

THE PATENTS ACT, 1970

Section 25(1)

In the matter of an
Application for Patent Number
3939/KOLNP/2010
Dated 21/10/2010
And

In the matter of
Pre-Grant Opposition to the Grant of Patent thereon
u/s 25(1) of The Patents Act, 1970 as amended by
The Patents (Amendment) Act, 2005 &
In the matter of Patents Rules, 2003 as amended by
The Patents (Amendment) Rules, 2006.

Applicant of the Impugned Application:	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-chome, Chuoku, Osaka-shi, Osaka
Applicant's Agent:	LEXORBIS 709/710, Tolstoy House 15-17, Tolstoy Marg New Delhi – 110001 India

Opponent 1:	Cancer Patients Aid Association (CPAA)
Opponent-1 's Agent:	Gopakumar Nair Associates 3rd floor, Shivmangal, Next to Big Bazaar, Akurli Road, Kandivli (East), Mumbai-400101 Maharashtra, India. Phone: 91-22-40895454 E-mail: gopanair@gnaipr.net
Opponent 2:	Mita Sheikh, A001, Nitesh Central Park, Bagalur Cross, Yelahanka, Bengaluru-64, Karnataka, India.
Opponent-2 's Agent:	Mr. Tarun Khurana Khurana and Khurana Advocates and IP Attorneys E-13, UPSIDC-Site-IV, Kasna Road, Greater Noida- 201308, Uttar Pradesh, India. Email: info@khuranaandkhurana.com

Date of Hearing u/s 25(1):	19/05/2022
Person(s) Present in the hearing:	
For the Applicant	For the opponent
PRADEEP KUMAR KAMAL (IN/PA-1306) VARUN SHARMA (IN/PA-4234)	Opponent 1: MANISH CHEMBURKAR (IN/PA-2761) ANDREYA FERNANDES (IN/PA-1777) BINA DANDEKAR (IN/PA-2917)-SUB PA
	Opponent 2: MR. TAPAN SHAH (IN-PA/2553) MR. SHASHI KANT VERMA (IN-PA/3609) GARIMA GARG (IN/PA-3480)

The Impugned Application is with the following prosecution timeline:

Date of the Event	Event Particulars
21/10/2010	Filing of Patent Application No. 3939/KOLNP/2010
24/12/2010	Publication of the Application
17/05/2012	Request for Examination Filed
15/02/2016	Issuance of the First Examination Report
22/08/2016	Reply to the First Examination Report
10/07/2017	Pre-Grant opposition under section 25(1) has filed; By "Opponent 1"
11/09/2018	Pre-Grant opposition under section 25(1) has filed; By "Opponent 2"
19/05/2022	Oral Hearing in pursuance of Hearing Notice u/s 25(1)
03/06/2022	Written Submissions w.r.t the Oral Hearing u/s 25(1) by the "Applicant"
03/06/2022	Written Submissions w.r.t the Oral Hearing u/s 25(1) by the "Opponent 1"
03/06/2022	Written Submissions w.r.t the Oral Hearing u/s 25(1) by the "Opponent 2"

DECISION

1. The patent application number 3939/KOLNP/2010 was filed on 21/10/2010 by **Takeda Pharmaceutical Company Limited** (Hereinafter "Applicant") of **1-1, Doshomachi 4-chome, Chuoku, Osaka-shi, Osaka** through the agent **LEXORBIS; 709/710, Tolstoy House, 15-17, Tolstoy Marg New Delhi – 110001 India.**

2. (i) A pre-grant opposition under section 25(1) of The Patent Act, 1970 was filed by **Cancer Patients Aid Association (CPAA)** (Hereinafter "Opponent-1") on 10/07/2017 against the above said application through the agent **Gopakumar Nair Associates; 3rd floor, Shivmangal, Next to Big Bazaar, Akurli Road, Kandivli (East), Mumbai-400101 Maharashtra, India.**

(ii) Another pre-grant opposition under section 25(1) of The Patent Act, 1970 was filed by **Mita Sheikh** (Hereinafter "Opponent-2") of **A001, Nitesh Central Park, Bagalur Cross, Yelahanka, Bengaluru-64, Karnataka, India;** on 11/09/2018 against the above said application through the agent **Mr. Tarun Khurana; Khurana and Khurana Advocates and IP Attorneys, E-13, UPSIDC-Site-IV, Kasna Road, Greater Noida- 201308, Uttar Pradesh, India.**

3. The pre-grant opposition under section 25(1) of The Patent Act, 1970 was filed by the "Opponents", on the following grounds:

Sec. 25(1)(b)/(d)	that the invention claimed in the complete specification is not Novel
Sec. 25(1)(e)	that the invention claimed in the complete specification is obvious and clearly does not involve any Inventive Step .
Sec. 25(1)(f)	that the subject of claim of the complete specification, is not an invention within the meaning of this act or is not patentable under this act.
Sec. 25(1)(g)	that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

But, in hearing opponent 1 has admitted withdrawal of grounds of oppositions under Section 25(1)(b); and Section 25(1)(d), and thereby maintaining opposition only on grounds of Section 25(1)(e); Section 25(1)(f); and Section 25(1)(g). While opponent 2 has admitted withdrawal of ground of oppositions under Section 25(1)(f), and thereby maintaining opposition only on grounds of Section 25(1)(e); and Section 25(1)(g). Therefore, consolidated discussion/decision given herein on the grounds under **Section 25(1)(e); Section 25(1)(f); and Section 25(1)(g).**

By referring the following documents:

Opponent 1	Opponent 2
Exhibit A: WO03/078404	-----
Exhibit B: WO2004/080980	D1: WO 2004/080980 A1
Exhibit C: Galkin, et al “Identification of NVP-TAE684, a potent, selective and efficacious inhibitor of NPM-ALK” (2007) Proceedings of the National Academy of Sciences of the United States of America 104(1): 270–75.	-----
Exhibit D: Zhao, et al. “The synthesis of novel acetolactate synthase inhibitors, N-(asymmetrically disubstituted phosphoryl)-N’-(4,6-dimethoxypyrimidin-2-yl) Ureas”, (1999) Heteroatom Chemistry 10(3): 237–41.	D2: Zhao et al., “The synthesis of novel acetolactate synthase inhibitors, N-(asymmetrically disubstituted phosphoryl)-N’-(4,6-dimethoxypyrimidin-2-yl) urea”, Heteroatom Chemistry, Volume 10, Number 3, 1999, pages 237-241
Exhibit E: Zhao, et al., “Bioisostere of sulfonyl moiety – The synthesis of new ALS inhibitors N-(asymmetry disubstituted phosphoryl)-N’-(4,6-dimethoxypyrimidin-2-yl) Ureas”, (1998) Chinese Chemical Letters 5: 455–58.	D3: Zhao et al., “Bioisostere of Sulfonyl Moiety- The Synthesis of New ALS Inhibitors N-(Asymmetry Disubstituted Phosphoryl)- N’-(4,6-dimethoxypyrimidin-2-yl) Ureas”, Chinese Chemical Letters, 1998, Issue 5, Pages 455-458.
Exhibit F: Zhao, et al., “Bioisoterism between sulfonyl group and phosphoryl group – The synthesis of new ALS inhibitors N-(arylamino hydroxyl phosphoryl)-N’-(4,6-dimethoxypyrimidine-2-yl) ureas”, (1998) Chinese Chemical Letters 8: 723–24 + 275	D4: Zhao et al., “Bioisosterism between sulfonyl group and phosphoryl group - The synthesis of new ALS inhibitors N’-(arylamino hydroxyl phosphoryl)-N’-(4,6-dimethoxypyrimidine- 2-yl) ureas”, Chinese Chemical Letters, 1998, Issue 8, Pages 723-724+275
Exhibit G: Schneider and Benner, “Building blocks for oligonucleotide analogs with dimethylene-sulfide, -sulfoxide, and -sulfone groups replacing phosphodiester linkages” (1990) Tetrahedron Letters 31(3): 335–38.	D5: Schneider et al., “Building blocks for oligonucleotide analogs with dimethylene-sulfide, -sulfoxide, and -sulfone groups replacing phosphodiester linkages”, Tetrahedron Letters, Volume 31, Issue 3, 1990, Pages 335-338.

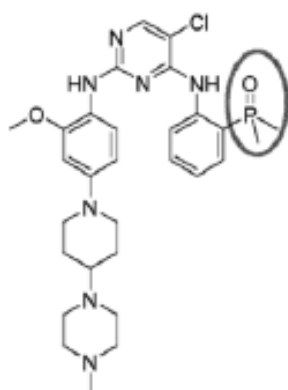
For the sake of convenience, the patent prior arts will be referred to by the last 3 digits (as summarized in the table below).

Prior Art	Abbreviated	Publication Date
WO03/078404	WO'404	25/09/2003
WO2004/080980	WO'980	23/09/2004
Galkin, et. al. "Identification of NVP-TAE684, a potent, selective and efficacious inhibitor of NPM-ALK"	Galkin et al.	2007
Zhao et al. Heteroatom Chemistry, Volume 10, Number 3, 1999, pages 237-241	Zhao et al. 1999	1999
Zhao et al. Chinese Chemical Letters, 1998, Issue 5, Pages 455-458	Zhao et al. 1998_5	1998
Zhao et al. Chinese Chemical Letters, 1998, Issue 8, Pages 723-724+275	Zhao et al. 1998_8	1998
Schneider et al. Tetrahedron Letters, Volume 31, Issue 3, 1990, Pages 335-338	Schneider et al.	1990

4. After completion of the procedure prescribed under section 25(1) to be read with Rule 55 under prevailing Rules a hearing was scheduled on 19/05/2022. After completion of the hearing, both the applicant and opponents, were directed to file written note of arguments and all the parties have submitted the same within the statutory period.

The subject matter of claim 1 of the Impugned Application relates to (Claim 1):

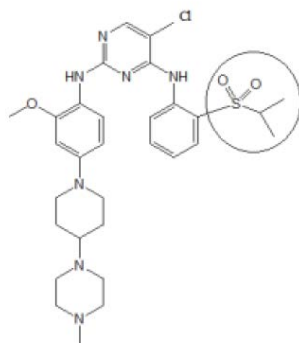
A compound of following formula: (Brigatinib) use as **ALK inhibitors**



Observation on Sec. 25(1)(e) i.e. on Inventive step vis-à-vis the cited documents:

WO'404 discloses the 2,4-diaminopyrimidine derivatives, used as inhibitors of protein tyrosine kinase specifically ALK inhibition, useful against neoplastic diseases, inflammatory disorders, etc. that comprise of the genus of the structure claimed in the present Application.

WO'980 discloses a compound with following structure (TAE-684), exhibiting powerful inhibition of tyrosine kinase activity of Anaplastic Lymphoma Kinase (ALK).



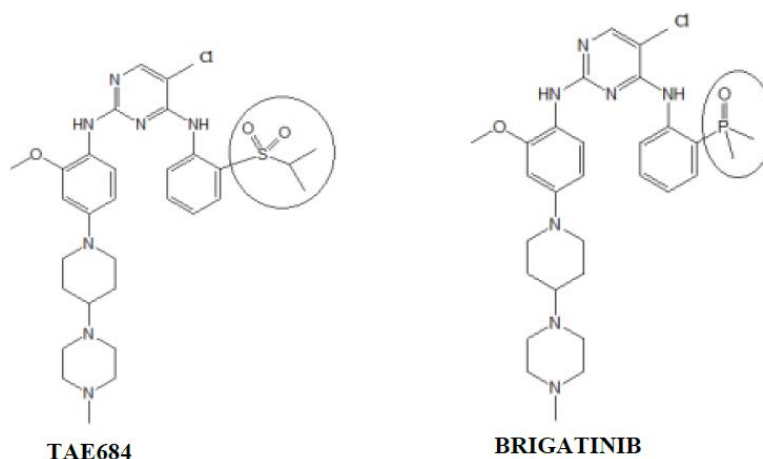
Galkin, et al., discloses the ALK-inhibiting activity of TAE-684; also discloses the inhibited growth of NPM-ALK-transformed cells with an IC₅₀ of approx. 3nM. The opponent also states that Galkin, et al. reported greater selectivity, (in fact 100-fold difference in selectivity), of TAE-684 for ALK over InsR. Galkin, et al. also discloses a difference in the InS-R inhibition as reported by in vitro tests and cellular assays. They show that though TAE-684 discloses a low IC₅₀ value (10–20nM) for InS-R inhibition in the in vitro kinase assay, a higher IC₅₀ is reported in cellular assays (1.2 μM) for InS-R inhibition. They further state that “These results indicate that, at least in cellular systems at its therapeutic IC₅₀, TAE684 is a potent and selective NPM-ALK kinase inhibitor, without exhibiting significant cross-reactivity against other kinases tested in this study, including the highly homologous InsR”. Galkin also discloses selectivity of TAE684 for ALK over other kinases including Ins-R as well.

Zhao et al. 1999 discloses the close homology between the sulfonyl and phosphoryl groups in terms of size, bond angle, bond length, and configuration which establish a good degree of Bioisosterism exhibited by sulfonyl and phosphoryl group.

Zhao et al. 1998 5 & Zhao et al. 1998 8 disclose the Bioisosterism between the ‘sulfonyl group’ and the ‘phosphoryl group’.

Schneider et al. discloses that they had successfully implemented and reported a reverse strategy of replacing phosphodiester linkage with sulfonyl group to overcome the drawbacks associated with the phosphodiester bond. It also discloses that the sulphones are non-ionic, achiral, isoteric analogs of phosphate diesters, make them ideal analogs for phosphate esters on other grounds as well.

From the above discussion the office finds that WO'404 discloses the 2,4-diaminopyrimidine derivatives (generic structure), which seems less relevant for the present claimed subject matter. However, WO'980 & Galkin et al. are found to be most relevant and closest prior art (**applicant has also admitted the same**) which discloses structurally very similar compound i.e. TAE-684:



From the above displayed two structures it can be seen that the present alleged invention differs in the presence of 'phosphoryl group' to get the compound 'Brigatinib' (as claimed in claim 1) instead of 'sulfonyl group' of the prior arts (WO'980 & Galkin, et al.) i.e. compound **TAE-684**.

Thus, the technical problem underlying the present application has to be seen the provision of further alternate compounds having an unexpected effect with regard to the closest prior art compound **TAE-684**. For the present case the 'technical advancement' may be regarded as 'increase in the selectivity' of 'Brigatinib' for ALK over InS-R (as per the applicant's submission).

In view of the above discussion for analysing section 2(1)(ja) the following question has erupted:

- that whether the replacement of 'sulfonyl group' by 'phosphoryl group' is obvious or not, in view of the cited prior arts? If the answer of the first question is affirmative whether said replacement gives rise to any 'technical advancement'. Not to mention herein again that the said technical advancement should be mentioned in the originally filed specification

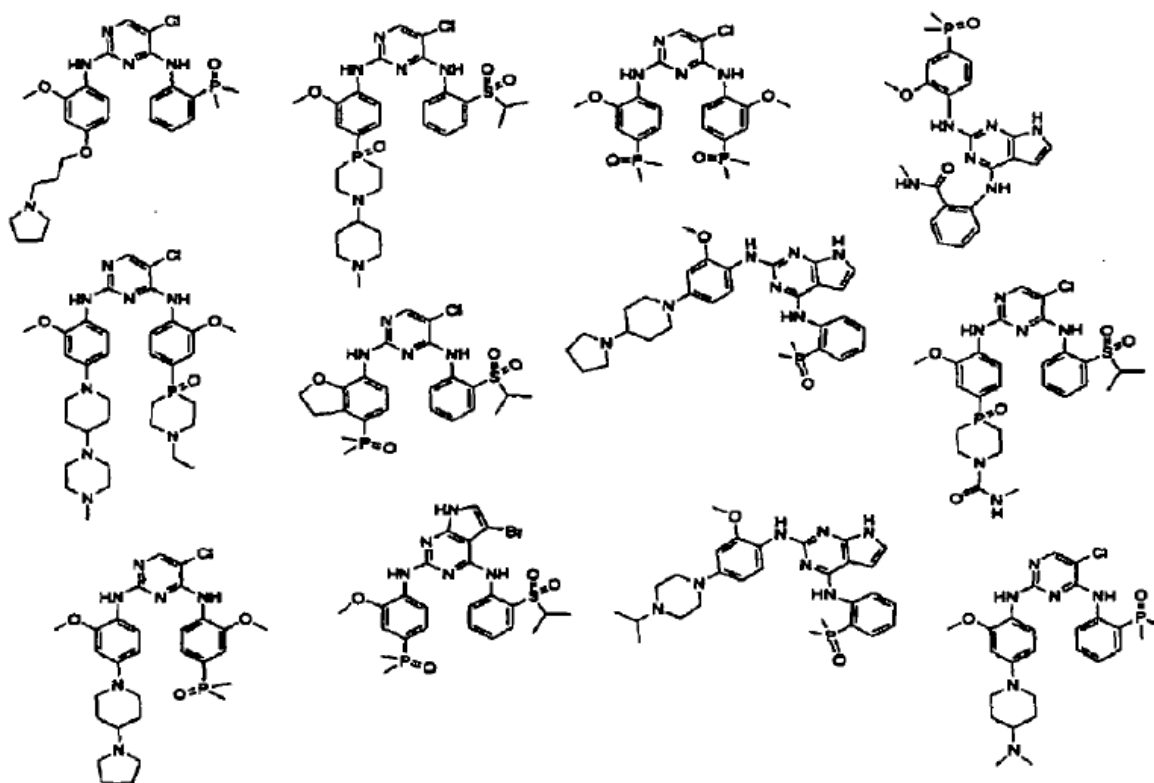
The question can be answered from the concept of "Bioisosterism" which says that "Bioisosterism is a unique approach used by medicinal chemists for the reasonable modification of lead compounds into safer, more clinically effective, economical, and therapeutically attractive drugs". Further details regarding "Bioisosterism" can be obtained from the disclosure of Zhao et al. 1999, Zhao et al. 1998 5, Zhao et al. 1998 8 and Schneider et al.

Zhao et al. 1999 discloses the close homology between the sulfonyl and phosphoryl groups in terms of size, bond angle, bond length, and configuration which establish a good degree of Bioisosterism exhibited by sulfonyl and phosphoryl group. Zhao et al. 1998_5 & Zhao et

al. 1998_8 also disclose the **Bioisosterism** between the ‘sulfonyl group’ and the ‘phosphoryl group’. Schneider et al. also discloses that sulphones and phosphate esters are ideal analogs.

Therefore, the office concludes that, replacement of **‘sulfonyl group’ by ‘phosphoryl group’** is obvious for a person skilled in the art from the disclosure of Zhao et al. 1999 and/or Zhao et al. 1998_5 and/or Zhao et al. 1998_8 and/or Schneider et al. Hence, from the disclosure of WO’980 and/or Galkin et al.; and from the disclosure of Zhao et al. 1999 and/or Zhao et al. 1998_5 and/or Zhao et al. 1998_8 and/or Schneider et al., a person skilled in the art could easily reach to the compound “Brigatinib” as claimed in claim 1.

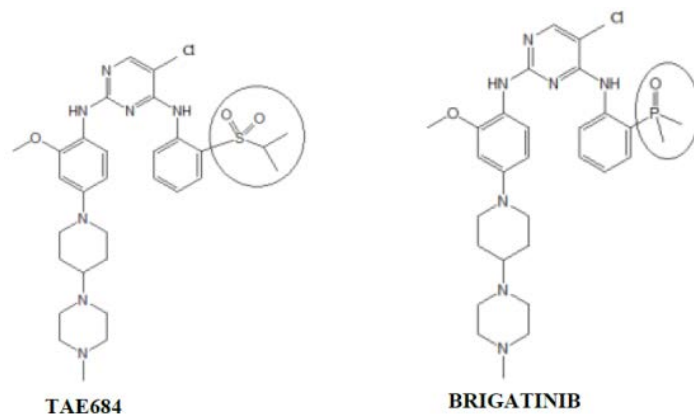
Notwithstanding the issue discussed regarding obviousness, the office also analyses the alleged technical advancement of the replacement. Now, in this regards the office finds that **“the applicant has not furnished any evidence of technical advancement in the as filed specification”**. The office is in the opinion that, the technical advancement must be described and demonstrated as part of the as-filed specification. Moreover, page 235 of the as filed specification discloses the effectiveness of few exemplified compounds (as displayed below) which shows the IC50 value less than 1nM. However, among those examples, **‘Brigatinib’** which has been claimed in claim 1, is not been mentioned. Hence, the office is in the opinion that, the applicant was not aware about the effectiveness of the compound viz **‘Brigatinib’**, at the time of filing the complete specification. Therefore, the office concludes that, the applicant has not furnished any evidence for technical advancement to show convincingly that the unexpected effect indeed has its origin in the distinguishing feature.



In view of the above discussion the office is in the same opinion with both the opponents view that “replacement of ‘sulfonyl group’ by ‘phosphoryl group’ is obvious for a person skilled in the art from the disclosure of WO’980 and/or Galkin et al.; and from the disclosure of Zhao et al. 1999 and/or Zhao et al. 1998 5 and/or Zhao et al. 1998 8 and/or Schneider et al., and “Inventive step” for the claim 1 has not been acknowledged.

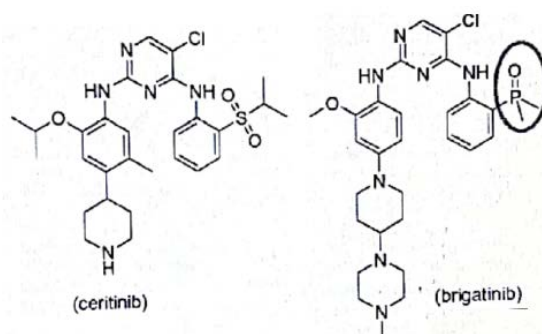
Without prejudice to the above discussion; on later stage, the applicant has submitted two affidavits as follows:-

Affidavit-1 submitted on 28/06/2017 to establish the effectiveness of the “Brigatinib” over TAE-684; particularly it shows that “Brigatinib” is less selective towards ‘InsR’ in comparison to TAE-684 (of prior art).



And

Affidavit-2 submitted on 16/12/2020 to establish the effectiveness of the “Brigatinib” over “Ceritinib”.



From page 235 of the as filed specification, it can be noted that none of the tested compounds pertains to the compound being claimed in the pending claim (i.e. Brigatinib) of the impugned application, making it clear that - at the time of filing of the impugned application, the Applicant was not aware if “Brigatinib” exhibits any ALK inhibitory activity. Moreover, from Page 53, Line 15-17 of the as filed specification the office finds that the

existence as well as ALK inhibitory activity of the compound TAE684 was very well known to the Applicant at the time of filing of the impugned application. However, the impugned application fails to disclose ALK-inhibitory activity of Brigatinib, establishing technical advancement over the prior-art known ALK inhibitor compound TAE684.

Therefore, the office considers that the effectiveness of the particular compound “Brigatinib” is a ‘later accrued knowledge’ (as discussed in the preceding para), both the affidavits cannot be taken on record.

Observation on Sec. 25 (1) (f) i.e. the subject matter of the impugned Application is not patentable under Section 3(d) of the Act:

From the above discussion it can be seen that, the present claimed compound “Brigatinib” is differs in the presence of ‘phosphoryl group’ instead of ‘sulfonyl group’ of the prior arts (WO’980 & Galkin, et al.) i.e. compound **TAE-684**.

As the applicant has failed to furnish any evidence for technical advancement in the as filed specification, the office considers the claimed compound as a mere derivatives of known substance **TAE-684**. (Detailed reason(s) mentioned in the preceding para).

Therefore, the office is in the same opinion with the opponent-1, that the claimed subject matter is not allowable u/s 3(d) of The Patent Act 1970.

Observation on Sec. 25 (1) (g) i.e. “Insufficiency of Disclosure”:

The office finds that, the applicant has disclosed a process for preparation of “Brigatinib”, (Example 122 at page 205). However, as the present claimed subject matter relates to a compound (drug), by displaying a process (only) for preparation of the said drug does not fulfil the requirements of sec 10(4). From the detailed discussion made in the preceding para the office has already concludes that the Applicant was not aware if “Brigatinib” exhibits any ALK inhibitory activity.

Therefore, the office is in the same opinion with both the opponents view that the as-filed specification to meet the requirement of sec 10(4) of The Patent Act 1970.

Conclusions:

After going through the post hearing submissions by the Applicant & both the Opponents and the cited documents, the office reaches to the following conclusions:-

- (i) The office is in the same opinion with both the Opponent's view on Sec. 25 (1) (e) and finds that the replacement of 'sulfonyl group' by 'phosphoryl group' is obvious for a person skilled in the art; and Inventive step u/s 2(1)(ja) cannot be acknowledged.
- (ii) The office is in the same opinion with the opponent 1's view on Sec. 25 (1) (f) and finds that the claimed compound as claimed in claim 1 is a mere derivatives of known substance TAE-684 and the alleged claimed invention is not patentable under Section 3(d) of The Patent Act 1970.
- (iii) The office is in the same opinion with both the opponent's view on Sec. 25 (1) (g) and finds that, the as-filed specification to meet the requirement of sec 10(4) of The Patent Act 1970.

Therefore, the office **accepts** the representation filed by the opponent under section 25(1) & rule 55(1) and proceeds with the impugned application accordingly.

Dated, 12th April, 2023

For

Controller General of Patents, Designs & Trademarks (CGPDTM)