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trans-3,4-Dimethyl-4-(3-carboxamidophenyl)piperidines: A Novel Class of μ-Selective Opioid Antagonists

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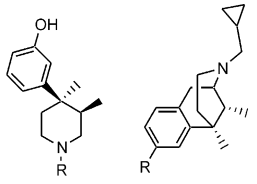
Abstract—*trans*-3,4-Dimethyl-4-(3-carboxamidophenyl)piperidines constitute a novel class of μ opioid receptor antagonists. The $CONH_2$ group was found to be an effective isostere of the phenolic OH moiety. Structure–activity relationships at the piperidine nitrogen position led to the identification of several ligands displaying high affinity toward the cloned human μ opioid receptors, good selectivity μ/δ, μ/κ, and potent in vitro antagonist activity.

In 1978, Zimmerman and collaborators described the discovery of opioid antagonist activity in a series of *trans* - 3,4 - dimethyl - 4 - (3 - hydroxyphenyl)piperidines (Formula **A**).[1]



A

1: R = OH
2: R = $CONH_2$

These 4-phenyl piperidine antagonists were structurally unique, since prior to their discovery, opioid antagonists were generally *N*-allyl or *N*-methylcyclopropyl analogues of morphine. The opioid antagonist activity in the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines was a consequence of substitution at the 3-position of the piperidine ring. Structure–activity relationship (SAR) in this *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine series has been focused largely on the substitution of the piperidine nitrogen.[2–5] Hence, modification of the OH phenolic position of the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines has never been described in the scientific literature.[6] Recently, Wentland and collaborators explored the SAR at the 8-position of cyclazocine (**1**), a mixed μ/κ agonist, in order to identify a potential bioisostere of the phenolic OH group.[7–9] Results from these studies showed that the 8-carboxamido analogue of cyclazocine (**2**) was found to have high affinity and agonist activity at the μ and κ opioid receptors, comparable to cyclazocine.

We now wish to report the synthesis, opioid receptor binding properties and in vitro functional activity of a series of *trans*-3,4-dimethyl-4-(3-substituted-phenyl)piperidines. The *N*-phenethyl *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (**3**, Table 1) has been previously reported to bind opioid receptors with good affinity [$K_i(\mu) = 1.5$ nM; $K_i(\kappa) = 52$ nM].[2] The in vitro affinity of **3** measured at cloned human opioid receptors was in agreement with literature data. On the basis of the structure of **3**, the phenolic OH group was replaced by various moieties (Table 1) in order to define the SAR at the phenolic OH position.

The target compounds **4**–**11** were prepared according to Scheme 1. Condensation of (+)-4(*R*)-(3-hydroxyphenyl)-3(*R*),4-dimethyl-1-piperidine[10] (**12**) with phenylacetaldehyde under reductive amination conditions afforded the derivative **3**. Palladium catalyzed carbonylation of the triflate derived from **3** provided the methyl ester **9**, which was hydrolyzed under basic conditions to give the carboxylic acid **11**. Coupling of **11**

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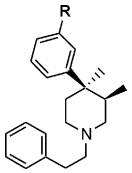
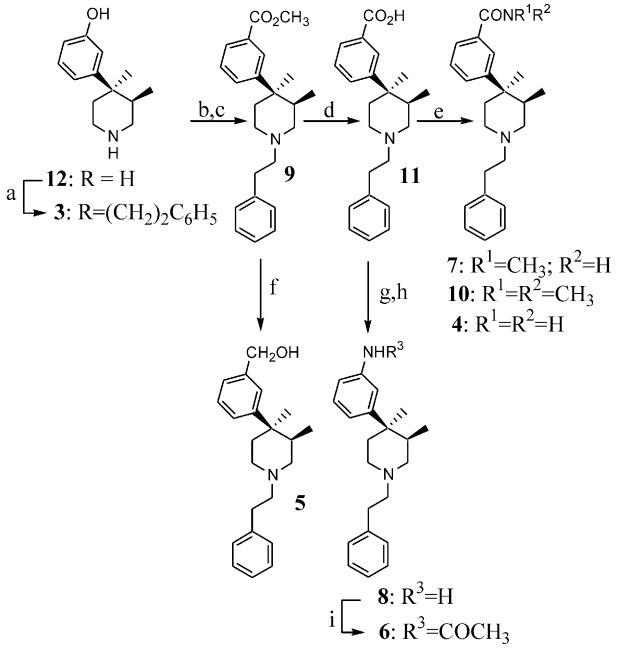
Table 1. Opioid receptor (μ, κ and δ) binding data and in vitro antagonist activity (μ) of *N*-phenethyl-*trans*-3,4-dimethyl-4-(3-substituted-phenyl) piperidines



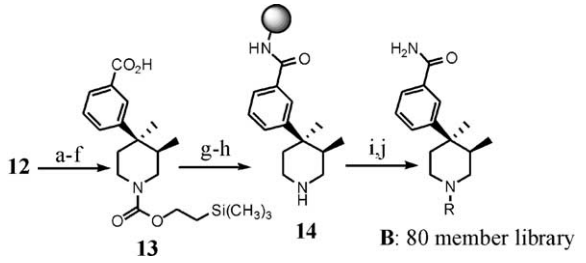
Compd	R	K_i(μ) (nM)[a] or % inh.@10 μM[c]	IC_{50}(μ) (nM)[b]	K_i(κ) (nM)[a] or % inh.@10 μM[c]	K_i(δ) (nM)[a] or % inh.@10 μM[c]
Naloxone		3.7	7.3	9.2	33
3	OH	1.9	2.0	17	33
4	$CONH_2$	4.7	1.9	95	72
5	CH_2OH	11	2.1	840	270
6	$NHCOCH_3$	68	16	1100	51%
7	$CONHCH_3$	71	24	1300	1200
8	NH_2	150	nd[d]	1400	50%
9	CO_2CH_3	850	nd	44%	18%
10	$CON(CH_3)_2$	1200	nd	23%	17%
11	CO_2H	25%	nd	9%	8%

[a]The potencies of the compounds were determined by testing the ability of a range of concentrations of each compound to inhibit the binding of the non-selective opioid antagonist, [^{3}H]diprenorphine, to cloned human μ, κ, and δ opioid receptors, expressed in separate cell lines.[11] K_i values are geometric means computed from at least three separate determinations.
[b]The potencies of the antagonists were assessed by their abilities to inhibit agonist (loperamide) stimulated [^{35}S]GTPγS binding to membranes containing the cloned human μ opioid receptor.
[c]% inhibition of [^{3}H]diprenorphine binding to the cloned human μ, κ, and δ opioid receptors using a concentration of the competitor of 10 μM.
[d]Not determined.



Scheme 1. Reagents and conditions: (a) $C_6H_5CH_2CHO$, BH_3/C_5H_5N, EtOH, 25 °C, 71%; (b) $C_6H_5N(SO_2CF_3)_2$, Et_3N, CH_2Cl_2, 25 °C, 67%; (c) CO(g), $Pd(OAc)_2$, DPPF, Et_3N, DMSO/MeOH, 65 °C, 92%; (d) aq NaOH, THF, reflux, 95%; (e) CH_3NH_2·HCl, $(CH_3)_2NH$ or NH_4Cl, EDCI, HOBt, Et_3N, DMF, 25 °C, 63% (**7**), 63% (**10**), 50% (**4**); (f) $LiAlH_4$, THF, 25 °C, 63%; (g) DPPA, Et_3N, molecular sieves, *t*-BuOH, reflux, 53%; (h) HCl/diethyl ether, MeOH, reflux, 96%; (i) CH_3COCl, Et_3N, CH_2Cl_2, 25 °C, 87%.

with methylamine, dimethylamine or ammonium chloride afforded the secondary, tertiary or primary amides **7**, **10** and **4**, respectively. The primary alcohol **5** was prepared by reduction of the methyl ester **9** using lithium aluminum hydride. Curtius rearrangement of the carboxylic acid **11** followed by acidic deprotection



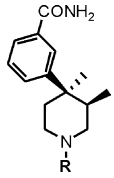
Scheme 2. Reagents and conditions: (a) Boc_2O, Et_3N, THF, 25 °C, 100%; (b) $C_6H_5N(SO_2CF_3)_2$, Et_3N, CH_2Cl_2, 25 °C, 74%; (c) CO(g), $Pd(OAc)_2$, DPPF, Et_3N, DMSO/MeOH, 65 °C, 75%; (d) HCl/Et_2O, MeOH, reflux, 98%; (e) 2-(trimethylsilyl)ethyl-*p*-nitrophenylcarbonate, $(iPr)_2EtN$, CH_3CN, 25 °C, 92%; (f) LiOH, H_2O/THF, 25 °C, 97%; (g) Fmoc-deprotected Rink amide resin, HATU, HOBt, $(iPr)_2EtN$, CH_2Cl_2/DMF, 25 °C; (h) TBAF, THF, 25 °C; (i) aldehyde or ketone, NMP/EtOH, BH_3/C_5H_5N, 25 °C; (j) TFA/CH_2Cl_2.

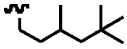
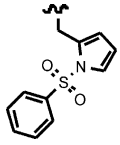
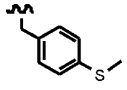
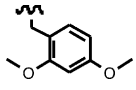
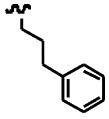
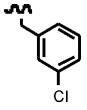
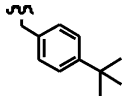
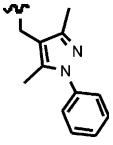
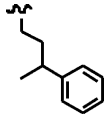
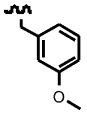
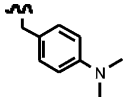
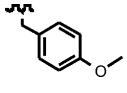
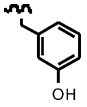
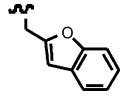
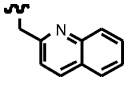
of the resulting Boc protected aniline derivative afforded the derivative **8**. Acylation of **8** with acetyl chloride in the presence of triethylamine provided the amide **6**.

Opioid receptor binding data are found in Table 1.[11] Compounds **3**–**11** were tested for their affinities toward the cloned human μ, δ and κ opioid receptors as measured by their abilities to displace [^{3}H]-diprenorphine from its specific binding sites.[11] The antagonist potencies of selected compounds (K_i < 100 nM) were assessed by their abilities to inhibit agonist (loperamide)-stimulated guanosine 5′ - *O* - (3 - [^{35}S]thio)triphosphate ([^{35}S]GTPγS) binding to membranes containing μ opioid receptors.[11] The antagonist potencies of these selected compounds were expressed as IC_{50} values. No agonist activity was detectable for compounds **3**–**11** at concentrations up to 10 μM. The primary carboxamido analogue **4** derived from **3** displayed high affinity for the cloned human μ opioid receptor, and good κ and δ

selectivity. Furthermore, compound **4** displayed potent in vitro μ antagonist activity ($IC_{50} = 1.9$ nM) that was comparable to that of its phenolic counterpart **3** ($IC_{50} = 2.0$ nM). When the carboxamido nitrogen of **4** was substituted by a single methyl group as in **7**, the affinity for the μ opioid receptor decreased 15-fold. The affinity for μ further decreased 17-fold when the carboxamido nitrogen of **4** was replaced by two methyl groups (**10**). These data indicated that both H-atoms of the carboxamide are important for μ binding. The primary alcohol derivative **5**, which also has the potential for H-bond donation, displayed high affinity for the μ

Table 2. Opioid receptor (μ, κ and δ) binding data of *N*-substituted-*trans*-3,4-dimethyl-4-(3-carboxamido)phenyl piperidines



Compd	R[c]	K_i(μ) (nM)[a]	K_i(κ) (nM)[a] or % inh.@10 μM[b]	K_i(δ) (nM)[a] or % inh.@10 μM[b]	Compd	R[c]	K_i(μ) (nM)[a]	K_i(κ) (nM)[a] or % inh.@10 μM[b]	K_i(δ) (nM)[a] or % inh.@10 μM[b]
15		0.5 (**0.7**[d])	5.4 (**8.1**[d])	14 (**19**[d])	**24**		8.3	210	62%
16		1.7	120	110	**25**		8.8	67%	59%
17		3.1[e] (**1.8**[d])	140 (**160**[d])	73 (**53**[d])	**26**		9.7	190	57%
18		3.2	120	70%	**27**		13	71%	74%
19		5.0	100	310	**28**		15	58%	32%
20		5.3	460	70%	**29**		16	210	42%
21		5.5 (**11**[d])	220 (**380**[d])	71% (**76%**[d])	**30**		29	140	59%
22		6.2 (**12**[d])	300 (**480**[d])	72% (**400**[d])	**31**		53	140	58%
23		8.0 (**13**[d])	600 (**750**[d])	220 (**420**[d])	**32**		69	64%	24%

[a]See Table 1, footnote a.
[b]See Table 1, footnote c.
[c]UV purity (library compounds) >90%; UV detector; Waters 996 PDA. 200–300 nm. Total scan; compound identity was established by MS analysis.
[d]Biological data of purified library compound expressed as the geometric mean of at least three separate determinations.
[e]UV purity of library compound: 73%.

opioid receptor, good receptor selectivity and potent μ in vitro antagonist activity. The methyl ester derivative **9** displayed only weak affinity ($K_i = 850$ nM) toward the μ opioid receptor, while the carboxylic acid analogue (**11**) was devoid of appreciable opioid receptor binding. In the previously reported agonist series, the 8-amino analogue of cyclazocine had significant affinity for the μ and κ opioid receptors.[12] In our antagonist series, the aniline derivative **8** displayed only modest affinity ($K_i = 150$ nM) for the μ opioid receptor. Interestingly, acetylation of **8** was accompanied by a 2-fold increase in the affinity toward the μ opioid receptor (**6**: $K_i = 68$ nM). Of the substituents examined, $CONH_2$ appeared to be an effective bioisostere of OH in this series of *trans*-3,4-dimethyl-4-(3-substituted-phenyl)piperidines.

With the identification of **4** as a novel μ antagonist, the SAR at the piperidine nitrogen was investigated. Thus, an 80 member library of tertiary amines, that is *N*-substituted *trans*-3,4-dimethyl-4-(3-carboxamidophenyl)piperidines (general formula **B**), was synthesized according to Scheme 2. The key intermediate **13**, used as starting material for the solid phase synthesis of compounds of Formula **B**, was prepared in six steps from (+)-4(*R*)-(3-hydroxyphenyl)-3(*R*),4-dimethyl-1-piperidine **12**. Coupling of the acid **13** with the Fmoc-deprotected Rink amide resin, followed by removal of the Teoc protecting group using TBAF, provided the resin **14**. Condensation of **14** with a selected range of aldehydes and ketones under reductive amination conditions in *N*-methylpyrrolidinone/ethanol (3:1) using borane/pyridine as reducing agent afforded the corresponding resin-bound tertiary amines. Compound cleavage was carried out using a mixture of trifluoroacetic acid/dichloromethane 1:1, yielding the desired carboxamide derivatives (Formula **B**). The purity of the cleaved products was generally >90% as determined by LC/MS. The library compounds were tested for their affinities toward cloned human μ, δ and κ opioid receptors. The biological data obtained for selected compounds **15**–**32** are summarized in Table 2. Representative compounds (**15**, **17** and **21**–**23**) were resynthesized according to Scheme 2 and further purified by preparative HPLC in order to confirm the binding data obtained for the library compounds. The K_i values obtained for the purified products were generally within 2–3-fold of the K_i values obtained for the library compounds. The various substituted benzyl derivatives **16**, **18**, **20**, **21**, **25**, **26**, **28**–**30** (Table 2) displayed nanomolar range affinity ($K_i < 30$ nM) toward the human cloned μ opioid receptor, suggesting that the μ opioid receptor seems to accommodate various lipophilic sustituents at this position. Similar results have been reported by Zimmerman and collaborators for the phenolic compounds.[2] Replacement of the phenyl ring of **29** by various heterocycles (compounds **22**–**24**, **27**) provided ligands with good affinity and selectivity for the μ opioid receptor. For example, the quinoline derivative **23** bound to the μ opioid receptor with high affinity ($K_i = 13$ nM) and was a potent μ antagonist in vitro (IC_{50} (μ) = 16 nM). It has been previously determined in the phenolic series that maximum potency and selectivity for the μ opioid receptor was achieved when the *N*-substituent incorporated a lipophilic entity (phenyl ring or cyclohexyl) separated from the piperidine nitrogen by three atoms.[2] Similarly, in the new carboxamide series, the 3-phenylpropyl derivative **17** bound with a higher affinity ($K_i = 1.8$ nM) to μ opioid receptors than its phenylethyl (**4**) ($K_i = 4.7$ nM) or benzyl (**29**) analogues ($K_i = 16$ nM). With regard to *N*-alkyl substitution, increasing the alkyl length to 5, 6 and 7 carbons was previously shown in the phenolic series to increase opioid antagonist potencies.[2] Similar results were found in the carboxamide series. In particular, the most active compound, the (3,5,5)-trimethylhexyl derivative **15** (diastereomeric mixture), displayed high affinity toward the μ opioid receptor ($K_i = 0.7$ nM) and potent in vitro antagonist activity ($IC_{50} = 2.2$ nM).

In summary, this study showed that the new series of *trans*-3,4-dimethyl-4-(3-carboxamidophenyl) piperidines provides ligands with good affinity toward the μ opioid receptor and potent in vitro antagonist activity. The carboxamide moiety was found to be an effective bioisostere of the phenolic OH. These results extend the earlier work of Wentland on μ/κ agonists to selective μ antagonists. In drug substances, phenolic groups are generally prone to sulfonation and glucuronidation, both of which facilitate rapid excretion of the active compounds, resulting in short half lives. In this regard, future in vivo evaluation of the *trans*-3,4-dimethyl-4-(3-carboxamidophenyl) piperidines in vivo will be of particular interest.

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