Interactive SAR Studies: Rational Discovery of Super-Potent and Highly Selective Dopamine D3 Receptor Antagonists and Partial Agonists

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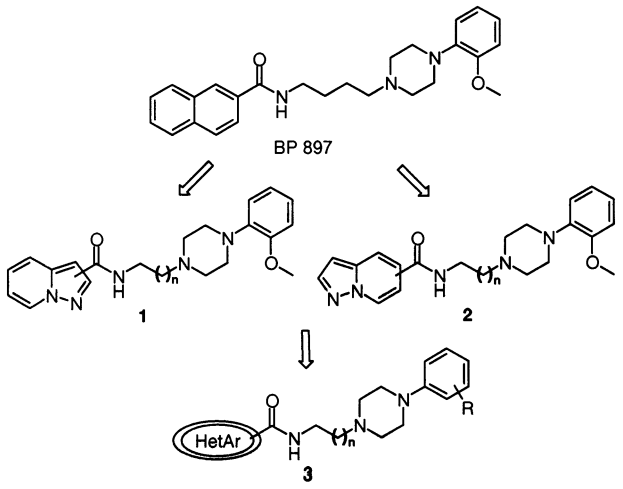
Abstract: Starting from dopamine receptor ligand BP897, an interactive drug discovery process leading to heterocyclic bioisosteres is demonstrated. The four step strategy involved a careful optimization of geometric and electronic properties by systematic modification of the attachment points and heteroatoms, respectively. Efficacy tuning by modification of the phenyl substituents led to both D3 partial agonists and full antagonists. The benzothiophenes **3c** (FAUC346) and **3d** (FAUC365) revealed outstanding D3 affinity and subtype selectivity.

Introduction. The dopamine D3 receptor identified in 1990 by Sokoloff, Schwartz, and co-workers is preferentially expressed in the nucleus accumbens, where dopamine is released by neurons originating from the ventral tegmental area.[1] Convincing pharmacological studies implicate D3-mediated neurotransmission in the reinforcing effects of cocaine.[2] Very recently, the preferential dopamine D3 receptor partial agonist BP 897 (Chart 1) was designed and investigated inhibiting cocaine-seeking behavior without revealing any intrinsic, primary rewarding effects.[3]

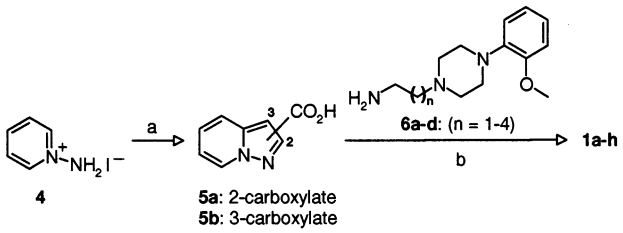
On the basis of the lead structure of BP 897 and related dopaminergic benzamides,[4,5] we started to develop more selective D3 partial agonists. Our plan of investigation involved the incorporation of the pyrazolo[1,5-*a*]pyridine unit as a heterocyclic bioisostere that proved to be excellent for a fine-tuning of selectivity and ligand efficacy within our recent structure−activity relationship (SAR) studies.[6] To modify the spatial orientation of the ring system, all of the possible attachment points of the five- and six-membered partial structures should be exploited leading to regioisomers of types **1** and **2**, respectively. Furthermore, the length of the chain connecting the arylamide function with the methoxyphenylpiperazine unit should be optimized. Within subsequent interactive SAR studies, further suitable heteroarenes and phenyl substitutents, which are taken into account within formula **3**, should be evaluated.

Results and Discussion. For the synthesis of the test compounds of type **1**, we started from *N*-aminopyridinium iodide **4**[7] when 1,3-dipolar cycloaddition with ethyl propiolate under oxidative conditions and subsequent saponification afforded the pyrazolo[1,5-*a*]pyridine derivative **5b** (Scheme 1).[8] Employing dimethyl acetylenedicarboxylate as a dipolarophile, the regioisomer **5a** could be isolated after hydrolysis and site selective decarboxylation.[9]

Chart 1



Scheme 1[a]



[a] Reagents and conditions: (a) Refs 8 and 9; (b) (1) $(COCl)_2$, toluene, 40 °C until gas development, and then 1 h at room temperature, and then 4 h at 60 °C; (2) **6a**−**d**, CH_2Cl_2, −60 °C to room temperature, 30 min (from **5a**: **1a**, $n = 1$, 97%; **1b**, $n = 2$, 99%; **1c**, $n = 3$, 93%; **1d**, $n = 4$, 84%; from **5b**: **1e**, $n = 1$, 78%; **1f**, $n = 2$, 88%; **1g**, $n = 3$, 76%; **1h**, $n = 4$, 74%).

For our initial investigations, we chose the aminoethyl-, aminopropyl-, aminobutyl-, and aminopentyl-substituted arylpiperazines **6a**−**d** as suitable building blocks, which were readily prepared by *N*-alkylation of *o*-methoxyphenylpiperazine with phthaloyl-protected alkyl bromides and subsequent hydrazinolysis, following previously described protocols.[10] Amide bond formation was performed by oxalyl chloride-induced activation of the heterocyclic carboxylic acids **5a**,**b** and addition of the primary amines **6a**−**d** to the crude acid chloride when the final products **1a**−**h** were formed in 74−99% yield. As central intermediates for the synthesis of the target compounds of type **2**, we needed to prepare the respective pyrazolo[1,5-*a*]pyridine carbaldehydes regiospecifically. In the case of the 5-substituted isomer **8c**, we started from 4-hydroxymethylpyridine, which could be *N*-aminated by hydroxylamine-*O*-mesitylenesulfonate to give the 1,3-dipolar intermediate **7** (Scheme 2). Subsequent cycloaddition with methyl propiolate furnished the 7a-azaindole **8a** that could be transformed into the degradation product **8b** under acidic conditions.[6a] Oxidation of the primary alcohol function succeeded by MnO_2 in dichloromethane gave access to the carbaldehyde **8c**.

Employing identical reaction conditions, the regioisomers **9** and **10** were obtained from their hydroxymethyl-substituted precursors[6a] whereas the 7-carbaldehyde **11** was prepared by ortho-directed metalation

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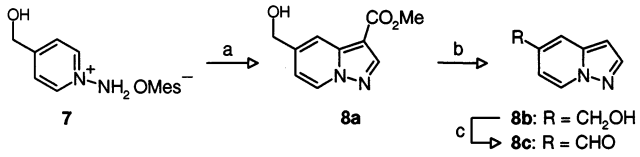
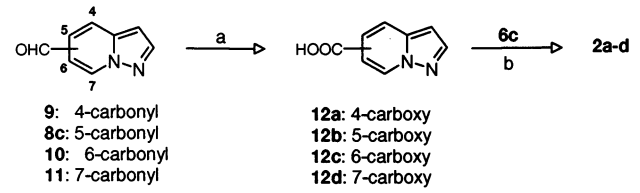
Scheme 2[a]



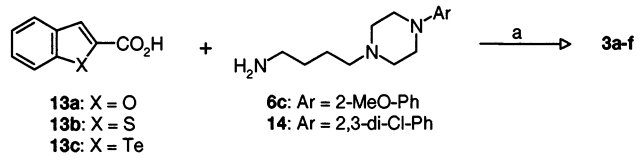
[a] Reagents and conditions: (a) Methyl propiolate, K_2CO_3, air−O_2, DMF, room temperature, 2 h (21%). (b) H_2SO_4 (v/v 40%), 110 °C, 3 h (90%). (c) MnO_2, CH_2Cl_2, room temperature, 19 h (91%).

Scheme 3[a]



[a] Reagents and conditions: (a) (1) MnO_2, NaCN, AcOH, MeOH, room temperature, 3 h; (2) NaOH (v/v 50%), reflux, 1 h (**12a**, 90%; **12b**, 72%; **12c**, 89%; **12d**, 33%). (b) Compound **6c**, HOAt, DCC, CH_2Cl_2, room temperature, 23 h (**2a**, 64%); **6c**, HOBt/H_2O, DCC, CH_2Cl_2−DMF (9:1), room temperature, 23 h (**2b**, 90%; **2c**, 86%; **2d**, 88%).

Scheme 4[a]



[a] Reagents and conditions: $SOCl_2$, DMF, $CHCl_3$−toluene (1:1), 90 °C, 30 min. Compound **6c** or **14**, Et_3N, $CHCl_3$, 0 °C, 30 min (**3a**: X = O, Ar = 2-MeO−Ph, 68%; **3b**: X = O, Ar = 2,3-di-Cl−Ph, 57%; **3c**: X = S, Ar = 2-MeO−Ph, 50%; **3d**: X = S, Ar = 2,3-di-Cl−Ph, 68%). Compound **6c**, HATU−HOAt (1:1), DIPEA, DMF, 0 °C, 4 h (**3e**: X = Te, Ar = 2-MeO−Ph, 58%); **14**, HATU, DIPEA, DMF, 0 °C, 2 h (**3f**: X = Te, Ar = 2,3-di-Cl−Ph, 45%).

and formylation following a recently described protocol (Scheme 3).[11]

Smooth transformation into the carboxylic acids **12a**−**d** was accomplished by utilizing a reaction mixture composed of MnO_2, sodium cyanide, acetic acid, and methanol[12] furnishing the respective methyl carboxylates, which were saponified by NaOH to give the building blocks **12a**−**d**. Finally, DCC coupling assisted by HOBt or HOAt[13] resulted in formation of the test compounds **2a**−**d** when utilizing the diaminobutane derivative **6c**. Benzofuran-2-carboxylic acid (**13a**) as well as the thia- and tellura-analogues **13b**,**c**, respectively, were activated by thionyl chloride or HATU[13] and subsequently reacted with **6c** and the 2,3-dichlorophenyl analogue **14** to give the potential dopamine receptor ligands **3a**−**f** (Scheme 4).

Radioligand binding assays and mitogenesis experiments were employed to analyze affinity, selectivity profiles, and ligand efficacy of the target compounds. The binding data were generated by measuring their ability to compete with [^{3}H]spiperone for the cloned human dopamine receptor subtypes $D2_{long}$, $D2_{short}$,[14] D3,[15] and D4.4[16] stably expressed in Chinese hamster ovary cells (CHO).[17] D1 receptor affinities were determined utilizing porcine striatal membranes and the D1 selective radioligand [^{3}H]SCH 23390.[17] The resulting K_i values are listed in Table 1 as compared to the dopaminergic lead compound BP 897. Because of the observation that the cocaine-seeking behavior inhibiting lead compound BP 897 reveals serotoninergic and adrenergic activity as well,[3] selected test compounds were investigated for their potency to displace [^{3}H]8-OH-DPAT and [^{3}H]ketanserin when employing porcine 5-$HT1_A$, 5-HT-2, and α1 receptors (Table 2).

The first steps of our interactive SAR studies should be directed to the optimization of the chain length controlling the spatial relationship of the heteroarylcarboxamide and the methoxypiperazine moiety when the investigations involved the pyrazolo[1,5-*a*]pyridines of type **1**. With respect to the D3 affinities, both the 2- and 3-substituted regioisomers showed only moderate receptor recognition when $n = 1$, 2, and 4. On the other hand, substantial D3 binding was observed for the aminobutyl derivatives **1c**,**g** ($n = 3$) resulting in K_i values of 4.3 and 18 nM, respectively. It was interesting to see that the attachment position 2 of the 7a-azaindole system proved to be advantageous as compared to position 3 causing a more bent orientation of the π-system. Actually, the carboxamide **1c** (D1/D3 = 350, $D2_{long}$/D3 = 72, $D2_{short}$/D3 = 72, and D4/D3 = 30) showed a binding profile that was comparable to the naphththalene-2-carboxamide BP 897 ($K_i = 1.4$ nM, D1/D3 = 540, $D2_{long}$/D3 = 150, $D2_{short}$/D3 = 150, and D4/D3 = 28). Substantial 5-$HT1_A$ and α1 binding was detected for both regioisomers. On the other hand, 5-HT2 receptor recognition was only weak. It is interesting to note that the 3-substituted test compounds **1e** ($n = 1$) and **1f** ($n = 2$) displayed strong and selective D4 ($K_i = 0.67$ nM) and D2 binding ($K_i = 11$ nM for $D2_{long}$ and 3.9 nM for $D2_{short}$), respectively. To further evaluate the relationship between the regiochemistry of the heteroaromatic unit and D3 binding, we pharmacologically characterized the target compounds of type **2** (for $n = 3$). For the 5- and 6-substituted regioisomers, the data indicated receptor binding profiles that were similar to **1c**. By contrast, the attachment positions 4 and 7 exerted reduced affinity and selectivity. On the basis of these observations, we concluded that the bent geometry that is a common structural feature of the 3-, 4-, and 7-substituted derivatives disfavors D3 binding whereas a more linear shape that is associated with the attachment positions 2, 5, and 6 is favorable. A schematic representation of both structural families is depicted in Figure 1.

As a measure of functional activity, ligand efficacy of **1c** was confirmed by a mitogenesis assay measuring the rate of [^{3}H]thymidine incorporation into growing CHO dhfr$^-$ cells stably expressing the human D3 receptor.[18,19] The data listed in Table 3 clearly show substantial ligand efficacy of **1c** (52%, 1.4 nM) that proved to be similar to those we obtained for the partial agonist BP 897 with respect to both intrinsic activity and EC_{50} values. Starting from the pyrazolopyridine-2-carboxamide **1c** (FAUC 329) that combines substantial D3 affinity and subtype selectivity and intrinsic activity, we tried to further improve the pharmacological profiles by modifying the electronic properties of the heteroaromatic unit. Within the pyrazolo[1,5-*a*]pyridine nucleus, the nitrogen atom in position 8 is part of the aromatic 10π-system whereas the lone pair of the nitrogen in position 1 induces a negative electrostatic potential that might influence the receptor recognition process. We

Table 1. Receptor Binding and Selectivity Ratios for **1a**−**3f** and BP 897 Employing Porcine D1 as Well as Human $D2_{long}$, $D2_{short}$, D3, and D4.4 Receptors[a]

compd					K_i values (nM)					ratio of K_i values		
					[3H]SCH 23390	[3H]spiperone						
no.	X	pos	*n*	R	pD1	$hD2_{long}$	$hD2_{short}$	hD3	hD4	$D2_{long}/3$	$D2_{short}/3$	D4/3
1a		2	1		1200 ± 100	520 ± 110	480 ± 40	250 ± 45	30 ± 5.0	2.1	1.9	0.12
1b		2	2		1200 ± 0	830 ± 120	970 ± 5.0	650 ± 180	41 ± 10	1.3	1.5	0.063
1c		2	3		1500 ± 50	310 ± 34	310 ± 30	4.3 ± 0.29	130 ± 16	72	72	30
1d		2	4		1400 ± 200	71 ± 0.50	76 ± 3.0	51 ± 1. 0	78 ± 11	1.4	1.5	1.5
1e		3	1		1200 ± 0	290 ± 60	140 ± 8.2	360 ± 9.6	0.67 ± 0.19	0.81	0.39	0.0019
1f		3	2		2200 ± 200	11 ± 1.4	3.9 ± 0.41	150 ± 17	14 ± 2.5	0.07	0.026	0.093
1g		3	3		1500 ± 100	110 ± 0	65 ± 4.2	18 ± 1.3	44 ± 7.4	6.1	3.6	2.4
1h		3	4		1100 ± 160	30 ± 1.2	25 ± 2.5	64 ± 6.0	68 ± 5.5	0.47	0.39	1.1
2a		4	3		2300 ± 150	270 ± 16	180 ± 14	20 ± 1.6	87 ± 10	14	9	4.4
2b		5	3		1500 ± 50	190 ± 12	120 ± 12	2.8 ± 0.48	67 ± 8.7	68	43	24
2c		6	3		2000 ± 100	140 ± 14	84 ± 9.7	4.3 ± 0.68	40 ± 4.1	33	20	9.3
2d		7	3		1200 ± 0	150 ± 18	98 ± 6.3	29 ± 4.7	8.9 ± 1.5	5.2	3.4	0.31
3a	O	2	3	2-MeO	1100 ± 50	110 ± 0	84 ± 6.0	1.1 ± 0.048	30 ± 8.0	100	76	27
3b	O	2	3	2,3-di-Cl	2900 ± 150	320 ± 10	80 ± 31	1.5 ± 0.22	93 ± 18	210	53	62
3c	S	2	3	2-MeO	670 ± 15	87 ± 0.50	52 ± 1.0	0.23 ± 0.016	15 ± 1.5	380	230	65
3d	S	2	3	2,3-di-Cl	8800 ± 1300	3600 ± 950	2600 ± 730	0.50 ± 0.12	340 ± 10	7200	5200	680
3e	Te	2	3	2-MeO	380 ± 15	63 ± 7.5	39 ± 6.0	0.68 ± 0.061	35 ± 8.5	93	57	51
3f	Te	2	3	2,3-di-Cl	1400 ± 720	91 ± 20	48 ± 5.5	0.55 ± 0.10	150 ± 0	170	87	270
BP897					760 ± 60	210 ± 18	210 ± 28	1.4 ± 0.075	39 ± 4.1	150	150	28

[a] K_i values in nM ± SEM are based on the means of 2−9 experiments each done in triplicate.

Table 2. Receptor Binding Data for Selected Test Compounds in Comparison to BP 897 Employing Porcine 5-$HT1_A$, 5-HT-2, and α1 Receptors[a]

	K_i values (nM ± SEM)		
	[3H]8-OH-DPAT	[3H]ketanserin	
compd	5-$HT1_A$	5-HT2	α1[c]
1c	24 ± 3.4	1200 ± 50[b]	26 ± 9.7
1g	14 ± 0.50	1300 ± 50[b]	48 ± 9.0
2a	11 ± 1.3	1600 ± 300[b]	28 ± 8.3
2b	15 ± 1.0	740 ± 70[b]	32 ± 10
2c	19 ± 0	950 ± 55[b]	19 ± 5.8
2d	22 ± 7.0	2000 ± 200[b]	18 ± 4.0
3a	17 ± 1.0	660 ± 10[b]	8.6 ± 1.7
3b	480 ± 5.0	11 000 ± 500	>10 000
3c	41 ± 4.2	350 ± 70[b]	15 ± 6.0
3d	360 ± 10	2000 ± 600	>2000
3e	69 ± 11	500 ± 110[b]	15 ± 5.0
3f	125 ± 5.0	730 ± 190	>1000
BP897	81 ± 8.0	840 ± 120[b]	25 ± 6.9

[a] K_i values as means of 2−5 experiments each done in duplicate or triplicate. [b] Determined in the presence of 10 μM prazosine.[c] K_i values derived from the high affinity binding site of a biphasic curve when labeled with [3H]ketanserin.

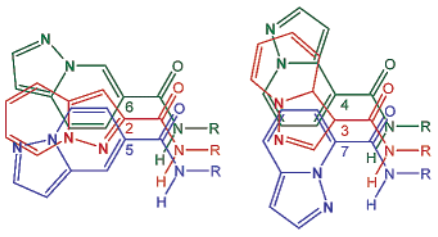


Figure 1. Schematic presentation of the different structural features of 2-,5-,6- and 3-,4-,7-substituted heteroarene carboxamides showing linear (left) or bent geometry (right), respectively.

were intrigued by the question whether oxa-, thia-, or even tellura-analogues might serve as bioisosteres. According to ab initio molecular orbital calculations that we performed on the 3-21G level of theory for the 2-aminocarbonyl substituted pyrazolo[1,5-*a*]pyridine, benzo[*b*]furan, benzo[*b*]thiophene, and benzo[*b*]tellurophene ring systems, negative partial charges were

Table 3. Intrinsic D3 Activities of **1c**, **3a**−**f**, and BP 897 Derived from the Stimulating Effect on Mitogenesis of D3 Receptor Expressing CHO Cells

test compd	agonist effect[a]	EC_{50} (nM)[b]	test compd	agonist effect[a]	EC_{50} (nM)[b]
1c	52%	1.4	**3e**	no effect	
3a	53%	1.5	**3f**	no effect	
3b	no effect		BP 897	56%	1.8
3c	49%	0.36	quinpirole	100%	3.1
3d	no effect				

[a] Rate of [3H]thymidine uptake related to the full agonist quinpirole (100%); quadruplicates from 4 to 12 experiments. [b] EC_{50} values derived from mean curve of all experiments.

observed for the nitrogen- and oxygen-containing heterocycles. For the less electronegative sulfur and tellurium analogues, positive ESP charges were calculated (for 3D representations including the resulting MEP maps, see the Supporting Information). To find out whether the resulting electrostatic properties might control the receptor activity profiles, the methoxyphenylpiperazinylbutylamides **3a**,**c**,**e** were included in our study. Interestingly, D3 binding significantly increased, especially for the thia-derivative **3c** that showed a K_i of 0.23 nM and a 380, 230, and 65-fold selectivity over $D2_{long}$, $D2_{short}$, and D4, respectively. Unless organo tellurium derivatives are scarcely described as phamacologically active compounds,[20] the tellurophene carboxamide **3e** displayed superior D3 affinity (K_i = 0.68 nM). Finally, exchange of the 2-methoxyphenylpiperazine substructure by a 2,3-dichlorophenylpiperazine moiety, which showed to be a highly suitable framework according to recent findings in the field of D3 antagonists,[4a] was performed. As a matter of fact, the dichloro derivatives **3b**,**d**,**f** revealed D3 affinities that are comparable to the methoxy-substituted analogues; however, the selectivities over 5HT-1_A, 5-HT2, and α1 were substantially higher. Interestingly, extraordinary selectivity ratios of 17 600, 7200, 5200, and 680 over D1, $D2_{long}$, $D2_{short}$, and D4, respectively, were determined for thebenzothiophene-2-carboxamide **3d** (K_i = 0.50 nM). To the best of our knowledge, the family of compounds presented herein shows by far the highest D3 selectiv-

ites reported yet. The intrinsic activities determined within the mitogenesis assays were also highly structure-dependent. The benzothiophene **3c** (FAUC 346) and its oxa analogue **3a** proved partial agonist character with EC_{50} values at 0.36 and 1.5 nM, respectively. On the other hand, exchange of the methoxyphenyl group by a dichlorophenyl moiety or introduction of the tellurium into the heteroarene led to a complete loss of ligand efficacy.

In conclusion, highly selective dopamine D3 partial agonists and also complete antagonists including the pyrazolo[1,5-*a*]pyridine FAUC 329 (**1c**) and the benzothiophenes FAUC 346 (**3c**) and FAUC 365 (**3d**) were discovered by a rational and interactive SAR sequence. Whereas the antagonists are of potential interest for the treatment of schizophrenia, the partial agonists could be exploited for the therapy of psychostimulant addiction.

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Supporting Information Available: Complete Experimental Section including details on synthesis, analytical characterization, and biological studies, as well as a graphical representation of molecular electrostatic isopotential maps. This material is available free of charge via the Internet at http://pubs.acs.org.

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