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THERAPEUTIC VALUE OF 1, 2 – BENZISOXAZOLES

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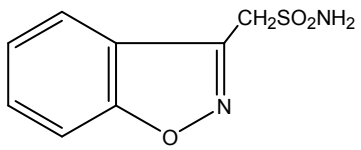
INTRODUCTION

The study of heterocycles is an evergreen field in the branch of organic chemistry and always attracts the attention of scientists working not only in the area of natural products but also in the synthetic organic chemistry. Moreover, many useful drugs have emerged from the successful investigations carried out in this branch. Besides this, spectacular advances have been made furtherance the knowledge of relationship between chemical and biological activity. In fact, this tendency is reflected by the voluminous data available in literature on heterocyclic chemistry. Thus, the successful applications in various fields ensure a limitless scope for the development of structurally novel compounds of this type with a wide range of physio-chemical and biological properties.

Heterocyclic compounds promote the life on earth[1]. These are widely distributed in nature and essential to life as they play important roles. Heterocyclic compounds are well known for their medicinal and biochemical activities[2, 3]. Benzisoxazole derivatives have recently attracted attention as an important class of heterocyclic compounds in the field of drugs and pharmaceutical properties. Benzisoxazole is composed of benzene-fused isoxazole ring structure. It is used primarily in industry and research.

Being a heterocyclic compound benzisoxazole finds use in research as a starting material for the synthesis of larger, usually bioactive structures. It is found within the chemical structures of pharmaceutical drugs such as the antipsychotic risperidone and the anticonvulsant Zonisamide. Its aromaticity makes it relatively stable, although as a heterocycle, it has reactive sites which allow for funtionalization. 1, 2-benzisoxazole moieties are isosteric with indoles and can mimic/bind to biologically important enzymes in a manner similar to indole derivatives.

Out of many biologically active compounds, Zonisamide is widely prescribed as an antiepileptic drug[4]. It was developed by Dianippon of Japan. These compounds are widely used as analgesic[5], anticonvulsant[6, 7] antipsychotic[8, 9], and antimicrobial[10] agents.



Zonisamide

FIGURE 1

A number of benzisoxazoles show physiological activity and have been tested for pharmacological uses. The derivatives of 6-acetamidobenzisoxazole-3-acetic acid have been reported to have tuberculostatic activity[11]. Compounds belonging to 3-aminobenzisoxazole series have been shown to possess sedative and analgesic properties[12]. Some compounds have been found to possess trypanocidal activity[13].

4,5,6,7-Tetrahydro derivatives were tested as analeptics[14]. Some derivatives of napthisoxazolyl phosphotioate have been used as acricides, insecticides and larvicides[15].

In view of the diverse type of biological activity and medicinal importance of benzisoxazoles we discuss some important activities of 1,2-benzisoxazoles:

ANTIMICROBIAL ACTIVITIES

An antimicrobial[16] is a substance that kills or inhibits the growth of microorganisms such as bacteria, fungi, or protozoans. Antimicrobial drugs either kill microbes (microbiocidal) or prevent the growth of microbes (microbiostatic). Disinfectants are antimicrobial substances used on non-living objects or outside the body.

Shastri et al.[17]synthesized a series of 3-propene 1,2-benzisoxazoles derivatives by microwave assisted eco-friendly method. The compounds were screened for their antimicrobial activities against E. coli, S. typhi, S. aureus and B. subtilis and for antifungal activities against A. niger, A. flavus, P. chrysogenum, F. moneliforme. The derivatives were found to possess antibacterial and antifungal activities.

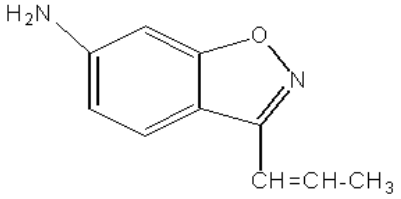


FIGURE 2

3-substituted(1,2,4)-triazolo(3,4-b)-1,2-benzisoxazole were found to possess antimicrobial activity[18].

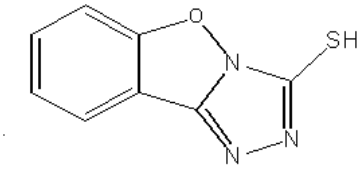


FIGURE 3

Sharma et al.[19] have discovered a novel series of 3-substituted 1,2-benzisoxazole and evaluated them for the antimicrobial activity in vitro. E. coli, P. aeruginosa, S. typhae are gram negative bacteria and S. aureus, B. subtilis, S. cohini are gram positive bacteria. All these synthesized compounds showed significant antimicrobial activity against all the test microorganisms. Among the tested compounds some showed relatively better antimicrobial activity.

The antifungal and antibacterial activities were observed by Thakar and coworkers[20,21] in the nitro substituted and formyl substituted 1, 2-benzisoxazoles. Some of the 5-nitro derivatives show inhibitory action on phytophathogenic bacteria.

Jadhav et al.[22] synthesized 3-alkyl-5-chlorosulphonyl-1,2-benzisoxazoles and their derivatives. All the synthesized compounds exhibited significant to moderate antibacterial activity.
3H-N- substituted phenyl-1,2-benzisoxazole derivatives were screened for their antifungal activities against two pathogens F. oxysporium and S. rolfsii by radial growth method using food poison technique at two concentrations 500 and 1000 ppm. All these compounds show higher activity against fungus F. oxysporium and weak inhibitory activities against S. rolfsii.[23]
Raut et al.[24] synthesized N-substituted benzisoxazolines by reacting substituted (α-arylimino) ethylbenzenes (Schiff's base) with DMSO-I_2-H_2SO_4. These benzisoxazolines were found to possess antimicrobial activities against S. typhi, S. paratyphi, P. vulgaries, X. spp., F. solnii and Botrytis. It has been found that compounds having both bromo and nitro groups are more active than simple benzisoxazolines.

ANTICONVULSANT ACTIVITIES

Anticonvulsants are traditionally used for the treatment of seizures but have also been found to beneficially treat neuropathic pain and even some mood disorders. The goal of an anticonvulsant is to suppress the rapid and excessive firing of neurons that start a seizure. Failing this, an effective anticonvulsant would prevent the spread of the seizure within the brain and offer protection against possible excitotoxic effects that may result in brain damage.
Zonisamide, a 1, 2 benzisoxazole derivative is a structurally novel antiepileptic drug (AED) with a broad spectrum of antiseizure activity[25,26]. Zonisamide has been available in Japan since 1989, where it is widely used both as monotherapy and adjunctive therapy (i.e. as Add on) for various seizure types and syndromes in adults and children[27, 28].
Leppik et al. [29] observed a 52% reduction in seizure frequency in a historical-control, open-label, multicenter study. However, development of kidney stones in 3.7% of patients enrolled in this study led to the temporary termination of US development efforts. Testing resumed in the 1990s, and zonisamide was approved by the US Food and Drug Administration (FDA) in March 2000 as adjunctive treatment for refractory partialon-set seizures in adults(aged>16years).
Several 3-(sulfamoylmethyl)-1,2-benzisoxazole derivatives were synthesized from 3-(bromomethyl)-1,2-benzisoxazole by the reaction with sodium bisulfite followed by chlorination and amination. Some of them displayed marked anticonvulsant activity in mice. The introduction of a halogen atom to the 5 position of the benzisoxazole ring caused increased activity and neurotoxicity; the substitution of a sulfamoyl group caused decreased activity. The activity of monoalkylated compounds might be the result of biotransformation. Among these compounds, 3-(sulfamoylmethyl)-1,2-benzisoxazole was thought to be the most promising as an anticonvulsant from the ratio of NTD50 and ED50.[30]
The anticonvulsant and neurotoxic properties of 3-sulfamoylmethyl-1,2-benzisoxazole (AD-810) have been demonstrated. AD-810 suppressed electrically and chemically induced maximal seizures but did not prevent minimal seizures in experimental animals. In rats, rabbits and dogs, the anticonvulsant activity of AD-810 against maximal electroshock seizures was more potent than those of diphenylhydantoin and carbamazepine. In rats, AD-810 showed more rapid onset as well as longer duration of anticonvulsant activity than the above two drugs. The anticonvulsant effect of AD-810 was reduced but not abolished by reserpine. No tolerance developed to the anticonvulsant action of AD-810 by consecutive treatment. The compound showed much less neurotoxicity and lethal toxicity than the existing antiepileptic drugs for grand mal, and also showed the least hypnotic effect by itself or by combination with hexobarbital. Thus, AD-810 possesses a profile of anticonvulsant activity most similar to that of

diphenylhydantoin or carbamazepine, providing a high protective index as well as other favorable properties[31].

ANTICANCER ACTIVITIES

According to the recent studies 1.9% of the total population in the world suffers from cancer. It is estimated that in India around 25 lakh people are suffering from Cancer. More than 70% of all Cancer deaths occur in developing countries, where resources available for prevention, diagnosis and treatment of Cancer are limited or non- existent. More than 2.5 million cancer patients are in India and nearly one in three die from disease. Based on projection, death due to cancer will continue to rise with an estimated 9 million people by 2015, and 11.4 million by 2030. Cancer is a disease in which a cell loses control of its growth. Only one cancer cell is enough to form significant tumor, growth which can potentially kill a person. To develop into a tumor, this one cancer cell must escape the body's defense against it.

A series of 1, 2-benzisoxazole[32] phosphorodiamidates have been synthesized and designed as prodrugs of phosphoramide mustard requiring bioreductive activation. Enzymatic reduction of 1, 2-benziosoxazole moiety is expected to result in the formation of imine intermediate due to the cleavage of the N-O bond. The imine should then be spontaneously hydrolyzed to a ketone metabolite, thereby facilitating base-catalyzed ,elimination of cytotoxic phosphoramide mustard.

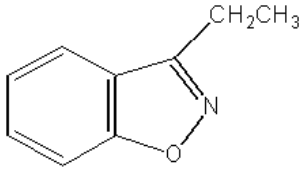


FIGURE 4

The anti-DNA damaging activity was analyzed by carrying out the reaction of 6-fluoro-3-(4-piperidinyl)-1, 2-benzisoxazole with different L-amino acids. The synthesized 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole analogues were evaluated for their anti-DNA damaging activity by using biophysical techniques such as agarose gel, thermal melting temperature (Tm) and ethidium bromide binding to DNA by using fluorescence spectrophotometer. Series of novel 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole L-amino acid derivatives were synthesized by varying substitution at N-position of the 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole[33].

Phenyl-2,1-benzisoxazoles are useful for the treatment of cancer. The inhibition of melanoma and other implanted tumors by 5- chloro-3-phenyl-2,1-benzisoxazoles was demonstrated in mice. The percentage inhibition was found to be 34.9[34].

Suhasrabudhe et al.[35] synthesized alkoxy derivatives of 6-hydroxy-3-methyl-1,2-benzisoxazole which were found to show antituber activity. 3-aryl-1,2-benzisoxazole derivatives are used as anticancer agents.

DIURETICS

Substances that augment "diuresis," or the removal of fluids from the body through urination are considered diuretics. More commonly known as "water pills" diuretics may be prescription or over the counter drugs. Diuretics are used for many reasons. They may be indicated for people who suffer from edema, an intense accumulation of fluids in the body's tissues, and those who suffer from high blood pressure or other heart related diseases. Increasing the production of urine

not only releases fluid, but also helps rid the body of excess salts and may reduce blood volume. Some people use diuretics as a weight loss aid, usually when a large amount of weight needs to be lost in a short amount of time. Diuretics are used to treat heart failure, liver cirrhosis, hypertension and certain kidney diseases.

A series of substituted 5, 6-dihydrofuro[3,2-f]-1,2-benzisoxazole were prepared and evaluated for their diuretic and uricosuric properties. Pharmacological evaluation of these compounds was carried out in mice, rats, dogs, and monkeys. The diuretic nature of these compounds was observed in all species, where as uricosuric activity was best seen in the cebus monkey[36].

A series of substituted 7,8-dihydrofuro[2,3-g]-1,2-benzisoxazole-7-carboxylic acids and 7,8-dihydrofuro[2,3-g]benzoxazole-7-carboxylic acids were synthesized and evaluated for uricosuric and diuretic activities in rats. Many of the benzisoxazole derivatives showed uricosuric and only weak diuretic activities. Among these compounds, 5-chloro-7,8-dihydro-3-phenylfuro[2,3-g]-1,2-benzisoxazole-7-carboxylic acid was found to be a potent uricosuric agent without diuretic activity and was selected for further development[37].

Kitzen et al.[38], reported the diuretic and uricosuric activity of [(7-bromo-3-(2-fluorophenyl)-1,2-benzisoxazol-6yl]oxyacetic acid.

Shutske et al.[39] synthesized indazole, benzisoxazole and benzisothazole 1,1-dioxide analogues of [7-chloro-3-(2-fluorophenyl)-1,2-benisoxazol-6-yl] oxyacetic acid and tested for diuretic activity.

ANTIPSYCHOTIC ACTIVITIES

Antipsychotics are among the most widely used drugs in psychiatric practice. They were originally intended primarily for the treatment of schizophrenia, but over the years their use has spread to other psychotic spectrum disorders, bipolar disorder, anxiety and related disorders, posttraumatic stress disorder, delirium, and personality disorders.

A series of 3-substituted-6-fluoro-1,2-benzisoxazoles were synthesized and evaluated for potential antipsychotic activity[40]. Many of the compounds displayed potent antipsychotic-like activity in the apomorphine induced climbing in mice (CMA) or spiroperidol binding assays, and compound (HRP 392, 1-[3-(6-fluoro-1,2-benzisoxazol-3-yl)propyl]-4-(2-methoxyphenyl) piperazine) was selected for more detailed antipsychotic evaluation in a battery of preclinical assays. The results of these studies suggest that this compound is a potential antipsychotic drug with less propensity for EPS than some standard neuroleptics in monkeys. The compound was advanced for toxicological evaluation.

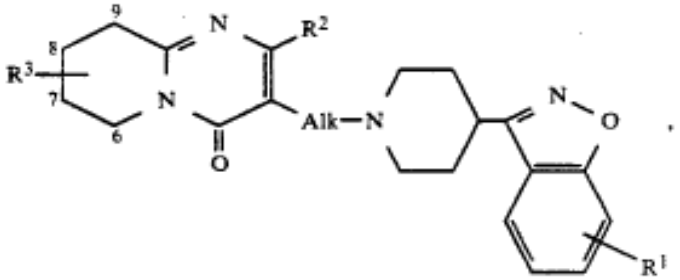
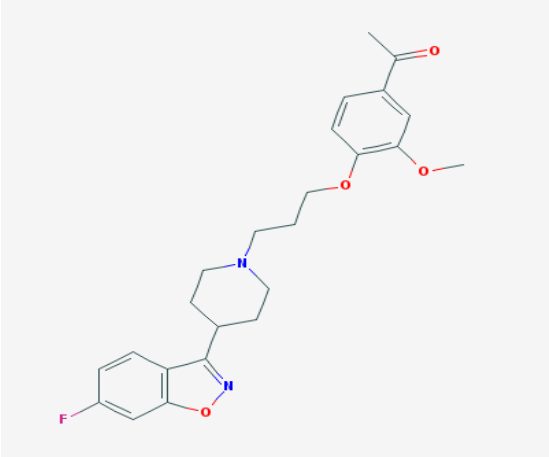


FIGURE 5

3-piperidinyl-1, 2-benzisoxazoles having long-acting antipsychotic properties and it is useful in the treatment of warm-blooded animals suffering from psychotic diseases. In particular, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl)ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one ("9-hydroxy-Risperidone") is disclosed[41].

A series of 3-[[(aryloxy)alkyl]piperidinyl]-1,2-benzisoxazoles[42] were synthesized and evaluated as potential antipsychotic D2/5-HT2 antagonists. Most of these compounds showed potent antipsychotic-like activity in an apomorphine-induced climbing mouse paradigm, with many also showing preferential mesolimbic activity, as indicated by their weaker effects in an apomorphine-induced stereotype model. In receptor binding assays, many displayed a moderate affinity for the D2 receptor coupled with a significantly greater affinity for the 5-HT2 receptor. a property that has been suggested as necessary for a typicality. From this series, compound 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone (iloperidone, HP 873), was further evaluated in a battery of in vivo and in vitro assays. This compound showed a 300-fold greater potency in inhibition of climbing than in inhibition of stereotype or induction of catalepsy, and when evaluated chronically in an electrophysiological model, this also caused a depolarization blockade of dopamine neurons in the A10 area of the rat brain but not in the A9 area. Additionally, it showed positive activity in a social interaction paradigm, suggesting potential efficacy against asociality, a component of the negative symptoms of schizophrenia. In chronic ex vivo studies, this is, similar to clozapine, caused a down regulation of 5-HT2 receptors but had no effect on the number of D2 receptors.



Iloperidone

FIGURE 6

HRP 913 {1 - [3 - (6 – fluoro - 1,2 - benzisoxazole – 3 - yl) propyl] – 4 - (2 – oxo -1 - benzimidazolinyl)} piperidine demonstrated preclinical antipsychotic activity with features that may provide a clinical advantage over current therapy[43].

3 - substituted 1,2 - benzisoxazole[44] are synthesized and evaluated in many pharmacological C.N.S. tests, show interesting neuroleptic activity but inferior to those of haloperidol and chlorpromazine.

ANALGESIC ACTIVITIES

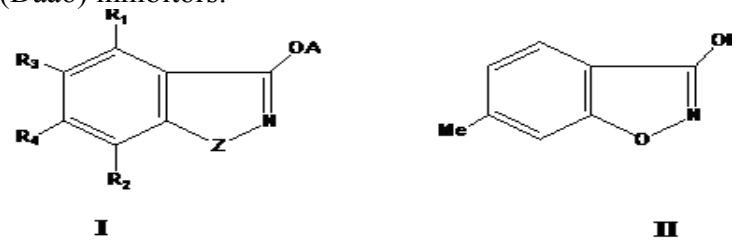
Analgesics are a class of drugs used to relieve pain. The pain relief induced by analgesics occurs either by blocking pain signals going to the brain or by interfering with the brain's interpretation of the signals, without producing anesthesia or loss of consciousness. There are basically two kinds of analgesics: non-narcotics and narcotics.

The 6 – fluoro – 3 - [3 - (1 - heterocyclo) propyl] - 1,2 - benzisoxazoles[45] are useful as analgesic agents due to their ability to alleviate pain in mammals.

Strupczewski et al.[46] synthesized 3-(4-piperidyl) 1,2 – benzisoxazoles and their salts by the cyclisation of 1-methyl-4-(2-fluorobenzoyl piperidine with NH_2OH which possess analgesic activity.

NEUROLEPTIC PROPERTY AND D-AMINO ACID OXIDASE (DAAO) INHIBITORS.

Fang Q Kevin et al.[47] prepared 1, 2-benzisoxazole derivatives of formula I and II useful as D-amino acid oxidase (Daao) inhibitors.



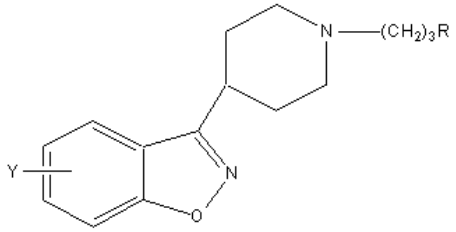
I II

R_1, R_2 = H, OH, alkoxy

R_3, R_4 = halogen, OH

FIGURE 7

Joseph T. Strupczewski et al.[48] synthesized and carried out the neuroleptic activity of 3-(1-substituted-4-piperidinyl)-1,2-benzisoxazoles.



MISCELLANEOUS ACTIVITIES

Sato et al.[49] synthesized thirty seven new N-(α-alkyl- α-methylbenzyl)-1,2-benisoxazole-3-acetamide and related compounds. Out of which twenty compounds were screened against seven field weeds and rice. In compounds having halogen at α-position are found to be more active.

Jackson et al.[50] prepared benzisoxazole of following type by stiring a mixture of 1-[5-(2fluoro-4-bromophenoxy)phenyl]ethanoneoxime, $K_2CO_3$and DMSO which were used as herbicides for grain crops.

A series of benzisoxazole-alkanoic acids, differing in the length of the side-chain, have been synthesized and their activity tested on pea stem elongation, flax root growth and shoot regeneration from tomato cotyledon explants. All compounds had little or no effect on cell elongation or root growth, but a stimulating effect on shoot induction in vitro, thus showing that their activity, like that of 1,2-benzisoxazole acetic acid, is partly independent of the side-chain and is linked to the structure of the benzisoxazolic ring[51].

Branca et al.[52] tested the activity of 1,2-benzisoxazole-3-one, a compound similar to1,2-benzisoxazole acetic acid but lacking the lateral carbon chain. The tests were made on the regeneration of tomato and on pea stem elongation.

The 2 - (1,2 – benzisoxazole – 3 - yl) - 3{ω - (dialkyl - amino) alkoxyphenyl} acrylonitrile which showed antisplasmodic activities in vitro and in vivo studies[53].
Bhat et al.[54] prepared 6-(3-amino-2-hydroxypropoxy)-3-methyl-1,2-benzisoxazoles and reported anesthetic and β-adrenergic blocking activity.

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