Executive Summary

A team of experts collaborated to transform potent and selective lead compounds that had been hampered by development issues into viable drug candidates. A fit-for-purpose strategy was designed to overcome the pharmacokinetic and toxicological issues. Using available computational models of the hERG channel and DA D₃ receptors, key amino acidic residues, responsible for the ligand interactions, were identified. This led to the identification of new templates in which the hERG and the D₃ Structure Activity Relationships started to diverge.

The strategy led to a new series of derivatives which greatly improved their physico-chemical, Drug Metabolism and Pharmacokinetics (DMPK) and developability characteristics. Significantly, additional refinement of these templates identified optimal development candidates which could be brought to humans.

Following the isolation and characterization of the cDNA for the dopamine DA D₃ receptor, subsequent studies indicated that D₃ receptors, as well as D₃ receptor mRNA, are primarily localized in limbic regions of the rat²³ and humanBrain. This indicated that D₃ receptors may be involved in the pathophysiology of drug addiction and schizophrenia.
**The Challenge**

Different templates were available as “selective” DA D₃ antagonists, but the research of a drug candidate was hampered by a lack in their development parameters. Two molecules demonstrated real selectivity versus the DA D₃. These compounds demonstrated excellent potency and selectivity profiles in vitro and good activity in vivo in different preclinical models. While these molecules proved to be very useful for target validation, part of their overall development profile, including hERG (human ether-a-go-go K⁺ channel) affinity and the potentially related modification of the QTc profile, were sub-optimal for further development. The challenge was to identify new chemical entities endowed with drug-like properties.

**The Solution**

Two molecules (Figure 2) showed excellent potency and selectivity profiles in vitro and good activity in vivo in different preclinical models.

**Figure 1**

The screening cascade was appropriately revised in agreement with the involved disciplines to bring forward the critical test for the progression of the compounds. A fit-for-purpose strategy was designed to tackle and overcome the pharmacokinetic and toxicological issues.
The exploitation of the available computational models of the hERG channel and of the DA D₃ receptor allowed for the identification of key amino acidic residues that were responsible for the ligand interactions.

This important discovery led to the identification of new templates in which the hERG and the D₃ Structure Activity Relationships, till then completely parallel, started to diverge.

**Figure 2**
The careful application of the Medicinal Chemistry strategy led to the discovery of a new series of derivatives⁹-¹¹ which greatly improved their physico-chemical, DMPK and development characteristics (Derivatives 1-3, Figure 2). QTc liability was no longer present in these newly developed scaffolds. Their efficacy in the *in vivo* preclinical models was very high. High potency and selectivity for the DA D₃ receptor was maintained.

Moreover, exploiting the above described principles, the integrated lead optimization process led to an additional refinement of these templates to identify “optimal” development candidates which could be brought to humans.

The full exploitation of the revised screening cascade and of the computational models allowed the identification of additional new scaffolds endowed with exceptional potency, selectivity and development profiles (Derivatives 4-5, Figure 2)¹²,¹³.
Conclusion
A team of experts collaborated to achieve viable drug candidates by overcoming the development issues that were hampering their use. Profiles were vastly improved for subsequent use in humans and the start of clinical trials.

The study demonstrates our capability to provide drug discovery and development services that include integrated research and development distinguished by fit for purpose strategies to overcome the most challenging pharmacokinetic and toxicological issues.

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REFERENCES