MMP13 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

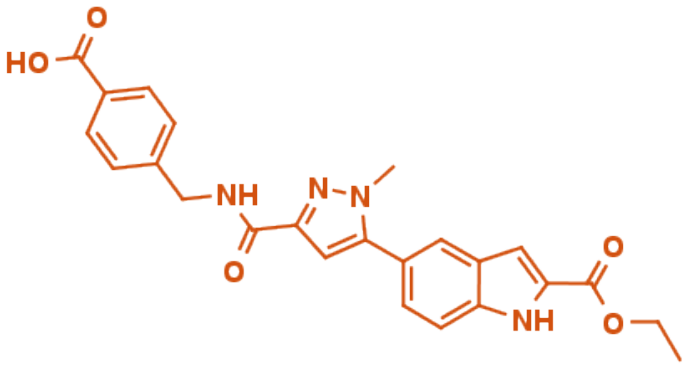

Figure 1: 2-D structure of BI-4394, a MMP13 antagonist

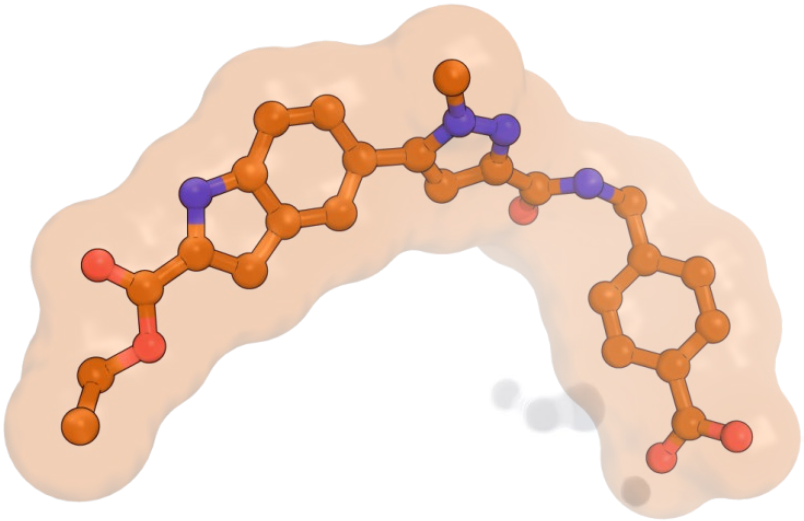

Figure 2: BI-4394, 3D conformation

Highlights

BI-4394 is a highly potent inhibitor of matrix metalloproteinase MMP-13 (IC_{50} = 1 nM) with excellent selectivity (> 1,000-fold) against several other matrix metalloproteinases. This compound is a high-quality tool to test, in vitro, biological hypothesis involving this target. According to the UK Third Generation Cannabinoid Act, the molecule cannot be shipped to the United Kingdom.

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.

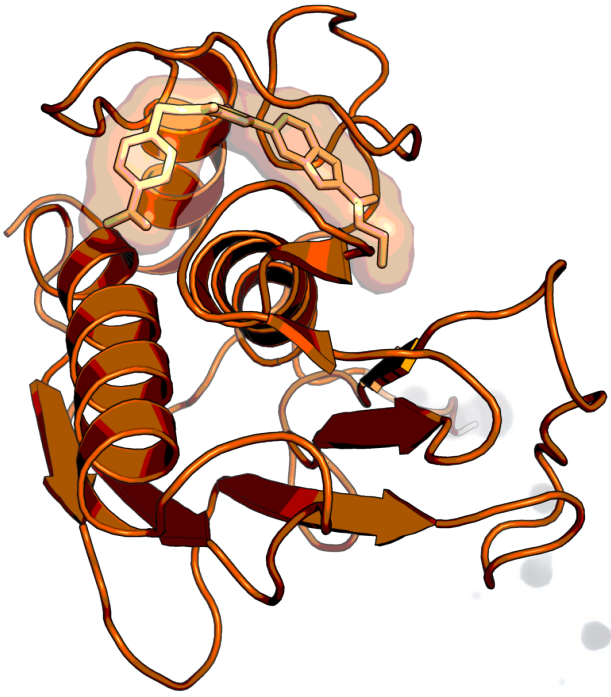

Figure 3: BI-4394 bound to MMP13, as observed by X-ray crystallography (PDB code: 5BPA)

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 @pH7.4 [$*10^{-6}$ 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 *i.v.* dose [h]	0.5
F [%]	39
V_{ss} [l/kg]	0.4

[b] *i.v.* dose: 1 mg/kg

Negative control

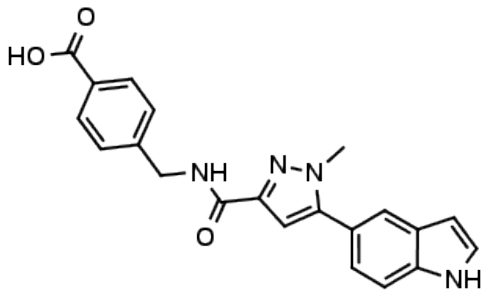

Figure 4: BI-4395 which serves as a negative control

Selectivity

BI-4394 is highly (>1,000 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

SELECTIVITY DATA AVAILABLE	BI-4394	BI-4395
SafetyScreen44™ with kind support of eurofins	Yes	Yes
Invitrogen®	Yes	No
DiscoverX®	No	No
Dundee	No	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).

Supplementary data

Selectivity data can be downloaded free of charge from opnMe.

References

1. Parks W. C., Wilson C. L., López-Boado Y. S. Matrix Metalloproteinases as Modulators of Inflammation and Innate Immunity, *Nature Reviews Immunology* **2004**, *4*, 617. doi:10.1038/nri1418, PubMed.
2. Taylor S. J., Abeywardane A., Liang S., Muegge I., Padyana A. K., Xiong Z., Hill-Drzewi M., Farmer B., Li X., Collins B., Li J. X., Heim-Riether A., Proudfoot J., Zhang Q., Goldberg D., Zuvela-Jelaska L., Zaher H., Li J., Farrow N. A. Fragment-Based Discovery of Indole Inhibitors of Matrix Metalloproteinase-13, *J. Med. Chem*. **2011**, *54*, 8174. dx.doi.org/10.1021/jm201129m, PubMed.
3. Heim-Riether A, Taylor S. J., Liang S., Gao D. A., Xiong Z., Michael August E., Collins B. K., Farmer B. T. 2nd, Haverty K., Hill-Drzewi M., Junker H. D., Mariana Margarit S., Moss N., Neumann T., Proudfoot J. R., Keenan L. S., Sekul R., Zhang Q., Li J., Farrow N. A. Improving potency and selectivity of a new class of non-Zn-chelating MMP-13 inhibitors, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5321. doi:10.1016/j.bmcl.2009.07.151, PubMed.
4. Gao D.A., Xiong Z., Heim-Riether A., Amodeo L., August E. M., Cao X., Ciccarelli L., Collins B. K., Harrington K., Haverty K., Hill-Drzewi M., Li X., Liang S., Margarit S.M., Moss N., Nagaraja N., Proudfoot J., Roman R., Schlyer S., Keenan L.S., Taylor S., Wellenzohn B., Wiedenmayer D., Li J., Farrow N. A. SAR studies of non-zinc-chelating MMP-13 inhibitors: Improving selectivity and metabolic stability, *Bioorg. Med. Chem. Lett.* **2010**, 20, *5039*. http://dx.doi.org/10.1016/j.bmcl.2010.07.036, PubMed.
5. Ruminski P. G., Massa M., Strohbach J., Hanau C. E., Schmidt M., Scholten J. A., Fletcher T. R., Hamper B. C., Carroll J. N., Shieh H. S., Caspers N., Collins B., Grapperhaus M., Palmquist K. E., Collins J., Baldus J. E., Hitchcock J., Kleine H. P., Rogers M. D., McDonald J., Munie G. E., Messing D. M., Portolan S., Whiteley L. O., Sunyer T., Schnute M. E. Discovery of N-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2S,5R)- 5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2H-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide. A Highly Selective and Orally Bioavailable Matrix Metalloproteinase-13 Inhibitor for the Potential Treatment of Osteoarthritis, *J. Med. Chem.* **2016**, *59*, 313. http://dx.doi.org/10.1021/acs.jmedchem.5b01434, PubMed.