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PYRROLE A VERSATILE SCAFFOLD: SYNTHETIC METHODOLOGIES, REACTION CHEMISTRY, AND PHARMACEUTICAL APPLICATIONS.

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Abstract:
Pyrrole is a five membered aromatic heterocyclic compound containing one nitrogen atom. It serves as an important structural motif in numerous natural products, biologically active molecules, lead compounds and drugs. Its aromaticity arises from the delocalization of six π electrons, including the lone pair of electrons on the nitrogen atom which imparts unique electronic and physicochemical properties. Due to its electron-rich nature and ease of structural modification, the pyrrole scaffold has gained significant importance in medicinal chemistry. Pyrrole based compounds have been extensively explored in drug discovery and development, leading to the identification of several clinically useful therapeutic agents. This review highlights the chemistry, synthesis, biological activities, and therapeutic potential of pyrrole derivatives in modern drug discovery.

Key words: *Pyrrole, Properties, Synthesis, Drugs, Biological activities.*

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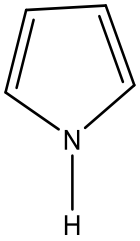
INTRODUCTION:

Heterocyclic compounds constitute one of the largest and most diverse classes of organic molecules and have attracted considerable attention owing to their wide range of synthetic and biological applications [1]. These compounds find extensive applications in medicinal chemistry, biochemistry, photochemistry, materials science, and environmental science [2]. Among the various heterocyclic systems, pyrrole (C_4H_5N) is an important five-membered aromatic ring containing one nitrogen atom. The pyrrole moiety is ubiquitous in nature and occurs in numerous biologically important molecules in both the plant and animal kingdoms. It serves as a structural subunit of hemes and chlorophylls, which are essential for oxygen transport and photosynthesis, respectively. Vitamin B_{12} is also biosynthetically related to tetrapyrrolic systems, as are the animal and plant bile pigments. Monopyrrolic natural products include porphobilinogen, the precursor of natural porphyrin and corrin pigments, and several antibiotics such as the tripyrrolicprodigiosins, which possess a different biosynthetic origin. The widespread occurrence of pyrrole-containing molecules in biological systems is attributed to their ability to polymerize and to form intermolecular N–H···π hydrogen bonds with neighboring molecules [3]. Pyrrole is a colorless volatile liquid that readily darkens on exposure to air and undergoes polymerization in the presence of light. It exhibits lower basicity than amines and pyridine because the lone pair of electrons on the nitrogen atom is delocalized over the aromatic ring. Consequently, pyrrole is a very weak base (pKa ≈ –3.8), and protonation results in the loss of aromaticity. Furthermore, both the N–H proton and the α-carbon hydrogen atoms possess moderate acidity and can be deprotonated by strong bases, thereby rendering pyrrole nucleophilic in nature [4].



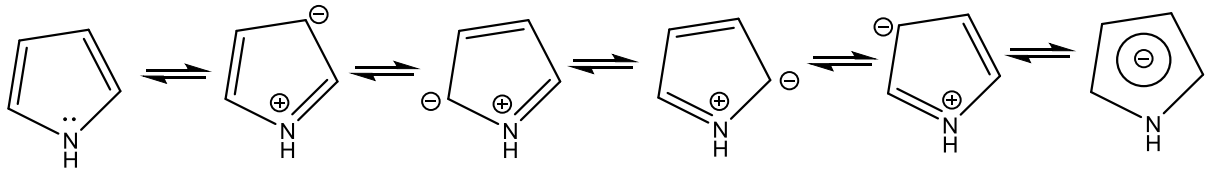
Pyrrole

Aromaticity

The aromaticity of five-membered heterocycles is influenced by the electronegativity of the heteroatom. In pyrrole, the nitrogen atom is more electronegative than carbon, resulting in polarization of electron density within the ring. Nevertheless, the nitrogen lone pair participates in the conjugated π-system, contributing two electrons to the aromatic sextet and providing significant aromatic stabilization. The interplay between heteroatom electronegativity and electron delocalization governs the aromatic character and reactivity of pyrrole [5].

ASE	HOMA	NICS(1)	TRE[β]	MRE[β]	RC[a]	X_G[b]
20.57	0.876	-10.60	0.2462	0.2094	0.6240	0.4132

The aromatic nature and extra-stability ofpyrrole can also be supported by the formation of its different resonating structures as shown in below figure. The structure of pyrrole is the resonance hybrid of all resonating structure [6].



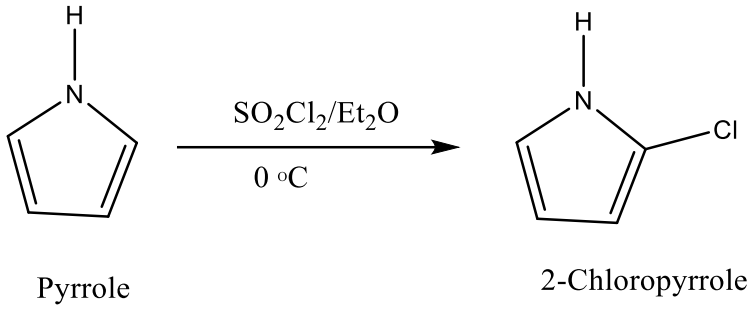
Physical properties

- Pyrrole is a colorless.
- Volatile liquid that becomes dark upon exposure to air.
- It has a low pKa of about - 3.8 which determines its weak basicity [4].

Chemical Reaction

1. **Halogenation**

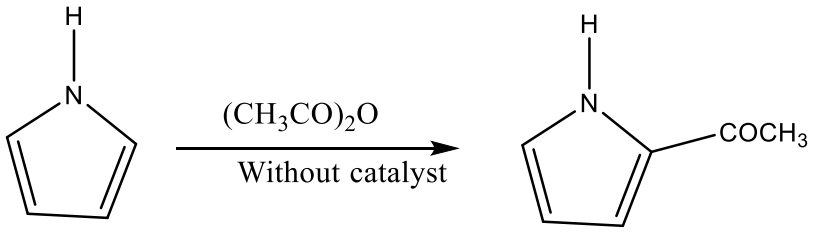
Pyrrole readily undergoes chlorination with thionyl chloride (SO_2Cl_2) in diethyl ether at 0 °C to give 2-chloropyrrole**.** The reaction occurs preferentially at the α-position(C-2) of the pyrrole ring because this position is more electron-rich and highly reactive toward electrophilic substitution.



Pyrrole 2-Chloropyrrole

2. **Friedel-Crafts acylation**

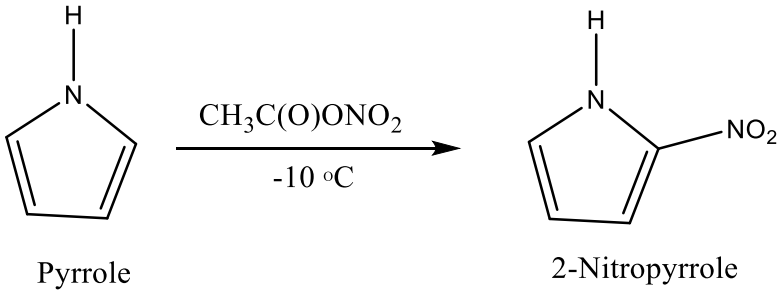
Pyrrole undergoes direct acetylation with acetic anhydride in the absence of a catalyst to afford 2-acetylpyrrole. Due to the high electron density at the α-position, the acetyl group is introduced preferentially at the C-2 position of the pyrrole ring.



Pyrrole 2-Acetylpyrrole

3. **Nitration**

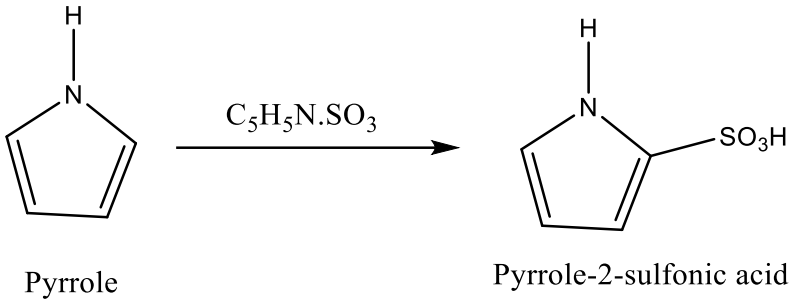
Pyrrole undergoes mild nitration with acetyl nitrate $CH_3C(O)ONO_2$ at -10 °C to give 2-nitropyrrole. The nitro group is introduced preferentially at the α-position (C-2) of the pyrrole ring owing to its higher electron density and enhanced reactivity toward electrophilic substitution.



Pyrrole 2-Nitropyrrole

4. **Sulfonation**

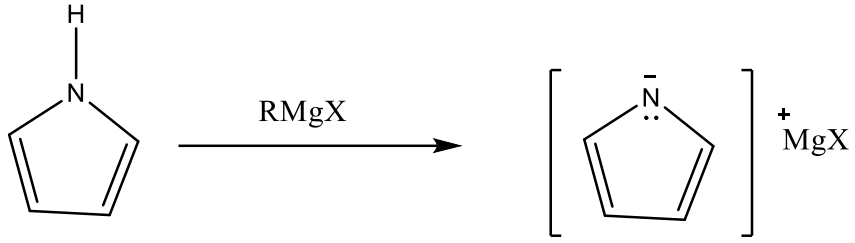
Pyrrole undergoes sulfonation with the pyridine-sulfur trioxide complex ($C_5H_5N{\cdot}SO_3$) to yield pyrrole-2-sulfonic acid. The sulfonic acid group is introduced selectively at the α-position (C-2) of the pyrrole ring because of its greater electron density and susceptibility toward electrophilic substitution.



Pyrrole Pyrrole-2-sulfonic acid

5. Grignard reaction

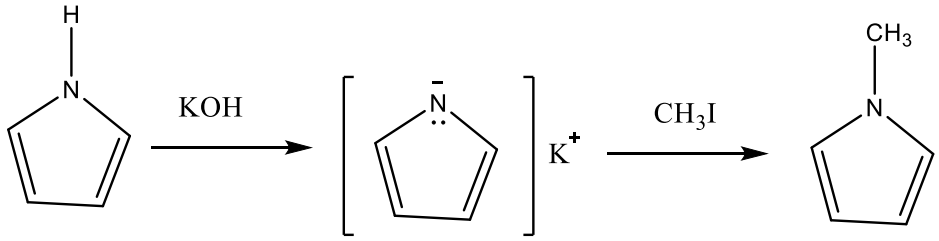
Pyrrole reacts with Grignard reagents (RMgX) to form pyrrolyl magnesium halide through deprotonation of the N–H group. This magnesium salt serves as a useful intermediate for the synthesis of various N-substituted and functionalized pyrrole derivatives.



Pyrrole Pyrrolyl magnesium halide

6. N-Alkylation

Pyrrole is readily deprotonated by potassium hydroxide to generate potassium pyrrolide, which subsequently reacts with methyl iodide to afford N-methylpyrrole**.** This transformation represents a simple and efficient method for the N-alkylation of pyrrole.

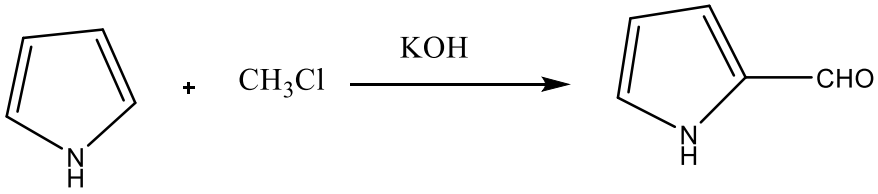


Pyrrole N-Methylation

7. Reimer-Tiemann Reaction

Reduction

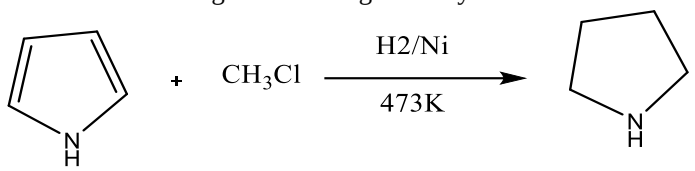
Pyrrole undergoes formylation to give 2-formylpyrrole, with the aldehyde group being introduced preferentially at the α-position of the ring. This reaction provides an important intermediate for the synthesis of various biologically active compounds.



Pyrrole 2-Formylpyrrole

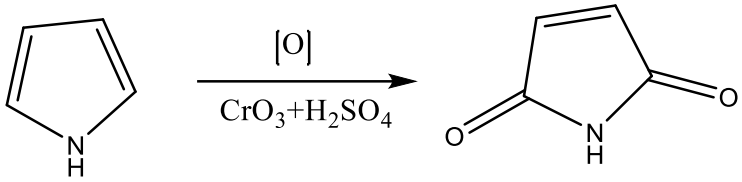
Oxidation

Catalytic hydrogenation of pyrrole in the presence of H_2/Ni at 473 K leads to the formation of pyrrolidine through complete saturation of the aromatic ring. This conversion is widely employed for the preparation of saturated nitrogen-containing heterocycles.



Pyrrole Pyrrolidine

Oxidation of pyrrole with chromium trioxide in sulfuric acid affords pyrrole-2,5-dione (maleimide). The reaction involves oxidation at the 2- and 5-positions of the pyrrole ring, yielding an important building block used in organic and medicinal chemistry.

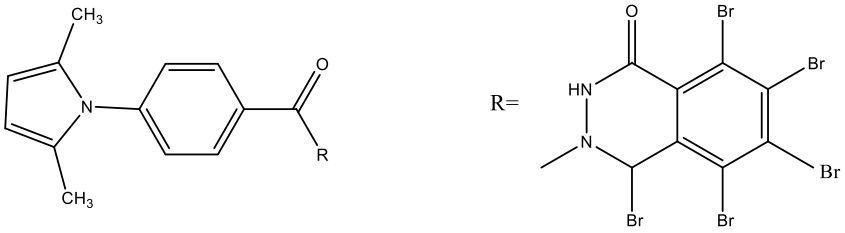


Pyrrole Pyrrole-2,5-dione(Malecimide)

Different biological activities of pyrrole

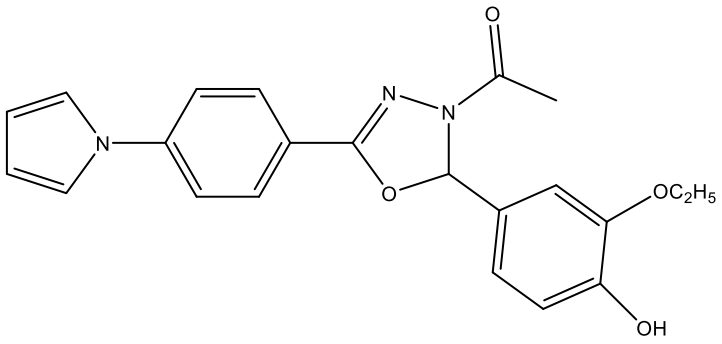
1. **Antituberculosis activity**

Joshi SD. *et.al.,* have reported the chemical synthesis and in silico molecular modeling of novel pyrrolyl benzohydrazide derivatives: their biological evaluation against enoyl ACP reductase (InhA) and m*ycobacterium tuberculosis.*The model suggests one or twoH-bonding interactions between the compounds and the InhA enzyme. Some compounds**1** exhibited goodactivities against InhA in addition to promising activities against M. tuberculosis [7].



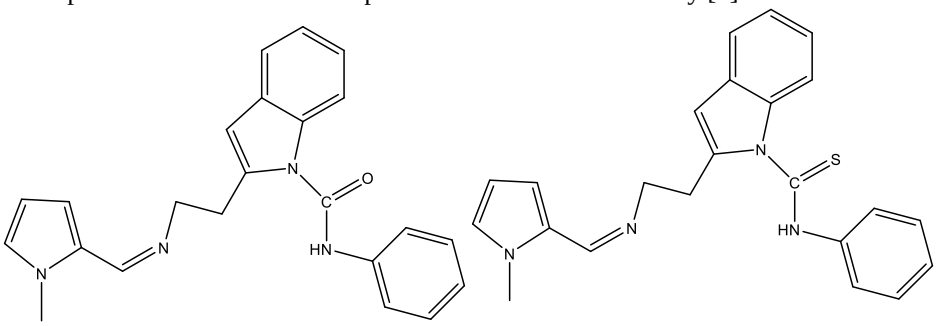
1

Joshi SD. *et.al.,* have reported the synthesis and molecular modeling studies of novel pyrrole analogs as antimycobacterial agents.In this studythe newly synthesizedcompounds were evaluated for their antimicrobial as well as antimycobacterial activities. Among the tested compounds,**2**displayed promising anti-tubercular activity [8].



2

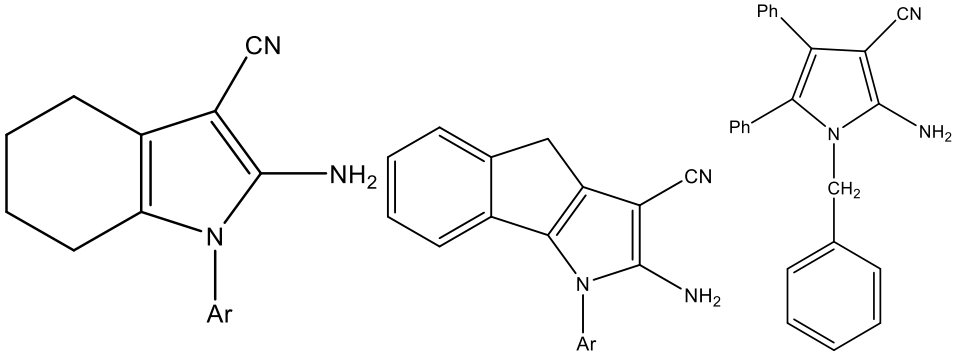
Boobal Arasu Velu*et al.*,havereported design and synthesis of novel pyrrole coupled tryptamine derivatives as contenders against staphylococcus aureus. Among the synthesised compounds, compound **3** and **4**have showed potent anti tuberculosis activity [9].



3 4

2. Anticancer and antioxidant activity

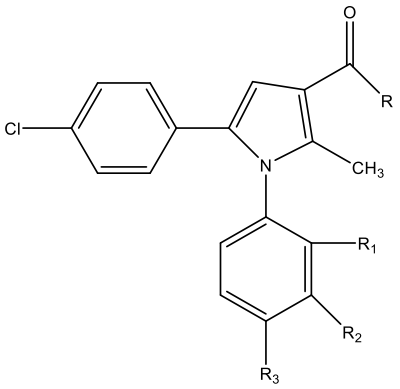
Samar Said Fatahalaa*et al.,* have reported apromising anti-cancer and anti-oxidant agents based on the pyrrole and fused pyrrole: Synthesis, Docking Studies and Biological Evaluation. All the synthesised molecules**(5, 6, 7)**showed the anticancer and antioxidant activity [10].



5 6 7

3. Anti-inflammatory activity

Hristina Zlatanova*et al.,* have reported experimental screening for analgesic and anti-inflammatory effect of novel compounds with a pyrrole heterocycle. In this studythe six novel pyrrolic compounds demonstrate analgesic effects against chemical stimuli in experimental conditions, impacting both peripheral and inflammatory nociceptive responses**(8, 9)** [11].

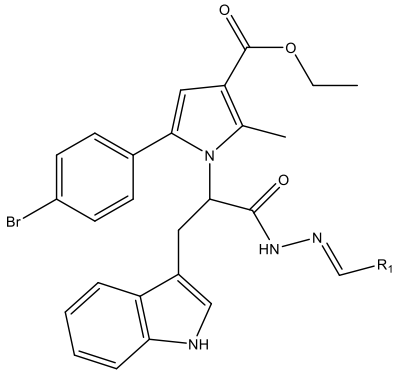


8: R=OC2H5: R1=H: R2=H: R3=Cl
9: R=CH3: R1=H: R2=H: R3=Cl

4. Anti-oxidant activity

Emilio Mateev*et al.,* have reported the design, microwave-assisted synthesis, biological evaluation, molecular docking, and ADME studies of pyrrole-based hydrazide-hydrazones as potential antioxidant agents. The free radical scavenging assays demonstrated that the hydrazide-hydrazone pyrrole-based compound comprising the 4-hydroxy moiety **(10)** is the most prominent. Moreover, the latter ligand

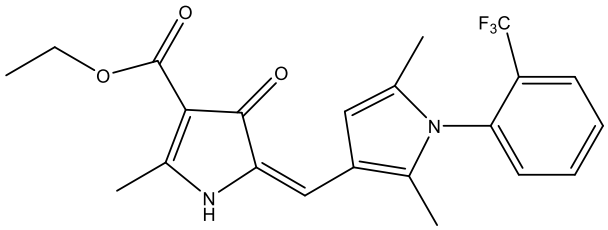
formed a stable complex with the active site of NO. The virtual simulation demonstrated that the hydroxyl moiety plays an important role in the antioxidant activity of the hydrazide-hydrazone [12].



10

5. Antimalarial activity

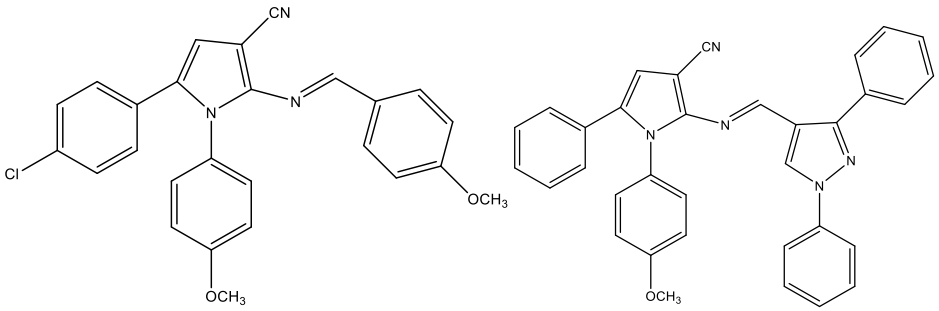
Dinakaran Murugesan *et al.*,havereporteddiscovery and structure- activity relationships of pyrrolone antimalarials. The phenotypic screening a series of pyrrolones derivatives have been identified with good *in vitro* activity against *P. falciparum* combined with good selectivity relative to the L6 mammalian cell line. While some pyrroloneshave shown good *in vivo* activity in a *P. berghei* mouse model when administered by the intraperitoneal route, oral activity has so far proved elusive, likely resulting from a combination of poor absorption due to the low aqueous solubility and rapid first-pass metabolism through cytochrome P450-mediated oxidation and/ or esterase cleavage**(11)**[13].



11

6. Antiviral activity

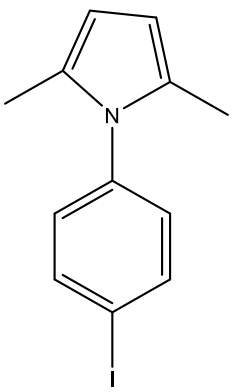
Khalid M. H. Hilmy*et al.,* have reported the synthesis and molecular modelling study of novel pyrrole schiff bases as anti-HSV-1 agents. The tested compounds **12** and **13** demonstrated potent antiviral activity against HSV-1 more than the standard drug.**13** could be a potential ligand to target /inhibit TK of herpes simplex virus [14].



12 **13**

7. Anti-convulsant activity

Vaishali m. Patil*et al.,* have reported the synthesis and anticonvulsant activities of small N- substituted 2, 5-dimethyl pyrrole and bipyrrole. In this study the two pyrrole derivatives**(14,15)**shows the potent anticonvulsant activity [15].



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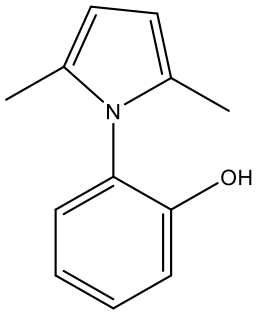
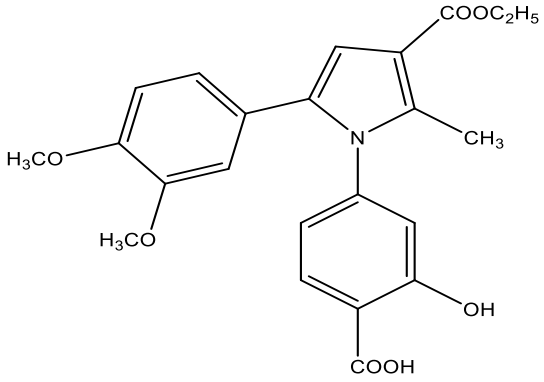


15

8. Analgesic activity

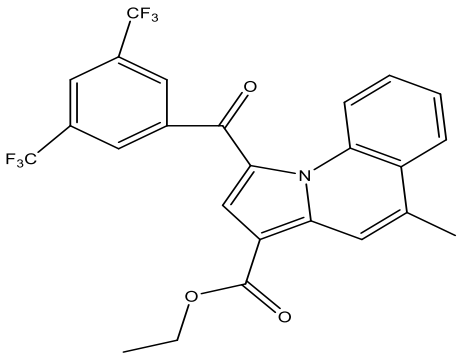
Nikolai Danchev*et al.,* have reported the synthesis, acute toxicity, and analgesic activity of new derivatives of pyrrole. Among the synthesized pyrrole derivatives, compound **16**exhibited the highest analgesic activity in the acetic acid-induced writhing model. Owing to its pronounced pain-relieving effect and comparatively low acute toxicity, this compound has been recognized as a promising candidate for the development of new analgesic agents [16].



16

9. Anti alzheimer's activity

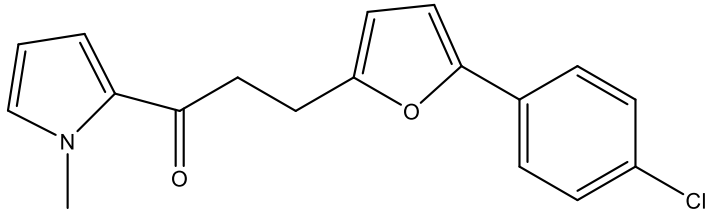
Pramod N Patil*et al.*,have reported the Anti-Alzheimer's and Anti-Fungal Activities of Pyrrolo[1,2-a] Quinoline Derivatives. Among the synthesized pyrrolo[1,2-a]quinoline derivatives, compound **17** demonstrated the strongest anti-Alzheimer's activity, exhibiting superior acetylcholinesterase inhibition compared to the reference drug tacrine. The presence of fluorine substituents on the benzene ring significantly contributes to enhancing their therapeutic potential against Alzheimer's disease [17].



17

10.Antidepressant activity

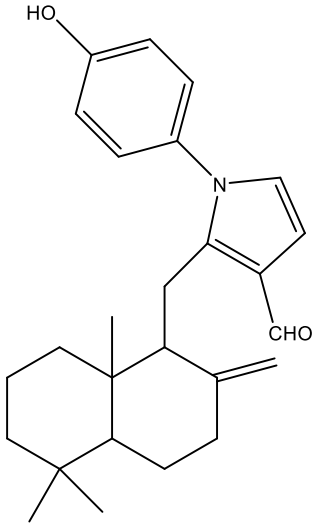
Mehlika d. Altintop*et al.*,have reported the design, synthesis, in vitro and in silico evaluation of new pyrrole derivatives as monoamine oxidase inhibitors. Compound **18**exhibited the highest and most selective MAO-A inhibitory activity (IC_{50} = 0.162 μM), suggestingits potential as a lead compound for the development of antidepressant agents [18].



18

11.Anti hyperlipidemic activity

Renjitha Jalaja *et al.*, have reported the anti-hyperlipidemic potential of natural product based labdane-pyrroles via inhibition of cholesterol and triglycerides synthesis. Among the synthesised compound 17 displayed the highest antihyperlipidemic activity among the synthesized (E)-Labda-8(17),12-diene-15,16-dial-derived pyrrole analogues. Its activity was found to be comparable to those of the clinically used drugs fenofibrate, atorvastatin, and pravastatin, suggesting its potential as a promising candidate for further therapeutic development**(19)** [19].

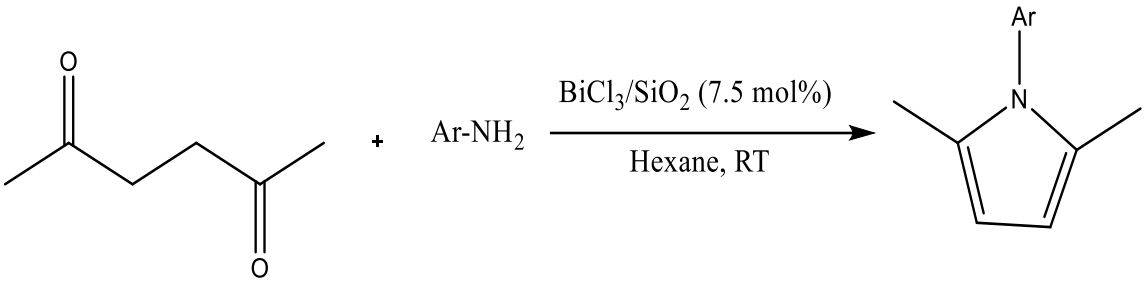


19

Synthesis

1. **Paal-knorr synthesis**

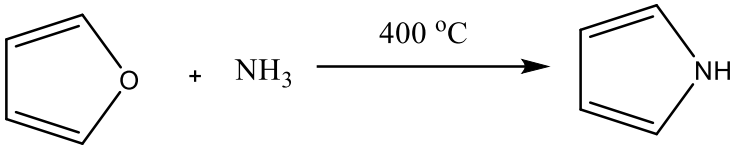
   The Paal–Knorr synthesis of N-aryl-2,5-dimethylpyrroles was accomplished by the condensation of hexane-2,5-dione with aromatic amines in the presence of silica-supported bismuth(III) chloride ($BiCl_3/SiO_2$, 7.5 mol%) in hexane at room temperature, affording the corresponding pyrrole derivatives in good yields [6].



hexane-2,5-dione Amine Pyrrole derivative

2. From furan

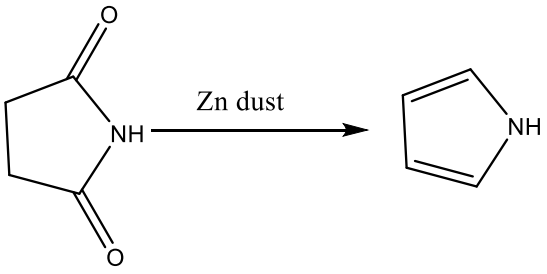
Pyrrole can be synthesized by the high-temperature reaction of furan with ammonia at 400 °C, wherein the oxygen atom of the furan ring is replaced by nitrogen through a heteroatom exchange process, leading to the formation of the pyrrole nucleus [6].



Furan Ammonia Pyrrole

3. From succinimide

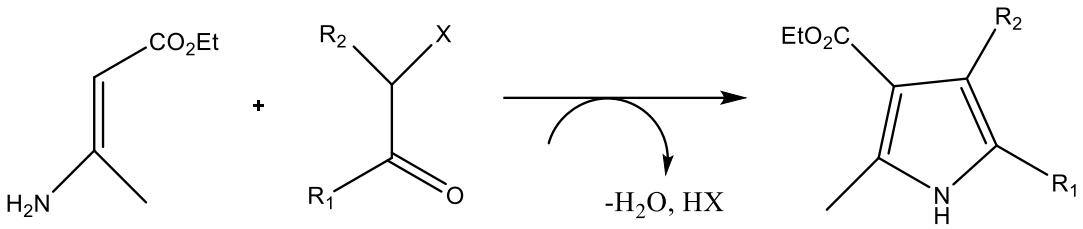
Pyrrole can be prepared by the reductive distillation of succinimide with zinc dust, which converts the cyclic imide into the corresponding pyrrole ring [6].



Succinimide Pyrrole

4. Hantzsch synthesis

The Hantzsch pyrrole synthesis involves the cyclocondensation of β-enamino esters, such as ethyl (E)-3-aminobut-2-enoate, with α-haloketones to afford substituted pyrrole derivatives with the elimination of water and hydrogen halide [20].



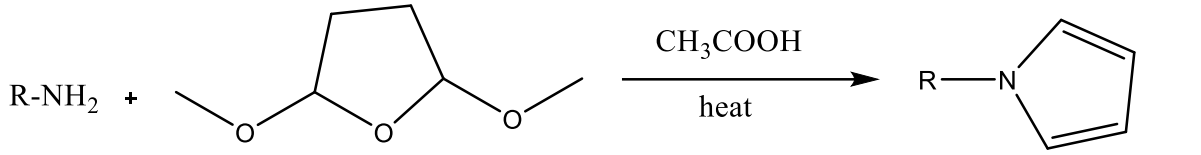
X= Cl, Br

ethyl (*E*)-3-aminobut-2-enoate

N-substituted pyrrole

5. Clauson-Kaas synthesis

The Clauson–Kaas reaction offers a straightforward approach to N-substituted pyrroles through the acid-catalyzed condensation of primary amines with 2,5-dimethoxytetrahydrofuran under heating conditions [21].



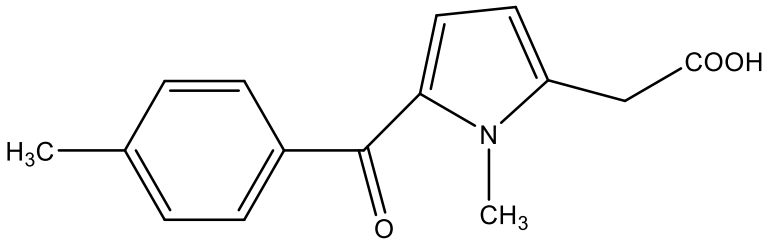
Amine 2,5-dimethoxytetrahydrofuran

N-substituted pyrrole

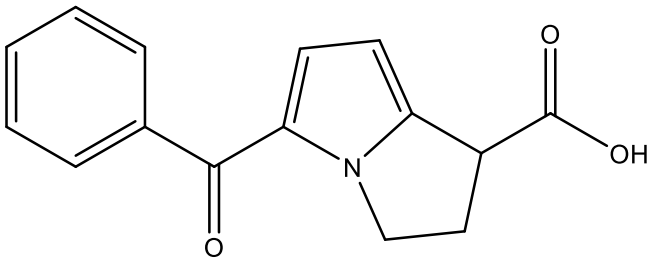
Pharmacologically active drugs containing the pyrrole nucleus

Anti-inflammatory agents

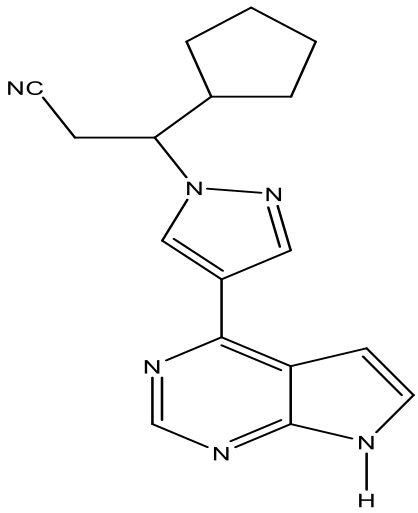
1. Tolmetin



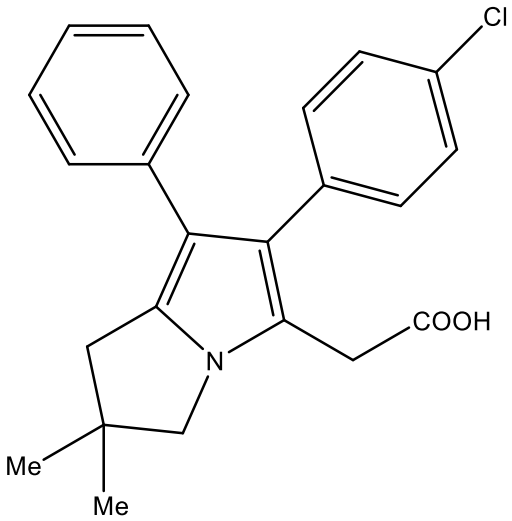
2. Ketorolac



3. Ruxolitinib

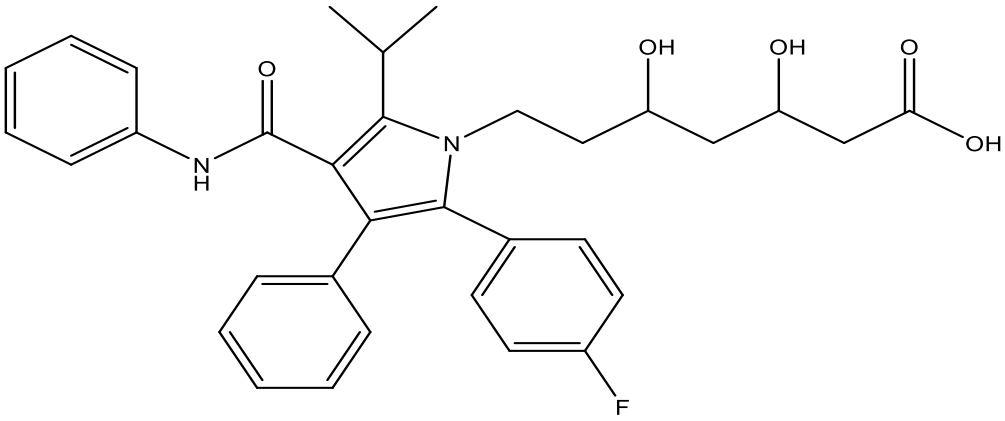


4. Licofelone



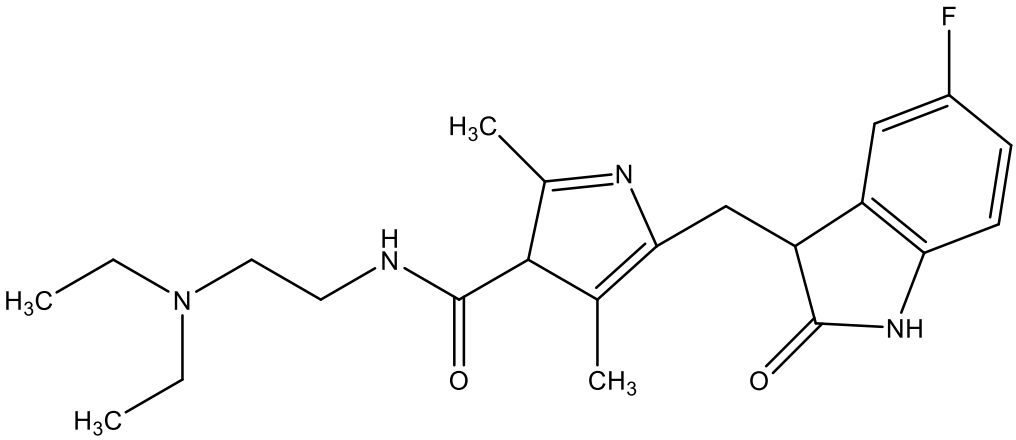
Statins

1. Atorvastatin

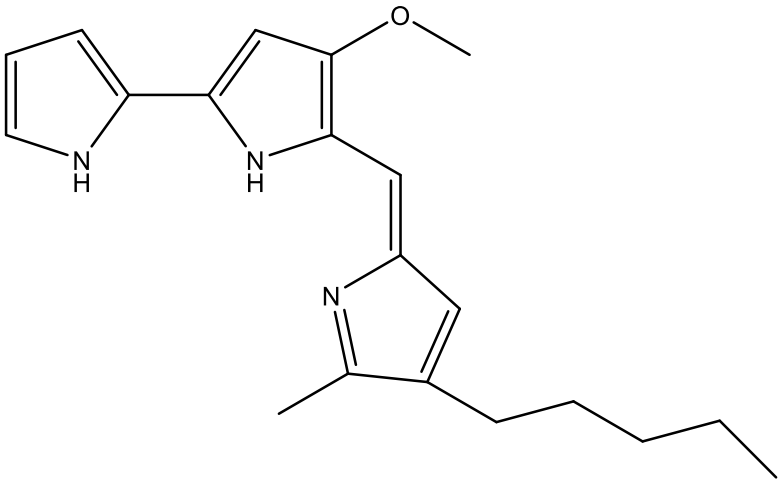


Anticancer agents

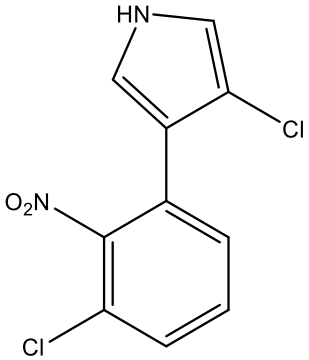
1. **Sunitinib**



2. Prodigiosin

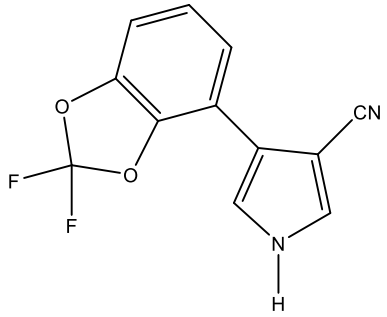


Antifungal agent
Pyrrolnitrin

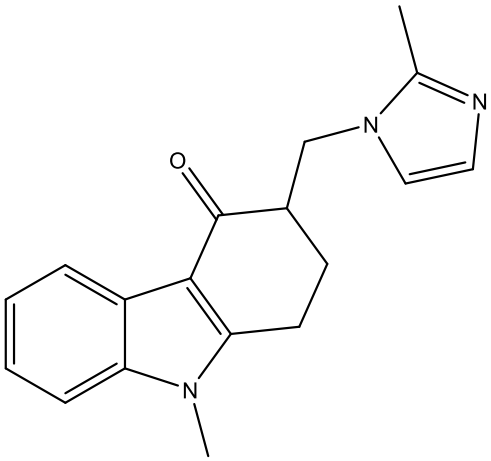


Fungicidal

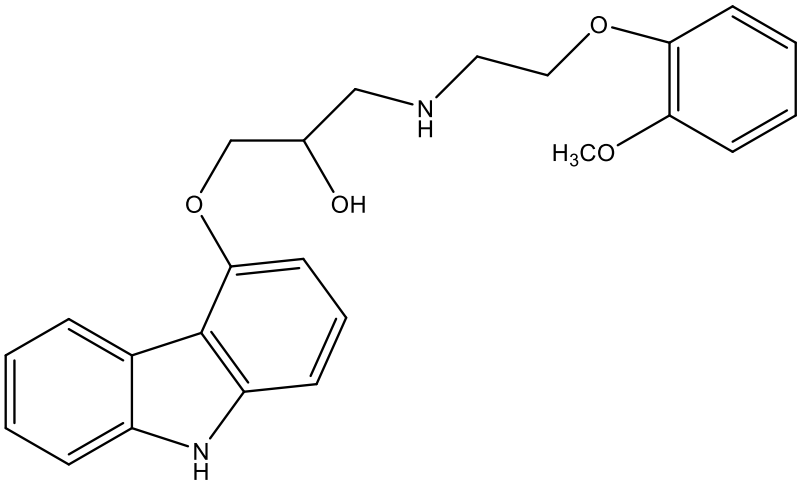
Fludioxonil



Antiemetic activity
Ondansetron



Antihypertensive agent
Carvedilol



CONCLUSION:

Pyrrole represents one of the most significant nitrogen-containing heterocyclic scaffolds in modern medicinal chemistry, owing to its unique aromatic nature, synthetic versatility, and remarkable pharmacological potential. The wide range of synthetic methodologies available for the construction and functionalization of the pyrrole nucleus has enabled the development of numerous biologically active derivatives. Pyrrole-based compounds have demonstrated diverse therapeutic activities, including antitubercular, anticancer,

anti-inflammatory, antioxidant, antiviral, antimalarial, anticonvulsant, and neuroprotective effects. Furthermore, the incorporation of the pyrrole moiety in several clinically approved drugs highlights its crucial role in drug discovery and development. Continuous advancements in synthetic chemistry, molecular modeling, and structure–activity relationship studies are expected to further expand the therapeutic applications of pyrrole derivatives. Therefore, the pyrrole nucleus remains a privileged and promising pharmacophore for the design of next-generation therapeutic agents with improved efficacy, selectivity, and safety profiles.

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