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N-Methylbenzanilide Derivatives as a Novel Class of Selective V_{1A} Receptor Antagonists

Akio Kakefuda,[a,*] Junko Tsukada,[b] Toshiyuki Kusayama,[a] Atsuo Tahara[a] and Shin-ichi Tsukamoto[a]

[a]*Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co. Ltd., 21 Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan*
[b]*Clinical Development Dept., Yamanouchi Pharmaceutical Co. Ltd., 3-17-1 Hasune, Itabashi, Tokyo 174-8612, Japan*

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Abstract—During our efforts to develop a novel class of selective V_{1A} receptor antagonists, the *N*-methylbenzanilide structure was applied to a 4,4-difluoro-1-benzazepine derivative, **4**, which is a selective V_{1A} receptor antagonist. Further structural modifications gave **16a** with high V_{1A} affinity and V_2/V_{1A} selectivity ($K_i = 5.71$ nM, $V_2/V_{1A} = 140$) and potent V_{1A} receptor antagonist activity ($ID_{50} = 0.0080$ mg/kg iv).

Introduction

Arginine vasopressin (AVP) is a peptide hormone which is released from the posterior pituitary and exerts a variety of biological effects in mammals. So far, two AVP receptor subtypes (V_{1A} and V_2) have been identified, in periphery.[1] The V_{1A} receptor mediates phospholipase C activation and intracellular calcium mobilization, which causes various known AVP actions, such as vasoconstriction, platelet aggregation, and growth of vascular smooth muscle cell.[1] The V_2 receptor is positively coupled to adenylate cyclase and plays a predominant role in the antidiuretic response to AVP which promotes water reabsorption.[2]

AVP may play a role in several diseases and disorders, such as heart failure, hypertension, coronary renal vasospasm, hyponatremia, and dysmenorrhea.[3,4] Therefore, the development of subtype selective AVP receptor antagonists is essential to investigate the pathophysiological roles of AVP and could lead to new therapeutic tools. Recently, two nonpeptide selective V_{1A} receptor antagonists, OPC-21268 (**1**)[5,6] and SR49059 (**2**)[7] have been reported (Fig. 1). They have undergone clinical testing.

In the course of the search for AVP antagonists at our laboratories, the 4,4-difluoro-5-methylene-2,3,4,5-tetrahydro-1*H*-1-benzazepine derivative, **3** (V_{1A} $K_i = 0.160$ nM, V_2 $K_i = 0.770$ nM), was discovered as a V_{1A} and V_2 receptor dual antagonist.[8] We moved into the next research program which addressed the development of selective V_{1A} receptor antagonists. Extensive study of the 4,4-difluoro-1-benzazepine derivatives afforded a series of compounds with the selectivity for the V_{1A} receptor versus the V_2 receptor, such as the 2-methyl-3-furyl derivative, **4** (V_{1A} $K_i = 0.102$ nM, V_2 $K_i = 33.9$ nM, $V_2/V_{1A} = 330$).[9] On the other hand, Ohkawa et al. reported the *N*-methylbenzanilide derivative, FR179544 (**5**), as a V_{1A} and V_2 receptor dual antagonist.[10] This report prompted us to apply the *N*-methylbenzanilide structure to **4**, which might afford a novel class of selective V_{1A} receptor antagonists. Subsequently, we attempted modifications of the tether linking the *N*-methylbenzanilide template with the terminal amide part, and the 2-methyl-3-furyl part. In this paper, we describe the synthesis and pharmacological evaluation of *N*-methylbenzanilide derivatives.

Chemistry

The basic structure of the novel compounds was constructed by condensation of a *N*-methylaniline with a 4-acylaminobenzoyl chloride (Scheme 1) or condensation of a *N*-methyl-4′-aminobenzanilide with a substituted benzoyl chloride (Scheme 2). Scheme 1 shows the preparation of compounds **9a**–**c** and **12a**–**d**. The *N*-methylaniline (**6**) was coupled with a 4-[(2-methyl-3-furyl)carboxamido]benzoyl chloride to afford the *N*-

*Corresponding author. Tel.: +81-298-54-1545; fax: +81-298-53-5387; e-mail: kakefuda@yamanouchi.co.jp

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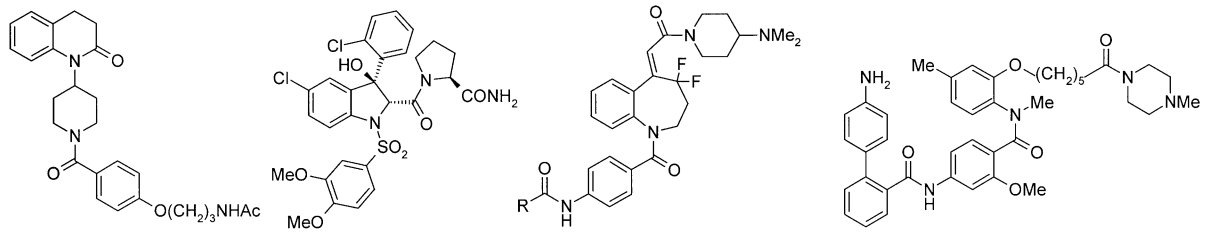
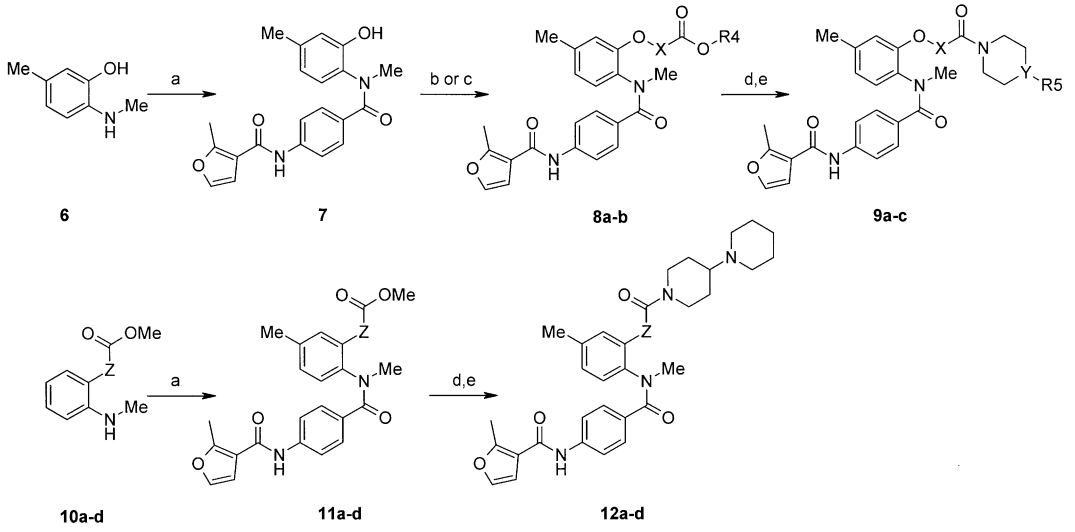
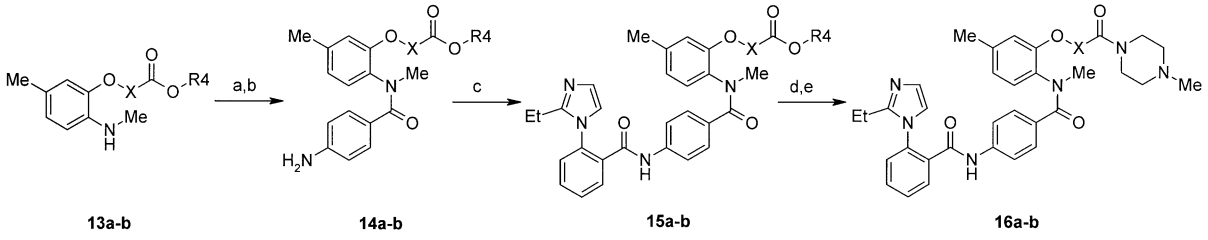


Figure 1. Known AVP antagonists.



Scheme 1. (a) 4-[(2-Methylfuran-3-yl)carboxamido]benzoyl chloride, pyridine, $Cl(CH_2)_2Cl$; (b) $Br(CH_2)_5CO_2Et$, K_2CO_3, CH_3CN, reflux; (c) 4-$BrCH_2C_6H_4CO_2Me$, K_2CO_3, CH_3CN, reflux: (d) 1 N NaOH aq, EtOH; (e) *N*-methylpiperazine or 4-(piperidino)piperidine, EDC•HCl, HOBt, $Cl(CH_2)_2Cl$.



Scheme 2. (a) 4-$O_2NC_6H_4COCl$, pyridine, $Cl(CH_2)_2Cl$; (b) H_2, Pd/C or PtO_2, EtOH–THF; (c) 2-(2-ethyl-1-imidazolyl)benzoyl chloride, pyridine, $Cl(CH_2)_2Cl$; (d) 1 N NaOH aq, EtOH; (e) *N*-methylpiperazine, EDC•HCl, HOBt, $Cl(CH_2)_2Cl$.

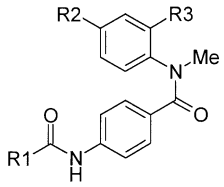
methylbenzanilide (**7**). The anilide **7** was finally transformed to the target compounds, **9a**–**c**, by *O*-alkylation, hydrolysis, and condensation with amines. Compounds **12a**–**d** were synthesized from *N*-methylanilines (**10a**–**d**) by a similar procedure described for **9a**–**c**. The synthesis of **16a**–**b** was illustrated in Scheme 2. The *N*-methylaniline (**13a**–**b**) was converted to the *N*-methyl-4-aminobenzanilide (**14a**–**b**) by benzoylation followed by hydrogenation. Compounds **14a**–**b** were coupled with 2-(2-ethyl-1-imidazolyl)benzoyl chloride[11] to give **15a**–**b**. Compounds **15a**–**b** were transformed to the target compounds, **16a**–**b**, by hydrolysis and condensation with amines.[12]

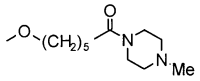
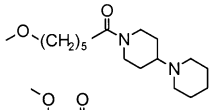
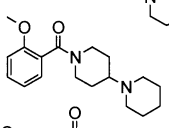
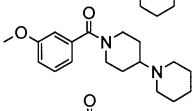
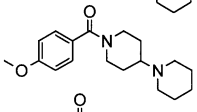
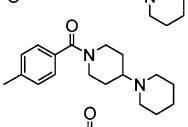
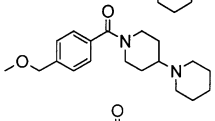
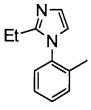
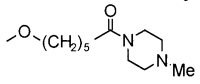
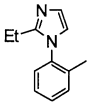
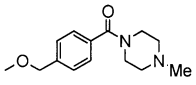
Results and Discussion

The synthesized compounds were primarily evaluated for their binding affinities for the V_{1A} and V_2 receptors on membranes using [^{3}H]AVP (rat liver for V_{1A} and rat kidney for V_2).[13] The results were expressed as K_i values and selectivity (K_i ratio, V_2/V_{1A}) in Table 1.

Initially, we examined the 2-methyl-3-furyl derivative (**9a**). Compound **9a** showed high V_{1A} affinity ($K_i = 8.77$ nM) and moderate V_2/V_{1A} selectivity ($V_2/V_{1A} = 8.4$). The structure–activity relationships (SAR) of **3** and its

Table 1. Binding affinities of *N*-methylbenzanilide derivatives for V_{1A} and V_2 receptors



Compd	R1	R2	R3	K_i[a] (nM)		Selectivity K_i ratio V_2/V_{1A}
				V_{1A}	V_2	
9a		Me		8.77±0.66	73.4±11	8.4
9b		Me		4.97±0.73	94.5±20	19
12a		H		1140±230	2250±160	2.0
12b		H		491±34	1360±270	2.8
12c		H		78.6±11	168±22	2.1
12d		H		335±93	2040±420	6.1
9c		Me		2.93±0.24	41.5±9.3	14
16a		Me		5.71±0.83	782±110	140
16b		Me		7.59±0.48	445±36	59
1				23.5±4.39	>10,000	>430
3				0.620±0.23	1.19±0.02	1.9
4				0.102[b]	33.9[b]	330

[a]K_i values were obtained from two or more independent experiments. Each value indicates mean ± SEM.
[b]Mean from two experiments.

derivatives revealed that the 4-aminopiperidine ring as the terminal basic part is superior to the 4-alkylpiperazine ring with respect to the V_2/V_{1A} selectivity.[14] Thus, we utilized these results to **9a** having a 4-methylpiperazine to obtain the 4-piperidinopiperidine derivative (**9b**). As a result, compound **9b** exhibited improved V_{1A} affinity and V_2/V_{1A} selectivity ($K_i = 4.97$ nM, $V_2/V_{1A} = 19$) in comparison to **9a**. This result was similar to the SAR of **3** and its derivatives.

We then modified the tether linking the *N*-methylbenzanilide template with the terminal amide of **9b**. The comparison of the binding results of the phenoxy derivatives (**12a**–**c**) demonstrated that the rank of order of potency in their V_{1A} affinities was 1,4- > 1,3- > 1,2-substitution pattern. Therefore, we examined another aromatic tethers with 1,4-substitution pattern. The phenyl derivative (**12d**) showed considerably weak V_{1A} affinity. In contrast, the benzyloxy derivative (**9c**) exhibited high V_{1A} affinity ($K_i = 2.93$ nM), being better than that of **9b**. These results suggested that the distance between the terminal basic moiety and the *N*-methylbenzanilide template might be important to exert high V_{1A} affinity and that the 4-benzyloxy moiety might be suitable for the tether.

Next, we converted the 2-methyl-3-furyl part of **9** into another heterocycle utilizing the SAR of **3**.[14] The 2-(2-ethyl-1-imidazolyl)phenyl derivatives (**16a**–**b**) showed similar V_{1A} affinities, but reduced V_2 affinities compared

Table 2. In vivo activities of *N*-methylbenzanilide derivatives

Compd	ID_{50}[a] (mg/kg iv)	*n*
9a	0.11±0.01	3
9c	0.038±0.002	4
16a	0.0080±0.002	4
16b	0.015±0.005	4
1	0.34±0.05	6

[a]ID_{50} represents the dose of the compounds required to inhibit AVP-induced pressor response in pithed rats by 50%. Each value indicates mean±SEM.

to **9a**, which resulted in an improvement of V_2/V_{1A} selectivity. Especially, compound **16a** had high V_2/V_{1A} selectivity ($V_2/V_{1A}=140$).

Thus, application of *N*-methylbenzanilide structure to **4** and further structural modifications utilizing the SAR of **3** led to novel compounds which had high V_{1A} affinity and V_2/V_{1A} selectivity.

From the results of the binging assay, some compounds were selected for in vivo evaluation[13] (Table 2). All the tested compounds dose-dependently antagonized an increase in DBP induced by AVP (30 mU/kg iv) via the V_{1A} receptor. In particular, compound **16a**, which had the highest V_2/V_{1A} selectivity in this series, exhibited potent V_{1A} receptor antagonist activity with an ID_{50} value of 0.0080 mg/kg, which was 43-fold more potent than that of **1**.

Conclusion

Application of the *N*-methylbenzanilide structure to a selective V_{1A} receptor antagonist, **4**, gave the novel 2-methyl-3-furyl derivative (**9a**) which showed high V_{1A} affinity and moderate V_2/V_{1A} selectivity. Further modifications utilizing the SAR of **3** gave novel compounds which exhibit high V_{1A} affinity and high V_2/V_{1A} selectivity, such as the 2-(2-ethyl-1-imidazolyl)phenyl derivative (**16a**). Compound **16a** showed potent V_{1A} receptor antagonist activity in vivo and was 43-fold more potent than **1**. This study would provide a novel approach to selective V_{1A} receptor antagonists, which might be useful in the treatment of diseases in which AVP is involved via the V_{1A} receptor.

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12. Satisfactory analytical data were obtained for all the target compounds. For example, **16a**: colorless amorphous powder: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.16 (3H, t, $J=7.6$ Hz), 1.43–1.47 (2H, m), 1.53–1.61 (2H, m), 1.69–1.76 (2H, m), 2.22 (3H, s), 2.39 (2H, t, $J=7.6$ Hz), 2.73 (5H, br s), 3.02–3.51 (8H, m), 3.15 (3H, s), 3.87–3.93 (2H, m), 6.63 (1H, d, $J=8.0$ Hz), 6.79 (1H, s), 6.99 (1H, d, $J=8.0$ Hz), 7.19 (2H, d, $J=8.0$ Hz), 7.42 (2H, d, $J=8.0$ Hz), 7.71–7.81 (5H, m), 7.93–7.95 (1H, m), 10.81 (1H, s), 11.41 (1H, br s), 15.05 (1H, br s); MS (FAB) *m*/*z* 651 (MH^+). Anal. calcd for $C_{38}H_{46}N_6O_4{\cdot}2HCl{\cdot}1.8H_2O$: C, 60.36, H, 6.88, N, 11.11; Cl, 9.38. Found: C, 60.32, H, 7.15, N, 11.00, Cl, 9.45.
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