An aminophenothiazine inhibitor of the NCS-1/Ric8a complex regulates synaptic function in fragile X syndrome

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The protein complex formed by the Ca^{2+} sensor neuronal calcium sensor 1 (NCS-1) and the guanine exchange factor protein Ric8a co-regulates synapse number and probability of neurotransmitter release, emerging as a potential therapeutic target for diseases affecting synapses such as Fragile X syndrome (FXS), the most common heritable autism disorder [1,2]. Using crystallographic data and the virtual screening of a chemical library [3], we identified a set of heterocyclic small molecules as potential inhibitors of the NCS-1/Ric8a interaction. The aminophenothiazine FD44 interferes with NCS-1/Ric8a binding and it restores normal synapse number and associative learning in a *Drosophila* FXS model [4]. The crystal structure of NCS-1 bound to FD44 and the structure-function studies performed with structurally close but inactive analogues explain the FD44 specificity and how this small compound can inhibit such big protein-protein interface: FD44 stabilizes NCS-1 in a conformation that impedes Ric8a recognition [4]. Our study demonstrates the druggability of the NCS-1/Ric8a interface and uncovers a suitable region in NCS-1 for development of additional drugs of potential use on FXS. Since other neuronal disorders share with FXS the synaptic density and morphology abnormalities, we believe that our compounds would be also useful for a whole range of synaptopathies, such as Rett Syndrome, ADS, schizophrenia or bipolar disorder. Given the therapeutic potential of compound FD44, we have protected our findings with a patent [5].

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