Pyrazoline as a medicinal scaffold.

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Abstract: Heterocyclic Chemistry is the backbone of medicinal compounds that exhibits numerous biological activities. Pyrazole and its derivatives possess nitrogen atom along with carbon atom as a substitution and show a diversity of biological activities such as antibacterial, antimicrobial, anti-inflammatory, antioxidant, antidiabetic, anticancer, antifungal, antidepressant, anticonvulsant, analgesic, and monoamine oxidases (MAOs) as shown by pyrazoline prepared from chalcone (intermediate). The synthesized compounds are checked by the TLC and further analyzed by the IR, NMR, and UV spectroscopy.

KeyWords: Anti-microbial, heterocyclic, and pyrazoles, biological activity.

Introduction

Pyrazole, well known heterocyclic compound with two adjacent nitrogen atoms within the ring and having a five-membered ring carries one endocyclic double bonds and essential in nature, represented by the molecular formula C3H4N2. Pyrazole melts at 70°C, in spite of its low molecular weight. Clinically the substitution derivatives at 3 and five positions are indistinguishable from one another whereas the properties disappear the hydrogen atom on the nitrogen atom immediately is replaced by an alkyl group3.

Figure 1. Pyrazole representation with two adjacent nitrogen atoms within the ring.

In 1883, Ludwig Knorr coined the term pyrazole, which is a weak base, acquires pKb 11.5 (pKa value of the conjugated acid 2.49 at 25°C). Pyrazole having unique pharmacological effects on human beings and from watermelon seeds, 1-pyrazolylalanine was isolated and then classified as alkaloids on composition, first natural pyrazole in 19594.

Pyrazole exhibits various biological activities and also has a potent medicinal scaffold5. Pyrazoline and its derivatives are having an antibacterial6, antimicrobial7, anti-inflammatory8, antioxidant9, antidiabetic10, anticancer11, antifungal12, antidepressant13, anticonvulsant14, analgesic15, and monoamine oxidases (MAOs)16.

Chemistry and Synthetic approaches

In medicinal chemistry, heterocyclic rings such as Pyrazole containing active pharmacophore agents play an essential role in refined and efficient ways to make these heterocyclic heads. Pyrazole includes two nitrogen atoms also carry a π-excessive heterocycle, as seen in pyrrole at position 1 and pyridine at positions 2. Pyrazole subsists in three partially reduced forms.

Figure 2. Pyrazole contains two nitrogen atoms also carry a π-excessive heterocycle, as seen in pyrrole at position 1 and pyridine at positions 2.

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Synthetic approach to the pyrazole

1-(4,5-disubstitutedpyrazol-1-yl)-ethanone Synthesis: On the contrary, pyrazoles have been carried out by the reaction of β-formyl enamides with hydroxylamine hydrochloride catalyzed by potassium dihydrogen phosphate in acidic medium and become novel synthesis18.

3,5-substituted-1H-pyrazole Synthesis: From tosyldiimides, α, β-unsaturated carbonyl compounds synthesis of pyrazole derivatives possessing a β-hydrogen is proposed and exploiting microwave activation coupled with solvent-free reaction conditions and appears as novel approach18.

Tri- and tetra-substituted pyrazoles Synthesis: For the facile synthesis of tri- and tetra-substituted pyrazoles using Dioxygen gas as the oxidant undergoing intramolecular oxidation coupling with the help of tetrazole and sodium hypochlorite to give novel products19.
oxidative CN coupling method catalyzed by A ruthenium (II) carried out the transformation, and the reaction demonstrates excellent reactivity, functional group tolerance, and high yields. For the Regio, selective synthesis; By the reaction of diarylhydrazones and vicinal diols via the route of 1,3- and 1,3,5-substituted pyrazoles undergoes iron-catalyzed synthesis of 1, 3-substituted pyrazoles.

Synthesis of 1,3,5-trisubstituted-1H-pyrazole: An easily accessible reaction 1, 3-bisaryl-monothio-1,3-diketone or 3-(methylthio)-1,3-bisaryl-2-proponens gives 1-aryl-3,5-bisarylpyrazoles with arylhydrazines and with complementary Regioselectivity at position 3 and 5.

General procedure for synthesizing pyrazoline

A substituted Chalcone (0.01 mole) mixed with hydrazine hydrate (0.012 moles) and acetic acid(10ml) in methanol for five hours. The reaction mixture was poured in chilled water, and solid separated was filtered and recrystallized from ethanol. Again, the reaction completion was confirmed by the TLC and monitored.

Pharmacological activity

The usefulness and great therapeutic value of pyrazole nucleus have been recognized, and the most comprehensive range of activities of this nucleus evaluated for a long time. However, as the first synthetic organic compound carries pyrazoline-5-one nucleus to find use as an essential drug.

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Dipankar et al. studied the reports of twelve 2-pyrazoline derivatives against \( S. \) aureus and \( A. \) niger thoroughly (Table 1). Two varieties of acetophenones were condensed with three varieties of substituted benzimidazole derivatives to get six chalcone derivatives, which undergo condensation followed by cyclization with isoniazid and 1-(2-naphthoxyacetate) hydrazine two get the final 2-pyrazoline derivatives. Compound D7 exhibited the highest antibacterial activity, and compound D12 exhibited highest anti-fungal activity as well as comparable to the antibacterial activity and antifungal activity of the standard drugs at 200 \( \mu \)g/mL. These compounds were characterized by IR, 1H-NMR and Mass spectral studies. The synthesized compounds were found to have good antimicrobial activity in the range of 20-70 \( \mu \)g/mL.

| Compounds         | Minimum inhibitory concentration (\( \mu \)g/mL) |
|-------------------|-----------------------------------------------|
|                   | Bacteria | Fungi \( S. \) aureus | \( A. \) niger |
| D12               | 50       | 20                        |
| Ciprofloxacin     | 12.5     | -                         |
| Ketaconazole      | -        | 10                         |

Table 1. Reports of twelve 2-pyrazoline derivatives against \( S. \) aureus and \( A. \) niger.

N.C. Desai et al. synthesized a series of compounds 2-[5-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(aryl)-4,5-dihydro-1Hpyrazol-1-yl] thiazol-4(5H)-ones (4a–q) and screened in vitro synthesized against the representative panel of Gram-positive (\( Staphylococcus aureus \), \( Streptococcus pyogenes \)) and Gram-negative (\( Escherichia coli \), \( Pseudomonas aeruginosa \)) bacteria. These compounds were also tested for their inhibitory action against strains of fungi (\( Candida albicans \), \( Aspergillus niger \), \( Aspergillus clavatus \)). The synthesized compounds showed potent inhibitory action against the test organisms by the use of an electron-withdrawing group on the benzene ring in basic structures was worthy. Compounds bearing 2-Cl, 4-Cl, 2-F, 3-F, 4-F, 2-NO2, and 4-NO2 exhibited more pronounced activity.

Antidepressant activity

B. K. Kaymakçıoğlu, S. Gumru, N. Beyhan, F. Arıcıoğlu investigated a series of new 2-pyrazoline derivatives and activity was evaluated by using tail suspension test. Compounds 3d and 3e were effective and a significant reduction in immobility time was observed as compared to results of imipramine, as the reference standard drug. Compounds 3d and 3e remarked the potential for the treatment of depression.

Anti-convulsant activity

Ahsan synthesized 3-substituted-N-aryl-6,7-dimethoxy-3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide and assayed the anticonvulsant activity and neuroprotection according to Antiepileptic Drug Development Programme protocol. Compound 4b showed neuroprotection activity with 26.2 ± 1.9% of total propidium iodide uptake at 100 \( \mu \)M, and inhibitory concentration 50 (IC50) of the compound was found to be 159.20 ± 1.21 \( \mu \)M.

Sudhakararao G et al., Synthesized compounds and then evaluated to suppress seizures and provide neuroprotection by minimizing the effects of the seizure attacks. To attain this some chalcone and chalcone based pyrazolines were evaluated for their anticonvulsant activity and then structural elucidation was taken on the basis of the elemental analysis and spectroscopic studies (NMR, IR and Mass Spectroscopy). Among all compounds only compounds Ph1, Ph2, Py 3 and Py 4 shown to be good anticonvulsant activity with dose level of 4mg/kg b.w.

Abdel-Aziz et al., have described two synthetic paths for the formation of diacylhydrazines, 5-amino-1-substituted pyrazole-3,3,4-tricarbonitriles and oxadiazole, pyrazoline derivatives, Compounds 4a and 4b showed good activity in comparison to imipramine at a dose of 10 mg/kg dose level and showing antidepressant activity using tail suspension behavioural despair test and anticonvulsant activity against pentylenetetrazol induced seizures in mice.

Monoaminoxidase activity

F. Manna et al., have synthesized a series of 1-acetyl-3-(4-hydroxy- and 2,4-dihydroxyphenyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole derivatives and investigated their ability to selectively inhibit the activity of the isoforms of MAO and created a...
novelty. The newly synthesized compound proved to be more reversible, potent, and selective inhibitors of MAO-A than of MAO-Compounds 6 and 11 were found to be most potent. Activities against 14α-demethylase were investigated by molecular docking using the HEX docking software. These compounds docked into the active site of the receptor (PDB code, 1E9X) using Hex docking tools software, which showed good affinity for the enzyme when compared with the binding energies of standard drugs such as clotrimazole (-24.05) and griseofulvin (-36.57). Among all the designed compounds, compound 7 shows more binding energy values (-59.85).

Kumar R and Joshi Y. C. synthesized β-diketones/β-ketoesters, 4a–e on condensation with different β-diketones/β-ketoesters, 3a–e in the presence of sodium hydroxide from the diazonium salt of 4-amino-1-methyl-3-propyl-1H-pyrazole-5-carboxamide. The β-diketones/β-ketoesters 4a–e were condensed with o-phenylenediamine (o-PDA) in the presence of p-toluene sulfonic acid/SiO2 to give biologically active 3H-1,5-benzodiazepines, 5a–e. Crofloxin and ciclopirox olamine were used as reference standards for comparison of the antibacterial and antifungal activities, respectively. Compound 5c exhibited greater antimicrobial and antifungal activities than the standard drugs, whereas compounds 5d and 5e showed significant anthelmintic activity. All the newly synthesized compounds were characterized by elemental analysis and spectral studies and screened for their antimicrobial, antifungal and anthelmintic activities.

Deng et al., synthesized a series of 1,3,5-trisubstituted-2-pyrazoline derivatives by introducing the furan rings. Among all compounds, compounds 4, 7, 9, 12, 18 and 19 displayed excellent antifungal activity against Rhizoctonia solani and tried to discover some more potent antifungal compounds. Additionally, at site 3 and site 5 of the pyrazoline in the compounds 9 and 19 bearing two furan rings respectively and with the help of bioactivity results pyrazoline derivatives receives a template for the further structural optimization.

Antiepileptic activity

Maruthi Rao B et al., prepared two varieties of acetophenones were condensed with two varieties of aromatic benzaldehydes to get four chalcone derivatives by undergoing condensation followed by cyclisation with isoniazid to get the final four 2-pyrazoline derivatives. Compounds T1 and T2 having 2-furyl derivatives names of T2 (5-(furan-2-yl)-4,5-dihydro-3-(4-hydroxyphenyl) pyrazol-1-yl) (pyridin-4-yl) methanone and T1,3-(4-chlorophenyl)-5-(furan-2-yl)-4,5-dihydropyrazol-1-yl) (pyridin-4-yl) methanone has prominent anti-epileptic activity on hydroxy-2 and furyl have the most potential anti-epileptic activity.
Anticancer Activity

M. Shaharyar et al. synthesized series of benzimidazole which carries 2-pyrazolines and then tested as well as belonging to different panels these compounds against various cancer cell lines such as renal, breast, colon, melanoma, prostate, and so on. The most active compound of the series was found to be 2-[5-(3,4-dimethoxyphenyl)-1-phenyl-4,5-dihydro-1H-3-pyrazolyl]-1H-benzimidazole. Based on close examination of the substituent it was concluded that the role of electron donating group on the phenyl ring at C5 of the phenyl ring had a great influence on anticancer activity.

Eman M. Fiefel et al. primarily synthesized a newly substituted pyrazole, thiazole, and 1, 2, 4-triazole derivatives and then reported. Among all the sugar hydrazones and their acetylated derivatives as yet derived acyclic C-nucleoside analogs, and the thioglycosides of the 1, 2, 4-triazole derivatives were also prepared. Compounds that were synthesized as well as studied and several compounds showed significant antitumor activities in the tested results.

Conclusions

Pyrazoline, a heterocyclic compound that exhibits a two nitrogen in the ring nucleus which synthesized via cyclization of chalcone from the reaction of substituted aldehydes and ketones in the presence of basic conditions. Medicinally pyrazoline and its derivatives showed the diversity of biological activities such as antibacterial, antimicrobial, anti-inflammatory, antioxidant, antidiabetic, anticancer, antifungal, antidepressant, anticonvulsant, analgesic, and monoamine oxidases (MAOs) and elucidated by spectral analysis and also characterized by elemental analysis.

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