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Synthesis and Structure–Activity Relationship of Novel Aminotetralin Derivatives with High μ Selective Opioid Affinity

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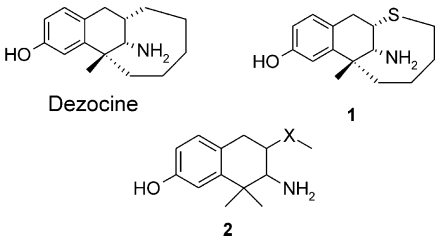
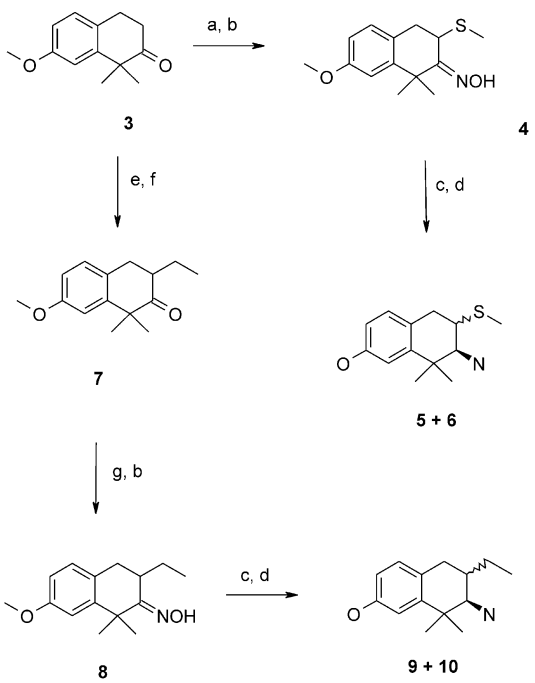
Abstract—Several novel racemic aminotetralin derivatives have been prepared using a stereoselective aziridine ring opening reactions and were evaluated for their μ-opioid receptor binding affinity. Selectivity index towards other opioid receptors and antinociceptive activity in mice have been evaluated for the most potent derivatives.

Inspired by analgesic proprieties of Dezocine, thiomorphinane **1**[1] was synthesized. Compound **1** has showed very good μ receptor affinity (Table 2) and the antinociceptive activity[2] (Table 3). We became interested in preparing the structurally related but simpler aminotetralins **2** bearing different side chains next to the amino group to try to improve or retain the opioid receptor affinity observed with **1**.



All compounds were prepared from dimethyl tetralone derivative **3** (Scheme 1) which was obtained in 80% yield from the commercially available 7-methoxy-2-tetralone by a double alkylaltion with methyl iodide and sodium hydride.[2] Racemic *cis* and *trans* thiomethyl ether derivatives **5** and **6** were prepared in four steps. Tetralone **3** was first treated with LiHMDS and methyl methanethiosulfonate[3] followed by hydroxylamine



Scheme 1. (a) LiHMDS, THF, $CH_3SSO_2CH_3$, −78 °C to rt, 89%; (b) NH_3OHCl, Pyr, 80 °C, 63–84%; (c) $TiCl_4$, $NaBH_4$, DME, 85 °C, 35–60%; (d) BBr_3, CH_2Cl_2, −78 °C to rt, 70–80%; (e) $(CH_3O)_2CO$, NaH 0–90 °C, 92%; (f) CH_3CH_2I, Cs_2CO_3, CH_3CN, 60 °C, 100%; (g) KOH 5%, MeOH, 80 °C, 70%.

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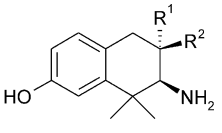
hydrochloride in pyridine[4] to give **4** in 67% overall yield. Oxime **4** was reduced using a mixture of sodium borohydride and titanium tetrachloride in DME[5] to produce a 1:1 mixture of *cis* and *trans* aminothioether in 60% yield. Both isomers were separated by flash chromatography and the methylether group was cleaved with boron tribromide in dichloromethane[6] to give **5** and **6** in 70% yield for both isomers. Racemic *cis* and *trans* ethyl derivatives **9** and **10** were easily prepared in six steps according to a known procedure.[7] Compound **3** was treated with methyl carbonate and sodium hydride followed by ethyl iodide and cesium carbonate to give **7** in 92% overall yield. The β-ketoester **7** was reacted with potassium hydroxide and then treated with hydroxylamine hydrochloride to form oxime **8** in 44% overall yield. The final products **9** and **10** were obtained after oxime reduction and demethylation of the methylether using conditions previously described for compounds **5** and **6**.

Preliminary results for binding affiunity to μ receptor (Table 1) revealed that both *trans* isomers **5** and **9** show a better affinity than their *cis* counterpart. The *trans* thiomethylether derivative **5** is almost 300 times more potent than the *cis* isomer **6** with a $K_i\mu$ of 1.1 nM, whereas **9** is 6-fold better than *cis* isomer **10** but 20-fold less potent than **5** with a $K_i\mu$ of 21 nM. The presence of a heteroatom next to the amino group seems to be important for enhancing μ receptor affinity. Based on these results, a stereospecific synthesis of *trans* aminotetralin, like **5,** was undertaken using an aziridine opening reaction as the key step. The starting tetralone **3** (Scheme 2) was treated with hydroxylamine hydrochloride in pyridine to form the oxime which was reacted with $LiAlH_4$ in the presence of diethylamine in THF under reflux[8] to produce aziridine **11** in 60% yield.

In order to facilitate analogue synthesis, the methylether group was replaced by a *t*-butyloxycarbonyl group in 75% overall conversion. The resulting protected aziridine **12** was used to prepare stereoselectively *trans* derivative **13**, **14**, and **16**. Aziridine **12** was reacted under very mild condition, in a regio and stereoselective manner, to produce the desired analogues in high yield. Thus, the preparation of the amino alcohol **13**[9] was achieved via the introduction of the C-hydroxyl group in the presence of PPTS, water in acetonitrile in 77% yield after purification, followed by concomitant, rapid deprotection of the two Boc groups by a short treatment with TFA in CH_2Cl_2. The compound **12** in methanol with PPTS gave, after deprotection, the amino ether **16** in 80% yield. Similarly, **12** was reacted with thioacetic acid and the resulting *trans* amino thioacetate was obtained in 74% yield. Acetate cleavage with sodium methoxide in methanol gave **14**, which upon acidic treatment afforded the *trans* amino thiol **15** in very good overall yield. The stereoselective synthesis of **5** was also carried out by treatment of the free thiol intermediate **14** with methyl iodide and K_2CO_3 in acetone under reflux, followed by deprotection. Oxidation of **17** with trichlorooxobis (triphenylphosphine)rhenium(V),[10] phenyl sulfoxide in chloroform gave a separated mixture of the sulfoxide. **18A** and **18B** were obtained by boc deprotection in the usual condition. Finally, the corresponding sulfone **19** was prepared from **17** by a treatment with MCPBA, Na_2CO_3 in CH_2Cl_2,[11] followed by deprotection.

Table 1. Binding affinity for μ receptor



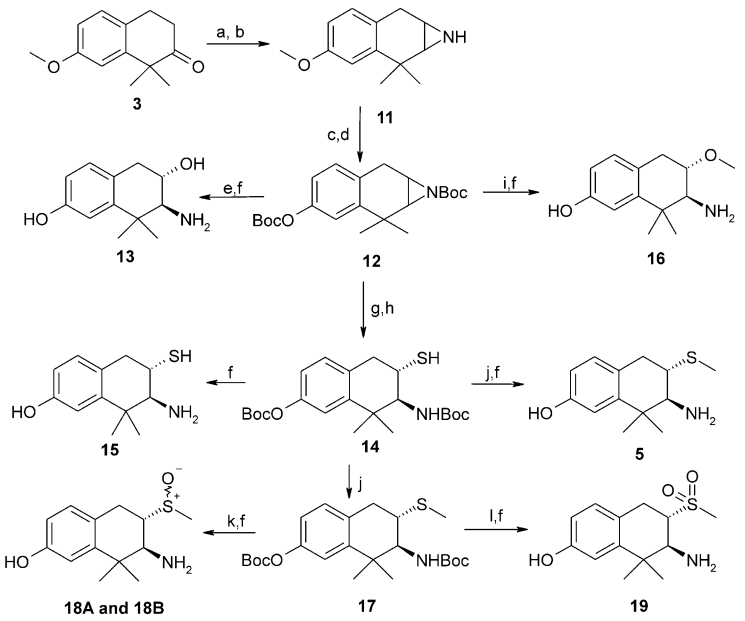
Compd	R^1	R^2	$K_i\mu$ = nM
5	H	SCH_3	1.1
6	SCH_3	H	286
9	H	CH_2CH_3	21
10	CH_2CH_3	H	135
13	H	OH	204
15	H	SH	163
16	H	OCH_3	1.8
18A	H	$SOCH_3$	1056
18B	H	$SOCH_3$	2000
19	H	SO_2CH_3	1151

The binding affinity for μ receptor (Table 1) was obtained for all these new *trans* amino tetralin derivatives and most of them showed marginal binding affinities. In fact, the ethyl derivative **9** and the methyl ether derivative **16** showed good binding affinity with a $K_i\mu$ of 21 and 1.8 nM, respectively. The free alcohol **13** and thiol **15** displayed a $K_i\mu$ 100-fold less potent than their corresponding methylated derivatives **16** and **5**. Oxidation of the sulfur atom to the sulphoxides **18A** and **18B** and sulphone **19** also reduced significantly the binding affinity for μ receptor. In regard to this loss of μ affinity binding, no further effort was involved in the characterization of **18A** and **18B**.

The affinity for δ and κ opioid receptors have been obtained for the most potent compounds **5**, **9,** and **16** (Table 2). All compounds have displayed better selectivity than morphine[14] towards the μ receptor. The thioether **5** showed 60-fold and more than 300-fold selectivity to μ when compared to κ and δ receptors, respectively. The alkyl derivative **9** showed 16-fold and more than 200-fold selectivity to μ when compared to κ and δ respectively. The methyl ether **16** has displayed the best results with selectivity to μ of 100-fold and almost 3000-fold when compared to κ and δ.

The antinociceptive activity (Table 3) in mice has been evaluated for compounds **5**, **9** and **16** using two different models: the tail flick[12] and the PBQ assay.[13] Compounds **5** and **16** showed good antinociceptive activity which was as good or better than morphine[15] and **1**.

We have identified a simple class of aminotetralins with very good μ receptor affinity and good selectivity towards the μ opioid receptors. A *trans* relationship between amino group and ether or thioether side chain is crucial for optimum affinity to the μ receptor. A stereoselective synthesis of the *trans* isomers was achieved using a ring opening reaction of aziridine with different nucleophiles. Further studies related to this new interesting class of compounds will be described in the near future.



Scheme 2. (a) NH_3OHCl, Pyr, 80 °C, 94%; (b) $LiAlH_4$, Et_2NH, THF, 80 °C, 60%; (c) BBr_3, CH_2Cl_2, −78 °C to rt, 66–80%; (d) $(Boc)_2O$, NEt_3, DMAP, CH_2Cl_2, rt, 100%; (e) H_2O, CH_3CN, PPTS, rt, 77%; (f) TFA, CH_2Cl_2, rt, 95–100%; (g) CH_3COSH, rt, 74%; (h) $CH_3O^-Na^+$, CH_3OH, 0 °C, 100%; (i) PPTS, CH_3OH, rt, 80%; (j) MeI, K_2CO_3, Acetone, 56 °C, 73%; (k) $[(C_6H_5)_2P]_2ReOCl_3$, Ph_2SO, $CHCl_3$, rt, 68%; (l) MCPBA, Na_2CO_3, CH_2Cl_2, rt, 73%.

Table 2. Affinity for different opioid receptors

Compd	$K_i\mu$ (nM)±SEM	$K_i\kappa$ (nM)	$K_i\delta$ (nM)
1	0.79±0.12	43.4	420
5	1.1±0.4	66	349
9	21±11.8	345	4507
16	1.8±0.2	184	5216
Morphine	3.96	52.14	113.3

Table 3. Antinociceptive activity in mice

Compd	Tail flick ED_{50} μmol/Kg (sc)	PBQ ED_{50} μmol/kg (sc)
1		0.33
5	0.58	0.14
9	10.4	4.8
16	16	1.1
Morphine	1.2	1.6

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