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# Synthesis and SAR of highly potent and selective dopamine $D_3$-receptor antagonists: Variations on the 1*H*-pyrimidin-2-one theme

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**Abstract**—In our efforts to further pursue one of the most selective dopamine $D_3$-receptor antagonists reported to date, we now describe the synthesis and SAR of novel and highly selective dopamine $D_3$ antagonists based on a 1*H*-pyridin-2-one or on a urea scaffold. The most potent compounds exhibited $K_i$ values toward the $D_3$ receptor in the nano- to subnanomolar range and high selectivity versus the related $D_2$ dopamine receptor. Thus, 1*H*-pyridin-2-one **7b** displays oral bioavailability ($F = 37\%$) as well as brain penetration (brain plasma ratio 3.7) in rat. Within the urea series, an excellent $D_3$ versus $D_2$ selectivity (>100-fold) could be achieved by removal of one NH group (compound **6**), although bioavailability (rat) was suboptimal ($F < 10\%$). These data significantly enhance our understanding of the $D_3$ pharmacophore and are expected to lead to novel approaches for the treatment of schizophrenia.


One of the best characterized, selective $D_3$ antagonists to date is ABT-925 (also known as A-437203 or BSF-201640[1]). This compound has high affinity for the human $D_3$ receptor ($K_i$ 2.9 nM), with at least 100-fold selectivity over the human $D_2$ and other receptors, enzymes, and ion channels. It readily crosses the blood–brain barrier and exhibits efficacy in a variety of animal models predictive of antipsychotic activity without inducing catalepsy or raising plasma prolactin levels. A program in our laboratories has been aimed at exploring further the potential of the pyrimidyl-piperazine core (Q) of ABT-925 (Fig. 1) to come up with follow-on candidates.[2,3]

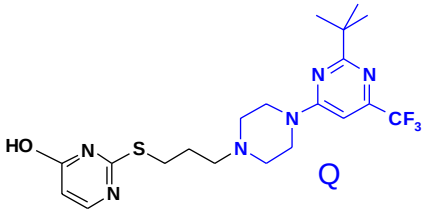


**Figure 1.** ABT-925.

In the course of our studies, we identified a series of compounds having nanomolar $K_i$ values toward the cloned human dopamine $D_3$-receptor, high selectivity versus related dopamine receptors, especially the cloned human $D_{2L}$-receptor, and in vivo efficacy in rat after po application.[2] Here, we present two new series of compounds derived from the same 1*H*-pyrimidin-2-one motif: 1*H*-pyridin-2-one derivatives, where the nitrogen atom from position 3 was omitted (Tables 1 and 2) and substituted ureas, designed by ring opening of the 1*H*-pyrimidin-2-one pharmacophore (Fig. 2).

The same synthetic route, discussed in detail for the 1*H*-pyrimidin-2-one derivatives,[2] was chosen to prepare the 1*H*-pyridin-2-ones. Starting materials were commercially

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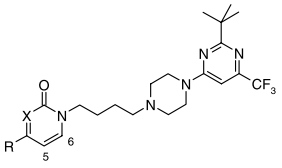
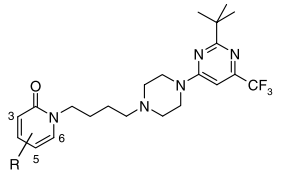
**Table 1.** Comparison of 1*H*-pyrimidin-2-ones (X = N)/1*H*-pyridin-2-ones (X = CH)



| Compound | R | X | $K_i$ (nM) | | Sel. versus $D_2$[b] | clog *P* | PSA |
|---|---|---|---|---|---|---|---|
| | | | $D_3$[a] | $D_2$[a] | | | |
| **7a**[2] | Me | N | 4.4 | 307 | 71 | 2.9 | 67 |
| **7b** | Me | CH | 0.8 | 62.6 | 81 | 4.0 | 54 |
| **8a**[2] | OH | N | 1.9 | 196 | 104 | 2.3 | 87 |
| **8b** | OH | CH | 1.1 | 25.5 | 23 | 3.2 | 74 |
| **9a**[2] | $CF_3$ | N | 14.5 | 936 | 64 | 3.6 | 67 |
| **9b** | $CF_3$ | CH | 11.4 | 231 | 20 | 4.5 | 54 |
| **10a**[2] | Ph | N | 1.4 | 168 | 122 | 4.4 | 67 |
| **10b** | Ph | CH | 7.9 | 527 | 67 | 5.3 | 54 |

[a] Values are means of 2–3 experiments. Standard deviation of max 30% of the mean.
[b] $K_i$ $D_2$/$K_i$ $D_3$.

**Table 2.** Variation of the substitution of the 1*H*-pyridin-2-one core

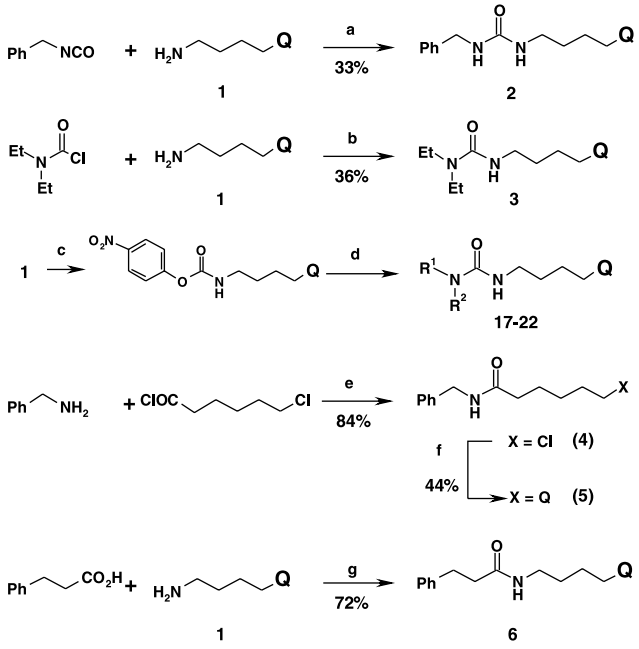


| Compound | R | $K_i$ (nM) | | Sel. versus $D_2$[b] |
|---|---|---|---|---|
| | | $D_3$[a] | $D_2$[a] | |
| **11** | 3-OMe | 2.2 | 168 | 77 |
| **12** | 3-Me | 2.3 | 171 | 73 |
| **13** | 3-$CF_3$ | 9.3 | 409 | 44 |
| **14** | 5-$CF_3$ | 35.7 | 399 | 11 |
| **15** | 5-Cl | 32.2 | 128 | 4 |
| **16** | 6-Me | 12.1 | 195 | 16 |

[a] Values are means of 2–3 experiments. Standard deviation of max 30% of the mean.
[b] $K_i$ $D_2$/$K_i$ $D_3$.

available with the exception of 4-phenyl-pyridin-2-ol, which was generated using a modified Suzuki cross-coupling reaction between sodium tetraphenylborate and 4-chloro-pyridin-2-ol.[4] 'Classical' Suzuki coupling with phenylboronic acid failed in that case.

As exemplified in Scheme 1, urea derivatives of types **2** and **3** were prepared from the corresponding amine **1** by




**Scheme 1.** Reagents and conditions: (a) DIPEA, $CH_2Cl_2$, 2 h, reflux; (b) $Et_3N$, $CHCl_3$, 2 days, 25 °C; (c) *p*-nitrophenylchloroformate (1.1 equiv), DIEA (1.1 equiv), DMA/DCM (1/1), 1 h, rt; (d) $NHR^1R^2$ (1.25 equiv), DIEA (2.2 equiv), 12 h, 55 °C; (e) $Et_3N$, THF, 12 h, 25 °C; (f) QH, NaBr, DIPEA, NMP, 5 h, 120 °C; (g) EDCI, DMAP, $CH_2Cl_2$, 8 h, 25 °C.

reaction with an isocyanate or a carbamoyl chloride. Chemical diversity was increased using parallel synthesis (exemplified by compounds **17**–**22**), whereby the intermediate *p*-nitrophenylcarbamate of amine **1** was generated in situ and combined with a diverse set of amines.[5] The amides **5** and **6**, designed by removing one NH group from the previously described ureas, were obtained as depicted in Scheme 1. Benzylamine was first coupled with 6-chlorohexanoyl chloride and the piperazine-pyrimidine moiety (QH) was introduced by nucleophilic substitution to yield **5**. In the second case, **6** was readily prepared by coupling amine **1** with 3-phenylpropionic acid.

Receptor affinities for the compounds described have been determined in binding assays[2] using human cloned dopamine $D_3$ and $D_2$ receptors. Compounds with a $K_i$ below 10 nM and a selectivity versus $D_2$ above 50-fold were analyzed in vitro for their functional properties with a $hD_3$-GTPγS binding assay:[6] all compounds tested displayed antagonistic activities ($E_{max}$ < 10%).

*1H-Pyridin-2-one derivatives (Tables 1 and 2)*: As shown in a previous paper,[2] $N^3$-methylation within the 1*H*-pyr-

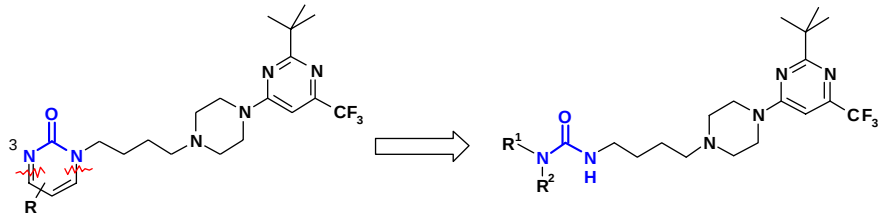


**Figure 2.** From the 1*H*-pyrimidin-2-one series[2] to the urea series.

imidin-2-one series decreased $D_3$ affinity, whereas the impact on the $D_2$ affinity was less pronounced. Here, we report on the 1*H*-pyridin-2-one class of compounds, where the nitrogen atom from position 3 was omitted. Unlike the effect of $N^3$-methylation, the impact was in general more pronounced on the $D_2$ affinity (compounds **7b**–**10b**): $D_2$ binding was increased up to 8 times compared to the corresponding 1*H*-pyrimidin-2-one derivatives (**7a**–**10a**).[2] This led to a significant decrease of the selectivity versus $D_2$, with the exception of the 4-methyl derivative **7b**, where $D_2$- and $D_3$-affinity increased simultaneously. As regards the 4-phenyl derivative **10b**, loss of selectivity versus $D_2$ is less significant as it is the result of both a decrease of $D_2$- and $D_3$-affinity. In general, compared to the corresponding 1*H*-pyrimidin-2-ones, 1*H*-pyridin-2-ones displayed higher clog*P*[7] (4.0–5.3, average increase of 1 unit) reflecting increased lipophilicity, whereas calculated polar surface area (PSA)[8] was significantly decreased (in average 13 Å$^2$) and ranged between 54 and 74 Å$^2$: values less than 75 being favorable for brain penetration.[8]

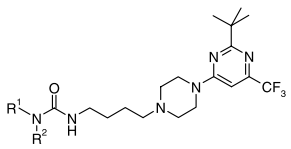
Positions 3, 5, and 6 of the 1*H*-pyridin-2-one were then screened (Table 2). In contrast to the effect of the $N^3$-methylation,[2] substitution in position 3 was favorable and led to compounds **11**–**13** with low nM $D_3$ affinity and high selectivity versus $D_2$. Examples with 5- (**14** and **15**) and 6-substituents (**16**) did not look promising enough for broader variation as they exhibited low $D_3$ binding affinity as well as low selectivity versus $D_2$.

Compound **7b** was further characterized and displayed in vitro metabolic stability in human liver microsomes (>97% recovery),[9] but very low in vitro microsomal stability in rat and dog (74% and 59%,[9] respectively), high permeability in the Caco-2 model ($P_{app}$ $5.0 \times 10^{-6}$ cm/s (pH 7.2)),[10] oral bioavailability ($F = 37\%$),[11] and brain penetration (brain plasma ratio 3.7)[11] in rat.

*Ureas and amides (Tables 3 and 4)*: Ureas were designed by ring opening of the 1*H*-pyrimidin-2-one pharmacophore (Fig. 2). Molecular modeling (in the $D_3$ receptor model)[2] suggests a strong interaction, already observed for the 1*H*-pyrimidin-2-one structural class,[2] of the urea carbonyl with Thr 368 on TM7 (Fig. 3)[12] and therefore supports high affinity for the $D_3$ receptor.

Seventeen of the 30 prepared ureas revealed $D_3$ affinity below 10 nM. Table 3 depicts binding data of selected examples. Insertion of a methylene unit, especially in the case of Ph (compounds **19** and **2**), did not influence $D_3$ binding but decreased $D_2$ affinity and therefore increased the selectivity versus $D_2$. Changing the benzyl moiety to a phenethyl (compound **20**) as well as saturation of the aromatic ring (compound **21**) led to decreased selectivity versus $D_2$. Replacement of the phenyl ring by various heterocyclic groups, substitution of the phenyl ring or of the methylene spacer did not give significant improvements of the selectivity versus $D_2$ (data not shown). Disubstitution ($R^2$ = Et) looked very promising with respect to $D_3$ affinity (subnanomolar level), as exhibited by the di-Et derivative **3**. However, this effect was not observed for the Bn derivative **22**,

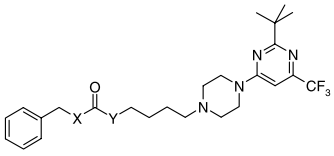
**Table 3.** Ureas



| Compound | $R^1$ | $R^2$ | $K_i$ (nM) | | Sel. versus $D_2$[b] |
|---|---|---|---|---|---|
| | | | $D_3$[a] | $D_2$[a] | |
| **17** | *t*-Bu | H | 4.0 | 65.8 | 17 |
| **18** | $CH_2$-*t*-Bu | H | 5.5 | 91.3 | 17 |
| **19** | Ph | H | 3.2 | 59.1 | 18 |
| **2** | Bn | H | 2.7 | 137 | 51 |
| **20** | $CH_2$-Bn | H | 7.2 | 234 | 32 |
| **21** | $CH_2$-cyclohex. | H | 6.7 | 159 | 24 |
| **3** | Et | Et | 0.9 | 17.3 | 19 |
| **22** | Bn | Et | 8.3 | 212 | 26 |

[a] Values are means of 2–3 experiments. Standard deviation of max 30% of the mean.
[b] $K_i$ $D_2$/$K_i$ $D_3$.

**Table 4.** Ureas and amides



| Compound | X | Y | $K_i$ (nM) | | Sel. versus $D_2$[b] |
|---|---|---|---|---|---|
| | | | $D_3$[a] | $D_2$[a] | |
| **2** | NH | NH | 2.7 | 137 | 51 |
| **5** | NH | $CH_2$ | 6.2 | 174 | 28 |
| **6** | $CH_2$ | NH | 1.6 | 244 | 149 |

[a] Values are means of 2–3 experiments. Standard deviation of max 30% of the mean.
[b] $K_i$ $D_2$/$K_i$ $D_3$.

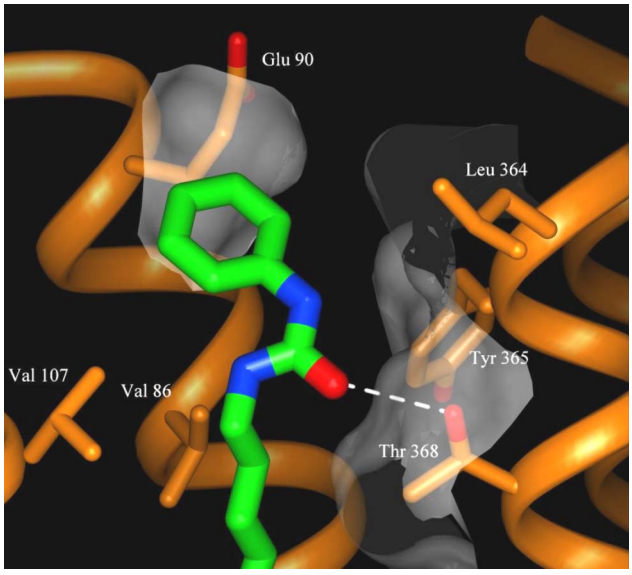



**Figure 3.** Compound **19** (in stick presentation) in the $D_3$ model. Interactions with the urea moiety.[12] The semitransparent white surface represents the molecular surface of the protein and the dashed line the interactions with Thr 368.

and selectivity versus $D_2$ was thus maintained at an insufficient level. Interestingly, when comparing **2** with **22**, disubstitution ($R^2 \neq H$) induced an increase of clog $P$[7] (from 4.7 up to 5.1) and in parallel a decrease of PSA (from 73 Å$^2$ down to 65 Å$^2$).[8]

Unexpectedly, removal of one NH group (compound **6**, X = $CH_2$, Table 4) facilitated high discrimination of the two receptors (>100-fold).[13] Such high selectivities versus $D_2$ were rarely observed within the parent 1*H*-pyridin-2-one series (X = CH, Tables 1 and 2). As exemplified by **5**, the other NH group seemed to be required for high selectivity versus $D_2$. Finally, given the suboptimal PK of **6** ($F < 10\%$),[14] activities on that series were terminated.

In summary, two novel series of potent and selective dopamine $D_3$ antagonists have been reported. Within the 1*H*-pyridin-2-one series, substitution in position 3 led to compounds (**11**–**13**) with low nM $D_3$ affinity and high selectivity versus $D_2$. Moreover, **7b** displayed oral bioavailability as well as brain penetration in rat. Within the urea series, removal of one NH group (compound **6**) facilitated high discrimination of the $D_3$ and $D_2$ receptors, although bioavailability (rat) was suboptimal. These data significantly enhance our understanding of the $D_3$ pharmacophore and are expected to lead to novel approaches for the treatment of schizophrenia. Further optimization of these two series (1*H*-pyridin-2-ones and ureas) will be reported in due course.

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11. After iv- and po-dosing (2 and 10 mg/kg, respectively).
12. The interactions with the other parts of the molecule are not shown and not discussed in detail, as they have already been published for other $D_3$ ligands.[2]
13. Numerous amides, mostly (hetero)arylamides, are known in the literature as dopamine $D_3$-receptor antagonists: see, for example: Hackling, A.; Ghosh, R.; Perachon, S.; Mann, A.; Höltje, H.-D.; Wermuth, C. G.; Schwartz, J.-C.; Sippl, W.; Sokoloff, P.; Stark, H. *J. Med. Chem.* **2003**, *46*, 3883, and references cited therein. The closest analog to **6**, a 3-phenyl-propionamide described by Hackling et al displayed a low selectivity versus $D_2$ (ratio $K_i$ ($D_2$)/$K_i$ ($D_3$) of 10).
14. Despite in vitro microsomal stability (rat-human 94–96%).[9]