

Fragment-based Drug Design and Drug Repositioning
Using Multiple Ligand Simultaneous Docking (MLSD):
Identifying Celecoxib and Template Compounds as
Novel Inhibitors of Signal Transducer and Activator of
Transcription 3 (STAT3)

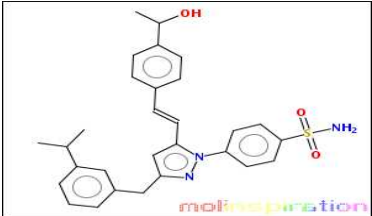
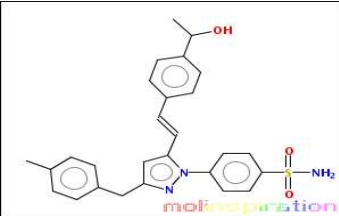
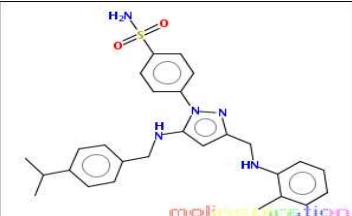
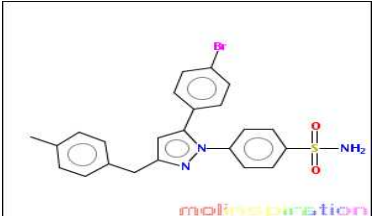
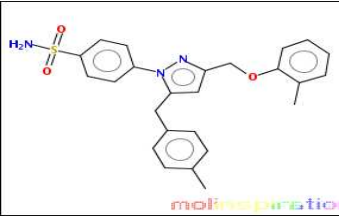
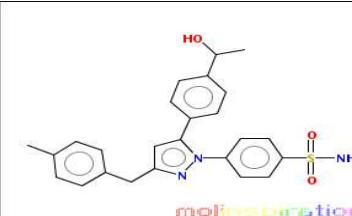
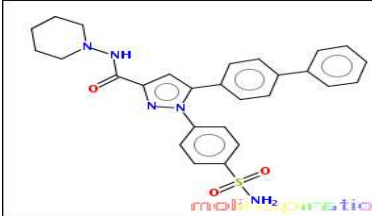
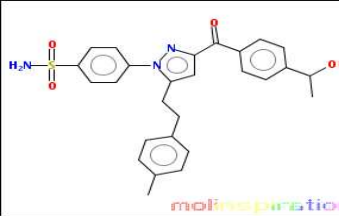
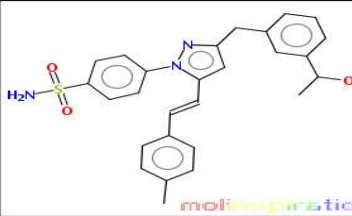
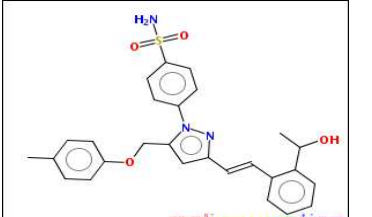
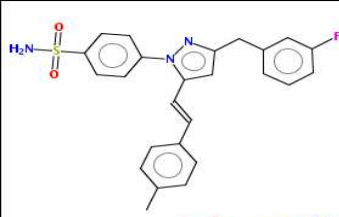
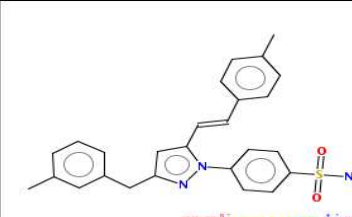
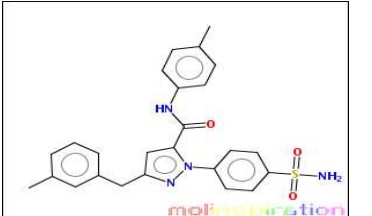
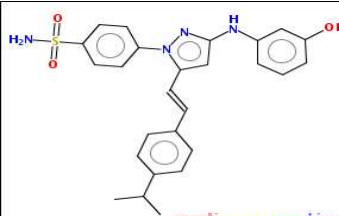
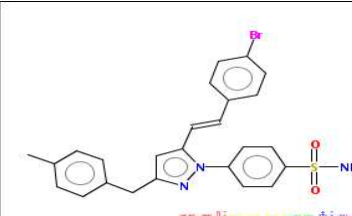
Huameng Li¹, Aiguo Liu^{3,4}, Zhenjiang Zhao⁵, Yufang Xu⁵, Jiayuh Lin³, David Jou³,

and Chenglong Li^{1,2}*

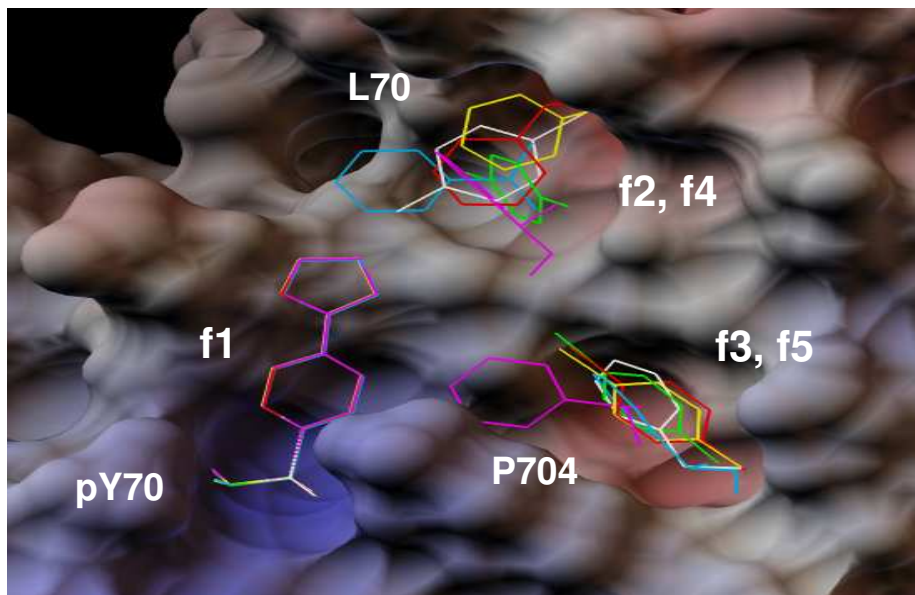
Contents of SI

- 2** Structures and docking energies of template compounds obtained by linking fragments in hits H1 (f1, f2 and f3) and H2 (f1, f4 and f5)
- 3** Binding modes cluster of hit H1 (f1, f2 and f3) and hit H2 (f1, f4 and f5)
- 4-5** Scheme of synthesis of hit compounds **T2 and T3**

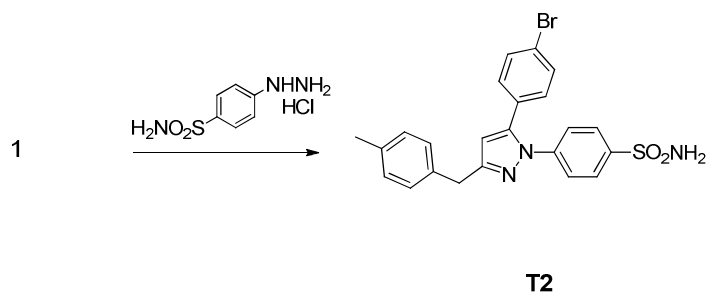
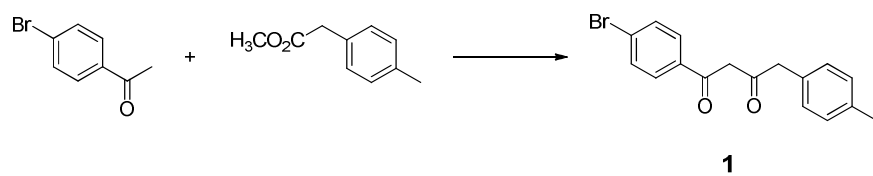
Supplementary Table S1. Structures and docking energies (ΔE) of template compounds obtained by linking fragments in hits H1 (f1, f2 and f3) and H2 (f1, f4 and f5)

Compound (ΔE , kcal/mol) Structure	Compound (ΔE , kcal/mol) Structure	Compound (ΔE , kcal/mol) Structure
T1 (-12.0) 	T6 (-10.1) 	T11 (-8.2) 
T2 (-8.6) 	T7 (-10.6) 	T12 (-8.8) 
T3 (-9.3) 	T8 (-10.3) 	T13 (-10.9) 
T4 (-10.1) 	T9 (-10.7) 	T14 (-11.0) 
T5 (-9.5) 	T10 (-9.9) 	T15 (-11.0) 

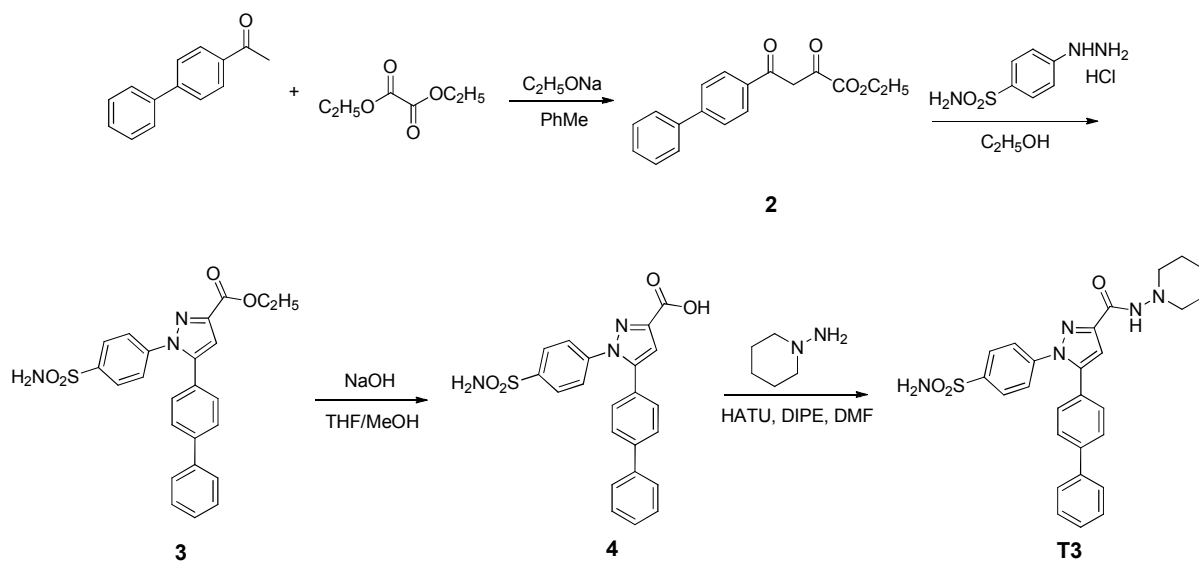
Supplementary Figure S2. Binding modes cluster of hit H1 (f1, f2 and f3) and hit H2 (f1, f4 and f5). Fragments are thin colored lines. The binding energies in the cluster were in the range of -12.1 kcal/mol to -12.5 kcal/mol. Fragment f1 showed a relatively fixed binding mode in pocket pY705, while the aromatic fragments f2, f4, f3 and f5 showed more dynamic and flexible binding modes in sub-pocket P704 or L706.



Supplementary Scheme S3. Synthesis of template compound T2.



Supplementary Scheme S4. Synthesis of template compound T3



Synthesis of intermediate compounds 2, 3 and 4. To a solution of $\text{C}_2\text{H}_5\text{ONa}$ (1.96g, 28mmol) in toluene (25 mL) was added diethyl oxalate 2.5mL by dropwise under ice-water cooling. A suspension of 4-phenyl acetophenone (1.96g, 10mmol) in 25 mL toluene was added at the same condition 10 min later. After about 4 h the reaction was checked by TLC and was determined to be complete. The resulting mixture was filtered, washed by water and petroleum ether, and dried to obtain the crude **2** as white solid.

A mixture of **2** (1.18 g, 4 mmol) in 80 mL $\text{C}_2\text{H}_5\text{OH}$ and p-Sulfonamide-phenylhydrazine hydrochloride (0.98 g, 4.4 mmol) was refluxed for 24 h, followed by cooling, recrystallization from $\text{C}_2\text{H}_5\text{OH}$ to produce compound **3** (0.89g, 50%) as yellow solid.

5-biphenyl-1-(4-aminosulfonylphenyl)pyrazole-3-Carboxylic acid (4). A mixture of compound **3** (178 mg, 0.3 mmol) and NaOH (28 mg, 0.6 mmol) in solvents of 5 mL $\text{C}_2\text{H}_5\text{OH}$, 5mL THF and 2 mL water was stirred 15 h. Acidification with diluted HCl, and concentration in vacuo of the reaction mixture gave crude compound **4** as white solid.