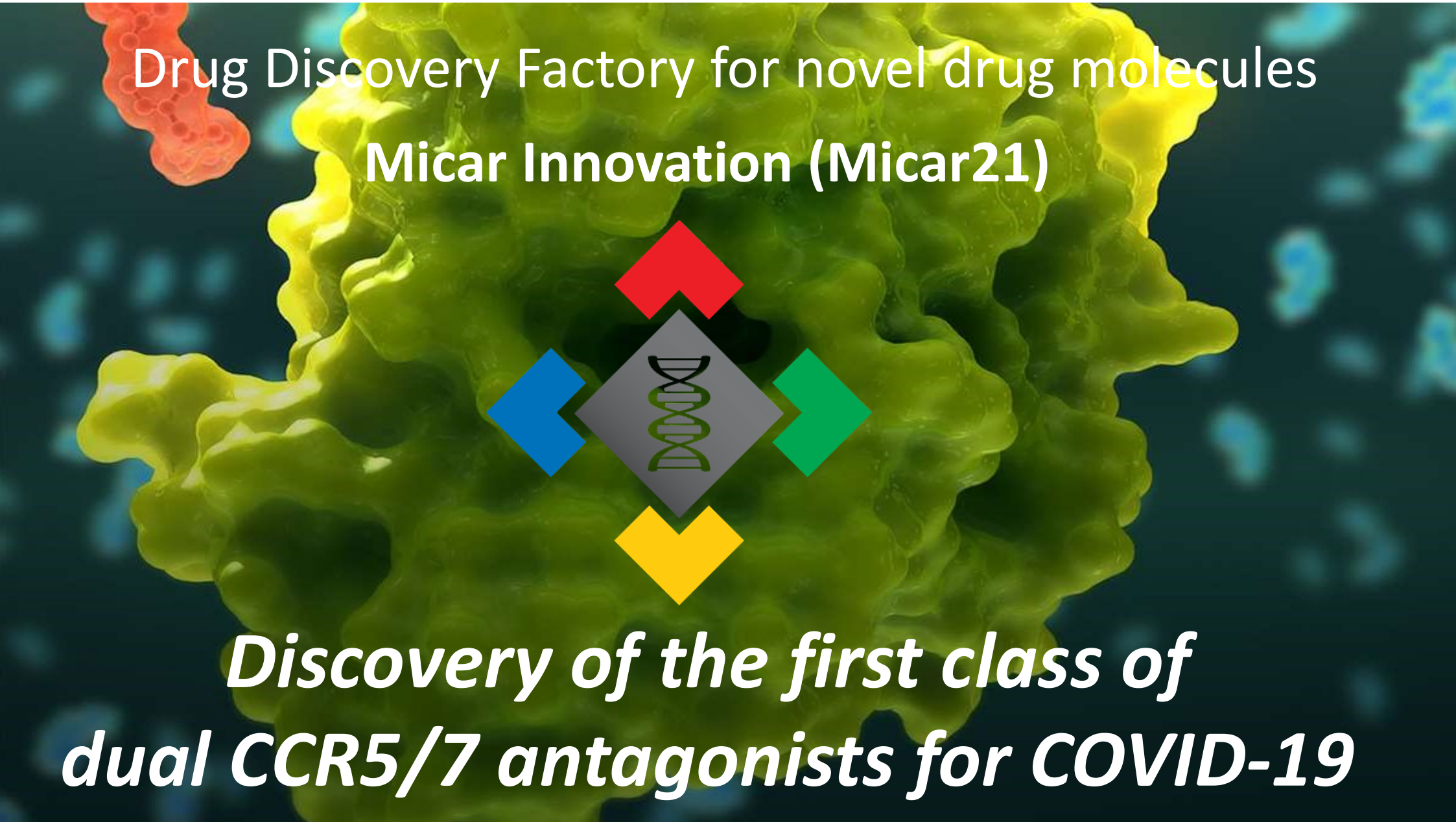
Drug Discovery Factory for novel drug molecules
Micar Innovation (Micar21)
Discovery of the first class of
dual CCR5/7 antagonists for COVID-19

CCR5/7 project

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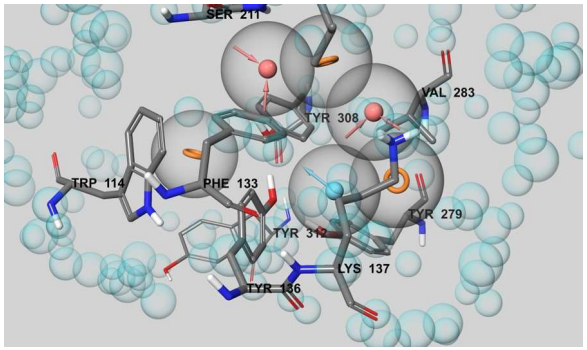
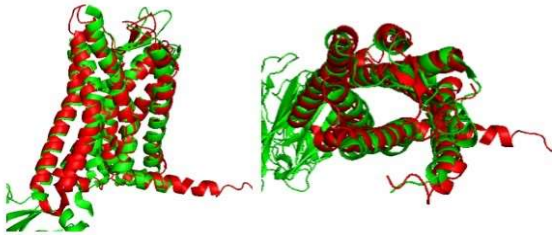
- Despite that CCR5/7 are a key targets for HIV, Coronavirus, Cancer metastasis and many other diseases only few antagonists have been developed up to date for CCR5 and non for CCR7. However, one of CCR5 antagonists is under clinical trial in US now (phase 2).
- We aimed to identify the fist class of dual CCR5/CCR7 small molecule antagonists
- We used intensive MD simulations (several 1 µs runs) to obtain the CCR5 and 7 structures
- A combination of structural based pharmacophore, docking, IFD and MD approaches were employed in a virtual screen of 4 million compounds
- The most promising compounds have been sent to ThermoFisher companies for bioassays to study both their binding capability and biological response; i.e. whether they are agonists or antagonists
- The compounds have been also studied for their cascade biological response paths: Ca+ mobilization and cAMP assays
- The biological response of most promising hit to the ERK path and GTPyS binding is currently under evaluation in a lab located in Belgium.



CCR5 pharmacophore model employed (top) and binding mode of one of the identified possible VS hits (bottom)



Alignment of MD optimized homology model (rendered in red) vs X-Ray (rendered in green)

CCR5/7 antagonists – Lead1

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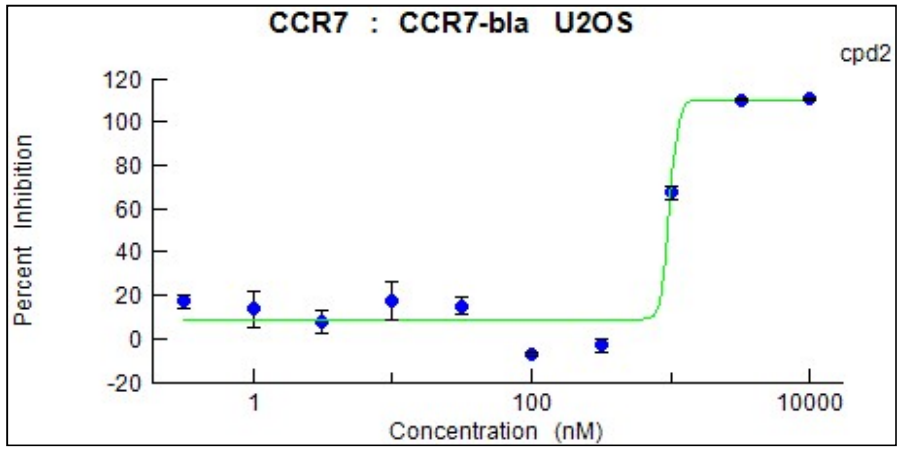
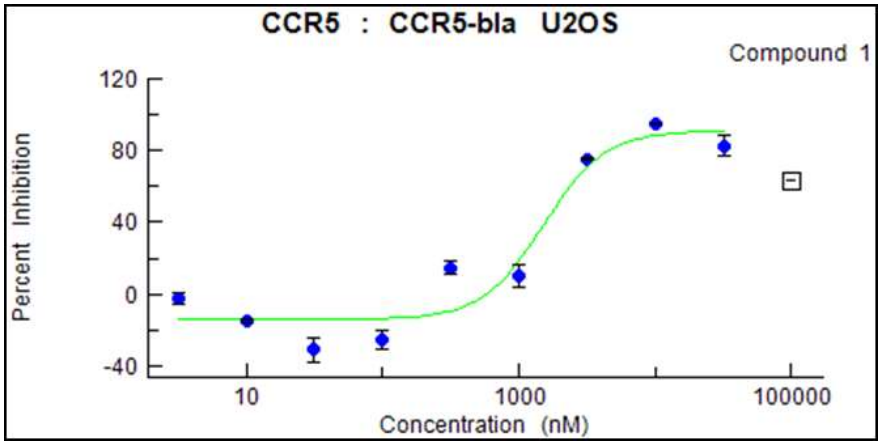
Thermo Fisher Scientific's SelectScreen™ Profiling Service: 10-point Titration Antagonist Results (β-arrestin binding assay)

Series of biological tests showed that Lead 1 (cpd2) is an antagonist of CCR7; No any agonist activity was detected



IC_{50} = 980 nM

Series of biological tests showed also that Lead 1 (compound 1) is an antagonist of CCR5



IC_{50} = 1.9 µM

Nano and micro molar activity have been detected for CCR7 and CCR5 respectively

CCR5/7 antagonists – Lead1

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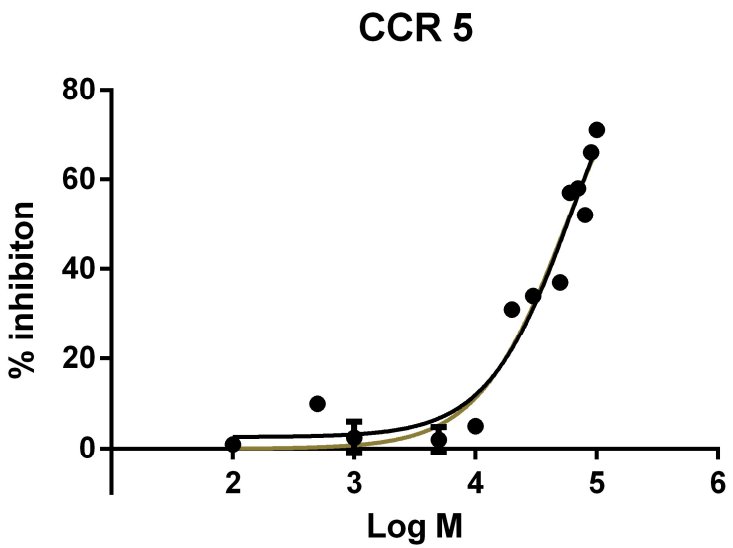
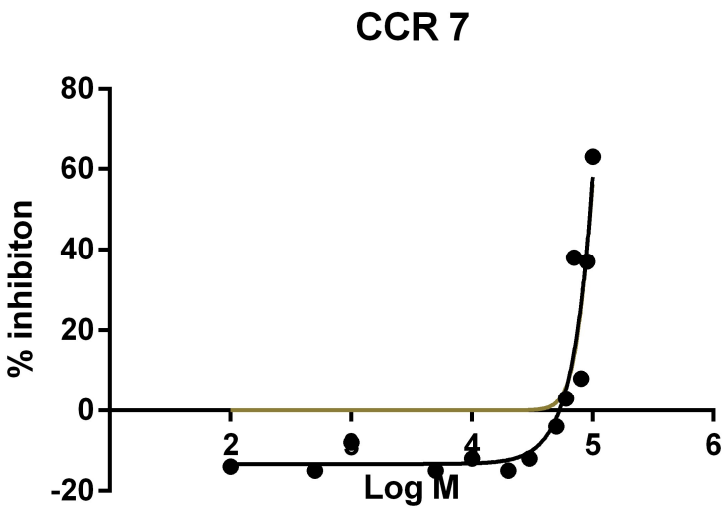
EuroFines Ca+ mobilization and cAMP assays proved that the our lead compound has a biological response

cAMP response of lead1 to CCR5



Ca+ response to CCR7



Micro molar activity have been detected for CCR7 and CCR5 respectively

CCR5/7 antagonists

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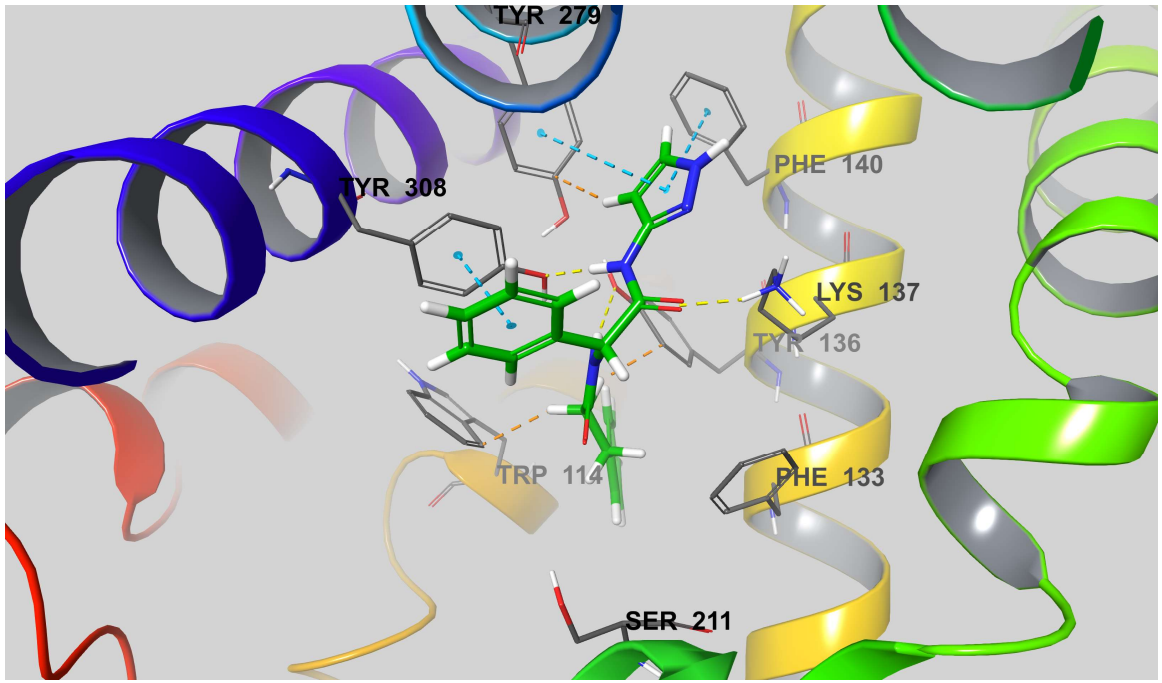
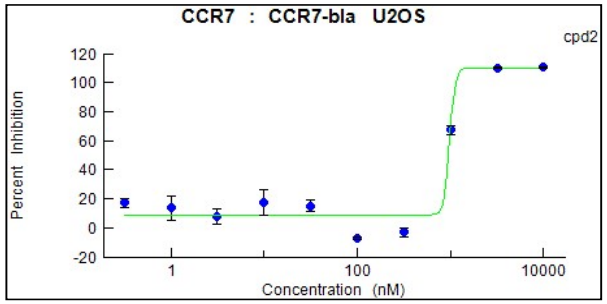
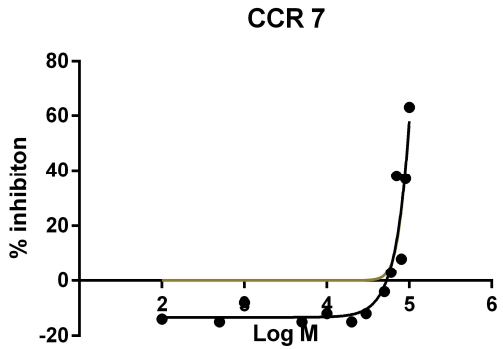
The intensive molecular modelling and biological data indicate that lead 1 binds to both ortho and allosteric sites

Binding mode of one of the compounds to CCR7



Dose-response to CCR7





Hill coefficient greater than 15 and 7 were obtained for β-arrestin binding and Ca+ assays

CCR5 and CCR7 hit compounds

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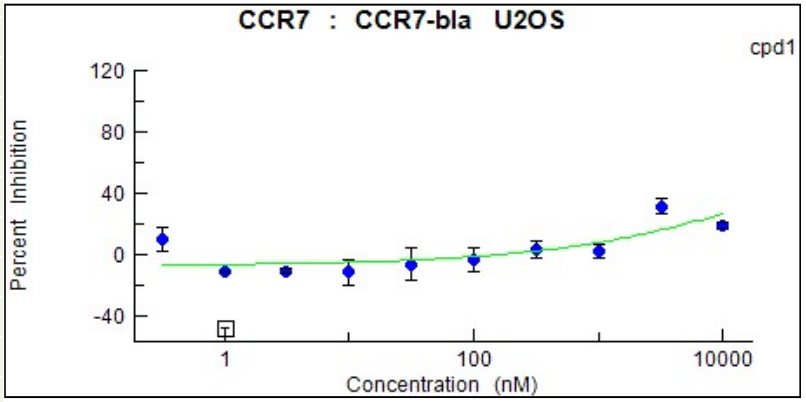
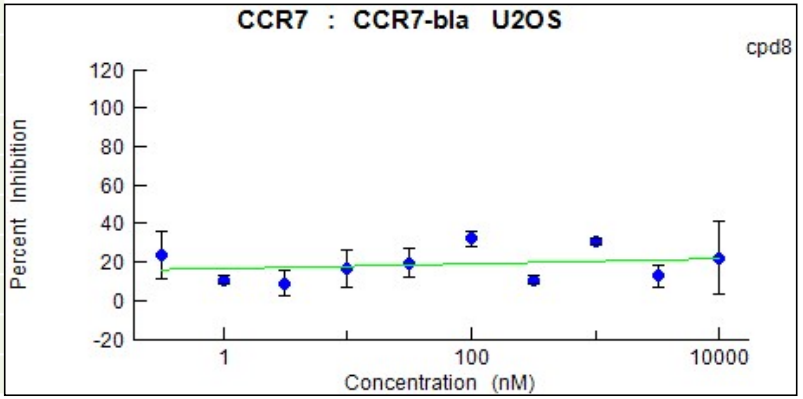
Thermo Fisher Scientific's SelectScreen™ Profiling Service: 10-point Titration Antagonist Results

		SelectScreen Scientist:	Matt Blattner				Date:	28-Jun-2019				
		Quality Assurance Review:	Aaron Bergsma				Date:	28-Jun-2019				
Project #	Cmpd Name	GPCR	Cell Line Tested	Cell Line Part# / Lot#	Stim	IC50 (nM)	Hillslope	R² Value	[Cmpd] (nM)	% Inhibition Point 1	% Inhibition Point 2	Z'
SSCG13438_45359	cpd1	CCR7	CCR7-bla U2OS	KV1531A/41370	Mip3-beta	>10000	0.45	0.6077	10000	17	21	0.40
SSCG13438_45359	cpd1	CCR7	CCR7-bla U2OS	KV1531A/41370	Mip3-beta	>10000	0.45	0.6077	3160	37	26	0.40
SSCG13438_45359	cpd1	CCR7	CCR7-bla U2OS	KV1531A/41370	Mip3-beta	>10000	0.45	0.6077	1000	6	-2	0.40
SSCG13438_45359	cpd1	CCR7	CCR7-bla U2OS	KV1531A/41370	Mip3-beta	>10000	0.45	0.6077	316	-3	9	0.40
SSCG13438_45359	cpd1	CCR7	CCR7-bla U2OS	KV1531A/41370	Mip3-beta	>10000	0.45	0.6077	100	5	-11	0.40
SSCG13438_45359	cpd1	CCR7	CCR7-bla U2OS	KV1531A/41370	Mip3-beta	>10000	0.45	0.6077	31.6	-16	4	0.40
SSCG13438_45359	cpd1	CCR7	CCR7-bla U2OS	KV1531A/41370	Mip3-beta	>10000	0.45	0.6077	10.0	-20	-3	0.40
SSCG13438_45359	cpd1	CCR7	CCR7-bla U2OS	KV1531A/41370	Mip3-beta	>10000	0.45	0.6077	3.16	-9	-12	0.40
SSCG13438_45359	cpd1	CCR7	CCR7-bla U2OS	KV1531A/41370	Mip3-beta	>10000	0.45	0.6077	1.00	-47	-11	0.40
SSCG13438_45359	cpd1	CCR7	CCR7-bla U2OS	KV1531A/41370	Mip3-beta	>10000	0.45	0.6077	0.316	3	18	0.40
SSCG13438_45359	cpd8	CCR7	CCR7-bla U2OS	KV1531A/41370	Mip3-beta	>10000	0.04	0.0500	10000	3	41	0.56
SSCG13438_45359	cpd8	CCR7	CCR7-bla U2OS	KV1531A/41370	Mip3-beta	>10000	0.04	0.0500	3160	7	18	0.56
SSCG13438_45359	cpd8	CCR7	CCR7-bla U2OS	KV1531A/41370	Mip3-beta	>10000	0.04	0.0500	1000	32	29	0.56
SSCG13438_45359	cpd8	CCR7	CCR7-bla U2OS	KV1531A/41370	Mip3-beta	>10000	0.04	0.0500	316	13	8	0.56
SSCG13438_45359	cpd8	CCR7	CCR7-bla U2OS	KV1531A/41370	Mip3-beta	>10000	0.04	0.0500	100	36	28	0.56
SSCG13438_45359	cpd8	CCR7	CCR7-bla U2OS	KV1531A/41370	Mip3-beta	>10000	0.04	0.0500	31.6	27	12	0.56
SSCG13438_45359	cpd8	CCR7	CCR7-bla U2OS	KV1531A/41370	Mip3-beta	>10000	0.04	0.0500	10.0	7	27	0.56
SSCG13438_45359	cpd8	CCR7	CCR7-bla U2OS	KV1531A/41370	Mip3-beta	>10000	0.04	0.0500	3.16	3	16	0.56
SSCG13438_45359	cpd8	CCR7	CCR7-bla U2OS	KV1531A/41370	Mip3-beta	>10000	0.04	0.0500	1.00	13	8	0.56
SSCG13438_45359	cpd8	CCR7	CCR7-bla U2OS	KV1531A/41370	Mip3-beta	>10000	0.04	0.0500	0.316	11	36	0.56

Several other less potent hits were also found





Further steps

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Lead 1 has a good ADMET profile, is not expensive and eventually can be directly used as a topical solution

FEP+ guided Lead 1 optimization for both activity and selectivity will be further performed

Preclinical studies of optimized molecules should be performed

Preclinical studies and hopefully clinical studies are beyond the Micar21 capabilities at the moment. Thus, we are open and looking for collaboration, licensing and/or M&A

A brief description of the scientific approaches which Micar21 employ can be found in the next slides. We are in a process of hit identification and lead optimization of several molecules, such as for example GlyT2 inhibitors, and look for a collaboration in these directions too.


Thank you for your attention!
Micar21
We are here to listen.
small molecule is the key
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