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Neuropharmacological profile of *indole* derivatives

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ABSTRACT

Epilepsy, multiple sclerosis, parkinson's disease etc. are the neurological disorders which inflict great pain and suffering on patients and their families. A report of a population-based neuroepidemiological study of 102,557 individuals in urban and rural of Bangalore in Southern India showed that the neurological disorders were detected in 3,206 persons resulting in crude and age-adjusted frequency rates of 3,126 and 3,355 per 100,000 population, respectively. The prevalence rate was 2,653,3,932, and 5,012 per 100,000 population, respectively among children, middle-aged (31-40 years old) and elderly persons. It has been postulated that the neurological disorders were twice as frequent in rural areas as in urban. To avert and treat neurological disorders, biopharmaceutical research companies are recently developing 444 medicines. Indoles, aromatic heterocyclic organic compound became the precursor to many pharmacological agents. Different biological evaluation of the new compounds as acetylcholinesterase inhibitors has been performed. Most of the compounds have been claimed to have potent acetylcholinesterase inhibitor activity.

INTRODUCTION

Epilepsy, multiple sclerosis and parkinson's disease are the neurological disorders which inflict great pain and suffering on patients and their families. To avert and treat neurological disorders, biopharmaceutical research companies are recently developing 444 medicines (Table 1) (Burnstock and De Ryck, 2008; Medicines in Development Neurological Disorders 2013).

Table 1. Medicines developed for neurological disorders.

S. No.	No. of medicine	Diseases	Number of people diagnosed
1	82	Alzheimer's disease	5 Million American
2	82	Chronic pain	100 Million American
3	62	Brain Tumor	Nearly 70,000 American
4	28	Epilepsy and seizure	More than 3 million American
5	38	Multiple Scleroses	Estimated 5,00,00 American
6	27	Parkinson's disease	1 Million
7	25	Headache including migraine	37 Million people

Findings and studies by various researchers in neurological disorder, medicines are in development to target amyotrophic lateral scl anderosis (ALS), brain injuries, Huntington's disease, spinal cord injury, cerebral palsy, and stroke. Among the 444 innovative medicines recently developing in the United States, many present innovative new ways to fight from diseases (Burnstock and De Ryck, 2008; Medicines in Development Neurological Disorders 2013). Few of them comprise of a gene therapy to restore neuronal function in Alzheimer's disease. It is planned for a specific purpose i.e. the treatment of Alzheimer's disease in clinical trials and also aims at the nerve growth factor (NGF) to the brain because NGF is a naturally occurring protein necessary for neuron survival. In the gene treatment it is injected into the brain region where neuron degeneration occurs in Alzheimer's disease (Jain, 2011).

EPIDEMIOLOGY

A report of a population-based neuroepidemiological study of 102,557 individuals in urban and rural of Bangalore in Southern India showed that the neurological disorders were detected in 3,206 persons resulting in crude and age-adjusted frequency rates of 3126 and 3355 per 100000 population, respectively (Gourie-Devi et al., 2004). The prevalence rate was 26533932, and 5012 per 100000 population respectively among children, middle-aged (31-40 years old) and elderly persons (Gourie-Devi et al., 2004). The prevalence of neurological disorders among women (3,617) was higher compared with men (2, 657). The prevalence rate in urban and rural populations

was 2190 and 4070/100000, respectively. It has been postulated that the neurological disorders were twice as frequent in rural areas as in urban (Zhang et al., 2010; Gourie-Devi et al., 2004).

CURRENT RESEARCH STATUS OF NEUROPHARMACOLOGICAL DISORDERS

Table 2. Current research status of neuropharmacological disorders.

S. no.	Author(s)	Findings
1.	Cai et al., 2014	Potential therapeutic effects of neurotrophins for acute and chronic neurological diseases
2.	Laquérriere et al., 2014	Mutations in CNTNAP1 and ADCY6 are responsible for severe arthrogryposis multiplex congenita with axoglial defects
3.	Hoffmann et al., 2014	Emerging targets in migraine.
4.	Malik et al., 2013	Design, synthesis and anticonvulsant evaluation of N-(benzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide derivatives: a hybrid pharmacophore approach.
5.	Hu et al., 2013	Evaluation of blood-brain barrier and blood-cerebrospinal fluid barrier permeability of 2-phenoxy-indan-1-one derivatives using in vitro cell models.
6.	Lee et al., 2013	Fluoxetine inhibits transient global ischemia-induced hippocampal neuronal death and memory impairment by preventing blood-brain barrier disruption
7.	Jensen, et al., 2013	The neurological disease ontology
8.	Locher, et al., 2013	TUBB3: Neuronal marker or melanocyte mimic?
9.	Leicht, et al., 2013	Spinal cord injury: known and possible influences on the immune response to exercise.
10.	Cui, et al., 2011	Synthesis and biological evaluation of indole-chalcone derivatives as ß-amyloid imaging probe
11.	Soret et al., 2005	Selective modification of alternative splicing by indole derivatives that target serine-arginine-rich protein splicing

Anticonvulsant

Novel N-(benzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide derivatives have been evaluated for their anticonvulsant effects using variety of models of experimental epilepsy. Initial anticonvulsant activities of the compounds were investigated using intraperitoneal (i.p.) maximal electroshock shock (MES), subcutaneous pentylenetetrazole (scPTZ) seizure models in mice. The quantitative assessment after oral administration in rats showed that the most active was 2-methyl-4-oxo-N-(6-(trifluoromethoxy)benzo[d]thiazol-2-ylcarbamoyl)quinazoline-3(4H)-carbothioamide (SA 24) with ED50 values of 82.5 µmol/kg (MES) and 510.5 µmol/kg (scPTZ). This molecule was more potent than phenytoin and ethosuximide which were used as orientation antiepileptic drugs (Malik et al., 2013).

Alzhiemer

2-Phenoxy-indan-1-one derivatives (PIOs) are a series of novel central-acting cholinesterase inhibitors for the treatment of Alzheimer's disease (AD). The adequate distribution of PIOs to the central nervous system (CNS) is essential for its effectiveness. However, their permeability in terms of CNS penetration across the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB) have not been found (Hu et al., 2013).

Congenital with axoglial defect

Non-syndromic arthrogryposis multiplex congenita (AMC) is characterized by multiple congenital contractures resulting from reduced fetal mobility. Genetic mapping and whole exome sequencing (WES) were performed in 31 multiplex and/or consanguineous undiagnosed AMC families (Laquérriere et al., 2014).

Migraine

The development of serotonin 5-HT1B/1D receptor agonists ("triptans") substantially improved the acute treatment of migraine attacks. However, many migraineurs do not react suitably to triptans and cardiovascular co-morbidities limit their use in a significant number of patients (Hoffmann et al., 2014).

Hippocampal neuronal death

In a report by Lee et al. (2013), fluoxetine treatment (10 mg/kg) after global ischemia significantly inhibited mRNA expression of MMP-2 and -9 and reduced MMP-9 activity. By Evan blue examine, fluoxetine reduced ischemia-induced BBB permeability (Lee, et al., 2013).

Neurological disease ontology

Developing the neurological disease ontology (ND) to provide a framework to enable representation of aspects of neurological diseases that are relevant to their treatment and learn. ND is a representative tool that addresses the need for unmistakable annotation, storage, and retrieval of data associated with the treatment and study of neurological diseases (Jensen, et al., 2013).

Neuronal marker

Identifying neuronal derivatives of stem cells is essential for both basic research and future applications in regenerative medicine targeting neurodegenerative diseases. Stem cell and neurobiology researchers widely regard the class III?? tubulin protein (TUBB3), a member of the microtubule family, as being selectively expressed in neuronal cells (Locher et al., 2013).

Spinal cord injury

A spinal cord injury (SCI) can increase the risk of infection by impacting on many aspects of immune function; one particularly well-documented observation is a reduction in lymphocyte numbers (Leicht, et al., 2013)

ß-amyloid imaging probe

A series of chalcone derivatives containing an indole moiety were evaluated in competitive binding assays with Aß(1-42) aggregates versus [(125)I]IMPY (Cui et al., 2011).

Serine-arginine-rich protein splicing

Soret et al. (2005) reported the indole derivatives as potent inhibitors of the splicing reaction. Highly important, compounds of this family specifically inhibit exonic splicing enhancer (ESE) dependent splicing, because they interrelate directly and selectively with members of the serine-arginine-rich protein (Soret et al., 2005).

CURRENT RESEARCH STATUS OF INDOLE DERIVATIVES

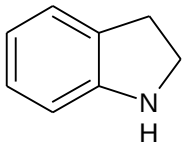


Figure 1. Indole.

The chemistry of indole is one of the most active areas of heterocyclic chemistry. The indole moiety remains at the front position of biological and medicinal chemistry. The main ever-present of the bioactive alkaloids recognized are based on the indole nucleus. Since the 3-position of indole is the favored site for electrophilic substitution reaction 3-alkyl or acyl indoles are adaptable intermediates for the synthesis of a broad range of indole derivatives. The simple and direct method for the synthesis of 3-alkylated indoles engage the conjugate addition of indoles to a, b-unsaturated compounds. 2-Substituted indoles are also potential intermediates for many alkaloids and pharmacologically significant substances (Cavdar et al., 2005; Radwan et al., 2007).

3,4-dihydroxy-1H-Indole 3yl-2-oxymethylpiperidin-4-yl-benzamide

Several indole derivatives, that were highly potent ligands of GluN2B-subunit-containing N-methyl-D-aspartate (NMDA) receptor, also verified antioxidant properties in ABTS technique. The 2-(4-benzylpiperidin-1-yl)-1-(5-hydroxy-1H-indol-3-yl) ethanone proved to be a dual-effective neuroprotective exactly (Buemi, et al., 2013).

***N*-hombivalent beta-carboline**

It has been established that some of these bivalent ß-carbolines were effective NR blockers. The most promising compound was a N^9-homobivalent ß-carboline with a nonylene spacer, which displayed IC_{50} values of 0.5 nM for AChE, 5.7 nM for BChE, and 1.4 µM for NR, respectively (Rook et al., 2013).

1-(2-hydroxyp ropyl)-2-phenyl1-4(2-phenyl lindolin-3-yl) methylene-1H-Imidazole5 (4H)-One)

A series of indole derivatives (3-6 & 8a) have been synthesized from 2-phenyl-1H-indole with an aim to get promising anticonvulsant agents. The compounds have been characterized on the basis of their IR, 1H NMR and Mass spectral data results. The compounds have been screened for their anticonvulsant action in MES and scPTZ animal models (Khan et al., 2012).

3-(l-{2-[5-(Acetylamino)-2-methylphenyl]ethyl}piperidin-4-yl)-6-chloro-lH-indole

The compounds of the invention are useful in the treatment of certain psychiatric and neurological disorders, i.e. schizophrenia, psychoses, anxiety, depression, migraine, cognitive, ADHD and sleep improvement (Andersen et al., 2001).

(+)-(R)-2-cyano-N, N-dipropyl-8-amino-6,7,8,9-tetrahydro-3H- benz[e]indole

The synthesis of (+)-(R)-2-cyano-N,N-dipropyl-8-amino-6,7,8,9-tetrahydro-3H- benz[e]indole [(R)-14, U92016A], a strong 5-HT1A agonist, and related analogs is described. *In-vitro* binding studies showed that the (R)-enantiomers of this series possess the highest potency for the 5-HT1A receptor (Romero et al., 1993).

Pyrano[3,2-c]quinoline-6-chlorotacrine

Two isomeric series of dual binding site acetylcholinesterase (AChE) inhibitors have been designed, synthesized, and tested for their aptitude to reduce AChE, butyrylcholinesterase, acetycholine estrase-induced and self-induced beta-amyloid (Abeta) aggregation, and beta-secretase (BACE-1) and to cross blood-brain blockade. The novel hybrids consist of a unit of 6-chlorotacrine and a multicomponent reaction-derived pyrano[3,2-c]quinoline gallows as the active-site and peripheral-site interact moieties, respectively, connected through an oligomethylene linker containing an amido group at changeable position. Indeed, molecular modeling and kinetic studies have confirmed the dual site binding of these compounds (Camps et al., 2009).

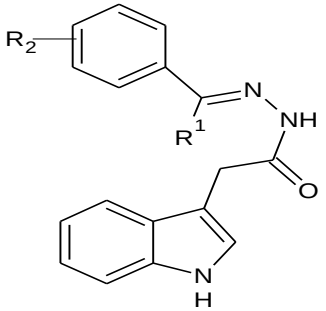
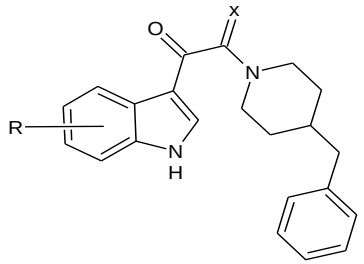
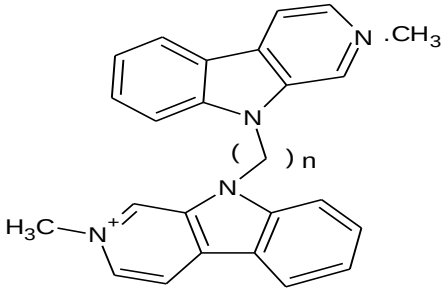
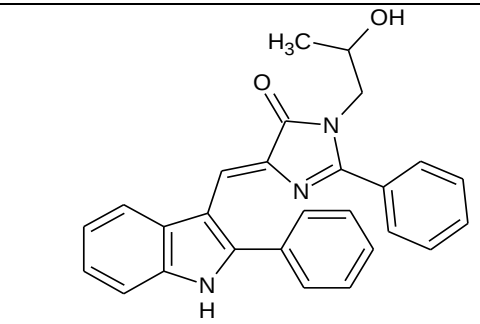
Indole derivative of BODIPY

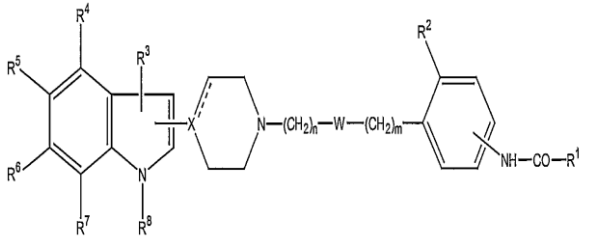
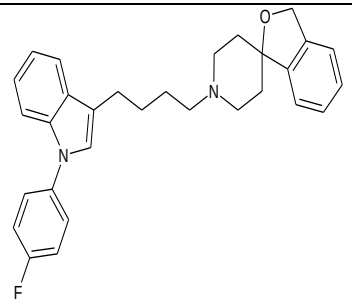
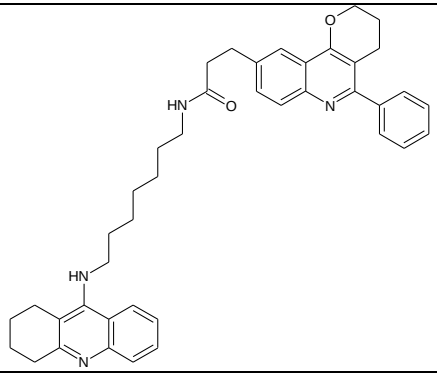
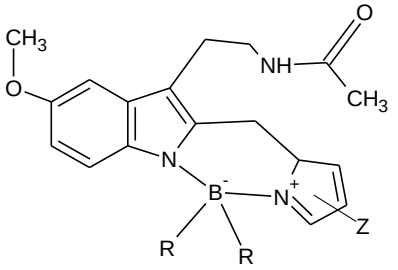
An original design and synthesis of fluorescent ligands for melatonin receptor studies is presented and consists in the fusion of the endogenous ligand with the fluorescent BODIPY core. Probes I–IV show high affinity for MT1 and MT2 melatonin receptors and exhibit fluorescence properties compatible with cell observation (Thireau et al., 2014).

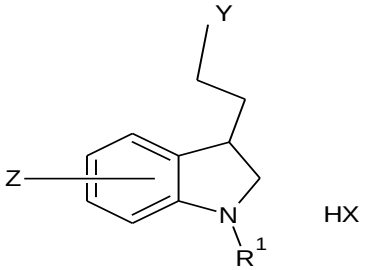
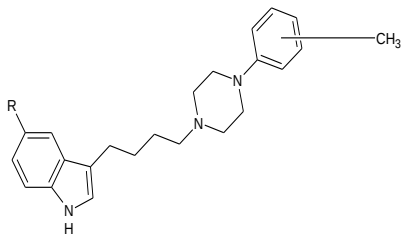
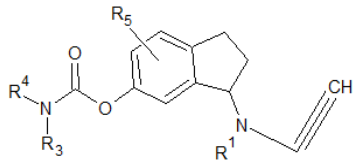
I.Y Indole

The flow of events that occurs in Alzheimer's disease involving oxidative pressure and the reduction in cholinergic show can be better addressed by multifunctional drugs than cholinesterase inhibitors alone. For this reason, researchers prepared a huge number of derivatives of indoline-3-propionic acids and esters. They showed scavenge activity against different radicals in solution and significant protection against cytotoxicity in cardiomyocytes and primary cultures of neuronal cells exposed to H2O2 species and serum deprivation at concentrations ranging from 1 nM to 10 µM depending on the molecule. For most of the indoline-3-propionic acid derivatives, introduction of N-methyl-N-ethyl or N-methyl-N-(4-methoxyphenyl) carbamate moieties at positions 4, 6, or 7 conferred both acetyl

Table 3. Current research status of indole derivative.

S. no.	Author(s)	Chemical name	Finding	Structure
	Yar et al., 2014	Indole derivative of hydrazide	Design and synthesis of new dual binding site cholinesterase inhibitors: *in vitro* inhibition studies with in silico docking	
1	Buemi et al., 2013	3,4-dihydroxy-1H-Indole-3yl-2-oxymethylpipeeridin-4-yl-benzamide	Dual –effective agents for the treatment of neurogenrative diseases	
2	Rook et al., 2013	*N*-hombivalent beta-carboline	Bivalent ß-carbolines as potential multitarget anti-alzheimer agents	
3	Khan et al., 2012	1-(2-hydroxypropyl)-2-phenyl1-4(2-phenyl lindolin-3-yl)methylene-1H-Imidazole5 (4H)-One	Anticonvulsant agents	

4	Andersen et al., 2001	3-(l-{2-[5-(Acetylamino)-2-methylphenyl]ethyl}piperidin-4-yl)-6-chloro-lH-indole	psychiatric and neurologic disorders	
5	Romero et al., 1993	Siramesine	Anxiolytic and antidepressant	
6	Camps et al., 2009	Pyrano[3,2-c]quinoline-6-chlorotacrine hybrids	Pyrano[3,2-c]quinoline-6-chlorotacrine hybrids as a novel family of acetylcholinesterase- and beta-amyloid-directed anti-Alzheimer compounds.	
7	Thireau et al., 2014	Indole derivative of bodipy	Affinities for MT1 and MT2 melatonin receptors	

8	Yanovsky et al., 2012	I.Y Indole	Neuroprotective agents	
9	Heinrich et al., 2004	1-4(indol-3-yl-butyl)-4-arylpiperazine	Studies of mood disorder	
10	Sterling et al., 2002	Carbamate derivatives Of N-Propargylaminnoidans	In treatment of Alzheimer's diseases	

(AChE) and butyryl (BuChE) cholinesterase inhibitory activities at similar concentrations to those that showed antioxidant activity. The most potent Acetycholinestrase inhibitors were 120 (3-(2-aminoethyl) indolin-4-yl ethyl(methyl)carbamate dihydrochloride) and 94 (3-(3-methoxy-3-oxopropyl)-4-(((4-methoxyphenyl)(methyl) carbamoyl)oxy)indolin-1-ium hydrochloride) with IC50s of 0.4 and 1.2 μM, correspondingly (Yanovsky et al., 2012).

1-4(indol-3-yl-butyl)-4 -arylpiperazine

A series of new 1-[4-(indol-3-yl)butyl]-4-arylpiperazines has been prepared to identify highly selective and potent 5-HT(1A) agonists as potential pharmacological tools in studies of mood disorders. The combination of structural elements (indole-alkyl-amine and aryl-piperazine) known to introduce 5-HT(1A) receptor affinity and the proper selection of substituents (R on the indole moiety and R' on the aryl moiety) led to compounds with high receptor specificity and affinity. In exacting, the beginning of the methyl ether or the un-substituted carboxamide as substituents in position 5 of the indole (R) guaranteed serotonergic 5-HT(1A) affinity compared to the un-substituted analogue. Para-substituted arylpiperazines (R') decreased dopaminergic D(2) binding and increased selectivity for the 5-HT(1A) receptor. Activater 5-HT(1A) receptor activity was confirmed *in-vivo* in the ultrasonic vocalization examination, and the results suggest that the preface of the carboxamide residue leads to better bioavailability than the corresponding methyl ether. 3-[4-[4-(4-Carbamoylphenyl)piperazin-1-yl]butyl]-1H-indole-5-carboxamide 54 was identified as a highly selective 5-HT(1A) receptor agonist [GTPgammaS, ED(50) = 4.7 nM] with nanomolar 5-HT(1A) affinity [IC(50) = 0.9 nM] and selectivity [D(2), IC(50) > 850 nM]. 3-[4-[4-(4-Methoxyphenyl)piperazin-1-yl]butyl]-1H-indole-5-carboxamide 45 is one of the most potent and selective 5-HT(1A) agonists known [5-HT(1A), IC(50) = 0.09 nM; D(2), IC(50) = 140 nM] (Heinrich et al., 2004).

Carbamate derivatives of N-propargylaminoindane

Carbamate derivatives of N-propargylaminoindans (Series I) and N-propargylphenethylamines (Series II) have been synthesized via multistep procedures from the corresponding hydroxy precursors. The individual rasagiline- and selegiline-related series has been designed to combine inhibitory activities of both acetylcholine esterase (AChE) and monoamine oxidase (MAO) by virtue of their carbamoyl and

propargylamine pharmacophores. A carbamate moiety has been established to be necessary for AChE inhibition, which was not present in the equivalent hydroxy precursor. The propargyl group caused 2-70-fold lessen in AChE inhibitory activity (depending on the position of the carbamoyl group) of Series I, but had small or no effect in Series II. Hence, the 6- and 7-carbamyloxyphenyls in series I were either equipotent to, or slightly (2- to 5-fold) less active as AChE inhibitors than, the analogous compounds in Series II, as the 4-carbamyloxyphenyls were more strong (Sterling et al., 2002).

CONCLUSION

Indole alkaloids are a class of alkaloids containing a structural moiety of indole; many indole alkaloids also include isoprene groups. Containing more than 4100 known different compounds, it is one of the largest classes of alkaloids. Many of them possess significant physiological activity and some of them are used in medicine. These compounds include indoleamines (melatonin), carbazoles (carvedilol), carbolines (tetrahydrocarbolines), pyrimidoindoles, vinpocetine etc. Special attention is paid to the γ-carboline stobadine.

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