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Therapeutic Activities of Pyrazole

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Abstract:-The aim of this review is to provide an overview of diverse pharmacological activities of pyrazole moiety. Pyrazole are well known and important nitrogen containing 5-membered heterocyclic compounds. Pyrazole chemically known as 1, 2-diazole . Numerous pyrazole derivatives have been found to possess a broad spectrum of biological activities,which stimulated the research activity in this field. Pyrazoles and its derivatives represent one of the most active classes of compounds, which possess wide range of biological activities like anti-bacterial, anti-convulsant, analgesic, anti-microbial, antiinflammatory, anti diabetic, sedative,anti-rheumatic, anticancer, and anti-tubercular activities.The purpose of this review was to collate literature work reported by researchers on pyrazole for their various pharmacological activities and also reported recent efforts made on this moiety.In the present review our main interest is to emphasize the chemistry reported by researchers on pyrazole for their various pharmacological activities.

Key words:-Pyrazole, physical & chemical state, pharmaceutical activity of pyrazoles

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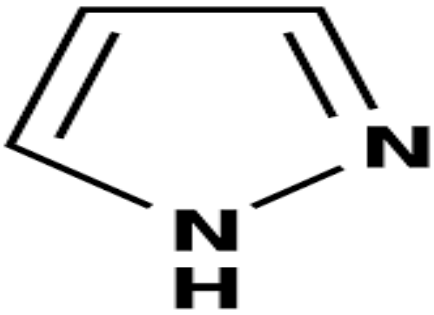
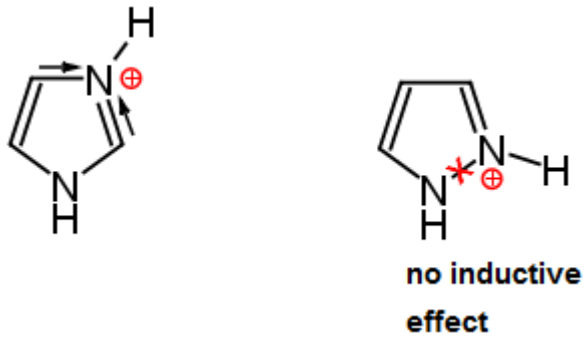
Introduction :-Pyrazole is an organic compound with the formula $C_3H_3N_2H$. Pyrazoles are five member ring heterocyclic compounds, have some structural features with two nitrogen atoms in adjacent position and are also called as azoles [1] .The chemical reactivity of the pyrazole molecule can be explained by the effect of individual atoms. The N-atom at position 2 with two electrons is basic and therefore reacts with electrophiles. The N-atom at position 1 is unreactive, but loses its proton in the presence of base. The combined two N-atoms reduce the charge density at C3 and C5, making C4 available for electrophilic attack. Deprotonation at C3can occur in the presence of strong base, leading to ring opening. Protonation of pyrazoles leads to pyrazoliumcations that are less likely to undergo electrophilic attack at C4, but attack at C3 is facilitated. The pyrazole anion is much less reactive toward nucleophiles, but the reactivity to electrophiles is increased [2] Pyrazoles are aromatic molecules due 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 [3] . Like other nitrogen involving heterocycles, different tautomeric structures can be written for pyrazoles. Unsubstitutedpyrazole can be represented in three tautomeric forms [4] .The molecule is planar; bond lengths and bond angles have been calculated from microwave spectra. It was found from the structural formula that the bond between atoms 3 and 4 is the longest



Pic:1

Physical and chemical properties of Pyrazole moieties: Pyrazole is a π-excessive heterocycle and contains two nitrogen atoms; pyrrole type and pyridine type, at positions 1 and 2. Pyrazole exists in three partially reduced forms. . Pyrazole is a weak base, with pK_b 11.5 (pK_a of the conjugated acid 2.49 at 25 °C). Pyrazoles are also a class of compounds that have the ring C_3N_2 with adjacent nitrogen atoms. Notable drugs containing a pyrazole ring are celecoxib (Celebrex) and the anabolic steroid stanozolol.Pyrazole is a colourless solid with m.p. 69-70° C(compared with 1-alkyl or aryl substituted pyrazoles) is due to intermolecular hydrogen bonding which results in a dimmer., boiling point of pyrazole (186-188° C) is due to intermolecular hydrogen bonding, Pyrazole exist in two identical and non-separable tautomers due to rapid interconversion of tautomers.



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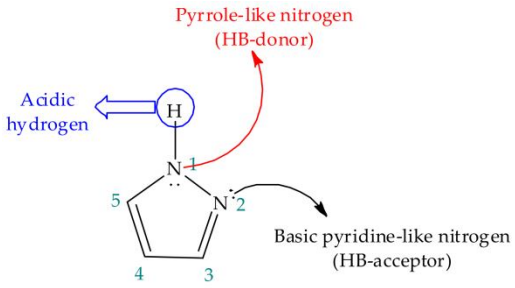
Pyrazoline contain two types of nitrogen atom, pyrrole and pyridine at position 1 and 2 respectively. Pyridine type nitrogen is susceptible to electrophilic attack, and the hydrogen atom attached to the nitrogen at position 1 is more acidic than pyrrolic N-H, so easily removed by nucleophiles. Pyrazole is weaker base (pKa= 2.52), lower basicity is due to extra destabilization of π-bonding after protonation. Pyrazole is very weak acid (pKa=14.21), introduction of electron withdrawing group (-I & -M effect) increase the acidity.



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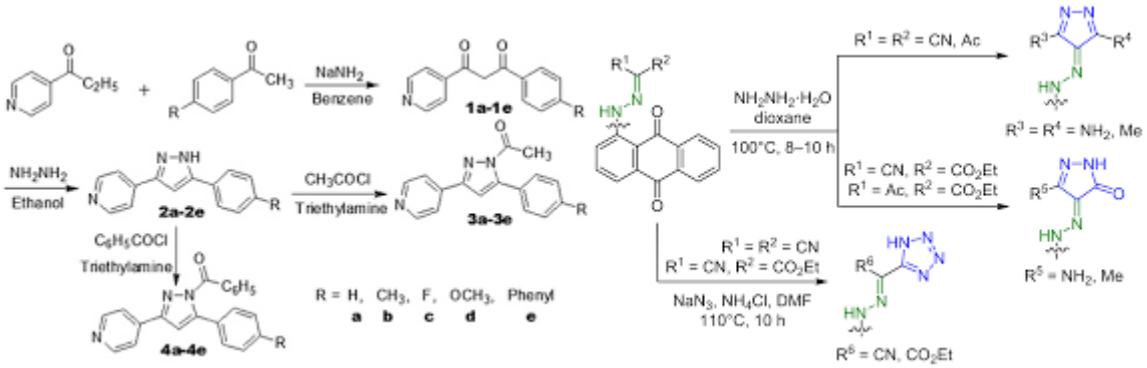
Synthesis of pyrazole:-



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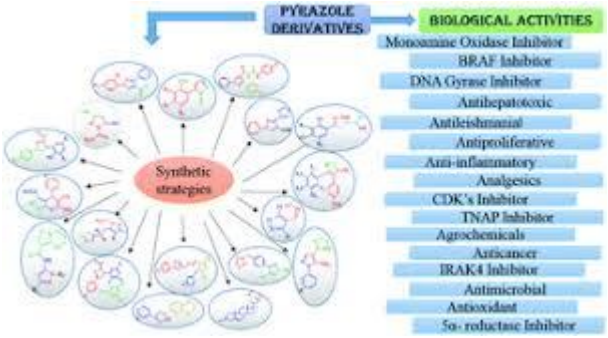
Literature review onPharmacological activity of pyrazole:-



Pic:5

Alan X.WangQinghuaXieBenLaneKarlW.MollisonGinC.HsiehKennanMarshMichaelP.SheetsJayR.LulyMichaelJ.Coghlan*, Bioorganic & Medicinal Chemistry LettersVolume 8, Issue 19, 6 October 1998, Pages 2787-2792(5)
A series of novel pyrazolecarboxamides is disclosed that demonstrate strong immunosuppressant activity in rodent and human mixed leukocyte response (MLR) assays. The synthesis, biological activity, mode of action, and pharmacokinetic properties of this new lead series are discussed.A series of novel pyrazolecarboxamides is disclosed that demonstrate strong immunosuppressant activity in rodent and human mixed leukocyte response (MLR) assays . The synthesis, biological activity, mode of action, and pharmacokinetic properties of this new lead series are discussed.

RuoxiLan,QianLiu,PushengFan,SonyuanLin,Susanthi R. Fernando,DeirdreMcCallion,RogerPertwee,AlexandrosMakriyannis, journal of medicinal chemistry, February 6, 1999(6),As a potent, specific antagonist for the brain cannabinoid receptor (CB1), the biarylpyrazole *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (SR141716A; 1) was the lead compound for initiating studies designed to examine the structure−activity relationships of related compounds and to search for more selective and potent cannabimimetic ligands. A series of pyrazole derivatives was designed and synthesized to aid in the characterization of the cannabinoid receptor binding sites and also to serve as potentially useful pharmacological probes. Therapeutically, such compounds may have the ability to antagonize harmful side effects of cannabinoids and cannabimimetic agents.

McDonald, Edward; Jones, Keith; Brough, Paul A.; Drysdale, Martin J.; Workman, Paul , Current Topics in Medicinal Chemistry, Volume 6, Number 11, 2006, pp. 1193-1203(7).This explains why the chaperone Hsp90 is an exciting protein target for the discovery of new drugs to treat cancer in the clinic, and summarises the properties of natural product derived inhibitors before relating the discovery and current state of development of synthetic pyrazole compounds. Blockade of Hsp90 results in reduced cellular levels of several proteins implicated in cancer including CDK4, ERBB2 and C-RAF, and causes simultaneous inhibition of cancer cell proliferation in culture and of tumor xenograft growth in vivo. Hsp90 has an ATPase domain that is necessary for its Hsp chaperone function, and X-ray crystallography has shown that natural product inhibitors (geldanamycin, radicicol) of Hsp90 function bind to this domain.

NesrinGökhanKelekçi,SamiyeYabanoğlu,EsraKüpeli,UmutSalgın,ÖzenÖzgen,GülberkUçar,Erdem Yeşilada,EnginKendi,AkgülYeşilada,A. AltanBilgin,Bioorganic & Medicinal ChemistryVolume 15, Issue 17, 1 September 2007, Pages 5775-5786(8)
It was shown that monoamine oxidase-B (MAO-B) inhibitors and anti-inflammatory agents might be effective in treating Alzheimer's disease. Therefore, a novel series of 1-thiocarbamoyl-3-substituted phenyl-5-(2-pyrrolyl)-4,5-dihydro-(1*H*)-pyrazole derivatives as promising MAO-B inhibitors was synthesized and investigated for the ability to inhibit selectively the activity of the A and B isoforms of monoamine oxidase (MAO). Most of the synthesized compounds showed high activity against both the MAO-A and the MAO-B . All the synthesized compounds were also tested for their in vivo anti-inflammatory activity by two different bioassays namely, carrageenan-induced oedema and acetic acid-induced increase in capillary permeability in mice. In addition, analgesic and ulcerogenic activities were determined.

Frankline K. Keter, StonardKanyanda, Sylvester S. L. Lyantagaye, James Darkwa, D. Jasper G. Rees & Mervin Meyer ,*Cancer ChemotherapyandPharmacology* volume 63, pages127–138(2008)(9)Apoptosis contributes significantly to the cytotoxic effects of anticancer agents such as cisplatin; therefore in this study the potential anticancer properties of a series of pyrazole palladium(II) and platinum(II) complexes. Cisplatin (*cis*-diamminedichloroplatinum) was first identified for its anti-bacterial activity, and was later also shown to be an efficient anticancer agent. However, the therapeutic use of this anticancer drug is somewhat limited by its toxic side effects, which include nephrotoxicity, nausea, and vomiting. Furthermore the development of drug-resistant tumours is commonly observed followingtherapy with cisplatin. Hence there is a need for improved platinum derived drugs to overcome these limitations.

R.M.Claramunt,L.Bouissane,M.P.Cabildo,M.P.Cornago,J.Elguero,A.Radziwon,C.Medina,Bioorganic & Medicinal ChemistryVolume 17, Issue 3, 1 February 2009, Pages 1290-1296,(10)Seven N-unsubstitutedcurcuminoidpyrazoles have been synthesized from the corresponding β-diketones (including curcumin). Then the possibility of curcuminoidpyrazoles regulating the activity of matrix metalloproteinases (MMPs) is evaluated by human intestinal epithelial cells in vitro. Zymographic analysis revealed that three compounds significantly down-regulated MMP-9 activity on inflammation-induced intestinal epithelial cells, making them original candidates for the treatment of inflammatory bowel disease (IBD).

MarcoBonesia,MonicaR.LoizzoaGiancarlo,A.Stattia,SylvieMichel,bFrançois,Tillequin,bFrancesco,Menichinia ,Bioorganic & Medicinal Chemistry Letters,Volume 20, Issue 6, 15 March 2010, Pages 1990-1993,(11)A series of chalcones (1–9) and pyrazoles (10–18) was prepared to investigate their potential activity as Angiotensin I-Converting Enzyme (ACE) inhibitors. Their structures were verified by elemental analysis, UV, IR, MS, ^{1}H NMR, ^{13}C NMR, and 2D NMR experiments. Among tested compounds, chalcone 7 exerted the highest activity with an IC_{50} value of 0.219 mM, while the most potent pyrazole was 15 (IC_{50} value of 0.213 mM).

RamaiyanManikannana,RamaiyanVenkatesana,ShanmugamMuthusubramaniana,PerumalYogeeswarib,DharmarajanSriramb,Bioorganic & Medicinal Chemistry Letters

Volume 20, Issue 23, 1 December 2010, Pages 6920-6924,(12)Azines derived from substituted phenacyl aryl/cyclohexyl sulfide on treatment with excess phosphorous oxychloride in *N*,*N*-dimethylformamide have been found to yield two isomeric pyrazolesin each case. A plausible mechanism has been suggested for the formation of the products. The antimycobacterial activity of the isomeric compounds has been tested against *Mycobacterium tuberculosis* (MTB).

Samir M. El-Moghazy, Flora F. Barsoum, Hamdy M. Abdel-Rahman & Adel A. Marzouk ,*Medicinal Chemistry Research* **volume 21**, pages1722–1733(2012)(13),A novel series of pyrazoles containing benzenesulfonamides, 1,3,4-oxadiazole-2-thiones, 4-substituted-1,2,4-triazole-3-thiones, and 2-substituted-1,3,4-thiadiazoles has been synthesized. Anti-inflammatory activity of some synthesized compounds was evaluated in vivo utilizing a standard acute carrageenan-induced paw edema method. The most active anti-inflammatory agents were evaluated for ulcerogenic liability in rats compared to indomethacin and celecoxib as reference standards. Molecular modeling studies were initiated herein to validate the attained pharmacological data and provide understandable evidence for the observed anti-inflammatory behavior.

BurcuÇalışkan, Akın Yılmaz, İlkerEvren, SevdaMenevşe, OrhanUludag & ErdenBanoglu ,*Medicinal Chemistry Research* **volume 22**, pages782–793(2013)(14)In this article, a series of novel 1-benzyl-5(3)-*p*-tolyl-1*H*-pyrazole-3(5)-carboxylic acid derivatives are synthesized and characterized by IR, ^{1}H NMR, and mass spectroscopy. Compounds were evaluated for their in vivo analgesic and anti-inflammatory activity using the *p*-benzoquinone-induced writhing test and the carrageenan-induced paw edema model, respectively. Out of 14 compounds tested those exhibited potent analgesic and/or anti-inflammatory activity as compared to reference drugs aspirin and indomethacin. Anticancer activity of these compounds was assessed against five cancer cell lines with the MTT assay. Compounds with high anti-inflammatory activity and also with mild anti-inflammatory activity exhibited promising anticancer activity against some selected cell lines.

Ashraf M. Mohamed, Weal A. El-Sayed, Musaed A. Alsharari, Husam R. M. Al-Qalawi & Mousa O. Germoush *Archives of Pharmacal Research* **volume 36**, pages1055–1065(2013)(15),A series of pyrazolopyridine and pyridopyrimidine derivatives were newly synthesized using 3,5-bisarylmethylene-1-methylpiperidone as the starting material. The anticancer activities of the synthesized compounds were evaluated using 59 different human tumor cell lines, representing cancers of CNS, ovary, renal, breast, colon, lung, leukemia, and melanoma, prostate as well as kidney. Some of the tested compounds, especially those with a fluorine substituent at the para-position in the phenyl ring and those with a pyridopyrimidine-2-thione with a free –NH or –SH, exhibited greater in vitro anti-tumor activities at low against the human tumor cell lines. Additionally, some of the compounds had moderate inhibitory effects on the growth of the cancer cell lines. The detailed synthesis, spectroscopic data and antitumor properties of the synthesized compounds are reported.

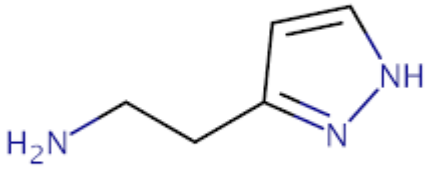
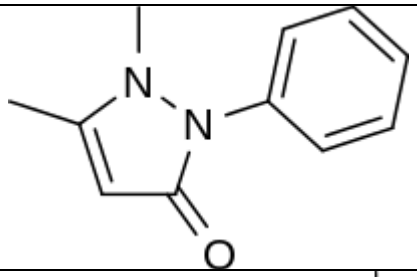
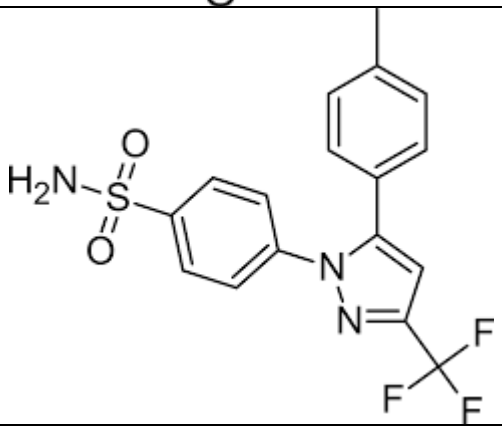
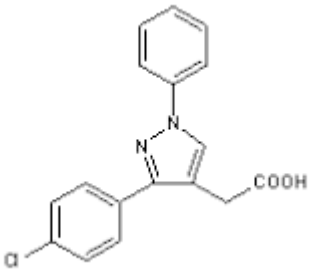
KEN Tzanetou, S.AHaroutounian - Frontiers in chemistry, 2014 (16)- frontiersin.org Angiogenesis is a mulit-step process by which new blood vessels are formed from preexisting vasculature. It is a key rate limiting factor in tumor growth since new blood vessels are necessary

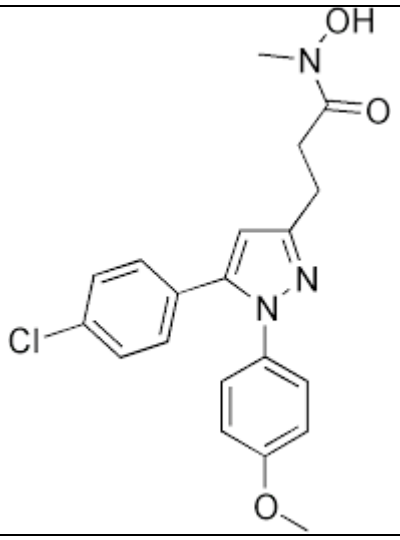
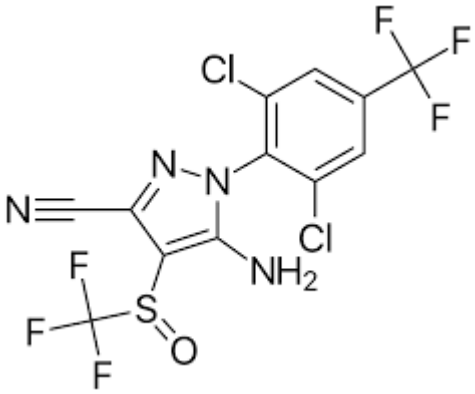
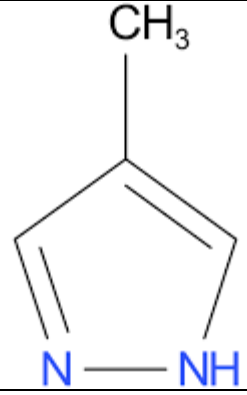
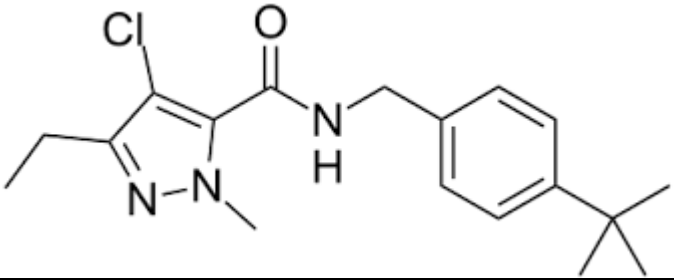
to increase tumor size. In this context it has been shown that anti-angiogenic factors can be used in cancer therapy. Among the plethora of heterocyclic compounds administered as anti-angiogenesis agents, pyrazoles constitute one of the bottlenecks of this category. Currently, several pyrazole based compounds are administered or are in Phase II and III trials and new targets emerge. It is highly possible that the advent of the next two decades will lead to the discovery and use of additional pyrazoles whose anti-angiogenic profile will position them in the forefront of the battle of various malignancies. The present review is an attempt to focus on those pyrazoles that arise as anti-angiogenesis agents commenting both on the chemistry and bioactivity that these exhibit aiming to contribute to the perspectives that they hold for future research.

ungHeeJoo, Jeong-Eun Huh, Jee Hyun Lee, Doo Ri Park, Seul Gee Lee, Sun Choi, HwaJeong Lee, Seong-Won Song, YongmiJeong, Ja-Il Goo, Yongseok Choi, Hye Kyung Baek, Sun Shin Yi, Soo Jin Park, JiEun Lee, SaeKwang Ku, Won Jae Lee, Kee-In Lee, Soo Young Lee & Yun SooBae ,*Scientific Reports* volume 6, Article number: 22389 (2016)(17),Osteoclast cells (OCs) are differentiated from bone marrow-derived macrophages (BMMs) by activation of receptor activator of nuclear factor ligand .Activation of NADPH oxidase (Nox) isozymes is involved in implicating Noxisozymes as therapeutic targets for treatment of osteoporosis. Here,apyrazole derivative, Ewha-18278 has high inhibitory potency on Noxisozymes. Blocking the activity of Noxincluding reactive oxygen species (ROS) generation, activation of mitogen-activated protein (MAP) kinases and NF-κB, and OC differentiation. To evaluate the anti-osteoporotic function of Ewha-18278, the derivative was applied to estrogen-deficient ovariectomized (OVX) ddY mice. Oral administration of Ewha-18278 (10 mg/kg/daily, 4 weeks) into the mice recovered bone mineral density, trabecular bone volume, trabecular bone length, number and thickness, compared to control OVX ddY mice. Moreover, treatment of OVX ddY mice with Ewha-18278 increased bone strength by increasing cortical bone thickness. We provide that Ewha-18278 displayed Nox inhibition and blocked the RANKL-dependent cell signaling cascade leading to reduced differentiation of OCs. Our results implicate Ewha-18278 as a novel therapeutic agent for the treatment of osteoporosis.

ZhiXuaChuan,GaobQing-ChengRenb,Xu-Feng,SongcLian-Shun,FengbZao-ShengLva,European Journal of Medicinal Chemistry,Volume 139, 20 October 2017, Pages 429-440,(18)The co-infection between the mainly pathogen *Mycobacterium tuberculosis* (MTB) and HIV, and the incidence of drug-resistant TB, multi-drug resistant TB, extensively drug-resistant TB as well as totally drug-resistant TB have further aggravated the mortality and spread of this disease. Thus, there is an urgent need to develop novel anti-TB agents against both drug-susceptible and drug-resistant TB. The wide spectrum of biological activities and successful utilization of pyrazole-containing drugs in clinic have inspired more and more attention towards this kind of heterocycles. Numerous of pyrazole-containing derivatives have been synthesized for searching new anti-TB agents, and some of them showed promising potency and may have novel mechanism of action.

Table: Marketed products of pyrazole with pharmacological activities (19)

Betazole is a H2 receptor agonist. It is used clinically to test gastric secretory function	
Phenazone (INN), antipyrine (USAN, or analgesic is an analgesic and antipyretic.	
Celecoxib is a non-steroidal antiinflammatory drug (NSAID) used in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms.	
Lonazolac is a non-steroidal antiinflammatory drug.	

Tepoxalin is a non steroidal anti Inflammatory drug approved for veterinary use in the United States and the European Union.	
Fipronil is a broad spectrum insecticide that disrupts the insect central nervous system by blocking the passage of chloride ions through the GABA receptor and glutamate-gated chloride channels (GluCl), components of the central nervous system.	
Fomepizole or 4-methylpyrazole is indicated for use as an antidote in confirmed or suspected methanol or ethylene glycol poisioning. A part from medicinal uses, the role of 4-methylpyrazole in coordination chemistry has been studied.	
Tebufenpyrad is a strong mitochondrial complex I inhibitor. Like Rotenone, it inhibits electron transport chain by inhibiting the complex I enzymes of mitochondria which ultimately leads to lack of ATP production and finally cell death.	

Conclusion:-The reviewed Pyrazole is a unique template that is associated with several biological activities. The various substituted pyridine and are having antibacterial, anticonvulsant, analgesic, antimicrobial, anti-inflammatory, ant diabetic, sedative antirheumatic, anticancer, and antitubercular activities. This article high lightened research work of many researchers reported in literature for different pharmacological activities on pyrazole compounds synthesized. The review has presented comprehensive details of pyrazole analogues, potent compounds reported for particular pharmacological activity and the method or technique involved in evaluation process. More investigations must be carried out to evaluate more activities of pyrazole for many diseases.

References:-

1. T, Eicher, S.Hauptmann, Edition IInd, 'The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and applications', Wiley-(2003).

2. Raj K Bansal. Heterocyclic chemistry. 4th ed.: New international publishers; 2007.

3. Krygowski, T. M.; Anulewicz, R.; Cyrafiski, M. K.; Puchala, A.; Rasata, D.Tetrahedron, 1998, 54, 12295. 4. Behr, L. C.; Fusco, R.; Jarboe, C. H., The Chemistry of Heterocyclic Chemistry: Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and CondensedRings; Wiley & Sons: London, 1967.

5. Alan X.WangQinghuaXieBenLaneKarlW.MollisonGinC.HsiehKennanMarshMichaelP.SheetsJayR.LulyMichael J.Coghlan*,Bioorganic & Medicinal Chemistry LettersVolume 8, Issue 19, 6 October 1998, Pages 2787-2792

6.RuoxiLan,QianLiu,PushengFan,SonyuanLin,Susanthi R. Fernando,DeirdreMcCallion,RogerPertwee,AlexandrosMakriyannis, journal of medicinal chemistry, February 6, 1999

7.McDonald, Edward; Jones, Keith; Brough, Paul A.; Drysdale, Martin J.; Workman, Paul , Current Topics in Medicinal Chemistry, Volume 6, Number 11, 2006, pp. 1193-1203

8.NesrinGökhanKelekçi[a]SamiyeYabanoğlu[b]EsraKüpeli[c]UmutSalgın[a]ÖzenÖzgen[d]GülberkUçar[b]ErdemYeşilada[e]EnginKendi[d]AkgülYeşilada[f]A. AltanBilgin[a], Bioorganic & Medicinal ChemistryVolume 15, Issue 17, 1 September 2007, Pages 5775-5786

9. Frankline K. Keter, StonardKanyanda, Sylvester S. L. Lyantagaye, James Darkwa, D. Jasper G. Rees & Mervin Meyer ,*Cancer ChemotherapyandPharmacology* volume 63, pages127–138(2008)

10.R.M.Claramunt[a]L.Bouissane[a]M.P.Cabildo[a]M.P.Cornago[a]J.Elguero[b]A.Radziwon[c]C.Medina[c]Bioorganic & Medicinal ChemistryVolume 17, Issue 3, 1 February 2009, Pages 1290-1296

11.MarcoBonesi[a]MonicaR.Loizzo[a]Giancarlo,A.Statti[a]SylvieMichel[b]FrançoisTillequin[b]Francesco Menichini[a] ,Bioorganic & Medicinal Chemistry Letters,Volume 20, Issue 6, 15 March 2010, Pages 1990-1993

12. RamaiyanManikannan[a]RamaiyanVenkatesan[a]ShanmugamMuthusubramanian[a]PerumalYogeeswari[b]DharmarajanSriram[b]Bioorganic & Medicinal Chemistry Letters Volume 20, Issue 23, 1 December 2010, Pages 6920-6924

13. Samir M. El-Moghazy, Flora F. Barsoum, Hamdy M. Abdel-Rahman & Adel A. Marzouk ,*Medicinal Chemistry Research* **volume 21**, pages1722–1733(2012)

14. BurcuÇalışkan, Akın Yılmaz, İlkerEvren, SevdaMenevşe, OrhanUludag & ErdenBanoglu ,*Medicinal Chemistry Research* **volume 22**, pages782–793(2013)

15. Ashraf M. Mohamed, Weal A. El-Sayed, Musaed A. Alsharari, Husam R. M. Al-Qalawi & Mousa O. Germoush *Archives of Pharmacal Research* **volume 36**, pages1055–1065(2013)

16. KEN Tzanetou, SA Haroutounian - Frontiers in chemistry, 2014

17.ungHeeJoo, Jeong-Eun Huh, Jee Hyun Lee, Doo Ri Park, Seul Gee Lee, Sun Choi, HwaJeong Lee, Seong-Won Song, YongmiJeong, Ja-Il Goo, Yongseok Choi, Hye Kyung Baek, Sun Shin Yi, Soo Jin Park, JiEun Lee, SaeKwang Ku, Won Jae Lee, Kee-In Lee, Soo Young Lee & Yun SooBae ,*Scientific Reports* volume 6, Article number: 22389 (2016)

18. ZhiXu[a]ChuanGao[b]Qing-ChengRen[b]Xu-FengSong[c]Lian-ShunFeng[b]Zao-ShengLv[a]**,**European Journal of Medicinal Chemistry**,**Volume 139, 20 October 2017, Pages 429-440

19. wikipedia.com/pyrazoles on 6-08-2013.