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Synthesis and analgesic activity of secondary amine analogues of pyridylmethylamine and positional isomeric analogues of ABT-594

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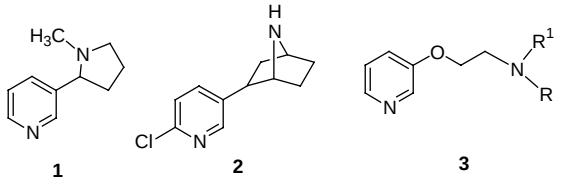
Abstract—A series of highly sterically hindered secondary amine analogues of pyridylmethylamine (**7a–f**, **8a–c)** and positional isomeric analogues of ABT-594 (**9a–c**) were synthesized and evaluated for their in vivo analgesic activity. The compounds **7a** and **7d** show potent analgesic activity and lower toxicity. Some interesting structure–activity relationships have been revealed.

Nicotine **1** produces many effects via interaction with nicotinic cholinergic (nACh) receptors.[1] There is also considerable evidence suggesting that selective neuronal nicotinic acetylcholine receptor (nAChR) agonists may have therapeutic potential in CNS disorders such as Alzheimer's and Parkinson's diseases, schizophrenia, and depression.[2] Antinociceptive effects of nicotine have been known for some time, but the most important discovery of the alkaloid epibatidine **2** (one of bridge nicotinoids, isolated from South American frogs by Daly in 1992) as a potent analgesic that acts via neuronal nAChRs has stimulated renewed interest in targeting nAChRs for analgesia.[3] However, the potential therapeutic actions of epibatidine and older nicotinic agonists are accompanied by evident adverse effects, such as high toxicity, hypertension, neuromuscular paralysis, dependence, and seizure.[4]

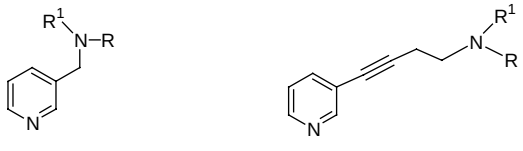
Several populations of nACh receptors have been identified, the emerging diversity of nAChR subtypes supporting the possibility of developing receptor subtype selective therapeutic agents that lack or have substantially reduced side effects.[5] The $\alpha_4\beta_2$ subtype is one of the most abundant nAChR subtypes within the CNS and has been the primary focus of high affinity ligand design.[6] To date, numerous structure–activity relationship studies based on the structures of nicotine **1** and epibatidine **2** have been performed in search of highly efficient analgesic agents and simple structure with lower toxicity.[7]

Among them, a series of representative ring-opened analogues (**3–5**) of nicotine **1** and epibatidine **2** show that different kinds of amines could influence the affinity



1 **2** **3**

3a R = H, R^1 = Me, *Ki* = 35 nM
3b R= R^1 = Me, *Ki* = 21 nM



4 **5**

4a R = H, R^1 = Me, *Ki* > 10,000 nM
4b R= R^1 = Me, *Ki* =540 nM
4c R = Me, R^1 = Et, *Ki* =28 nM

5a R = H, R^1 = Me, *Ki*= 113 nM
5b R= R^1 = Me, *Ki* =510 nM
5c R = Me, R^1 = Et, *Ki* =1770 nM

Keywords: Nicotinic cholinergic receptor; Analgesic activity; Highly sterically hindered secondary amine analogues of pyridylmethylamine; Synthesis.
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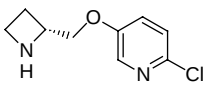
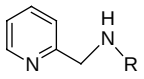
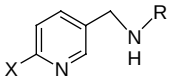


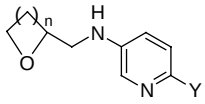
ABT-594 (6)



8a (X = H, R = cyclopentyl)
8b (X = H, R = furfurylmethyl)
8c (X = H, R =tetrahydrofurfurylmethyl)



7a (X = H, R = cyclopentyl)
7b (X = H, R = furfurylmethyl)
7c (X = H, R =tetrahydrofurfurylmethyl)
7d (X = Cl, R = cyclopentyl)
7e (X = Cl, R = furfurylmethyl)
7f (X = Cl, R = tetrahydrofurfurylmethyl)



9a (n = 0, Y = H)
9b (n = 0, Y = Cl)
9c (n = 2, Y = Cl)

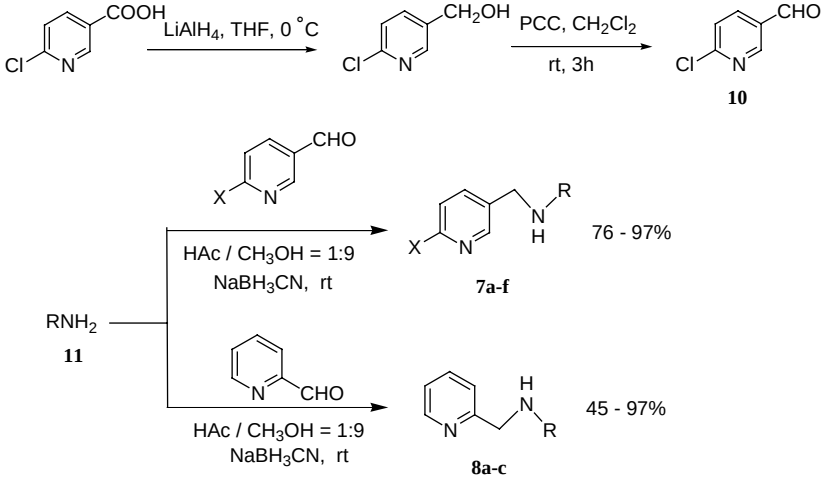
significantly.[8] For 3-pyridyl ethers **3** (3-PE), the secondary amine (e.g., **3a**) and tertiary amine (i.e., **3b**) show similar affinity for the $\alpha_4\beta_2$ receptor. However, for 3-pyridylmethylamines **4** (3-PMA), the tertiary amines (i.e., **4b** and **4c**) are typically favored over secondary amines (i.e., **4a**) for $\alpha_4\beta_2$ receptor binding. In contrast, for 3-pyridylbutynylamines **5** (3-PBA), the secondary amines (e.g., **5a**) bind with affinity higher than those of corresponding tertiary amines (i.e., **5b** and **5c**). Therefore, it is of interest to examine how secondary amine analogues of 3-PMA with larger cyclic substituent influence the affinity. Also, because (*R*)-5-(2-azetidinylmethoxy)-2-chloropyridine (ABT-594, **6**) has potent antinociceptive properties in different animal models and demonstrates superior selectivity for neuronal nAChRs,[9] we are interested in exploring whether these properties could remain if the 'O' and 'NH' in the molecule are exchanged. Meantime, we hope to determine the difference between 3-pyridylmethylamines (3-PMA) and 2-pyridylmethylamines (2-PMA) for the affinity, because only a few papers reported the influence of the positional isomeric chain-extended analogues of nicotine (**1**) on affinity.[8c]

On the basis of the above ideas, 3-pyridylmethylamines **7** and 2-pyridylmethylamines **8** with a highly sterically hindered secondary amino group, as well as the chain extended 3-pyridylamine oxacycle analogs **9a–c** of ABT-594, were synthesized and evaluated for their in vivo analgesic activity. The results are reported in this paper.

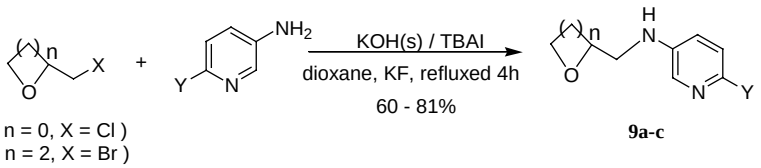
As shown in Scheme 1, the reduction of 6-chloronicotinic acid with $LiAlH_4$ gave 6-chloro-3-pyridylmethanol,[10] subsequent PCC oxidation affording the key intermediate 6-chloro-3-pyridylaldehyde **10**. The compounds **7a–f** and **8a–c** were obtained by the reductive amination of 6-chloro-3-pyridylaldehyde, 3-pyridylaldehyde or 2-pyridylaldehyde with the corresponding primary amines **11** and sodium cyanoborohydride.

The synthesis of compounds **9a–c** is outlined in Scheme 2. The N-alkylation of 3-pyridylamine or 6-chloro-3-pyridylamine with epichlorohydrin (**12a**) or tetrahydrofurfurylmethyl bromide (**12b**) was performed under solid–liquid-phase transfer catalysis conditions in 60–81% yields. The TBAI was used as catalyst, dioxane as solvent, KOH as base, and KF as activating agent.

All newly synthesized compounds **7a–f**, **8a–c**, and **9a–c** were evaluated for their in vivo analgesic activity and



Scheme 1. Synthesis of secondary amine analogues of pyridylmethylamine **7a–f** and **8a–c**.



Scheme 2. Synthesis of compounds **9a**–**c**.

Table 1. The biological activities of compounds **7a**–**f**, **8a**–**c**, and **9a**–**c**

Compound	Dose (mg/kg sc)	Inhibitory rate[a] (%)[b]	Rate of death (%)
Nicotine	20	—	100
	10	100	50
	5	88	25
7a	20	61	0
	10	0	0
7b	20	50	0
	10	0	0
7c	20	56	0
	10	23	0
7d	20	66	0
	10	37	0
7e	20	46	0
	10	41	0
7f	20	35	0
8a	20	0	0
8b	20	0	0
8c	20	0	0
9a	20	0	0
9b	20	20.5	0
9c	20	0	0

[a] Acetic acid writhing test was used on mice.

[b] % inhibition = 100 − (A/B × 100), where A = incidence of writhing in the treated group; and B = incidence of writhing in the control group, occurring from the 5th to 10th min after administration of the noxious agents.

toxicity according to our reported method.[11] The results are summarized in Table 1.

As shown in Table 1, all the 3-pyridylmethylamine ring-opened nicotine analogues **7a**–**f** displayed significantly analgesic activity, especially the compounds **7a** and **7d** showing a remarkable potency and efficacy. This result demonstrates that higher sterically substituted secondary amine derivatives of 3-pyridylmethylamine are favorable to increase the analgesic activities. Comparing the biological results of compounds **7a**–**c** with those of **7d**–**f**, there is no obvious difference. Therefore, the introduction of 6-chloro at pyridyl ring has little impact on analgesic activity.

The compounds **8a**–**c**, the corresponding positional isomers of **7a**–**c**, completely lost the analgesic activity. It indicates that the substituted position of aminomethyl group in this kind of compounds is one of critical factors influencing analgesic activity.

Among the positional isomeric analogues of ABT-594 (**9a**–**c**), only compound **9b** shows weak analgesic activity (23% analgesic activity at a dose of 20 mg/kg), and compounds **9a** and **9c** are devoid of any analgesic activity. So it is very important to keep the suitable distance between two nitrogens in the molecular.

The results of the present investigation also confirmed that all tested compounds showed toxicity lower than that of nicotine. Just as, the rats died in 100% at dose of 20 mg/kg of nicotine; however, no dead rat was found at the same dose of tested compound.

In summary, a series of novel ring-opened secondary pyridylmethylamine analogues of nicotine and positional isomeric analogues of ABT-594 have been prepared. The highly sterically hindered secondary amine analogues (**7a**–**f**) of 3-pyridylmethylamine show potent analgesic activity and lower toxicity, especially the compounds **7a** and **7d**. The further structure–activity relationship studies of this class of compounds might offer the opportunity for the discovery of analgesics with more potent activity and lower toxicity.

Acknowledgments

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