



Human olfactory receptors deorphanization

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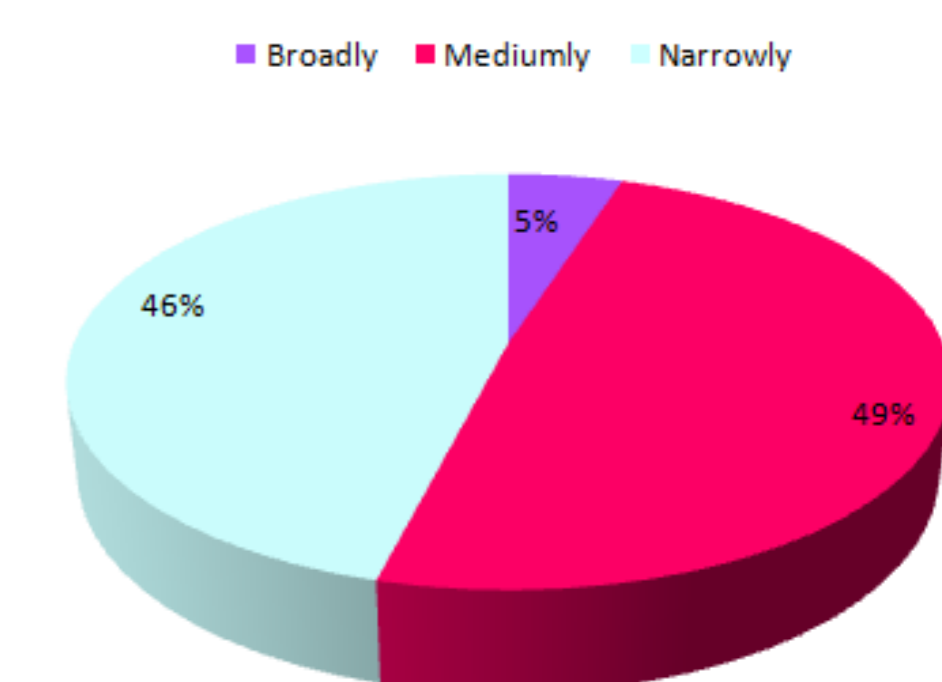


Figure 1. – Categories of ORs deorphanized at ChemCom. ORs are considered as broadly tuned when responding to more than 80 agonists having different chemical and organoleptic properties. ORs are considered as narrowly tuned when responding to less than 6 agonists from the same chemical and organoleptic properties.

Abstract:

ChemCom progresses towards its objective of deorphanizing the whole repertoire of human olfactory receptors (ORs). Relying on (i) its proprietary technology, (ii) libraries of thousands of odorant compounds and (iii) an efficient screening system, ChemCom is currently identifying and characterizing new modulating molecules (enhancers or blockers) and novel odorant compounds for the whole range of human ORs. The profiling of expression OR gene in the whole olfactory mucosa and the analysis of its distribution in the human population recently achieved at ChemCom, provides a unique opportunity to select among 273 frequently expressed ORs in view of a systematic deorphanization¹. At ChemCom, more than 100 ORs have been robustly and specifically deorphanized. The number of odorant molecules quoted as agonists for these ORs largely exceeds 1,000, with an average of 19 agonists per OR and a maximum of 216 activators for a single OR. By contrast, one molecule activates 2 different ORs in average and a number of 13 ORs activated by the same molecule has been observed as the upper limit. So far, only 5% of the ORs were found to respond to more than 80 agonists possessing different chemical and organoleptic properties and are therefore considered as broadly tuned. The remaining ORs are considered as moderately (>5 agonists per OR; 49%) or narrowly (≤5 agonists per OR; 46%) tuned. Interestingly, most of the ORs deorphanized to date belong to the expressed OR gene set. Indeed, among the 47 deorphanized receptors reported in publications²⁻¹¹, 43 are found to be expressed. Here, we present a data sheet for twelve highly expressed and deorphanized ORs which respond to representative molecules such as Musks, Ionone, Carvone, Sotolon, Lactone, Geraniol, Vanillin, Androstenone, Pyrazines, Thiols, Carboxylic acids,... Besides the results presented in this poster, Chemcom holds confidential data on ORs responding to pleasant odor of interest (e.g. amber, marine, green, floral, fruity, spicy, anisic...) and also to typical malodors (e.g. sweat, mildew, animal, fishy, sulfurous, beverage and food off-notes,...).

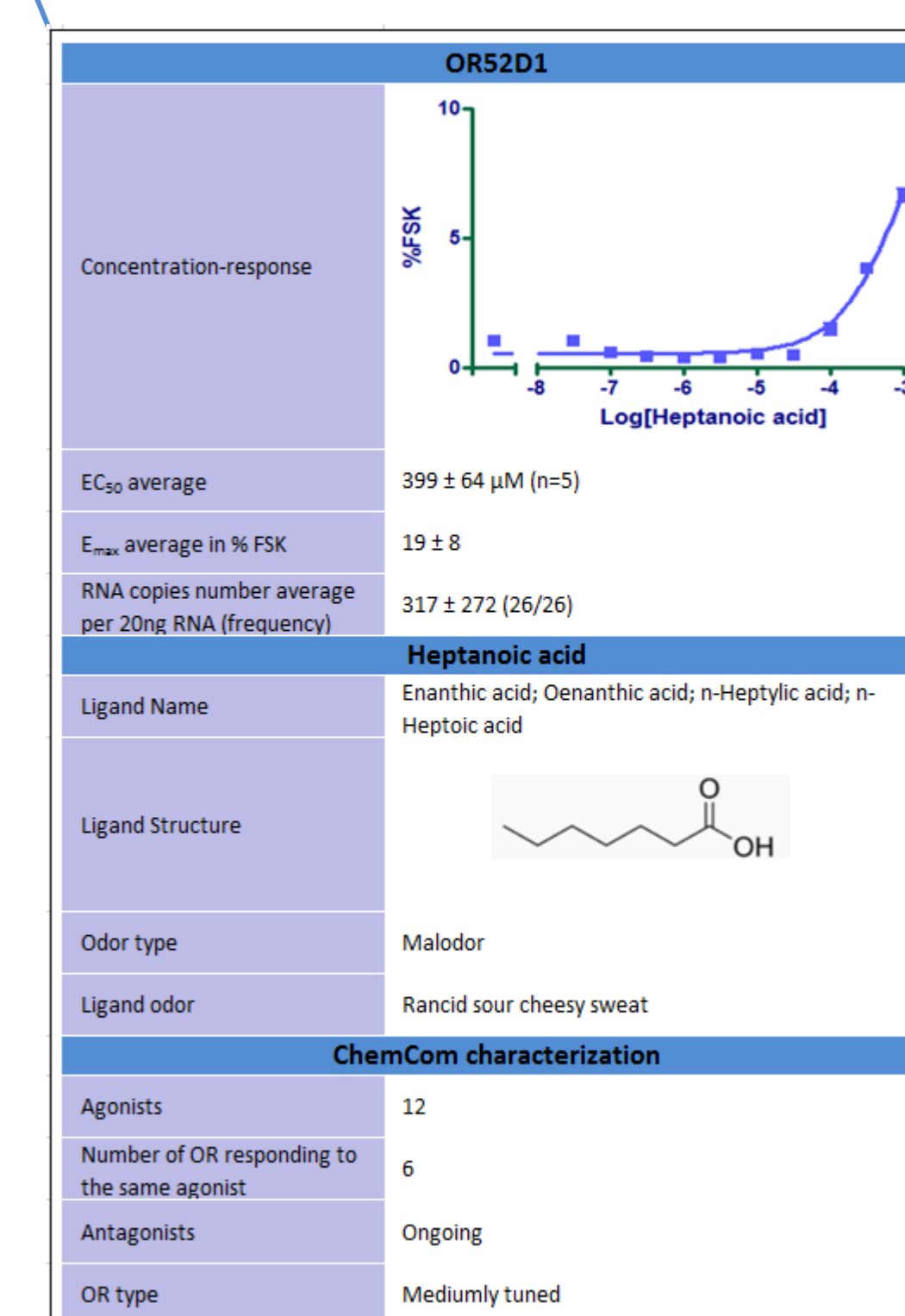
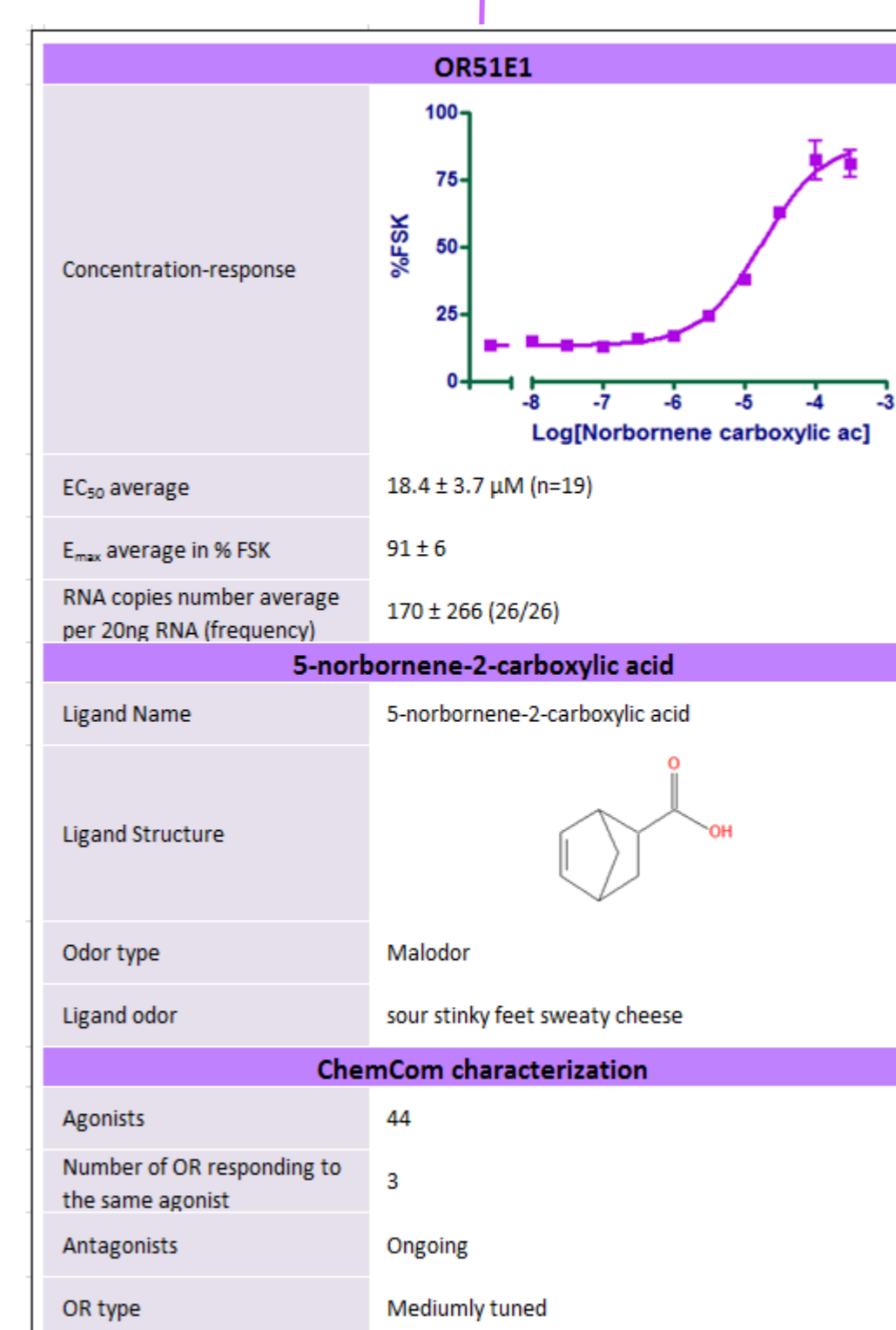
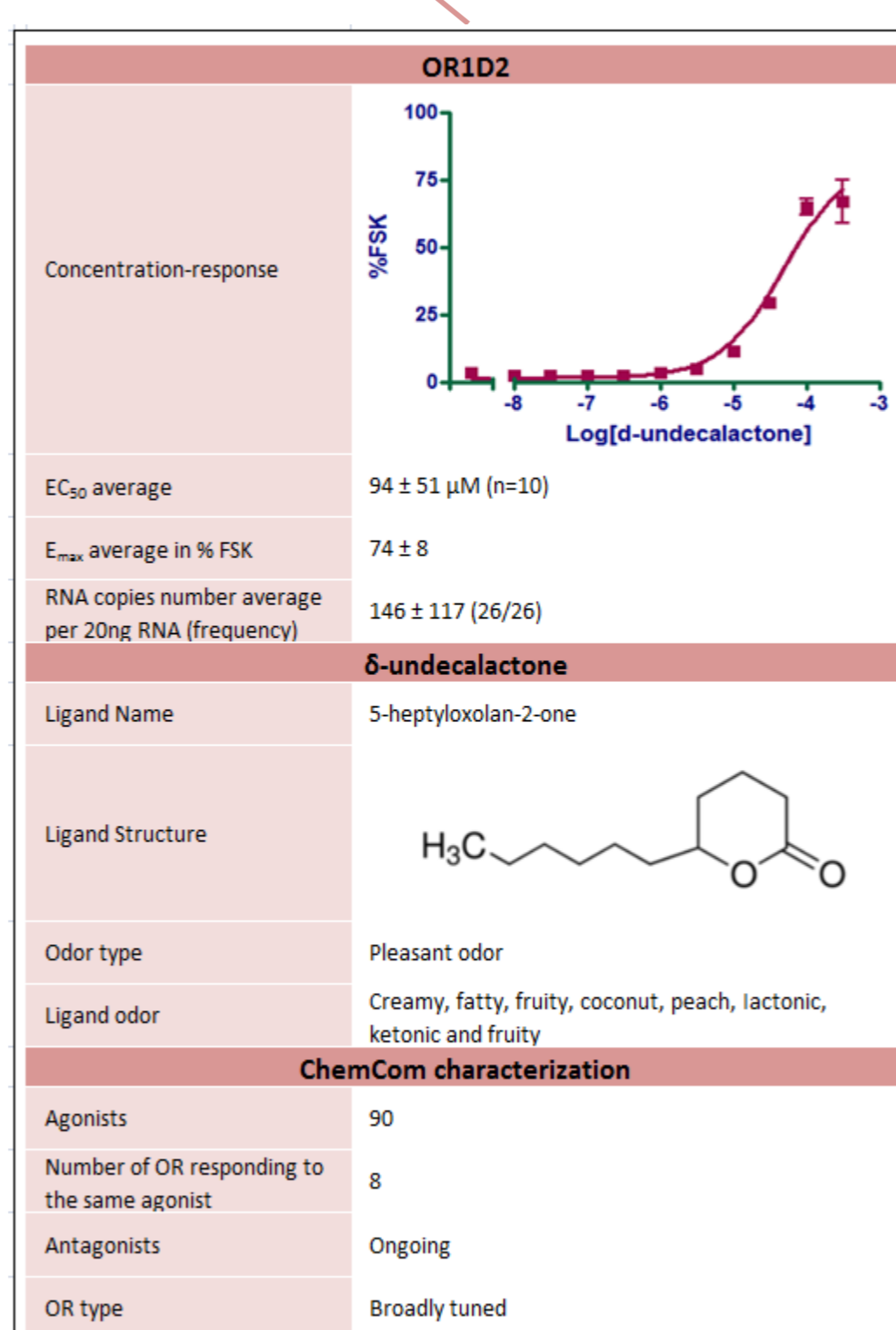
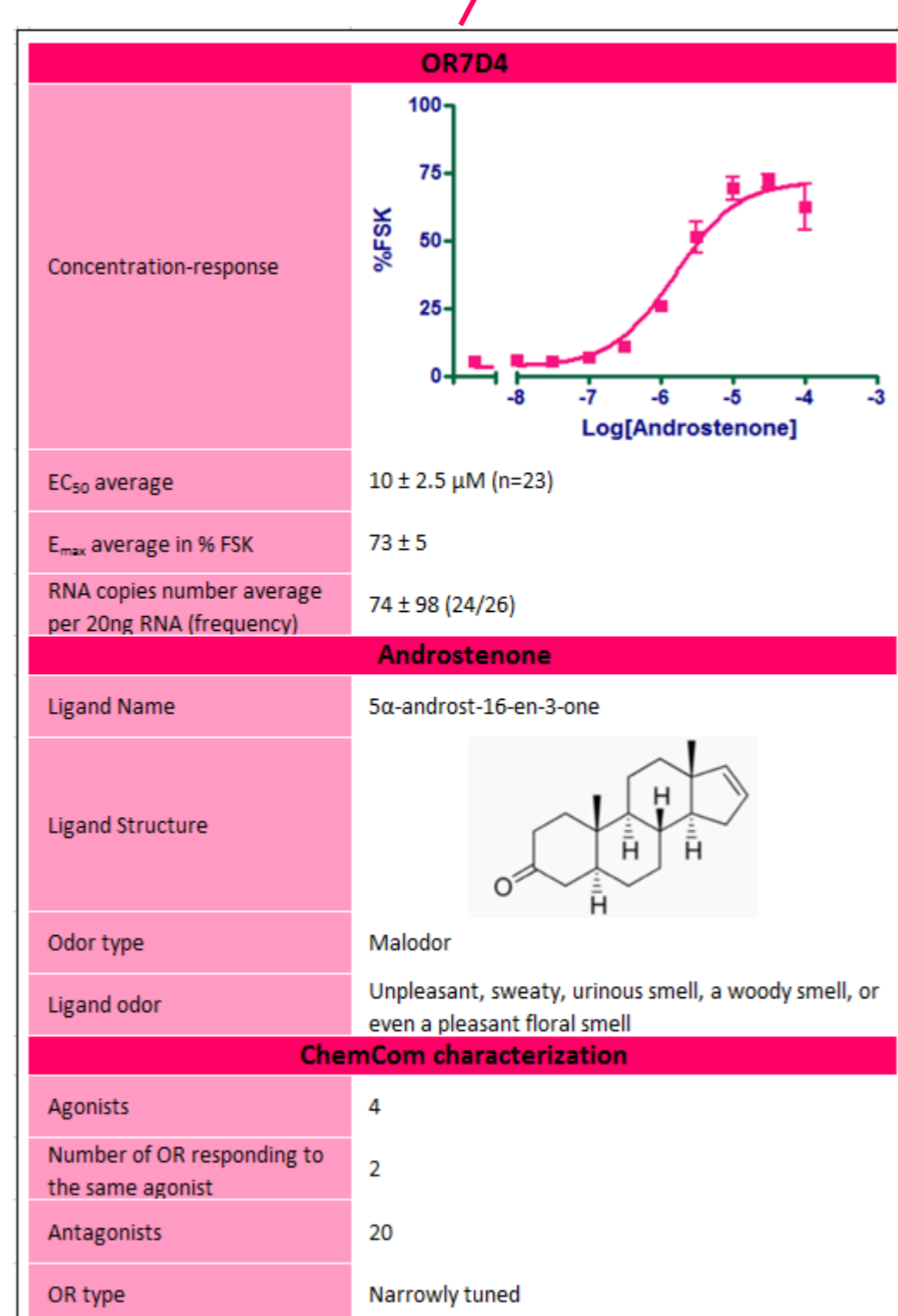
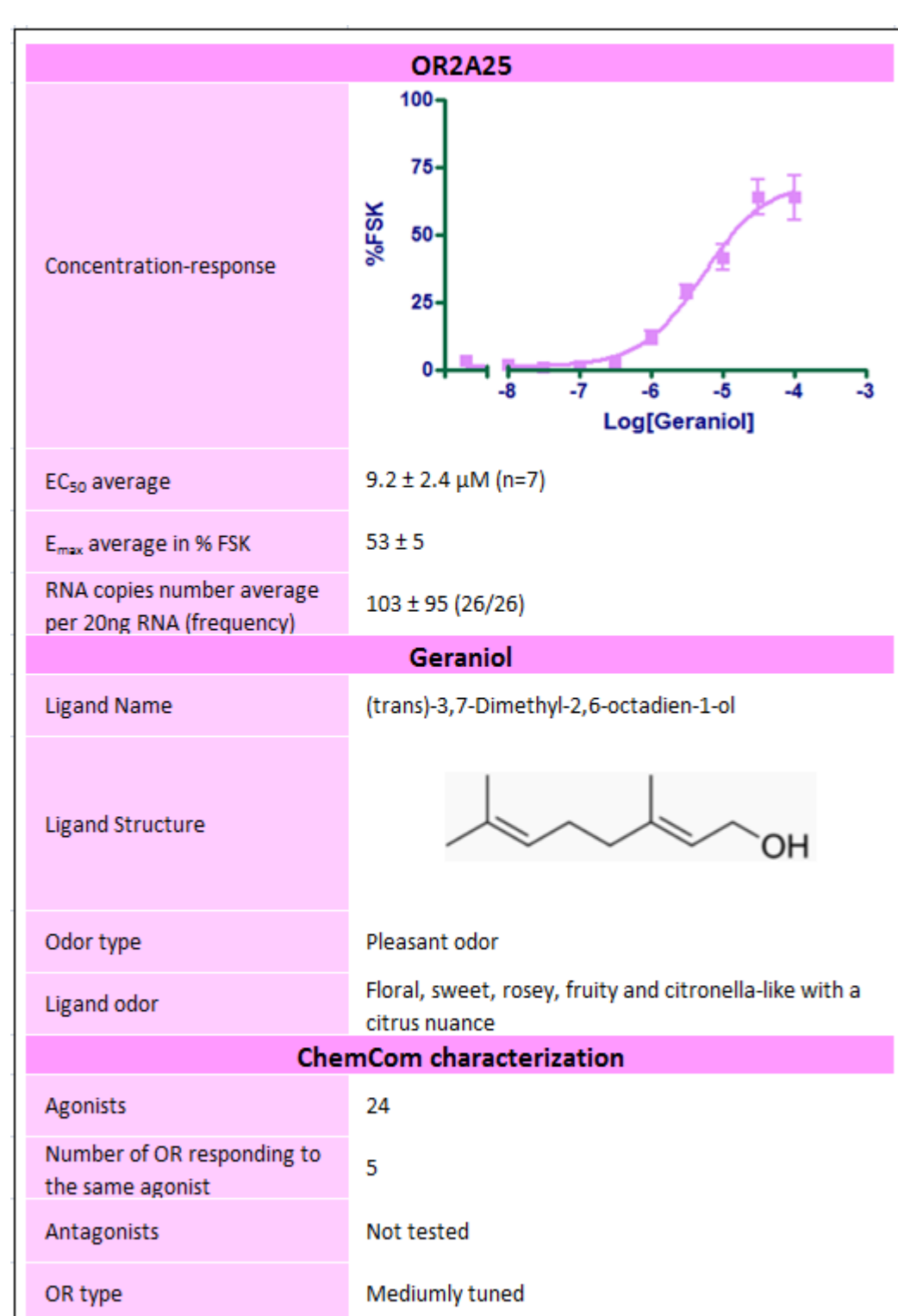
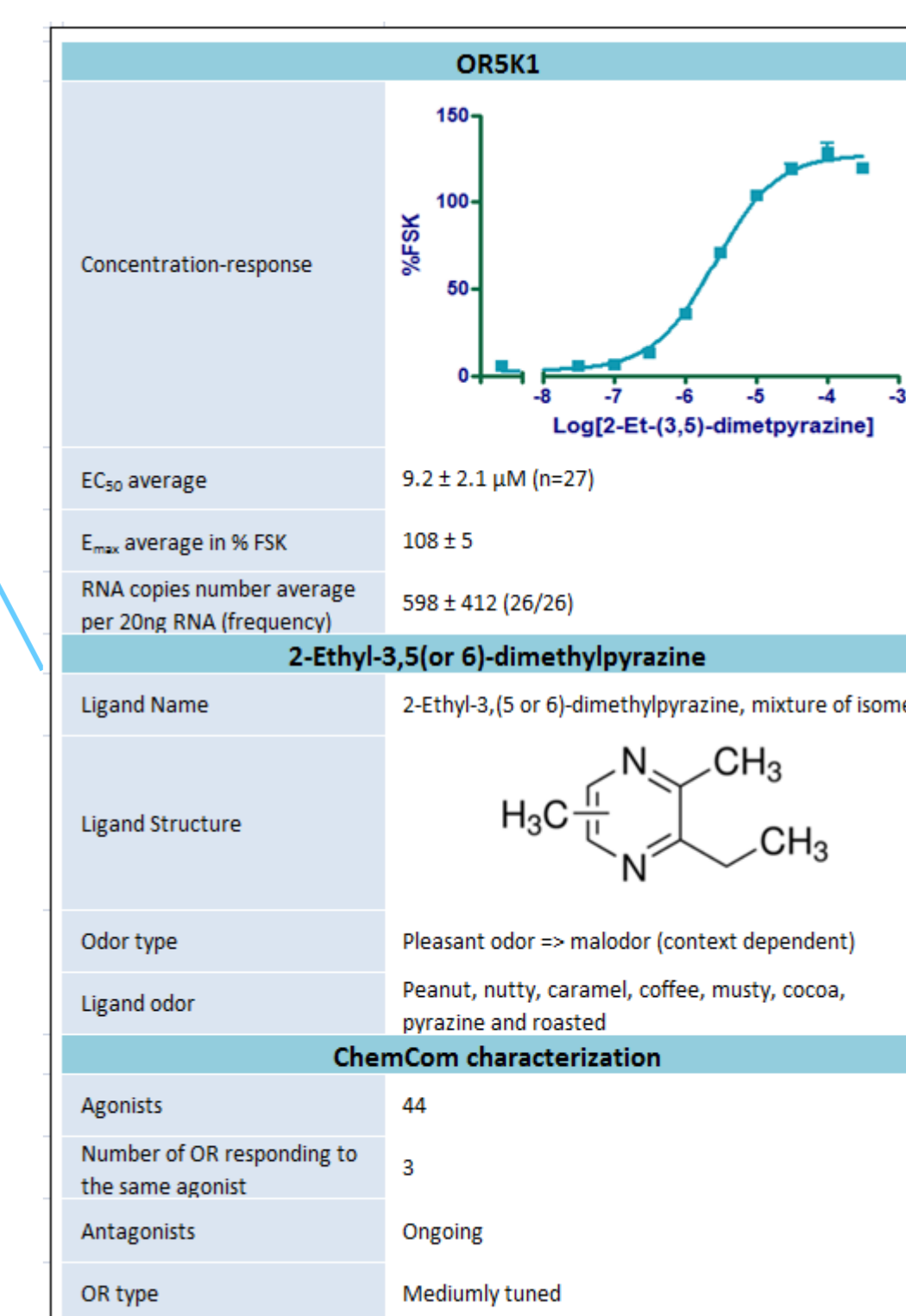
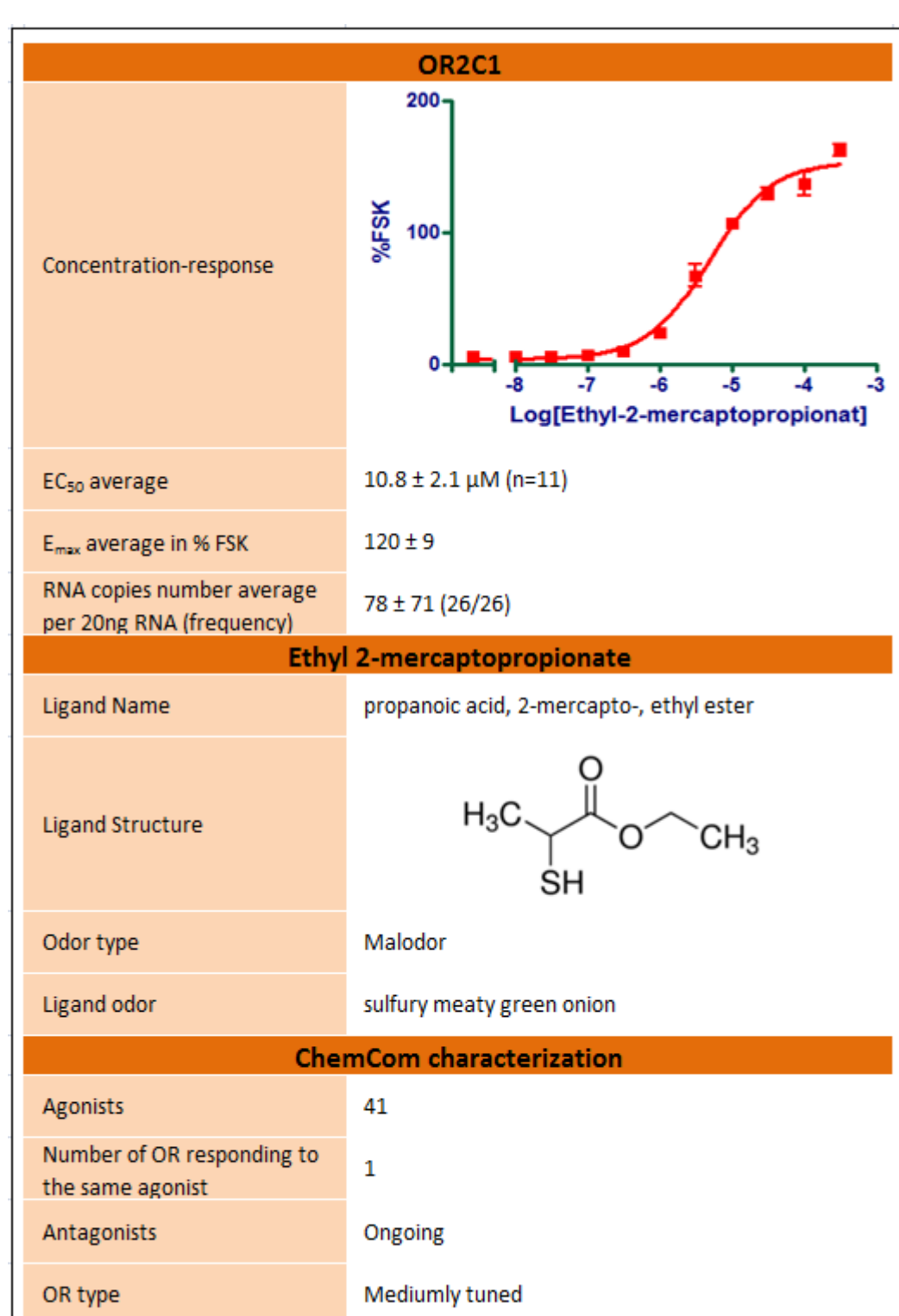
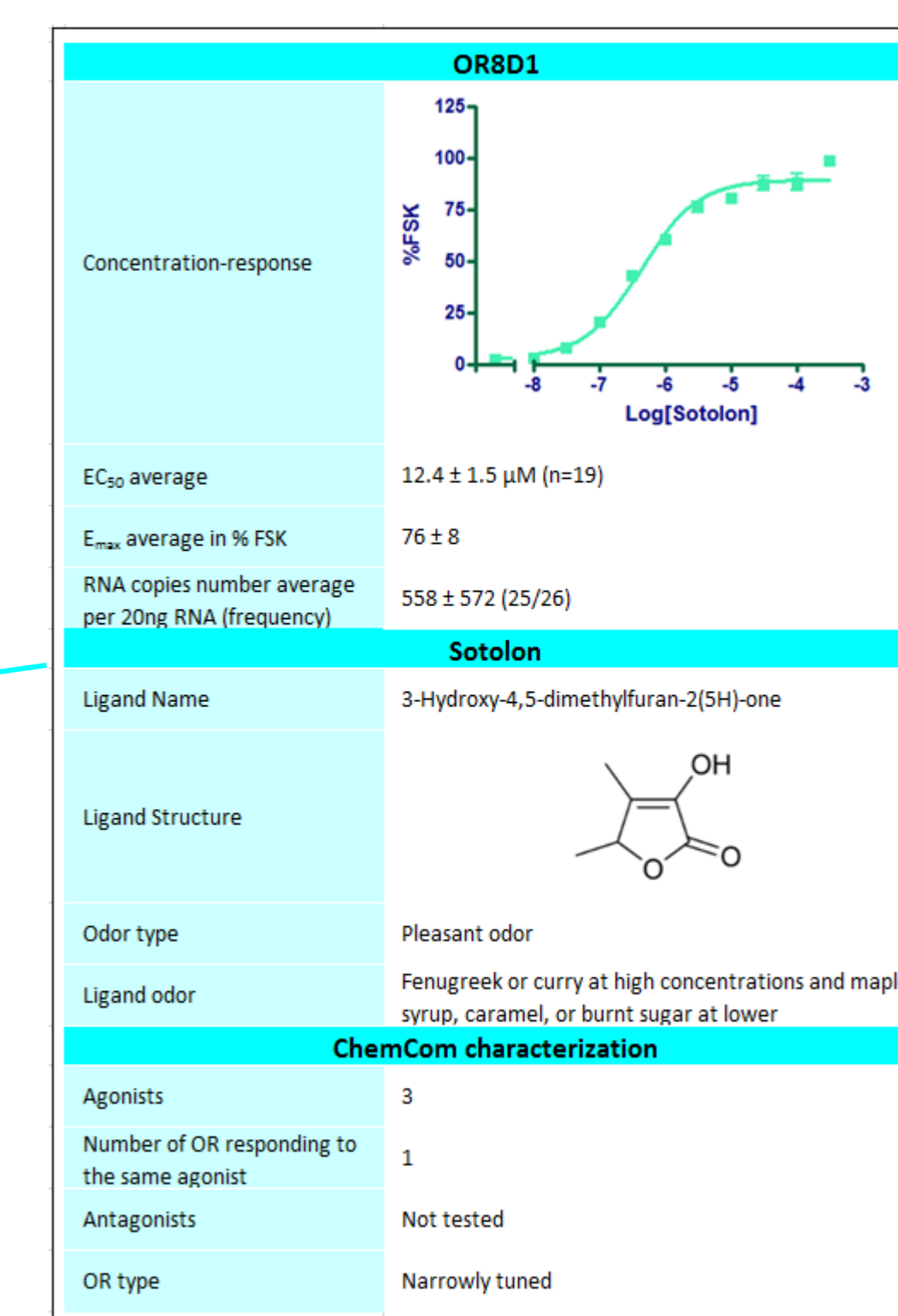
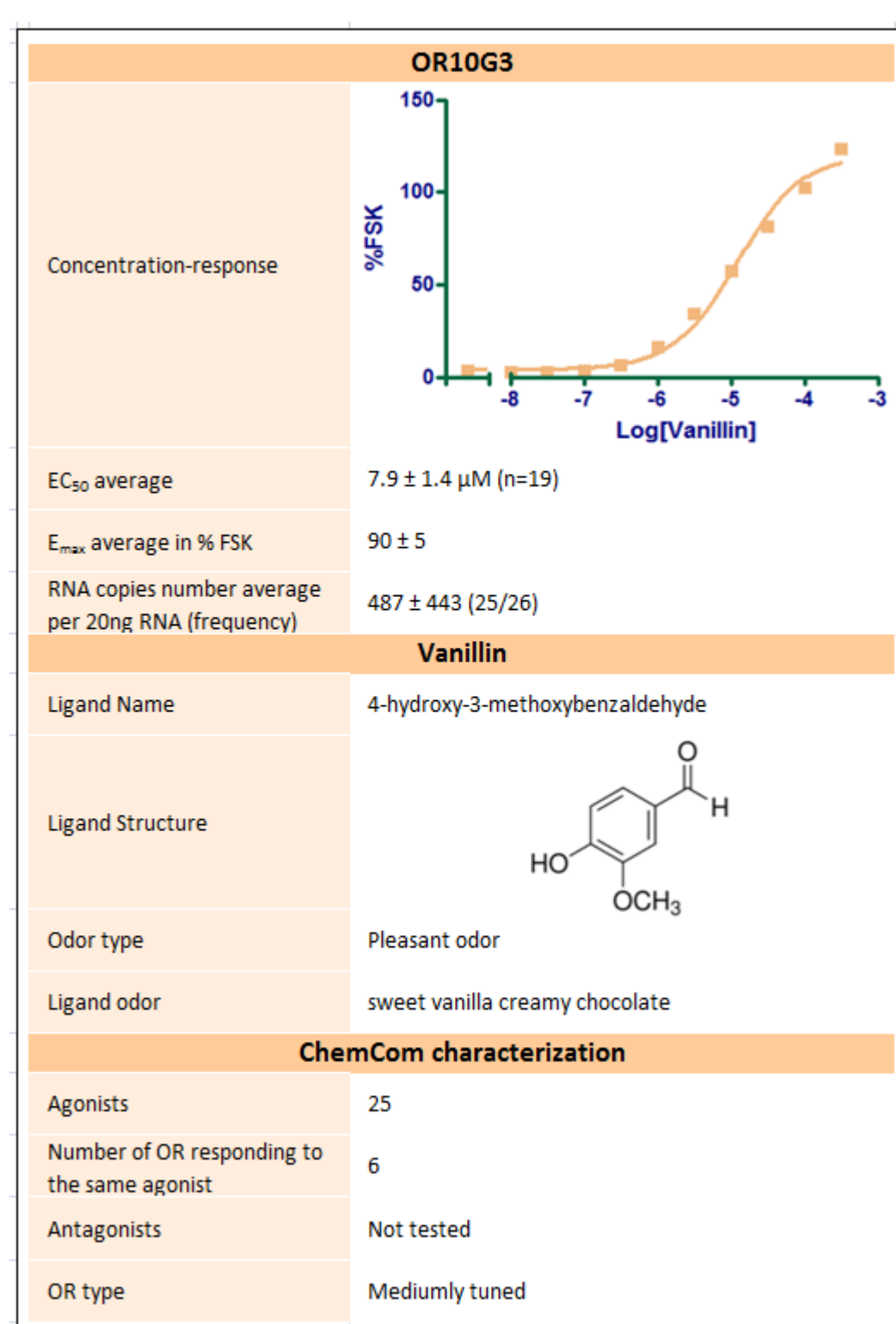
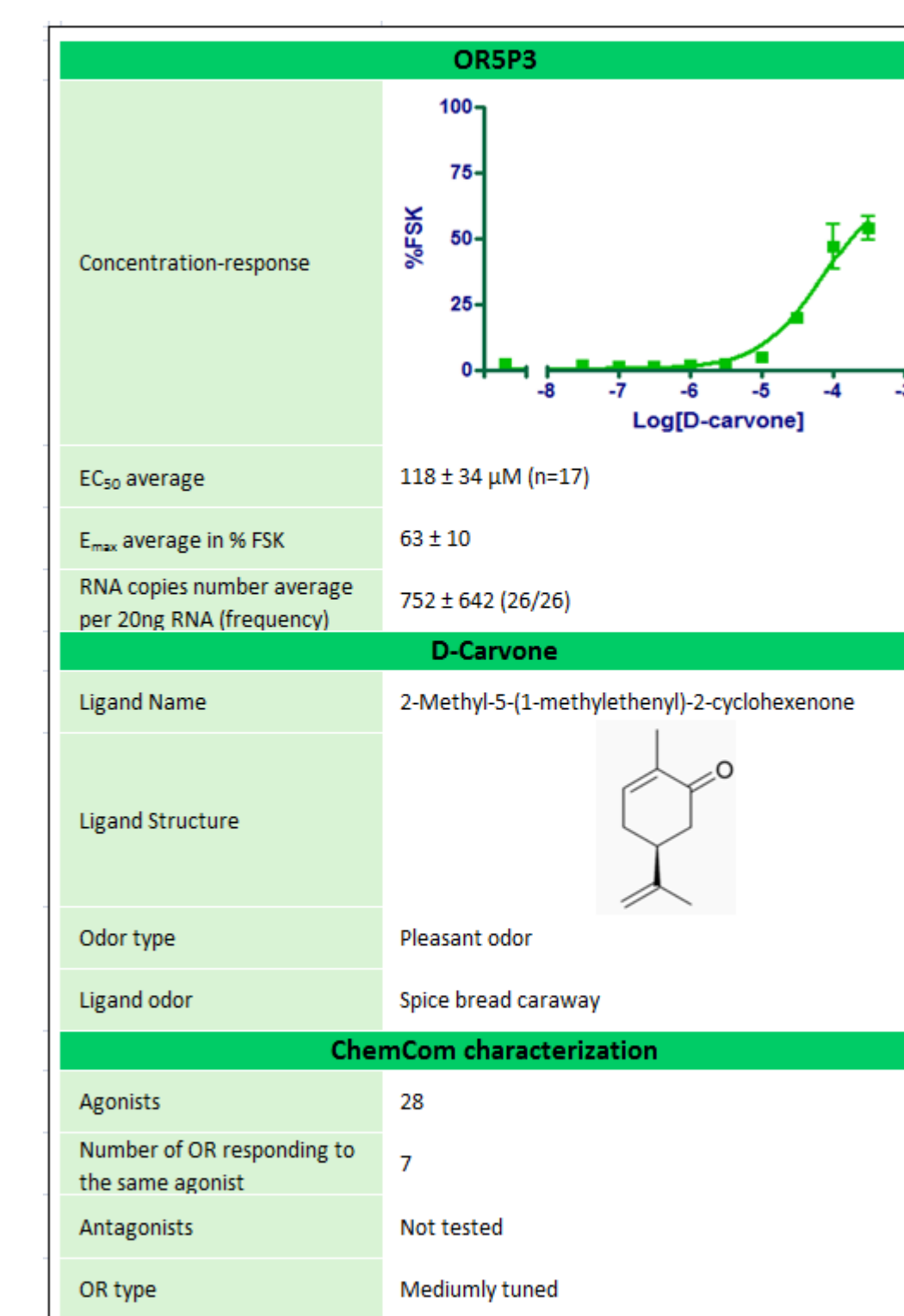
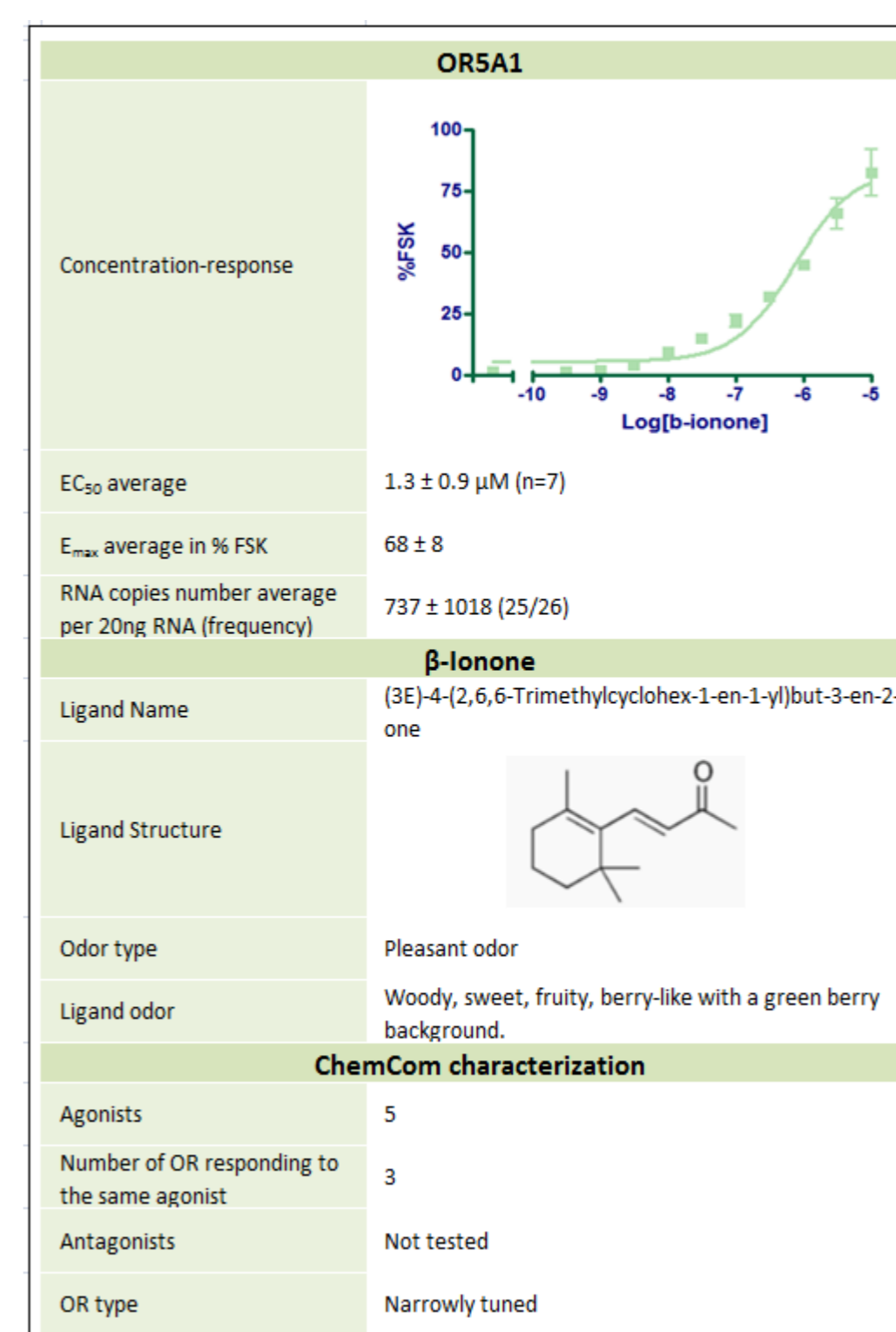
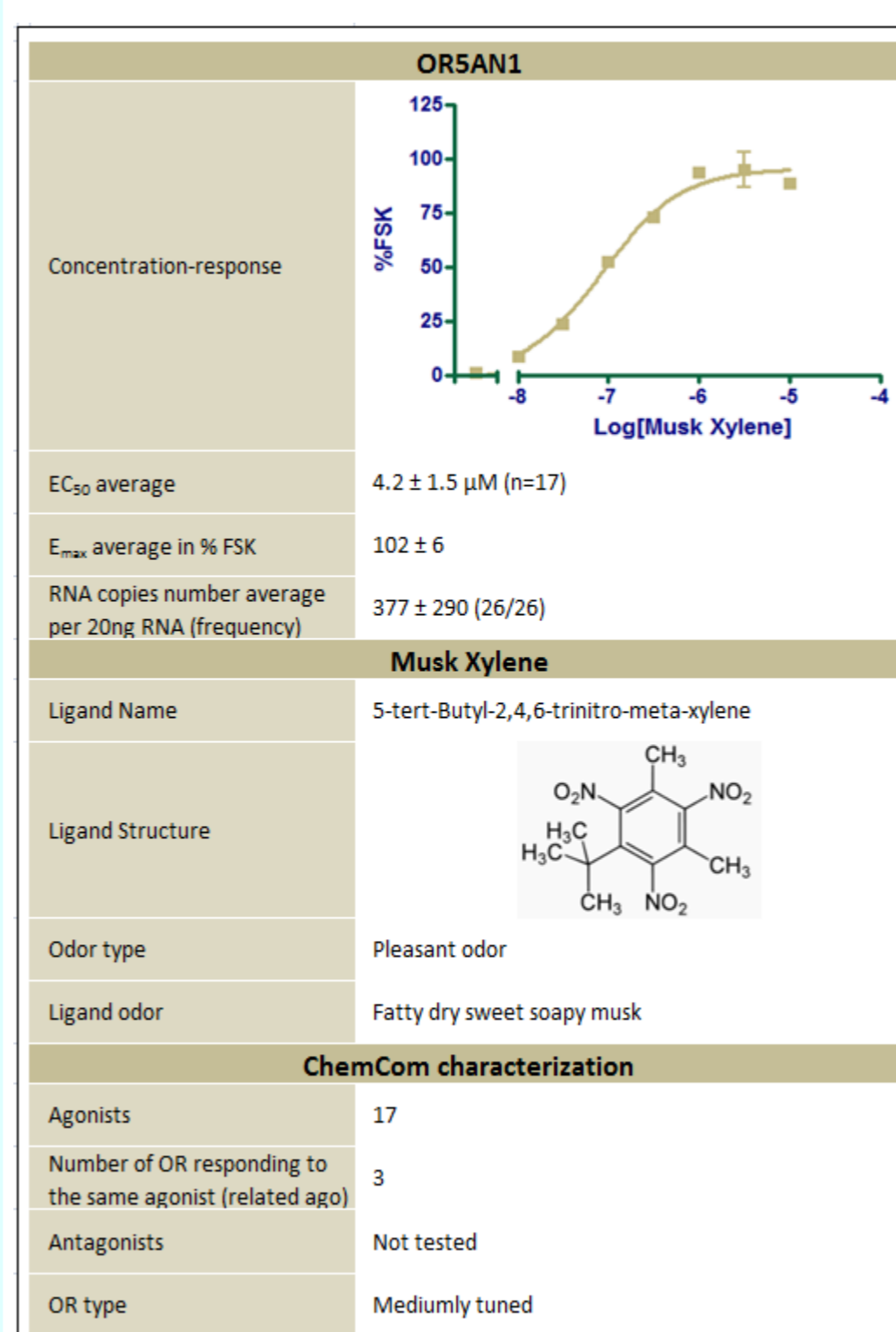


Figure 2. – Cladogram of human olfactory receptors. In black are indicated the robustly and specifically already deorphanized ORs by ChemCom. In color, the data sheets for twelve highly expressed and deorphanized olfactory receptors which respond to molecules of interest.

Methods:

Deorphanization screening was performed in HEK293T-hRTP1S/hRTP2 cells with CRE-luciferase reporter assay system¹². Briefly, cells plated one day before, were transfected with OR and pGL4.29 plasmids using TransIT[®]-LT1 (Mirus) according to the manufacturer's protocol. Twenty hours after transfection and four hours after incubation with compounds, cells were lysed and processed for luminescence measurement using a Spectra Max M5 reader (Molecular Devices). Results were expressed as percentage of the response induced by 10 μM of Forskolin (FSK). Statistical analysis and curve fitting was done by the Hill's equation using Microsoft Excel. Before being considered as true agonist of the tested OR, odorants are tested on mock cells to confirm the specific activation of the receptor.

Acknowledgements : This work is supported by the Brussels Institute for Research and Innovation (InnovIris).

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