Neurotrophic Natural Products
Review by E. A. Theodorakis et al.

Hybrid Surfactants
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Highlights: Alkaloid-Synthesis · Ingenol Synthesis · Switchable Surfaces
Neurotrophic Natural Products: Chemistry and Biology

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Keywords:
Alzheimer’s disease · dementia · drug discovery · neurodegenerative disease · total synthesis

Dedicated to Professor Samuel J. Danishefsky
Neurodegenerative diseases and spinal cord injury affect approximately 50 million people worldwide, bringing the total healthcare cost to over 600 billion dollars per year. Nervous system growth factors, that is, neurotrophins, are a potential solution to these disorders, since they could promote nerve regeneration. An average of 500 publications per year attests to the significance of neurotrophins in biomedical sciences and underlines their potential for therapeutic applications. Nonetheless, the poor pharmacokinetic profile of neurotrophins severely restricts their clinical use. On the other hand, small molecules that modulate neurotrophic activity offer a promising therapeutic approach against neurological disorders. Nature has provided an impressive array of natural products that have potent neurotrophic activities. This Review highlights the current synthetic strategies toward these compounds and summarizes their ability to induce neuronal growth and rehabilitation. It is anticipated that neurotrophic natural products could be used not only as starting points in drug design but also as tools to study the next frontier in biomedical sciences: the brain activity map project.

1. Introduction

Neurons are the basic building blocks of the nervous system, which includes the brain, the spinal cord, and the peripheral ganglia. Neurodegenerative disease (NDD) is a catchall term for heterogeneous and often sporadic disorders that are characterized by progressive nervous system dysfunction resulting from loss of neural structure and function as well as from neural death. Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, and amyotrophic lateral sclerosis are notable examples of these disorders. On the other hand, spinal cord injury arises from extreme trauma to the spinal cord. Currently, neurodegenerative diseases and spinal cord injuries affect about 50 million people worldwide bringing the total annual healthcare cost to over 600 billion dollars.

Efforts to understand the progression of these diseases point to a series of molecular and cellular events, such as accumulation of misfolded proteins, protofibril formation, dysfunction of the ubiquitin-proteasome system, mitochondrial damage, oxidative stress, and synaptic failure. Nonetheless, the etiologies of these diseases still remain under investigation.

Typically, a neuron consists of a cell body, dendrites, and an axon. Although the selective pruning of exuberant neural projections is a fundamental mechanism for maintaining neural plasticity, aberrant axon degeneration, neuronal atrophy, and loss of synapses are a common scenario of acute injury or chronic NDDs. Currently, the therapies for NDDs and spinal cord injuries mainly relieve disease symptoms and control the damage. It is well-known that promoting the regeneration of neural axons, dendrites, and synapses within the adult nervous system would be a highly desirable therapeutic approach. Nonetheless, at present such therapeutic strategies have not yet been successful.

Neurotrophins are a family of proteins that regulate neuron survival, development, and function. Despite their overall promise, the advancement of neurotrophins as therapeutics has encountered significant problems, likely because of their suboptimal pharmacological properties. These include poor serum stability, poor oral bioavailability, and limited penetration of the central nervous system (CNS). On the other hand, small molecules, such as dopamine, γ-aminobutyric acid (GABA), and acetylcholine (ACH), can overcome these limitations and were shown to play an important role in the management of NDDs. Nature has yielded a fascinating collection of small molecules that are able to mimic neurotrophins or modulate neural cellular signaling. Thus, therapeutic strategies based on neurotrophic small molecules could bypass the limitations of protein-based therapeutics and could lead to clinical applications.

In this Review we will introduce the representative neurodegenerative diseases and spinal cord injuries as well as the major neurotrophins. We will then highlight the main families of neurotrophic natural products, focusing in particular on compounds that have been shown to enhance neurite outgrowth, and will summarize approaches toward their chemical syntheses and biological profiles.

1.1. Neurodegenerative Diseases and Spinal Cord Injury

1.1.1. Alzheimer’s Disease

Alzheimer’s disease (AD) is the most common form of dementia and affects approximately 36 million people world-
From a biological standpoint, pathogenic aggregation of amyloid-β (Aβ) and tau protein in the form of extracellular amyloid plaques and intracellular neurofibrillary tangles characterize this disease. As these aggregations advance, the neurons gradually undergo dysfunction and cell death, thereby resulting in memory loss, cognitive deficit and ultimately death. Neuronal death in AD occurs mainly in the hippocampus and cerebral cortex. Currently, there are several hypotheses of pathological pathways of AD that include the cholinergic, the amyloid-β, and the tau protein hypotheses. The cholinergic hypothesis implicates decrease of acetylcholine levels as a significant factor in AD pathogenesis, based on the fact that the level of this neurotransmitter is significantly low in AD patients. The second hypothesis involves accumulation of Aβ aggregates, formed upon cleavage of amyloid precursor protein by two secretase enzymes, that form toxic oligomeric species and plaques in neuronal tissue, ultimately resulting in loss of cognitive function. The third hypothesis attributes the pathology of AD to hyperphosphorylation of the microtubule-associated protein tau. These hypotheses have led to the evaluation of small-molecule-based inhibitors of cholinesterase, secretase, and tau aggregation. Although these compounds have shown symptom improvements or slowed disease progress, they are not capable of stopping, reversing, or curing AD.

1.1.2. Parkinson’s Disease

Parkinson’s disease (PD) is considered to be one of the most common neurodegenerative diseases and affects approximately 1% of the population over 65 years of age. Death of dopamine-secreting neural cells (dopaminergic neurons) in the substantia nigra, has been proposed to occur early in PD pathogenesis. The distinctive feature of PD that differentiates it from other NDDs is the development of intraneuronal proteinaceous cytoplasmic inclusions (referred to as Lewy bodies) in the affected brain area. Certain genetic mutations have been suggested to cause PD, such as mutations in genes for α-synuclein and ubiquitin C-terminal hydrolase like 1 (UCH-L1), parkin (PRKN), PINK1, and DJ-1. The encoded proteins from the above genes are thought to contribute significantly to the three major dysfunctions observed in PD, which are oxidative stress, mitochondrial failure, and proteasomal dysfunction. The most common treatment of PD is targeting the dopamine receptors with various receptor agonists. Nevertheless, this strategy does not slow or stop the progressive neuron death and, more disturbingly, it produces several severe side effects. Moreover, monoamine oxidase (MAO) inhibitors, catechol-O-methyl transferase (COMT) inhibitors, and amantadine are also used to manage the progression of PD.

1.1.3. Huntington’s Disease

Huntington’s disease (HD) is the most common genetic neurodegenerative disease and affects about 4 to 8 persons per 100,000 people. HD is characterized by progressive motor, cognitive, and psychiatric symptoms. At its early stage, HD affects the striatum and subsequently other areas of the brain. This disease is characterized by expansion of a cytosine-adenine-guanine (CAG) repeat in the coding area of the huntingtin gene located on chromosome 4. These CAG repeats are translated into a polyglutamine sequence in the N-terminal region of huntingtin (HTT) that interferes with the various regulatory processes of HTT and produces the defects associated with HD. Currently available therapies only relieve HD symptoms. For example, a small synthetic...
molecule, tetrabenazine, is currently used to combat the chorea symptoms.\[^{[31]}\]

### 1.1.4. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS or Lou Gehrig’s disease) affects roughly 2 in 100,000 individuals annually.\[^{[32]}\] Pathologically, ALS is characterized by degeneration of the large pyramidal neurons in the motor cortex, loss of large motoneurons of the anterior horns in the spinal cord, and motor nuclei in the brainstem.\[^{[33-35]}\] The progressive degeneration of the motor neurons weakens the nervous and muscular system, resulting in paralysis, respiratory dysfunction, and eventually death.\[^{[32]}\] The cause of ALS remains unknown, although several specific gene mutations or immune responses associated with this disease have been suggested. For example, mutations in the gene encoding Cu/Zn superoxide dismutase (SOD1) have been implicated in certain cases of familial ALS.\[^{[36]}\] Recently, mutations of the TDP-43\[^{[37]}\] and FUS\[^{[38]}\] genes have also been linked to ALS. Current drug therapies of ALS\[^{[7g]}\] only help to alleviate the general symptoms, but do not target the disease itself. For example, riluzole is the only FDA approved drug for this condition which acts on ion channels.\[^{[39]}\] Moreover, encouraging phase II clinical data have been reported with dexpramipexole, a putative mitochondrial regulator.\[^{[40]}\] Nonetheless, these agents do not provide direct treatment of the motor neuron degeneration.

### 1.1.5. Spinal Cord Injury

Approximately 2.5 million people live with spinal cord injury (SCI), and more than 130,000 new injuries are reported annually.\[^{[2a]}\] Unlike NDDs, SCI is produced by direct trauma to the spinal cord, which commonly results in paralysis and death. Damage to the spinal cord results in the production of various growth inhibitors from the myelin and glial scars, which generate an undesirable environment for the regeneration of nerve cells.\[^{[41,42]}\] Potential therapeutic strategies include the control of glial scars, the inhibition of myelin-associated proteins, the use of neurotrophic factors and related small molecules, as well as cell replacements and transplantation of peripheral nerves, Schwann cells, and stem cells.\[^{[7a,42a,43]}\] Nevertheless, at present there is no effective method for fully regenerating healthy neuronal cells or regaining full mobility.\[^{[41,42]}\] Figure 1 shows a summary of neurodegenerative diseases and spinal cord injuries.

### 1.2. Neurotrophins and Cell Signaling

Neurotrophins are a class of small proteins that act on cell membrane receptors that elicit cell growth, differentiation, and survival.\[^{[8]}\] Well-known neurotrophins include nerve growth factor (NGF), brain-derived growth factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5).\[^{[45]}\] Each neurotrophin binds selectively to its tyrosine kinase receptor (Trk) and nonselectively to a 75 kDa neurotrophin receptor (p75\[^{NTR}\]). Figure 2. Trk signaling occurs through two major pathways: the mitogen-activated protein kinase (MAPK) pathway and the phosphoinositide 3-kinase (PI3) pathway. These pathways regulate the fate of neurotrophin signaling in terms of cell survival and cell differentiation.\[^{[46]}\] On the other hand, neurotrophin binding to p75\[^{NTR}\] can trigger neuron apoptosis.\[^{[47]}\]
cell line Neuro 2A. Specifically, cells treated with lactacystin for one day displayed a predominantly bipolar (two-neurite-bearing) morphology, in which two neurites project at opposite sites of the cell body. Upon longer exposure (3–4 days) the cells displayed a multipolar (multiple-neurite-bearing) morphology, while the neurites became increasingly branched. Lactacystin was found to increase intracellular cAMP levels at a time point that coincides with the development of maximal bipolar morphology, but did not affect protein kinase C (PKC) and did not inhibit proteinases such as thrombin and the plasminogen activator. The lactacystin-induced neurite outgrowth appears to depend upon microtubule assembly, actin polymerization, and de novo protein synthesis.

The promising biological profile of lactacystin (1) and its interesting γ-lactam thioester motif triggered numerous biological and synthetic efforts. The first total synthesis of (+)-lactacystin was accomplished by Corey et al. one year after its isolation. The C5–C9 trans-amino moiety of key intermediate 3 was achieved through an aldol reaction between oxazolidine 2 and isobutyraldehyde (Scheme 1). Another key synthetic step was a MgI₂-mediated Mukaiyama aldol reaction between oxazolidine aldehyde 5 and the TMS enolate 6 that produced the desired C6 and C7 stereocenters in 7. Subsequent to this pioneering synthesis by Corey et al., several additional syntheses and formal syntheses of 1 were reported.

Studies on the structure–activity relationships on lactacystin have been reported by Corey, Schreiber, and co-workers as well as by the Omura and Smith research groups. Biological investigation of lactone 1 by Corey et al., several additional syntheses and formal syntheses of 1 were reported. Studies on the structure–activity relationships on lactacystin have been reported by Corey, Schreiber, and co-workers as well as by the Omura and Smith research groups. Biological investigation of lactone 1 by Corey et al., several additional syntheses and formal syntheses of 1 were reported.

Important information regarding the mechanism of action of lactacystin was disclosed by Schreiber and co-workers. Working with Neuro 2A and MG-63 osteosarcoma cells, these authors found that 1 inhibits cell-cycle progression at both the G₂/M and G₂ phases of the cell cycle. Based on structure–activity relationship screening studies, the authors suggested that the mode of action of 1 could involve acylation of a cellular target through attack of the β-lactone by a nucleophilic group on the target molecule and subsequent opening of the β-lactone ring. To identify the target of lactacystin, the authors synthesized radiolabeled versions of 1 and used them as covalent affinity labels. This strategy allowed identification of the 20S proteasome as the main observed target of 1. In particular, the N-terminal threonine residue of the mammalian proteasome subunit X (also known as MB1) was found to be esterified on its side-chain hydroxy group by 1. This acylation results in inhibition of several proteasome peptidase activities that are critical to protein degradation, cellular differentiation, and apoptosis. In turn, these findings point to a connection between proteasome inhibition and neuronal differentiation. Fellutamide B (12; Figure 4), a marine fungal metabolite, provides further evidence in support of this connection; this compound binds to the 20S proteasome at a distinct site, which results in inhibition of its hydrolytic activity and at a concentration of 10 μM induces synthesis of NGF in fibroblasts and cultured brain cells. Perhaps more importantly, these findings suggest that controlled inhibition of proteasome activity by small molecules represents a promising therapeutic approach against various diseases, including NDDs.

2.2. Illicium Sesquiterpenes

The Illicium family of natural products has attracted considerable attention since several of its members possess potent neurotrophic activities. These include merrillactone A (13), jiadifenin (14), jiadifenolide (15), (1R,10S)-2-
oxo-3,4-dehydroxyneomajucin (16, ODNM), jiadifenoxolan A (17), (2R)-hydroxy-11-O-debenzyllashironin (19), tricycloillicinone (21), and bicycloillicinone (22) (Figure 5). In addition to their complex caged architectures, several natural products of this family were shown to promote neurite outgrowth at low nanomolar to low micromolar concentration in primary cultures of cortical neurons of fetal rats.

Isolated from *Illicium merrillianum*, a plant indigenous to China and Myanmar, merrilactone A (13) was found to promote neurite outgrowth in primary cultures of cortical neurons of fetal rats at concentrations ranging from 0.1 to 10 μM. A pioneering synthesis of 13 was reported by the Danishefsky research group that allowed synthetic access to several *Illicium* natural products (Scheme 2). This approach builds upon an intermolecular Diels–Alder reaction between 23 and 24 to afford 25. A subsequent ozonolysis of 26 produced the corresponding dialdehyde, which underwent an intramolecular aldol condensation to yield 27, which contains the BC ring system of the natural product. After formation of the D ring, an impressive AIBN/TBu3SnH-induced free-radical cyclization allowed formation of the A ring of 29 from vinyl bromide 28.

The synthesis of merrilactone by Inoue, Hirama et al. is highlighted by an intramolecular aldol reaction that forms the AB ring system in 34 from diketone 33 (Scheme 3). The latter compound was obtained from cyclic anhydride 32 which, in turn, was assembled from a [2+2] photocycloaddition between trans-1,2-dichloroethylene (30) and 31. The D ring of 36 was formed by an intramolecular radical cyclization of alkyl bromide 35. Interestingly, in subsequent studies, the authors reported that both enantiomers of 13 are equally active in primary cultures of cortical neurons of fetal rats.

The synthesis of (+)-13 by Mehta and Singh relied on a ring-closing metathesis (RCM) to build the A ring and a [2+2] photocyclization to furnish the C-ring framework (Scheme 4). The cyclobutene motif of 40 was then subjected

**Figure 5.** Representative neurotrophic *Illicium* sesquiterpenes.

**Scheme 2.** Part of the total synthesis of merrilactone A (13) by Danishefsky and co-workers. AIBN = azobis(isobutyronitrile), TFA = trifluoroacetic acid.

**Scheme 3.** Part of the total synthesis of merrilactone A (13) by Inoue, Hirama and co-workers. LiHMDS = lithium hexamethyldisilazide.

**Scheme 4.** Part of the total synthesis of (+)-merrilactone A (13) by Mehta and Singh. PCC = pyridinium chlorochromate.
to a ring-expansion strategy that proceeded through ozonolysis and lactol oxidation to afford advanced intermediate 41.

Formation of the B ring of 44 by a Nazarov cyclization[78] constitutes the key step of the total synthesis of (±)-13 reported by Frontier and co-workers.[79] IrIII complex 43[80] was pivotal for the success of this cyclization.[81] After removal of the TMS group, alkyne 45 was subjected to an AIBN/nBu3SnH-induced free-radical cyclization to afford the critical C9 quaternary center in 46 (Scheme 5).

More recently, an interesting synthesis of (±)-13 was described by the Zhai research group,[84] in which a hetero-Pauson–Khand reaction[85] was employed to convert alkyne 52 into the D-ring lactone motif in the presence of [Mo(CO)3-(DMF)]3/CO (Scheme 7). Subsequently, the A-ring framework of 55 was constructed through a sequence of reactions that included formation of the extended enol silyl ether 54, conjugate addition of 54 to methyl vinyl ketone (MVK), and SmI2-mediated reductive radical cyclization.[86]

Recently, the Greaney research group reported two interesting synthetic strategies toward (±)-merrilactone A (13).[82] Key to the first-generation synthesis was a Cp2TiCl2/Zn-triggered reductive epoxide cleavage followed by radical cyclization, which furnished the A ring of 48 containing the C9 quaternary center. The second-generation synthesis was based on a cyanide 1,4-addition/aldol reaction cascade[83] that constructed the A ring and the C9 quaternary center. Intermediate 50 then underwent a one-pot elimination/cyanide hydrolysis/lactonization upon treatment with a Lewis acid and heating (Scheme 6).

Jiadifenin (14) and ODNM (16) were isolated from the East-Asian plants *Illicium jiadifengpi*,[64] and *Illicium majus*,[66] respectively. 14 was shown to promote neurite outgrowth in primary cultures of cortical neurons of fetal rats at a concentration of 0.1 µM. The first synthesis of (±)-14 was elegantly accomplished by Danishefsky and co-workers (Scheme 8).[87]

Central to the strategy was an intramolecular Horner–Wadsworth–Emmons reaction that formed the A ring of 58. Subsequent formation of the C ring led to construction of key intermediate 59.

Recently, the Theodorakis research group reported an enantioselective synthesis of (−)-jiadifenin (14) from 60, which was obtained by an organocatalyzed[88] asymmetric
Robinson annulation.\(^9\) Palladium-mediated carbomethoxylation\(^9\) followed by an oxidation/epoxide opening cascade was used to build the C/D ring system of 64, an advanced intermediate toward 14 (Scheme 9).

Another enantioselective route toward \((-\)\(C0\)-14 was recently reported by the Zhai research group (Scheme 10).\(^9\) Critical to this strategy was an Ireland–Claisen rearrangement\(^9\) to form the C ring of 66 followed by a Pauson–Khand reaction\(^8\) to construct the A ring. Subsequent treatment of allylic alcohol 70 with mCPBA afforded epoxide 71 in a diastereoselective manner. \(^9\)71 was then treated with Dess–Martin periodinane to produce the corresponding C1 ketone, which underwent epoxide opening followed by a C4 translactonization to furnish the desired five-membered lactone 72. Further functionalization of the A ring furnished trilate 73, which underwent a Pd\(^0\)-mediated methylation to install the C1 methyl group in 74. This compound represents a fully functionalized framework of jiadifenolide.

The above strategies paved the way to evaluate structure–activity relationship issues of jiadifenin (Figure 6). Notably, the Danishefsky\(^8\) and Theodorakis research groups\(^9\) have independently performed such studies on jiadifenin structural motif and have identified several compounds, such as 75, ODNM (16), 76, and 77, which are more potent than the parent natural products in promoting neurite outgrowth. The neurotrophic effects were evaluated by measuring the stimulation of NGF-mediated neurite outgrowth in PC-12 cells.\(^9\)\(^7\) These studies suggest that: a) removal of the

\[\text{Scheme 9. Part of the total synthesis of \((-\)jiadifenin (14) by Theodorakis and co-workers.}^9\]

\[\text{Scheme 10. Part of the total synthesis of \((-\)jiadifenin (14) by Zhai and co-workers.}^9\]

\[\text{Scheme 11. Part of the total synthesis of \((-\)jiadifenolide (15) by Theodorakis and co-workers.}^9\]

\[\text{Figure 6. Representative structure–activity relationship studies on jiadifenin and analogues. The numbers in parenthesis indicate the extent of neurite outgrowth compared to a control; inactive indicates less than 110% neurite outgrowth as compared to control.}\]
C1 methyl group increases the neurotrophic activity of the jiadifenin motif, as shown by comparing 14 with 75, and 76 with 77; and b) the α substitution at the C10-position is critical for the activity (Figure 6). These compounds are likely to upregulate NGF signaling rather than mimicking NGF.[87,89,184]

11-O-Debenzoyltashironin (19, Scheme 12) and its benzoate ester (tashironin, 20) were isolated from pericarps of *Illicium merrillianum*.[68,98] 19 was found to induce neurite outgrowth in cortical neurons of fetal rats at concentrations of as low as 0.1 μM, while 20 was inactive in this assay. Danishefsky and co-workers reported an impressive total synthesis of (±)-19.[99] The key step of their approach is a remarkable oxidative dearomatization/transannular Diels–Alder reaction cascade. This transformation was achieved using PhI(OAc)₂ followed by a microwave-assisted intramolecular Diels–Alder reaction.[100] The enantioselective construction of propargyl alcohol 79 led to an asymmetric synthesis of 19.[101] A synthesis of 11-O-methyldebenzoyltashironin has also been reported by the Mehta research group.[102]

Tricycloillicinone (21) and bicycloillicinone (22) were isolated from the extracts of *Illicium tashiroi* by Fukuyama et al.[69,70] Interestingly, these compounds have been shown to enhance choline acetyltransferase (ChAT) activity at concentrations as low as 30 μM.[69,70] There is significant evidence that ChAT upregulation induces neurite outgrowth.[103] Specifically, it has been shown that the level of acetylcholine (ACh) is low in AD patients, thus suggesting that upregulation of ChAT represents a possible strategy for the treatment of AD.[104] In 1998, Danishefsky and co-workers reported the first total synthesis of 21.[105] Highlights of their strategy include an aromatic Claisen rearrangement followed by a MnIII-promoted oxidative radical cyclization (Scheme 13). Heating protected phenol 83 in toluene produced the rearranged cyclohexadienone 84 in nearly quantitative yield. In turn, 84 was oxidized by MnIII in the presence of CoII as a co-oxidant to afford a resonance-stabilized radical[107] at C2, which underwent a cyclization cascade to yield the cyclic core of 85. A biomimetic transformation of 21 from its likely biosynthetic precursor illicinone A (86) was initially described by Furukawa et al.[108] and later optimized by Danishefsky and co-workers.[109] A synthesis of ent-21 has also been reported by the Terashima research group[109] by using a Pauson–Khand reaction[85] to generate the challenging C2 quaternary center (conversion of 87 into 88). In addition, Danishefsky and co-workers have reported the synthesis of bicycloillicinone aldehyde.[108b]

2.3. Lycopodium Alkaloids

Several members of the Lycopodium alkaloids,[111] such as huperzine A (89),[112] lyconadins (90 and 91),[113] complanadiane A (94)[114] and B (95),[115] and nankakurine A (92) and B (93), display highly promising neurotrophic profiles (Figure 7).[116] Huperzine A (89) was originally isolated from the Chinese plant *Huperzia serrate* by Liu et al. in 1986.[112] Huperzi...
ne A has been found to potently inhibit acetylcholinesterase (AChE)\(^{[117]}\) and effectively cross the blood–brain barrier with no signs of cytotoxicity and minimal side effects.\(^{[118]}\) Both NGF and P75NTR levels increased in the presence of \(^89\) in studies performed in PC-12 cells.\(^{[119,120]}\) Huperzine A was shown to prevent oxidative damage in SHSY5Y cells, presumably as a result of its ability to increase NGF production.\(^{[121]}\) Studies in mice demonstrated that huperzine A, administered at 0.2 mg kg\(^{-1}\), increases the concentration of various proteins, including NGF, BDNF, and phosphorylated MAPK.\(^{[121]}\) Interestingly, \(^89\) was also reported to promote hippocampal neurogenesis in vitro and in vivo.\(^{[120]}\) Moreover, \(^89\) is an approved drug in China to treat cognitive deficiencies associated with AD, and is being offered as a herbal supplement in the USA.\(^{[123]}\) The pharmacology and therapeutic potential of huperzine A has recently been reviewed.\(^{[124]}\)

The total synthesis of (±)-\(^89\) was independently accomplished by Kozikowski and Xia\(^{[125]}\) as well as Qian and Ji\(^{[126]}\) by using an almost identical strategy to construct the huperzine A core. Specifically, a one-pot Michael addition/aldol reaction of \(97\) with methacrolein formed the desired carbon bridge of \(98\) (Scheme 14).

The Fukuyama research group has also reported a synthesis of (±)-\(^89\)\(^{[127]}\) (Scheme 15). Key to this strategy was a TIOH-catalyzed cationic ene cyclization that produced tricyclic lactone \(102\). Precursor \(100\) could be constructed from readily available \(99\) in one step.

The growing pharmacological interest in (−)-huperzine A (\(^89\)) prompted two efficient syntheses of this molecule by using palladium-catalyzed coupling reactions as a key step (Scheme 16).\(^{[128]}\) Specifically, Herzon and co-workers reported a scalable synthesis of huperzine A\(^{[129]}\) that relies on a modified intramolecular Heck coupling of \(\alpha\)-cyanoketone \(103\) to assemble the carbon bridge of \(104\).\(^{[130]}\) Lin and co-workers also disclosed a synthesis of \(89\)\(^{[131]}\) by using a Buchwald–Hartwig coupling reaction\(^{[132]}\) between enol triflate \(105\) and Boc-NH\(_2\) to form enamine \(106\). A subsequent intramolecular Heck reaction\(^{[133]}\) of \(107\) led to the bridged motif of \(108\). Several other syntheses and formal syntheses of huperzine A (\(^89\)) have also been reported.\(^{[134]}\)

Lyconadins (\(90\) and \(91\))\(^{[113]}\) and complanadines (\(94\) and \(95\))\(^{[114,115,135]}\) are particularly attractive small molecules since they enhance the mRNA expression of NGF in human glial cells.\(^{[113b,115]}\) In addition, \(90\) displayed modest cytotoxicity against murine lymphoma L1210 and human epidermoid carcinoma KB cells,\(^{[113a]}\) while \(94\) exhibited modest cytotoxicity against murine lymphoma L1210 cells.\(^{[114]}\)

From a structural point of view, lyconadins possess a pyridinone-fused tetracyclic caged framework, which constitutes the central synthetic challenge for \(90\). The Smith research group reported the first total synthesis of (+)-\(90\) and (−)-\(91\) (Scheme 17).\(^{[136]}\) The tricyclic intermediate \(110\) was crafted by an aldol/1,4-addition reaction cascade from aldehyde \(109\). After a few synthetic steps, amine \(111\) underwent a NIS-induced cyclization to furnish the tetracyclic motif \(112\). One year later, the Sarpong research group reported the synthesis of (±)- and (+)-\(90\)\(^{[137]}\) Double deprotonation of \(114\) formed dianion \(115\), which was oxidized with iodine to form the critical C–N bond of \(116\). This bond formation can also be accomplished by an NIS-mediated S_N2 reaction (Scheme 18).
Another interesting synthesis of (+)-90 and (−)-B (91) by Beshore and Smith.[136] Cbz = carboxybenzyl, NIS = N-iodosuccinimide.

Scheme 17. Part of the total synthesis of (+)-lyconadin A (90) and (−)-B (91) by Beshore and Smith.[136] Cbz = carboxybenzyl, NIS = N-iodosuccinimide.

Siegel research groups have yielded two intriguing strategies for the synthesis of (+)-complanadine A. In the former study, Fischer and Sarpong started the synthesis of 123 following the procedure developed by Schumann and Naumann (Scheme 20).[141] The authors converted triflated lycodine derivative 124 into boronic ester 125 under reductive detriflation conditions, followed by an Ir(I)-catalyzed Miyaura–Hartwig C–H borylation.[142] Pd-based cross-coupling between 125 and triflate 124, followed by cleavage of the Boc group, produced (+)-94. A synthesis of complanadine B (95) has also been reported by similar strategies.[143]

In parallel, the Siegel research group reported a synthesis of (+)-94 (Scheme 21).[144] Key to this strategy was a [2+2+2] cycloaddition of 126 with 127 to produce lycodine analogue 129. This compound was then coupled with 130 to yield complanadine precursor 131. Notably, it was found that both the presence of PPh₃ and the formyl motif of 130 were essential for the regioselectivity of the second cycloaddition. More recently, Tsukano and co-workers reported a synthesis of (+)-complanadine A and B[145] by a Pd-catalyzed coupling of N-oxolycodine with a -bromolycodine.[147]

Nankakurine A (92), another Lycopodium natural product, was reported to possess neurotrophic activity in human astrocytoma cells.[116b] 92 was isolated from Lycopodium hamiltonii in 2004,[116a] and its originally proposed structure was revised two years later.[116b] The Overman research group reported the first synthesis of (+)-nankakurine A (92) and B (93), thereby establishing their absolute configurations (Scheme 22).[148] Critical to the synthetic strategy was an intramolecular azomethine imine [3+2] cycloaddition of 133 that installed the two nitrogen atoms at C5 and C13 in

Another interesting synthesis of (+)-90 and (−)-lyconadins B and C was reported by the Fukuyama research group (Scheme 19).[138] The authors utilized dibromocyclopropane 119 as the key motif, which was prepared from amine 117 by an aza-Prins reaction followed by a dibromocyclopropanation. Subsequently, 119 underwent an acid-promoted ring expansion to produce the tetracyclic core of 120.

Complanadine A (94) is an unsymmetric dimer of lycodine (96),[139] while complanadine B (95) can be considered as a pseudodimer of 96. Independent studies by the Sarpong and Beshore-Sarpong group started the synthesis from tetracyclic compound 123 following the procedure developed by Schumann and Naumann (Scheme 20). The authors converted triflated lycodine derivative 124 into boronic ester 125 under reductive detriflation conditions, followed by an Ir(I)-catalyzed Miyaura–Hartwig C–H borylation. Pd-based cross-coupling between 125 and triflate 124, followed by cleavage of the Boc group, produced (+)-94. A synthesis of complanadine B (95) has also been reported by similar strategies.[143]

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Nankakurine A (92), another Lycopodium natural product, was reported to possess neurotrophic activity in human astrocytoma cells.[116b] 92 was isolated from Lycopodium hamiltonii in 2004,[116a] and its originally proposed structure was revised two years later.[116b] The Overman research group reported the first synthesis of (+)-nankakurine A (92) and B (93), thereby establishing their absolute configurations (Scheme 22).[148] Critical to the synthetic strategy was an intramolecular azomethine imine [3+2] cycloaddition of 133 that installed the two nitrogen atoms at C5 and C13 in
a stereoselective manner. Reductive cleavage of the N–N bond in 134 released the free amine at C13, which was reductively methylated to form 135.

Cheng and Waters reported a short synthesis of (±)-nankakurines by Overman and co-workers.\textsuperscript{[149]} Amine 139 was derived from an intermolecular Diels–Alder reaction between 136 and 137 followed by reductive amination of the resulting ketone 138. Upon treatment with formaldehyde, a Mannich-type cyclization produced luciduline (140), a known precursor of nankakurines.\textsuperscript{[150]}

In a recent study, Overman and co-workers reported that 92 and 93 showed no effect on neurite outgrowth in rat hippocampus H-19 cells,\textsuperscript{[148b]} which stands in contrast to the previously reported results.\textsuperscript{[116b]} Certainly, further biological investigation of these intricate \textit{Lycodium} alkaloids would be necessary to unveil their biological potential.

### 2.4. Cyathane Diterpenoids

Isolated from fungi, sponges, and fruiting plants, cyathane diterpenes possess a variety of bioactivities including antimicrobial activity and cytotoxicity against certain tumor cells.\textsuperscript{[151]} In addition, erinacines\textsuperscript{[152]} scabronines\textsuperscript{[153]} and cyrneines\textsuperscript{[154]} were found to induce NGF synthesis in 1321N1 human astrocytoma cells and mouse astroglial cells as well as promote neurite outgrowth in PC-12 cells at low micromolar concentrations. From a chemical point of view, the cyathane natural product family possess a skeleton with 20 carbon atoms (141) and a 5-6-7 fused tricyclic ring system (Figure 8).

Erinacines A–F (142–147; Figure 8) were isolated from the cultured mycelia of \textit{Hericium erinaceum} by Kawagishi et al.\textsuperscript{[152]} These cyathane xylosides are able to stimulate NGF secretion in mouse astroglial cells, albeit at rather high concentrations (1–5 mM). The in vivo effect of erinacine A (142) was also studied. Specifically, rats treated with 142 showed an increase in the levels of both noradrenaline and homovanillic acid, and displayed enhanced NGF secretions in both the locus coeruleus and hippocampus.\textsuperscript{[156]} Moreover, erinacine E is a selective agonist of κ-opioid receptors,\textsuperscript{[157]} which are present on the peripheral terminals of primary afferent neurons. It has been reported that activation of these receptors reduces hyperalgesia in a rat model of inflammation.\textsuperscript{[158]}

An efficient synthesis of (±)-erinacine A (142), was reported by the Snider research group (Scheme 24).\textsuperscript{[159]} Key to this strategy was an intramolecular carbonyl-ene reaction\textsuperscript{[160]} of 157 that furnished erinacine A aglycon (140). The synthesis of 158, also known as allocyathin B\textsubscript{2}, has also been reported by various research groups.\textsuperscript{[161]}

Nakada and co-workers recently disclosed a divergent synthesis of (−)-erinacines B (143)\textsuperscript{[162]} and \textit{E} (146),\textsuperscript{[162e,163]} by using 161 as the common intermediate (Scheme 25). The tricyclic motif of 161 was constructed through a sequence of three steps that included: a) carbomethoxylation of ketone 159 with Mander's reagent,\textsuperscript{[164]} b) cyclopropanation, and c) SmI\textsubscript{2}-assisted ring expansion. Interestingly, the D ring of...
could be constructed during a Swern oxidation of diol 162, presumably through the presence of triethylamine. In turn, a well-designed biomimetic intramolecular aldol reaction [163] followed by a 1,2-migration of a benzoyl group (Scheme 25) produced the motif 164, thus paving the way for the synthesis of erinacine E (146).

Scabronines A–C (148–150), E (151), and G (152) were isolated from the mushroom Sarcodon scabrosus. Compounds 148 and 152 potently induce NGF synthesis in 1321N1 human astrocytoma cells in a concentration-dependent manner. It was also found that 148 and 152 enhanced NGF mRNA by 3.2-fold and 3.6-fold, respectively, in the same cell line. However, it was observed that the concentration of NGF synthesized in response to these compounds was not sufficient to induce differentiation of PC12 cells. Based on this finding, the authors suggested that other neurotrophic growth factors might be involved in the PC12 cell differentiation process.

The Danishefsky research group initiated a synthesis of (-)-scabronine G (152) from enone 165, which is available from the Wieland–Miescher ketone (Scheme 26). Nazarov cyclization of 165 produced the A-ring motif of 166 which was transformed into 167 over several steps. 167 was then subjected to lithiated (methoxymethyl)phenyl sulfide to afford alcohol 168. Treatment of 168 with HgCl₂ under acidic conditions facilitated the desired one-carbon-atom
expansion of the C ring to furnish conjugated cycloheptenone
169, which was then converted into 152.[167]

In 2011 another synthesis of (−)-scabronine G (152) was
reported by the Kanoh, Iwabuchi et al. (Scheme 27).[168] Key
to this synthesis was an intramolecular double 1,4-addition of
170 under TMSI/HMDS conditions, which afforded the bridged tricyclic scaffold of 171. Another critical step was
a Lewis acid induced Prins cyclization of 172 to construct the
seven-membered ring of 173.[159] More recently, the Nakada
research group reported a divergent synthesis of (−)-scabronines A (148) and G (152).[169]

In addition, the scabronine G methyl ester (153) was
synthesized from 152 and biologically evaluated by the
Nakahata research group.[170] This compound displayed
stronger neurite outgrowth activity and NGF-synthesis-
inducing activity than scabronine G in 1321N cells and PC-
12 cells (in the 153-conditioned 1321N cell medium). Similar
activities have been reported by Danishefsky and co-work-
ers.[165] Furthermore, the synthetic analogue 169 was found to
possess a 30% greater neurite-outgrowth activity than 153.[169] Additiona l studies on the effe ct of 153 on NGF synthesis in
1321N cells were reported by Nakahata and co-workers.[170]
These authors suggested that the 153-induced NGF synthesis
is mediated by the activation of PKC−ζ, an isoform of protein kinase C.[170]

Interestingly, scabronine M (174) significantly inhibited
NGF-induced neurite outgrowth in PC-12 cells without
showing any cytotoxicity at the concentrations tested
(Figure 9). Gao and co-workers suggested that this activity
might be due to suppressing the phosphorylation of TrkA and
ERK. Moreover, the epoxide motif of 174 was proposed to be
the reason for the potent inhibition of neurite outgrowth.

Cyreneines A (154) and B (155) were isolated from the mushroom Sar-
codon cypreus in 2006.[194] Both compounds
induced moderate neurite outgrowth in PC-12 cells at high micromolar con-
centrations without significant toxicity.[194] It was reported that 154 upregulates the
transcription factors activator protein-1 (AP-1) and NF-κB. Moreover, the activity
of Rac-1, a small GTPase protein
that regulates actin dynamics, was increased, while expression
of a dominant-negative Rac-1 mutant significantly inhibited
the 154-induced neurite outgrowth in PC-12 cells. Based on these
findings, it was suggested that 154 promotes neurite
outgrowth through a Rac-1-dependent mechanism.[172]

The Gademann research group recently reported a total
synthesis of (+)-cyreneine A (154) starting from commercially
available (R)-carvone.[173] Critical to this strategy is an
intramolecular Heck coupling reaction that constructed the
tricyclic core of 176. Treatment of 176 with lithiated dibromo-
methane followed by lithium/halogen exchange resulted in
a one-carbon-atom ring expansion to form the desired tricyclic motif of 178 (Scheme 28).

Figure 9. Structure of scabronine M (174).

Figure 10. Neurotrophic trichothecanes.
2.6. Manzamine Alkaloids

Isolated from marine sponges of the genera *Haliclon* and *Pellina*, the manzamine family is comprised of various structurally complex indole alkaloids. Among them, manzamine A (195) displays a broad biological profile that includes antitumor, antibacterial, insecticidal, antimalarial, anti-inflammatory, and anti-HIV activities. In addition, manzamines A (195), E (197), F (198), and 8-hydroxymanzamine A (196) were shown to exhibit potent neurotrophic activities in Neuro 2A cells at concentrations as low as 1 μM (Figure 11). Furthermore, it was proposed that 195 could act through the same mechanism reported for lactacystin (1).
the tetrahydropyridine motif of 199. The transiently formed cyclobutane ring of 200 underwent a retro-Mannich fragmentation, and the resulting iminium ion was trapped by the C11 enol to form aminal 201. The corresponding C—O rearrangement furnished the crucial tetracyclic motif 202 in pyridine/AcOH at elevated temperature.

Martin and co-workers also reported an efficient synthesis of (+)-195. The AB ring system of 195 was constructed through a one-pot Stille coupling between vinyl bromide 203 and vinyltributylstannane. This reaction produced in situ the corresponding diene, which underwent an intramolecular Diels–Alder cyclization to form 204. In turn, the macroyclic ring of 206 was built through the assistance of a Z-selective (ca. 8:1) ring-closing metathesis (RCM) reaction of the two terminal alkenes of 205. Interestingly, the C32/C33 terminal alkenes of 205 did not interfere with the formation of this 13-membered ring (Scheme 32).

Another interesting synthesis of (+)-195 was reported by the Fukuyama research group. An intermolecular Diels–Alder reaction between the Danishefsky-diene-like motif 207 and chiral butenolide 208 provided the B ring of 209. Subsequently, a well-designed [3,3] sigmatropic rearrangement of allyl cyanate 210 furnished the desired pyrrolidine motif of 211. Notably, the stereocentrivity of the preformed macrocycle dictated the stereoselectivity during the subsequent chemical steps (Scheme 33).

An alternative synthesis of (+)-195 was recently accomplished by Dixon and co-workers. Highlights of this synthesis include: a) a three-component nitro-Mannich lactamization cascade between 212, formaldehyde, and amine 213 to form the A-ring motif of 214; and b) a novel reductive nitro-Mannich cyclization between the C12 alkyl nitrate and the five-membered lactam moiety of 215 in the presence of Ti(OiPr)4/PhSiH2 to generate the B ring of 216 (Scheme 34).

In addition to its neurotrophic activities, 195 was found to be a potent non-ATP competitive inhibitor of GSK-3β, a serine-threonine kinase known to phosphorylate the microtubule-associated protein tau in mammalian cells. It has been found that overexpression of GSK-3 leads to abnormally hyperphosphorylated tau protein, which can no longer bind to microtubules but instead are free and available to undergo filament assembly. Such hyperphosphorylation is believed to be an early event in various neuropathological conditions including brain impairment, learning/memory deficits, depression, AD, and ALS. Thus, inhibiting the abnormally upregulated GSK-3 activity has become an important strategy for NDD treatment. A potential binding site of 195 to GSK-3 was reported.

Scheme 32. Part of the total synthesis of (+)-manzamine A (195) by Martin et al.[187]

Scheme 33. Part of the total synthesis of (+)-manzamine A (195) by Fukuyama and co-workers.[184] PMP = p-methoxyphenyl.

Scheme 34. Part of the total synthesis of (+)-manzamine A (195) by Dixon and co-workers.[190]
2.7. Steroids

Various steroids, such as NGA0187 (217) and withanolide A (218), display interesting neurotrophic activities (Figure 12). NGA0187 was isolated from Acremonium sp. TF-0356 and is considered to be the first neurotrophic steroid.[194,195] It was found that 217 induces neurite outgrowth in PC-12 cells at a concentration of 30–60 μM.[194,195] The Danishefsky research group reported a synthesis of (−)-217 starting from adrenosterone (Scheme 35).[195] The strategy is highlighted by a conjugate addition of the lithium-copper complex of 220 to enone 219 to produce advanced intermediate 221. Moreover, several C17 side chain truncated analogues of 217 have been synthesized and evaluated. These analogues have shown no appreciable activities, which suggests that the C17 side chain may play a critical role in the neurotrophic activity of NGA0187.[195]

Withanolide A (218) and related steroids were isolated from the roots of Withania somnifera and have shown potent neurite outgrowth activities in human neuroblastoma SH-SYSY cells at 1 μM.[196] The Gademann research group designed a synthesis of (−)-218 starting from pregnenolone (224; Scheme 36).[197] Crucial steps of this approach include: a) a vinylogous aldol reaction between aldehyde 225 and the lithium enolate of 226 to afford lactone 227; and b) an elegant singlet oxygen-ene reaction to produce the C5 tertiary alcohol of 228. The singlet oxygen was generated in situ from oxygen under irradiation with a Na lamp in the presence of meso-tetraphenylporphyrin (TPP) as the sensitizer. It has been demonstrated that 218 significantly induces axonal/dendritic regeneration and synaptic reconstruction in the impaired mouse brain and damaged rat cortical neurons.[196a] However, conflicting results precluded a clearer view of the mechanism of action of 218[197a,199].

Certain steroids, such as β-estradiol, were shown to induce neurite outgrowth through the MAPK pathway (Figure 2)[200] and enhance synaptophysin expression via membrane estrogen receptor and p44 MAP kinase.[201] In addition to 217 and 218, several other steroids[202] such as deoxygedunin,[203] allopregnanolone,[204] and S19159,[205] have been reported to possess neurotrophic activities.[206] The signaling mechanisms of these steroids are likely similar to that of β-estradiol.[196b,206]

2.8. Polyprenylated Acylphloroglucinols

Polyprenylated acylphloroglucinols (PPAPs) possess an intricate polycyclic structure and a broad range of important bioactivities.[207] Hyperforin (229) and garsubellin A (230) are two representative samples (Figure 13). The neurite outgrowth effects of hyperforin (229) have been well documented.[208] On the other hand, garsubellin A (230), isolated from the wood of Garcinia subelliptica, was proposed to
display potent neurotrophic activities by enhancing choline acetyltransferase (ChAT) activity in P10 septal neurons of cultures rats (154% relative to control).\[209\]

Hyperforin (229) was isolated from the herb St. John’s wort (Hypericum perforatum) in 1971.\[210\] In addition to other bioactivities,\[211\] 229 was shown to induce promising neurological effects. For example, the antidepressant activity of 229 was attributed to its ability to inhibit neuronal uptake of various neurotransmitters.\[208a–f\] Furthermore, 229 is known to induce neurite outgrowth (10 μM)\[206f\] by directly and selectively activating a member of the canonical transient receptor potential (TRPC) family of ion channels.\[206g,212\] Moreover, 229 was reported to affect the processing of the amyloid precursor protein (APP)\[213\] and to prevent formation of the amyloid-β (Aβ) deposit, Aβ neurotoxicity, and spatial memory impairments.\[214\] In addition, 229 stimulates the expression of TrkB, the selective BDNF receptor.\[215\]

A total synthesis of (−)-229 was accomplished by Kanai, Shibasaki, and co-workers.\[216\] This approach stems from a catalytic asymmetric Diels–Alder reaction\[217\] between dienophile 231 and diene 232 promoted by an FeIII complex with PyBOX ligand 233 (Scheme 37). Claisen rearrangement\[92\] of allyl enol ether 235 installed the C1 quaternary center of 236. The C5 quaternary center of 238 was set through an intramolecular aldol reaction of 237.

Shair and co-workers reported an efficient approach of (+)-229 (Scheme 38).\[218\] Key to the hyperforin core 240 was the use of a TMSOTf-mediated epoxide-opening cyclization cascade. During this cyclization, the chair transition state is favored over the boat conformation, which offers perfect stereocontrol. Another key step involves a Keck radical allylation under allyl-SnBu3/BEt3/air conditions. This step was followed by olefin metathesis using the Hoveyda-Grubbs second-generation catalyst in the presence of 2-methyl-2-butene to yield advanced intermediate 242. More recently, the Nakada research group reported a total synthesis of (−)-229.\[219\]

Kanai, Shibasaki, and co-workers also reported a total synthesis of (±)-garsubellin A (230).\[220\] The B ring of this compound was set through a Claisen rearrangement\[92\] of 243 followed by a ring-closing metathesis. Cleavage of the carbonate group in 245 and a subsequent Wacker-type oxidative cyclization gave rise to the tricyclic motif of 246 (Scheme 39).

In the total synthesis of (±)-230 by Danishefsky and co-workers the A ring was formed by an iodine-induced cyclization between the C6 center and the C7-C8 olefin of 247 (Scheme 40).\[222\] A subsequent oxidative iodination installed the vinyl iodide motif in 248 that, upon metalation and
allylation, allowed installation of the C2 side chain. A similar sequence was implemented for the conversion of 250 into 251.

A formal synthesis of (±)-garsubellin A (230) was accomplished by the Simpkins research group. (224)

2.9. Tricholomalides

Tricholomalides A–C (252–254) were isolated from the mushroom *Tricholoma* sp. and were found to promote neurite outgrowth in PC-12 cell lines at concentrations of 100 μM (Figure 14). (225) A total synthesis of (±)-252 and (±)-253 was reported by Danishefsky and co-workers, thus allowing revision of the C2 configuration (Scheme 41). (226) The bicyclic motif of 258 was produced through a homo-Robinson annulation. (226b) Compound 259 was then subjected to a [2+2] cycloaddition followed by dechlorination to afford the tricyclic motif of 260. Subsequently, the cyclobutanone motif of 260 underwent a Baeyer–Villiger oxidation (227) under basic TBHP conditions to yield lactone 261.

The first total synthesis of (±)-neovibsanin B (263) was accomplished by Imagawa, Nishizawa et al. (229b) This synthesis is based on the formation of lactone 265 through an intramolecular Diels–Alder reaction (72) to yield a mixture of two isomers 265a and 265b, which were both carried forward (Scheme 42). A conjugate addition/lactonization cascade reaction was used to convert 266 into 267. The neurotrophic activity of the racemic 263 was evaluated in PC-12 cells and its activity was found to be comparable to that of enantiomerically pure 263. (229b)

An enantioselective synthesis of (+)-neovibsanin B (263) was accomplished by Esumi, Fukuyama et al. (229c) The strategy features a stereocontrolled conjugate vinylation of chiral oxazolidinone 268 to form the C11 quaternary center (Scheme 43). This reaction was followed by a Pd-mediated carbonylation/carbamethoxylolation cascade reaction to furnish the A ring of 271.

Moreover, the Williams research group reported the synthesis of (±)-4,5-bis-epi-neovibsanin A and B. (230) These

Neovibsanin A (262) and B (263) were isolated from the leaves of the poisonous plants *Viburnum awabuki* (Figure 15). (228) Both compounds were reported to induce NGF-mediated neurite outgrowth in PC-12 cells at 40 μM. (229)
effects.[235] As a consequence of its promising biological profiles, various synthetic studies of 273 have been reported.[236] 14-Norpseurotin (274)[237] was isolated from the marine-derived fungus Aspergillus sydowi PFW 1-13 and was reported to induce neurite outgrowth of PC-12 lines at concentrations of 10 µM.[238] A member of the flavonoid family, 7,8-dihydroxyflavone (275), was recently found to be a selective TrkB agonist through Erk1/2 and Akt activation.[239] Moreover, its neuroprotective effects[239,240] and optimized analogues[241] have been recorded. In addition, several other natural flavonoids have been reported to possess activities to promote neurite outgrowth or neurogenesis.[242] Aspermyatin A (276) was isolated from a marine-derived fungus Aspergillus sp. and was found to display neurotrophic effects in PC-12 cells at a concentration of 50 µM.[243] A synthesis of 276 has been reported by the Shishido research group.[244] Gelsemiol (277)[245] was isolated from the Paraguayan plant Verbena littoralis H. B. K. and was shown to promote NGF-mediated neurite outgrowth in PC-12 cells at concentrations between 100 and 300 µM. Gademann and co-workers have reported an efficient synthesis of 277.[246]

Various protein kinase C (PKC) activators, such as phorbol ester (PMA, 278)[247] and bryostatin 1 (279)[248] were found to significantly promote neurite outgrowth in PC-12 cell lines[249] and primary culture of chicken dorsal root ganglion (DRG) neurons.[250] Other notable neurotrophic PMA natural analogues include kirkinine (280).[251] kirkinine B, mezerein, and synaptolepis factor K7.[252] Pioneering syntheses of phorbol and related daphnane natural products have been reported by the research groups of Wender,[253] and Cha.[254] In addition, multiple impressive syntheses of bryostatin 1 (270)[255] and its natural analogues have been reported by the research groups of Kek,[256] Masamune,[257] Evans,[258] Nishiyama/Yamamura,[259] Trost,[260] Kri- sche,[261] and Wender.[262]

Caryolanemagnol (281) and clovanemagnol (282) were isolated from Magnolia obovata and have been found to enhance neurite outgrowth as well as increase ChAT activity at a concentration of 0.1 µM.[263] Studies conducted by Siegel and co-workers have led to a bioinspired synthesis of 281 and 282.[264] The authors also confirmed the potent neurotrophic activity of 273 in embryonic hippocampal and cortical neurons at concentrations of 10 nM.[265] A member of the caged Garcinia xanthones,[266] gambogic amide (283), has shown significant neurotrophic activity at a low nanomolar concentration by binding to and activating TrkA, thereby promoting its dimerization and autophosphorylation.[267] In addition, 283 also exhibited neuroprotective effects.[268]

The clerodane diterpenoid[269] pychonal (284) was isolated from Psychotria olacoides as a mixture of the hemiacetal and aldehyde form.[269] This equilibrium mixture was shown to exhibit neurite outgrowth promoting activities on NGF-mediated PC-12 cells at concentrations ranging from 0.1 to 10.0 µM. The neurotrophic metabolite epolactaene (285) was isolated from the fungal strain Penicillium sp. BM 1689-p.[270] 285 was shown to promote neurite outgrowth in a human neuroblastoma cell line (SH-SY5Y) at concentrations ranging from 10 µM to 25 µM.[271,272] As a result of its promising biological activity, various syntheses have been

2.11. Miscellaneous Natural Products

In addition to the above-mentioned natural products, nature has produced other fascinating small molecules that possess various levels of architectural complexity, yet they share a similar level of exciting neurotrophic activity. Representative examples of such natural products are shown in Figure 16.

Panaxytritol (272) is an active component of red Ginseng[232] and its chemical synthesis has been reported by several research groups.[233] Among them, Danishefsky and co-workers have shown that 272 promotes NGF-induced neurite outgrowth in PC-12 cells at a concentration of 60 µM.[234] Talauminid (273) is a tetrahydrofuran neolignan that was isolated from the roots of Aristolochia arcuata.[235] It promotes neurite outgrowth of cultured rat cortical neurons at a concentration of 1–30 µM and exhibits neuroprotective
Deoxygedunin (286), a natural product isolated from Indian neem trees (Azadirachta indica), was found to act as a BDNF mimic and exhibited TrkB activation in rat hippocampal neurons at nanomolar concentrations.[203] Kansuinin E (287),[270] a macrocyclic jatrophane diterpene,[270,271] was found to promote neurotrophic activity, presumably through TrkA activation.[271c] A related study has also suggested that activation of cyclooxygenase plays an essential role in NGF synthesis.[271b] Tripchlorolide (288), an immunosuppressive extract of Chinese herb Tripterygium wilfordii Hook F, was reported to induce neurotrophic activity in embryonic mesencephalic neurons of rats and displayed neuroprotective effects in dopaminergic neurons from 1 pM to 10 nM.[288] It was reported to stimulate BDNF mRNA expression.[273] Moreover, its neuroprotective properties have been evaluated in several studies.[272,273] The neurological activity of 288 might be similar to another immunosuppressant FK506 (tacrolimus).[274]

A series of pyridone alkaloids (289),[275] such as tenellins,[276] bassianins,[276a–c] farinosones,[277] and militarinones,[278] share a common chemical skeleton and promising neurotrophic activities. In 1982, the Williams research group reported an efficient synthesis of tenellin.[279] More recently, a divergent synthesis of various neurotrophic pyridone alkaloids was reported by Gademann and co-workers.[275d,280] The related farinosone C (290)[277] also promotes neurite outgrowth in NGF-mediated PC-12 cell lines at a concentration of 50 μM.[281] The authors reported a synthesis of 290 and have disclosed that L-tyrosinolamide represents its pharmacophore.[281] Studies in PC12 cells suggest that certain militarinones induce persistent neuritic differentiation by elevating the intracellular cAMP levels that, in turn, affect TrkA receptor signaling.[278c] Such persistent activation of the PI3/Akt and MEK/ERK pathways was shown to upregulate p53 and induce the release of AIF from mitochondria, ultimately resulting in cell apoptosis in Neuro 2a mouse neuroblastoma cells. Based on these findings, the authors concluded that the effect of militarinones depends on the basal expression of p53; specifically, these compounds induce apoptosis in cells with high p53 expression but prompt...
neuritic differentiation in cells where the p53 levels are low.\cite{276}

Various macrolides, such as amphotericin B (291) and FK506 (tacrolimus, 292), exhibit remarkable neurotrophic profiles. 291 was originally isolated from the filamentous bacterium Streptomyces nodosus\cite{282,284} and is often used as an antifungal agent.\cite{285} The exciting neurological activity of 291 was recently revealed.\cite{286} This compound was shown to promote neurite outgrowth in rat postnatal cerebellar neurons and rat embryonic cortical neurons. It was also found to prevent the activities of the major myelin- and glial-associated inhibitors, which are the crucial factors that suppress neuron regeneration upon spinal cord injury.\cite{274} A stereoselective synthesis of 291 has been reported by Nicolau et al.\cite{287} A recent mechanistic study suggested that 291 antagonizes CNS inhibitors to promote axon growth through the activation of the Akt pathway, which suppresses the activity of GSK-3.\cite{286}

FK506 (tacrolimus, 292) was isolated from Streptomyces tsukubaensis in 1987.\cite{288} In addition to its remarkable function in the immune system, 292 has also shown intriguing neuroprotective and neurotrophic activities, including promotion of neurite outgrowth in PC-12 cells and peripheral neurons.\cite{289} 292 was shown to induce functional improvements of peripheral nerve damage and spinal cord injury.\cite{274} Furthermore, it was reported that 292 promotes the proliferation of cultured Schwann cells and NGF secretion at a concentration of 10 nM.\cite{290} In addition, 292 was reported to promote NGF-induced neurite outgrowth through the MAP kinase pathway.\cite{291} The neuroprotective potential of 292 following CNS injury has been evaluated.\cite{274} Although the detailed mechanism remains unclear, it is noted that binding to two members of the immunophilin family, FKBP-12 and FKBP-52, are critical for its neuroprotective effects.\cite{292} Since CNS injury is associated with the activation of the immune response, it is suggested that the immunosuppressive activity of 292 could induce the observed neuroprotective effects.\cite{274} Indeed, it has been shown that immunophilin ligands possess neurotrophic activities.\cite{292,293} Therefore, it is reasonable to find that several natural or synthetic analogues of 292, such as rapamycin\cite{289,290} and FK1706,\cite{295} promote neurite outgrowth in PC-12 cells (rapamycin, 1 nM) and human neuroblastoma SH-SY5Y cells (FK1706, 1 nM). Several total syntheses of 292 have been accomplished by Merrck,\cite{296} Schreiber and co-workers,\cite{297} and Ireland et al.\cite{298} In addition, the research groups of Danishefsky,\cite{299} Shi,\cite{300} and Smith\cite{301} have completed formal total syntheses. The synthetic efforts toward 292 have been reviewed by Nakata\cite{302} and Ley and co-workers.\cite{303}

Stolonidiol (293) was isolated from the Okinawan marine soft coral Clavularia sp.\cite{103,304} Aside from its potent cytotoxicity to P388 leukemia cells, 293 was reported to possess significant ChAT activity in primary cultured basal forebrain cells and clonal septal SN49 cells at a concentration of 0.3 μM.\cite{105} A synthesis of stolonidiol was reported by Yamada and co-workers.\cite{305} Xanthofulvin (SM-216289, 294) and vinaxanthone (295) were isolated from the cultured broth of a fungus Penicillium sp. SPF-3059.\cite{306} Significantly, these two compounds were found to strongly inhibit the activity of semaphorin3A (Sema3A), an inhibitor of axonal regeneration, with no observable cytotoxicity. Studies in animals validated the clinical promise of 294.\cite{307} These findings may pave the way for the development of agents to treat injured spinal cords. Recently, Siegel and co-workers have reported an impressive synthesis of 294 and 295.\cite{308}

3. Conclusions and Perspectives

It is widely accepted that natural products have evolved to perform, often in synergy, a wide array of functions that are beneficial to the producing organism. In fact, they are considered to be “privileged structures”\cite{299} which, upon subtle changes aimed to improve their pharmacokinetic and pharmacodynamic profile, can lead to the development of new medicines.\cite{310} For example, natural products and their structural relatives still comprise more than 50% of the drugs used clinically.\cite{311} Equally important is the role of natural products as tools in chemical biology, where the aims are to develop new bioassays, to characterize cell signaling pathways, and to chemically evaluate biological events.

Neurodegenerative diseases is a generic term applied to a variety of conditions that arise from a chronic breakdown and deterioration of the nerve cells, in particular those of the central nervous system.\cite{312} Most commonly, these diseases manifest in elderly people and in industrialized societies, where the life expectancy is long, and they impose severe strains on the social welfare systems. Preventive approaches against neurodegeneration require consideration of various genetic and epidemiological studies that are not easy to correlate. In addition, such approaches are difficult to implement in the case of a traumatic event, such as spinal cord injury. Research into the underlying cause of neurodegeneration is far from complete and no cures for these diseases have been found. The current approach is to produce symptomatic relief or correct neurotransmitter deficiencies and enzymatic breakdown.\cite{313,314}

Neurotrophins have been identified as promoters of neuronal survival, development, and function, including synapse formation and remodeling of the synaptic network.\cite{315} The importance of these molecules is underscored by the severe neurological effects observed in animals in which neurotrophins or their receptors have been deleted.\cite{316} Despite their unambiguous importance in biology and physiology, drug development approaches based on neurotrophins have encountered several problems associated with oral availability, insufficient delivery to the brain, and high manufacturing cost.\cite{317,318} Natural products and related molecules with neurotrophic activity can, in principle, overcome these obstacles.\cite{10,11,319} In fact, several compounds are currently in clinical trials for neurodegenerative diseases.\cite{318} A recent example is bryostatin 1 (297),\cite{317,318} which, in turn, highlights the importance of developing robust synthetic strategies that can be used to evaluate and optimize the biological properties of the parent structure.\cite{319}

The synthetic strategies reviewed above offer confidence that the privileged motifs of various neurotrophic natural products can be constructed in the laboratory. Constant advances in the area of synthetic methods promise to further improve these strategies, particularly as they relate to
efficiency, flexibility, and overall cost. Apart from certain notable exceptions that have been discussed in this Review, the chemical biology of neurotrophic natural products has not been explored methodically. This could be due to the complexity of pathways that account for neural degeneration and the difficulties related to conducting biological experiments in primary neural cells. On the other hand, several key proteins that regulate neuronal growth have been identified as potential targets for therapeutic intervention against neurodegeneration. In addition, advances in high-throughput screening, cellular phenotype imaging, stem cell technology, and regenerative medicine promise to facilitate and accelerate such studies. It is critical to take advantage of this progress on all fronts and push the frontiers of chemical neurobiology further. This task is particularly important and timely due to the recently announced Brain Activity Map (BAM) project. Reminiscent of the Human Genome Project, this initiative will attempt to reconstruct the entire neural activity in the brain. With such an ambitious goal in mind, chemical neurotrophins are expected to play a critical role in the chemical evaluation of neural circuit remodeling, cognitive functions, and behavior.

Financial support from the National Institutes of Health (CA 133002) is gratefully acknowledged. We also thank the U.S. Department of Education for a Fellowship to M.H.L. through GAANN grant P200A120223. We thank the National Science Foundation for instrumentation grants CHE9709183 and CHE0741968. We also thank Dr. Lynnie Trzoss, Weng K. Chang, and Prof. William C. Mobley for contributions to the research described in this Review, and Professors Jerry Yang and Carlos A. Guerrero (UCSD) for useful comments.

Received: March 17, 2013
Published online: December 18, 2013

Neurotrophic Natural Products


