BEFORE THE CONTROLLER OF PATENTS

THE PATENT OFFICE BRANCH, DELHI

In the matter of:

Section 25(1) of The Patents Act,1970 as amended by
The Patents (Amendment) Act 2005;

and

Rule 55 of Patents Rules 2003 as amended by the Patent (Amendment) Rules, 2017

and

Indian Patent Application 4759/DELNP/2012, dated 29/05/2012
in the name of ABBVIE INC. of
1 North Waukegan Road, North Chicago, Illinois 60064, U.S.A.

REPRESENTATION BY WAY OF PRE-GRANT OPPOSITION:

Neha Sahu **.....OPPONENT**

vs.

Abbvie INC. **.....APPLICANT**

I, Neha Sahu, an Indian citizen, age about 36 years, r/o BG-6/7C, Block BG 6, Paschim Vihar, Delhi 110 063, hereby give my representation of opposition to grant of patent on IN 4759/DELNP/2012 dated 29.05.2012 titled "Novel Tricyclic Compounds".

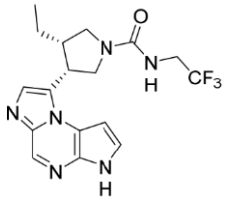
STATEMENT OF CASE OF OPPONENT

I. BACKGROUND & BIBLIOGRAPHIC INFORMATION:

1. The Opponent, in this pre-grant opposition requests that the grant of patent on IN 4759/DELNP/2012 [**IN'4759**] filed on 29.05.2012 titled "Novel Tricyclic Compounds" be refused. IN'4759 is a national phase entry of PCT/US2010/058572 [publ. as WO 2011/068881 on 09.06.2011]. It claims priority from US application Nos. 61/265,563 of 01.12.2009 and 61/364,116 of 14.07.2010.

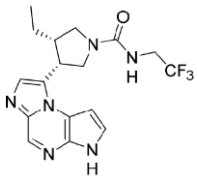
2. IN'4759 appears to be currently pending with 2 claims [as of 25.03.2018]:

1. *A compound represented by the following structure:*



or a pharmaceutically acceptable salt thereof.

2. *The compound as claimed in claim 1, represented by following structure:*



3. The compound represented by the chemical structure shown above has the International Non-Proprietary Name (INN) of UPADACITINIB.

4. Opponent places the following documents as part of this pre-grant opposition and will rely on such documents in this opposition.

Exhibit No.	**Particulars**
Exhibit 1	Claims pending on IN'4759
Exhibit 2	First Examination Report on IN'4759 [***FER***]
Exhibit 3	Applicant's Response to FER
Exhibit 4	Front Page of WO 2011/068881 [**WO'881**]
Exhibit 5	Copy of EPO Opposition Board decision on corresponding EPA 10835061.2 [**EP'061**]
Annexure No.	**Particulars**
Annexure 1	Complete Specification & Claims of IN292307 [IN 195/DELNP/2008] – **IN'307**
Annexure 2	WO 2009/152133 – **WO'133**
Annexure 3	US Patent 8962629 – US'629
Annexure 4	Copy of USFDA Orange Book for Upadacitinib – **Upada-OB**
Annexure 5	Lucet et. al., *The structural basis of Janus kinase 2 inhibition by a potent and specific pan–Janus kinase inhibitor*, BLOOD, 1 JANUARY 2006 VOLUME 107, NUMBER 1 – hereinafter ***Lucet et al***
Annexure 6	Williams et. al., *Dissecting Specificity in the Janus Kinases: The Structures of JAK-Specific Inhibitors Complexed to the JAK1 and JAK2 Protein Tyrosine Kinase Domains*, J. Mol. Biol. (Jan 2009) 387, 219–232 – hereinafter ***Williams et al***
Annexure 7	Stephen et al., *Advances in the Discovery of Small Molecule JAK3 Inhibitors*, Annual Reports in Medicinal Chemistry, Vol. 44 2009 Elsevier Inc. ISSN: 0065-7743, DOI 10.1016/S0065-7743(09)04412-1 – hereinafter ***Stephen et al***
Annexure 8	US2007/0203142 – hereinafter ***US'142***

II. GROUNDS OF OPPOSITION

5. Opponent submits that IN'4759 is invalid and grant of patent ought to be refused. The following grounds are relied on for this purpose herein:

i. **Section 25(1)(c) –** the invention so far as claimed in any claim of the complete specification is claimed in a claim of a complete specification published on or after priority date of the applicant's claim and filed in pursuance of an application for a patent in India, being a claim of which the priority date is earlier than that of the applicant's claim.

ii. **Section 25(1)(b) –** the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim (i) in any specification filed in pursuance of an application for a patent made in India on or after 01.01.1912; or (ii) in India or elsewhere, in any other document.

iii. **Section 25(1)(e)** – the invention claimed in the impugned application is obvious and also clearly does not involve any inventive step.

iv. **Section 25(1)(f)** – the subject of any claim of the complete specification, is not an invention within the meaning of this act or is not patentable under this act.

v. **Section 25(1)(g)** – the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

vi. **Section 25(1)(h) –** the patentee has failed to disclose to the Controller the information required by Section 8 or has furnished information which in any material particular was false to his knowledge.

III. PRELIMINARY SUBMISSIONS

6. IN'4759 was filed claiming priority from two US applications, US61/265,563 dated 01.12.2009 and US61/364,116 dated 14.07.2010 [PD-1 & PD-2 respectively]. Irrespective of whatever may have been filed as a claim set at the time of filing/national phase entry of IN'4759, as of today, the application has only two claims: Upadacitinib and a pharmaceutically acceptable salt thereof [Claim 1] and Upadacitinib per se [Claim 2].

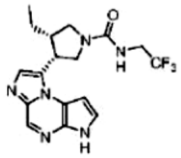
7. Neither PD-1 nor PD-2 provides any support in terms of any disclosure, let alone a fair disclosure, in respect of Upadacitinib or any pharmaceutically acceptable salt thereof. In simple terms, Upadacitinib or a pharmaceutically acceptable salt thereof cannot be either found or derived from either of the two US provisional applications viz., PD-1 and PD-2 from which priority is claimed.

8. Upadacitinib was disclosed for the first time only on 01.12.2010 in WO'881, i.e., the PCT Publication which was filed as PCT/US2010/058572 – the PCT Application which forms the basis for national phase entry for IN'4759.

9. Section 11 of The Patents Act, 1970 [hereinafter ***TPA***] is categorical on the priority date claimable for a claim. A reading of each of the clauses of Section 11 makes it clear that Claims 1 and 2 as of today are only entitled to a priority date of 01.12.2010 i.e., filing date of WO'881 since this is the first document where there is some semblance of a basis for Upadacitinib in terms of disclosure.

10. IN'4759 is not entitled to statutory or any benefit of a priority date of PD-1 [i.e. 01.12.2009] or of PD-2 [i.e., 14.07.2010]., and at best can only be entitled to a priority date being the actual date of filing i.e., 01.12.2010. It is only in WO'881, that Upadacitinib is disclosed as a structure with characterisation data [Page 41 and page 363 of WO'881, corr. to Page 42 and Page 364 of IN'4759].

(3*S*,4*R*)-3-Ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-pyrrolidine-1-carboxylic acid (2,2,2-trifluoro-ethyl)-amide.

Stereoisomers [Chiral Separation Method]	Structure	Ex. #	R_t min (method)	*m/z* ESI+ $(M+H)^+$
(*cis*)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-*N*-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide (prepared using **J.1** with Preparation #F.1.1 and 2,2,2-trifluoroethanamine, and **D** with NaOH). [Table 2, Method **69**, R_t = 15.5 min, or = negative]		AA.1.160	1.52 (**a**)	381

11. Thus, any document published prior to 01.12.2010 is available to be cited as prior art against IN'4759, and any examination of IN'4759 is required to proceed on the basis that the only priority date it is entitled to at best is 01.12.2010.

12. Absence of basis for claimed priority dates of 01.12.2009 [PD-1] or 14.07.2010 [PD-2] is also supported by findings in jurisdictions such as EPO and China where applications were challenged and there are definitive rulings on this point.

13. In opposition proceedings on corresponding EP application 10835061.2, the EPO Opposition Board held that since Upadacitinib is not disclosed in either PD-1 or PD-2, the priority date for this compound is filing date of WO'881 where it was first

disclosed. Applicant did not contest this position and instead decided to remain silent, thus accepting that priority could not have been claimed from either US provisional Applications US'563 or US'116. The decision of Opposition Board rendered on priority is on page 8 thereof.

14. Similarly, in an invalidation against the corresponding Chinese application CNIPA (China National Intellectual Property Administration) issued decision No. 561725 wherein CNIPA declared the patentee's compound patent ZL201080062920.6 invalid in its entirety including invalidating the claimed priority date. This decision appears to have not been challenged or overturned as yet. CNIPA also declared the corresponding CN patent invalid on grounds of lack of inventive step and lack of sufficiency. With respect to priority date, CNIPA held that Upadacitinib could not benefit from an earlier priority date of 01.12.2009 due to absence of description in the said priority document viz. US'563.

15. The fact that EP 10835061.2 and CN: ZL201080062920.6 correspond to and belong to the same family derived from WO'881 is borne out by the various Forms 3 filed by Applicant on IN'4759. Accordingly, the priority date of IN'4759 can and must be held to be 01.12.2010 i.e. the date of the corresponding PCT application and not as claimed.

16. Opponent respectfully further now sets out hereinbelow the grounds of opposition relied on with supporting averments.

IV. ANTICIPATION BY PRIOR CLAIMING [Section 25(1)(c)]

17. Section 25(1)(c) stipulates that if an alleged invention so far as claimed in any claim of an impugned application is claimed in a claim of a complete specification of an Indian application published on or after the priority date of the applicant's claim but has an earlier priority date, then the impugned claim is invalid for prior claiming.

18. Thus, all that is required to be shown is that the cited document is an Indian patent application which

a. Has an earlier priority date

b. Is published on or after the priority date of IN'4759

c. Has a claim(s) in which protection for Upadacitinib is available/was claimed.

19. Opponent stipulates that this ground is irrespective of the priority date challenge in the Preliminary Submissions above. Reliance is placed on IN 292307 [earlier IN 195/DELNP/2011] [**Annexure 1, IN'307**].

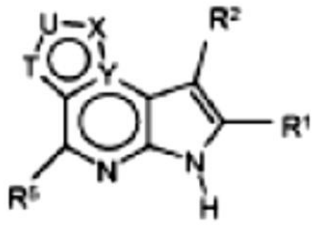
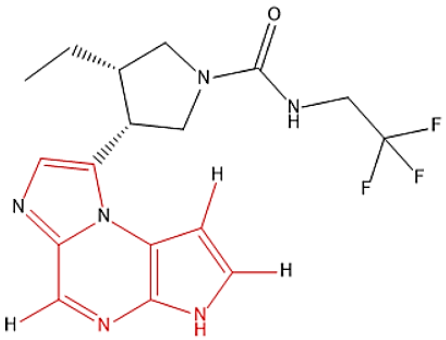
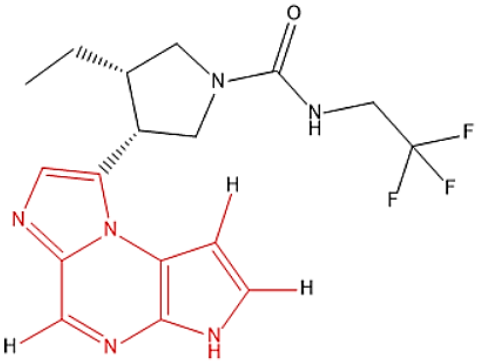
20. IN'307 which belongs to the same Applicant viz., Abbvie is also titled Novel Tricyclic Compounds, and

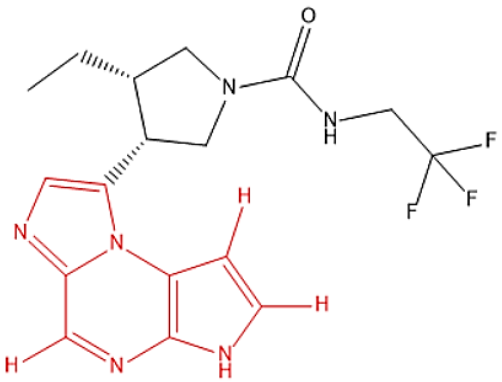
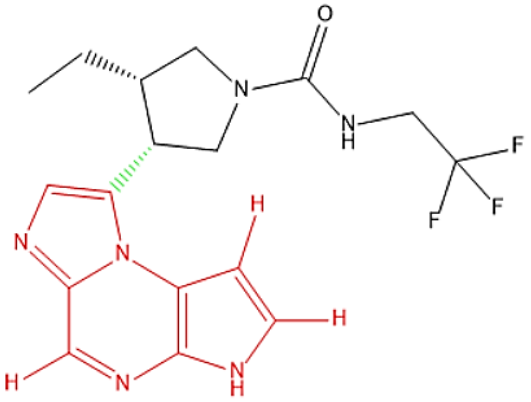
a. has a claimed priority date of 10.06.2008 i.e., earlier than the claimed priority dates of 01.12.2009 and 14.07.2010 on IN'4759;

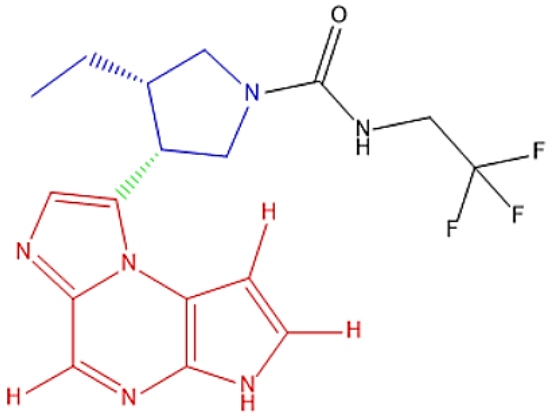
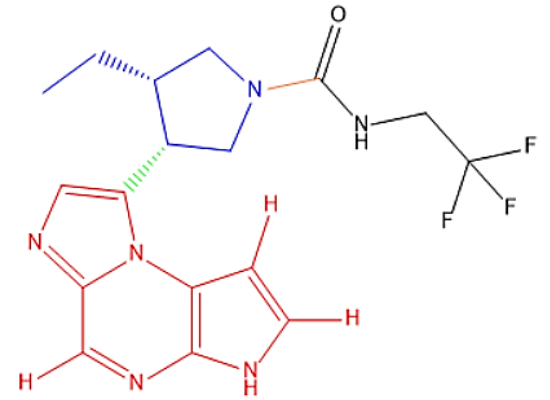
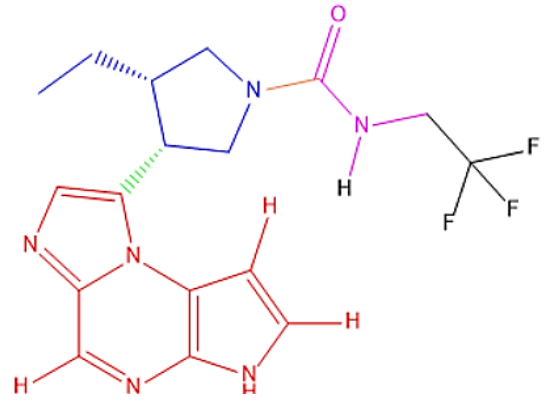
b. was published on 16.12.2011 i.e., after the claimed as well as actual priority date(s) of IN'4759; and

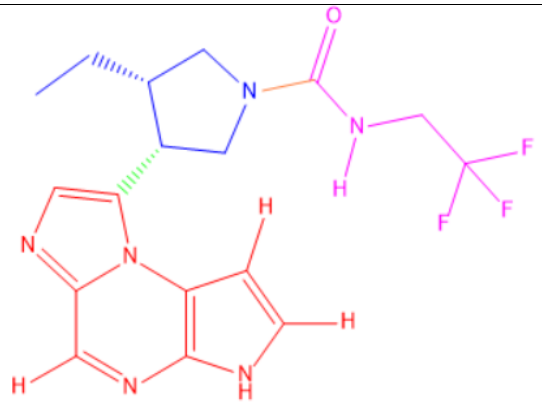
c. has a claim or claims through which protection is available/claimed by Abbvie.

21. Updacitinib as claimed in Claim 1 and 2 of IN'4759 and a pharmaceutically acceptable salt thereof is prior claimed in IN'307 i.e., Application No. 195/DELNP/2011 in the following manner:

Claim 1 of as filed 195/DELNP/2011	**Claimed compound Upadacitinib**
In a first embodiment the invention provides a compound of Formula (I)  Formula (I)	
pharmaceutically acceptable salts, pro-drugs, biologically active metabolites, stereoisomers and isomers thereof wherein T is N, U is N, X is CR3 and Y is N; or T is CR6, U is N, X is CR3 and Y is N; or **T is N, U is CR4, X is CR3 and Y is N**; or T is CR6, U is CR4, X is CR3 and Y is N; or T is CR6, U is N, X is NR3 and Y is C; or T is O, U is N, X is CR3 and Y is C; or T is NR6, U is N, X is CR3 and Y is C; or	

T is CR6, U is CR4, X is NR3 and Y is C; or T is S, U is N, X is CR3 and Y is C;	
R1 , R2 and R5 are each independently hydrogen, deuterium, -N(Ra)(Rb), halogen, - ORa , -SRa , -S(O)Ra , -S(O)2R a , -NO2, -C(O)ORa , -CN, -C(O)N(Ra)(Rb), - N(Ra)C(O)(Rb), -C(O)Ra , -C(OH)RaR b , -N(Ra)S(O)2-R b , -S(O)2N(Ra)(Rb), -CF3, - OCF3, optionally substituted (C1-C6)alkyl, optionally substituted (C2-C6)alkenyl, optionally substituted (C2-C6)alkynyl, optionally substituted (C3-C10)cycloalkyl, optionally substituted (C1-C10)heteroaryl, optionally substituted (C1-C10) heterocyclyl, or optionally substituted (C6-C10)aryl; wherein in a moiety containing -N(Ra)(Rb), the nitrogen, Ra and Rb may form a ring such that -N(Ra)(Rb) represents an optionally substituted (C2-C10)heterocyclyl or optionally substituted (C1-C10)heteroaryl linked through a nitrogen;	
R3 is hydrogen, an optionally substituted bridged (C5-C12)cycloalkyl, optionally substituted bridged (C2-C10)heterocyclyl, optionally substituted (C1-C8)alkyl, optionally substituted (C3-C10)cycloalkyl, optionally substituted (C3- C8)cycloalkenyl, optionally substituted (C6-C10)aryl, optionally substituted (C1- C10)heteroaryl, optionally substituted (C2-C10)heterocyclyl; or **R3 is -A-D-E-G, wherein A is attached to X and: A is a bond,** -C(O)-, optionally substituted (C1-C6)alkylene, optionally substituted (C2-C6)alkenylene, optionally substituted (C2-C6)alkynylene, optionally substituted (C3- C12)cycloalkylene, optionally substituted (C2-C6)heterocyclylene, -C(O)N(Ra)-R e -, -N(Ra)C(O)-R e -, -O-R e -, -N(Ra)-R e -, -S-R e -, -S(O)2-R 6 -, -S(O)R6 -, -C(O-R a)(Rb)-R 6 -, - S(O)2N(Ra)-R 6 -, -N(Ra)S(O)2-R 6 - or -N(Ra)C(O)N(Rb)-R 6 -;	

D is an optionally substituted (C1-C8)alkylene, optionally substituted bridged (C5- C12)cycloalkylene, optionally substituted (C3-C10)cycloalkylene, optionally substituted bridged (C5-C10)cycloalkenylene, optionally substituted (C3- C10)cycloalkenylene, optionally substituted (C6-C10)arylene, optionally substituted (C1-C10)heteroarylene, optionally substituted bridged (C2-C10)heterocyclylene or **an optionally substituted (C2-C10)heterocyclylene;**	
E is a bond, -R 6 -, -R 6 -C(O)-R 6 -, -R 6 -C(O)C(O)-R 6 -, -R 6 -C(O)O-R 6 -, -R 6 -C(O)C(O)N(Ra)-R 6 -, -R 6 -N(Ra)-C(O)C(O)-R 6 -, -R 6 -O-R 6 -, -R 6 -S(O)2-R 6 -, -R 6 -S(O)- R 6 -, -R 6 -S-R 6 -, -R 6 -N(Ra)-R 6 -, -R 6 -N(Ra)C(O)-R 6 -, -R 6C(O)N(Ra)R6 -, -R 6 - OC(O)N(Ra)-R 6 -, -R 6 -N(Ra)C(O)OR6 -, -R 6 -OC(O)-R 6 , -R 6 -N(Ra)C(O)N(Rb)-R 6 -, -R 6 - N(Ra)S(O)2-R 6 -, or -R 6 -S(O)2N(Ra)-R 6 -;	
G is hydrogen, deuterium, -N(Ra)(Rb), halogen, -ORa , -SRa , -S(O)Ra , -S(O)2R a , -NO2, - C(O)ORa , -CN, **-C(O)N(Ra)(Rb)**, -N(Ra)C(O)Rb , -N(Ra)C(O)ORb , -OC(O)N(Ra), - N(Ra)C(O)N(Rb)2, -C(O-R a)(Rb)2, -C(O)Ra , -CF3, -OCF3, -N(Ra)S(O)2R b , - S(O)2N(Ra)(Rb), -S(O)2N(Ra)C(O)Rb , an optionally substituted -(C1-C6)alkyl, an optionally substituted -(C2-C6)alkenyl, an optionally substituted -(C2-C6)alkynyl, an optionally substituted -(C3-C10)cycloalkyl, an optionally substituted -(C1- C10)heteroaryl, an optionally substituted -(C1-C10) heterocyclyl, an optionally substituted -(Ce-C10)aryl, an optionally substituted -(C1-C6)alkyl-(C3- C10)cycloalkyl, an optionally substituted -(C1-C6)alkyl-(C6-C10)aryl, an optionally substituted -(C1-C6)alkyl-(C1-C10)heteroaryl, or an optionally substituted -(C1- C6)alkyl-(C1-C10)heterocyclyl;	

Ra and Rb are each independently hydrogen, deuterium, **an optionally substituted (C1-C10)alkyl**, an optionally substituted (C2-C10)alkenyl, an optionally substituted (C2-C10)alkynyl, an optionally substituted (C1-C10)alkyl-O-(C1-C10)alkyl, an optionally substituted (C3-C10)cycloalkyl, an optionally substituted (C6-C10)aryl, an optionally substituted (C1-C10)heteroaryl, an optionally substituted (C1- C10)heterocyclyl, an optionally substituted -(C1-C6)alkylene-(C3-C10)cycloalkyl, an optionally substituted -(C1-C6)alkylene-(C6-C10)aiyl, an optionally substituted -(C1-C6)alkylene-(C1-C10)heteroaryl, or an optionally substituted -(C1-C6)alkylene-(C1- C10)heterocyclyl;	

22. IN'307 is a national phase entry out of WO 2009/152133 [**Annexure 2 – WO'133**] which is also the equivalent of US Patent 8962629 [**Annexure 3 – US'629**]. A bare comparison of the claims granted on US'629 will show that they are pari materia with the claims of IN'307, i.e, they cover the same claim scope.

23. Support for the objection/ground of prior claiming is also evident from the fact that it is Abbvie Inc., viz., the Applicant herein which itself declared US'629 as the patent claiming Upadacitinib to the US Food & Drug Administration for the purposes of notice of patent exclusivity rights. Thus, it is Abbvie's admission that US'629 claims Upadacitinib.

24. Given that the claims of US'629 are pari materia with the claims of IN'307, what is self-evident is that Upadacitinib [and pharmaceutically acceptable salt thereof] is also protected/claimed/covered [all synonymous] in the claims of IN'307.

25. Thus, IN;4759, i.e., application impugned in this pre-grant stands anticipated by prior claiming through the claims as filed, as well as, as granted in IN'307. On this ground alone, IN'4759 deserves refusal. It is pertinent in this context that in fact, the ground set out in Section 25(1)(c) also has a place in regular examination procedures through Section 13(1)(b).

V. ANTICIPATION BY PRIOR PUBLICATION [Section 25(1)(b)]:

26. For the purposes of anticipation by prior publication, Opponent relies on the disclosure in WO2009/152133 (**Annexure 2 – WO'133**). The following are material for purposes of assessment of this ground [para (a) below is also relevant and material for an assessment of the ground of anticipation by prior claiming].

a. the inventorship of WO'133 and IN'4759/WO'881 are absolutely identical;

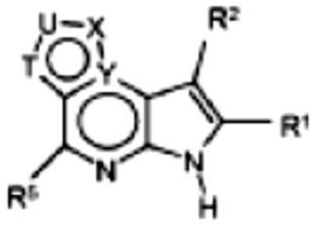
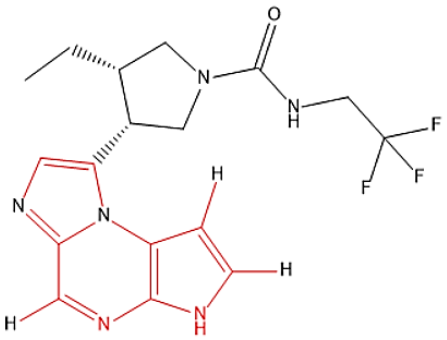
b. the written description texts including the alleged detailed description portions are largely identical. Most of the compounds identified as falling within the Markush Formula of IN'4759 are also disclosed in WO'133.

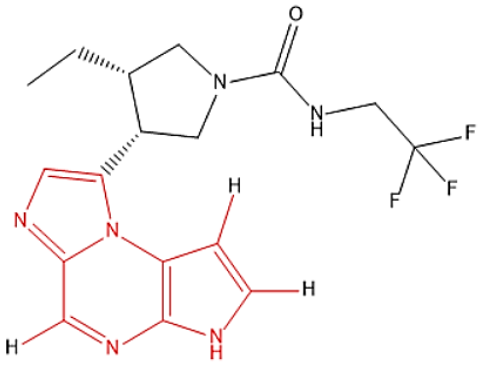
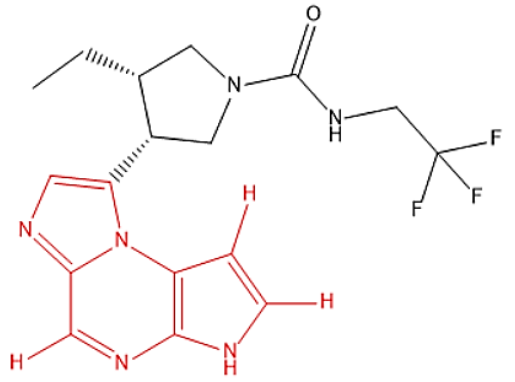
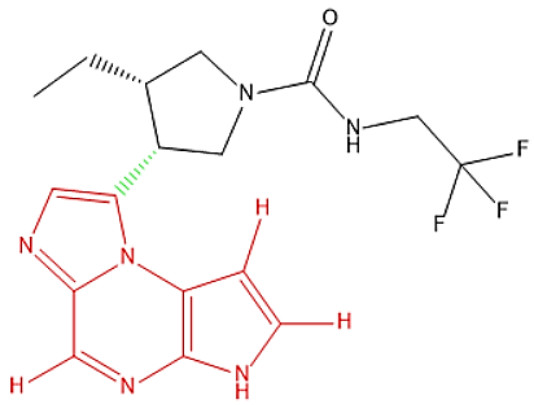
c. The examples, including what limited data points are present, also overlap significantly.

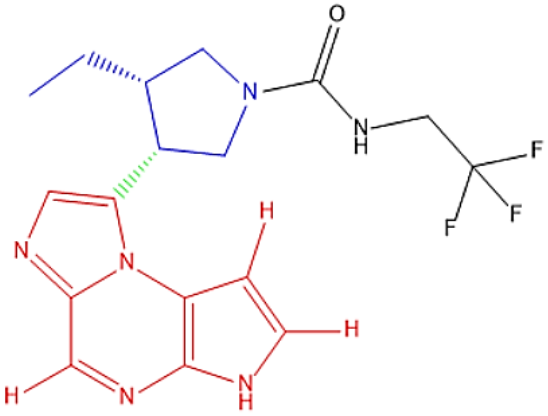
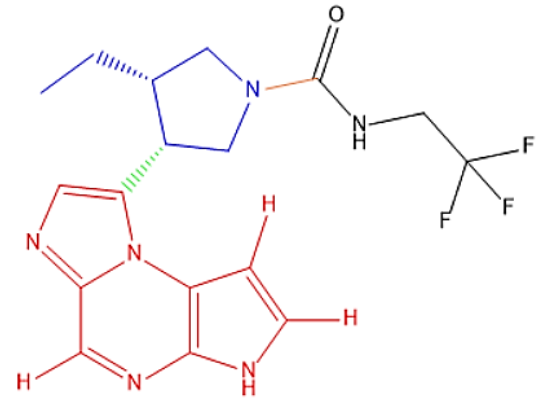
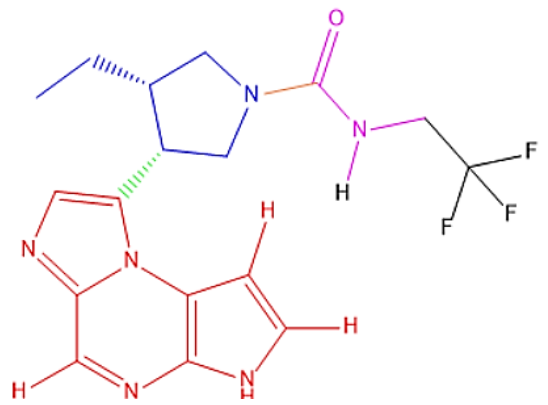
d. The mode of preparation [best method or otherwise] in both documents i.e., IN'4759 and WO'133 are practically identical as can be seen from a bare reading of the respective documents.

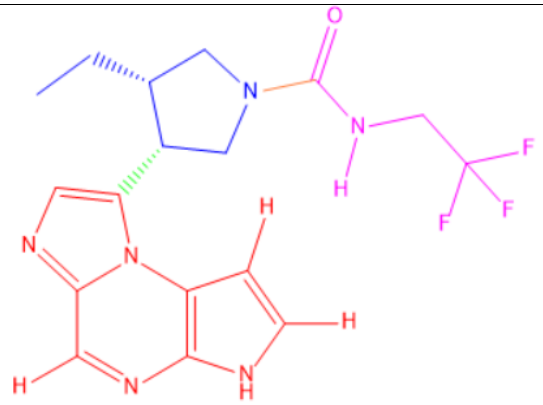
27. Firstly, if Upadacitinib is independent of its separate identification and characterisation, also protected/covered/claimed vide the original Markush structure of IN'4759 used at the time of filing, then, it is equally present in the self-same Markush structure of WO'133.

28. In any event, and without prejudice to any of the above, WO'133 discloses the claimed compound in the manner as represented in the table below:

Disclosure of WO'133	**Claimed compound Upadacitinib**
In a first embodiment the invention provides a compound of Formula (I)  Formula (I)	

pharmaceutically acceptable salts, pro-drugs, biologically active metabolites, stereoisomers and isomers thereof wherein T is N, U is N, X is CR3 and Y is N; or T is CR6, U is N, X is CR3 and Y is N; or **T is N, U is CR4, X is CR3 and Y is N**; or T is CR6, U is CR4, X is CR3 and Y is N; or T is CR6, U is N, X is NR3 and Y is C; or T is O, U is N, X is CR3 and Y is C; or T is NR6, U is N, X is CR3 and Y is C; or T is CR6, U is CR4, X is NR3 and Y is C; or T is S, U is N, X is CR3 and Y is C;	
R1 , R2 and R5 are each independently hydrogen, deuterium, -N(Ra)(Rb), halogen, - ORa , -SRa , -S(O)Ra , -S(O)2R a , -NO2, -C(O)ORa , -CN, -C(O)N(Ra)(Rb), - N(Ra)C(O)(Rb), -C(O)Ra , -C(OH)RaR b , -N(Ra)S(O)2-R b , -S(O)2N(Ra)(Rb), -CF3, - OCF3, optionally substituted (C1-C6)alkyl, optionally substituted (C2-C6)alkenyl, optionally substituted (C2-C6)alkynyl, optionally substituted (C3-C10)cycloalkyl, optionally substituted (C1-C10)heteroaryl, optionally substituted (C1-C10) heterocyclyl, or optionally substituted (C6-C10)aryl; wherein in a moiety containing -N(Ra)(Rb), the nitrogen, Ra and Rb may form a ring such that -N(Ra)(Rb) represents an optionally substituted (C2-C10)heterocyclyl or optionally substituted (C1-C10)heteroaryl linked through a nitrogen;	
R3 is hydrogen, an optionally substituted bridged (C5-C12)cycloalkyl, optionally substituted bridged (C2-C10)heterocyclyl, optionally substituted (C1-C8)alkyl, optionally substituted (C3-C10)cycloalkyl, optionally substituted (C3- C8)cycloalkenyl, optionally substituted (C6-C10)aryl, optionally substituted (C1- C10)heteroaryl, optionally substituted (C2-C10)heterocyclyl; or **R3 is -A-D-E-G, wherein A is attached to X and: A is a bond,** -C(O)-, optionally substituted (C1-C6)alkylene, optionally substituted (C2-C6)alkenylene, optionally substituted (C2-C6)alkynylene, optionally substituted (C3- C12)cycloalkylene, optionally substituted (C2-	

C6)heterocyclylene, -C(O)N(Ra)-R e -, - N(Ra)C(O)-R e -, -O-R e -, -N(Ra)-R e -, -S-R e -, -S(O)2-R 6 -, -S(O)R6 -, -C(O-R a)(Rb)-R 6 -, -S(O)2N(Ra)-R 6 -, -N(Ra)S(O)2-R 6 - or -N(Ra)C(O)N(Rb)-R 6 -;	
D is an optionally substituted (C1-C8)alkylene, optionally substituted bridged (C5- C12)cycloalkylene, optionally substituted (C3-C10)cycloalkylene, optionally substituted bridged (C5-C10)cycloalkenylene, optionally substituted (C3- C10)cycloalkenylene, optionally substituted (C6-C10)arylene, optionally substituted (C1-C10)heteroarylene, optionally substituted bridged (C2-C10)heterocyclylene or **an optionally substituted (C2-C10)heterocyclylene;**	
E is a bond, -R 6 -, -R 6 -C(O)-R 6 -, -R 6 -C(O)C(O)-R 6 -, -R 6 -C(O)O-R 6 -, -R 6 -C(O)C(O)N(Ra)-R 6 -, -R 6 -N(Ra)-C(O)C(O)-R 6 -, -R 6 -O-R 6 -, -R 6 -S(O)2-R 6 -, -R 6 -S(O)- R 6 -, -R 6 -S-R 6 -, -R 6 -N(Ra)-R 6 -, -R 6 -N(Ra)C(O)-R 6 -, -R 6C(O)N(Ra)R6 -, -R 6 -OC(O)N(Ra)-R 6 -, -R 6 -N(Ra)C(O)OR6 -, -R 6 -OC(O)-R 6 , -R 6 -N(Ra)C(O)N(Rb)-R 6 -, -R 6 - N(Ra)S(O)2-R 6 -, or -R 6 -S(O)2N(Ra)-R 6 -;	
G is hydrogen, deuterium, -N(Ra)(Rb), halogen, -ORa , -SRa , -S(O)Ra , -S(O)2R a , -NO2, - C(O)ORa , -CN, **-C(O)N(Ra)(Rb)**, -N(Ra)C(O)Rb , -N(Ra)C(O)ORb , -OC(O)N(Ra), -N(Ra)C(O)N(Rb)2, -C(O-R a)(Rb)2, -C(O)Ra , -CF3, -OCF3, -N(Ra)S(O)2R b , - S(O)2N(Ra)(Rb), -S(O)2N(Ra)C(O)Rb , an optionally substituted -(C1-C6)alkyl, an optionally substituted -(C2-C6)alkenyl, an optionally substituted -(C2-C6)alkynyl, an optionally substituted -(C3-C10)cycloalkyl, an optionally substituted -(C1- C10)heteroaryl, an optionally substituted -(C1-C10) heterocyclyl, an optionally substituted -(Ce-C10)aryl, an optionally substituted -(C1-C6)alkyl-(C3- C10)cycloalkyl, an optionally substituted -(C1-C6)alkyl-(C6-C10)aryl, an optionally substituted -(C1-C6)alkyl-(C1-	

C10)heteroaryl, or an optionally substituted -(C1- C6)alkyl-(C1-C10)heterocyclyl;	
Ra and Rb are each independently hydrogen, deuterium, **an optionally substituted (C1-C10)alkyl**, an optionally substituted (C2-C10)alkenyl, an optionally substituted (C2-C10)alkynyl, an optionally substituted (C1-C10)alkyl-O-(C1-C10)alkyl, an optionally substituted (C3-C10)cycloalkyl, an optionally substituted (C6-C10)aryl, an optionally substituted (C1-C10)heteroaryl, an optionally substituted (C1-C10)heterocyclyl, an optionally substituted -(C1-C6)alkylene-(C3-C10)cycloalkyl, an optionally substituted -(C1-C6)alkylene-(C6-C10)aiyl, an optionally substituted -(C1-C6)alkylene-(C1-C10)heteroaryl, or an optionally substituted -(C1-C6)alkylene-(C1-C10)heterocyclyl;	

29. Apart from the fact that the disclosure of WO'133 categorically and comprehensively discloses each and every element of the substitutions of Upadacitinib [and of its pharmaceutically acceptable salts], there is sufficient teaching and guidance in terms of signposts in WO'133 [such as the reaction schema, the bioassay data points, etc.] all of which give Upadacitinib and its properties.

30. It is not open to Abbvie today to claim that Upadacitinib is a selection from the Markush structure of WO'133 in as much as the US patent corresponding to WO'133 [i.e., US'629 which is = IN'307] has been stated by them as claiming Upadacitinib. Further, it also cannot be that the same Markush structure and description of IN'4759 provides sufficient enablement to make Upadacitinib while that of WO'133 i.e., the cited documents and of the same inventors does not.

31. WO'133 claims priority dates of 10.06.2008, 25.08.2008 and 05.12.2008, and was published on 17.12.2009. While this date is 16 days after the earliest priority date of 01.12.2009 claimed on IN'4759 [PD-1], what remains is that IN'4759 is not even entitled to the claimed priority date. The actual priority date of IN'4759 necessarily has to be 01.12.2010 – the date on which the structure and characterisation of

Upadacitinib was first identified in WO'881/IN'4759. WO'133 is therefore, prior art relevant for purposes of novelty assessment of the claims pending on IN'4759.

32. In view of the above, what is claimed in IN'4759, i.e, Upadacitinib [and its pharmaceutically acceptable salt] through claims 1 and 2 stands anticipated by the disclosure of WO'133. Thus, IN'4759 is liable to be refused on this ground alone.

VI. OBVIOUSNESS / LACK OF INVENTIVE STEP [Section 25(1)(e)]:

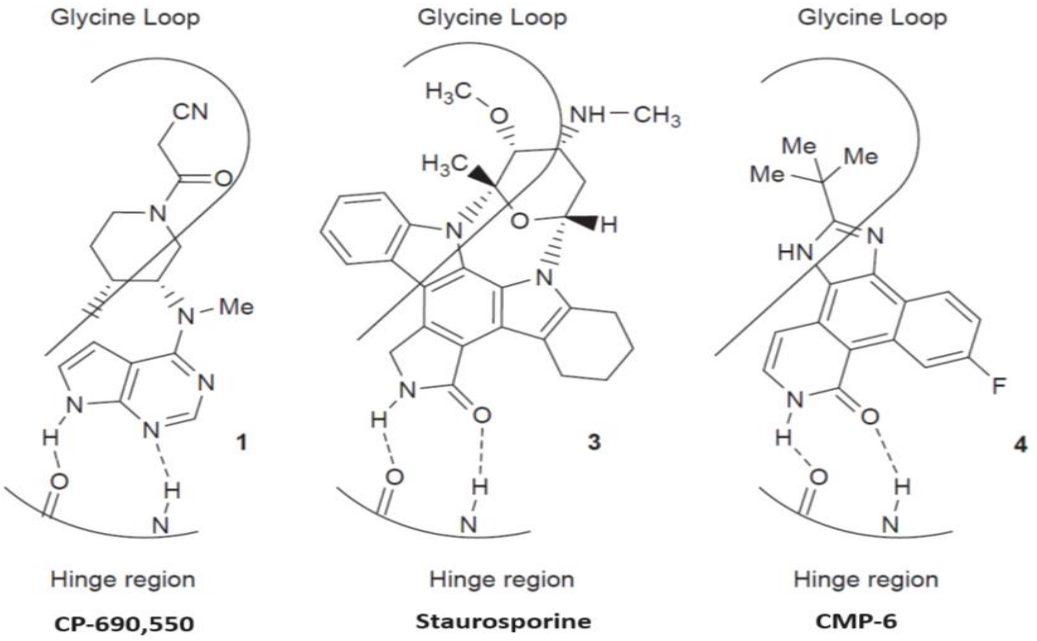
33. Without prejudice and in the alternative to the above, the Opponent states that the subject matter claimed in IN'4759 lacks inventive merit and is independently obvious to a person of skill in the art in view of prior art documents annexed in the instant pre-grant opposition and as explained hereinbelow.

34. The lack of inventive step of the impugned application will be discussed herein under two subheadings namely

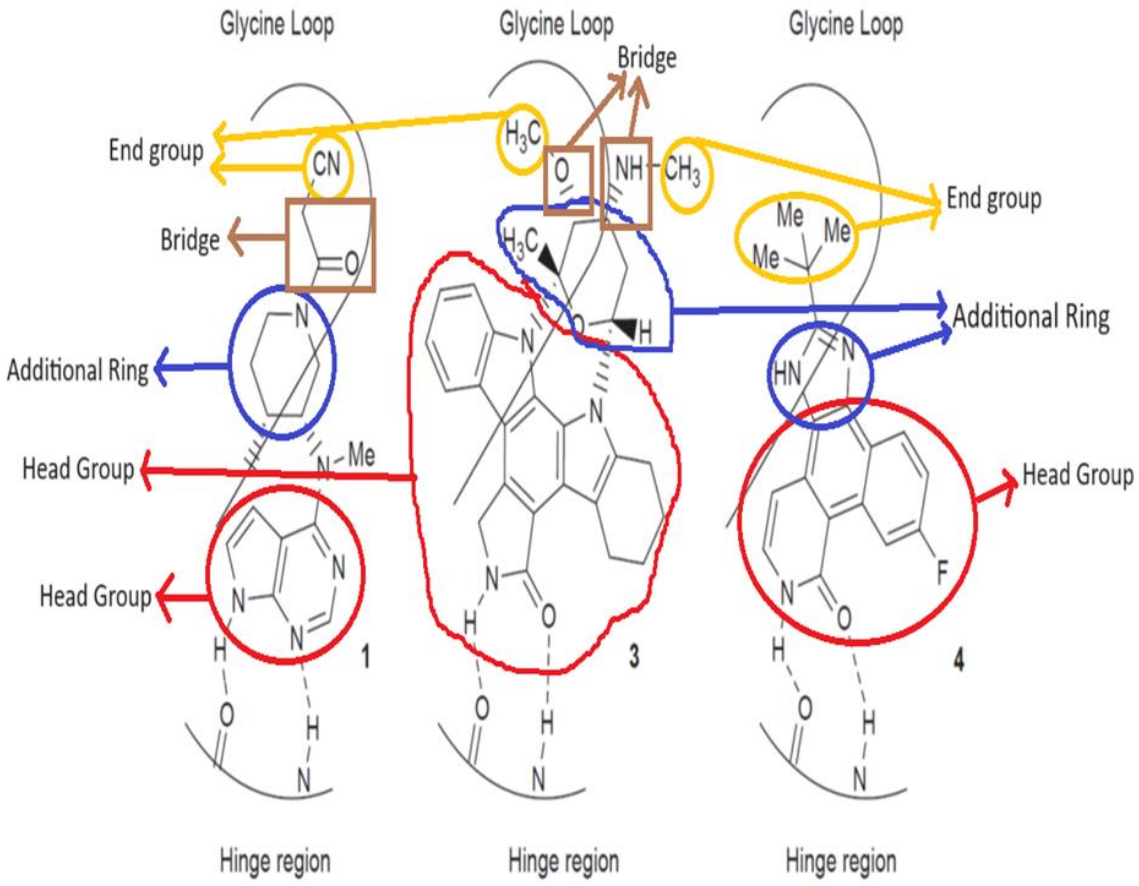
A. Obvious to a person skilled in the art.

B. Lack of Technical Advancement over the existing knowledge.

[#NOTE: for ease of reference regarding structural features of compounds referred in below paragraphs herein, certain nomenclature has been adopted which is explained by using the example of three known JAK inhibitors namely CP-690,550, Staurosporine, CMP-6 shown in below diagram bound in the JAK binding site.]



Three known JAK inhibitors CP-690,550; Staurosprine, and CMP-6 are shown above bound in the JAK binding site



The same three compounds as shown in above diagram are shown here with the adopted nomenclature used to address the different structural features used in present opposition

A. Obvious to a person skilled in the art.

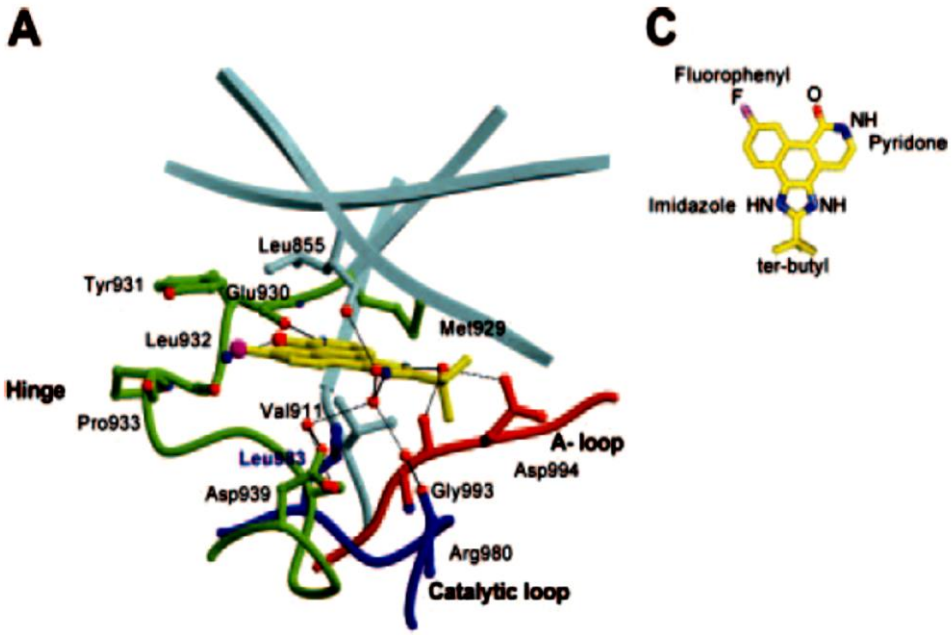
35. Annexure 5, i.e., Lucet et. al. of 2006 discloses that JAKs coordinate specifically to different receptors. For example, JAK3 appears to be associated with cytokine receptors that include the γc chain of the interleukin-2 (IL-2) receptor (eg, IL-4, IL-7, etc), whereas JAK2 is associated with a wide range of cytokine receptors, including those activated by growth hormone, erythropoietin, prolactin, granulocyte colony-stimulating factor (G-CSF), and IL-3, as well as some G-protein-coupled receptors. Lucet et. al. discloses that the 2.0 Å resolution crystal structure of JAK2 kinase domain in complex with the JAK-specific inhibitor 2-tert-butyl-9-fluoro-3,6-dihydro-7H-benzo[h]imidazo-[4,5-f]isoquinoline-7-one. The structure provides not only critical insights into how this molecule exerts its JAK specificity but also an important first step in trying to understand the mechanism by which JAK kinases are regulated.

36. JAK-specific inhibitor sits snugly within the constricted ATP-binding site that lies deep between the 2 lobes, occupying a site where the adenine base resides. The

inhibitor is well ordered; moreover, the mode of binding of the inhibitor within the JAK2 PTK domain structure is unambiguous, as evidenced by electron density maps. The inhibitor is orientated such that the fluorophenyl moiety points toward the bulk solvent, the pyridone moiety is orientated toward the gatekeeper residue (Met 929), and the tert-butyl group points toward the tip of the glycine loop. There is high shape complementarity between the planar ring system of the inhibitor and the JAK2 PTK, in which the inhibitor buries 225 Å2 of its available 516 Å2 surface area, thereby making numerous contacts with the residues lining the active site.

37. CMP6 is predominantly hydrophobic and, accordingly, forms a large number of van der Waals interactions with JAK2 PTK domain. The planar ring system of the inhibitor is sandwiched between the hydrophobic residues of the N-terminal lobe (Leu 855, Val 863, Ala 880, Val 911), the C-terminal lobe (Leu 983 and Gly 935), and the hinge (Met 929, Tyr 931). In addition, the pyridone ring forms 2 direct hydrogen bonds, with the hinge region between the N- and C-lobes of JAK2 PTK (pyridoneN2 and pyridoneO interacts with Glu 930O and Leu 932N, respectively) that mimic those observed between the adenine group of ATP and other PTKs. The imidazole moiety participates in a network of water-mediated hydrogen bonds, the imidazoleN1 group interacting with Asp 939OD1, Ser 936N,OG, Leu855O, and Arg 980O; the imidazole NO interacting with Gly 993O and Asp 994OD1. Interestingly, the carbonyl group of Gly 993 points toward the ATPbinding pocket, whereas in all the PTK structures examined (including JAK3), the corresponding carbonyl group points toward the core of the C-terminal lobe. The hydrophobic t-butyl group of the inhibitor is not well accommodated in the JAK2 active site, being located within and adjacent to a polar pocket that includes Asp 994, Arg 980, Asn 981, Asn 859, and Lys 882, a pocket that typically coordinates Mg2+ ions. The glycine loop was observed not to participate in inhibitor contacts in JAK2 PTK domain, with the Phe 860 residue pointing away from the active site. Instead, the glycine loop collapses over and restricts the active site, with Asn 859 making a water-mediated hydrogen bond to the conserved Asp 994 and a hydrogen bond to the conserved catalytic residue Asp 976 of the C-terminal lobe.

38. Previously, induced-fit binding of inhibitors to PTKs are described and a similar conformation of this loop is observed in both fibroblast growth factor receptor tyrosine kinase (FGFR1) in complex with a high-affinity inhibitor, and Abl kinase in complex with Glivec. Neither ATP nor pan-kinase inhibitor staurosporine can be accommodated within the observed active site of JAK2 PTK without having to invoke conformational changes in either glycine loop or Asp 994 - indicative of JAK2 PTK being able to exhibit a degree of malleability in accommodating substrates and inhibitors.



39. A person of skill in the art gets the teaching from Lucet et. al. about the changes in the structure of a compound that can be done to reduce its affinity for JAK2 since this document teaches which structural components of the known JAK2 inhibitor CMP6 interact with JAK2 binding site. Thus, a person skilled in the art engaged in designing an inhibitor with reduced affinity to JAK2 is taught since CMP6 is a planar well-ordered molecule, it snugly fits within the constricted ATP-binding site that lies deep between the 2 lobes, occupying a site where the adenine base resides. Hence, a molecule with non-planar ring structure will have less capability of fitting in the ATP binding site of JAK2.

40. Further, it is taught that the inhibitor CMP6 is orientated such that the fluorophenyl moiety points toward the bulk solvent, the pyridone moiety is orientated toward the gatekeeper residue (Met 929), and the tert-butyl group points

toward the tip of the glycine loop. There is high shape complementarity between the planar ring system of the inhibitor and the JAK2 PTK, in which the inhibitor buries 225 Å2 of its available 516 Å2 surface area, thereby making numerous contacts with the residues lining the active site. CMP6 is predominantly hydrophobic and, accordingly, forms a large number of van der Waals interactions with JAK2 PTK domain. The hydrophobic t-butyl group of the inhibitor is not well accommodated in the JAK2 active site, being located within and adjacent to a polar pocket that includes Asp 994, Arg 980, Asn 981, Asn 859, and Lys 882, a pocket that typically coordinates Mg2+ ions. The glycine loop was observed not to participate in inhibitor contacts in the JAK2 PTK domain, with the Phe 860 residue pointing away from the active site. Instead, the glycine loop collapses over and restricts the active site, with Asn 859 making a water-mediated hydrogen bond to the conserved Asp 994 and a hydrogen bond to the conserved catalytic residue Asp 976 of the C-terminal lobe.

41. Hence, a person skilled in the art is taught that a compound with following structural characteristics will have less affinity for JAK2 namely: 1. a compound wherein there is no substituent on the first ring of the headgroup, 2. a compound wherein the fourth ring is not in planar configuration with the head group and is consequently not directly attached to the tricyclic head group, 3. the compound should be less hydrophobic and have higher polarity especially in the head group so heterocyclic rings preferably nitrogen containing heterocyclic rings in head group will have lesser binding with the binding domain of Jak2, 4. the last group of the compound oriented towards the glycine loop should be either longer than tert-butyl and/or with negative polarity so as to disorient the restriction of the active site formed by the glycine group.

42. The preference to have the last group of the compound oriented towards the glycine loop should be either longer than tert-butyl and/or with negative polarity so as to disorient the restriction of the active site formed by the glycine group is also reinforced by the observations made by of Lucet et. al. on superposition of JAK2/CMP6 complex with the recently reported JAK3/AFN94153 complex. They observed that JAK2/CMP6 complex exemplifies the “closed” conformation that JAK2 adopts when bound to CMP6. Significant differences are seen in the conformations

of the hinge region, the glycine loop, the activation loop, and the JAK insertion loop. In the reported JAK3 structure, the presence of a DTT molecule in the phosphate-binding region, in addition to bulky staurosporine analog, appears to push the glycine loop away from the active site, resulting in a loss of contacts with the activation and catalytic loop and a more open site than constricted site seen in JAK2. Furthermore, the activation loops differ markedly just before the APE motif, while by contrast the phosphorylated tyrosines adopt a similar conformation in both structures.

43. Lucet et. al. also did a comparison of our JAK2/CMP6 complex structure with the recently published JAK3/AFN941 complex structure exemplifies how the size and shape of the ligand can impact binding characteristics and potency. They teach that the presence of the indolocarbazole ring system of staurosporine would displace the side chain of Asp 994 and disrupt the interaction between Asp 994 and Lys 882. In addition, the presence of the tetrahydroindole ring and the inherent rigidity of staurosporine is likely to relate to the outward movement of the hinge region observed in the JAK3 structure, which results in a more open structure, a reduction in shape complementarity, and therefore a decrease in potency for the pan-kinase inhibitor. These observations further confirm the teachings about structural modification of a molecule for reducing its binding with JAK2 as discussed in para 20 and 22 above.

44. Lucet et al thus teaches that although the hinge region is well conserved between members of the JAK family, subtle yet significant differences could be exploited for the design of selective JAK inhibitors.

45. Lucet et al. also disclose that there is a 15-fold difference in the relative potency of this inhibitor for JAK2 versus JAK1 and that the examination of the contacts between the inhibitor and the JAK2 PTK active site, together with the residual alignment of the JAK PTK active site, highlights a constellation of residues (853, 857, 859, 862, 865, 931, 934, 938, 979, and 982) that may account for the observed differences in the binding affinity of CMP6 to JAK1 and JAK2. Of these, 857 and 931 are the sole locations that make contact with the inhibitor in the JAK2 crystal structure. Lys 857, located in the phosphate-binding region of JAK2, makes a number of Van der Waals contacts with the inhibitor. In JAK1 and TYK2, lysine is replaced by a

glutamic acid residue, which may alter the strength and nature of the enzyme contacts with the tert-butyl moiety. This again points to replacement of the head group, fourth ring, and the bridge to be more polar with positive polarity since glutamic acid is a negative polarity amino acid.

46. It is further taught that position 931 located in the adenine binding region of the hinge, is the only unique residual difference between JAK1 and the rest of the JAK family that makes direct contact with CMP6. In JAK2, JAK3, and TYK2, this residue is a tyrosine, while in JAK1 it is a phenylalanine. Presence of an intermolecular halogen bond between the fluorophenyl moiety of inhibitor and hydroxyl of Y931 may contribute to observed difference in activity. This teaches a person skilled in the art to avoid any substituents especially negative polarity substituents on the head group.

47. Lucet et. al also teach the way in JAK 2 and JAK 1 differ in their residues in the binding domain and which can serve to differentiate the affinity of an inhibitor molecule towards JAK 1 or JAK 2. They teach that there a number of changes in JAK 1 and JAK 2 that may serve to indirectly impact the binding affinity of the inhibitor to JAK2 and JAK1. Asn859His, Ser862Lys of the glycine loop; Gln853Arg, Met865Leu, and Tyr934Ser of the solvent accessible region; Arg938Lys, Thr979Ala of the sugar region; and Ile982Val of the adenine binding region may all have the capacity to alter the environment of their adjacent residues that interact with the various moieties of the tetracyclic pyridone. It is taught in the document that it is the sum of these subtle changes that may account for the differences in the binding affinity of CMP6 to JAK1 and the other members of the JAK family. These differences teach a person skilled in the art to have modifications in the structure of CMP6 which has the polarity of substituents and ring systems capable of interacting with the residues in JAK1 which are different from JAK2 as well as it teaches a person skilled in the art to avoid the substituents and ring systems which interact with the residues present in the binding site of JAK2 and absent in JAK1.

48. Annexure 6, i.e., Williams et. al. 2009 discloses that there is was an increasing realization in the field that each member of the JAK family has an individual role in the oncogenesis and pathology of the immune system, and because of this there is a

pressing need to develop potent and specific inhibitors for each member of this family, and targeting the conserved ATP-binding site of each specific JAK represents one such approach. To meet this end, the authors of document D2 disclose that the crystal structure of the JAK2 PTK domain in complex with a pan-JAK inhibitor, 2-t-butyl-9-fluoro-3,6-dihydro-7H-benz[h]- imidaz[4,5-f]isoquinoline-7-one37 (CMP6) developed by Merck Research Laboratories, and that of the JAK3 PTK domain in complex with a pan-PTK inhibitor was studied.

49. Williams et al also discloses that fragment-based lead identification coupled with crystallography was being used to design potent JAK2 inhibitors. These studies provided some insight into the function of the ATP binding domains and the mode of their inhibition in each particular type of JAK.

50. Williams et al discloses that developing specific inhibitors towards each JAK member remains a challenge and the development of JAK1 specific inhibitors, or inhibitors with reduced off-target JAK1 activity, was being hampered by the lack of structural data on the JAK1 PTK domain. To solve this issue, the authors of this document determined crystal structures of the JAK1 PTK domain in complex with two JAK-specific inhibitors, CMP6 and CP-690,550, to 2.0 and 1.9 Å, respectively, as well as the JAK2 PTK domain in complex with CP-690,550 to 2.4 Å resolution. Collectively, these structural data complement the knowledge of this important class of PTKs and provide an invaluable tool for future structure-based development of novel, potent and specific therapeutics against the JAK family.

51. Williams et. al. report the high-resolution crystal structures of the “active form” of the JAK1 PTK domain in complex with two JAK inhibitors, a tetracyclic pyridone 2-t-butyl-9-fluoro-3,6-dihydro-7H-benz[h]-imidaz[4,5-f]isoquinoline-7-one (CMP6) and (3R,4R)-3-[4-methyl-3-[N-methyl-N-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropionitrile (CP-690,550), and compare them with the corresponding JAK2 PTK inhibitor complexes. Both inhibitors bound in a similar manner to JAK1, namely buried deep within a constricted ATP-binding site, thereby providing a basis for the potent inhibition of JAK1. As expected, the mode of inhibitor binding in JAK1 was very similar to that observed in JAK2, highlighting the challenges

in developing JAK-specific inhibitors that target the ATP-binding site. Nevertheless, differences surrounding the JAK1 and JAK2 ATP-binding sites were apparent, thereby providing a platform for the rational design of JAK2- and JAK1-specific inhibitors.

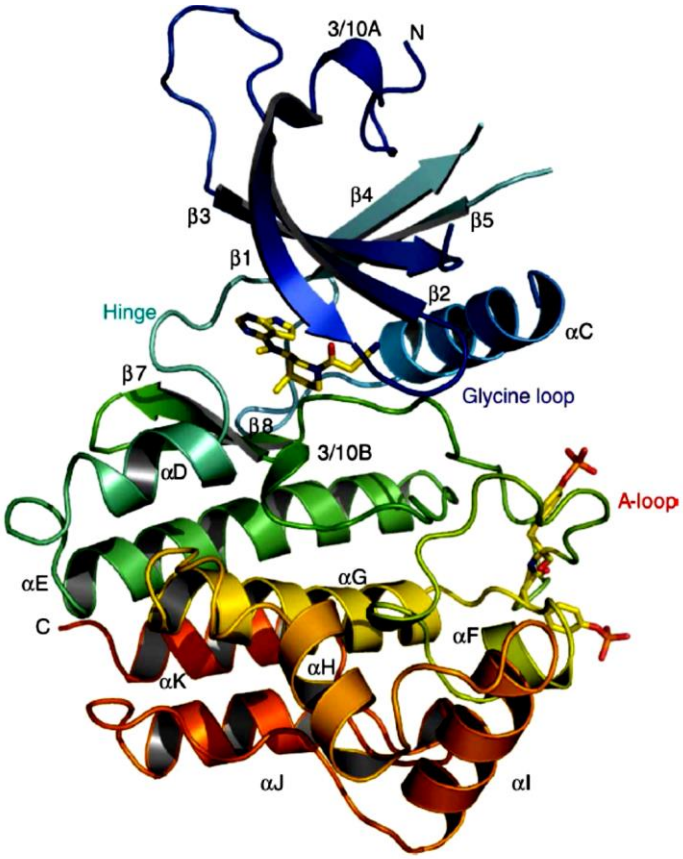


Fig. 1. Overview of the crystal structure of JAK1. Ribbon representation of the crystal structure of the JAK1 PTK domain in complex with CP-690,550. The N-terminal lobe (residues 865–958) comprises a five-stranded antiparallel β-sheet (β1 to β5) and one α-helix (αC). The larger C-terminal lobe (residues 595–1154) is predominantly helical with eight α-helices (αD to αK) and three 3/10 helices (3/10B, 3/10C and 3/10D), with one main pair of antiparallel β-strands (β7–β8). Locations of the hinge region, glycine loop and activation loop (A-loop) are indicated. The bound CP-690,550 and P-Tyr residues 1034 and 1035 are presented in a ball-and-stick representation with carbon atoms in yellow, oxygen atoms in red, nitrogen atoms in blue and phosphorus atoms in orange.

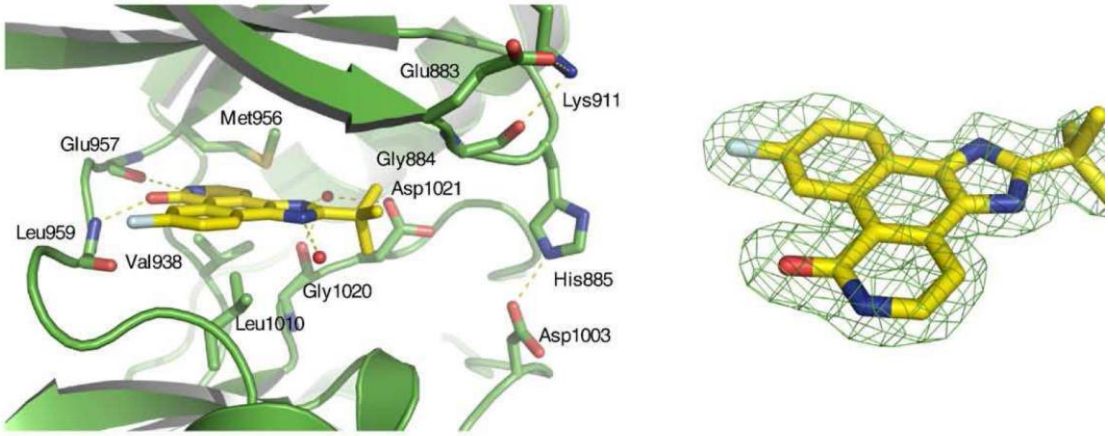
52. Comparative analysis of the overall structures of the JAK family The JAK1 PTK domain shares 53% and 50% sequence identity to JAK2 and JAK3, respectively. Accordingly, there is a high degree of similarity in their overall structures. Almost all the residues in the ATP-binding site are conserved between these three enzymes. The most significant differences in sequence are observed in the hinge region, glycine loop and activation loop. By measuring the interdomain angle between respective N-terminal and C-terminal lobes, it was found that JAK2 PTK is significantly more "closed" in comparison with other PTK structures. Similarly, after superposing the N-terminal lobe of JAK1 PTK onto the N-terminal lobe of JAK2 PTK, a 3.3° rotation (calculated using the program LSQMAN) is required to superpose the corresponding C-terminal lobes. While JAK1 is slightly more "open" with respect to JAK2, the tip of the glycine loop (consensus sequence G-x-G-x-Φ-G, where Φ is usually F or Y) of JAK1

is oriented more towards the activation loop than was the case with JAK2, resulting in a similarly narrow opening of the JAK1 and JAK2 ATP-binding sites. Comparison of the electrostatic surface potentials in the vicinity of the ATP-binding sites revealed a marked charge difference between JAK1 and JAK2, with JAK2 displaying much more positively charged potential than JAK1. By comparison, JAK3 seems to have less overall charge in the same region. The residues in this vicinity contributing to the greater electronegativity of JAK1 are D880, E883, D1042, S1080 and D1081, corresponding to Q854, K857, E1015, K1053 and S1054, respectively, of JAK2 and to Q827, K830, Q988, K1026 and S1027, respectively, of JAK3.

53. In JAK1–CMP6, CMP6 is sandwiched within the ATP-binding cleft of JAK1 and oriented such that the fluorophenyl ring points towards the bulk solvent, the pyridone moiety is buried in a deep hydrophobic pocket and the tbutyl group points towards the glycine loop (Fig. 4a and d). There is high shape complementarity between CMP6 and JAK1 PTK with the inhibitor burying 250 Å2 of its available 495 Å2 surface area. Accordingly, the planar hydrophobic ring system of CMP6 makes van der Waals contacts with Leu881, Val889, Ala906 and Val938 of the N-terminal lobe, Met956 and Phe958 of the hinge and Gly962 and Leu1010 of the C-terminal lobe. There are two hydrogen bonds between the hinge region of JAK1 and CMP6, linking Glu957O with pyridoneN2 and Leu959N with pyridoneO0. Additionally, the imidazole moiety of CMP6 is involved in a water-mediated hydrogen bond network through water molecules, with the imidazoleN0 group making water-mediated hydrogen bonds (W51) with Gly1020 and the conserved Asp1021 of the DFG motif. Although the glycine loop does not interact with CMP6, as observed in the JAK2–CMP6 structure, the tip of the glycine loop collapses over the ATP binding, stabilized in JAK1 by the non-conserved residue His885, making a hydrogen bond with the conserved catalytic aspartate Asp1003, thus connecting the N-terminal and Cterminal lobes. Lys911, another residue not conserved between JAK1 and JAK2, from the loop connecting β3 and αC, extends across the glycine loop, making a salt bridge with Glu883 and a hydrogen bond with Gly884. The mode of CMP6–JAK1 inhibitor binding is extremely similar to that found with JAK2, with nearly identical points of inhibitor

contacts between JAK1 and JAK2, and this is consistent with it being a pan-JAK inhibitor.

(a)



54. The teachings of Williams et al resonate with the teachings of Lucet et al and reverberate the motivations regarding structural changes of an inhibitor compound which a person skilled in the art perceives on reading the Lucet et al.

55. In Williams, binding of another JAK inhibitor CP-690,550 with the binding site of JAK 1 was studied. While CMP6 is a known JAK2 inhibitor with higher selectivity for JAK 2 binding site, CP-690,550 is a known pan JAK inhibitor but with higher affinity towards JAK 1 binding site as compared to AMP6. The structure of CP-690,550 is as shown below.

56. Williams teaches that in JAK 1 binding site CP-690,550 is orientated such that the pyrrolopyrimidine rings point towards the hinge, the methyl group points towards the bulk solvent, the piperidine ring is located in the polar pocket with its methyl group pointing towards the C-terminal lobe and the nitrile group points buried beneath the tip of the glycine loop.

57. The teachings of Williams follow some of the teachings of Lucet et al wherein the head group has rings with more polarity, particularly more positive polarity = both the rings in the head group are heterocyclic rings with nitrogen, the additional ring is merged with the head group thus creating a more non-planar structure = the head group is a bicyclic pyrrolopyrimidine structure and the additional ring i.e. a pyridine is not directly attached to the head group, the end substituent is more polar with

higher positive polarity to have better attachment in the cavity formed by and around the glycine loop = the ned substituent is nitrile, the end substituent is joined to the additional ring via bridge which lengths the group at this position and helps to better disorient and open up the cavity formed by glycine loop = the pyridine additional ring is attached to nitrile group by a carbonyl methyl bridge.

58. It was observed by Williams et al that although CP-690,550 is not planar, there is high shape complementarity between the inhibitor and the JAK1 ATP binding site (240 Å2 buried of its available 510 Å2 surface area), thereby making numerous contacts with the residues lining the active site. The pyrrolopyrimidine rings form two direct hydrogen bonds with the hinge region between the N-terminal and C-terminal lobes of JAK1 PTK (the nitrogen atoms N12,N17 from the five- and six-member rings of the group interact with Glu957O and Leu959N , which mimic those observed between the adenine group of ATP and other PTKs). PyrrolopyrimidineN19 interacts indirectly with hinge Pro960 and β1 Arg879 through water-mediated hydrogen bonds.

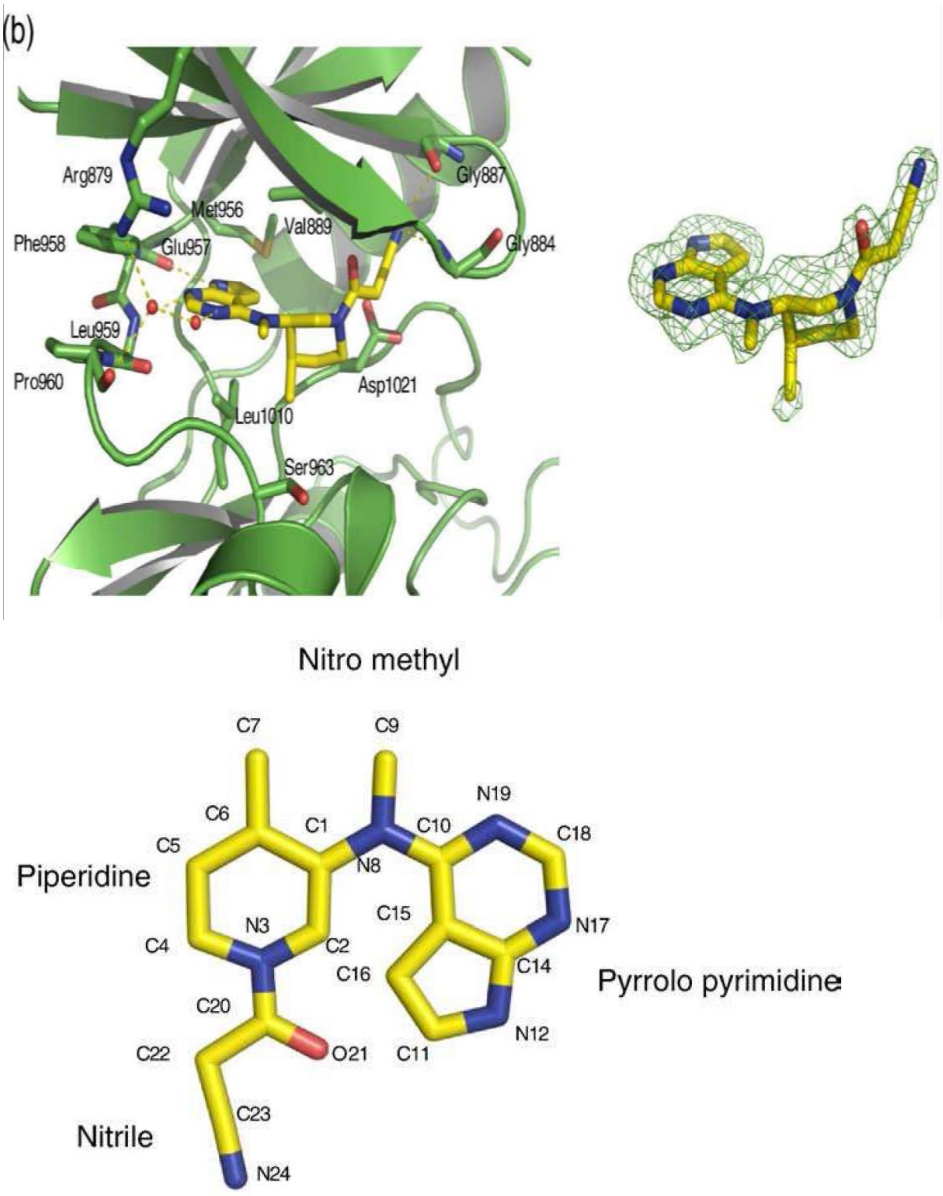
59. The above conforms that having a molecule with a head group and additional rings in a non-planar conformation helps better binding in the binding site of JAK1 contrary to the conformational requirement for JAK2 binding site wherein more planar structure have better binding. The above also confirms that having more polar head group as well as additional ring i.e. having a more polar molecular structure with more positive polarity helps make more bonds with the residues lining the binding site of JAK1 as opposed to what was observed for JAK2 wherein the more hydrophobic the compound, the better affinity it had for JAK2 binding site.

60. It was also observed in Williams et al that the oxygen and nitrile groups of CP-690,550 are well accommodated in the JAK1 active site, being located within and adjacent to a polar pocket that includes Asp1021 and Lys908, a pocket that typically coordinates Mg2+. Therefore, unlike CMP6, CP-690,550 makes numerous contacts with the glycine loop with both the oxygenO21 and the nitrileN24 forming hydrogen bonds with conserved Gly residues from the glycine loop (Gly882, Gly884, Gly887) and making van der Waals contacts with several residues, including non-conserved Glu883 and Lys888.

61. The above observations teach a person skilled in the art that the presence of more polar end groups helps make better bond formation with residues present around the glycine loop. It also teaches that majority of the residues present in the groove made by the glycine group are positive residues (Gly882, Gly884, Gly887, Glu883, Lys888) and therefore, having not just a polar end group but an end group which has more negative polarity will be able make more bonds with the residues present in the groove formed by the glycine loop. The above observation also teaches that presence of the carbonyl and nitrogen in the bridge connecting the additional ring and end is helpful in bond formation with the surrounding residues, thus, motivating a person skilled in the art to have bridge system like urea or amide connecting the additional ring and the end group. Another teaching gleaned from the observations mentioned in above para is that lengthening the distance between the additional ring and the end group is beneficial for better affinity with JAK 1 binding site such as in CP-690,550 the bridge is formed by a carbonyl methyl group.

62. A large number of van der Waals interactions with the JAK1 PTK domain also stabilize the inhibitor. Both the pyrrolopyrimidine and piperidine rings (chair conformation) are sandwiched between the hydrophobic residues of the N-terminal lobe (Leu881, Val889, Ala906, Val938), the C-terminal lobe (Leu1010) and the hinge (Met956, Phe958, Leu959). The methyl group of the piperidine ring points towards the C-terminal lobe, making van der Waals contacts with Ser963, Arg1007, Asn1008, Val1009 and Leu1010.

63. The above mentioned observations teach a person skilled in the art that van der waals interactions in the JAK binding domain help to stabilize the inhibitor which implies that having head groups with more number of rings would be better such a compound with tricyclic head group and additional ring will have more van der waals interactions in the binding domain than a compound with bicyclic head group and additional ring. The observations mentioned in above para also teach a person skilled in the art that having a small alkyl group like methyl on the additional ring is beneficial in forming bonds in the binding site increasing the affinity.



64. Williams teaches that there are differences in the binding of CMP-6 inhibitor (selective JAK2 inhibitor) as compared to binding of CMP-6 with JAK1. It was observed that the JAK1–CMP6 structure is not as “closed” as the JAK2–CMP6 structure. This variation in the juxtapositioning of the N-terminal and C-terminal lobes between JAK1 and JAK2 may contribute to the observed difference in affinities between JAK1 and JAK2 for CMP6. A close examination of the contacts between CMP6 and the JAK1 active site reveals that positions 883 (Glu) and 958 (Phe) in JAK1 (corresponding to Lys857 and Tyr931 in JAK2) are the only unique residues that make direct contacts with the inhibitor. Both of these residues form numerous van der Waals interactions with the inhibitor mediated through backbone and side chains, and these differences may alter the strength of CMP6 binding.

65. Williams concludes that the direct contacts made between CP-690,550 and the JAK1 and JAK2 active sites highlights four residue differences. These residues are located in the glycine loop (Glu883/Lys857, Lys888/Ser862, His885/Asn859) and hinge region (Phe958/Tyr931). Although all these residues interact with the inhibitor through their main-chain atoms, this sequence variability may contribute to a difference between the two proteins in the plasticity of the hinge region and the glycine loop. Interestingly, in inspecting the residues located outside the ATP-binding site, we found that in both inhibitor structures, JAK1 Lys911 (Gln885 in JAK2 and Gln858 in JAK3) located at the tip of β3 extends over the glycine loop to form a salt bridge with Glu883in a manner not seen in JAK2 and JAK3–AFN941. Additionally, pyrrolopyrimidine N19 of CP-690,550 participates in a network of water-mediated hydrogen bonds connecting the N-terminal lobe residue Arg879 with hinge residue Pro960. In JAK2 and JAK3, Arg879 is replaced by shorter sidechain residues (Gln853 in JAK2 and Ser826 in JAK3) unlikely to promote such a network of water-mediated hydrogen bonds with the inhibitor.

66. Williams et al also provides the direction of further work in preparing inhibitors with better selectivity for JAK1. It is stated in the document that "To enhance discrimination between the JAK active sites, the next generation of inhibitors must exploit the identified non-conserved residues by including interactions with their side chains. The proximity to the inhibitor-binding site of the unique JAK1 residues Phe958, Arg879 and His885 may be most useful in this regard. More subtle variations between the JAK proteins, such as electrostatic potential differences around the active site, might also be useful when fine-tuning relative binding affinities of therapeutics for enhanced selectivity and reduced off-target activity. Thus, the determination of the crystal structure of the JAK1 and JAK2 PTK domains in complex with two pan-JAK inhibitors (CMP6 and CP-690,550) not only provides insight into how these inhibitors exert their specificity but also reveals important structural differences surrounding the ATP-binding site, which could be exploited for the development of more JAK member-specific compounds."

67. The observations and conclusions of Williams mentioned in the above two paras teach a person skilled in the art that having a tricyclic head group in a inhibitor

compound will be better because the extra ring will be able to participate in hydrogen bond formation with Phe958, Arg879 residues in the hinge region. A person skilled in the art is also taught in the end group it would be better to have a substituent which is more negatively polar and with broader spatial configuration in order for it form bonds with the His885, Lys911, and Glu883 in the salt bridge formed by the glycine loop. The parson skilled in the art is also taught to retain the pyrrolopyramide in the head group while designing better inhibitor so as to maintain the participation of pyrrolopyrimidine in a network of water-mediated hydrogen bonds connecting the N-terminal lobe residue Arg879 with hinge residue Pro960.

68. Annexure 7, i.e., Stephen et. al., 2009 studied the comparison between binding of inhibitors to the binding site of JAK 2 and JAK3 and it is disclosed that the inhibitors bind within the ATP-binding site of JAKs and form dual H-bonds to the hinge region of the protein. In addition, the N-terminal portion of the activation loop that contains the highly conserved Asp-Phe-Gly (DFG) motif adopts the 'inward' conformation characteristic of active kinases.

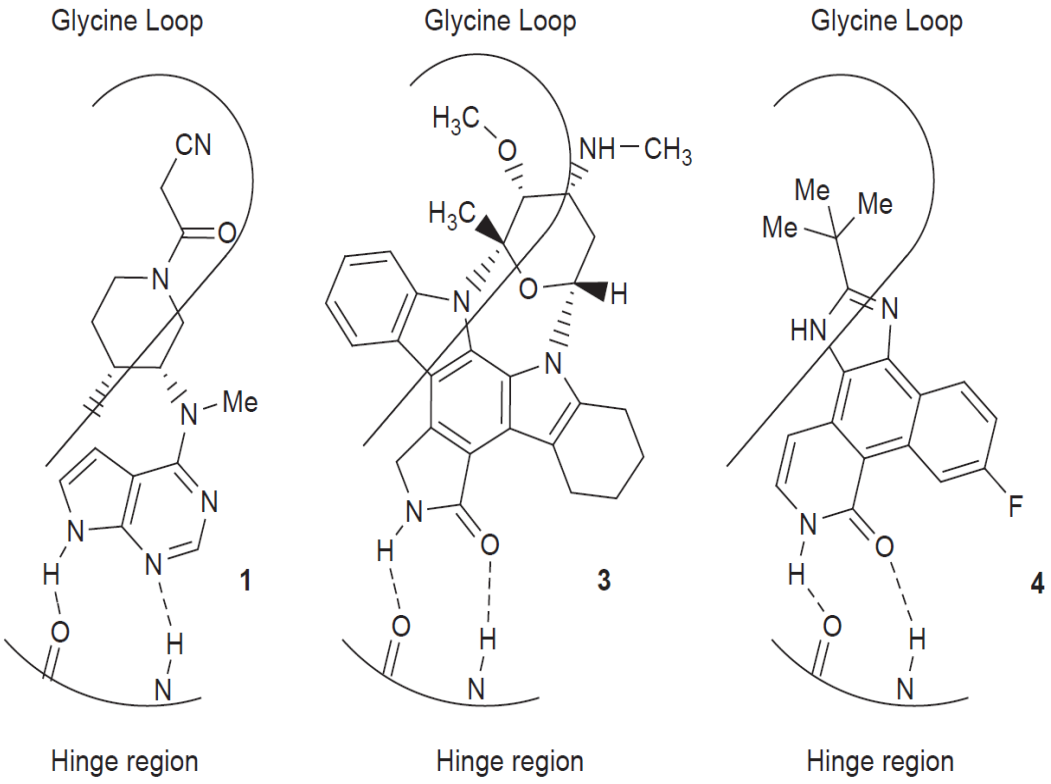


Figure 2 Schematic of compounds 1, 3 and 4 illustrating key hydrogen bonds to hinge region in a generic JAK family active site.

69. However, on the basis of the JAK3 X-ray structure of compound 3, a sequence alignment analysis of the active site residues that are in proximity to the complexed inhibitor revealed only two differences that the authors believed could be exploited to provide selectivity between JAK3 and its most closely related isoform JAK2.

70. Based on the observed difference, Stephen et al reasoned that JAK2-selective compounds could be designed to exploit the extra space afforded by the difference between an active site glycine (JAK2) and Ala966 (JAK3). A subsequent report disclosing the JAK2 structure with compound 4 also revealed that the JAK2 glycine carbonyl is in a flipped conformation relative to that found in all other tyrosine kinase structures including the JAK3 structure with compound 3. In addition, exploiting the residue difference between Cys909 (JAK3) and an analogous serine residue in JAK2 has been suggested as a potential strategy for obtaining JAK3 selectivity over JAK2. Several JAK3 inhibitors have been reported, which might interact with Cys909.

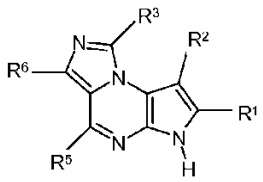
71. Stephen et al also reiterates the teaching of Williams with regard to JAK 1 since it teaches that three JAK1 residues Phe958, Arg879 and His885 differ when compared to JAK2, although these residues are in proximity to the active site. The authors also postulate that subtle variations in the electrostatic potential differences in the active site might also be useful to consider in the design of more selective compounds.

72. Annexure 2, i.e., WO 2009/152133 [WO'133] discloses that Jak kinases transduce signals for many different cytokine families and hence potentially play roles in diseases with widely different pathologies. It is further disclosed that both Jakl and Jak3 control signalling of the so-called common gamma chain cytokines (IL2, IL4, IL7, IL9, IL15 and IL21), hence simultaneous inhibition of either Jakl or Jak3 could be predicted to impact ThI mediated diseases such as rheumatoid arthritis via blockade of IL2, IL7 and IL 15 signalling. Moreover, several pathologically significant cytokines signal via Jakl alone.and blockade of one of these, IL6, using an IL6R neutralizing antibody, has been shown to significantly improve disease scores in human rheumatoid arthritis patients. Similarly, blockaded of GCSF signalling, which is also mediated by Jakl alone, using neutralizing monoclonal antibodies or target gene deletion protects mice from experimental arthritis.

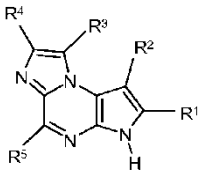
73. Accordingly, WO'133 relates to identification of small-molecule compounds that inhibit, regulate and/or modulate the signal transduction of kinases, such as Jakl, as a desirable means to prevent or treat autoimmune diseases or other diseases related to aberrant Jakl function such as rheumatoid arthritis.

74. WO'133 also discloses that Jak kinases also transmit signals regulating essential physiological processes whose inhibition could be undesirable for example Jak2 mediates the signalling of Erythropoetin (Epo) and Granulocyte/Monocyte-Colony Stimulating Factor. Individuals with genetic, congenital or acquired defects in these signalling pathways can develop potentially life-threatening complications such as anaemia and neutrophil dysfunction. **Accordingly, one non-limiting aspect of WO'133 disclosed therein relates to identifying compounds that may have a favourable safety profile as a result of them selectively avoiding inhibition of Jak2.**

75. With regard to structure of inhibitor compounds WO'133 teaches that a headgroup structure preferred in said document is imidazopyrrolopyrazine since this is the only headgroup structure for which three schemes of synthesis have been provided in the document namely Scheme III, XII, IV. Further, two of the general formula Formula (Ib) and (Ic) are both imidazopyrrolopyrazine headgroups. Thus, imidazopyrrolopyrazine is a preferred head group as per WO'133 and either of the Formula (Ib) or (Ic) is obvious to try for a person skilled in the art.



Formula (Ib)



Formula (Ic)

76. The commonly used substituent on the head group is either a cycloalkyl ring or a heterocyclic ring and when the substituent is a heterocyclic ring, the ring is either a pyrrole or a pyrazine ring. There are number of exemplified compounds in WO'133 which have pyrrole ring [Example I.1.5, I.1.7, L.3.6, N.1.13, N.1.15], making pyrrole ring an obvious to try choice.

77. Furthermore, it can be seen from the exemplified compounds of WO'133 that the substituent on heterocyclic ring such as pyrrole is 1. an alkyl and 2. a substituent joined to the heterocyclic ring via a bridge which is either carbonyl or amide. Among the alkyl group which is direct substituent on the heterocyclic ring, methyl and ethyl have been commonly used. Among the substituent which is joined to the heterocyclic group via a carbonyl or amide bridge, there is either a cycloalkyl group such as cyclopropyl which has been frequently used or among the non-cyclic substituents methyl nitrile and methyl -CF3 were commonly used. Thus, nitrile and -CF3 become obvious to try substituents on the amide or carbonyl bridge. [please see Table 4 in WO'133 for reference to the submissions in this para].

78. Considering that WO'133 specifically addresses the technical problem of designing JAK inhibitors which have high specificity for JAK1 and have a higher safety profile due to avoiding JAK2 inhibition, a person skilled in the art engaged in designing alternate compounds with same effect and safety is motivated to use the head group taught by WO'133 and then make minor structural modifications to rest of the substituents while conforming to the same structural framework defined therein.

79. The **VX-509** was advanced molecule, which showed a high selective inhibition of Janus Kinase 3 (JAK 3). It was submitted for Phase-2 Clinical trial (@clinicaltrials.gov) on 18.01.2010 i.e. before the correct Upadacitinib priority of 01.12.2010. A person skilled in the art, in search of the structure of VX-509, would have arrived at **US7767816B2** (US2007/0203142, i.e., Annexure 8) by Vertex, which discloses a series of compounds that are **more selective towards JAK3** than **JAK2**.

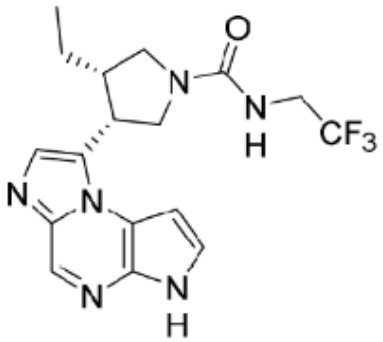
80. **VX-509** and related compounds of US'142 motivates that a **trifluoroethyl carboxamide** can lead to a highly selective inhibitor of Janus kinase 3 (JAK3). Thus, a person skilled in the art would be motivated to try trifluoroethyl-carboxamide as 'upper half" of the tricyclic system in order to improve selectivity of compound as disclosed in WO'133 and per se Example 19.

81. Also, as discussed above, Lucet et al, Williams et al, and Stephen et al, explicitly teach the detailed structure including the specific amino acid residues present in the binding sites of JAK1, JAK2. These documents also teach in explicit

detail how different inhibitors interact with the various amino acid residues in the binding sites of different JAKs. Most notably, WO'133 follows and reinforces the teachings of preceding documents in terms of the various structural requirements to be followed and structural groups to be used while designing an inhibitor which has high affinity for JAK1 but low affinity for JAK 2. The teachings of the prior art documents with respect to the preferred structure of the compound with high affinity for JAK1 but low affinity for JAK 2 is as follows:

- the head group is a tricyclic system as compared to the bicyclic system of CP-690550 whereby the head group can form additional hydrogen bonds with Phe958, Arg879 and His885 in the hinge region of JAK1 as taught by Lucet and Williams.
- the additional ring is not merged with the head group which makes the compound a more non-planar configuration as taught in Lucet which results in the inhibitor with high affinity for JAK 1 and less affinity for JAK 2, as taught by Lucet, Williams and Stephen.
- the additional ring is a nitrogen containing heterocyclic ring i.e. its polar and hence makes bonds in the binding cavity similar to pyridine does in CP-690,550 as taught in Williams and Stephen.
- the presence of small alkyl group ethyl on the additional ring points towards the C-terminal lobe making van der Waals contacts with Ser963, Arg1007, Asn1008, Val1009 and Leu1010, as taught in Lucet, resulting in more bond formation as compared to methyl in CP-690,550.
- presence of bridge between additional ring and end group and this bridge contains O and N in form of amide or urea forming hydrogen bonds with conserved Gly residues from the glycine loop (Gly882, Gly884, Gly887), as taught in Lucet.
- the presence of end group such as -CF3 forms bonds with His885, Lys911, and Glu883 in the salt bridge formed by the glycine loop, as taught in Williams and Stephen. This results in higher affinity for JAK1 and less binding with JAK2, as taught by Williams, Stephen and Lucet, respectively.
- the bridge between the additional ring and the end group is lengthened by presence of methyl amide linkage which results in more opening of the cavity formed by the glycine loop forming better affinity with JAK 1 and lesser affinity with JAK2, as taught by Lucet, Williams and Stephen.

82. In light of the teachings of prior documents Lucet, Williams, Stephen, WO'133 and US'142, as discussed above, a person skilled in the art understands that the compound with the structure shown below has reasonable expectation of having high affinity for JAK1 but low affinity for JAK 2:



83. Therefore, in view of the combined teachings of the prior art documents relied on above Upadacitinib i.e. the compound claimed in IN'4759 is obvious to a person of skill in the art, and IN'4759 is liable to be refused on this ground alone.

B. Lack of Technical Advancement over the existing knowledge.

84. IN'4759 states that the alleged technical problem addressed therein is designing JAK inhibitor compounds which will be useful in inhibiting JAK 1 but will have very less affinity for JAK 2 resulting in reduced inhibition of JAK 2 and consequently reduced toxicity of the claimed inhibitor compounds. Abbvie, through purported additional data seeks to show that Upadacitinib also has high affinity for JAK 3 but low affinity for Jak 2.

85. As discussed in detail above WO'133 relates to the same technical problem as IN'4759 and provides the same solution claiming to be provided by IN'4759 [given that the alleged inventors are identical].

86. WO'133 also relates to designing of compounds which have high affinity for JAK 1 and JAK 3 but low affinity for JAK 2. This is evident from the disclosure of WO'133 in:-

- Line 34 to 37 on page 45 and lines 1 to 9, 12-15 on page 46 that "*Both Jakl and Jak3 control signalling of the so-called common gamma chain cytokines (IL2, IL4, IL7, IL9, IL15 and IL21), hence simultaneous inhibition of either Jakl or Jak3 could be predicted to impact ThI mediated diseases such as rheumatoid arthritis via blockade*

of IL2, IL7 and IL 15 signalling. On the other hand, IL2 signalling has recently been shown to be essential for development and homeostasis of T- regulatory cells (Malek TR et ah, Immunity, 2002, 17(2), p.167-78). Thus, based on genetic data, blockade of IL2 signalling alone is predicted to result in autoimmunity (Yamanouchi J et ah, Nat Genet., 2007, 39(3), p.329-37, and Willerford DM et ah, Immunity, 1995, 3(4), p.521-30). Th2 mediated diseases such as asthma or atopic dermatitis via IL4 and IL9 signalling blockade. Jakl and Tyk2 mediate signalling of IL 13 (see Int. Immunity, 2000, 12, p. 1499). Hence, blockade of these may also be predicted to have a therapeutic effect in asthma. These two kinases are also thought to mediate Type I interferon signalling; their blockade could therefore be predicted to reduce the severity of systemic lupus erythematosus (SLE)…… In summary, this invention describes small-molecule compounds that inhibit, regulate and/or modulate Jak family kinase activity that is pivotal to several mechanisms thought critical to the progression of autoimmune diseases including, but not limited to, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), Crohn's disease, psoriasis and asthma."

- line 8-10 on page 47 that **one non-limiting aspect of WO'133 disclosed therein relates to identifying compounds that may have a favourable safety profile as a result of them selectively avoiding inhibition of Jak2.**
- on page 82 where it is described that the compounds of WO'133 were tested for effect in rheumatoid arthritis using the test "*Collagen Induced Arthritis (CIA) in Lewis Rat*"

87. Accordingly, WO'133 relates to identification of small-molecule compounds that inhibit, regulate and/or modulate the signal transduction of kinases, such as Jak l, as a desirable means to prevent or treat autoimmune diseases or other diseases related to aberrant JAK l and JAK3 function such as rheumatoid arthritis and identifying compounds that may have a favourable safety profile as a result of them selectively avoiding inhibition of JAK2.

88. In light of existing knowledge of compounds such as compounds disclosed in WO'133 which have high affinity for JAK1 and low affinity for JAK2 because of which these compounds have a favourable safety profile as a result of them selectively

avoiding inhibition of Jak2, it was incumbent upon the Applicant to establish technical advancement of the claimed compounds of the impugned specification. Abbvie however, signally fails to provide any data in the complete specification to show that what is claimed in IN'4759, i.e, Upadacitinib has any technical advancement over the existing knowledge particularly that of WO'133. There does not appear to be any reference at all to the WO'133 family including its priority forming US Provisional Applications which is surprising given that the alleged inventors are the same.

89. Abbvie, through post-filed data attempts a comparison of Example 19 of WO'133 with Upadacitinib and avers that Upadacitinib has lower IC50 value for JAK1 and higher IC50 value for JAK 2 than the compound of Example 19 of WO'133.

90. However, Upadacitinib is a pharmaceutical compound whose industrial utility has to be established in terms of its effect on various diseases such as rheumatoid arthritis. Hence, the technical advancement of what is claimed in IN'4759 should also be based and be assessed on its pharmaceutical usage. This is sorely missing in the complete specification of IN'4759.

91. In this regard, the difference in IC50 value of Upadacitinib versus IC50 of the compound of Example 19 of WO'133 is insufficient to establish technical advancement of the claimed invention over existing knowledge since IC50 values are determined in vitro wherein a sample of relevant purified protein, JAK 1 or 2 in present case, is directly exposed to the test compound. However, practically a compound when administered to a patient undergoes a very tortuous journey to reach the target receptor and in this journey the compound is exposed many different enzymes, plasma proteins and metabolic pathways which degrade, bind, and metabolize the compound thereby decreasing the amount of compound which actually reaches the target receptor. This is also the reason why hundreds of test compounds demonstrate great IC50 values in-vitro tests but fail in in-vivo tests.

92. It is submitted that WO'133 discloses various in vivo tests for assessing the in-vivo efficacy of the compounds disclosed therein, for example, one such test is collagen induced arthritis in Lewis rat which is an animal model test for Rheumatoid

Arthritis. Notably, the impugned specification also provides the same in vivo tests for assessing the in-vivo efficacy of the compounds disclosed therein as those disclosed in WO'133 including collagen induced arthritis in Lewis rat.

93. Therefore, the correct and scientifically rationalistic method of establishing the technical advancement of the invention claimed in the impugned invention would have been to determine the effect of claimed compound compared to the effect obtained from compound of Example 19 of WO'133 using one of the in-vivo tests described therein and in IN'4759 such as "collagen induced arthritis in Lewis rat".

94. It is also critical to note that the statement with regard to the supposed technical advancement of an invention should be stated in the specification at the time of filing. However, in IN'4759 there is no mention of either the data of inhibition of JAK 1 or of any data of inhibition of JAK 2. IN'4759 is conspicuous not only just in its absence of any comparative data establishing technical advancement over existing knowledge but even in absence of any data demonstrating the purported technical solution i.e. higher affinity the compounds for JAK 1 and lower affinity for JAK2.

95. In fact, it is stated in IN'4759 in first paragraph on page 51 of the specification that JAK 2 mediates signalling of IL12 and IL23 and blockade of this pathway by inhibition of JAK2 is useful in treatment of psoriasis. It is further stated in IN'4759 in last line of page 55 of the specification that the compounds thereof are useful in treating psoriasis type I and psoriasis type II. Hence, it is understood that the compounds of IN'4759 or at least 'some' of the compounds thereof are effective JAK2 inhibitors and which can be used in JAK2 mediated diseases such as psoriasis. This understanding leads to following conclusions:

- not all compounds disclosed or described in IN'4759 solve the technical problem of having a inhibitor with low JAK 2 affinity and thereby higher safety profile.
- as discussed above, since no such activity is stated in IN'4759 for Upadacitinib and no generalization can be made that all compounds of IN'4759 have said activity, it is clear that alleged inventors could not state with any certainty that Upadacitinib definitely possesses the property of high affinity for JAK1 and low affinity for JAK2.

- hence, the alleged inventors of IN'4759 were not in possession of the alleged invention which today is being asserted as "inventive".

- the selection of Upadacitinib is at best a an arbitrary selection with no demonstrated superiority over the other disclaimed compounds of IN'4759. This is especially pertinent given the fact that IN'4759 was filed with a broad Markush claim and subsequently restricted to a single compound in the face of various challenged thereagainst in India as well as in Europe and in China.

- as discussed above, since IC50 values have no direct correlation with in vivo effect of a compound and can only be considered to be at best indicative of the farthest extent of actual effect of a compound. Abbvie fails to establish that Upadacitinib provides a solution to the purported technical problem stated in IN'4759 or that it is technically superior to the existing knowledge in the art, both in comparison to the compounds described in WO'133 and to the compounds of IN'4759 which have been disclaimed via responses to the various challenges thereto.

96. Thus, in light of the above submissions it is submitted that Abbvie has failed to prove the technical advancement of the claimed subject matter over the existing knowledge. Therefore, what is claimed in IN'4759 lacks lacks inventive step in view of the combination of teachings of prior art documents cited and relied on above and is liable to be refused on this ground alone.

VII. *NOT AN INVENTION/ NOT PATENTABLE [Section 25(1)(f)]:*

Not Patentable u/s 3(d)

97. The subject-matter of claims of IN'4759 falls under the ambit of Section 3(d) of the Act as explained below. Section 3(d) of the Indian Patent Act bars patentability of a subject matter wherein such subject-matter is

> "*the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.*
> *Explanation—For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy;*".

98. It is submitted that WO'133 discloses compounds which have high affinity for JAK 1 and JAK 3 but low affinity for JAK 2. This is evident from the disclosure therein:-

- Line 34 to 37 on page 45 and lines 1 to 9, 12-15 on page 46 that "*Both Jakl and Jak3 control signalling of the so-called common gamma chain cytokines (IL2, IL4, IL7, IL9, IL15 and IL21), hence simultaneous inhibition of either Jakl or Jak3 could be predicted to impact ThI mediated diseases such as rheumatoid arthritis via blockade of IL2, IL7 and IL 15 signalling. On the other hand, IL2 signalling has recently been shown to be essential for development and homeostasis of T- regulatory cells (Malek TR et ah, Immunity, 2002, 17(2), p.167-78). Thus, based on genetic data, blockade of IL2 signalling alone is predicted to result in autoimmunity (Yamanouchi J et ah, Nat Genet., 2007, 39(3), p.329-37, and Willerford DM et ah, Immunity, 1995, 3(4), p.521-30). Th2 mediated diseases such as asthma or atopic dermatitis via IL4 and IL9 signalling blockade. Jakl and Tyk2 mediate signalling of IL 13 (see Int. Immunity, 2000, 12, p. 1499). Hence, blockade of these may also be predicted to have a therapeutic effect in asthma. These two kinases are also thought to mediate Type I interferon signalling; their blockade could therefore be predicted to reduce the severity of systemic lupus erythematosus (SLE)…… In summary, this invention describes small-molecule compounds that inhibit, regulate and/or modulate Jak family kinase activity that is pivotal to several mechanisms thought critical to the progression of autoimmune diseases including, but not limited to, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), Crohn's disease, psoriasis and asthma*."

- line 8-10 on page 47 that **one non-limiting aspect of WO'133 as disclosed therein relates to identifying compounds that may have a favourable safety profile as a result of them selectively avoiding inhibition of Jak2.**

- on page 82 where it is described that the compounds thereof were tested for effect in rheumatoid arthritis using "*Collagen Induced Arthritis (CIA) in Lewis Rat*".

99. Accordingly, WO'133 relates to identification of small-molecule compounds that inhibit, regulate and/or modulate the signal transduction of kinases, such as Jak l, as a desirable means to prevent or treat autoimmune diseases or other diseases related to aberrant JAK l and JAK3 function such as rheumatoid arthritis and

identifying compounds that may have a favourable safety profile as a result of them selectively avoiding inhibition of JAK2.

100. Abbvie, in IN'4759 as well as in its responses to various challenges thereto including response to the FER and in Europe, states that the alleged invention lies in providing compounds which have high potency of inhibition of JAK1 and low potency of inhibition of JAK 2 which results in said compounds possessing better safety profile and higher therapeutic index when used for treatment of diseases mediated by JAK 1 (and JAK3) such as rheumatoid arthritis.

101. As discussed above, the therapeutic property alleged to be possessed by Upadacitinib is already known to be exhibited by the compounds of WO'133.

102. The compound exemplified as Example 19 in WO'133 for example has also been accepted by the Applicant to be the closest prior art. Hence, the claimed compound is a mere derivative of the known substance "compound of Example 19 of WO'133".

103. As per section 3(d) of the Act, the onus is on the Applicant to establish in the complete specification that the claimed composition has enhanced therapeutic efficacy as compared to the known substance. Abbvie has failed to provide any data or even information establishing that the claimed compound has enhanced efficacy as compared to the known compound of Example 19 of WO'133.

104. The complete specification of IN'4759 has no reference or mention of either the data of inhibition of JAK 1 or of inhibition of JAK 2. It does not provide any data demonstrating the purported technical solution i.e. higher affinity the compounds for JAK 1 and lower affinity for JAK2 nor is there any comparative data establishing enhanced therapeutic efficacy over known compound such as Example 19 of WO'133. In fact, there appears to be no mention of WO'133 or its family equivalents at all – which is strange given that the alleged inventors are the same.

105. In post-filed data Abbvie provides a comparison of Example 19 of WO'133 with Upadacitinib and asserts stated that the claimed compound has lower IC50 value for

JAK1 and higher IC50 value for JAK 2 than compound of Example 19 of WO'133. This data according to Abbvie is representative of enhanced therapeutic efficacy.

106. However, as discussed above, IC50 values are determined in vitro wherein a sample of relevant purified protein, JAK 1 or 2 in present case, is directly exposed to the test compound. On the other hand, in reality a compound administered to a patient undergoes a very tortuous journey to reach the target receptor and in this journey the compound is exposed to many different enzymes, plasma proteins and metabolic pathways which degrade, bind, and metabolize the compound thereby decreasing amount of compound which actually reaches target receptor. This is why hundreds of test compounds demonstrate great IC50 values in-vitro tests but fail in in-vivo tests. Therapeutic efficacy comes into existence and can be measured only in in-vivo conditions i.e. when a compound is inside a "body" and not in in-vitro.

107. Thus, IC50 value or potency is not a measure of the therapeutic effect of a compound and the difference in IC50 value of the claimed compound versus the IC50 of compound of Example 19 of WO'133 does not prove enhanced therapeutic efficacy let alone significant enhancement of therapeutic efficacy.

108. It is submitted that WO'133 discloses various in vivo tests for assessing the in-vivo efficacy of the compounds disclosed therein, for example, one such test is collagen induced arthritis in Lewis rat which is an animal model test for Rheumatoid Arthritis. The impugned specification also provides the same in vivo tests for assessing the in-vivo efficacy of the compounds as those disclosed in WO'133 including collagen induced arthritis in Lewis rat.

109. Therefore, the correct method of establishing enhanced therapeutic efficacy of Upadacitinib would have been to determine effect thereof and of compound of Example 19 of WO'133 using one of the in-vivo tests described in WO'133 as well as in IN'4759 such as the test "collagen induced arthritis in Lewis rat". However, till date, Abbvie has not provided any such tests or data to show therapeutic efficacy of Upadacitinib or data establishing significant enhancement in therapeutic efficacy thereof over known compounds such as compound of Example 19 of WO'133.

110. Hence, the claimed subject matter of IN'4759 falls under the prohibition of Section 3(d) of the Act and ought to be rejected on this basis alone.

VIII. LACK OF SUFFICIENT DISCLOSURE [Section 25(1)(g)]

111. Independent claim 1 is not enabled because the specification of IN'4759 does not disclose the alleged invention sufficiently for a person of average skill in the art to carry out the invention without undue experimentation.

112. While the complete specification may describe broad schemes of synthesis of the compounds described therein, and while specific routes of synthesis may have been provided for about 40 exemplified compounds, there is no synthesis procedure provided in respect of Upadacitinib. None of the 40 exemplified compounds for which specific routes of synthesis are provided are structurally close to Upadacitinib.

113. The general scheme of synthesis and general procedures described in IN'4759, a person of ordinary skill in the art gets no information about the exact starting material, intermediates, and reagents to be used for preparation of Upadacitinib. All information about these process parameters then requires extensive determination by a person of average skill. Hence, the impugned specification serves, at best, as a generic guidance document requiring extensive effort by a person of average skill to determine the best method of working the alleged invention that is claimed i.e., Upadacitinib. The lacunae in information in the general scheme of synthesis provided for the claimed compound is detailed below.

114. Upadacitinib is identified in IN'4759 as Example AA.1.160 for which the process of preparation is described as "*prepared using J.1 with Preparation #F.1.1 and 2,2,2-trifluoroethanamine, and D with NaOH*" (page 364 of specification). To follow the route of synthesis for AA.1.160, it is required to read the general procedure J.1, general preparation#F.1.1 and general connotation D. The general procedure J.1 is provided on page 291 of IN'4759 and is reproduced below for ready reference:

General Procedure J.1: Formation of a urea or a thiourea using CDI or thiocarbonyldiimidazole, respectively

To a solution or slurry of an amine or amine salt (1-3 equiv, preferably 1-2 equiv) in an organic solvent such as DCM, THF, or DMF (preferably DMF) at about 20 – 80 °C (preferably about 65 °C) is optionally added an organic base, such as TEA, DIEA, pyridine (preferably TEA) (1-10 equiv, preferably 1-5 equiv) followed by CDI or 1,1'-thiocarbonyldiimidazole (0.5-2 equiv, preferably 1 equiv). After about 0.5-24 h (preferably about 1-3 h), a second amine or amine salt (1-10 equiv, preferably 1-3 equiv) is added neat or as a solution or slurry in an organic solvent such as DCM, THF, or DMF (preferably DMF). The reaction is held at about 20 – 80 °C (preferably about 65 °C) for about 2 – 24 h (preferably about 3 h). If the reaction mixture is heated, it is cooled to ambient temperature. The reaction mixture is partitioned between an organic solvent (such as EtOAc, DCM or 1,4-dioxane) and an aqueous base (such as saturated aqueous $NaHCO_3$ or saturated aqueous Na_2CO_3, preferably saturated aqueous $NaHCO_3$). Optionally, the reaction mixture is concd under reduced pressure and the residue is partitioned as above. In either case, the aqueous layer is then optionally extracted with additional organic solvent such as EtOAc or DCM. The combined organic layers may optionally be washed with brine and concd *in vacuo* or dried over anhydrous Na_2SO_4 or $MgSO_4$ and then decanted or filtered prior to concentrating under reduced pressure to give the target compound. Optionally, the reaction mixture is concd under reduced pressure and the residue is directly purified.

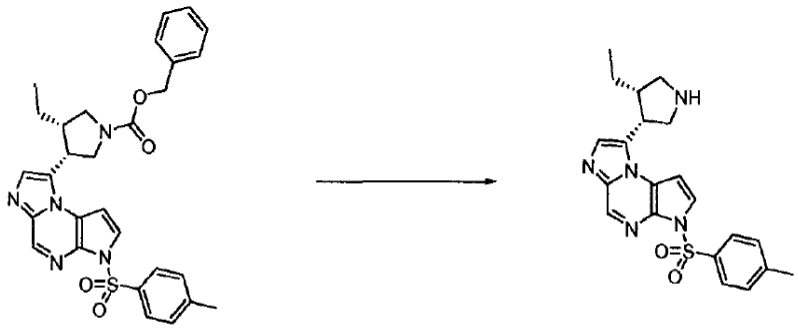
115. The general procedure J.1 provides no information about:-

- which amine or amine salt is to be used. There is no information on which is the second amine or amine salt to be used in the procedure. No criteria for selection of such “amine or amine salt” and “second amine or amine salt” has been provided.
- what is the preferred duration of reaction for preparation of Upadacitinib. The general procedure provides a very broad range of duration of reaction such as for addition of second amine or amine salt [stated that the addition is to be done after 0.5 to 24 hrs]. Similarly, for holding reaction at 20-80°C it is stated that the reaction is to be held for about 2 to 24 hrs. It can be easily appreciated that the difference in duration from **0.5 hrs** to **24 hrs** is significantly large and too drastic. While IN’4759 identifies certain values as preferred, it is not specified or even clear whether these preferred values are also preferred for Upadacitinib i.e. compound AA.1.160 as well.
- the procedure provides choices to be made in selection of organic solvents and some preferences have been stated but there is no indication of which organic solvent would be particularly suitable for compound AA.1.160.

116. General preparation #F.1.1 is provided on page 274-275 of IN'4759 is reproduced below for ready reference:

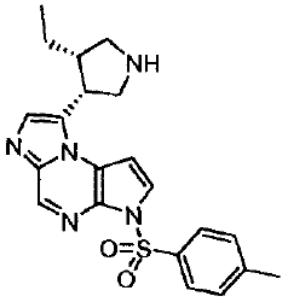
Illustration of General Procedure F.1

Preparation #F.1.1: 8-((*cis*)-4-ethylpyrrolidin-3-yl)-3-tosyl-3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazine

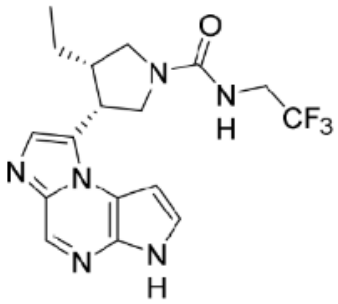


To a solution of (cis)-benzyl 3-ethyl-4-(3-tosyl-3*H*-imidazo[1,2-*a*]pyrrolo[2,3-e]pyrazin-8-yl)pyrrolidine-1-carboxylate (0.838 g, 1.541 mmol, prepared using **E** from Example #36 Step D with TFA, **N**, **R**, **S.1** with Example #3 Step E, and **T** with Lawesson's reagent) was added a solution of HBr (2.50 mL, 15.19 mmol, 33% in acetic acid). The reaction mixture was stirred at ambient temperature for about 1 h. The reaction was diluted with Et_2O (50 mL) and water (20 mL). The layers were stirred for about 3 min and the organic layer was decanted then the procedure was repeated 5 times. The aqueous layer was cooled to about 0 °C was basified with saturated aqueous $NaHCO_3$ solution (10 mL) to about pH 7. The aqueous layer was extracted with EtOAc (3 x 50 mL), combined, and dried over anhydrous Na_2SO_4, filtered and concd to give a brown solid. The solid was dissolved in DCM (50 mL) and washed with water (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concd to afford *8-((cis)-4-ethylpyrrolidin-3-yl)-3-tosyl-3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazine* (0.453, 61%) as a brown residue: LC/MS (Table 1, Method **a**) R_t = 1.73 min; MS *m/z*: 410 $(M+H)^+$.

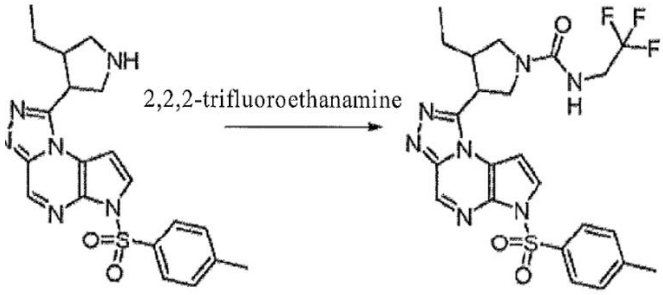
117. At the outset it is seen that Preparation #F.1.1 is for preparation of a specific compound 8-((cis)-4ethylpyrrolidin-3-yl)-3-tosyl-3H-imidazo[1,2-a]pyrrolo[2,3-e] pyrazine, the structure of which is show below



118. On the other hand the structure of the presently claimed compound is as follows:



119. As is self-evident, Preparation #F.1.1 cannot read upon or lead to Upadacitinib since it pertains to a compound which is structurally very different. Even if the compound shown in para 101 is reacted with 2,2,2-trifluoroethanamine the reaction would be as follows:



120. As far as "D" is concerned it is unclear what is being referred to since there is no "D" in the list of abbreviations and elsewhere in the specification "D" is stated as either as "D from Preparation #BBBBB.l" or "D from Preparation #YYYY.l" or "D from Preparation #Q.l" or "D from Preparation #25" or "D from Preparation #EEEE.l".

121. However, in the process of preparation of AA.1.160 merely a "D" is mentioned, the reference of which cannot be found in IN'4759.

122. Thus, the process of preparation stated for example AA.1.160 which is the presently claimed compound is fraught with lacunae which a person of ordinary skill in the art engaged in arriving at the claimed invention would have to work out on his own by doing extensive experimentation.

123. Hence, it is evident from the above submissions that IN'4759 in its complete specification fails to disclose the claimed invention fully and sufficiently or its best

method of preparation so as to enable a person of ordinary skill in the art to arrive thereat without facing the burden of undue experimentation.

124. What is also clear is that a person of average skill has to do undue experimentation to arrive at Upadacitinib and also that what is claimed are non-worked embodiments. Hence, IN'4759 is liable to be rejected on this ground alone.

IX. INFORMATION RELATING TO CORRESPONDING APPLICATIONS UNDER SECTION 8 [SECTION 25(1)(h)]

125. The Applicant has failed to disclose to the Patent Office the information required under Section 8. The Applicant is required to provide all the information regarding the prosecution of the equivalent applications till the grant of the Indian application to the Patent Office in writing from time to time and also within the prescribed time.

126. Applicant has not provided information about updated status of corresponding applications in Form-3 to the Patent Office. In particular, refusal of priority date claim in Europe or China [including refusal in China of the corresponding patent] do not appear to have been disclosed. Pertinently, such failure does not appear to be inadvertent. It is for Abbvie to show that such failure was inadvertent – on the contrary given that it has contested challenges including prior art challenges globally, it cannot be said that it was either unaware of such prior art or status of foreign applications, or that it accidentally failed to provide such information. The presumption has to be that it deliberately withheld such information.

127. Therefore, the applicant has failed to comply with the requirements of Section 8 of the Act and IN'4759 should be rejected on this ground also. The opponent craves leave to file further submissions and evidence with respect to this ground.

CONCLUSION

128. In view of the above, the claimed subject matter of IN'4759 is not inventive, non-patentable, is anticipated by prior claiming and prior publication separately, and further impugned specification is insufficient. The pre-grant opposition as filed may be allowed and the subject patent application may be refused.

HEARING REQUESTED

129. Opponent hereby requests a hearing under section 25(1) of The Patents Act, 1970 and Rule 55 of the Patents Rules 2013. It is submitted that no adverse decision, whether at prima facie consideration or final consideration be taken without providing Opponent an opportunity of being heard. It is further submitted that Opponent be advised or informed of any amendments/submissions of Applicant on IN'4759 and opportunity be provided to address such amendments/submissions.

P R A Y E R

In the fact and circumstances of the case, the Opponent prays as follows:

i. that the present Opposition be taken on record and Indian Patent Application 4759/DELNP/2012 be rejected under the various grounds of Section 25(1) taken above;

ii. that Opponent may be allowed to file further documents and evidence if necessary to support their averments;

iii. that Opponent may be allowed to file rejoinder and affidavit if necessary to support their averments;

iv. that the Opponent may be granted an opportunity of being heard in the matter before any preliminary or final orders are passed;

v. that the Opponent may be allowed to make further submissions in case the Applicant makes any amendments in the claims;

vi. any other reliefs considering the facts and circumstances may be granted in favour of the Opponent in the interest of justice.

Dated this 28th day of April, 2025

Neha Sahu
Opponent
Through

G. Nataraj
Advocate for Opponent
D/536/1993

To,
The Controller of Patents
The Patent Office, Delhi