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Patent Highlight

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Plasma Kallikrein Inhibitors for the Treatment of Retinal Vascular Permeability Associated with Diabetic Retinopathy and Diabetic Macular Edema

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Patent Application Title:	Heteroarylcarboxamide derivatives as plasma kallikrein inhibitors		
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Priority Application:	EP 15191757.2	**Priority date:**	27 October 2015
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Applicant:	Boehringer Ingelheim International GMBH; Binger Strasse 173, 55216 Ingelheim Am Rhein (DE)		
Disease Area:	Diabetic complications, particularly retinal vascular permeability associated with diabetic retinopathy and diabetic macular edema	**Biological Target:**	Plasma kallikrein (KLKB1)

Summary:

The invention in this patent application relates to five-membered heteroarylcarboxamide derivatives represented generally by formula I. These compounds are plasma kallikrein inhibitors and may be used for the treatment and/or prophylaxis of diabetic complications, particularly retinal vascular permeability associated with diabetic retinopathy and diabetic macular edema.

Plasma kallikrein (KLKB1) is a trypsin-like serine protease. It is secreted by the hepatocytes in the liver as an inactive precursor named plasma prekallikrein (PK). PK remains in the plasma either as a free zymogen or as a heterodimeric complex with the high molecular weight kininogen. This heterodimeric complex is activated by factor XII (FXII) to generate the active plasma kallikrein; this activation affects the release of kinins (including bradykinin) from kininogens. Kinins are potent mediators of inflammation that act through G protein-coupled receptors such as bradykinin receptors.

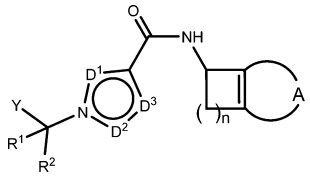
Available data implicate plasma kallikrein activities in a number of inflammatory disorders such as diabetic macular edema (DME) and hereditary angioedema (HAE) among many others. The high levels of blood sugar can damage blood vessels in the retina of diabetes patients causing them to leak fluids into the retina, which is a disorder known as diabetic retinopathy. DME occurs when fluids from the damaged blood vessels leak into the macula. This disorder is a main cause of vision impairment or loss in diabetes patients. HAE is a rare disease that is caused by an inherited deficiency or mutation of the C1-inhibitor protein. This protein is a physiological inhibitor of the plasma kallikrein protease. The disease occurs because of excessive production of bradykinin in a process mediated by plasma kallikrein. It is characterized by recurrent painful edema that affect different parts of the body such as the hands, feet, face, and abdomen.

The inventors mentioned a very long list of additional inflammatory disorders that may be caused by the activities of plasma kallikrein including proliferative and nonproliferative retinopathy, clinically significant macular edema (CSME), cystoid macular edema (CME), CME following cataract extraction, CME induced by cryotherapy, CME induced by uveitis, endophthalmitis, CME following vascular occlusion (e.g., central retinal vein occlusion, branch retinal vein occlusion, or hemiretinal vein occlusion), retinal edema, complications related to cataract surgery in diabetic retinopathy, hypertensive retinopathy, retinal trauma, dry and wet aged-related macular degeneration (AMD), polypoidal choroidal vasculopathy (PCV), intracerebral hemorrhage, hemorrhagic transformation of ischemic stroke, cerebral trauma associated with injury or surgery, brain aneurysm, and many more.

Therefore, the inhibition of plasma kallikrein may be a useful therapeutic target to develop medicaments for the treatments of many of these disorders, particularly those associated with edema formation such as edema related to ischemic reperfusion injuries, DME, HAE, and brain edema. Plasma kallikrein inhibitors may particularly be useful in the treatment of retinopathy, e.g., retinopathy associated with diabetes and/or hypertension, and in the treatment of macular edema, e.g., macular edema associated with diabetes and/or hypertension.

While there are plasma kallikrein inhibitors already known in the art; there exists a need for inhibitors with enhanced potency and bioavailability, high metabolic and/or chemical stability, high selectivity and tolerability, desirable plasma protein binding, and improved pharmacokinetic profiles. The compounds of formula I in this patent application are described to possess these properties and may potentially provide needed useful treatments for many of the above-mentioned disorders, particularly in reducing retinal vascular permeability associated with diabetic retinopathy and DME retinopathy or edema-associated diseases. Kallikrein inhibitors may treat additional diabetes complications such as cerebral hemorrhage, nephropathy, cardiomyopathy, and neuropathy.

Important Compound Classes:



Formula I

Key Structures: The inventors described 16 examples of formula I including the following representative examples:

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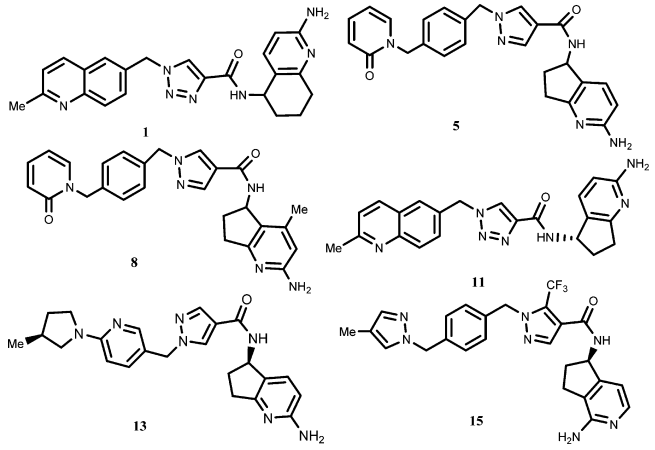

Biological Assay: The following are some of the assays reported by the inventors:

- Evaluation of the inhibition of KLKB1 using an end point assay
- Evaluation of the inhibition of human KLKB1 in Dextransulfat activated human PPP
- Evaluation of the inhibition of KLKB1 (K_i)
- Evaluation of the inhibition of FXIIa (K_i)

Biological Data: The IC_{50} values for the inhibition of KLKB1 obtained from testing the above representative examples are listed in the following table:

IC_{50} data for the inhibition of human Plasma Kallikrein (KLKB1)			
Compound	IC_{50} (nM)	Compound	IC_{50} (nM)
1	900	**11**	1900
5	9	**13**	19
8	4	**15**	1

Recent Review Articles:

1 Kolte, D.; Shariat-Madar, Z. *Cardiol. Rev.* **2016**, *24* (3), 99−109.

2 Murakami, T. *Diabetes* **2015**, *64* (10), 3350−3352.

3 Masuda, T.; Shimazawa, M.; Hara, H. *Eur. J. Pharmacol.* **2015**, *749*, 161−163.

4 Feener, E. P.; Zhou, Q.; Fickweiler, W. *Thromb. Hemost.* **2013**, *110* (3), 434−441.

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Notes

The author declares no competing financial interest.

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