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Pharmacological and Biological Activities of Azetidinone models: A Brief Overview

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Abstract: ***Azetidinones represent a four-membered heterocyclic ring system with nitrogen as the heteroatom and a carbonyl group integrated within its structure. These compounds are also commonly referred to as β-lactams. Their broad-spectrum antibacterial activity encompasses both gram-positive and gram-negative bacteria. Beyond their antibacterial properties, this review also explores the antimicrobial, anti-tubercular, anti-convulsant, anti-cancer, anti-depressant, anti-inflammatory, and central nervous system (CNS) activity of azetidinones. The various pharmacological traits connected to the monocyclic 2-azetidinone moiety are the main focus of this review. The most current and pertinent references have been covered with care.***

Keywords: Azetidinones, Biological activity, Anti-bacterial

1. Introduction

The age of antibiotics is said to have begun with Sir Alexander Fleming's discovery of penicillin in 1929. Waksman offered the generally used definition of an antibiotic as a chemical produced by microbes with the ability to prevent the growth and even the destruction of other microorganisms in 1942. Controlling and preventing diseases brought on by microbes in humans becomes crucial as a result.

Azetidinones, commonly known as 2-azetidinones or -lactams, are carbonyl derivatives of azetidine that contain the carbonyl group at position 2. Despite the ring system being Although being well-known since 1907, the study of their chemistry began only in 1947. Currently, these are employed for antibiotic treatment for bacterial infections. choosing only bacterial cell wall production is inhibited is what gives it its distinct and deadly antibacterial effect [1].

The pencillins, cephalosporins, carbapenems, and monobactams are the main antibiotic families that include the beta-lactam ring, which is why these families are also known as beta-lactam antibiotics. Almost all antibiotics function by preventing the development of bacterial cell walls. Bacteria are wiped out by this.

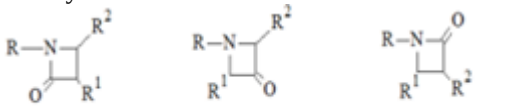
The population of bacteria does, however, contain a lesser number of germs that are resistant to beta-lactam antibiotics. They accomplish this by activating one of several beta-lactamase genes. In distinct bacterial species, more than 1000 different -lactamase enzymes have been identified. These enzymes exhibit a wide range of chemical compositions and catalytic performances. Treatment with beta-lactams can make the resistant strain more frequent and thus more virulent when bacterial populations contain these resistant subgroups.

2. Chemistry of Azetidinones

Azetidine makes up the parent heterocyclic ring of azetidinones. The hetero atom in the four-member heterocyclic ring structure of azetidine is nitrogen. The heterocyclic ring 2-azetidinone, usually referred to as a "-lactam," is one of the most prevalent heterocyclic rings discovered in antibiotics. The second position of a carbonyl group is present in 2-azetidinones.

3. Numbering of Azetidinones

Azetidin-2-one, Azetidin-3-one, and Azetidin-4-ones are all conceivable derivatives of the azetidine ring, depending on the position of the carbonyl group. The first place will be given to the heteroatom, nitrogen in the -lactam ring, and the second position will be given to the carbonyl group. For azetidin-3-ones and azetidin-4-ones, respectively, the position of the carbonyl group will be represented as 3 and 4, respectively.



4. Physical Properties

Azetidin-2-ones are a colorless, hydrolytically vulnerable solid. Their melting point is between 73 and 74 °C. Low melting solids or oils are some other straight forward azetidin-2-ones. A variety of monocyclicazetidinones were subjected to x-raycrystallographic examinations, and the results showed that, aside from places where steric constraints require significant deviations from planarity, the ring is largely planar with the N2 atomsome what off of the mean plane of its substituent's. As opposed to azetidinones, which show a distance of 1.38, typical amides show a distance of 1.32 [2].

5. Pharmacological Activity

5.1 Anti-depressant & Nootropic

Azetidinones **(4a-k)** was synthesised by the stirring and sonication methods which involves the cyclocondensation of

the Schiff's base of Isonicotinyl Hydrazone **(3a-k)** with Chloroacetyl chloride, Triethylamine. These synthesised compounds were tested for the activity on swiss albino mice. Forced swim test and tail suspension test was carried out in which the synthesised compounds **3k** and **4k** which had 2,5-dimethoxy substitution had the highest anti-depressant activity in a dose-dependent manner. Elevated plus maze test and passive avoidance test is carried out for nootropic activity. The compounds **3d** and **4d** containing a nitro group at para position showed highest nootropic activity compared to the other compounds but all the compounds showed lesser activity than the standard drug Piracetam. The synthesised compounds were found to be active against the Scopolamine-induced memory deficit. Significant nootropic activity was exhibited by all the compounds in the passive avoidance and elevated plus maze test as well [3].

Azetidinone **(23-42)** compounds was synthesised by treating the Schiff's bases of Indole compounds with Chloroacetyl chloride and triethylamine. These synthesised compounds were tested for anti-depressant activity by Forced Swim test at a definite concentration with Fluoxetine as the standard drug. The results showed that the compounds **26** (Nitro phenyl) and **36** (Chloro phenyl) was found to be more potent with 66.82 and 65.61% of inhibition respectively compared to the standard drug with inhibition of 70.93%. This revealed that presence of electron withdrawing substituent at ortho position to the phenyl ring increased the anti-depressant activity [4].

5.2 Anti-tubercular

Schiff's base was condensed of Phenothiazines with triethyl amine and chloroacetyl chloride in presence of 1,4-dioxane to form the Azetidinones**(4a-g)**. The synthesized compounds were tested against *Mycobacterium tuberculosis* strain H37Rv at different concentrations using Lowenstein-Jensen medium method with Pyrazinamide as the standard drug. The results confirmed that all the compounds **(4a-g)** were found to be active against the organism in all the different concentrations [5].

Azetidinones was synthesized based on Quinoline nucleus. Chloroquniloine compounds on reacting with triethylamine with 1, 4-dioxane in presence of chloroacetyl chloride yields the Quinoline based Azetidinones **(5a-l).** The synthesized compounds were tested against *Mycobacterium tuberculosis* strain H37Rv by Lowenstein- Jensen method. The compound **5l** which had amino methyl thiazole moiety was found to be inhibiting the most with an MIC value of 12.5µg/ml. The compound **5k** with a Fluoro derivative was found to inhibiting at an MIC value of 25µg/ml. Further compounds **5i** and **5g** with para-nitro and meta-chloro aniline substituent exhibited moderate inhibitory activity at an MIC of 50µg/ml.

5l- 3-Chloro-4-(2-chloro-quinoline-3-yl)-1-(5-methyl-thiazol2-yl)- azetidin-2-one

5k- 3-Chloro-4-(2-chloro-quinoline-3-yl)-1-(4-fluoro-phenyl) - azetidin-2-one

5i- 3-Chloro-1-(3-chloro-phenyl)-4-(2-chloro-quinoline-3-yl) - azetidin-2-one

5g- 3-Chloro-4-(2-chloro-quinoline-3-yl)-1-(4-nitro-phenyl) - azetidin-2-one [6].

Azetidinone compounds was synthesized from the Schiff's base made of Isoniazid. The Schiff's base on treatment with Chloroacetyl chloride with triethylamine in presence of 1, 4-dioxane yields Azetidinone (**10a-j**) compounds. These synthesized compounds were tested for anti-mycobacterial activity on *Mycobacterium fortuitum*CA10 and *Mycobacterium tuberculosis* CIP, H37Rv strain by agar dilution method with Pyrazinamide as standard drug. Results showed that compounds **10b** (4-Pyridyl) and **10i** (4-Fluorophenyl) exhibited potent anti-mycobacterial activity in which **10i** had the most potent activity with an MIC value of 2.21µg/ml.[7]

5.3 Anti-convulsant

Azetidinones (**14-18**) was synthesised from Oxadiazole moieties by cyclocondensing with triethylamine and acetyl chloride in presence of dioxane. Further these azetidinones are treated with formaldehyde and various substituted anilines to yield Azetidinones couple with Amino methylenes (**19-33**). All the synthesised compounds were tested for anti-convulsant activity by Maximal Electroshock induced Seizures (MES) with Phenytoin as the standard drug. The results showed that the compound **29** (4-Methoxy at both phenyl rings) was found to be most potent with 80% inhibition to that of standard drug. [8]

Schiff's base was synthesised from pyridine-3-carbonyl hydrazine. These Schiff's base on treatment with Chloroacetyl chloride and triethylamine by the stirring method yields azetidinones **(IV a-e)**. The compounds were administered to the mice in different groups with Diazepam as the standard drug. The percentage of the tonus and clonus mortality was found to be low in the compounds **IVa**(16.78%) and **IVd**(16.67%) compared to the other three compounds. [9]

5.4 Anti-bacterial

The azetidinones **(2a-k)** that are coupled with benzothiazepine nucleus are synthesised by the reaction of the thiazepine derivatives with chloroacetyl chloride and thioglycolic acid under mild reaction conditions. The synthesised compounds were tested for anti-bacterial activity against several pathogenic microorganisms. The compound **2d** which had three methoxy groups at 3,4,5 positions exhibited very good activity against *Escherichia coli* with an MIC value of 62.5µg/ml compared to the standard drug Ampicillin with an MIC value of 100µg/ml. All the other compounds exhibited moderate anti-microbial activity. From this, it is known that compounds with Nitro, Halogen, Methyl, and Methoxy substitutions exhibits anti-microbial activity. **2d-** 3-chloro-1-(dibenzo [1, 4] thiazepin-11-yl amino)-4-(3, 4, 5-trimethoxy phenyl)azetidin -2-one.[10]

Azetidinones**(Saz 1-5)**was synthesized from the Schiff's base of Naphthylamine moiety (Acetyl hydrazide) using chloroacetyl chloride and triethyl amine in presence of dioxane. The synthesized azetidinones were tested against *Bacillus subtilis, Escherichia coli* and *Pseudomonas aeruginosa* with Ampicillin as the standard drug. The determination of the zones of inhibition of the different compounds showed that the compounds **Saz 2** (Chloro) and

Saz 3 (Methoxy) were found to be more potent against the organisms than the other compounds. This showed that the presence of chloro and methoxy group on azetidinone may be responsible for the activity.
Saz 2-N 1 -[3-chloro-4(4-chloro-phenyl)-2-oxo-azetidin-1-yl]-2(naphthylamine)acetamide
Saz 3- N 1 -[3-chloro-4(4-methoxyphenyl)-2-oxo-azetidin-1- yl]-2(naphthylamine) acetamide [11].

Hydrazone compounds was synthesized from the acid hydrazides. These hydrazone compounds on treatment with triethylamine in dioxane with chloroacetyl chloride yields azetidinone**(5a-e)** compounds. The synthesized compounds were tested for interaction studies by molecular docking method on the DNA gyrase protein. The docking score of the compound **5b** (Chloro substitution) was -6.467631 which was nearer to the standard docking score (-7.636035) and it had the better affinity and interaction with the DNA gyrase protein than other compounds. The anti-bacterial activity was tested on various organisms which showed all the compounds **(5a-e)** had moderate anti-bacterial activity compared to standard drug Ciprofloxacin.
5b- 4-chloro-N-(3-chloro-2-(4-(difluoromethoxy)-3-hydroxyphenyl)- 4- oxoazetidin-1-yl) benzamide [12].

Azetidiniones**(4a-m)** wassynthesised by reacting Thiazolyl amino hydrazone compounds with Chloroacetyl chloride and triethylamine in a magnetic stirrer. The synthesised compounds were tested against *E.coli, K.pneumonia* , *S.aureus* and *B.subtilis*with Streptomycin as the standard drug. The results revealed that the compounds containing Nitro group **(4h, 4i** and **4j)** was found to be more potent than the compounds with chloro group **(4c** and **4d)** and Bromo group **(4e** and **4f).** The activities of the compounds depend on the electron withdrawing nature of the substituent groups.All the compounds other than this showed moderate to low activity [13].

Azetidinones**(1a-1e)** wassynthesized from the Schiff's base made of phenyl hydrazines. The Schiff's base made from phenyl hydrazines on treatment with Chloroacetyl chloride in presence of triethylamine and dioxane yields the Azetidinone compounds. The synthesized compounds were tested for anti-microbial activity on *Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, etc*by Agar diffusion cup plate method with Amoxicillin as the standard drug. The compound **1b** (Hydroxyl) was found to be active against *Pseudomonas aeruginosa* and compound **1c** (Methoxy) was active against *Escherichia coli*[14].

5.5 Anti-fungal

Cyclocondensation of4-(1H-naphtho[1,8-de][1,2,3]triazin-1-ylsulfonyl)-N-arylideneaniline **(2a-g)** with triethyl amine and chloroacetyl chloride in presence of 1,4-dioxane to yield azetidinones**(3a-g)**. The synthesized compounds were tested against plant pathogenic strains such as *Rhizopusnigricum, Nigrospora sp.* and *Fusariumoxysporum*on potato dextrose agar (PDA) medium. The zone of inhibition of the compounds on different strains showed that compounds **3b** with Chlorine substituted aryl ring and **3f** with Hydroxyl group substituted aryl ring was found to be more active than other compounds[15].

5.6 Anti-oxidant

The azetidinones **(4a-c)** are synthesised by the cyclocondensation of the thiazole derivatives with Chloroacetyl chloride in presence of triethyl amine. The antioxidant activity was tested by Ferric Ions (Fe^{3+}) Reducing Antioxidant Power (FRAP) method. The reductive power of the compounds was tested at different concentrations. The compounds **4b** (Methyl)and **4c** (Hydrogen)were found to be having the most reductive power since it showed the ability of electron donor to scavenge the free radicals. By using metal ion chelating activity method for the determination of anti-oxidant activity showed that compounds **4a** (Chloro)and **4b** (Methyl) had good chelating activity better than that of standard drug Ferrozine.
4a- 3-chloro-1-[4-(4-chlorophenyl] thiazol-2-yl)-4-(2-phenyl1H-indol-3-yl) azetidin-2-one
4b- 3-chloro-1-[4-(4-Tolyl) thiazol-2-yl]-4-(2-phenyl-1H-indol3-yl) azetidin-2-one
4c- 3-chloro-1-[(4-Phenyl) thiazol-2-yl]-4-(2-phenyl-1H-indol3-yl) azetidin-2-one [16].

The Researcherstreated 3-((phenylimino) methyl) quinoline-2-thiol (pyrimidine amine) with chloroacetyl chloride and triethyl amine in presence of 1,4-dioxane to afford the azetidinones. The anti-oxidant activity was tested by the DPPH radical scavenging activity of the compounds at different concentrations. The percentage inhibition of the free radicals was calculated and the compounds **7h, 7i** and **7j** with Chloro groups at 8,7 and 6^{th} position respectively showed good radical scavenging activity with IC_{50} values of 17.72, 17.21 and 16.92µg/ml than the standard drug Ascorbic acid because of the presence of mild electron donating groups with it.
7h- 1-(3-(4-(Pyridin-3-yl)pyrimidin-2-ylamino)-4-methylphenyl)-3-chloro-4-(8-chloro-2-mercaptoquinolin-3-yl)azetidin-2-one
7i- 1-(3-(4-(Pyridin-3-yl)pyrimidin-2-ylamino)-4-methylphenyl)-3-chloro-4-(7-chloro-2-mercaptoquinolin-3-yl)azetidin-2-one
7j- 1-(3-(4-(Pyridin-3-yl)pyrimidin-2-ylamino)-4-methylphenyl)-3-chloro-4-(6-chloro-2-mercaptoquinolin-3-yl)azetidin-2-one [17].

Sulfonamides **($4a_{1-6}$, $4b_{1-6}$)** wassynthesized from Sulfadiazine **(4a, 5a)** and Sulfisoxazole**(4b, 5b)** derivatives. Azetidinones**($5a_{1-6}$, $5b_{1-6}$)** were synthesizedby reacting Sulfonamides with chloroacetyl chloride in presence of triethylamine. The synthesized compounds were tested for DPPH radical scavenging activity with a methanol solution as a control sample and Ascorbic acid as the standard drug. The results showed that all the compounds had potent anti-oxidant activity with certain compounds having activity similar to that of Ascorbic acid. The compounds made of Sulfadiazine **($4a_{1-6}$, $5a_{1-6}$)** moiety were found to have better activity than that of compounds with Sulfisoxazole**($4b_{1-6}$, $5b_{1-6}$)** moiety [18].

5.7 Anti cancer

The azetidinones**(1)**was synthesised and then coupled with retinoid derivatives which produces a hybrid molecule

azetidinone-retinoid which is tested as an HDAC8 inhibitor. The hybrid molecule is synthesised by the convergent synthesis of 4-alkylidene-azetidinone carboxy acid and retinoid amine which yields two geometric isomers **2E** and **2Z** of the molecule. The synthesised compounds **1,2E** and **2Z** were tested for anti cancer activity by using MTT assay method on the SH-SY5Y neuroblastoma cells. The compounds of group **2E** and **2Z** showed significant reduction in the cell proliferation. All the compounds showed some anti-proliferative effect in a time dependent manner better than the control.
2E & 2Z- (2Z)-N-((2EZ, 4E)-3-Methyl-5-(2,6,6-trimethylcyclohex-1- enyl)penta-2,4-dienyl)-2-(4-oxoaze tidin-2-ylidene)acetamide [19].

Azetidinones**(9a-h)** was synthesized by treatment of Hydrazone compounds with Chloroacetyl chloride and triethylamine. The synthesized compounds were tested for anti-cancer activity against HeLa cells by Trypan blue exclusion method with Cyclophosphamide as the standard drug. Certain compounds exhibited good to moderate anti-cancer activity such as compound **9a**(4-Chloro phenyl) and **9b**(Biphenyl) found to inhibit the HeLa cells at different concentrations with IC_{50} values in the range 11.44-11.77µg/ml. Molecular docking studies of the compound **9a** and **9b** showed it inhibited β-Tubulin well with a great affinity [20].

Schiff's bases wassynthesized of Quinoline compounds which are reacting with Chloroacetyl chloride and triethlyamine in presence of dichloromethane affords a series of Azetidinones**(6a-o)** which is a hybrid Quinoline-Azetidinone. These synthesized compounds were tested for anti-proliferative activity by testing against Hep-G2 and Hep-3B cancer cell lines. The results showed that the compound **6f** (Hydroxy group at C4 position) exhibited the most potent anti-proliferant activity with an IC_{50} value of 0.04µM compared to the standard drug Paclitaxel which had 0.30µM against Hep-G2 cells. The compound **6j** (3, 4-Dichloro substitution) showed better activity with an IC_{50} value of 0.66µM compared to the standard drug against Hep-3B cells. It was also reported that the synthesized compounds were found to be safe against normal cells [21].

Piperazine coupled Azetidinones**(5a-h)** was synthesized from the reaction of Piperazines with Chloroacetyl chloride and triethylamine in presence of dioxane. The synthesized compounds were tested for anti-cancer activity on HeLa cervical cancer cells by MTT assay method with 5-Fluorouracil as the standard drug. The compound **5e** (Nitro phenyl) showed the most potent activity among the compounds with IC_{50} value of 29.44µg/ml. This compound was also found to induce apoptosis by arresting the G_2/M phase of cell cycle [22].

Azetidinone (**5a-o**) was synthesized compounds by the reaction of 4-Bromo coumarins with iminomethyl phenols. All the synthesized compounds were tested for Cytotoxic activity by Brine shrimp bioassay method with *Artemiasalina*eggs. The results of the assay showed that the compound **5h** (6-Chloro) showed the most potent cytotoxic activity against *Artemiasalina* with LD_{50} value of 7.154 x 10^{-4} and compounds **5m** and **5f** showed moderate cytotoxic activity [23].

5.8 Calcium channel blocker

Several compounds in the series of spiro-piperidineazetidines and azetidinones were synthesised. The enolate of esters were treated with N-Akly or Aryl aldimines to yield Azetidinones which on reducing affords Azetidines. Two different isomers **2a** and **2b** were obtained from the spiro-piperidineazetidines of which the **2a** was found to be more potent calcium channel blocker by Ionworks HT and manual voltage clamp assays. The aryl urea substituted azetidinones showed some improvement in the pharmacokinetic profile but there was loss in the potency. The azetidinone series was found to be potent than the azetidine series compounds in calcium channel blocking activity and a good TRPV1 selectivity. It is concluded that by structural modifications of azetidine and azetidinones provided compounds with altering calcium channel blocking potency, good pharmacokinetic profile, improved TRPV1 selectivity [24].

5.9 Acetylcholine esterase inhibitor (AchI),

They synthesised Schiff's base with Acetazolamide moiety which on treatment with triethylamine in dioxane with the addition of chloroacetyl chloride yields the Acetazolamide condensed Azetidinones**(5a-k)**. The acetylcholine esterase (AChE) and Butylcholine esterase (BuChE) assay was carried out under phosphate buffer at pH-8. All the synthesised compounds showed some inhibitory activity against AChE and BuChE in which the compound **5c** (4-Fluorophenyl) showed good inhibitory activity against the choline esterases.
5c- N-(5-{[3-chloro-2-(4-fluorophenyl)-4-oxoazetidin-1-yl]sulfonyl}-1,3,4-thiadiazol-2-yl)acetamide [25].

5.10 Anti inflammatory

Schiff's base **(3a-j)** was synthesised from 6-Nitro-1H indazole moiety. These Schiff's base on treatment with chloroacetyl chloride in the presence of triethylamine affords Azetidinones**(4a-j)**. These compounds were tested for anti-inflammatory activity by Carrageenan induced rat paw edema method with Phenylbutazone as the standard drug. The results showed all the compounds had inhibitory activity against inflammation while the compound **4i** (3-nitro) exhibited the highest percentage inhibition with 68.75% and compound **4j** (2-nitro) with 65.63% with best activities which was calculated using Newbould formula [26].

Schiff's base of Indoles was synthesized which on further treatment with Chlororacteyl chloride and triethylamine to give the Azetidinones (**8a-h**). All the synthesized compounds were tested for anti-inflammatory activity by carrageenan induced rat paw edema method with Indomethacin and Phenylbutazone as the standard drug. The compound **8g** (2-Chlorophenyl) showed the most potent anti-inflammatory and analgesic activity with COX-1 and COX-2 inhibition at 69.13% and 93.34% respectively [27].

5.11Anti-viral

Amido/Imido acid hydrazoneswas synthesized which on treatment with Phenoxy acetic acid and Thionyl chloride yields Azetidinones (**6a-f**). The synthesized compounds were tested on Japanese encephalitis virus (JEV), Herpes simplex virus (HSV) and Tobacco mosaic virus (TMV) for evaluation. The compound **6d** (Salicylamide substitution) showed lower order activity against JEV and HSV whereas against the TMV from *Nicotianaglutinosa* the compound **6c** (Nicotinamide substitution) showed the highest inhibition in both *in vitro* and *in vivo* models [28].

5.12Analgesic activity

Azetidinones (**2a-h**) was synthesized by treating Dinitrophenylhydrazine derivatives with chlororacetyl chloride and triethylamine. The synthesised compounds were tested for analgesic activity by Eddy's hot plate method with Morphine as the standard drug. The results showed that the compound **2h** (2, 4-Dichlorophenyl) showed the most excellent activity among the compounds with the reaction time at 12.4 seconds which is greater than other compounds and the standard drug Morphine injected animals exhibited reaction time at 14 seconds [29].

Benzimidazole substituted benzenamines was synthesized which on treatment with triethylamine and chloroacetyl chloride in presence of 1, 4-dioxane yields Azetidinones (**3a-h**). The synthesized compounds were tested for analgesic activity by acetic acid induced writhing on mice with Nimesulide as the reference drug. The compound **3e** (4-Hydroxyphenyl) and **3h** (4-Methoxyphenyl) was found to be potent with 46.20 and 43.67% inhibition of the writhing reflexes compared to Nimesulide with 52.54% of inhibition. Molecular docking studies exhibited that the compounds **3e** and **3h** had docking scores of -11.82 and -12.74 respectively against COX-2 which showed it excellent analgesic activity [30].

5.13 Anthelminthic activity

Two types of Azetidinones were synthesized from different Schiff's bases made of aldehyde and ketone. Schiff's base of aldehyde gave rise to Azetidinone (**4a-c**) while of ketone gave rise to Azetidinones (**8a-e**). All the synthesized compounds were tested for anthelminthic activity at different concentrations against Indian earthworm *Pheretimaposthuma* with Piperazinehexahydrate as the standard drug. The compounds **4b** (Methoxy), **8a** (R_1-Phenyl, R_2-Methyl, R_3-Nitro, R_4-Chloro) and **8e** (R_1-Ethyl, R_2-Methyl, R_3-Nitro, R_4-Chloro) was found to have most potent anthelminthic activity by recording the time of death of the worms [31].

5.14 Anti-parkinsonian activity

Azetidinone (**7a-l**) compounds was synthesized by the treatment of Quinazolinone derivatives with chloroacetyl chloride in presence of triethylamine. The synthesized compounds were tested for anti-parkinson activity by Rigidity, Oxotremorine induced Tremors which exhibited the compound **7f** (Hydrogen) was found to show better anti-parkinsonian activity and it was found to be equipotent to the standard drug L-Dopa [32].

5.15Anti-plasmodial activity

The author evaluated a series of Azetidinone compounds which are functionalized at 3rd position to determine their activity against malarial organisms of different strains of *Plasmodium falciparum* such as 3D-7(Chloroquine sensitive), K1(Chloroquine resistant) and W2(Chloroquine resistant). The results showed that the Azetidinone compounds with Azide substitution were found to have better activity than that with amine substitution. The compound **2d** (Cyclohexyl) and **2e** (Benzyl) showed IC_{50}values of 2.36 and 4.70µM respectively [33].

5.16 Anti-diabetic activity

Azetidinones (**5a-o**) was synthesized by the cyclocondensation of Imines and Ketenes in presence of triethylamine. The synthesized compounds were tested for anti-diabetic activity on Wistar rats by Alloxan induced hyperglycemia with Gliclazide as the standard drug. The results showed decrease in serum glucose levels and prevention of decrease in liver glycogen contents were found to be decreased in animals treated with the synthesized compounds. The compound **5a** was found to have better anti-diabetic activity than all other synthesized compounds [34].

5.17 Human Leukocyte Elastase inhibitory activity

The authors evaluated the Human Leukocyte Elastase (HLE) inhibitory activity by a series of monocyclic β-lactams known as Azetidinones. The study was focused on synthesizing potent and stable HLE inhibitors by β-lactam hydrolysis. A series of Azetidinone compounds differing in substitution at the urea group were synthesized and HLE inhibitory activity was tested *in vivo* on Hamster Lung haemorrhage assay which exhibited that the compounds with Methyl and Methoxy group in para position found to be the most potent HLE inhibitors [35].

Conflict of Interest

The author declares no potential conflict of interest.

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