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REVIEW ON HETEROCYCLIC COMPOUNDS SYNTHESIS AND EVALUATION

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Keywords:

Indole, Pyrazole, Antimicrobial activity, Anti-inflammatory activity

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ABSTRACT: Among all the organic compounds, heterocyclic compounds are the most common and varied class. It has been possible to synthesis a considerable number of heterocyclic molecules thus far. Heterocyclic compounds are getting more and more prevalent due to extensive synthetic study and their synthetic utility. In the realm of medical chemistry, these molecules are useful in several ways. Some common uses include dyes, disinfectants, corrosion inhibitors, antioxidants, and copolymer production. An effective strategy for synthesizing recently identified heterocyclic compounds and their moieties always has some distinctive features. The importance of heterocyclic compounds in curative chemistry has been shown through their neoteric advancements. These compounds exhibit biological activities such as anti-convulsant, anti-HIV, antiviral, anti-allergic, anti-cancer, anti-inflammatory, and antifungal properties. This article gives comprehensive information about these heterocyclic compounds.

INTRODUCTION: The field of medicinal chemistry is very vast and includes the aspects of various types of chemistry, biology and computations [1]. The increase in drug resistance towards antimicrobial therapeutics has pressurized medicinal chemist to unearth novel drug candidates for the treatment of resistant diseases [2]. Inflammation is a physiological reaction which cause reddened, swollen, hot, and often painful, especially as a reaction to injury or infection on body parts and it is associate with many chronic diseases, including allergy, arthritis and auto-immune disease [3]. Heterocyclic chemistry deals with heterocyclic compounds which constitute about sixty-five percent of organic chemistry literature. A large number of heterocyclic compounds, both synthetic and natural, are pharmacologically active and are in clinical use [4].

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Heterocyclic Compounds: Heterocycles are an extraordinarily important and unique class of compounds; they make up more than half of all known organic compounds and have a wide range of physical, chemical and biological properties spanning a broad spectrum of reactivity and stability [5]. Heterocyclic chemistry is the branch of organic chemistry dealing with the synthesis, properties, and applications of these heterocycles [6].

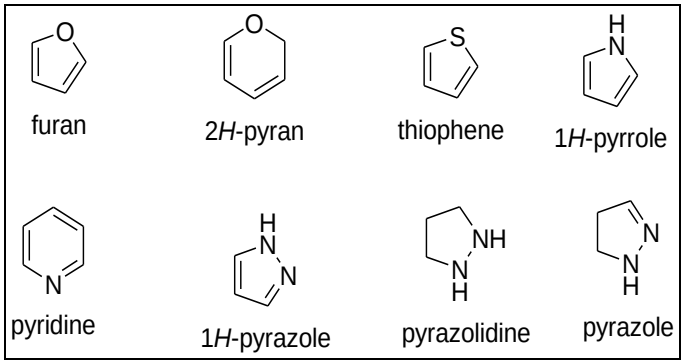


FIG. 1: STRUCTURE OF VARIOUS HETEROCYCLIC COMPOUNDS

Pyrazole: The term pyrazole was given to this class of compounds by German chemist Ludwig Knorr in 1883. In a classic method developed by German chemist Hans von Pechmann in 1898, pyrazole was synthesized from acetylene and diazomethane [7]. Pyrazoles are five member ring heterocyclic compounds, have some structural features with two nitrogen atoms in adjacent position and are also called as azoles [8]. Pyrazoles are aromatic molecules by to their planar conjugated ring structures with six delocalized π-electrons. Therefore, many important properties of these molecules were analyzed by comparing with the properties of benzene derivatives [9].

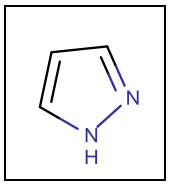
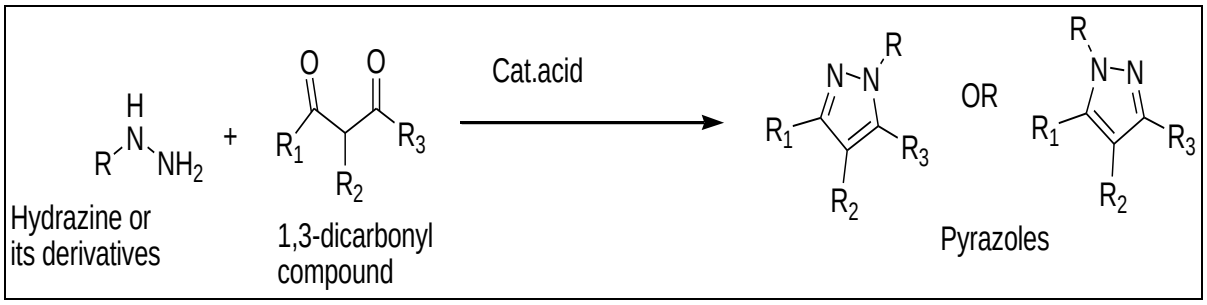


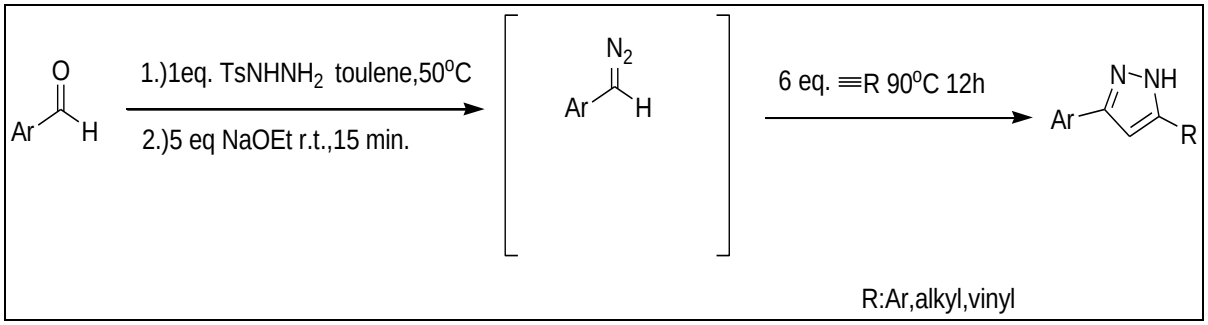
FIG. 2: STRUCTURE OF PYRAZOLE

Some Synthetic Methods of Pyrazole:

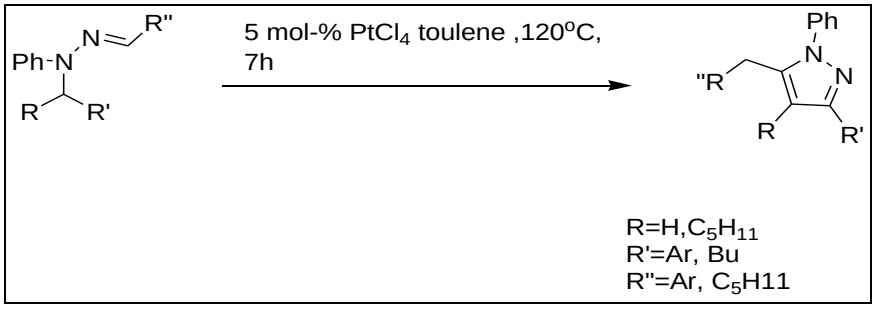
Knorr Pyrazole Synthesis: The Knorr pyrazole synthesis is an organic reaction used to convert a hydrazine or its derivatives and a 1,3-dicarbonyl compound to a pyrazole using an acid catalyst. The mechanism begins with an acid catalyzed imine formation, where in the case of hydrazine derivatives the attack can happen on either carbonyl carbon and result in two possible products. The other nitrogen of the hydrazine derivative then attacks the other carbonyl group which has also been protonated by the acid and forms a second imine group. This diimine compound gets deprotonated to regenerate the acid catalyst and provide the final pyrazole product.



3,5-disubstituted 1*H*-pyrazoles can be prepared by condensation of substituted aromatic aldehydes and to sylhydrazine followed by cycloaddition reaction with terminal alkynes. The reaction is one pot, highly efficient, general and bears a variety of functional groups and sterically hindered substrates to make the pyrazole [67].



A very efficient [3,3] sigmatropic rearrangement of *N*-propargylhydrazones affords convenient access to different functionalized pyrazoles [68].



4-substituted 1*H*-pyrazole-5-carboxylates can be made by the cyclocondensation of unsymmetrical enaminodiketones with *tert*-butylhydrazine hydrochloride or carboxy-methylhydrazine. The regiospecific pyrazoles are formed in good yields [69].

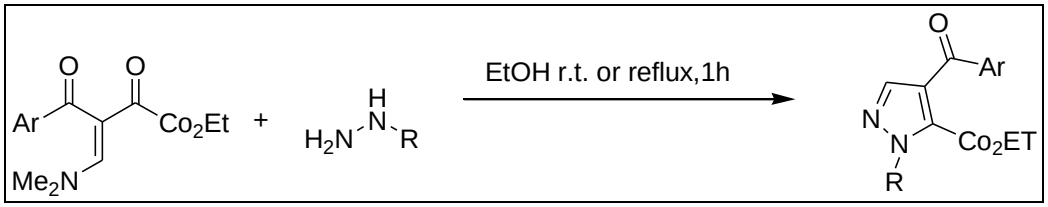


FIG. 3: KNORR PYRAZOLE SYNTHESIS

Indole: Development of indole chemistry started with the study of the indigo dye. Indigo may be transformed to isatin and after that to oxindole. In 1866, Adolf von Baeyer prepared indole by reducing oxindole to indole using zinc dust [14].

Certain indole derivatives were significant dyestuffs until the end of the 19th century. In the 1930s, concern in indole intensified when it became known that the indole substituent is present in many essential alkaoloids (e.g., tryptophan and auxins), and it remains an active area of research today [15].

Indole is an aromatic heterocyclic organic compound with the formula. It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered pyrrole ring. Indole is brodly distributed in the nature and can be produced by a range of bacteria. As an intercellular signal molecule, indole regulates various aspects of bacterial physiology, as well as spore formation, plasmid stability, resistance to drugs, biofilm formation, and virulence [16]. The amino acid tryptophan is an indole derivative and the precursor of the neurotransmitter serotonin [17].

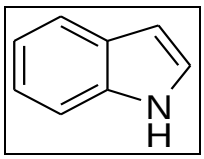


FIG. 4: STRUCTURE OF INDOLE

Some Synthetic Method of Indole:

Leimgruber –Batcho Indole Synthesis: The Leimgruber-Batcho indole synthesis is a series of organic reaction that produce indoles from o-nitrotoluenes [18]. The first step is the formation of an enamine 2 using N,N-dimethylformamide dimethyl acetal and pyrrolidine [19]. The desired indole 3 is then formed in a second step by reductive cyclisation.

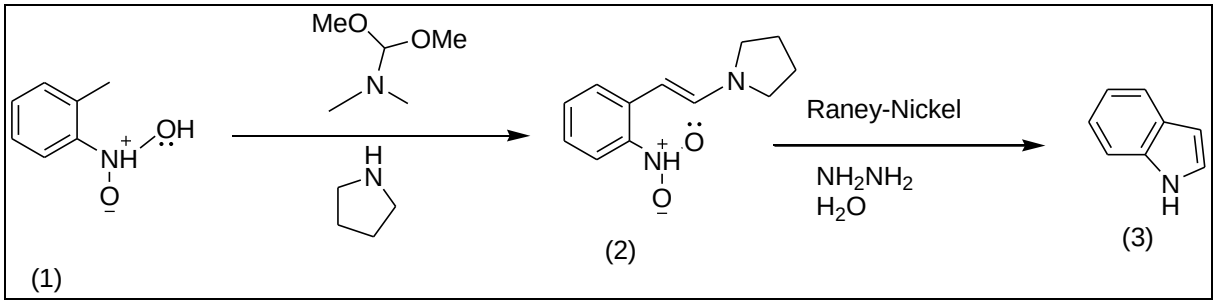


FIG. 5: LEIMGRUBER-BATCHO INDOLE SYNTHESIS

In the above scheme, the reductive cyclisation is effected by Raney nickel and hydrazine. Palladium on carbon and hydrogen, stannous chloride, sodium hydrpsulfite [20] or ironin acetic acid [21] are also effective reducing agents.

Fischer Indole Synthesis: The Fischer indole synthesis is a chemical reaction that generate the aromatic heterocycle indole from a (substituted) phentlhydrazine and an aldehyde or ketone under acidic condition [22].

The reaction was discovered in 1883 by Hermann Emil Fischer. Antimigraine drugs of the triptan class are often synthesized by this method.

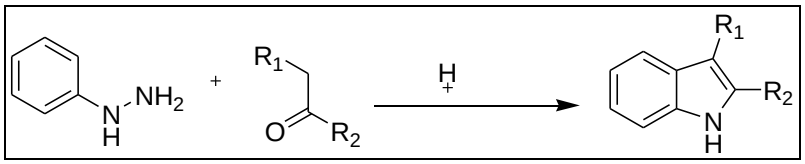


FIG. 6: FISCHER INDOLE SYNTHESIS

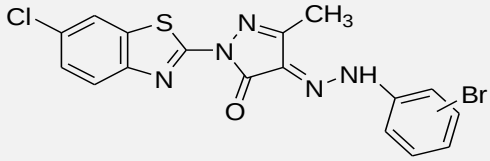
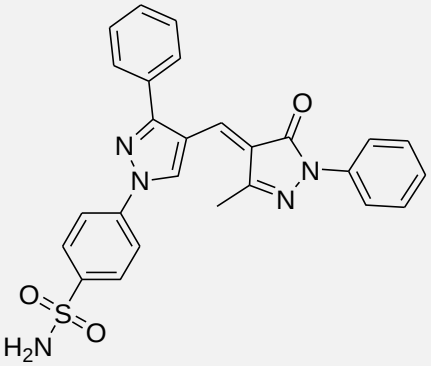
The choice of acid catalyst is very important. Brønsted acids such as HCl, H2SO4, polyphosphoric acid and p-toluenesulfonic acid have been used successfully. Lewis acidssuch as boron trifluoride, zinc chloride, iron chloride, and aluminium chloride are also useful catalysts for this reaction

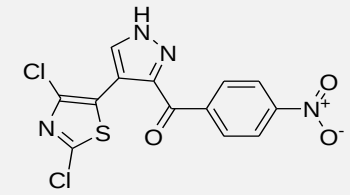
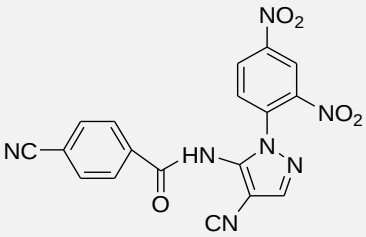
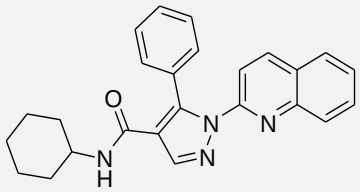
The available literature reports on pyrazole, indole and its derivatives were collected and they are compiled in the following table to get an over view of the knowledge already available on these derivatives and to plan for new pyrazole and indole derivatives.

Literature Review: The Pyrazole and indole moieties were searched in various journals and website extensively. Some interesting reports on derivatives of these nuclei are shown below

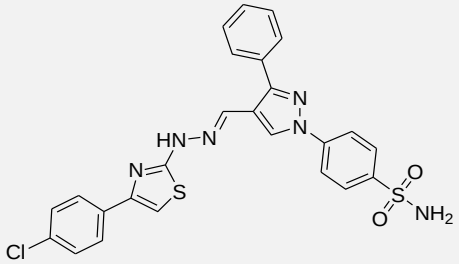
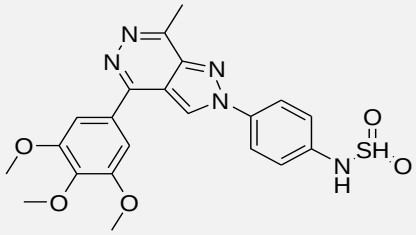
Pyrazole:
Antimicrobial Activity:

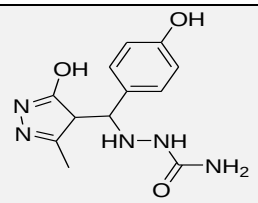
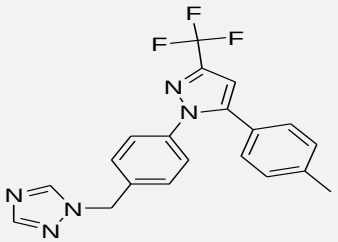
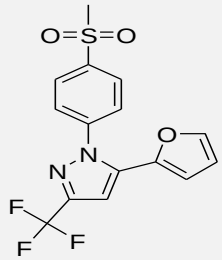
TABLE 1: LITERATURE REPORTS ON PYRAZOLE AND INDOLE DERIVATIVES AND THEIR BIOLOGICAL POTENTIAL

Sr. no.	Author	Year	Active molecules
1	Amir *et. al.*[23]	2011	1-(6'-Chlorobenzothiazol-2-yl)-3-methyl-4(4"bromophenylhydrazono)-2-pyrazolin-5-one. 
2	Khloya *et. al.*[24]	2013	be 4-[4-[(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4H-pyrazol-4-ylidene)methyl]-3-phenyl-1H-pyrazol-1-yl]benzenesulfonamide 
3	Basha et. al.[25]	2015	(4-(2,4-dichlorothiazol-5-yl)-1Hpyrazol-3-yl)(4-nitrophenyl) methanone.

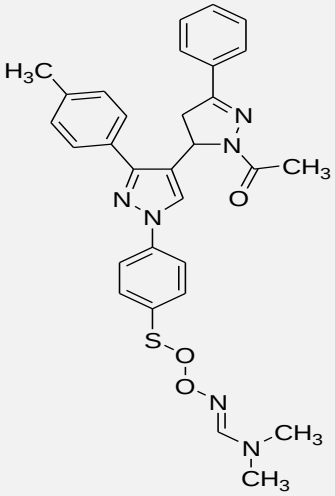
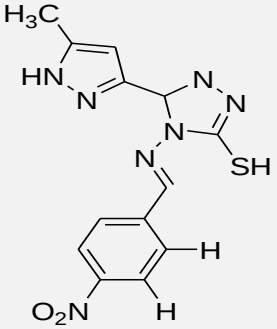
4	Rahimizadeh et.al.[26]	2010	N1-[4-cyano-1-(2,4-dinitrophenyl)-1H-5-pyrazolyl]-4cyanobenzamide 
5	Laxmi et.al.[27]	2013	5-((3-(6-Bromo-2-oxo-2H-chromene-3-yl)-1 phenyl 1H pyrazol4yl) methylene) pyrimidine2,4,6(1H,3H,5H)-trione. 
6	Isloor et.al.[28]	2012	N-cyclohexyl-5-phenyl-1-(quinolin-2-yl)-1H-pyrazole-4-carboxamide. 

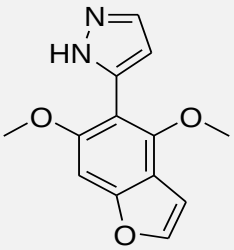
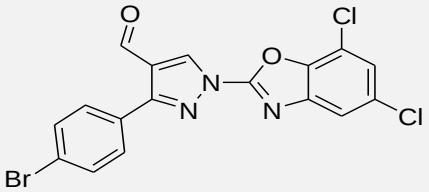
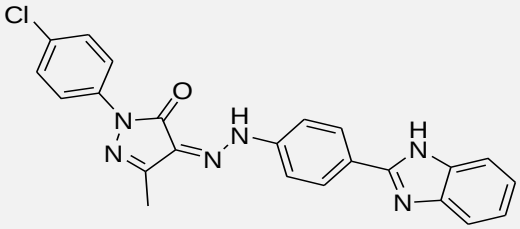
Anti-inflammatory activity

Sr. no.	Author	Year	Active molecules
1	Kumar et.al.[29]	2012	4-(4-{[2-(4-(4-Chlorophenyl)-1,3-thiazol-2yl)hydrazono]methyl}-3-phenyl-1H-pyrazol-1yl)benzenesulfonamide. 
2	Mashooq A. et.al.[30]	2017	7-Methyl-2-(4-sulfonamidophenyl)-4-(3,4,5 trimethoxyphenyl)-2H-pyrazolo[3,4-d] pyridazin. 
3	Kumar et.al.[31]	2016	2-((3-hydroxy-5-methyl-4H-pyrazol-4-yl)(4-hydroxyphenyl)methyl)hydrazinecarboxamide.

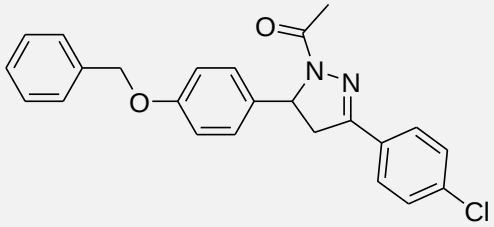
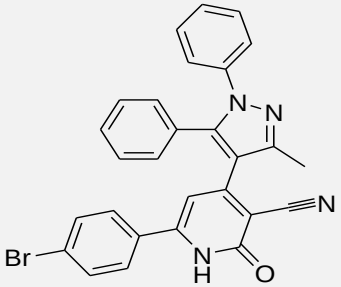
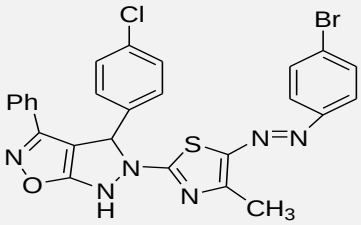
4	Chandna et.al.[32]	2014	 1-{4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzyl}-1H-1,2,4-triazole.
5	Khaled R.et.al.[33]	2015	 5-Furan-2-yl-1-(4-methanesulfonylphenyl)-3-trifluoromethyl1H-pyrazole.
			

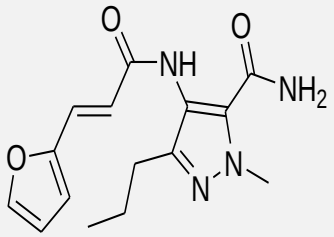
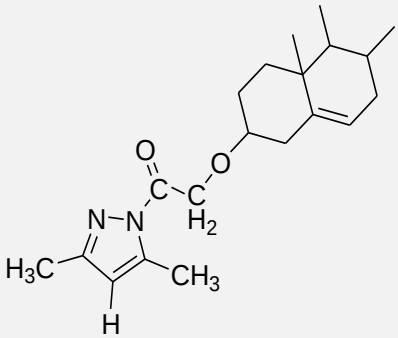
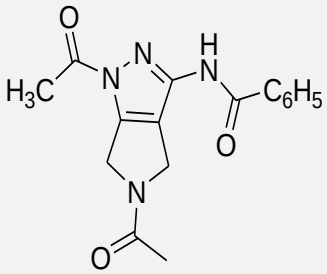
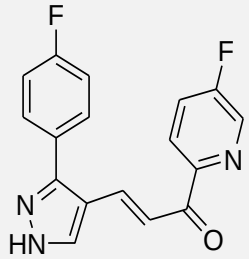
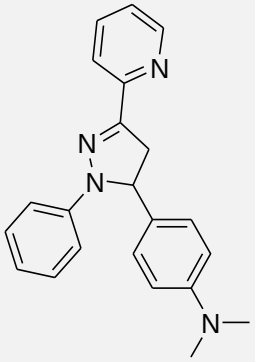
Analgesic Activity

Sr. no.	Author	Year	Active molecules
1	Domiati.et.al.[34]	2016	(E)-N'-(4-(4-(1-acetyl-3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)-3-p-tolyl-1H-pyrazol-1-yl)phenylthioperoxy)-N,N-dimethylformamidine. 
2	Karrouchi et.al.[35]	2016	be 5-(5(3)-methyl-1H-pyrazol-3(5)-yl)-4-((4-nitrobenzylidene)amino)-4H-1,2,4-triazole-3-thiol. 

3	Kumar et.al.[36]	2013	5-(4,6-Dimethoxybenzofuran-5-yl)-1H-pyrazole. 
4	Jayanna et.al.[37]	2013	1-(5,7-Dichloro-1,3-benzoxazol-2-yl)-3-(4-bromophenyl)-1H-pyrazole-4-carbaldehyde. 
5	Chikkula.et.al.[38]	2017	4-(2-(4-(1H-Benzimidazol-2-yl)phenyl)hydrazono)-1-(4-chlorophenyl)-3-methyl-1H-pyrazol-5(4H)-one. 

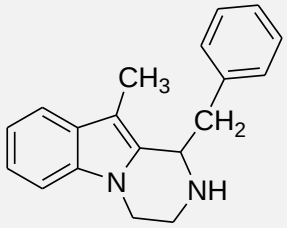
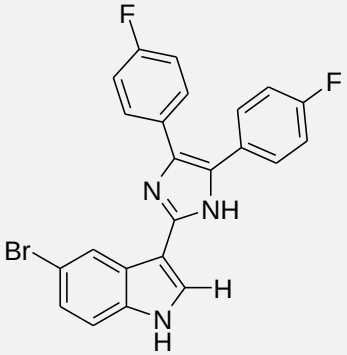
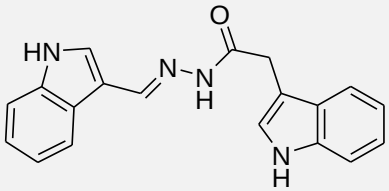
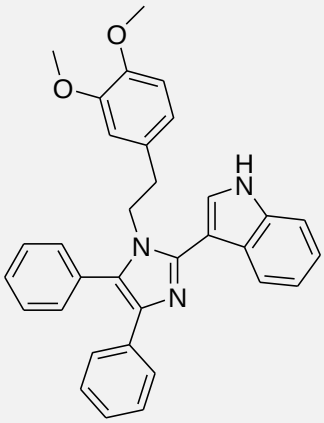
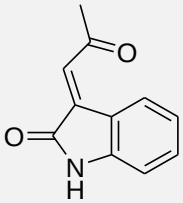
Antiviral activity

Sr. no.	Author	Year	Active molecules
1	Sabbagh.et.al.[39]	2009	1-Acetyl-5-(4-(benzyloxy)phenyl)-3-(4-chlorophenyl)-4,5- dihydro-(1H)-pyrazole 
2	Tantawy et.al.[40]	2012	be6-(4-bromophenyl)-4-(3-methyl-1,5-diphenyl-1H-pyrazol4-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile. 
3	Gomha et.al.[41]	2014	(E)-1-(4-bromophenyl)-2-(2-(4-(4-chlorophenyl)-3-phenyl-4H-pyrazolo[4,3-d]isoxazol-5(6H)-yl)-4-methylthiazol-5-yl)diazene. 

Anticancer activity			
Sr. no.	**Author**	**Year**	**Active molecule**
1	Shi et.al.[42]	2015	(E)-4-(3-(Furan-2-yl) acrylamido)-1-methyl-3-propyl 1H-pyrazole-5-carboxamide. 
2	Siddiqui et.al.[43]	2015	3β-[3',5'-Dimethyl pyrazole-1-yl]carbonylmethoxycholest-5-ene. 
3	Bai et.al.[44]	2012	N-(1,5-diacetyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-yl)benzamide. 
4	Rai U.et.al.[45]	2014	(E)-3-(3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(5-fluoropyridin-2-yl)prop-2-en-1-one. 
5	Sham et.al.[46]	2012	N,N-dimethyl-4[1-phenyl-3-(pyridin-2-yl)-4,5-dihydro-1H pyrazol-5-yl] benzenamine. 

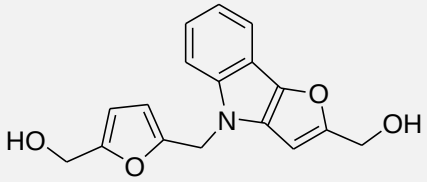
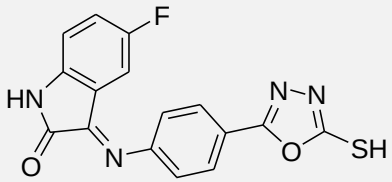
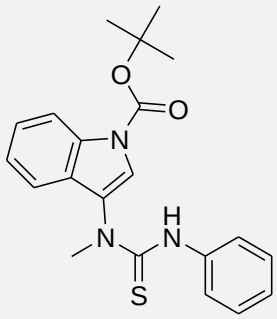
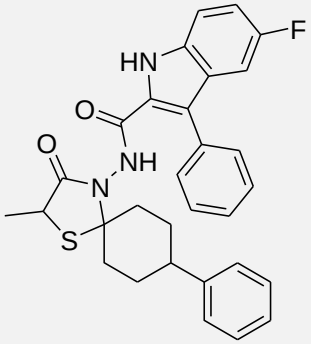
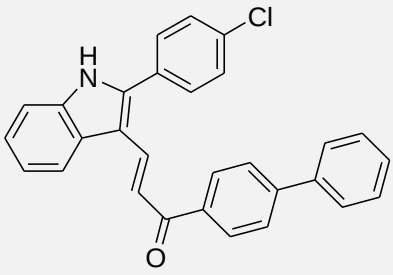
Indole:

Antimicrobial Activity:

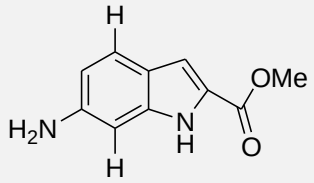
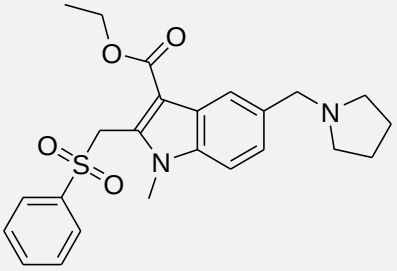
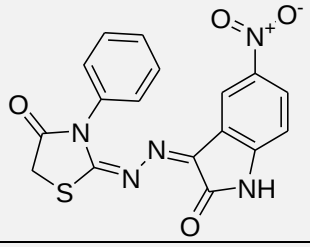
Sr. no.	Author	Year	Active molecules
1	Tiwari et.al.[47]	2005	1-benzyl-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole. 
2	Qawasmeh et.al. [48]	2010	[3-(4,5-bis(4-fluorophenyl)-1H-imidazol-2-yl)-5-bromo-1H-indole]. 
3	Choppara et. al. [49]	2015	N'-((1H-indol-3-yl)methylene)-2-(1H-indol-3-yl)acetohydrazide. 
4	Rajaraman et.al. [50]	2016	3-(1-(3,4-dimethoxyphenethyl)-4,5-diphenyl-1H-imidazol-2-yl)-1H-indole 
5	Majik et.al. [51]	2014	(E)-3-(2-Oxopropylidene)indolin-2-one 

Anticancer activity

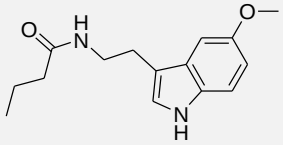
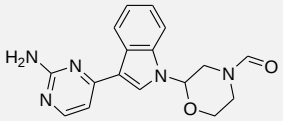
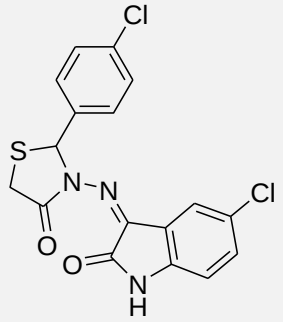
Sr. no.	Author	Year	Active molecules

1	Zhuang et.al.[52]	2013	(5-((2-(Hydroxymethyl)-4H-furo[3,2-b]indol-4-yl)methyl) furan-2-yl) methanol 
2	Gudipati et.al. [53]	2011	3-(4-[5-Mercapto-1,3,4-oxadiazole-2-yl] phenylimino)-5-flouro-indolin-2-one 
3	Budovská et. al. [54]	2013	N-[1-(tert-Butoxycarbonyl)indol-3-yl]methyl-N' -phenylthiourea 
4	Gokce et.al.[55]	2012	5-Fluoro-N-(2-methyl-8-phenyl-3-oxo-1-thia-4-azaspiro[4. 5] dec-4-yl)-3-phenyl-1H-indole-2-carboxamide 
5	H zahran et.al.[56]	2009	(E)-1-Biphenyl-4-yl-3-[2-(4-chlorophenyl)-1Hindol-3-yl]-prop-2-e 

Anti viral activity			
Sr. no.	**Author**	**Year**	**Active molecule**
1	Gao et.al.[57]	2014	Methyl-6-amino-1H-indole-2-caboxylate

			
2	Sellito et.al.[58]	2010	ethyl-1-methyl-2-((phenylsulfonyl)methyl)-5-((pyrrolidin-1yl)methy -oxylate
			
3	Terzioglu et.al.[59]	2006	5-Nitro-3-[(3-phenyl-4-thiazolidinone-2-ylidene)hydrazono]-1H-2-indo
			

Anti-malarial activity

Sr. no.	Author	Year	Active molecules
1	Schuck et.al.[60]	2014	N-(2-(5-methoxy-1H-indol-3-yl)ethyl)butanamide
			
2	Bharate et. al.[61]	2013	(3-(2-Aminopyrimidin-4-yl)-1H-indol-1-yl)(morpholino) methanone
			
3	Shingade et.al.[62]	2013	3-(5-chloro-2-oxoindolin-3-ylideneamino)-2-(4-chlorophenyl)thiazolidin-4-one
			

CONCULSION: One of the most important classes of organic molecules in medical chemistry are heterocyclic compounds, which are utilized as drugs to treat a variety of illnesses. Heterocyclic compounds have been demonstrated to have a broad range of medicinal pharmacological uses through a number of remarkable achievements. Because of their fascinating biological activity, heterocyclic molecules are useful synthetic targets and important structural elements in organic synthesis and medicinal chemistry. The pharmaceutical world is very interested in the

prospective uses of heterocycles as antiviral, anticancer, anti-inflammatory, antifungal, antibacterial, anti-Alzheimer's, and antidiabetic medicines, among other uses. It's interesting to note that in continuing drug development, a growing number of heterocycles have been identified as possible therapeutic candidates.

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