Luncheon Roundtable
Follow-on pharmaceutical innovation and patents
…lessons from around the world

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Why Patents for inventions?

Patent

- Negative Right granted a sovereign or state to an inventor for his invention for a limited period of time to stop others from making, selling, vending, offering for sale or using the said invention, having disclosed the invention in a patent specification such that a person skilled in the art can reproduce the invention.
- The invention must satisfy the patentability criteria as per the law of the land
- In some developing countries (like India), the patentee is obligated to make the invention available to the public to satisfy the reasonable requirements of the public and at affordable prices to the public

Thus the Patent Law seeks to strike a balance between the rights of a patentee and the obligations of the patentee towards to society.

Follow on Inventions…What are they?

A. Typically first in class products are unique but fail to harness full therapeutic potential Subsequent products improve this significantly.

Some examples.

1. **Losartan vs subsequent sartans e.g. Telmisartan. (Angiotensin receptor blockers for hypertension)**
2. **Gefitinib vs Osimertinib (EGFR inhibitors for lung cancer)**
3. **Pegaptinib vs Aflibercept (VEGF inhibitors for macular degeneration)**
4. **Lovastatin vs Atorvastatin (HMG co enzyme inhibitors for lipid lowering)**
5. **Enbrel vs Adalimumab (anti- TNF for inflammatory disease).**
6. **Captopril vs Enalapri (ACE inhibitor for hypertension).**

The subsequent product has advantage of knowledge of previous products and its deficiency at the same time it enters into a market created by the first in class and so need not spend significant resources to create its market

Initially US FDA were granting approval to all products based on safety and efficacy. This led to increase expenditure in health care. Now the new drug has to demonstrate significant advantage over approved product.

Follow on Inventions…What are they?

B. Typically first in class products are unique but fail to harness full therapeutic potential Subsequent products improve this significantly.

Formulations for delivery systems and also combination of drugs

Some examples.

1. A stable oral pharmaceutical composition of Atenalol, Simvastatin, Ramipril, hydrochlorothiazide and optionally Asprin which is separated by coating

Indian Patent No. IN 283909

There are hundreds of patents granted in the Indian Patent Office on such follow-on inventions

In the Context of the Indian Patents (Amendment) Act 2005

- Section 2 (ja) “Inventive step” means a feature of **an invention that involves technical advance as compared to the existing knowledge or having economic significance or both and** that makes the invention not obvious to a person skilled in the art;

- **“New invention” means any invention or technology which has not been anticipated by publication in any document or used in the country or elsewhere in the world before the date of filing of patent application with complete specification, i.e., the subject matter has not fallen in public domain or that it does not form part of the state of the art.**

Points for Debate

- 1970 Act the and earlier Acts did not have a definition for “inventive step”.

  This was made up for in Section 3 by way of exceptions to patentability most of which were in effect related to the inventive step.

- The 2005 Amendment defined “inventive step”.

Therefore one has to question the need for additional exception other than those that may be included to exploit the flexibilities of Article 27. 2 and 27.3 of the TRIPS Agreement.

Debate:

a) In view of the above are some of the clauses in Section 3 are now logically redundant.

Interestingly, no Member Country has challenged any of the subsections (clauses) of Section 3 in the last 15 years.

b) How has Section 3 impacted innovations and patentability of inventions in India?

Exceptions to Patentability
What is not an invention within the meaning of the Act

Section 3 (d): 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 to Section 3 (d): “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.

Exceptions to Patentability
What is not an invention within the meaning of the Act

- Section 3(e):

  a substance obtained by mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance

- Section 3(f):

  the mere arrangement or re-arrangement or duplication of known devices each functioning independently of one another in a known way.

Note: these imply the lack of inventive step!

Exceptions to Patentability
What is not an invention within the meaning of the Act

Section 3 (k):

A mathematical or business method or a computer programme *per se or algorithm*

Exceptions to Patentability
What is not an invention within the meaning of the Act

Section 3 (p): an invention that is in effect , is traditional knowledge or which is an aggregation or duplication of known properties of traditionally known component or components

Position of IPAB on Section 3d

Section 3(d) of the Act applies only in respect of the new form of a 'known' substance and the Hon'ble Intellectual Property Appellate Board (IPAB), whose decisions and judgments are binding on the Controller, has held in *Fresenius Kabi Oncology Limited vs. Glaxo Group Limited (Order No. 162 of 2013), para.56* that to raise a challenge or an objection under Section 3(d), one has to specifically allege and identify at least the following three:

(i) What is the specific 'known' substance in question?

(ii) How and why the claimed molecule(s) or substance(s) is a derivative or is otherwise a new form of a known substance?

(iii) Basis to assert that the alleged 'known' substance and the claimed molecule or substance have the same 'known' efficacy?

Where did Novartis Fail? Any lessons learnt?

- **Misinterpreted the meaning of Section 3(d)**

Compared the Beta imatinib mesylate with imatinib

Should have compared Beta imatinib mesylate with imatinib mesylate to fall out of the ambit of Section 3d.

Also challenged the Indian Patent Law in the Wrong Forum

Design the research to overcome potential objections under Section 3d

On molecules (NCEs)

i) Indian Patent No. IN 301788 and
ii) Indian Patent No. IN 276375

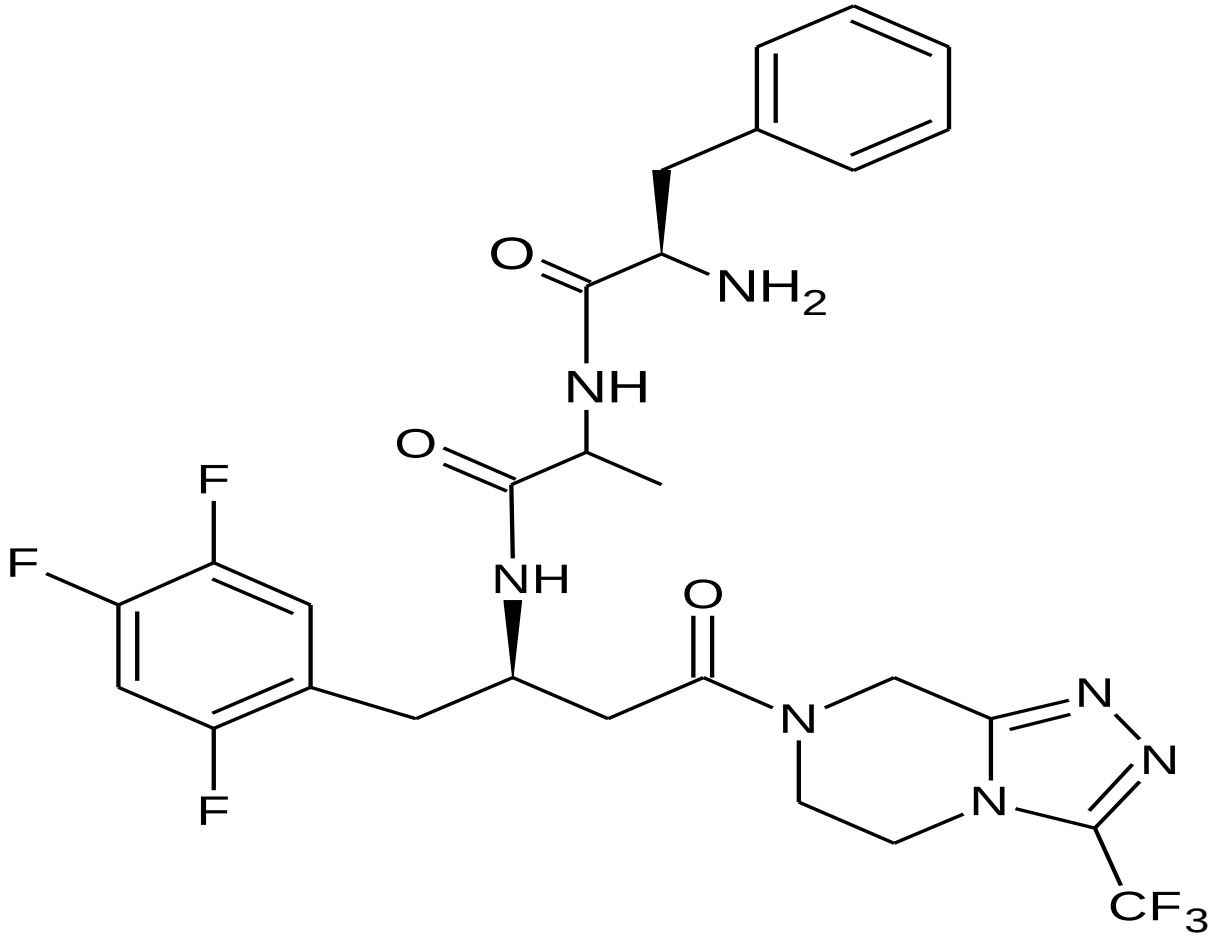
This is only a representative example of the many patents granted in India on NCEs

Therapeutic efficacy of the claimed NCEs

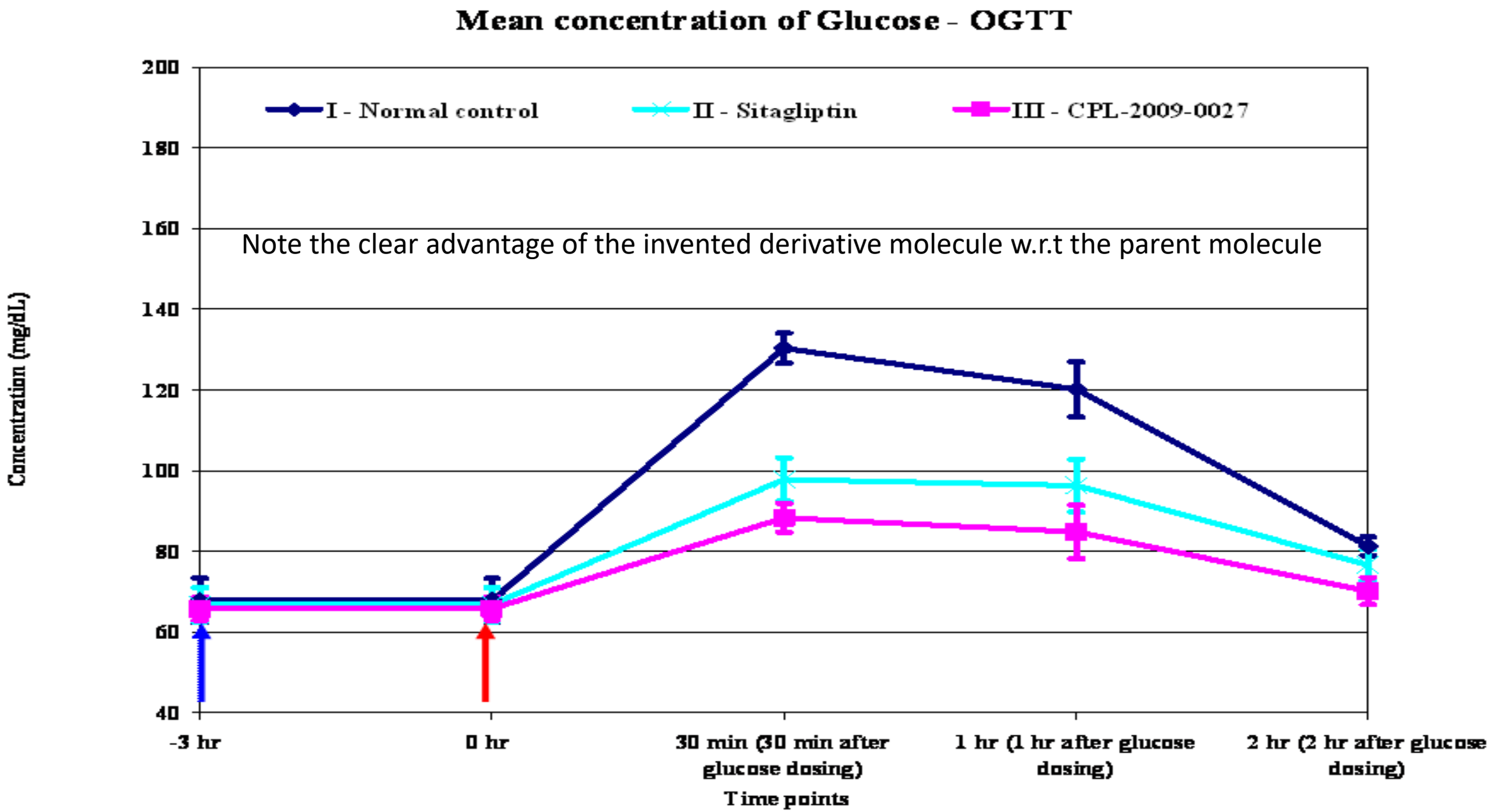
- The inventors have demonstrated that the claimed derivatives show significantly high DPP- IV inhibition activity.

- Research was designed to demonstrate the enhanced therapeutic activity of Sitagliptin derivatives of the invention with respect to Sitagliptin (as such)

CPL-2009-0027

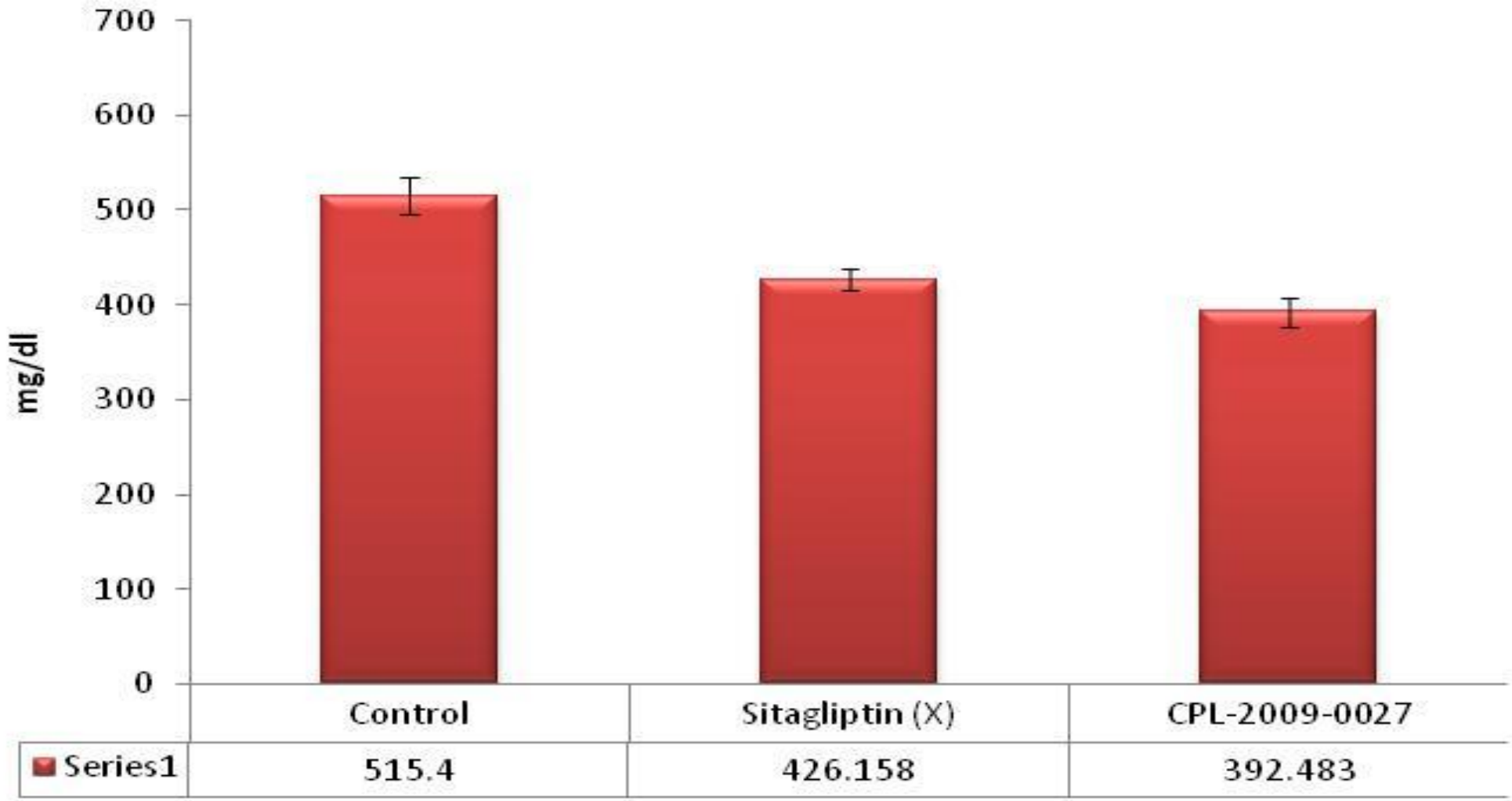


L-Phe-Ala-Sitagliptin

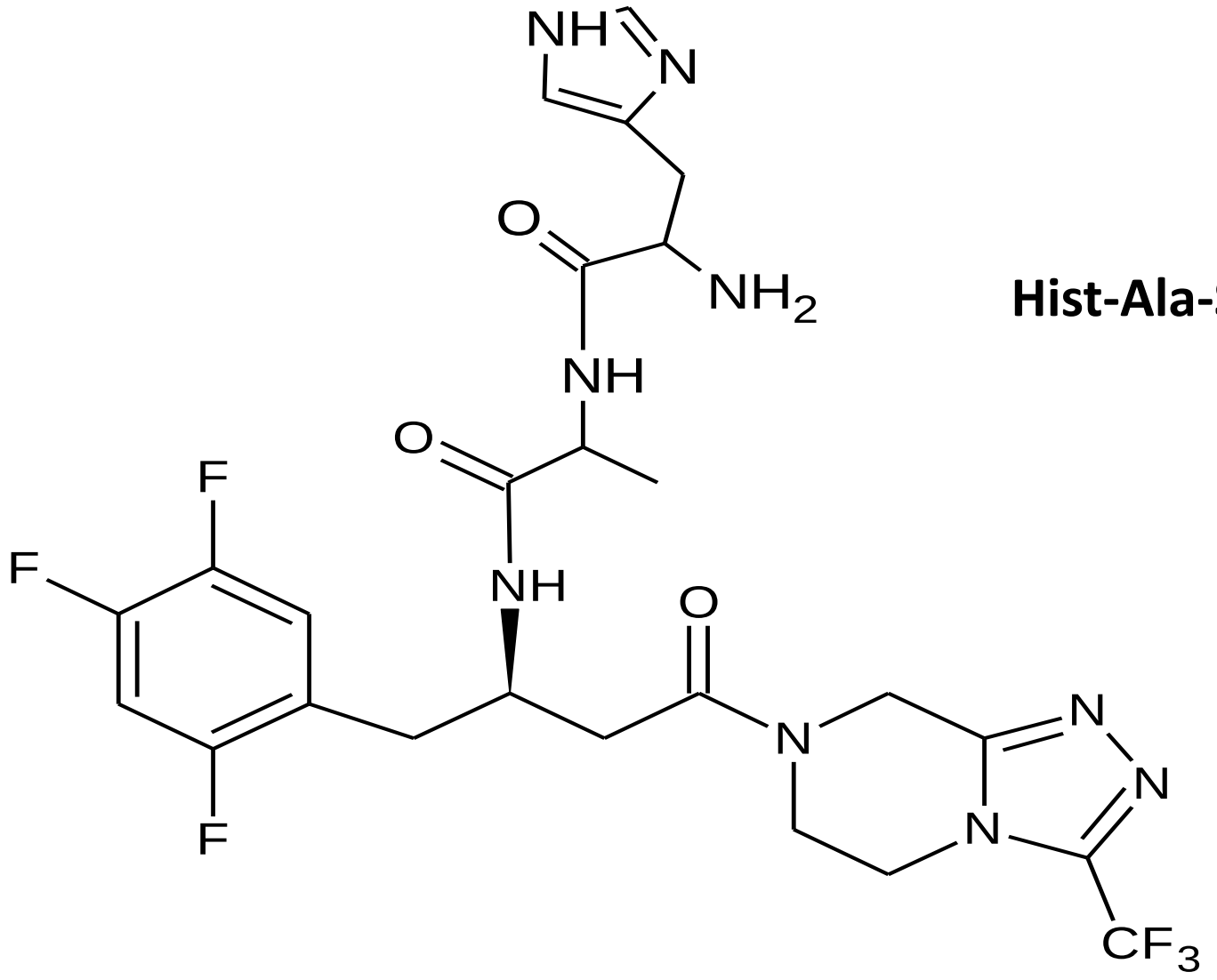

Mean concentration of Glucose - OGTT
I - Normal control
II - Sitagliptin
III - CPL-2009-0027
Note the clear advantage of the invented derivative molecule w.r.t the parent molecule
Concentration (mg/dL)
200
180
160
140
120
100
80
60
40
-3 hr
0 hr
30 min (30 min after glucose dosing)
1 hr (1 hr after glucose dosing)
2 hr (2 hr after glucose dosing)
Time points

AUC last of glucose

Note the clear advantage of the invented derivative molecule w.r.t the parent molecule



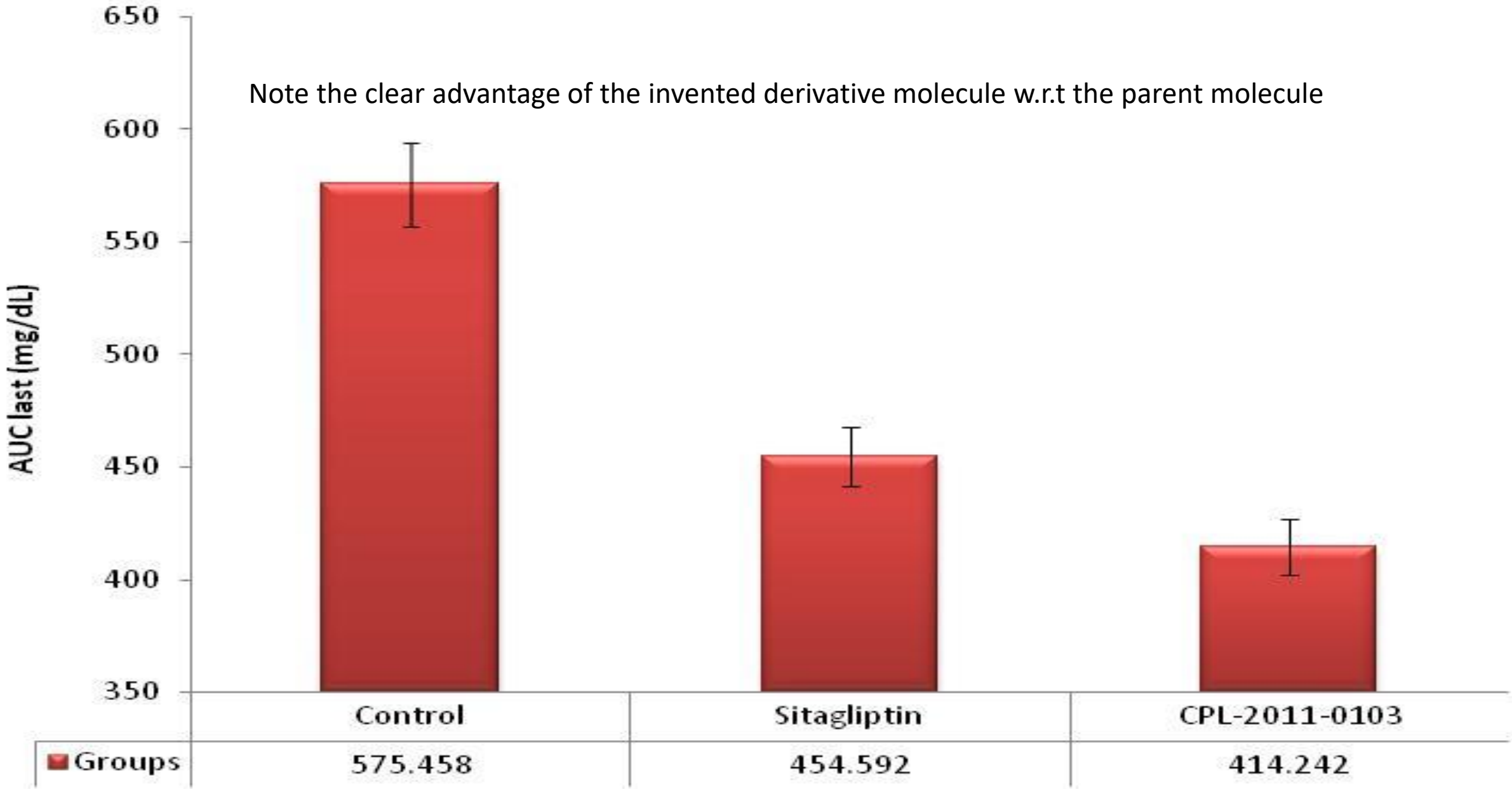
CPL-2011-0103



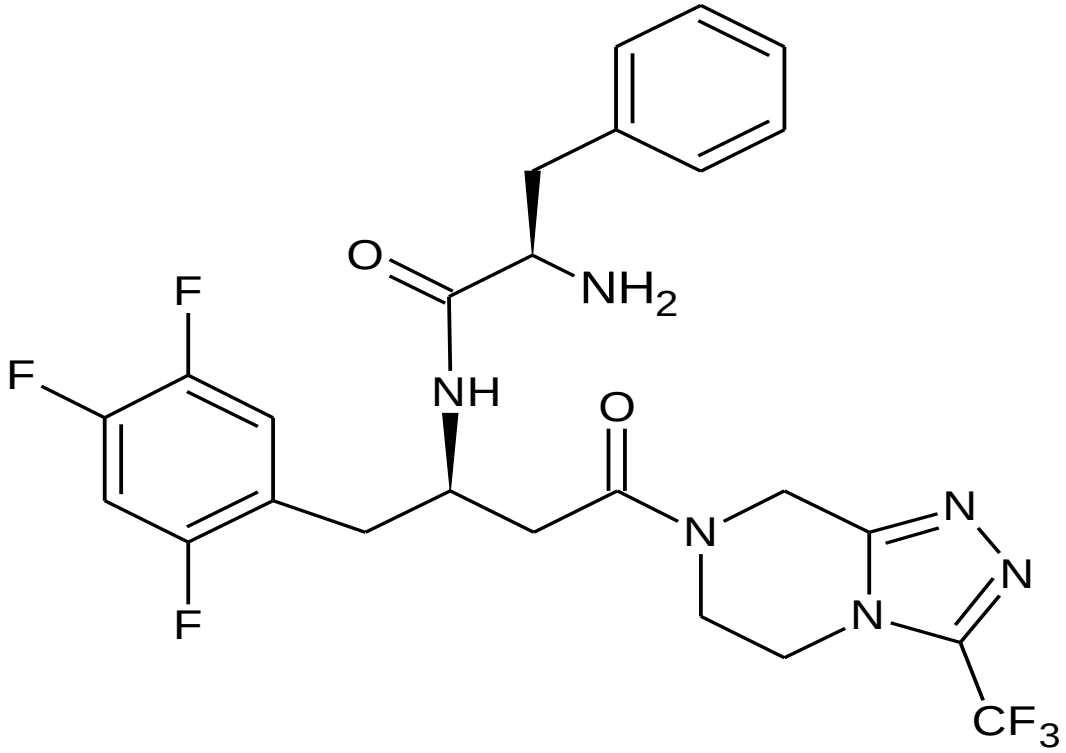
Hist-Ala-Sitagliptin

AUC last of glucose

Note the clear advantage of the invented derivative molecule w.r.t the parent molecule



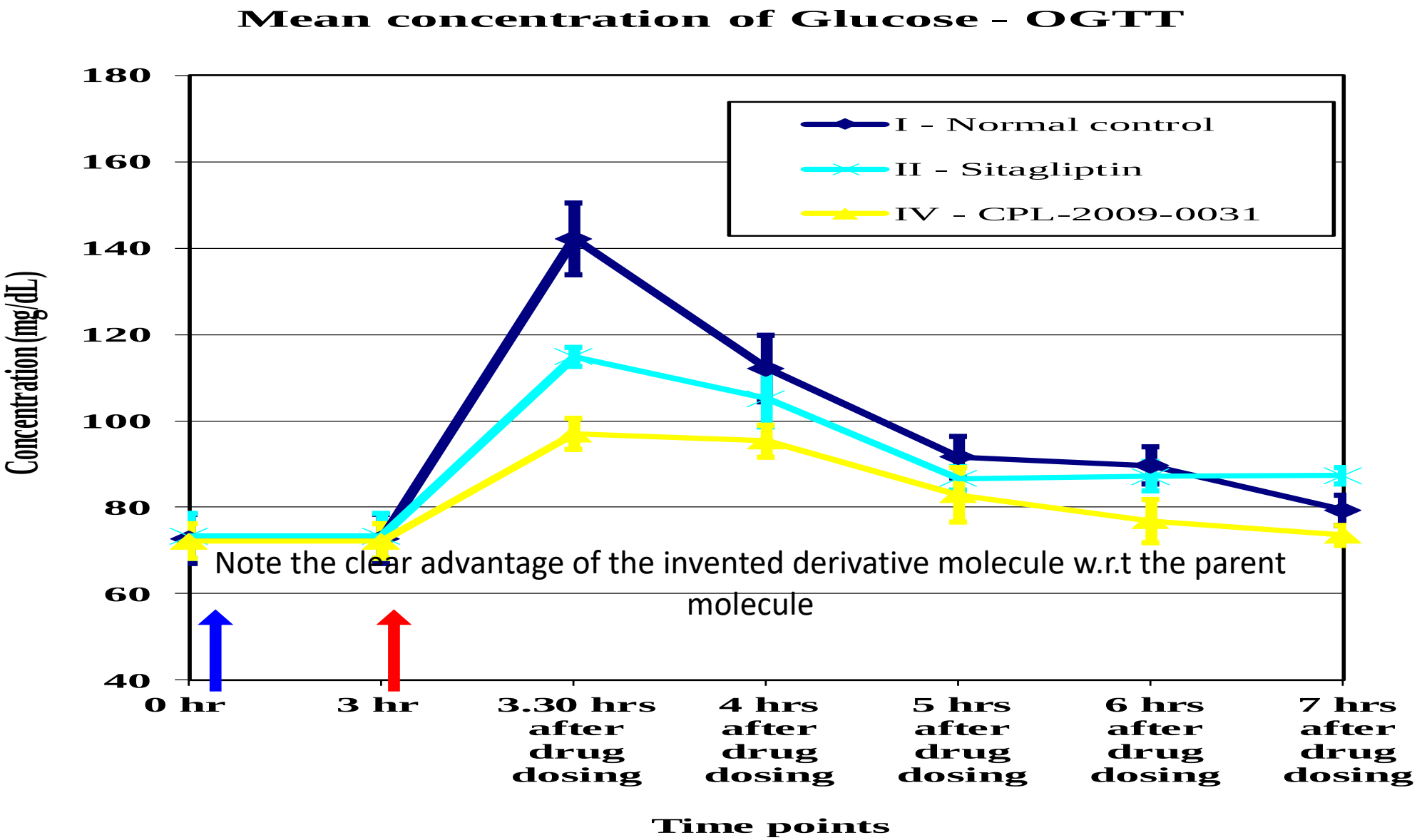
CPL-2009-0031



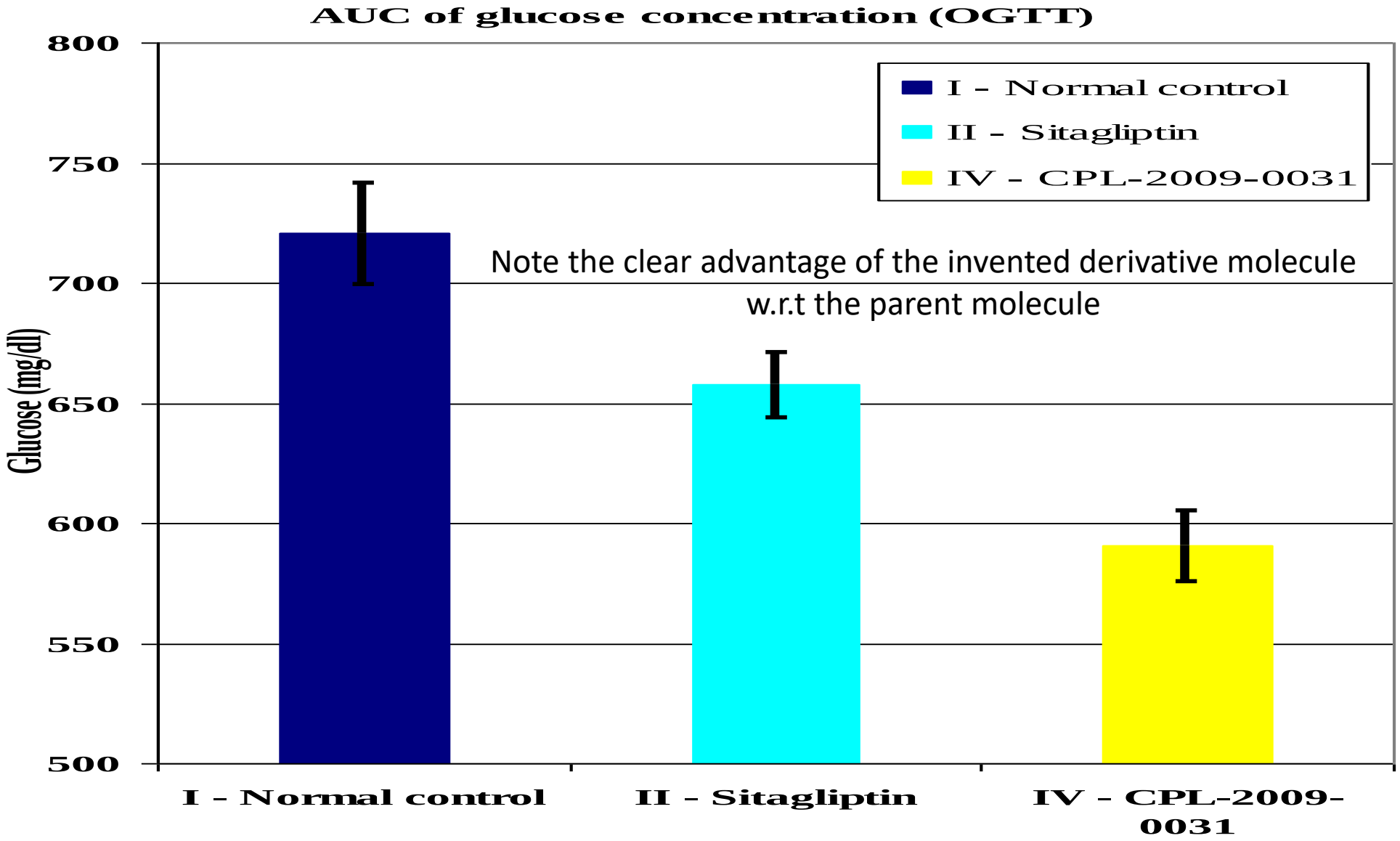
L-Phe-Sitagliptin

M. Wt. 554.48

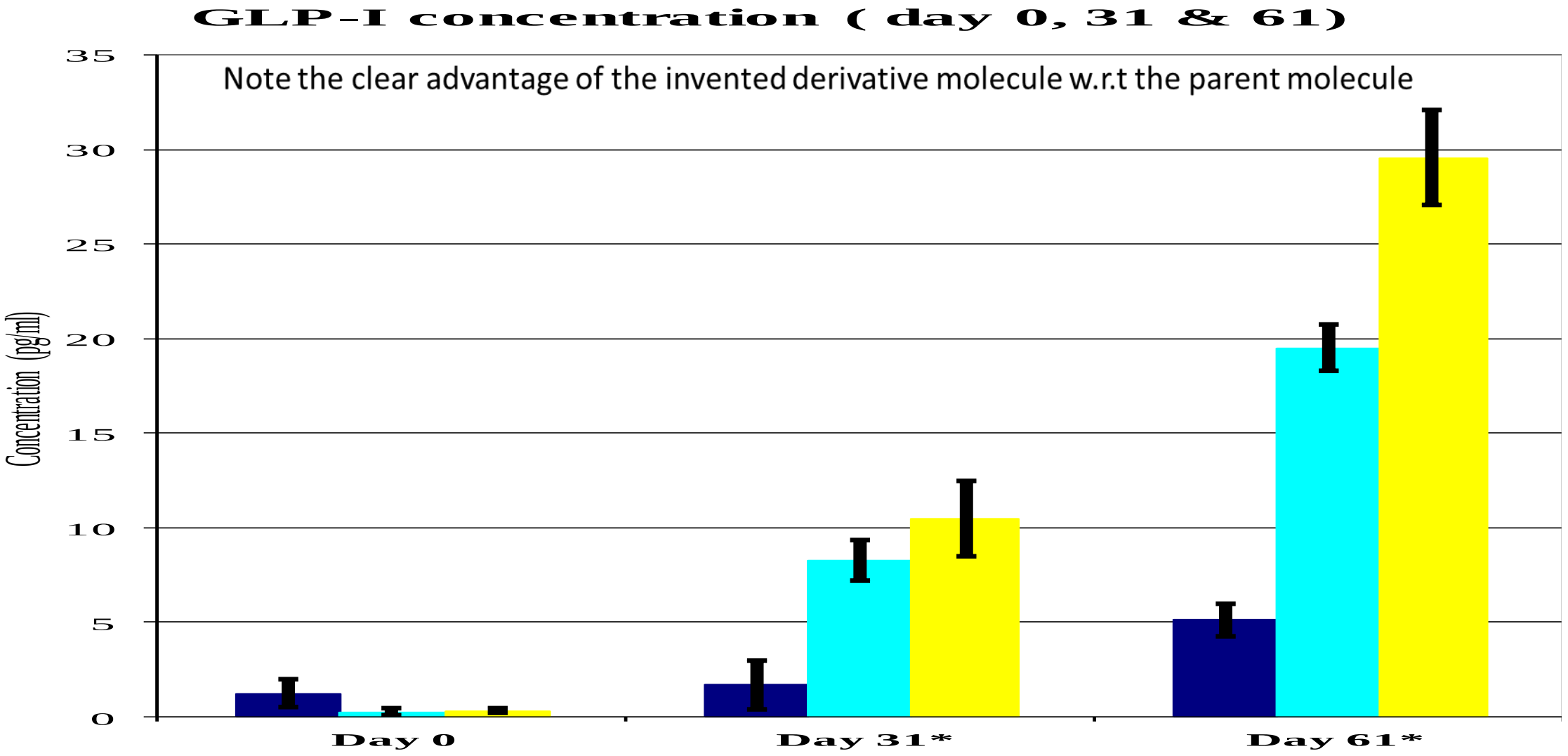
Results of OGTT in normal Wistar Rats



Results of OGTT in normal Wistar Rats



Summary of efficacy study in nSTZ rats



Case of Formulation and combination of drugs

Indian Patent No: IN 283909

Excellent Example of a formulation comprising combination of Drugs with demonstrated enhanced stability due to synergistically combining the various known ingredients in an inventive way

I. A stable solid oral pharmaceutical composition comprising Atenolol in amount of 6mg to 100mg, Simvastatin in amount of 5mg to 80mg, Ramipril in amount of 1.25mg to 20mg, hydrochlorothiazide in amount of 6mg to 50mg and optionally aspirin which is separated by coating,

wherein:

a. the Simvastatin has been granulated separately using an alcoholic binder solution;

b. the Atenolol has been granulated separately using an alcoholic binder solution; and

c. the granules of Simvastatin and Atenolol do not contain any organic acid.

Indian Patent No: IN 283909

➢Patent Office Objection under Section 3(e):

Response by Patent Applicant: The amended claim 1 is related a **stable composition with essential feature (a), (b) and (c), over the prior art** and not related to mere combination of active ingredients.

1. A stable solid oral pharmaceutical composition comprising Atenolol in amount of 6mg to 100mg, Simvastatin in amount of 5mg to 80mg, Ramipril in amount of 1.25mg to 20mg, hydrochlorothiazide in amount of 6mg to 50mg and optionally aspirin which is separated by coating,

wherein:

a. the Simvastatin has been granulated separately using an alcoholic binder solution;

b. the Atenolol has been granulated separately using an alcoholic binder solution; and

c. the granules of Simvastatin and Atenolol do not contain any organic acid.

The research was designed to demonstrate the claimed stability with all the features claims in the patent application

Indian Patent No: IN 283909

Novartis: Granted Indian Patent No 312642

- Bicyclic Fused Hetero Aryl or Aryl compounds and their use as IRAK4 Inhibitors

The object of the present invention overcomes the provision of new phosphoinositide-3 kinase (PI3K) inhibitors for the treatment of e.g. rheumatoid arthritis, multiple sclerosis, allergy (atopic dermatitis, contact dermatitis, allergic rhinitis), transplant rejection, cancers of haematopoietic origin, severe and cerebral malaria. This problem has been solved with the claimed compounds. The description discloses exemplary compounds as well as pharmacological data that substantiates the fact that the problem has been solved essentially over the whole of the claimed scope.

In other words, the law in relation to section 3(d) is very clear. If there is a known substance that known substance, it should have known efficacy. It is not enough for Section 3(d) to be attracted to show that there is some known compound in the prior art which allegedly bears some structural resemblance to the claimed compound.

Examples of Patents Granted to Pfizer by the Indian Patent Office

inPASS Indian Patent Advanced Search System (http://ipindia.nic.in/index.htm)

INTELLECTUAL PROPERTY INDIA PATENTS | DESIGNS | TRADE MARKS GEOGRAPHICAL INDICATIONS (http://ipinc

Patent Search

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Total Document(s): 754

Page: First <<

Application Number	Title	Application Date	Status		
201617033027	BICYCLIC FUSED HETEROARYL OR ARYL COMPOUNDS AND THEIR USE AS IRAK4 INHIBITORS	27/09/2016	Granted	E-Register	A
201617020814	PRE MOISTENED WIPES FOR USE IN TREATING ANAL RECTAL IRRITATIONS AND DISORDERS	17/06/2016	Granted	E-Register	A
201617017215	PYRROLO[2 3 D]PYRIMIDINYL PYRROLO[2 3 B]PYRAZINYL AND PYRROLO[2 3 D]PYRIDINYL ACRYLAMIDES	18/05/2016	Granted	E-Register	A
201617005421	HETEROBICYCLOARYL RORC2 INHIBITORS AND METHODS OF USE THEREOF	16/02/2016	Granted	E-Register	A
7226/DELNP/2015	ENHANCED STABILITY OF NOVEL LIQUID COMPOSITIONS	14/08/2015	Granted	E-Register	A
6803/DELNP/2015	PYRROLO [2 3 D]PYRIMIDINE DERIVATIVES AS INHIBITORS OF JANUS RELATED KINASES (JAK)	03/08/2015	Granted	E-Register	A
4262/DELNP/2015	GLYCOCONJUGATION PROCESS	19/05/2015	Granted	E-Register	A
2877/DELNP/2015	PROCESS FOR THE PREPARATION OF VORICONAZOLE AND ANALOGUES THEREOF	07/04/2015	Granted	E-Register	A
10186/DELNP/2014	IMPROVED ANTAGONIST ANTIBODIES AGAINST GDF 8 AND USES THEREFOR	28/11/2014	Granted	E-Register	A
7205/CHENP/2014	MACROCYCLIC DERIVATIVES FOR THE TREATMENT OF PROLIFERATIVE DISEASES	26/09/2014	Granted	E-Register	A

Boehringer Ingelheim Pharma GMBH & co. vs Intermed Laboratories Pvt Ltd ..... Decision of Pre-grant Opposition Dated 6th Nov,2012

This comparison shown that the crystalline monohydrate did not undergo particle growth and remained stable during micronization , whereas the compound of the prior art undergone reduction in the small size particles i.e. shown significant particle size growth. The compound of the present invention was more stable and maintained stability and uniform particle size during micronization and during the storage, which was an essential feature for successful administration of the drug for powder inhalation.

The opposition was rejected by the Patent Office as there was enough evidence to demonstrate the therapeutic effect

Lessons Learnt

- Clauses under Section 3(d), (e), (i) etc., not necessarily a hindrance to follow-on innovations and grant of Patents in India
- Challenge to the innovators to demonstrate credible utility

  Design research to overcome potential objections
- Argue appropriately to defend the patent application
- As regards the change in the present law, one will have to consider all the techno-legal features coupled with the socio-economic aspects at the appropriate national policy making body in the government.

  These can also be debated at the major international for a such as the WIPO, WTO, WHO., etc.