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Synthesis and Biological Evaluation of Pyranone Analogues of Territrem B

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Abstract: 23 compounds containing pyranone pharmacophore of territrem B were designed and synthesized. Some of the analogues showed IC_{50} values of AChE inhibition at 10^{-5} mol/L.

Keywords: 2H-Pyran-2-one, territrim B, synthesis, AChE inhibitor.

As a highly selective and potent acetylcholinesterase (AChE) inhibitor, territrem B was isolated by Ling *et al.* from a strain of *Aspergillus terreus* in 1979[1,2]. Zhao *et al.* reported mimic preparation of territrem B analogues from triterpenoids and found that the enone moiety and aromatic ring played important roles in their synthetic compounds[3,4]. To further detect essential pharmacophors for AChE inhibitors, we simplified the A/B ring system of territrem B and synthesized a number of pyranone pharmacophore derivatives, including 3-N-aminomethyl-6-substiuted phenyl-2H-pyran-2-one **9** and 3-*O*-hydroxymethyl-6-substiuted phenyl-2H-pyran-2-one **10**.

The synthetic route started from ethyl acetoacetate **1**, which was reacted with iodomethane to give ethyl 2-methylacetoacetate **2** (**Scheme 1**). The resulted **2** was condensed with 3,4-dimethoxybenzaldehyde to afford **3**, which was reduced to a diol **4**. **4** was then subjected to hydrolysis to give an acid **5**. Intromolecular esterification of **5** provided tetrahydro-α-pyrone **6**. This step could be carried out *via* two different methods. Esterification catalyzed by *p*-toluenesulfonic acid provided 31% yield of **6**, while esterification catalyzed by dicyclohexylcarbodiimide (DCC) and 4-dimethylamino-pyridine (DMAP) could promote the yield to 61%. Two paths (path A and path B) were performed to prepare the dihydro-2H-pyran-2-one **7** (**Scheme 1**). In path A, **6** was reacted with mesyl chloride then treated with 1,8-diazacyclo[5.4.0]undec-7-ene (DBU) at room temperature to provide a dihydropyranone **7** in a 47% yield. In path B, the hydroxyl was directly eliminated under the catalysis of *p*-toluenesulfonic acid to provide **7** with a lower yield (*ca*. 35%).

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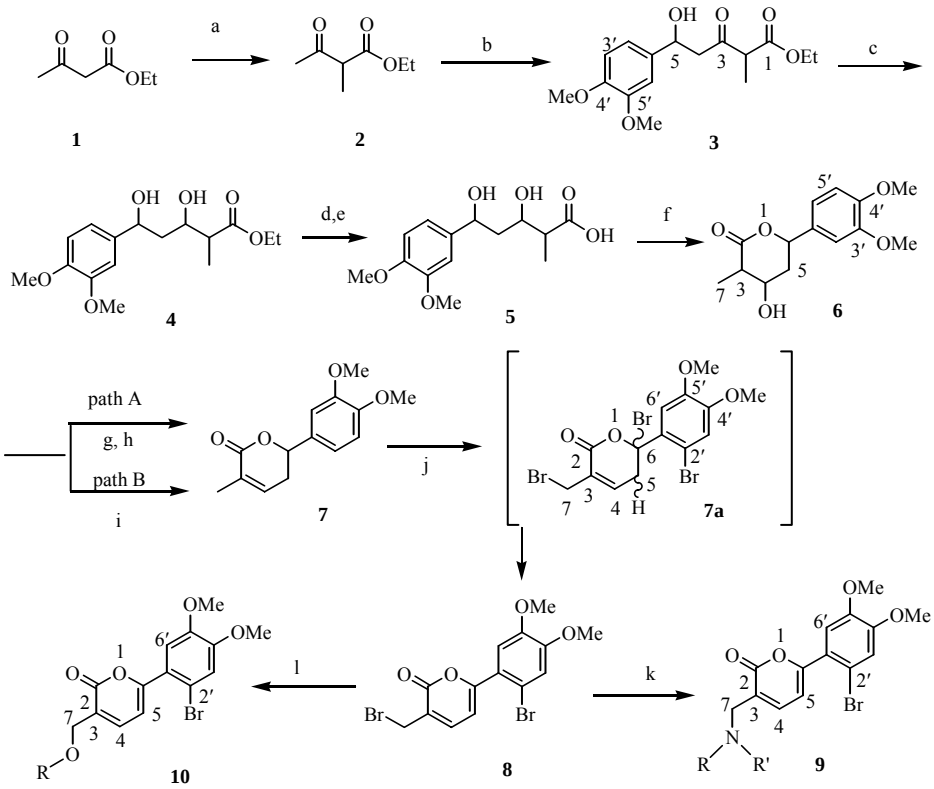
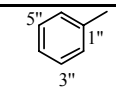
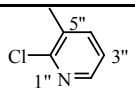
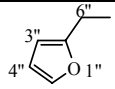
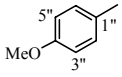
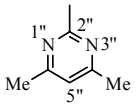
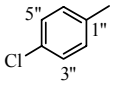
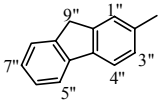
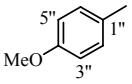
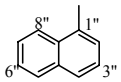
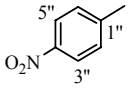
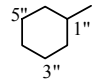
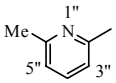
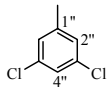
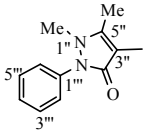
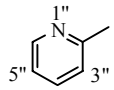
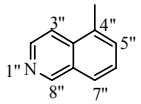
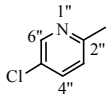
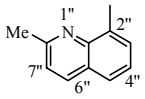
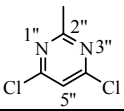
Scheme 1



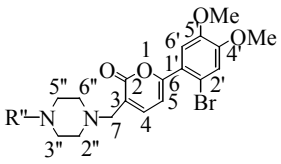
Reagents and conditions: a) MeI, Na, EtOH, reflux, 56%; b) 3,4-dimethoxybenzaldehyde, NaH, *n*-BuLi, THF, -20°C, 72%; c) $NaBH_4$, MeOH, 0°C; d) 1 mol/L LiOH, EtOH, rt.; e) HCl, H_2O; f) *p*-TsOH, THF, rt., 4 steps total yield 35%; or DCC, DMAP, CH_2Cl_2, rt., 4 steps total yield 64%; path A: g) MsCl, Et_3N, CH_2Cl_2, 0°C; h) DBU, toluene, rt., 47% in two steps; path B: i) *p*-TsOH, THF, 50-60°C, 35%; j) NBS, AIBN, CCl_4, 44%; k) RNH_2 or R(R′)NH (for **9o**, **9p** and **9r**), MeCN, rt.; l) K_2CO_3, Me_2CO, ROH, rt.

The bromide **8** was then obtained by reaction of **7** with N-bromosuccinimide (NBS) and 2,2-azobisisobutyronitrile (AIBN) in carbon tetrachloride. It was quite nteresting that this step not only induced bromination on the 4-methyl and C-2′ of aromatic ring, but also accelerated an elimination of the dihydropyran-2-one to a pyran-2-one. According to the analysis of the by-products of this bromination reaction at different temperatures, it could be deduced that the bromination first happened on the aryl part before occurring on the 3-methyl and C-6 methine to form a tribromide **7a** as an unstable intermediate (**Scheme 1**). The bromine hydride molecule was then eliminated from C-5 and C-6 to form the dibromide **8**, which was reacted with different amines or different substituted phenols to give the corresponding derivatives of **9** and **10** (**Table 1** and **Table 2**).

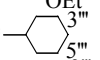
Table 1 Structures of compounds **9a-r** and **10a-e**

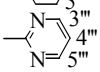
Compd.	R	R′	Compd.	R	R′	Compd.	R	R′
9a		H	**9i**		H	**9q**		H
9b		H	**9j**		H	**9r***	/	/
9c		H	**9k**		H	**10a**		/
9d		H	**9l**		H	**10b**		/
9e		H	**9m**		H	**10c**		/
9f		H	**9n**		H	**10d**		/
9g		H	**9o***	/	/	**10e**		/
9h		H	**9p***	/	/			

* For compounds **9o**, **9p** and **9r**, the structures are:



9o R"= 

9p R"= 

9r R"= 

All of the synthesized pyranone analogues of territrem B were evaluated on their AChE inhibitory activities. It was found that **9r** exhibited an IC_{50} of 7.2×10^{-5} mol/L and compounds **9p** and **9e** also showed inhibitory potency at 10^{-5} mol/L scale. These inhibitory activities suggested that the pyranone moiety is perhaps another pharmacophor for AChE inhibition.

Table 2 The m.p. and yields of **9a-r** and **10a-e**

Compd.	mp (°C)	yield (%)	Compd.	m.p. (°C)	yield (%)	Compd.	m.p. (°C)	yield (%)
9a	105-108	47.6	**9i**	160-161	11.1	**9q**	/*	76.2
9b	129-131	76.2	**9j**	66-68	35.9	**9r**	203-205	88.5
9c	138-141	69.0	**9k**	/*	35.7	**10a**	140-142	64.4
9d	70-73	75.6	**9l**	108-109	35.9	**10b**	204-205	79.6
9e	/*	50.0	**9m**	143-145	11.6	**10c**	148-151	84.7
9f	35-37	56.6	**9n**	110-113	12.0	**10d**	181-182	55.6
9g	113-114	<10.0	**9o**	109-112	83.3	**10e**	/*	40.6
9h	157-159	20.5	**9p**	93-94	73.3			

*. "/" implies that corresponding compound is colorless gem.

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References and Notes

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4. J. Zhao, F. Zhao, Y. Wang, *et al*., *Helv. Chim. Acta*, **2004**, *87*, 1832.
5. Selected data of compounds: **9a.** puff powder; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.93 (s, 3H, 4′-OMe), 3.95 (s, 3H, 5′-OMe), 4.25 (s, 2H, H-7), 6.64 (d, 2H, *J*=8.0 Hz, H-2″, H-6″), 6.78 (t, 1H, *J*=7.6 Hz, H-4″), 6.94 (d, 1H, *J*=8.8 Hz, H-5), 7.22 (dd, 2H, *J*=8.4, 8.0 Hz, H-3″, H-5″), 7.34 (s, 1H, H-6′), 7.49 (d, 1H, *J*=8.8 Hz, H-4) , 7.49 (s, 1H, H-3′); MS (ESI) *m/z* 416 $(M+1)^+$. **9b.** puff powder; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.76 (s, 3H, 4″-OMe), 3.93 (s, 3H, 4′-OMe), 3.95 (s, 3H, 5′-OMe), 4.21 (s, 2H, H-7), 6.65 (d, 2H, *J*=8.8 Hz, H-3″, H-5″), 6.82 (d, 2H, *J*=8.8 Hz, H-2″, H-6″), 6.94 (d, 1H, *J*=8.8 Hz, H-5), 7.34 (d, 1H, *J*=2.0 Hz, H-6′), 7.49 (dd, 1H, *J*=8.8, 2.0 Hz, H-4), 7.50 (s, 1H, H-3′); MS (ESI) *m/z* 446 $(M+1)^+$. **9c.** puff powder; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.93 (s, 3H, 4′-OMe), 3.95 (s, 3H, 5′-OMe), 4.23 (s, 2H, H-7), 6.57(d, 2H, *J*=9.2 Hz, H-2″, H-6″), 6.93 (d, 1H, *J*=8.4 Hz, H-5), 7.17 (d, 2H, *J*=9.2 Hz, H-3″, H-5″), 7.34 (d, 1H, *J*=2.0 Hz, H-6′), 7.45 (s, 1H, H-3′), 7.51 (dd, 1H, *J*=8.4, 2.0 Hz, H-4); MS (ESI) *m/z* 450 $(M+1)^+$. **10a.** colorless amorphous powder; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.79 (s, 3H, 4″-OMe), 3.94 (s, 3H, 4′-OMe), 3.96 (s, 3H, 5′-OMe), 4.92(s, 2H, H-7), 6.88 (d, 2H, *J*=9.2 Hz, H-3″, H-5″), 6.95 (m, 3H, H-2″, H-6″, H-5), 7.26 (s, 1H, H-6′), 7.52 (dd, 1H, *J*=6.8, 1.6 Hz, H-4), 7.73 (s, 1H, H-3′); MS (ESI) *m/z* 447 $(M+1)^+$.

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