It's about time: novel drug discovery concepts for the molecular pharmacological characterization fo the cannabinoid CB2 receptor

Bouma, J.

List of publications

Part of this thesis

Bouma, J., Kumar, S.S., van den Berg, B.J.W., van der Horst, C., Hoare, S.R.J., Guba, W., Wittwer, M., Grether, U., van der Stelt, M., Heitman, L.H. (2024). Kinetic multiplex assay to assess biased signaling of clinical agonists at the cannabinoid CB_2 receptor. *Manuscript in preparation*.

Bouma, J., Broekhuis, J.D., van der Horst, C., Kumar, P., Ligresti, A., van der Stelt, M., & Heitman, L.H. (2023). Dual allosteric and orthosteric pharmacology of synthetic analog cannabidiol-dimethylheptyl, but not cannabidiol, on the cannabinoid CB_2 receptor. *Biochemical Pharmacology*, **218**, 115924.

Li, X.*, Chang, H.*, **Bouma, J.***, de Paus, L. V., Mukhopadhyay, P., Paloczi, J., Mustafa, M., van der Horst, C., Kumar, S.S., Wu, L., Yu, Y., van den Berg, R.J.B.H.N., Janssen, A.P.A., Lichtman, A., Liu, Z.-J., Pacher, P., van der Stelt, M., Heitman, L.H., Hua, T. (2023). Structural basis of selective cannabinoid CB_2 receptor activation. *Nature Communications*, **14**(1), 1447.

Bouma, J., Soethoudt, M., van Gils, N., Xia, L., van der Stelt, M., & Heitman, L.H. (2022). Cellular assay to study β-arrestin recruitment by the cannabinoid receptors 1 and 2. In *Endocannabinoid Signaling: Methods in Molecular Biology* (pp. 189-199). New York, NY: Springer US.

** These authors contributed equally*

Other publications

Mach, L., Omran, A., **Bouma, J.**, Radetzki, S., Sykes, D. A., Guba, W., Li, X., Höffelmeyer, C., Hentsch, A., Gazzi, T., Mostinski, Y., Wasinska-Kalwa, M., de Molnier, F., van der Horst, C., von Kries, J.P., Vendrell, M., Hua, T., Veprintsev, D.B., Heitman, L.H., Nazare, M. (2024). Highly Selective Drug-Derived Fluorescent Probes for the Cannabinoid Receptor Type 1 (CB1R). *Manuscript accepted; Journal of Medicinal Chemistry.*

Wasinka-Kalwa, M., Omran, A., Mach, L., **Bouma, J.**, Scipioni, L., Li, X., Radetzki, S., Mostinski. Y., Schippers, M., Gazzi, T., van der Horst, C., Brennecke, B., Hanske, A., Kolomeets, Y., Guba, W., Sykes, D., von Kries, J.P., Broichhagen, J., Hua, T., Veprintsev, D., Heitman, L.H., Oddi, S., Maccarrone, M., Grether, U., Nazare, M. (2024). Visualization of membrane localization and functional state of CB2R pools by matched agonist and inverse agonist probe pairs. *Manuscript submitted.*

Vlachodimou, A., **Bouma, J.**, De Cleyn, M., Berthelot, D., Pype, S., Bosmans, J.P., van Vlijmen. H., Wroblowski, B., Heitman, L.H., IJzerman, A.P. (2023). Kinetic profiling of novel spirobenzo-oxazinepiperidinone derivatives as equilibrative nucleoside transporter 1 inhibitors. *Purinergic Signalling*, 1-13.

Nakladal, D., Buikema, H., Romero, A.R., Lambooy, S.P.H., **Bouma, J.**, Krenning, G., Vogelaar, P., van der Graaf, A.C., Groves, M.R., Kyselovic, J., Henning, R.H., Deelman, L.E. (2019). The (*R*)-enantiomer of the 6-chromanol derivate SUL-121 improves renal graft perfusion via antagonism of the α_1-adrenoceptor. *Scientific Reports*, **9**(1), 13.

Oral and poster communications

Biased signaling of clinical CB_2R agonists

2023 **Oncornet2.0 Final symposium** (*poster*)
Amsterdam, the Netherlands

2023 **ACS Fall 2023** (*oral*)
Hybrid, online presentation

2023 **Gordon Research Conference "Cannabinoid Function in the CNS"** (*poster*)
Barcelona, Spain

2023 **Gordon Research Seminar "Cannabinoid Function in the CNS"** (*poster*)
Barcelona, Spain

Structural basis of CB_2R activation

2023 **LACDR Spring symposium** (*poster*)
Leiden, the Netherlands

2023 **Oncode TU/e meeting** (*oral*)
Leiden, the Netherlands

2023 **Guest lecture at F. Hoffmann-La Roche Ltd.** (*oral*)
Basel, Switzerland

2022 **ULLA Summer school** (*poster*)
Uppsala, Sweden

2022 **International Cannabinoid Research Society Meeting** (*oral*)
Galway, Ireland
Awarded predoctoral presentation award

2022 **FIGON Dutch Medicines Day & EUFEPS Annual meeting** (*oral*)
Leiden, the Netherlands
Awarded EUFEPS WIPS Women in Pharmaceutical Sciences Award 2022

Allosteric modulation of CB_2R

2022 **LACDR Spring symposium** (*poster*)
Leiden, the Netherlands

2021 **FIGON Dutch Medicines Day** (*poster*)
Leiden, the Netherlands

2021 **LACDR Spring symposium** (*poster*)
Online

2020 **LACDR Spring symposium** (*poster*)
Online

Curriculum vitae

Jara Bouma was born in Woerden, the Netherlands, on April 4th 1996. She graduated from pre-university education at Stellingwerf College, Oosterwolde (Friesland, the Netherlands) in 2014, after which she continued with the Bachelor's program Life Science & Technology at the University of Groningen (Groningen, the Netherlands) with a major in Medical Pharmaceutical Sciences. Her Bachelor internship into the molecular mechanisms of a novel α_1-adrenoceptor antagonist under supervision of dr. Dalibor Nakladal, dr. Leo Deelman and dr. Hendrik Buikema at the Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen (Groningen, the Netherlands), resulted in a co-authorship on a publication. During these three years, she also took the opportunity to attend a semester at Umeå University (Umeå, Sweden).

After graduating in 2017, she started the Master's program Bio-Pharmaceutical Sciences at Leiden University (Leiden, the Netherlands). As part of her Master's, she performed a nine-month internship at the division of Medicinal Chemistry (formerly known as Drug Discovery and Safety) under supervision of dr. Anna Vlachodimou and prof.dr. Laura H. Heitman. This project focused on the characterization of structure-affinity and structure-kinetic relationships of inhibitors for the equilibrative nucleoside transporter 1 (ENT1), which resulted in co-authorship on a publication. A second internship was performed at the Central Laboratory Animal Facility/Department of Anatomy and Embryology at Leiden University Medical Center (Leiden, the Netherlands) under the supervision of prof. dr. Daniela Salvatori where she performed a comparative analysis of stem-cell derived xenografts and human germ cell tumors. During the second year of her Master's Jara also joined the Leiden Leadership Program, an extracurricular honours program at Leiden University, for which she performed a consultancy project at insurance company Zorg en Zekerheid (Leiden, the Netherlands).

In 2019 she started as a PhD candidate at the division of Medicinal Chemistry of the LACDR under supervision of prof. dr. Laura H. Heitman and prof. dr. Mario van der Stelt. Her project focused on the molecular pharmacological characterization of the cannabinoid CB_2 receptor by applying novel drug discovery concepts. This project was funded by the Dutch Research Council (NWO Vidi #16573) and as such she frequently shared her research findings with experts in the field as part of the User Committee. Her PhD project was highly collaborative in nature, while she also took part in multiple external collaborations, reflected by the publications listed in this thesis. Moreover, she presented her work at national and international conferences. In 2022 she was awarded the EUFEPS Women in Pharmaceutical Sciences Award at the FIGON Dutch Medicines Days, as well as the predoctoral presentation award at the International Cannabinoid Research Society Meeting for her presentation 'Molecular basis for selective activation and target engagement of cannabinoid CB_2 receptor agonists'. In 2023 she visited the Pharma Research and Early Development site of F. Hoffmann-La Roche (Basel, Switzerland) as guest scientist for two weeks to get acquainted with preclinical drug research in the pharmaceutical industry.

Jara is currently working as program manager at ZonMw in Den Haag.

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My PhD projects relied greatly on collaborations with various academic and industrial partners. I would like to convey my thanks to Xiaoting Li, Tian Hua (iHuman Institute, ShanghaiTech University), Pal Pacher (NIH), Anthe Janssen (Leiden Institute of Chemistry), Alessia Ligresti (National Research Council of Italy), Wolfgang Guba, Matthias Wittwer (Roche), Isabelle Geron (Revvity) and Sam Hoare (Pharmechanics) for their significant theoretical, practical and analytical input. Your contributions have been key for the successful completion of my PhD. I wish to extend my appreciation to Ad IJzerman (LACDR), Herman van Vlijmen (Johnson & Johnson), Arne Rufer, Uwe Grether (Roche) and Rob Hermans (NWO), for their endless advice and support during all our Vidi meetings. I would like to give special credit to Uwe for initiating and inviting me to join many collaborations and welcoming me into his home whilst visiting Roche.

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