Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 2041–2044

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Phenyloxazoles and Phenylthiazoles as Benzamide Bioisosteres: Synthesis and Dopamine Receptor Binding Profiles†

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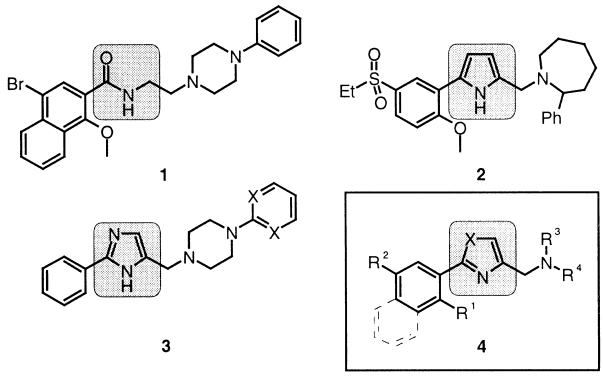
Received 10 May 2000; revised 3 July 2000; accepted 7 July 2000

Abstract—Conformationally restricted benzamide bioisosteres were investigated when the aminomethylpyrrolidine derivative **4o** proved D3 as well as D4 binding properties which were comparable to those of the atypical neuroleptics sulpiride and clozapine, respectively. © 2000 Elsevier Science Ltd. All rights reserved.

SAR studies in the field of selective dopamine D3 and D4 receptor antagonists are known as a promising strategy for the development of atypical neuroleptics.[1,2] Compounds of this type possibly offer the chance to treat both positive and negative symptoms of schizophrenia without causing extrapyramidal side effects, which are attributed to dopamine D2 receptor blockade in striatal regions of the brain.[3] A variety of structural families was evaluated when the benzamide functionality turned out to be a valuable pharmacophore. Besides the well established neuroleptics sulpiride[4] and amisulpride[5] showing limbic selectivity in vivo, methoxynaphthamides of type **1** proved to have high dopamine D3 receptor affinity.[6] Furthermore, bioisosteric replacement of the amide substructure by a pyrrole nucleus was successful for the design of D3 antagonists (**2**).[7,8] On the other hand, the phenylimidazole derivatives **3** which are known as potent D4 receptor ligands can also be regarded as conformationally restricted benzamide surrogates.[9]

In order to recognize the essential structural features of the systems we were intrigued by the question whether oxazole or thiazole moieties could be employed as an alternative with substantially different electronic properties being, furthermore, devoid of a H-donating group. These deliberations led us to compounds of type **4** when we planned to incorporate *N*-phenylpiperazinylmethyl, *N*-benzylpiperazinylmethyl or *N*-benzylpiperidinylaminomethyl side chains. In order to modify the spatial orientation of the diamine substructure and to examine the influence of chirality on the receptor binding profiles, amino- and aminoalkylpyrrolidine derivatives were anticipated as further promising building blocks, according to our recent studies in the field of dopamine receptor binding benzamides.[10] The 5-bromo-2-methoxy substitution pattern[11] was chosen for the phenyl group. Furthermore, the bromomethoxynaphthyl and the unsubstituted phenyl moieties of the lead compounds **1** and **3**, respectively, were selected.



The synthesis of the target compounds was envisioned by *N*-alkylation of various diamines when chloromethyl substituted oxazole and thiazole derivatives should be used as electrophiles (Scheme 1). For the coupling of primary amines, aromatic carbaldehydes should be employed to facilitate controlled alkylations under reductive conditions. In detail, the chloromethyloxazole derivative **6a** was prepared from the amide **5a**, according to a previously reported protocol which proved also applicable for the synthesis of the bromomethoxy analogue **6b**.[12] In this case, treatment of the benzamide **5b**, which was readily available from the 5-bromo-2-

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†Dedicated to Professor Fritz Eiden on the occasion of his 75th birthday.

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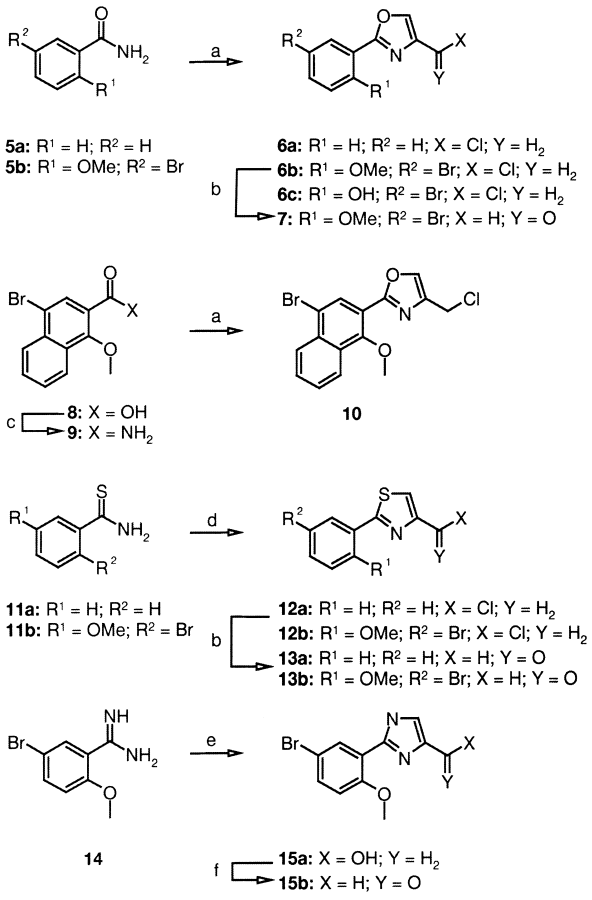
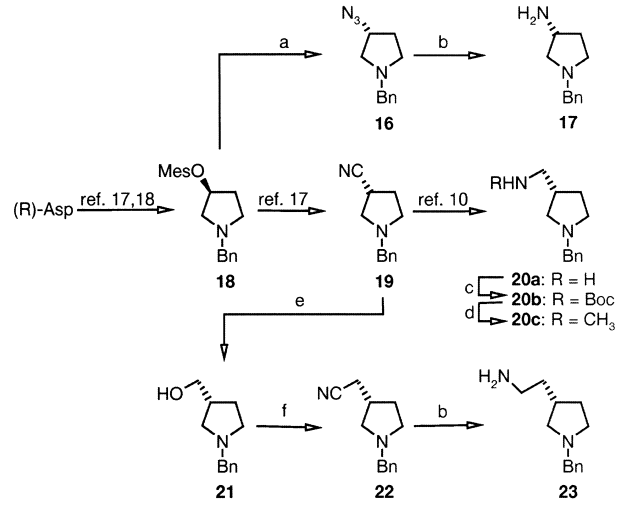
PII: S0960-894X(00)00405-4



Scheme 1. (a) 1,3-Dichloroacetone, 130 °C, 1 h (**6a**: 81%; **6b**: 72%; **10**: 60%); 150 °C, 0.5 h (**6b**: 37%; **6c**: 5%); (b) $NaHCO_3$, DMSO, 130 °C, 1 h (**7**: 70%; **13a**: 60%; **13b**: 64%); (c) 1. $SOCl_2$, toluene, cat-DMF, 65 °C, 1 h; 2. Et_2O, 25% aq NH_3, rt, 10 min (99%); (d) 1. 1,3-dichloroacetone, acetone, rt, 16 h; 2. concd H_2SO_4, rt, 45 min (**12a**: 78%, **12b**: 74%); (e) 1,3-dihydroxyacetone dimer, NH_4Cl, 25% aq NH_3, 80 °C, 30 min (65%); (f) MnO_2, CH_2Cl_2, rt, 1.5 h (75%).

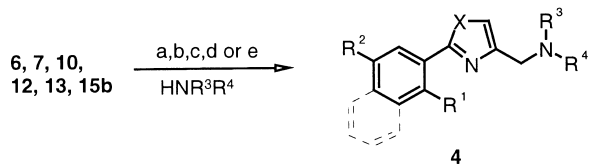


Scheme 2. (a) NaN_3, DMSO, 60 °C, 5h (78%); (b) $LiAlH_4$, Et_2O, 0 ° to rt, 0.5 h (**17**: 92%; **23**: 98%); (c) Boc_2O, CH_2Cl_2, rt (97%); (d) $LiAlH_4$, THF, reflux, 4 h (crude); (e) 1. concd HCl, reflux, 0.5 h; 2. MeOH, $SOCl_2$, −50 °C to rt, 16 h (98%), 3. $LiAlH_4$, Et_2O, −30 °C (87%); (f) 1. MesCl, NEt_3, THF, −23 °C, 0.5 h; 2. NaCN, DMSO, 60 °C, 5 h (95%).

methoxycarbonitrile,[13] with 1,3-dichloroacetone gave oxazole formation in 72% yield. It was necessary to control the reaction temperature, because more drastic conditions resulted in ether cleavage and formation of the phenol **6c** as a side product. Transformation of the naphthoic acid **8**[14] into the carboxamide **9** and subsequent condensation with 1,3-dichloroacetone gave the naphthyloxazole **10**. Analogous cyclization reactions yielded the thiazoles **12a,b** starting from the thioamides **11a,b**.[15] Kornblum oxidation[16] of the alkyl halides **6b** and **12a,b** afforded the carbaldehydes **7** and **13a,b**. The imidazolecarbaldehyde **15b** was obtained by MnO_2 oxidation of the alcohol **15a** which was readily available from the amidine **14**.[13]

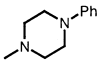
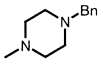
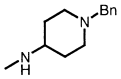
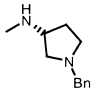
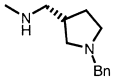
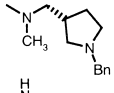
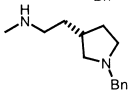
Besides the commercially available piperidine and piperazine derived building blocks, we intended to incorporate the chiral diamines **17**, **20a,c** and **23** (Scheme 2). We were intrigued by the question whether the mesyloxypyrrolidine **18**, which was recently developed in this laboratory as a central intermediate for the synthesis of β-proline,[17,18] and the 1,3-diamine **20a**[10] gave also access to the 1,2-diamine **17**[19] and to the 1,4-diamino homologue **23**. Starting from the (*R*)-aspartic acid derivative **18**, nucleophilic displacement with NaN_3 gave the azide **16** which was subsequently reduced by $LiAlH_4$ to afford the primary amine **17**. The aminomethylpyrrolidine **20a**, which was prepared through the nitrile **19**,[17] was transformed into the secondary amine **20c** by treatment with Boc_2O to give the carbamate **20b** and subsequent reduction with $LiAlH_4$. Synthesis of the aminoethylpyrrolidine **23** was performed by hydrolysis of the nitrile **19**, followed by esterification and reduction to give the primary alcohol **21**.[20] Activation by MesCl and nucleophilic displacement with NaCN resulted in formation of the homologation product **22**.[21] $LiAlH_4$ reduction gave the 1,4-diamine **23**.[22] The optical antipodes **ent17**, **ent20a** and **ent23** were prepared from natural aspartic acid.

Starting from the chloromethyloxazoles **6a–c** and **10** and the chloromethylthiazoles **12a**,**b**, the secondary amines **20c**, *N*-phenylpiperazine and *N*-benzylpiperazine were subjected to the nucleophilic displacement conditions a–d to afford the target compounds **4a–i** and **4t**. S_N2 reactions of primary amines affording the products **4j–m** and **4p** worked less efficiently. Starting from the aldehydes **7**, **13a**,**b** and **15b**, reductive amination in the presence of $NaBH(OAc)_3$[23] turned out advantageous when the monoalkylated products **4n**,**o**,[24]**q**,**r**,**s**,**u** (**ent4n**, **o**,**q**,**r**,**u**) were isolated (Scheme 3, Table 1).



Scheme 3. (a) DMF, 40°C, 1 h; (b) DMSO, NEt_3, 0°C to rt, 2d; (c) DMF, NEt_3, 40°C, 2d; (d) CH_2Cl_2, NEt_3, reflux, 5d; (e) $NaBH(OAc)_3$, $(CH_2)_2Cl_2$, rt, 3 h.

Table 1. Chemical reaction and receptor binding data (Ki values [nM] based on the means of 2–4 experiments performed in triplicate at eight concentrations)

Product	-NR^3R^4	Electrophile	X	R^1	R^2	Yield (%)	Method	D1	$D2_{long}$	$D2_{short}$	D3	D4
4a		6a	O	H	H	92	a	11,500	3000	1750	3950	250
4b		6b	O	OMe	Br	66	a	4850	690	330	660	370
4c		6c	O	OH	Br	40	a	17,500	6650	4400	7600	580
4d		12a	S	H	H	83	a	19,500	2300	1060	2050	450
4e		12b	S	OMe	Br	85	a	1250	610	440	1190	590
4f		6a	O	H	H	99	a	72,000	27,500	21,500	8400	1450
4g		6b	O	OMe	Br	97	a	15500	1500	790	1050	710
4h		12a	S	H	H	88	a	9200	28,000	19,500	5250	590
4i		12b	S	OMe	Br	94	a	10,500	210	85	640	370
4j		6a	O	H	H	25	d	30,000	14,000	8650	6100	350
4k		6b	O	OMe	Br	12	c	12,500	940	630	580	390
4l		12a	S	H	H	40	b	6800	23,000	13,500	2300	53
4m		12b	S	OMe	Br	25	c	4500	195	105	205	400
4n		7	O	OMe	Br	62	e	8000	2450	2000	1700	39
ent4n		7	O	OMe	Br		e	16,000	8250	6600	1850	510
4o		7	O	OMe	Br	48	e	3500	320	245	65	11
ent4o		7	O	OMe	Br		e	6750	510	210	83	20
4p (Naphth.)		10	O	OMe	Br	15	b	100,000	45,500	17,500	5850	15,500
4q		13a	S	H	H	76	e	8850	7900	5050	660	390
ent4q		13a	S	H	H		e	13,500	7950	6400	880	390
4r		13b	S	OMe	Br	91	e	4950	420	280	115	170
ent4r		13b	S	OMe	Br		e	4000	185	92	220	150
4s		15b	NH	OMe	Br	57	e	8900	6250	2750	1300	1110
4t		7	O	OMe	Br	18	c	5450	3800	3250	1200	650
4u		7	O	OMe	Br	60	e	8950	1070	1100	120	170
ent4u		7	O	OMe	Br		e	6600	510	310	75	150
Clozapine								420	39	28	960	16
(*S*)-Sulpiride								50,000	120	51	88	2100

The final products of type **4** and the atypical neuroleptics clozapine and sulpiride were evaluated in vitro for their abilities to displace [^{3}H]spiperone from the cloned human dopamine receptors $D2_{long}$, $D2_{short}$,[25] D3[26] and D4.4 [27] being stably expressed in CHO cells (see Table 1).[28] The D1 affinities were determined by employing bovine striatal membrane preparations and the D1 selective antagonist [^{3}H]SCH 23390.[28] The phenylpiperazines **4a**–**e**, the benzylpiperazines **4f**–**h** and the 4-amino-1-benzylpiperidines **4j**,**k**,**m** revealed only moderate affinity in the radioligand binding experiments except the benzylpiperazine **4i** and the aminopiperidine **4l** which proved fairly good $D2_{long}$ (Ki = 85 nM) and D4.4 (Ki = 53 nM) binding, respectively. Among the pyrrolidines investigated, the (*S*)-aminomethyl derivative **4o** exhibited strong D3 (Ki = 65 nM) and D4 (Ki = 11 nM) affinity. It is interesting to note, that **4o** combines the D3 binding properties of the benzamide (*S*)-sulpiride (Ki = 88 nM) with those of the D4 antagonist clozapine (Ki = 16 nM). However, the test compound **4o** revealed substantially higher selectivity over the D2 isoforms.[29] The (*R*)-configured enantiomers **ent4o**,**q**,**r** showed binding profiles comparable to those of their enantiomers which might be due to a high conformational flexibility. Shortening and homologation of the side chain by CH_2 resulted in reduction of dopamine receptor binding for **ent4n**, **4u** and **ent4u**. **4n** indicated substantial D4 affinity. *N*-Methylation to give the tertiary amine **4t** as well as exchange of the oxazole template by thiazole and imidazole (**4q**, **ent4q**, **4r**, **ent4r** and **4s**) and extension of the benzene nucleus (**4p**) led to significantly reduced receptor binding when compared to the D3/D4 ligand **4o**.

In conclusion, SAR investigations on conformationally restricted benzamide bioisosteres led to dopamine receptor ligands with interesting binding profiles. In contrast to previously reported D3 and D4 ligands, the oxazole derivative **4o** exhibiting combined D3/D4 binding incorporates a secondary amine structure which is crucial for the receptor recognition. Interestingly, the imidazole derivative **4s** which is structurally related to the D4 ligands of type **3** showed only weak receptor binding.

Acknowledgements

We thank Dr. J.-C. Schwartz and Dr. P. Sokoloff (INSERM, Paris), Dr. H. H. M. Van Tol (Clarke Institute of Psychiatry, Toronto) and Dr. J. Shine (The Garvan Institute of Medical Research, Sydney) for providing D3, D4.4 and D2 receptor expressing cell lines.

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24. **4o**: ^{1}H NMR ($CDCl_3$, 360 MHz): $\delta = 1.51$ (dddd, $J = 12.7$, 8.0, 6.5, 6.0 Hz, 1H, H-4a), 2.03 (dddd, $J = 12.7$, 9.0, 8.0, 6.5 Hz, 1H, H-4b), 2.28 (dd, $J = 9.3$, 6.5 Hz, 1H, H-2a), 2.39 (ddddt, $J = 7.5$, 6.5, 6.5, 6.0, 7.2 Hz, 1H, H-3), 2.56 (ddd, $J = 8.5$, 8.0, 6.5 Hz, 1H, H-5a), 2.62–2.71 (m, 3H, H-5b and $NHCH_2CH$), 2.83 (dd, $J = 9.3$, 7.5 Hz, 1H, H-2b), 3.62 (d, $J = 12.7$ Hz, 1H, NCH_2Ph), 3.66 (d, $J = 12.7$ Hz, 1H, NCH_2Ph), 3.77 (s, 2H, oxazole-CH_2), 3.91 (s, 3H, OCH_3), 6.89 (d, $J = 8.9$ Hz, 1H, Ar), 7.22–7.34 (m, 5H, Ph), 7.49 (dd, $J = 8.9$, 2.4 Hz, Ar), 7.60 (s, 1H, oxazole), 8.06 (d, $J = 2.4$ Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$, 90 MHz): $\delta = 28.9$, 37.6, 45.3, 53.6, 54.3, 56.3, 58.5, 60.3, 112.8, 113.7, 118.4, 127.1, 128.3, 129.0, 132.8, 134.1, 135.3, 138.3, 140.4, 156.5, 159.0.
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29. Based on **4o**, further SAR studies are in progress.