THE PATENT ACT 1970

AS AMENDED BY THE PATENTS (AMENDMENT) ACT, 2005

SECTION 25(1)

In the matter of application for Patent No.**6000/DELNP/2007**

and

In the matter of an opposition thereon to the

grant of a patent thereon.

TAISHO PHARMACEUTICAL CO.LTD. Applicant

Vs

1.ROHAN CHOPRA

2.BHAWANA JOSHI Opponents

3.TAPAN SHAH

4.RITU SHARMA

VIDEO CONFERENCE HEARING HELD ON 27.11.2019 BEFORE

Dr. BINDHU JACOB, ASST. CONTROLLER OF PATENTS & DESIGNS

Opponent 1 :	Represented by : 1.Mr. Deepak Srinivas & 2.Ms. Pragya Thakur)
Opponents 2-4 :	Not represented
Applicant :	Represented by : 1.Ms. Archana Shanker; 2.Mr. Devinder Singh Rawat & 3. Dr. Sachin Malik

Examiner : Mr.Veera Raghavalu Kattula

DECISION

1. BRIEF HISTORY OF THE CASE

(i) An Application for Patent was filed on 01-08-2007 by Taisho Pharmaceutical co., Ltd.(herein referred to as the "Applicant") for their invention " 1-THIO-D-GLUCITOL DERIVATIVES" . As per the provision under Section 11A of Patents Act, the said application was published on 17/08/2007. A request for examination under Section 11-B was filed on 06/01/2009. The application was examined under Section 12 and 13 of Patents Act and First Examination Report was forwarded on 03/08/2017 and the applicant's agent filed response on 02/02/2018.

2. PREGRANT OPPOSITION DETAILS

OPPONENTS	1. Rohan Chopra	2.Bhawana Joshi	3.Tapan Shah	4.Ritu Sharma
Opposition filed	04-Jul-2017	19-Feb-2018	25-Aug-2018	24-Jul-2019
Reply statement	01-Nov-2017	01-Nov-2018	06-Mar-2019	13-Sep-2019

(ii)Pre-grant hearing has been fixed which got adjourned twice on request from the parties. Later the hearing was fixed on 27/11/2019 and the Applicant has attended the scheduled hearing, while from the Opponent side, only Rohan Chopra (represented by Mr. Deepak Srinivas & Ms. Pragya Thakur have attended the hearing.

3. GROUNDS OF OPPOSITION (Combined from all the opponents)

(a) Section 25(1)(e): Lack of inventive step

(b) Section 25(1)(f): Invention is not patentable under section 3(d)

(c) Section 25(1)(g): The complete specification does not sufficiently and clearly describe the invention.

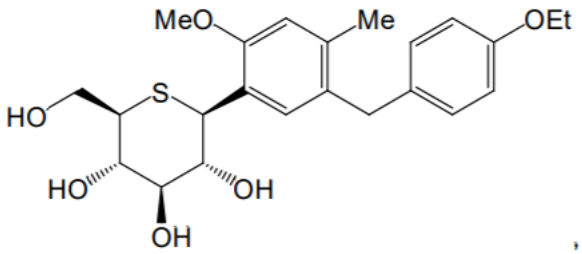
(d) Section 25(1)(h): The Applicant has failed to disclose to the Controller the information required under Section 8.

4. BACKGROUND OF THE INVENTION

The amended claims of present invention are directed to the compound ((1S)-1,5-anhydro-1-[3-(4-ethoxybenzyl)-6-methoxy-4-methylphenyl]-1-thio-D-glucitol), i.e., **Luseogliflozin** , which is supposedly SGLT2 inhibitor, (which is identified in the patent specification as "Compound 89" on page 191 of the specification).

PENDING CLAIM

1. The 1-thio-D-glucitol compound represented by the following formula:



or the pharmaceutically acceptable salt thereof, or a hydrate of the compound or the salt.

GROUNDS OF OPPOSITION-DISCUSSION

(a) Section 25(1)(e): Lack of inventive step

DOCUMENTS RELIED UPON BY THE OPPONENTS:

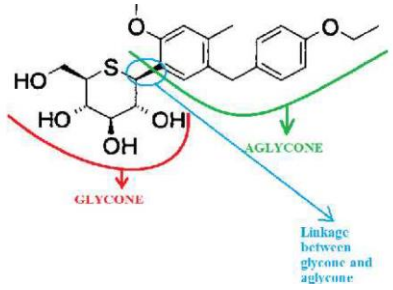
1. WO 2004014931
2. US 6414126
3. Link and Sorensen
4. US 6515117
5. WO 2004080990
6. Yao et al
7. Kajimoto et al
8. Hirayama et al.
9. WO 2004063209

OPPONENT'S ARGUMENTS

Explanation on Citations: (The detailed explanations and comparison over the impugned patent claim over the cited documents are not recited herein for the sake of brevity).

Comparison with WO 2004014931

The counsel for the opponents argued that WO'931 segments the structure of the molecule into the following three parts. WO'931 discloses SGLT2 inhibitors with following Markush wherein stress has been laid on replacement of O glucose glycone ring with thioglucose which is attached to aryl aglycone part via a linkage.



The SGLT2 inhibitor molecules of impugned application are prepared by joining aglycone and glycone by a linkage - *Scheme 1, page 58; Scheme 2, page 60; Scheme 3, page 61*

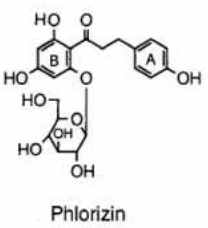
Also, the process of preparation disclosed in prior art US'126 and WO'209 also discloses that SGLT2 inhibitor molecules are prepared by joining aglycone and glycone by a linkage. Apart from the above, all SGLT inhibitor compounds upon oral administration, are prone to hydrolysis in gut by glycoside enzyme into glycone moiety and aglycone moiety.

Also, it has been shown that since the basic compound has two or more discrete structures which are to be linked, the research in SGLT2 inhibitors also progressed in the same manner i.e. directed towards the **following three modifications**:

(a)Modifications of the aglycone moiety;

perusal of the work done in the field reveals that:

(i) Phlorizin has a hydroxyl group at the same place on the second phenyl ring i.e. on A ring and has two hydroxyl groups at the same places on the first phenyl ring i.e. on B ring as the claimed compound of impugned application, Luseogliflozin.

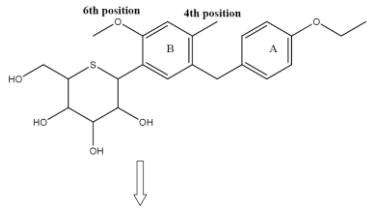


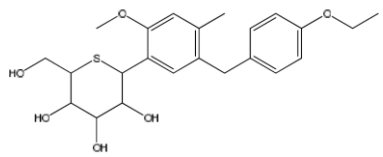
Phlorizin

WO02/064606 recommends one substitution (at the same place) on the A ring and has two substitutions (at the same places) on the B ring. Modifications in the SGLT inhibitor molecules done over the last two decades in relation to the substitutions on the aglycone moiety, it can be observed that the hydroxyl group present on the A ring is exchangeable and if exchanged with "OMe" gives drastically better results (Tsujihara et al., 1996).

Even though Tsujihara et al., 1996 did not state anything about the hydroxyl group present at the ortho position in B ring, US'117 as well as WO'209 furthermore replaced the hydroxyl group present at the ortho position in B ring. Thus, it can be seen from the prior arts it had become customary practice to replace all the three hydroxyl group present in the aglycone moiety.

They further submitted that continuing with the teaching of Tsujihara, WO02/064606 also teaches methyl or methoxy as substituents at 6th position of B ring. Thus, in light of teachings of prior art, the combination of methoxy (at 6th position of B ring) and methyl (at 4th position of B ring) in the compound of impugned application is obvious:





LUSEOGLIFLOZIN

(b) Modifications of the glycone moiety

- research that took place in relation to glycone moiety is disclosed in WO'931; Yao et al.; and Kajimoto et al. All these documents clearly indicate replacement of "O" of glycone moiety with "S".
- Kajimoto and Yao teach replacement of O-glucose with S glucose (i.e. thioglucose). Both the documents disclose that the thioglucose is stronger inhibitor of glycosidase enzyme compared to O glucose. Kajimoto et al discloses thioglucose molecule as compound 25 in Chart 1and its inhibitory effect on glucosidase is given Table 1 on page 149: Yao et al discloses in Table 2, page 140 that thioglucose is more potent inhibitor of glycosidase enzyme than O-glucose.

➢ The opponent reiterated that the crux of WO'931 is that a glycone moiety having a "S" instead of "O" linked to any aglycone moiety via any position (whether 1or 2) would give good results i.e. will be a good SGLT2 inhibitor. Therefore, it would be obvious and natural for a person skilled in the art to replace "a O-substituted glycone moiety" with "a S-substituted glycone moiety", as in US'126.

(c) **Modifications of the linkage between the aglycone and glycone moiety.**

The opponent argued that it was common general knowledge in art that C-glycosidic linkage is more stable than Oglycosidic linkage. Link and Sorenson, 2000 states that;

"*we became interested in designing phlorizin(1) analogs in which the glycosidic bond was replaced by a more stable connection. One classic method for achieving this goal is to construct a related C-glycoside*". Further, WO'931 discloses in fifth para on page 57 that: ….*synthesize a compound having a glycosidic bond converted to carbon to prevent decomposition.*

Comparison with US '126

They further stated that US'126 discloses a direct bond (or C-glycosidic bond) between glycone and aglycone moieties and the position of the bond is at 1st position ("meta" to the aglycone link) and **NOT** at 2nd position ("ortho" to the aglycone link).

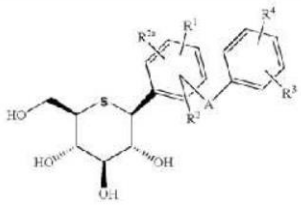
As per US'126, the aglycone moiety is characterized by two aryl rings linked by a methyl bond, wherein both the aryl groups can be substituted. In particular,

- the first aryl ring may (at max) be substituted at three positions (that are available), and
- the second ring can have a maximum of two substitutions.

Hence, a person skilled in the art learns that compounds in which glycone and aglycone moieties are joined by a C-glycosidic linkage are more stable to enzymatic hydrolysis than compounds in which glycone and aglycone moieties are joined by an O-glycosidic linkage.

WO '931 and US'126

In view of the above teachings, it is obvious for a person skilled in the art to combine the teachings of US'126 and that of '931, as depicted below:

Compound as per the combined teaching of US'126 and WO'931


Expert Affidavits submitted by Applicant

The Opponent opined the following with respect to the affidavits submitted by the Applicant: They argued that the following compounds have been disclosed by the given affidavits,

Koji Yamamoto -Compound 74

Dr. Hideya Yuasa-Compound 75

Fusayo IO -Compound 75

Dr.Hiroyuki Kakinuma-Compound-76

- None of the affidavits given by the Applicant pertain to the claimed compound Luseogliflozin (**Compound 89**) and are therefore, of no relevance to present opposition.

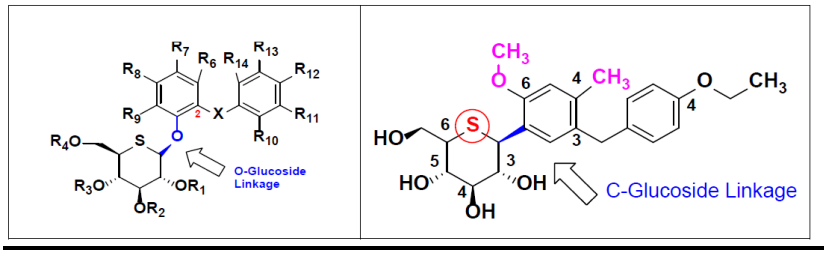
Dapagliflozin and Luseogliflozin: US'117

The applicant has submitted data for pharmacokinetic parameters of Dapagliflozin and Luseogliflozin. In continuation of their arguments the agent for the opponent argued that the opponent has never asserted that Dapagliflozin (glycone ring is O-glucose) is the closest structurally similar compound to Luseogliflozin and therefore, any comparison between Dapagliflozin and Luseogliflozin by applicant is arbitrary and misleading. Further, it is submitted that market acceptance of the claimed compound is not an indicator of inventive merit in the claimed compound.

APPLICANT'S RESPONSE ON INVENTIVE STEP

The Applicant made the following statements with respect to Inventive step arguments.

EXPLANATION OVER WO '931 : relates to 5 thio-O-glucoside compounds that are structurally different from the compounds disclosed in instant invention.



Further, the phenyl ring that is attached with O-Glucoside group in WO '931 is further substituted at 2-position to another phenyl group via linker 'X'. In contrast, the compounds of the present invention, the phenyl ring which is attached to the C-thio glucoside is further substituted to another phenyl group at 3-position. WO '931 discloses various compound by way of Markush structure and specifically exemplified 92 compounds. All the exemplified compounds are O-gluciside except compound 35 that is N-glucoside linkage. The biological data is provided in Table 2 indicating that the two best active compounds, (Compound 9 having IC50 value of 0.16µM and Compound 1 having IC 50 value of 0.20 µM).

Structural features of WO'931 compound:

1. They are thio O-glucoside compounds.

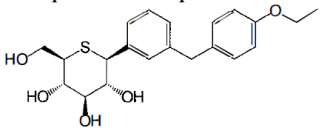
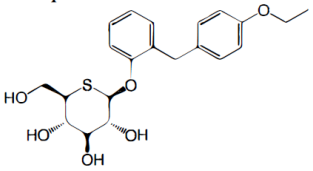
2. The exemplified compounds of WO '931 does not contains both "6-methoxy" and "4-methyl" group as the substituent on the phenyl ring that is attached to the thio-O-glucoside group.
3. The second phenyl ring is attached at 2- position on the phenyl ring that is attached to the thio-O-glucoside group and not at the 3-position as in Luseogliflozin.

The Applicant stated that the Opponent has ignored the actual teachings of WO '931 and instead created a hypothetical compound having seen the compound Luseogliflozin (by hindsight) . However, a person skilled in the art would look for the best active compound(s) for further investigation. Thus there is no reason for a person skilled in the art to consider a hypothetical compound instead of the compound 9 or compound 1 that possess good biological activity, i.e., IC50 value of 0.16μM and 0.16μM, respectively.

EVIDENCE RELIED BY THE APPLICANT

The details of the evidence provided by the Applicant are reproduced below:

No	Evidence	details
1	**Dr. Koji Yamamoto** **(**To demonstrate the difference in SGLT2 inhibition activity of C- aryl-thioglucoside (IN '6000) and aryl C-glucoside (USP 6,414,126)).	1) Compared example 1E of US '126 with compound 74 of the present invention Example IE of USP 6,414,126 2) The difference in structure between the invention of the subject application **compound 74** and compound Example IE (USP 6,414,126) is that the former is an aryl C-thioglucoside whereas the latter is an aryl C-glucoside. 3) Compound 1E has 57% inhibition at a concentration of 10 μM, i.e., IC50 of 10 μM. 4) Compound 74 of the present invention has high SGLT2 inhibitory activity (IC50 1.190 μM) as shown in Table 3 of the specification of the subject application. Referring to the above affidavit: 1) With regard to US '126, demonstrates that it is unpredictable from the nature of thiosugar to show the SGLT2 inhibition activity. 2) Additionally, with regard to US '126 the expert shows that the compounds of the present invention have remarkably better Physiochemical properties over US '126 due to the replacement of ring oxygen atom with sulphur atom.

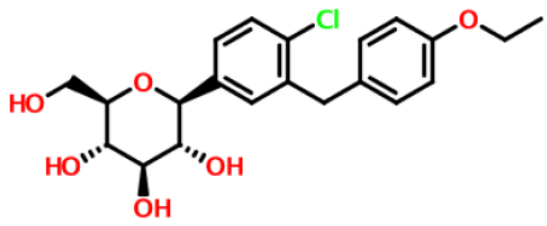
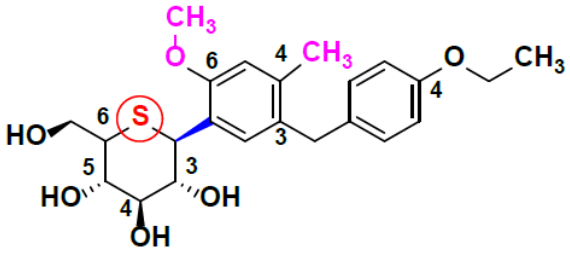
		3) Therefore aryl-C-thioglucoside compounds are better than aryl C-glucoside disclosed in US '126 and have unexpectedly higher crystanillity and unexpectedly high SGLT2 inhibitory activity.
2	**Ms. Fusayo IO(I) [Taisho]** (Studies the hyoglycemic effect on streptozocin induced diabetic rats).	Compound of the present invention (Compound 75)  Compound of WO2004/014931 (Compound 5)  Compound 75 of the IN '6000 application, -C- glucoside bond Compound 5 of WO 2004/014931:-O- glucoside bond **Conclusion:** WO '931: The expert refers to the affidavit of Ms. Fusayo IO(I) wherein compound 75 of present invention was compared to compound 5 of WO '931 to show the difference in activity between C-thioglucoside (compound 75) versus O-thioglucoside (Compound 5) of WO '931. This results shows that the O-glucoside bond plays an essential role in the biosynthesis and metabolism of oligosaccharides.
3	**Ms. Fusayo IO (III)** (Comparison of C-thioglucoside (Luseogliflozin) Versus O-thioglucoside (analog of Luseogliflozin) – Hypoglycemic effect test:)	Studies conducted to determine the hypoglycemic effect of C-thioglucoside. The O-glucoside of Luseogliflozin (compound 9) is not a prior art compound and the experiments were carried out only to demonstrate that even for Luseogliflozin (Cglucoside), the hypoglycemic effects are not the same as their O-glucoside analog. Therefore it is difficult to predict that O-glucoside of a different compound which is not a luseogliflozin would have same results.
4	**Dr. Hiroyuki Kakinuma**	1) The data shows compounds are highly crystalline. 2) As shown in the comparative data in [O 106] and [O 107] of the specification of the subject application, the aryl C-glucoside compound B (Z=O) is glassy and has low

	(studied melting point of C-thioglucosides to support superior physiochemical properties over US 64144126).	crystallinity. Compound B is regarded as a glassy substance, i.e. amorphous from the disclosure of [0189] of US2002/0137903. On the other hand, compound 76 (Z=S) of the present invention which is the aryl C-thioglucoside is colorless powdery crystal having a melting point of79.0 to 83.0°C. 3) The aryl C-glucoside compounds disclosed in USP 6,414,126 are mostly amorphous substances, which need to be crystallized with suitable amino acids, such as phenylalanine and proline, during pharmaceutical manufacturing. However, the compounds of the present having glucose converted into thioglucose are highly crystalline and need not be co-crystallized with amino acids. 4) Melting points of compound 76 and other compounds were determined on a Yanaco MP-500D melting point apparatus and the obtained data are reproduced unaltered in the following table. (table given), shows compounds are highly crystalline **Conclusion:** Also refers to crystallinity of Dr. Hiroyuki Kakinuma. Compound 75 of the present invention showed a significantly stronger blood lowering effect than compound 5 disclosed in WO2004/01493 l. This result suggests that the C-thioglucoside derivative of the invention of the subject application is metabolically more stable in vivo and expected to show a stronger pharmacological action than the O-thioglucoside disclosed in WO2004/014931.
5	**Dr. Hideya Yuasa**	Hideya Yuasa explained that the C-thioglucoside of the present invention is very significant in terms of both chemical and biological properties over the prior art glucoside and Othioglucoside. US '126 does not disclose C-thio-glucoside compounds. The compound of US '126 contains "glucoside" moiety in contrast, Luseogliflozin contains the "thio-glucoside" moiety. None of the exemplified compound of US '126 contain the phenylene moiety that has substituents '**6-methoxy-4 methyl-3 (4-ethoxy benzyl)**'. US '126 contain various substituents on phenyl and benzyl ring. However, in the absence of biological data a person skilled in the art would not have any direction to select a particular compound as a starting point. ➢ Explains that C-thioglucoside of present invention is critical for both chemical and biological

		properties over prior art glucoside and O-thioglucoside.

EXPLANATION OVER 'US'117

The Applicant argued that **US '117 does not disclose C-thio-glucoside compounds and it** discloses the compound Dapagliflozin having the structure below:

Dapagliflozin	Luseogliflozin
	

The Applicant stated that the compounds Dapagliflozin is structurally different from Luseogliflozin in the following respects: a) Thio glucoside ring vs. glucoside ring b) The phenyl ring in Dapagliflozin contains chloro substituent at 4-position in contrast Luseogliflozin contains substituents at 4- and 6-position as "methyl" and "methoxy" respectively. c) No biological activity

Therefore, in order to arrive at the compound Luseogliflozin starting from the compound Dapagliflozin, a person skilled in the art has to make the several modifications:

a) Firstly, one has to change the glucose ring to thio-glucose ring;

b) Secondly one has to replace the electron withdrawing group, Cl, at 4-position with the non-polar 'methyl' group in the phenyl ring, which is directly attached to the thio-glucose ring;

c) Thirdly, one has to put the 'methoxy group' at 6-position of the phenyl ring which is directly attached to the thio-glucose ring.

Data has been provided on the comparison Between Dapagliflozin And Luseogliflozin for their Effect On Urinary Glucose Excretion, which shows, **Luseogliflozin has:**

a) Slower metabolic rate; b) Higher plasma concentration; c) Superior to Dapagliflozin in pharmacokinetic term (AUC & Clearance); and d) Greater therapeutic efficacy in small amount.

EXPLANATION OVER WO'990

The Applicant submitted the following:

a) WO ‘990 discloses C-aryl glucoside compounds that contain the glucoside ring and not the ‘thio glucoside’ ring as disclosed in the present invention.

b) The ring ‘B’ in the compounds of WO’990 is a fused bicyclic, (heterocyclic) ring.

c) None of the 188 exemplified compound of WO ‘990 (Table 7 to 39) contains ‘4-ethoxy benzyl’ group attached to the phenyl ring (ring A).

d) None of the exemplified compound of WO ‘990 contains the ‘6-methoxy’ and ‘4-methyl’ substituents attached on the phenyl ring, i.e., ring ‘A’.

- WO ‘990 discloses C-aryl glucoside compounds that contain the glucoside ring and not the ‘thio glucoside’ ring. There are 188 exemplified compounds disclosed in WO ‘990. Further, the biological activity in term of IC50 value has been reported in Table 4 for six compounds (117, 134, 141, 142, 150 and 174). The example 141 is the most active compound having IC50 value of 3.8nM. As it can be seen the compounds having biological data contains hetero-bicyclic (fused heterocyclic) ring substituted 3- position of phenyl ring. Example 150 contains the ‘4-ethyl benzyl’ ring, however, in this case the ring ‘A’ is pyrazine (heterocyclic) ring and not the phenyl ring. Further, the exemplified compounds as disclosed in Table 7 to 39, majority of them contains the hetero-bicyclic (fused heterocyclic) ring substituted 3- position of phenyl ring.

EXPLANATION OVER ‘967

WO ‘967, relates to heteroaryl 5-thio-beta-d-glucopyranoside derivatives: compounds 3 and 20, contain the following features:

a) Thio-glucose ring is attached via oxygen linker to the heterocyclic ring;

b) Compound 3 and compound 20 contain a pyridine ring and a pyrazolo ring, respectively;

c) The methyl group on the phenyl ring is attached at the position adjacent to the oxygen linkage attached to thio-glucose;

d) The phenyl ring is substituted with ‘4-ethyl’ in compound 3 and with ‘3-fluoro and 4-methyl’ in compound 20. Whereas,

Luseogliflozin is a “1-Thio-C-Glucoside” compound with the following specific features.

a) “thiol-glucosyl” ring;

b) C-Glucosidic bond to attach “phenylene ring” with ‘thio-glucosyl” moiety; and

c) Phenylene ring is substituted with “6-methoxy-4-methyl-3-(4-ethoxybenzyl)” group.

- There is no teaching / suggestion or motivation in WO '967 for a person skilled in the art to modify compounds 3 / 20 in such a manner as to arrive at Luseogliflozin.
- WO '967, is irrelevant for an inventive step analysis of the present invention because the basic core moiety in the compound of present invention is different. The compound of the present invention contains the 'thio-C-glucoside' ring directly attached to the 'phenyl' ring. In contrast, in the compound of '967, the 'thio-glucoside' ring is attached to the'heterocyclic' ring via 'oxy' linkage.

Response on Link et al.,

The Applicant stated that Link et al., does not disclose SGLT-2 inhibitors instead is directed to α-glycosidase inhibitors. Link et.al, is in relation to preparing C-glucoside analogues of 'Phlorizin", which is a β aryl glucoside compound and has been demonstrated to lower blood glucose level. However, Phlorizin as it is inactivated via conversion to 'Phloretin" by β-glycosidase in the intestine. The analogues of Phloretin has been created (TI095A and T1095) that inhibit renal SGLT.

Link et. al. design phlorizin analogs in which the glucosidic bond was replaced by a more stable connection, such as related C-glucoside. Such derivatives would be stable to glycosidases while maintaining a similar structure to phlorizin (1). However, in vitro examination of C-glucosides 18 and 23 in several assays indicated these compounds were much weaker inhibitors of SGLT than phlorizin (1), indicating the importance of the glucosidic **oxygen** in this family of SGLT inhibitors.

- Thus, the teaching of Link et al., would lead a person skilled in the art to prepare 'O-glucoside' compounds and not "C-glucoside or C-thioglucoside' compounds.

Yao et al and Kajimoto et al (discloses Glucosidase inhibitor (alpha glucosidase inhibitors)

Alpha-glucosidase inhibitors are saccharides that act as competitive inhibitors of enzymes needed to digest carbohydrates: specifically, alpha-glucosidase enzymes in the brush border of the small intestines. The membrane-bound intestinal alpha-glucosidases hydrolyze oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the small intestine.

Yao et al., is in relation to inhibition of α-glucosidase activity by D-glucose analog. The activity thus represented in the cited reference is in relation to inhibition of α glucosidase and not with respect to SGL2 inhibition.

- A person skilled in the art who is inclined to develop new SGLT2 inhibitor would not consider the teaching of Yao et al, as being a non-analogous art. The activity of a compound

disclosed in Yao et al., has no relevance to SGLT2 inhibition. Further, even if one look for this article would be directed to "1-Deoxynojirimycin"

Hirayama et al., British J Pharmacology, 2001, 134, 484 – 495)

Hirayama et. al. discloses an electrophysiological method to investigate the interaction of inhibitors with the human Na+ /glucose (hSGLT1) and Na+ /Cl-/GABA (hGAT1) cotransporters and have correlated the structure of the inhibitors resulted in a pharmacophore for glycoside binding to hSGLTI: the aglycone is coplanar with the pyranose ring, and binds to a hydrophobic/ aromatic surface. However, there is no empirical study with regard to designing novel hSGLT inhibitors. A person skilled in the art would not be able to design novel SGLT2 inhibitor purely on the basis of the biophysical characteristics of co-transporters.

Direction of the teaching in the cited prior art documents

The Applicant contended that the directions of the teaching of the cited prior art, WO '931, US '126, US '117, Link et. al and WO '990 is totally opposite to what has been alleged by the Opponent. In this regard the Applicant provided the timeline at which these cited prior art come into public domain to describe the direction of teaching.

Sl.no.	Document name	Publication date	Priority date	Type of linkage preferred
1	WO'931	19/02/2004	09/08/2002	a. O-Glucoside b. S-Thioglucoside ring
2	US'126	02/07/2002	12/10/1999	a. C-Glucoside b. O-Glucoside ring
3	Link et.al.	2000		O-Glucoside bond
4	US'117	04/02/2003	12/10/1999	a. C-Glucoside b. O-Glucoside ring
5	WO'990	23/09/2004	14/03/2003	a. C-Glucoside b. O-Glucoside ring

As can be seen from the above timeline, the teaching of the documents is in relation to "C-glucoside" bond and retaining "O-glucoside ring". Thus, the contention of the Opponent is totally flawed, as a person skilled in the art from Link et al., would be inclined to retain the "O-Glucoside" bond and not to change it to "C-Glucoside" bond.

Based on the above explanations, the Applicant summarizes their arguments on obviousness as follows:

1. The Opponent has miserably failed to establish the ground for the lack of inventive step for the compound Luseogliflozin. The inventive step allegation of the Opponent starts and finishes by focusing only on the thio-glucose / glucose ring structure and the glucosidic linkage, and yet the Opponent has miserably failed in their allegation.
2. There is no single document that demonstrates that a person skilled in the art based on his common general knowledge and the prior art document cited by the Opponent would consider a 5-thio-glucose as being interchangeable with glucose.
3. The Opponent has failed to demonstrate as to why a person skilled in the art would change 'O' glucoside linkage to a C-glucoside linkage without any teaching of any of the prior art documents.
4. The Opponent has completely ignored the remaining part of the molecule and the substitution pattern on the phenyl ring that is linked by glucosidic bond to the thio-glucose. The said phenyl ring is substituted with '4-ethoxy benzyl' group at 3-position, 'methyl' group at 4-position, and 'methoxy' group at 6-postion.

INVENTIVE STEP ANALYSIS

On consideration of the written and oral arguments of the parties, my observation and conclusion regarding inventive step of the presently claimed invention is as follows: The question of obviousness and lack of inventive step have assessed in the light of cited documents and the evidence submitted.

The cited prior art by the Opponents: US '126, US '117 and WO '931 discloses SGLT2 inhibitor having "C-Glucosidic" bond and the compounds of WO '931 contains "O-glucosidic" bond. It has been observed that none of the prior arts, including the non-patent literature like Link et.al, Yao et.al, Hirayamo et.al etc. include a 5-thio-glucose for SGLT2 inhibition.

I am of the opinion that the above documents do not explicitly disclose the compound of the claimed invention. And it is not easy for a person skilled in the art to conceive of modifying the prior art O-glucoside compound to arrive at Luseogliflozin, the C-glucoside compound. The cited documents do not ascertain clear and definite directions to make the compound in the claimed invention.

- **The information provided by the Opponent to modify the glycone/aglycone/linkage between the glycone-aglycon moiety may be relevant, but not appropriate to obtain the compound of the present invention.**

Also, the Opponent was focusing only on the thio-glucose / glucose ring structure and the glucosidic linkage and has failed to demonstrate as to why a person skilled in the art would change 'O' glucosidic linkage to a C-glucosidic linkage without any teaching of any of the prior art documents.

- I am relying on the opinion of the Applicant that a document is to read as a whole and not in isolation. Therefore, a person skilled in the art would not randomly select the particular substituent on a particular position of the molecule and ignore the rest of the molecule.

It is imperative to note that a compound's chemical and pharmacological properties do not result solely from its core or from individual substituents, but rather from the entirety of the molecule and how all its component atoms interact. Thus, the biological activity of a compound is based on the structure of the molecule as a whole. (**Merck vs Glenmark 2015**).

From the above analysis, and considering all the expert affidavits relied by the Applicant, I have concluded that a person skilled in art will not be motivated to arrive at the present invention based on the prior art references alone or any of its combination. It is evident that the Opponent has failed to establish the grounds of obviousness or lack of inventive step. Hence inventive step is acknowledged for the impugned application.

The remaining opponents (who were absent during the pre-grant hearing) have also raised the same grounds and citations as of Opponent -1, the detailed explanation and Applicant's response in this regard has not been reiterated here.

(b) SECTION 25(1)(f): INVENTION IS NOT PATENTABLE UNDER SECTION 3(d)

The following submissions have been made by the Opponent: There is no data for enhanced therapeutic efficacy in the impugned application with regard to the compound Luseogliflozin compared to SGLT2 inhibitor compounds known in prior art.

- The applicant has merely given IC50 values of inhibition of SGLT2, SGLT1 and SGLT2/SGLT1. However, there is no data in the impugned application establishing

enhanced therapeutic efficacy of the compound Luseogliflozin over other compounds known in the art.

Several compounds in Table 3 of the impugned application have been shown to have lower IC50 for SGLT2 and more selectivity for SGLT1 e.g. compound 78, compound 96, compound 99, compound 103, compound 105. Yet, the Patentee claims that compound No. 89 (Luseogliflozin) without any data establishing enhanced efficacy of compound 89 over compound 78, compound 96, compound 99, compound 103, compound 105. The basis thereof is not known from the specification. In view of the above, no enhanced therapeutic efficacy is demonstrated.

APPLICANT'S RESPONSE

Countering the objection under section 3(d) of the Patents Act, the agent for the applicant argued that the application is in relation to **new chemical entity** that claims a novel compound, Luseogliflozin. The patentability criteria in relation to the said application and specifically with regard to Luseogliflozin, includes novelty, inventive steps and industrial applications of the compound Luseogliflozin as required under section 2(1)(j).

There is no patentability requirement that specification of new chemical entity patent application must include data about therapeutic efficacy or clinical trial data. In this regard the Applicant has relied on the following case laws: **a) Roche vs. CIPLA, 2015, DHC, RFA (OS) 92/2012 & 103/2012**

SECTION 3(d) ANALYSIS

From the response provided by the Applicant, I am of an opinion that the claims of the present application relate to a new chemical entity, **Luseogliflozin** and is not a mere discovery of a known substance and cannot be derived from any of the prior art compounds.

(c)GROUND 4: SECTION 25(1)(H):

The Opponent argued that: the applicant has deliberately ignored the requirement as set out in the Section 8, Rule 12 and submitted the required information in Form 3 after marked delay of approx. 7 years without any explanation for such delay. Till date the applicant has not filed a single petition for condonation of irregularity in filing information of corresponding applications in Form 3.

APPLICANT'S RESPONSE

The Applicants argued that they have complied with the Section 8(1) requirement and have submitted updated details of the corresponding foreign application. Further, Applicants have provided search and examination report of the major patent office and hence have complied with the Section 8 requirement.

DECISION

After having considered all the circumstance of this case, representation of opponents, reply statement and evidence of the applicants, written submissions and arguments in the hearing made by the parties and also my discussion and findings as mention above, I am of the opinion that the opponents have failed to prove any of the grounds relied upon by them. In view of the above, I reject the representation and dispose off the opposition.

Dated 19th November 2020 Dr. BINDHU JACOB

Assistant Controller of Patents & Designs