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Synthesis and local anesthetic activity of fluoro-substituted imipramine and its analogues

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Abstract—A series of fluoro-substituted imipramines and its analogues, **6a**–**6e**, were synthesized and evaluated for their in vitro local anesthetic activity. Compound **6b** was found to have potency, onset, and duration of action comparable to those of lidocaine (lidocaine hydrochloride, CAS:6108-05-0). Dissociation constants (pK_a) of these compounds have been determined to be 7.6–7.9.

Local anesthetics interrupt conduction of neural messages in sensory, motor, and autonomic nerves. They prevent both the generation and conduction of the nerve impulse in a circumscribed area by binding to the sodium channel and blocking sodium entry into neuron.

Tri-cyclic antidepressants (TCAs) have been widely used in treating major depressive disorders. Recent studies further demonstrated that TCAs have potent sodium channel blocking effect.[1–6] For example, imipramine at 5 mM elicited a longer complete sciatic nerve blockade than that of bupivacaine at 15.4 mM (0.5%).[7] About 50 new substituted local anesthetics where the benzene ring is substituted by fluorine in the *o*-, *m*-, and *p*-positions were synthesized in our previous work. Some of these compounds exhibited infiltration and surface local anesthetic actions, and the potency was higher than that of lidocaine. When fluorine is at position 1 of the phenyl ring, amitriptyline exhibits substantially increased antidepressant activity and significantly decreased anticholinergic toxicity.[8] So far, there were no reports about the change of the sodium channel blocking effect of fluorine substituted amitriptyline. The biological properties of fluoro-TCAs raised our interest to focus on their derivations as potential long-acting local anesthetics.

Five fluoro-substituted imipramines and its analogues which were mainly modified at positions 3 and 7 with two fluorines on phenyl ring and different substitutions on the amines were designed and synthesized. Their in vitro local anesthetic activity was evaluated by sciatic nerve block.

The target compounds **6a**–**6e** were prepared as shown in Scheme 1.

4-Fluoro-2-nitro-toluene was condensed with each other in the presence of sodium methoxide in petroleum ether at 5–15 °C to give the 4,4′-difluoro-dinitrodibenzyl (**2**) in a yield of 72%. It was reduced to give compound **3** in ethanol at 60 °C by Fe powder as reductive agent under acidic condition in a yield of 76%. The compound **3** was condensed at 290 °C for 1 h to obtain compound **4** in a yield of 5%. Other resultants were removed by trituration of the reaction mixture between petroleum ether and water. Treatment of **4** with $NaNH_2$ in refluxing toluene, followed by the addition of *N*,*N*-dimethyl-3-chloride propylamine with further refluxing, gave compound **5** in a yield of 67%. An excess of reactant was removed using column chromatography on silica gel. Compound **5** was dissolved in anhydrous ether and dried gas of hydrogen chloride was added at rt for 5 min, **5** was transformed into **6a**.[9] Compounds **6b**–**6e**[10] were prepared by following the same procedure as shown in Scheme 1.

3,7-Difluoro-10,11-dihydro-5H-dibenz[b,f]azepine (compound **4**) was the key intermediate. The parent 10,11-dihydro-5H-dibenz[b,f]azepine was first synthesized in

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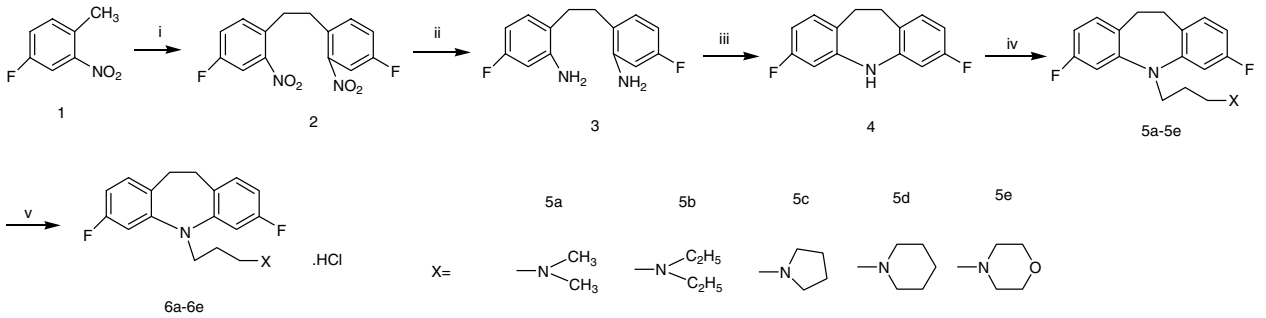

Scheme 1. Synthesis procedure for compounds **5a**–**5e**. Reagents and conditions: (i) CH_3ONa, 5–15 °C, 4–5 h; (ii) Fe/HCl, 60–70 °C, 3 h; (iii) 290 °C, 1 h; (iv) $NaNH_2/ClCH_2CH_2CH_2NR_1R_2$, 110 °C, 12 h; (v) HCl, rt, 5 min.

1899 by Thiele and Holzinger[11] and since then many substituted 10,11-dihydro-5H-dibenz[b,f]azepines have been prepared.[12] The derivatives have been made either directly by substitution reactions on the parent unsubstituted tricycle or by ring synthesis starting from substituted synthons. Most direct substitution reactions, for example, nitration,[13] bromination[14] and Friedel-Crafts acylation,[15] are possible, but in general proceed in low yields and either give mixtures of regioisomers or limit to only one accessible position on the ring system. Ring synthesis of 10,11-dihydro-5H-dibenz[b,f]azepines has been approached in a few different ways.[16] All methods require relatively harsh conditions or inconvenient multi-steps with very low yields. We obtained compound **4** by only three steps from 4-fluoro-2-nitro-toluene through the ring synthesis method which differs from the methods mentioned above. The yield of the key step is only 5% because the great mass of reactant was carbonized at the reactive temperature. Compound **4** was dissolved in petroleum ether while the carbonizations did not, so carbonizations could be easily removed by the trituration of the reaction mixture between petroleum ether and water conveniently. A facile, flexible, and easily accessible synthetic route toward 3,7-difluoro-10,11-dihydro-5H-dibenz[b,f]azepine is still under investigation.

Dissociation constant (pK_a) is an important physicochemical parameter for local anesthetic. Most of the clinically useful local anesthetics have pK_a values of 7.5–9.0. This implies that compounds with pK_a values below 7.0 are not sufficiently ionized at physiological pH to be effective in bringing about anesthesia even though they can penetrate the axon. In contrast, drugs with pK_a values above 9.5 are almost fully ionized at physiological pH. Consequently, these drugs are less effective because they have difficulty in penetrating the cell membrane. The pK_a values of these compounds have been determined by potentiometric titration method.[17] A graph was plotted for volume of hydrochloric acid added versus pH of the solution. The dissociation constant (pK_a) values were obtained from the pH at half neutralization point of the titration curves. The pK_a of compounds **5a**–**5e** obtained from this method were 7.7, 7.7, 7.9, 7.6, and 7.6, respectively. This means compounds **5a**–**5e** have the appropriate pK_a values for use as potent Na-channel blockader.

All target compounds **6a**–**6e** were evaluated for their local anesthetic effects of sciatic nerve block in toads.[18–20] Electrophysiological experimental data were obtained on Doctor-95 Super Lab (Jingsu Medicine technological institute). All of the experiments were performed with wild adult toads (two available isolated sciatic nerves of one toad). Lidocaine (lidocaine hydrochloride, CAS: 6108-05-0) was obtained from Shanghai Xidi Biotech. Co., Ltd and was used after dissolving in Ringer's solutions. Experimental data[21] and results are summarized in Table 1.

The new compounds increased the ED_{50} (%) to the electric stimuli applied on the injected area with value ranging between 0.018 and 0.094. Under the same conditions lidocaine had an effect equal to 0.019. The analysis of the results showed that the most active compound which produced an effect versus lidocaine hydrochloride was **6b** with 105.5. Its analogues **6d**, **6e** also exhibited significant efficacy with 48.7 and 65.5, respectively. Compounds **6a** and **6c** (20.2, 27.5) were less effective than lidocaine. The latent period of these compounds was 30.7–40.6 min, which were very close to that of lidocaine (37.2 min) at the same test conditions.

Structurally, the most active compound was characterized by the presence of the diethyl amine group on the side chain. The least active compound **6a** had 20.2 of the lidocaine action, which possesses the dimethyl amine group. The side chain of compounds **6c**, **6d**, and **6e** was tetrahydropyrrolyl, piperidino, and morpholine group, respectively.

To summarize, a series of fluoro-substituted imipramines and its analogues, **6a**–**6e**, were synthesized and eval-

Table 1. Sciatic nerve block activities of compounds **6a**–**6e**

Compound	ED_{50} (%)	Latent period (min)	Effect versus lidocaine 0.019 = 100
6a	0.094	30.7	20.2
6b	0.018	38.2	105.5
6c	0.069	40.6	27.5
6d	0.039	39.8	48.7
6e	0.029	37.3	65.5
Lidocaine	0.019	37.2	100

uated for their in vitro local anesthetic activity. The compounds **6a**–**6e** were obtained starting from 4-fluoro-2-nitro-toluene. The in vitro local anesthetic activity was evaluated by sciatic nerve block. Dissociation constants (pK_a) of these compounds have been determined to be 7.6–7.9. These compounds have different degrees of local anesthetic action. Compound **6b** was found to have potency, onset, and duration of action comparable to those of lidocaine. The new compound **6b** may deserve further evaluation as potential local anesthetic.

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9. Compound **6a**: (CD_3OD) δ 2.02 (2H, m, 2-CH_2), 2.82 (6H, s, 1′-NCH_3), 3.18 (4H, m, $ArCH_2$–), 3.32 (2H, m, 3-CH_2N), 3.82 (2H, t, J = 7 Hz, 1-NCH_2), 6.72 (2H, m, ArH), 6.94 (2H, m, ArH), 7.13 (2H, m, ArH).
10. Compound **6b**: (CD_3OD) δ 1.22 (6H, t, J = 6.5 Hz, 2′-CH_3), 2.03 (2H, m, 2-CH_2), 3.14 (4H, m, 1′-NCH_2), 3.18 (4H, m, $ArCH_2$–), 3.32 (2H, m, 3-CH_2N), 3.88 (2H, t, J = 6.5 Hz, 1-NCH_2), 6.76 (2H, m, ArH), 6.99 (2H, m, ArH), 7.18 (2H, m, ArH). Compound **6c**: (CD_3OD) δ 2.02 (2H, m, 2-CH_2), 2.06 (2H, m, 2′-CH_2), 2.15 (2H, m, 3′-CH_2), 3.16 (2H, m, 4′-CH_2N), 3.28 (4H, m, $ArCH_2$–), 3.35 (2H, m, 3-CH_2N), 3.36 (2H, m, 1′-NCH_2), 3.86 (2H, t, J = 7 Hz, 1-NCH_2), 6.76 (2H, m, ArH), 6.97 (2H, m, ArH), 7.16 (2H, m, ArH). Compound **6d**: (CD_3OD) δ 1.22 (2H, m, 3′-CH_2), 1.77 (2H, m, 2′-CH_2), 1.91 (2H, m, 4′-CH_2), 2.07 (2H, m, 2-CH_2), 2.90 (2H, m, 5′-CH_2N), 3.10 (2H, m, 1′-CH_2N), 3.18 (4H, m, $ArCH_2$–), 3.35 (2H, m, 3-CH_2N), 3.86 (2H, t, J = 7 Hz, 1-NCH_2), 6.76 (2H, m, ArH), 6.97 (2H, m, ArH), 7.16 (2H, m, ArH). Compound **6e**: (CD_3OD) δ 2.00 (2H, m, 2-CH_2), 3.05 (6H, m, 3-CH_2N, 1′-NCH_2, 5′-CH_2N), 3.18 (4H, m, $ArCH_2$), 3.65 (2H, m, 2′-CH_2O–), 3.80 (2H, t, J = 7 Hz, 1-NCH_2), 3.97 (2H, m, 4′-CH_2O–), 6.70 (2H, m, ArH), 6.90 (2H, m, ArH), 7.10 (2H, m, ArH).
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