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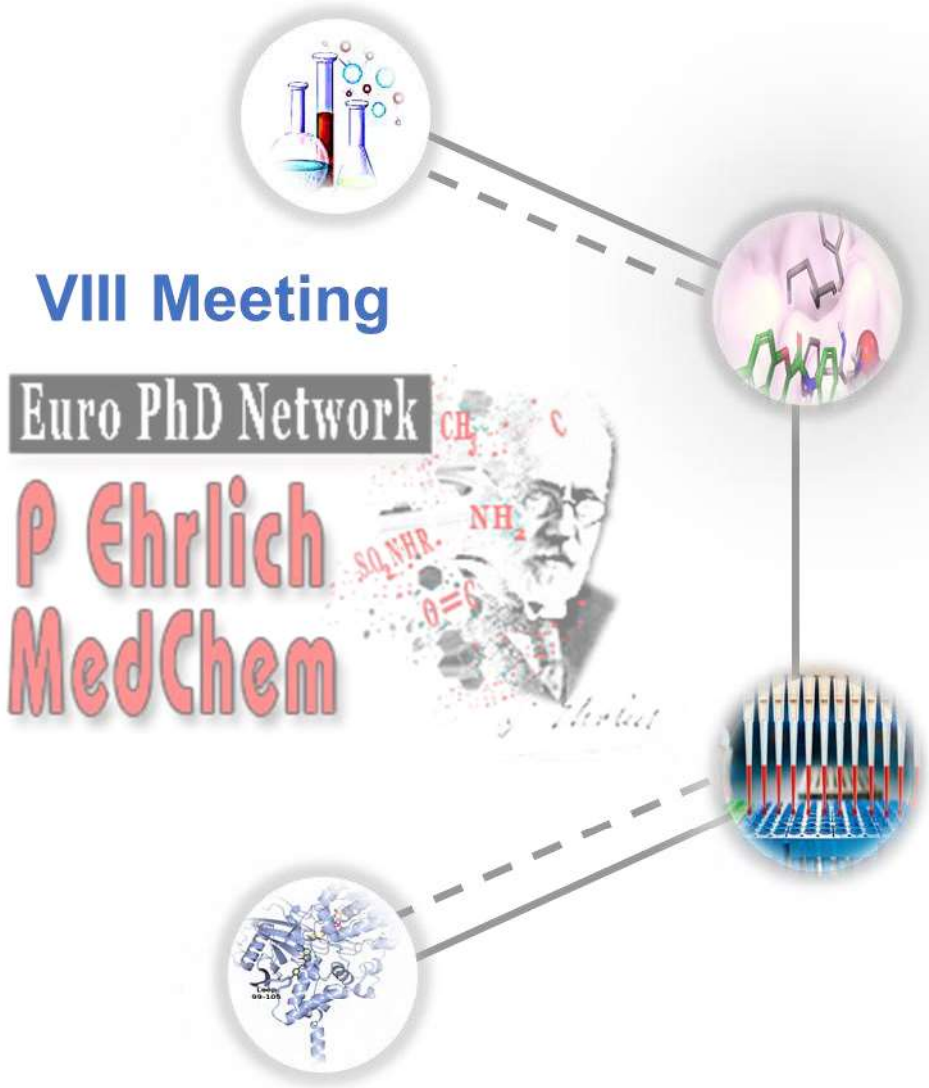

BOOK OF ABSTRACTS

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Constrained 1,4-dialkylpiperazines as monoamine transporters inhibitors for cocaine-related abuse

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Cocaine abuse and addiction remain grave health and societal problems with nearly 11,000 overdose deaths in 2015. Despite the high prevalence of cocaine use, no FDA-approved therapeutic for treating cocaine addiction has been achieved. The primary target for cocaine is dopamine transporter (DAT) and the rewarding and reinforcing effects of cocaine are mediated predominantly by its inhibition, with a consequent 'reverse agonist' effect. Several DAT inhibitors have been proposed as potential drugs for cocaine abuse.[1-2] One of the most studied DAT inhibitors, GBR12909 (Ki_{DAT} = 3.7 nM), is able to slightly increase DA level and to blunt the cocaine-induced elevation of extracellular DA *in vivo* without exerting the central exciting effects of cocaine and addiction. Unfortunately, the phase I clinical trials failed, due to its cardiotoxicity.[3-4] In a lead optimisation program focused to identify novel and safe GBR12909 analogues, nine constrained derivatives were design and synthesized in a ligand based approach. Maintaining unaltered the fluoro-phenyl and phenylpropylpiperazine moiety, the rigidification of the ethylene ether, by means of tetrahydrofuran, dioxolane, dioxane, oxathiolane and dithiolane ring, was investigated in a focused SAR study (Fig. 1).

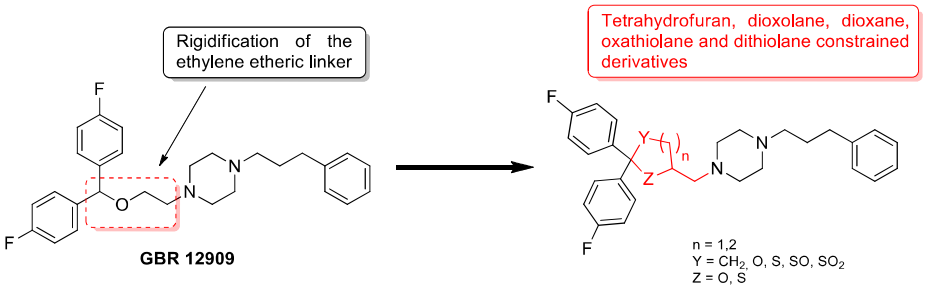

Fig. 1: Structural modification of the lead compound GBR12909.

All the compounds were assayed for the determination of the binding affinity for DAT, NET and SERT. In particular, two dioxolane derivatives displayed a binding affinity comparable to that of GBR12909, with *Ki* of 21.2 and 13.9 nM for DAT, and a selectivity ratio SERT/DAT > 30. Since the cyclization introduces one chiral centre, the two enantiomers of one racemic mixture were prepared following enantioselective synthetic procedures. The (R)- and (S)-forms showed a binding affinity comparable to the one determined for the racemate (Ki_{DAT} of 16 and 46 nM, respectively), suggesting that the configuration of the stereocenters slightly affect the binding to the DAT transporter. For the most interesting derivatives, uptake inhibition assays were conducted in rat brain synaptosomes. It was observed that the potency trend parallel the affinity values.

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