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Microtubule Stabilizing Agents as Potential Treatment for Alzheimer's Disease and Related Neurodegenerative Tauopathies

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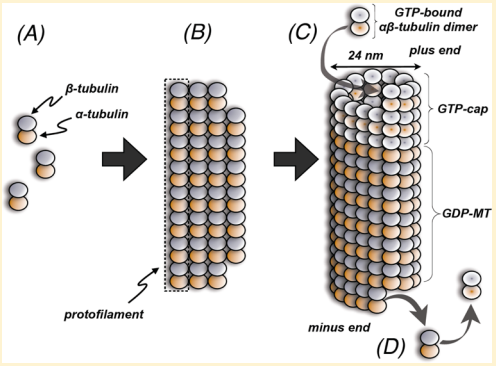
ABSTRACT: The microtubule (MT) associated protein tau, which is highly expressed in the axons of neurons, is an endogenous MT-stabilizing agent that plays an important role in axonal transport. Loss of MT-stabilizing tau function, caused by misfolding, hyperphosphorylation, and sequestration of tau into insoluble aggregates, leads to axonal transport deficits with neuropathological consequences. Several in vitro and preclinical in vivo studies have shown that MT-stabilizing drugs can be utilized to compensate for the loss of tau function and to maintain/restore effective axonal transport. These findings indicate that MT-stabilizing compounds hold considerable promise for the treatment of Alzheimer disease and related tauopathies. The present article provides a synopsis of the key findings demonstrating the therapeutic potential of MT-stabilizing drugs in the context of neurodegenerative tauopathies, as well as an overview of the different classes of MT-stabilizing compounds.



MICROTUBULE (MT) DYNAMICS, AXONAL TRANSPORT, AND NEURODEGENERATIVE TAUOPATHIES

Microtubules (MTs), essential constituents of the cytoskeleton in eukaryotic cells, are involved in a number of important structural and regulatory functions, including the maintenance of cell shape, intracellular transport machinery, as well as cell growth and division. Structurally, MTs are hollow tubes of approximately 24 nm in diameter that result from the head-to-tail polymerization of α- and β-tubulin heterodimers (Figure 1).[1]

MTs are highly dynamic structures that alternate between growing and shrinking phases.[2] Because of this dynamic nature, MTs can undergo relatively rapid turnover and form a variety of different arrays within cells. The presence of various tubulin isoforms, post-translational modifications, and interactions with MT-associated proteins (MAPs) play an important role in determining the morphology, stability, and ultimately, the particular function of the MT lattice in different cell types.

In the axons of neurons, MTs form polarized linear arrays with the plus ends directed toward the synapses and the minus ends toward the cell body. Such an organization of axonal MTs provides both structural support and directionality for the intracellular transport of proteins and vesicles to and from the cell body and the synapses (Figure 2). This cytoskeletal structure, together with molecular motors such as kinesins and dyneins, forms the axonal transport machinery, which is critical to the viability of neurons,[3] and notably, axonal transport defects are observed in several neurodegenerative diseases.[4] In the case of tauopathies, which are a group of neurodegenerative diseases that include Alzheimer's disease (AD) and related forms of frontotemporal lobar degeneration (FTLD), axonal transport deficits are thought to arise at least in part from the misfolding and aggregation of the MT-associated protein (MAP) tau.[5] These tau aggregates form intracellular filamentous inclusions, known as neurofibrillary tangles (NFTs) and neuropil threads, which together with the senile plaques comprising amyloid β (Aβ) peptides, constitute the characteristic lesions that are diagnostic of AD. Furthermore, the presence of tau aggregates in the absence of deposits of Aβ peptides or other proteinaceous inclusions comprises the defining lesions of other tauopathies, such as Pick's disease, progressive supranuclear palsy (PSP), and corticobasal degeneration, which are the most common forms of FTLD.[5]

The protein tau is expressed particularly in the axons of neurons with the primary function to promote MT stabilization.[6] Under physiological conditions, the vast majority of tau molecules are bound to MTs. However, in neurons affected by tauopathies, tau becomes progressively disengaged from the axonal MTs, possibly because of hyperphosphorylation, which is known to reduce the binding affinity of this

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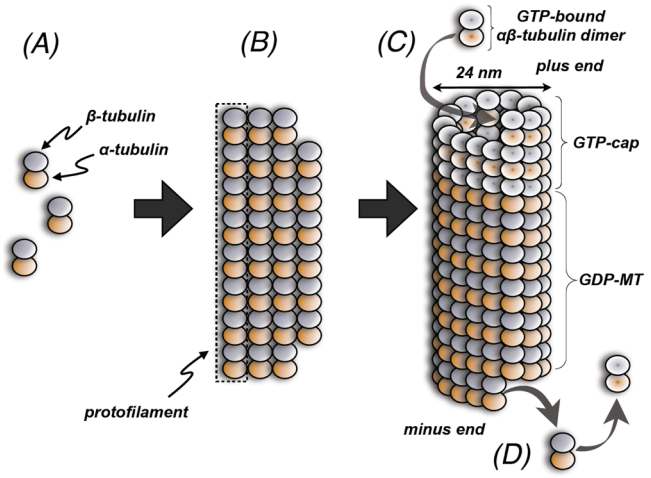

Figure 1. Schematic of the tubulin polymerization process. (A) Head-to-tail polymerization of α- and β-tubulin heterodimers results in the formation of protofilaments. (B) Lateral interactions between protofilaments enable them to assemble into sheets of tubulin, which fold on themselves to form hollow MT structures typically comprising 13 protofilaments per MT. (C) During MT-polymerization, guanosine 5′-triphosphate (GTP)-bound α,β-tubulin heterodimers are added at the polymerizing end of the MT. Concomitantly or soon after incorporation into the MT, GTP-bound to β-tubulin is hydrolyzed to the corresponding diphosphate (GDP-MT). The GTP to GDP hydrolysis is not required for MT polymerization; however, this conversion plays an important role in determining the dynamic instability of the MT, as GTP-tubulin forms more stable interactions, while GDP-tubulin establishes comparatively weaker intersubunit interactions and is therefore prone to depolymerization. The presence of a GTP-bound tubulin at the growing end of the MT (GTP cap) protects the MT from depolymerization. Removal of the GTP cap can trigger rapid depolymerization events. (D) Upon depolymerization, released tubulin heterodimers can exchange GDP with GTP and re-enter the polymerization cycle.

protein for the MTs.[7,8] An abnormal detachment of tau from the MTs is thought to alter the dynamics and organization of the axonal MTs, which in turn can trigger or exacerbate axonal transport defects.[3] Furthermore, once detached from MTs and hyperphosphorylated, tau becomes considerably more prone to misfolding and aggregation.[9,10] This misfolded and/or aggregated tau can in turn recruit additional functional tau proteins into the aggregation cascade, contributing further to the destabilization of axonal MTs.[11] Thus, on the basis of the relationship between tau pathology and the appearance of MT[12] and axonal transport deficits, a possible strategy for the treatment of AD and related tauopathies is to employ exogenous MT-stabilizing agents that could compensate for loss of tau maintenance of the appropriate organization and dynamics of the axonal MTs.[13] Such an approach would hold the promise of restoring effective axonal transport in neurons affected by tauopathy and, as a result, prevent synaptic dysfunctions and neuron loss.[13,14]

Over the past several decades, several classes of MT-stabilizing natural products have been discovered (Table 1) with the majority of these having been extensively characterized as cancer therapeutics because of the essential role of MTs in cell division. In contrast, as shown in Table 1, a comprehensive evaluation of the different classes of natural products in the context of neurodegenerative tauopathies has not as yet been achieved. A critical challenge facing the development of CNS-directed MT-stabilizing therapies to treat tauopathies is identifying brain-penetrant compounds that would be effective at nontoxic doses. Indeed, the blood−brain barrier (BBB), which is equipped with relatively impermeable intercellular tight junctions, as well as with active transporters such as the P-glycoprotein (Pgp),[15] is known to be a remarkable obstacle in the development of any CNS-directed therapy.[16] It is estimated that <2% of all potential drug candidates can permeate across the BBB.[17] In addition, MT-stabilizing drugs, which are routinely used in cancer chemotherapy, are known to cause a number of debilitating side effects, which are directly linked to the MT-stabilizing properties of these compounds and include neutropenia[18] and peripheral neuropathy.[19] Thus, even if brain-penetration issues were solved, long-term treatment of tauopathy patients with this class of therapeutics might be difficult because of dose-limiting toxicities. Despite these important challenges, different lines of research have validated the potential utility of MT stabilization as a therapeutic approach to treat tauopathies. In vitro, MT-stabilizing agents have been found to protect cultured neurons against tau-[20,21]

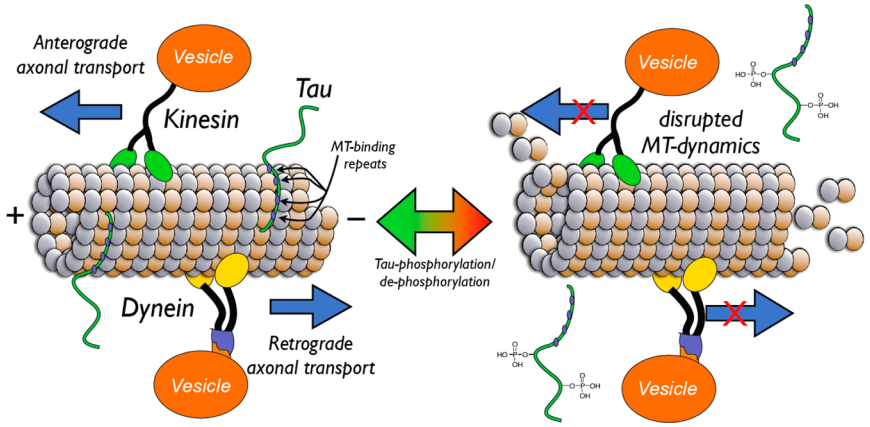

Figure 2. Schematic representation of the axonal transport machinery, which comprises MTs, motor proteins (kinesins and dyneins), and cargos. Kinesins and dyneins move toward the plus and the minus ends of the MTs, respectively, and are involved in either the anterograde (kinesins) or retrograde (dyneins) axonal transport. The MT-stabilizing function of tau plays an important role in the organization and dynamics of axonal MTs and, as such, is critical for axonal transport. Under pathological conditions, hyperphosphorylation of tau leads to an abnormal disengagement of tau from the MTs, which results in disruption of MT dynamics and impaired axonal transport.

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Table 1. Different Classes of MT-Stabilizing Natural Products and Their Stage of Development as Potential Candidates for Neurodegenerative Tauopathies

compd class	brain penetration	stage of development in the context of tauopathies
taxanes	Paclitaxel, docetaxel, and several related analogues are not brain penetrant. Selected analogues and/or prodrugs are reported to exhibit improved brain penetration.[32−35]	Paclitaxel was evaluated in an animal model of tauopathies.[25] Lack of brain penetration prevented further development of this compound.
epothilones	several examples reported to be brain penetrant[36−38]	Epothilone D was evaluated in animal models[26,27] and recently entered phase Ib clinical trial for AD.[28]
discodermolide	not reported	not reported
dictyostatin	not reported	not reported
eleuthesides	not reported	not reported
laulimalide	not reported	not reported
peloruside	not reported	cell-based studies[21]
cyclostreptin	not reported	not reported
taccalonolides	not reported	not reported
zampanolide	not reported	not reported
ceratamines	not reported	not reported

and Aβ-mediated[22−24] neurotoxicity. In vivo, the first demonstration of the therapeutic potential of this type of compounds was reported in 2005,[25] when paclitaxel treatment was found to restore fast axonal transport (FAT) and increase MT density in L5 axons that project from spinal motor neurons to lower limb muscles of T44 tau transgenic (Tg) mice affected by spinal cord tau pathology. Importantly, paclitaxel treatment produced an improvement in the motor weakness phenotype of these Tg mice because of uptake at neuromuscular junctions and retrograde transport.[25] However, paclitaxel does not cross the BBB and is thus unsuitable as a therapeutic candidate for human tauopathies where tau pathology is primarily in the brain. More recently, a series of studies from our laboratories[26,27] and subsequently from Bristol-Myers Squibb[28] (BMS) provided further validation of this therapeutic approach using the brain-penetrant MT-stabilizing agent epothilone D to prevent and ameliorate disease in other lines of Tg mouse models with tau pathology in the brain that resembles that observed in tauopathy patients. In our studies, administration of low weekly doses of epothilone D by intraperitoneal (ip) injections into PS19 mice, which have NFT-like inclusions in the brain,[29] produced normalization of MT density, restoration of FAT, reduction in axonal dystrophy, and decrease in neuronal pathology and death, with consequent improvement in cognitive performance.[26,27] Notably, these effects were seen in both preventative and interventional studies in which epothilone D was administered to PS19 mice either before or after the onset of tau pathology. Similar outcomes on neuropathology and cognition were observed in the BMS studies in which epothilone D was administered to rTg4510 and 3× tau Tg mice.[28]

One important observation that was made in both the paclitaxel[25] and epothilone D in vivo studies[26,28] is that the dose−response curves appeared to be U-shaped, with relatively low doses of the compounds (e.g., 100 times below the cumulative cancer chemotherapeutic dose, in the case of epothilone D[26−28]) being most efficacious. This result indicates that low doses of MT-stabilizing agents may be both necessary and sufficient to restore the dynamics of axonal MTs and normalize FAT to physiological levels and thus produce optimal therapeutic effects. Overstabilization of MTs on the other hand may in fact be counterproductive and could be accompanied by side effects such as peripheral neuropathy. Thus, an important outcome of the sustained low dose treatments with MT-stabilizing drugs is that Tg animals did not show signs of toxicities,[26−28] including peripheral neuropathy and neutropenia.

Collectively, these findings indicate that brain-penetrant MT-stabilizing agents may be useful for the treatment of AD and related FTLD tauopathies. Importantly, BMS has recently initiated a phase Ib clinical trial in which epothilone D is being evaluated in AD patients.[30] Moreover, since ∼80% of Parkinson's disease (PD) patients develop dementia (PDD) by ∼10 years after onset of PD and since AD-like tau pathology is associated with cognitive impairment in PDD, MT-stabilizing agents could be of therapeutic benefit to PDD patients.[31]

The highly promising results obtained from the epothilone D studies in our tau Tg animal models raise the possibility that other MT-stabilizing agents may be identified as alternative and potentially improved clinical candidates. As summarized in Table 1, although a growing number of MT-stabilizing natural products continue to be discovered, to date, only a few selected compounds have been characterized as potential candidates for the treatment of neurodegenerative diseases. In the sections below, we provide an overview of the different classes of MT-stabilizing agents, including natural products and fully synthetic compounds, with a particular focus on those that might be useful to treat AD and other tauopathies.

MT-STABILIZING NATURAL PRODUCTS AND ANALOGUES THEREOF

Taxanes. Paclitaxel (Taxol, **1**, Figure 3), which was isolated in the 1960s from the stem bark of the Western yew, *Taxus brevifolia*,[39] as well as from other species of the Taxus genus, was found to exhibit potent antitumor properties. The structure of paclitaxel was reported in 1971,[40] but the MT-stabilizing properties of this compound remained unknown until 1979, when the Horwitz laboratory in pioneering studies demonstrated that paclitaxel is able to promote MT assembly in vitro.[41] Paclitaxel binds to the lumen (i.e., the inside) of the MT at a binding site found in the β-tubulin subunit,[42] although initial binding of this compound to the outer wall of the MT has been proposed, which may precede the translocation of this drug into the lumen of the MT.[43,44] The luminal binding site, which is commonly referred to as the taxane binding site, is also targeted by the MT-binding repeats of tau;[45] importantly, paclitaxel is found to displace tau from MTs.[46] The binding of paclitaxel within the taxane site in β-tubulin is believed to promote MT stabilization by inducing conformational changes

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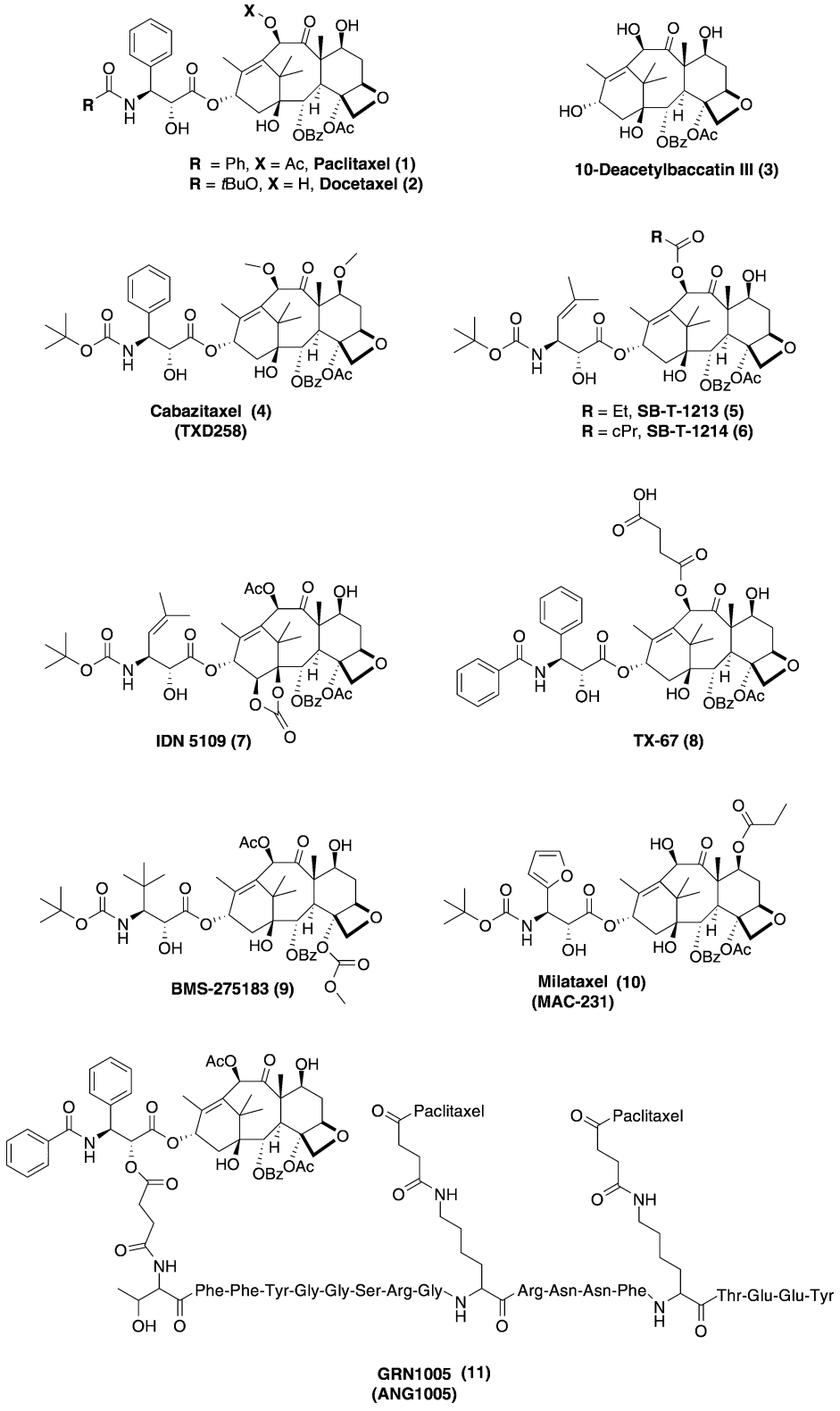

Figure 3. Structures of paclitaxel, docetaxel, 10-deacetylbaccatin III, and selected examples of Pgp-insensitive taxanes.

of the M-loop of β-tubulin that result in more stable lateral interactions between adjacent protofilaments.[47]

Because of the potent antimitotic properties, paclitaxel has been widely used for the treatment of cancer.[48] Much of the interest surrounding the MT-stabilizing class of therapeutics is arguably due to the success of paclitaxel and the closely related analogue docetaxel (Taxotere, **2**, Figure 3) in cancer chemotherapy.[49] Although paclitaxel could be obtained only in limited quantities from the bark of *Taxus brevifolia*, the issue of supply was elegantly solved by semisynthesis from more readily available 10-deacetylbaccatin III (**3**, Figure 3).[50,51] Among the various reported tactics to obtain paclitaxel from **3** (reviewed by Kingston et al.[52]), the Ojima–Holton β-lactam strategy for the coupling of the phenylisoserine side chain proved to be most

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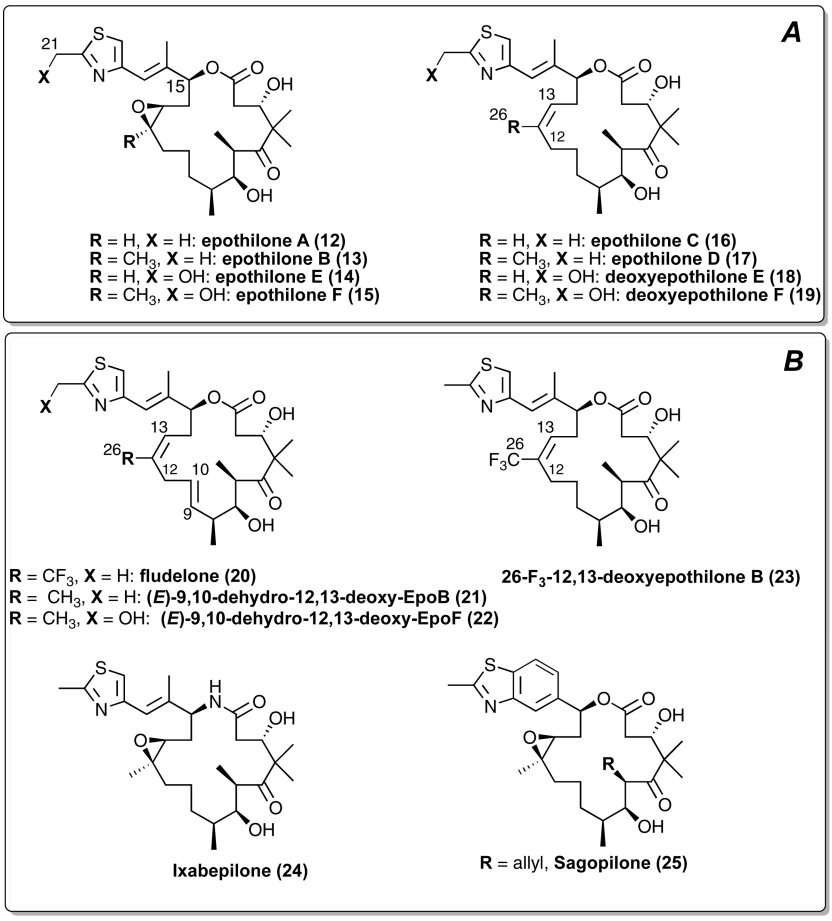

Figure 4. Naturally occurring epothilones (A) and selected examples of synthetic epothilones (B).

effective.[53−56] In addition to these semisynthetic approaches, biotechnological methods of taxane production proved to be successful.[57]

Paclitaxel was the first MT-stabilizing agent to be investigated in an animal model of neurodegenerative tauopathies, the T44 tau Tg mouse, which exhibits tau pathology in spinal motor neurons that project outside the BBB to innervate striated muscles where there is no BBB equivalent.[25] However, the lack of brain penetration of paclitaxel precluded further investigations of this compound in mouse models of tauopathies that, unlike T44 tau Tg mice, more closely resemble human tauopathies with tau pathology in the brain.[36] The limited ability of paclitaxel and docetaxel to diffuse across the BBB is believed to be caused at least in part by the Pgp efflux pump,[58,59] which is highly expressed in the BBB.[60] Thus, taxane analogues capable of overcoming Pgp-mediated transport may result in improved brain penetration. Several examples of compounds of this type have been reported, which include (a) weak Pgp substrates, such as cabazitaxel[32] (**4**, Figure 3), an FDA approved semisynthetic taxane that can saturate the active transporter;[61] (b) taxoids that are also Pgp-inhibitors,[62−64] such as SB-T-1213,[65] SB-T-1214,[66] and IDN-5109[67] (**5**, **6**, and **7**, respectively, Figure 3); and (c) taxoids that are devoid of Pgp-interactions, such as TX-67[34,68] (**8**, Figure 3). Among these Pgp-insensitive taxanes, **7** was found to exhibit greater brain penetration than paclitaxel.[33] Furthermore, pharmacokinetic (PK) studies with **4** revealed that drug exposure in the brain could be significantly enhanced by administering the compound via rapid infusions that resulted in plasma drug levels that are above the threshold needed to saturate Pgp.[61] Other examples of taxanes capable of circumventing Pgp-mediated efflux are orally active BMS-275183[69,70] (**9**, Figure 3) and milataxel,[71,72] also known as MAC-321 (**10**, Figure 3).

In addition to these semisynthetic taxanes, promising results have been reported with brain targeted delivery approaches. An example of this strategy is the paclitaxel−peptide conjugate GRN1005[35] (**11**, Figure 3), a Pgp-insensitive prodrug that exploits the low density lipoprotein receptor-related protein 1 (LRP-1),[73] which is highly expressed in the BBB, to deliver paclitaxel into the brain via receptor-mediated uptake. Compound **11** was recently reported to be active in patients with advanced solid tumors with brain metastases.[74]

Epothilones. Epothilones A and B (**12** and **13**, respectively, Figure 4), originally discovered by Höfle and Reichenbach as antifungal agents produced by the soil bacterium *Sorangium cellulolus*,[75] were later found by scientists at Merck to promote MT assembly.[76] The same studies revealed that the epothilones compete with paclitaxel for the taxane binding site on β-tubulin, suggesting that this class of compounds may act on MTs in a paclitaxel-like manner.[76] This observation led to the hypothesis that epothilones, taxanes, and other classes of MT-stabilizing natural products may share a similar pharmacophore.[77] NMR[78] and computational studies[79] supported this common pharmacophore model; however, an evaluation by electron crystallography of the complex of epothilone A with tubulin polymerized in zinc-stabilized sheets demonstrated that epothilone A and paclitaxel interact in substantially different ways within the same binding pocket in β-tubulin.[80] Such differences in the binding

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modes provide a possible explanation of why the epothilones, but not paclitaxel, retain generally high levels of antimitotic activity in cell lines that are resistant to taxanes because of point mutations in the β-tubulin subunit.[81] An additional distinctive feature of many of the epothilones is that these compounds, unlike paclitaxel and docetaxel, are active against cell lines with multidrug resistance (MDR) caused by the overexpression of Pgp.

In addition to epothilones A and B, several other naturally occurring congeners have been isolated as minor components of fermentation of myxobacteria (**14**–**19**, Figure 4 A).[82] Among these, epothilone D (**17**, Figure 4 A) exhibited a number of promising properties, including a greater therapeutic index as a chemotherapeutic agent, compared to **13**.[83] Clinical trials with this compound, however, were halted because of severe side effects, which included CNS toxicities.[84] These CNS side effects are possibly the earliest evidence that **17** is a brain-penetrant compound, and reports from the patent literature indicated that this is indeed the case.[85] Furthermore, in 2006 epothilone D was reported to be effective in an animal model of schizophrenia, the STOP-null mouse model, which both lacks a MAP known as STOP (stable tubule only polypeptide) and exhibits cytoskeletal defects in CNS neurons.[86] The selection of **17** as preferred candidate compound for efficacy studies in tau Tg animals followed a comparative study in which selected taxanes and epothilone D congeners, including deoxyepothilone F[87] and fludelone[88] (**19** and **20**, respectively, Figure 4), were evaluated for their ability to diffuse across cellular membranes in vitro and enter the brain in vivo. In addition, these compounds were tested for their ability to elicit MT stabilization in the CNS of normal mice, as determined by the elevation in acetylated α-tubulin (AcTub), which is known to be a marker of stable MTs.[89,90] Interestingly, PK studies revealed that significant concentrations of these epothilones in the brain were achieved.[36] Furthermore, these studies showed that **17** exhibits a considerably longer half-life in the brain than in plasma. Similar PK properties have been described for **13**.[38] The ability of **17** to be retained selectively in the brain for relatively prolonged periods of time permitted infrequent (i.e., weekly) administration of the compound in efficacy studies and likely reduced the potential for systemic toxicities in tau Tg mice.[26,27]

After the first total syntheses of **12** by the groups of Danishefsky,[91] Nicolaou,[92] and Schinzer[93] between 1996 and 1997, several synthetic strategies for the efficient synthesis of epothilone analogues have been developed (for comprehensive overview, see Altmann et al.[94] and references therein). Collectively, these studies enabled the synthesis and evaluation of several hundred analogues. Among these, the epothilone lactam ixabepilone (Ixempra, **24**, Figure 4 B) was the first epothilone to receive FDA approval for the treatment of metastatic breast cancer.[95] Other synthetic epothilones in clinical development include sagopilone (**25**, Figure 4 B),[96] which is characterized by the presence of the benzimidazole side chain. Compound **25** was found to be more potent in vitro than **13**, as well as highly effective in mouse tumor xenograft models.[96,97] Notably, this compound has been found to be brain-penetrant.[37]

Discodermolide. (+)-Discodermolide (**26**, Figure 5), a cytotoxic polyketide isolated by Gunasekera and co-workers from the deep-water Caribbean sponge *Discodermia dissoluta*,[98] was initially reported to be an immunosuppressant agent.[99,100] The MT-stabilizing properties of this compound were discovered in 1996,[101,102] when it was found that **26** is even more potent than paclitaxel in promoting the nucleation phase of tubulin assembly. Further studies revealed that discodermolide, unlike paclitaxel, retains potent antimitotic activity against Pgp-overexpressing cancer cell lines.[103] Mechanistically, **26** was found to compete with paclitaxel for the taxane binding site on β-tubulin,[102,103] and photoaffinity labeling experiments by Horwitz, Smith, and co-workers confirmed that the discodermolide binding site is in proximity to the taxane site.[104] Interestingly, the bioactive conformation of **26** is believed to be U-shaped, where the C19 side chain comes close to the lactone moiety.[105] Overlays of this folded conformation of **26** and the bioactive conformation of paclitaxel highlight the similarities between the two 3D structures, supporting the possibility that both compounds adhere to a common pharmacophore.[105] However, unlike paclitaxel, tubulin-bound discodermolide is thought to interact with the N-terminal H1-S2 loop[106] and not with the M-loop, which is believed to be a key mediator of paclitaxel induced MT stabilization.[47] This observation suggests that the MT-stabilizing effects of paclitaxel and discodermolide may be complementary,[106] thus providing an explanation for the observed synergistic effects of **26** and paclitaxel both in vitro and in vivo.[107−109] Notably, **26** is the only example among the taxane site MT-stabilizing agents that shows synergy with paclitaxel.

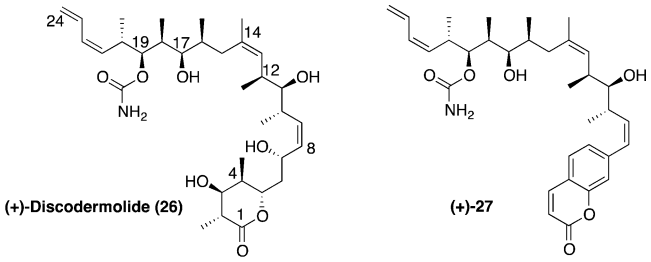

Figure 5. Structure of discodermolide and a biologically active, structurally simplified analogue (**27**).

The first total synthesis of discodermolide was reported by the Schreiber laboratory, which reported the synthesis of the natural product[110] and, prior to that, the synthesis of the unnatural (−) antipode.[111] Several other syntheses of **26** have been reported (reviewed by Smith and Freeze[112]). Notably, the gram-scale synthesis devised by Smith and co-workers,[113,114] combined with Paterson's first generation endgame,[115] was licensed to Novartis to permit the synthesis of 60 g of material needed to conduct a phase I clinical trial.[116] In addition to discodermolide, these synthetic efforts produced numerous analogues, including discodermolide−dictyostatin[117] and discodermolide−paclitaxel[118] hybrid structures. Interestingly, structural changes that impede the active U-shaped conformation proved to be highly detrimental to the biological activity. On the other hand, relatively substantial structural simplifications that maintain the characteristic folded conformation of **26** produced several interesting analogues (e.g., **27**, Figure 5) with biological activities comparable to that of the parent compound.[119,120]

Dictyostatin. (−)-Dictyostatin (**28**, Figure 6), which was first isolated from a Maldives marine sponge *Spongia* sp. by Pettit and co-workers,[121] was found to be highly potent against a variety of human cancer cell lines with a GI_{50} in the 50 pM to 1 nM range. The MT-stabilizing properties of this compound were reported by the Harbor Branch Oceanographic

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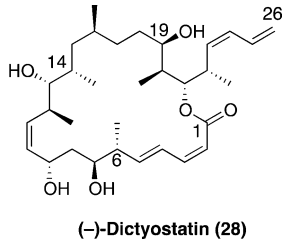

Figure 6. Structure of dictyostatin.

Institute.[122] The same studies also demonstrated that **28** is active against paclitaxel-resistant cell lines that overexpress Pgp. Competition studies revealed that **28** binds to the taxane binding site.[123] Interestingly, the configurational assignment for dictyostatin is fully consistent with a common biogenesis for the structurally related, but open-chain, discodermolide. Indeed there is an exact configurational match of the C19–C26 and C6–C14 regions of **28** with those at C17–C24 and C4–C12 of discodermolide, respectively. Moreover, it has been shown that the preferred conformation for **28** in solution closely resembles the conformation that was determined for discodermolide both in the solid state and in solution,[124] strongly suggesting that dictyostatin and discodermolide interact in a similar fashion with the taxane binding site on β-tubulin.[125,126]

The first total syntheses of (−)-dictyostatin were reported concurrently by the laboratories of Paterson[127] and Curran.[128] Other approaches to the natural product were later reported.[129−131] Dictyostatin currently represents a promising antimitotic natural product lead for development in cancer chemotherapy. To date, the ability of this compound and/or related analogues to gain access to the CNS has not been reported.

Eleutherobin, Sarcodyctins, and Related Eleuthesides. Eleutherobin[132,133] (**29**, Figure 7) and sarcodyctins[134,135] (**30**–**33** Figure 7) are structurally related, coral-derived antimitotic agents isolated from *Eleutherobia* sp. and *Sarcodictyon roseum*, respectively. The abilities of these eleuthesides to promote MT-stabilization were described by Long et al.[133] (eleutherobin) and Ciomei et al.[136] (sarcodyctins). Competition binding studies revealed that these MT-stabilizing agents interact with β-tubulin at the taxane binding site.[133,137] Like paclitaxel, **29** was found to be a substrates for the Pgp.[133] The carbohydrate moiety of this compound is thought to be important for the eleutherobin–Pgp interaction, as indicated by the observation that analogues lacking this fragment,[138] such as SKBII.296 and SKB.294 (**34** and **35**, respectively, Figure 7), did not appear to be sensitive to Pgp-mediated efflux.[138]

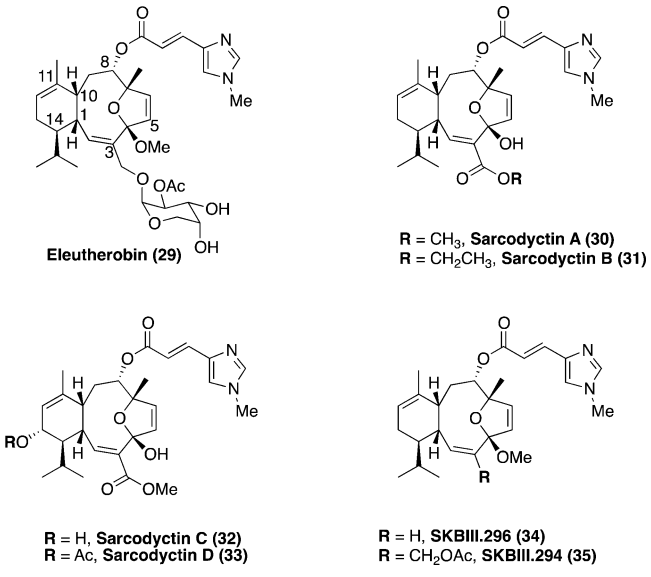

Figure 7. Eleutherobin, sarcodyctins, and selected synthetic derivatives.

Total syntheses of eleutherobin and sarcodyctins have been reported by the Nicolaou[139−142] and Danishefsky laboratories.[143−145] To date, no studies describing the evaluation of these compounds in either cell or animal models of neurodegenerative tauopathy have appeared.

Laulimalide. Laulimalide and the rearrangement product isolaulimalide (**36** and **37**, respectively, Figure 8) were isolated from marine sponges collected in Indonesia,[146] Vanatau,[147] and the island of Okinawa.[148] These compounds were described as cytotoxic agents; however, their mode of action was unknown until 1999, when Mooberry and co-workers reported that these compounds exhibit paclitaxel-like MT-stabilizing properties.[149] In addition, the same studies demonstrated that **36** retains strong antimitotic activity against cancer cell lines over-expressing Pgp.[149,150] Interestingly, competition studies with radiolabeled or fluorescently labeled paclitaxel revealed that **36** does not compete for the taxane binding site.[150] Furthermore, consistent with this observation, **36** was found to be active against cell lines with β-tubulin mutations[151] that cause resistance to both taxanes and epothilones.[150] In addition, synergistic effects of laulimalide with taxane drugs have been reported.[152] Taken together, these results clearly indicate the existence of a distinct tubulin binding site for this compound. Recent studies revealed that **36** binds to the exterior of the MT on β-tubulin.[153]

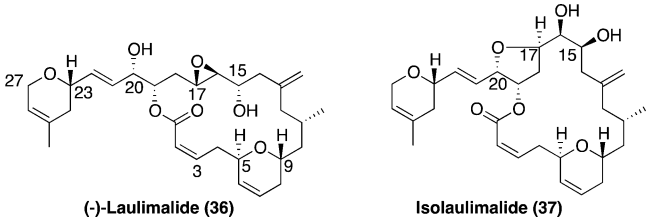

Figure 8. Laulimalide and isolaulimalide.

Because of these promising biological activities and because of the limited natural supply, laulimalide became an attractive synthetic target. The first total synthesis of **36** was reported by Ghosh and co-workers.[154] Several other synthetic approaches, reviewed by Mulzer and Ohler,[155] have been developed. Notably, scientists at the Eisai Research Institute were able to synthesize sufficient quantities of laulimalide to enable in vivo efficacy studies.[156] Somewhat surprisingly, despite the promising in vitro anticancer activity and PK properties, **36** did not produce a statistically significant tumor growth inhibition. The reasons for the lack of in vivo anticancer effects of laulimalide remain unclear but may be explained, at least in part, by the relatively high mitotic block reversibility ratio observed for this compound. A high reversibility of the antimitotic effect would imply that, in vivo, cancer cells exposed to laulimalide may resume mitosis soon after the circulating drug levels becomes sufficiently low.[157] Furthermore, this lack of in vivo anticancer activity was accompanied by severe toxicities indicating that **36**

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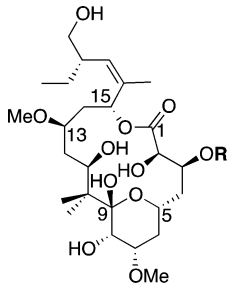
may not be a viable candidate for cancer chemotherapy.[157] However, subsequent studies in a different animal model demonstrated a significant inhibition of tumor growth.[158]

Peloruside A. Isolated in New Zealand from the marine sponge *Mycale hentscheli*, peloruside A (**38**, Figure 9) was identified as a potent cytotoxic agent with paclitaxel-like activities.[159,160] In addition to the antimitotic activity, this natural product was found to be not affected by the overexpression of Pgp or by tubulin mutations that are known to affect the activity of paclitaxel.[161] Competition binding experiments revealed that **38** does not bind to the taxane site in β-tubulin, while the observation that laulimalide can displace **38** clearly suggests that these two compounds may have overlapping binding sites.[161,162] In line with these results, **38** did not show synergistic effects with laulimalide, but like the latter, it was found to synergize with other taxane site drugs in both polymerizing purified tubulin[152] and cellular activity.[163]



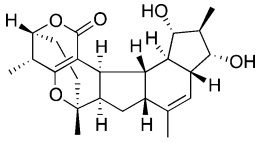
R = CH_3, **Peloruside A (38)**
R = H, **Peloruside B (39)**

Figure 9. Pelorusides A and B.

The first total synthesis of peloruside A was reported in 2003 by De Brandander and co-workers.[164] Several other approaches to this natural product were later developed.[165−171] In addition to **38**, other naturally occurring congeners have been isolated,[172,173] including peloruside B (**39**, Figure 9), which exhibits similar MT-stabilizing and biological activities as **38**.[172]

Recent studies have shown that **38** protects cultured neurons against okadaic acid induced tau phosphorylation.[21] These results suggest that in addition to the epothilones, other MT-stabilizing agents, including those that do not target the taxane binding site on β-tubulin, such as peloruside and laulimalide, may be considered potential candidates for the treatment of tauopathies. However, there are presently no reports on the brain penetration of **38**.[21]

Cyclostreptin. (−)-Cyclostreptin (**40**, Figure 10), a bacterial natural product also known as WS9885B and FR182877, was originally identified as a compound with paclitaxel-like biological activities using a cell-based screen for novel antimitotic agents.[174,175] Structurally, **40** is characterized by an unusual ring system featuring a constrained α,β-unsaturated lactone. The natural product was initially assigned the opposite configuration.[176] Total syntheses of both (+) and (−)-cyclostreptin, as reported by the laboratories of Sorensen[177,178] and Evans,[179] confirmed the (−)-enantiomer to be the natural product.

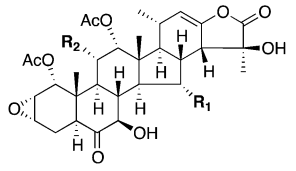


(−)-Cyclostreptin (40)

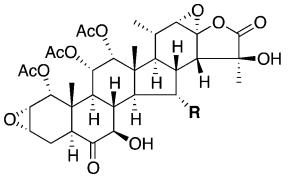
Figure 10. Structure of (−)-cyclostreptin.

Cytotoxicity studies revealed that **40**, although ∼10 times less potent than paclitaxel in paclitaxel-sensitive cell lines, is considerably more effective than paclitaxel against Pgp-overexpressing cell lines.[180] Furthermore, these studies demonstrated that **40** is not affected by tubulin mutations that are known to cause resistance to both paclitaxel and epothilone A.[180] Interestingly, whereas cyclostreptin was found to be an effective competitive inhibitor of the binding of paclitaxel to MTs, significant differences were observed in the MT-stabilizing properties of these two compounds. While cyclostreptin-treated MTs are more stable to depolymerizing conditions than those resulting from paclitaxel treatment, cyclostreptin-induced MT-stabilization requires the presence of MAPs and GTP, which are not necessary for paclitaxel-induced MT-assembly.[180] Subsequent studies revealed that **40** interacts covalently with specific amino acid residues of β-tubulin in both MTs and tubulin dimers. These residues are Asn228, which resides in the proximity of the taxane binding site, and Thr220 at the outer surface of a pore[43] in the MT wall.[181] Computational studies suggested that the covalent attachment of **40** to Thr220 may prevent the diffusion of paclitaxel and other taxane-binding drugs across the MT pore into the taxane binding site.[182] This model provides an explanation of why **40** can prevent the binding of paclitaxel to β-tubulin despite the relatively weak tubulin polymerization properties compared to paclitaxel. Cyclostreptin is the first example of a MT-stabilizing agent found to interact irreversibly with tubulin. Similar mode of action has recently been reported for zampanolide[183] (vide infra). To date, there are no reports of **40** being evaluated in cell models and/or animal models of tauopathies; thus, it is not clear yet whether the particular mode of action of cyclostreptin, which involves covalent modification of tubulin, may be effective in restoring axonal transport deficits in neurons affected by tauopathy.

Taccalonolides. Taccalonolides are steroidal natural products that were originally isolated in 1963 from the tubers of *Tacca leontopetaloides*.[184] The structures of these compounds were fully elucidated in 1987 when Chen and co-worker characterized taccalonolides A and B (**41** and **42**, respectively, Figure 11) from *Tacca plantaginea*.[185] Since then, several other members of the taccalonolide class have been discovered (e.g., **43** and **44**, Figure 11).[186−189] The MT-stabilizing properties of the taccalonolides were first recognized in 2003 when



	R_1	R_2
(41) Taccalonolide A	OAc	OAc
(42) Taccalonolide B	OH	OAc
(43) Taccalonolide E	OAc	H
(44) Taccalonolide N	OH	H



R = OAc, **Taccalonolide AF (45)**
R = OH, **Taccalonolide AJ (46)**

Figure 11. Selected taccanolides.

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taccalonolides A and E were found to cause paclitaxel-like MT-bundling in dividing cells.[190] Furthermore, the taccalonolides were found to be poor substrates for the Pgp and exhibit only limited cross-resistance with paclitaxel.[190,191]

The mode of action of this class of natural products remains an active area of investigation. Studies with **41** and **42** revealed that the taccalonolides do not bind to either tubulin or MTs[192] and that the MT-stabilizing properties of these compounds are observed only in intact cells but not in cell extracts or purified tubulin preparations.[192,193] Recent studies, however, reported the identification of considerably more potent MT-stabilizing members of the taccalonolide family, such as taccalonolides AF and AJ (**45** and **46**, respectively, Figure 11), which promote MT assembly from purified tubulin.[189] Further studies are needed to elucidate the mode of action of taccalonolides and to evaluate the potential of taccalonolides in the context of neurodegenerative disorders.

To date, there are no reports describing the total synthesis of taccalonolides.

Zampanolide and Dactylolide. (−)-Zampanolide and (+)-dactylolide (**47** and **48**, respectively, Figure 12) are

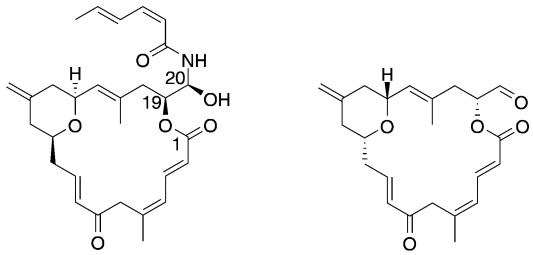

Figure 12. Structures of naturally occurring (−)-zampanolide and (+)-dactylolide.

structurally related natural products isolated, respectively, from *Fasciospongia rimosa*,[194] the same sponge found on the island of Okinawa that yielded laulimalide,[148] and from *Dactylospongia* sp.[195] These two compounds share the same highly unsaturated macrolactone core but with opposite absolute configuration. In addition, zampanolide features a characteristic *N*-acyl hemiaminal side chain. The total synthesis and assignment of absolute configuration of both antipodes of **47** and **48** were reported first by the Smith and then Hoye laboratories.[196−205]

In 2009, **47** was reported to stabilize MTs in cells and to promote the polymerization of purified tubulin in cell-free assays.[206] The same studies revealed that **47** exhibits low nanomolar IC_{50} against several cell lines, including those that overexpress the Pgp.[206] Similar MT-stabilizing properties have been described for **48**,[207] although this compound was found to be considerably less cytotoxic than **47**, with IC_{50} values in the low micromolar range.[195] Competition binding studies revealed that **47** targets the taxane site and does not interfere with the binding of laulimalide with MTs.[183] Interestingly, these studies also revealed that the mode of action of **47** and **48**, like cyclostreptin, involves covalent modification of specific residues (Asn228 and His229) found in the taxane binding site. However, compared to cyclostreptin, **47** is a considerably more potent MT-stabilizing agent. As in the case of cyclostreptin, the therapeutic potential of **47** as a treatment for tauopathies may be limited because of the alkylating properties of this compound.

Ceratamines. Ceratamines A and B (**49** and **50**, respectively, Figure 13), originally isolated from marine sponge

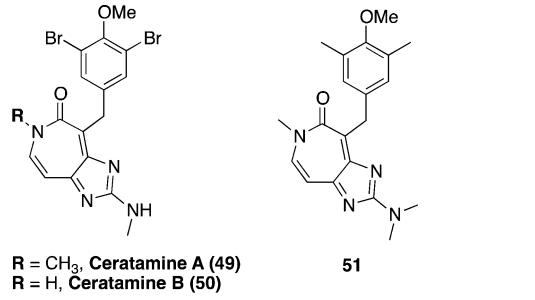

Figure 13. Structures of naturally occurring ceratamine A and B and of a synthetic congener (**51**).

Pseudoceratina sp. collected in Papua New Guinea, are antimitotic heterocyclic alkaloids characterized by an unusual imidazo[4,5-*d*]azepine core.[208] These compounds were found to promote the polymerization of purified tubulin in the absence of MAPs, although less potently than paclitaxel.[209] Competition binding studies revealed that the ceratamines do not act as competitive inhibitors of paclitaxel binding.[209]

Interestingly, ceratamines are the only nonchiral examples among all MT-stabilizing natural products. Because of this and because of the comparatively simpler structure, ceratamines are considered as promising lead compounds for cancer chemotherapy.[209] Such attributes also suggest that compounds from this class may be identified as CNS-active candidates for the treatment of tauopathies. The syntheses of the natural products have been described by Coleman and co-workers,[210] with several analogues constructed and evaluated.[211,212] This effort resulted in the identification of selected derivatives (e.g., **51**, Figure 13) with improved antimitotic and MT-stabilizing properties.[211]

Other Naturally Occurring Compounds with Reported MT-Stabilizing Properties. In addition to the different classes of natural products discussed above, a number of other naturally occurring compounds, or derivatives thereof, have been reported to exhibit MT-stabilizing properties (Figure 14). These include dicumarol (**52**),[213] jatrophanes (**53**−**55**),[214] tubercidin (**56**),[215] xanthophylls (e.g., lutein, **57**),[216] as well as the NAP peptide (**58**), also known as davunetide, which is a short peptide fragment (NAPVSIPQ) derived from the activity-dependent neuroprotective protein (ADNP).[217] However, as reported by Buey and co-workers,[192] who conducted a comparative study involving different classes of MT-stabilizing agents, the MT-stabilizing properties of most of these compounds (i.e., **52**−**55**, **57**) were not confirmed. Likewise, the NAP peptide, which has been found to be neuroprotective in many different animal models (reviewed by Gozes and co-workers[218−220]) and is currently in phase II/III clinical trials for AD and progressive supranuclear palsy (PSP), was reported to be a MT-stabilizing agent.[221,222] However, recent studies indicate that this peptide may not directly impact MT dynamics.[223]

Synthetic MT-Stabilizing Agents. Although the vast majority of known MT-stabilizing agents are structurally complex natural products, progress has been made in the identification of small synthetic molecules with MT-stabilizing properties. These compounds, which include GS-164 (**59**), identified by scientists at Takeda Chemical Industries Ltd.,[224]

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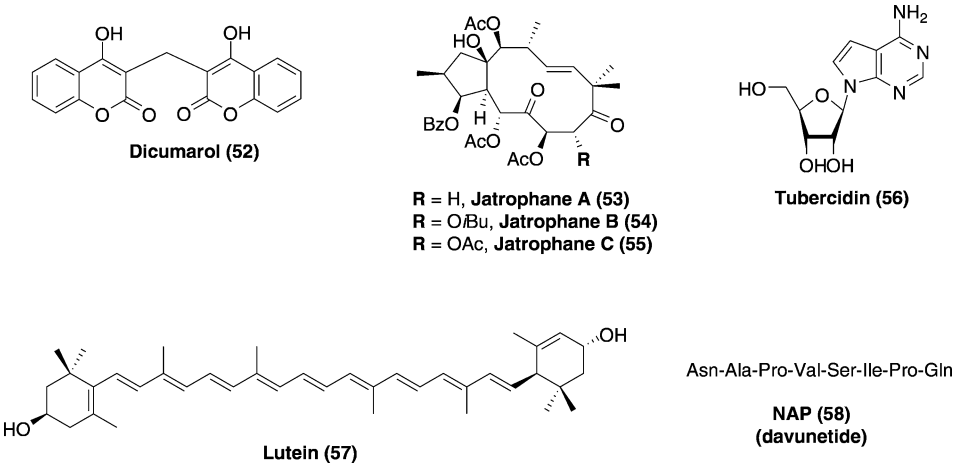

Figure 14. Natural products with reported MT-stabilizing properties.

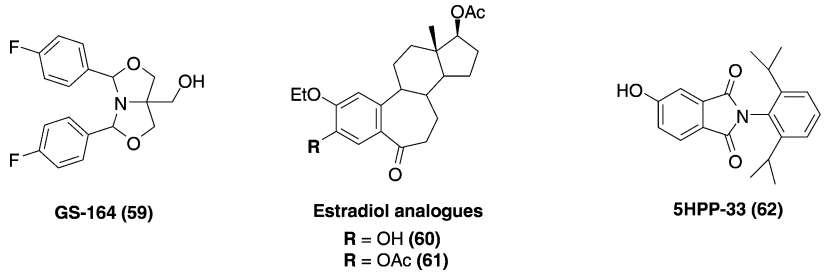

Figure 15. MT-stabilizing **59**, estradiol derivatives **60** and **61**, and thalidomide analogue **62**.

selected estradiol derivatives,[225] such as **60** and **61**, and a derivative of thalidomide, 5HPP-33 (**62**),[226] could be considered as potentially interesting leads for AD drug discovery programs (Figure 15).

Furthermore, screening programs directed at the discovery of antifungal agents identified multiple series of synthetic mono- and diheterocyclic compounds with MT-stabilizing properties, including certain triazolopyrimidines typified by cevipabulin[227] (also known as TTI-237, **63**, Figure 16A), as well as some structurally related phenylpyrimidines[228] (Figure 16B), pyridopyridazines,[229] pyridotriazines[230] (Figure 16C), and pyridazines[231] (e.g., **64**, Figure 16D).

Although the vast majority of these synthetic MT-stabilizing agents have been investigated only as antifungal agents, in recent years there have been reports of compounds of this type being explored as potential anticancer drugs. Among these, **63** displayed excellent anticancer activities in several nude mouse tumor xenograft models.[227] Moreover, **63** was found to exhibit excellent pharmaceutical properties, including oral bioavailability, metabolic stability, and water solubility.[227] Interestingly, the mechanism by which these heterocyclic compounds promote MT-stabilization appears to be distinct from that of other classes of MT-stabilizing natural products.[232,233] In fact, radioligand binding studies demonstrated that **63** does not compete for the taxane binding site on β-tubulin.[232] Instead, this compound appears to affect vinblastine binding to β-tubulin, although it is not clear yet whether this results from overlapping binding sites or a distinct allosteric cevipabulin site.[232] However, in sharp contrast to the mechanism of vinblastine, vincristine, and other vinca alkaloids, which destabilize MTs, **63** and related congeners promote the polymerization of tubulin into MTs.[232,233] Cevipabulin is currently undergoing clinical trials as an anticancer agent.[234]

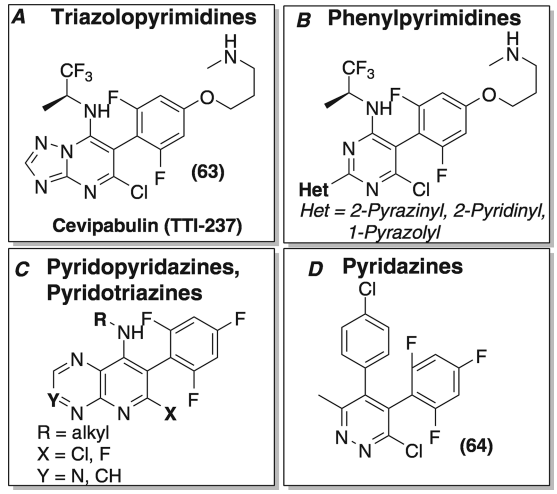

Figure 16. Representative mono- and diheterocyclic MT-stabilizing agents.

However, because of the MT-stabilizing ability, favorable physical–chemical properties, and synthetic accessibility, **63** and/or related analogues may hold promise in the development of CNS-active MT-stabilizing therapies.

■ CONCLUDING REMARKS

Over the past several years, remarkable progress has been made in the development of tau focused therapies from target identification toward clinical trials for AD and related FTLD tauopathies (see Lee et al.[235]). Among a growing number of potentially druggable targets that could abrogate tau-mediated neurodegeneration,[236] counteracting the functional loss of tau

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with MT-stabilizing agents is one of the most biologically and pathologically well grounded. Thus, these agents appear to be among the most compelling as potential treatments for neurodegenerative tauopathies. The promising results obtained from the epothilone D studies in tau Tg animal models, summarized here, provide important validation of this therapeutic strategy and, notably, have resulted in the selection of epothilone D as a clinical candidate for the treatment of AD.[30]

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ABBREVIATIONS USED:

MT, microtubule; AD, Alzheimer's disease; PD, Parkinson's disease; CNS, central nervous system; FTLD, frontotemporal lobar degeneration; PSP, progressive supranuclear palsy; NFT, neurofibrillary tangle; BBB, blood–brain barrier; FAT, fast axonal transport; Pgp, P-glycoprotein; Tg, transgenic; MDR, multidrug resistance; FDA, Food and Drug Administration; SAR, structure–activity relationship; *B*/*P*, brain to plasma ratio; PK, pharmacokinetic; PD, pharmacodynamic; BMS, Bristol-Myers Squibb; ADNP, activity dependent neuroprotective protein

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