Indo Global Journal of Pharmaceutical Sciences, 2019; 9(1): 42-53

INDO GLOBAL JOURNAL OF PHARMACEUTICAL SCIENCES
ISSN 2249- 1023

A Review on the Urease Inhibition Potential of Various Compounds

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Received: 22.07.2018
Accepted: 05.02.2019

Keywords
Urease; Urease inhibitors; Gallic acid derivatives.

ABSTRACT: Urease is a nickel containing metalloenzyme which is found in many bacteria, fungi, algae, plants, soil and some invertibrates. Urease catalyzes the hydrolysis of urea causing a pH increase of its environment which may be noxious for human tissues and causes many serious disorders/diseases. In this context, a number of natural and synthetic urease inhibitors were reviewed. There are a number of gallic acid derivatives which have different pharmacological activities reviewed from the literature.

Cite this article as: Parvinder; Kakkar, S.; Khatkar, A. A review on the urease inhibition potential of various compounds. Indo Global J. Pharm. Sci., 2019; 9(1): 42-53. **DOI**: http://doi.org/10.35652/IGJPS.2019.9106 .

INTRODUCTION

Urease (EC 3.5.1.5) is a nickel containing metalloenzyme of high molecular weight [1] belonging to the superfamily of amidohydrolases and phosphotriesterases [2]. *Urease* was the first crystallized enzymatic protein [3] which is found in many bacteria [1], fungi [4], algae, plants [5] and some invertibrates [6] as well as in soil, as a soil enzyme. It is widely distributed in soil, water, human and animal body [1].

Urease catalyzes the hydrolysis of urea ~10^{15} times superior than the rate of uncatalyzed reaction [7] in which it produces ammonia and carbonic acid causing a pH increase of its environment [8]. Excess production of ammonia via urea hydrolysis, may be noxious for human tissues [9,10] and causes many serious disorders/diseases which include urinary stones occurrence and catheters blocking, pyelonephritis, ammonia and hepatic encephalopathy, hepatic coma [11,12] rheumatoid arthritis or atherosclerosis as well as cardiovascular disease [13]. *Urease* also contributes in the ecological cycling of a variety of nitrogen compounds, in addition to urea based fertilizers. In disparity to the pathogenic property of microbial *ureases*, these are significant enzymes in ruminant metabolism and in ecological conversions of definite nitrogenous compounds [1]. It is found in human sera as an immunogenic protein and acts as antibodies. *Urease* is also used for diagnostic purposes in the diagnosis of several bacteria like *Helicobacter pylori* [14,15]. *Helicobacter pylori* get benefits of the increase in pH to stay alive in the acidic environment of the host's stomach, as a result causes stomach ulcers, after a while leading to cancer [16,17].

From a very long time natural products are used as a source of medicines [18]. Amongst wide range of natural products phenolic acids are compounds of huge importance having broad range of biological activities [19]. Phenolic acids belong to non-flavonoid family having large number of phenolic compounds [20] which get absorbed rapidly after oral, parentral administration [21]. Among all the phenolic acid contents gallic acid is a compound of great interest as it possesses a number of biological activities like antioxidant [22], antimicrobial [23], anti-inflammatory [24], antitumour [25] and antidiabetic [26].

Gallic acid is a trihydroxybenzoic acid, also known as 3,4,5-trihydroxybenzoic acid. It occurs as a white, yellowish-white, or pale fawn-colored crystals having molar mass – 170.12 g/mol and molecular formula $C_7H_6O_5$. It is obtained from

gallnuts, sumac, witch hazel, tea leaves, oak bark, and some other plants [25].

INHIBITORS OF *UREASE* ENZYME

Implications of the *urease* are mounting in the developing countries, while in some parts of the world more than 50% of the population is reported to be infected with *helicobacter pylori* [27]. Due to the assorted functions of *urease* enzyme, its inhibition by potent and specific compounds could lead to the treatment of infections caused by *urease*-producing bacteria [28]. There are many reported natural *urease* inhibitors which are given in (**Table 1**):

S.No.	Source	Family/ Category	Part used/ Phytoconstituents	Model	References
1.	*Artemisia scoparia*	Asteraceae	Shoot extracts	*Canavalia ensiformis*	[29]
2.	*Rheum ribes*	Polygonaceae	Root extracts	-	[30]
3.	*Sambucus ebulus*	Adoxaceae	Fruit extracts	-	[30]
4.	*Camelia sinensis*	Thaceae	Leaf extracts	*Helicobacter Pylori*	[31]
5	*Matricaria recutita*	Asteraceae	Flower extracts	*Helicobacter Pylori*	[31]
6.	*Fagonia arabica*	Zygophyllaceae	Whole plant extracts	*Helicobacter Pylori*	[32]
7.	*Lonicera japonica*	Caprifoliaceae	Flower extracts	*Helicobacter Pylori*	[33]
8.	*Brassica oleraceae*	Brassicaceae	Cabbage juice	Jack bean urease	[34]
9.	*Vernonia cinerascens*	Terpenoids	Root extracts (Vernonione 3β-acetoxy-5α-angeloyloxy-7-deoxy-carvotacetone)	Jack bean urease	[35]
10.	*Plumeria rubra*	Terpenoids	Plant extracts (Rubrajaleelol & Rubrajaleelic acid)	Human urease	[36]
11.	*Zygophyllum fabago linn*	Terpenoids	Ariel part (Zygofaboside A)	*Bacillus pasteurii*	[29]
12.	*Stereospermum acuminatissimum k. schum*	Phenols	Stem (Syringaldehyde)	Jack bean urease	[37]
13.	*Paeonia lactiflora*	Phenolic acids	Root extracts (Methyl gallate & 1,2,3,4,6-Penta-o-galloyl-β-D-glucopyranose)	*Helicobacter Pylori*	[38]
14.	*Stereospermumacumin atissimum k. schum*	Phenolic acids	Stem bark (Atranorin & Ellagic acid)	Jack bean urease	[37]
15.	*Mallotus philippensis*	Phenolic acids	Bark extracts (Bergenin)	*Bacillus pasteurii*	[39]
16.	*Daphne retusa*	Flavones & their glycosides	Plant extracts (5,7-Dihydroxyflavone)	Jack bean urease	[40]
17.	*Scutellaria glucuronide*	Flavones O-glycosides	Root extracts (Baicalin)	Jack bean urease	[41]
18.	*Erigeron breviscapus*	Flavones O-glycosides	Scutellarin	Jack bean urease	[42]
19.	*Hypericum oblongifolium*	Xanthones	Root extract (Hypericorin C and 1,2-Dihydroxy-8-methoxyxanthone)	Jack bean urease	[43]
20.	*Corydalis govaniana*	Alkaloids	Plant extract (Govaniadine,Caseadine,Caseamine and Protopine)	Jack bean urease	[44]
21.	*Lawsonia alba lam*	Quinones	Stem extract (2-(β-D-glucopyranosyloxy)-1,4-naphthoquinone	Jack bean urease	[45]
22.	*Viola betonicifolia*	Quinones	Plant extract (3-Methoxydalbergione)	*Bacillus pasteurii*	[46]
23.	*Pityriasis rubra*	Iridoids	Rubradoid,Plumieride p-z-coumarate	Human urease	[36]
24.	*Pityriasis rubra*	Sphingolipids	Rubranin	Human urease	[36]
25.	*Indigofera gerardiana*	Phenols	Plant extracts (Indigoferin-B & Indigoferin-C)	Jack bean urease	[47]
26.	*Vernonia cinerascens*	Phenols	Herb extracts (2-Hydroxy-3-methoxy-5-(2-propenyl)-phenol)	Jack bean urease	[35]
27.	*Vitis vinifera*	Stilbenes	Resveratrol	*Helicobacter Pylori*	[48]
28.	*Celtis africana*	Flavones C-glycosides	Vitexin,Orientin & Isoswertisin	Jack bean urease	[49]

Table 1: Natural Inhibitors of *urease* enzyme

Synthetic *urease* inhibitors contain (**Table-2**):

Sr. No.	Chemical constituents	Model	References
1.	3,4,5-Trihydroxybenzohydrazone	Jack bean urease	[50]
2.	Carbazole substituted pyrimidine derivatives	Jack bean urease	[51]
3.	Barbituric acid derivatives	Jack bean urease	[52]
4.	2,5-Substituted-1,4-benzoquinone	*Helicobacter Pylori*	[53]
5.	Hydroxamic acids	*Helicobacter Pylori*	[54]
6.	Isatin derived bis-schiff bases and their copper complexes	Jack bean urease	[55]
7.	1,3,4-Oxadiazole derivatives	Jack bean urease	[56]
8.	Substituted aminomethane p-hydroxymethyl-phosphonic acids		[57]
9.	5,6-Dihydropyridine derivatives	Jack bean urease	[58]
10.	N-analogs of 1,2-diarylethane	*Helicobacter Pylori*	[59]
11.	3-Arylpropionylhydroxamic acid derivatives	*Helicobacter Pylori*	[60]
12.	1,2-Benzisoselenazol-3-one derivatives	*Sporosarcina Pasteurii* and *Helicobacter Pylori*	[61]
13.	β-Hydroxy-β-phenylpropionyl-hydroxamic acid	*Helicobacter Pylori*	[33]
14.	2-Methoxybenzoylhydrazones	-	[62]
15.	Oxindole derivatives	-	[63]
16.	Benzothiazole derivatives	*Helicobacter Pylori*	[64]

Table 2: Synthetic Inhibitors of *urease* enzyme

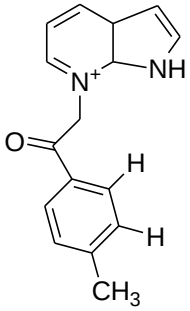
Pharmacological activities of gallic acid derivatives (**Table-3**):

Sr. No.	Chemical constituents	Biological activity	References
1.	4 Medicinal plant extracts [guava (*Psidium guajava*) leaf, capillary wormwood (*Artemisia capillaries* Thunb.), Chinese goldthread (*Coptis chinensis*), and dandelion (*Taraxacum platycarpum*)]	Anti-inflammatory	[24]
2.	Gallic acid based steroidal phenstatin analogues	Anticancer	[25]
3.	Gallic acid purified from *Terminalia nigrovenulosa* bark against *Fusarium solani*	Antifungal	[12]
4.	A bioactive derivative of chitooligosaccharides was synthesized via grafting of gallic acid onto chitooligosaccharides (G-COS)	Antiallergic	[65]
5.	Gallic acid and catechin against *Helicobacter pylori* by an agar-well diffusion method	Antimicrobial	[23]
6.	3,4,5-Trihydroxybenzoic acid, a major bioactive polyphenol present in Cyamopsis tetragonoloba, exhibited antihyperglycemic activity.	Antidiabetic	[26]
7.	Ellagic acid	Antioxidant	[22]
8.	Chitosan-gallic acid films by the log reduction method	Antimicrobial	[66]
9.	Quinolin-8-yl 3,4,5-trihydroxybenzoate	Antimicrobial	[67]

Table 3: Different pharmacological activities of gallic acid derivatives

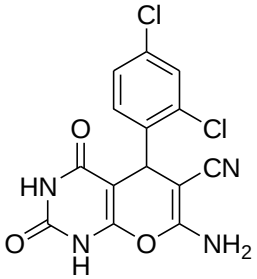
BIOLOGICAL PROFILE OF *UREASE* INHIBITORS

Saify *et al*., studied the synthesis of (1*H*-pyrrolo [2,3-*b*] pyridine) 7-azaindole derivatives and screened for their *urease*, phosphodiesterase and beta-glucuronidase inhibitory activity. *Urease* inhibitory activity was measured by using the indophenols method. Beta-glucuronidase inhibitory activity was measured by using the spectrophotmetric method. Phosphodiesterase inhibitory activity was determined by using the lysophospholipids. Out of all 7-azaindole derivatives, compound 7-[2-(4-methoxy-phenyl)-2-oxo-ethyl]-1*H*-pyrrolo[2,3-*b*]pyridine-7-ium (1) with IC_{50}=2.19 ± 0.37µM was found to be highly active against jack bean urease as compared with reference drug thiourea (IC_{50}=21.00 ± 0.01µM) [68].



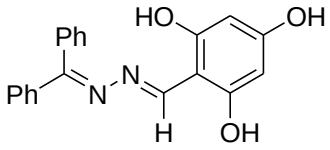
(1)

Ziarani *et al*., synthesized the pyrano (2,3-*d*)-pyrimidine dione derivatives facilitated by sulfonic acid nanoporous silica (SBA-Pr-SO_3H) as a nanocatalyst. These derivatives were screened for their *urease* inhibitory potential using the indophenols method. Binding free energies of the pyrano (2,3-*d*)-pyrimidine derivatives revealed that out of all derivatives, 7-amino-5-(2,4-dichlorophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1*H*-pyrano [2,3-*d*] pyridine-6-carbonitirile (2) was found to be most active with IC_{50}=19.45µM, when compared with standard drug thiourea with IC_{50}=21 µM [69].



(2)

Khan *et al*., synthesized the benzophenone hydrazone derivatives and screened for them antioxidant and *urease* inhibition activities. Antioxidant activity of synthesized compounds was determined by using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) mehod. *Urease* inhibition activity was measured by using the indophenol method. Studies revealed that 2,4,6-trihydroxy substituted (3) and 2,6-dihydroxy substituted (4) derivatives showed potent activity against jack bean urease with IC_{50}=36.36 ± 0.94µM, and 55.5 ± 0.69µM respectively as compared with standard drug thiourea with IC_{50}=21 ± 0.11µM [70].



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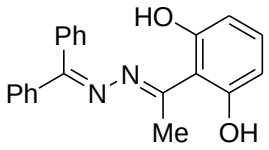
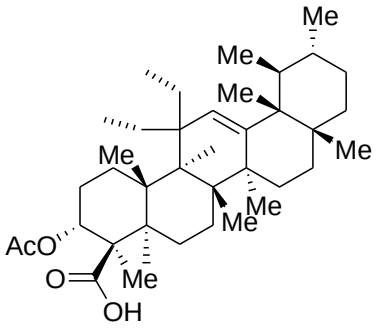


(4)

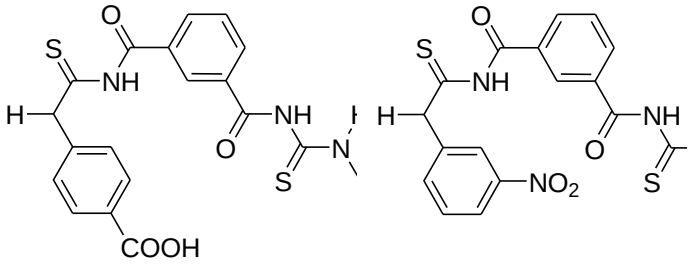
Ahmed *et al*., studied the methanolic extract and sub-fractions in different solvents of *Melilotus indicus* (Linn.) All., these extracts or fractions were evaluated for α-*amylase* and *urease* inhibition activities. *Urease* inhibition potential was measured by using the Indophenols method. Studies revealed that chloroform fraction showed the potent activity with IC_{50}=0.89µM against jack bean urease compared with positive control thiourea with IC_{50}=0.97µM [71].

Golbabaei *et al*., studied the four β-boswilic acid derivatives isolated from *Baswellia carterii*. These compounds were charaacterised by NMR and Mass spectroscopic techniques and were screened for their *urease* inhibitory potential. Docking and pharmacophore analysis were performed by using Autodock 4.2 and ligandscout 3.03 programs to measure the possible interaction between isolated compounds and *urease* enzyme. *Urease* inhibition activity was determined by using the indophenols method. Studies revealed that compound (3R,4R,4aR,6aS,6bS,8aR,11R,12S,12aR,14aS,14bS)-3-acetoxy-14,14-diethyl 4,4a,6a,6b,8a,11,12,12a,14a,14b-decamethyl-1,2,3,4,4a,5,6,6a,7,8,8a,9,10,11,12,12a,14,14a,14b-icosahydropicene-4-carboxylic acid (5) showed the potent activity with IC_{50}=6.27 ± 0.03µM, when compared with the positive control thiourea with IC_{50}=21.1 ± 0.3µM against jack bean urease [72].



(5)

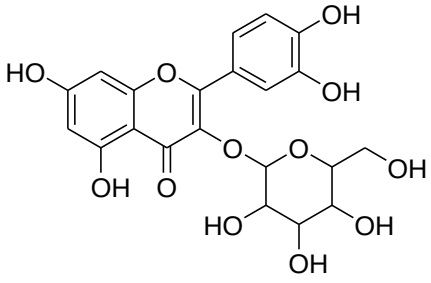
Jamil *et al*., synthesized a number of N^3, $N^{3'}$–*bis*-(disubstituted) isophthalyl-*bis*-(thioureas) derivatives and characterized by using the elemental analysis, infrared and ^1H NMR spectroscopy. The synthesized compounds were evaluated for antibacterial and antiurease activities. Antibacterial potential was measured by using the disc diffusion method against some Gram positive and Gram negative bacteria. *Urease* inhibition activity was measured by using the indophenol method. Studies revealed that out of all bis-thiourea derivatives compounds N^3,$N^{3'}$-*bis*-(4-carboxyphenyl)isophthalyl-*bis*-(thiourea) (6), N^3,$N^{3'}$-*bis*-(3-nitrophenyl)isophthalyl-*bis*-(thiourea) (7), showed potent activity, exhibiting IC_{50}=26.3 ± 0.5µM and 26.7 ± 0.5µM against jack bean urease compared with thiourea IC_{50}=21.1 ± 0.1µM. It was also found that some derivatives had potent anti-bacterial activity [73].



(6)

(7)

Ullah *et al*., evaluated the *urease* inhibitory capacity of extract/fractions and isolated compounds of *Monotheca buxifolia* fruit. *Urease* inhibiting activity was determined by using the indophinol method and their molecular docking studies. Out of all extract/fractions, ethyl acetate fraction showed the maximum inhibition of 61.7% compared with thiourea 98.2% and from isolated compounds isoquercetin (8) exhibiting IC_{50}=51.6 ± 1.46µM showed maximum potential when compared with thiourea exhibiting IC_{50}=21 ± 0.11µM against jack bean urease. After evaluated the compounds it was proved that *Monotheca buxifolia* fruit was very useful in gastritis and urinary tract infections [74].



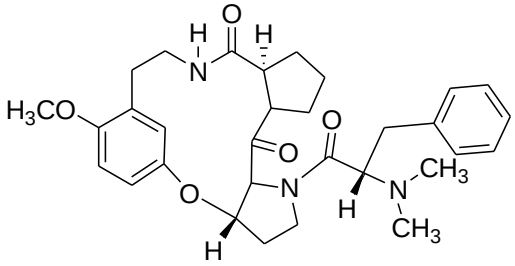
(8)

Ahmed *et al*., studied the phenolic content, *urease* and α-*amylase* inhibitory potentials of methanolic extracts of *Rumex acetosella* roots and its fractions in different solvents. The methanolic extract and its fractions in chloroform, ethyl acetate, n-butanol and water were evaluated for their *urease* and α-*amylase* inhibitory activities. Total phenolic content was determined by using the Folin-ciocalten calorimetric method. α-*amylase* inhibitory potential was measured in comparison with the positive control acarbose. *Urease* inhibitory potential was determined by using the indophenols method. Studies revealed that aqueous fraction of methanolic extract of *Rumex acetosella* roots showed potent activity i.e. 97.36 ± 0.13% inhibition at 20µg/ml against jack bean urease when compared with standard drug thiourea which showed 95.03 ± 3.94% inhibition at 20µg/ml [75].

Sr. No.	Extracts/Fraction	IC_{50} (µg/ml)
1.	Crude methanolic extracts	0.99
2.	Chloroform	3.89
3.	Ethyl acetate	1.76
4.	n-Butanol	0.91
5.	Aqueous	0.85
6.	Thiourea	0.97

Table 4: IC_{50} values of extract/fractions

Kaleem *et al*., studied the *urease* inhibitory potential of *Zizyphus oxyphylla* edgew. extracts and isolated compounds. Methanolic extracts and some fractions were obtained from the stem and three compounds were isolated from the roots by using the column chromatography. These compounds were screened for their *urease* inhibition capacity using indophenol method. Studies revealed that extracts obtained from the *zizyphus* stem, ethyl acetate fraction showed the maximum inhibition of 86.7 ± 0.03% when compared with the standard drug thiourea which showed *urease* inhibition of 98.1 ± 0.02%. Out of all isolated compounds from the roots of *zizyphus oxyphylla*, oxyphylline(D) (9) with IC_{50}=420.1 ± 1.22µM showed the potent inhibitory activity compared with thiourea with IC_{50}=21 ± 0.011µM against jack bean urease [76].



(9)

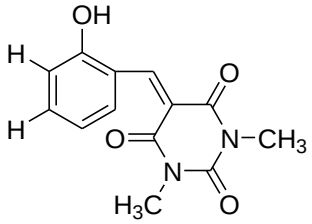
Sr. No.	Compounds	Percentage Inhibition
1.	Oxyphylline(D)	58.2±0.02
2.	Nummularin(C)	29.3±0.01
3.	Nummularin (R)	35.7±0.02
4.	Thiourea	98.1±0.2

Table 5 : Percentage inhibition of isolated compounds

Zahid *et al*., studied the antioxidant and *urease* inhibition activity of methanolic extracts of *Hibiscus schizopetalus* (Mask) Hook. Antioxidant assay was performed using the DPPH radical scavenging and nitric oxide scavenging activity. *Urease* inhibition potential was determined by using the indophenol method. Studies revealed that *Hibiscus schizopetalus* flower extracts showed the maximum inhibition capacity of 55.5% with IC_{50} =80.1 ± 0.87µg/ml, when compared with the standard drug thiourea which showed inhibition of 98.2% with IC_{50} =88.2 ± 0.1µg/ml, and ascorbic acid showed 81.02% inhibition against jack bean urease, where as *Hibiscus schizopetalus* leaves extracts showed the minimum inhibition activity i.e. 22.2%. Extracts obtained from *Hibiscus schizopetalus* (Mask) Hook were found to be useful in gastric and urinary tract infections [77].

Khan *et al*., studied the aerial parts of *Artemisia scoparia* including crude methanolic extract, extracts of sterols, flavonoids and aqueous fraction. These parts are evaluated for *urease* inhibition activity using *in-vitro* study. Drugs synthesized from *Artemisia scoparia* are being used in the treatment of ulcers. *Urease* inhibition activity was measured by determining the production of ammonia using indophenols method. Studies revealed that flavanoidal extracts with IC_{50} =2.10 ± 0.01mg/ml showed higher inhibition activity against jack bean urease when compared with standard drug thiourea which showed dose dependent activity with maximum inhibition of 91% at 100µg/ml and flavanoidal extracts showed maximum inhibition of 86.17% at 10mg/ml, whereas sterol extracts showed least *urease* inhibition activity with IC_{50} =8.04 ± 0.09mg/ml [29].

Sokmen *et al*., carried out the synthesis of derivatives of arylidene barbiturates and these compounds were investigated for their antiurease, antibacterial, and antioxidant potential. *Urease* inhibition activity was determined by using indophenol method. Studies revealed that compounds 5-(2-hydroxybenzylidene)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (10) and 5-(3-hydroxybenzylidene)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (11) with IC_{50}=0.036 ± 0.002µM and 0.033 ± 0.151µM respectively showed potent activity, when compared with the standard drug thiourea with IC_{50}=8.825 ± 1.601µM and hydroxyurea with IC_{50}=7.418 ± 0.012µM against jack bean urease. Some synthesized derivatives of arylidene barbiturates showed good antibacterial and antioxidant activities. Because of their good antiurease, antibacterial, and antiurease activity, the synthesized *arylidene* barbiturates can be used in the industries and agriculture [78].



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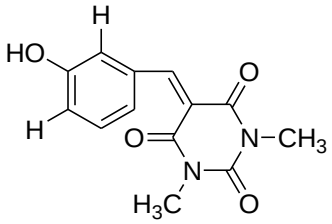
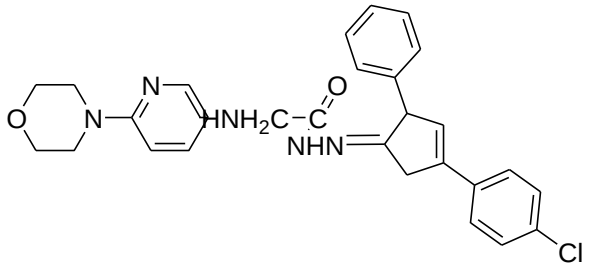


(11)

Bektas *et al*., synthesized morpholine derivatives containing an azole ring from the starting compound 6-morpholin-4-ylpyridin-3-amine. Structures of morpholine derivatives were elucidated by using FTIR, EIMS, ^{1}H-NMR, ^{13}C-NMR spectroscopic techniques and elemental analysis. Synthesized derivatives were evaluated for their *urease* inhibition and antimicrobial potentials. Studies revealed that few derivatives were found to have good *urease* inhibition and antimicrobial potentials against *Mycobacterium smegmatis*, *Candida albicans*, and *Saccharomyces cerevisiae*. Compound *N*'-((5-(4-chlorophenyl)-3-phenyl-1,3-thiazole-2(3*H*)-ylidene)-2-((6-morpholine-4-ylpyridin-3-yl)amino)acetohydrazide (12) showed potent *urease* inhibition activity with IC_{50}=2.37 ± 0.19µM [79].



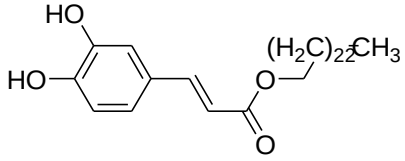
(12)

Amin et *al*., carried out the anti-*helicobacter pylori* and *urease* inhibition potentials of some traditional medicinal plants like *Acacia nilotica* (L) Delile, *Calotropis procera* (W.T.) Aiton, *Adhatoda vasica Nees*, *Fagoniaar abica* L. and *Casuarinas equisetifolia* L. etc. Methanol, acetone and water extracts of the plants were evaluated by phenol red method for determination of their *helicobacter pylori* and *urease* inhibition activities. Agar dilution method was used to obtaine the minimum inhibitory concentration (MIC) of the plants extracts and compared with standard antibiotics like amoxicillin, clarithromycin, tetracycline and metronidazole. Methanol and acetone extracts of some medicinal plants showed stronger anti-*helicobacter pylori* activity like *Acacia*

nilotica calotropis plant than metronidazole and approximately similar activity as tetracycline [32].

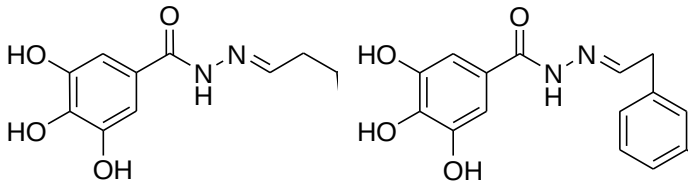
Lateef *et al*., evaluated the roots of *Glycyrrhiza glabra* for antioxidant and *urease* inhibition activities. Methanolic extract was used for *urease* inhibition activity. Ethyl acetate, chloroform and butanol were used for fractionation of methanolic extracts. Antioxidant acivity was measured by using the DPPH radical scavenging activity. *Urease* inhibition activity was measured by using indophenol method. Out of all fractions, ethylacetate fraction showed the maximum inhibition i.e. 72% when compared with the standard drug thiourea which showed 94% inhibition against jack bean urease. Studies revealed that roots of *Glycyrrhiza glabra* is a potential source of antioxidant and *urease* inhibitors. Thus, our study validated the traditional use of *Glycyrrhiza glabra* in the treatment of ulcer [80].

Arfan *et al*., carried out the *urease* inhibition activity of the compounds isolated from *Hypericum oblongifolium* WALL. Various fractions were obtained after extraction with hexane (F_1), ethyl acetate (F_2), and methanol. Methanolic fraction was further extracted with n-butanol after suspending in water and obtained fractions of butanol (F_3) and water (F_4). Three compounds were isolated from fractionation of *Hypericum oblongifolium*. Structures of these derivatives were screened by NMR and mass spectroscopic techniques. *Urease* inhibition activity was measured by using the indophenols method against jack bean urease. Studies revealed that ethyl acetate and water fractions showed potent inhibitory activity with IC_{50}= 140.37 ± 1.93 and 167.43 ± 3.03 µM, when compared with standard inhibitor thiourea with IC_{50}=21.01 ± 0.51 µM. Out of all isolated compounds, tetracosyl 3-(3,4-dihydroxyphenyl) acrylate (13) was observed to show highest *urease* inhibitory activity with IC_{50}=20.96 ± 0.93 µM [81].



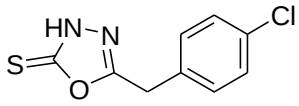
(13)

Taha *et al*., synthesized the 3,4,5-trihydroxybenzohydrazones from 3,4,5-trihydroxybenzohydrazide and evaluated them for *urease* inhibition activity. 3,4,5-trihydroxybenzohdrazide was synthesized from methyl-3,4,5-trihydroxybenzoate after refluxing with hydrazine hydrate. All synthesized derivatives were characterized by NMR and mass spectroscopic techniques. *Urease* inhibition activity was determined by using the indophenol mehod. Kinetic studies showed that (*E*)-*N*'-(furan-2-ylmethylene)-3,4,5-trihydroxybenzohydrazide (14) and (*E*)-3,4,5-trihydroxy-*N*-(3-hydroxybenzylidene) benzohydrazide (15) derivatives had potent inhibitory activities with IC_{50}=28.09 ± 1.2 µM and 27.20 ± 1.2 µM against jack bean urease when compared with positive control thiourea with IC_{50}=21.20 ± 1.30 µM [63].



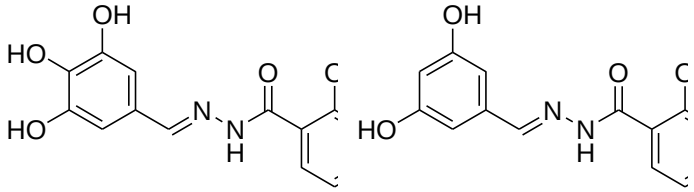
(14) (15)

Muhammad *et al*., studied the synthesis of eighteen 1,3,4-oxadiazole derivatives and these derivatives were screened for their *urease* inhibition, antioxidant, and anti-bacterial activities. *Urease* inhibition activity was measured by using indophenol method. Molecular docking studies were also performed to observed the mode of interaction of synthesized derivatives. Studies revealed that 5-(4-chlorobenzyl)-1,3,4-oxadiazole-2(3*H*)-thione (16) with IC_{50}=1.15 ± 0.2 µM was found to have potent activity against jack bean urease when compared with positive control thiourea with IC_{50}=22.3 ± 1.2 µM. Some derivatives also showed good antioxidant and antibacterial activities [46].



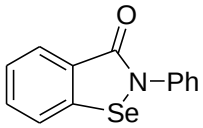
(16)

Taha *et al*., carried out the synthesis of a series of 2-methoxybenzoylhydrazone derivatives and these compounds were evaluated for *urease* and α-*glucosidase* inhibition activities. *Urease* inhibition activity was measured by using indophenol method. Studies revealed that compounds *N*'-(3,4,5-trihydroxybenzylidiene)-2-methoxybenzohydrazide (17) and *N*'-(3,5-dihydroxybenzylidene)-2-methoxybenzohydrazide (18) had potent activity with IC_{50}=21.6 ± 0.6 µM and 19.6 ± 1.0 µM when compared with positive control thiourea with IC_{50}=21.8 ± 1.6 µM. Some derivatives were found to have good α-*glucosidase* inhibition activity when compared with acarbose [62].



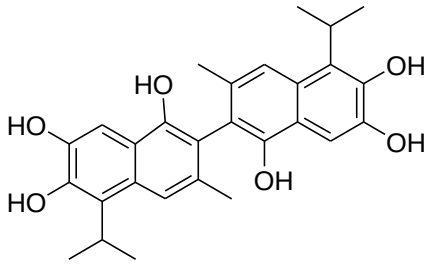
(17) (18)

Macegoniuk *et al*., studied the synthesis of 1,2-benzisoselenazol-3(2*H*)-one derivatives as inhibitors of bacterial *ureases*. These compounds were evaluated for inhibition activity against *Sporosarcina pasteurii* and *Helicobactor pylori ureases* and measured the production of ammonia using phenol-hypochlorite method. Kinetic parameters were measured by using the Michaelis-Menten equation, which gave the Ki value of compound 2-phenyl-1,2-benzisoselenazol-3(2*H*)-one (ebselen) i.e. 2.11 ± 0.18nM against *Sporosarcina pasteurii* and 226 ± 16nM against *Helicobacter pylori urease* in comparison with standard acetohydroxamic acid (*Ki* is 3300 ± 400nM). Studies indicated ebselen (19) as one of the low molecular weight inhibitor which showed potent activity against bacterial *ureases*. Studies of *urease* inhibition in whole *Helicobactor pylori* J99 strain also showed the potent activity of the studied 1,2-benzisoselenazol-3(2*H*)-one derivatives as inhibitors of bacterial *ureases* [61].



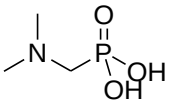
(19)

Chen *et al*., studied the derivatives of gossypol inhibitors of jack bean urease and these compounds were evaluated experimently and theoretically for inhibition activity. The binding free energies, action sites, inhibition constants and hydrogen bonds were calculated using Autodock. The binding free energies of gossypol (-4.39Kcal/mol), gossypolone (-4.91Kcal/mol), and apogossypol (-7.07Kcal/mol) were determined. *Urease* inhibition activity was determined by indophenols red method. From experimental data IC_{50} values were calculated i.e. 110µM for gossypol, 51.7µM for gossypolone and 9.8µM for apogossypol, respectively. From the docking and experimental data it was indicated that the phenolic hydroxyl groups of gossypol i.e. 1,1'-OH, gossypolone i.e. 6,6'-OH, and apogossypol i.e. 7,7'-OH played an important role in the jack bean *urease* inhibition. Out of all gossypol derivatives apogossypol (20) showed the most potent inhibitory activity against jack bean *urease* [82].

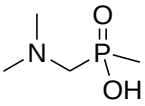


(20)

Berlicki *et al*., synthesized the *N*-substituted derivatives of aminomethanephosphonic and aminomethane-*p*-methylphosphinic acids. These derivatives were evaluated for urease inhibitior activity using indophenols method against *Canavalia ensiformis* and *Bacillus pasteurii urease*. Studies revealed compounds *N,N*-dimethylaminomethanephosphonic acid (21) and *N,N*-dimethylaminomethane-*p*-methylphosphinic acid (22) with IC_{50}=82 ± 26 and 14.4 ± 4.8µm against *Canavalia ensiformis urease*, IC_{50}=49 ± 1.7 and 3.8 ± 0.4µm against *Bacillus pasteurii urease* when compared with standard inhibitor acetohydroxamic acid with IC_{50}=64.6 ± 3µm. Whole cell activity showed that derivatives of aminomethane-*p*-methylphosphinic acid had higher inhibition activity than *N,N*-dimethyl derivatives [83].

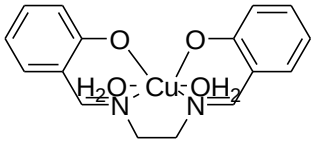


(21)



(22)

Afza *et al*., studied the schiff base ligand and its complex whose structure was characterized by elemental analysis, molar conductance, ^{1}H-NMR, FTIR and FAB-Mass spectroscopic techniques and these were evaluated for *urease* inhibition activity using indophenol method. Studies revealed that 2-{[(2-{[(*E*)-(2-hydroxyphenyl) methylidene] amino} ethyl) imino] methyl} phenol-copper (II) complex (23) with IC_{50}=19.0µM was found to be potent inhibitor when compared with positive control thiourea with IC_{50}=21.6µM [84].

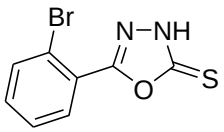


(23)

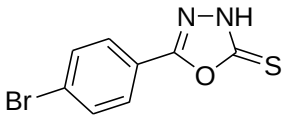
Bekiracan *et al*., studied the synthesis of new fluorine-containing 1,2,4-triazole-5-one derivatives and structure of these compounds were characterized by IR, ^{1}H and ^{13}C NMR techniques and were evaluated for antiurease, antixanthine oxidase and antioxidant activities. *Urease* inhibition activity was determined by using indophenol method. Studies revealed that compounds 4-amino-5-(2-fluorobenzyl)-2-({4-[(4-trifluoromethoxyphenylamino)methyl]-5-thioxo-1,3,4-oxadiazol-2-yl}methyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one and 4-Amino-5-(4-fluorobenzyl)-2-({4-[(4-trifluoromethoxyphenylamino)methyl]-5-thioxo-1,3,4-oxadiazol-2-yl}methyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one with IC_{50}=29.34 ± 0.36 and 28.89 ± 0.11µm were found good inhibitors of jack bean urease when compared with standard drug thiourea with IC_{50}=63.72 ± 0.23µm. Some derivatives also showed good antixanthine oxidase and antioxidant activity [85].

Shi *et al*., synthesized two Schiff base zinc (II) complexes and structure of these complexes were clarified by IR and NMR techniques. These complexes were screened for *urease* inhibition potential using indophenols method. Studies revealed that $ZnBr_2L^2$ complex showed 35.63 ± 1.45% inhibition, when compared with positive control acetohydroxamic acid which showed 88.23 ± 2.08% inhibition against jack bean urease [86].

Shahzad *et al*., studied microwave-assisted solvent free efficient synthesis of 5-substituted-1,2,4-oxadiazole-2(3*H*)-thiones derivatives which were screened for *urease* inhibition activity using indophenol method. Out of all derivatives 5(2′-bromophenyl-1,3,4-oxadiazole-2(3*H*)-thione (24) and 5(4′-bromophenyl-1,3,4-oxadiazole-2(3*H*)-thione (25) with IC_{50}=12.60 ± 0.92 and 13.03 ± 1.80µM were found most active inhibitors of jack bean urease compared with standard drug thiourea with IC_{50}=21µM [87].

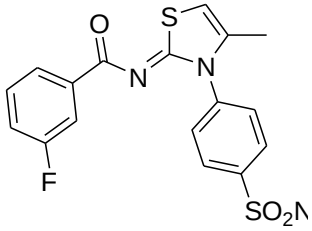


(24)

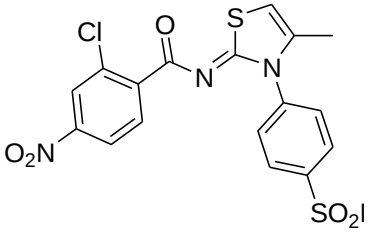


(25)

Saeed *et al*., carried out the synthesis of some iminothiazoline-sulfonamide hybrids and these derivatives were screened for *urease* inhibition potential using indophenols method. Studies revealed that (*Z*)-*N*-(3-(4-aminosulfonylphenyl)-4-methylthiazol-2(3*H*)-ylidene)-3-flourobenzamide (26) and (*Z*)-*N*-(3-(4-aminosulfonylphenyl)-4-methylthiazol-2(3*H*)-ylidene)-2-chloro-4-nitrobenzamide (27) with IC_{50}=0.064 ± 0.01 and 0.058 ± 0.011µM were found potent inhibitors of jack bean urease when compared with positive control thiourea with IC_{50}=20.9 ± 0.92µM. The kinetic mechanism studies showed that (*Z*)-*N*-(3-(4-aminosulfonylphenyl)-4-methylthiazol-2(3*H*)-ylidene)-3-flourobenzamide is a mixed type inhibitor but (*Z*)-*N*-(3-(4-aminosulfonylphenyl)-4-methylthiazol-2(3*H*)-ylidene)-2-chloro-4-nitrobenzamide is a competitive inhibitor [88].



(26)

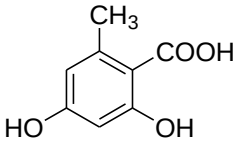


(27)

Barakat *et al*., synthesized several barbituric acid derivatives and structure of these compounds were characterized using IR, ^1H and ^{13}C NMR and mass spectroscopic techniques. These derivatives were evaluated for *urease* inhibitory activity using indophenol method. Out of all derivatives 4-((6-hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl), (6-hydroxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)benzaldehyde diethylaminium salt and 5,5′-(*p*-tolylmethylene)bis(6-hydroxypyrimidine-2,4(1*H*,3*H*)-dione) diethylaminium salt with IC_{50}=17.2 ± 0.44 and 17.6 ± 0.23µM showed excellent jack bean urease inhibiting activity when compared with positive control thiourea with IC_{50}=21.2 ± 1.3µM. Molecular dynamic stimulation was also carried out to measure the binding interaction of synthesized derivatives with *urease* which showed that enol form was more established due to their coordination [52].

You *et al*., synthesized 2,5-disubstituted-1,4-benzoquinone derivatives and the structure of these derivatives were confirmed by IR, ^1H and ^{13}C NMR and single crystal X-ray determination techniques. These derivatives were evaluated for *urease* inhibition activity using indophenol method. Studies revealed that 2,5-*bis*(2-morpholin-4-ylethylamino)-[1,4] benzoquinone with IC_{50}=27.30 ± 2.17µM was found active against *Helicobacter pylori urease*. Molecular docking studies were also carried out to analyze the binding interaction of between enzyme active centre with synthesized derivatives in which compound 2,5-*bis*(2-morpholin-4-ylethylamino)-[1,4] benzoquinone was found as potent inhibitor [53].

Thadhani *et al*., synthesized several mononuclear phenolic lichen compounds and these were evaluated for *urease* inhibition activity using indophenol method. Out of all compounds orsellinic acid (28) and orcinol (29) with IC_{50}=4.50 ± 0.14 and 11.2 ± 0.2µM were found excellent *urease* inhibitor when compared with standard inhibitor thiourea with IC_{50}=21.01 ± 0.5µM. This study proved that polyphenolic lichen compounds were potent *urease* inhibitors [89].



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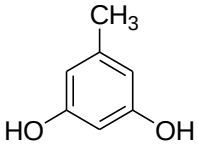

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