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Heterocycles, their Synthesis and Industrial Applications: A Review

Kwa Clovis Dze[1], Fayad Samad[2]
[1]*Lead College of Management*

Abstract: ***Aromatic heterocycles are planar rings of atoms containing at least one non-carbon atom (N, S, O) and contains (4n+2)π electrons. A vast number of different classes exists for example pyrrole, thiophene, furan, pyridine, azoles, indoles, Isoindoles, quinolines, isoquinolines, Benzofurans, Isobenzofurans, benzothiophenes, Isobenzothiophenes, pteridines, purines. These ring compounds possess interesting pharmacological and biological activities which include: anti-malarial, analgesic, anti-inflammatory, anticancer, antifungal, antibacterial and are also used as pesticides: herbicides, fungicides, insecticides, rodenticides, and as stimulators and regulators of plant growth as well as fluorescence materials, ionic liquids, dyes and pigments. There are several established methods for their synthesis. This research paper aims at highlighting these very diversities of these ring compounds and the different methods by which they could be synthesized.***
Keywords: Aromatic heterocycles, Aromaticity, heteroatom, pharmacological activity, fluorescence applications.

I. INTRODUCTION

Heterocyclic chemistry is a branch of chemistry that deals with the properties, synthesis and applications of heterocycles (Alvarez-Builla et al., 2011). A cyclic compound is that which contains a ring of atoms, if all the atoms in the ring are the same, the compound is homocyclic (eg cyclohexane) but if atoms of different elements are involved in the ring it is heterocyclic (eg aziridine) (Daintith, 2005). Therefore, a ring atom that is not carbon is called a heteroatom from the Greek word heteros which means different (Bruice, 2005). Organic compounds in which one carbon is common to two rings are called spirocyclic compounds eg spiro pentane and those for which two or more carbon atoms are common to more than one ring are called polycyclic compounds eg bicyclobutane. These molecules are classified as bicyclic, tricyclic, tetracyclic… according to the number of bond cleavages required to generate a noncyclic structure (Carey, 2000). Cyclic compounds could be saturated, that is containing no double or tipple bonds (eg oxirane) or unsaturated and contain double or triple bonds (eg dihydropyran) (Clayden et al., 2001). Unsaturated cyclic compounds are either aromatic (that is, are planar rings of atoms linked by alternate double and single bonds (Daintith, 2005)) or nonaromatic

1) The Huckel molecular orbital theory which states that, planar completely conjugated hydrocarbons will be aromatic if the ring contains (4n+2)π electrons where n is an integer n=0, 1, 2, 3, …(Carey and sundberg, 2007).
2) The Mobius aromaticity which states that, 4nπ electron annulenes consisting of planar cyclic array of p-orbitals could distribute π-twisting more readily without a loss in π electron energy (Mckee *et al*., 2013) and for 12, 16 or 20 carbon atoms the Mobius twist results in there being one point in the ring at which the atomic orbitals have a phase reversal (node).

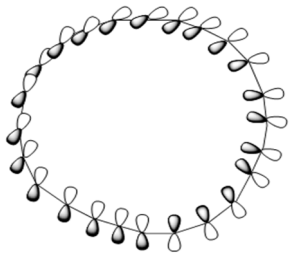

Fig 1 Mobius Twist

In such systems provided the twist is small the Huckel rule is reversed and aromaticity is observed for the 4nπ electron system (Carey and Sundberg, 2007). Based on these rules, conjugated heterocyclic compounds containing (4n+2)π electrons are aromatic (hence referred to as hetero aromatics in order to be able to recognize their heterocyclic and aromatic nature while those containing 4nπ electrons cannot be aromatic even though they may be cyclic, planar and conjugated and are said to be anti- aromatic as delocalization of their π-electrons will instead lead to destabilization (McMurry, 2008).

By definition an aromatic compound is a planar ring of atoms linked by alternate single and double bonds. Delocalization of the π-electrons of aromatic systems is a major contribution to the stabilization of these molecules and yield properties that are characteristic of aromaticity such as diamagnetic ring current. The Huckel molecular orbital theory is often used to express the relationship between a molecular orbital description of the structure and aromaticity.

There are three criteria used for evaluating aromaticity and include;

a) Energy data indicating thermodynamic stabilization or destabilization.
b) Structural data that relate to bond lengths indicating delocalized structures.
c) Electronic properties which are; energy levels, electron distribution, and polarizability.

These include the response of electrons to a magnetic field. Magnetic susceptibility measurements or NMR spectroscopy (in which aromatic compounds exhibit a diamagnetic ring
Current) could be used as important experimental tools for assessing or observing aromaticity. The following orbital representations show delocalization in pyridine, pyrrole and thiophene which are all aromatic.

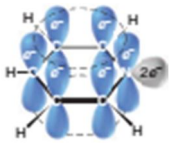
Fig 1.a Pyridine

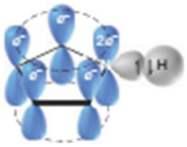
Fig 1.b Pyrrole


Fig 1.c Furan

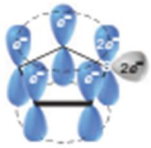
Fig 1.d Thiophene

Fig 2 Orbital representations showing delocalization (Graham and Craig, 2011)

II. HETEROCYCLIC NOMENCLATURE

The names of heterocyclic compounds are derived from a system of nomenclature made up of three parts.

1) The name of the heteroatom; “az” for N, “ox” for O, “thi” for S.
2) The ring size; -ir- = 3, -et- = 4, -ol- = 5, -ep- = 7.
3) The degree of saturation; -ene or –ine for unsaturated heterocycles, -idine or –ane for saturated heterocycles (Clayden *et al.*, 2001).

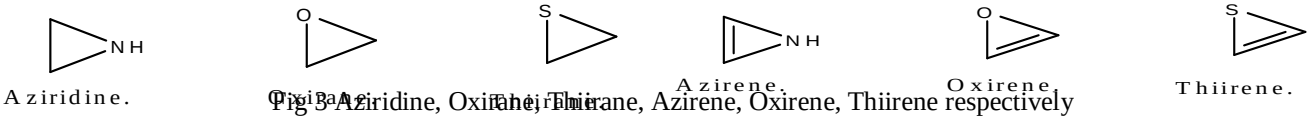

Fig 3 Aziridine, Oxirane, Thiirane, Azirene, Oxirene, Thiirene respectively

Homocyclic aromatic hydrocarbons are generally designated [n]annulenes with n referring to the number of carbon atoms in the ring eg [6]-annulene being benzene (Roberts *et al.*, 1971).
Heterocyclic compounds containing N, S or O are the most important (Graham and Craig, 2011) and these systems are obtained by inserting into aromatic hydrocarbons certain structural units containing heteroatoms eg –CH=N-, -N=N-, -O-, -S-, -NR-, to replace –CH=CH- in an aromatic ring in such a way that the system remains conjugated and isoelectronic with the original hydrocarbon. Heterocycles that have more than one hetero atom are called poly heterocycles and greatly occur naturally particularly in natural products like; nucleic acids, plant alkaloids, flavones, haem pigment, chlorophyll, vitamins, carbohydrates and some proteins (Norman *et al.*, 1995). Heteroaromatic compounds occur as rings containing one or more heteroatoms (Dewick, 2006).

A. *Structure and Names Of Aromatic Heterocycles*

1) *Five-membered ring Aromatic Heterocycles:* Five-membered ring aromatic heterocycles containing one hetero atom include; Pyrrole (N), Furan (O) and Thiophene (S) whereas five-membered ring aromatic heterocycles containing two, three, four or five heteroatoms are called Azoles.

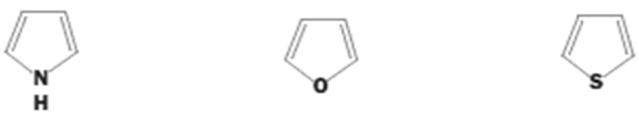

Fig 4 Five membered ring aromatic heterocycles with one heteroatom. Purole, Furan and Thiophene respectively

Five-membered ring aromatic heterocycles containing two heteroatoms are generally called Azoles. They contain a N-atom and an additional heteroatom which could be –NH, -O-, -S- (Alvarez-Builla *et al.*, 2011). They are as follows.

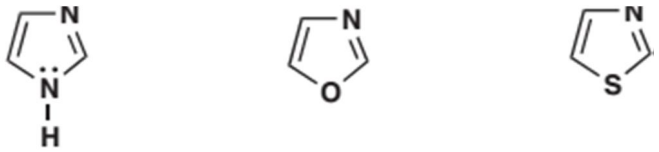

Fig 5 Five-membered ring aromatic heterocycles containing two heteroatoms. 1,3 Azoles -Imidazole, Oxazole, Thiazole respectively.

2) Five-membered ring Aromatic Heterocycles with three hetero Atoms

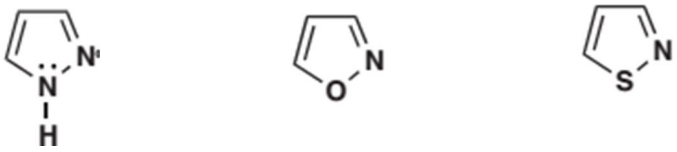

Fig 6 1,2 Azoles - Pyrazole, Isoxazole, Isothiazole respectively (Wyatt and Warren, 2007)

Fig 7 Trizoles - 1,2,4-triazole (wyatt and Warren 2007) and 1,2,3-triazole (Clayden et al., 2001)

3) Five-membered ring aromatic heterocycles with four or five heteroatoms

Fig 8 Oxidiazoles -1,2,3-oxidiazole, 1,2,5-oxidiazole, 1,2,4-oxidiazole, 1,3,4-oxidiazole respectively

Fig 9 Thiadiazoles - 1,2,3-thiadiazole, 1,2,5-thaidiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole

Fig 10 1H-tetrazole 1H-pentazole (Frija et al., 2010)

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4) Six-membered Ring Aromatic Heterocycles

Fig 11 Six membered ring aromatic heterocycles with one heteroatom Pyridine, Pyridinium ion,α-Pyrone, γ-Pyrone. (Roberts et al., 1971).

5) Six-membered ring Aromatic heterocycles with two Heteroatoms

These compounds are called *Diazines* (Wyatt and Warren, 2007) and include; (Alvarez-Builla *et al*., 2011).

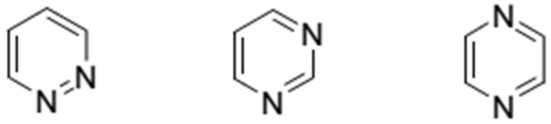
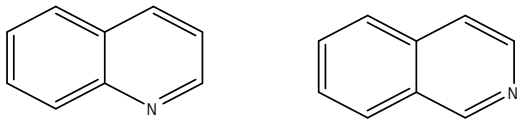


Fig 12 Six-membered ring aromatic heterocycles with two heteroatoms
Pyridiazine, Pyrimidine, Pyrazine

6) Aromatic Heterocycles fused to Benzene

a) Quinolines and Isoquinolines



QUINOLINE ISOQUINOLINE

Fig 13 Quinolines and Isoquinolines (Pandeya and Tyagi, 2011).

b) Indoles and Isoindoles

Fig 14 Indole, (Speck and Magauer, 2013) Isoindole (Inman and Moody, 2013).

c) Benzofurans and Isobenzofurans

BENZOFURAN ISOBENZOFURAN

Fig 15 Benzofuran and Isobenzofuran (Abu-Hashem et al, 2014)

d) Benzothiophene and Isobenzothiophene

Fig 16 Benzothiophene and Isobenzothiophene (Martinez et al., 2003).

e) Fused Aromatic Heterocycles

Fig 17 Pteridine (Sayed et al., 2014), Purine (Bruice, 2005)

B. Relevance of Aromatic Heterocycles

Because most aromatic heterocycles contain N, S and/or O, as heteroatoms which are the core constituents of a range of natural products such as: Nucleic acids, vitamins, amino acids, carbohydrates and alkaloids and because Medicinal Chemistry efforts often evolve around simulating such structural motifs, aromatic heterocycles containing N, S, and O, are therefore of intrinsic pharmacological and biological importance and are used for the synthesis of pharmaceuticals and agrochemicals (Gomtsyan, 2012; Arora *et al.*, 2012). Also aromatic heterocycles have fluorescence-based applications and are used as: molecular probes (for biochemical research, traditional textile and polymer fields and for photo-conducting materials (Rahimidazeh *et al.*, 2010)), biosensors (for metals, anionic species and pharmaceutical analysis (Costa *et al.*, 2007)) and biomarkers.

Aromatic heterocycles also find relevance in ionic liquids, sanitizers, antioxidants, corrosion inhibitors, and copolymers (Arora *et al.*, 2012) and because of the extended conjugation present in aromatic heterocycles they are used in dyes and pigments (Arunkumar, 2015).

III. SYNTHESES OF AROMATIC HETEROCYCLES.

Synthesis is the production of chemical compounds from other compounds (Daintith, 2005). The ensuing review is limited to the syntheses of five-membered (pyrroles, thiophenes and furans), six-membered (pyridines) ring aromatic heterocycles together with benzo-fused analogs (indoles, quinolines and isoquinolines) each containing one heteroatom. Many varied synthetic methods have been presented with a few discussed. Generally most of the methods involve condensations, cyclization and subsequent aromatization.

A. Synthesis of Five-Membered Ring Aromatic Heterocycles Containing One Heteroatom

1) Synthesis Of Pyrroles: Pyrroles are synthesized through the following ways

a) Van-Leusen Synthesis: A stable tosylmethylisocyanide (TOsMIC) under basic conditions reacts with α,β-unsaturated ketones, esters or nitriles in a Michael fashion to give substituted pyrroles (Leusen, 1972).

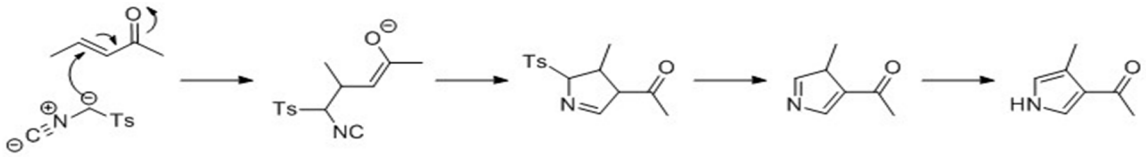


Fig 18 Van-Leusen synthesis

b) Knorr Pyrrole Synthesis: When an α-amino keto ester reacts with a β-ketoester having a reactive methylene group, an aldol-dehydration takes place in which the amino group attacks the carbonyl carbon to yield an enamine which on cyclization followed by dehydration yields pyrrole derivatives. (Arun et al., 2006; Dewick, 2006).

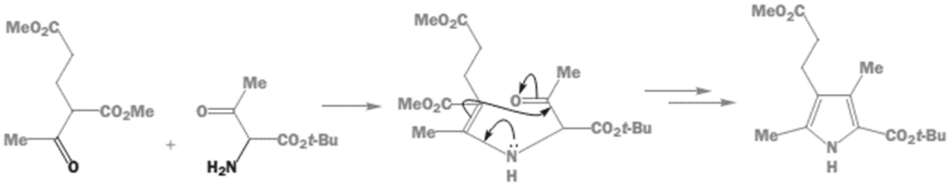


Fig 19 Knorr pyrrole synthesis (Clayden et al., 2001)

c) Barton-Zard pyrrole synthesis: This is the synthesis of 2-substituted pyrroles through the base-induced reaction of α, β-unsaturated nitroalkenes with alkyl α-isocyanoacetates in a Michael fashion to give substituted pyrroles (Wang, 2010;). In the improved Barton-Zard synthesis K_2CO_3 is used as the base (Bobal and Lightner, 2001).

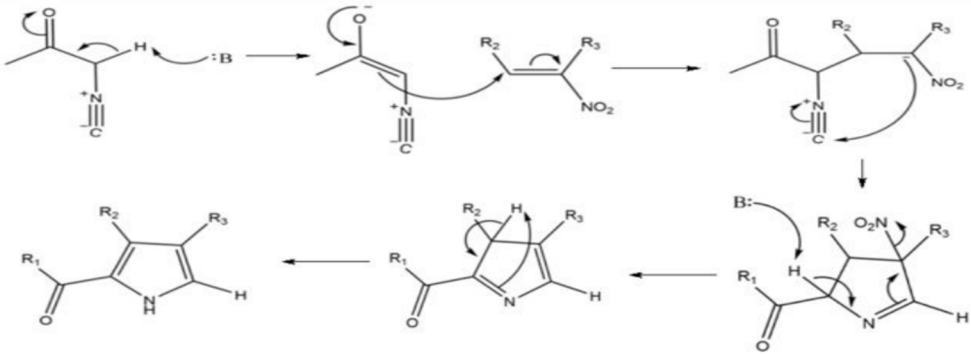


Fig 20 Barton-Zard pyrrole synthesis (Arun et al., 2006)

d) Piloty-Robinson synthesis: This is the synthesis of substituted pyrroles by the direct combination of hydrazine and aldehydes or ketones in the presence of acid at high temperatures (Milgram, 2007; Joules, 2010).

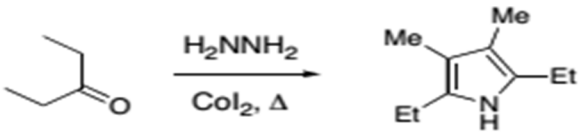


Fig 21 Piloty-Robinson synthesis

e) Trofimov synthesis of pyrroles: The synthesis of pyrroles (eg steroid pyrroles) by reaction of ketoximes with acetylene in the super basic system of KOH/DMSO (Trofimov et al., 2014). When dimethylacetylene dicarboxylate is used in the presence of europium (lll) triflate as catalyst, polyfunctionalized pyrroles are produced (Madabhushi et al., 2012, Zaitsev et al., 2014)

Other methods for pyrrole synthesis include

- The Paal-Knorr pyrrole synthesis: prepares pyrroles by an aldol-dehydration condensation of α-amino ketone and a 1,4-dicarbonyl compound (Dewick, 2006)
- the Hantzsch pyrrole synthesis: It is a solvent- and catalyst free synthesis of

Fig 22 Trofimov synthesis

Penta-substituted pyrroles based on the three-component reaction between primary amines alkylacetoacetates and fumaryl chloride. The mechanism is initiated by the formation of β-enaminone followed by its Michael addition onto a molecule of fumaryl chloride and then intramolecular attack of the enamine's nitrogen onto the acyl chloride function leading to cyclization and dehydration (Estevez *et al.*, 2010; Norman *et al.*, 1995)

2) *Synthesis Of Thiophenes: Industrially thiophenes are produced by the gas-phase reaction of C_4 hydrocarbons with sulfur at 600^0C (*Wolf and Folkers, 1951*).*

a) *Paal-Knorr Thiophene Synthesis:* When 1,4-dicarbonyl compounds are treated with a source of sulfur eg the sulfides of phosphorus called Lawesson's reagent in the presence of a strong acid an aldol-dehydration takes place to yield thiophene via the thioenol. (Joules and Mills, 2010)

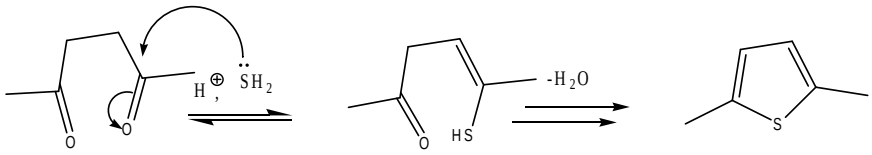


Fig 23 Paal-Knorr Thiophene Synthesis (Mishra et al., 2011)

b) *Fiesselmann Thiophene synthesis:* This is an extension of the Woodward condensation and involves the reaction of Thioglycolic acid and α,β-acetylenic esters in the presence of base (NaOMe) to form 3-hydroxythiophenedicarboxylate. This synthesis proceeds through consecutive base-catalyzed 1,4-conjugate addition reactions to form thioacetal which is then treated with NaOMe to form an enolate, intramolecular reaction through Dieckmann condensation leads to the formation of a ketone. Elimination of methylthioglycolate and tautomerization favored by aromaticity provides 3-hydroxythiophene dicarboxylate. (Jie, 2009).

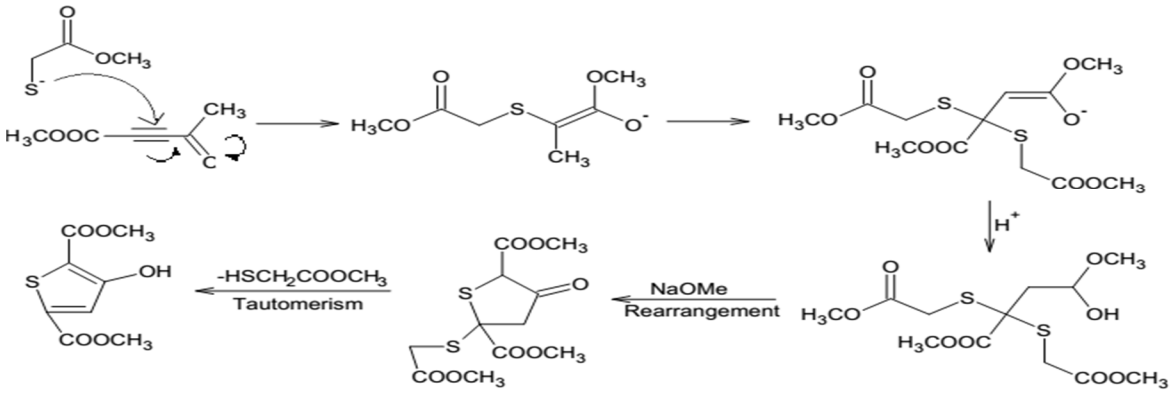


Fig 24 Fiesselmann Thiophene synthesis

c) *Hinsberg synthesis:* This method involves two consecutive aldol condensation reactions between a 1,2-dicarbonyl compound and diethylthiodiacetates to give thiophenes. Though the immediate product is often an ester-acid obtained by the Stobbe-type mechanism, hydrolysis is carried out to then obtain an isolated diacid (Mishra et al., 2011).

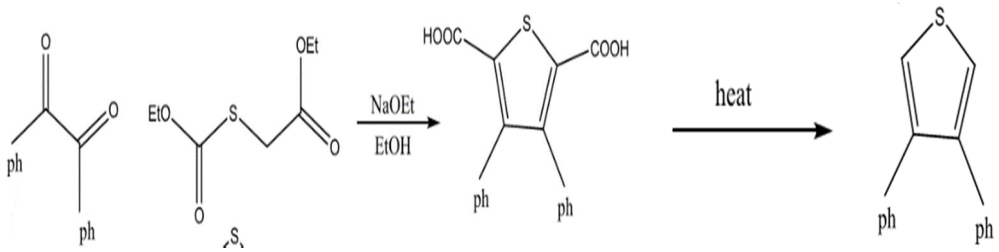


Fig 25 Gewald aminothiophene synthesis

d) Gewald Aminothiophene Synthesis: This consists the base-catalyzed condensation of a ketone having a -CH_2- group with a β-ketonitrile. The first step is the Knoevenagel condensation of an activated nitrile with a ketone or an aldehyde to give acrylonitrile which is then thiolated at the methylene position with elemental sulfur. The resulting compound undergoes a cyclization reaction via mercaptide attack at the cyano-group. Base-catalyzed tautomerization then affords 2-aminothiophenes (Mishra et al., 2011; Gribble, 2012).

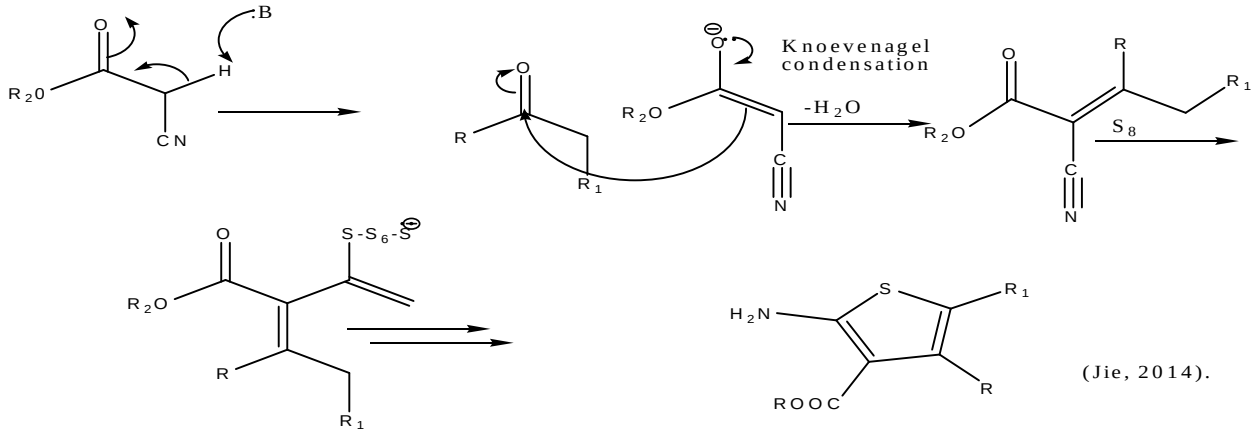


Fig 26

Other methods include

- From thiocarbonyl compounds: 2-ketothiols added to alkenyl phosphonium ions.

followed by ring closure via wittig reaction gives 2,5-dihydroxythiophenes .

- Industrially, thiophene is prepared by passing a mixture of acetylene sulfide through a tube containing alumina at 400^0C.

Fig 27 Industrial thiophene preperation reaction

3) Synthesis Of Furans

a) Paal-Knorr synthesis of furan: When a 1, 4-dicarbonyl compound is treated with a strong acid or a dehydrating agent like P_2O_5 at 100^0C, an aldol-dehydration occurs to yield furan via an enol (Streitwiester, 1985).

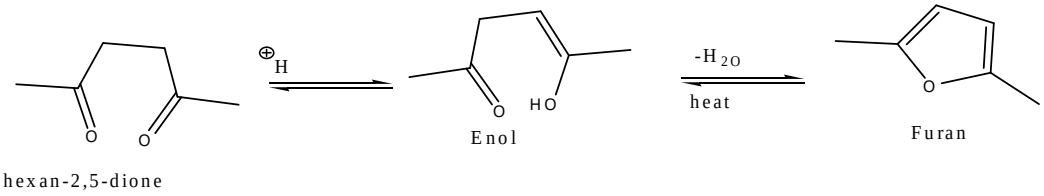


Fig 28 Paal-Knorr synthesis of furan

b) Feist-Benary Synthesis of Furan: This involves the condensation of a β-ketoester with an α-haloketone in the presence of pyridine or NH_4OAc/ethanol to produce furans. The first step is a Knoevenagel condensation between the enolate of a β-ketoester with an α-haloketone to yield an adduct which undergoes intramolecular cyclization by displacing HX in a nucleophilic aliphatic substitution to produce dihydrofuran which is then converted to furan by elimination of water (Ghazvini et al., 2016)

Furans could equally be obtained from: the Cu-catalyzed cyclo-isomerization of alkynyl ketones (Kel'en 2002),

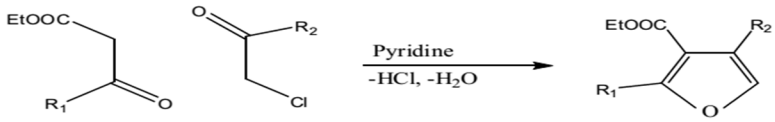


Fig 29 Feist-Benary synthesis of furan (Ghazvini et al., 2016).

B. Syntheses of Six-Membered Ring Aromatic Heterocycles With One Heteroatom

1) Synthesis Of Pyridines

a) Hantzsch Synthesis of Pyridines: It is a four-component reaction involving two keto-esters, an aldehyde and ammonia. A reasonable sequence of the reaction is an aldol condensation followed by a Michael addition that generates in situ 1,5-dicarbonyl compound (Bossart *et al.*, 1981). (Clayden *et al.*, 2001)

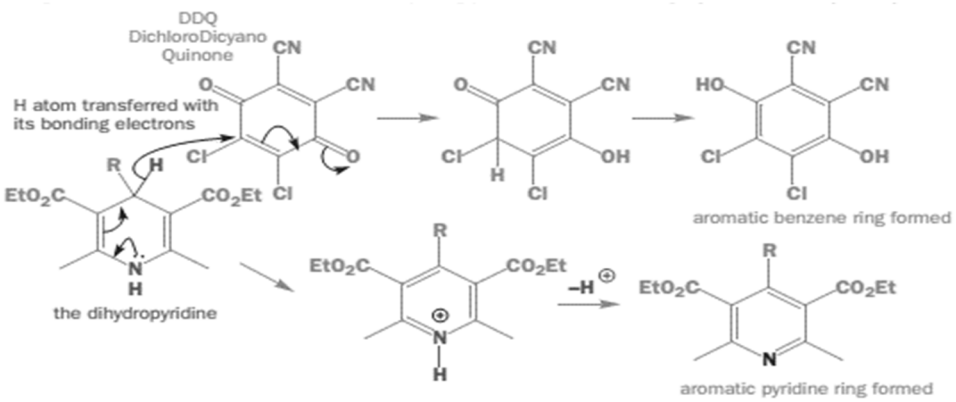


Fig 30 Hantzsch synthesis of pyridines

b) Boger Pyridine Synthesis: This is pyridine synthesis via hetero Diels-alder reaction between 1,2,4-triazines and dieonophiles (enamines) followed by extrusion of N_2

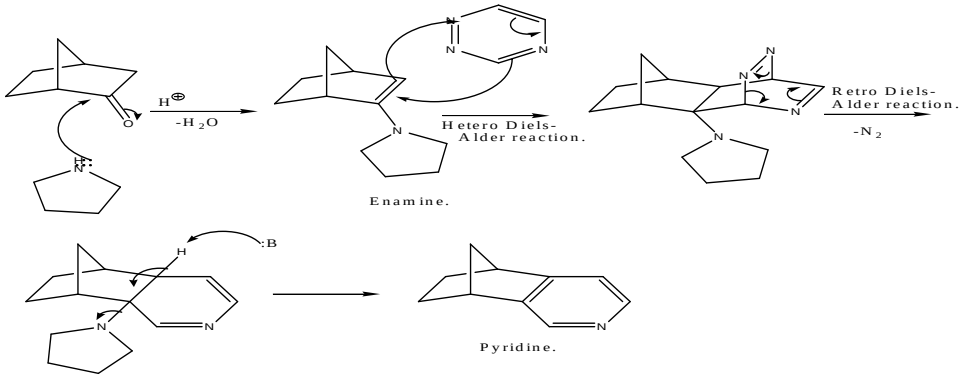


Fig 31 Boger pyridine synthesis (Jie, 2009).

c) Chichibabin Pyridine Synthesis: This is the condensation of aldehydes, ketone or α,β-unsaturated carbonyls with ammonia to afford pyridine. The first step of the reaction is an aldol condensation followed by a Michael addition and then cyclization (Franck et al.,1949; Jie, 2009). The reaction occurs in the gas phase on a solid acid catalyst such as alumina (Shimizu, 1998)

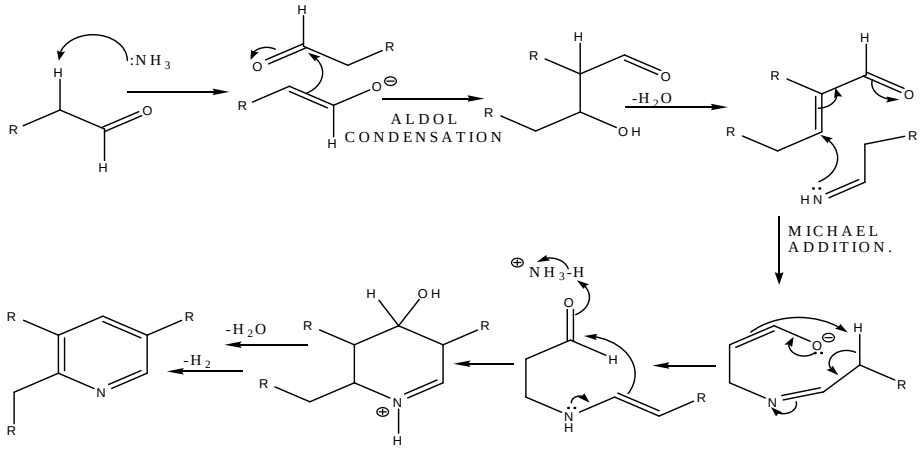


Fig 32 Chichibabin pyridine synthesis (Jie, 2009).

Other methods include

- The Ciamician-Dennstedt Rearrangement: This is the transformation of pyrroles to pyridines by heating with chloroform in alkaline solution. The intermediate is a carbene which rearranges to halogenopyridines on loss of HCl (Ciamician, 1881).
- Gattermann-Skita pyridine synthesis: This is the synthesis of substituted pyridines by Cyclocondensation of sodium malonic ester with dichloromethylamine (Hollins, 1924; Gattermann 1916).
- Guareschi-thorpe pyridine synthesis: Here a N-containing component such as cyanoacetamide reacts with 1,3-diketone in the presence of K_2CO_3 (Galatsis, 2005).

C. Synthesis of Aromatic Heterocycles Fused to Benzene

1) Synthesis Of Indoles

a) Fischer Indole Synthesis: It is the cyclization of arylhydrazone of a carbonyl compound by an acid or heating at elevated temperatures to form indole (Arun et al., 2012). This reaction proceeds via an initial acid-catalyzed tautomerization of an aromatic phenylhydrazone (formed from the condensation of phenylhydrazine and an aldehyde or ketone (Sajjadifar et al., 2010)) to an ene-hydrazine that undergoes a [3,3]-sigmatropic rearrangement to produce bis-imine. Subsequent aromatization and loss of ammonia affords indoles (Matsumoto et al., 2015; Inman and Moody, 2013).

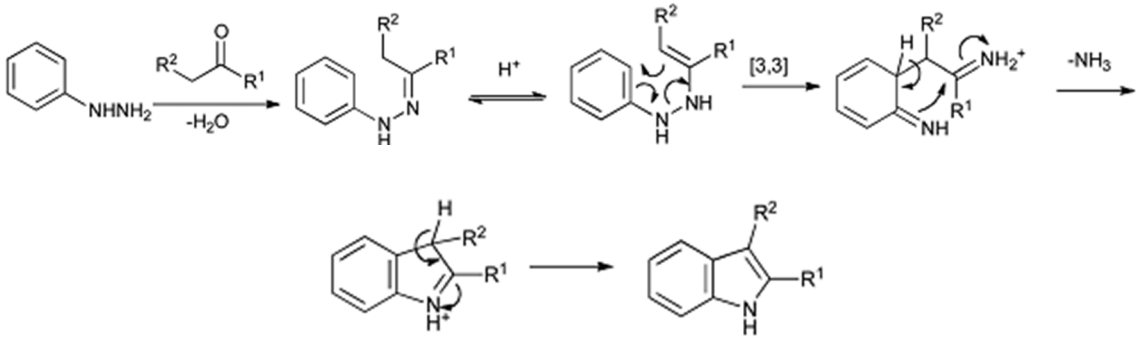


Fig 33 Fischer indole synthesis (Inman and Moody, 2000).

b) Nenitzescu Indole Synthesis: Preparation of 5-hydroxyindoles by the condensation of p-benzoquinones with β-aminocrotonic ester (enamine). The mechanism involves five steps. 1) Conjugated addition of enamine to p-quinone, 2) Isomerization, 3) Oxidation, 4) Nucleophilic addition and cyclization, 5) Reduction as shown below (Arun et al., 2006).

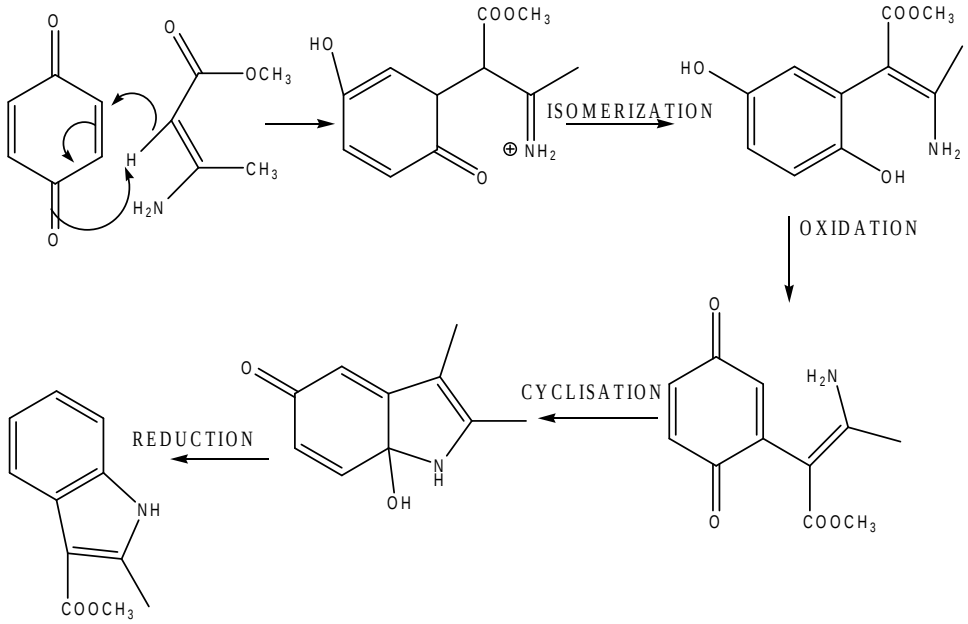


Fig 34 Nenitzescu indole synthesis (Arun et al., 2006).

c) *Reissert Indole Synthesis:* This is a nucleophilic addition reaction between the carbanion of o-nitrotoluene and the carbonyl group of ethyl oxalate in the presence of sodium ethoxide to produce an α-keto ester that is hydrolyzed in acid to form phenyl pyruvic acid derivatives which undergo reductive cyclization in the presence of Zn/acetic acid aromatization to yield indoles

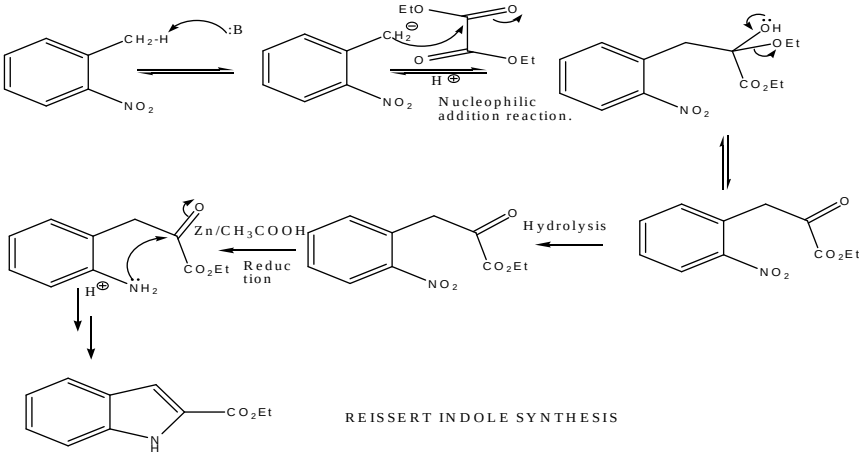


Fig 35 Reissert indole synthesis (Jie, 2009).

d) *Other Methods Include:* The Madelung indole synthesis. It's a non-catalytic process (Inman et al., 2000) involving the intramolecular cyclization of N-phenylamides in the presence of sodium ethoxide at elevated temperaures (360^0C-380^0C) to produce indoles. The Verley modification uses $NaNH_2$ /K^+ tert-BuO^- (Taber et al., 2011).

2) *Synthesis of Quinolines*

a) *Friedlander Quinoline Synthesis:* When 2-aminobenzaldehyde reacts with an enolizable ketone or aldehyde, in the presence of base eg KOH, poly substituted quinolines are produced (Xuefeng et al., 2015; Martinez et al., 2008). The first step of the reaction is the formation of enamine followed by a slow intermolecular Aldol-condensation. The Aldol adduct undergoes a rapid cyclization and dehydration to form 2,3-disubstituted quinolines (Kiss et al., 2008; Muchowski et al., 2004; Alireza et al., 2011).

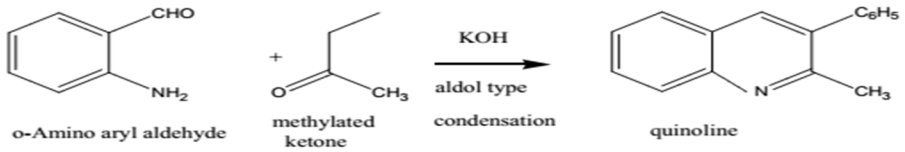


Fig 36 Friedlander quinoline synthesis

b) *Combes Quinoline Synthesis:* This is the acid-catalyzed condensation of β-diketones with primary arylamines to furnish the quinoline skeleton (Arun et al., 2006). The reaction proceeds with the formation of enamine via an intermediate Schiff base followed by acid-catalyzed cyclization to form substituted quinolines (Yamashkin et al., 1992).

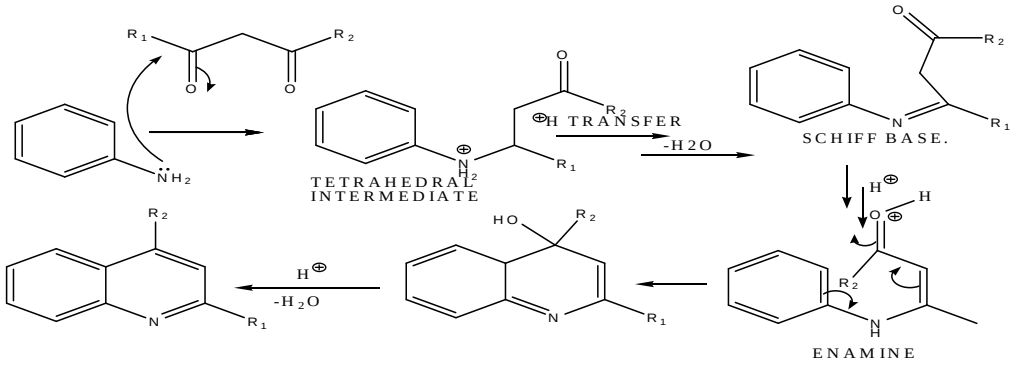


Fig 37 Combes quinoline synthesis (Jie, 2009).

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c) *Pfitzinger Quinoline Synthesis:* It is a modification of the Friedlander method (Norman et al., 1995) and is a base-promoted condensation Between isatin or it derivatives with ketones and aldehydes that contain $–CH_2CO-$ group (Hatem et al., 2009). The reaction is initiated by the hydroxide hydrolysis of isatin's amide bond to form isatinate whose $–NH_2-$ group reacts with an enolizable carbonyl compound by nucleophilic addition to yield an enamine which is cyclized and dehydrated to the corresponding quinoline (Sangshetti et al., 2014; Wang, 2010).

The below mechanism is from (Sangshetti *et al.,* 2014)

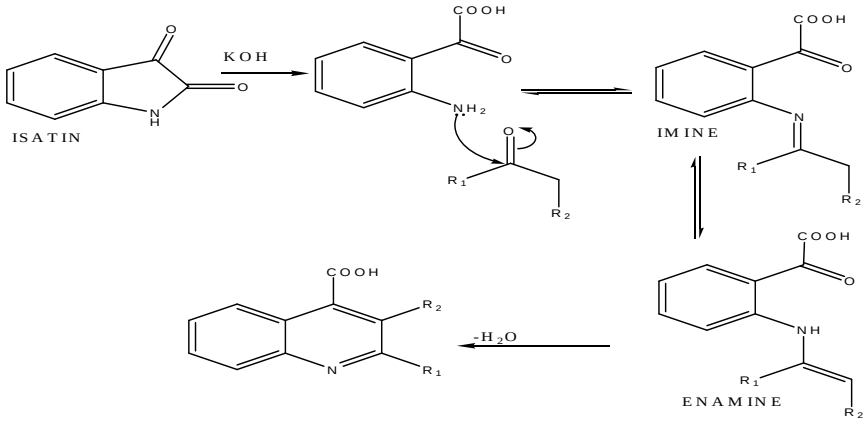

Fig 38 Pfitzinger quinoline synthesis

d) *Doebner-Von miller Synthesis:* Formation of quinolines by heating anilines with α,β-unsaturated carbonyls in the presence of H_2SO_4 (Bergstrom, 1994).

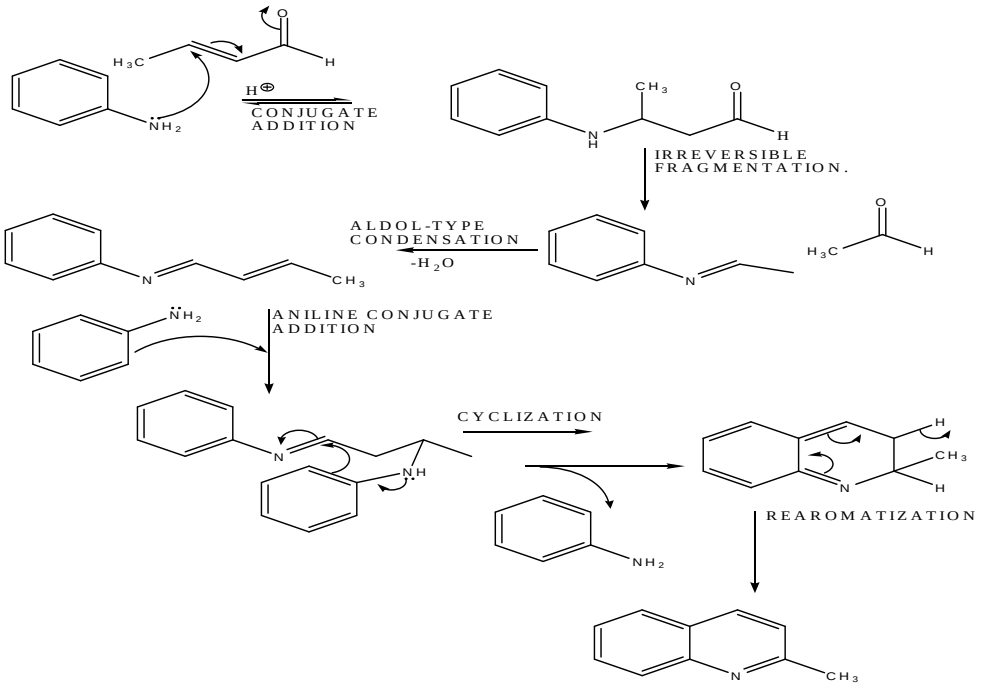

Fig 39 Doebner-Von miller synthesis (Heravi et al., 2014)

e) *Other Methods Include:* Skraup synthesis. Formation of quinolines nucleus by heating aniline with γ-aryl-β, γ-unsaturated α-ketoesters in the presence of HCl

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3) Synthesis of Isoquinolines

a) Pomeranz-Fritsch Reaction: The synthesis of isoquinolines via an acid-promoted electrophilic cyclization of benzalaminoacetal prepared from benzaldehyde and aminoacetal to form isoquinoline (Brown, 1977; Gensler, 2011).

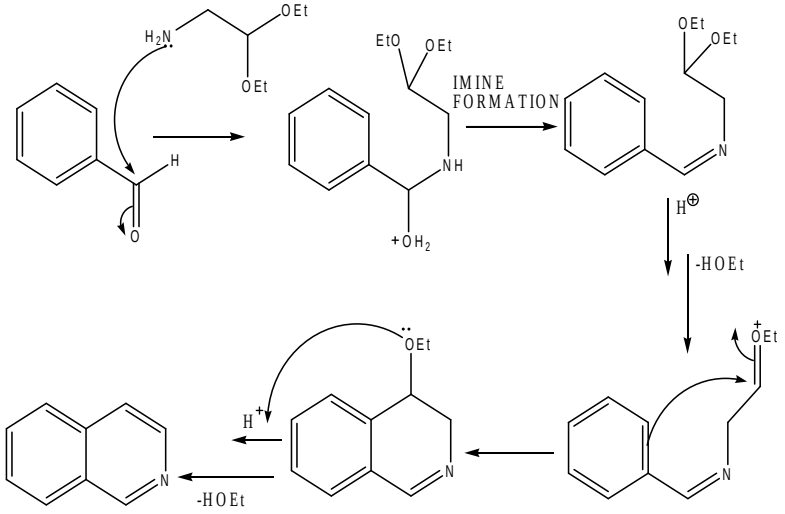

Fig 40 Pomeranz-Fritsch Reaction (Jie, 2009).

b) Bischler-Napieralski Reaction: It is a two steps process for preparing substituted isoquinolines by the cyclization of β-phenethylamide (derived from the nucleophilic acyl substitution reaction between β-phenylamine and methanoyl chloride) using dehydrating agents such as phosphorus pentoxide or phosphorus oxychloride. The lower temperature and use of mild condensing agent improves the yield. (Nagubandi, 1980;).

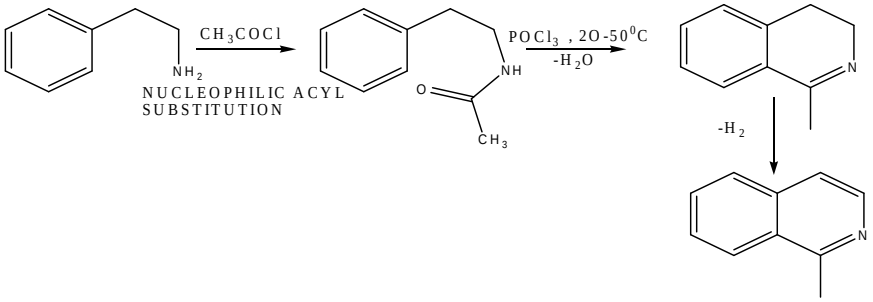

Fig 41 Bischler-Napieralski Reaction (Arun et al., 2006).

c) Pictet-Gams Isoquinoline Synthesis: This reaction is a modification of the Bischler-Napieralski reaction and involves the cyclization of N-acyl derivative of β-hydroxy-β-phenylethylamine in the presence of Lewis acid or P_2O_5 or phosphorus oxychloride under reflux in an inert solvent such as decalin produces isoquinolines (Jie, 2006).

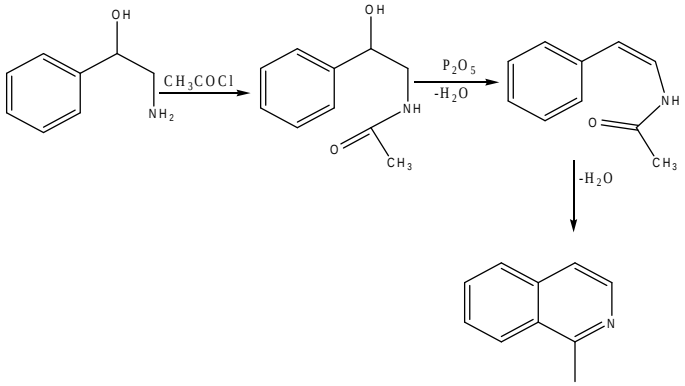

Fig 42 Pictet-Gams Isoquinoline synthesis

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IV. APPLICATIONS OF HETEROCYCLES AND AROMATIC COMPOUNDS

A. Applications of Heterocycles

Heterocycles are common fragments of the vast majority of marketed drugs and they play an essential role in modern drug synthesis. They could serve as useful tools to manipulate;

Lipophilicity, polarity and hydrogen bonding capacity of molecules thus leading to improved pharmacological, pharmacokinetic, toxicological and physicochemical properties of drug candidates and ultimately drugs. (Gomtsyan, 2012).

They have the following pharmacological applications.

1) *Antimalarial Activity:* Malaria is caused by the Protozoan parasites of the genus Plasmodium (species falciparium, vivax, ovale, malariae) and spread by the bite of an infested female anopheles mosquito. The life cycle of the asexual parasite, plasmodium, consists of two phases; the tissue phase called exoerythrocytic phase and the blood phase called erythrocytic phase. The 4-amino quinoline derivatives, Chloroquine (1) and hydroxychloroquine (2), are antimalarial drugs which work by inhibiting the parasitic enzyme heme polymerase that converts the toxic heme into non-toxic hemazoin, thereby resulting in the accumulation of toxic heme within the parasite and thus raises the p^H of the parasite. They also interfere the biosynthesis of nucleic acids by inhibiting DNA and RNA polymerase of parasite (Lilley et al., 2007). Another malarial drug is 8-aminoquinoline (3) which have the ability to bind to and alter parasitic DNA.

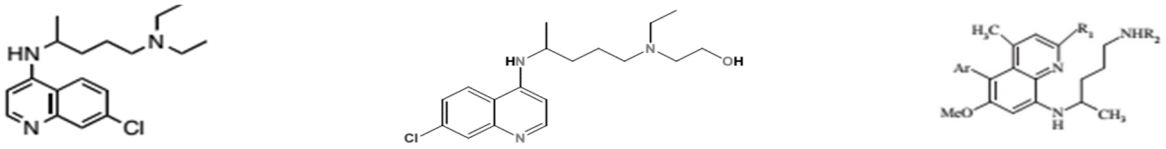

Fig 43 (1).Chloroquine, (2). hydroxychloroquine, (3).8-aminoquinoline

2) *Analgesic Activity:* This refers to the property of a substance or treatment to remedy pain by regulating the balance of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species. ROS are free radicals produced by the mitochondrial electron transport in biological systems and include $O_2^{\cdot-}$ and $HO^{\cdot}$. RNS species is peroxynitrite ($ONOO^-$) formed by the reaction of nitric oxide with $O_2^{\cdot-}$. RNS could lead to the nitration of mitochondrial proteins of the respiratory chain, reduction of Adenosin triphosphate (ATP) synthesis, alteration of mitochondrial membrane potential with subsequent release of apoptogenic proteins such as caspases and nucleic acid disintegration. Therefore high levels of ROS and RNS are major contributors to apoptosis underlying pain as these species activate and sensitize the polymodal nociceptor, Transient Receptor Potential Vanilloid 1 (TRPV1) which enhances the further production of $O_2^{\cdot-}$ and $HO^{\cdot}$. Capsazepine (4) a TRPV1 inhibitor is a free radical scavenger with analgesic properties (Salat et al., 2013).

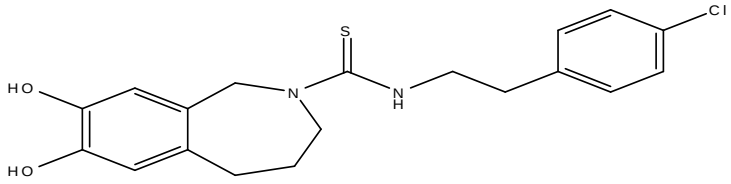

Fig 44 Capsazepine (Salat et al., 2013).

3) *Anti-Inflammatory Activity:* Anti-inflammatory drugs are a group of analgesics, remedying pain by reducing inflammation. Inflammation is body's response to tissue repair and is triggered by release of chemical mediators such as amines: histamine and serotonin, lipids such as prostaglandins and small peptides such as kinins. Inflammatory response occurs through the following mechanism: A transient material called the acute inflammatory exudates occupies the affected area. The exudates carry proteins, fluid and cells from local blood vessels into the damaged area to mediate local proteins. If an infective causative agent (e.g. bacteria) is present in the damaged area it can be destroyed and eliminated by components of the exudates. The damaged tissue can be broken down and partially liquefied and the debris removed from the site of damage. Quinoxaline ring is a part of number of antibiotics which are known to inhibit the growth of Gram Positive bacteria. (Noorulla et al., 2011). eg Triostin (5) (Katagiri et al., 1975).

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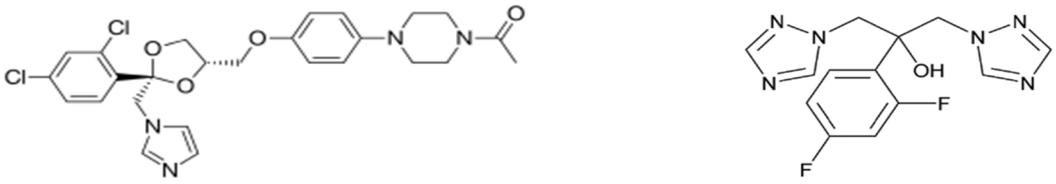

Fig 45 Triostin

4) *Antifungal Activity: Fungi are heterotropic organisms that lack photosynthetic ability and include all yeasts and molds (Saini et al., 2013). The infections caused by fungus is a mycosis and four types of mycotic infections exist:*

a) Systemic infections (eg Cryptococcosis caused by *Cryptococcus neoformans*).
b) Cutaneous infections (eg Candidiasis caused by *Candida albicans* and *Candida tropicatis).*
c) Subcutaneous infections (eg Dermatophytes caused by *Epidermophyton spp).*
d) Superficial infections (eg Tinea versicolor caused by *Malassezia furfur).*

Azole antifungals eg Ketoconazole (6) and fluconazole (7) kill fungi by interfering with the formation of fungal cell wall (Lilley *et al.*, 2007; Ursu *et al.*, 2006).

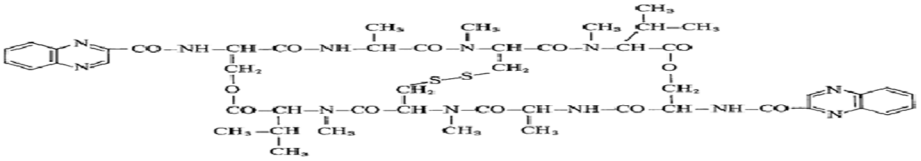

Fig 46 Ketoconazole, fluconazole

5) *Anticancer Activity:* Cancer is a disease in which there is uncontrolled multiplication and spread within the body of abnomal forms of the body's own cells. A normal cell turns into a cancer cell because of one or more mutations in its DNA, which could be inherited or acquired. The proliferation of tumour cells are not subject to normal regulatory processes. eg an inherited single defective copy of the tumour supressor genes could lead to breast cancer. Anastrozole (8) is an aromatase-inhibiting drug approved for the treatment of breast cancer. The severity of breast cancer is increased by estrogen, as sex hormones cause hyperplasia, and differentiation at estrogen receptor sites. Anastrozole works by inhibiting the synthesis of estrogen (Rang et al., 2007).

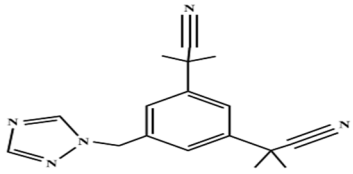

Fig 47 Anastrozole (Rang et al., 2007).

6) *Antibacterial Activity:* Bacteria are the simplest unicellular organisms found individually or in clusters (Saini et al., 2013). They are classified as Gram-positive or Gram-negative based on whether the organism do or do not stain with Gram's stain. For example Neisseria gonorrhoea causes gonorrhoea, E coli causes infections of the urinary tract (Rang et al., 2003). 3-aryl-2-oxazolidinones are synthetic antibacterial agents, having a mechanism of action which involves very early inhibition of bacterial protein synthesis (Bricner et al., 1996).

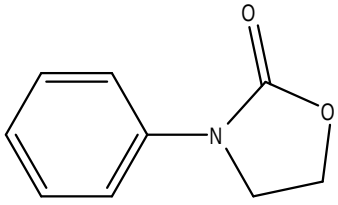

Fig 48 (Bricner et al., 1996).

B. Applications of Aromatic Heterocycles in Agriculture

Most of the food intended for humans is consumed or spoiled by pests such as rodents, insects, microorganisms and weeds. Though biological methods of plant protection are of great potential importance, chemical control is still the main approach utilized. Chemical control of pests is carried out by compounds known as pesticides and include: Herbicides (agents for killing weeds), insecticides, fungicides and rodenticides. Stimulators and regulators of plant growth are also of paramount importance. Because heterocyclic compounds participate in many biological systems its therefore not surprising that a majority of pesticides are heterocyclic compounds

1) *Herbicides:* Herbicides are widely used for weed control though their application contaminates the environment and their use in crop cultivation may affect subsequent crops. They have a selective phototoxic action on different plant species (Kutuzova *et al*., 2006) and are classified into three main groups based on the nature of the biological target of the agent.

a) Anti-photosynthetics (substances that prevent photosynthesis).

b) Chemicals which disturb the biosynthesis or destroy chlorophyll and other photosynthetic pigments like carotenoids within the cells.

c) Chemicals that inhibit the biosynthesis of essential amino acids or inhibit "dark" metabolic reactions

Examples of anti-photosynthetic herbicides include Azoles like 3-Amino-1,2,4-triazole (10), chlorflurazole (11),

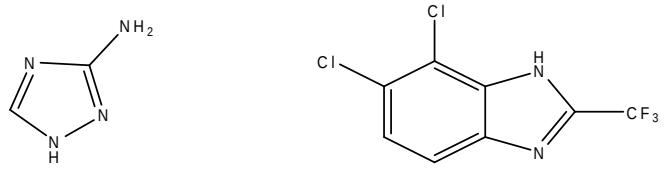

Fig 49 3-Amino-1,2,4-triazole, chlorflurazole (Pozharski et al., 2011)

Heterocyclic plant stimulators and regulators include the growth hormones: Hetero-auxins (12) and cytokinins (13), Uniconazole (14), (George *et al*., 2008).

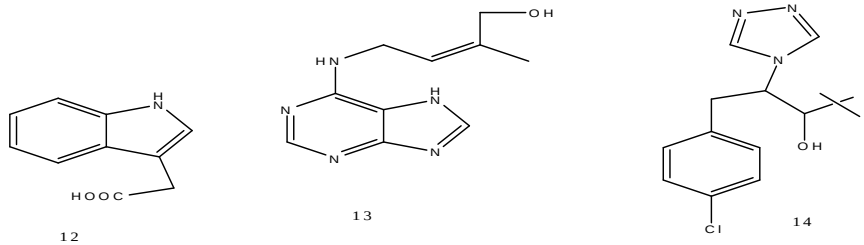

Fig 50 Hetero-auxins, Cytokinins, Uniconazole (George et al., 2008).

2) *Insecticides: These are agents used to kill insects. Pyridine alkaloids Anabasine (15) and nicotine (16) which affect the central nervous system of the insect are widely used active components of insecticides.*

Fig 51 Anabasine, Nicotine (Pozharski et al., 2011)

3) *Fungicides*

The following heterocyclic compounds serve as fungicides: Chimethionat (17) and penconazole (18)

Penconazole is a fungicide that has preventative and curative effects. It stops the development of fungi by interfering with the biosynthesis of sterols in the cell membranes it is used in the cultivation of fruits especially in viniculture (El-Sharkawy, 2012; Schwack *et al*., 1994).

Fig 52 Chimethionat, Penconazole (Tomlin, 2000).

4) *Fluoresnce-Based Applications:* Fluorescence is the absorption of radiation by atoms or molecules followed by immediate emission of electromagnetic radiation as the particles make transitions to lower energy states (Daintith 2005). Fluorescent heterocyclic compounds are of great importance in many disciplines such as emitters for electroluminescence devices (Hunger 2003), fluorescent whitening agents (Belgodere et al., 1985), fluorescent and/or colorimetric sensors for metals, anionic species and pharmaceutical analysis (Costa et al., 2007), molecular probes for biochemical research, traditional textile and polymer fields and for photo-conducting materials (Rahimizadeh et al., 2010). Examples of heterocyclic fluorescent compounds include, derivatives of imidazopyridinium salts which are used to prepare styryl dyes.

A wide range of organic compounds are used in the manufacture of electroluminescence cells eg Pyrazoloquinolines (19), Pyrazoloquinoxalines (20), Bis-pyrazolopyridine (21) and Benzoxazoles (22). These compounds were at first used in photocopiers.

Fig 53 Pyrazoloquinolines, Pyrazoloquinoxalines, Bis-pyrazolopyridine, Benzoxazoles (Danel 2010).

Another application of aromatic heterocycles is in ionic liquids: quaternary salts of some heterocyclic bases. They find application as high boiling polar solvents for extraction or as reaction media eg salts of imidazole.

Also aromatic heterocycles display the extended conjugation so important in the development of new dyes and pigments eg 3-substituted 5-amino-4-arylazopyrazoles (26) (Arunkumar 2015; Rizk *et al.*, 2011).

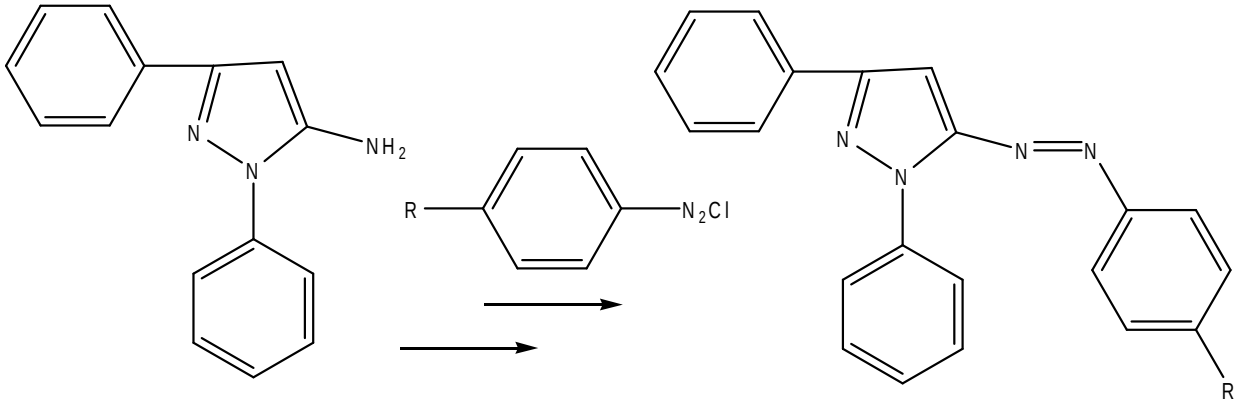

Fig 54 3-substituted 5-amino-4-arylazopyrazoles (Rizk et al., 2011).

V. CONCLUSION

A cyclic compound containing at least one ring atom different from carbon is a heterocycle.

Aromaticity is described in molecular orbital terms, that is, Huckel's rule and Mobius rule, a heterocycle is aromatic if it contains $(4n+2)\pi$ electrons n = 1,2,3… and antiaromatic if it contains $4n\pi$ electrons.

Five-membered ring aromatic heterocycles are pyrrole, furan thiophene and the azoles while six-membered ring aromatic heterocycles are pyridine, pyridinium ion, α-pyrone, γ-pyrone and the Diazines: pyridazine, pyrimidine, and pyrazine.

Aromatic heterocycles fused to benzene include; quinolines, isoquinolines, indoles, Isoindoles, benzothiophenes, isobenzothiophenes, Benzofurans and isobenzofurans. Different synthetic methods for these heterocycles have been reviewed

Fused aromatic heterocycles include; pteridine and purine.

Because most aromatic heterocycles contain N, S and/or O, as heteroatoms which are the core constituents of a range of natural products such as: Nucleic acids, vitamins, amino acids, carbohydrates and alkaloids and because Medicinal Chemistry efforts often evolve around simulating such structural motifs, aromatic heterocycles containing N, S, and O, therefore possess important pharmacological and biological activities such as, anti-malarial, analgesic, anti-inflammatory, anticancer, antifungal, antibacterial. They are therefore used for the synthesis of pharmaceuticals and agrochemicals which are pesticides: herbicides, fungicides, insecticides, rodenticides, and stimulators and regulators of plant growth. Heterocycles also possess fluorescence applications, are used as ionic liquids, dyes and pigments.

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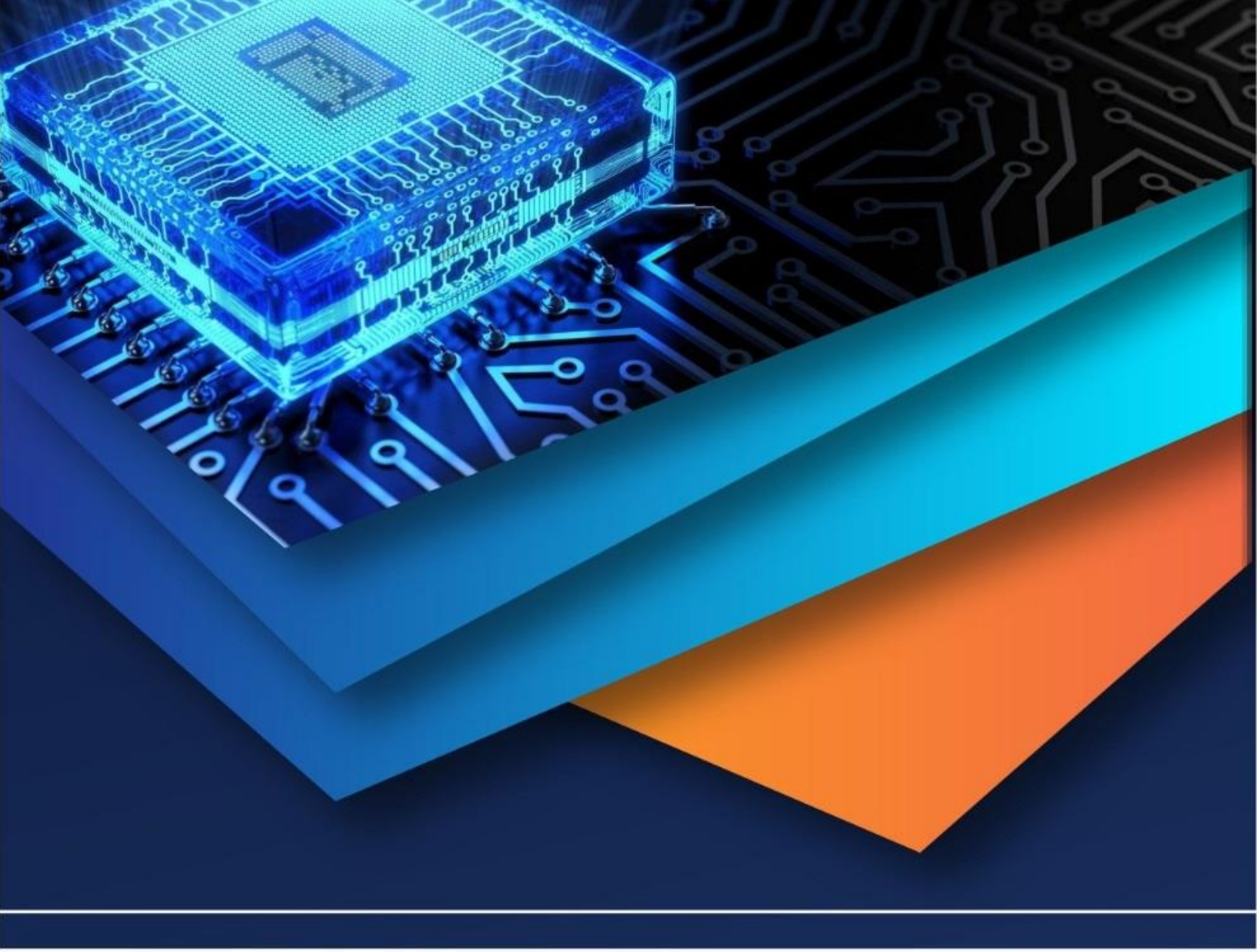

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