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Excellent Acceleration of the Diels-Alder Reaction by Microwave Irradiation for the Synthesis of New Fluorine-Substituted Ligands of NMDA Receptor

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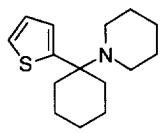
Abstract: A series of 6,11-ethanobenzo[*b*]quinolizinium derivatives was synthesized through the Diels-Alder reaction between azoniaanthracne and the corresponding 1,1-disubstituted olefin. After a systematic investigation for achieving rapid synthesis, it was found that the reaction is accelerated in polar media such as H_2O and trifluoroethanol. In particular, excellent acceleration was effected by microwave irradiation. The new fluorine-substituted ligands thus obtained exhibited potential affinity toward NMDA receptors.

The NMDA receptor is a member of ion channel-type receptors for L-glutamate, an excitatory amino acid in the mammalian central nervous system (CNS), and is characterized by activation with *N*-methyl-*D*-aspartate which increases the influx of Ca^{2+} through the ion channel of the receptor. NMDA-type glutamate receptors play a significant role in the CNS function such as synaptic transmission, learning and memory, and so on. It is now widely accepted that disorders of NMDA receptors are included in ischeameic, hypoxic, hypoglycaemic, and traumatic insults epilepsy, AIDS dementia, and Huntington's and Alzheimer's diseases; therefore, the selective inhibitors for NMDA receptors are expected to be useful for therapeutic treatment.[1)]



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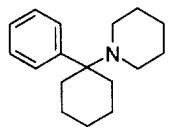

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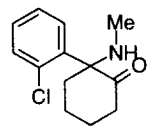

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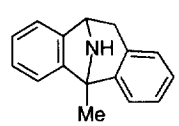

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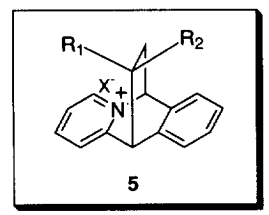

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On the other hand, radioactive ligands which have selective affinity to NMDA receptors *in vivo* will be useful for non-invasive diagnosis of such diseases as associated with disorder of NMDA receptors. TCP (**1**), PCP (**2**), ketamine (**3**), and MK801 (**4**) are representative antagonists which noncompetitively inhibit the NMDA receptor at a site within the receptor-ion channel *in vitro*, the so-called TCP site. However, studies on *in vivo* biodistribution of their radio-labeled derivatives have suggested predominant non-specific binding in the brain.[2)] Recently a new type of highly hydrophilic TCP-site ligands, 6,11-ethanobenzo[*b*]quinolizinium derivatives (**5**), was reported to be specific to the open state of the NMDA ion channel.[3)] In the course of our continuing search for NMDA receptor specific radioligands,[4)] especially those labeled with ^{18}F of short half-life ($t_{1/2}$=110 min) for use in PET (positron emmition tomography), we chose this new skeleton as a new lead structure. We wish to report here that the Diels-Alder reaction between azoniaanthracene and bis-substituted olefin leading to 6,11-ethanobenzo-[*b*]quinolizinium was highly accelerated under microwave irradiation so that the reaction may be applicable to the labeling with ^{18}F of short half-life. In addition, potential inhibitory

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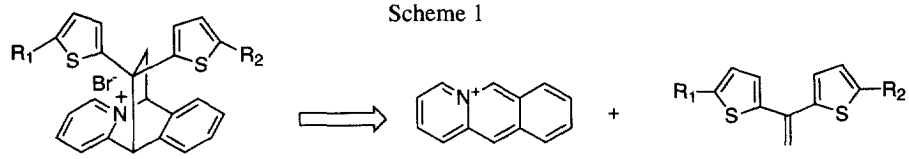
activity toward NMDA receptors of a series of the new ligands, including fluorine-substituted ones, thus obtained is also described.

Scheme 1

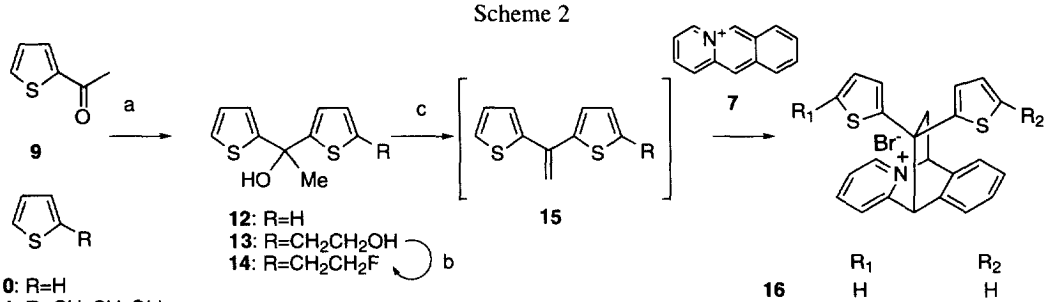


6 **7** **8**

R_1, R_2=H, CH_2CH_2F R_1, R_2=H, CH_2CH_2OH, CH_2CH_2F

We designed new fluorinated ligands **6** based on the 6,11-ethanobenzo[*b*]quinolizinium skeleton **5**. In our preliminary investigation, radio-fluorination *via* S*N*2 displacement of the mesylate (**6**; R_1 or R_2=CH_2CH_2OMs) using the complex of ^{18}FK with Kriptofix[2.2.2] was unsuccessful, probably because the ^{18}F-anion was trapped by the ammonium cation. Then, an alternative synthetic route was devised to include early fluorination of dienophile prior to the Diels-Alder reaction (Scheme 1). As the half-life of ^{18}F-radionuclide is as short as 110 minutes, synthesis time of **8** and the subsequent Diels-Alder reaction with **7** are required to complete within this period. Therefore, we first investigated rate acceleration of this D-A reaction.

Scheme 2



10: R=H
11: R=CH_2CH_2OLi

12: R=H
13: R=CH_2CH_2OH
14: R=CH_2CH_2F

15

a) **10** or **11**, *n*BuLi, THF, then **9**, 92% for **12**, 69% for **13**, b) i) TsCl, TEA, CH_2Cl_2, 76%, ii) *n*Bu_4NF, THF, 30%, c) TFE, reflux, 57-60% (**18**:**19**=1:1, **20**:**21**=1:1).

	R_1	R_2
16	H	H
17	CH_2CH_2OH	CH_2CH_2OH
18	H	CH_2CH_2F
19	CH_2CH_2F	H
20	H	CH_2CH_2OH
21	CH_2CH_2OH	H

Bisthiophene-substituted ethylene derivatives were previously obtained *via* multistep transformation including Wittig olefination to the corresponding ketone.[3] Our synthesis was started with commercially available thiophene derivatives (**9**-**11**). Thiophene **10** was lithiated with *n*-BuLi and reacted with acetylthiophene (**9**) to give the corresponding alchohol **12**. An attempt to isolate the eliminated olefin (**15**, R=H) was unsuccessful, because the bisthiophene-substituted ethylene was unstable and easily polymerized. Then, thermal elimination of **12** and *in-situ* trapping by the D-A reaction with **7** was examined. Thus, a mixture of **7** and **12** was heated in CH_3CN under reflux for 24 h to give **16** in 60% yield. It should be noted that the same reaction proceeded much faster in H_2O, and the reaction completed within 2 hours and the adduct was isolated in 76% yield.[5] We next examined further acceleration of the D-A reaction using different solvent systems or heating methods (Table 1).

When the reaction mixture was heated at 50°C, hydroxylated bisthienyl derivative **12** was insufficiently soluble to give the D-A adduct (entry 3). The reaction occurred only slowly in DMSO (entry 4), and rate

acceleration was observed in the order of CH_3CN, MeOH, 10% AcOH-MeOH, and trifluoroethanol (TFE), (entries 5-9). As almost no olefinic product **15** was detected by ^{1}H-NMR measurements of a solution of **12** after heating, D_2O at 80°C, d_6-DMSO at 80°C, or CD_3OD at 60°C, it was assumed that **12** and **15** might be in an equilibrium state in the media, and that the solvent effects might primarily work on the rate of the D-A reaction of **15**.[5] It is remarkable that microwave irradiation enhanced the reaction to a greater extent (entries 10-12).[6] Thus, the most efficient reaction took place in 10% AcOH-TFE under microwave irradiation, and some 200 times faster reaction was achieved compared to that in CH_3CN. Under the condition of microwave irradiation, almost 100 % conversion from **12** to **15** was observed in 10% AcOH-TFE after 1.5 min, but no olefin **15** was present in TFE even after 10 min. These results suggest that microwave irradiation to a TFE solution mainly effected acceleration of the D-A reaction and that to a TFE solution containing acetic acid enhanced the formation of olefin **15** as well. Eventually, we established a very efficient D-A reaction, which will be applicable to the synthesis of radio-labeled ligands with short half-life of ^{18}F-fluoride.[7]

Table 1. Comparison of the Rate of Deals-Alder Reaction Between **7** and **12**.[a]

Entry	Solvent	Condition	$t_{1/2}$ (hr)	notes
1	CH_3CN	reflux	-	60% (24 h)[b]
2	H_2O	reflux	-	76% (2 h)[b]
3	H_2O	50 °C	-	**12** was not soluble
4	DMSO	50 °C	17	
5	CH_3CN	50 °C	3	
6	H_2O/MeOH	50 °C	3	
7	MeOH	50 °C	2.5	
8	10% AcOH in MeOH	50 °C	2	
9	TFE	50 °C	1.5	
10	H_2O/TFE(1/1)	microwave[c]	~ 0.1	58% (10 min)[b]
11	TFE	microwave[c]	~ 0.05	76% (10 min)[b]
12	10% AcOH in TFE	microwave[c]	< 0.015	78% (3 min)[b]

a) The reaction was done using 50 mM each of **7** and **12**, and the formation of **16** was followed by TLC. The half-life ($t_{1/2}$) was obtained by the analysis of TLC with a densitometer at 254 nm, b) Isolated yield at indicated time, c) A kitchen-type microwave oven (500W) was used.

Several new 6,11-ethanobenzo[*b*]quinolizinium derivatives were synthesized as described above using substituted bisthienyl dienophile precursors (**12-14**) (Scheme 2). Hydroxyethyl-substituted thienyl derivative **13** was fluorinated by tosylation following fluoride anion substitution with nBu$_4$NF. These dienophile precursors were heated in TFE in the presence of **7** to give the corresponding D-A adducts.[8] Their structures were unambiguously determined by H-H COSY as well as NOESY spectra. The compound **17** was also obtained *via* a similar D-A reaction using the symmetric bis(hydroxyethylthienyl)ethanol (**24**).[9] Table 2 summarizes their binding affinities to the TCP site of NMDA receptors. Orientation of the substituent on the thienyl ring did not cause a significant difference in affinity (**18** *vs* **19**, **20** *vs* **21**), but introduction of bisethanol groups (compound **17**) caused disappearance of affinity . As fluorine-containing compounds (**18** and **19**) retain affinity to a similar extent with PCP, their ^{18}F-labeled derivatives may be expected as candidates for use *in vivo* study.

Table 2. Binding affinity of new 6,11-ethanobenzo[*b*]quinolizinium derivatives to TCP Site of NMDA Receptor.

Compound	R_1	R_2	IC_{50} (nM)[a]
16	H	H	3.6 ± 1.6
17	CH_2CH_2OH	CH_2CH_2OH	12360 ± 1910
18	H	CH_2CH_2F	47 ± 10
19	CH_2CH_2F	H	89 ± 7.6
20	H	CH_2CH_2OH	61 ± 32
21	CH_2CH_2OH	H	141 ± 39
PCP	-	-	47 ± 7.5

a) IC_{50} Values indicate concentrations necessary for 50% displacement of [^{3}H]TCP bound to NMDA receptors of rat brain homogenates.

In conclusion, we have established excellent acceleration of the Diels-Alder reaction by microwave irradiation in polar media, and several fluorine-substituted 6,11-ethanobenzo[*b*]quinolizinium derivatives were synthesized. Furthermore, these new compounds were shown to have high affinity to the TCP site of NMDA receptors. *In vivo* study for investigation of biodistribution in the brain are now ongoing with ^{18}F-labeled ligands.

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7) In a preliminary radiochemical synthesis using ^{18}FK•Kriptofix[2.2.2] complex in CH_3CN, [^{18}F]**14** was obtained in 70% radiochemical yield from the tosylate of **13** at the reaction time of 25 min including purification with Sepack Silica. The following D-A reaction under microwave irradiation in AcOH/TFE for 20 min gave [^{18}F]**18** and **19** in 20% radiochemical yield in 1:1 ratio at the synthesis time of 77 min including HPLC purification.
8) Microwave irradiation was not applied to the large scale synthesis in order to avoid accidental scattering of the reaction mixture. All new compounds (**17-21**) were purified by reverse-phase HPLC (ODS), and showed satisfactory 1D- and 2D- (COSY and NOESY) ^{1}H-NMR, IR as well as high resolution FAB mass spectra.
9) **17** was synthesized by the following scheme.