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Review Article

VERSATILE ACTIVITIES OF PYRAZOLES: MINI REVIEW

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ABSTRACT

Pyrazoles and their derivatives are an important class of five member nitrogen containing hetrocyclic compounds having much importance on account of their biological activities.These compounds have shown much attention recently due to their diverse biological profile.The importance of the pyrazole nucleus in the field of medicinal chemistry has given a great impetus to search for new potential drugs.

Keyword: Biological activities, Pyrazoles

INTRODUCTION

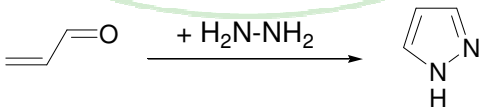
Chemistry

Pyrazoles are heterocyclic compounds containing a five-membered ring consisting of three carbon atoms united to two nitrogen atoms, thus: the derivatives are orientated from the imino group, the second position being at the other nitrogen atom. Pyrazole, $C_3H_4N_2$, was obtained by E. Buchner by heating pyrazole 3,4,5-tricarboxylic acid; and by L. Balbiano, who condensed epichlorhydrin with hydrazine hydrate in the presence of zinc chloride:

$$C_3H_6OCl + 2N_2H_4 = C_3H_4N_2 + N_2H_4.HCl + H_2O + H_2$$

It may also be prepared by the union of diazomethane with acetylene, and by warming the acetal of propargyl aldehyde with an aqueous solution of hydrazine sulphate. It crystallizes in colourless needles, is very stable and behaves as a weak base. It does not combine with the alkyl iodides.

Pyrazoles are produced synthetically through the reaction of α,β-unsaturated aldehydes with hydrazine and subsequent dehydrogenation.



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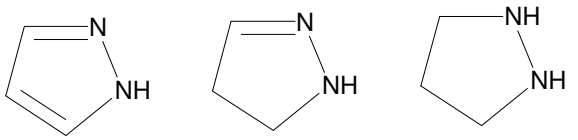
In medicine, pyrazoles are used for their analgesic, anti-inflammatory, antipyretic, antiarrhythmic, tranquilizing, muscle relaxing, psychoanaleptic,anticonvulsant, monoamineoxidase inhibiting, antidiabetic and antibacterial activities. Pyrazoles react with

potassium borohydride to form a class of ligands known as Scorpionates.

Structurally related compounds are pyrazoline and pyrazolidine.

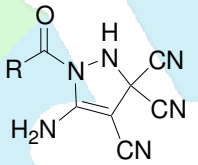


pyrazole pyrazoline pyrazolidine

Biological activities

Anticonvulsant

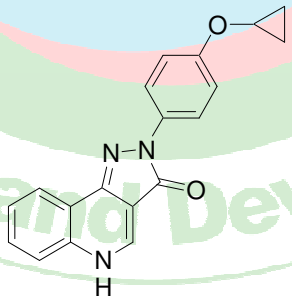
Abdel-Aziz *et al* synthesized some newer pyrazole derivatives (**1**) and tested them for the anticonvulsant activity against PTZ induced seizures in mice. Three compounds exhibited remarkable protective effect against clonic seizures induced by ip injection of PTZ at a dose level of 20 mg kg^{-1}. The results of anticonvulsant activity are nearly close to phenobarbital sodium at a dose level of 30 mg $kg^{-1}$and more potent than phenytoin sodium at a dose level of 30 mg kg^{-1}.[1]



R = H, CH_3, OCH_3, NH_2

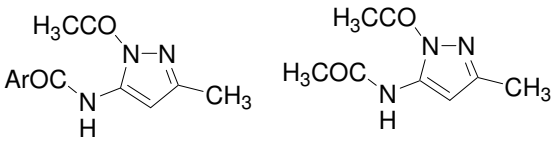
(**1**)

Mitchinson *et al* synthesized 2,5-dihydropyrazolo[4,3-*c*]pyridin-3-ones (**2**) that were $GABA_A$ receptor benzodiazepine binding site ligands with functional selectivity for the α3 subtype over the α1 subtype. SAR studies to optimize this functional selectivity were described.[2]



(**2**)

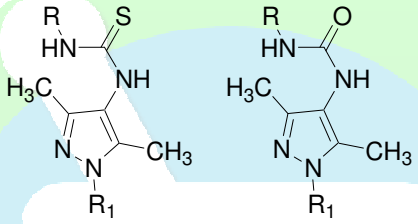
Some unsymmetrical R_i-exocyclic and *N*-endocyclic derivatives (**3**, **4**) from benzoylation of 3- and 5-aminopyrazole were prepared by Michon *et al* with the aim of comparing their anticonvulsant activity towards the MES and scMET tests. Unambiguous proof of their structure was obtained from heteronuclear long-range correlation spectroscopy and NOE difference spectra. Only the *N*-exe-pyrazole benzamides showed good protection with respect to these tests.[3]



(**3**) (**4**)

Ar = Ph, MePh, OMePh

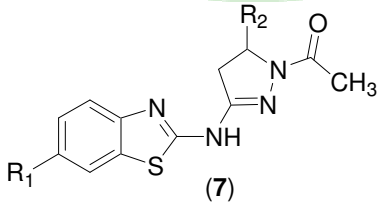
Several thiourea and urea derivatives (**5**, **6**) were prepared by the reaction of 4-aminopyrazoles with substituted isothiocyanates or isocyanates. The novel compounds were tested anticonvulsant activity using by pentylenetetrazole-induced seizure (PTZ) and maximal electroshock seizure (MES) tests. Among the tested compounds, thiourea derivatives were afforded 90 and 100% protection in PTZ and MES tests at 50 mg/kg, respectively. Urea derivatives were afforded 82 and 100% protection both at 25 and 50 mg/kg. [4]



(**5**) (**6**)

R = CH_3, C_2H_5, C_3H_7, cyclohexyl, benzyl, phenyl
R_1 = H, CH_3

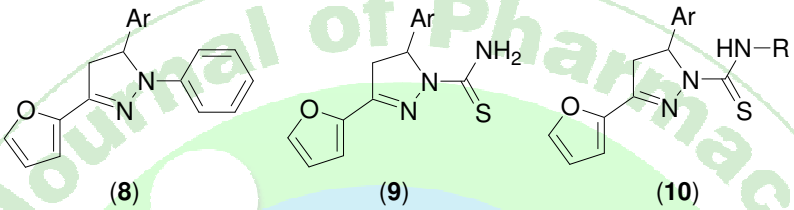
A series of 6-substituted-2- [(1-acetyl-5-substituted)-2-pyrazolin-3-yl]aminobenzothiazole (**7**) were synthesized using appropriate synthetic route and evaluated experimentally against maximal electroshock test. Selected compounds were evaluated for neurotoxicity, hepatotoxicity and behavioral study. The most active compound, 6-methyl-2-[(1-acetyl-5-(4-chlorophenyl))-2-pyrazolin-3-yl]aminobenzothiazole exhibited an ED_{50} of 25.49 mmol/kg, TD_{50} of 123.87 mmol/kg and high protective index (PI) of 4.86 compared to standard drug phenytoin. The 3D-QSAR analysiswas carried out by PHASE program and a statistically reliable model with good predictive power (r2¼ 0.9220, q2¼ 0.8144) was achieved. The 3D-QSAR plots illustrated insights into the structure activity relationship of these compounds which may aid in the design of potent aminobenzothiazole derivatives as anticonvulsant agents.[5]



(**7**)

R_1 = H, Cl, NO_2, CH_3
R_2 = C_6H_5, 4-Cl-C_6H_4, 4-OH-C_6H_4, C_4H_3O, 4-OMe-C_6H_4

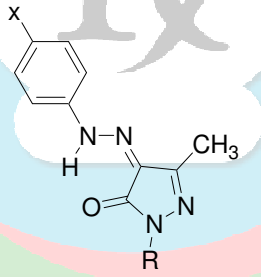
Twelve 1-phenyl-, 1-thiocarbamoyl- and 1-*N*-substituted thiocarbamoyl-3-(2-furyl)-5-phenyl/(2-furyl)-2-pyrazoline derivatives (**8-10**) were synthesized. Anticonvulsant activities of the compounds were determined by maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (metrazol) (scMet.) tests, neurotoxicities were determined by rotarod toxicity test on albino mice. 1,5-Diphenyl-3-(2-furyl)-2-pyrazoline, 1-*N*-allylthiocarbamoyl-3-(2-furyl)-5-phenyl-2-pyrazoline, 1-*N*-allylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline and 1-*N*-phenylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline were active at 100-300 mg/kg dose levels. 1-Thiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline, 1-*N*-methylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline and 1-*N*-ethylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline were found protective against MES and scMet. at 30-300 mg/kg dose levels.



(**8**) (**9**) (**10**)

Ar = C_6H_5, 2-furyl
R = CH_3, C_2H_5, C_3H_5, C_6H_5

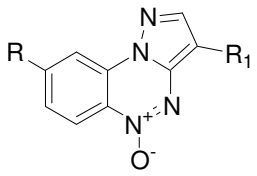
The synthesis of a new series of 4-arylhydrazono-2-pyrazoline-5-ones (**11**) was described by Kucukguzela *et al*. Compounds were evaluated for anticonvulsant activity. One compound showed 40% protection against pentylenetetrazole-induced seizures in albino Swiss mice.[7]



(**11**)

R = H, CH_2-CH_2OH, C_6H_5
X = triazole, oxadiazole

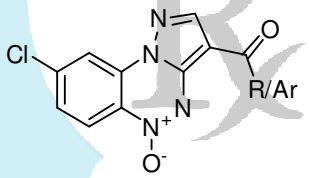
The synthesis and the binding study of new 3-arylesters and 3-heteroarylpyrazolo[5,1-c][1,2,4]benzotriazine 5-oxide 8-substituted (**12**) were reported by Guerrini *et al*. The nature of these substituents (in terms of lipophilic and electronic features) seemed to influence the binding affinity. High-affinity ligands were studied in mice *in vivo* for their pharmacological effects, considering six potential benzodiazepine actions: anxiolytic-like effects, muscle relaxant effects, motor coordination, anticonvulsant action, spontaneous motor activity, and ethanol-potentiating action. Two compounds showed an inverse-agonist profile. These compounds were evaluated also for their binding at benzodiazepine site on $GABA_A$ receptor complex ($GABA_A$/BzR complex) subtype to evaluate their subtype selectivity. [8]



(**12**)

R = Br, I, Me, OEt, OMe, SMe
R_1 = 2-furyl, 3-furyl

Guerrini *et al* further reported the synthesis and binding studies of a series of 3-acylpyrazolo[5,1-c][1,2,4]benzotriazine 5-oxides 8-substituted (**13**). High-affinity ligands at benzodiazepine site on GABAA receptor complex ($GABA_A$/BzR complex) were obtained when the 3-aroyl substituent is represented by a five-member heteroaroyl ring (furoyl-, thenoyl-, and pyrroyl-). Moreover the type of heteroaroyl ring at position 3 influences the feature of the substituent at position 8 to obtain high-affinity ligands: a 'hydrogen-bond acceptor ring' at position 3 is synergic with an electron donor substituent at position 8, while a 'hydrogen-bond donor ring' is synergic with a withdrawing substituent. Three compounds were deeply studied *in vivo* for their pharmacological effects considering six potential benzodiazepine actions: motor coordination, anticonvulsant action, spontaneous motor activity and explorative activity, anxiolytic-like effects, mouse learning and memory modulation, and ethanol-potentiating action. To rationalize and qualitatively interpret the $GABA_A$/Bz binding affinities of compounds a dynamic molecular modeling study has been performed, with the aim of assessing the preferred geometry of protein–ligand complex.[9]

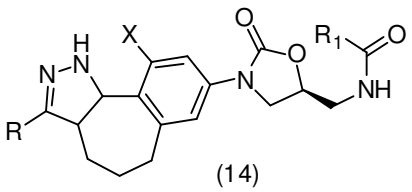


(**13**)

R/Ar = H, CH_3, Ph, *o*-OCH_3Ph, *p*-OCH_3Ph
3-pyridyl, 2-furyl, 2-thienyl, 2-pyrrolyl

Antimicrobial

Boyer *et al* developed a novel series of conformationally-restricted oxazolidinones (**14**) which possessed a fused pyrazole ring substituted with various alkyl, aryl and heteroaryl substituents. A number of analogs exhibited potent activity against both Gram-positive and fastidious Gram-negative organisms.[10]

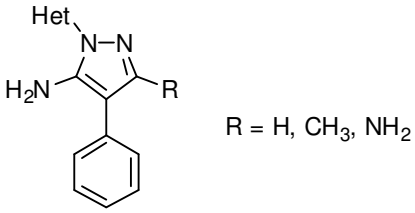


(14)

R = H, alkyl, or heteroaryl
R_1 = alkyl, aryl, or heteroaryl
X = H, F

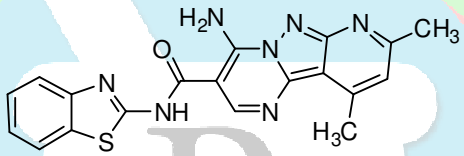
The regioselective synthesis of 1-heteroaryl-5-amino-4-phenylpyrazoles and 1-heteroaryl-5-amino-3-methyl-4-phenylpyrazoles (**15**) was achieved by the treatment of heteroarylhydrazines with α-phenylformylacetonitrile and α-

phenylacetylacetonitrile, respectively by Aggarwal *et al*. All the fourteen compounds were tested for their *in vitro* antibacterial activity against three Gram-positive and two Gram-negative bacteria. Six compounds from this series were found to be equipotent or more potent than the commercial antibiotics (Linezolid and Cefroxime axetil).[11]



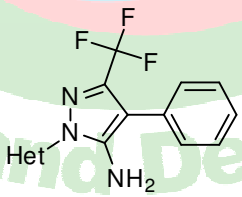
(**15**)

Bondock *et al* used enaminonitrile as key intermediate for the synthesis of polyfunctionally substituted heterocycles (e.g. pyrazoles, isoxazole, pyrimidines, thiazolo[3,2-*a*]pyrimidine, tetrazolo[1,5-*a*]pyrimidine, pyrido[1,2-*a*]pyrimidine, 1,5-benzodiazepine, and pyrazolo[1,5-*a*]pyrimidine) incorporating benzothiazole moiety (**16**) *via* its reactions with some *N*-nucleophiles. Representative compounds of the synthesized products were tested and evaluated as antimicrobial agents.[12]



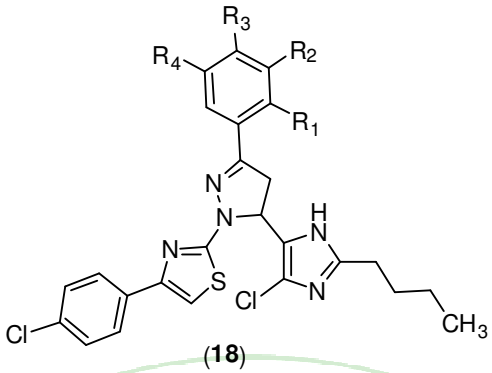
(**16**)

Kumar *et al* treated 1,1,1-trifluoromethyl-3-cyano-3-phenylpropanone with several heteroarylhydrazines in refluxing ethanol that afforded 1-heteroaryl-5-amino-4-phenyl-3-trifluoromethylpyrazoles (**17**) in a regioselective manner. The compounds were tested for their antibacterial property against six Gram-positive and three Gram-negative bacteria. Two compounds, namely 1-(benzothiazol-2′-yl)-5-amino-4-phenyl-3-trifluoromethylpyrazole and 1-(6′-methylbenzothiazol-2′-yl)-5-amino-4-phenyl-3-trifluoromethylpyrazole have displayed antibacterial activity comparable to the commercial antibiotics.[13]



(**17**)

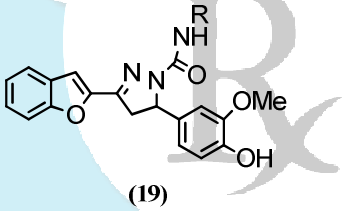
Dawane *et al* prepared several 1-(4-(4'-chlorophenyl)-2-thiazolyl)-3-aryl-5-(2-butyl-4-chloro-1*H*-imidazol-5yl)-2-pyrazoline derivatives (**18**) by the base catalyzed treatment of appropriate chalcones with 4-(4'-chlorophenyl)-2-hydrazino-thiazole in polyethylene glycol (PEG-400) as an alternative reaction solvent. All the synthesized compounds were tested for their antimicrobial activities against *Escherichia coli* (MTCC 2939), *Salmonella typhi* (MTCC 98), *Staphylococcus aureus* (MTCC 96), *Bacillus subtilis* (MTCC 441), *Aspergillus niger* (MTCC 281), *Trichoderma viridae* (MTCC 167), *Penicillium chrysogenum* (MTCC 160), *Fusarium moniliforme* (MTCC 156) and *Candida albicans* (MTCC 183). Most of the compounds showed potent antibacterial and antifungal activity.[14]



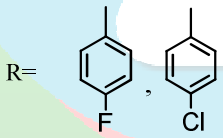
(**18**)

R_1 = H, OH; R_2 = H, I, Br, Cl
R_3 = H, Cl, Me, NH_2, OMe
R_4 = H, Cl, Me, I, Br

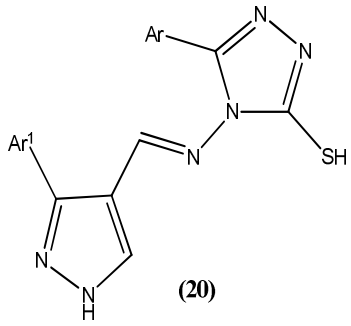
In search for a new antimicrobial agent, a series of benzufuran based 1,3,5-substituted analogues (**19**) were synthesized by *Rangaswamy et al*.The tested compounds exhibited good antimicrobial acivity at concentration 1.0 and 0.5mg/ml compared with standard, streptomycin and fluconazole respectively.[15]



(**19**)



Vijesh *et al,* synthesized the new pyrazole derivatives containing triazoles and benzoxazoles as potent antimicrobials.The compound **(20)** having 2,5-dichlorothiophene substituent on pyrazole moiety and a triazole ring showed significant antimicrobial activity.[16]



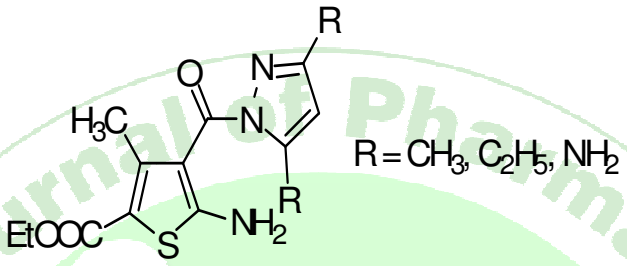
(**20**)

Ar=2,4-Dichlorophenyl, 4-Thioanisyl, 2,5-Dichlorothiophene, Biphenyl

Ar^1=1-Naphthyloxymethyl, Isonicotinyl, 6-Methylnicotinyl

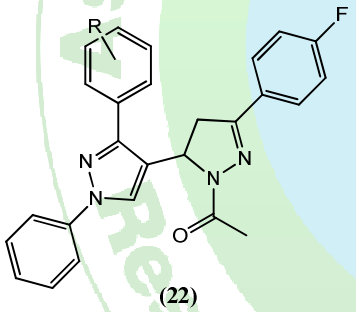
Anti-inflammatory

A series of 5-ethyl-2-amino-3-pyrazolyl-4-methylthiophenecarboxylate (**21**) were prepared by Hafez *et al*. The compounds were evaluated for anti-inflammatory, analgesic and ulcerogenic activities. Among the compounds studied, compounds containing the substituted hydrazide at C-3 position showed more potent anti-inflammatory activity than the standard drug (Indomethacin and Aspirin), without ulcerogenity.While other compounds showed moderate activities.[17]



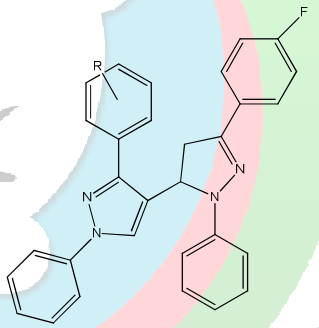
(21)

Jadhav *et al* synthesized a new series of fluoro substituted pyrazoline derivatives (**22**) and (**23**).The newly synthesized compounds were characterized and screened for their in vivo anti-inflammatory activity.Compounds were found to be more potent than standard drug Diclofenac.[18]



(22)

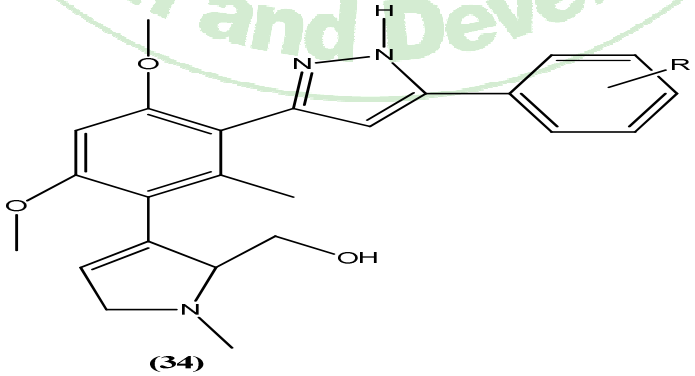
R=4-F,4-Cl,4-Br,4-Me,4-OMe,3-NO_2,H



(23)

R=4-F,4-Br,4-Cl,4-Me,3-NO_2,H,4-OMe

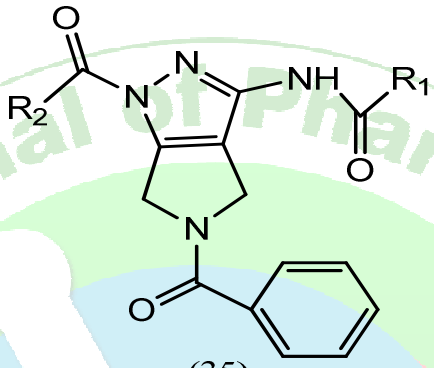
Anticancer



(34)

R- 2-Cl, 2-Cl-4-NO_2

Bai et al synthesized a new series of novel 1-acyl-3-amino-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole derivatives were designed and synthesized. These derivatives were initially evaluated for their in vitro anticancer activity against human colon carcinoma HCT-116 cell line, and compounds **(35)** was chosen for further evaluation their in vitro activity against other five human cancer cell lines. The result indicate that most of the target compounds have considerable in vitro anticancer activity. The most active compound 11a was found to be 4- to 28-fold more potent than (R)-roscovitine against six human cancer cell lines.The compound 11a was assessed for its activity against 12 kinases, and then evaluated for its interaction mode by docking experiments with cyclin-dependent kinase 5 (CDK5) and glycogen synthase kinase-3b (GSK3b).[24]

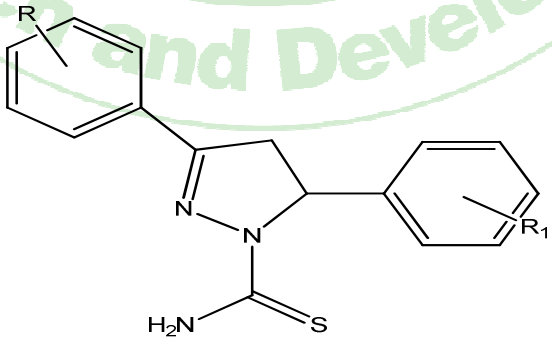


(35)

R_1- Phenyl

R_2- CH_3

Two series of pyrazole derivatives designing for potential EGFR kinase inhibitors have been discovered by *Lv et al*.Compond exhibited significant EGFR inhibitory activity. Compound 3-(3,4-dimethylphenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide **(36)** displayed the most potent EGFR inhibitory activity with IC_{50} of 0.07 lM, which was comparable to the positive control erlotinib. Docking simulation was performed to position compound C5 into the EGFR active site to determine the probable binding model. Antiproliferative assay results indicating that some of the pyrazole derivatives own high antiproliferative activity against MCF-7. Compound C5 showed significant antiproliferative activity against MCF-7 with IC_{50} of 0.08 lM. Therefore, compound C5 with potent inhibitory activity in tumor growth inhibition would be a potential anticancer agent.[25]



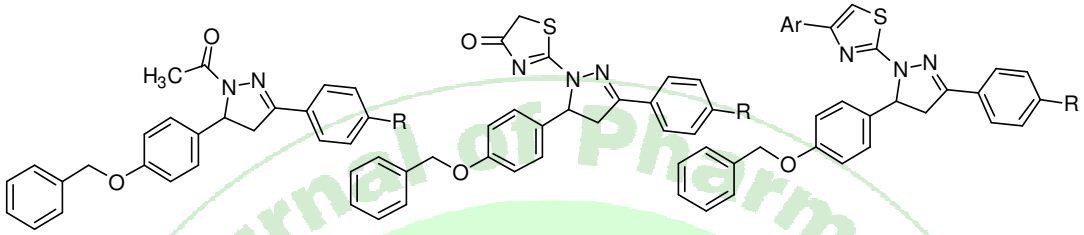
(36)

R- 3,4-$2CH_3$

R_1-4-OCH_3

Antiviral

New *N*-acetyl and *N*-thiocarbamoyl derivatives of 4,5-dihydropyrazole (**37-39**) were synthesized by Sabbagh *et al* starting from α,β-unsaturated ketones under the effect of hydrazine hydrate and thiosemicarbazide, respectively. The antiviral activity for such novel compounds against a broad panel of viruses in different cell cultures revealed that *N*-acetyl 4,5-dihydropyrazole was the only active one at subtoxic concentrations against vaccinia virus (Lederle strain) in HEL cell cultures with a 50% effective concentration (EC_{50}) value of 7 µg/ml.[26]



(**37**) (**38**) (**39**)

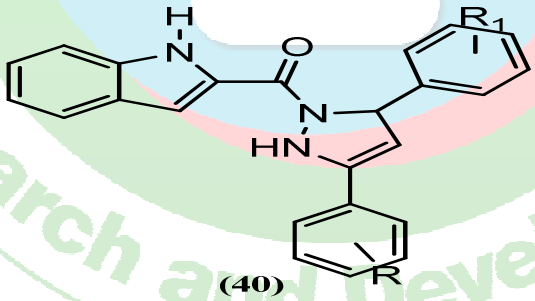
R = H, halo, nitro, alkyl, alkoxy

Antidiabetic

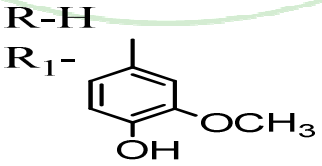
A novel Zn mononuclear complex with 3-carboxy-pyrazole ligand has been prepared by Viseras *et al*.This compound exhibits a potential *in vivo* antidiabetic activity and the *in vitro* toxicity can be considered negligible.[27]

Antioxidant

The structures of newly synthesized compounds were elucidated by spectroscopic methods such as IR, ^{1}H NMR, ^{13}C NMR, mass, ^{1}H NMR spectra and elemental analysis by Sharath *et al.* Antioxidant assays like 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging, 2,2-azinobis (3 ethylbenzothiazoline-6-sulfonic acid) (ABTS _þ) radical ion decolorization assay and lipid peroxidation activity (LPO) were performed. Among the synthesized analogues compound **(40)** revealed broad spectrum of antioxidant activity.[28]



(40)



CONCLUSION

In conclusion, the structural diversity and biological importance of pyrazoles have made them attractive targets in designing and synthesis of pyrazole derivatives as new class of structural entities of medicinal importance.

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