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Synthesis and Binding Affinities of 4-Diarylaminotropanes, a New Class of Delta Opioid Agonists

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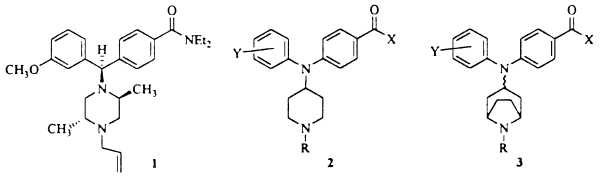
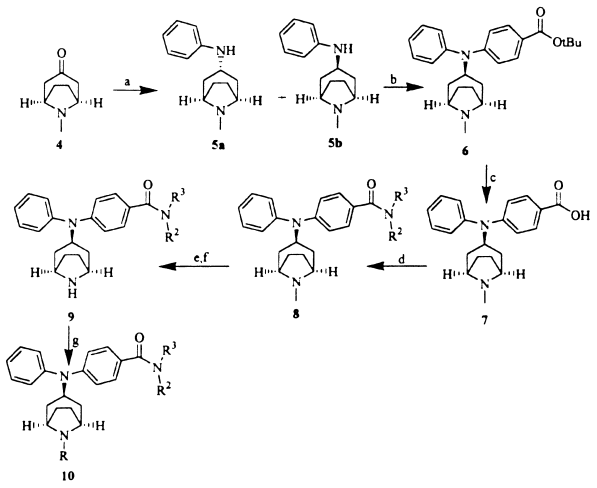
Abstract—A series of 4-diarylaminotropanes has been prepared. Both *endo* and *exo* diastereomeric forms bound to the delta opioid receptor but the *endo* isomers were more potent and selective versus the μ opioid receptor than the *exo* isomers. The most potent delta opioid agonist (**14**) exhibited a delta opioid K_i of 0.2 nM and was 860-fold selective over mu.

A number of selective delta (δ) opioid agonists have been reported in the literature.[1] These compounds were pursued as potential analgesic agents with fewer side effects than classic mu (μ) opioid agonists. Many of these δ agonists are piperazines or piperidines and resemble the earlier mu opioid agonists but incorporate an additional aromatic 'address functionality'.[2] A piperazine that has been widely studied as a δ agonist is SNC 80 (**1**).[3] Transposition of nitrogen and carbon at the head of SNC 80 gives rise to diarylaminopiperidines (**2**), another class of compounds with δ agonist activity.[4–7] We sought to investigate the role of stereochemistry in δ agonists by preparing and evaluating a series of bridged compounds, the 4-diarylaminotropanes (**3**).



A synthetic pathway to compounds of type **3** is shown in Scheme 1. Tropinone (**4**) was subjected to reductive alkylation with aniline. The reducing agent employed determined the stereochemistry of the new bond formed. Sodium borohydride, sodium triacetoxyborohydride, or catalytic reduction gave exclusively the *endo* isomer (**5b**) while sodium metal in ethanol produced both isomers[8] (**5a** and **5b**) which could be separated by flash chromatography.



Scheme 1. General syntehsis of diarylaminotropanes. Reagents and conditions: (a) aniline, Na, EtOH; (b) *t*-butyl 4-bromobenzoate, Pd_2dba_3, (*t*-butyl)$_3$P, NaO*t*Bu, toluene; (c) 6 N HCl; (d) HATU, HNR^2R^3; (e) 1-chloroethylchloroformate, DCE, reflux, 2 h; (f) MeOH, reflux; (g) carbonyl compound, $NaBH(OAc)_3$, DCE.

Once separated, the individual isomers underwent arylation[9] with *t*-butyl 4-bromobenzoate to produce the 4-(diaryl)aminotropane (**6**). The ester was hydrolyzed with HCl and the resulting acid (**7**) was converted to the desired amide (**8**) by one of two ways. Coupling utilizing HATU (*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate)[10] produced the desired

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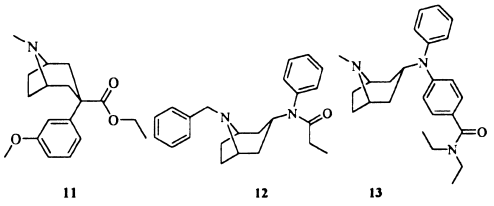
amides in quantitative yield. Conversion of the acid to the acid chloride followed by Schotten–Baumann reaction with the appropriate amine proved successful as well. Compounds (**10**) with different substituents on the tropane nitrogen were acquired by alkylation after demethylation of compound **9** with 1-chloroethylchloroformate.

Tropanes have been studied as μ opioid agonists.[11–14] NMR studies indicated an axial phenyl in a chair configuration for the meperidine analogue (**11**)[11,12] while the bridged fentanyl analogue (**12**) adopted the equatorial boat configuration.[14] The lack of an NOE between the aromatic protons and the protons on the bridge indicate that *endo* diarylamino function of **13** is in the equatorial boat configuration analogous to **12**.



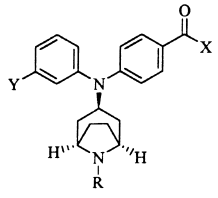
11 **12** **13**

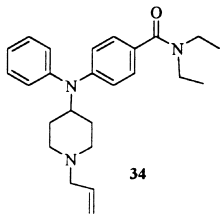
A summary of biological data is listed in Tables 1 and 2. The δ opioid receptor affinity was calculated from the inhibition of ^{3}H-DPDPE binding to δ opioid receptors from rat brain membranes. The μ opioid receptor affinity was calculated from the inhibition of ^{3}H-DAMGO binding to μ opioid receptors from rat brain membranes.[15] The binding affinities of morphine[16] and SNC 80 are listed as μ and δ agonist representatives.

This new class of compounds can exhibit low nanomolar binding affinity for the δ opioid receptor. Some of the *endo* isomers (Table 1) are among the most potent and selective nonpeptidic δ agonists to be published to date. Compounds **14**, **15** and **16** are more potent and selective than SNC 80. The *endo* tropanes are, in general, more potent and selective than their nonbridged counterparts, the piperidines (**16** vs **34**).[6]

The structure–activity relationships of this class parallel the SAR of previously published δ opioid agonists.[17–21] The small 'R' groups on nitrogen, H (**15**), allyl (**16**), methyl (**19**), and propyl (**20**), typical of δ agonists analogous to SNC 80, elicit high δ receptor affinity. The

Table 1. Binding affinity of the *endo* isomers to δ and μ opioid receptor





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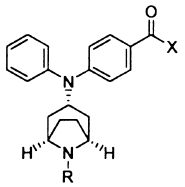
Compound	R	X	Y	δ K_I nm	μ K_I nm	μ/δ ratio
Morphine				90	1.8	0.02
SNC 80				1.7	1300	760
14	3,4-Methylenedioxybz	NEt_2	H	0.2	172	860
15	H	NEt_2	H	0.4	5040	14000
16	Allyl	NEt_2	H	0.5	1820	3640
17	Cy	NEt_2	H	2	817	355
18	Phenethyl	NEt(2-Me)allyl	H	2	1185	546
19	Me	NEt(2-Me)allyl	H	2	2555	1122
20	Pr	NEt_2	H	3	5790	1776
21	Phenethyl	NMePr	H	4	293	75
22	Phenethyl	NMePr	H	4	308	77
23	Phenethyl	NPr_2	H	4	818	200
24	Phenethyl	NMeEt	H	5	113	24
25	Phenethyl	NEtBu	H	5	244	50
26	Me	NMePh	H	6	2773	473
13	Me	NEt_2	H	7	4830	733
27	Phenethyl	NEt_2	H	8	124	16
28	Me	NPrBu	H	8	1725	220
29	Me	NEt_2	SCH_3	9	2770	235
30	Me	NEt(4-Me)Bn	H	10	1205	119
31	Me	NMeEt	H	18	4346	240
32	Me	NPr_2	H	18	Inact.	Inact.
33	Me	NEt_2	OCH_3	21	3700	180
34				24	1155	481
35	Phenethyl	NMe_2	H	30	128	4.3
36	Me	1-pyrrolidinyl	H	34	1400	41
37	Me	NMe_2	H	53	3018	57
38	Phenethyl	1-pyrrolidinyl	H	93	1343	14
39	Phenethyl	OH	H	356	249	0.7
40	Me	OH	H	363	7500	21
41	Me	O*t*-butyl	H	2260	Inact.	Inact.

Table 2. Binding affinity of the *exo* isomers to δ and μ opioid receptor



Compound	R	X	δ K_I nm	μ K_I nm	μ/δ ratio
SNC 80			1.7	1300	760
Morphine			90	1.8	0.02
41	PhenylPr	NEt_2	4	23	6.3
42	3,4-Methylene dioxybz	NEt_2	4	704	186
43	2-Furylmethyl	NEt_2	6	845	136
44	3,4-Dimethoxy- phenethyl	NEt_2	9	350	39
45	3,3-Dimethallyl	NEt_2	12	94	8
46	H	NEt_2	19	1590	85
47	4-Fluoro phenethyl	NEt_2	24	311	13
48	Hexyl	NEt_2	33	130	4
49	2-EtBu	NEt_2	42	975	23
50	Phenethyl	NPr_2	61	370	6
51	Phenethyl	NEt_2	72	13	0.2
52	Cyclohexyl-methyl	NEt_2	77	371	5
53	H	NPr_2	131	2950	23
54	Pr	NEt_2	151	1850	12
55	Me	NEt_2	305	6350	21
56	2,2-Diphenyl ethyl	NEt_2	550	1420	3

3,4-methylenedioxy substituent[22] imparts very good potency. Compounds with an *N*-phenethyl substituent are, in general, less selective. The C=O(X) functionality associated with the address[2] portion of the molecule is optimally a tertiary amide. Optimal activity and selectivity are achieved with the diethylamide. Activity and selectivity are lost when the amide is *N*,*N*-dimethyl (**37**) or CO-pyrrolidinyl (**36**). Activity is greatly diminished when the C=O(X) substituent is ester or acid.

The *exo* isomers (Table 2) are less potent and less selective for the δ opioid receptor. The structure–activity relationship of this set of compounds is quite different from the *endo* isomer. Small alkyl 'R' groups on the tropane nitrogen result in a loss of activity (**45**, **47**, and **49**).

In summary, the generation of this class of compounds has developed a greater understanding of the spacial relationships between the δ opioid receptor and its agonists. The binding site of the receptor is highly influenced by the stereochemistry of the agonist. These findings indicate that investigation into steric barriers designed into the framework of the molecule is likely to lead to additional potent and selective δ opioid agonists.

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