VEDIC RESEARCH INTERNATIONAL
Biolological Medicinal Chemistry
JOURNAL HOME PAGE AT WWW.VEDICJOURNALS.COM
eISSN 2330-7250

REVIEW

DOI: http://dx.doi.org/10.14259/bmc.v1i1.4

Thiazoles as Imperative Molecules for Potential Therapeutic Importance

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Article Info
Received: May 18th, 2013
Accepted: June 6th, 2013

Keywords
Heterocycles,
Biological significance,
Medicinal significance.

ABSTRACT

This article outlines the biological significance of one of the most important heterocycles, the thiazoles. An attempt has been made to cover most of the physiologically as well as medicinally important compounds containing thiazole derivatives.

INTRODUCTION

Thiazoles are an important moietywhich is present in a wide variety of drugs and chemicals. Thousands of molecules containing the thiazole nucleus are been tested and evaluated showing a wide range of activities like fungicide and parasiticide, NSAID, sedative and hypnotic, anticancer, antihistaminic, respiratory stimulant, dopamine agonist, xanthine oxidase inhibitor, antibacterials, antihelmintic, veterinary use, etc. Hence, this moiety requires a large exploration in the field of drug discovery and evaluation.

Therapeutic Importance

Thioflavin *(a)* can refer to either of two dyes used for histology staining. Thioflavin T (Basic Yellow 1 or CI 49005) is used to visualize plaques composed of amyloid beta found in the brains of Alzheimer's disease patients as well as other amyloid proteins [1]. Thioflavin S is also used to stain Alzheimer's plaques. Like Thioflavin T, it binds to amyloid fibrils but not monomers and gives a distinct spectral shift upon binding [1].

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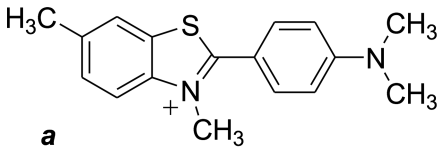
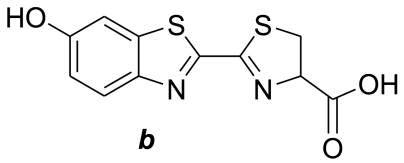


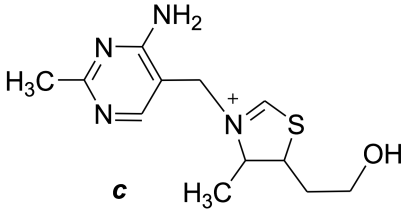
a

Luciferin *(b)* is a class of light-emitting biological pigments found in organisms that cause bioluminescence. The term is used generically to refer to any light-emitting molecule utilized by a luciferase or photoprotein [2]. There are many types of luciferins, yet all share the use of reactive oxygen species to emit light [3].



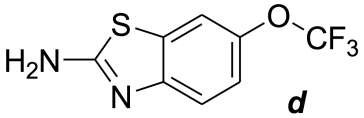
b

Thiamine *(c)* is named as the "thio-vitamine" (sulfur-containing vitamin) is a water-soluble vitamin of the B complex. In less severe deficiency, nonspecific signs include malaise, weight loss, irritability and confusion [4].



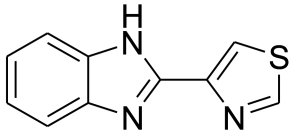
c

Riluzole *(d)* is a drug used to treat amyotrophic lateral sclerosis. It delays the onset of ventilator-dependence or tracheostomy in selected patients and may increase the survival by 3–5 months. Riluzole preferentially blocks TTX sensitive sodium channels, which are associated with damaged neurons [5]. This indirectly prevents stimulation of glutamate receptors [6]. Its antiglutamate action is still detectable in the presence of sodium channel blockers, its potent glutamate uptake activator activity seems to mediate many of its effects [7,8].



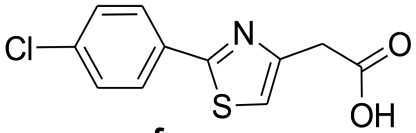
d

Tiabendazole *(e)* is a fungicide and parasiticide and use in treatment of Aspergillus has been reported [9]. It controls roundworms [10], hookworms, and other helminth species which attack wild animals, livestock and humans [11].



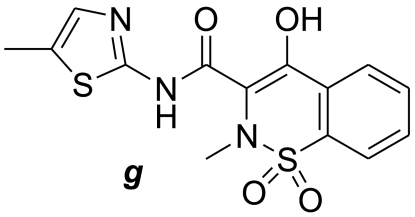
e

Fenclozic acid *(f)* is an analgesic, antipyretic and anti-inflammatory drug [12].



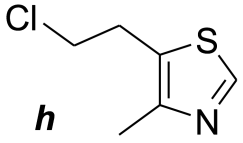
f

Meloxicam *(g)* is a nonsteroidal, anti-inflammatory drug. Meloxicam selectively inhibits COX-2 over COX-1 [13].



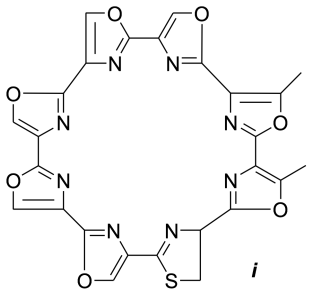
g

Clomethiazole *(h)* is a sedative and hypnotic used in treating and preventing symptoms of acute alcohol withdrawal. It acts like a sedative, hypnotic, muscle relaxant and anticonvulsant. It is also used for the management of agitation, restlessness, short-terminsomnia and Parkinson's disease in the elderly [14,15].



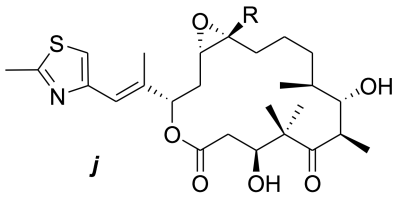
h

Telomestatin *(i)* is a macrocyclic chemical compound that acts by inhibiting the telomerase activity of the cancer cells [16]. There will be a decrease in the activity of the telomerase, which is involved in the replication of the telomeres and as a result the cell dies due to Hayflick type senescence.



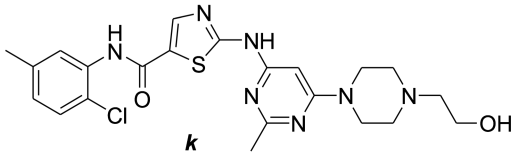
i

Ixabepilone *(j)* is an epothilone B analog [17] developed as a cancer drug produced by *Sorangium cellulosum* [18]. Ixabepilone, in combination with capecitabine, has demonstrated effectiveness in the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline and a taxane [19]. It has been investigated for use in treatment of non-Hodgkin's lymphoma [20]. Epothilones prevent cancer cells from dividing by interfering with tubulin [21].



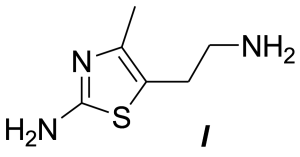
j

Dasatinib *(k)* is a cancer drug of Src family of tyrosine kinases inhibitor approved for use in patients with chronic myelogenous leukemia (CML). It is being evaluated for use in numerous other cancers, including advanced prostate cancer [22].



k

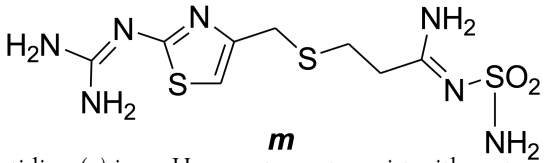
Amthamine *(l)* is a histamine agonist selective for the H_2 subtype [23]. It has been used *invitro* and *invivo* to study gastric secretion [24], as well as other functions of the H_2 receptor [25-27].



l

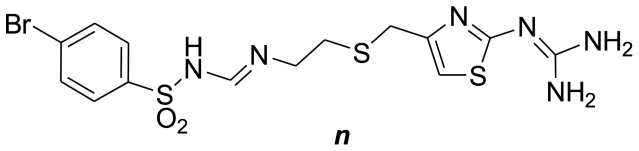
Famotidine *(m)* is a histamine H_2 receptor antagonist that inhibits stomach acid production and it is commonly used in the treatment of peptic ulcer disease and gastroesophageal reflux disease. Famotidine is given to surgery patients before operations to prevent post-operation nausea and to reduce the risk of aspiration pneumonitis. It serves as an alternative to Proton-pump inhibitor. Famotidine has also been used in combination with an H_1 antagonist to treat and prevent urticaria caused by an

acute allergic reaction [28].



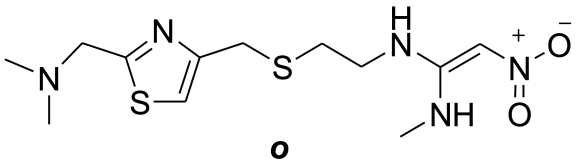
m

Ebrotidine (*n*) is an H_2 receptor antagonist with gastroprotective activity. It has a gastro-protective action against ethanol-, aspirin- or stress-induced gastric mucosal damage. Ebrotidine has anti-*Helicobacter pylori* activity *via* inhibition of the urease enzyme and the proteolytic and mucolytic activities of the bacterium. Ebrotidine is used for the treatment of gastric or duodenal ulcers or erosive reflux oesophagitis, with significantly better ulcer healing rates in those who smoke [29].



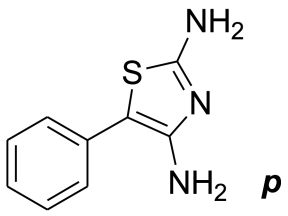
n

Nizatidine (*o*) is a histamine H_2 receptor antagonist that inhibits stomach acid production and commonly used in the treatment of peptic ulcer disease and gastroesophageal reflux disease. Nizatadine has been used to control weight gain associated with some antipsychotic medication [30].



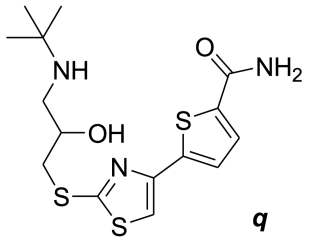
o

Amiphenazole (*p*) is a respiratory stimulant traditionally used as an antidote for barbiturate or opiate overdose, usually in combination with bemegride [31,32], as well as poisoning from other sedative drugs [33,34] and treatment of respiratory failure from other causes [35]. It was considered particularly useful as it could counteract the sedation and respiratory depression produced by morphine but with less effect on analgesia [36,37]. It is still rarely used in medicine in some countries, although it has largely been replaced by more effective respiratory stimulants such as doxapram and specific opioid antagonists such as naloxone [38].



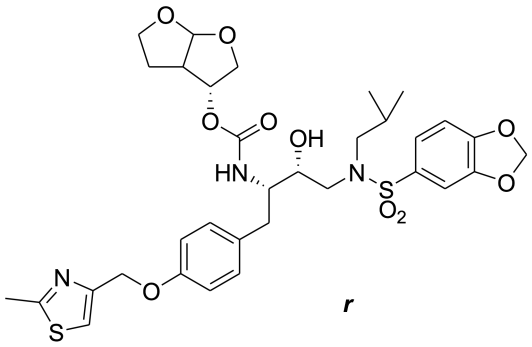
p

Arotinolol (*q*) is a medication in the class of mixed alpha/beta blockers used in the treatment of high blood pressure [39,40]. It has been proposed for use in treatment of essential tremor [41].



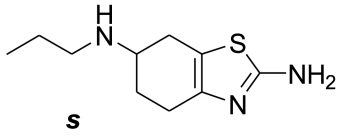
q

Brecanavir (*r*) is a protease inhibitor which has been used for the treatment of HIV [42].



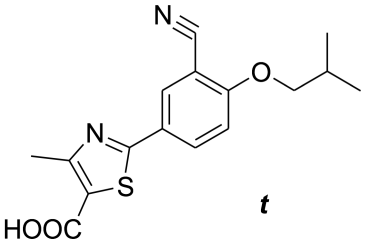
r

Pramipexole (*s*) is a non-ergoline dopamine agonist indicated for treating early-stage Parkinson's disease and restless legs syndrome. It is used to counteract the problems with sexual dysfunction [43]. It is also being investigated for the treatment of clinical depression and fibromyalgia [44-46].



s

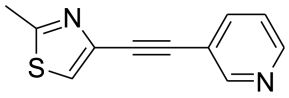
Febuxostat (*t*) is an inhibitor of xanthine oxidase that is indicated for use in the treatment of hyperuricemia and gout [47]. Febuxostat decreases levels of uric acid [48].



t

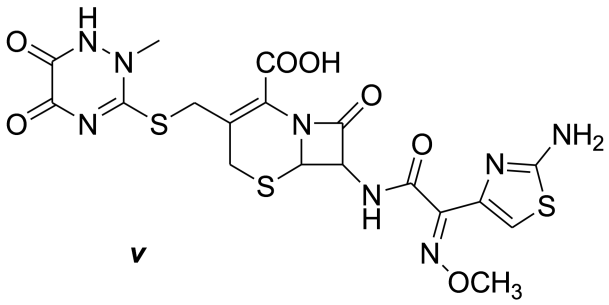
3-((2-Methyl-4-thiazolyl)ethynyl)pyridine (*u*) acts as a selective allosteric antagonist of the metabotropic glutamate receptor subtype $mGluR_5$ [49]. It is more potent and more selective as a $mGluR_5$ antagonist [50] and produces similar neuroprotective [51], antidepressant [52], analgesic [53,54] and anxiolytic effects [55]. It has anti-addictive effects in a variety of animal models

[56] and also decreasing the addictive effects of nicotine, cocaine and methamphetamine [57].



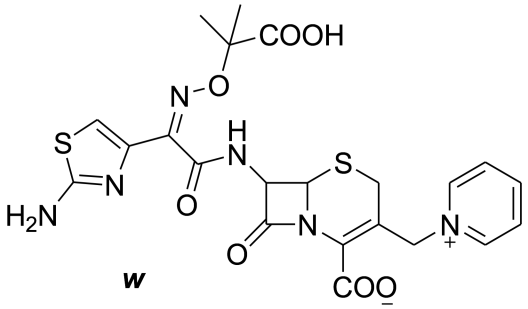
u

Ceftriaxone (*v*) is a third-generation cephalosporin antibiotic having broad spectrum activity against Gram-positive and Gram-negative bacteria. Ceftriaxone is often used for the treatment of community-acquired or mild to moderate health care-associated pneumonia. It is also a choice drug for treatment of bacterial meningitis. In pediatrics, it is commonly used in febrile infants between 4 and 8 weeks of age who are admitted to the hospital to exclude sepsis. It is also used for the treatment of gonorrhea [58]. Ceftriaxone has also been investigated for efficacy in preventing relapse to cocaine addiction [59].



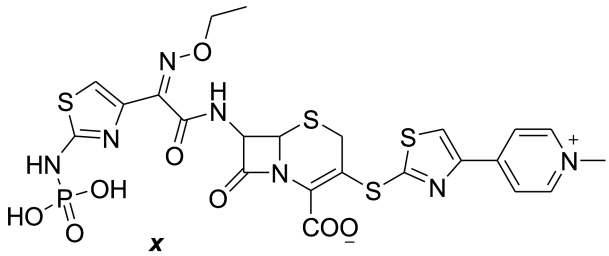
v

Ceftazidime (*w*) is a third-generation cephalosporin antibiotic having broad spectrum activity against Gram-positive and Gram-negative bacteria. Ceftazidime is usually reserved for the treatment of infections caused by Pseudomonas aeruginosa. It is also used in the empirical therapy of febrile neutropenia, in combination with other antibiotics. It is used in infection severity, and/or renal function of the recipient. Ceftazidine is first line treatment for the rare tropical infection, melioidosis [60].



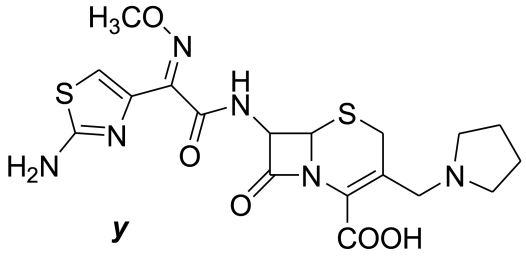
w

Ceftaroline fosamil (*x*) is an advanced generation [61] cephalosporin antibiotic active against methicillin resistant Staphy*lococcus aureus* and Gram positive bacteria. It retains the activity of later generation cephalosporins having broad spectrum activity against Gram negative bacteria. It is currently being investigated for community acquired pneumonia and complicated skin and skin structure infection [62]. It is also used for the treatment of community-acquired bacterial pneumonia



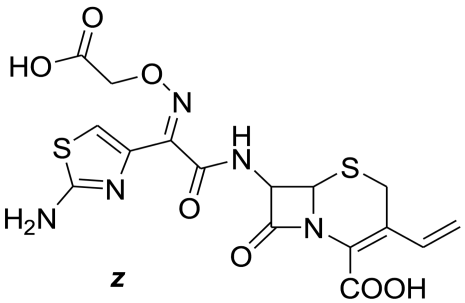
x

Cefepime (*y*) is a fourth-generation cephalosporin antibiotic having extended spectrum of activity against Gram-positive and Gram-negative bacteria [64]. Cefepime is usually reserved to treat moderate to severe nosocomial pneumonia, infections caused by multi-resistant microorganisms and empirical treatment of febrile neutropenia [65].



y

Cefixime (*z*) is an oral third generation cephalosporin antibiotic used to treat gonorrhea [66], tonsillitis and pharyngitis [67].



z

Conclusion

Thiazoles occupy a distinct and unique place in our life. This heterocyclic moiety has great biological and medicinal significance. A large number of thiazole drugs possess a variety of medicinal properties. These properties include amyotrophic lateral sclerosis, Fungicide and parasiticide, NSAIDs, Sedative and hypnotic, anticancer, histaminic agonists, antihistaminic, respiratory stimulant, alpha/beta blockers, protease inhibitor, dopamine agonist, xanthine oxidase inhibitor, metabotropic glutamate receptor subtype $mGluR_5$ antagonist, antibacterials, antihelmintic and veterinary use.

Abbreviations

COX-1: Cyclo-oxygenase-1; COX-2: Cyclo-oxygenase-2; HIV: Human Immunodeficiency Virus; $mGluR_5$: Metabotropic glutamate receptor 5; NSAIDs: Non-steroidal Anti-inflammatory Drugs; TTX: Tetrodotoxin.

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