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Unique Spirocyclopiperazinium Salt. Part 2: Synthesis and Structure–Activity Relationship of Dispirocyclopiperazinium Salts as Analgesics

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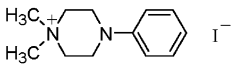
Abstract—Three series of spirocyclopiperazinium derivatives **5a–d**, **6a–f** and **17a–d** were synthesized and evaluated for their in vivo analgesic activities. Compounds **5a**, **17a** and **17b** exhibited excellent analgesic activity. Two important structure–activity relationships were observed from this study: (1) the quaternary ammonium functionality is a critical pharmacophore for analgesic activity; (2) it is important to adjust the lipophilic property of compounds to improve analgesic activity.

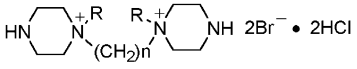
Introduction

N^1,N^1-Dimethyl-N^4-phenylpiperazinium iodide (DMPP, **1**) is a well-known nicotinic agonist[1–3] that does not fit any proposed pharmacophore for nicotinic binding. This quaternary salt does not cross the blood–brain barrier (BBB) as required for drugs useful to treat neurodegenerative diseases, however, it present 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).[4] 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[5,6] and the pharmacokinetic properties[7,8] of DMPP.

In the previous papers, we reported several classes of piperazinium salts with significant analgesic activity (**2–4**),[9–12] and their structures are similar to that of DMPP. As an extension of our research, herein, we report the synthesis of two series of new dispirocyclopiperazinium salts **5a–d** and **6a–f**. According to the analgesic activity of compounds **5a–d** and **6a–f**, compound **5a** was selected as lead compound. Compounds **17a–d**, a series of **5a** derivatives, were further designed and prepared to improve the ability across the blood–brain barrier.

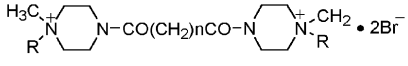


1



R=alkyl,phenzyl
n=2, 4, 6, 8, 10

2



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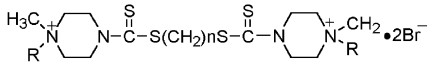

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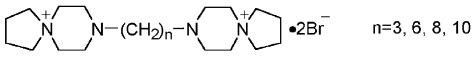
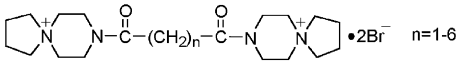


n=3, 6, 8, 10

5



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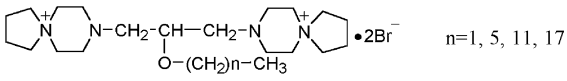
6



n=1, 5, 11, 17

17

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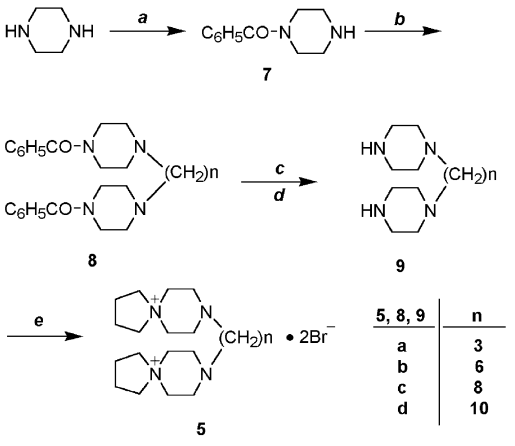
Chemistry

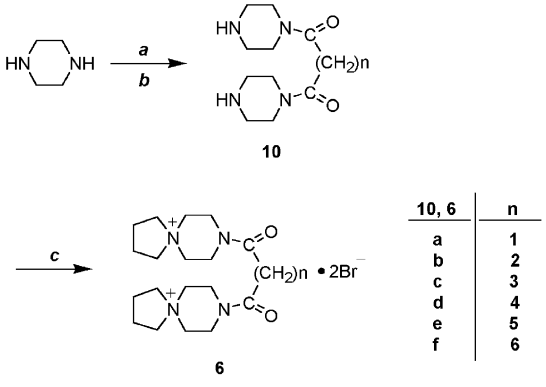
Compounds **5a–d** were synthesized as outlined in Scheme 1. The reaction of two equivalents of 1-benzoyl piperazine **7**[13] with one equivalent of the corresponding α,ω-dibromoalkanes in the presence of sodium bicarbonate provided the key intermediates **8a–d**. Deprotection of **8** in 10% hydrochloric acid, followed by neutralization with aqueous sodium hydroxide gave the α,ω-di(1-piperazyl)alkanes **9a–d**. One equivalent of **9a–d** was reacted with two equivalents of 1,4-dibromobutane to yield the corresponding spirocyclopiperazinium bromides **5a–d**.

The synthesis of compounds **6a–f** was outlined in Scheme 2. The key intermediates **10a–f** were obtained by the reaction of piperazine with α,ω-diacyl chlorides at room temperature in good yields. It is crucial to scrupulously control the pH = 4–5 in the reaction system. Final compounds **6a–f** were synthesized from intermediates **10a–f** utilizing the similar procedure as described above for the preparation of **5a–d**.

The compounds **17a–d** was prepared as illustrated in Scheme 3. The glycerol was treated with phenyl aldehyde to give the 1,3-dihydroxyl protected glycerol **11**.[14]



Scheme 1. Synthesis of compounds **5a–d**. Reagents and conditions: (a) C_6H_5COCl, AcOH; (b) $Br(CH_2)_nBr$(1 equiv), $KHCO_3$, EtOH; (c) 10% HCl; (d) NaOH; (e) $Br(CH_2)_4Br$(2 equiv), $NaHCO_3$, EtOH, reflux.

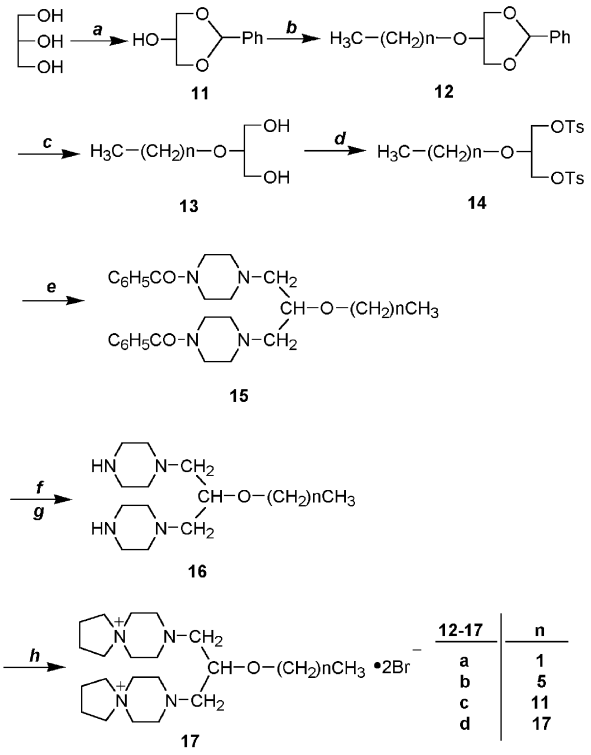


Scheme 2. Synthesis of compounds **6a–f**: (a) HCl, PH = 4.5, rt; (b) $ClCO(CH_2)_nCOCl$, 10% ag NaOH, rt; (c) $Br(CH_2)_4Br$, $NaHCO_3$, EtOH, reflux.

Reaction of **11** with R-X under basic condition provided the corresponding compounds **12a–d**.[15] Compounds **12a–d** were deprotected and then reacted with TsCl to afford the key intermediates **14a–d**.[16,17] The preparation of **17a–d** from **14a–d** was also similar to the preparation of **5a–d**.

Pharmacology

All newly synthesized compounds **5a–d**, **6a–f** and **17a–d** were tested for their in vivo analgesic and/or sedative activity utilizing our reported method.[11] The results were summarized in Tables 1–3. In order to further prove the potency of quaternary ammonium cation for



Scheme 3. Synthesis of compounds **17a–d**. Reagents and conditions: (a) C_6H_5CHO, H_2SO_4; (b) $CH_3(CH_2)nCl$, NaH; (c) $HOAc/H_2O$; (d) TsCl; (e) 1-benzoyl piperazine; (f) 10% HCl; (g) NaOH; (h) $Br(CH_2)_4Br$ (2 equiv), $NaHCO_3$, EtOH, reflux.

Table 1. The biological activities of compounds **5a–d**

Compd	*n*	Dose (mg/kg sc)	Sedative activity[a] (%)[b]	Analgesic activity[a] (%)[c]
5a	3	10	4.7	96.0
		5	0	45.5
5b	6	2	72.4	56.6
5c	8	2	98.6	0
5d	10	2	84.6	0

[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.

Table 2. The biological activities of compounds **6a–f**

Compd	*n*	Dose (mg/kg sc)	Sedative activity[a] (%)[b]	Analgesic activity[a] (%)[c]	Death dose (mg/kg sc)
6a	1	2	0	0	40
6b	2	2	47.7	0	20
6c	3	2	67.4	0	20
6d	4	0.2	8.1	70.4	2
6e	5	0.02	0	0	0.2
6f	6	0.02	27.5	0	0.2

[a,b,c]As defined in Table 1.

Table 3. The biological activities of compounds **17a–d**

Compd	*n*	Dose (mg/kg sc)	Analgesic activity[a] (%)[c]
17a	1	20	90
		10	46
		5	34
17b	5	20	100
		10	91
		5	61
		2.5	49
17c	11	20	18
17d	17	20	24

[a,c]As defined in Table 1.

analgesic activity, compound **10d**, the hexanedioyl bi(4-methyl-1-piperazine) dihydrochloride **18** and the hexanedioyl bi(4,4-dimethyl-1-piperazine) dibromide **19** were also tested for their analgesic activity (Table 4).

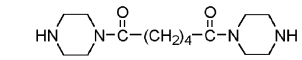
Results and Discussion

Most of the compounds tested displayed definite analgesic or sedative activity. The results reported in Table 1 clearly show that the distance between two spirocyclopiperaziniums obviously affected the biological activities. The analgesic activity increases as *n* decreases, and the sedative activity increases as *n* increases. Thus, analgesic activity and sedative activity of compound **5a** ($n=3$) is 96 and 4.7% separately at the dose of 10 mg/kg sc. On the contrary, compound **5c** ($n=8$) exhibited high sedative activity (98.6%) and no analgesic activity at the dose of 0.2 mg/kg sc.

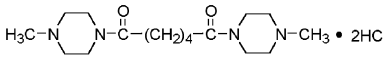
When two spirocyclopiperazinium cations were linked with α,ω-diacyl in a series of compounds **6**, only compound **6d** ($n=4$) was found to show significant analgesic activity (70.4%, dose 0.2 mg/kg), and the others did not show analgesic activity and various sedative activity (Table 2). The death doses of derivatives **6a–f** were also tested. It is apparent from the results that the toxicity was raised with the increase of *n*.

Compared with the analgesic activity of compounds **5a–d** and **6a–f**, compound **5a** is the most potent lead. In order to improve the ability to across the blood–brain barrier (BBB), a new class of **5a** analogue, **17a–d**, in which a different length of carbon chain was introduced into compound **5a** through an ether bond, was designed and synthesized. The data of analgesic activity were listed in Table 3.

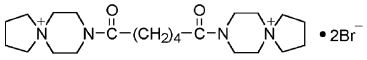
Table 4. The biological activities of compounds **10d**, **18**, **19** and **6d**



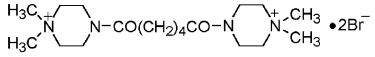
10d



18



6d



19

Compd	Dose (mg/kg sc)	Analgesic activity[a] (%)[c]
6d	0.2	70.4
18	10	10.9
10d	5	34.5
19	0.05	60.1

[a,c]As defined in Table 1.

As shown in Table 3, the introduction of suitable lipophilic group was favorable to improve the analgesic activity. Thus, compounds **17a** and **17b** exhibited good analgesic activity and dose–effect relationship, however, the analgesic activity of compounds **17c** and **17d** was very weak.

It could be found from Table 4 that the secondary amine hydrochloride **10d** and tertiary amine hydrochloride **18** only exhibited weak analgesic activity; however, the quaternary ammoniums **19** and **6d** showed higher activity. This result demonstrates that the quaternary ammonium functionality is a critical pharmacophore for the analgesics.

In summary, three series of dispirocyclopiperazinium salts synthesized in this study showed analgesic and/or sedative effects, especially, compounds **5a**, **17a** and **17b** which processed excellent analgesic activity. Two important structure–activity relationships were observed from this study: (1) the quaternary ammonium functionality is a critical pharmacophore for the analgesics; (2) it is important to adjust the lipophilic properties of compounds for the improvement of analgesic activity.

Acknowledgements

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