MMP-13 antagonist | BI-4394

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Summary

BI-4394 is a potent and highly selective inhibitor of MMP-13 that can be used as tool compound to test biological hypotheses *in vitro*.

Chemical Structure

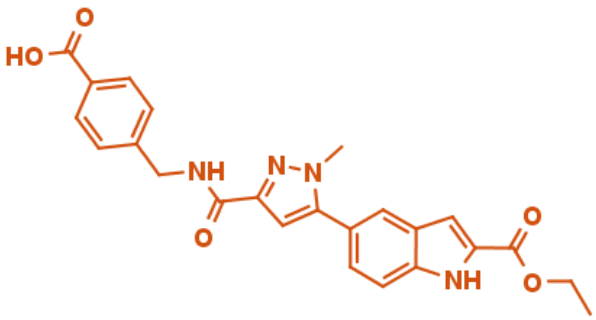

Figure 1: 2-D structure of BI-4394, a MMP-13 antagonist

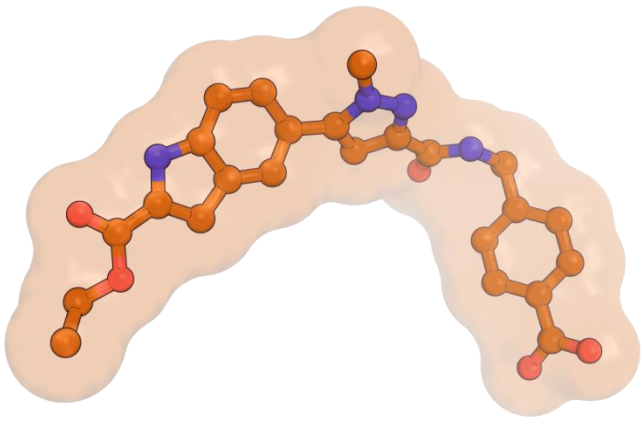

Figure 2: BI-4394, 3D conformation

Highlights

BI-4394 is a highly potent inhibitor of MMP-13 (IC_{50} = 1 nM) with excellent (>1000 fold) selectivity against several other metalloproteinases and is thus a high quality tool compound for testing biological hypotheses involving this target.

Target information

Matrix metalloproteinases (MMPs) are zinc- and calcium-dependent peptidases, involved in the cleavage of collagen, gelatin and other proteins in the extracellular matrix and tissue remodelling. There are approximately 23 known human MMPs that are grouped into subtypes based on their substrates. MMPs have a conserved active site motif where a tris(histidine)-bound zinc(II) acts as the catalytic site for substrate hydrolysis. MMP-13 (also known as collagenase 3, CLG3) is the most efficient enzyme of this class at degrading collagen II, the committed step in articular cartilage degradation and progressive joint damage associated with rheumatoid arthritis (RA). Broad-spectrum MMP inhibitors have failed in clinical trials at least in part due to a joint-stiffening side effect, termed musculoskeletal syndrome (MSS). This was likely due to inhibition of MMPs other than MMP-13 and high selectivity for MMP-13 over other MMPs is therefore favourable.

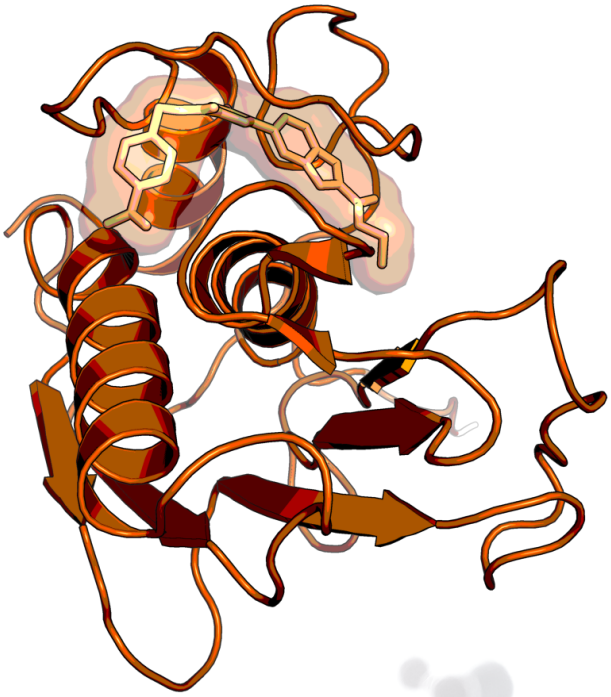

Figure 3: BI-4394 bound to MMP-13, as observed by X-ray crystallography (PDB code: 5BPA)

In vitro activity

BI-4394 is a potent inhibitor of MMP-13 with an IC_{50} value of 1 nM.

PROBE NAME / NEGATIVE CONTROL	BI-4394	BI-4395
MW [Da]	446.5	374.4
Inhibition of MMP-13 (IC_{50}) [nM]	1	>26,000
Inhibition of bovine nasal cartilage with human full length MMP-13 (IC_{50}) [nM]	31	n.d.

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BI-4394		BI-4395	
logP (pH 2)	1.9		n.d.	
Solubility @ pH 7.4 [µg/ml]	60		>96 (pH 7)	
Solubility @ pH 4 [µg/ml]	<0.1		<0.1	
CACO permeability @ pH 7.4 [$*10^{-6}$ cm/s]	0.6		n.d.	
CACO efflux ratio	27		n.d.	
Microsomal stability (human/rat) [% Q_H]	40	41	25	n.d.
Plasma protein binding (human) [%]	98		n.d.	

In vivo DMPK parameters

BI-4394	RAT
Clearance [ml/(min*kg)][b]	39
Mean residence time after *iv* dose [h]	0.5
F [%]	39
Vss [l/kg]	0.4

[b] *iv* dose: 1 mg/kg

Negative control

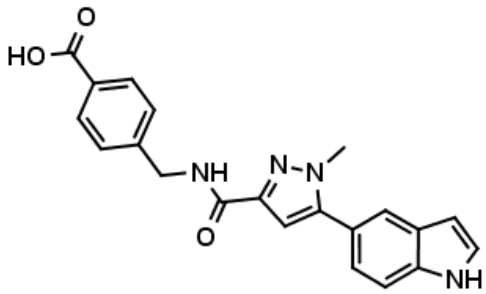

Figure 4: BI-4395 which serves as a negative control

Selectivity

BI-4394 is highly (>1000 fold) selective against other matrix metalloproteinases (MMP-1, 2, 3, 7, 8, 9, 10, 12, 14):

MMP	1	2	3	7	8	9	10	12	13	14
IC_{50} [µM]	>22	18	>22	>22	>22	8.9	16	>22	0.001	8.3

BI-4394	SELECTIVITY DATA AVAILABLE
Cerep®	Yes
Panlabs®	No
Invitrogen®	Yes
DiscoverX®	No
Dundee	No

Invitrogen:

18/56 kinases hit >50 inhibition at 10 µM: STK6 (99%), MAPKAPK2 (99%), RPS6KA3 (95%), MAPK14 (94%), GSK3B (94%), AMPK A1B1G1 (92%), PRKACA (90%), PIM1 (86%), KDR (83%), AKT1 (76%), SRC (75%), DYRK3 (72%), MAP4K4 (68%), MET (57%), JAK3 (56%), IKBKB (52%), ABL1 (52%), NEK1 (51%).

Co-crystal structure of the Boehringer Ingelheim probe compound and the target protein.

X-Ray co-crystal structure of BI-4394 bound to MMP-13 is available (see Figure 3, PDB code: 5BPA).

Summary

Matrix metalloproteinases (MMPs) are zinc-dependent peptidases involved in collagen degradation in the extracellular matrix. They play an important role in cartilage homeostasis and are involved in arthritic diseases. BI-4394 is a highly potent inhibitor of MMP-13 (IC_{50} = 1nM), displays excellent selectivity over other MMPs, and inhibits the degradation of bovine nasal cartilage with human full length MMP-13 with an IC_{50} value of 31 nM. Thus, BI-4394 is high quality tool for testing biological hypotheses involving MMP-13.

Supplementary data

Selectivity data can be downloaded free of charge from opnMe.

References

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