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New fused benzazepine as selective D_3 receptor antagonists. Synthesis and biological evaluation. Part one: [h]-fused tricyclic systems

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Abstract—The synthesis and SAR of a new series of potent and selective dopamine D_3 receptor antagonists is reported. The introduction of a tricyclic [h]-fused benzazepine moiety on the recently disclosed scaffold of 1,2,4-triazol-3-yl-thiopropyl-tetrahydrobenzazepines is reported. A full rat pharmacokinetic characterization is also reported.

Following the isolation and characterization of the cDNA for the dopamine D_3 receptor,[1] a number of non-selective and selective dopamine D_3 receptor antagonists have been reported.[2] Growing evidence suggests that selective antagonists at dopamine D_3 receptor can reduce the reinforcing efficacy of drugs of abuse, reverse cognitive deficits, and show efficacy in animal models of schizophrenia.[2a] GSK showed a long-standing interest in this field and contributed to the discovery of selective D_3 receptor antagonists.[3–5] While SB-277011[3] (**1**, Fig. 1) represented an excellent tool to the purpose of target validation, the recently disclosed benzazepine derivative **2**[5–10] (Fig. 1) represents a more balanced molecule with improved developability criteria. In the present study we investigated the possibility to 'fuse' the pendant heterocycles attached to the benzazepine (BAZ) template of the series to which **2**[5–10] belongs with the BAZ moiety itself to develop tricyclic derivatives. Depending on the bond on which the fusion is achieved, this task can lead to [h]-fused or [g]-fused derivatives. This manuscript deals with the former class, while the latter one will be the topic of the second part.

Each new chemical entity (NCE) prepared was assayed for its agonistic versus antagonistic properties using a functional GTPγS assay expressing the human dopamine D_3 receptor.[5] All the compounds here reported proved to be antagonists at the D_3 receptor.[5] The objective of the screening cascade for this specific series was to identify molecules having at least 100-fold selectivity versus dopamine D_2 and histamine H_1 receptors (functional assays), and being endowed with 100-fold selectivity versus the hERG ion channel (Dofetilide binding assay).[5] Generic developability screens such as CYPEX bactosome P450 inhibition and rat and human in vitro clearance in liver microsomes (Cli) were included early in the screening cascade. Substituted 3-[(3-chloropropyl)thio]-4-methyl-5-aryl-4 *H*-1,2,4-triazoles

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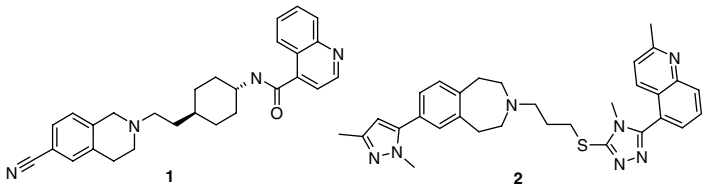


Figure 1. GSK selective D_3 antagonist.

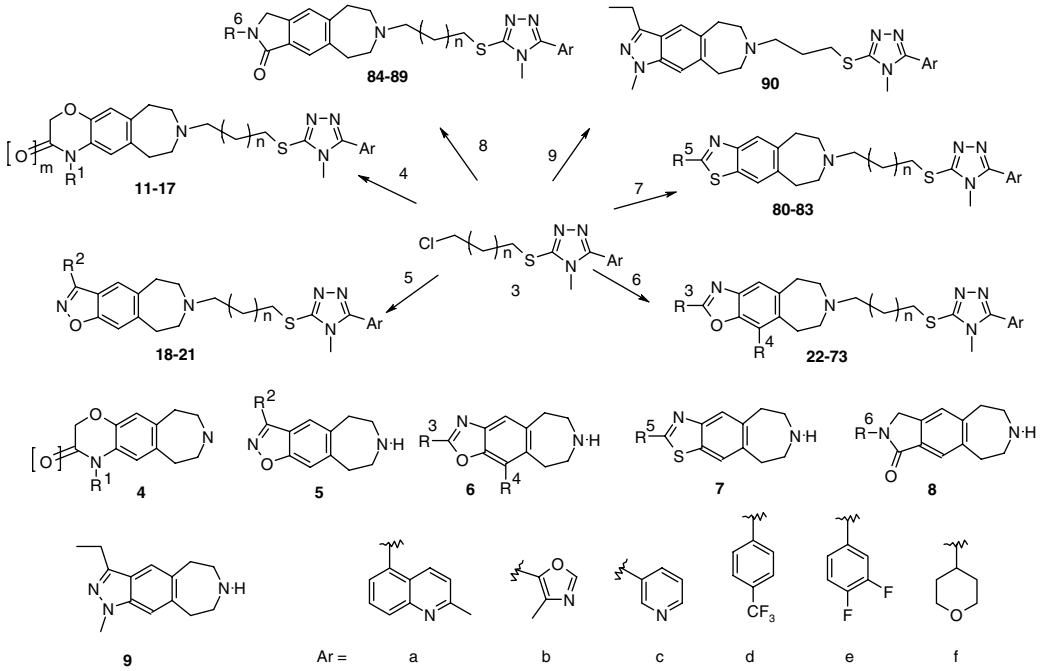
were reacted[5–10] with tricyclic derivatives, according to the general Scheme 1, at 60 °C in DMF using K_2CO_3 overnight and purified through column chromatography to obtain the products described in Tables 1–7.

For the preparation of the alpha-substituted derivatives, reductive ammination was used as depicted in Scheme 2. The introduction of an oxazinone system (**4**) on the thiotriazole scaffold (**11**, **12**) led to a marked increase in PSA[11] (values > 90 $\AA^2$ with respect to 65 $\AA^2$ for derivative **2**) and was detrimental both to the desired D_3 affinity and to the selectivity of the molecule, leading to an increased unwanted interaction with the hERG channel (Table 1). This could have been due to either a potential detrimental effect of a hydrogen bond (HB) donor (morpholinone N–H) or to the presence of an additional HB acceptor (morpholinone C=O). The first hypothesis may find some support in the fact that N-methylation (**13**, **14**) allowed some recovery in terms of D_3 affinity and significantly reduced hERG affinity. On the other hand, while the sulfonamide (**15**) further increased the desired affinity with the removal of both features, the acetamide (**16**) had a similar profile to **11** in terms of D_3 affinity having introduced again a carbonyl group into the system. However, the [1,4]oxazino[2,3-h][3]benzazepine derivative (**17**), where none of the features (i.e., carbonyl group and acidic NH) were present, showed an excellent D_3 potency and selectivity versus D_2 receptor.

Unfortunately, the hERG value did not match the selectivity criteria described in the screening cascade.

In this series it is important to highlight that the heterocyclic decoration on the thiotriazole moiety can be modified with no significant loss in terms of D_3 affinity (**12** vs. **11**, **14** vs. **13**). Taking into account the high PSA values displayed by derivatives **11**–**17** (ranging from 90 to 130 $\AA^2$), the pharmacokinetic (PK) properties of **15** were assessed in vivo in the rat.[12] The compound showed low blood clearance (Clb = 32 ml/min/kg), moderate half life ($T_{1/2}$ = 1.2 h), and low distribution volume (V_d = 2.4 l/kg). One may assume that this parameter (V_d), coupled with the high PSA value mentioned above, led to low brain penetration: the brain to blood (B/B) ratio, measured through sampling of the blood and brain[12] 1 h after i.v. administration, was actually equal to 0.2.

Consequently, it was decided to move from 6-membered anellated BAZ to 5-membered anellated BAZ to modulate the PSA parameter and the isoxazolo[4,5-h][3]benzazepine scaffold was designed (Table 2).



Scheme 1. Reagents and conditions: K_2CO_3, DMF 60 °C, cat NaI and appropriate tricyclic **4**–**8**, overnight. n = 0, 1, 2. m = 0, 1. R as defined in each table.