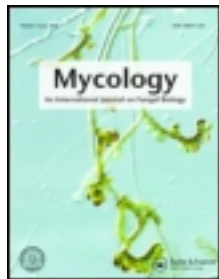


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Hericenones and erinacines: stimulators of nerve growth factor (NGF) biosynthesis in *Herichium erinaceus*

Bing-Ji Ma ^a , Jin-Wen Shen ^a , Hai-You Yu ^a , Yuan Ruan ^a , Ting-Ting Wu ^a & Xu Zhao ^a

^a Department of Traditional Chinese Medicine , Agronomy College of Henan Agricultural University , Zhengzhou, 450002, Henan Province, China

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Hericenones and erinacines: stimulators of nerve growth factor (NGF) biosynthesis in *Hericium erinaceus*

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Department of Traditional Chinese Medicine, Agronomy College of Henan Agricultural University, Zhengzhou 450002, Henan Province, China

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This review surveys the chemical and biological literature dealing with the isolation, structural elucidation and bioactivity of hericenones and erinacines from the fruiting body and mycelium of *Hericium erinaceus*, concentrating on work that has appeared in the literature up to December 2009.

Keywords: *Hericium erinaceus*; hericenones; erinacines; structures; bioactivities

1. Introduction

Nerve growth factor (NGF) has potent biological activities, such as preventing neuronal death and promoting neurite outgrowth, and is essential to maintain and organize neurons functionally (Obara and Nakahata 2002). It is assumed that functional deficiency of NGF is related to Alzheimer's disease and plays a part in the etiology of the disease process (Allen and Dawbarn 2006). NGF is expected to be applied to the treatment of Alzheimer's disease (Takei et al. 1989). However, NGFs are proteins and so are unable to cross the blood–brain barrier; it is also easily metabolized by peptidases. Therefore, its application as a medicine for treatment of neurodegenerative disorders will be difficult. Alternatively, research has been carried out on low-molecular weight compounds that promote NGF biosynthesis, such as catecholamines (Furukawa et al. 1986), scabronins (Obara et al. 1999), cyrneines (Marcotullio et al. 2007), hericenones and erinacines.

Hericium erinaceus is a mushroom belonging to the family Hericiaceae and has been known as Chinese medicine or food in China and Japan without harmful effects. *H. erinaceus* grows on old or dead broadleaf trees and has been used as a medicine for treatment of gastricism in traditional Chinese medicine for more than 1000 years (Mizuno et al. 1999). Recently, the chemical constituents of *H. erinaceus* have been investigated for its interesting and significant bioactivities. Hericenones and erinacines were isolated from the fruiting body and mycelium of *H. erinaceus*, respectively, and most of the compounds promote NGF biosynthesis in rodent cultured astrocytes (Table 1). These results suggest the value of *H. erinaceus* for the treatment and prevention of dementia. However, there has been no review article on bioactive compounds

isolated from *H. erinaceus* to date. This report covers the isolation and structural elucidation of hericenones and erinacines from the fruiting body and mycelium, and their biological activity of stimulating NGF biosynthesis. In addition, this report examines the research on erinacines produced by *H. erinaceus* grown in mycelial culture and the cultural conditions for the fermentation of *H. erinaceus*.

2. Hericenones in the fruiting body of *H. erinaceus*

Hericenones are aromatic compounds isolated from the fruiting body of *H. erinaceus*. Fresh fruiting bodies of the fungus were extracted with acetone. Repeated chromatography of the chloroform-soluble fraction obtained by solvent partitions (chloroform and then ethyl acetate) of the extract with silica gel followed by HPLC with ODS column gave hericenones. Hericenones A (1), B (2) (Kawagishi et al. 1990), C (3), D (4), E (5) (Kawagishi et al. 1991), F (6), G (7), H (8) (Kawagishi et al. 1993), hericenones A–C (9–11) (Alberto et al. 1995) and hericerin (12) (Kimura et al. 1991) were isolated from the mushroom *H. erinaceus*. Hericenones C, D and E exhibited stimulating activity for the biosynthesis of NGF in vitro. In the presence of hericenones C, D, E and H at 33 µg/ml, mouse astroglial cells secreted 23.5 ± 1.0, 10.8 ± 0.8, 13.9 ± 2.1 and 45.1 ± 1.1 pg/ml NGF into the culture medium, respectively. The degree of activity for hericenones D was almost at the same level as the potent stimulator, epinephrine. It is of interest that the difference of the activity among those compounds was dependent on the nature of the fatty acid (Scheme 1).

*Corresponding author. Email: mbj123@sina.com

Table 1. List of hericenones and erinacines in *Hericium erinaceus*.

No.	Name	Occurrence*	References
1	Hericenone A	a	Kawagishi et al. 1990
2	Hericenone B	a	Kawagishi et al. 1990
3	Hericenone C	a	Kawagishi et al. 1991
4	Hericenone D	a	Kawagishi et al. 1991
5	Hericenone E	a	Kawagishi et al. 1991
6	Hericenone F	a	Kawagishi et al. 1993
7	Hericenone G	a	Kawagishi et al. 1993
8	Hericenone H	a	Kawagishi et al. 1993
9	Hericene A	a	Alberto et al. 1995
10	Hericene B	a	Alberto et al. 1995
11	Hericene C	a	Alberto et al. 1995
12	Hericerin	a	Kimura et al. 1991
13	Erinacerin A	a	Yaoita et al. 2005
14	Erinacerin B	a	Yaoita et al. 2005
15	3-Hydroxyhericenone F	a	Ueda et al. 2008
16	Hericenone I	a	Ueda et al. 2008
17	Hericenone J	a	Ueda et al. 2008
18	Erinacine A	b	Kawagishi et al. 1994
19	Erinacine B	b	Kawagishi et al. 1994
20	Erinacine C	b	Kawagishi et al. 1994
21	Erinacine D	b	Kawagishi et al. 1996
22	Erinacine E	b	Kawagishi et al. 1996
23	Erinacine F	b	Kawagishi et al. 1996
24	Erinacine G	b	Kawagishi et al. 1996
25	Erinacine H	b	Lee et al. 2000
26	Erinacine I	b	Lee et al. 2000
27	Erinacine P	b	Kenmoku et al. 2000
28	Erinacine Q	b	Lee et al. 2002
29	Erinacine J	b	Kawagishi et al. 2006
30	Erinacine K	b	Kawagishi et al. 2006
31	Erinacine R	b	Ma et al. 2008
32	Erinacol	b	Kenmoku et al. 2004
33		b	Shimada et al. 1996
34		b	Shimada et al. 1996
35		b	Kawagishi et al. 1995
36		b	Kawagishi et al. 1995
37	Cyatha-3,12-diene	b	Kenmoku et al. 2001
38	Cyatha-3,12-diene	b	Kenmoku et al. 2001
39	CP-412,065	b	Saito et al. 1998

*Occurrence: a = fruiting body; b = mycelium.

Erinacerin A (**13**) and B (**14**) were also isolated from the fruiting bodies of *H. erinaceus*. It was found that erinacerin A occurred as a racemate (Yaoita et al. 2005). 3-Hydroxyhericenone F (**15**), hericenone I (**16**) and hericenone J (**17**) were isolated from the same mushroom. 3-Hydroxyhericenone F showed the protective activity against endoplasmic reticulum stress-dependent Neuro2a cell death (Ueda et al. 2008) (Scheme 2).

3. Erinacines in the mycelium of *H. erinaceum*

A number of cythane-type diterpenoids with potent inductive activity for NGF synthesis were isolated from the mushroom, for example scabronines A (Ohta et al. 1998), B–F (Kita et al. 1998) isolated from the fruiting bodies of *Sarcodon scabrosus*, and the cyrneines A, B

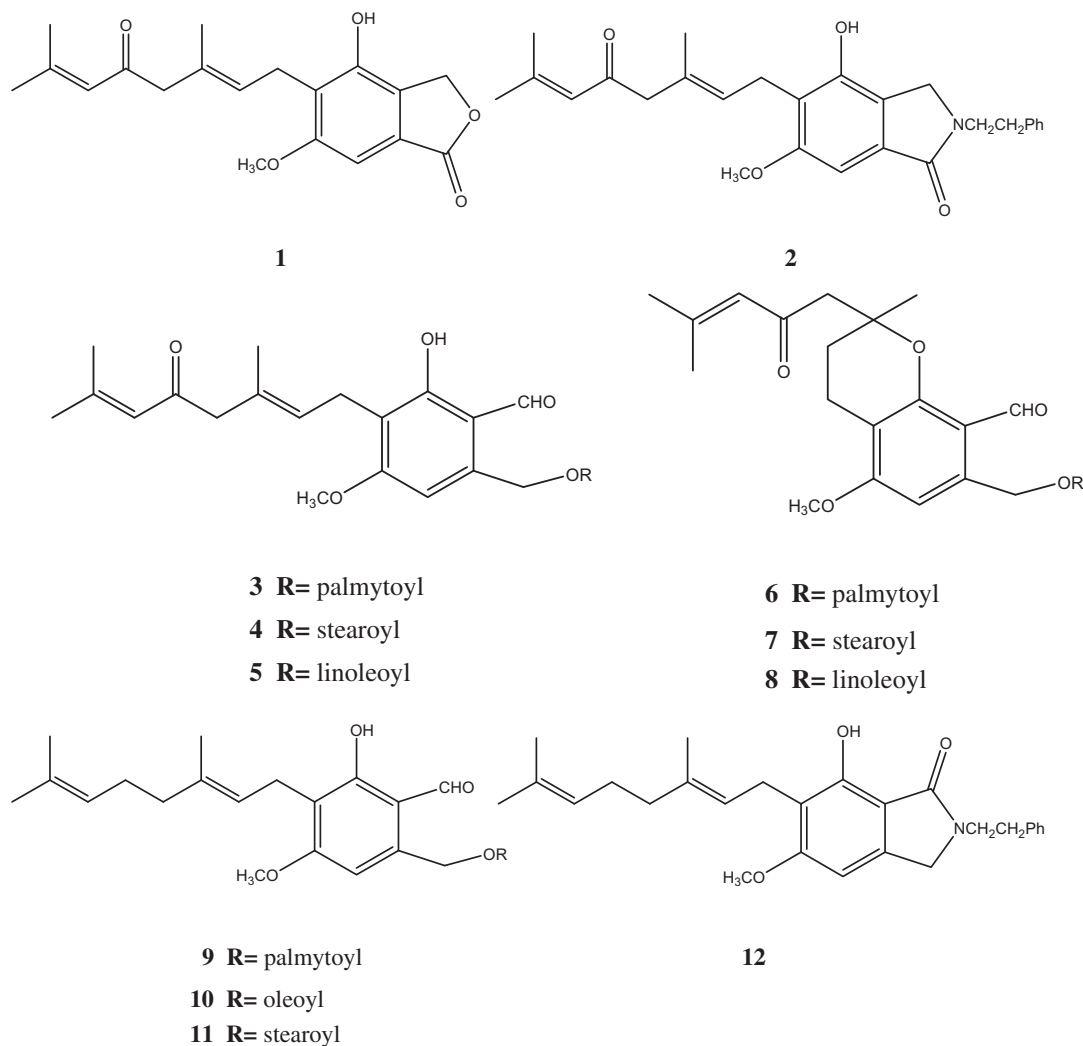
(Marcotullio et al. 2006; Obara et al. 2007), C, D (Marcotullio et al. 2007) isolated from the fruiting bodies of *Sarcodon cyrneus*. All erinacines possess a cythane skeleton consisting of angularly condensed five-, six-, and seven-membered rings. Erinacines A (**18**), B (**19**), C (**20**) (Kawagishi et al. 1994), D (**21**) (Kawagishi et al. 1996a), E (**22**), F (**23**), G (**24**) (Kawagishi et al. 1996b), H (**25**), I (**26**) (Lee et al. 2000), P (**27**) (Kenmoku et al. 2000), Q (**28**) (Kenmoku et al. 2002), J (**29**), K (**30**) (Kawagishi et al. 2006), R (**31**) (Ma et al. 2008) and erinacol (**32**) (Kenmoku et al. 2004), isolated from the mycelia of *H. erinaceus*, show stimulating activity for NGF biosynthesis. The fungus was cultivated by shaking at 30°C for 4 weeks; then the culture was centrifuged and the mycelia were extracted with ethanol. The extract, after concentrating the solvent, was fractionated by solvent partition between ethyl acetate and water. Repeated silica gel chromatography and HPLC of the ethyl acetate extract gave erinacines. Erinacine F was a diastereomer of erinacine E in the sugar part. However, the stereochemistry of the sugar part in erinacine F remained undetermined since NIOSY experiments did not give any valuable information. In the bioassay using mouse astroglial cell, the amounts of NGF secreted into the medium in the presence of erinacines A, B, and C at 1.0 mM were 250.1 ± 36.2 , 129.7 ± 6.5 and 299.1 ± 59.6 pg/ml, respectively. The amounts of NGF secreted into the medium in the presence of erinacines E and F at 5.0 mM were 105 ± 5.2 and 175 ± 5.2 pg/ml, respectively. These activities were much stronger than that (69.2 ± 17.2 mM) of a known potent stimulator, epinephrine, used as a positive control in the bioassay.

Two erinacine derivatives (**33**, **34**) isolated from the mycelia of *H. erinaceus* were claimed to induce the biosynthesis of NGF, which were expected to be applicable for the treatment of dementia (Shimada et al. 1996). Another two erinacine diterpenoids (**35**, **36**) (Kawagishi et al. 1995), isolated from the mycelia of *H. erinaceus*, were also claimed to induce the production of NGF (Scheme 3).

Cyatha-3, 12-diene (**37**), together with its isomer (**38**), was isolated from the mycelia of *H. erinaceus* as a biosynthetic intermediate of cythane diterpenoids (Kenmoku et al. 2001). Biotransformation of erinacine E was examined using 81 microorganisms. One of them, *Caladario-myces fumago* ATCC 16373, was found to transform erinacine E to a new analog CP-412,065 (**39**) at a conversion rate of 29% (Saito et al. 1998) (Scheme 4).

4. Discussion

Hericenones and erinacines are two natural products isolated from the fruiting body and mycelium of *H. erinaceus*, respectively, and most compounds exhibit the

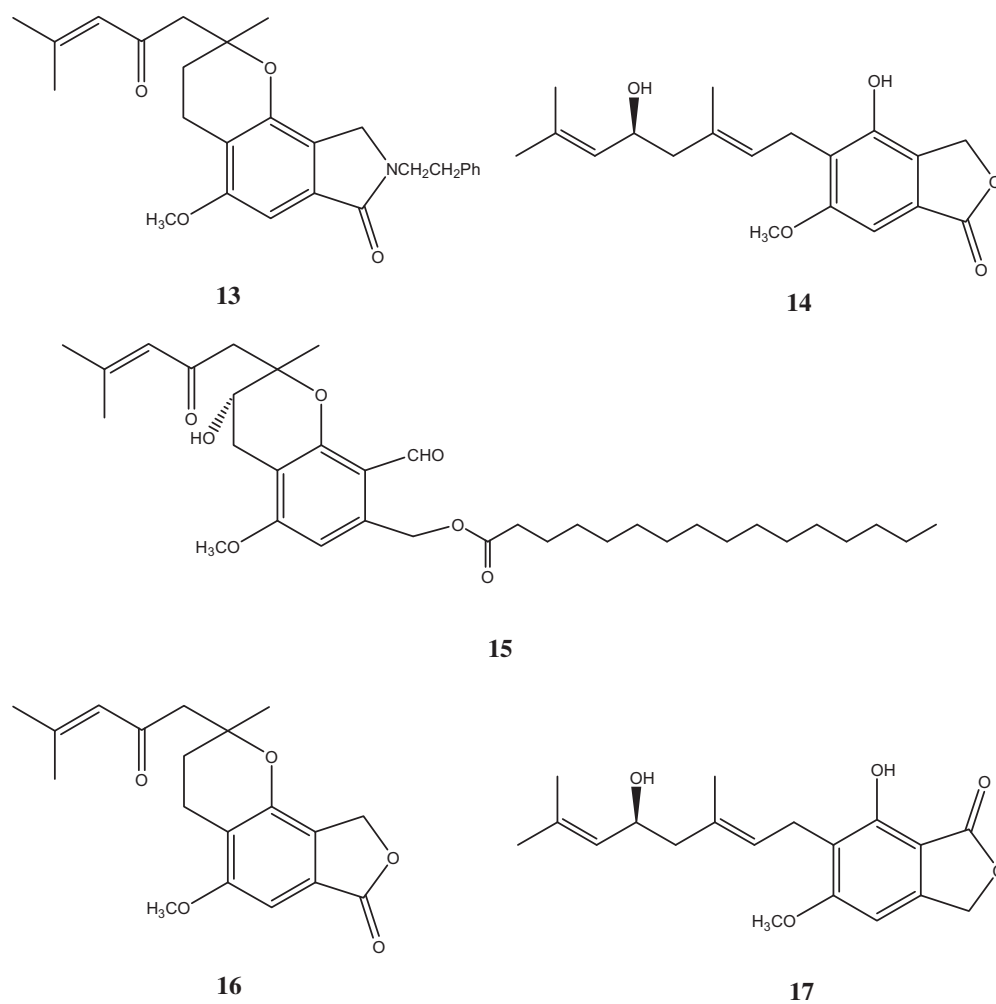
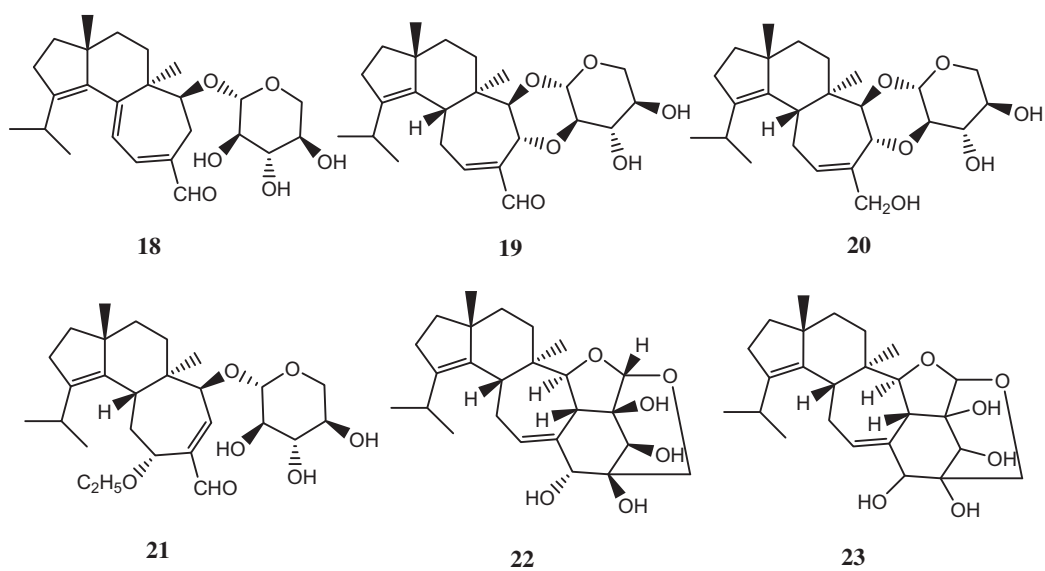


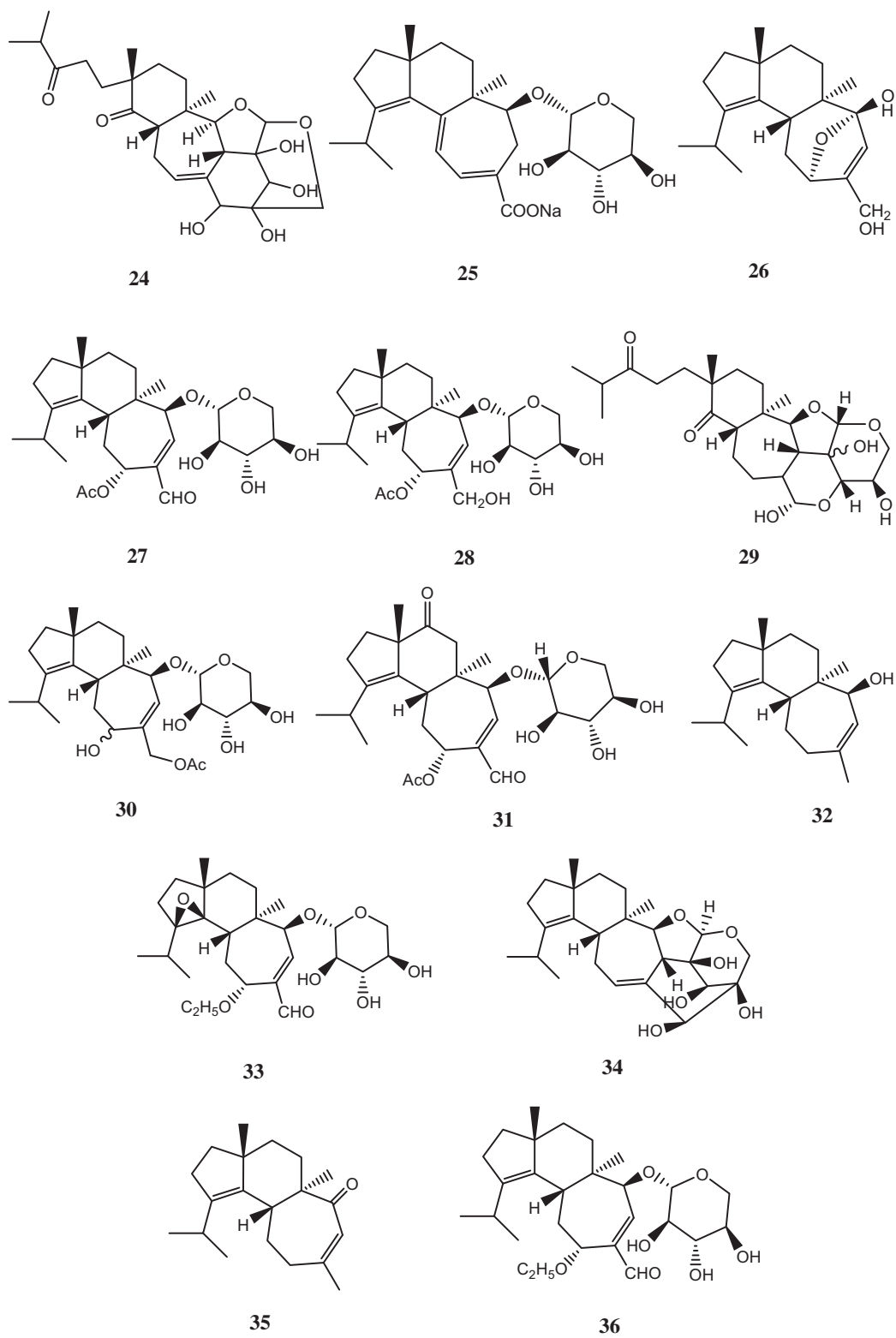
Scheme 1. Structures of compounds 1–12.

activity of promoting NGF synthesis. Hericenones and erinacines are low-molecular weight compounds that easily cross the blood–brain barrier. In a bioassay using mouse astroglial cell, the amounts of NGF secreted into the medium in the presence of erinacines were greater than for hericenones. There is debate as to whether hericenones are active components stimulating biosynthesis of NGF and the recent result have shown that hericenone C, D and E did not increase NGF mRNA expression at 10–100 $\mu\text{g/ml}$ in 1321 N1 cells (Mori et al. 2008). Therefore, erinacines have potential as medicines for degenerative neuronal disorders such as Alzheimer's disease and peripheral nerve regeneration. It has been reported that oral administration of erinacine A significantly increases the level of NGF in the rat locus coeruleus and hippocampus, but not in the cerebral cortex (Shimbo et al. 2005). However, the detailed mechanism by which erinacines induces NGF

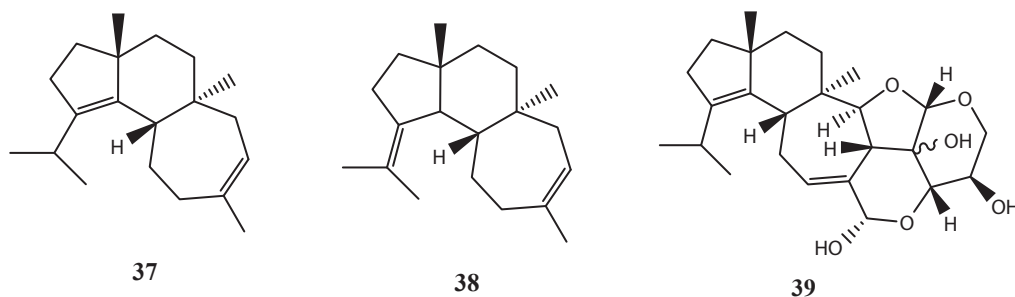
synthesis remains unknown. It is interesting that hericenones have been only reported in the fruiting bodies of *H. erinaceus* and erinacines only in the mycelia.

Biosynthesis of natural products is complex and the expression of many of the key synthase genes is affected by a number of factors. Biosynthetic studies on the cyathane skeleton, which does not follow the isoprene rule, was carried out by Ayer and co-workers in the late 1970s (Ayer et al., 1978; Kenmoku et al. 2001). However, the search for fungal cyathadiene cyclases is still in progress. The structural novelty and significant biological activities displayed by the erinacines have also made members of this family attractive targets for total synthesis. Testimony to this is found in the number and diversity of approaches that have been developed to construct these fascinating natural products (Wright and Whitehead 2000; Takano et al. 2004; Trost et al. 2005), and construction of

Scheme 2. Structures of compounds **13**–**17**.Scheme 3. Structures of compounds **18**–**36**.



Scheme 3. (Continued)



Scheme 4. Structures of compounds 37–39.

the 5-6-7 tricyclic core of the erinacines is the key step. However, the low yield, multi-step synthetic methods restrict their commercial application. Currently, fermentation is perhaps the best way to provide erinacines for further exploitation.

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