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Cyclic Amidines as Benzamide Bioisosteres: EPC Synthesis and SAR Studies Leading to the Selective Dopamine D4 Receptor Agonist FAUC 312

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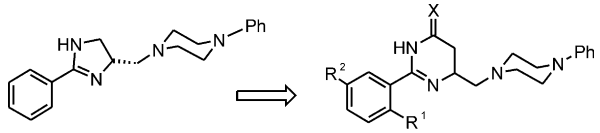
Abstract—Investigation of conformationally restricted benzamide bioisosteres led to the chiral phenyltetrahydropyrimidine derivative **ent2a** (FAUC 312) displaying strong and highly selective dopamine D4 receptor binding ($K_{i_{high}} = 1.5$ nM). Mitogenesis experiments indicated 83% ligand efficacy when compared to the unselective agonist quinpirole. The target compounds of type **2** and **3** were synthesized in enantiopure form starting from asparagine.

Very recently, we have reported on the dihydroimidazole derivative FAUC 179 (**1**) showing highly selective dopamine D4 receptor binding in combination with partial agonist properties (42% ligand efficacy).[1] Drugs exhibiting that kind of activity profile are supposed to be beneficial for an effective pharmacotherapy of ADHD (attention deficit hyperactivity disorders).[2]

In conjunction with our current efforts focused on the efficacy tuning of dopaminergics,[3] we were intrigued by the question, whether modifications of the dihydroimidazole substructure led to a significant change of intrinsic activity. Conserving the basicity of the amidine function, we decided to expand the dihydroimidazole moiety by one carbon atom resulting in tetrahydropyrimidine derivatives of type **2**. The modified geometry of the six-membered ring was expected to influence the spatial orientation of the phenylpiperazinylmethyl side chain. This could affect the interaction with both the binding sites of the active and inactive receptor state thus enhancing or reducing the intrinsic activity. To evaluate the effect of an electron withdrawing carbonyl function, the neutral 5,6-dihydro-3*H*-pyrimidin-2-one substructure of the analogue **3** should be investigated for its ability to serve as a suitable bioisostere.

Since the receptor binding of FAUC 179 (**1**) proved to be strongly stereoselective,[1] we planned to establish effective EPC syntheses giving access to both enantiomers. Thus, the target compounds of type **2** and **3** should be prepared optically pure starting from (*S*)-asparagine and its unnatural antipode.



1 (FAUC179) **2**: (X = H_2) **3**: (X = O)

Whereas the synthesis of the tetrahydropyrimidine derivatives **2** was envisioned by reaction of a benzimidate with a suitable 1,3-diamine building block, the pyrimidinone derivative **3** should be prepared by condensation with the appropriate β-alanine equivalent. The elaboration of smooth cyclization conditions were regarded to be crucial, because we expected a high temperature sensitivity of the chiral building blocks. In detail, the preparation of the chiral 1,3-diamine derivative **10a** was possible by two alternative pathways. Starting from (*S*)-asparagine (**4**), a previously developed protocol gave access to the aldehyde derivative **5**.[4] Reductive amination to give the

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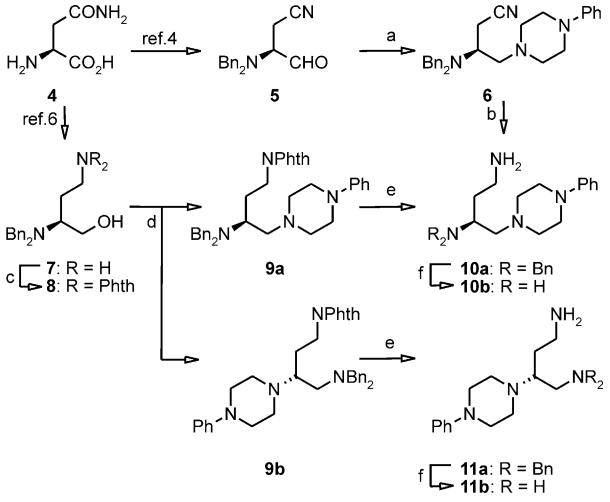
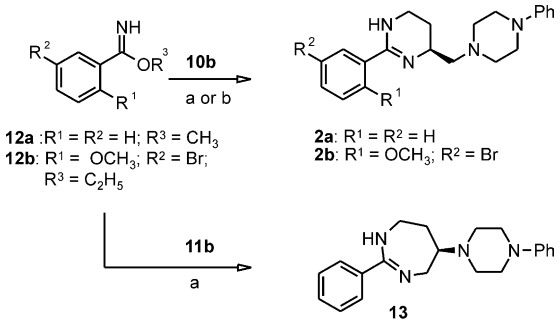
piperazine derivative **6** and subsequent reduction with $LiAlH_4$ afforded the diamine **10a** with high enantiomeric purity.[5] Overall yields could be increased by exploiting the 1,3-diaminoalcohol derivative **7** as a central intermediate, readily available from (*S*)-asparagine.[6] The protection of the primary amine to give the phthalimide derivative **8** was achieved by the reaction with phthalic acid anhydride applying Dean-Stark conditions.[7] Our first attempts to perform a Dess-Martin oxidation[8] of the alcohol and subsequent reductive amination using phenylpiperazine hydrochloride resulted in disappointing yields. Thus, we preferred an activation of the hydroxy group by methanesulfonic chloride followed by a nucleophilic displacement with phenylpiperazine. This reaction sequence furnished 59% yield of the desired product **9a** and 7% of the regioisomer **9b**, obviously formed via an aziridinium intermediate.[9] Hydazinolysis of both isomers afforded the primary amine derivatives **10a** and **11a**. Derivatization of **10a** with (*R*)-phenylethyl isocyanate and careful HPLC investigation proved the isomeric integrity of the reaction sequence.[10] Debenzylation under reductive conditions gave access to the fully deprotected diamine building blocks **10b** and **11b** (Scheme 1).



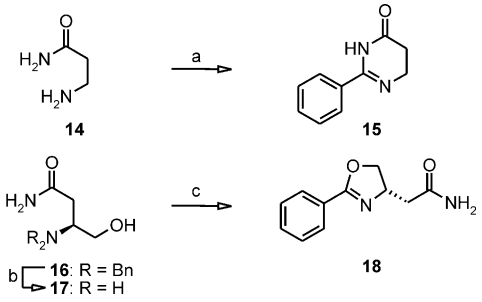
Scheme 1. (a) Phenylpiperazine HCl, $NaBH_3CN$, MeOH, rt, 24 h (30%); (b) $LiAlH_4$, Et_2O, 0 °C–rt (crude: 99%); (c) phthalic acid anhydride, NEt_3, toluene, Dean-Stark, 5 h (91%); (d) (1) MesCl, NEt_3, THF, −23 °C, 1 h; (2) phenylpiperazine, DMF/THF, 0 °C–rt, 24 h (**9a**: 59%, **9b**: 7%); (e) $N_2H_4xH_2O$, EtOH, reflux, 3 h (**10a**: 96%, **11a**: 64%); (f) H_2, $Pd(OH)_2/C$, MeOH, rt, 24 h (**10b**: 92%, **11b**: 79%).

Employing cyclization conditions that proved suitable for the synthesis of dihydroimidazole derivatives,[11] we were able to proceed a smooth formation of the tetrahydropyrimidine **2a**[12] by condensation of the 1,3-diamine **10b** with methyl benzimidate (**12a**)[13] (Scheme 2). In an analogous way, the isomer **13** was available. For the 5-bromo-2-methoxy derivative **2b**, it turned out advantageous to react the 1,3-diamine **10b** and the corresponding imidate **5b** (available by the reaction of 5-bromo-2-methoxy benzamide[14] with Meerwein's salt[15]) in refluxing 1,2-dichloroethane.



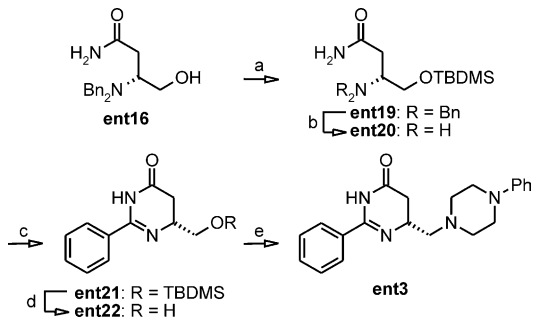
Scheme 2. (a) **12a**, MeOH, rt, 72 h (**2a, 13**: 44%); (b) **12b**, $(CH_2Cl)_2$, reflux, 2 h, (72%).

As a model reaction for the synthesis of the 5,6-dihydro-3*H*-pyrimidin-4-one scaffold, we decided to react suitable β-alanine equivalents with methyl benzimidate (**12a**). While the condensation with β-alanine and β-amino propionitrile required extremely high temperatures, the ring closure with β-alanine amide (**14**)[16] proceeded in refluxing ethanol to give 2-phenyl-5,6-dihydro-3*H*-pyrimidin-4-one (**15**) (Scheme 3). Since the position of the double bond in the amidine substructure was not actually clear,[17] we performed an ab initio molecular orbital calculation favoring unambiguously the tautomer **15**.[18]



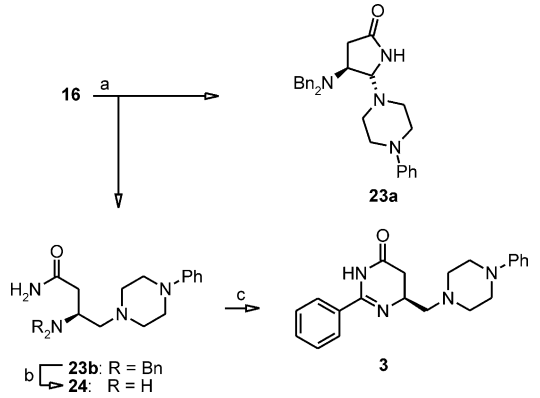
Scheme 3. (a) **12a**, EtOH, reflux, 12 h (34%); (b) H_2, $Pd(OH)_2/C$, 12 h, rt (100% crude); (c) **12a**, EtOH, reflux, 1 h (28%).

The initial strategy for the synthesis of the target compounds **3** was to build up the pyrimidinone scaffold, followed by the introduction of phenylpiperazine. In detail, the dibenzylamino derivative **16**, being accessible from (*S*)-asparagine in two steps,[19] gave rise to the β-alanine amide derivative **17** by reductive deprotection. Unfortunately, the condensation with methyl benzimidate **12a** resulted in a complete formation of the oxazoline derivative **18**, obviously due to kinetic reaction control. In order to induce the desired regiocontrol of the ring closure, *O*-protection of **ent16** to give silyl ether **ent19** was performed. Indeed, subsequent debenzylation and ring closure of the precursor **ent20** furnished the pyrimidone derivative **ent21** (Scheme 4). Finally, desilylation to give the primary alcohol **ent22**, subsequent conversion into the respective methanesulfonate and S_N2 reaction with phenylpiperazine afforded 7% of the test compound **ent3** over three steps.



Scheme 4. (a) TBDMS-Cl, imidazole, DMF, 0 °C–rt, 2 h (100%); (b) H_2, $Pd(OH)_2$/C, rt, 6 h, (97%, crude); (c) **12a**, EtOH, reflux, 72 h (49%); (d) NBu_4F, THF, 0 °C, 30 min (95%); (e) (1) MesCl, NEt_3, THF, −23 °C, 30 min (2) phenylpiperazine, DMF, 45 °C, 12 h, 75 °C, 2 h (7%).

To improve the yield, we changed the reaction sequence towards a completely functionalized β-alanine building block. Starting from alcohol **16**, periodinane promoted oxidation and subsequent reductive amination with phenylpiperazine hydrochloride furnished the dibenzylamine **23b**. During the process, the cyclic *N,N*-acetal **23a** was formed as a side product. Careful hydrogenolysis of **23b** to give the primary amine **24** and subsequent condensation with methyl benzimidate (**12a**) afforded the target compound **3** in high optical purity (Scheme 5).[20] The enantiomers **ent2a**, **ent2b**, **ent3** and **ent13** were prepared analogously starting from (*R*)-asparagine.

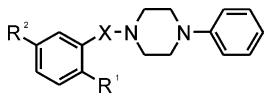


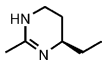
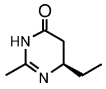
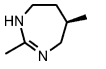
Scheme 5. (a) (1) DMP, CH_2Cl_2, 0 °C, 1 h; (2) $NaHCO_3/Na_2S_2O_3$ (1:1), H_2O, Et_2O (27%); (3) phenylpiperazine–HCl, $NaBH_3CN$, MeOH, rt, 24 h (26%); (b) H_2, $Pd(OH)_2$/C, rt, 6 h, (97%, crude); (c) **2a**, EtOH, reflux, 5 h (52%).

The test compounds **2a**,**b**, **3** and **13** and the optical antipodes **ent2a**,**b** **ent3** and **ent13** as well as the dopamine receptor agonist quinpirole were evaluated in vitro for their abilities to displace [^{3}H]spiperone from the cloned human dopamine receptors $D2_{long}$, $D2_{short}$,[21] D3[22] and D4.4[23] being stably expressed in CHO cells (see Table 1).[24] D1 affinity was determined by employing bovine striatal membrane preparations and the D1 selective antagonist [^{3}H]SCH 23390.[24]

All test compounds showed only weak D1, D2 and D3 receptor binding. Investigation of the D4 binding properties clearly indicated that the tetrahydropyrimidine **ent2a** (FAUC 312) revealed high D4 affinity, when careful analysis of the competition experiments employing a large number of test concentrations showed a biphasic curve ($K_{i_{high}} = 1.5$ nM and $K_{i_{low}} = 27$ nM). These data are comparable to the D4 binding properties of the unselective dopamine receptor agonist quinpirole. However, selectivity over $D2_{long}$, $D2_{short}$ and D3 was approximately 500-fold higher. On the other hand, receptor binding of the enantiomer **2a** was significantly reduced. Surprisingly, only weak affinity was observed when investigating the 5-bromo-2-methoxy derivatives **2b** and **ent2b**. Introducing the electron withdrawing carbonyl group to give the pyrimidone derivatives **3** and **ent3** resulted in reduced D4 affinity, when **ent3**, showing the same spatial orientation of the phenylpiperazinylmethyl side chain as **ent2a**, turned out to be the more active isomer. The diazepine derivative **13** showed moderate D4 binding ($K_i = 120$ nM), while the affinity of **ent13** was low.

Table 1. Receptor binding data [K_i values (nM) based on the means of 2–4 experiments each performed in triplicate]



Compd	-X-	R^1	R^2	D1	$D2_{long}$	$D2_{short}$	D3	D4
2a		H	H	39,000	29,000	30,000	13,000	310
ent2a		H	H	29,000	25,000	32,000	13,000	1.5/27
2b		OMe	Br	9100	16,000	14,000	1900	3500
ent2b		OMe	Br	15,000	44,000	43,000	7400	1600
3		H	H	8900	18,000	6400	20,000	3700
ent3		H	H	19,000	7300	2800	12,000	460
21		H	H	23,000	10,000	4200	12,000	120
ent21		H	H	23,000	19,000	14,000	3300	4400
Quinpirole				nd	64/3100	52/4000	24/420	1.8/53

To investigate the intrinsic effect of FAUC 312 (**ent2a**), an in vitro functional assay measuring the [^{3}H]thymidine uptake in growing CHO cells stably expressing the dopamine D4.2 receptor was performed.[25] In fact, a 83% stimulation of mitogenesis (compared to the full agonist quinpirole and the D4 antagonist clozapine) was determined ($EC_{50} = 50$ nM) (Table 2).

Table 2. Agonist effects of the tetrahydropyrimidine **ent2a**, quinpirole and clozapine at the D4.2 receptor investigated by measuring the stimulation of mitogenesis

	Test compounds		
	ent2a	Quinpirole	Clozapine
Agonist effect (%)[a]	83	100	0
EC50 (nM)[b]	50	9.9	nd

[a]Rate of incorporation of [^{3}H]thymidine (in %) relative to the maximal effect of the full agonist quinpirole (100%); the results are the means of quadruplicates from 10 experiments.
[b]EC50 values derived from the mean curves of 10 experiments; nd, not determined.

In conclusion, SAR studies on cyclic amidine benzamide bioisosteres led to the highly selective dopamine D4 receptor partial agonist **ent2a** (FAUC 312) incorporating a chiral tetrahydropyrimidine substructure. Thus, expanding the imidazoline moiety of FAUC 179 (**1**) by one carbon atom did not significantly change the D4 binding, if the spatial orientation of the phenylpiperazinylmethyl side chain was maintained. On the other hand, the intrinsic activity was increased from 42 to 83%. Further modifications including the introduction of a carbonyl group or a substitution of the phenyl group resulted in a significantly reduced affinity.

Acknowledgements

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