REVIEW OF LITERATURE

BIOACTIVE BENZOFURAN BASED MARINE ALKALOIDS

Natural products play important roles in drug discovery and chemical biology as well as drugs which are derived from natural sources (Wipf P. et al., 2007; Metzger J. V. et al., 1979). Benzofurans, often found in naturally occurring and synthetic compounds, are attractive to chemists for their biological activities and roles in plant defence systems. The hydroxylated benzofuran cicerfuran 8 was obtained from the roots of a wild species of chickpea, *Cicer bijugum* and reported to be a major factor in the defence system against *Fusarium wilt*.
Mometasone 9 is one of the examples for pharmaceutical drugs that contain a furan ring. Mometasone is a moderately potent glucocorticoid used for the treatment of inflammatory skin disorders, asthma and allergic rhinitis (Price B. J. et al., 1983).

![Mometasone](image)

Amiodarone (Cordarone) 10 is an antiarrhythmic drug containing a benzofuran ring system (Witczak M. et al., 2005; Wang H. et al., 2006; Ha H. R. et al., 2000).

![Amiodarone](image)

Ceftiofur 11 is an antibiotic of the cephalosporin type (third generation) which the most commonly used antibiotics in the treatment of enteritis were in calve (Donaldson S.C. et al., 2006).
The manzamine alkaloids containing benzofuran ring 12 showed potent biological activities such as anticancer, antibacterial and antimalarial activities. (Tokumaru K. et al., 2016)

Morus, a genus of flowering plants in the family Moraceae, comprises 10-16 species of deciduous trees commonly known as mulberries. The root bark, stem bark and leaves of Morus alba, M. lhau, Morus macroura are the main sources for arylbenzofuran derivatives 13. They show biological activity, which include anticancer, antimicrobial, immunomodulatory and antioxidant and anti inflammatory properties (Naik R. et al., 2015).
Ganodone, a bioactive benzofuran 14 obtained from the extracts of Ganoderma tsugae, also known as the Hemlock varnish shelf mushroom and related Reishi mushrooms, which are well documented in traditional Chinese medicine. Several Ganoderma sp. are currently cultivated for use in coffee, teas, and dietary supplements. James J. La Clair, et al., reported the isolation and characterization of an unprecedented benzofuran, ganodone from the fruiting bodies of Ganoderma tsugae (La Clair J. J. et al., 2011).

BIOACTIVE BENZOFURAN DERIVATIVES

The compounds containing benzofuran show antimicrobial, enzyme inhibition, enzyme activation, receptor agonist and antagonist, anti-inflammatory, anticancer, antiviral, antitubercular, antioxidant, anticonvulsant, anti-alzheimer, complement system inhibitors, anti-ulcerogenic, ischemic cell death inhibitors and dopamine uptake inhibitor activities. Benzofuran has a great value in medicinal chemistry (Nevagi R. J. et al., 2014)

The benzofuran derivative 15 was AMP-activated protein kinase enzyme activator and were considered as anti-obesity and antidiabetic agents (Nguyen P. H. et al., 2010).
Marlon Cowart and co-workers synthesized 2-aminoethylbenzofuran compound 16 and found to consist of antagonist activity (Cowart M. et al., 2005).

The Benzofuran 17 was synthesized and evaluated for anti-inflammatory activity by using rat carrageenan induced foot paw edema model and found to have remarkable anti-inflammatory activity (Tirlapur V. K. et al., 2010).
Shrey Parekh et al. synthesized novel benzofuran-2-yl-(4,5-dihydro-3,5-substituted diphenylpyrazol-1-yl)methanones 18 evaluated the compounds for antiproliferative activity. The compounds possess good activity (Parekh S.. et al., 2011).

![Chemical structure of compound 18](image)

The spiro-benzofuran derivative 19 was synthesized and evaluated for their antiviral activity against influenza virus. The compounds have notable activities (Rida S. M. et al., 2006).

![Chemical structure of compound 19](image)

Kuntal Manna and Yadvendra K. Agrawal synthesized benzofuranpyrazolyl-pyridine 20 and tested for antitubercular activity against multidrug-resistant M. tuberculosis stains (in-vitro and in-vivo). In in-vivo assay, reduction in bacterial count in lung and spleen tissues has been measured (Manna K. & Agrawal Y. K., 2010).
Benzofuran-1,3-thiazolidin-4-one derivative 21 was synthesized and evaluated for antioxidant properties using 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity. The compounds showed excellent antioxidant activity (Latif N. A. et al., 2013).

The I-123 labelled benzofuran derivatives 22 were used as diagnostic imaging agents targeting amyloid plaques in Alzheimer’s disease (Ono M. et al., 2002).

Complement system inhibitors plays an important role in host-defence response against infection. Controlled activation of this system leads to the proper response, but improper activation leads to xenograft rejection, necrosis of infracted heart tissue and brain damage. So inhibitors of this system play an important
physiological role. Natural complement inhibitor K76-COOH 23 contains benzofuran ring. (Larghi E. L. et al., 2009).

The benzofuran derivative 24 was synthesized and their anti-ulcerogenic activity was studied by using acetic acid-induced ulcerative colitis model in rats. Benzofuran 24 showed anti-ulcerogenic effect in ulcerative colitis (Hassan G. S. and Soliman G. A., 2010).

The benzofuran derivative, 3-substituted-benzofuran-2-carboxylic ester 25 was synthesized by Jeehee Suh. et al., 2010 and evaluated for ischemic cell death inhibitors in H9c2 cells and found good activity (Suh J. et al., 2010).
Benzofuran derivative 26 was investigated for dopamine uptake inhibitory activity in nanomolar concentration but it was found to have remarkable activity (Loriga G. et al., 2007).

The compound which have benzofuran ring, 4,6-dimethoxy-5-(heterocycles)benzofuran 27 was synthesized by El-Sawy E. R. et al. and were tested for their anti-inflammatory, analgesic and anticonvulsant activities. The results show that the newly synthesized compounds possess significant anti-inflammatory, analgesic and anticonvulsant activities (El-Sawy E. R. et al., 2014).
Kamal M. Dawood and co-workers synthesized 1-(benzofuran-2-yl)-2-(benzotriazol-1-yl)ethanone 28 from 2-bromoacetylbenzofuran. The newly synthesized compounds were found to possess anticonvulsant and anti-inflammatory activities (Dawood K. M. et al., 2006).

Jadhav V. B. et al. synthesized 2-(6-methyl-benzofuran-3-ylmethyl)-imidazo[2,1-b][1,3,4]thiadiazoles 29 and tested for their in vivo analgesic and anti-inflammatory activities. A qualitative structure activity relationship (SAR) studies indicate that the chloro substitution in the imidazole ring and introduction of formyl group at C-5 position of the imidazole ring increased the anti-inflammatory and analgesic activity (Jadhav V. B. et al., 2008).

Rekha Rani and Makrandi J. K. obtained 2-(benzo-furan-2-yl)-7-(substituted)imidazo(2,1-b)benzothiazoles 30 by the condensation of 2-(2-bromoacetyl)benzofurans and various 2-amino-7-(substituted)benzothiazoles under normal thermal condition as well as microwave irradiations. The antibacterial and antifungal activities of synthesized compounds were moderate (Rani R. and Makrandi J.K., 2009).
Lisha Huang et al. synthesized benzofuran-2(3\textit{H})-ones 31 and observed that the compounds possess remarkable biological activities (Huang L. et al., 2015).

Photochromic diarylethene derivatives 32 having benzofuran heteroaryl groups were synthesized and compound exhibited tremendous photochromic reactivity (Yamaguch T. & Irie M., 2005).

The compounds 2\textit{H},3\textit{H}-spiro[benzofuran-3,2′-naphthoquinones] 33 were synthesized from 2-aryloxymethyl-1,4-naphthoquinones and palladium(II)-catalyst and the compounds possess remarkable biological activities (Claes P. et al., 2013).
Xizhen Jiang and co-workers synthesized benzofuran derivatives 34. The compounds were screened for their antibacterial and antifungal activities. The compounds were found to exhibit favourable antibacterial activities which were better than the control drugs (Jiang X. et al., 2011).

Rindhe S. S. et al. synthesized benzofuran derivatives 35 from substituted phenacyl bromide and 2-hydroxy-5-niro acetophenone in presence of K$_2$CO$_3$ in DMF. The synthesized compounds were tested for in vitro antioxidant and antimicrobial activity and reported that they possess good activity (Rindhe S. S. et al., 2010).
Mycophenolic acid 36 containing benzofuran ring, produced by *Penicillium brevicompactum* species, has antibiotic, antiviral and immunosuppressive properties (Fardis M. *et al.*, 2006).

![Mycophenolic acid 36](image)

Suparna Sengupta and co-workers identified 4-amino-5-benzoyl-2-(4-methoxyphenylamino)thiazole 37 as bioactive compounds. These compounds showed good anticancer activity and used to develop antimitotic agents for the control of cytoskeletal functions and cell proliferation. It would also be an interesting probe for the structure-function studies of tubulin - microtubule system (Sengupta S. *et al.*, 2005).

![4-amino-5-benzoyl-2-(4-methoxyphenylamino)thiazole 37](image)

The reaction of ethyl 4-(benzofuran-2-yl)-2,4-dioxobutanoate and hydrazine hydrate afforded 5-(benzofuran-2-yl)-1H-pyrazole-3-carbohydrazide, while its reaction with equimolar amount of phenylhydrazine gave ester which then converted to 5-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbohydrazide 38 & 39. The new compounds are tested for their antimicrobial activity and found to have better activity than the control (Abdel-Wahab B. F. *et al.*, 2008).
Benzofuran based new compound 3-(glycinamido)-benzofuran-2-carboxamide and 3-(β-alanamido)-benzofuran-2-carboxamide derivatives 40 were synthesized for the purpose of developing the new bioactive chemical entities and evaluated for their in vitro, antimicrobial, anti-inflammatory and DPPH radical scavenging activities. The synthesized compounds were found to have magnificent activities. (Lavanya A. et al., 2015)

Ryuta Inagaki and co-workers synthesized furonaphthoquinones 41 by effective one-pot cascade reactions of 3-phenyliodonio-1,2,4-trioxo-1,2,3,4-tetrahydronaphthalenides with 3-butyn-2-ol in the presence of palladium and cuprous catalysts via Sonogashira coupling and intramolecular cyclization. Furonaphthoquinones isolated from Tabebuia Plants. Furonaphthoquinones showed
moderate cytotoxicity against human leukemia U937 and HL-60 cells. (Inagaki R. et al., 2013)

Paul V. Murphy et al., 2008 synthesized benzofurans 42 & 43, which showed remarkable biological activities (Murphy P. V. et al., 2008).

Pevzner L. M. reported the reaction of formylfurancarboxylates with excess ethylene glycol in the presence of p-toluenesulfonic acid that gives rise to (1, 3-dioxolan-2-yl)furancarboxylates 44. All synthesized compounds characterized by $^1$H-NMR analysis and evaluated for antibacterial activities and reported that all possess excellent activities (Pevzner L. M. et al., 2008).

Naphtho[1,2-b]furan-4,5-dione (NFD) 45 was prepared from 2-hydroxy-1,4-naphthoquinone and chloroacetaldehyde in an efficient one-pot reaction and the
compound exhibits anti-carcinogenic effect. The present study shows that NFD 45 inhibited the proliferation of breast cancer MDA-MB-231 cells through the induction of S-phase arrest and apoptosis (Lin K. L. et al., 2008).

Bidyut Kumar Senapati and Dipakranjan Mal reported (4+2) cycloaddition reaction between furan sulfoxide and 2-cyclohexenone. The reaction produced dihydro naphtho[2,3-b]furanone derivative 46. The naphtho[2,3-b]furans possess broad anticancer activities (Senapati B. K. and Dipakranjan M., 2015).

Kuntal Manna. and Yadendra K. Agrawal. synthesized pyrazolyl benzofuran derivatives 47 using microwave assisted route. All the synthesized compounds show good antibacterial activity compared with the standards sparfloxacin and norfloxacin (Manna K.. & Agrawal Y. K. et al., 2009).
Benzofuran derivatives containing tumor necrosis factor-α (TNF-α) converting enzyme (TACE) inhibitors 48 were synthesized and evaluated for the biological activity, TACE is a Zn-dependent metalloprotein, which is important in the synthesis of TNF-α, a cytokine important for an inflammatory response. TACE is having an important role in rheumatoid arthritis drug discovery (Lu Z. et al., 2008).

Benzofuran derivatives 49 can be synthesized through Michael addition and intramolecular cyclization reaction of ketones with 1,4-benzoquinones by using triethyl orthoformate as an additive. In the presence of Sc(OTf)₃ as catalyst, triethyl orthoformate may be utilized to convert enolizable ketone into ethyl vinyl ether. The compound possess remarkable biological activities (Wu F. et al., 2016).
Hui Yu and coworkers synthesized 2-aminobenzofuran-3(2H)-one 50, which was obtained from 2-acylphenols by the treatment with secondary amines using TBHP/I₂ as catalyst in good yields. The compound has fabulous biological activities (Yu H. et al., 2014).

Nagaraja naik et al. reported 4-methoxy-2-acetylbenzofuran based chalcones 51, which were synthesized by aldol condensation reaction between 2-hydroxy-3-methoxybenzaldehyde with chloroacetone. The synthesized compounds were characterized by IR, ¹H NMR, ¹³C NMR, mass and elemental analysis and were evaluated for their antioxidant potential using 2,2-diphenyl-1-picrylhydrazyl (DPPH). Butylated hydroxy anisole (BHA) was used as a reference compound and the comparative study with the newly synthesized compounds was also performed. All the newly synthesized analogues show good antioxidant activity (naik N. et al., 2013).
Yun Kwon and co-workers reported that three new secondary metabolites, amycofuran, amycocyclopiazonic acid and amycolactam 52, 53 & 54 were isolated from the sponge-associated rare actinomycete *amycolatopsis* sp. The absolute configurations were deduced by electronic circular dichroism (ECD) calculations, modified using Mosher method. Amycolactam 54 displayed significant cytotoxicity against the gastric cancer cell line SNU638 and the colon cancer cell line HCT116. (Kwon Y. *et al.*, 2014).

Ling-Guo Meng and co-workers obtained 2-aminobenzofuran-3-(2H)-one derivatives 55 using cyclization reaction of 2-azido-1-(2-hydroxyphenyl)ethanones with terminal alkynoates catalyzed by 4-dimethylaminopyridine (DMAP) under optimized condition produce compound in good yield. The 2-aminobenzofuran-3(2H)-one derivatives were tested for antibacterial and antifungal activities. The result of biological study was satisfactory. (Meng L. G. *et al.*, 2011).
Mizoroki-Heck cross-coupling reactions of 2-acetyl-5-bromobenzofuran 56 as well as activated and deactivated aryl bromides with various olefins were investigated under both thermal as well as microwave irradiating conditions in open air using water solvent under different conditions. The compounds show remarkable biological activity (Shaaban M. R. et al., 2010).

Xin Li et al. reported Michael addition reaction of 3-phenylbenzofuran-2(3H)-one and maleimide under the optimal conditions and obtained 3-substituted benzofuran-2(3H)-ones derivatives 57. The synthesized compounds were characterized, determined by X-ray crystal studies, evaluated for anticancer activity and found good activity (Li X. et al., 2010).
Martin Tiano and Philippe Belmont reported powerful aminobenzannulation reaction for the synthesis of amino-substituted quinolines, benzofurans and carbazole 58. All compounds show broad biological and antitumor activities (Tiano M. & Belmon P. et al., 2008).

Y = O, NH  
R = Alkyl, Aryl

Abdel Hafez O. M. and co-workers synthesized benzofuran derivatives 59 obtained from 5-acetyl-6-hydroxy-4-methoxybenzofuran (visnaginone) by the reaction with 2-diethylaminoethylchloride and aromatic aldehyde. All synthesized chalcone derivatives were characterized and found to have good antibacterial, antifungal activity (Abdel Hafez O. M. et al., 2001).

Gurubasavaraja Swamy P.M and Agasimundin Y.S. reported 3-hydroxybenzofuran derivatives 60 obtained from 2-acetyl-3-hydroxybenzofuran by the reaction with aromatic aldehydes in ethanol. The structures of reported compounds have been established on the basis of analytical and spectral data. The
synthesized compounds were screened for antibacterial activity and have moderate activity. (Gurubasavaraja Swamy P. M. & Agasimundin Y.S., 2008).

Weiming Luo and co-workers reported the synthesis of benzofuran derivative 61 and studied structure activity relationship. The compound 61 show good anticholinesterase activity by the use of computer aided molecular modelling using Sybyl version 7 (Luo W. et al., 2006).

Nazan Ocak Iskeleli et al. reported 2-acetyl-3-(benzoylamino)-1-benzofuran 62, which was synthesized from the reaction of 2-acetyl-3-aminobenzofuran with benzoyl chloride in dry acetone and the compound showed remarkable biological activity (Iskeleli N. O. et al., 2005).
Ahmed Hamdy Halawa synthesized novel 5-bromobenzofuran-based heterocycles 63 & 64 were obtained by the condensation of 2-acetyl-5-bromobenzofuran with methyl hydrazinecarbodithioate and thiosemicarbazide in ethanol. The newly synthesized compounds showed promising antimicrobial activity (Halawa A. H, 2014).

The benzofurans 65 & 66 are synthesized by the reaction of 1-(1-benzofuran-2-yl)-2-bromoethanones with 4-phenyl-1,3-thiazol-2-amines and 4-benzofurano-1,3-thiazol-2-amines respectively are characterized by IR, $^1$H NMR and mass spectroscopic studies and were screened for antimicrobial activities. Both compounds possess tremendous biological activities (Shankerrao S. et al., 2012).
The benzofuran derivative 67 was screened for antibacterial and antifungal activity and found to have excellent activities (Abdel-Wahab B. F. et al., 2009).

Javarappa Rangaswamy et al., reported the synthesis of benzofuran derivative 68 which possess antioxidant and antimicrobial activities (Rangaswamy J. et al., 2014).
The synthesis and characterization of radio iodinated benzofuran derivative 69 was done by Masahiro Ono et al. in 2013. The in vitro binding experiments and biodistribution studies with normal mice suggested that both compounds show high affinity (Ono M. et al., 2013).

![Image of compound 69]

Monoamine oxidase (MAO) is an important drug target for the treatment of neurological disorders. A series of 2-arylbenzofuran and evaluated as inhibitors of both MAO isoforms, MAO-A and MAO-B. Docking experiments for the most active compound 70 provided new information about the enzyme-inhibitor interaction and the potential therapeutic application of these scaffolds (Ferino G. et al., 2013).

![Image of compound 70]

Ya-Qiang Xie et al. in 2014, reported the synthesis and bio-assay of benzofuran derivatives 71. The synthesized compounds were characterised by $^1$H NMR, $^{13}$C NMR, MS and HRMS. The target compounds exhibited tremendous fungicidal activities (Xie Y. Q. et al., 2014).
Gao Wentao and co-workers reported new heterocyclic systems of benzofuran derivatives 72, from salicylaldehydes. All the synthesized compounds possess remarkable biological activity (Wentao G. et al., 2012).

The benzofuran derivative, 5-(2-aminopropyl)benzofuran (5-APB) 73 is a psychoactive compound (Nakagawa Y. et al., 2016).

Amel Haouas et al., reported spiro benzofuran derivative 74 & 75, which shows anti-inflammatory property (Haouas A. et al., 2013).
Shoichi Nakamura and co-workers reported the synthesis of porphyrin analogues containing benzofuran 76, which possesses in vitro cytotoxicity against Human Cancer Cell Lines (Nakamura S. et al., 2013).

Lin Li et al. synthesized benzofuran derivatives 77, which was found useful as anticancer drug against lung cancer cell line (Li L. et al., 2015).

Feng-Quan Yuan and Fu-She Han reported the substituted benzofuran 78, which were synthesized directly from phenolic compounds and propargylic alcohols in the presence of iron catalyst. The compound showed significant antifungal activity (Yuan F. Q. and Han F. S., 2013).
Charlotte Mallet. *et al.*, (2013) reported the synthesis of three new oligomers bearing benzofuran, furan or thiophene 79, which showed remarkable antibacterial and antifungal activities (Mallet C. *et al.*, 2013).

\[ X = \text{O, S etc.} \]

Chatterjea J. N. *et al.*, in 1980, synthesized benzofuran derivatives 80 & 81, which were found to possess anticancer property (Chatterjea J. N. *et al.*, 1980).

The benzofuran derivatives 82 possess anticancer activity against human cancer cell lines, namely, breast cancer, leukemia, prostate and lung cancer (Barluenga J. *et al.*, 2006).

The benzofuran derivative 83 showed anti-bacterial activity (Sakae M. *et al.*, 2014).
Sandip Kundal et al., in 2015 reported the synthesis and biological evaluation of 3-alkylbenzofuran derivatives 84. The compounds were found to have remarkable activity (Kundal S. et al., 2015).

The benzofuran derivatives 85 were screened by diphenyl-2-picrylhydrazyl radical scavenging and ferric ion reducing potential assays compared with the synthetic antioxidants 2-tert-butylhydroquinone and butylated hydroxytoluene. The compounds showed good antioxidant properties (Ghotbabadi H. S. et al., 2015).

Benzofuran derivatives 86 were synthesized through Michael addition and cyclization reaction. All the synthesized compounds were evaluated for antibacterial and antifungal activity and possess tremendous activities (Wu F. et al., 2016).
Treguier *et al* in 2011 synthesized benzofurans 87, which posses significant anticancer activity (Tréguier B. *et al.*, 2011).

Marina Ionita *et al.* synthesized 3-arylbenzofuran derivatives 88, which have antiulcer activity (Ionita M. *et al.*, 2010).

Maud Jacubert *et al.*, in 2010 synthesis of 2- substituted 3-bromobenzofurans derivatives 89 show remarkable antibacterial activity (Jacubert M. *et al.*, 2010).
The compounds 5-(2-aminopropyl)benzofuran (5-APB) \( 90 \) & \( 91 \) were reported by UK authorities to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in 2010, to produce a combination of stimulant and entactogenic effects. (Stanczuk A. et al., 2012).

\[ \text{\includegraphics[width=0.5\textwidth]{compound90_91.png}} \]

Pratima Yadav et al. reported benzofuran derivatives \( 92 \). The compounds \( 92 \) served as good anti-inflammatory agents (Yadav P. et al., 2014).

\[ \text{\includegraphics[width=0.5\textwidth]{compound92.png}} \]

Maria J. Moure et al. synthesized benzofuran derivative \( 93 \), which posses antiinflammatory activity (Moure M. J. et al., 2012).

\[ \text{\includegraphics[width=0.5\textwidth]{compound93.png}} \]

The benzofuran compounds \( 94 \) showed good antimicrobial activity (Rahmatpour A. et al., 2009).
Purushottamachar P. and co-workers reported benzofuran derivative \( \text{95} \) which was examined to determine the structural requirements of N-myristoyltransferase enzyme inhibition by three-dimensional quantitative structure–activity relationship using comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis. The synthesized compound is evaluated for antifungal activity and reported that they have good activity (Purushottamachar P. and Kulkarni V. M. 2003).

The benzofuran derivatives \( \text{96} \) were synthesized, a three-dimensional quantitative structure–activity relationship (3D-QSAR) and molecular docking were carried out and found that they can be Candida albicans N-myristoyl transferase Inhibitors (Telvekar V. N. \textit{et al}., 2008).
The benzofuran derivative 97 was designed, synthesized and evaluated as butyrylcholinesterase inhibitors. The synthesized compound was found to be a mixed-type inhibitor as determined by kinetic analysis. Molecular dynamics simulations revealed that compound binds to both the catalytic anionic site (CAS) and peripheral anionic site (PAS) of butyrylcholinesterase (BChE) and it displayed the best interaction energy value, in agreement with our experimental data (Delogu G. L. et al., 2016).

Kevin W. Wellington et al., in 2013 reported 5,6-dihydroxylated Benzofurans derivatives 98 were screened against anticancer cell lines renal, melanoma breast and cervical cancer cell lines (Wellington K. W. et al., 2013).

The in vivo antihyperlipidemic activity test of benzofuran derivatives 99 was carried out using Triton-WR-1339-induced hyperlipidemic rats as an experimental
model. The results revealed that the compound has excellent activity (Al-Qirim T. et al., 2012).

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The benzofuranones 100 showed a broad range of biological and pharmaceutical activities (Li Y. et al., 2013).

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**BIOACTIVE THIAZOLE BASED MARINE ALKALOIDS**

Another heterocyclic system that is very common in marine as well as terrestrial biomolecules is the thiazole ring. Marine sources have been especially rich in highly bioactive thiazole containing alkaloids and peptoids. Some of these cyclic peptides such as dolastatins have been stated to be the most potent cytotoxic natural peptide derivative isolated so far. Dolastatins isolated from marine sponges showed powerful cell-growth inhibition of leukemia cell lines. It has been reported that dolastatin 3 101 has a surprisingly low $ED_{50}$ value of 0.1 pg/mL (Pettit G. R. et al., 1982).
The acyclic marine natural product dolastatin 10 102 is another thiazole containing potent antineoplastic agent. This acyclic peptide derivative bears only one thiazole ring (Pettit G. R. et al., 1987).

Other potent cyclic peptides that bear multiazole units have been isolated from marine tunicates. Examples are lissoclinamides 103 with one pyrrole, one oxazole and two thiazole units (Zabriskie T. M. et al., 1988; Degnam B. M. et al., 1989;

These are also strongly cytotoxic against cancer cell lines with IC$_{50}$ values of 0.8 to 0.01 µg/mL for lissoclinamides 103 and ulithiacyclamide 104.

Simple thiazoles have also been isolated from marine sources. Thus anguibactin 105 has been isolated from the fish pathogen *Vibrio anguillarium* (Jalal M. A. F. *et al.*, 1989).
Other such simple thiazole derivatives from the sea are the thiolactone 106 and the alcohol 107 (Arabshahi L. et al., 1988).

The antibiotic cystothiazole A 108 was isolated by Sakagami and co-workers from the myxobacterium culture broth of *Cystobacter fuscus* which are structurally similar to the myxothiazoles 109 and melithiazoles 110. Cystothiazole A possesses potent activity against a large range of fungi, including *Candida albicans* with no effect on bacterial growth. When compared with myxothiazole A, cytothiazole A was more active and less cytotoxic against fungi. Cytothiazole A possesses cytotoxicity activity against colon carcinoma and Leukaemia (Ojika M. et al., 1998; Suzuki Y. et al., 1998; Gerth K. et al., 1980; Trowitzch W. et al., 1980; Bohlendorf B. et al., 1999).
Natural macrolactam products containing heterocyclic amino acids composed of thiazole, oxazole, thiazolines and oxazolines with a wide range of biological activities. Bistratamides 111 are a family of macrolactams isolated from *Lissoclinum bistratum* that possess moderate cytotoxic activity against a human colon tumor (Davidson Davidson B. S., 1993; Wipf P., 1995; Degnan B. M. *et al.*, 1989; Foster M. P. *et al.*, 1992; Perez L.J., 2003).

Hectochlorin 112 is a marine natural fungicide isolated from *Lynbya majuscule*. Hectochlorin possesses antifungal activity against *Candida albicans* and antiproliferative activity in the NCI 60-cell line assay (Cetusic J. R. P. *et al.*, 2002).
Bacillamide A 113 was isolated from *Bacillus endophyticus* obtained from a bahamian hypersaline microbial mat and shows antibiotic activity against target isolates of hypersaline pond *Bacillus sp.* (Aaron M. S. *et al.*, 2007).

Pateamine A 114 is a thiazole-containing dilactone macrolide isolated from the marine sponge *Mycale sp.* is cytotoxic and has immunosuppressive activity. (Northcote P.T., 1991; Rzasa R.M., 1995).
BIOACTIVE THIAZOLE DERIVATIVES

Thiazole ring system is a common structural motif found in many biologically active molecules (Kurzer F. et al., 1970). Recent reports indicate a continued recognition of thiazole as a pharmacophore unit. Among thiazole derivatives, 2-aminothiazole seems to possess remarkable pharmacophore activity. A large number of 2-aminothiazole derivatives are in recent clinical use or under development as therapeutics. Thus, 2-aminothiazole ring system is a long-recognised and useful structural unit in medicinal chemistry and has found very broad application in drug development as can be amply demonstrated by the examples given below.

One of the first commercial synthetic drugs containing thiazole was sulphathiazole, which is a simple sulphonamide antibiotic derived from 2-aminothiazole 115 (Lowe P. A. et al., 1980).

The 2-aminothiazole derivative 116 is reported to be useful in the treatment of neurobiological illness and inflammation (Geronikaki A. A. et al., 1998).
Niridazole 117 is another 2-aminothiazole derivative with a masked amino group, which is one of the most active schistosomicidal drugs in clinical use currently (Werbel L. M. et al., 1991).

Simple aminonitrothiazole derivatives that show useful bioactivities include the 5-nitrothiazole 118 which has antiparasital, antibacterial, antifungal and antiviral activities (Rossignol J. F. et al., 1996).

Rather simple 2-aminothiazole derivatives such as 2-amino-4-arylthiazole 119 also shows promising bioactivities. For example 119 have antibacterial and fungitoxicity activities (Agarwal N. et al., 1997).
The 2-amino-4-arylthiazole 120 possesses antifungal and antibacterial activities (Shrivastava A. K. et al., 1997)

![Diagram of 2-amino-4-arylthiazole 120]

The 2-amino-4-arylthiazole 121 shows antifungal activity (Varma R. S. et al., 2001).

![Diagram of 2-amino-4-arylthiazole 121]

The 2-aminothiazole derivative 122 has antibacterial, antitubercular and antifungal activities (Vingkar S. K. et al., 2001)

![Diagram of 2-aminothiazole derivative 122]

Many 2-aminothiazoles show anticancer activity. One such example of a 2-aminothiazole derivative with anticancer activity is the flavone 123 (Bhatti S. P. et al., 2000).

![Diagram of flavone 123]
The biheterocyclic thiazole derivative **124** has been found useful as an antitumor agent (Lago M. A. *et al.*, 2000).

![Image of molecule 124]

The 2-amino-4-arylthiazole derivative **125** inhibited kinases at IC\(_{50}\) value of 2 nM level and are potentially useful for the treatment of cytokine-mediated and adenosine receptor-mediated diseases (Ohkawa S. *et al.*, 2001).

![Image of molecule 125]

The dithiazolylurea derivative **126** exhibits antitumor activity and cdk\(_2\)-cyclin and cdk\(_5\)-cyclin kinase inhibition activity with IC\(_{50}\) < 50 \(\mu\)M (Santora V. *et al.*, 2002).

![Image of molecule 126]

The 2-ureidothiazole derivatives **127** and **128** are useful for controlling kinase activity and thus useful in treating cancer, Alzheimer’s disease, viral infections, autoimmune disease and neurodegenerative disorders (Pevarella P. *et al.*, 2000).

![Image of molecule 127 and 128]
The thioureidothiazole 129 is a potential agent for the treatment of HIV infection (Uckun F. M. et al., 2002).

The thioureidothiazole 130 has antineoplastic activity with a low GI<sub>50</sub> value of 9.5 μM (El-Subbagh H. I. et al., 1996).

The 2-guanidinothiazole derivatives 131 (Fukumi H. et al., 1996) and 132 (Fujisawa, 1997) shows antiulcer and antibacterial activities.
Guanidinothiazoles such as 133 show antioxidant property and are useful as protective agents against lipid peroxidation (Matsui T. et al., 1997).

![Chemical structure of Guanidinothiazole 133](image)

Famotidine 134, which is a 2-guanidino derivative of thiazole inhibits gastric acids and is clinically used in the treatment of gastric ulcers (Anglada L. et al., 1988).

![Chemical structure of Famotidine 134](image)

Guanidinothiazole 135 has also been reported to be active against lung carcinomas (Schnur R. C. et al., 1991).

![Chemical structure of Guanidinothiazole 135](image)

The hydrazonothiazole derivative 136 exhibits bactericidal and fungicidal activities (Zaharia D. et al., 1997).

![Chemical structure of Hydrazonothiazole 136](image)
The 2-amino-4-(substituted)thiazole derivative 137 is useful as intermediates for cephalosporin antibiotics (Matsunaga T. et al., 2002).

Another example of bioactive 2-amino-4-(substituted)thiazole derivative is the 2-aminothiazole derivative 138 that shows anticonvulsive activity (Bezugly P. A. et al., 2001).

The 2-(4-chlorophenyl)thiazol-4-ylacetic acid 139 possesses antiinflammatory properties (Foulkes D. M., 1969)

The 2-aminothiazole derivatives 140 (Kawamoto I. et al., 1998) and 141 (Iwasaki F. et al., 1998) are established intermediates for cephem antibiotics.

\[ 	ext{Ad} = 1\text{-adamantyl} \]
The 2-sulphonamidothiazole 142 is useful for the treatment and prevention of diabetes, glaucoma, hyperlipidemia, hyperglycemia, osteoporosis and inflammatory disorders (Barf T. et al., 2002).

Shilong Zheng and co-workers synthesized thiazole derivatives 144 as novel inhibitors of metastatic cancer cell migration and invasion can potentially lead to clinical applications as therapy to block tumor metastasis, the primary cause of death in cancer patients (Zheng S. et al., 2013).

Chi B. Vu et al. reported imidazo[1,2]thiazole derivatives 144 & 145, which activate the NAD+ nicotinamide adenine dinucleotide dependent deacetylase SIRT1 and a potential new therapeutic target to treat various metabolic disorders (Chi B. V. et al., 2009).
Shilong Zheng et al. synthesized thiazole derivatives 146 from sodium hydride and N-alkylation of the amides in tetrahydrofuran. All the thiazole analogues were biologically evaluated to determine their cytotoxicity, antimigration, and anti-invasion activities and showed strong antiangiogenesis activity (Zheng S. et al., 2014).

Girish A. Hampannavar et al., synthesized thiazole derivative 147. The in vitro anti-mycobacterial activity of synthesized compound was evaluated against Mycobacterium tuberculosis H37Rv strain as promising class of anti-mycobacterial agents (Hampannavar G. A. et al., 2016).

Junsheng Zhu and co-workers reported thiazole-derivatives 148 as selective inhibitors against Human Dihydroorotate Dehydrogenase (HsDHODH) through structure based lead optimization. HsDHODH is a flavin-dependent mitochondrial
enzyme, which has been certified as a potential therapeutic target for the treatment of rheumatoid arthritis and other autoimmune diseases (Zhu J. et al., 2015).

Thiasporine A is a natural product with a 5 hydroxy-4H-1,3-thiazin-4-one moiety, along with two new thiazole derivatives, thiasporines B and C were isolated from the marine-derived *Actinomycetospora chlora*. Thiasporine A showed cytotoxicity against the non-small-cell lung cancer cell line (Fu P. and MacMillan J. B. et al., 2014).
Sobhi M. Gomha and co-workers reported bioactive 1,3,4-thiazole derivatives \textbf{151} \& \textbf{152}. The synthesized bioactive compounds showed promising cytotoxic activity against the Hepatic carcinoma cell line (HepG-2). The binding mode of the active compounds was interpreted by a molecular docking study (Gomha S. M. \textit{et al.}, 2016).

El-Subbagh and co-worker synthesized thiazole \textbf{153} and tested the compound for their \textit{in vitro} antitumor activity against human tumor cell lines and found that the compound has remarkable activities (El-Subbagh \textit{et al.}, 1999).
Kouatly O. A. et al., synthesized thiazole derivative 154 and tested for anti-inflammatory activity as well as lipoxygenase and cyclooxygenase inhibitory actions. The compounds have very good biological activities (Kouatly O. A. et al., 2009).

Both Kuanoniamine A and dendrodoine incorporate a dihetary ketone moiety with one of the hetaryl ring being an azole unit and the other benzofused nitrogen containing hetaryl moiety. In addition dendrodoine is an aminoazole derivative. Both are known to be cytotoxic against cancer cell lines. On the basis of this realization we reasoned that suitably designed aminothiazolyl benzofuryl ketone might show interesting cytotoxic properties. This hypothesis forms the basis of the work incorporated into this thesis are described in the subsequent sections.
Objectives

The main objectives of the present study are

- To develop a viable route to synthesize new analogs of dendrodoine viz. 2-(2-alkyl/arylamino-4-aminothiazol-5-oyl)benzofurans, 2-(2-alkyl/arylaminothiazol-5-oyl)benzofurans, 2-(2-alkyl/arylamino-4-phenylthiazol-5-oyl)benzofurans.
- To identify on its basis suitable precursors and to develop or select practical methods for their preparation.
- To develop the suitable reaction conditions and thus prepare several examples of the target structure.
- To characterize the new analogs by elemental analysis and spectral techniques like IR, $^1$H NMR, $^{13}$C NMR and mass spectra.
- To calculate bond length, bond angle, dihedral angle, vibrational frequencies of targeted molecules using Gaussian 09 software.
- To carry out molecular docking studies and
- To assay these new compounds for biomedical application like anti-bacterial anti-fungal, anticancer and antioxidant activities.