Supplementary Data

Supplementary Table S1. JAK selectivity, mode of binding, and approved indications of abrocitinib, baricitinib, filgotinib, peficitinib, tofacitinib, and upadacitinib

	JAK selectivity	Mode of binding [1][a]			Indication	Year of first approval (country of approval)
		JAK1	JAK2	Other		
Abrocitinib	JAK1 [2]	• Three hydrogen bonds (with Glu957, Leu 959, and Asn1008)	• Four hydrogen bonds (with Glu930, Leu932, Arg980, and Asn981) • One carbon–hydrogen bond (with Leu932)	–	Atopic dermatitis [2]	2021 (UK) [3]

		• Three carbon–hydrogen bonds (Leu881 and Leu959) • Several hydrophobic interactions with amino acids	• Hydrophobic interactions with Leu855, Val863, Ala880, Val911, and Leu 983			
Baricitinib	JAK1, JAK2 [4]	• No data	• One hydrogen bond (Leu932)	–	Rheumatoid arthritis [4] Atopic dermatitis [4]	2017 (EU) [5] 2020 (EU) [6]

			• Three carbon–hydrogen bonds (Ser862, Lys882, and Asp994) • One pi-sulfur interaction (Met929) • Several hydrophobic interactions of the pi-sigma and pi-alkyl types		Alopecia areata [4]	2022 (EU) [7]
Filgotinib	JAK1 [8]	• Two hydrogen bonds (Leu932) • One carbon–hydrogen	–	–	Rheumatoid arthritis [8] Ulcerative colitis [8]	2020 (EU/Japan) [9] 2021 (EU) [10]

		bond (Lys882)				
Peficitinib	Pan-JAK inhibitor [11]	• Three hydrogen bonds (Leu959 and Asn1008)	• Two hydrogen bonds (Glu930 and Leu932) • One carbon–hydrogen bond (Glu930)	• JAK3 ○ Two hydrogen bonds (Glu903 and Leu905) ○ One carbon–hydrogen bond (Glu903) • TYK2 ○ Four hydrogen bonds (Val981, Glu979, Asn1028, and Asp1041)	Rheumatoid arthritis [11]	2019 (Japan) [12]
Tofacitinib	JAK1, JAK2, JAK3 [13]	• Two hydrogen bonds	• Two hydrogen bonds (Gly858 and Leu932)	• JAK3 ○ One hydrogen bond (Leu905)	Rheumatoid arthritis [14]	2012 (USA) [15]

		(Gly884 and Leu959)	• Three carbon–hydrogen bonds (Leu855, Arg980, and Asn981)	○ Four carbon–hydrogen bonds (Leu828, Lys855, Arg953, and Asn954) • TYK2 ○ Two hydrogen bonds (Gly906 and Val981)	Psoriatic arthritis [14] Ulcerative colitis [14] Juvenile idiopathic arthritis [14] Ankylosing spondylitis [14]	2017 (USA) [16] 2019 (USA) [17] 2020 (USA) [18] 2021 (EU) [19]
Upadacitinib	JAK1 [20]	• No data[b]	–	–	Rheumatoid arthritis [20] Psoriatic arthritis [20]	2019 (USA) [21] 2021 (EU) [22]

		Ankylosing spondylitis [20]	2021 (EU) [22]
		Atopic dermatitis [20]	2021 (EU) [23]
		Ulcerative colitis and Crohn's disease [20]	2022 (USA) [24]

[a]Based on crystal structures of JAK inhibitors complexed with target JAKs [1]. [b]To our knowledge, a crystal structure of upadacitinib bound to its target JAK has yet to be reported. It is hypothesized that upadacitinib achieves JAK1-selective competitive inhibition by interacting with the canonical glycine-rich loop in the ATP-binding pocket, which assumes a "closed" conformation in JAK1 but not in JAK2. A trifluoromethyl group within upadacitinib was predicted to occupy the van der Waals interaction space under the loop to provide an induced fit into JAK1, thereby conferring JAK1 selectivity [25].
ATP: adenosine-5´-triphosphate; JAK: Janus kinase.

Supplementary Table S2. Summary of IC_{50} values and average daily STAT inhibition from McInnes *et al*. [26]

	IC_{50} values (nM)			Average daily STAT inhibition (%)		
	Baricitinib	**Tofacitinib**	**Upadacitinib**	**Baricitinib 4 mg**	**Tofacitinib 10 mg**	**Upadacitinib 15 mg**
JAK1/JAK2-dependent cytokines						
IL-6/pSTAT3	48–61	40–56	43–58	29–32	54–61	22–27
IFN-γ/pSTAT1[a]	38	46	30	37	61	34
JAK1/JAK3-dependent cytokines						
IL-2/pSTAT5	29–44	11–15	10–27	34–44	85–89	36–60
IL-4/pSTAT6	22–48	8–35	8–22	30–52	70–91	40–61
IL-15/pSTAT5	40–67	15–22	17–40	24–36	79–85	27–47
IL-21/pSTAT3	62–85	21–37	20–34	22–27	63–76	34–44
JAK1/TYK2-dependent cytokines						
IFN-α/pSTAT1	64–97	121–163	40–69	21–29	32–37	21–32
IFN-α/pSTAT3	14–27	23–51	6–17	45–62	55–76	48–72
IFN-α/pSTAT5	13–23	22–36	5–14	50–67	64–78	52–75
IL-10/pSTAT3	68–142	55–104	80–124	14–23	40–53	14–21
JAK2/TYK2-dependent cytokines						
G-CSF/pSTAT3[a]	65	97	84	25	40	17
JAK2/2-dependent cytokines						
IL-3/pSTAT5[a]	26	102	12	47	42	52
GM-CSF/pSTAT5[a]	30	97	13	45	37	55

Adapted from Tables 1 and 3 of McInnes *et al*. [26].
IC_{50} values and average daily percent STAT inhibition were determined in CD4+ T cells, NK cells, and monocytes.
[a]Data obtained from monocytes only.

G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; IC_{50}: half maximal inhibitory concentration; IFN: interferon; IL: interleukin; JAK: Janus kinase; NK: natural killer; pSTAT: phosphorylated signal transducer and activator of transcription; STAT: signal transducer and activator of transcription; TYK: tyrosine kinase.

Supplementary Table S3. Predicted average daily percent STAT inhibition results from Traves *et al*. [27]

	Predicted average daily STAT inhibition (%)			
	Filgotinib 200 mg	Baricitinib 4 mg	Tofacitinib 10 mg	Upadacitinib 15 mg
JAK1/JAK2-dependent cytokines				
IL-6/pSTAT1	53	52	59	55
IFN-γ/pSTAT1	24	37***	46***	40***
JAK1/JAK3-dependent cytokines				
IL-4/pSTAT6	26	35	63***	44***
JAK1/TYK2-dependent cytokines				
IFN-α/pSTAT5	55	59	72***	61*
JAK2/TYK2-dependent cytokines				
G-CSF/pSTAT3	16	34***	32***	29***
JAK2/2-dependent cytokines				
GM-CSF/pSTAT5	6	21***	17***	27***

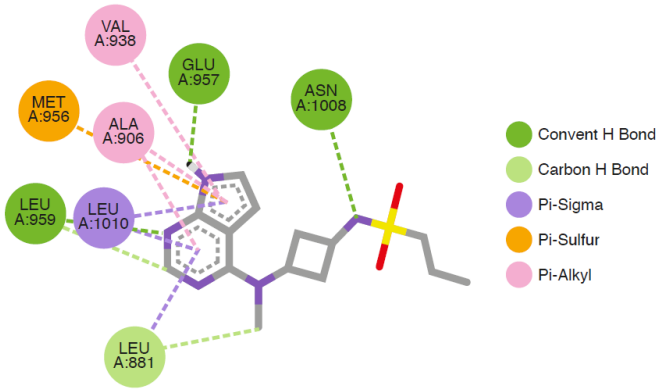
Adapted from Fig. 4 of Traves *et al*. [27].
Predicted average daily percent STAT inhibition was determined in monocytes (IL-6/pSTAT1; G-CSF/pSTAT3; GM-CSF/pSTAT5), CD4+ T cells (IFN α/pSTAT5; IL-4/pSTAT6), and neutrophils (IFN-γ/pSTAT1).
*$P < 0.05$ *vs* filgotinib; ***$P < 0.001$ *vs* filgotinib.
G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; IFN: interferon; IL: interleukin; JAK: Janus kinase; pSTAT: phosphorylated signal transducer and activator of transcription; STAT: signal transducer and activator of transcription; TYK: tyrosine kinase.

Supplementary Table S4. Search criteria

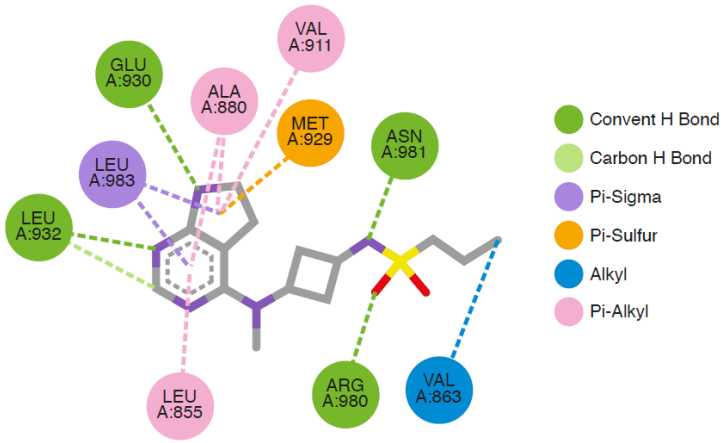
"Janus kinase inhibitor" "abrocitinib" "baricitinib" "filgotinib" "peficitinib" "tofacitinib" "upadacitinib" "selectivity" "chemical structure" "crystal structure" "catalytic domain" "platelet" "neutrophil" "lymphocyte" "haemoglobin" "carcinogenicity" "DNA damage repair" "reproductive system" "metabolized" "renal impairment" "hepatic impairment"
Additional articles were identified from key review papers
Only papers published in English were included

Supplementary Fig. S1 The 2-dimensional binding modes of JAK inhibitors in the catalytic cleft of target JAKs. Adapted from Shawky *et al*. (2022) [1] unless otherwise stated.

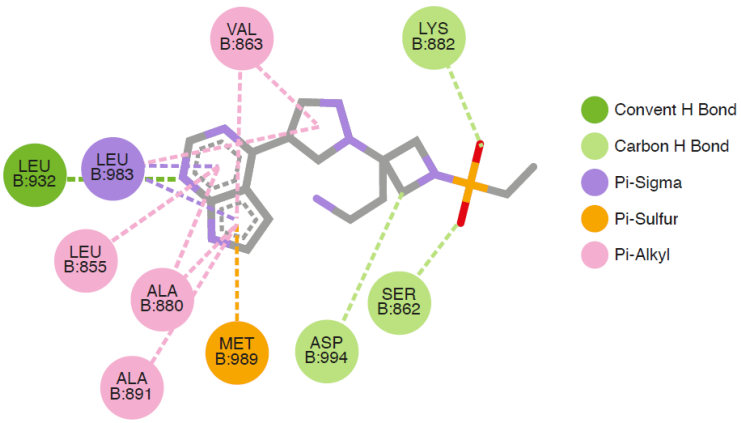
Abrocitinib bound to JAK1



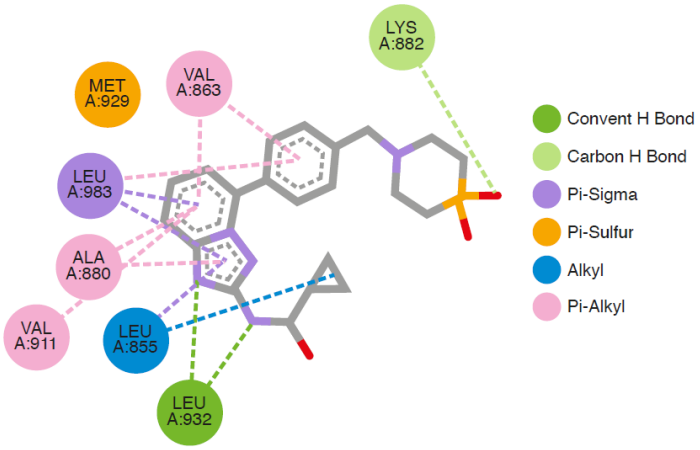
Abrocitinib bound to JAK2



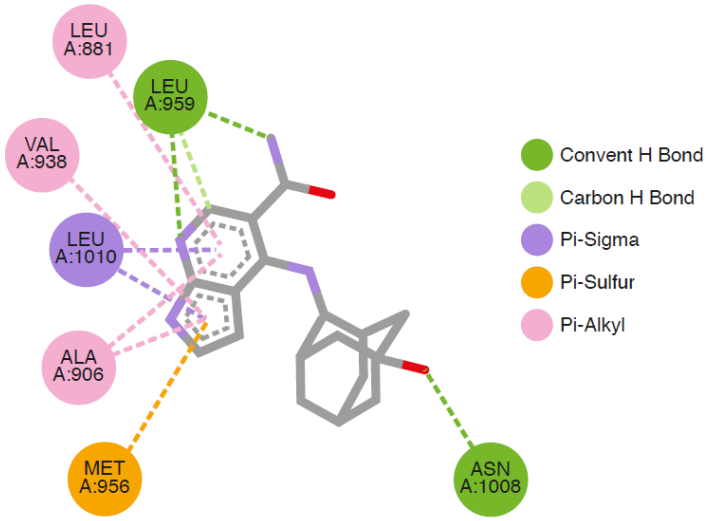
Baricitinib bound to JAK2


VAL
B:863
LYS
B:882
LEU
B:932
LEU
B:983
LEU
B:855
ALA
B:880
MET
B:989
ASP
B:994
SER
B:862
ALA
B:891
Convent H Bond
Carbon H Bond
Pi-Sigma
Pi-Sulfur
Pi-Alkyl

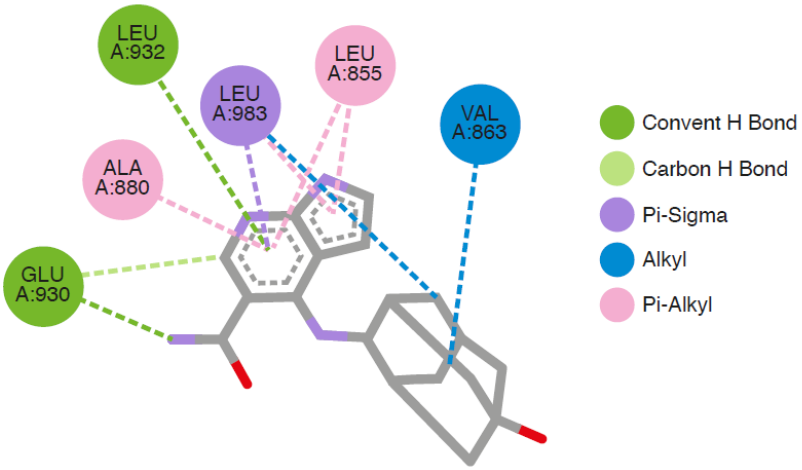
Filgotinib bound to JAK1



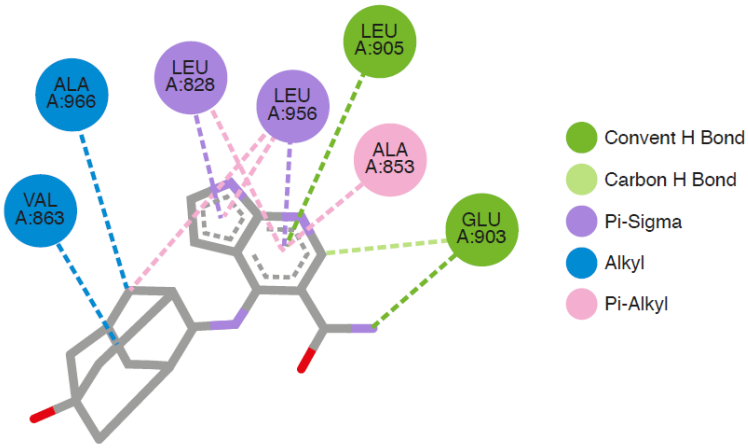
Peficitinib bound to JAK1



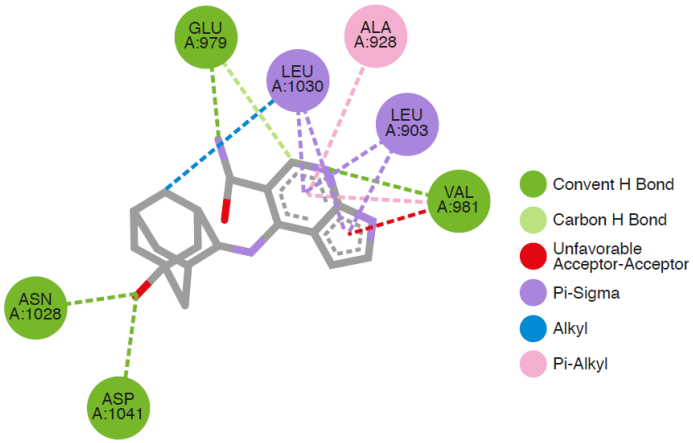
Peficitinib bound to JAK2


LEU
A:932
LEU
A:983
LEU
A:855
VAL
A:863
ALA
A:880
GLU
A:930
Convent H Bond
Carbon H Bond
Pi-Sigma
Alkyl
Pi-Alkyl

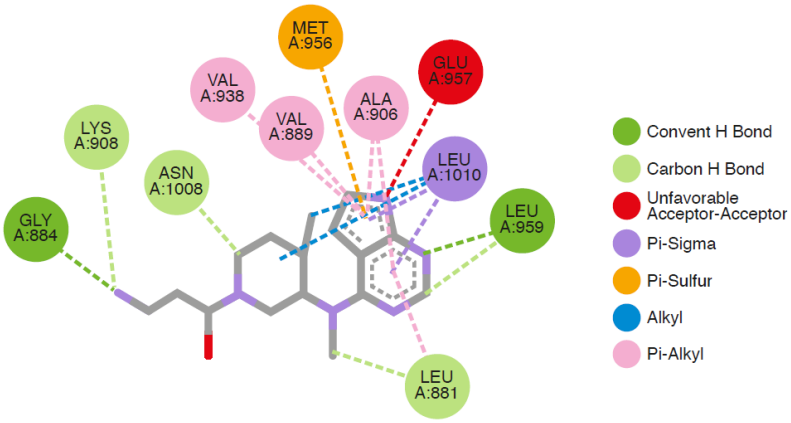
Peficitinib bound to JAK3



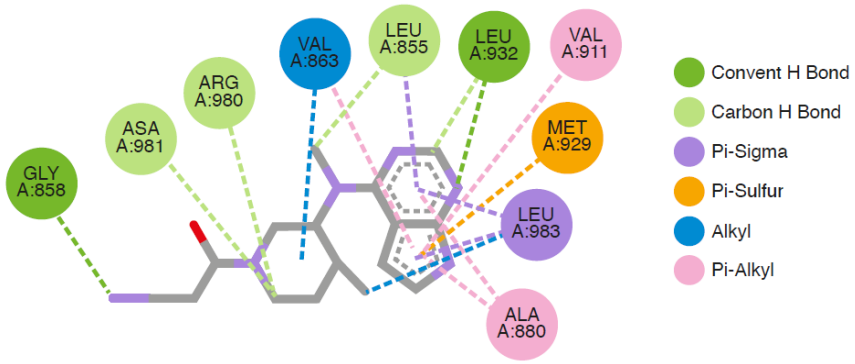
Peficitinib bound to TYK2



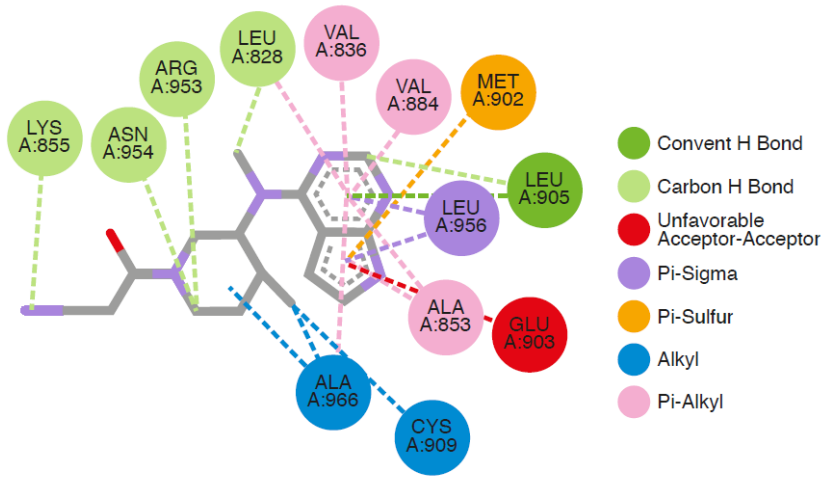
Tofacitinib bound to JAK1


MET
A:956
GLU
A:957
VAL
A:938
ALA
A:906
VAL
A:889
LYS
A:908
LEU
A:1010
ASN
A:1008
GLY
A:884
LEU
A:959
LEU
A:881
Convent H Bond
Carbon H Bond
Unfavorable
Acceptor-Acceptor
Pi-Sigma
Pi-Sulfur
Alkyl
Pi-Alkyl

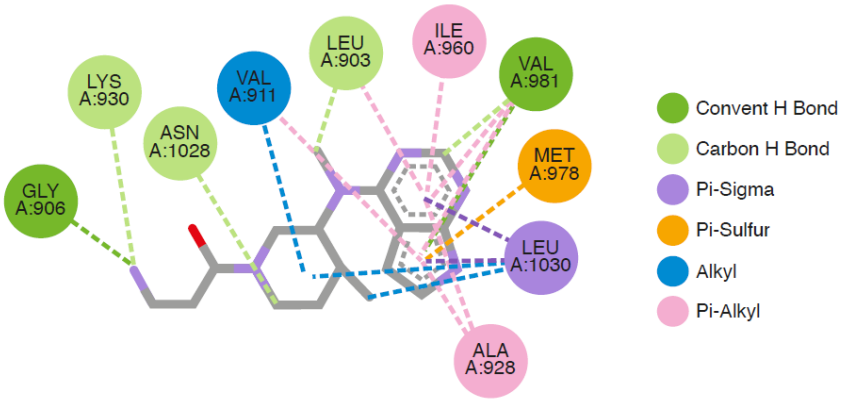
Tofacitinib bound to JAK2



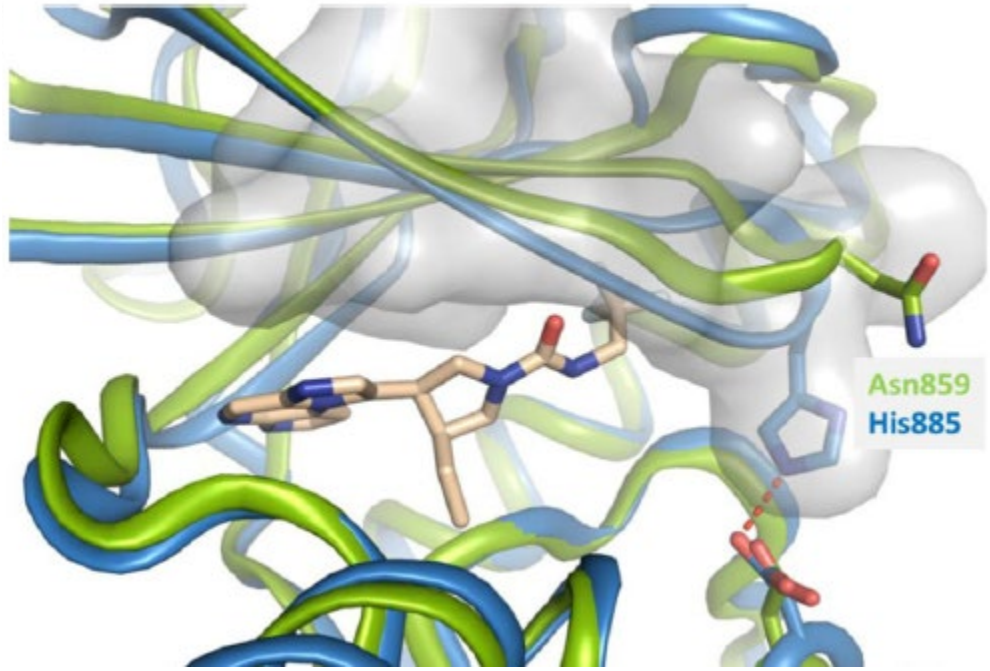
Tofacitinib bound to JAK3



Tofacitinib bound to TYK2


LEU
A:903
ILE
A:960
LYS
A:930
VAL
A:911
VAL
A:981
ASN
A:1028
MET
A:978
GLY
A:906
LEU
A:1030
ALA
A:928
Convent H Bond
Carbon H Bond
Pi-Sigma
Pi-Sulfur
Alkyl
Pi-Alkyl

Upadacitinib bound to JAK1



A model of upadacitinib bound to JAK1 (in blue); JAK2 is overlaid in green. Adapted from Parmentier *et al*. (2018) [25] under https://creativecommons.org/licenses/by/4.0/

JAK: Janus kinase.

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