

# [Alogliptin, was to discover the favoured stereochemistry at](https://assignbuster.com/alogliptin-was-to-discover-the-favoured-stereochemistry-at/)

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Alogliptin, a pyrimidinedionebased potent and selective DPP 4 inhibitor was discovered by Syrrx (Takeda) inorder to treat patients suffering from type 2 diabetes. There were a lot ofproblems faced prior to the development and discovery of Alogliptin. One of themain problems was to identify a suitable heterocyclic scaffold that could beused clinically. Alogliptin discovery begun from a xanthine derivative whichwas, 7-(2-chlorobenzyl)-1, 3-dimethyl-8-(piperazin1-yl)-1H-purine-2, 6(3H, 7H)-dione. This was chosen from 80 co-crystal structures which had been collected fromhigh throughput crystallography. (Zhang et al.

, 2011) The 2-chlorobenzyl group hadbeen substituted by a 2-cyanobenzyl moiety, this caused a polar interactionbetween the cyano group and Arg125. Furthermore the piperazinyl group had beensubstituted by a 3-aminopiperidine moiety, this caused in increase in potency. Aselective and potent inhibitor was provided by substitution of the central ringby a quinazolinone scaffold which lead to inhibition of CP450 and hERGblockade. In order to conquer these problems further SAR studies were conducted. Alogliptin was produced from substitution of the quinazoline ring by apyrimidinone moiety which changed to a pyrimidinedione ring. Another problemfaced was to discover the favoured stereochemistry at the C-3 position of theaminopiperidine moiety. Prior to this the favoured R-stereochemistry was discoveredby preparation of both of the enantiomers of the xanthine-based inhibitor and testingthem for their in vitro inhibitory properties. Another issue which needed to besolved was the favoured orientation of the 3-amino group.

The 3 amino groupfavoured an axial orientation on the piperidine ring which was discovered bythe co-complex of Alogliptin with the active site of DPP IV. Calculations suchas the ab initio which took place on the axial and equatorial conformationindicated a major stabilization of the axial conformation. This was as a resultof the nitrile amine interaction. A chair form was displayed in the axialconformer and a boat form was noted in the equatorial conformer of the piperidinering. In conclusion task of the axial chair conformer aided by numerouscalculations had met the desired fit to the binding site.

Once this was done andtoxicology assessments had been conducted to assess the in vivo profile ofAlogliptin in rats and dogs, Alogliptin had been considered for developmentclinically. (Parsa and Pal, 2011)Teneligliptin was discoveredthrough a series of processes. (Yoshida et al., 2012) Firstly investigationstook place on the connections between bicyclic heteroarylpiperazines replacedat the ?-position of the proline structure while investigatingl-prolylthiazolidines. As a result of this a very potent, selective, longlasting and orally active DPP-4 inhibitor was discovered known as 3-(2S, 4S)-4-4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-ylpyrrolidin-2-ylcarbonylthiazolidine(8 g). This has a distinctive structure consisting of 5 consecutive rings.

DPP4 potency had been increased as well as selectivity. This was found by an x-rayco-crystal structure of 8 g in DPP-4 showing the prime interaction amongst thephenyl ring on the pyrazole and the S(2) extensive subsite of DPP-4. Thecompound 8g, at 0. 03mg/kg or even at a higher dose showed notable inhibitoryeffects on the increase of plasma glucose levels following an oral glucose loadin Zucker fatty rats. The compound 8g now known as Teneligliptin has beenapproved in treating type 2 diabetes in Japanese patients.

(Singh, 2017)Structural baseddrug design was used in order to aid the discovery process of trelagliptin. Co -complex x ray crystal structures were acquired which showed Trelagliptin binding to DPP 4. Fig 1 displays the co-complexstructures of trelagliptin in the active site of DPP-4. Observations of this led to thefact that the aminopiperidine creates a salt bridge to Glu205/206. On the otherhand the cyanobenzyl group occupies the S1 pocket and upon doing so it has an interactionwith Arg125. A key hydrogen bond is formed as a result of 2-position carbonylinteracting with the backbone NH of Tyr631. Furthermore the uracil ring pistacks with Tyr547.

One of the key features of the atomic structure oftrelagliptin is that there is a fluorine atom at the 5-position of thecyanobenzyl group. By looking at the area near the fluorine atom one can notethat the DPP 4 active site shows the proximity of the following residues Trp659, Tyr631, and Val656. Fig 2After observing the radius of theelements it was found that Van der Waals distance of the fluorine dictated thathydrogen atoms are the only residues that fit this category.

A permanentpartial positive charge is held by the hydrogen atoms this is because of theposition the aromatic rings of Trp659 and Tyr631 take. Furthermore another positivecharge is present which is inducible and occurs on the side chain of Val656. In comparison to hydrogen atomsat the 5-position, fluorine contains a persistent partial negative changetherefore they would be able to produce an added attractive force betweenligands and proteins. Although the added attractionwould be relatively low in terms of its effectiveness it might still be accountablefor the 4-fold potency rise in trelagliptin. Trelagliptin binds to DPP-4non-covalently and does not cause toxicity.  (Grimshaw et al., 2016) Dipeptidyl peptidase-4 (DPP – 4) inhibitors are a class oforal hypoglycaemic drugs, used in the treatment of type 2 diabetes mellitus.

They aim to inhibit the action of an enzyme known as DPP – 4which destroys the hormone incretin. Incretins aid the body by producing an increased amount ofinsulin when required, additionally incretin reduces glucose levels whenglucose is not needed. The incretin hormone is released during the day and theamount of incretin released is higher during meals.

DPP – 4 inhibitors exert their therapeutic effects byincreasing incretin which inhibits the release of glucagon. This causes anincrease in insulin secretion leading to a decrease of gastric emptying and areduction of blood glucose levels. As a result of this DPP 4 inhibitors make it easier tocontrol glycaemia increasing active incretin levels. A physiological mechanism is used by DPP 4 inhibitors inorder to control hyperglycaemia. The mechanism works by stimulation of the secretion ofinsulin from B – cells. This leads to a decrease in secretion of glucagon frompancreatic A – cells which causes a reduction in the build up of glucose by theliver. DPP 4 inhibitors are also known to improve liver dysfunction in thosewhom suffer from type 2 diabetes. The level of efficacy is high in DPP 4 inhibitors in termsof keeping levels of glycosylated haemoglobin at a low constant.

Studiesconducted in vitro and on animals have shown that DPP 4 inhibitors can blockapoptosis of B – cells which can be beneficial for their regeneration anddifferentiation. The benefits of taking DPP 4 inhibitors rather than someother anti-diabetic agents is that DPP 4 inhibitors do not affect the bodyweight and have a low risk of hypoglycaemia. The first DPP 4 inhibitor Sitagliptin was FDA approved inthe year of 2006A recently approved DPP 4 inhibitor Omarigliptin wasapproved in Japan in the year 2015.  Astudy was conducted in order to assess the safety and efficacy of omarigliptinin comparison to Sitagliptin. The sample tested upon were Japanese patients of whomsuffered from type 2 diabetes.

Randomized control trials was the method usedfor this study which took place over a time period of 24 weeks. The sample sizeconsisted of 414 patients whom were split into groups either taking omarigliptin25mg once weekly, Sitagliptin 50mg once daily or a placebo. One of thehypotheses tested was that omarigliptin is non inferior to Sitagliptin inreducing HbA1c levels. Results were in correlation to this hypothesis, this wasas the results showed that the least squares mean difference in the baselinechanges of HbA1c of omarigliptin and Sitagliptin was only -0.

02%. Due to theirbeing such a small difference this met the criteria for omarigliptin not beinginferior to Sitagliptin. Also to note over the 24 week period of time therewasn’t any clinically important differences in the incidence rates of the drugsamongst the patients. However there was 1 incident were symptomatichypoglycaemia occurred in the Sitagliptin group, one the other hand no incidentsoccurred in the omarigliptin group. Moreover body weight had not been effectedas a result of taking omarigliptin. There isn’t any major difference between the DPP 4 inhibitorsSitagliptin and Omarigliptin in terms of their therapeutic effects.    DPP 4 inhibitors such as Vildagliptin, Sitagliptin andSaxagliptin are efficient when taken on their own and can be taken alongsideother oral anti diabetic drug such as metformin and acarboseA pooled analysis study consisting of 25 randomised clinicaltrials was conducted which showed that Sitagliptin does not lead to anycardiovascular risks in sufferers of type 2 diabetes. A clinical trial was conducted to assess the efficacy andsafety of omarigliptin.

Patients whom suffer from type 2 diabetes who currently usemetformin and glimepiride were tested on with omarigliptin. Tests took placefor 24 weeks and findings showed that taking omarigliptin once weekly improvedglycaemic control and was tolerated well. Furthermore omarigliptin was found tobe better than the former drugs used which were metformin and glimepiride. Omarigliptin was taken once weekly amongst 4202 patients of type 2 diabetes inorder to assess whether or not there were any cardiovascular side effectsassociated with consuming this drug. After 96 weeks results indicated that thedrug omarigliptin was well tolerated amongst consumers and it did not increasethe risks of cardiovascular problems such as heart failure. A meta-analysis was conducted to investigate the relationshipbetween DPP 4 inhibitors and risks associated with them causing heart failurein patients with type 2 diabetes. The methods used were randomized controltrials.

Findings showed that the risks of heart failure upon dosing withVildagliptin, Sitagliptin or Saxagliptin were low. However there was arelatively high risk of heart failure with Alogliptin. The order of safest toleast safe in terms of causing heart failure was from Vildagliptin, Saxagliptin, Sitagliptin, Linagliptin and AlogliptinA major difference between Linagliptin and other DPP 4inhibitors is that Linagliptin has a largely non renal excretion routetherefore adjustment of dose is not required when given to patients sufferingfrom renal impairment. Furthermore dose adjustments are also not required forpatients suffering from hepatic impairment. This could be due to Linagliptinpossessing a large therapeutic window. In DPP 4 inhibitors Sitagliptin, Saxagliptin and Alogliptin dose adjustment would have to be required forpatients suffering from renal impairmentWarning labels were added to the DPP 4 inhibitorssitagliptin, saxagliptin, linagliptin and alogliptin as they have the potentialto cause severe joint pain that may be disabling. A meta-analysis conducted by scientists Marfella, Barbieri, Grella, Rizzo, Nicoletti and Paolisso to compare the effects of DPP-4inhibitors, Sitagliptin and Vildagliptin had been executedFindings from this study had shown that there had beensimilar reductions in HbA1c of both drugs. Although evidence showed thatVildagliptin had decreased the glycaemic changes at a greater magnitude thanthat of Sitagliptin.

The development process of DPP – 4 inhibitors started whenDPP-4 inhibitors were used as a therapeutic agent for the treatment of type 2diabetes. This was based upon the fact that DPP-4 is the primaryenzyme used in the regulation of the incretin hormone GLP-1 which is used fortreatment of type 2 diabetes.  From these findings a hypothesis was made that inhibition ofDPP-4 could cause increased GLP-1 circulationThis hypothesis was confirmed by research scientists Balkan, Kwasnik, Miserendino, Holst and Li whom used Zucker fatty rats for testingDPP-4 inhibitors on and had found that glucose tolerance and insulin secretionhad improved as a result of this. This was caused by an increase in GLP-1 which occurred dueto DPP-4 inhibitors. GLP-1 stimulates release of insulin and causes inhibition ofglucagon production in a way which relies upon glucose therefore the mechanismis believed to have a low risk of hypoglycaemia. In the year of 2002 a 4 week study had been conducted inorder to learn about the inhibitory effects of Dipeptidyl Peptidase IV onmetabolic control in type 2 diabetes.

Findings had shown that HbA1c had reducedby 0. 6% in patients after being treat with DPP 4 inhibitorsThis study did not discover the underlying mechanismsresponsible for the beneficiary effects of DPP -4 inhibitors on the glycaemiccontrol in humans however. A systematic review and meta-analysis study was conducted byLing Li and colleaguesThe aim of this review was to investigate the possibility ofDPP-4 inhibitors causing heart failure in patients suffering from type 2diabetes. Findings from this study showed that risks of DPP 4 inhibitorscausing heart failure in patients suffering from type 2 diabetes is unknown. This is due to a lack of relevant evidence in support of either DPP 4inhibitors causing heart failure or not. However evidence was found whichindicated that DPP 4 inhibitors may have detrimental effects on those alreadysuffering from cardiovascular diseases.

Specifically the drugs which were responsible for slightincreased risks of heart failure were Saxagliptin and Alogliptin, this lead tothe FDA to attach warning labels on these drug packages. The drug Saxagliptin was tentatively approved which meansthat even though the drug meets the safety, efficacy and manufacturingstandards it still cannot be sold in the US. Saxagliptin has also been rejected in India due to patentingissues. Comparisons between different DPP 4 inhibitors on theirtherapeutic effects, metabolic properties and dosage differences are scarce. Current data used in order to compare and contrast the properties of DPP 4inhibitors shows that almost all obtainable DPP 4 inhibitors have similareffects and efficacy. Teneligliptin, a DPP 4 inhibitor approved in Japan in the year2012 hasn’t been in the market for long enough therefore post marketingsurveillance is still ongoing. In order to draw a comparison betweenteneligliptin and other DPP 4 inhibitors additional time would be required tosee whether any new discoveries on the drug are found.

In the year of 1993 in vitro studies were performed, thesestudies found that DPP 4 causes both gip and glp – 1 to become n-terminallydegraded to an inactive metabolite. In the year of 1995 DPP 4 inhibition begunto be something which was considered in order to treat sufferers of type 2diabetes. In 2001 a study was conducted on type 2 diabetes patients, from thisstudy clinical evidence showed glucose to become decreased along with fastingblood glucose and HbA1c after consumption of an early DPP 4 inhibitor by thepharmaceutical company Novartis. This provoked further research which led totesting Vildagliptin for 52 weeks.

GLP 1 levels are increased as a result of DPP 4 inhibitionwhich causes a prevention and inactivation of GLP 1. Increase in GLP 1 ispresent within 24 hours of consumption.  Studies conducted on animals show that DPP 4 inhibition doesnot improve glucose homeostasis. Rather GLP 1 stimulates insulin secretion which causes animprovement in the acute B cell function by inhibition of DPP 4. Reports forVildagliptin have supported this. Inhibition of glucagon secretionby DPP 4 inhibition is also an important mechanism in improvement of glycaemiccontrol. This has been shown when Vildagliptin at 100mg was consumed for 4weeks. Furthermore, a study showed thatthe glucagon profile for a whole 24-hour period is reduced by Vildagliptin.

A recent study found that byreducing glucagon levels due to an increase of insulin secretion by consumptionof 100mg Vildagliptin on patients with type 2 diabetes, had caused aninhibition of hepatic glucose production.  DPP 4 inhibitions might alsoimprove insulin sensitivity, findings have supported this as treatment withVildagliptin using both direct and indirect measure insulin sensitivity alongwith a hyperinsulinemia euglycemic clamp test. This could be due to a reductionof levels of glucagon as a result of DPP 4 inhibition that causes animprovement of insulin action by improved metabolic control. A DPP 4 inhibitor program at Merck was provoked in the year1999 due to the emergence of glucagon-like peptide 1 (GLP-1) as a valid advancein treating patients suffering from diabetes. The programme started with thelicensing of DPP-4 inhibitors threo- andallo-isoleucyl thiazolidide, although problems faced with these chemicals leadto their development to become discontinued. The problems associated withboth of these DPP 4 inhibitors were that they produced toxicity which wasconfirmed by studies conducted on rats and dogs. An observation was made asboth of the compounds inhibited the proline peptidases DPP8 and DPP9 this ledto the hypothesis that inhibition of DPP8 and/or DPP9 could cause toxiceffects.

This lead to attempts based ondiscovering a selective DPP 4 inhibitor. Work begun on isoleucyl thiazolididewhich was later discontinued as the chemical compound lacked selectivity. Structural studies took place on two screening leads which led to the discoveryof a very selective B- amino acid piperazine. In order to keep the piperazinemoiety balanced, a number of bicyclic derivatives were arranged, extensivemetabolization occurred in vivo. This was done until a potent and selectivetriazolopiperazine series could be discovered. These anologs presented greatpharmacokinetic effects in the preclinical speciesThe discovery of Sitagliptin whichis a very selective DPP 4 inhibitor was made due to the optimization of theseseries of clinical trials.