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Chemistry and Pharmacological Exploration of Benzoxazole Derivatives

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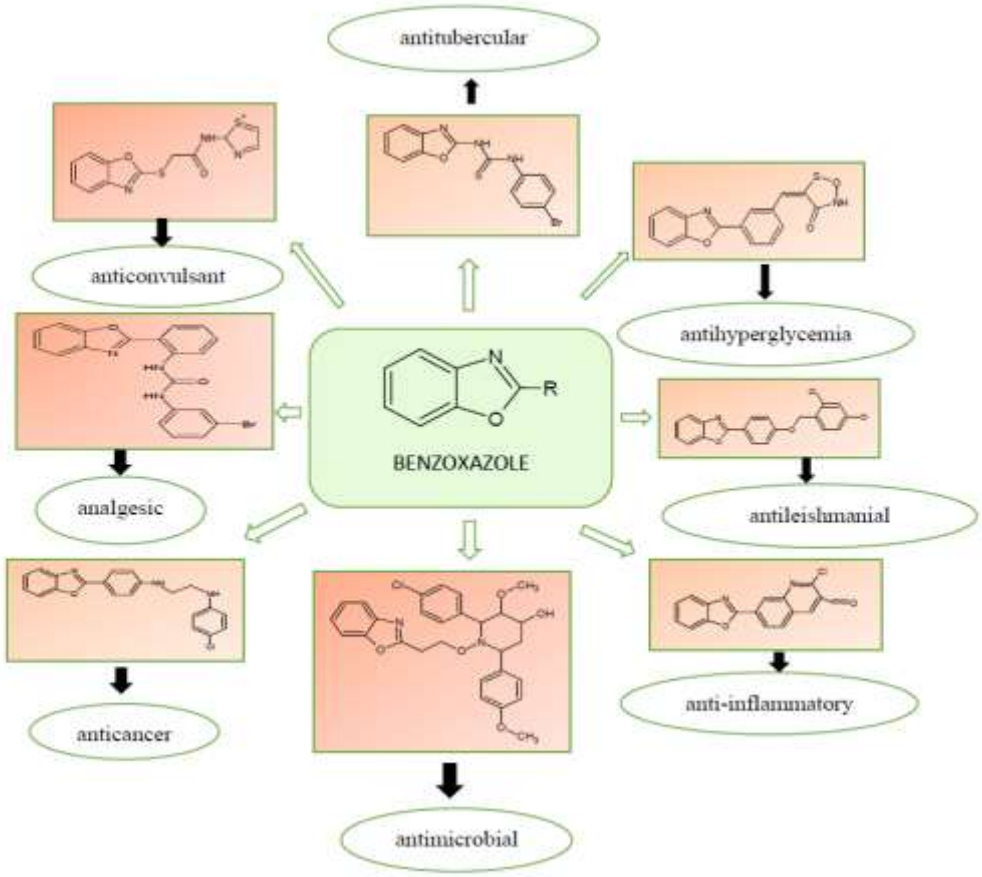
GRAPHICAL ABSTRACT



Benzene attached with oxazole moiety constitutes extensive range of pharmacological activity. Numerous pharmacological actions including anticancer, analgesic, anti-inflammatory, antihyperglycemic, antimicrobial, antitubercular, anticonvulsant have been associated with benzoxazole scaffold.

ABSTRACT

Benzoxazole is one of the most prominent heterocyclic structures and is found in an extensive range of biologically active compounds. It is one of the often occurring heterocyclic nitrogen-containing moieties that perform as the primary active elements of pharmaceutical compounds. It can be viewed as isosteres of the naturally occurring guanine and adenine nucleic bases since they interact effectively with the polymeric components of biological systems. A wide range of biological features, including analgesic, antibacterial, anti-inflammatory, anti-hyperglycemic, anticancer, antiviral, antifungal, antileishmanial, and antitubercular activities, they are significantly influenced by heterocyclic compounds with a benzoxazole nucleus.

KEYWORDS: Benzoxazole, anticancer, antihyperglycemic, antibacterial, caboxamycin, pseudopteroxazole

1.INTRODUCTION

A heterocyclic compound is a cyclic molecule that contains at least two distinct elemental atoms as members of its ring. Benzoxazole (fig: 1) belongs to the most prominent heterocyclic compounds having exceptional pharmacological activity within all heterocyclic compounds.[1]

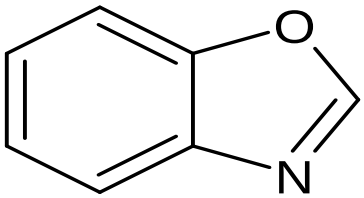
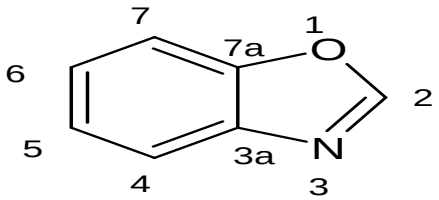


Figure 1: structure of benzoxazole

Due to its extraordinary pharmacological characteristics, which include antibiotic, antifungal, antiviral, antitumor, antiulcer, antibacterial, anti-inflammatory, anti-tubercular, and analgesic effects, it is of significant importance. This constituent is found in a diverse range of organic products. Because of its diverse biological characteristics, benzoxazole has indeed been used as a crucial pharmacophore and substructure in numerous pharmaceutical drugs. It is a fundamental component in the production of physiologically active medicinal molecules because it can exhibit the appropriate pharmacological action.[2]

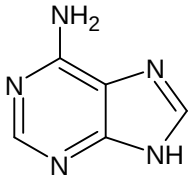
2. Chemistry

Chemically, benzoxazole is a known as 1-Oxa-3-aza-1H-indene. Oxazole ring structure consists of 3a,7a position fused benzene ring.

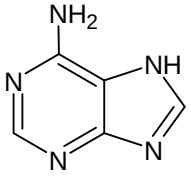


It is a planar cyclic molecule having conjugated π electrons. Due to the nitrogen lone pair of electrons' coplanar position with the heterocyclic ring and their absence from the delocalization process, the benzoxazole exhibits weak basic properties. They often only react at the C-2,5,6 positions. Electrophilic substitutions of benzoxazole primarily occur at the C-6 position, with C-5 position being less reactive. 2- substituted benzoxazole greatly alter the pharmacological activities, whereas substitution at position 5 significantly alters the strength of the particular biological activity.

They play a vital function in the creation of physiologically active medicinal molecules since it be liable to contain the appropriate pharmacological characteristics. This ring is often considered the structural bioisosteres of the guanine and guanine nucleobases. These nucleobases are heterocyclic molecules that make up the structure of nucleic acids. This important property of the benzoxazole skeleton favors interactions between derivatives of benzoxazole and biopolymers in biological systems. Based on the structural similarity, it is hypothesized that the derivatives may exhibit microbiological activity by inhibiting nucleic acid synthesis. This chemical may further explain the broad pharmacological activity of its derivatives.[1,2,3]



(a)Guanine



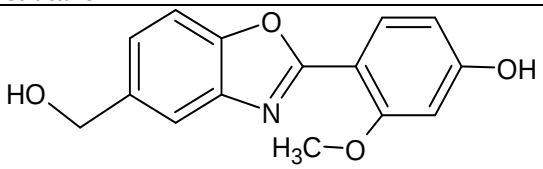
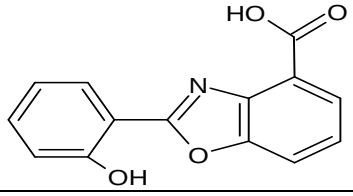
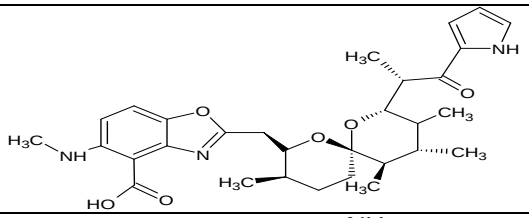
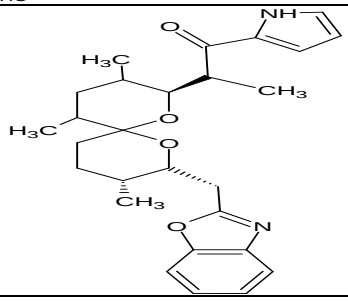
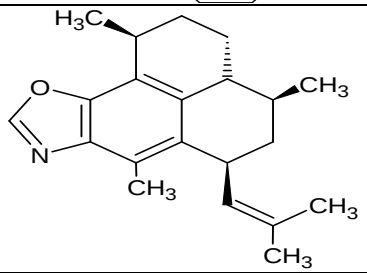
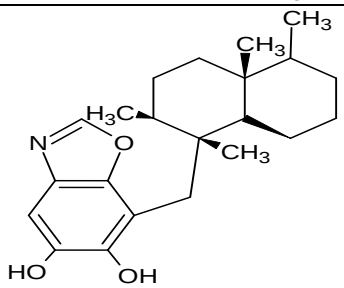
(b) adenine

Figure 2. Structure of (a) guanine nucleobase and (b) adenine nucleobase

3. Occurrence of benzoxazole

The first naturally occurring alkaloids of benzoxazole were reported in 1972, however benzoxazoles have been recognized prior 1900. Many of these alkaloids have significant physiological properties that make them prospective therapeutic targets.

According to their origin, alkaloids are widely categorised as having (i) plant, (ii) fungal, (iii) marine, origins.[2,4]

No	Benzoxazole alkaloid	Structure	Origin	Biological activity
1.	Nocarbenzoxazole G		Fungal	Anticancer
2.	Caboxamycin		Fungal	Anticancer, antibacterial
3.	Calcimycin		Fungal	Antibacterial, antifungal
4.	Cezomycin		Fungal	Antibacterial
5.	Pseudopteroxazole		Marine	Antitubercular
6.	Nakijinol B		Marine	Anticancer

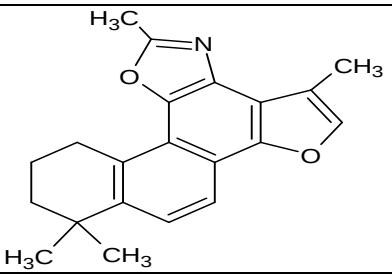
7.	Neosalvianen		Plant	Anticancer

Table no 1: Benzoxazole alkaloids and their chemical structure, origin and biological activity [3]

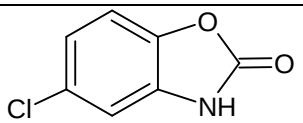
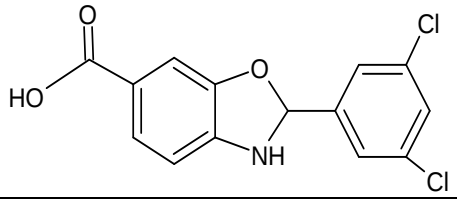
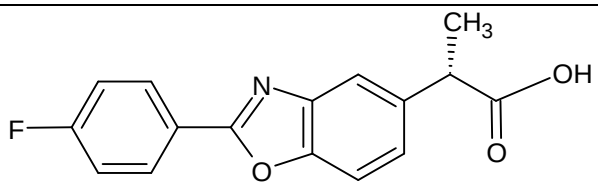
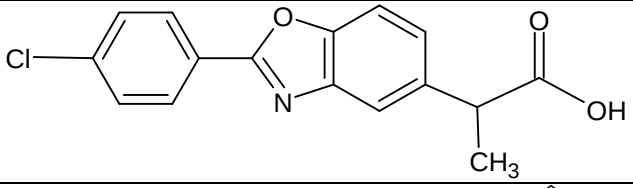
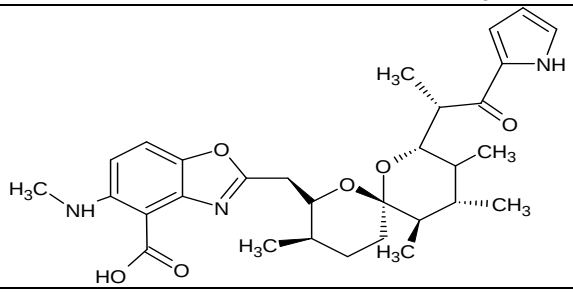
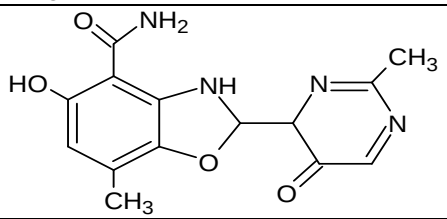
.	Name of drug	Structure	Biological activity
1.	Chlorzoxazone		Muscle relaxant
2.	Tafamidis		Transthyretin stabilizer for transthyretin amyloid cardiomyopathy
3.	Flunoxaprofen		Anti-inflammatory
4.	Benoxaprofen		Anti-inflammatory
5.	Calcimycin		Antifungal, antibacterial, pro-inflammatory and pro-allergic activities
6.	Boxazomycin B		Antibacterial

Table no 2: marketed drugs and their biological activity of benzoxazole moiety[3,4]

4.Pharmacological activity

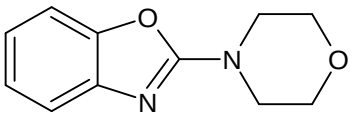
4.1. Antibacterial activity

Antibacterial agent is an agent that inhibits the growth and kills the bacteria. This agent has the capability to supress reproduction of bacteria.

Raju et al. (2015) was designed 12 derivatives of 2-(cyclic amine)-1,3-benzoxazole. Their antibacterial activities were assessed by using minimum inhibitory concentration (MIC) in comparison with standard drugs amphotericin-B and

streptomycin using serial dilution method and culture medium of broth nutrient for bacterial growth. The findings indicated that compounds of 2-(morpholin-4-yl)-1,- 3-benzoxazole(1), 2-(1,4- diazepan-1-yl)-1,3benzoxazole(2), 2-(1,3-benzoxazol2-yl)piperazino]-1-ethanol(3) exhibit good antimicrobial activity. Increased occurrences of these compounds was substituted with N-(2- hydroxyethyl), amine and oxygen group at the para position of a cyclic amine compound. The remaining compounds show no activity.[3]

Janardhan et al.(2012) was reported novel substituted 5-([1,2,4] triazolo [3,4-b] [1,3,4] thiadiazol-3-yl)-1,3-benzoxazole derivatives. The synthesized derivatives were screened for their antibacterial activities by the cup plate method against some species of gram negative and gram positive bacteria. Streptomycin was utilized as a comparison control for this study. The findings showed that compound 5-(6-phenyl-[1,2,4] triazolo [3,4-b] [1,3,4]thiadiazol-3-yl)benzoxazole(4) exhibit good antibacterial activity against gram positive strains of S aureus, B subtilis with % zone of inhibition 21 and 16mm and gram negative strains of Proteus vulgaris and E coli with 25 and 30 mm % zone of inhibition. The remaining compounds showed moderate to low activities. In above mentioned compound, Structure activity relationship (SAR) studies revealed that introduction of phenyl group in basic nucleus antibacterial activity increases.[3]



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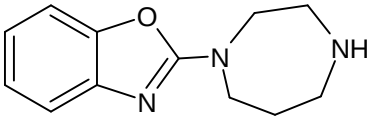

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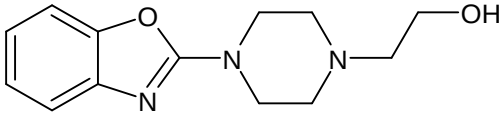

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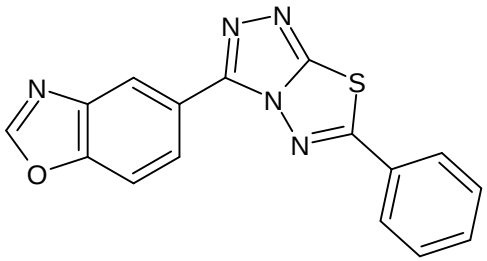
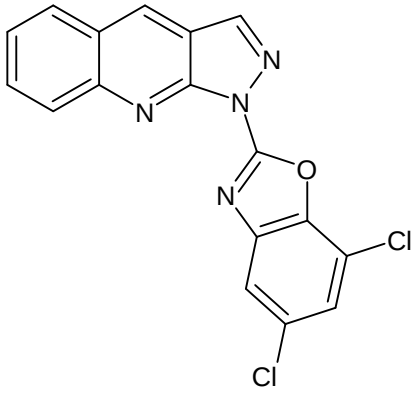


(4)

5-(6-phenyl-[1,2,4] triazolo [3,4-b] [1,3,4]thiadiazol-3-yl)benzoxazole Jayana and coworkers (2013) synthesized six derivatives of 1-(5,- 7-dichloro-1,3-benzoxazol-2-yl)-1H-pyrazolo[3,4-b]quinolone. These synthesized compounds were evaluated 2 by agar well diffusion method in comparsion to Ciprofloxacin as standard drug against different strains of bacteria for their antibacterial. Results showed that two compounds 5,7-dichloro-2-(1H-pyrazolo[3,4-b]quinolin-1-yl)benzo[d] oxazole(5) and 5,7-dichloro-2-(6-methoxy-1H-pyrazolo [3,4-b]quinolin-1-yl)benzo[d]oxazole(6) exhibit good antibacterial activity against Vibrio cholera, S aureus, Klebsiella pneumonia, Pseudomonas aeruginosa, Bacillus cereus, E coli, and S Flexner with values of inhibition zone (cm) in the range of 2.5 to 2.8 for compound and 2.3 to 2.7 for compound respectively. The improved activity of two of these compounds is by absence of substitution of methoxy group or due to electron donating of methoxy group.[3]



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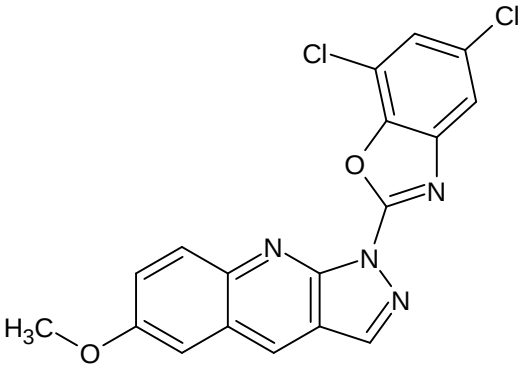
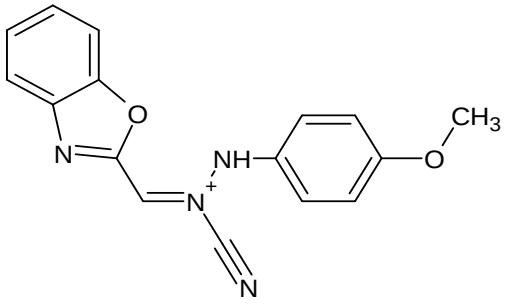


(6)

Figure no 3. Benzoxazole derivatives with antibacterial activity

4.2. Anticancer activity

2-substituted derivatives of benzoxazole were designed by Jauhari et al and revealed their activity against the hela, widr, hepg2, and MCF-7 human cancer cell lines. This study findings showed that compounds 7 and 8 against all four cancer lines exposed higher antioxidant activities.[5,6].



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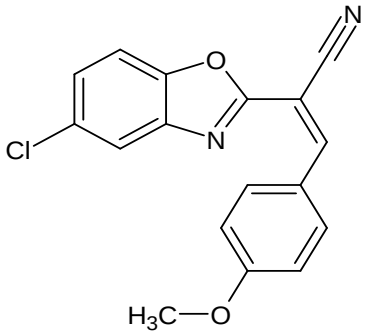
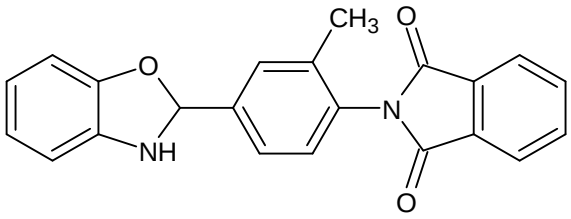


(8)

The anticancer activity of benzoxazole derivatives with phthalimide core was tested on hepg2 and MCF-7 cell lines by Philoppes and Lamiet. With IC50 values of 0.011 and 0.006, respectively, researchers determined that compound 9 had a better anticancer potential for both cancer cell lines.[5,7]

Reddy et al. Created a new sequence of substituted benzoxazoles fused with combretastatin. The in vitro anticancer efficacy of these molecules against human cancer cell lines was evaluated. These substances displayed GI50 values between 0.1 and 34.6 M. However, compound (E)-4-(2-(4,5-dimethoxybenzoxazol-2-yl)- 2-(3,4,5-trimethoxyphenyl)vinyl)-2-methoxyphenol (10) was discovered to have higher affinity than standard medicine etoposide with GI range0.1 to 0.13 M. Some derivatives shown substantial anticancer activity against numerous cancer cells.[3]



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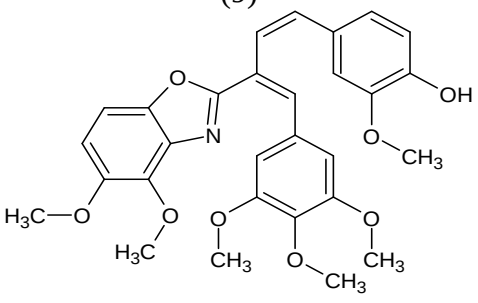
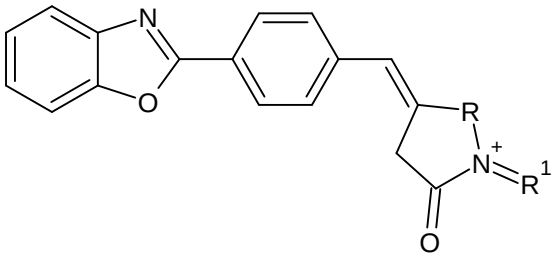


(10)

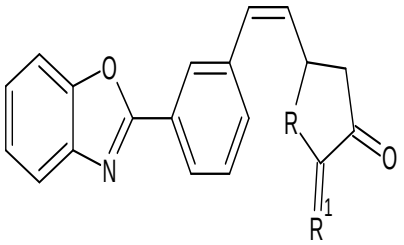
Figure no 4. Benzoxazole derivatives with anticancer activity

4.3. Antihyperglycaemic activity

Singh et al. Generated benzoxazole analogues (11a-11d and 12a-12d) and investigated their inhibitory effect against - amyloglucosidase. While other compounds exhibited moderate potential, compounds 12a and 12c demonstrated the least inhibitory activity against - amyloglucosidase with IC50 values of 22.00 1.21 and 29.03 1.11 M. Compounds 11b and 12b also demonstrated significant IC50 values in the range of 0.24 0.01-0.94 0.01 M. In this investigation, acarbose was utilised as a positive control. [5,8]



11a -11d



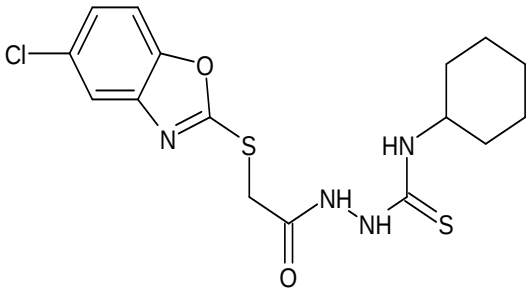
12a-12d

Compounds	R	R^1
11a and 12a	S	O
11b and 11c	S	S
11c and 12c	NH	O
11d and 12d	NH	S

Figure no 5. Benzoxazole derivatives with antihyperglycaemic activity

4.4. Anticonvulsant activity

Ibrahim et al. Produced pentylenetetrazole-induced seizures in mice and tested the anticonvulsant effect of 5-chloro-2-substituted sulfanylbenzoxazole. Additionally, researchers have explored synthetic drugs' molecular docking in order to assess their binding to the KCNQ2 receptor affinities. This study's findings indicated that compounds 13, 14, 15, and 16 had the best anticonvulsant potential and the highest binding affinities to the KCNQ2 receptor.



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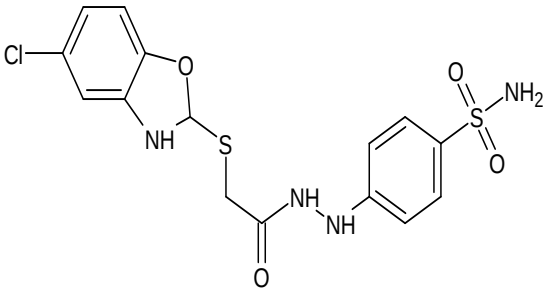

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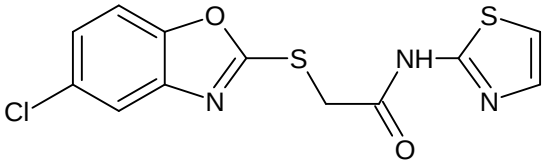

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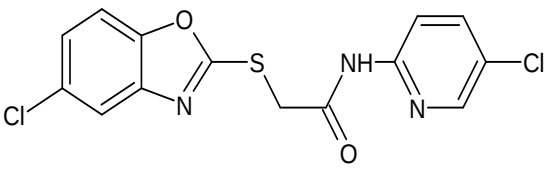

(16)

Figure no.6: Benzoxazole derivatives with anticonvulsant activity

5.CONCLUSIONS

In this review, concluded the benzoxazole is naturally occurring alkaloids found in plant, fungal and marine origins. It has so many pharmacological actions that is antibacterial, antihyperglycaemic, antitubercular, antimicrobial, anticonvulsant, anti-inflammatory activities.

Declaration by Authors
Ethical Approval: Not Applicable
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

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