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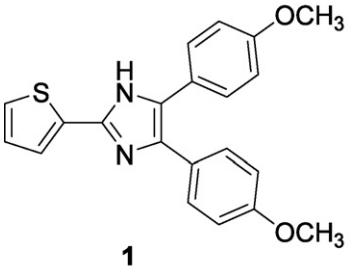
Discovery of PDE10A inhibitor, PF-2545920

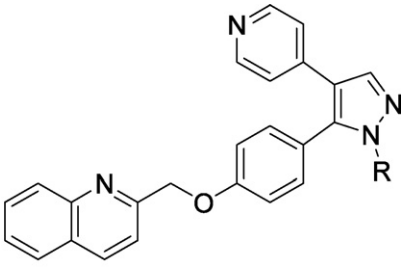
Since it is highly expressed in the medium spiny neurons of the striatum, inhibition of phosphodiesterase 10A (PDE10A) has emerged as a potential new target for the treatment of schizophrenia [1]. The first compound reported to enter the clinic for this indication was PF-2545920, a PDE10A inhibitor discovered by Pfizer, which is currently in Phase II trials. In a recent paper [2], the medicinal chemistry effort involved in the initial hit-to-lead program leading to the ultimate identification of PF-2545920 as a clinical candidate is detailed. In addition, the unique binding properties that play a role in the selectivity of this compound over other PDEs is demonstrated using X-ray crystallography.



1

The initial phase of the program focused screen yielded **1**, which not only had desirable activity against PDE10A (PDE10A IC_{50} = 35 nM), but also demonstrated >100-fold selectivity over other PDEs. The reason for the selectivity became apparent when a co-crystal X-ray structure of the compound bound to PDE10A was determined. The structure showed a unique binding configuration compared to standard PDE inhibitors. First, **1** associated with Gln-726 via a π–nitrogen interaction, rather than an H-bond, which is standard for conventional PDE inhibitors. In addition, it made use of a unique H-bond to Tyr-693, a residue that is found in only one other PDE. Finally, the X-ray structure revealed that PDE10A possesses a selectivity pocket not found in the 21 other known PDEs, which, in the case of **1**, is occupied by the thiophene ring.

Further rounds of screening were launched using X-ray crystallography and physiochemical properties (mw < 400, *c* log $P \leq 4$ and low number of H-bond donors) as filters to guide the selection of lead compounds, which made use of the selectivity pocket and were expected to have sufficient brain uptake. Among several potential lead series, the pyrazole-based chemotype, exemplified by **2**, eventually stood out. This chemotype takes advantage of the same binding configuration utilized by **1**, but in this case the quinoline group occupies the selectivity pocket and Tyr-693 interacts with the quinoline nitrogen. Moreover, this compound also takes advantage of an additional interaction with a structural water which forms an H-bond to the pyridine ring. Although **2** displayed most of the desired properties for a clinical candidate (PDE10A IC_{50} = 0.42 nM, > 100-fold selectivity over other PDEs, mw = 378 and *c* log *P* = 3.9) it had poor brain penetration (brain/plasma ratio = 0.21), which would require high plasma exposure to achieve efficacy. Nonetheless capping the pyrazole with methyl retained activity (PDE10A IC_{50} = 0.37 nM) and selectivity (>1000-fold) and improved the brain to plasma ratio to 0.86. The *in vivo* activity of PF-2545920 (**3**) in the conditioned avoidance response assay (ED_{50} = 1 mg/kg sc) and favorable PK properties in preclinical species (rat, dog and monkey) led to its nomination as a clinical candidate.



2 (R = H)
3 PF-2545920, (R = CH_3)

1 Menniti, F.S. *et al.* (2007) Phosphodiesterase 10A inhibitors: a novel approach to the treatment of the symptoms of schizophrenia. *Curr. Opin. Investig. Drugs* 8, 54–59

2 Verhoest, P.R. *et al.* (2009) Discovery of a novel class of phosphodiesterase 10A inhibitors and identification of clinical candidate 2-[4-(1-methyl-4-pyridin-4-yl-1H-pyrazol-3-yl)-phenoxymethyl]-quinoline (PF-2545920) for the treatment of schizophrenia. *J. Med. Chem.* 52, 5188

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