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Synthesis of the pyridone analogues of territrem B

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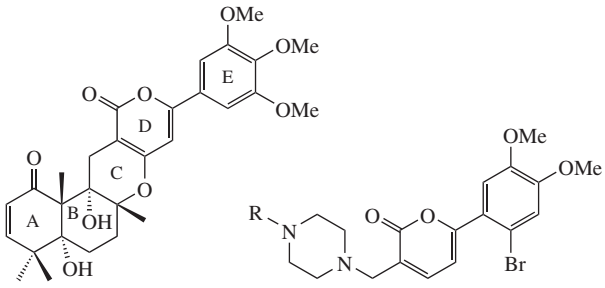
Two series of territrem B analogues were synthesised in nine linear steps from commercially available starting materials.

Territrem B **1** (Figure 1), as an acetylcholinesterase (AChE) inhibitor isolated from the rice cultures of *Aspergillus terreus* 23-1,[1] is 20 times more potent than neostigmine.[2] A preliminary study showed that both the enone and the pyrone moieties play important roles in inhibitory activity on electric eel AChE.[3] To further disclose essential pharmacophores of territrem B (rare from natural sources), we have prepared A/B ring analogues of territrem B starting from triterpenoid jujubogenin. However, only a few synthetic analogues were found to exhibit satisfactory inhibitory activity against AChE.[4] In our continued investigations, the A/B/C ring system with multiple stereocenters was simplified and a number of pyranone derivatives of territrem B were synthesised.[5] The experimental results and molecular modeling studies indicated that an additional piperazine ring (see compounds **2**) (Figure 1) might favour a planar conformation and could enhance the inhibitory effects on AChE. From the viewpoint of medicinal chemistry, the bromine of aromatic moiety in **2** was abandoned because the bromoarenes are more prone than others to yield unwanted toxic metabolites.[6] To testify this proposition, territrem B analogues, 6-arylpyridin-2(1*H*)-ones **3** and their derivatives **10**, were designed and synthesised.

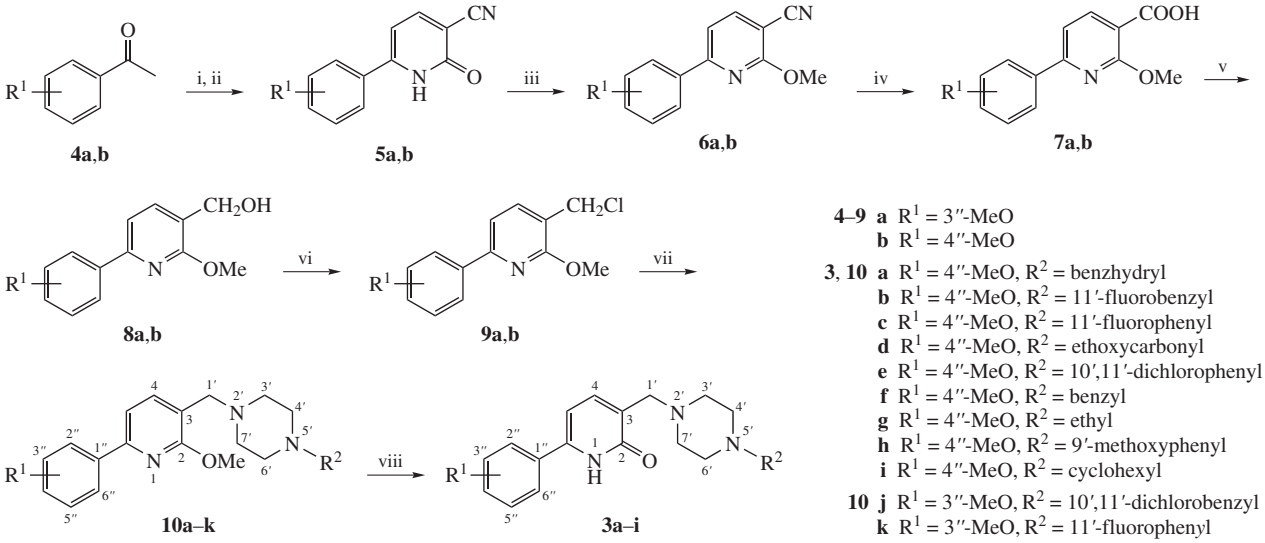


1 Territrem B

2 R = EtOC(O), cyclohexyl, pyrimidin-2-yl

Figure 1 Structures of compounds **1** and **2**.

The syntheses of **3** and their derivatives are outlined in Scheme 1. Acetophenone **4a** was prepared from *m*-hydroxyacetophenone with dimethyl sulfate and **4b** from commercially available anisole with acetic anhydride and $ZnCl_2$ as a catalyst. Treatment of acetophenone **4** with ethyl formate employing the standard Claisen–Schmidt reaction gave intermediate sodium formylacetophenones,[7] which were cyclised (without purification) with cyanoacetamide to afford pyridones **5**. The pyridones were then refluxed with *N*,*N*-dimethylformamide dimethyl acetal (DMF DMA) in DMF to afford methyl-protected pyridones **6**. Compounds **6** were then hydrolysed with a 30% KOH aqueous



Scheme 1 *Reagents and conditions*: i, HCOOEt, Na, MeOH, Et_2O, 0 °C → room temperature; ii, $CNCH_2CONH_2$, H_2O, reflux, 8 h; iii, DMF DMA, DMF, reflux, 12 h; iv, 30% KOH, EtOH–H_2O (1:1), reflux, 12 h, then 6 M HCl; v, $LiAlH_4$, THF, 0 °C → room temperature; vi, Et_3N, MsCl, CH_2Cl_2, 0 °C → room temperature, 12 h; vii, K_2CO_3, substituted piperazine, MeCN, 60–80 °C, 1–6 h; viii, 40% HBr, AcOH, 50–80 °C.

ethanol solution to yield corresponding acids **7**, which were reduced with $LiAlH_4$ to give desired alcohols **8**. In the presence of Et_3N, alcohols **8** reacted with mesyl chloride (MsCl) in CH_2Cl_2 to give chlorides **9**.[8] The latter reacted with substituted piperazines to afford compounds **10a–k**. Compounds **10a–i** were selectively demethylated to provide pyridinones **3a–i** (Scheme 1).

The structures of **10a–k** and **3a–i**, as well as all of the intermediates involved (Scheme 1), were confirmed by ^{1}H NMR and ESI-MS data.† The proton signal of the methoxy group linked at C-2 in compounds **10** appeared at δ 3.99–4.07 (s, 3H) owing to the electron-deficient pyridine ring. This signal is absent from the spectra of compounds **3**; therefore, it was concluded that the methoxy group linked to the pyridine ring of compounds **10a–i** was selectively demethylated.[9]

In summary, two series of territrem B analogues were designed and synthesised based on previous molecular modeling studies.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2008.07.004.

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† **3h**: yield 89%, pale yellow solid, mp 151–152 °C (MeCN). R_f 0.46 (CH_2Cl_2–MeOH, 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.81 (br. s, 4H, H-3′, H-7′), 3.15 (br. s, 4H, H-4′, H-6′), 3.66 (s, 2H, H-1′), 3.86 (s, 6H, 4″-MeO, 9′-MeO), 6.58 (d, 1H, H-5, *J* 6.8 Hz), 6.85–7.01 (m, 6H, H-10′, H-11′, H-12′, H-13′, H-3″, H-5″), 7.57 (d, 1H, H-4, *J* 6.8 Hz), 7.67 (d, 2H, H-2″, H-6″, *J* 8.4 Hz). ESI-MS (*m*/*z*): 406 ([M + 1]$^+$). Calc. for $C_{24}H_{27}N_3O_3$, *M* = 405.21.

3i: yield 86%, pale yellow solid, mp 125–127 °C (MeCN). R_f 0.30 (CH_2Cl_2–MeOH, 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.08–1.90 (m, 10H, H-9′, H-10′, H-11′, H-12′, H-13′), 2.24 (br. s, 1H, H-8′), 2.64 (br. s, 8H, H-3′, H-4′, H-6′, H-7′), 3.56 (s, 2H, H-1′), 3.86 (s, 3H, 4″-MeO), 6.59 (d, 1H, H-5, *J* 7.2 Hz), 6.99 (d, 2H, H-3″, H-5″, *J* 8.8 Hz), 7.48 (d, 1H, H-4, *J* 7.2 Hz), 7.67 (d, 2H, H-2″, H-6″, *J* 8.8 Hz). ESI-MS (*m*/*z*): 382 ([M + 1]$^+$). Calc. for $C_{23}H_{31}N_3O_2$, *M* = 381.24.

10h: yield 73%, white solid, mp 73–74 °C (EtOH), R_f 0.35 (light petroleum–EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.74 (br. s, 4H, H-3′, H-7′), 3.12 (br. s, 4H, H-4′, H-6′), 3.64 (s, 2H, H-1′), 3.87 (s, 6H, 4″-MeO, 9′-MeO), 4.05 (s, 3H, 2-MeO), 6.85–7.02 (m, 6H, H-10′, H-11′, H-12′, H-13′, H-3″, H-5″), 7.29 (d, 1H, H-5, *J* 7.2 Hz), 7.69 (d, 1H, H-4, *J* 7.2 Hz), 8.01 (d, 2H, H-2″, H-6″, *J* 7.6 Hz). ESI-MS (*m*/*z*): 420 ([M + 1]$^+$). Calc. for $C_{25}H_{29}N_3O_3$, *M* = 419.22.

10j: yield 65%, colourless oil, R_f 0.36 (light petroleum–EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.50 (br. d, 8H, H-3′, H-4′, H-6′, H-7′), 3.46 (s, 2H, H-8′), 3.57 (s, 2H, H-1′), 3.89 (s, 3H, 3″-MeO), 4.04 (s, 3H, 2-MeO), 6.93 (dd, 1H, H-14′, *J* 2.4 and 8.0 Hz), 7.16 (d, 1H, H-5, *J* 8.4 Hz), 7.32–7.38 (m, 3H, H-10′, H-13′, H-4″), 7.43 (s, 1H, H-2″), 7.60 (d, 1H, H-4, *J* 8.4 Hz), 7.66 (m, 2H, H-5″, H-6″). ESI-MS (*m*/*z*): 472 ([M + 1]$^+$). Calc. for $C_{25}H_{27}Cl_2N_3O_2$, *M* = 471.15.

For ^{1}H NMR and ESI-MS spectral data for compounds **3a–g**, **9a**,**b** and **10a–g**,**i**,**k** see Online Supplementary Materials.