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PYRAZOLINE DERIVATIVES AND ITS PHARMACOLOGICAL POTENTIAL-REVIEW

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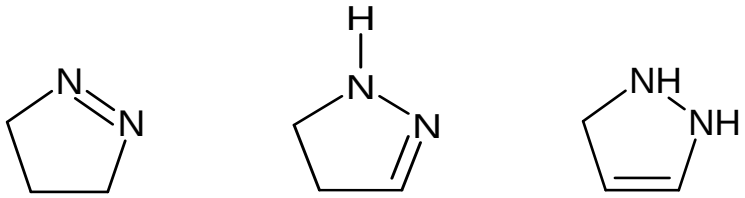
ABSTRACT

Pyrazoline is an important scaffold in the drug discovery process. Various synthetic derivatives of pyrazoline are prepared and evaluated for their various biological activities in a different model. Some analogs of the pyrazoline derivatives are more potent than the corresponding standard drugs. Hence the pyrazoline is considered to be a lead molecule for future drugs. The present review articles discuss the pharmacological activities of pyrazoline derivatives such as Antineoplastic, Antimicrobial, Anti-inflammatory, 5α-reductase inhibitor, Cyclo-oxygenase inhibitor, Anti-malarial, Hypoglycemic and etc.

KEYWORDS: Pyrazoline, Pyrazoline derivatives, Antineoplastic, Antimicrobial, Anti-inflammatory, 5α-reductase inhibitor and anti-malarial.

INTRODUCTION



1-Pyrazoline 2-Pyrazoline 3-Pyrazoline

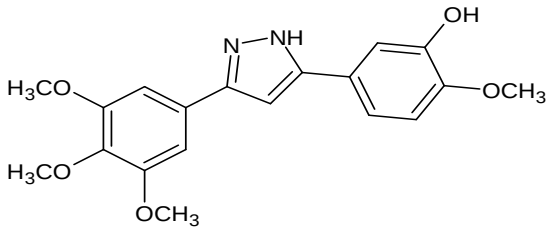
Pyrazolines is a heterocyclic chemical compound with the molecular formula $C_3H_6N_2$ containing three carbon atoms and two adjacent nitrogen atoms. Pyrazoline has three possible

tautomeric forms, specially 1-pyrazoline, 2-pyrazoline, and 3-pyrazoline. Pyrazoline has less stable than the corresponding pyrazoles. It is also called the five-membered heterocyclic ring which has two nitrogen atoms in nearby position and contains two endocyclic double bonds. Noteworthy consideration has been concentrated on pyrazolines and pyrazoline derivatives due to important pharmacological actions as antineoplastic, antimicrobial, anti-fungal, anti-inflammatory, 5α-reductase inhibitor, Cyclo-oxygenase inhibitor, Anti-malarial, Hypoglycemic properties.

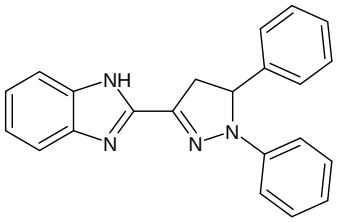
Pharmacological Activities

Anti-cancer activity

Marlie Johnson et.al reported the synthesis of 2-methoxy-5-[3-(3,4,5-trimethoxyphenyl)-1*H*-pyrazol-5-yl] phenol derivatives show anti-cancer activity.[1]

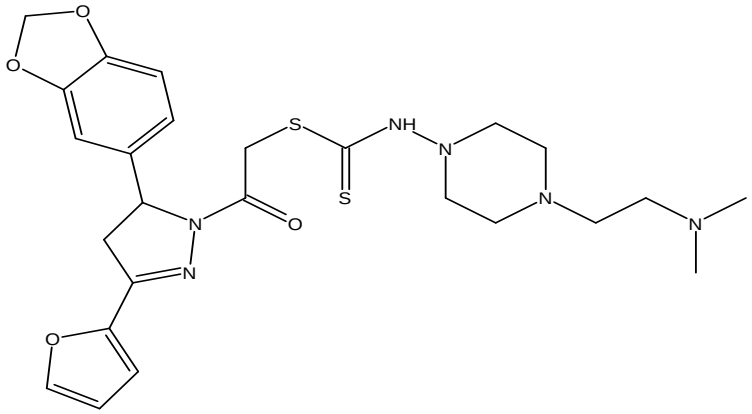


X.-H. Liu, B.-F. Ruan, J.Li, F.-H. Chen, B.-A. song, H.-L. Zhu, P.S. Bhadury, and J. Zhao[2] reported the synthesis and biological activity of chiral dihydro pyrazole such as 2-(1,5-diphenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-1*H*-benzimidazole show promising activity was observed against Leukemia CCRF-CEM and RPMI-8226 cell lines with GI_{50} values of 2.23 and 2.76 µM.



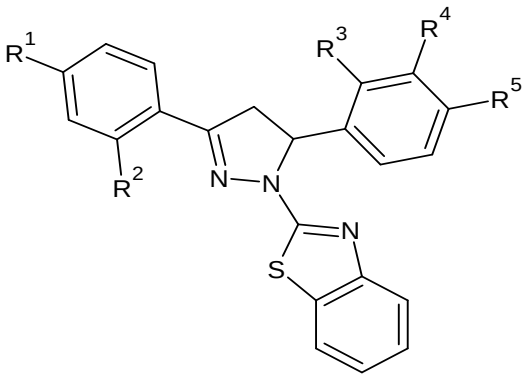
Mehlika et al., (2013) synthesized new novel pyrazoline derivatives were synthesized via the reaction of 1-(chloroacetyl)-3-(2-furyl)-5-aryl-2-pyrazoline with sodium salts of N, N-disubstituted dithiocarbamic acids. Each derivative was evaluated for its ability to inhibit acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) using a modification of Ellman's spectrophotometric method. The compound was also investigated for its cytotoxic

properties using the MIT assay. The most potent AChE inhibitor was found as compound 7 was 1-(((4-(2-Dimethylaminoethyl)piperazin-1-yl)- thiocarbamoylthio)acetyl)-3-(2-furyl)-5-(3,4-methylene- dioxyphenyl)-2-pyrazoline. These compounds bearing 2-dimethylaminoethyl and 3,4-methylenedioxyphenyl moieties were also found to be the most effective inhibitor of BuChE. The MTT assay indicated that the effective concentration of compound 7 was lower than its cytotoxic concentration.[3]



Anti-Microbial activity

Vandana et al.,(2009) synthesized series of 3,5-diaryl-1-benzolopyrazoline derivatives by the reaction of appropriately substituted chalcones and 2-hydrazinobenzthiazole in ethanol. These compounds are tested for biological activity against a variety of test organisms. The compounds 23, 28, 32,36,37,38,39 showed a broad range of activity as inhibition zone was found against all plant and human bacteria and fungi.[4]



23: R_1=Cl, R_2= R_3= R_4= R_5=H

28: R_1=Cl, R_2= R_5= R_4=H, R_3=OH

32: R_1=Cl, R_2= R_3= R_4=H, R_5=OCH_3

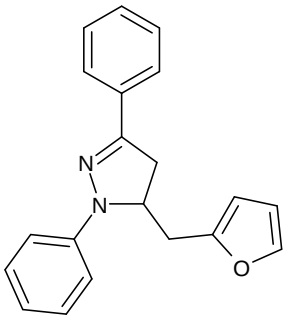
36: R_1= R_5=Cl, R_2= R_3= R_4=H

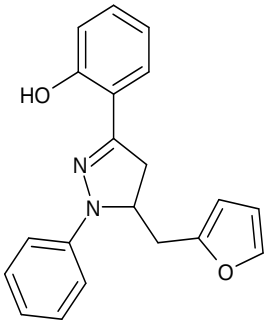
37: R_1= CH_3, R_2= R_3= R_4=H, R_5=Cl

38: R_1=OCH_3, R_2= R_3= R_4=H, R_5=Cl

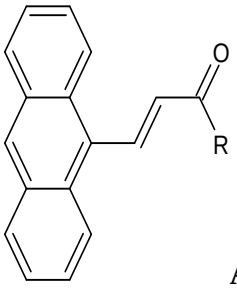
39: R_1=Cl, R_2= R_3= H, R_4=R_5=OCH_3

Biswajit Chandra Das, Debjit Bhowmik, Chiranjib B, G. Mariappan[5] reported Synthesis, biological evaluation of some new pyrazoline compounds such as (I).1,3 (diphenyl)-5-(furfuryl)-2-pyrazoline, (II).2-{5-[(furan-2-yl)methyl]-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}phenol shows both anthelmintic and anti-microbial activity.

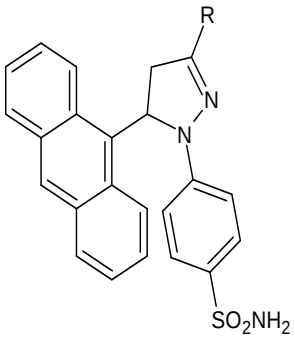


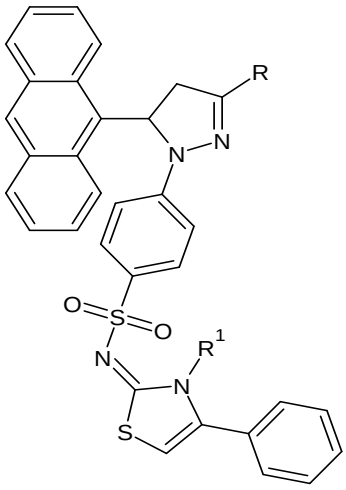


A series of di- and tri-substituted pyrazoles were synthesized by Salem et al., (1997) and the compounds are screened for their antibacterial and antifungal activity[6] following agar-diffusion-method, using gram-positive bacteria Staphylococcus aureus and gram-negative bacteria Escherichia coli. The antifungal testing was carried out against Candida Albicans.



A

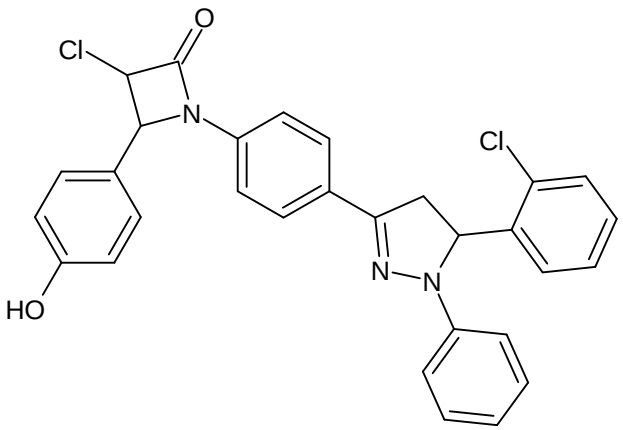




C

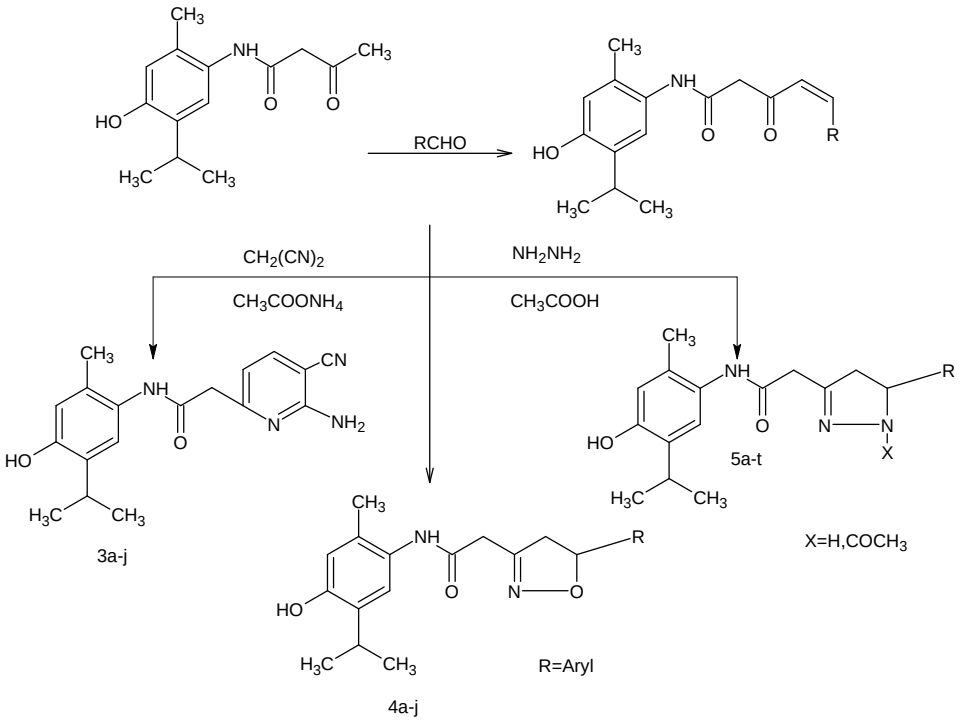
R		R^1
A	C_6H_5	C_6H_5
B	p-$CH_3C_6H_4$	cyclohexyl
C	p-BrC_6H_4	α-Naphthyl

Shailesh et al., (2012) synthesized some novel phenyl pyrazoline derivatives[7] were synthesized by reacting 3-chloro-1-(4-(3-(substituted-phenyl)prop-2-enoyl)phenyl)-4-(4-hydroxyphenyl)azetidine-2-one (0.01 M) and phenylhydrazine (0.001 M) in presence of acetic acid (glacial). All synthesized products were evaluated for their antimicrobial activity. All the products were tested for their antibacterial and antifungal activities by the broth dilution method. MIC valued revealed that amongst newly synthesized compound having chlorophenyl type linkage such as 3-chloro-1-(4-(5-(2-chlorophenyl)-4,5-dihydro-1-phenyl-1*H*-pyrazol-3-yl)phenyl)-4-(4-hydroxyphenyl)azetidin-2-one has shown good activity against bacterial strains rest of all compounds exhibit moderate improvement in activity against some of the pathogenic strains.

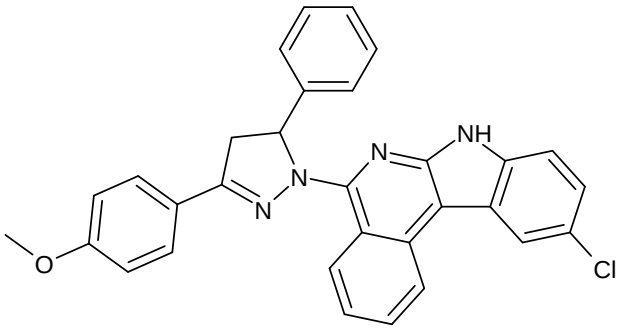


3-chloro-1-(4-(5-(2-chlorophenyl)-4,5-dihydro-1-phenyl-1*H*-pyrazol-3-yl)phenyl)-4-(4-hydroxyphenyl) azetidin-2-one

J M Desai et al., synthesized some of the pyrazoline derivatives 5a-t that have been screened for antimicrobial activity.[8] The product showed moderate to good activities.

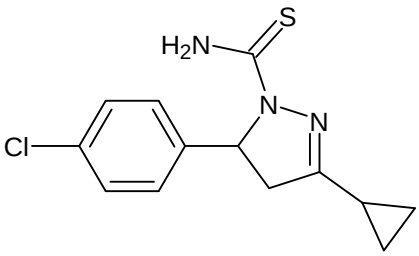


Based on the biological activities exhibited by pyrazoline compounds, Hiremath et al., (2001) reported the synthesis and biological activities of new 5-hydrazino-10-substituted-7H-indolo(2,3-c) isoquinolin-5-yl)-3,5-disubstituted pyrazoles, -3-methyl pyrazol-5-ones and-3, 5-disubstituted pyrazolines from that 1-(10-chloro-7H-indolo(2,3-c) isoquinoline-5-yl)-3-(p-methoxyphenyl)5-phenyl pyrazoline compound shows moderate to highly active against E. coli, S. aureus, P. aeruginosa, and P. Vulgaris.[9]

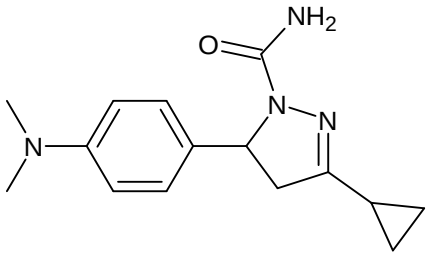


Anti-Inflammatory Activity

Nadia A. Khalil et al. (2012) synthesized (I).5-(4-chlorophenyl)-3-cyclopropyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide and (II).3-cyclopropyl-5-[4-(dimethylamino) phenyl]-4,5-dihydro-1*H*-pyrazole-1-carboxamide shows the highest free-radical scavenging and anti-inflammatory activities[10], thus can be useful in the prevention of oxidative stress and anti-inflammation-related disorders.

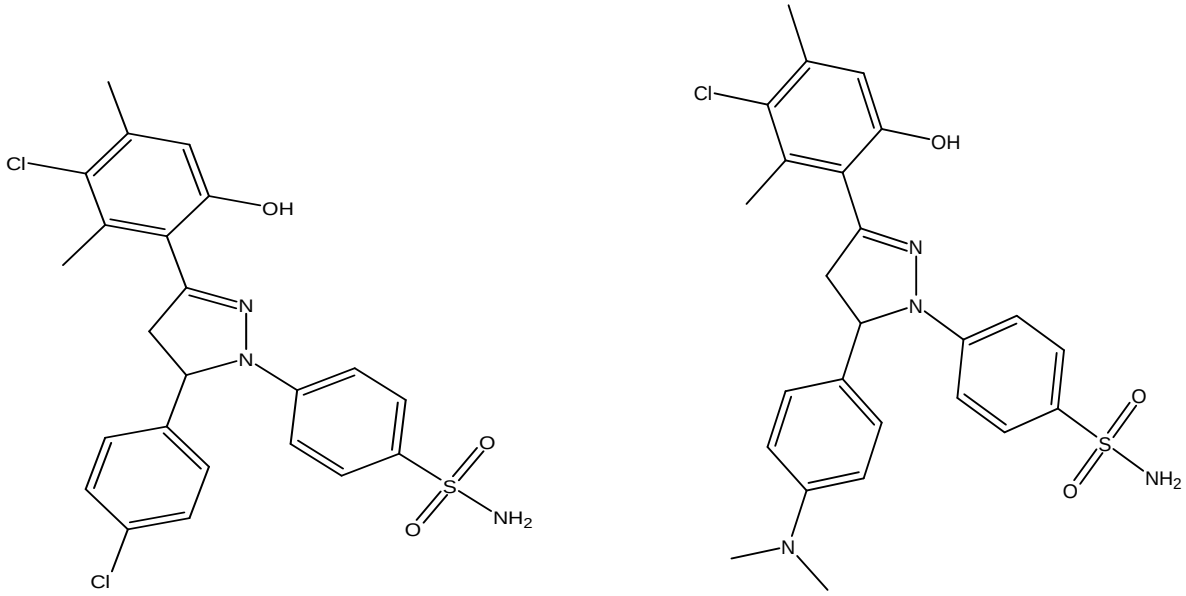


(I)

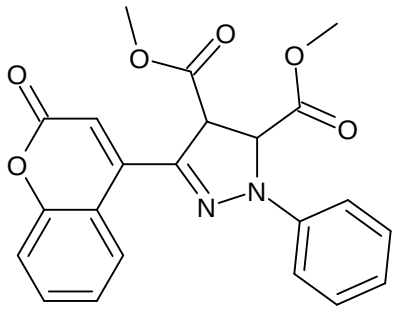


(II)

Sameena et al., (2011) synthesized some new 2-pyrazolines bearing benzenesulfonamide compounds from appropriate chalcones/flavanones with 4-hydrazinobenzenesulfonamide hydrochloride and these compounds were then screened for their anti-inflammatory and anti-cancer activity.**[11]** All the compounds exhibit good activity. The compounds such as 3-(5'-chloro-2'-hydroxy-4',6'-dimethylphenyl)-5-(4-chlorophenyl)-1-(p-sulfamylphenyl)-Δ^2-pyrazoline and 3-(5'-chloro-2'-hydroxy-4',6'-dimethylphenyl)-5-(4-(N,N-dimethylamino) phenyl)-1-(p- sulfamylphenyl)- Δ^2- pyrazoline exhibited antitumor activities against the entire tumour cell lines. They show effective growth inhibition GI_{50} (MG-MID) values of 15.13 and 15.13µM respectively. especially compound 2 exhibited promising anti-proliferative activity with GI_{50}.



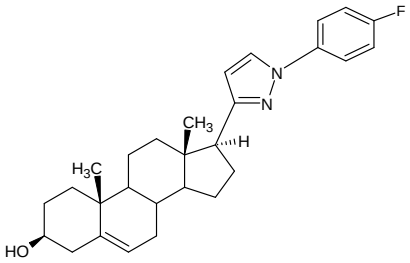
Based on the report to have multiple biological coumarins. Anne et al(2001). synthesized series of 3-(coumarin-4-yl) dihydropyrazole derivatives. These coumarin derivatives were isolated, characterized, and evaluated in vitro for their ability to inhibit trypsin, β-glucuronidase, soybean lipoxygenase and to interact with stable radical 1,1-diphenyl-2-picrylhydrazyl. The compound was tested in vivo as anti-inflammatory agents in the rat carrageenin paw edema assay. dimethyl 1-phenyl-3-(2-oxo-2H-(1) benzopyran-4-yl)-4,5-dihydropyrazol-4,5-dicarboxylate seems to be a lead molecule to be modified to improve the lipoxygenase inhibition.[12] The results are discussed in terms of structural characteristics.

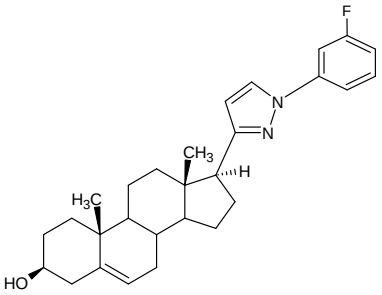


dimethyl 1-phenyl-3-(2-oxo-2H-(1) benzopyran-4-yl)-4,5-dihydropyrazol-4,5-dicarboxylate

5α-reductase inhibitor

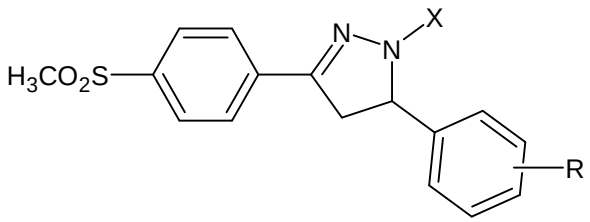
Abid H. Banday, Shameen A. Shameem, Salik Jeelani[13] reported the synthesized D-ring substituted pyrazolyl pregnenolones shows inhibition of the 5α-reductase enzyme.





Cyclo-oxygenase inhibitor

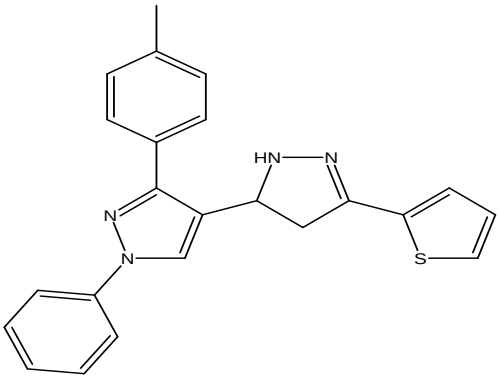
Rossella et al., (2014) synthesized some new N-substituted-3,5-diphenyl-2-pyrazolines and cyclo-oxygenase (COX-1 and COX-2) inhibitory activities[14] have been evaluated. New pyrazoline derivatives were synthesized by replacing pyrazole moiety, with a dihydro pyrazole nucleus, liked in C3 and C5 with a phenyl group. In particular, we have introduced 4-methylsulfonyl phenyl, in the C3 position, which seems important in interaction with secondary pockets of the cox-2 active site.



R=H=4-Cl=4-CH_3=4-OCH_3

Anti-Malarial activity

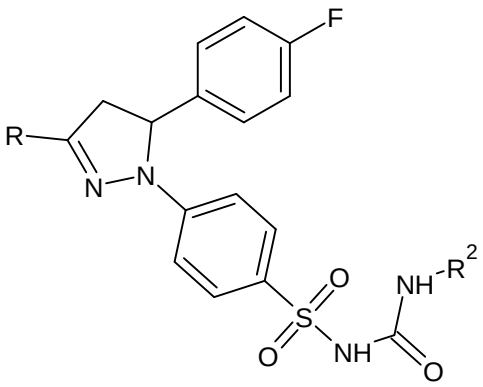
Based on the biological activity exhibited by Pyrazoline compounds. Abdu et al., (2014) synthesized some pyrazoline derivatives by using aldol condensation and subsequent cyclization reactions. The results showed that all the synthesized compounds had lower activity than the standard drug chloroquine phosphate.[15] Compound 1-phenyl-4-(3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-5-yl)-3-p- tolyl-1H-pyrazole, showed relatively the highest % suppression, 63.40%.



1-phenyl-4-(3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-5-yl)-3-p-tolyl-1H-pyrazole

Hypoglycemic activity

A series of fluoropyrazolesulfonylurea derivatives were synthesized by Hassan et al.,(2016) through condensation of 4-hydrazino benzenesulfonamide hydrochloride with fluorochalcones to give pyrazoline derivatives which upon oxidation with bromine water afforded corresponding pyrazoles. The final product screened for biological activity. Preliminary biological testing of these compounds revealed that compounds 6,7,10,11 and 14 showed marked hypoglycemic activities.[16]



6, R= 4-BrC_6H_4; R^1/R^2= C_6H_5

7: R= 4-$CH_3C_6H_4$; R^1/R^2= C_6H_5

10: R= 4- BrC_6H_4; R^1/R^2= p-ClC_6H_4

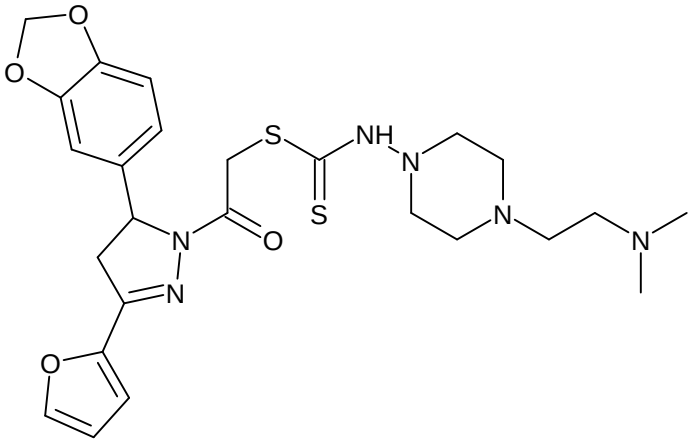
11: R= 4-$CH_3C_6H_4$; R^1/R^2= p-ClC_6H_4

14: R= 4- BrC_6H_4; R^1/R^2=Cyclohexyl

Acetylcholinesterase inhibitor

Mehlika et al., (2013) synthesized new pyrazoline derivatives via the reaction of 1-chloroacetyl)-3-(2-furyl)-5-aryl-2-pyrazolines with sodium salts of N,N-disubstituted dithiocarbamic acids. Each derivative was evaluated for its ability to inhibit acetylcholinesterase(AChE) and butyrlcholinesterase (BuChE) using a modification of

Ellman's spectrophotometric method. The compounds were also investigated for their cytotoxic properties using the MTT assay. The most potent AChE inhibitors[17] was found namely 1-[[(4-(2-dimethylaminoethyl)piperazin-1-yl)- thiocarbamoylthio]acetyl]-3-(2-furyl)-5-(3,4-methylenedioxyphenyl)-2-pyrazoline.



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