Short Communication

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Pharmacology profile of F17464, a dopamine D3 receptor preferential antagonist

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F17464(N-(3-{4-[4-(8-Oxo-8H-[1,3]-dioxolo-[4,5-g]-chromen-7-yl)-butyl]-piperazin-1-yl}phenyl)-methanesulfonamide, hydrochloride) is a new potential antipsychotic with a unique profile: it is a > 50 fold D3 over D2 receptor preferential antagonist and a 5-HT1a receptor partial agonist. The efficacy of F17464 has been demonstrated in patients with an acute exacerbation of schizophrenia, within a phase 2 study, with a favourable safety profile (Blier et al, 2019) and selective D3 receptor occupancy has been demonstrated in a human PET imaging study (Slifstein et al., 2020). In animal models, F17464 reversed psychotomimetic-induced hyperactivity mimicking positive symptoms of schizophrenia, improved social deficits, and cognition (Sokoloff and Le Foll, 2017). Previously reported F17464 behavioral work been expanded here (see below) to show target engagement, neurochemical properties, the effect on NMDA - glutamatergic alterations and the effects in a rodent model for autism (Cosi et al., 2021). F17464 exhibits high affinity for the human dopamine receptor subtype 3 (hD3) (Ki = 0.17 nM) and the serotonin receptor subtype 1a (5-HT1a) (Ki = 0.16 nM) and a > 50 fold lower affinity for the human dopamine receptor subtype 2 short and long form (hD2s/l) (Ki = 8.9 and 12.1 nM, respectively). [14C] F17464 dynamic studies show a slower dissociation rate from hD3 receptor (t1/2 = 110 min) than from hD2s receptor (t1/2 = 1.4 min) and functional studies demonstrate that F17464 is a D3 receptor antagonist, 5-HT1a receptor partial agonist. In human dopaminergic neurons F17464 blocks ketamine induced morphological changes, an effect D3 receptor mediated. In vivo F17464 target engagement of both D2 and 5-HT1a receptors is demonstrated in displacement studies in the mouse brain. F17464 increases dopamine release in the rat prefrontal cortex and mouse lateral forebrain - dorsal striatum and reduces the effect of MK801 on % c-fos mRNA medium expressing neurons in cortical and subcortical regions. F17464 also rescues valproate induced impairment in social interaction, a rat model of autism. All the neurochemistry and behavioural effects of F17464 are observed in the dose range 0.32– 2.5 mg/kg i.p. in both rats and mice. The in vitro - in vivo pharmacology profile of F17464 in preclinical models is discussed in support of a therapeutic use of the compound in schizophrenia and autism.

Biography:

Cristina Cosi is a biologist and pharmacologist, biochemist by training, with a Master in Science (Doctor in Biology) from the University of Florence, Italy, and a PhD in Pharmacology from the University of Toulouse, France, 1997, she has an extensive working experience in the Neuroscience research field, mostly in industry at Pierre Fabre, France, but also in academic environments, in Italy, University of Florence and Verona, and US, NIH. She has focused her career on the understanding of neurodegenerative processes and mechanisms of neuronal plasticity in order to find medications that might be beneficial against neurodegenerative and neurodevelopmental diseases and pain. She has done pioneering work in the poly (ADP-ribose) polymerase (PARP) inhibitors preclinical research field, by showing evidence of the neuroprotective activity of these compounds, for the first time. She has contributed to the discovery and development of neurotrophins receptors TRKA/B inhibitors as potential analgesics and D3 antagonists/5-HT1A agonists as potential antipsychotics.