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SYNTHESIS AND IN VITRO GASTROINTESTINAL MOTILITY ENHANCING ACTIVITY OF 3-ARYL-2-IMIDAZOLIDINYLIDENE PROPANEDINITRILE DERIVATIVES

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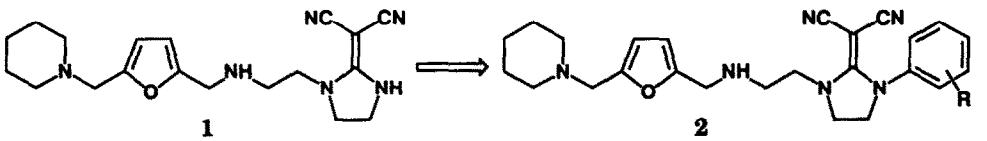
Abstract: Novel *N*-3-arylated imidazolidinylidene propanedinitrile derivatives **2a–f** were prepared by a new intramolecular cyclization method and their AChE inhibitory activity and in vitro gastrointestinal motility enhancing activity were evaluated. All compounds except **2f** were found to be potent in both activities.

Introduction: It is well known that disturbance of gastrointestinal motility is associated with many symptoms of digestive disease, such as gastric stasis, vomiting, abdominal pain, paralytic ileus, and constipation. Many gastrointestinal motility enhancing agents have been used to treat these symptoms.[1] Recently, it has been reported that ranitidine, a histamine H_2-receptor antagonist, enhances antroduodenal motility in man.[2] Conversely, we reported that a novel ranitidine derivative **1** (fumarate: KW-5092) showed a potent gastrointestinal motility enhancing activity mainly by inhibition of acetylcholinesterase (AChE).[3] During further modification of **1**, we became very interested in *N*-3 arylated compounds because an exchange of 2-nitro-1,1-ethenediamine moiety in ranitidine for phenyl groups led to remarkable increase in AChE inhibitory activity.[4] In this paper, the synthesis of novel 3-aryl-2-imidazolidinylidene propanedinitrile derivatives **2** and their enhancing activities of gastrointestinal motility are described.



1 **2**

Chemistry: A crucial step in the synthesis of **2** involves the introduction of phenyl groups to the nitrogen in the 3-position of imidazolidinylidene propanedinitrile moiety. We examined the intramolecular cyclization of a model compound **4**, which was readily prepared from ketenedithioacetal **3** (Scheme I). Reaction of **4** with methanesulfonyl chloride in pyridine,

followed by treatment with DBU in THF at 0 °C afforded the desired *N*-benzyl-2-imidazolidinylidene propanedinitrile **5** in good yield (80% from **4**).[5] In this cyclization reaction, the aziridine derivative was not detected.

On the basis of these results, target compounds **2a–f** were synthesized as depicted in Scheme II.[6] The intramolecular cyclization reaction of the alcohols **7** also proceeded to give **8** in excellent yield (80–90%). Introduction of a chloroethyl moiety to **8** with 1-bromo-2-chloroethane in the presence of NaH, followed by reaction with NaN_3 in DMF afforded the azides **10**. After reduction of the azide group, a reductive alkylation of the resulting amines **11** with furfural **13** yielded the target compounds **2a–f**.[7]

Pharmacological Results and Discussion: The compounds synthesized were evaluated for AChE inhibitory activity and in vitro gastrointestinal motility enhancing activity. The AChE (from rat brain) inhibitory activity was measured at 25 °C and pH 8.0 by the photometric method of Ellman et al.[8] using acetylthiocholine (ATCh) as a substrate. The inhibitory activity was expressed as IC_{50} value. The in vitro gastrointestinal motility enhancing activity was determined by the potentiating action on electrically evoked contractions of the isolated guinea pig ileum.[3] The results were represented by EC_{30} that was the concentration of the tested compounds producing a 30% potentiation of the contractions induced by electrical stimulation. These results are summarized in Table I.

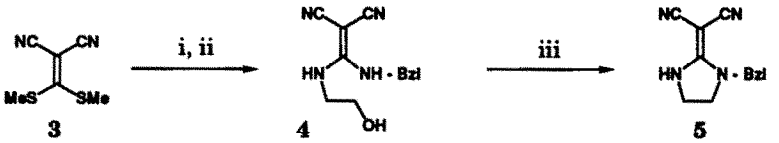
Introduction of a benzene ring to the *N*-3 position of the imidazolidinylidene propanedinitrile moiety (giving **2a**) enhanced AChE inhibitory activity and the potentiating effect on electrically induced contractions in comparison with the parent compound **1**. Substitution of methyl or methoxy groups at *para* or *meta* positions on the benzene ring had no significant effect on the activities, whereas compound **2f** possessing an *o*-methoxy group showed decrease in both assays. This suggests that substituents at the *ortho* position of the benzene ring were not tolerated sterically.

In conclusion, novel *N*-3 arylated imidazolidinylidene propanedinitrile derivatives **2a–f**, that were synthesized by a newly established cyclization method, showed potent AChE inhibitory activity and potentiating activity of electrically evoked contractions. Synthesis and investigation of biological activity of further series of *N*-3 substituted imidazolidinylidene propanedinitrile derivatives are now in progress.

Typical Procedure of Intramolecular Cyclization

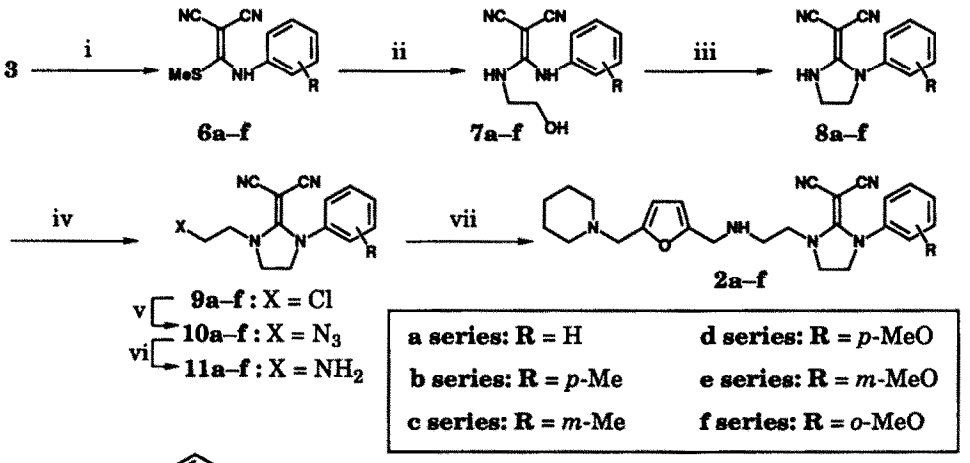
To a stirred solution of **7b** (R = *p*-MeO; 3.39 g, 14 mmol) in anhydrous pyridine (25 mL) was added dropwise methanesulfonyl chloride (2.2 mL, 28.4 mmol) under ice-cooling. After the reaction mixture was stirred for 1 h, the solvent was evaporated. The resulting residue was dissolved in THF (25 mL) and the solution was cooled in an ice-bath. DBU (2.3 mL, 15.4 mmol) was added dropwise to the cooled solution. The mixture was stirred at 4 °C for 1 h, and then the solvent was evaporated to dryness. The resulting residue was dissolved in CH_2Cl_2 and washed with diluted HCl, saturated aqueous $NaHCO_3$ solution and brine. The

Scheme I



(i) $BzlNH_2$, $CHCl_3$; (ii) $HO(CH_2)_2NH_2$, 80 °C; (iii) CH_3SO_2Cl, pyridine, 0 °C, then DBU, THF, 0 °C

Scheme II



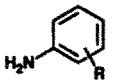
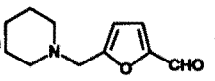
(i)  **12**, DBU, THF, reflux; (ii) $HO(CH_2)_2NH_2$, 80 °C; (iii) CH_3SO_2Cl, pyridine, 0 °C, then DBU, THF, 0 °C; (iv) $Cl(CH_2)_2Br$, NaH, DMF, 80 °C; (v) NaN_3, DMF, 70 °C; (vi) PPh_3, AcOEt / H_2O, 70 °C; (vii)  **13**, TEA, EtOH, then $NaBH_4$.

Table I. Pharmacological Data for Compounds **2a–f** and **1**

no.	R	AChE IC_{50} (nM) [a]	ES. EC_{30} (nM) [b]
2a	H	14 ± 0.7	10
b	*p*-Me	22 ± 1.2	52
c	*m*-Me	13 ± 0.7	19
d	*p*-MeO	19 ± 1.5	12
e	*m*-MeO	14 ± 1.3	14
f	*o*-MeO	66 ± 1.5	490
1		30 ± 0.3	16

[a] The IC_{50} values are means ± SE of three separate experiments done with four different concentrations. [b] Electrical stimulation; The mean concentration of three experiments producing a 30% potentiation of the electrically evoked contraction of the isolated guinea pig ileum.

organic layer was dried, and concentrated to yield a crude solid of **8b**. This was recrystallized from AcOEt–*i*-Pr_2O to give 2.74 g (87%) of **8b** as a pale yellow powder.

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References and Notes:

1. For a recent review of gastrointestinal motility enhancing agents, see: (a) Gidda, J. S.; Monkovic, I. *Annu. Rep. Med. Chem.* **1985**, *20*, 117–125. (b) King, F. D.; Sanger, G. J. *Annu. Rep. Med. Chem.* **1988**, *23*, 201–210.
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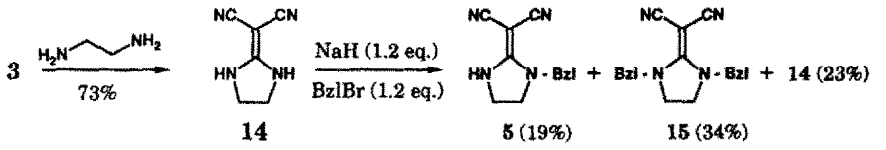
5. (a) Compound **5** has been described in "Wisterowicz, K.; Foks, H.; Strzalkowska-Grad, H.; Hac, E.; Janowiec, M.; Zwolska-Kwiek, Z. *Acta Pol. Pharm.* **1986**, *43*, 25–31; *Chem. Abstr.* **1987**, *106*, 156351h, 679."
(b) Compound **5** was prepared to elucidate its structure by the route as illustrated below. The spectroscopic data of **5** obtained by *this* method were identical with **5** by the intramolecular cyclization reaction.



(c) Selected data for **5**: mp 171.1–171.8 °C; EIMS m/z 224 (M^+); ^1H NMR ($CDCl_3$)7.26–7.43 (5H, m), 6.11 (1H, bs), 4.82 (2H, s), 3.59 (4H, s); IR (KBr) 2200, 2160 (both CN) cm^{-1}.
6. Aniline **12** possessing electron withdrawing group, such as *p*-nitroaniline, failed to react with **3** because of its poor nucleophilicity.
7. All new compounds were characterized spectroscopically.
Selected data for the **b** series (R = *p*-Me): **6b**; mp 278 °C (dec); ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 7.21 (2H, d, *J* = 8.6 Hz), 7.14 (2H, d, *J* = 8.6 Hz), 3.23 (3H, s), 2.32 (3H, s). **7b**; mp 158.1–159.7 °C; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 9.19 (1H, bs), 7.15 (2H, d, *J* = 8.6 Hz), 7.03 (2H, d, *J* = 8.6 Hz), 5.27 (1H, bs), 3.69 (2H, m), 3.41 (2H, dd, *J* = 9.6, 5.3Hz), 2.32 (3H, s). **8b**; mp 213.6–216.2 °C; ^1H NMR ($CDCl_3$) δ 7.26 (2H, d, *J* = 8.6 Hz), 7.18 (2H, d, *J* = 8.6 Hz), 6.27 (1H, bs), 4.03 (2H, m), 3.78 (2H, m), 2.38 (3H, s). **9b**; mp 151.3–151.7 °C; ^1H NMR ($CDCl_3$) δ 7.26 (2H, d, *J* = 8.6 Hz), 7.15 (2H, d, *J* = 8.6 Hz), 4.02 (2H, m), 3.95 (4H, m), 3.95 (4H, s), 3.90 (2H, m), 2.38 (3H, s). **10b**; mp 143.2–143.8 °C; ^1H NMR ($CDCl_3$) δ 7.26 (2H, d, *J* = 8.6 Hz), 7.15 (2H, d, *J* = 8.6 Hz), 3.91 (4H, m), 3.79 (4H, m), 2.38 (3H, s). **11b** mp 185.6–186 °C (0.5 fumarate/ethanol); ^1H NMR (DMSO-d_6; 0.5 fumarate) δ 7.23 (2H, d, *J* = 8.6 Hz), 7.19 (2H, d, *J* = 8.6 Hz), 6.51 (2 5 0.5H, s), 3.89 (4H, m), 3.72 (2H, t, *J* = 6.3 Hz), 3.04 (2H, t, *J* = 6.3 Hz), 2.34 (3H, s). **2b**; mp 151–152.5 °C (1.5 oxalate, 0.5 hydrate/*i*-PrOH); EIMS m/z 444 (M^+); ^1H NMR ($CDCl_3$, free base) δ 7.23 (2H, d, *J* = 8.6 Hz), 7.14 (2H, d, *J* = 8.6 Hz), 6.14 (1H, d, *J* = 3.0 Hz), 6.11 (1H, d, *J* = 3.0 Hz), 3.85 (4H, m), 3.81 (2H, s), 3.73 (2H, t, *J* = 6.3 Hz), 3.47 (2H, s), 2.98 (2H, t, *J* = 6.3 Hz), 2.39 (4H, m), 2.36 (3H, s), 1.59 (4H, m), 1.42 (2H, m); IR (KBr) 2200, 2160 (both CN) cm^{-1}.
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