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REVIEW ARTICLE

# Exploring the potential of natural and synthetic neuroprotective steroids against neurodegenerative disorders: A literature review

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## Abstract

Neurodegeneration is a complex process, which leads to progressive brain damage due to loss of neurons. Despite exhaustive research, the cause of neuronal loss in various degenerative disorders is not entirely understood. Neuroprotective steroids constitute an important line of attack, which could play a major role against the common mechanisms associated with various neurodegenerative disorders like Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. Natural endogenous steroids induce the neuroprotection by protecting the nerve cells from neuronal injury through multiple mechanisms, therefore the structural modifications of the endogenous steroids could be helpful in the generation of new therapeutically useful neuroprotective agents. The review article will keep the readers apprised of the detailed description of natural as well as synthetic neuroprotective steroids from the medicinal chemistry point of view, which would be helpful in drug discovery efforts aimed toward neurodegenerative diseases.

KEYWORDS

Alzheimer's disease, neuroprotection, neuroprotective steroids, oxidative stress, Parkinson's disease

## 1 | INTRODUCTION

The term "neurodegeneration" is composed of two words—"neuro," which refers to nerve cells or neurons and "degeneration," which implies the progressive damage of structural or functional activities of the tissues or organs. Neurodegeneration is a key aspect responsible for progressive degeneration and/or death of nerve cells within the brain, resulting into incurable and debilitating circumstances known as "neurodegenerative disorders."[1] Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington disease (HD), multiple sclerosis (MS), and stroke represent some major neurodegenerative diseases arising as a result of neurodegenerative processes.[2,3] Both endogenous and synthetic neuroprotective steroids attenuate neural degeneration by reducing cell oxidation,

excitotoxicity, and apoptosis and positively modulate cognitive and locomotor functions to treat several neurodegenerative disorders.[4,5] The attentions of researchers have been largely inclined toward the phytochemicals due to their minimal side effects. Therefore natural neuroprotective steroids, which are endogenous regulators of neuronal excitability and offer remarkable prospects for developing therapeutic approaches, have been widely explored by the scientists. However several disadvantages associated with endogenous steroids such as short biological half-life, lack of specificity and selectivity with rapid metabolism, and low oral bioavailability have instigated the researchers to further investigate this area for new synthetic or natural therapeutic candidates. Although few research efforts have also been directed toward the development of synthetic analogues of endogenous neurosteroids to produce novel agents for the treatment of several neurodegenerative disorders, there is still lot of scope to achieve drug discovery breakthroughs in this area. The review article provides detailed survey on the potential of natural and synthetic steroids as neuroprotective agents for the treatment of neurodegenerative diseases.

## 1.1 | Alzheimer's disease

It is the most common form of dementia or memory loss along with impairment of intellectual abilities, disorientation (easily get lost), mood swings, loss of motivation, and behavioral issues that drastically affect the daily chores of an indiviual.[6] It is a chronic neurodegenerative disease characterized by the deposition of amyloid-$\beta$ (A$\beta$) plaques in the brain parenchyma and neurofibrillary tangles within the neurons leading to neuronal dysfunction, cytoskeleton changes, and cellular death.[7,8]

## 1.2 | Parkinson's disease

It is a chronic and progressive neurodegenerative disorder mainly affecting the motor system (part of the central nervous system (CNS) that controls voluntary and involuntary movement) and characterized by symptoms that include tremors of the hands, arms, legs, jaw and face, bradykinesia (slowness of movement), rigidity (stiffness of the limbs and trunk), postural instability (impaired balance and coordination), and cognitive deficits.[9] In majority of people, PD remains idiopathic (with no specific known cause) but mutation in genetic factors such as $\alpha$-synuclein, parkin, leucine-rich repeat kinase 2 (LRRK2), PTEN (phosphatase and tensin homolog)-induced putative kinase 1 (PINK1), DJ-1, and ATP13A2 are mainly involved in the pathology of PD.[10]

## 1.3 | Amyotrophic lateral sclerosis

ALS is a specific neurodegenerative disorder involving the death of motor neurons. Muscles stiffness, muscle twitching, and gradual muscle weakness are the main symptoms associated with progressive decrease in the size of muscle, which leads to difficulty in speaking, swallowing, and eventually breathing.[11] The exact pathophysiology of ALS is still unclear and the diagnosis is mainly based on symptomatic behavior. About 5–10% of cases have a genetic component, which involves inheritance of the traits of patient's parents due to defect in chromosome 21, which codes for a powerful antioxidant, superoxide dismutase 1 (SOD 1).[12,13]

## 1.4 | Huntington disease

It is an inherited disease resulting in the progressive breakdown (degeneration) of nerve cells in the brain and mainly affect the functional abilities of a person such as impairment in muscle coordination, loss of cognitive abilities, and alteration of behavioral symptoms.[12] The pathogenesis of HD is linked with mutation in two copies of the Huntingtin genes (Hd and IT15) resulting in abnormal sequencing of cytosine, adenine, and guanine (CAG) trinucleotides.[14,15]

## 1.5 | Multiple sclerosis

MS is a demyelinating autoimmune disease of the central nervous system. The neuroinflammation is the one of the main components involved in the pathogenesis of MS.[16] The inflammatory process is caused by T cells that gain entry into the brain through disrupted BBB. T cells recognize myelin sheath as foreign body. The autoantibodies and autoreactive T cells against the myelin have been detected in MS patients.[17,18] Recently various research efforts have been targeted toward downregulation of the immune response, including inhibitory receptors on cells of the immune system and regulatory T cells, which could help in prevention or suppression of neuroinflammatory response in MS.[19,20]

## 1.6 | Diabetic neuropathy

Diabetic neuropathy (DN) is associated with decreasing nerve functionality and nerve blood perfusion leading to numbness, burning and tingling sensation, and intractable pain. This neurodegenerative disorder, which is linked with diabetes mellitus, results in malnourished nerves and ultimately permanent nerve damage.[21] In chronic hyperglycemia, neuropathic pain results from the nerve injuries of the peripheral or the central nervous system or of both.[22] Chronic hyperglycemia results in structural loss of neurons including alteration in myelin protein by infiltration of monocytes, macrophages, neutrophils from the blood circulation, and activation of glial cells within the CNS.[23] In addition, accumulation of advanced glycation end products (AGEs) of proteins and lipids along with transcription factor NF-$\kappa$B stimulate release of inflammatory mediators like cytokines (TNF-$\alpha$, IL-1, IL-6, IL-17), complement proteins (C-1, C-reactive protein), and chemokines (CCL-2, CXC). The stimulated monocytes, immune cells, and inflammatory cytokines damage the structure and functional abilities of the peripheral nerves leading to the diabetic peripheral neuropathy and are also responsible for the induction of neuronal apoptosis.[24]

## 1.7 | Stroke

A stroke occurs due to reduced blood flow to the brain. This brain attack results in cell death and mainly affects the area of brain that controls the memory and muscular abilities. Ischemic stroke arises due to reduced blood flow, whereas hemorrhagic stroke occurs due to excessive bleeding.[25] Obstruction within a blood vessel supplying blood to the brain results in less blood flow, which enhances the production of oxygen free radicals and other reactive oxygen species (ROS) through ischemic stress. Free radicals directly initiate elements for the programmed cell death by damaging a number of cellular and extracellular elements. Reduced supply of oxygen due to thrombus and embolus in the arterial blood stream of brain (infarction) slows down the production of adenosine triphosphate (ATP) resulting in cellular injuries within the brain.[26] Both ischemia and infarction contributes to cerebral edema through the release of protease enzymes such as metalloproteases.[25] In addition, the release of the excitatory neurotransmitter glutamate promotes the influx of calcium that activates the enzymes that digest the proteins, lipids, and nuclear material of brain cells and cause programmed cell death.[27] On the other side, hemorrhagic stroke is initiated either by trauma or after rupturing of cerebral aneurysm. The blood released in brain after hemorrhage produce direct toxic effects on brain tissue and vasculature. Further inflammation promotes the secondary brain injury after hemorrhage.[28]

## 1.8 | Traumatic brain injury

Traumatic brain injury (TBI), also known as intracranial injury, occurs when an external force injures the brain. TBI can result in physical, cognitive, social, emotional, and behavioral symptoms and the outcome could be ranging from complete recovery to permanent disability or death. The main causes of TBI include falls, vehicle collisions, and violence.[29] TBI is graded as mild, moderate, or severe on the basis of the level of consciousness or Glasgow Coma Scale (GCS) score after resuscitation (panel).[30] On other hand, pathological classification depends upon the lesions that may be extra-axial (occurring within the skull but outside of the brain) or intra-axial (occurring within the brain tissue). In case of severe TBI (comatose), patients have a significant risk of hypotension, hypoxemia, and brain swelling. The risk of death is increased if these sequelae are not prevented or treated properly.[31]

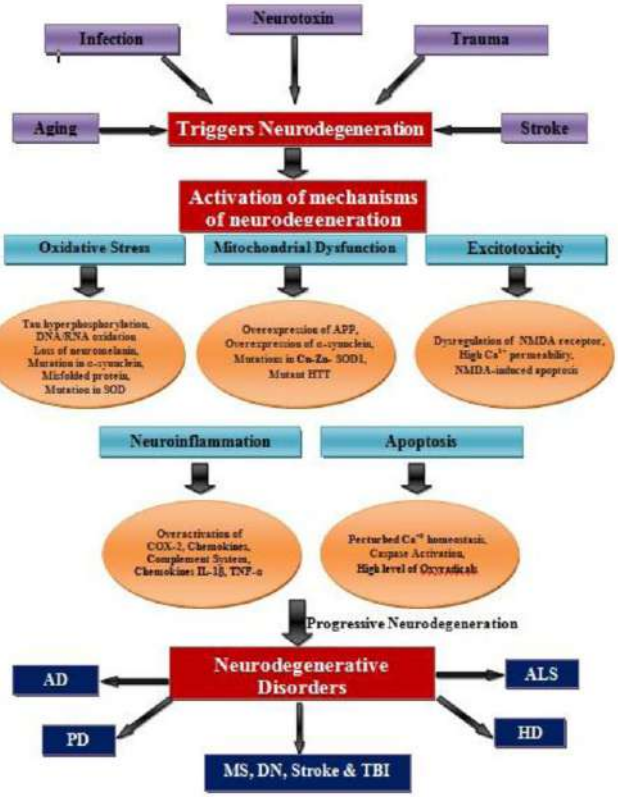



**FIGURE 1** Various neurodegenerative mechanisms in the central nervous system

## 2 | MECHANISM OF NEURODEGENERATION

All the neurodegenerative diseases manifest with specific clinical features but the cellular mechanisms appear to be similar leading to progressive brain damage. The mechanisms mainly include oxidative stress, mitochondrial dysfunction, excitotoxicity, and neuroinflammation responsible for the alteration of neuronal integrity as well as neuronal loss over the time, which promotes the pathogenesis of neurodegenerative disorders (Fig. 1).[32,33]

### 2.1 | Oxidative stress

It is a consequence of the deleterious events mainly involved in the generation of harmful ROS resulting in imbalance of pro-oxidant/antioxidant homeostasis. Oxidative stress acts as a pathological marker for the neuronal cell death, which further manifests in the form of neuropathological conditions like AD, PD, and ALS.[34–37] ROS contains highly reactive unpaired electrons (free radicals) such as superoxide ($O_2^{\bullet -}$), nitric oxide ($NO^{\bullet}$), and hydroxyl radical ($OH^{\bullet}$) including other molecular species like hydrogen peroxide ($H_2O_2$) and peroxynitrite ($ONOO^-$).[38]

### 2.2 | Mitochondrial dysfunction

Mitochondria generally known as "powerhouses of the cell," are responsible for the production of energy in the form of ATP.[39] In eukaryotic cells, fusion process is responsible for the proper distribution of mitochondrial components such as mitochondrial DNA (mtDNA), lipid membranes, and oxidative phosphorylation complexes. The GTPase proteins OPA1, Mfn1, and Mfn2 are involved in the fusion process by regulating mitochondrial trafficking through inner and outer membranes.[40–42] Alteration in fusion proteins causes mitochondrial elongation and an imbalance in fission

proteins induce excessive mitochondrial fragmentation, which ultimately leads to mitochondrial dysfunction, a factor in the etiology of AD, PD, ALS, and HD.[43]

### 2.3 | Excitotoxicity

It is a pathological process that damages or kills the nerve cells by excessive neuronal excitation of ionotropic glutamate receptors such as *N*-methyl-D-aspartic acid (NMDA), $\alpha$-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA), and kainic acid (KA) receptors.[44,45] The excitotoxins like NMDA and KA and high glutamate levels cause excessive activation of these receptors by allowing high levels of calcium ions ($Ca^{2+}$) to enter into cell, which activates number of enzymes like phospholipases, endonucleases, and proteases resulting in neuronal dysfunction and death by damaging cell structures, which ultimately induce neurodegeneration.[46,47] In addition, metabotropic glutamate receptors (mGluRs), which belong to the subfamily C of G-protein-coupled receptors designated as Group I (mGlu1 and mGlu5), Group II (mGlu2 and mGlu3), and Group III (mGlu4, mGlu6, mGlu7, and mGlu8), are also implicated in several neurodegenerative diseases including AD, PD, and HD.[48,49] Recent research reports suggest that agonists and antagonists as well as positive and negative allosteric modulators of mGluRs represent important therapeutic agents to treat neurodegenerative diseases.[50,51]

### 2.4 | Neuroinflammation

Inflammation of the nervous tissues in the CNS due to a specialized immune response results in neurodegeneration, which manifests in the form of AD, PD, HD, ALS, and MS.[52] Neuroinflammation is mainly responsible for longstanding activation of microglia as well as subsequent sustained release of inflammatory mediators, which promote oxidative and nitrosative stress within the brain.[53] Thus, it is responsible for the injury to nervous cells within the CNS and is characterized by the sustained activation of glial cells as well as recruitment of other immune cells in the brain leading to neurodegenerative conditions.[54]

### 2.5 | Apoptosis

Neuronal apoptosis is a normal physiological process that is an essential and integral part of neurogenesis. To maintain a constant size and to function properly, the older cells must die to make the way for new ones. Such programmed cell death involves a sequence of biochemical and morphological changes that allows the cell to die without adversely affecting its neighbors.[55] Age- and disease-related stressors promote excessive activation of apoptosis through oxidative stress, perturbed calcium homeostasis, mitochondrial dysfunction, and activation of cysteine proteases (caspases) leading to the neurodegeneration. The overactivation of glutamate receptors under oxidative stress (ROS) or reduced availability of energy (ATP) promotes the $Ca^{2+}$ influx. The excessive cytoplasmic entry of $Ca^{2+}$ induces apoptotic cascades that involve production of Par-4, translocation of proapoptotic Bcl-2 family members (Bax and Bad) to the mitochondrial membrane, and activation of certain caspases (caspase-8). The increased mitochondrial $Ca^{2+}$ and oxyradical levels results in the formation of permeability transition pores (PTP) in the mitochondrial membrane and release of cytochrome c into the cytosol that forms a complex with apoptotic protease-activating factor 1 (Apaf-1) and caspase-9. This results in caspase-3 activation and execution of the cell death process.[56,57] Unfortunately, many people experience excessive death of one or more populations of neurons leading to neurodegenerative disorders. For example, death of hippocampal and cortical neurons is responsible for the symptoms of AD; death of midbrain neurons causes PD, death of neurons in the striatum, which control body movements result in HD and death of lower motor neurons manifests as ALS.[58]

## 3 | NEUROPROTECTION

Neuroprotection refers to the mechanisms and strategies involved in the preservation of neuronal structure and its functions and prevention of the neurodegeneration involved in the pathogenesis of various neurodegenerative

disorders.[59] Neuroprotection mainly aims to reduce or prevent the common mechanisms associated with the neurodegeneration such as oxidative stress, mitochondrial dysfunction, excitotoxicity, neuroinflammatory change, and protein aggregation leading to slow disease progression and also delays the transition from the preclinical to the clinical stage.[60] A plethora of endogenous neuroprotective mechanisms are demonstrated by neuronal, glial, and other type of cells on activation against various types of neuronal damage.[61] The main endogenous protective mechanisms include (i) binding of pituitary adenylate cyclase-activating polypeptide (PACAP), a hypothalamic neuropeptide to three different G-protein-coupled receptors, that is, PAC1, vasoactive intestinal polypeptide receptor 1 (VPAC1), and VPAC2. These three receptors are widely distributed in the different regions of the CNS. PACAP acts as a neuroprotectant by blocking neuronal death induced by the excitotoxin *N*-methyl-D-aspartate (NMDA) or serum deprivation in cortical neuron culture and by promoting cortical neurogenesis as neurotrophic factor,[62,63] (ii) prevention of nuclear translocation of apoptosis inducing factor and overexpression of NMDA to stop cell death by hepatocyte growth factor (HGF) and the c-Met receptors,[64] (iii) secretion of apolipoprotein (apo) E containing lipoproteins to produce neuroprotective effects against trophic factor-withdrawal and excitotoxicity-induced apoptosis in primary cultured retinal ganglion cells. Binding of apo E containing lipoproteins to lipoprotein receptor related protein 1 (LRP1) prevents the intracellular calcium overload through NMDA receptors,[65,66] (iv) neuroprotection by erythropoietin (EPO), a glycoprotein, against apoptosis and/or neuroinflammation induced by nerve injuries or disorders. Morishita and co-workers reported that the EPO administration protected primary cultured cortical and hippocampal neurons from glutamate-induced neurotoxicity.[67] Furthermore, EPO rescued cultured hippocampal neurons from NO-induced damage suggesting that the neuroprotective effects of EPO are exerted due to prevention of the NO-mediated formation of free radicals.[68] Literature reports indicate that neuronal apoptosis induced by the neurotoxicant trimethyltin is inhibited by the EPO treatment in the primary cultured hippocampal neurons.[69] In addition EPO promotes the transcription of the cAMP responsive element binding protein as well as the expression and the production of BDNF,[69] (v) neuroprotective effects by several neurotrophins against oxidative stress and apoptosis-induced neuronal cell death.[70–80] The neurotrophins mainly include brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), insulin-like growth factor-1 (IGF-1), glial cell derived factor neurotrophic factor (GDNF), vascular endothelial growth factor (VEGF), ciliary neurotrophic factor (CNTF) neurotrophin-3, neurotrophin-4. The neurotrophins BDNF and NGF have been extensively explored with respect to their protective effects on neuron survival in neurodegenerative conditions.[70–77] BDNF and NGF protect the hippocampal progenitor cells from staurosporine-induced apoptosis by stimulating the phosphatidylinositol-3-kinase/Akt pathway through tropomyosin-related kinase Trk receptors.[72] In cultured hippocampal neurons, exogenous treatment of BDNF or NGF attenuated glutamate-induced neurotoxicity by increasing the activity of antioxidant enzymes and decreasing the intracellular concentration of calcium ion.[73] Furthermore, an experimental study using neurotrophin-deficient mice have shown that BDNF and neurotrophin-3 are crucial for the survival of developing neurons in the cerebellum.[74] Recently, it was investigated that BDNF promotes the neurite outgrowth and cell survival via likes of PI3-K and Erk1/2 pathways, which is useful for normal neural and cognitive development in neonates.[75] Tandon and co-workers suggest that BDNF protects developing brain from seizure-induced excitotoxicity and enhance the neuronal development and survival rate.[76] Recently another clinical study demonstrated the improvement in motor and cognitive functions in children suffering from hypoxic-ischemic brain injuries (HIBI) by intraventricular NGF administration.[77]

Several other epidemiologic studies have shown that daily intake of dietary products like pomegranate, blueberries, turmeric, and *ginko biloba* produce the neuroprotective effects against PD and AD.[81] Recent investigations suggest that drinking green tea, coffee, and red wine reduce risk of neurodegenerative disorders.[82] All of these products promote the neuroprotective mechanisms by indirect activation of transcription factors, antioxidant enzymes, and anti-inflammatory activities within the CNS and also act as potent oxygen and nitric radical scavengers.[81–83]

Various synthetic therapeutic agents, which prevent death of vulnerable neurons and impede the disease progression are also used as neuroprotective agents.[84] These agents mainly include antioxidants, anti-inflammatory drugs, glutamate antagonists, cholinesterase inhibitors, dopamine agonists, antiapoptotic, neuroprotective steroids, and some

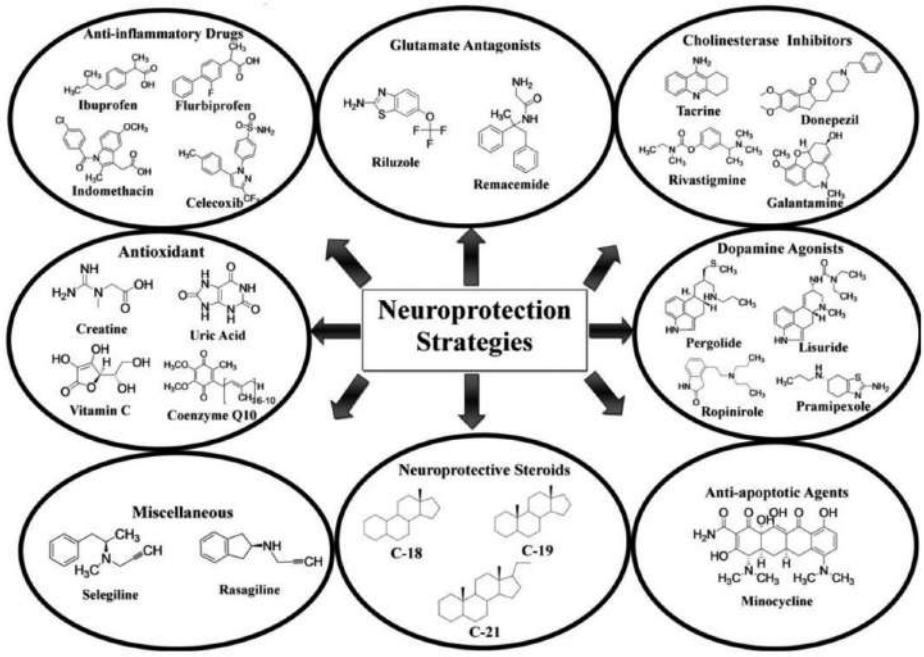



**FIGURE 2** An overview of various neuroprotective agents

miscellaneous drugs. An overview of various categories of neuroprotective agents along with the representative examples has been provided in Figure 2.[85,86]

## 3.1 | Antioxidants

These are the agents that inhibit the formation of ROS by scavenging the free radicals or their precursors and also upregulate the endogenous antioxidant defense. Antioxidants are mainly of two types: (i) enzymes such as SOD, catalase and glutathione peroxidase and (ii) low molecular weight antioxidants that include creatinine, uric acid, vitamin C (ascorbic acid), and coenzyme Q10.[87–99]

## 3.2 | Anti-inflammatory drugs

These mainly include nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, flurbiprofen, indomethacin, celecoxib, and steroidal anti-inflammatory drugs (glucocorticoids) like prednisone and dexamethasone. These drugs mainly prevent the COX activity leading to decreased prostaglandin levels and also prevent the release of proinflammatory mediators (IL-1$\beta$, TNF-$\alpha$, and IL-6). They are known to act as ROS and NOS (NO synthase) scavengers.[100–112]

## 3.3 | Glutamate antagonists

Glutamate is a potent excitatory neurotransmitter. The loss of glutamate transporters or the overactivation of NMDA receptors leads to accumulation of extracellular glutamate that is responsible for the cell death through excitotoxicity mechanism.[113] Glutamate antagonists are useful in preventing glutamate toxicity. Glutamate antagonists mainly include the drugs like riluzole, which cause indirect antagonism of glutamate receptors as well as inactivation of neuronal voltage-gated $Na^+$ channels.[114] Remacemideh acts as a low-affinity NMDA receptor antagonist and does not cause the behavioral and neuropathological side effects.[115]

### 3.4 | Cholinesterase inhibitors

These are the agents that inhibit acetylcholinesterase (AChE) and prevent the hydrolysis of acetylcholine (ACh), which ultimately increase both the level and duration of action of ACh for the neurotransmission. They help in combating the loss of ACh due to the depletion of the cholinergic neurons and useful in symptomatic treatment of AD. Moreover, AChEIs also protect cells from the free radical toxicity and $\beta$-amyloid-induced cell injury by promoting the antioxidant defense. Tacrine, donepezil, rivastigmine, and galantamine are commonly used as reversible AChEIs for the pharmacotherapy of AD.[116,117]

### 3.5 | Dopamine agonists

Dopamine agonists are the compounds that activate dopamine receptors (D1- and D2-type receptors) and exert antiparkinsonian effect by restoring dopaminergic function in the striatum. They mainly comprise ergoline dopamine agonists, for example, pergolide and lisuride whereas nonergoline agonists include ropinirole and pramipexole.[118,119]

### 3.6 | Antiapoptotic agents

Apoptosis is a process of programmed cell death widely implicated in a variety of neurodegenerative disorders. Therefore antiapoptotic agents are developed to counter the apoptosis mechanism. Minocycline has recently shown neuroprotective effects in various animal models of stroke/ischemic injury, HD, and PD. The neuroprotective effects of minocycline are mainly associated with marked reduction in the apoptotic factors like inducible NOS (iNOS) and caspase 1 expression.[120–123]

### 3.7 | Miscellaneous

**(i)** MAO-B inhibitors such as selegiline and rasagiline enhance the dopamine level in the basal ganglia by blocking its metabolism. These drugs mainly inhibit monoamine oxidase B (MAO-B) that is involved in the depletion of dopamine and leads to increased L-dopa level in the striatum.[124]

**(ii)** Lipid-lowering medications such as statins could also be used to inhibit amyloidogenic pathway by decreasing the ability of A$\beta$ to form fibrils.[125]

## 4 | NEUROPROTECTIVE STEROIDS

Neuroactive steroids include endogenous and synthetic steroidal compounds that act as physiological regulators and protective agents in the nervous system. They mainly protect the central and peripheral nervous system from neurodegeneration, hence termed as "neuroprotective steroids." The endogenous or natural neuroactive steroids, which are produced by the steroidogenic peripheral glands include hormonal steroids such as dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), testosterone, estradiol, pregnenolone, and progesterone, whereas the ones that are directly produced in the CNS are allopregnanolone and tetrahydrodeoxycorticosterone.[126]

Steroidal biosynthesis in central nervous system takes place within the mitochondria as described in Figure 3. In the first step of the biosynthesis process, cholesterol is converted to pregnenolone by cytochrome P450 within the mitochondria. Pregnenolone either inside the mitochondria or in cytoplasmic compartment is converted to progesterone and DHEA by 3$\beta$-hydroxysteroid dehydrogenases (3$\beta$-HSDs) and cytochrome P450 17$\alpha$-hydroxylase (Cyp17), respectively. The conversion of progesterone into 5$\alpha$-dihydroprogesterone (5$\alpha$-DHP) and deoxycoticosterone is catalyzed by 5$\alpha$-reductase and 21-hydroxylase, respectively. Further, allopregnanolone (3$\alpha$,5$\alpha$-tetrahydroprogesterone) is generated from 5$\alpha$-dihydroprogesterone by the catalytic action of 3$\beta$-HSDs and deoxycoticosterone is converted into 5$\alpha$-dihydrodeoxycoticosterone (5$\alpha$-dihyroDOC) and then to 3$\alpha$,5$\alpha$ tetrahydrodeoxycoticosterone

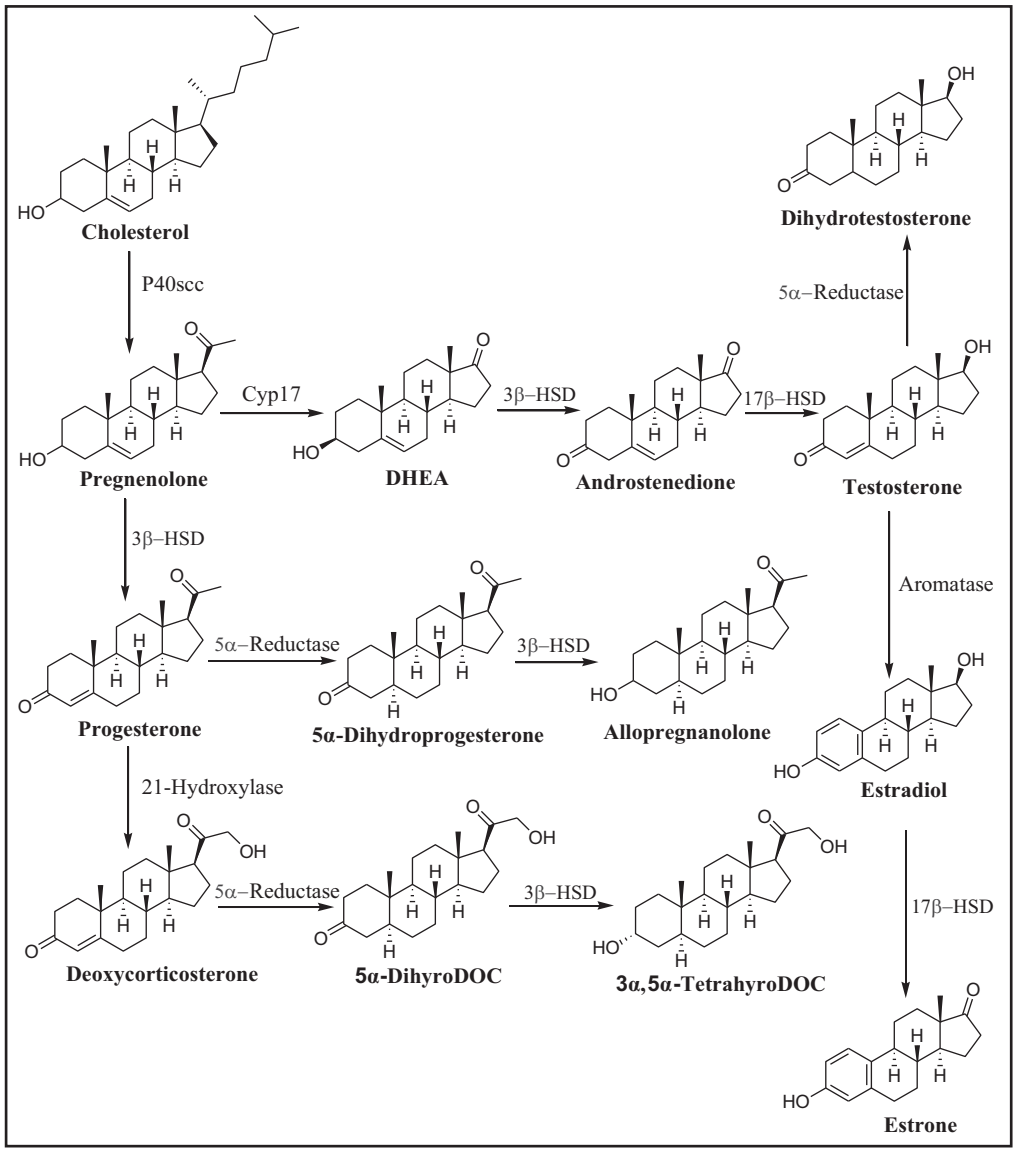



**FIGURE 3** Steroidal biosynthesis pathway within the central nervous system

(3$\alpha$,5$\alpha$-tetrahydroDOC) under the influence of enzymes 5$\alpha$-reductase and 3$\beta$-HSDs. On the other hand, DHEA gives androstenedione through 3$\beta$-HSDs, which further generates testosterone in the presence of 17$\beta$-HSDs. Aromatase enzyme catalyzes conversion of testosterone to estradiol, whereas 5$\alpha$-reductase converts testosterone to dihydrotestosterone. Estradiol is further converted to estrone in the presence of 17$\beta$-HSDs.[127] The concentration levels of these steroids in the brain mainly depend upon their hormonal source along with their local synthesis and metabolism. The neuroprotective action of steroids is exerted through both steroid receptor dependent and independent mechanisms within cell nucleus, plasma membrane, mitochondria, glial cells, and blood vessels. Neuroprotective steroids mainly protect the neurons from oxidative stress, excitotoxicity, and neuroinflammation, which are mainly involved in the death of neuronal cells and also promote the neurotransmission, repair processes such as neurogenesis, myelination, and expression of antiapoptotic factors.[128,129] They also regulate the expression of phosphatases, kinases, and transcription of genes leading to decreased apoptosis, excitotoxicity, and oxidative stress. Neuroprotective steroids

reduce reactive gliosis and the release of proinflammatory cytokines such as TNF-$\alpha$, IL-1$\beta$, and IL-6 in altered neuronal conditions. These steroids play an important role in controlling the function of the neurovascular units via astrocytes and endothelial cells, which helps to reduce brain edema and promote neurogenesis in the injured brain. All these course of actions are linked with therapeutic management of neurodegenerative disorders and could be useful for the chemical exploration of neuroprotective steroids in preventing the progression of neurodegeneration or neurodegenerative diseases.[130]

Neuroprotective steroids modulate brain functions primarily by interacting with neurotransmitter receptors, for example, $\gamma$-amino butyric acid type A and B ($GABA_A$ receptor, $GABA_B$ receptor), serotonin type 3 (5-HT3), NMDA, $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate receptor, and an atypical receptor like the sigma 1 within the brain.[131]

Sex has a great impact on the neuroprotective action of steroids within the CNS. Sex differences influence the structural and functional activities of neuronal cells in the brain and the spinal cord. Differences in hormonal levels of males and females are usually associated with the outcomes of the pathological insults to the nervous system as well as prevalence of neuropathological disorders.[132] Experimental studies in animal models have shown the fluctuations in hormonal levels during the estrous cycle, which affect the brain response to pathological insults.[133–135] This indicates the effect of endogenous fluctuations of gonadal hormones during the estrous cycle on the neuronal loss. It is also observed that ischemic events occur with greater frequency in men than in women before the age of 85 years.[136] The ovarian hormones might be involved in the sex differences pertaining to brain damage as ovariectomy enhances the effect in female animals.[137]

The influence on the response of the brain to exogenously administered steroids with sex differences has been shown by several experimental studies.[134–142] The differential effects of neuroactive steroids in the male and female neural cells may be a consequence of differences in steroid receptors or in the mechanisms of steroid signaling.

## 4.1 | Natural neuroprotective steroids

DHEA, testosterone, estradiol, and progesterone are the natural neuroprotective steroids, which promote the neuronal survival by activating various mechanisms in the CNS. These mainly enhance the activity of ion channels associated with neurotransmitter receptors, promote the antioxidant effects via steroid receptor independent mechanisms, and regulate the cell survival and metabolism by steroid receptor signaling initiated in the mitochondria. All these mechanisms increase life of the neuronal cells by preventing the apoptosis, excitotoxicity, and production of toxic free radicals.[128,143–145] From the chemical structural point of view, various natural neuroprotective steroids could be divided into various classes as follows.

### 4.1.1 | C-18 steroids

Estradiol is a sex hormone essential for the development and maintenance of female reproductive tissues. It plays an important role in the regulation of the estrous and menstrual cycles of female reproductive process. It is also produced within the brain from its steroid precursors to produce the neuroprotective effects. Estradiol mainly regulates the cholinergic neurotransmission, promotes neuronal survival, and also stimulates synaptic transmission in different experimental situations.[143,146,147]

Recently, it has been reported that estrogen treatment in experimental autoimmune encephalomyelitis (EAE) animals reduce the proinflammatory cytokines such as TNF-$\alpha$, IFN-$\gamma$, and IL6, chemokines and their receptors and increase the anti-inflammatory transforming growth factor (TGF)-$\beta$2 and $\beta$3.[148] Experimental findings indicate that estradiol targets important landmarks involved in the pathophysiology of AD. Estradiol regulates $\beta$-amyloid accumulation in the brain of experimental animals and also protects the neuronal cells from $\beta$-amyloid damage through variety of mechanisms such as regulation of the expression of proteins involved in apoptotic process and inhibition of excitotoxic neuronal death. Estradiol is also able to prevent the pathological hyperphosphorylation of tau protein that is a characteristic feature of AD. All these experimental findings support the protective role of estradiol in AD.[149] In addition, estradiol also provides the neuroprotective effects against PD and MS by increasing the ratio of antiapoptotic Bcl-2

proteins, promoting the release of growth factors such as BDNF and IGF-1 and by regulating the expression of myelin protein in the experimental animal models of PD and MS.[150,151]

### 4.1.2 | C-19 steroids

DHEA is the most abundant circulating endogenous steroid hormone in the human body and is mainly produced in adrenal glands and gonads. DHEA is reversibly converted into its sulfate ester DHEAS under the influence of enzyme sulfotransferase. Both DHEA and DHEAS are imported into the brain from the circulation but small portion of these are also produced locally in the brain.[152,153] DHEA easily cross the blood–brain barrier (BBB), whereas its sulfated form does not penetrate from the blood into the brain through BBB. However penetration of DHEAS into the hypothalamus, which is not protected by the BBB cannot be ruled out. Moreover, an experimental study using labeled DHEA and DHEAS proved the possibility of transformation of DHEA to the sulfated form and vice versa for the easy accessibility through BBB.[152]

DHEA gets converted to either testosterone and dihydrotestosterone or estradiol and exerts its neuroprotective effects through androgen and estrogen receptors present within the brain. The recent studies provide enough evidence about clinical applications of DHEA as neuroprotective steroids, which mainly include antioxidant, anti-inflammatory, and antiapoptotic effects.[154] It also promotes neurogenesis and neuronal survival in response to brain injury. In animal models of AD and PD, DHEA also receive great attention due to its ability to improve the cognitive and locomotor functions.[155]

The A$\beta$ deposits produced from amyloid precursor protein (APP) cause the degeneration of brain cells in AD. The data from the clinical studies prove that DHEA treatment impede the processing of APP through nonamyloidogenic pathway, which prevents the gradual accumulation of toxic A$\beta$ proteins in AD patients. DHEA treatment also enhances the nonamyloidogenic secretion (nontoxic protein forms) that promotes the neurite outgrowth. Therefore, the age-associated decline in DHEA levels may contribute to the pathological amyloid precursor protein processing and eventually lead to the development of AD. Thus, there is a hope to protect the structure and function of ageing brains through long-term DHEA supplementation.[156–158]

The possible neuroprotective role of DHEA against the development of AD is also elucidated in experimental models in which the young female rats were ovariectomized and AD was developed by daily intraperitoneal administration of aluminum chloride ($AlCl_3$) at 4.2 mg/kg of body weight for 12 weeks. Half of them received DHEA orally (250 mg/kg, three times weekly) for 18 weeks. After treatment, the animals were analyzed for the cholinergic markers (AChE and ACh) and also for the biomarkers of oxidative stress. Results of experimental study revealed that the significant increase in the parameters of oxidative stress is directly associated with the decreased activities of antioxidant enzymes. Moreover, the elevation in brain AChE activity with significant reduction in ACh levels was recorded in same group of animals. DHEA-treated animals produce significant amelioration in all investigated parameters of $AlCl_3$-intoxicated ovariectomized rats, which was confirmed by histological examination of brain sections. The results clearly indicate the role of DHEA as a neuroprotective steroid against AD.[159]

DHEA administration significantly produces the anti-Parkinsonian effects in moderately and severely impaired MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) monkeys. In addition, DHEA in combination with a low dose of L-3,4-dihydroxyphenylalanine (L-DOPA) prevent the dopamine degeneration in the brains of females monkeys lesioned with MPTP. The metabolism of DHEA into estradiol within the brain can also improve the dopamine activity. Moreover, DHEA treatment helped in the recovery of locomotor abilities with proper left–right coordination and fine motor control.[154]

As reported earlier, neuroinflammation plays a major role in pathogenesis of neurodegenerative disorders. Secretion of inflammatory mediators by activated glial cells and infiltrating leukocytes initiates the neuropathological mechanisms leading to AD, PD, and HD.[52–54] A latest investigation suggests that DHEA and DHEAS induce the suppression of inflammatory gene expression for IL-1$\beta$, TNF-$\alpha$, and IL-6. DHEAS treatment reduces the transcription of inflammatory genes for CD3 and GFAP in brain of animals.[160] DHEA and DHEAS have been reported to act as neurotrophic factors by defending neurons against many harmful events mainly excitotoxicity.[128] DHEA also inhibit the

NMDA-induced NO production in hippocampal cells and modulate the calcium/NO signaling pathway. The protective effects of both DHEA and DHEAS can be mediated by protecting mitochondria against intracellular $Ca^{2+}$ overload in the in vivo model of cerebral ischemia in rats.[161] Nowadays it is generally accepted that DHEA serves as a protector against the neurodegenerative changes and is ultimately involved in neuroprotection by homeostasis within the brain.[162]

Testosterone is another C-19 steroid belonging to the category of gonadal sex hormone that plays an important role in neuroprotection. The recent research approaches prove that testosterone acts as a potent neuroprotective steroid in various experimental studies related to neurodegenerative disorders. Testosterone acts through androgen receptors (ARs) present in the brain as well as in prostate, testes, and ovaries. Being an endogenous agent, it easily crosses the BBB and influences the neuronal cells by acting directly via androgen pathway or indirectly through conversion into estrogen.[163] Recent investigations correlate declined level of testosterone with ageing leading to memory loss and impairment in cognitive function.[164,165] Therefore, exogenous supplements of testosterone in elderly patients produce the beneficial effects. The experimental studies in animals provide the useful information regarding the protective role of testosterone within CNS. It includes inhibition of NMDA excitotoxicity and upregulation of the level of NGF in the hippocampus and its receptor in the forebrain. It also reduces the overexpression of amyloid $\beta$ and inhibits the hyperphosphorylation of tau proteins in the animal models of AD. Testosterone enhances the neurite growth, neuronal size, plasticity, and synaptogenesis within the spinal nucleus and also protects the nerves cells from oxidative stress, neuroinflammation, and apoptosis.[166]

Baltimore Longitudinal Study of Aging (BLSA) provided most convincing evidence regarding the neuroprotective effects of testosterone against age-related cognitive decline in AD. Repeated neuropsychological assessments and morning testosterone levels were obtained from 407 men aging between 50 and 91 years. The findings suggest that higher level of endogenous testosterone is accountable for better visual, verbal memory, and visuospatial functioning in young ones versus elders and in men versus men having low testosterone levels. This may be due to increased blood flow in the hippocampus area.[167] In another study, effect of castration (gonadectomy) in dogs on loss of cognitive function was observed. The obtained results conclude that sexually intact male dogs were significantly less prone to mild to severe cognitive impairment than the neutered dogs that clearly indicate the relationship of cognitive function with role of circulating testosterone in sexually intact male dogs.[168]

Testosterone deficiency in older male population increased prevalence of Parkinson's like symptoms.[169] Testosterone therapy has been successfully used to improve the nonmotor symptoms of PD but there is evidence regarding the direct effect of testosterone on motor symptoms.[170] Mitchell et al. observed the significant improvement in the resting tremor and fine motor control after testosterone administration in a testosterone-deficient Parkinsonian patient.[171] MS is an inflammatory neurodegenerative disease of the CNS. Most of the medications reduce inflammatory activity but they have modest effect on long-term disability and gray matter atrophy. Kurth and his co-workers provide the useful information regarding potential neuroprotective effects of testosterone on cerebral gray matter in a pilot clinical trial. Focal gray matter loss was noted as a marker of neurodegeneration in MS. During the nontreatment phase, significant ratio of gray matter has been found to decrease in brains of patients. However, the testosterone treatment not only reduces the loss of gray matter within the brain but also significantly increase the density of gray matter in right frontal cortex. These observations supported the potential role of testosterone in the therapeutic management of MS.[172]

### 4.1.3 | C-21 steroids

Progesterone is primarily a female hormone produced in the ovarian corpus luteum and placenta of females, but is also present in the testes and adrenal glands of males. However, progesterone and its derivatives like allopregnanolone may also be synthesized de novo within the nervous system. Neuroprotective effects of progesterone mainly include the inhibition of neuronal death, edema, and improvement of functional recovery in males and females.[173] Other neuroprotective actions of progesterone include: downregulation of the inflammatory cascade by decelerating cytokine (IL-1$\beta$, IL-6, TNF-$\alpha$) induced reactions, reduced excitotoxicity by inhibition of glutamate receptors,

inhibition of glial cell activation in the CNS, and reduced oxidative stress via upregulation of antioxidant enzymes.[174] In experimental models of TBI model, treatment with progesterone leads to reduced edema, accumulation of the astrocytes in the cortex, and reduction in the expression of inflammatory mediators such as nuclear NFkB, active C3 fragments, IL1$\beta$, and TNF-$\alpha$. In addition, it also attenuates the response of reactive microglial/macrophage cells and reduces the activity of iNOS. All the observations give a clear indication regarding the positive influence of progesterone on the inflammatory events by suppressing the proinflammatory mediators and emphasizing the anti-inflammatory response within the CNS.[175]

Neuroprotective effects of progesterone in midbrain dopaminergic neurons of the rats are reoprted by Schumacher et al.[176] In this study, progesterone was also found to be a protective agent for dopaminergic neurons against degeneration induced by MPTP. Progesterone also activates signaling enzymes such as mitogen-activated protein kinase (MAPK), extracellular signal regulated kinase (ERK), and serine/threonine protein kinase associated with neuroprotection mechanism within in the brain. The investigation revealed that progesterone increased expression of the Bcl-2 antiapoptotic gene leading to prevention of cell death in rat hippocampal neuronal cultures. The administration of progesterone increased mRNA levels of antiapoptotic genes like Bcl-2 and Bcl-xL and their protein derivatives in the TBI model in rats.[177] The beneficial effects of progesterone were also seen in EAE model of MS. The mice treated with progesterone, starting 1 week before EAE induction, reduced the risk of demyelination in the spinal cord and infiltration of inflammatory cells. It also normalized the expression of neuronal proteins, and improved the clinical scores. Moreover, progesterone may help to repair the myelin sheath by promoting the endogenous population of oligodendrocyte precursor cells (OPCs).[178]

Allopregnanolone, a metabolite of progesterone also plays an important role in neuroprotection, though its precise role is still unclear.[179] In mouse model of AD, allopregnanolone had beneficial effects on disease markers with improved cognitive functions as well as reduced hyperphosphorylation of tau proteins. In the mouse model of Niemann–Pick C disease, administration of allopregnanolone increased the survival rates of cerebellar neurons and doubled the lifespan of the animals.[180] In rats after TBI, the treatment with allopregnanolone decreased the DNA fragmentation and expression of capase-3.[181] Moreover, it also prevents the apoptotic cell death in the human NT2 cell line cultures in NMDA-induced excitotoxicity.[182]

Pregnenolone is an another steroid hormone produced within brain and acts as a precursor for progestogens, glucocorticoids, mineralocorticoids, androgens, and estrogens.[183] Pregnenolone exhibits neuroprotective effects especially against glutamate and amyloid $\beta$ protein induced neurotoxicity.[128] In clonal mouse hippocampal cells, it stabilizes microtubules by enhancing their polymerization, improves myelination, and activates NGF.[184] Pregnenolone and DHEA together act as agonists of intracellular receptors like sigma 1 protein that is mainly involved in learning and memory processes. In addition, pregnenolone exerted neuroprotective effects against kainate-induced cell death in the hippocampus of gonadectomized rats.[185]

## 4.2 | Synthetic neuroprotective steroids

The disadvantages associated with natural neurosteroids mainly include their short biological half-lives, rapid metabolism, and low oral bioavailability. Therefore synthetic modifications of the natural neurosteroids are an attractive approach to produce potent neuroprotective agents for the treatment of various neurodegenerative disorders.[186]

### 4.2.1 | Estrane derivatives

Estradiol is a potent antioxidant having neuroprotective activity. It protects neural cells against glutamate and peroxide-mediated oxidative damage.[143] The structures of some of the estrane derivatives developed as neuroprotective agents have been shown in Figure 4. The 17$\beta$-*O*-alkyl derivatives **(1)** of estradiol have displayed improved neuroprotection in a dose-dependent manner against the glutamate-induced oxidative damage. 17$\beta$-*O*-alkyl ethers with alkyl substituents in a homologous series were obtained by treatment of 3-*O*-benzyl-17$\beta$-estradiol with sodium hydride/alkyl halide, followed by the removal of the *O*-benzyl protecting group via catalytic transfer hydrogena-

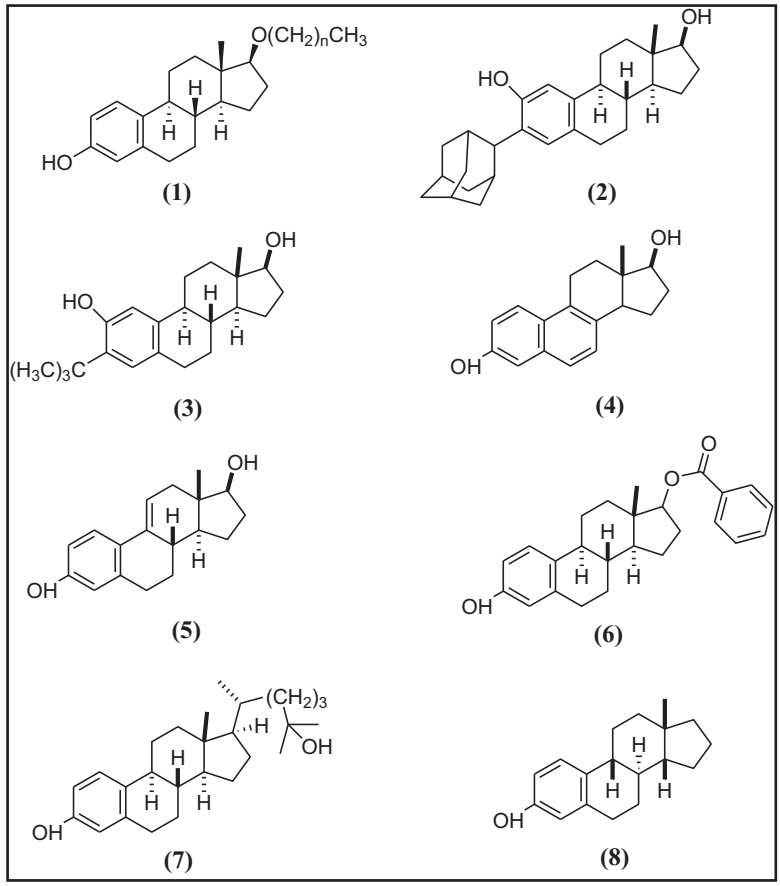



**FIGURE 4** Estrane derivatives as neuroprotective steroids

tion. The higher 17$\beta$-alkyl ethers of estradiol ($n = 3$ to $n = 8$) produced better protection in vitro against oxidative stress in HT-22 neural cells, whereas introduction of lower alkyl ethers ($n < 2$) decreased neuroprotective effects significantly.[187] In another study, a library of estrane derivatives was evaluated using in vitro models for their ability to inhibit cell toxicity against glutamate and iodoacetic acid (IAA) in HT-22 (a murine hippocampal cell line) neural cells. The structure–activity relationship (SAR) for this particular series of estrane derivatives has been established. The phenolic nature of the A-ring in estratriene analogues **1–3** is found to be necessary to protect the neuronal cells from death induced by glutamate or IAA. On the other hand addition of hydroxyl group on B or C ring enhances the hydrophilicity, which completely abolished the neuroprotective activity. The introduction of groups such as adamantyl (**2**) and *tert*-butyl (**3**) at the 3 position of steroidal nucleus drastically improved neuroprotective potencies as compared to 17$\beta$-estradiol, whereas the replacement of the hydrogen with such bulky alkyl groups at the 2- or 4-positions of the A-ring diminished the activity. The introduction of conjugated double bonds into the B (**4**) or C (**5**) rings results in most potent estrane derivatives against oxidative stress toxicity due to the increase in the stability of the phenoxy radical. Esterification **(6)** or introduction of the alkyl side chain **(7)** at the $C_{17}$ position of the estrane skeleton did not enhance the neuroprotection potency, whereas the complete removal of 17-substituent as in compound **8** improved the neuroprotective effects.[188]

### 4.2.2 | Androstane derivatives

Abdalla and co-workers carried out the structural modification on 16-arylideneandrostane to produce the steroidal derivatives **9–13** exhibiting remarkable changes in the biological activity against AD (Fig. 5). Synthetic modifica-

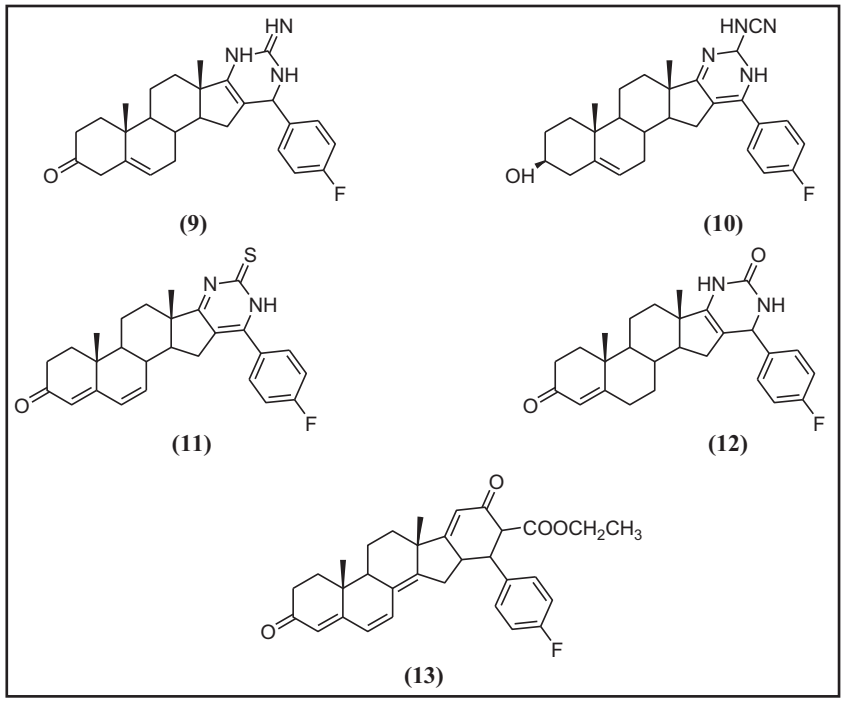



**FIGURE 5** D-ring substituted derivatives of epiandrosterone and androsterone

tions have been achieved by introducing multibasic entities on ring-D of the steroidal nucleus via fusion of different heterocyclic ring systems like pyrimidines, cyanopyrimidines, thiopyrimidines, and pyrimidones. The SAR studies suggest that all the synthesized derivatives act as proton acceptors to form hydrogen bonds with A$\beta$42 or A$\beta$40 and its precursors as well as with $\beta$ and $\gamma$ secretase enzymes leading to interference in biosynthetic pathways that prevent the formation of A$\beta$. Among these *N*-cyanoiminopyrimidine steroid **10** was found to display the highest activity ($IC_{50}$ = 3.28 nM) in A$\beta$42 and A$\beta$40 assays. Furthermore, the SAR studies conclude that the introduction of a double bond at 4 position of the steroidal nucleus (**11–13**) improves the activity in comparison to reduced ones. Increase in the degree of conjugation as in compounds **11** and **13** further enhances the activity. Moreover, the substituent with −I (Inductive) effects promote the anti-Alzheimer activity in comparison to those with −M (Mesomeric) effects while the latter is better tolerated than those with +M (Mesomeric) effects. The presence of 17-ester moiety in derivative **13** enhances the activities as compared to the ketone group by promoting the interaction with $\beta$ and $\gamma$ secretase receptors, thus reduce amyloid (A) formation.[189]

Recently Singh and Bansal reported the neuroprotective effects of 16-pyridylidene steroids and their 4-aza analogues in LPS (lipopolysaccharides)-treated animal models.[190] It was observed that the 16-arylidene steroidal derivatives significantly improve LPS-induced learning, memory, and movement deficits in animal models. In addition, the results of biochemical estimations of brain serum of treated animals have shown the suppression of oxidative and nitrosative stress, AChE activity, and reduction in TNF-$\alpha$ levels, which were induced through LPS-mediated neuroinflammatory mechanisms. Among all of the steroidal derivatives, 16-(4-pyridylidene) steroid **14** and its 4-aza analogue **15** (Fig. 6) were found to be the most active neuroprotective agents and produced effects comparable to standard drugs celecoxib and dexamethasone in terms of behavioral, biochemical, and molecular aspects.[190] DHEA analogues with spiro-epoxy modifications at C-3 or C-17 positions produce significant antiapoptotic and neuroprotective effects. Of the series, the spiro-epoxy steroidal derivatives **16–18** (Fig. 7) were found to be most potent with $IC_{50}$ values of 0.19 ± 0.01, 99.0 ± 4.6, and 6.4 ±0.3 nM, respectively, when evaluated for neuroprotective activity against the serumdeprivation-induced apoptosis using neural crest derived PC12 cell model. These compounds possess high affin-

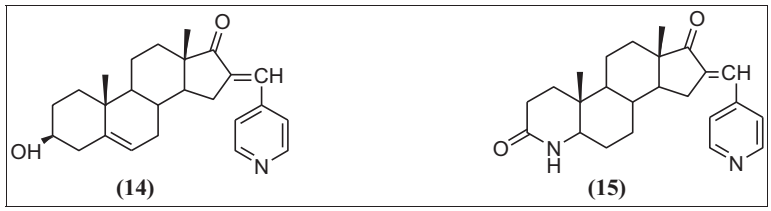



**FIGURE 6** 16-(4-Pyridylidene)androstane analogues as novel neuroprotective agents

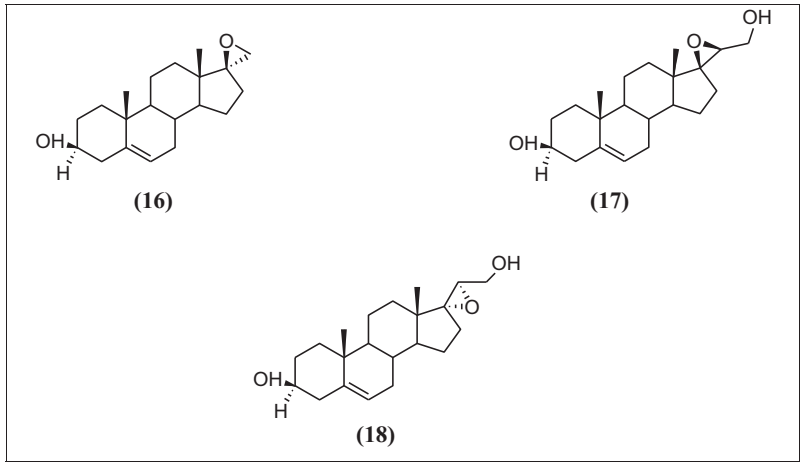



**FIGURE 7** Structures of neuroprotective spiro-epoxy analogues of DHEA

ity for the membrane receptors, that is, NMDA and $GABA_A$ receptors and mimic the release of antiapoptotic Bcl-2 proteins at nanomolar levels. Moreover the incubation of PC12 cells with spiro-epoxy neurosteroid analogues **16–18** increases dopamine level after 24 hr leading to increased de novo production of dopamine in dopaminergic neurons. The results of SAR studies revealed that substitution of epoxide group at C17 position in DHA derivatives **16–18** promotes the passage into the cell membrane, which facilitates the binding of steroidal analogues with estrogen receptors $\alpha$ and $\beta$. In addition, the presence of –OH at C21 position in steroids **17** and **18** promotes the hydrogen bond formation that results in better neuroprotective effects due to enhanced binding interactions of these steroidal derivatives with the NMDA and $GABA_A$ receptors.[191]

Androst-3$\beta$,5$\alpha$,6$\beta$-triol **(19)**, another hydroxy derivative of DHEA was examined for its effects on mitochondrial function and oxidative stress in the cultured cortical neurons exposed to hypoxia followed by reoxygenation. The obtained results suggest that pretreatment of neuronal tissue cultures with triol **19** protected the cortical neurons from hypoxia/reoxygenation exposure by reducing the neuronal viability. The steroid **19** promotes the mitochondrial membrane potential as well as ATP production and also enhances the protection against oxidative stress. Because of the lipophilic nature (logP = 3.31), the triol easily crosses the BBB and other membrane structures and produces neuroprotective effects within the brain. Hence the compound may be useful in the treatment of acute ischemic stroke.[192] SAR studies indicate that incorporation of a methylene moiety at C-17 position **(20)** results in weaker neuroprotection, whereas substitution of alkyl groups as in compounds **21** and **22** offered a better flexibility and promotes the bond formation with receptors, which ultimately enhances the neuroprotective activity (Fig. 8). The presence of electron-withdrawing groups at 17-position **(23)** also enhances the neuroprotective activity in comparison to the electron-donating groups.[193] Fluasterone (**24**) (DHEF, a novel analog of DHEA) is considered as a drug candidate that might be useful in the treatment of TBI. It was observed that DHEF improves the functional recovery in the rats through the possible mechanisms such as attenuation of free radical production, inhibition of NMDA, and KA receptor toxicity

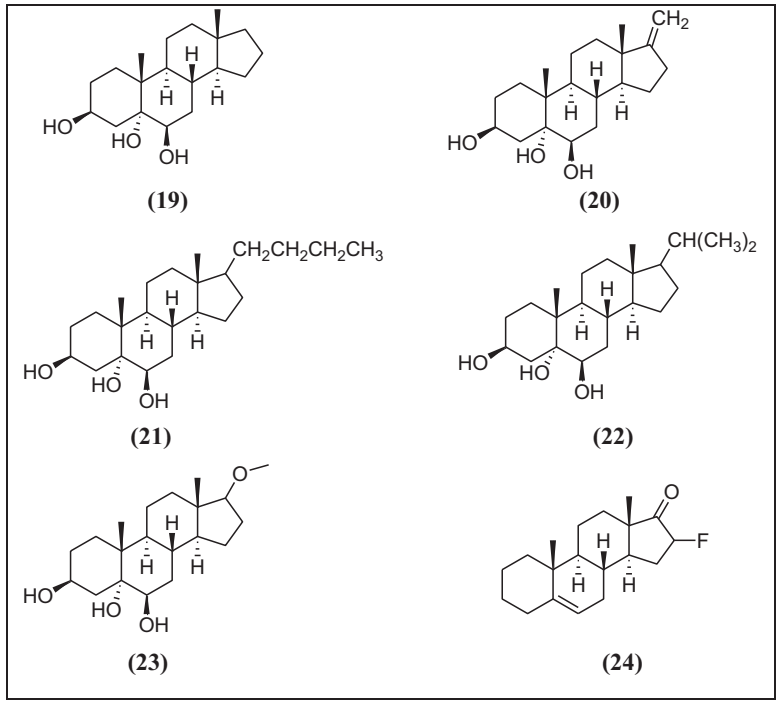



**FIGURE 8** Hydroxylated derivatives of DHEA as neuroprotective agents

in the animal models of TBI. DHEF also inhibited the activation of IL-1$\beta$-induced cyclooxygenase-2 and production of prostaglandin (PGE2) in cultured rat mesangial cells.[194]

### 4.2.3 | Pregnane derivatives

NMDA receptors act as glutamate-gated ion channels and are composed of GluN1, GluN2A–GluN2D GluN3A, and GluN3B subunits. Overactivation of NMDA receptors initiate the excitotoxic response within the brain, which causes neuronal cell death leading to AD, PD, and TBI.[195] Neurosteroids and their synthetic analogues act as useful therapeutic candidates against the overactivated response of NMDA receptors.[128,196] On the basis of this therapeutic approach, a new class of pregnanolone sulfate analogues **25a–k** (Fig. 9) have been synthesized by diverse structural modifications on the D-ring of steroid skeleton and evaluated on recombinant GluN1/GluN2B receptors to access the role of structural variation on activity profile. All the tested compounds **25a–k** were found to be potent inhibitors of NMDA receptors ($IC_{50}$ = 90 nM to 5.4 $\mu$M) in comparison to the endogenous neurosteroid pregnenolone sulfate ($IC_{50}$ = 24.6 $\mu$M). The in vitro activity data correlated strongly with SAR studies. The 20-oxo group on the acetyl pregnane moiety was not found crucial for the inhibition of NMDA-induced excitotoxicity as the removal of the 17-acetyl moiety in steroid **25a** resulted in more potent N-methyl-D-aspartate receptor (NMDAR) inhibition. Further the introduction of 17-alkyl substituents in **25b** and **25c** promotes the inhibition of NMDA-induced currents. However, the introduction of exocyclic or endocyclic double bond in the D-ring of steroids **(25d–h)** or the expansion of the D-ring **(25i)** did not produce any effect on the biological activity. The substitution of the halogens such as iodine **(25j)** or fluorine **(25k)** at C-17 position enhances the neuroprotective effects against the overactivated NMDA receptors.[197]

Jiang and co-workers[198] synthesized a new class of pregnenolone derivatives **(26–33)** substituted with various arylidene groups at C-21 position and having epoxy moiety at C-5, C-6 positions as represented in Figure 10. The neuroprotective effects have been evaluated against amyloid-$\beta_{25\text{-}35}$, $H_2O_2$-induced neurotoxicity in PC12 cells and oxygen-glucose deprivation (OGD) induced neurotoxicity in SH-SY5Y cells. The bioassay studies indicated that most of the derivatives displayed potent in vitro neuroprotective effects in different screening models. Among them, com-

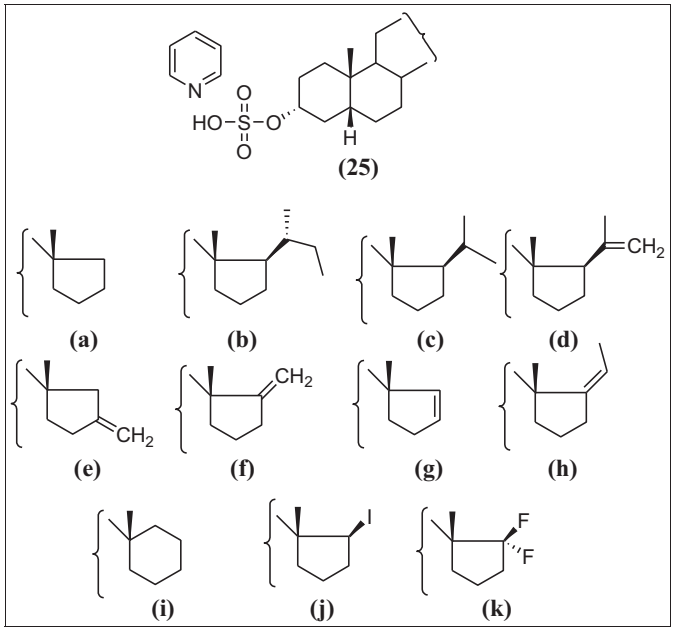



**FIGURE 9** A new class of pregnanolone sulfate analogues

pounds **26–28** exhibited the most potent neuroprotective effects against amyloid-$\beta_{25\text{-}35}$ and $H_2O_2$-induced neurotoxicity in PC12 cells and OGD-induced neurotoxicity in SH-SY5Y cells. The findings suggest that electron-releasing *ortho*-substituents such as methyl **(26)** or alkoxy groups **(27, 28)** increase neuroprotective effects while *para*-substituents like ch loro **(29)**, cyano **(30)**, nitro **(31)** moieties or incorporation of heterocyclic rings, for example, pyridine **(32)** and furan **(33)** could not produce significant impact on the neuroprotective activity of 21-arylidene steroids.

Much interest has been focused on the pharmacological agents having capability of selectively blocking the tonically activated NMDARs, while leaving the synaptically activated NMDARs intact. It is observed that synaptic activation of NMDARs plays a key role in synaptic transmission and plasticity, but the overexpression of NMDARs cause excitotoxicity leading to neurological disorders.[196] The endogenous neurosteroid pregnanolone sulfate acts as a selective potent inhibitor of tonically activated NMDARs. The synthetic pregnanolone derivatives represented by structure **34 (***n* = 1–*6)* have been prepared by substituting different carboxylic acid moieties at the terminal end of an aliphatic chain of varying length attached at C-3 position of the steroid skeleton. The results of in vivo biological activities have shown that steroidal derivative pregnanolone hemipimelate (*n* = 6) with the longest chain exhibited the highest potential against the tonically activated receptors without inducing psychomimetic side effects. This information provides valuable insights into the influence of synthetic neurosteroids on neuronal function and might be useful for the development of new therapeutic neurosteroid-based ligands with better clinical advantage over other known NMDAR inhibitors.[199] Another novel synthetic neurosteroid 3$\beta$-*p*-iodobenzoyloxypregnan-4,16-diene-6,20-dione (IBP) **(35)** has shown neuroprotective effects against markers of oxidative stress in animal models of HD. Treatment of male Wistar rats with IBP resulted in significant decrease in the concentrations of TBARS (thiobarbituric acid reactive substances—a end product of lipid peroxidation), $H_2O_2$, and total ATPase. The inhibition of the these biomarkers of oxidative stress protect the brain from the neurodegeneration.[200] Kapras and his co-workers reported a new novel synthetic steroidal derivative 20-oxo-5$\beta$-pregnan-3$\alpha$-yl-L-glutamyl-1-ester **(36)** as a potent inhibitor of the NMDA receptor, which is less susceptible to the fast metabolic deactivation caused by sulfatase and possesses better bioavailability as compared to pregnanolone sulfate. It antagonizes the NMDA receptor in a dose-dependent manner with high neuroprotective potential.[201] The structures of the potent steroidal NMDAR inhibitors are given in Figure 11.

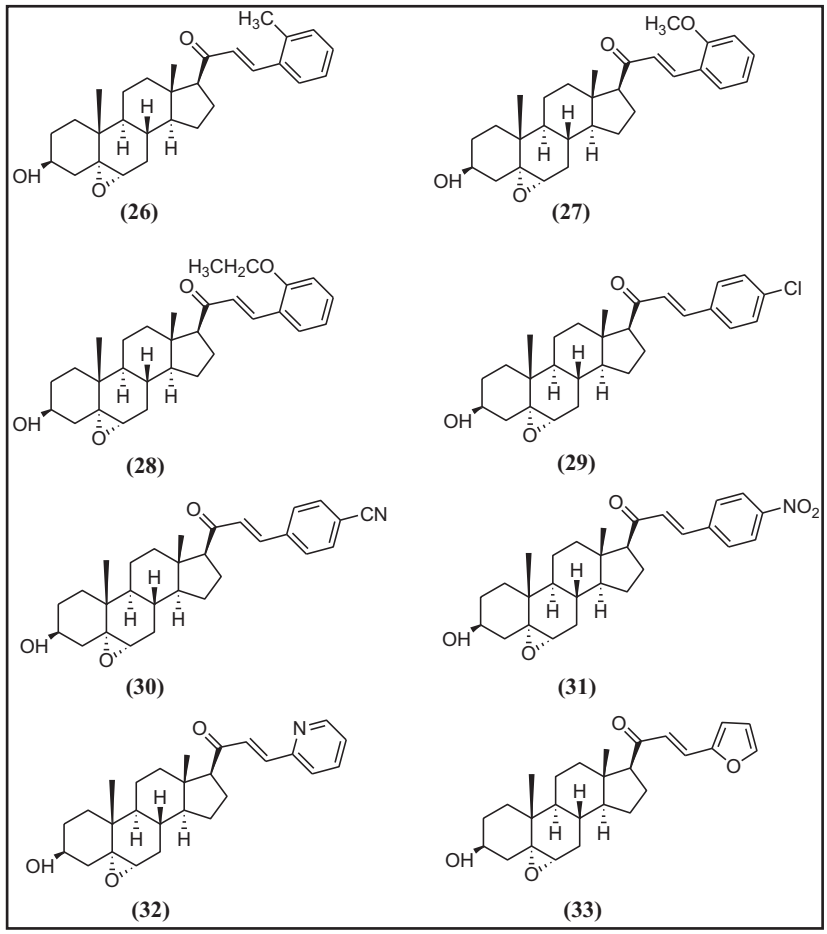



**FIGURE 10** 21-Arylidenepregnenolone derivatives and their corresponding epoxides

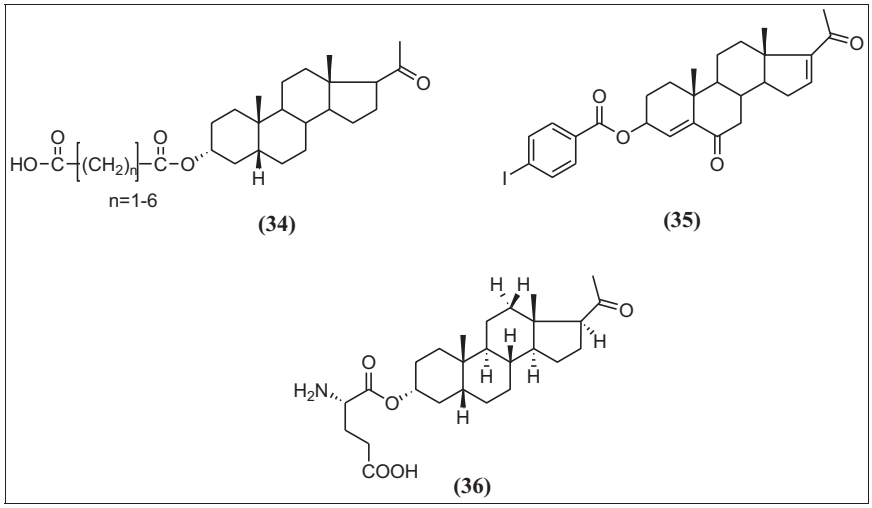



**FIGURE 11** C-3 substituted pregnanolone analogues as NMDAR inhibitors

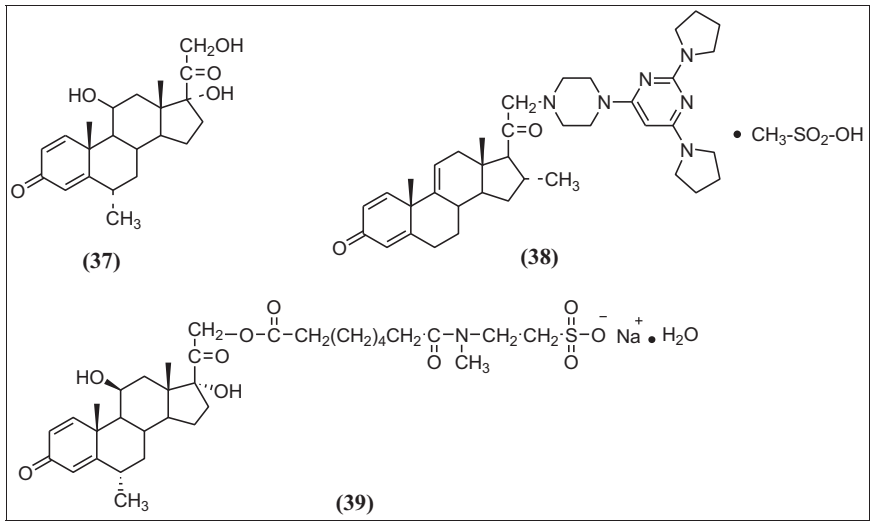



**FIGURE 12** Methylprednisolone and its prodrugs as neuroprotective steroids

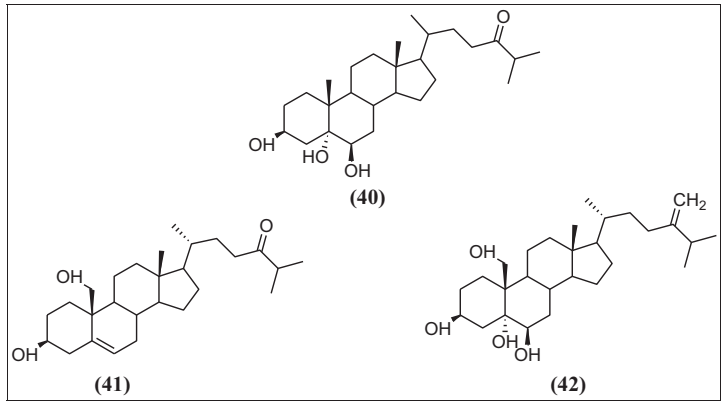



**FIGURE 13** Cholestane derivatives used as neuroprotective steroids

The neuroprotective effects of methylprednisolone include the inhibition of oxygen free radical induced lipid peroxidation and prevention of cerebral ischemia. Methylprednisolone **(37)** enhances neurological recovery in spinal cord injured patients after intravenous dosing within 8 hrs of an injury. However therapeutic window, optimum duration of treatment, and rational combination with other neuroprotective agents are the unresolved issues with methylprednisolone therapy. The novel nonglucocorticoid prodrugs 21-aminosteroid tirilazad mesylate (U-74006F) **(38)** and methylprednisolone sodium suleptanate (U-67590A) **(39)** have been developed with improved solution stability (Fig. 12).

After intravenous administration, prodrugs **38** and **39** are cleaved by esterase enzyme to liberate the free steroid methylprednisolone, which is presumably responsible for the neuroprotective effects on the injured CNS. It helped in surpassing lipid antioxidant effects of methylprednisolone without unwanted glucocorticoid properties.[202]

### 4.2.4 | Cholestane derivatives

Haiyan Hu and his co-workers reported the cholestane-3,5,6-triol (Triol) **(40)**, a major metabolite of cholesterol as an endogenous neuroprotectant.[203] Treatment of cultured neurons with Triol **40** protects the neuronal cells from injury

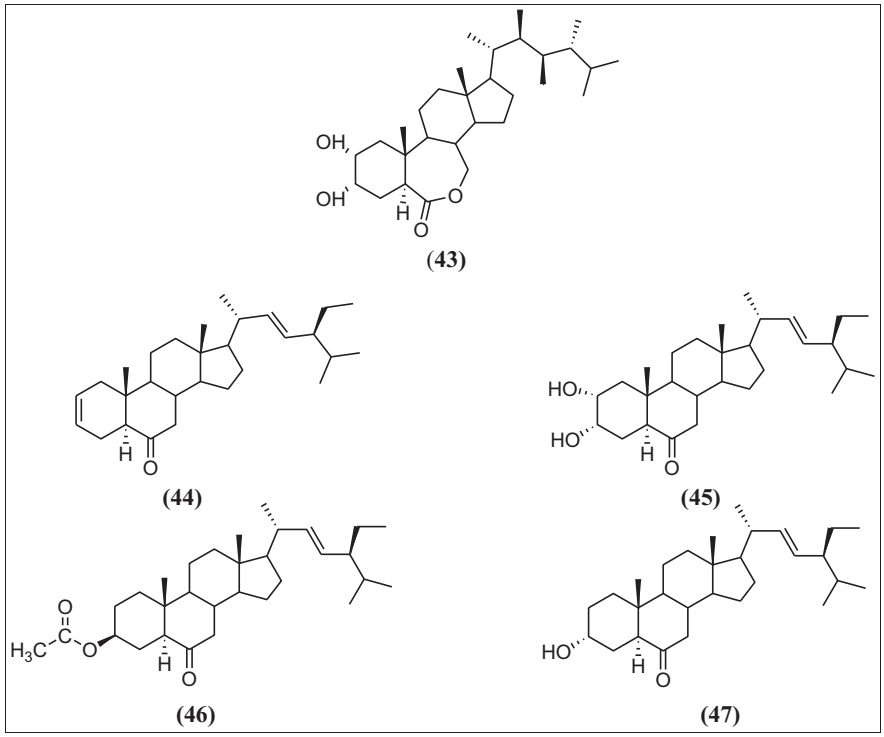
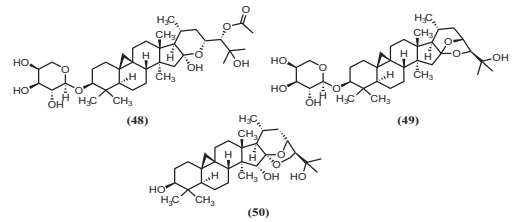
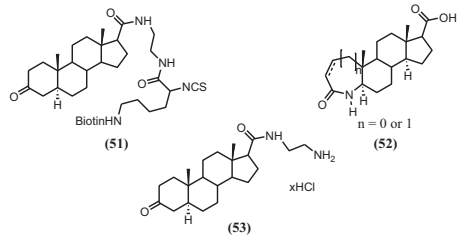
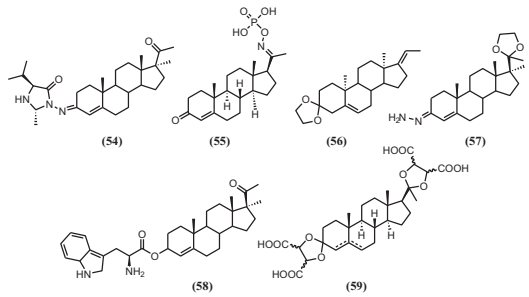
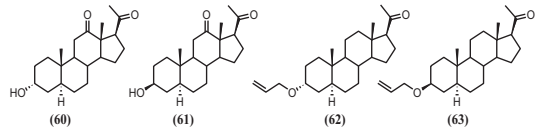
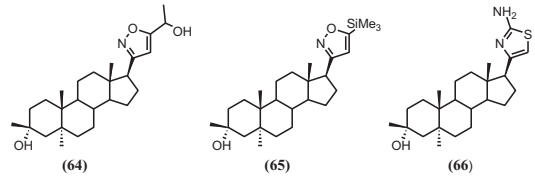



**FIGURE 14** Synthetic derivatives of brassinosteroids as neuroprotective agents

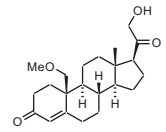
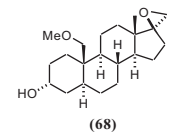
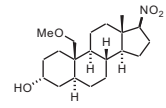
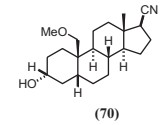
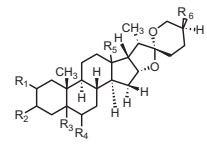
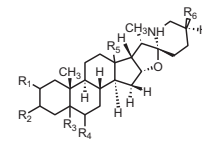
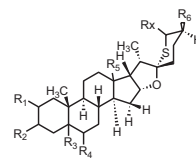
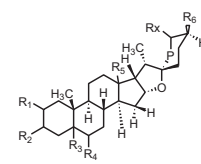
in both in vitro and in vivo animal models via negative modulation of NMDA receptors. It also decreases neuronal injury after spinal cord ischemia in rabbits and transient focal cerebral ischemia in rats. It has been concluded from the results that administration of Triol significantly attenuates intracellular concentration of calcium ions induced by glutamate and directly block the NMDA receptors, which may be responsible for neuroprotective effects. The findings suggest that Triol functions as an endogenous neuroprotectant that may provide novel insights into understanding and developing potential therapeutics for neurodegenerative disorders. Taking lead from significant neuroprotective effects of the Triol, recently, a promising candidate 24-keto-cholest-5-ene-3$\beta$,19-diol (Diol) **(41)** has been synthesized for the treatment of neurological disorders.[203] Diol was evaluated using in vitro models of hypoxia- and glutamate-induced neuronal injury and in vitro models of middle cerebral artery occlusion (MCAO) induced cerebral ischemia in mice. The treatment of animals with Diol enhanced the survival rate of cerebellar granule neurons against the glutamate or hypoxia-induced neuronal injury. Moreover, it was observed that the Diol treatment effectively decreased MCAO-induced infarction volume in mice. The obtained results suggest that Diol acts as a potent neuroprotectant and these types of synthetic approaches might be useful in the development of promising candidates for the treatment of stroke intervention.[204] A marine steroid 24-methylenecholestane-3$\beta$,5$\alpha$,6$\beta$,19-tetraol (Tetrol, **42)** has been recently investigated for its neuroprotective effects. It was synthesized through a multiple step reaction starting from hyodeoxycholic acid (HDCA) and evaluated against glutamate-induced neuronal injury using in vitro animal model. The results of the in vitro study showed increased survival rate of cerebellar granule neurons degenerated with the toxic concentration of glutamate on treatment with Tetrol. Tetrol significantly reduced glutamate-induced lactate dehydrogenase (LDH) release by inhibiting glutaminolysis at a threshold concentration of 2.5 $\mu$M. Tetrol attenuated NMDA-induced intracellular calcium $[Ca^{2+}]_i$ increase with an $IC_{50}$ of 7.8 $\pm$ 0.62 $\mu$M, and inhibited NMDA currents in cortical neurons with an $IC_{50}$ = 10.28 $\pm$ 0.71 $\mu$M. It was observed that Tetrol significantly decreased MCAO-induced infarction volume by 50% at 12 mg/kg in MCAO-induced cerebral ischemia model of rats that demonstrated the neuroprotective

**TABLE 1** Details of various patented inventions related to neuroprotective steroids

| Patent No. | Description of the patent | Structure |
|---|---|---|
| WO2006/ 124956 A1 | Findeis and co-workers[209] patented compounds **48-50** for their usefulness for the treatment or decreasing the severity of neurodegenerative disorders specially Alzheimer's disease. These compounds reduce the phosphorylation of amyloid precursor protein (APP) as well as inhibit the phosphorylation of amino acid residue tyrosine 668 of APP which is useful for treating or lessening the severity of AD. |  **(48)** **(49)** **(50)** |
| US2009/ 0170889 A1 | Another invention by Soskic and his co-workers[210] provide a new class of steroidal derivatives **51-53,** which could be explored as a medicament for the prevention and/or treatment of neurological diseases such as Parkinson's disease, Alzheimer's disease, dementia, schizophrenia or epilepsy. The results of *in vivo* and *in vitro* animal studies have shown neuroprotective effects by inhibiting MPTP induced neurotoxic response, modulating voltage-gated potassium channels and lowering the load of β-amyloid plaques. |  **(51)** **(52)** **(53)** |
| US2011/ 0263553 A1 | The invention by Christopher *et al.*[211] details the steroidal analogues **54-59** with functionalized polar substituents at the C3 and/or C20 positions of the steroid ring system leading to improved water solubility. These novel steroid analogues are useful for neuroproetcion/neurogenesis in response of traumatic brain injury and stroke due to any stress, infection or toxin within the central nervous system. In addition, the inventive steroid analogues can also prevent the undesired side effects such as sleepiness; reduced arousal and increased blood clotting that are typically seen after acute or prolonged treatment with progesterone. |  **(54)** **(55)** **(56)** **(57)** **(58)** **(59)** |
| US2014/ 0058079 A1 | Recently Nyagan *et al*. were granted a patent for their discovery of allopregnanolone and epiallopregnanolone derivatives BR053 **(60),** BR297 **(61)**, BR351 **(62)** and BR338 **(63)**. According to the invention, these molecules could be used for treatment of neuropathological disorders and in particular the neuropathies induced by the chemotherapy of cancer. These neurosteroids act as neuroprotectant with ability to prevent neuronal cell death and stimulates neuronal proliferation.[212] |  **(60)** **(61)** **(62)** **(63)** |
| US2014/ 0148412 A1 | Hogenkamp[213] patented his invention of the novel 17β-heteroaryl-substituted steroid compounds **64-66.** These compounds act as modulators of $GABA_A$ receptors and are therefore useful in the treatment and/or prevention of a variety of disorders of the CNS such as epilepsy, depressive or bipolar disorders, multiple sclerosis, cognitive dysfunction and in stroke. |  **(64)** **(65)** **(66)** |

(Continues)

**TABLE 1** (Continued)

| Patent No. | Description of the patent | Structure |
|---|---|---|
| US2014/0235600 A1 | Novel neuroactive 19-alkoxy-17-substituted steroids **67-70** were invented by Covey and Robichaud[214] and could be useful against the CNS disorders relating to GABA function and activity. More specifically the steroidal derivatives in this invention are neuroactive compounds which regulate the neuronal excitability, mood change and stress response through the GABA receptors. |  (67)  (68)  (69)  (70) |
| EP 2801581 A1 | This patented invention reports novel esterane derivatives fused with spirostane rings **(71-74)** having anti-inflammatory and anti-glutamatergic actions within the CNS. The inventors reported that all of these novel spirosteroidal derivatives can be used for the treatment of inflammatory, cerebrovascular, neurodegenerative, neuropsychiatric, and neurological diseases. This invention provides the new direction to chemical and pharmaceutical branches to synthesize novel molecular entities of estrane derivatives fused with spirostane rings and evaluate their biological effects on central nervous systems.[215] |  (71)  (72)  (73)  (74) |

effects of the marine steroid Tetrol.[205] The structures of prominent neuroprotective cholestane derivatives have been given in Figure 13.

### 4.2.5 | Brassinosteroids

Brassinosteroids (BRs) represent a class of growth-promoting plant steroids. Currently BRs are being studied intensively for their physiological effects in plants including activation of protein and nucleic acid synthesis, regulation of hormonal balance and enzyme activity.[206] It has also been reported that BRs such as 24-epibrassinolide **(43)** exhibit potent antioxidative properties against MPP+-induced oxidative stress and apoptosis. Therefore, the synthetic derivatives of BRs namely, (22*E*,24*S*)-stigmastan-2,22-dien-6-one **(44),** (22*E*,24*S*)-2$\alpha$,3$\alpha$-dihydroxy-5$\alpha$-stigmast-22-en-6-one **(45)**, (22*E*,24*S*)-3$\beta$-acetoxy-5$\alpha$-stigmast-22-en-6-one **(46)**, and (22*E*,24*S*)-3$\alpha$-hydroxy-5$\alpha$-stigmast-22-en-6-one **(47)** (Fig. 14) have been studied to assess if the neuroprotective effects are being derived from their antioxidative properties. The synthetic analogues were tested in neuronal PC12 cells against 1-methyl-4-phenylpyridinium (MPP+), a neurotoxin known to induce oxidative stress and degeneration of dopaminergic neurons in the brain of PD patient.[207] The results divulged that all the synthetic derivatives of BRs exhibit promising activity for the protection of neuronal PC12 cells against MPP+ toxicity. The SAR studies suggested that keto group at B ring and also the unsaturation at 22- and 23-positions of the steroidal nucleus promote their neuroprotective actions. However, the hydroxylation of the A ring at positions 2 and 3 does not seem to be important for neuroprotection against MPP+-induced toxicity.[208]

## 4.3 | Patent details

Recently, a large number of inventions related to synthesis and pharmacological profile of novel neuroprotective steroids have been patented.[209–215] The details of various patented inventions with brief description of their structural and pharmacological properties have been given in Table 1.

## 5 | FUTURE PERSPECTIVES

Neuroprotective steroids promote the neuronal survival by a variety of mechanisms including regulation of transcriptional activity within the cell nucleus, initiation of the cell survival and metabolism by steroid receptor signaling within the mitochondria, regulation of kinases and phosphatases at the plasma membrane, and induction of antioxidant effects against the oxidative stress. The protective actions of steroids within the brain provide the molecular basis for the development of such compounds in future against neurodegeneration. Both naturally occurring and synthetic neuroprotective steroids offer a considerable potential in the treatment of neuropathological disorders. The naturally occurring neurosteroids have short biological half-life, lack of specificity and selectivity with rapid metabolism, and low oral bioavailability. The future prospect in this field is the synthesis of novel neuroprotective steroids with extended biological half-life and specificity as well as selectivity toward steroid or neurotransmitter receptor. Steroids are highly lipophilic molecules in nature capable of easily transporting the different moieties across the BBB, which reduces systemic toxicity and improve specificity of therapy. Moreover, before conversion of natural steroids into their semisynthetic derivatives, precursors could be evaluated for their distinct pharmacological properties by using different in vivo or in vitro experimental studies. As a prerequisite, it remains to be determined if and to what extent synthetic neuroprotective steroids are effective (equally or even superior to the natural neuroprotective steroids) and produce side effects upon long-term administration that could prevent their further clinical exploitation. It may be possible to provide a lead for the development of novel therapeutic strategies in the treatment of neurodegenerative disorders. Future studies mainly focused toward exploring protective actions of neurosteroids of both natural and synthetic origin might help in maintaining homeostasis within the brain and also the behavioral consequences after the long-term administration.[216,217]

## 6 | CONCLUSION

Neuroprotective steroids mainly improve the neuronal function within the brain. Both natural and synthetic neuroprotective steroids prevent or reduce the effects of neurodegenerative mechanisms such as oxidative stress, neuronal excitability, and inflammatory responses. The therapeutic applications of natural neurosteroids are significantly limited by their rapid metabolism and short biological half-lives. Synthetic derivatives of natural neurosteroids might overcome the disadvantages of natural ones. Among these the D-ring substituted steroidal derivatives have been found to be the most effective against the various mechanisms of neurodegeneration. Although usage of neuroprotective steroids still remains a less explored defense against neurodegenerative disorders, the promising results in the preclinical studies have attracted the neuroscientists toward the development of neuroprotective steroids. The real hope lies in the effectiveness of neuroprotective steroids as an efficient strategy for the therapeutic management of AD, PD, ALS, and HD.

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