Natural Products in the Drug Discovery Programmes in Alzheimer’s: Impacts and Prospects

by Goutam Brahmachari

Laboratory of Natural Products and Organic Synthesis, Department of Chemistry, Visva-Bharati University, Santiniketan-732 235, West Bengal, India
brahmg2001@yahoo.co.in
In 1906 Dr. Alois Alzheimer, a German psychiatrist and neuropathologist, described the first published case of "presenile dementia" based on the observation of amyloid plaques, neurofibrillary tangles and vascular anomalies during the autopsy of his patient, Mrs. Auguste Deter who had died 7 months earlier with severe cognitive defects, and the disease became known as Alzheimer's disease (AD) or simply Alzheimer's after the name of the inventor. Alzheimer's, a progressive neurodegenerative disorder leading to the most common form of dementia, very particularly in elderly people, has already affected approximately 36 million population worldwide as of 2010; it is a matter of great concern that 1,000 new cases of AD are reported daily throughout the United States. Such neurodegenerative disease is characterized by progressive and irreversible decline of memory and other cognitive functions including language, judgment, reasoning along with progressive loss of physical functioning and associated neuropsychiatric symptoms, which become severe enough to impede social or occupational functioning.

Although other major causes of death have been decreasing, deaths attributable to AD have been rising dramatically. Between 2000 and 2006, cardiovascular mortality decreased 11.1%, stroke deaths decreased 18.2%, and prostate cancer-related deaths decreased 8.7%, whereas deaths attributed to AD increased 46.1%. In fact, the overall case number in developed countries is estimated to increase by 100% between 2001 and 2040, but by more than 300% in India and China. Recent estimates indicate that nearly 5 million additional new dementia cases are diagnosed per year. Alzheimer's is predicted to affect 1 in 85 people globally by 2050. The 2003 World Health Report estimates that dementing diseases contribute a greater overall burden of disability than cardiovascular disease, stroke, and cancer.

Neuropathology of AD

Despite decades of research and many significant advances, the precise neuropathology of AD is still not completely understood; however, amyloid plaques and neurofibrillary tangles are considered as the two primary pathological hallmarks of the disease. Histopathological studies of the AD brain revealed dramatic ultra-structural changes triggered by two classical lesions, the senile plaques, mainly composed of amyloid-β (Aβ) peptides, and the neurofibrillary tangles, composed of hyperphosphorylated tau proteins. Amyloid plaques are insoluble, dense cores of 5–10 nm fibrils containing aggregates of amyloid precursor protein (APP) fragments that are primarily composed 42-amino acid β-amyloid peptide (Aβ42) as found in AD patients. On the other hand, neurofibrillary tangles contain aggregates of phosphorylated tau, a microtubule-associated protein. Some hypotheses of Alzheimer's pathology suggest that the aggregation of hyperphosphorylated tau protein causes the degeneration of the microtubule network required for neuronal survival. Ultimately, the insoluble neurofibrillary tangle of tau protein is left as a "tombstone" for dead neurons.

Although neurofibrillary tangles can occur independently, and cause neuronal death in frontotemporal dementia, the presence of both lesions in the neocortex is essential to the diagnosis of AD. The pathogenesis of the disease is complex and is driven by both environmental and genetic factors. The molecular identification and characterization of different genes associated with familial AD has provided strong support to the so-called amyloid cascade hypothesis as a causative event in the pathogenesis of AD. This hypothesis states that Aβ generated from deregulated proteolysis of the amyloid precursor protein (APP) undergoes accelerated Aβ oligomerization, fibril formation, and amyloid deposition in a process that initiates the AD pathology. In the past ten years, the large majority of the pharmacological research on AD has focused on understanding how Aβ is generated from APP via β- and γ-secretase cleavages, with the goal of designing specific inhibitors that will block Aβ production and the associated pathology. Besides, newer approaches aimed at better understanding of various molecular pathways involved in Aβ clearance have been gaining considerable attention over the last several years.

The inflammatory response to the deposition of these amyloid plaques and neurofibrillary tangles is thought to play an important role in producing the "halo" of degenerated neurons, reactive astrocytes and activated microglia around these protein deposits that is observed in microscopic sections. Over time there is gross atrophy of affected regions, including the temporal, parietal, frontal lobes (in particular the...
ventral forebrain), and the cingulate gyrus. Eventually, neuronal loss leads to global neurotransmitter deficiencies, specifically in norepinephrine and acetylcholine.

One of the earliest molecular observations in AD was the finding of a deficiency of overall acetylcholine and decreased activity of enzymes involved in the synthesis and degradation of this neurotransmitter in AD autopsy and biopsy tissue.\textsuperscript{19,20} During the course of the disease plaques and tangles develop within the structure of the brain. This causes brain cells to die. Current models suggest a prodromal period of amyloid accumulation, followed by a progression of tau pathology, inflammation, and neurodegeneration that tracks cognitive decline. Oxidative damage to proteins, lipids, and DNA in the brains of AD patients likely accompanies the widespread inflammation.

Current Treatments

As Alzheimer’s progresses, brain cells die and connections among cells are lost, causing cognitive symptoms to worsen. While there is no cure for AD or stop the damage Alzheimer’s causes to brain cells, currently there are five prescription drugs (Figure 1) approved by the U.S. Food and Drug Administration (FDA) for its symptomatic treatments that may help lessen or stabilize cognitive symptoms such as memory loss and confusion, for a limited time by affecting certain chemicals involved in carrying messages among the brain’s nerve cells. Four of these drugs are acetylcholinesterase (AChE) inhibitors, while one modulates N-methyl-D-aspartic acid (NMDA) receptors. Donepezil (Aricept\textsuperscript{®}), galantamine (Razadyne\textsuperscript{®}), rivastigmine (Exelon\textsuperscript{®}) and tacrine (Cognex\textsuperscript{®}) are the four cholinesterase inhibitors prescribed to treat symptoms related to memory, thinking, language, judgment and other thought processes. Memantine (Namenda\textsuperscript{®}), the first Alzheimer drug of the NMDA receptor antagonist-type approved in the United States, is prescribed to improve memory, attention, reason, language and the ability to perform simple tasks; it is used to treat moderate to severe Alzheimer’s. However, these drugs have some adverse side effects that commonly include nausea, vomiting, loss of appetite, headache, constipation and dizziness.

Natural Products: Promising hope against Alzheimer’s

Natural products have been the source of most of the active ingredients of medicines.\textsuperscript{21} The search for new pharmacologically active agents obtained by screening natural sources such as plants, marines and microbes has led to the discovery of many clinically useful drugs that play a major role in the treatment of human diseases.\textsuperscript{22} Natural flora and fauna have always been and continue to be the important medical reservoirs, with considerable number of modern FDA-approved medications having been derived from natural sources.\textsuperscript{23-26} In the field of Alzheimer’s, several conclusions on the possibility of natural product leads have already been supported by the experimental outcomes; the majority of the compounds examined to date with a direct relevance to AD are primarily from plants, with comparatively few molecules derived from marine and microbial sources. Still to date, the greatest successes have been resulted from plant-based AChE discovery programs, which have provided two of the five currently approved drugs for the treatment of AD. Hence, multiple factors are likely the driving force for increased interest in natural supplementation and for use in Alzheimer’s and other neurodegenerative diseases; clearly the lack of a safe, effective, proven therapy is a primary driver for the search for alternatives.

There are so many raw plant extracts/herbal formulations that find immense uses as natural remedies in the treatment of AD.
and other neurodegenerative diseases. Essentially, all traditional natural medical systems including Chinese, Indian, Native American, and medieval European have had various "brain tonics" and memory enhancers. These include "Ashwagandha" (Withania somnifera; Solanaceae) and Brahmi (Bacopa monnieri; Pennell; Scophulariaceae) mentioned in Indian Ayurveda as memory enhancers, the common 'Sage' plants (Salvia species; Labiatae) described in Roman texts as being "good for the memory", and Gingko biloba (Ginkgoaceae) discussed in Chinese literature as a possible remedy for memory loss as early as 2800 BC. Indian turmeric (Curcuma longa; Zingiberaceae), which contains an antioxidant and anti-inflammatory compound called curcumin, is found to be very effective in the treatment of AD. Vegetables such as pumpkin, carrot and other foods and spices like zinger, sesame and sunflower seeds that contain various chemical agents find very useful for enhancing the function of the brain. Consumption of blueberries/grapes and pomegranate juice has recently been proven to have beneficial effect in AD. Food supplements of vitamin B6 & B12, folic acid, vitamin E, vitamin C and co-enzyme Q10 also have been found to exert beneficial effect in AD patients.

Numerous literatures are available on the chemical, pharmacological and clinical studies of natural substances used in the treatment of AD and related diseases, including their medicinal efficacy, safety, and other relevant matters. Good review articles have also been published detailing on the naturally occurring compounds of varying skeletons that showed potential efficacy against AD and other neurodegenerative disorders. More than 200 compounds of natural origin are reported so far to exert anti-AD activities; few representative chemical agents among them are presented in Figure 2 to get a glimpse of the major advances in this direction.

Natural product leads under clinical developments

Some promising natural product leads that have aroused our hope in controlling Alzheimer’s are summarized below:

Physostigmine

The ‘classic’ cholinesterase inhibitor is physostigmine (also called eserine; Fig. 3a), an alkaloid with a pyrroloindole skeleton first isolated from the Calabar Bean, the seeds of Physostigma venenosum Balf. (Leguminosae). It is a potent, short-acting
Figure 2. Chemical structures of some representative natural compounds showing significant Anti-Alzheimer’s potential: 1: 19,20-Dihydrotabernamine (plant-derived bis-indole alkaloid; Tabernanthea diversa; Apocynaceae); 2: Geissospermine (plant-derived indole alkaloid, Geissospernum vellosi; Apocynaceae); 3: Pseudocoptisine (plant-derived benzylisoquinoline alkaloid; Coptis species; Papaveraceae); 4: Nigellastrine I (plant-derived β-carboline alkaloid; Peganum nigellastrum; Zygophyllaceae); 5: Anhydrolycodoline (plant-derived alkaloid; Lycopodium annotinum; Lycopodiaceae); 6: Lycojapodine A (plant-derived alkaloid; Lycopodium japonicum; Lycopodiaceae); 7: Lycoperine A (plant-derived alkaloid; Lycopodium hamiltonii; Lycopodiaceae); 8: Piperine (plant-derived alkaloid; Piper species; Piperaceae); 9: Sinapine (plant-derived alkaloid; Raphanus sativus; Brassicaceae); 10: Tapsine (plant-derived protoalkaloid; Magnolia × soulangiana; Magnoliaceae); 11: Zeatin (a cytokinin phytohormone); 12: 16α-Hydroxy-5-N-acetylardeemin (fungus-derived alkaloid, Aspergillus terreus; Trichocomaceae); 13: 1,8-Cineole (13) and α-pinene (14), both are the terpenoid constituents of essential oils of Salvia species (Lamiaceae); 15: Limonene (15) and perillyl alcohol (16), both are the terpenoid constituents of essential oils of Citrus species (Rutaceae); 17: Taraxerol (plant-derived triterpenoid, Cilactus ternatus; Leguminosae); 18: Timosaponin All (plant-derived steroidal saponin; Anemarrhena asphodeloides Bunge; Asparagaceae); 19: Quercetin (19) and Tiroside (20), both are plant-derived flavonoid derivatives from Agrimonia pilosa (Rosaceae); 21: Icariin (plant-derived prenyllavone; Epimedium species; Berberidaceae); 22: Belidifolin (plant-derived xanthone; Gentiana compestris; Gentianaceae); 23: Macluraxanthone (plant-derived xanthone from various Guttiferae plants); 24: Hopeahainol A (plant-derived phenolic compound; Hopea hainanensis; Dipterocarpaceae); 25: Petrosamine, a marine-derived pentacyclic pyridoacridine alkaloid from the sponge Petrosia n. sp.; 26: Hispidin (fungus-derived polyketide; Phellinus linteus; Hymenochaetales); 27: Dictazole A (marine sponge-derived bis-2-amino-imidazoline alkaloid; Spongospongia cerebriformis Duchassaing & Michelotti; Thorectidae); 28: Bastadin 9, a marine natural product isolated from the sponge Halichona sp.; 29: Manzamine A, a marine-derived alkaloid isolated from an Okinawan sponge of the genus Halichona sp.; 30: Palminurin, a linear sesterterpene isolated from a marine sponge of the genus Ircinia Polejazief (Icriniiidae); 31: Withanolide A (a plant-derived steroidal lactone; Withania somnifera (Solanaceae); 32: Ginkgolide B (a plant-derived terpenic lactone; Ginkgo biloba (Ginkgoaceae).
and reversible inhibitor of acetylcholinesterase (AChE), and has been shown to improve cognitive functions in vivo and in both normal and AD patients. It can improve the pharmacokinetic profile and efficacy, there is a considerable history of the synthesis of analogues of physostigmine — although numerous synthetic derivatives have been developed, few of them have reached advanced stages of clinical developments for AD. The most therapeutically successful synthetic analogue is rivastigmine (Fig. 3b) which is now at Phase IIIb clinical trial; the drug inhibits the G1 form of AChE in the cortex and hippocampus, the brain areas involved in cognition in AD patients. Clinical studies have borne out the usefulness of rivastigmine (Exelon®) in mild to moderate AD and it has been licensed as a treatment for symptomatic relief of AD since 2000.

Galantamine

Galantamine (Fig. 4), a plant alkaloid, is found in members of the Amaryllidaceae family, e.g., the Chinese medicinal herb Lycoris radiata Herb. and the European Galanthus nivalis L. and Narcissus spp. It is under Phase IIIb clinical trial. The drug has already been licensed to treat symptoms of mild to moderate dementia in AD. Its main mechanism of action includes reversible inhibition of acetylcholinesterase (AChE) and allosteric potentiation of nicotinic ACh receptors. To date, seven large scale, double-blinded, placebo-controlled trials have been conducted with galantamine in mild to moderately severe AD patients. These multi-centre randomised clinical trials showed that it was well tolerated and significantly improved cognitive function, and the cognitive benefits appear to be sustained for at least 3 years, a much longer time than for other drugs of this type. Galantamine is well absorbed when given orally; approximately 75% of a dose of galantamine is metabolised in liver. It was launched onto the market as a selective AChE inhibitor for AD treatment, showing the process of neurologial degeneration by inhibiting AChE as well as binding to and modulating the nicotinic acetylcholine receptors in Austria as Nivalin® in 1996 and as Reminyl® in the rest of Europe and the US in 2002.

Numerous synthetic derivatives of galantamine have been investigated, with some inhibiting AChE more potently than galantamine, although their potential for clinical use is undetermined. Of particular therapeutic relevance is Memogain® (Gln-1062), a pro-drug of galantamine, which has improved cognitive effects in an animal model of amnesia and bioavailability (15-fold) in the brain compared to galantamine, with fewer adverse gastrointestinal effects.

Curcumin

Curcumin (Fig. 6), a well-known polyphenolic ingredient in traditional Indian cuisine from the turmeric plant Curcuma longa L. (Zingiberaceae), has recently attracted significant interest in the field of dementia, as it possesses certain properties that relate to the postulated neuropathology of AD. Curcumin has a long history of use as a traditional remedy and food in Asia. Many studies have reported that curcumin has various beneficial properties, such as antioxidant, antiinflammatory, and antitumor. Recent reports have suggested therapeutic potential of curcumin in the pathophysiology of Alzheimer’s disease (AD). In vitro studies, curcumin has been reported to inhibit amyloid-β-protein (Aβ) aggregation, and Aβ-induced inflammation, as well as the activities of β-secretase and acetylcholinesterase. In vivo studies, oral administration of curcumin has resulted in the inhibition of Aβ deposition, Aβ oligomerization, and tau phosphorylation in the brains of AD animal models, and improvements in behavioral impairment in animal models. These findings suggest that curcumin might be one of the most promising compounds for the development of AD therapies. Consumption of curcumin has been associated with lower risk of AD, which further supports its potential role in the treatment and prevention of AD.
of curcumin is associated with improved cognitive function\textsuperscript{[66]} and a lower prevalence of AD in some populations, which is suggested to be due to a curcumin-rich diet.\textsuperscript{[67]} Longvida\textsuperscript{®}, a curcumin formulation (developed by an Elite Group of University Neuroscientists at the University of California, Los Angeles), is being evaluated in a Phase II Alzheimer's clinical trial.\textsuperscript{[68]-[71]}

Resveratrol

Resveratrol (i.e. \textit{trans}-3,4',5 trihydroxystilbene; Fig. 7) occurs in various plants including grapes (\textit{Vitis vinifera} L. (Vitaceae)) and it produces a number of mechanistic effects, including antioxidant, relevant for AD treatment. This polyphenol promotes the decomposition and clearance of intracellular A\textsubscript{β} aggregates by resveratrol-enhanced proteasomal degradation of A\textsubscript{β} – it was also noted in this study that proteasome activity is reduced in an AD brain, supporting a possible novel therapeutic mechanism of resveratrol in AD.\textsuperscript{[72,73]} A recent study suggests resveratrol disrupts A\textsubscript{β}\textsubscript{42} hydrogen bonding thus preventing fibril formation, and it can destabilize preformed fA\textsubscript{β}\textsubscript{42} \textit{in vitro}, but does not prevent oligimerization.\textsuperscript{[74]} Specifically, it scavenges Reactive oxygen species (ROS), up-regulates cellular antioxidants including glutathione and is neuroprotective against oxidative stress \textit{in vitro} and \textit{in vivo}.\textsuperscript{[62,75,76]}

Resveratrol protects astrocytes in rat hippocampal slices from H\textsubscript{2}O\textsubscript{2}-induced oxidative stress by increasing glutathione levels, in addition to other mechanisms.\textsuperscript{[77]} It also prevents cognitive impairments and associated oxidative stress \textit{in vivo}\textsuperscript{[69,78]} and reduces plaque formation in a transgenic model of AD.\textsuperscript{[79]} It is apparent there is emerging evidence that resveratrol may modulate AD pathology due to antioxidant effects, or by various other mechanisms.\textsuperscript{[13,15,80]} Resveratrol is currently in Phase III clinical trials as a nutritional supplement in combination with glucose and malate. The underlying rationale is that the glucose and malate prime oxidative metabolism and the Krebs-cycle in the brain, which aids in regenerating the reduced form of resveratrol under normal brain cell metabolism.\textsuperscript{45}

Resveratrol, one particular constituent of red wine, is well known for its benefits in cardiovascular disorders, certain cancers, and in anti-aging therapy.\textsuperscript{[81]} In a recent study, the phenolic compound has been found to be a potent activator of Sirtuin 1 (SIRT1), genes encoding the human sirtuin family of proteins, through a molecular pathway that mimics the effects of caloric restriction (CR). Caloric restriction normally prepares the body to deal with stress; it is one of the few interventions well known to enhance overall longevity. Sirtuin 1 proteins affect the aging processes and are also involved in enhancing the function of mitochondria. The study also found that resveratrol was specifically capable of enhancing neuronal survival and preventing neurodegeneration in cell models of AD and amyotrophic lateral sclerosis (ALS).\textsuperscript{[82]} Although controlled human studies are lacking, the effects of resveratrol in model systems certainly appears to warrant further investigation.

Bryostatin-1

Bryostatin-1 (Fig. 8), a macrolide lactone first isolated by George Pettit from the bryozoan \textit{Bugula neritina} L. (Bugulidae), is currently under investigation as an anti-cancer agent and as a memory enhancing agent.\textsuperscript{[83]-[85]} Bryostatin-1 enhances \textalpha;-secretase activation in human fibroblast cells, reduces A\textsubscript{β}\textsubscript{42} levels, and reduces mortality of transgenic AD mice.\textsuperscript{[86]} It also reverses A\textsubscript{β}42 produced deficits of protein kinase C (PKC) and extracellular-signal-regulated kinase 1 and 2 (ERK1/2) phosphorylation in cellular models of AD. The macrolide has appeared very promising in enhancing memory in animal models; it has been found to be able to enhance the duration of memory retention of the marine slug \textit{Hemisnassa crassicornis} by over 500\%\textsuperscript{[87]} Additionally, the drug increased the rate of learning in rats as well.\textsuperscript{[88]} Currently bryostatin-1 is in clinical trial phase II for the treatment against AD; the ability of bryostatin-1 to alleviate brain damage in ischaemically brain-injured rats also seems promising and may open another therapeutic field for bryostatins.\textsuperscript{[89,90]}

Rifampicin

Rifampicin (Fig. 9a), a semisynthetic polykетide antibiotic originally derived from \textit{Amycolatopsis rifamycinica} Bala (Pseudonocardiaceae), is found to inhibit A\textsubscript{β} aggregation \textit{in vitro}.\textsuperscript{[91]} Recently, a randomized trial to assess the effectiveness of the combination therapy of rifampicin with another semisynthetic antibiotic doxycycline (Fig. 9b) over a three-month
ELND-005

Scylo-cyclohexanexol (Fig. 10), a chemical constituent of dogwood⁹⁹ Cornus florida L. Spach (Cornaceae) and coconut palm Cocos nucifera L. (Arecaceae), is being evaluated in Phase II clinical trials against Alzheimer’s by Transition Therapeutics and Élan Corporation, as ELND-005 (AZD-103) on its successful Phase I trial. Results of Phase I clinical trials suggested the compound was well-tolerated and resulted in Phase IIa trials at multiple doses for mild to moderate AD.¹⁰¹ ELND005 (AZD-103) is part of an emerging class of disease-modifying agents that have the potential to both reduce disease progression and improve symptoms such as cognitive function. ELND005 (AZD-103) breaks down neurotoxic fibrils, allowing amyloid peptides to clear the body rather than form amyloid plaques — a hallmark pathology of AD.

Bapineuzumab

Bapineuzumab [Molecular formula: C₃₆₄H₄₆₂N₁₇O₂₆S₄; Mol. mass 148.8 kDa (major glycoform)] is a humanized monoclonal antibody (from mouse) that acts on the nervous system and has found to have potential therapeutic value for the treatment of AD;¹⁰²,¹⁰³ the drug is an antibody to the beta-amyloid (Aβ) plaques that are believed to underlie Alzheimer’s neuropathology. It is widely considered one of the most promising candidates, and now at Phase III clinical trials.¹⁰⁴-¹⁰⁷ Bapineuzumab was being co-developed by the pharmaceutical companies Élan and Wyeth and entered Phase III trials in December 2007. In 2008 a Johnson & Johnson affiliate acquired a substantial portion of Élan’s assets related to the Alzheimer’s immunotherapy program, which Elan had shared with Wyeth. The program is continuing with Pfizer, which acquired Wyeth in 2009. Alzheimer disease is based on the ability of antibodies raised against Aβ peptides to bind to and clear Aβ from the brain, thus removing the peptide and inhibiting the damage to neurons that Aβ inflicts. Bapineuzumab has been designed to bind and remove the Aβ peptide that accumulates in the brain. It is a passive immunotherapy approach, in which patients are treated with humanized monoclonal antibodies with specificity to Aβ peptides. The treatment with antibodies should bind and clear Aβ, with the potential added benefit of a better safety and tolerability profile. Ponezumab (PF-04360365; Pfizer) is another antibody vaccination that successfully completed two Phase I studies in patients with mild to moderate AD.¹⁰⁷ This vaccination is now undergoing Phase II clinical trials.

Conclusions

Due to the insufficiency in understanding the exact pathophysiology of Alzheimer’s, still it is a great challenge in finding an appropriate treatment of this devastating disease. Several natural products are found to be useful chemotypes themselves or have provided lead compounds for the present treatment of Alzheimer’s and other neurodegenerative diseases; some natural compounds have already reached widespread clinical use as well. The majority of the compounds examined to date with a direct relevance to AD are primarily from plants, with comparatively few molecules derived from marine and microbial sources. The notable successes achieved so far have come from plant-based acetylcholinesterase discovery programmes, providing two of the five currently approved drugs for the treatment of AD. Natural molecules can also be subjected to ‘fine-tuning’ by chemical derivatisation and synthesis of analogues for better pharmacokinetics and efficacy. Natural products have always been and continue to be the important medical reservoirs, with considerable number of modern FDA-approved medications having been derived from natural sources. In the filed of Alzheimer’s, several conclusions on the possibility of natural product leads have already been supported by the experimental outcomes; hence, natural products have emerged as promising hope in the drug discovery programmes in Alzheimer’s. More emphasis should be given in finding clinically useful new chemical entities of natural origin in combination with evaluating safety and efficacy of such pure compounds or crude extracts as a whole. We are looking forward for a better medicinal scenario in controlling Alzheimer’s in days coming ahead, and we are hopeful indeed!
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About the Author

Goutam Brahmachari studied Chemistry at Visva-Bharati University in India from 1987–1992. Having obtained his Ph.D. degree in Natural Products Chemistry in 1997, he started his academic career in the next year at the same University, where he is now an Associate Professor of Chemistry. He has been deeply involved both in teaching and research during the last thirteen years. His research interests focus on chemical and biological studies of phytochemicals from medicinal plants, including organic synthesis. Besides publishing about fifty scientific research articles in the fields of organic chemistry in leading national and international journals, he has authored and edited several books from reputed National/International Presses; among the books, five are the major reference volumes in the field of natural products (Chemistry of Natural Products: Recent Trends & Developments-2006; Natural Products: Chemistry, Biochemistry and Pharmacology-2009; Handbook of Pharmaceutical Natural Products, Vol. 1 & 2 – 2010, Bioactive Natural Products: Opportunities & Challenges in Medicinal Chemistry -2011). He is a member of the Indian Association for the Cultivation of Science (IACS).