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MolTag 1st Funding Period.

Defensio: February 2016

Title: Unraveling the molecular pharmacology of 4-MEC and 4-MePPP- Insights into their mode of action

The growing abuse of psychoactive designer drugs worldwide requires scientific intervention to elucidate their pharmacological properties, physiological effects. It is important to bring forward crucial information about their abuse potential leading to awareness and effective ban on their use. My thesis focuses on two mephedrone analogues, 4-MEC and 4-MePPP, to investigate their neuropharmacological profile. I used a spectrum of techniques including in vitro models of rat brain synaptosomes, HEK293 cells and oocytes from Xenopus laevis to reveal their mode of action on their targets, the monoamine neurotransmitter transporters, the serotonin transporter (SERT) and the dopamine transporter (DAT). The work also looks at their effects in the rat brain by using in vivo microdialysis and monitors their effects on behavioral traits like motor locomotion and stereotypical locomotion.

The study sheds light to a distinctive pharmacological profile of 4-MEC and 4-MePPP and at the molecular mechanism of interaction between the drugs and their targets by using the tools of computational biology. The two drugs under investigation are popular drugs of abuse, which have flooded the market since the ban of mephedrone in 2010. The study reveals 4-MEC to possess an unique “hybrid” profile wherein it is effectively able to block the DAT and produce substrate mediated efflux at the SERT. It also produces SERT mediated inward current. In vivo studies revealed its potential to aggravate 5-HT neurotransmitter levels in the rat brain. 4-MePPP displays a different profile by blocking DAT effectively however showing less potency at the SERT. In the rat brain the drug was able to elevate the levels of dopamine without affecting the levels of serotonin. It also increases motor and stereotypical locomotion in rats. Their diverse profile captivated our imagination to seek an answer as to why they have different modes of action, which is striking considering their common ancestral lineage from mephedrone. Computational docking solved this puzzle and disclosed the reason behind 4-MePPP’s inactivity at the SERT. This was due to its structural constraint, namely its bulky pyrrolidine ring that could not accommodate itself into the binding pocket of SERT. The study reflects on the importance of structure function relationship of drugs and their profound influence on their pharmacological profile.

My thesis puts forward a comprehensive understanding of the mode of action of 4-MEC and 4-MePPP on the monoamine neurotransmitter transporters.

The study utilizes various tools and techniques at the molecular, cellular and at the systemic level to understand the biological potential of the drugs. This can be further extrapolated on to other drugs, which still remain a mystery regarding their mode of action as shown by at the later stage of my thesis.

In conclusion, my thesis celebrates the importance of research in deciphering the mechanism of action of drugs of abuse by using an array of scientific methods.

The work puts forward a model wherein drugs of abuse can be evaluated not only to reveal their biological influence and the molecular mechanism behind them but also point to a therapeutic potential towards a cure for drug addiction.