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FUSED HETEROCYCLES AS A POTENT BIOLOGICAL AGENTS; RECENT ADVANCEMENT

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ABSTRACT: Recently the synthesis of fused heterocyclic compounds seeks great attention of researchers in the field of medicinal chemistry. Majority of the drug compounds contains heterocyclic ring in their structures and these heterocyclic skeleton contributes significantly in the biological profile of drug. The heterocyclic compound play significant role in synthetic chemistry and many heterocyclic derivatives have been successfully synthesized as potent drug molecule. Many researchers have focused on the synthesis of fused heterocyclic compounds considering the beneficial property of fused derivatives and some of the fused heterocyclic compounds were found to possess potent biological action such as; antibacterial, antiallergic, anti-inflammatory, antitumor and antiparkinsonism etc. The basis of synthesizing fused heterocyclic derivatives resides in the fact that combination of two molecules or incorporation of new molecule in previously bio-active compound may potentiate action of each other synergistically, sometimes fusion leads formation of derivatives with newer biological profile other than the combining structure. This review article covers the most active heterocyclic compounds which possess considerable biological activities.

INTRODUCTION: Heterocyclic compounds belong from medicinally valuable family of organic compounds. Fused ring heterocycles are also important constituents of many available therapeutics agents. Naturally heterocyclic aromatic compounds are widely distributed in animal and plant tissues. More than 90% of new drugs contains heterocyclic ring¹. Heterocyclic compounds possess diversified biological activities, because they are having ability to bind reversibly to proteins. Medicinal chemistry involves great utilization of heterocyclic compounds by converting them into potent biological agents. Recently many researchers work to synthesize and screen fused heterocyclic compounds against a variety of different receptors, yielding several active compounds.

Many combinations of fused heterocyclic structures can be designed, to develop new chemical entity with versatile physical, chemical and biological properties. The rationale of fusion involve geometrically rigid polycyclic structures which possess three dimensional spatial orientation of substituent's which ultimately leads better biological profile due to the diversified binding ability²⁻⁴. Literature review revealed significant biological activities of these compounds such as; antibacterial, antiallergic, anti-inflammatory, antitumor, phosphodiesterase inhibition and antiparkinsonism etc.⁵⁻¹⁰. Till now many important discoveries have been made on the basis of rational drug development process considering heterocyclic structure as a lead moiety. This review article presents clinical importance of some fused heterocyclic compounds developed recently.

Antimalarial Activity:

Malaria is a major cause of morbidity and mortality throughout the world. The available treatments options involves utilization of drug and drug combinations but many of them becoming less effective due to parasite resistance; looking on this

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view many researchers recently workout of finding new drug as potent antimalarial agent. Gajanan et al synthesized and tested α -pyranochalcones and pyrazoline for their anti-malarial activity by evaluating growth of malaria parasite in culture using the microtiter plate based SYBR-Green-I assay. Amongst the synthesized derivatives the compound (*E*)-3-(3-(2,3,4-trimethoxyphenyl)-acryloyl)-2H-chromen-2-one (**Fig.1**) was found to

be most potent analog of the series, showed IC_{50} of 3.1 $\mu\text{g/ml}$ against chloroquine-sensitive (3D7) strain and IC_{50} of 1.1 $\mu\text{g/ml}$ against chloroquine-resistant field isolate (RKL9) of *Plasmodium falciparum*. Results of study revealed that the all series of synthesized compounds exhibited promising antimalarial activity against both chloroquine-sensitive strain (3D7) and chloroquine-resistant field isolate (RKL9) of *P. falciparum*¹¹.

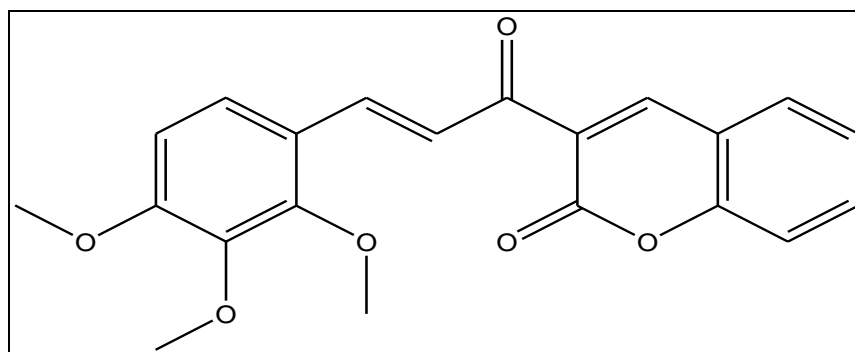


FIG.1: (*E*)-3-(3-(2,3,4-TRIMETHOXYPHENYL)-ACRYLOYL)-2H-CHROMEN-2-ONE

Eric M. Guantai et al synthesized targeted series of chalcone and dienone hybrid compounds containing aminoquinoline and nucleoside templates and evaluated these compounds for their *in vitro* antimalarial activity. Compound 3-{4-[1-(7-Chloro-quinolin-4-yl)-1H-[1,2,3] triazol - 4 -

ylmethoxy]-3-methoxy-phenyl}-1-(2,4-dimethoxy-phenyl)-propenone (**Fig. 2**) was found to be the most active, exhibiting submicromolar IC_{50} values against the various strains of *Plasmodium falciparum*¹².

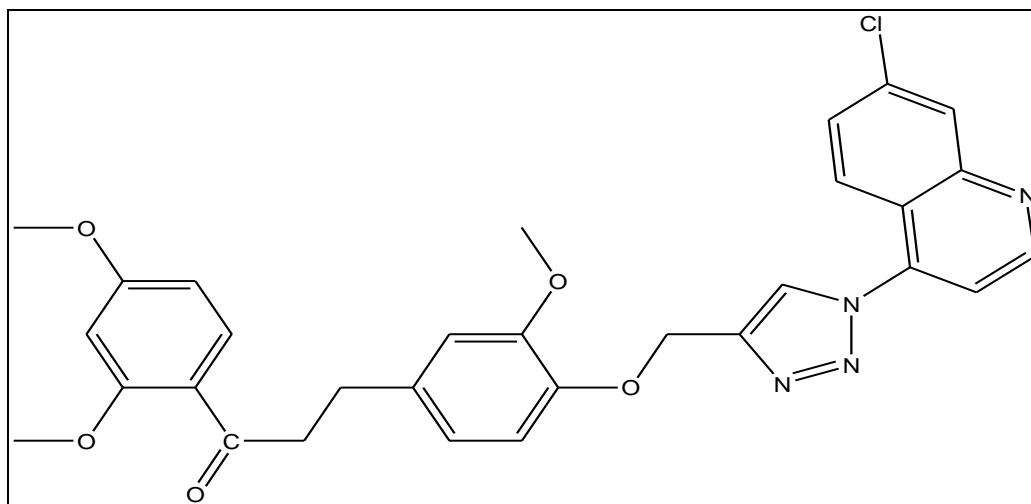


FIG.2:3-{4-[1-(7-CHLORO-QUINOLIN-4-YL)-1H-[1,2,3]TRIAZOL-4-YLMETHOXY]-3-METHOXY-PHENYL}-1-(2,4-DIMETHOXY-PHENYL)-PROPENONE

Renate H et al synthesized and evaluated two novel series of natural-product-like hybrids based on the chalcone, thiolactone and isatin. Results showed that the thiolactone-chalcones were more active against W2 strain *Plasmodium falciparum* with IC_{50} s ranging from 0.68 to 6.08 μM than the isatin-

chalcones with IC_{50} s of 14.9 μM or less. Study also confirmed the interaction capabilities of the isatin scaffold with the thiols of cysteine proteases¹³.

V. Tomar et al synthesized a series of novel chalcones bearing acridine moiety attached to the

amino group in their ring A through noncatalyzed nucleophilic aromatic substitution reaction. The synthesized chalcone derivatives have been characterized and screened for their *in vitro* antimalarial activity against *Plasmodium falciparum* NF-54. All the chalcones showed complete inhibition at concentration of 10 mg/mL and few of them showed significant inhibition at concentration of 2 mg/mL. Chalcone derivative 1-

(4-(Acridin-9-ylamino) phenyl) - 3 - (4-methoxyphenyl) prop- 2-en-1-one (**Fig. 3**) exhibited >71% inhibition at 2 mg/mL concentration. It was also observed that location and nature of the substituent(s) in ring B of the chalcone derivative play very important role. Author suggested derivative (**3**) as potent antimalarial drug after further refinement¹⁴.

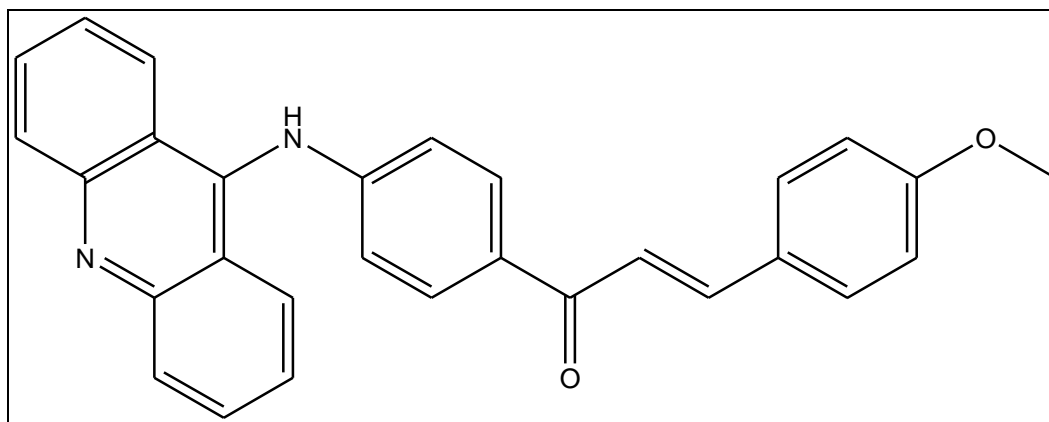


FIG. 3: 1-(4-(ACRIDIN-9-YLAMINO) PHENYL)-3-(4-METHOXYPHENYL)PROP- 2-EN-1-ONE

Anti-Cancer:

Koneni et al performed synthesis and *in vitro* cytotoxicity evaluation against a panel of four human cancer cell lines and normal fibroblasts (NIH3T3) of a series of coumarin–chalcone hybrids. The synthesis involved strong rational that; both coumarin and chalcone are known microtubule inhibitor with antimetabolic activity. Among synthesized compounds the compound (*E*-

ethyl 8-sec-butyl-2-oxo-6-(3-p-tolylacryloyl)-2H-chromene-4-carboxylate (**Fig. 4**) showed most promising activity around 30-fold more selectivity towards C33A (cervical carcinoma) cells over normal fibroblast NIH3T3 cells with an IC₅₀ value of 3.59 μM. The study was intended to develop new potent coumarin–chalcone hybrid prototypes for further optimization and development to get new leads for the treatment of cancer¹⁵.

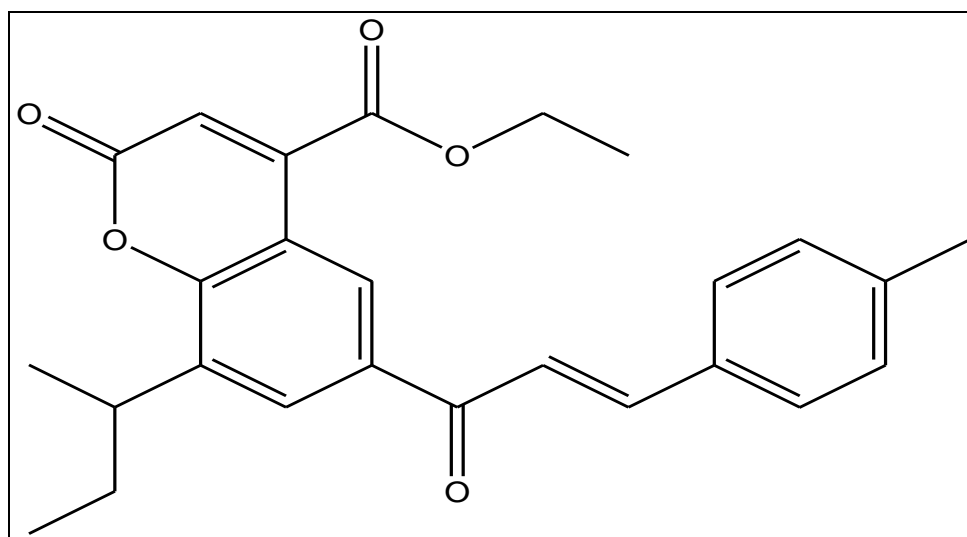


FIG.4: (*E*)-ETHYL 8-SEC-BUTYL-2-OXO-6-(3-P-TOLYLACRYLOYL)-2H-CHROMENE-4-CARBOXYLATE

Peng-Cheng et al discovered two series of pyrazole derivatives as potential EGFR kinase inhibitors. Some of them exhibited significant EGFR

inhibitory activity. Compound 3-(3,4-dimethylphenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**Fig. 5**)

displayed the most potent EGFR inhibitory activity with IC_{50} of 0.07 μ M, which was comparable to the positive control Erlotinib. Docking simulation was performed to determine the probable binding model. Results of antiproliferative assay indicated that some of the pyrazole derivatives own high

antiproliferative activity against MCF-7. Compound (5) showed significant antiproliferative activity against MCF-7 with IC_{50} of 0.08 μ M. Therefore, compound (5) was suggested potent anticancer agent¹⁶.

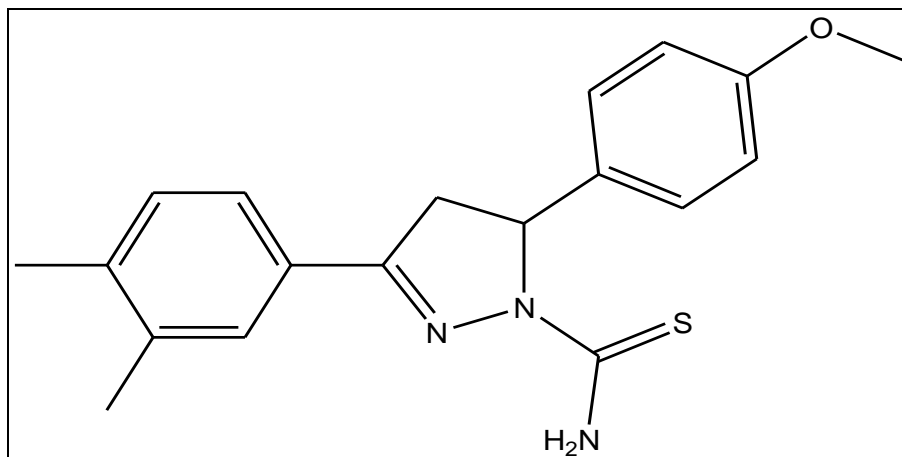


FIG. 5: 3-(3,4-DIMETHYLPHENYL)-5-(4-METHOXYPHENYL)-4,5-DIHYDRO-1H-PYRAZOLE-1-CARBOTHIOAMIDE

Antimicrobial Activities:

Bhaskar S. et al prepared some new 1-thiazolyl-2-pyrazoline derivatives by the base catalyzed condensation of 4-(2'-hydroxy-5'-chlorophenyl)-2-hydrazino-thiazole and pyrazole containing chalcones in polyethylene glycol (PEG-400) as a green reaction medium. All the synthesized compounds were tested for their antimicrobial activities.

Different 4-chloro-2-(2-(5-(1,3-diphenyl-1H-pyrazol-5-yl)-3-phenyl)-4,5-dihydropyrazol-1-yl)thiazol-4-yl) phenol derivatives were synthesized using various substituent such as; OH, Cl, Br and CH_3 etc. Compounds 4-(1-(4-(5-chloro-2-hydroxyphenyl)thiazol-2-yl)-5-(3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazol-5-yl)-4,5-dihydro-1H-pyrazol-3-yl)benzene-1,3-diol and 2,4-dichloro-6-(1-(4-(5-chloro-2-hydroxyphenyl)thiazol-2-yl)-5-(3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazol-5-yl)-4,5-dihydro-1H-pyrazol-3-yl)benzene-1,3-diol were found to possess significant antibacterial activity. Study concluded that hydroxyl substitution increases activity against *Proteus vulgaris*¹⁷.

Antinociceptive Activities:

Zafer Asim et al synthesized some pyrazoline derivatives and investigated their potential

antinociceptive activities. 1-[(Benzoxazole/benzimidazole-2-yl) thioacetyl] pyrazoline derivatives were obtained by reacting 3,5-diaryl-1-(2-chloroacetyl) pyrazolines with 2-mercaptobenzoxazole/benzimidazole. The chemical structures of the compounds were elucidated by IR, ¹H NMR and FAB-MS spectral data and Elemental Analysis. All of the compounds (100 mg/kg) exhibited significant antinociceptive activities in both hot plate and acetic acid-induced writhing tests.

Naloxone (5 mg/kg) pre-treatment reversed the antinociceptive activities suggesting the involvement of opioid system in the analgesic actions. Compound 2-(5-chlorobenzo[d]oxazol-2-ylthio)-1-(3-(3,4-dimethylphenyl)-5-phenyl-1H-pyrazol-1-yl)ethanone (Fig. 6) showed highest antinociceptive activities in nociception tests. Finally researchers suggested that, dimethyl substitution on phenyl at third position of the pyrazole ring increases the antinociceptive activities. Study concluded that benzoxazoles/benzimidazoles and pyrazoline-combined pyrazol derivatives possess centrally and peripherally mediated antinociceptive activities¹⁸.

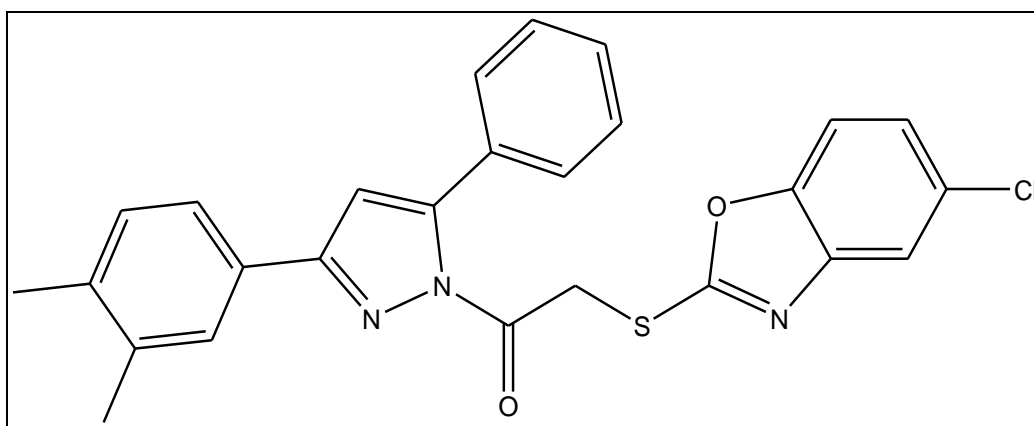


FIG.6: 2-(5-CHLORO BENZO [D] OXAZOL - 2 - YLTHIO) – 1 - (3-(3,4-DIMETHYLPHENYL) – 5 - PHENYL-1H-PYRAZOL-1YL)ETHANONE

Antiprotozoal Activity:

Asha Budakoti et al developed some new chalcones, amino-5-substituted-(3-phenyl(2-pyrazolinyl))methane-1-thione derivatives and 2-(5-substituted-3-phenyl - 2 - pyrazolinyl) -1,3-thiazolino[5,4-b]quinoxaline derivatives and evaluated for their *in vitro* antiamoebic activity against HM1:IMSS strain of *E. histolytica*. The structural features of compounds were established on the basis of IR, ¹H NMR and Mass Spectroscopic data. The MTT assay was performed on human kidney epithelial cell line to check the cytotoxicity of the compounds and the results were compared with metronidazole. Compound 2-{5-[2-

(Methylethyl) phenyl]-3-phenyl-2-pyrazolinyl}-1,3-thiazolino[5,4-b]quinoxaline (**Fig. 7**) showed better antiamoebic activity comparable to the metronidazole. Study suggested that the antiamoebic activity increases on modifying the structure of chalcones to the pyrazolines and further to quinoxalines (i.e; pyrazoline compound amino{5-[2-(methyl ethylphenyl) - 3 - phenyl (2-pyrazolinyl)] methane-1-thione was found to possess potent antiprotozoal activity but activity increases as modification towards quinoxalines since 2-(5-substituted-3-phenyl-2-pyrazolinyl)-1,3-thiazolino [5,4-b]quinoxaline derivatives were found to possess more potent antiprotozoal activity)¹⁹.

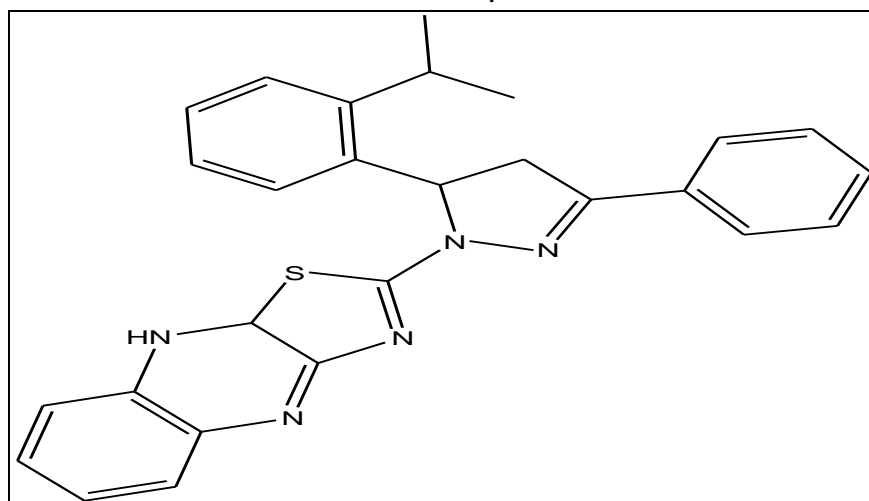


FIG. 7: 2-{5-[2-(METHYLETHYL) PHENYL]-3-PHENYL-2-PYRAZOLINYL}-1, 3-THIAZOLINO [5, 4-B] QUINOXALINE

Antiviral Activity:

Osama I. et al synthesized new N-acetyl and N-thiocarbamoyl derivatives of 4,5-dihydropyrazole from unsaturated ketones under the effect of hydrazine hydrate and thiosemicarbazide, respectively. N-Thiocarbamoylpyrazole derivatives

were cyclized using either ethyl bromoacetate or phenacyl bromides to afford the novel pyrazolothiazol-4(5H)-ones or pyrazolothiazoles. Synthesized compounds were evaluated for their antiviral activity against a broad panel of viruses in different cell cultures. The results of antiviral

activity revealed that the compound 1-Acetyl-5-(4-(benzyloxy)phenyl)-3-(4-chlorophenyl)-4,5-dihydro-(1H)-pyrazole (**Fig. 8**) was the only active one at subtoxic concentrations against *vaccinia*

virus (Lederle strain) in HEL cell cultures with a 50% effective concentration (EC₅₀) value of 7 mg/ml²⁰.

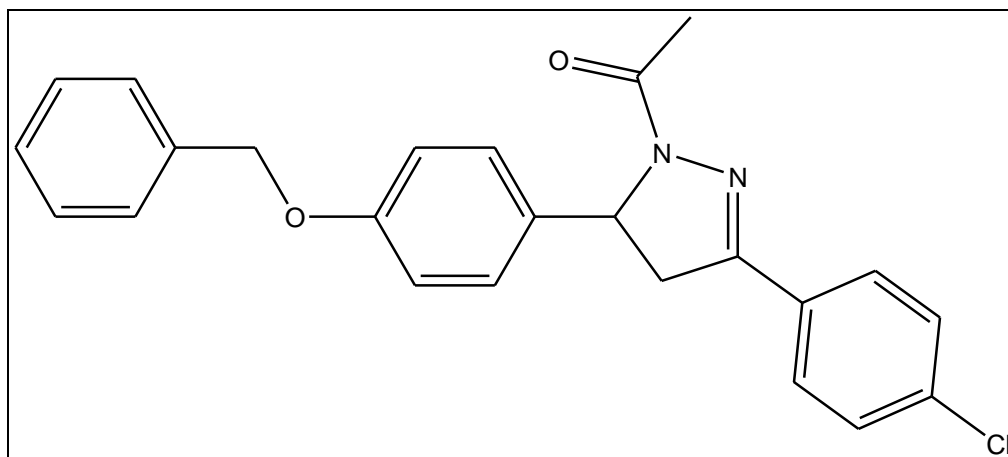


FIG.8:1-ACETYL-5-(4-(BENZYLOXY) PHENYL)-3-(4-CHLOROPHENYL)-4,5- DIHYDRO-(1H)-PYRAZOLE

Molluscicidal activity:

Raghunath. B. et al were synthesized a series of pyrazoline and isoxazoline derivatives to develop potent molluscicides. The synthesis was performed through cyclization of substituted chalcone derivatives. The synthesized compounds tested against *Machrochlamys indica* snails. The pyrazoline and isoxazoline derivatives showed good molluscicidal activity. Compound 3-[5-(3,

4Dimethoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl]-4-hydroxy-1-methyl-quinolin-2-(1H) one (**Fig.9**) was found to be most potent compound with LC₅₀ = 0.7876. It was also observed that all the synthesized compounds significantly controlled infection rate of *Machrochlamys indica* snails. Results of study suggested that pyrazolines and isoxazolines having *p*-OCH₃ group on phenyl ring possess potent molluscicidal activities²¹.

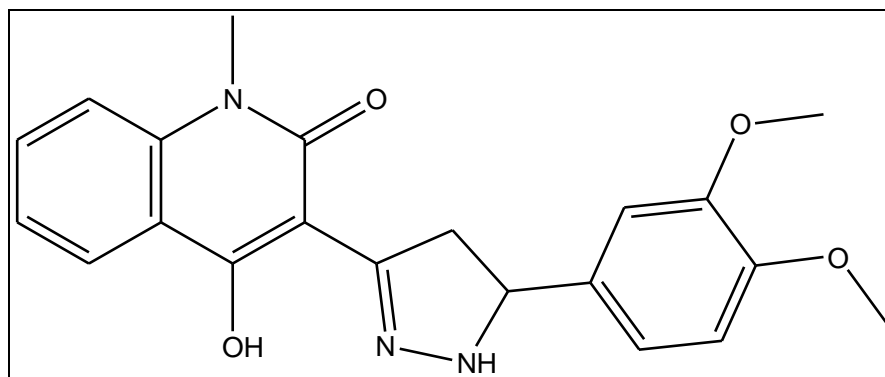


FIG.9: 3-[5-(3, 4DIMETHOXYPHENYL)-4,5-DIHYDRO-1H-PYRAZOL-3-YL]-4-HYDROXY-1-METHYL-QUINOLIN-2-(1H)ONE

CONCLUSION: In conclusion it can be said that the rational design of new chemical entities by the fusion of two active compounds is very effective strategy towards the drug development approaches. This approach becomes very useful when both compound having synergistic or additive activities. It has been observed that sometimes this strategy also play vital role when the active molecules being merged possess independent modes of action.

Another basis for hybridization is to facilitated transport mechanisms by joining bioactive units to moiety which can be actively transported into mammalian cells.

CONFLICT OF INTEREST: Here the author declared that there is no conflict of interest.

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