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Synthesis and Evaluation of Pyrrole Derivatives

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ABSTRACT :

It is well known that pyrrole is a physiologically active scaffold with a wide range of functions. More active compounds have been created by combining other pharmacophores with the pyrrole ring structure. Analogs of pyrrole are thought to be a possible source of physiologically active substances with a wide range of beneficial characteristics that are present in numerous natural goods. Numerous pharmacological effects, including antipsychotic, βadrenergic antagonist, anxiolytic, anticancer (including leukemia, lymphoma, and myelofibrosis), antibacterial, antifungal, antiprotozoal, antimalarial, and many more, are known to be present in commercially available medications that contain the pyrrole ring system. Pyrrole are organic cyclic compounds with an extensive and fascinating chemistry. These compounds have a wide structural variety and are an important basis in technological development as they can be used as drugs, dyes, catalysts, pesticides, etc. Therefore, the production of these heterocyclic compounds by efficient clean methodologies is a great achievement in contemporary chemistry.

Keywords: Pyrrole, green synthesis, heterocyclic compounds, Anticancer activity, Paal-Knorr synthesis.

INTRODUCTION

The pyrrole core is widely distributed in nature as the main structure of important molecules such as porphyrins and porphyrin analogues: hemoglobin, chlorophylls, vitamin B12, cytochromes, chlorine, bacteriochlorine,etc [1]. It is also a structural part of different secondary metabolites that have been used in therapeutic drugs [2]. The pyrrole derivatives and analogues have interesting biological activities, such as virus inhibition and specialized inhibition of HIV virus [3], hepatoprotective, antimycotic, antibacterial [4], cholesterol-lowering [5], antipsychotic, antihypertensive, anticarcinogen, antimalarial and anticonvulsant activity [6]. These compounds have an important role in other areas of technological advancement, being used in sensor development, semiconductor synthesis [7], catalysts [8], corrosion inhibitors [9], preservatives [10], luminescence chemistry [11], and spectrochemical analysis [12]. Pyrrole has an aromatic structure with five members, including a nitrogen atom. Compared with other heterocyclic compounds such as pyridine, where the hydrogen atom is not bonded to nitro gen, the pyrrole is a weakest base because the lone pair in the nitro gen contributes to the aromaticity in the structure. Pyrroles are unstable toward mineral acids and
are protonated in the 2-position. The resulting cation polymerizes easily produce pyrrole resins. The common reactions in pyrroles are electrophilic substitutions in 2, 5-position [1]. Pyrroles are obtained by three classical condensation methods: Hantzsch reaction [13], Knorr and Paal-Knorr reactions [14]. Other pyrrole synthesis methods include multicomponent, addition, annelation and Wittig reactions [15].

As the second leading cause of mortality globally, cancer represents one of the biggest threats to global health [16]. The search for new and efficient chemotherapeutic drugs with little to no damage to healthy cells is primarily fueled by the continually rising number of cancer patients and the expense of treatment [17]. The onset and progression of mutations in human genes are largely attributed to genetic illnesses brought on by heritance or hereditary factors [18]. Overall, cancer causes aberrant cell proliferation, cell cycle arrest, and the conversion of proto-oncogenes to oncogenes, all of which impact the function of essential genes [19].

Breast cancer, prostate cancer, colon cancer, lung cancer, colon and rectal cancer, and bladder cancer are among the most common cancer forms. The most prevalent tumor types in males and women are prostate and breast cancers, respectively [20]. The pharmacological treatment of cancer has not altered much in spite of the enormous work in the field of tumor cell biology, and the majority of the time, current chemotherapy does not distinguish between tumor and normal cells [21].

PYRROLECOMPOUNDS'IMPORTANCE

Pyrrole is a significant heterocyclic nitrogen-containing chemical with intriguing biological characteristics [22]. Numerous naturally occurring compounds, such as pyrroloquinoline quinone (PQQ), [23], ryanodine, [24], lamellarin, [25], prodigiosin, [26], sceptrin, [27], and others,alsoincludeit. A number of medications contain pyrrole as the primary heterocyclic component (Fig. 1), such as Lamellarin O (1), a pyrrole alkaloid that is known to selectively inhibit the breast cancer resistance protein (BCRP) [28].

As an inhibitor of HMG-CoA reductase (3-hydroxy-3-methylglutaryl-CoA reductase), atorvastatin (AVA) 2 is a popular pyrrole medication that lowers cholesterol. It is also used to treat cerebral malaria and exhibits good effectiveness against Plasmodium falciparum [29]. It has demonstrated strong anti-inflammatory and neuroprotective properties. Pyrrolnitrin 3 has antifungal properties throughout the body [30]. Licofelone 4 has strong anti-inflammatory, anti-asthmatic, and analgesic properties. [31] As an antibacterial and HIV-1 integrase inhibitor, pyrrole-2-carbaldehyde 5 is employed. [32] One of the most significant non-steroidal anti-inflammatory drugs (NSAIDs) is ketorolac 6. [33]

As a multi-targeted receptor tyrosine kinase inhibitor, sunitinib 7 is a commercially available medication that contains pyrrole and is used to treat renal cancer[34]. Significant antifungal efficacy against Candida species has been demonstrated by diguanidino-1-methyl 2,5-diaryl-1H-pyrrole derivatives 8[35]. One significant non-steroidal anti-inflammatory medicine (NSAID) is tolmetin 9, which functions by lowering the hormones that produce pain and inflammation in the body [36].

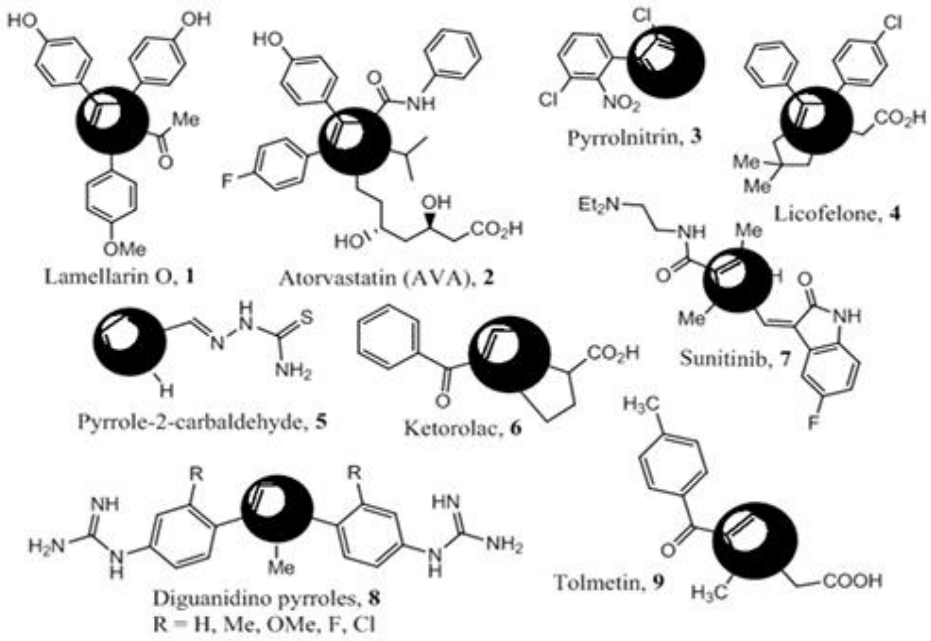
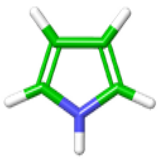
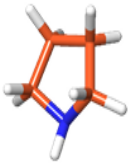


Fig. 1. Some biologically active pyrrole derivatives

Pyrrole – Anticancer Properties

Pyrrole is one of the N-containing heterocyclic scaffolds that has attracted a lot of attention because of its wide range of pharmacological effects and increasing prevalence in medicines, natural goods, and novel materials. With the chemical formula C4H5N, pyrrole is a five-membered heterocyclic molecule. When exposed to air, this volatile liquid takes on a black hue. Pyrrole was first discovered as a component of coal tar in 1834, but it was separated from a bone's pyrolysate 23 years later [37]. As an aromatic five-membered N-containing heterocycle, pyrrole differs from its saturated analog, pyrrolidine (Table 1), in a number of important physicochemical properties [38]. Table 1 lists the chemical characteristics and three-dimensional structures of pyrrole and pyrrolidine.

Table 1. 3D structures and molecular descriptors of pyrrole and pyrrolidine.

	
Pyrrole	**Pyrrolidine**
D – 2.930	*D* – 1.411
PSA – 13.364	*PSA* – 16.464
LogPo/w – 0.750	*LogPo/w* – 0.459
AcceptHB – 0.500	*AcceptHB* – 1.500
LogS - -0.175	*LogS* – 0.854

D – dipole moment of the molecule; *PSA* – power surface area; *LogPo/w* – octanol/water partition coefficient; *AcceptHB* – estimated number of hydrogen bonds accepted by the solute from water molecules in aqueous solutions; *LogS* – predicted aqueous solubility (in mold m -3).

In contrast to cyclopentane, the introduction of a nitrogen atom significantly boosts the polarity of the structures, producing a dipole moment and a notable power surface area (PSA) value. As can be seen above, pyrrole and pyrrolidine have comparable PSA and lipophilicity values. The main differences between the two N-containing molecules, however, are the planar shape, the shorter bond lengths, and the larger binding free energy. Consequently, pyrrolidine, a saturated heterocyclic system, increases the likelihood of producing structural diversity [39].

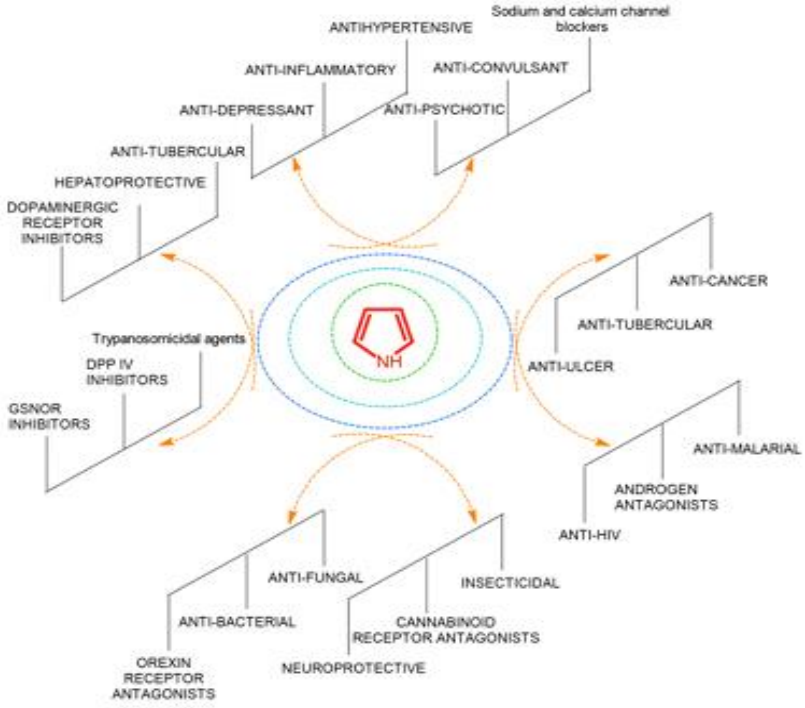


Figure 1. The pharmacological profile of pyrrole derivatives.

A study by Vitaku et al. [40] has verified the previously indicated claim. Furthermore, according to the study, the pyrrolidine ring is the fifth most prevalent five-membered N heterocycle, appearing in 37 approved medications. Interestingly, the former ring is not among the top 10 scaffolds found in approved medications because there are not enough FDA medications that contain pyrrole. Nonetheless, the live creature greatly depends on the pyrrole ring [41]. Chlorophyll, vitamin B12, myoglobin, and bile pigments all depend on the azo-containing heterocycle [42]. Furthermore, a wide range of recent investigations have shown interest in the pyrrole derivatives' broad pharmacological profile (Figure 1) [43].

Pharmacological Activity of Pyrrole and Its Derivatives

In both natural and medicinal chemistry, pyrrole and its derivatives are crucial. In the production of pharmaceuticals, medications, agrochemicals, dyes, photographic chemicals, fragrances, and other organic compounds, they are frequently employed as an intermediate. For instance, the porphyrin ring system's four pyrrole ring production produces the derivatives heme and chlorophyll (Fig. 1). They also serve as solvents for resins and terpenes, corrosion inhibitors, preservatives, catalysts for polymerization processes, standards in chromatographic analysis, and organic synthesis in the pharmaceutical sector. It is a crucial component of the structures of several pharmaceutical products and novel active agents with a range of pharmacological effects, such as the antihyperlipidemic atorvastatin, the Alzheimer's disease treatment aloracetam, the antipsychotic elopiprazole, the anxiolytic lorpiprazole, and the anti-inflammatory tolmetin (Fig. 2). [44]

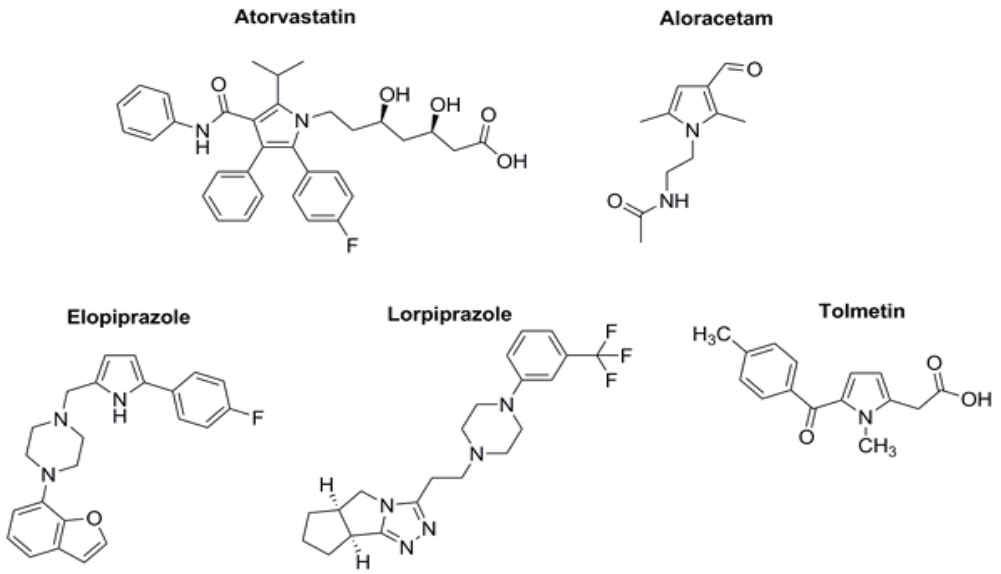


Fig. 2. Structure of drugs, containing pyrrole cycle.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Highly Substituted Pyrroles

Toluene (2.0 mL), 1,3-di carbonyl compounds [46] (0.6 mmol), propargylic alcohols [45] (0.5 mmol), and InCl3 (0.05 mmol) were added one after the other to a 10 mL flask. Primary amines [47] (0.6 mmol) were added after the reaction mixture had been allowed to stir at 608Cor at 708C and was periodically checked by TLC until it was finished. To ensure TLC completion, the reaction mixture was heated to reflux temperature for a further two to twenty-two hours. The reaction mixture was allowed to cool to room temperature before being quenched with 2 mL of 1M HCl, the organic and aqueous layers were separated, and the aqueous layer was extracted using 35 mL of Et2O. After being dried on MgSO4, the mixed organic layers were filtered. To obtain the corresponding highly substituted pyrroles, the filtrate was concentrated under vacuum, and the residue was subsequently purified using silica gel column chromatography (EtOAc/hexane) [48].

General instrumental methods

An HP 8453 spectrophotometer was used to record UV-visible spectra. A 400 MHz Bruker Avance III HD spectrometer fitted with a 5 mm BB/1H SmartProbe was used to record 1H NMR spectra, which were then compared to either residual CH2Cl2 at 5.32 ppm or residua1 CHCl3 at 7.26 ppm. An LTQ Orbitrap XL spectrometer was used to record high-resolution electrospray-ionization (HR-ESI) mass spectra using methanolic solutions, usually in positive ion mode. Elemental studies were performed by Atlantic Microlab Inc., USA33

An EG&G Model 263A potentiated with a three-electrode system—a saturated calomel reference electrode (SCE), a platinum wire counter electrode, and a glassy carbon working electrode—was used to perform cyclic voltammetry at 298 K. The supporting electrolyte was tetra(n-butyl)ammonium perchlorate (CAUTION!), which was recrystallized twice from pure ethanol and dried in a desiccator for at least two weeks. Aldrich's anhydrous CH2Cl2 was employed as the solvent. A fritted-glass bridge containing the solvent/supporting electrolyte mixture served as a barrier between the reference electrode and the bulk solution. Prior to all measurements, which were conducted under an argon blanket, the electrolyte solution was purged with argon for at least two minutes. The SCE was cited by all potentials.

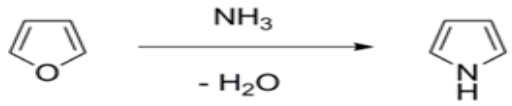
CLASSICAL APPROACHES FOR PYRROLE SYNTHESIS

Industrial preparation

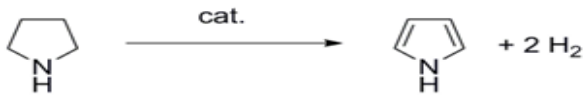
In the industrial setting, pyrrole is created by treating furan with ammonia while solid acid catalysts such as SiO2 and Al2 O3 are present (Scheme 3) [49]. Pyrrolidine can also be catalytically dehydrogenated to get pyrrole (Scheme 4).

Paal-Knorr pyrrole synthesis

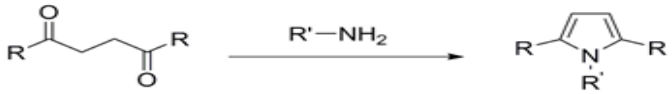
The most prominent and applied method for synthesis of pyrroles, furans and thiophenes, and their derivatives is the well-known Paal-Knorr synthesis, based on a reaction of a 1,4-dicarbonyl compound with ammonia or a primary amine to form pyrrole and substituted pyrrole, respectively (Scheme 5) [50-51].



Scheme 3. Industrial production of pyrrole.



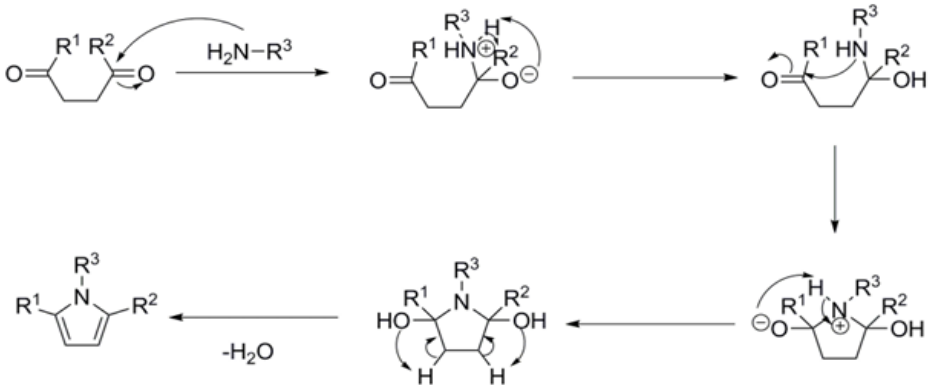
Scheme 4. Preparation of pyrrole by catalytic dehydrogenation of pyrrolidine.



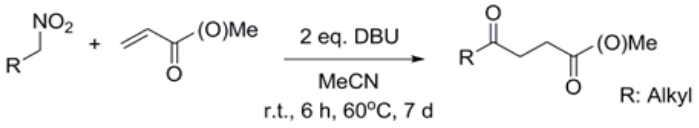
Scheme 5. Reaction of Paal-Knorr.

Mechanism of Paal-Knorr pyrrole synthesis

The mechanism of the Paal-Knorr reaction was proposed by V. Amarnath et al. [52] in 1991. It is based on the amine attacking the protonated carbonyl to generate a hemiaminal. After attacking the other carbonyl, the amine creates a derivative of 2,5-dihydroxytetrahydropyrrole, which is then further dehydrated to produce the matching substituted pyrrole [53]. (Scheme 6) presents the suggested mechanism. With a primary amine, the reaction is usually conducted under Lewis or protic acidic conditions. According to Paal, the US age of ammonium hydroxide or ammonium acetate yields N-unsubstituted pyrrole [53].



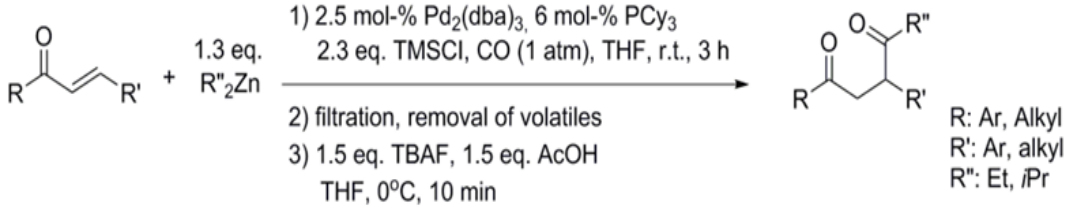
Scheme 6. Mechanism of Paal-Knorr reaction.



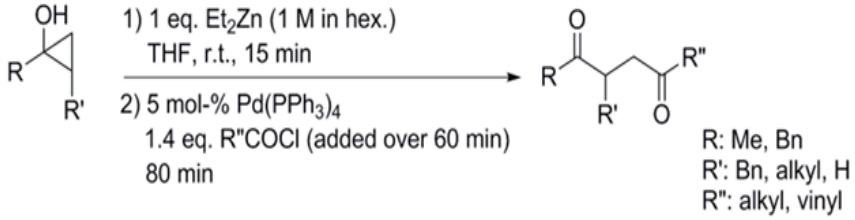
Scheme 7. Obtaining 1,4-diketones by one-pot synthesis.

SYNTHESIS OF 1,4-DIKETONES

There have been several documented techniques for synthesizing the 1,4-diketones required for cyclization: Conjugated addition of primary nitroalkanes to α,β-unsaturated ketones or esters yields γ-diketones or γ-keto esters in a single pot (Scheme 7) [54]. According to Schemes 8 and 9, 1,4-diketones can be obtained in good yield by Pd-catalyzed addition [55] and cross-coupling [56].



Scheme 8. Obtaining 1,4-diketones by Pd-catalyzed addition.



Scheme 9. Obtaining 1,4-diketones by cross-coupling.

CONCLUSION

In just a few seconds, moderate quantities (35–60%) of 5-(2-pyrrolyl) isocorroles are produced when free-base meso-triarylcorroles react with an excess of pyrrole in dichloromethane at room temperature when DDQ is present. Complexation with Cu (II) indicated metal coordination to each isocorrole ligand. Strong near-infrared absorption was observed in both the free ligands and their metal complexes, suggesting possible uses as sensitizers in photodynamic treatment. With a focus on recently published, environmentally friendly procedures, we have given a summary of the many multicomponent reactions (MCRs) based approaches for the synthesis of substituted pyrroles. Pyrrole is a crucial heterocyclic scaffold that has been used extensively in chemistry, particularly in drug development and medicinal chemistry.

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