, 49, D57, D58, D75** and **D98**.



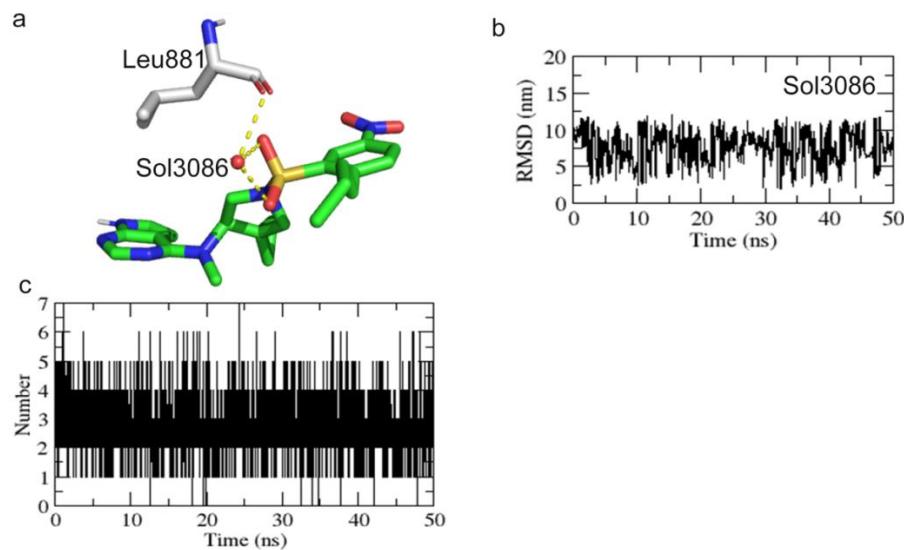
**Figure S6.** Analysis of the water molecules that participated in water mediated H-bond interactions between compound **D57** and JAK1. (a) The water mediated interactions observed between compound **D57** and JAK1. (b) The root mean square deviation (RMSD) of the water molecules (c) The number of H-bond interactions with water molecules observed throughout the MD simulation.



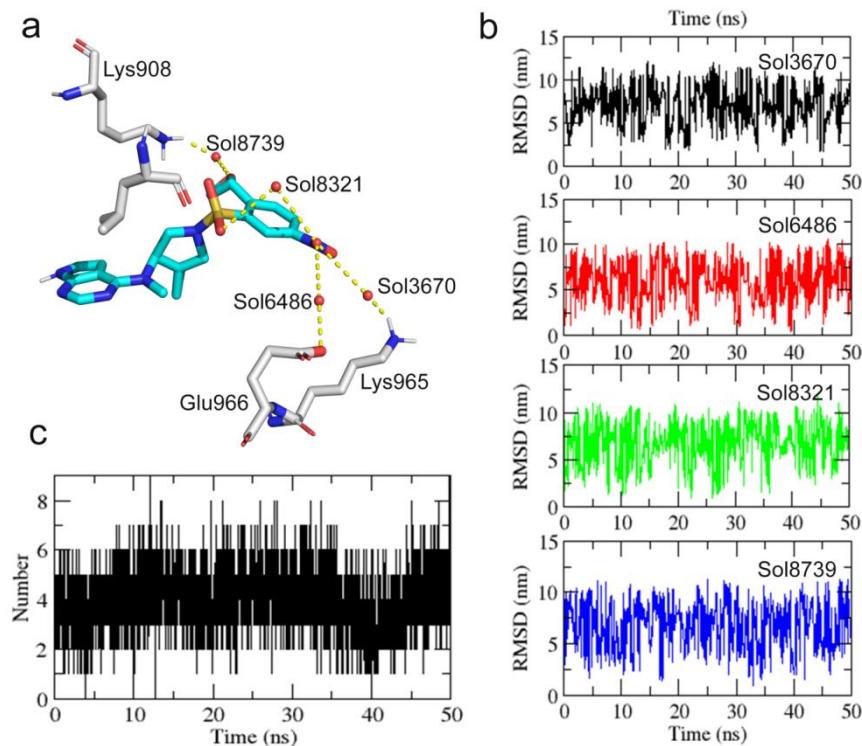
**Figure S7.** Analysis of the water molecules that participated in water mediated H-bond interactions between compound **D58** and JAK1. (a) The water mediated interactions observed between compound **D58** and JAK1. (b) The root mean square deviation (RMSD) of the water molecules (c) The number of H-bond interactions with water molecules observed throughout the MD simulation.



**Figure S8.** Analysis of the water molecules that participated in water mediated H-bond interactions between compound **D75** and JAK1. (a) The water mediated interactions observed between compound **D75** and JAK1. (b) The root mean square deviation (RMSD) of the water molecules (c) The number of H-bond interactions with water molecules observed throughout the MD simulation.



**Figure S9.** Analysis of the water molecules that participated in water mediated H-bond interactions between compound **D98** and JAK1. (a) The water mediated interactions observed between compound **D98** and JAK1. (b) The root mean square deviation (RMSD) of the water molecules (c) The number of H-bond interactions with water molecules observed throughout the MD simulation.



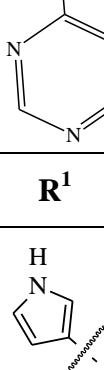
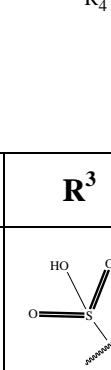
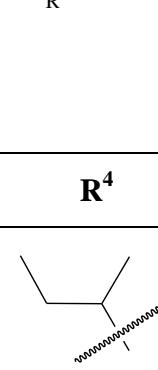
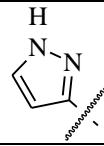
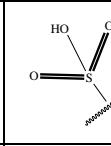
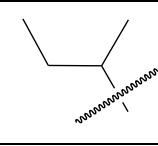
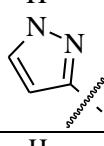
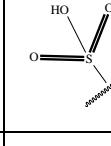
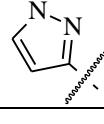
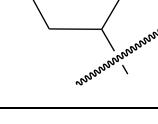
**Table S1.** The experimental/actual and predicted pIC<sub>50</sub> values with their residuals for the receptor-based CoMFA and the ligand-based CoMFA for JAK1.

Compound	Experimental pIC <sub>50</sub>	Receptor based model		Ligand-based model	
		Predicted pIC <sub>50</sub>	Residual	Predicted pIC <sub>50</sub>	Residual
<b>1</b>	8.03	8.10	-0.07	8.16	-0.13
<b>2</b> <sup>*</sup>	7.79	7.60	0.19	7.84	-0.05
<b>3</b>	7.77	7.87	-0.10	7.83	-0.06
<b>4</b> <sup>*</sup>	7.82	7.82	0.00	7.66	0.17
<b>5</b>	7.50	7.46	0.04	7.88	-0.38
<b>6</b> <sup>*</sup>	8.07	7.91	0.16	8.00	0.07
<b>7</b> <sup>*</sup>	5.85	6.02	-0.17	6.20	-0.35
<b>8</b>	6.64	7.02	-0.38	7.40	-0.76
<b>9</b>	6.92	6.83	0.09	7.04	-0.12
<b>10</b> <sup>*</sup>	7.68	7.48	0.21	6.87	0.81
<b>11</b>	7.11	7.22	-0.10	7.14	-0.02
<b>12</b>	6.77	7.56	-0.79	7.25	-0.48
<b>13</b>	6.77	6.89	-0.12	6.66	0.11
<b>14</b>	6.28	6.20	0.09	6.31	-0.03
<b>15</b> <sup>*</sup>	6.17	6.15	0.02	6.14	0.04
<b>16</b>	6.74	6.62	0.13	6.62	0.12
<b>17</b> <sup>*</sup>	7.27	7.77	-0.50	6.87	0.40
<b>18</b>	6.82	7.50	-0.68	6.98	-0.15
<b>19</b>	6.80	6.96	-0.17	6.87	-0.07
<b>20</b> <sup>*</sup>	6.85	7.64	-0.79	6.97	-0.12
<b>21</b>	7.00	7.06	-0.06	6.84	0.16
<b>22</b>	6.72	6.73	-0.01	6.88	-0.16
<b>23</b> <sup>*</sup>	6.30	6.27	0.03	6.34	-0.04
<b>24</b>	6.38	6.52	-0.14	6.62	-0.25
<b>25</b> <sup>*</sup>	7.70	7.75	-0.05	7.76	-0.07
<b>26</b>	7.47	7.49	-0.02	7.44	0.03
<b>27</b>	7.12	7.19	-0.07	7.44	-0.31
<b>28</b>	7.16	7.08	0.08	7.71	-0.55
<b>29</b> <sup>*</sup>	7.92	7.62	0.30	7.79	0.14
<b>30</b>	7.64	7.69	-0.05	7.67	-0.03
<b>31</b>	6.92	7.19	-0.27	7.24	-0.32
<b>32</b> <sup>*</sup>	7.40	7.45	-0.05	7.38	0.01
<b>33</b>	7.27	7.42	-0.15	7.22	0.05
<b>34</b>	7.13	7.23	-0.09	7.21	-0.08
<b>35</b>	7.07	7.84	-0.77	7.24	-0.17
<b>36</b> <sup>*</sup>	5.82	6.35	-0.53	6.30	-0.48
<b>37</b>	6.33	6.23	0.10	6.24	0.09
<b>38</b>	8.14	8.47	-0.33	8.28	-0.14
<b>39</b> <sup>*</sup>	7.70	7.59	0.11	7.66	0.04
<b>40</b> <sup>*</sup>	8.16	8.23	-0.07	8.29	-0.13
<b>41</b>	8.05	8.04	0.00	8.21	-0.17

<b>42</b>	7.89	7.75	0.14	7.72	0.17
<b>43</b>	8.55	8.33	0.22	8.24	0.32
<b>44</b>	8.02	8.65	-0.63	8.18	-0.16
<b>45</b>	7.30	7.35	-0.04	7.42	-0.12
<b>46</b>	8.24	8.25	-0.02	8.10	0.14
<b>47<sup>*</sup></b>	8.00	8.05	-0.05	8.09	-0.09
<b>48</b>	7.59	7.54	0.05	7.59	0.00
<b>49</b>	8.85	8.84	0.01	8.92	-0.07
<b>50<sup>*</sup></b>	8.20	8.74	-0.54	8.30	-0.10
<b>51</b>	7.92	7.93	-0.01	7.88	0.04

\* Test set compounds

**Table S2.** The chemical structures and the predicted  $\text{pIC}_{50}$  values of some of the newly designed compounds that showed  $\text{pIC}_{50}$  values greater than 8.0.

Compounds	<b>R<sup>1</sup></b>	<b>R<sup>2</sup></b>	<b>R<sup>3</sup></b>	<b>R<sup>4</sup></b>	<b>X</b>	<b>Predicted <math>\text{pIC}_{50}</math></b>
<b>D105</b>		-			N	8.1
<b>D106</b>		-			N	8.2
<b>D107</b>		-		Cyclohexane	N	8.2
<b>D108</b>		-	NO <sub>2</sub>		N	8.4

<b>D114</b>	NO <sub>2</sub>	-			N	8.2
<b>D115</b>	COCH <sub>2</sub> CH <sub>3</sub>	-	NO <sub>2</sub>	Cyclohexane	N	8.8
<b>D116</b>	NO <sub>2</sub>	-	NO <sub>2</sub>	Cyclohexane	N	8.6
<b>D117</b>	CONH <sub>2</sub>	-	NO <sub>2</sub>	Cyclohexane	N	8.6
<b>D119</b>	NO <sub>2</sub>	-	SO <sub>2</sub> NH <sub>2</sub>	(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	N	8.0
<b>D120</b>	N <sub>3</sub>	-	SO <sub>2</sub> NH <sub>2</sub>	(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	N	8.0