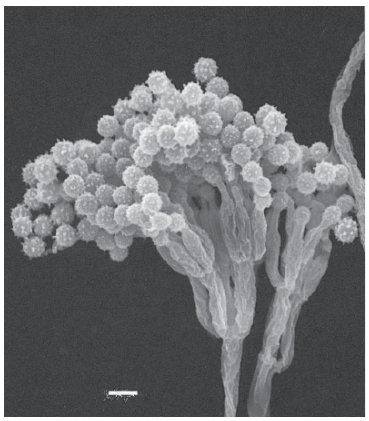
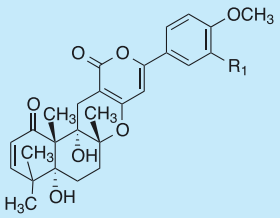
Arisugacin

1. Discovery, producing organism[1,2] and structures[1,3,7,8]

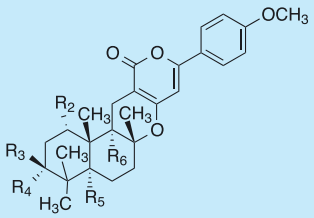
Arisugacins were isolated from the culture broth of *Penicillium echinulatum* FO-4259 and found to be selective acetylcholinesterase (AChE) inhibitors. The fungal strain FO-4259 was also found to produce the known compounds territrems B and C[4].



Penicillium sp. FO-4259
(*Penicillium echinulatum*
FO-4259)
Bar: 5 μm



	R_1
Arisugacin A	OCH_3
B	H



	R_2	R_3	R_4	R_5	R_6
Arisugacin C	OCH_3	=O		OH	H
D	H	H	$OCOCH_3$	OH	OH
E	H	H	OH	OH	H
F	H	OH	H	OH	H
G	H	=O		H	H
D	OH	H	$OCOCH_3$	OH	OH

2. Physical data (Arisugacin A)

White powder. $C_{28}H_{32}O_8$; mol wt 496.21. Sol. in MeOH, EtOH, $CHCl_3$. Insol. in H_2O, hexane.

3. Biological activity[2,5,9]

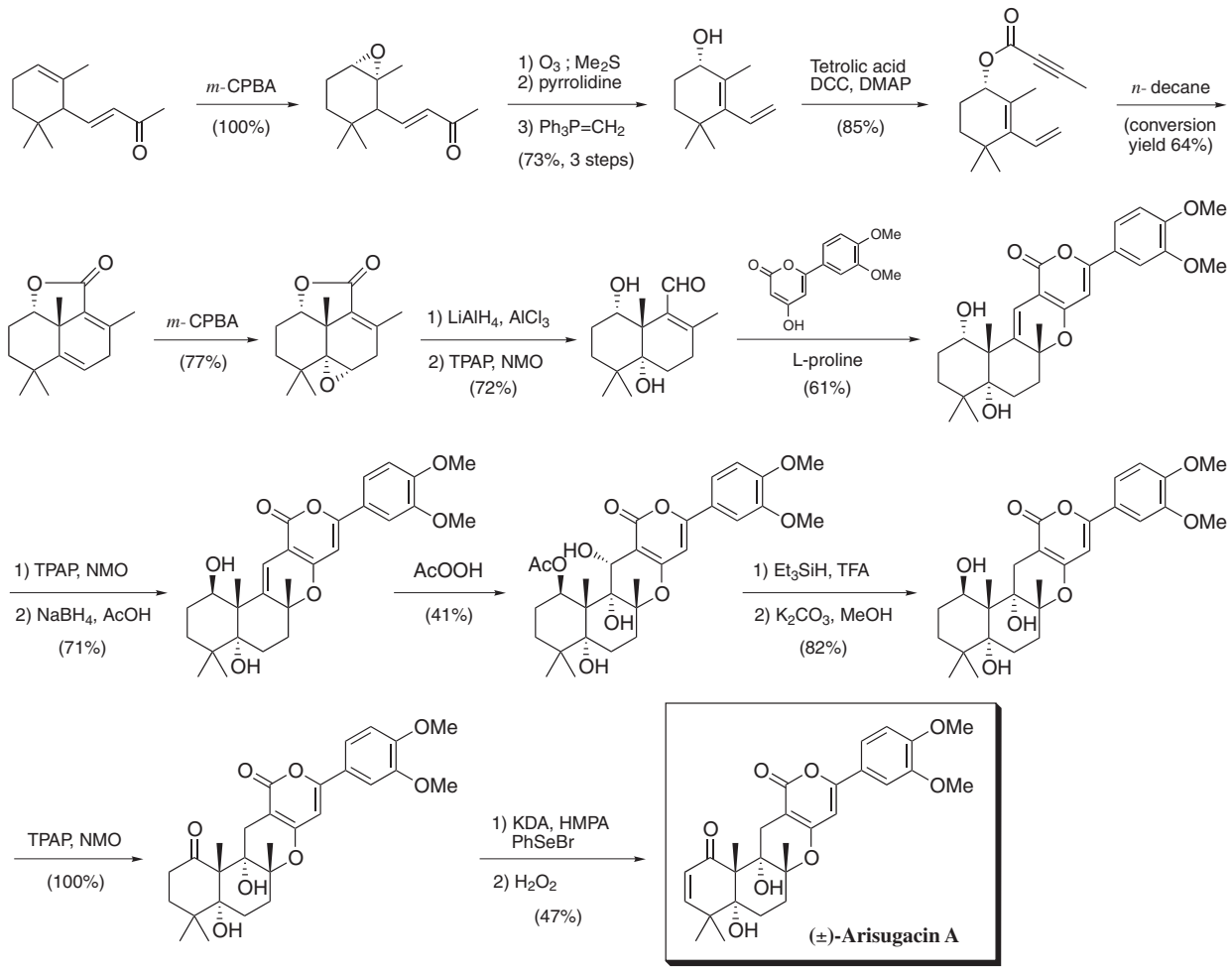
Inhibitory activities of arisugacins and the related compounds against AChE and butyrylcholinesterase (BuChE)

Compound		IC_{50} (nM)		Selectivity (BuChE/AChE)
		AChE*	BuChE**	
Arisugacin	A	1.0	>21,000	>21,000
	B	25.8	>516,000	>20,000
	C	2,500	30,000	12
	D	3,500	30,000	8.57
	E	>100,000	30,000	—
	F	>100,000	30,000	—
	G	>100,000	30,000	—
	H	>100,000	30,000	—
Territrem	B	7.6	>20,000	>2,632
	C	6.8	>26,000	>3,824
Tacrine***		200	12.0	0.06

* from human erythrocytes, ** from horse serum, *** clinically used

4. Total synthesis[6,10-13)]

The total synthesis of arisugacin A was reported by two groups. The following scheme is Ōmura's approach. (See Appendix-I)



Overall yield 1.5% in 18 steps

5. References

1. [583] S. Ōmura *et. al*., *J. Antibiot*. **48**, 745-746 (1995)
2. [623] F. Kuno *et. al*., *J. Antibiot*. **49**, 742-747 (1996)
3. [624] F. Kuno *et. al*., *J. Antibiot*. **49**, 748-751 (1996)
4. K. H. Ling *et. al*., *Appl. Environ. Microbiol*. **37**, 355-357 (1979)
5. [686] K. Otoguro *et. al*., *Phamacol. Ther*., **76**, 45-54 (1997)
6. [797] T. Sunazuka *et. al*., *Org. Lett*. **4**, 367-369 (2002)
7. [741] K. Otoguro *et al*., *J. Antibiot*. **53**, 50-57 (2000)
8. [778] M. Handa *et al*., *J. Antibiot*. **54**, 386-391 (2001)
9. Z. F. Al-Rashid & R. P. Hsung, *Bioorg. Med. Chem. Lett*. **21**, 2687-2691 (2011)
10. [986] T. Sunazuka *et al*., *Acc. Chem. Res*. **41**, 302-314 (2008)
11. [901] T. Sunazuka & S. Ōmura, *Chem. Rev*. **105**, 4559-4580 (2005)
12. T. Sunazuka, *Jpn. J. Antibiot*. **56**, 66-79 (2003)
13. [777] M. Handa *et al*., *J. Antibiot*. **54**, 382-385 (2001)