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N,*N*-Dialkyl-4-[(8-azabicyclo[3.2.1]-oct-3-ylidene)phenylmethyl]-benzamides, potent, selective δ opioid agonists

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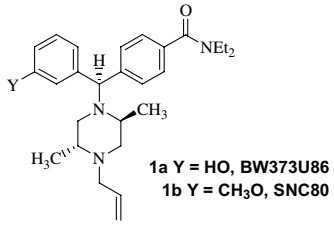
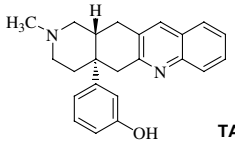
Abstract—A series of *N*,*N*-dialkyl-4-(9-aryltropanylidenemethyl)benzamides was prepared. The lead compounds, **15a** and **15c**, exhibited extremely high affinity for the δ opioid receptor with excellent selectivity versus the μ opioid receptor. They were full agonists at the δ opioid receptor, as assessed by stimulation of GTPγS binding, and displayed antinociceptive activity.

The discovery of multiple opioid subtypes in 1976[1] gave rise to hopes that new pain relieving medications lacking the side associated with morphine would be discovered. Studies with the potent, δ selective, cyclic peptide DPDPE, that showed good antinociceptive activity without concurrent effect on GI motility, amplified these hopes.[2] The discovery of the nonpeptide δ agonists BW373U86[3] (**1a**), TAN-67[4] (**2**), and SNC80[5] (**1b**) raised enthusiasm even higher.



1a Y = HO, BW373U86
1b Y = CH_3O, SNC80



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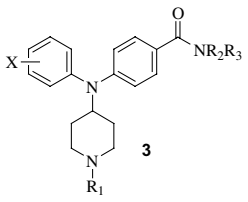
TAN-67

Upon further investigation, however, the expectations surrounding the nonpeptide δ agonists as analgesics have fallen short. SNC80 showed antinociceptive activity in mice in the models predictive of efficacy in severe pain but only by parenteral routes and only at high doses.[6] In addition, both BW373U86 and SNC80 induced convulsions in mice.[7] These results challenged the potential of δ opioid agonists as therapeutic agents.

Meanwhile, the search for new δ agonists has continued.[8,9] The structures of new nonpeptide δ agonists have generally fallen into two classes, the compounds related to TAN-67 from the GlaxoSmithKline group and the structures related to SNC80 such as **3**,[10,11] **4**,[12] and **5**.[13,14] Compounds of types **4** and **5** have shown impressive potency and selectivity. The challenges facing the creators of new structural classes of δ agonists, however, have been to overcome issues regarding safety and efficacy encountered with the first generation of nonpeptide δ agonists. With these objectives in mind, we prepared and evaluated a series of *N*,*N*-dialkyl-4-[(8-azabicyclo[3.2.1]-oct-3-ylidene)phenylmethyl]benzamides, **6**, which combine the structural features of **4** and **5**.



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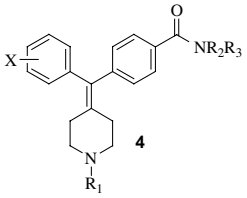

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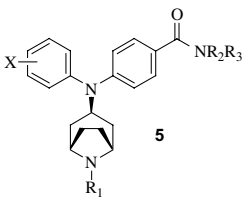

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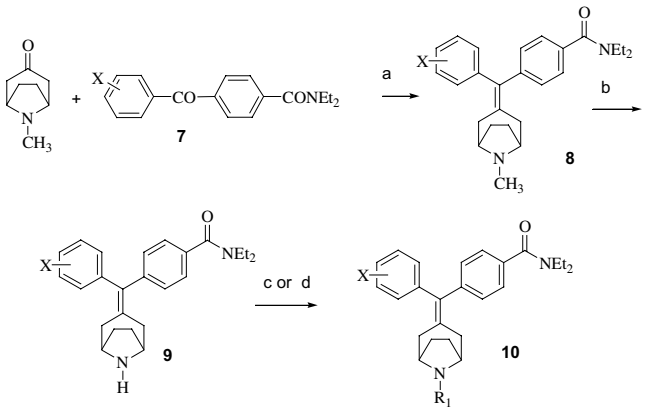
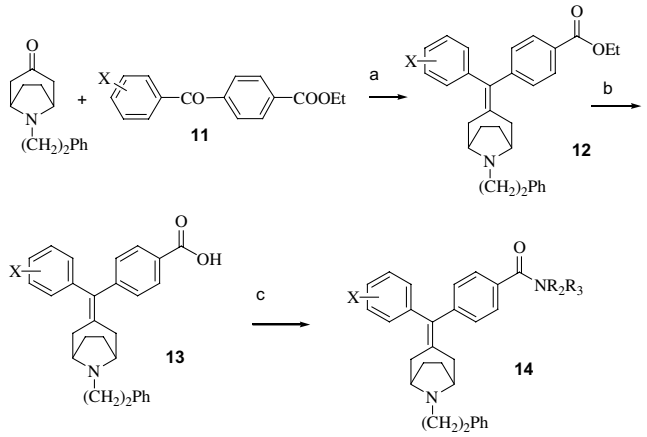
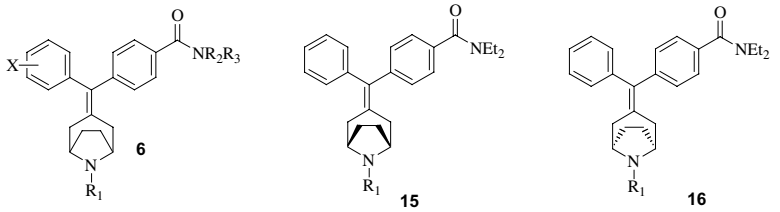


Scheme 1. Reagents and conditions: (a) $TiCl_4$, Zn; (b) (1) CCl_3CH_2OCOCl, (2) (2-Pr)$_2$*N*-Et (Zn); (c) RCHO, $NaBH(OAc)_3$ or R_1Br, K_2CO_3.



Scheme 2. Reagents and conditions: (a) $TiCl_4$, Zn; (b) NaOH; (c) (1) $SOCl_2$, (2) R_2R_3NH, NaOH.



The synthesis of compounds of type **6** was carried out by condensation of an appropriately substituted benzophenone **7** with tropinone under 'McMurray' conditions as shown in Scheme 1.[15] Compounds with a phenethyl group on the tropane nitrogen, varying in the carboxamide functionality, were prepared by McMurray condensation of *N*-phenethyl tropinone with ethyl 4-benzoylbenzoate and conversion of the resulting ester to the desired amides (Scheme 2). Compounds bearing a phenolic group were prepared by cleavage of the corresponding methoxy compound with BBr_3.

Compound **9** (X = H) was separated into enantiomers, **15a** and **16a**, by chiral HPLC. Other enantiomerically pure compounds (**15** and **16**) were prepared by alkylation or reductive alkylation of the enantiomers of **15a** and **16a**. Compounds **15d** and **16d** were also prepared by classical resolution as ditoluoyltartrate salts. The absolute configuration of **16d** was assigned by vibrational circular dichroism[16,17] and the assignment of configuration of **16a** was made by conversion to **16d**.

The opioid properties of the *N*,*N*-dialkyl-4-[(8-azabicylo[3.2.1]-oct-3-ylidene)phenylmethyl]benzamides, **6**, were examined (Table 1). Methodology used for the binding studies has been described.[18] Functional activity was measured by stimulation of [^{35}S]GTPγS binding. The procedure for these studies was adapted from that previously employed to study signal transduction pathways associated with bradykinin receptors.[19] The stimulation of [^{35}S]GTPγS binding in Chinese hamster ovary cells (CHO) transfected with the human δ opioid receptor following treatment with test compound was measured, and the efficacy relative to stimulation by SNC80 was calculated. Antinociceptive activity was assessed using the mouse abdominal irritant test (MAIT).[20]

A general SAR for SNC80 and close relatives such as **3** and **4** has been put forward.[21] One phenyl ring bearing an *N*,*N*-diethylcarboxamide, the Portoghese 'address' function,[22] is an obligatory feature for δ agonists of this class. They feature a second phenyl ring, which may or may not bear an oxygenated function. The central heterocyclic ring, which on SNC80 is dimethylpiperazine, may be varied[10–14] leading to compounds such as **4** and **5**, which may surpass SNC80 in potency and selectivity. The optimal groups on the heterocyclic ring nitrogen have been allyl and hydrogen. Groups which have imparted good activity as N substituents have generally been five carbon atoms or less.[12,13,23] An exception to this rule is the (1,3)-benzodioxol-5-ylmethyl group, which conferred high δ opioid affinity to a piperazine, albeit, resulting in little antinociceptive activity.[24]

Certain compounds of type **6** showed exceptional potency and selectivity. Compound **15a**, with a K_i value of 23 pM, was 400 times as potent as SNC80 and 13 times as potent as the analogous compound of type **5**. It was 37,000-fold selective for δ over μ receptor binding. The *N*-allyl compound, **15c**, was similarly of higher affinity than analogous compounds within this structural class, and nearly as selective. These compounds were full agonists at the δ opioid receptor, as assessed by GTPγS binding. Compounds with the 1*R*,5*S* (**15**) stereochemistry had higher affinity for the δ opioid

Table 1. Structure–activity relationships of δ opioid agonists

Compd	R_1	*N*-R_2,R_3	X	δ K_i (nM)	μ K_i (nM)	δ GTPγS		%*I* MAIT 150 μmol/kg po
						EC_{50} (nM)	Rel. eff.	
8a	CH_3	*N*-Et_2	3-CH_3O	5.9	693	65	0.87	
8b	CH_3	*N*-Et_2	3-OH	0.60	727	3	0.87	
8c	CH_3	*N*-Et_2	4-CH_3O	3.5	1499	27	0.85	
8d	CH_3	*N*-Et_2	4-OH	1.89	194	9	0.86	
9a	H	*N*-Et_2	4-OH	0.58	442	5	0.96	26.7
10a	*n*-Pr	*N*-Et_2	H	0.39	289	43	0.87	93.3
10b	2-(4-Fluorophenyl)ethyl	*N*-Et_2	H	2.62	393	27	0.76	26.7
10c	(1,3)-Benzodioxol-5-yl-methyl	*N*-Et_2	H	0.01	22.4	0.2	1.02	40
10d	2-Oxo-2-phenylethyl	*N*-Et_2	H	6.31	9643	173	0.68	
10e	3-Phenylpropyl	*N*-Et_2	H	0.56	104	112	0.88	13.3
10f	2-Phenoxyethyl	*N*-Et_2	H	0.38	630	623	0.84	
10g	2-(2-Thienyl)ethyl	*N*-Et_2	H	13.12	1281	1348	0.78	
10h	2-(1*H*-Indol-3yl)-ethyl	*N*-Et_2	H	3.48	337	16	0.91	
10i	2-Cyclohexylethyl	*N*-Et_2	H	1.36	451	228	0.92	
14a	2-Phenethyl	*N*-*n*-Pr_2	H	7.39	644	3557	0.82	
14b	2-Phenethyl	*N*-2-Pr_2	H	49.01	103	5041	0.92	
14c	2-Phenethyl	*N*-Ethyl,2-methylallyl	H	2.94	229	1081	0.9	33
14d	2-Phenethyl	*N*-Bis-(2-methoxyethyl)	H	16.61	294	403	0.71	
14e	2-Phenethyl	*N*-Ethyl,2-hydroxyethyl	H	3.2	291	548	0.77	
14f	2-Phenethyl	Pyrrolidinyl	H	24.1	276	1463	0.86	
14g	2-Phenethyl	*cis*-2,6-Dimethyl-piperidinyl	H	10.97	571	10,000		
14h	2-Phenethyl	Morpholinyl	H	35.2	237	350	0.76	
14i	2-Phenethyl	*N*-Et_2	3-CH_3O	1.36	417	218	0.8	
15a	H	*N*-Et_2	H	0.023	855	1.8	1.02	86.7
15b	CH_3	*N*-Et_2	H	5.7	2910	153	0.87	80
15c	Allyl	*N*-Et_2	H	0.025	322	0.5	1.05	100
15d	2-Phenethyl	*N*-Et_2	H	0.24	72.3	34	0.82	100
16a	H	*N*-Et_2	H	0.36	2310	53	1.00	86.7
16b	CH_3	*N*-Et_2	H	4.5	9730	149	0.85	90
16c	Allyl	*N*-Et_2	H	0.32	4400	177	0.83	100
16d	2-Phenethyl	*N*-Et_2	H	42.1	317	1387	0.88	90
1b	Allyl	*N*-Et_2	3-CH_3O	1.7	1300			
3a	H	*N*-Et_2	H	35	>10,000	458	0.76	
3b	Allyl	*N*-Et_2	H	24	11,565	21	0.81	
5a	H	*N*-Et_2	H	0.3	5040	12	0.95	
5b	Allyl	*N*-Et_2	H	0.5	3650	12	1.07	

receptor than compounds with the 1*S*,5*R* configuration (**16**). In general, the SAR pattern seen with SN80 analogues was followed.[15] An exception was the *N*-R_1 phenethyl compound (**15d**). The compound with this large group on nitrogen had a δ K_i of 0.23 nM and was active in the MAIT test. In an attempt to follow up on this finding, some amide variations (**14a–i**) were prepared. They were less potent and selective than the *N*,*N*-diethyl compound (**15d**). Some other large groups were tried on the tropanylidene nitrogen leading to compounds **10b–i**. Only the (1,3)-benzodioxol-5-ylmethyl group (**10c**) led to high affinity δ binding although this compound lacked antinociceptive activity.

In the course of evaluating compounds for antinociceptive activity in the MAIT test, each of 15 compounds of type **6** was administered orally to 15 mice at a dose of 150 μmol/kg. In no instances were any convulsions observed.

These findings suggest that convulsant activity is not an unavoidable consequence of activation of the δ opioid receptor. The only compound, which elicited 'straub tail' behavior, characteristic of μ opioid agonists, was **15d**.

In summary, we have prepared a series of *N*,*N*-dialkyl-4-[(8-azabicyclo[3.2.1]-oct-3-ylidene)phenylmethyl]benzamides (**6**). The lead compounds (**15a**,**c**) bind with exceptionally high affinity to the δ opioid receptor and are also highly selective for δ versus μ opioid binding. They are full δ agonists and are antinociceptive in the mouse abdominal irritant test. Importantly, they appear to have a lower convulsant liability than earlier δ agonists.

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