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Unique Spirocyclopiperazinium Salt I: Synthesis and Structure–Activity Relationship of Spirocyclopiperazinium Salts as Analgesics

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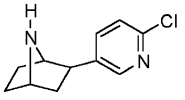
Abstract—Based on the structure of compound **3**, two series of spirocyclopiperazinium derivatives **7a**–**n** and **10a**–**h** were synthesized and evaluated for their in vivo analgesic and sedative activities. Compounds **7f** and **10c** were discovered to exhibit excellent analgesic activity. Structure–activity relationships revealed that anion of the quaternary salt affected the analgesic and sedative activity significantly; the allyl group is a most effective group among the compounds **7a**–**n**; the electron-released substitute on the aromatic ring is favorable to increase the analgesic activity.

Introduction

The discovery of high efficient analgesics without the side effects of drug dependency is highly desirable in pain management. In this respect, it has been suggested that selective neuronal nicotinic acetylcholine receptor (nAChR) agonists may be useful. Nicotine itself has long been known to have antinociceptive properties, but a variety of side effects make it a poor therapeutic choice.[1–4] The discovery of epibatidine[5–7] (**1**), a potent analgesic and nAChR modulator, brought about a renewed interest for compounds acting through nAChRs. N^1, N^1-dimethyl-N^4-phenylpiperazinium iodide (DMPP, 2) is a well-known nicotinic agonist[8–10] that does not fit any proposed pharmacophore for nicotinic binding. This quaternary salt does not cross the blood–brain barrier (BBB) as required for the drugs useful to treat neurodegenerative diseases; however, it presents a $K_i = 250$ nM as a nicotinic receptor of the rat brain labeled by [^{3}H]-cytisine (thought to be represented mainly by the $\alpha_4\beta_2$ subtype).[11] Therefore, it represents a unique ligand among the hundreds of nicotinic agonists studied in the past decades. Recently, more attention has been directed to the systematic modulation of the chemical structure and the pharmacokinetic properties of DMPP.[12–15]

During our study on the synthesis and biological activity of quaternary piperazinium salts,[16,17] compound **3**, whose structure is similar to the DMPP, was found to show significant analgesic activity. In an effort to explore the structure–activity relationships of this kind of compounds and look for the more potential analgesic compounds with low toxicity, a series of spirocyclopiperazinium derivatives **7a**–**n** and **10a**–**h** were prepared. Herein, we report their synthesis and in vivo analgesic and sedative activity.



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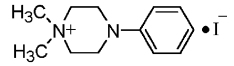

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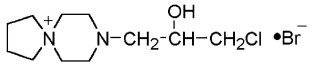

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Chemistry

The synthetic route of compounds **7a**–**n** was outlined in Scheme 1. The piperazine was reacted with benzoyl chloride in the presence of sodium acetate to give the intermediate 1-benzoyl piperazine **4**.[18] Reaction of **4** with various alkyl halides provided the corresponding 1-benzoyl-4-alkylpiperazine **5**. Compound **5** was deprotected by 10% hydrochloric acid, and then neutralized

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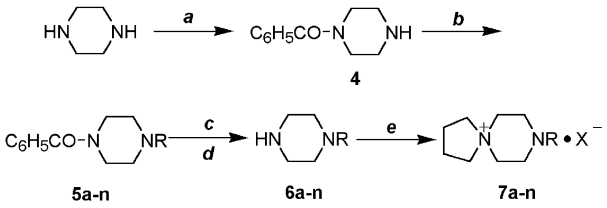
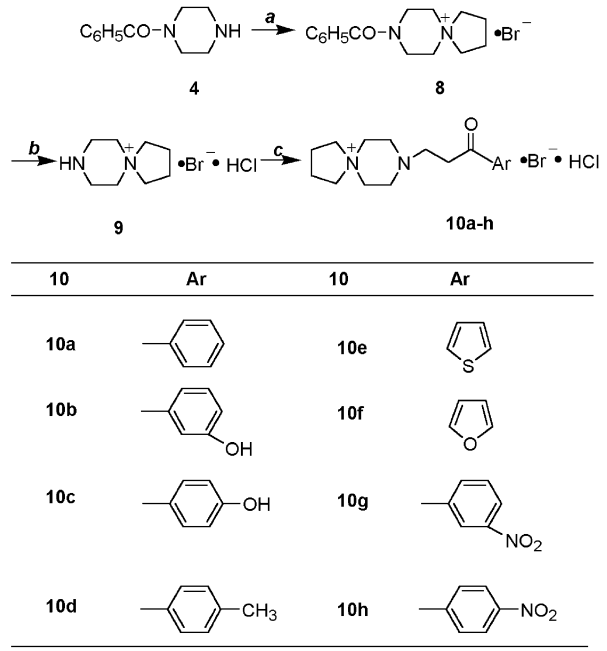


5,6,7	R	5,6,7	R
a	$CH_2CHOHCH_2Cl$	h	$(CH_2)_3$–N(CO)$_2$
b	CH_2CH_3	i	$CH_2CH{=}CHC_6H_5$
c	$CH_2C(CH_3){=}CH_2$	j	$CH_2CH{=}CHC_6H_4$-Cl–o
d	CH_2CH_2OH	k	$CH_2CH{=}CHC_6H_4$-Cl–m
e	$(CH_2)_4OC_6H_5$	l	$CH_2CH{=}CHC_6H_4$-Cl–p
f	$CH_2CH{=}CH_2$	m	$CH_2CH{=}CHC_6H_4NO_2$–m
g	CH_2CH_2CH(O)$_2$	n	$CH_2CH{=}CHC_6H_4NO_2$–p

Scheme 1. Synthesis of compounds **7a–n**. Reagents and conditions: (a) C_6H_5COCl, AcOH; (b) RX, $NaHCO_3$, EtOH; (c) 10% HCl, reflux; (d) NaOH; (e) $Cl(CH_2)_4Cl$(**7a**) or Br $(CH_2)_4Br$(**7b–n**), $NaHCO_3$, EtOH, reflux.

with NaOH aqueous solution gave the 1-alkyl piperazine **6**. The intermediate **6** was reacted with 1,4-dihalorobutane in the presence of sodium bicarbonate to yield target compounds **7a–n**.

As shown in Scheme 2, the reaction of benzoyl piperazine **4** with 1,4-dibromobutane gave 8-benzoyl-5,8-diaza-spiro[4.5] decane **8**. Deprotection of **8**, followed by neutralization,to afford the key intermediate **9**. The compounds **10a–h** were prepared from the Mannich reactions of **9** with formaldehyde and various acetophenones.



10	Ar	10	Ar
10a	Ph	10e	2-thienyl
10b	4-OH-Ph	10f	2-furyl
10c	2-OH-Ph	10g	3-NO_2-Ph
10d	4-CH_3-Ph	10h	4-NO_2-Ph

Scheme 2. Synthesis of compounds **10a–h**. Reagents and conditions: (a) $Br(CH_2)_4Br$, $NaHCO_3$, EtOH; (b) 10% HCl, reflux; (c) HCHO, MeCOAr, MeOH, reflux.

Table 1. The biological activities of compounds **7a–n**

Compd	Dose (mg/kg sc)	Analgesic activity[a] (%)[c]	Sedative activity[a] (%)[b]
3	20	64	57
7a	20	0	0
7b	20	0	0
7c	20	0	0
7d	20	10	0
7e	20	9	4
7f	20	100	0
	10	45	0
7g	20	36	25
7h	20	20	10
7i	20	0	33
7j	20	27	59
7k	20	42	51
7l	20	19	12
7m	20	32	12
7n	20	24	10

[a]Acetic acid writhing test was used on mice.
[b]% Inhibition = 100−(A/B×100), where A = spontaneous locomotion times in the treated group and B = spontaneous locomotion times in the control group.
[c]% 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.

Pharmacology

The in vivo analgesic and sedative activities of compounds **7a–n** and **10a–h,** summarized in Tables 1 and 2 respectively, were evaluated according to our reported method.[19]

Results and Discussion

Based on the Verma's report[20] that the anion of quaternary ammonium influenced the neuromuscular block activity obviously, we firstly wanted to explore whether it

Table 2. The biological activities of compounds **10a–h**

Compd	Dose (mg/kg sc)	Analgesic activity[a] (%)[c]	Sedative activity[a] (%)[b]
10a	20	25	11
10b	20	14	13
10c	20	100	85
	10	77	—
10d	20	25	14
10e	20	12	3
10f	20	15	0
10g	20	59	0
10h	20	12	35

[a,b,c]See footnotes in Table 1.

was also important for the analgesic activity. Therefore, compound **7a** (X = Cl) was synthesized to compare with compound **3** (X = Br). Comparing the biological results of compounds **3** and **7a**, the former showed better analgesic activity (64%) and sedative activity (57%) at the dose of 20 mg/kg, however, the compound **7a** did not show any activity at the same dose. Thus, it was revealed that the anion of quaternary ammonium also influenced the analgesic activity distinctively.

With the above result in mind, we selected compound **3** as the lead compound and synthesized its derivatives **7b–n** and **10a–h** to further study on the structure–activity relationship.

As seen from the Table 1, compound **7f** (R = allyl, X = Br) was the most potent analgesic, which not only possessed the analgesic activity of 100% and 45% at the dose of 20 and 10 mg/kg, respectively, but also showed no sedative activity at the same dose. However, the other compounds, no matter the allyl group in compound **7f** was replaced by saturated alkyls (**7b–d**, **7g–h**) or substituted cinnamyls (**7i–n**), showed weak or inactivity. These data demonstrated that the allyl group was a very effective group for the analgesic activity.

The data reported in Table 2 indicated that all the compounds (**10a–h**) showed the definite analgesic and/or sedative activity and, the best one was the compound **10c**. Comparing the 4-substituted derivatives **10a**, **10c–d**, and **10h**, it was found that the biological activity was affected by the property of substitute on the aromatic ring. The electron-releasing substitute is favorable to increases the analgesic activity (**10c**) and the electron-attracting substitute decreases the analgesic activity (**10h**). The position of the substitution on the aromatic ring also affected on the analgesic activity, however, it was no regular. For example, the 4-OH substituted compound **10c** exhibited higher analgesic activity (100%) than 3-OH substituted compound **10b** (14%); on the contrary, the 4-NO_2 substituted compound **10h** (12%) exhibited lower analgesic activity than 3-NO_2 substituted compound **10g** (59%).

In summary, two series of three analogues **7a–n** and **10a–h** were synthesized and evaluated for their in vivo analgesic and sedative activity. Compounds **7f** and **10c** were showed excellent analgesic activity. Some useful structure–activity relationships were revealed.

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