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HETEROCYCLIC COMPOUNDS WITH THEIR RECENT DEVELOPMENT: AN INTEGRATED APPROACH

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ABSTRACT: Organic chemist has developed the number of heterocyclic compounds. The heterocyclic compounds have gained more attention in medicinal and organic chemistry because of their numerous biological activities. There are various types of the heterocyclic compound available for several biological activities such as antibacterial activity, anticancer activity, antiepileptic activity, antipsychotic activity, antihypertensive activity, antiproliferative activity. Pyrrole, furan, benzimidazole, thiophenol, thiophene, imidazole and indole compounds became more popular heterocyclic compound due to their biological activities, beta-lactam ring system has important role in the design of different antibiotics as well as in the biological activities. Furthermore the recent advancement that occurred in the scheme of heterocyclic compound caught more attention in many product developments. The present review article focused on the heterocyclic compound, classification, nomenclature, importance of heterocyclic compound, history of heterocyclic compound and recent development in the scheme along with their biological activities.

INTRODUCTION: Organic chemist has developed different heterocyclic compounds they have provocative role in the Pharmaceuticals, agricultural as well in veterinary products [1]. Heterocyclic compound deals with innovation in the scheme of method and heterocyclic compound has potency, efficacy against bacterial infection. Heterocyclic compound are the cyclic compound which contains the heteroatom it includes nitrogen, sulphur and oxygen.

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Most of the heterocyclic compound does not have the any heteroatom like phosphorus tin, bromine silicone. Heterocyclic compounds are classified according to the number of atoms present in the ring system. Heterocyclic compounds are classified into aromatic and non-aromatic but the physical properties of heterocyclic compound are often different from each ring system. Heterocyclic compound is a unique and highly valuable category of compound. These compounds determine the physical, biological and chemical characteristic [2, 3].

History of Heterocyclic Compound [4, 51]: The history of heterocyclic compound began in year of 1800's although.

1818: Brugnatelli was isolated from alloxan

1832: Dobereiner was prepared by using starch and sulphuric acid.

1834: Runge synthesize pyrrole from bone oil by using dry distillation method.

1906: developed the indigo dye in synthetic chemistry and agricultural industry.

1936: Treibs synthesized different chlorophyll derivative from crude oil

1951: Chargaff's was explained the role of heterocyclic compound like purine and pyridine bases in genetic code [1].

General Properties of Heterocyclic Compound: The heterocyclic compounds having five membered, six membered and four membered ring system and they includes, pyrrole, furan, pyridine, thiophene, benzofuran and pyran, quinolone [1]. The five membered ring system contains heteroatom includes the furan, pyrrole and thiophene, in which the furan consists of four carbon atom and oxygen heteroatom, similarly the pyrrole has the four carbon atom and nitrogen as a heteroatom, thiophenecomprises four carbon atom and sulphur as a heteroatom [1, 5, 6]. The Heterocyclic compound used is used as a vehicle. They find application in preparation of sanitizer; antibiotics like cephalosporin, penicillin, anticancer drugs like reserpine, vincristine and vinblastine also have the heterocyclic moiety. The pyrrole and pyridine are heterocyclic compounds having six membered ring systems and having nitrogen as heteroatom. The pyridine and pyrrole found in the form of oily mixture and they were developed in 1820 from the strong heating of bone, but nowadays they are prepared synthetically. Pyridine is widely used as a solvent and dyestuff, waterproofing agent, alcohol denaturation [7, 8, 9].

The heterocyclic scaffold containing drug finds anthelmintic activity, it gets more attention in the field of medicinal chemistry. The Benzimidazole contains imidazole heterocyclic ring system. Piperazine was firstly developed during 19th century and it has more potency against helminthic infection /threadworm infection in small children as it is non-prescription medication. Diethyl carbamazepine drug have been used in intestinal nematode infection but its mechanism of action is still unknown hence it is withdrawn from the market [10, 11, 12, 13, 14, 15].

Nomenclature [15]: There are different ways of numbering to the heterocyclic ring system. The chemical abstract type of nomenclature is accepted.

Simple Heterocyclic Ring System Containing One Heteroatom:

1. The heteroatom in the ring system is numbered as one or start the numbering either in clockwise and anticlockwise direction.
2. If substituent present on the ring system then numbering should be in a way that the substituent has least possible number.
3. If more than one substituent is present on the ring system then numbering should be in an alphabetical order.
4. If heterocyclic ring system contains more than one heteroatom then numbering should be first number for oxygen, second number for sulphur and third number for nitrogen. If other heteroatoms are present they should bear least number. The order of preference in the following ways: O>S>N
5. If more than one nitrogen atom, one of them either saturated N-H imino group then imino group should bear the one number.

Classification of Heterocyclic Compounds: Depending upon the ring size and Degree of unsaturation. In case of non-aromatic heterocyclic ring system – The ketal and cyclic amine, ether, epoxide, cyclic acetal and cyclic ketal. The numbering starts from the heteroatom if the cycle has more than one heteroatom then numbering depending upon the atomic number of heteroatom e. g. in case of morpholine, the structure consist of oxygen and nitrogen as heteroatom so, the numbering begins from the oxygen atom and ends at the nitrogenatom.[16]furthermore the nomenclature of compound begins with aza and oxy and thia are widely acceptable.

Aromaticity: The pyridine and benzene are structurally resembles. The constitution of structure of benzene consists of CH bond and N heteroatom in the pyridine system.

We see the benzene structure; the atoms are SP2 hybridized and the remaining the singly occupied p orbital is moved right angle to the plane of ring and overlap to give delocalized Pie system, extending to closed loop moreever,in pyridine, the lone pair of electron is available in Sp2 hybridized form. Hence this structural changes leads to the stabilization. From investigation it was suggested that the benzene and pyridine conforms to the Huckel's rule [16].

Five Membered Ring Containing One Heteroatom:

Pyrrole [16]: The pyrrole is one of the most important five membered ring system contains nitrogen as a heteroatom because of its nucleus present in different natural compound such as vitamin B12, Chlorophyll and heamtin [17]. If we replace the CH2 group of cyclopentadiene by nitrogen atom hence Pyrrole is also known as azacyclopentadiene but the cyclopentadiene is not aromatic in nature but pyrrole has aromatic character because it contributes the two electrons, its lone Pair electron and its pie system [16].

It was observed that the resonance form of pyrrole shows the partial positive charge on nitrogen atom and electron rich carbon atom this is stronger than opposite inductive effect hence it reflects that pyrrole is basic in nature but the pyrrole is weak base because the pKa value of pyrrole is -3.8. The protonation of pyrrole will not be possible because the nitrogen already contributes its lone pair of electron, if we did protonation there may be chances of destroy of aromaticity of pyrrole ring but stabilization of resonance effect remains as it is.

Isolation of Pyrrole: Pyrrole is synthesized from coal tar and bone oil. The oil is washed successively with dilute acidic and alkaline solution to remove the acidic and alkaline compound the extract is subjected to distillation it is distill until and unless it boiled at 100-150 ^{0}C. Finally it is purified by using potassium hydroxide. Potassiopyrrole, so formed lastly it gives pure form of pyrrole [17].

Synthesis of Pyrrole from the Bone Oil [18]: The Pyrrole is isolated by various techniques /methods [18].

1. By passing acetylene through red hot tube
2. By passing mixture of furan, ammonia, aluminium oxide at temperature 480-490 it gives pyrrole
3. By the distillation of succinimide over zinc dust

Synthesis of Pyrrole Derivative: The various methods have been developed for synthesis of pyrrole derivatives.

Hantzsch Synthesis: It involves the condensation of alpha, beta ketoester and alpha chloro ketone in the presence of ammonia.

Properties of Pyrrole:

- Pyrrole is a colourless liquid. Is boiling point is 131 0C but it changes its colour in the presence of air
- It sparingly soluble in water and slightly soluble in alcohol and ether
- It shows red colour on a pine splint moistened with hydrochloric acid, pyrrole shows different canonical form
- The pyrrole has resonance energy is about 31kcal/mole, C-N bond length are 1.42A, C-C bond length is between C=C and C-C , dipole moment is 1.80D [17].

Mechanism [17]:

Pyrrole:

Substitution at Carbon:

- Protonation: The addition of proton occurs being faster at nitrogen atom, being faster at second carbon atom, third carbon atom. In gas phase system the protonation occurs on carbon atom in the presence of mild acidic reagent like $NH4^+$ but it has more affinity at second carbon atom than third carbon atom.
- The protonation of pyrrole occurs at second position hence formation of stable cation like 2-H pyrrolium ion than 1-H pyrrolium ion. Although the weak basicity of nitrogen produces the impact onthe mesomeric delocalization of charge in the 1-H pyrrolium ion.

- Similarly, sulphonation occurs on pyrrole ring leads to formation of pyrrole-3-sulphonic acid it seems like formation of more stable acid [19].

Pyrrole Derivatives with their Pharmacological Activity:

Goel: The synthesized derivative of2-methyl- 3, 4, 5-triphenyl pyrrole act as an antihyperglycemic agent. The 2-methyl- 3, 4, 5-triphenyl pyrrole was prepared by refluxing a mixture of benzyl acetate, benzyl methyl acetate in ammonium acetate in the presence of acetic acid. It was already reported that the by product was formed due to self – condensation of benzoin, ammonium acetate in presence of acetic acid, air. These byproduct was avoided by synthesis of 3,4,5-triphenyl-1*H*-pyrroles. The synthesized product was assessed for their antihyperglycemic activity by streptozotocin induced diabetic rat model. From the results it was predicted that the unsubstituted phenyl ring at 4, 5 position reduces the excessive sugar level similarly the substitution of phenyl ring at 3,4 position resulted the complete reduction of antihyperglycemic activity. The substitution of trifluoromethyl group at the 3 position of the aryl group hence it possessed the good antidiabetic activity [20, 21, 23, 24].

Pyrazole [25, 26, 27]: Pyrazole is considered as one of the most potential nitrogen containing heterocyclic compound. The oxazolidine compound is more adaptable lead compound to design and develop the potential biologically active compounds. It exhibited the antimicrobial, antimalarial, anti-inflammatory, lipid peroxidation inhibitor and genotoxic studies1, 3, 4.

Pyrazole derivatives are class of heterocyclic compounds consists of the five membered ring system with two adjacent nitrogen atom, the one nitrogen atom is proton acceptor and another nitrogen atom is proton donor Pyrazole acts as weak acid or weak base. Many drugs containing the pyrazole as a heterocyclic ring system like analgesic drug like antipyrine, Phenylbutazole which is used in treatment of th arthritis, Lonazolac, Rimonabant [25, 26, 27].

Synthesis of 1-phenyl-2-(1-phenylethylidene) Hydrazine: The substituted acetophenone was added to the solution methanol (30 ml) and mixed with phenyl hydrazine, concentrated acetic acid was added to the reaction mixture and it was employed from microwave irradiation for 20 min at 340 watt. The reaction mixture allowed to cool at the room temperature. The obtained precipitate was filtered, washed with methanol, collected, dried and used for next step.

Synthesize 1, 3-diphenyl-1H-pyrazole-4-Carbaldehyde: The dimethyl formamide is added to the phosphrousoxychloride solution. The reaction mixture was cooled. The phosphrousoxychloride was added drop wise to the solution of dimethyl formamide. The solution was warmed for 30 min. at 340 watt although Solution kept for microwave irradiation. The mixture was cooled at room temperature.

Indazole [28]: These are the newer compound. It found rarely in nature. The compound consists of nitrogen containing heterocyclic moiety furthermore it is also known as the isoindazole and benzpyrazole. It became more popular due to its various biological activities.

The indazole possessed different biological properties like anti-inflammatory, antiarthritic and antimicrobial agent, anticancer agent moreover the PPAR inhibitor, antihypertensive agent and HIV protease inhibitor. New 2,3- disubstituted tetrahydro-2H-indazoles were prepared and evaluated its biological activities like *in-vivo* anti-inflammatory activity by carrageenan induced edema and freunds adjuvant induced arthritis.

The mammalian concentrating enzyme mainly present in the central nervous system of vertebrate. MCH receptor mostly present in the hypothalamus which has main role in food intake and body weight regulation. This leads to the development of MCH antagonist which acts on central nervous system and it explored for obesity treatment. A number of different compound of urea based N1-(2-aminoethyl) indazoles for melanin concentrating hormone receptor 1 in both binding and functional assay [28].

Benzo-condensed Pyrrole, Furan and Thiophene:

Indole [29]: It is also known as 2,3-benzopyrrole. Indole is a very important pharmacophore.

Indole compound bears the benzonoid nucleus and has 10 pie electrons which reflects the aromatic character. Indole is heterocyclic ring system provide the skeleton to lysergic acid diethylamide, strychinine and alkaloid obtained from herbal species. The physical appearance of indole, it is colourless crystalline powder with specific odour. However the indole scaffolds containing compounds effective against the gram negative and gram positive bacteria. And it is effective against the viral infection and inhibits the HSV1.

The indole structure fused with 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine and 1,3-thiazole derivative, effective against the viral infection of HSV1 grown on viro cells. The number of derivative have been synthesized and tested to get good antiviral activity. The new lipophilic 1,2-annulated indole diketopiperazines were formulated. The various substituentsare attached on the parent structure of compound like OH and MeO. The obtained analog evaluated for their inhibitory activity against IAV and HCV RNA replication in sub genomic replicon assay. Pyrazino[1,2-a]indole1,3(2H,4H)-diones 1ca–cd following experimental protocol.it has anticancer activity.

Thiophenol [30]:

Shaima Ibraheem Chyad AL-Khazraji: Thiol is a moiety in which it contains the –SH group. The various organic and inorganic compounds have been prepared although thiol group are widely present in protein Thiophenol is a sulphur-containing heterocyclic compound and it is synthesized along with its derivative. The sh_1-sh_{16} compounds were synthesized by heating thethiazole compound with different reagent.

Scheme no.1 preparation of 2-phenylacetic Acid: 0.02 mole of potassium hydroxide was added in thiazole compound with 20 ml of absolute ethanol then monochloroacetic acid was added into the mixture, the mixture was refluxed for 8 hr. The obtained precipitate was washed and recrystallized with ethanol.

2-((phenylthio) methyl)-1Hbenzo[d] imidazole (Sh2) Preparation: 2-((phenylthio)methyl)-1Hbenzo[d]imidazole (Sh_2) preparation: The sh_2 compound leaved for 10hrs it was added with o-phenylenediamine, ammonia was added to neutralize the solution then The benzimidazole compound was filtered and recrystallized.

Preparation of ethyl 2-(phenylthio) Acetate (Sh_3): The ethylchloro acetate solution was added with hot solution of thiophenol, potassium carbonate in acetone solvent, the mixture was refluxed for 4hrs. Allow to stand for evaporation under reduced pressure, water was added to the crude extract. The extract was dried by using magnesium sulphate by evaporating the organic layer which gave the solid precipitate.

Preparation of 2-(2-(phenylthio) acetyl) hydrazine-1- carbothioamide (Sh_4): The stirred solution of sh_3 was added in 20 ml of absolute ethanol it was added to the thio-semicarbazide, themixture was refluxed for 4hr. the solution was filtered and recrystallized it.

5-(phenylthio) Methyl-4H-1, 2, 4-triazole-3-thiol (Sh_5): Extract of compound in 10 ml of 4% NaOH was heated and refluxed for 3hr then acidified with 10 %HCl then solid residue remains as it is. It is recrystallized with ethanol.

Preparation of Phenyl Hydrazine: A Thiophenol compound was added with hydrazine hydrate mixture and it was refluxed for 4 hr and it was added with 15 ml of absolute ethanol then further heated for 3 hr. After separation the retained residue, the wash the residue with cold water, and washed with ethanol.

Preparation of 1-(derivatives of benzylidene)-2-Phenyl hydrazine (sh7- sh9): A suspension of P-bromobenzaldehyde was added in 15 ml of ethanol and compound was mixed with two drops of glacial acetic acid, heated under reflux for 6hr product was collected after cooling and recrystallized with ethanol. Similarly the sh_{10}-sh_{12} were derived by the following method. 0.02 mole of Schiff base with mercaptoacetic acid, added with benzene furthermore the reaction mixture was refluxed for 12 hr. The precipitate was filtered and recrystallized.

Preparation of 2-phenylthion acetyl chloride (sh13): The freshly prepared the chloroacetyl chloride was added in benzene, along with gradually addition of thiophene in benzene solution.

The reaction mixture was refluxed for 2hr. The residue was washed with 5% sodium bicarbonate solution, finally washed with water.

Preparation of 2- phenyl thioacetohydrazide (sh14): 1.82 gm of compound was added to hydrazine-hydrate compound further heated with ethanol solution, refluxed for 7hr. furthermore the solution was filtered; recrystallization of compound was done by ethanol

Preparation of N`-(4-bromobenzylidene)-2-(phenylthio) acetohydrazide (sh15), N`-(4-bromobenzylidene)-2-(phenylthio) acetohydrazide (sh15) have been prepared .The synthesized compound were characterized by the NMR, FT-IR. Lastly the newly synthesized heterocyclic derivative have been prepared successfully and confirmed by NMR, FT-IR.

Five Membered Rings Containing One Hetero Atom:

Thiophene [31]:

Kang, D.; Ding, X.; Wu, G.; Huo, Z.; Zhou, Z.; Zhao, T.; Feng, D.; Wang, Z.; Tian, Y.; Daelemans, D.; De Clercq, E.; Pannecouque, C.; Zhan, P.; Liu, Had developed and synthesized a new class of thiophene [3,2-d]pyrimidine HIV-1 NNRTIs that target the NNIBP's tolerance region I, and tested their efficacy against HIV-1WT and mutant strains, as well as HIV-2 (ROD). With EC50 values ranging from 0.0071 to 0.196 M, all of the target compounds showed moderate to outstanding efficacy against WT HIV-1, and the two most powerful compounds. 9b and 9d were shown to be single-figure nanomolar inhibitors (EC50 = 9.2 and 7.1 nM, respectively), outperforming AZT. These two chemicals were also moderately effective against the majority of the mutant strains tested. They showed good efficacy against K103N (EC50 = 0.032 and 0.070 M, respectively) and E138K (EC50 = 0.035 and 0.045 M).The newly inserted sulfamide group, as opposed to its isostere amide could create more contacts with amino acid residues in the NNIBP's tolerant region I, according to molecular simulation. We expect that these findings will aid in the development of thiophenepyrimidine-based NNRTIs with increased potency against RT mutant HIV strains. The synthesis of 2-aminothiophene derivative was prepared by various reactions like Schmidt reaction, Beckmann reaction, and gewald reaction. Nowadays the gewald reaction has taken more attention but in ancient year, it was more difficult to perform the gewald reaction due to more chances of lesser yield and it was very difficult to prepare the [32-47].

Five Membered Rings Containing Two Heteroatom:

Thiazole [48]: Thiazole derivative caught more attention due to its biological activities like anti-inflammatory, antimicrobial, anticancer, antihyper-tensive, antioxidant and hepatoprotective activity [29-44].

Take 5 – acetyl – 4 – methyl – 2 – phenyl - thiazole compound, refluxed with 2-cyanoacetohydrazide Hence formation of single product like as 2-cyano-N0-(1-(4-methyl-2-phenylthiazol-5-yl) ethylidene)-acetohydrazide. The method for synthesis of 5-amino – 1 – aryl - 3-substituted-N0-(1-(4-methyl-2-phenyl thiazol-5-yl) ethylidene)-1H-pyrazole-4-carbohydrazides

Method A has been used in preparation of 5-amino-1 – aryl – 3 – substituted - N0 - (1 - (4-methyl-2-phenyl thiazol-5-yl) ethylidene)-1H-pyrazole-4-carbohydrazides, when hydrazone added to the hydrazonyl halide in diaxone containing TEA was subjected to radiation at 400 watt in a closed taflon vessel until the starting material has consumed furthermore the hot solution was allowed to coolat temperature and solid precipitate was formed and later washed with ethanol.

Method B has been used in preparation of 5-amino -1 – aryl – 3 -substituted-N0-(1-(4-methyl-2-phenyl thiazol-5-yl) ethylidene) - 1H – pyrazole – 4 - carbohydrazides, when hydrazone added with hydrazonyl halide in diaxone containing the grafted chitosan was subjected to radiation at 400 watt in a closed taflon vessel. Furthermore filter the hot mixture until all the taflon removed from the mixture. The mixture was triturated with methanol and washed with methanol. The product separated and it was subjected for the physical constant determination, infrared spectroscopy. The 3-Acetyl - 5 – amino - N0-(1-(4-methyl-2-phenylthiazol-5-yl) ethylidene) – 1 – phenyl - 1H – pyrazole - 4-carbohydrazide, 3 – Acetyl – 5 – amino - N0 -(1-

(4-methyl - 2 - phenylthiazol-5-yl) ethylidene)-1-(p-tolyl)-1H-pyrazole-4-carbo-hydrazide, 3-Acetyl-5-amino - 1 - (4 - methoxyphenyl) - N0-(1-(4-methyl-2 – phenylthiazol – 5 - yl) ethylidene)-1H-pyrazole-4-carbohydrazide, Ethyl-5-amino-4-(2-(1-(4 – methyl – 2 – phenylthiazol – 5 - yl) ethylidene) hydrazinecarbonyl) – 1 – phenyl - 1H-pyrazole-3-carboxylate were analyzed and evaluated for biological activities like anticancer, antifungal and antimicrobial activity.

Comparison of Aromatic Properties of Pyrrole, Furan and Thiophene: Heterocyclic compounds containing four carbon atom and pie electrons and two lone pair of electron on the heteroatom which added to form aromatic sextet, these compounds follow the Huckel's rule and it must show aromatic character. The relative reactivity of the compounds with respect to benzene is as follows

Furan> Pyrrole> Thiophene> Benzene. Hence we can say that thiophene is most aromatic in nature and least reactive although furan is least aromatic in nature and most reactive in nature.

1. When reaction of furan with the maleic anhydride, in this case the furan acts as a normal diene and gives a normal adduct but the pyrrole does not acts as normal diene even though it undergoes the addition reaction whereas the thiophene does not react at all.

2. The order of reduction in heterocyclic compound is pyrrole>furan>thiophene>benzene. Pyrrole is reduced under mild condition and form dihydroderivative and the furan is also undergo the reduction reaction to form the tetrahydrofuran whereas the thiophene resistant to the hydrogenation reaction.

3. When the pyrrole, furan and thiophene reacts with the mineral acids, therefore the furan undergoes polymerization, pyrrole forms salt which further undergoes the polymerization reaction whereas the thiophene does not react at all[17].

Six-membered Containing One Heteroatom

Pyridine [49, 50]: The pyridine is most common heterocyclic compound. Pyridine is a greek word derived from pyr means fire and idine indicates the aromatic bases. The structure is resembled with benzene. The pyridine was isolated from the picoline by Anderson in 1846 later Wilhelm Corner and James Dewar discovered the structure of pyridine. William had synthesized the pyridine based compound by combining acetylene with the hydrogen cynide in red hot conditions. The pyridine scaffold present in the plant resources (alkaloid) (Atropa belladonna) which is used as cholinergic drugs[50]. The structure of pyridine has planarsymmetry, the pyridine is less basic than aliphatic compound but more basic than pyrrole, aniline because the structure of pyridine consists of one nitrogen atom with lone pair of electron however the lone pair of electron is in sp2 hybridized orbital moreover the lone pair of electron makes available in sp2 hybridized orbital whereas the aniline is an aromatic compound which contains the –NH2 group along with lone pair of electron furthermore the lone of electron is in sp3 hybridized orbital. Electron stick the nucleus more tightly even if they are in sp2 hybridized orbital than that of sp3 hybridized orbital therefore the less number of lone pair of electron is available for protonation. The less basicity of pyrrole and aniline are depending the less availability of lone pair of electron on nitrogen atom hence such lone pair of electron involved in the delocalization of orbital [49, 50].

Five Membered Rings Containing Two Heteroatom:

Imidazole [51, 52]: Imidazole containing heterocyclic compound have provocative properties while using as medicinal agent. Imidazole structure consist of five membered ring system , in which it is soluble in polar solvent like water, it exist in two different form depending upon the position of nitrogen atom or the hydrogen atom has position on either of two nitrogen atom. Imidazole ring is a planar ring and it is aromatic in nature due to the presence of sextet of pie electron. Imidazole compounds are almighty compound due to its wide ranges biological activities like anticancer, anti-inflammatory, antiviral activities. The development of new imidazole containing compound has taken more demand.

Recently, Esmailvessally and his co-workers developed the derivative of imidazole by using N-propargyl-benzamidines with aryl halide via

tandem aminopalladation by isomerization reaction. Similarly, the PPh3 is used as a catalyst and CuI acts as a co-catalyst. The reaction was preceded in the presence of potassium carbonate in anhydrous DMF medium. The co-catalyst has imperative role in the progress of reaction furthermore if the reaction to be proceeds without use of co-catalyst then we will get lesser yield of product and it will take more time for their completion. In year of 2009, Pandeyetal, the compound 1, 3 – bis - (2 – propyl – imidazol – 1 - yl) propane was prepared from the 2-propyl imidazole and 1,3-dibromopropane in the presence of solvent like NaH at 0-30°C temperature for 4hrs.similarly the various derivative of imidazole were prepared but 1,3-bis-(2-propyl-imidazol-1-yl) propane have good antitubercular activity [53].

Amita Verma, Sunil Joshi, and Deepika Singh [54, 55], Imidazole nucleus forms different component of human organism like vitamin B12, amino acid, histamine, component of DNA and constituent of pyrimidine and purine bases, nucleic acids. Imidazole is amphoteric in nature it acts as an acid and base and it is aromatic in nature due to its sextet of π-electrons furthermore imidazole consists of two nitrogen atom with lone pair of electron either on the protonated hydrogen atom. Imidazole is soluble in water.

Total nine derivatives were prepared with substituted piperidine-4-one. The 17-26 derivatives were subjected to structural elucidation by Infrared spectroscopy and nuclear magnetic resonance in addition 21, 24 derivatives was analyzed by X-ray diffraction method. for example, *N*-(*N*-(1H-imidazo-1-yl) acetyl-2,6-diarylpiperidin-4-ones/1-[2-(1, 2, 3-benzotriazol-1-yl)acetyl)-2, 6-diarylpiperidin-4-ones was prepared from the 2,6-Diarylpiperidin-4-ones followed by the addition of imidazole and benzotriazole moiety. Furthermore, the derivatives were evaluated for in-vitro antibacterial and antifungal activities against the pathogenic microorganism (gram positive and gram negative strains) *Bacillus subtilis* and *Escherichia coli.* From the result it revealed that the compound number 19 and 24 had exhibited good antibacterial activity. The compound possesses inhibited growth of microorganism against *Bacillus subtilis* and *Escherichia coli.* N.C. Desai, A.S. Maheta, K.M. Rajpara, V.V. Joshi, H.V. Vaghani, H.M. Satodiya [56], Imidazole moiety has important role against the fungal, vaginal and ringworm infection, it is effective against the leishmania. The conventional and microwave method were employed for synthesis of 4-((2-chloroquinolin-3-yl) methylene)-2-phenyloxazol-5(4H)-one. In case of conventional method, when2-chloroquinoline-3-carbaldehyde, sodium acetate and acetic anhydride and hippuric acid mixture were heated until the mixture become liquefied and it was transferred into the water bath and further heated for 4 hrs. The 100 ml of ethanol was added very slowly into the reaction mixture and kept overnight in a refrigerator. The crystalline compound was formed and allowed to recrystallize with ethanol to remove impurities washed with ice-cold water.

Similarly, the 2-chloroquinoline-3-caraldehyde was heated with mixture of sodium acetate, hippuric acid and acetic anhydride mixed the mixture thoroughly. The mixture was irradiated at 300 W for 3 min. With continuous shaking with intermittent time of 30s. the progress of reaction was checked by performing the thin layer chromatography. Once the reaction was completed the mixture kept overnight in a refrigerator, the crystalline product was formed and filtered, washed with ice-cold alcohol then boiling with water and crude product was formed.

4 - ((2 – Chloroquinolin – 3 - yl) methylene) – 2 - phenyloxazol-5(4*H*)-one compound was prepared by conventional method. If equimolar concentration of N-aminoaryl carboxamides was heatedin the presence of pyridine (oil bath) at temperature150-155^{0}C. The excess of pyridine was poured off. The mixture was added into the ice cold water then concentrated hydrochloric acid was added to neutralize the mixture. The solid product was settled down at the bottom and kept overnight in refrigerator. Whereas same procedure was followed in the microwave method but in reaction mixture, 2-3 drops of DMF was added and the mixture was subjected for irradiation. Lastly the entire synthesized product was subjected to physical constant determination and characterized by IR and NMR and Mass spectroscopy. The synthesized compounds were employed for screening like antimicrobial assay, antibacterial and antifungal activity. The antibacterial activity was carried by serial broth dilution method.

The suspension is inoculated on the agar media. The synthesized compounds were evaluated against the gram positive and gram negative bacterial strains. The antibacterial activity was carried by using six sets against *E. coli*, *S. aureus*, *Pseudomonas aeruginosa* and *S. pyogenes* at different concentrations of 1000, 500, 200, 100, 50, 25 µg/mL. The ampicillin was used as standard drug and it showed 100, 100, 250 and 100 µg/mL Minimum inhibitory concentration against *E. coli*, *P. aeruginosa*, *S. aureus* and *S. pyogenes* respectively. The newly synthesized compounds were tested for antifungal activity in different six forms against *C. albicans*, *Aspergillusniger* and *Aspergillus clavatus.* Griseofulvin is used as standard drug.

Lu X, Liu X, Wan B, Franzblau SG, Chen L, Zhou C, You Q: A series of 4-(2,6-dichlorobenzyloxy) phenyl thiazole, oxazole and imidazole derivative were prepared. The synthesized derivative assessed for the tubercular activity against the mycobacterium tuberculi H37Rv using the microplatealmar blue assay and antibacterial activities against the *Escherichia coli penicillin resistant Staphylococcus pneumonia and Staphylococcus, aureus* by agar diffusion method. Among 15 compounds, the various derivatives possessing the good antituberculosis activity with MIC values between 1micro meter and 61.5 micrometer. Hence from the result it was suggest that thiazide containing moiety have good antituberculosis and antibacterial activity [57].

Benzotriazole:

Raju R. Kale, VirendraPrasad Prabhu P. Mohapatra Vinod K: Benzotriazole became more popular due to its usefulness and its more successful protocol and methodology. Bezotriazole is easily added into another molecule hence it activate the another biological effective component. This heterocycle has more advantages over another heterocyclic compound like it is non-toxic, inexpensive and more stable, it is easily introducing into the another molecule [58, 59].

Derivatives with their Pharmacological Activities: Vorozole and alizaprideis are the compounds which are used as ananti-inflammatory agents even though they are effective against nausea and vomiting respectively. Vorozole and alizapride compound consists of benzotriazoleheterocycle moiety. 1-substituted benzotriazole carboxylic acids have been recognized as the selective small-molecule agonists of the human orphan G-protein-coupled receptor GPR and the number of novel heterocyclic compound have been discovered even though they had effective action against the enzyme like kinase. A several compound has been prepared which are effective against the SARS 3CL protease. Additionally, the compound has property of DNA cleaving hence the compound have more interest in developing the new heterocycle containing compounds.

Azole:

Shravankumar Kankalaa,, Ranjith Kumar Kankalab, Prasad Gundepakac, d, Niranjan Thotae, Srinivas Nerellaa, Mohan Rao Gangulaa, Hanmanthu Gugulotha, Mukkanti Kaggad, Ravinder Vaddea, Chandra Sekhar Vasam: Azole heterocycle is a provocative structural moiety in different naturally occurring compound this moiety have important role in different biological activities like anti-inflammatory, anticancer, antihistamine, HIV-inhibitor, antioxidant, anthelmintic activities [61, 62, 63, 64].

N-propargyl 2-mercaptobenzimidazoles was obtained by performing three consecutive steps but firstly we have to synthesize the 2-mercaptobenzimidazole from the ortho phenylenediamine and carbon disulphide in the presence of sodium hydroxide as a base hence resulting in formation of 2-mercaptobenzimidazole, these compound was further treated with 2,4-dinitro-chlorobenzene in the presence of potassium hydroxide or in the presence of ethanol. The synthesized product was subjected for N-propargyltion therefore formation of N-propargyl 2-mercaptobenzimidazole. The terminal alkynes were subjected to cycloaddition reaction by using nitrile oxide in the presence of catalyst like N-heterocyclic carbene (NHC) to get product like N-isoxazole-bound 2-mercaptobenzimidazoles. Actually the cycloaddition reaction may produce the mixture of compound. N,N-ditertiary butyl imidazolium chloride is used as catalyst which increases the reactivity.

The synthesized 2-mercaptobenzimidazole containing 3, 5-disubstituted isoxazole compounds were subjected for analysis by Infrared spectroscopy and nuclear magnetic resonance. The ^{1}H NMR and ^{13}C NMR were used for the study but the ^{1}H NMR didn't show any signal at terminal alkyne position d=2.10 but it emerged new signal at d=6.30at 4 th C-H position of iso-oxazole which provided the support for the cycloaddition reaction. Similarly the same case happened with ^{13}C NMR didn't show any signal but it showed at d =99 after cycloaddition reaction. All the prepared compounds were employed for the analgesic and anti-inflammatory activity.

The analgesic activity was performed by measuring the responses of animals to the heat and thermal stimuli. The analgesic activity was performed by the hot plate method on mice. The analgesic activity was conducted at a dose of 100 mg/kg of body weight and all the result was compared with standard drug like pentazocin. The anti-inflammatory activity was performed by caragennan induced inflammation on rat hind paw. The study was conducted by comparing the drug with standard compound like diclofenac at dose of 50mg/kg. The animal study was conducted by following all the protocols of animal ethics committee.

β-lactam Ring [66, 67, 68, 69]: Among the heterocyclic compound, beta lactam ring has important scaffold in the design of different antibiotics. Beta lactam ring is building blocks for synthesis of different bioactive heterocycle. Beta lactam have important application in biological system for example ezetimide are cholesterol synthesis inhibitor and clavulanic acid is β-lactamase inhibitor.

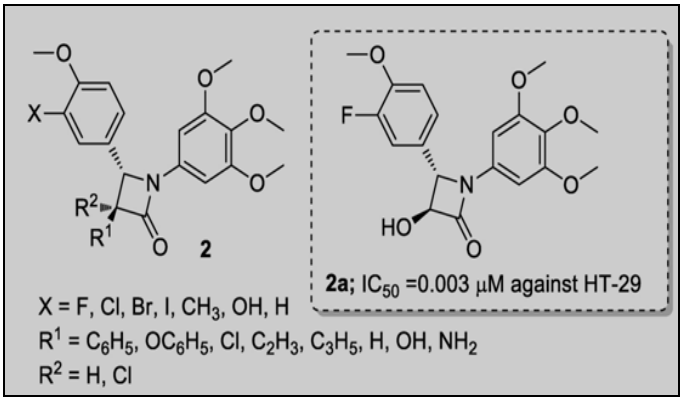

FIG. 1: ANTIPROLIFERATIVE ACTIVITY OF MOST OF B-LACTAM DERIVATIVE

In 2 number of structure, the several numbers of derivatives have been prepared and assessed for antiproliferative activity against the human colon and breast cancer cell lines.

When the hydroxyl group attached at 3-position of beta lactam and flourophenyl group at the 4 position of drug it exhibited the good antiproliferative activity with IC50 values at 0.022μm against the breast cancer cell lines and against the human colon at 0.03μm. the substitution of chloro, bromo and iodo group at 4 position, reduced the antiproliferative activity.

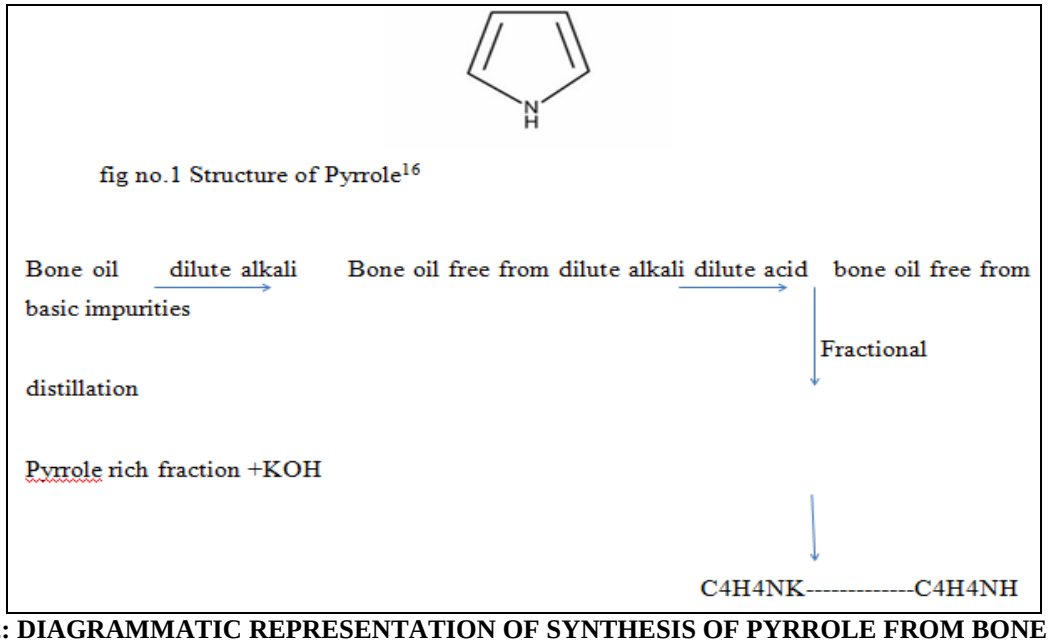

FIG. 2: DIAGRAMMATIC REPRESENTATION OF SYNTHESIS OF PYRROLE FROM BONE OIL[18]

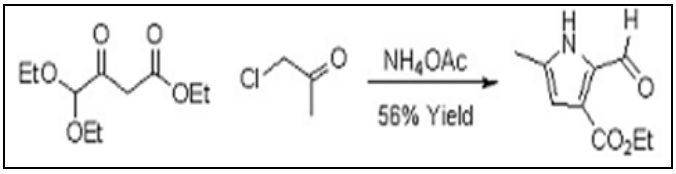

FIG. 3: SYNTHESIS OF PYRROLE DERIVATIVE FROM HANTZSCH METHOD

The bromine, chlorine iodine has antiproliferative activity against the human colon cell line. The introduction of fluorine at 4 positions, it may affect the physiochemical properties and physiological properties of drug like lipophilicity, metabolic and stability of drug. The another active compound 2a which induced the mitotic arrest in breast and colon cancer cell lines and inhibited the active site of colchicines from molecular modeling study it was revealed that active compound binds to the tubulin as similar to that of colchicine compound.

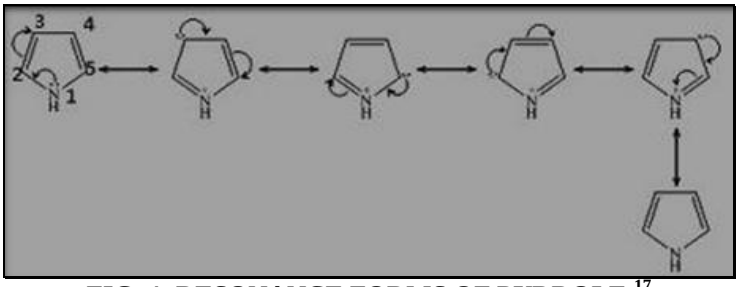

FIG. 4: RESONANCE FORMS OF PYRROLE [17]

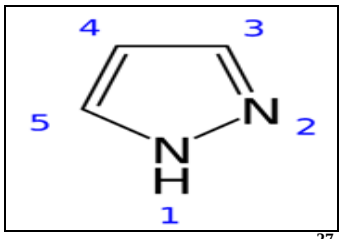

FIG. 5: STRUCTURE OF PYRAZOLE [27]

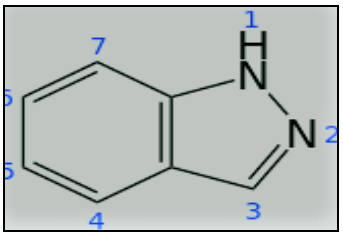

FIG. 6: STRUCTURE OF INDAZOLE [28]

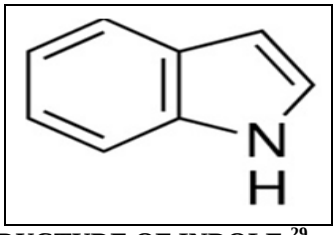

FIG. 7: STRUCTURE OF INDOLE [29]

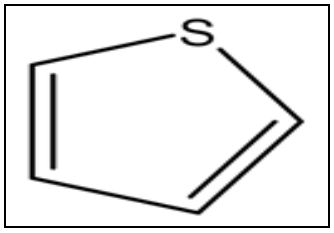

FIG. 8: STRUCTURE OF THIOPHENE [31]

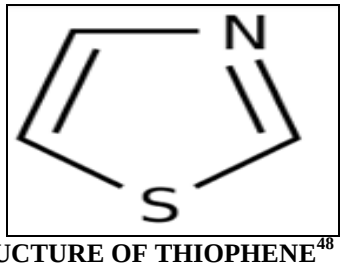

FIG. 9: STRUCTURE OF THIOPHENE[48]

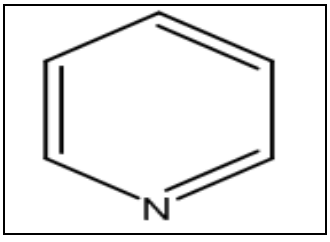

FIG. 10: STRUCTURE OF PYRIDINE[49]

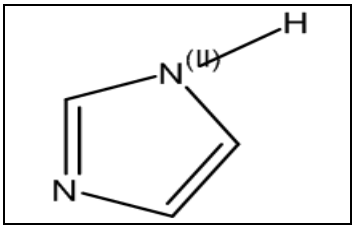

FIG. 11: STRUCTURE OF IMIDAZOLE [51, 52]

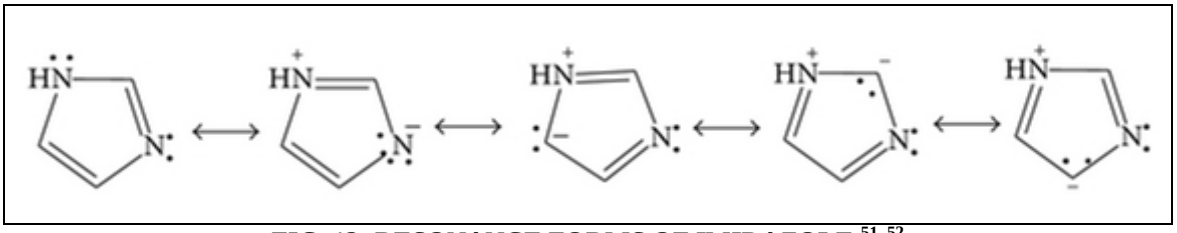

FIG. 12: RESONANCE FORMS OF IMIDAZOLE [51, 52]

CONCLUSION: Heterocyclic compounds caught more attention in the medicinal chemistry and organic chemistry. The different derivatives have been synthesized from four membered ring system, five membered ring system, six membered ring system which possesses the pharmacological activities like anticancer, antibacterial, antifungal. The recent advancement has been occurred in the scheme of derivative preparations which exhibited the various biological activities.

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