BEFORE CONTROLLER OF PATENTS

THE PATENT OFFICE, DELHI

THE PATENTS ACT, 1970 (AS AMENDED)

SECTION 15 & SECTION 25(1)

IN THE MATTER OF AN APPLICATION FOR PATENT, APPLICATION NO: 1430/DELNP/2011

Application Details	
APPLICATION NUMBER	1430/DELNP/2011
APPLICATION TYPE	PCT NATIONAL PHASE APPLICATION
DATE OF FILING	28/02/2011
APPLICANT NAME	**PFIZER INC.**
TITLE OF INVENTION	DIOXA-BICYCLO[3.2.1.]OCTANE-2,3,4-TRIOL DERIVATIVES,DIOXA-BICYCLO(3,2,1)OCTANE-2,3,4-TRIOL DERIVATIVES
PCT INTERNATIONAL APPLICATION NUMBER	PCT/IB2009/053626
PCT INTERNATIONAL FILING DATE	17/08/2009
PRIORITY DATE	28/08/2008
REQUEST FOR EXAMINATION DATE	28/02/2011
PUBLICATION DATE (U/S 11A)	09/12/2011
FIRST EXAMINATION REPORT DATE	27/10/2014
REPLY TO FER DATE	27/04/2015

1. Present application No. 1430/DELNP/2007 entitled "DIOXA-BICYCLO [3.2.1.]OCTANE-2, 3, 4-TRIOL DERIVATIVES,DIOXA-BICYCLO (3,2,1) OCTANE- 2,3,4-TRIOL DERIVATIVES" was filed on 28/02/2011 by the applicant "**PFIZER INC.**".
2. A pre-grant opposition u/s 25(1) was filed by Mr. Antony David on 20/08/2018.
3. The notice of representation by way of pre-grant opposition u/s 25(1) filed by Mr. Antony David on 20/08/2018 had been communicated to the applicant as per rule 55(3) on 07/09/2018.
4. As per Rule 55(4), the applicant had filed his reply statement along with evidences within three months of the said notice, on 06.12.2018 (Reply Statement along with evidence of Dr. David Earl Nichols), on 24.12.2018 (Apostille Affidavit of Dr. David Earl Nichols).
5. The Pre-Grant Opposition, filed with the grounds under Section 25(1)(e), Section 25(1)(f), Section 25(1)(g) enumerated in Section 25 (1) of the Patents Act 1970 and prior art documents are relied upon by the Opponent as follow:
   D1: WO 2008/013280 A1, January 31, 2008
   D1a: US 2011/0275703 A1 (which is an English translation of intl. application WO 2008/013280 A1 - D1), November 10, 2011
   D2: WO 1996/015796 A1, May 30, 1996
   D3: JP 2004/217600 A, August 05, 2004

D4: Miloslav C˘Erny, “Chemistry of Anhydro Sugars”, Advances in carbohydrate chemistry and biochemistry, vol. 58, 2003.

D5: M Bavin, Chemistry & Industry, 21 August 1989, Pages 527 - 529.

D6: ICH Guidelines Q6A - Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (6 October 1999).

D7: G.S. Banker, C.T. Rhodes; Modern Pharmaceutics; Fourth Edition, 2002, Pages 172-174.

D8: S. Byrn et al., Pharmaceutical Research 1995, 12(7), Pages 945- 954.

D9: L. Huang et al., Advanced Drug Delivery Reviews 2004, Volume 56, Issue 3, Pages 321-331.

D10: B C Hancock et al., Title: Molecular mobility of amorphous pharmaceutical solids below their glass transition temperatures. Pharmaceutical Research, June 1995, 12(6), 799 - 806.

D11: Rong Liu., “Water-Insoluble Drug Formulation”, Interpharm Press, Denver, Colorado, 2000, Pages 525, 557-561.

D12: US 6774112 B2. August 10, 2004.

6. As per procedure a pre-grant opposition hearing u/s 25(1) was offered on 19/09/2019 with due intimation to the applicant and opponent vide hearing notice dated 08/08/2019.
7. Applicant had filed a request of adjournment u/r 129A of the Act, on 12/09/2019, which is allowed and hearing was rescheduled on 05/11/2019.
8. Opponent informed to Controller via mail dated 17/09/2019 that “This email is in reference to the Pre-grant Opposition hearing scheduled for the afore-mentioned Patent Application1430/DELNP/2011 on 19th Sep, 2019. We would like to inform you that we will not attend the scheduled hearing”. Further same thing is informed via mail on 21/10/2019.

Decision based on hearing u/s 25 (1), u/r 55 of the Act.

9. Applicant’s agent Ms. Archana Shanker, Mr. Devinder Singh Rawat, Dr. Muthu Venkatesh Sudali attended hearing on 05/11/2019 and held discussion on pending objections contained in hearing letter u/s 14 as well as grounds of opposition u/s 25(1) of the patent act, 1970 (as amended).

10. Grounds of opposition u/s 25(1) and documents as discussed during hearing:
(a). **Obviousness: Section 25(1)(e):**

1. WO2008/013280A1 (WO ‘280),
2. WO1996/015796A1 (WO ‘796),
3. JP2004/217600A (JP ‘600),
4. “Chemistry of Anyhdro Sugars”, Advances in carbohydrate chemistry and biochemistry, Vol. 58, 2003.
5. Chemistry & Industry 1989, 527-529.
6. ICH Guidelines Q6A, 1999.
7. Modern Pharmaceutics, 2002, 172-174.
8. Pharmaceutical Research, 1995, 12(7), 945-954.
9. Advanced Drug Delivery Reviews, 2004, 56(3), 321-331.
10. Pharmaceutical Research, 1995, 12(6), 799-806.
11. Interpharm Press, 2000, 525, 557-561 3-7
12. US6774112B2 (US ‘112).

(b). **Not an Invention: Section 25(1)(f)**
(c). **Insufficiency: Section 25(1)(g)**

11. Applicant's agent submitted written submission to hearing held u/s 25(1), u/s 14 of the Act, on 19/11/2019 (which can be seen in electronic file-wrapper of the present Application). Applicant respectfully and humbly submits hearing submission in order to meet requirement of the Act as objected in hearing letter u/s 14 of the Act and grounds of opposition u/s 25(1) of the Act.

12. **(a). Regarding Ground I: Section 25(1)(e)-** applicant's agent submitted arguments over documents D1-D12 cited by opponent. D1 is same document as cited by opponent as well as by examiner in FER.
Opponent did not appear for hearing u/s 25(1) on dated 05/11/2029, but the documents cited by the opponent in representation by way of pre-grant opposition u/s 25(1) of the Act, are considered during proceeding, the document D1 is found relevant.

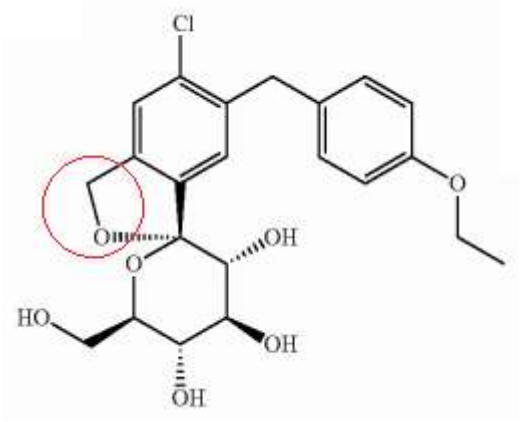
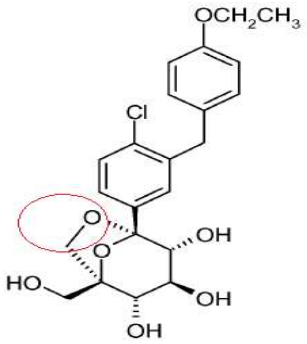
In representation by way of pre-grant opposition u/s 25(1), Opponent submits that the substituted spiroketal derivatives as disclosed in D1 and the ertugliflozin compound as claimed in the impugned application have very close structural similarities and similar utilities. The prior art document D1 therefore applies as the closest prior art. Hence, starting from D1, the technical problem to be solved was to provide an alternative chemical compound having SGLT2 inhibitory activity.

D1 discloses substituted spiroketal derivatives which inhibit sodium-glucose cotransporter 2 (SGLT2) and are thereby useful as preventive or therapeutic agents for diabetes such as insulin-dependent diabetes (Type 1 diabetes), non-insulin-dependent diabetes (Type 2 diabetes), diabetic complications and diseases caused by hyperglycemia such as obesity.

More specifically, D1 in Example-5 discloses a substituted spiroketal compound, which has very close structural similarities with the ertugliflozin compound claimed in the impugned application (see, D1, page 57, Table 1-1, Example-5).

D1 also describes that the compound disclosed in Example-5 is particularly useful as SGLT2 inhibitor for the treatment of type 2 diabetes (see, D1, pages 82-83, Table 2-1, Table 2-2 and Test example-2).

The structure of ertugliflozin compound claimed in claim 1 of the impugned application is compared with the structure of the compound disclosed in Example-5 of D1 in the following table:

Prior art D1 (WO 2008/013280 A1)	**Impugned '1430 application** (Claim 1)
 (Example-5, page 57)	 (4A) Ertugliflozin

It is clear from the above comparative table that the only difference between the compound of D1 and ertugliflozin is that in the compound of D1 the ketal (-O-CH2) on C1 of the sugar ring is appended to the 2-phenyl ring, whereas in the claimed compound, i.e. ertugliflozin, the ketal (-OCH2) on C1 of the sugar ring is appended to C5 of the sugar ring. The above comparison makes it clear that barring this modification, the ertugliflozin compound claimed in the impugned application under opposition is substantially same as the compound disclosed in Example-5 of D1.
Further, the compound disclosed in Example-5 of D1 is known to be a selective inhibitor of SGLT2 and is particularly useful for the treatment of type 2 diabetes. It would therefore have been clearly obvious to a person skilled in the art that similar compounds wherein the ketal (-OCH2) on C1 of the sugar ring is appended to C5 of the sugar ring (i.e., a 6,8-dioxabicyclo[3.2.1]octane structure) would also expectedly possess similar biological activity. It is therefore stated that the ertugliflozin compound as claimed in claim 1 of the impugned application is an obvious modified version of the Example-5 compound of D1.

Moreover, 6,8-dioxabicyclo[3.2.1]octane skeleton was very well known at the priority date of the impugned application and a skilled medicinal chemist would be aware that the spiroketal derivative exemplified in Example-5 of D1 could be modified in order to form a 6,8-dioxabicyclo[3.2.1]octane structure. The fact that 6,8-dioxabicyclo[3.2.1]octane skeleton is frequently used in medicinal chemistry is evident from, for example, documents D2 to D4.

Document D2 teaches that levoglucosan (i.e. 6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol) itself has excellent therapeutic properties (see, D2, page 2,lines 16-19).
Document D3 indicates that compounds with 6,8-dioxabicyclo[3.2.1]octane structure are effective for the treatment of diabetes (see, D3, page 36,compounds Ie-19, Ie-20 and Ie-21).

Document D4 describes the chemistry of anhydro sugars. D4 teaches that levoglucosan (i.e. 6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol) is a valuable starting material for the preparation

of various sugar derivatives, as well as compounds of biological importance (see, D4, page 134, first paragraph).

As is apparent from the above, documents D2 to D4 teach 6,8-dioxabicyclo[3.2.1]octane structure which is the skeleton of the presently claimed ertugliflozin compound. A skilled medicinal chemist is also taught by documents D2 to D4 that the structure of 6,8-dioxabicyclo[3.2.1]octane skeleton influences therapeutic activity and potency of chemical compounds. Hence, starting from D1, a skilled medicinal chemist would obviously turn to documents D2-D4 to find a solution to the problem of providing an alternative compound having SGLT2 inhibitory activity.

Therefore, starting from D1 and combining this with the teaching of any of documents D2 to D4, a skilled medicinal chemist would easily modify the Example-5 compound of D1 (that has already been proved to have SGLT2 inhibitory properties) by appending the ketal (-O-CH2) on C1 of the sugar ring to C5 of the sugar ring in the same way as in claim 1 when trying to form an alternative SGLT2 inhibitor compound with reasonable expectation of success. It is therefore respectfully submitted that the ertugliflozin compound as claimed in claim 1 is obvious to try with reasonable expectation of success and cannot be regarded as inventive in light of the disclosure of D1 combined with one or more of documents D2 to D4.
Further, as outlined before, the compound disclosed in Example-5 of D1 is known as selective inhibitor of SGLT2 and useful as therapeutic agent for the treatment of diabetes, hyperglycemia, diabetic complications and obesity. It would therefore have been clearly obvious to a person skilled in the art that similar compounds wherein the ketal (-O-CH2) on C1 of the sugar ring is appended to C5 of the sugar ring would also expectedly possess similar biological activity.

Therefore all the applicant has done in this case is appended the ketal (-O-CH2) on C1 of the sugar ring to C5 of the sugar ring to form the bridged ketal structure of compound of the impugned application in line with the impetus provided by the teachings of documents D1 to D4 and verified the results. Such verification of results cannot be considered as inventive. The Opponent further submits that obviousness cannot be avoided simply by showing of some degree of unpredictability in the art as long as there was a reasonable probability of success.
Thus, the ertugliflozin compound as claimed in claim 1 of the impugned application is obvious with respect to the disclosure and teachings of D1 combined with any of documents D2-D4.

Applicant's submission:

Applicant's agent submitted written submission on 19/11/2029 and presented arguments with reasoning and comparison of compound of formula 4 as claimed in present application with Example 5 of D1 (cited by opponent and examiner).
Applicant's agent submits "D2 is a non-analogous art, as it relates to medical conditions associated with micro-organisms such as virus and bacteria and that can be used for treatment of inflammatory conditions. The Opponent has simply identified Levoglucosan. It is submitted that the moiety in Ertuglifozin is not Levoglucosan. There is not even a single

document including document D2 that has an identical sugar moiety of Ertugliflozin and in this regard reference is made to paras above.
Document D3 is an irrelevant prior art that relates to novel compounds as inhibitors of nitrogen monoxide synthetase (iNOS), particularly the inducible NOS selectively inhibitory activity of formula (I).
Document D4 is also an irrelevant prior art as it relates to the synthesis of various anhydro sugars and the complex chemistry involved with it. It discuss about the anhydro sugars involving the anomeric carbon atom and also without anomeric carbon atom also with dianhydroaldoses and ketoses. Moreover, it also discusses about the rearrangement of these anhydro sugars.
Documents D5 to D12 have been relied upon by the Opponent to show that the crystals/polymorph/ L-proline of compound of formula Iva are well known in the art.
It is respectfully submitted that if the molecule is novel, it's co-crystals L-proline complex are also novel and inventive.
Therefore citing general state of art does not render the invention as lacking in inventive step. In view of the above submissions, we submit that the ground of lack of inventive step be dismissed".

The arguments of applicant's agent as submitted over documents D1-D12 cited by the opponent, are found persuasive.
Therefore the opponents objection u/s 25(1)(e) for obviousness over document D1-D12 is found not valid in view of arguments submitted in oral hearing as well as submitted in written submission dated 19/11/2019.

(b). **Regarding Ground II: Section 25(1)(f)-**
In representation by way of pre-grant opposition u/s 25(1), Opponent submits that "Claim 1 is directed to a compound with 6,8-dioxabicyclo[3.2.1]octane structure, useful as sodium-glucose transporter inhibitor, in particular SGLT2 inhibitor. As shown above in the comparative table, the only difference between the impugned structure of claim 1 and the compound of D1 is that in the compound of D1 the ketal (-O-CH2) on C1 of the sugar ring is appended to the 2-phenyl ring, whereas in the claimed compound, i.e. ertugliflozin, the ketal (-OCH2) on C1 of the sugar ring is appended to C5 of the sugar ring. Further, the compound of D1 is used in the treatment of diseases and disorders mediated by SGLT2 inhibitors, which is also the function of compound of claim 1 of the impugned application. Considering the very close structural similarities and similar utilities, it will only be fair to mention that the impugned structure of claim 1 is an alternative compound which is only a "derivative of known compound" and used for the inhibition of SGLT2 with no enhanced efficacy.

The Opponent states "that the ertugliflozin compound of claim 1 can be considered as patentable u/s 3(d) only if an enhancement of known efficacy is demonstrated by the Applicant.
The Applicant in its „1430 application has mentioned that the problem solved by his invention is to provide compounds that are useful as SGLT2 inhibitors and therefore useful in the treatment of diseases related to obesity, Type 2 diabetes, and obesity-related and diabetes-related comorbidities. However, the specification of the '1430 application lacks any

data/information demonstrating that the claimed ertugliflozin compound results in enhanced therapeutic efficacy over the efficacy achieved by previously known SGLT2 inhibitors, particularly the compound disclosed in Example-5 of D1".

Applicant's agent submitted reply submission and evidences as well as presented arguments during hearing and filed written submission on dated 19/11/2019 (not produced here for sake of brevity).

The patent specification provides the following:
i. Ertugliflozin is represented in the patent specification as "Example 4(A)" on page 4 of the specification and is prepared according to the process as that of "Example-4, Page 64-65" along with its isomer (Example 4(B)).
ii. The patent specification of IN '1430 contains extensive information with regard to the crystal structure, pharmaceutical composition and biological activity of Ertugliflozin, claimed in the invention.
iii. The patent specification of IN '1430 also contains process for cocrystallization of the claimed compound, Ertugliflozin (example 4(A)) with Lproline or L-pyroglutamic acid (Example 15-26, Page 86-110). Further, the biological activity of the co-crystallized compounds is disclosed.
iv. The IC50 value of Ertugliflozin i.e., example 4(A) is provided in (Table 3, Page 112-115 of the patent specification). An extensive in-vivo and pharmacokinetic studies of Ertugliflozin is provided at Tables 4 and 5, (Page 115-118 of the patent specification).

Applicant refers page 111 of the patent specification that clearly indicates that the selectivity of the compound of Formula 4a for SGLT2 is 1983.64 times more than SGLT1. This has been calculated on the following basis:

4A	1	1590	1.27
	2	1010	0.816
	3	1750	0.57
	4	>1000	0.922
	5	>1000	1.85
	6	2090	0.812
	7	1810	0.7
	8	2860	0.737
	9	2480	0.846
	10	2840	0.768

The average of 10 experiments:
IC_{50} (nM) value of SGLT1 is 1843
IC_{50} (nM) value of SGLT2 is 0.9291
Selectivity for SGLT2 = 1843/0.93 = 1983.64

Applicant's agent submits "Applicant clearly demonstrated that the compounds of the present invention have a better biological activity than the compounds of Example 5 of D1 and in this regard, refer to the activity of Example 5 given on page 39 of D1, Table 2-2.

TABLE 2-2

Test compound	hhSGLT2 IC_{50} value (nM)	hSGLT1 IC_{50} value (nM)	hSGLT2 selectivity
Comparative Compound 1	1.6	132	83
Example 1	1.3	201	155
Example 5	1.5	425	283
Example 7	1.7	381	224
Example 8	1.1	355	323
Example 9	2.3	1358	590
Example 15	1.7	1013	596
Example 21	2.0	682	341

The average of IC50 nM value for SGLT1 is 425; SGLT2 is 1.5 Therefore, the selectivity for SGLT2 = 425/1.5 = 283.

From the said Table it is clear that the selectivity of Example 5 for SGLT2 is only 283 fold whereas that of the present application is approximately 1983 fold. In view of the above, reconsideration of the objection is requested".

The arguments as submitted by the applicant are found persuasive in view of comparative data as presented in written submission dated 19/11/2019 and also in view of detailed reply submission and evidences submitted by the applicant on 06.12.2018 (Reply Statement along with evidence of Dr. David Earl Nichols), on 24.12.2018 (Apostille Affidavit of Dr. David Earl Nichols).
Therefore the objection u/s 25(1)(f) of the Act is rejected.

(c). Regarding Ground III: Section 25(1)(g)- Applicant's agent submits "With regard to objections relating to insufficiency, the Applicant has clearly demonstrated that a POSA based on the information provided in the specification and common general knowledge will easily be able to make the molecule of the present invention in accordance with Section 10(4) of the Indian Patents Act. In fact, Example 4 at page 64 provides method for preparation of compound of Formula 4A and at page 111 provides the biological activity of Ertugliflozin (Example 4A)".

The said ground of opposition is found invalid in view of disclosure in complete specification, discussion held during hearing and arguments as presented in reply submission.

13. The Pre-Grant Opposition, filed with the grounds under Section 25(1)(e), Section 25(1)(f), Section 25(1)(g) enumerated in Section 25 (1) of the Patents Act 1970 are relied upon by the Opponent, are dismissed after considering the hearing submission (oral as well as written) filed by the applicant on 19/11/2019 and also in view of detailed reply submission and evidences submitted by the applicant on 06.12.2018.

Decision u/s 15 based on hearing u/s 14.

14. The present application relates to dioxa-bicyclo[3.2.1]octane-2,3,4-triol compounds and their crystal structures as SGLT2 inhibitors.
15. Applicant's agent filed reply to FER on 27/04/2015 with amended claim 1-7 and other documents. Said amended claims were taken on records and further objections raised on the pending claim 1-7 filed dated 27/04/2015. Applicant is offered hearing in view of pending objections and Hearing notice u/s 14 containing statement of objections which had been discussed during hearing and complied consequently are as follows:

Objections

Invention u/s 2(1)(j)

1. Abstract of the subject matter should contain a concise summary of the matter contained in the specification as per requirements of Rule 13(7)(b) The Indian Patent rules, 2003

2. Subject matter of claims fall u/s section 3 of the Patents Act,1970 and are not inventions under the said section/Clause: Claims fall within the scope of such clause (d)of section 3 of Patents Act, 1970-the invention appears to lie in the selection of the groups of "R1,R2" which is already known in the prior art as shown above.Further, the present compounds do not differ significantly in properties with regard to efficacy with respect to the known compounds.Thus in the absence of the same it thus appears to be new use of known substance.

3. Subject matter of the claims does not constitute an invention under section 2[1(j)] of the Patents Act,1970 because it lacks inventive step in view of prior art citation nos D1. WO 2008/013280 A (CHUGAI PHARMACEUTICAL COL TD [JP]; SATO TSUTOMU [JP]; HONDA KIYOFUMI-[) 31 January 2008 (2008-01-31)

D2.TAKASH"I YAMANOI ET AL: "Trifluoromethanesulfonic Acid Efficiently Catalyzed the Intramolecular Glycosidation of 1-C-Aikyl-0-hexopyranoses to Form the Anhydroketopyranoses Having 6,8- Dioxabicyclo[3.2.1]octane Structures" SYNLETT, no. 19, 2005, pages 2973-2977,

The compound claimed in the claim 1 is well known product which commercial name 'is Ertugliflozin'. The invention as disclosed in claims 1-8 does not involve an inventive step over above cited documents.

Industrial Applicability The invention defined in the claims is considered to meet the requirements of Industrial Applicability. because it can be made by, or used in, industry.

16. An official hearing under Section 14 was appointed by the Ld. Controller on April 03, 2017. The said hearing was adjourned at the request of the Applicant's agent. In the meantime, the Applicant's agent filed a response to the hearing notice in the form of "Advance Hearing Submissions" on May 15, 2017.

17. Further hearing u/s 14 is offered to the applicant on 05/11/2019. Applicant's agent appeared for hearing on scheduled day and time.

18. With respect to objections as communicated in hearing notice u/s 14 of the Act, applicant's agent submitted written submission and amended claims 1-7 on 19/11/2019.

19. In view of arguments as presented in oral hearing as well as written submission submitted in advance dated 15/05/2017 (not produced here for sake of brevity) and hearing submission on 19/11/2019, the pending objections u/s 2(1)(ja), u/s 3(d) and rule 13(7) of the Act, are considered met.

Hence the written submission filed dated 15/05/2017 and 19/11/2019 with respect to objections contained in hearing letter are found to be correct and complied with all the objections raised. Based on the above facts, submissions, claim 1-7, observations and discussion in the case, all the objections raised in the hearing notice are met. There was a pre-grant opposition filed which has been disposed off.

Therefore I hereby proceed with grant of patent for the instant patent application No. 1430/DELNP/2011 with Seven (7) claims filed dated 19/11/2019.

Dated this 06th day of February, 2020

(Dr. Suman Verma)
Asst. Controller of Patents & Designs