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A Short Review on Pyrazole Derivatives and their Applications

Samet Mert[1], Rahmi Kasimogullari[1], Salim Ok*[2]

[1] Department of Chemistry, Faculty of Arts and Sciences, Dumlupinar University, 43100 Kutahya, Turkey,
[2] School of Earth Sciences, The Ohio State University, Columbus, OH 43210, USA
Email: *ok.12@osu.edu

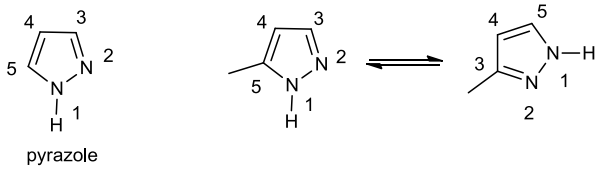
Abstract

Pyrazole is a heterocyclic organic compound having a 5-membered ring structure with three carbon atoms and two neighbor nitrogen atoms. There are several applications of pyrazole core based organic molecules in various areas including pharmacy and agro-chemical industries. There is an increase in the interest of synthesizing, analyzing different properties, and seeking possible applications of pyrazole derivatives. Our research efforts have been focusing on different aspects of pyrazoles including facile synthesis, their behavior in biodegradable polymers, and investigating their bioactivity. In this short review article, the aim is to show the trend in the research on pyrazole derivatives.

Keywords: applications, property characterization, pyrazole derivatives, synthesis

Introduction

Over the years increasing attention has been paid to pyrazole derivatives which are synthesized based on the pyrazole as the central core. The central core contains a five-membered heterocyclic organic compound with two adjacent nitrogen atoms [1] (See Scheme 1). Pyrazole derivatives have great interest in agrochemical, pharmaceutical, and chemical industries [2, 3]. In this short review, we want to cover the recent studies on pyrazole derivatives mostly published within the last 5 years. There are several aspects that will be explained referring to the works of the leading groups in the area of pyrazole derivatives: i) different approaches in synthesis, ii) characterization of various properties, iii) bioactivities of pyrazole derivatives, iv) other applications of pyrazole derivatives.

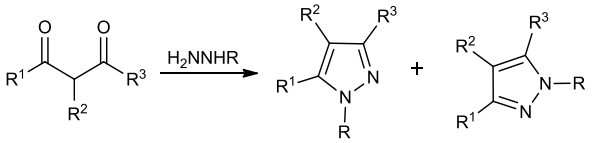


Scheme 1

Different Approaches in Synthesis

There are various synthetic approaches in synthesizing new pyrazole derivatives. The most common synthetic approach to pyrazole derivatives involves the reaction of 1,3-diketones with hydrazine derivatives [1, 4] (See Scheme 2). One of the major concerns is to exhibit simple routes for the synthesis of the pyrazole derivatives [5, 6]. The other important area of research in synthetic organic chemistry is “Green Chemistry”. The “Green Chemistry” here refers to the reactions that can be carried at room temperature with no organic solvent requirement, and no waste production [7]. For instance, solvent free heterocyclic compound synthesis includes ultrasound and microwave irradiation [8, 9]. Microwave (MW) irradiation has been widely exploited in the last decades to run various number of organic synthesis. Usually three types of solvent-free procedures can be coupled with dielectric heating provided by a microwave source: reactions among neat reagents, reactions among supported reagents on mineral solid supports and phase transfer catalysis reactions. Among the three types of solvent-free procedures, the neat reagent one is the most routinely employed due to its easy work-up and negligible use of solvents [10]. In particular, applying Microwave Assisted Organic Synthesis (MAOS) becomes more common in heterocyclic chemistry and especially in pyrazole derivative synthesis [11-13]. The other

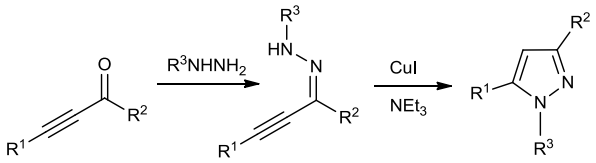
possibility in contributing to "green chemistry" is to carry the synthesis of pyrazole derivatives in aqueous medium [14]. The use of water has many advantages since water is cheap, easily available, and environmentally friendly. Water is preferable as a solvent from both an economical and environmental point of view [15]. The unique structure and physicochemical properties of water establish particular interactions of polarity, hydrogen-bonding, hydrophobic effects in addition to trans-phase interactions that might influence the course of a reaction [16].



R= alkyl, aryl, heteroaryl etc.

Scheme 2

Usually pyrazole derivatives are synthesized as a series of molecules. For this reason, combinatorial synthesis is also mentioned in the current literature [17]. In addition to "green chemistry" and combinatorial synthetic approaches to novel pyrazole derivatives generation, there are metal assisted synthetic methods developed [18-20]. Extension of metal-mediated cyclization reaction led to the synthesis of aluminated pyrazoles. Aluminated heteroles can be produced by in parallel addition/intra-molecular 5-endo-dig metal-mediated cyclization enabling the preparation of 1,3,5-trisubstituted 4-aluminopyrazoles [18]. Synthesis of pyrazoles via electrophilic cyclization of α,β-alkynic hydrazones by copper (I) iodide was reported. Upon reacting with copper(I) iodide in the presence of triethylamine in refluxing acetonitrile, α,β-alkynic hydrazones underwent electrophilic cyclization to result in novel pyrazole derivatives with high yields [19] (See Scheme 3). The other important sub-class of pyrazole derivatives are the fluorinated compounds [20]. There is transition-metal-mediated C-F bond formation that has high attention for the construction of organic fluoro compounds [21-23]. In this regard, palladium and gold are the most promising metals for C-F bond formation. For example, gold-catalyzed aminofluorination of alkynes yielded fluorinated pyrazoles at room temperature [20].



R^1= alkyl, aryl, ferrocenyl
R^2= H, methyl, phenyl
R^3= alkyl, aryl

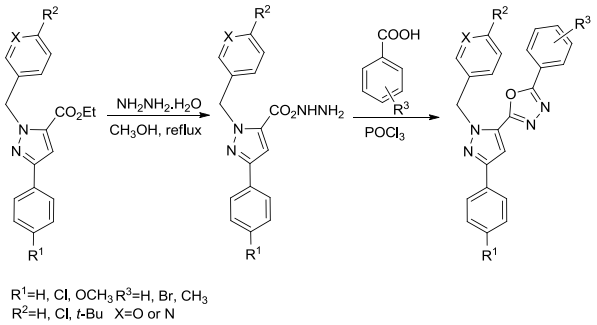
Scheme 3

This review is a short description of an ongoing research area of pyrazole synthesis, though there are a lot of synthetic methods developed for generating novel pyrazole derivatives. However, generally these methods need organic solvents [24, 25]. In addition to the use of organic solvents, low yield percentage is another major challenge in pyrazole synthesis. Solventless reactions are rapid, regio- or chemo-selective. These reactions result in high yields, and have environmental and economic advantages. We believe that these solventless reactions represent a possible solution to the challenges in the synthesis of pyrazole derivatives. The use of water will also be helpful in overcoming some major issues of pyrazole derivative synthesis [26].

Characterization of Various Properties

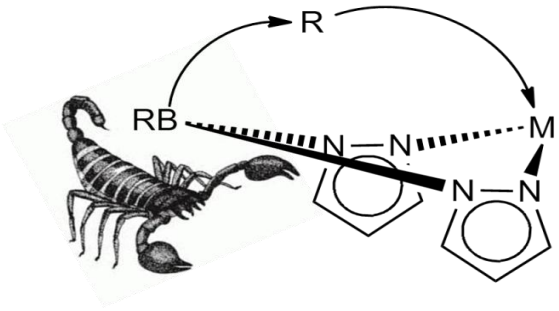
It is necessary to study different properties of pyrazole derivatives since investigation of these properties is compulsory because of wide biological activities of the derivatives. There are various physical properties of pyrazole derivatives which are important. For example, the photochemical property of phthalocyanines substituted with four 3,5-dimethylpyrazole-1-methoxy groups [27] and fluorescence activity of metal complexes of 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde Schiff bases have been reported

[28]. Cationic surfactants and their tin and copper complexes were derived based on the pyrazole core. Surface activity of these surfactants was studied. The presence of the heterocyclic core led to the relatively higher values of the surface tension of these surfactants [29]. In the study on phthalocyanines with and without metals typical electronic spectra with two strong absorption regions were observed. The peak around 300 nm is called "B" band, while the other peak at 600-750 nm is defined as "Q" band. The metallophthalocyanines have style single narrow Q bands and this supports the formation of phthalocyanine complexes [27]. Pyrazole derived metal complexes of carboxaldehyde Schiff bases were also characterized for thermal behavior and fluorescence activity. In the study by Sing et al. (2012) the decomposition of all the complexes ended with oxide formation. The Schiff bases showed dramatic decrease in fluorescence emission intensity upon complex formation with transition metals of cobalt, nickel, copper, and zinc [28]. In another similar study, on pyrazolyl 1,3,4-oxadiazole derivatives, the absorption spectra and fluorescence characteristics were correlated with substituents on benzene rings [30] (See Scheme 4). In a very recent report on pyrazole-metal complexes, UV-Vis was employed for controlling thermodynamic stability [31]. Such property characterization needs to be done in order to cross check the synthesis of the molecules and to figure out new applications of pyrazole derivatives. For example, UV-active pyrazole derivatives may have applications as dye molecules [5] or in polymer light emitting diodes [32].



Scheme 4

Scorpionates (Poly (pyrazolyl) borates) have proven to be extremely popular ligands since their introduction by Trofimenko. As in the case of the pincers of a scorpion (See Scheme 5), these versatile tripodal ligands bind a metal with nitrogen heteroatoms from two pyrazole rings attached to a central boron atom. The third pyrazole ring (or the R group), attached to the boron, rotates forwards like a scorpion's tail to "sting" the metal [33]. In another recent study, a new polydentate class of pyridyl-functionalized scorpionate ligands have been employed for the synthesis of complexes of Fe^{2+}, Zn^{2+}, Ni^{2+}, V^{4+}, Pd^{2+} [34]. The aim in that study was to design new multidentate tris (pyrazolyl) methane ligands bearing an additional *N*-donor group pending from the central methane carbon. The function of this extra unit was studied to figure out the potential of forming heteronuclear species. The new ligands toward Fe^{II}, Zn^{II}, Ni^{II}, Pd^{II}, and V^{III} centers were applied as doubly functionalized ligands to the preparation of hetero-bimetallic complexes of Fe^{II}/Pd^{II} and Fe^{II}/Cu^{II} centers.



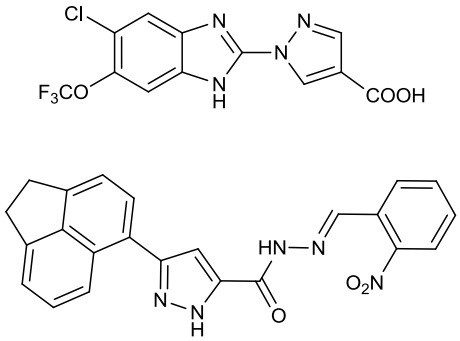
Scheme 5

Basic structural characterization of pyrazole derivatives includes spectroscopy, thermal analysis, and other aspects. Often detailed characterization by advanced techniques such as two-dimensional (2D) nuclear magnetic resonance (NMR) spectroscopy is not employed. Further, thermal analysis is done with the thin capillary method. In fact, thermo gravimetric analysis (TGA) measurements are required to be performed prior to melting temperature determination of new organic molecules by

differential scanning calorimeter (DSC). We think that the organic synthetic community, and especially the contributors of the synthesis of pyrazole derivatives literature need to benefit from such methods of 2D-NMR, TGA, and DSC in order to provide more reliable data on different physical properties of pyrazole derivatives. Overcoming such a challenge will be important for opening new routes for better understanding the properties of novel pyrazole core based organic molecules.

Bioactivities of Pyrazole Derivatives

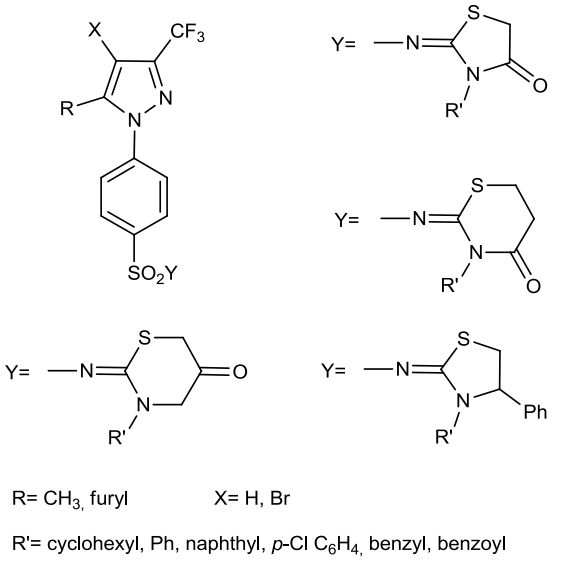
Pyrazole derivatives possess a wide range of bioactivities [3, 35], including anti-inflammatory [36], anticonvulsant [37], anticancer [38], and antifungal [39] behavior. In this section, we will describe some of the current studies about the inhibition ability of pyrazole derivatives. Barret et al. (2011) reported a fluorinated pyrazole derivative that was able to inhibit selective hypoxia-inducible factor prolyl hydroxylase [40]. Hypoxia-inducible factor-α (HIF-α) mediates the cells' transcriptional response to hypoxia [41]. There is a role of prolyl hydroxylase (PHD) enzymes in the process for the hypoxia-responsive nature of cellular HIF-1α content. The possibility of mimicking the body's coordinated response to hypoxia was shown by the PHD inhibitor, 1-(5-Chloro-6-trifluoromethoxy)-1H-benzoimidazol-2yl)-1*H*-pyrazole-4-carboxylic acid (JNJ-42041935). The JNJ-42041935 depicted great promise for the treatment of a range of anemic conditions [40] (See Scheme 6).



Scheme 6

In another study by Kasimogullari et al. (2010), some novel sulfonamides derived from pyrazole core exhibited antiglaucoma activity [42]. Glaucoma is a well-known sickness arising from fluid formation in the eye and leading to increase in intraocular pressure. In glaucoma treatment, there are several side effects of various drugs used. For this reason, there is a need for synthesizing novel molecules with antiglaucoma activity with less side effect. Some of these sulfonamides had higher inhibition ability with respect to drug molecules.

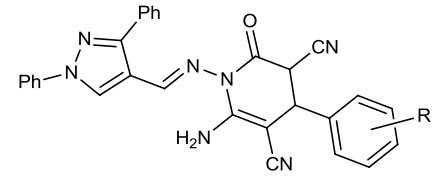
One of the important concerns in evaluating bioactivity of organic molecules is to work with lower concentrations in sub-micromolar range. Shih et al. (2010) reported BPR1P0034 as a pyrazole-based anti-influenza compound [43] (See Scheme 6). BPR1P0034 showed potent (sub-μM) antiviral activity. Such results have significance to develop new novel compounds for fighting against influenza viruses, a major cause of morbidity and mortality around the world.



Scheme 7

Further, new 3-trifluoropyrazole derivatives synthesized by the condensation of 4-hydrazino benzenesulfonamide hydrochloride with 1-trifluoromethyl diketones exhibited antimicrobial activities [44] (See Scheme 7). In a recent in vitro

study by Desai et al. (2013), some pyrazole derivatives encompassing 2-pyridene depicted potent antibacterial activity against bacterial strains such as Staphylococcus aureus at non-cytotoxic concentrations [45] (See Scheme 8). Finding such new organic molecules with antibacterial activity is important because of the resistance of pathogenic bacteria towards available antibiotics.

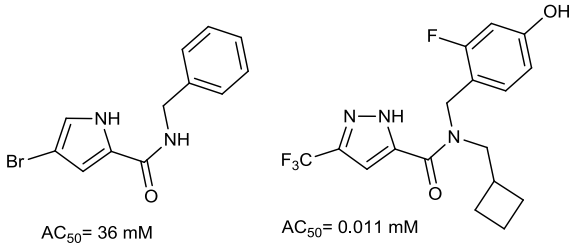


R= H, F, Br, NO_2, CH_2,CF_3, OH, OCH_2,

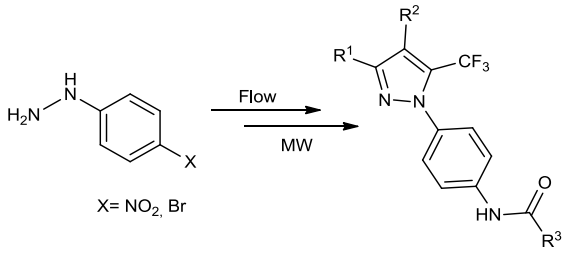
Scheme 8

In addition to inhibition ability, pyrazole derivatives also show activation talent. In a very recent report, Xu et al. (2014) optimized a weakly active screening hit to a structurally novel series of small molecule 3-(trifluoromthyl)-1H-pyrazole-5-carboxamides as potent PKM2 activators [46] (See Scheme 9). Pyruvate kinase (PK) is a key mediator of glycolysis and a rate-limiting enzyme catalyzing the last step of glycolysis. Among the four PK isoforms (PKL, PKR, PKM1, PKM2) in mammalian cells encoded by two genes of pkrl and pkm, PKM2 is found in highly proliferating cells including cancer and embryonic cells [47]. PKM2 may change cancer cell metabolism. In this regard, small molecule PKM2 activators stabilize the tetrameric form and may affect cancer metabolism. Thus, the activators may provide a novel anticancer therapeutic strategy. Obermayer et al. (2011) performed microwave-assisted synthesis of a series of 4-(pyrazol-1-yl) carboxanilides as inhibitors of canonical transient receptor potential channels [48] (See Scheme 10).

There are two major issues in studying the bioactivity of pyrazole derivatives. One of them is the concentration below which pyrazole derivatives show bioactivity. Generally, the concentration needs to be in sub-micro molar range.



Scheme 9



X= NO_2, Br

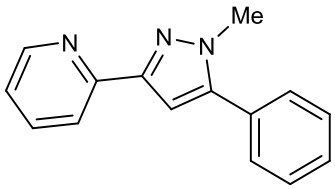
Scheme 10

The second issue is the structure-activity relationship (SAR) analysis. SAR analysis especially needs to be explored and extended by computational efforts.

Other Applications of Pyrazole Derivatives

The most studied property of pyrazoles is their bioactivity. In addition to bioactivity, pyrazoles have potential for other applications such as dyes and catalysts. Pyrazole based metal complexes for example have been studied as homogenous or supported catalysts [49]. Oxo-vanadium(IV) complexes derived from pyrazole were studied for oxidation of cyclohexane under mild conditions. The study focused on applying these complexes as catalyst precursors for the single-pot peroxidative cyclohexane oxidation to cyclohexane oxidation, then to cyclohexanol and to cyclohexanone at 25 °C under both homogeneous and heterogeneous conditions. The homogeneous reactions were faster than the heterogeneous ones.

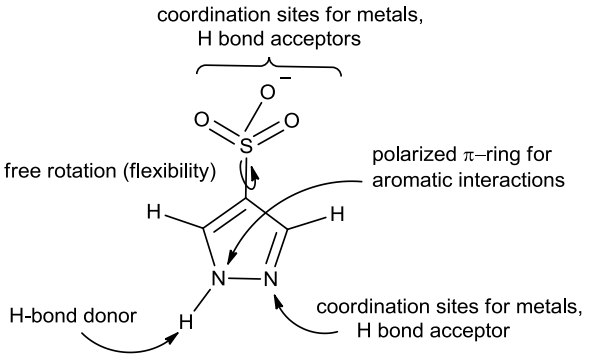
Since, in most cases, pyrazole derivatives are UV active molecules, one of the interesting applications of pyrazole derivatives is using them as dye molecules. Novel dyes were synthesized based on 1,5-dioxo pyrazolo[1,2-a]pyrazole 3-carboxylic acid aschomophonic systems. The dying properties of the pyrazole derivatives were investigated on cotton, wool and silk fabrics. The results assessed for dyeing indicated that the hetero-bifunctional monochlorotriazine/ sulphatoethylsulphone (MCT/SES) pyrazolo pyrazole 3-carboxylic acid derivatives showed higher exhaustion and fixation values, color yield and fastness properties than those of hetero-bifunctional MCT/SES 3-methyl pyrazolo pyrazole derivatives. This enhancement was attributed to the solubilizing groups [50].



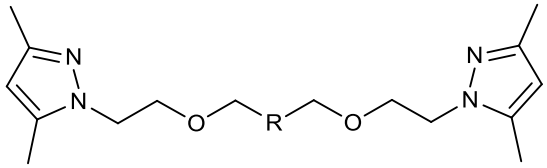
Scheme 11

Herve et al. (2010) performed the selective preparation of 3,4,5-trinitro-1*H*-pyrazole known as an aromatic explosive that is all-carbon nitrated and can be used in powerful ammunitions or in propellants exhibiting great thermal, chemical, and mechanical stability [51]. Cuipa et al. (2012) synthesized pyrazole based fluorescent sensors selective for Cd^{2+} and Zn^{2+} [52] (See Scheme 11). Fernando et al. (2010) have used inorganic–organic layered structure of pyrazole-4-sulfonate networks as inhibitors of copper corrosion [53] (See Scheme 12). Further, possibility of using pyrazole derivatives as efficient acceptors for organic solar cells was depicted [54].

There have been different applications of pyrazole derivatives in polymer research [55-59]. Monodisperse maghemite nanoparticles, templated in a novel, well-defined pyrazole-containing norbornene-based block copolymers, provided a super paramagnetic nanocomposite with high saturation magnetization [55]. Guerrero et al. have designed new N,O hybrid pyrazole derived ligands and they investigated their use as stabilizers for the synthesis of Pd nanoparticles [56] (See Scheme 13).



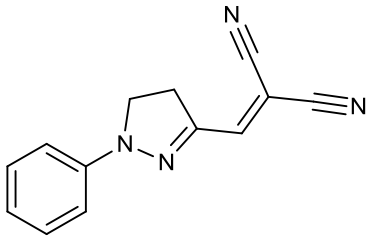
Scheme 12



Scheme 13

The block copolymer contained “chelating groups” in one block and “steric-stabilizing” block. The chelating block was for binding with the metal nanoparticles while the other block was utilized for preventing agglomeration. The anchoring group was synthesized by the versatility of oxirane ring-opening by the heterocycle pyrazole, forming a ligand to stabilize maghemite nanoparticles through strong coordination. Well-defined *N*,N-dimethyl pyrazole-functionalized norbornene-based diblock copolymers were effective in stabilizing in situ-generated maghemite nanoparticles. In another study, it was shown that synthetic pyrazole-containing polymer sorbents are promising for the recovery of gold and silver from cyanic solutions of complex compositions [57]. In a recent study, the role of various

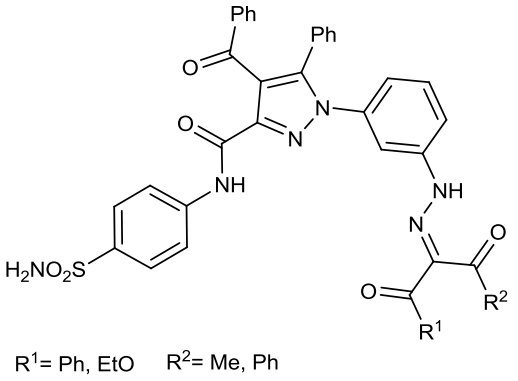
polymer matrix systems on the emissive properties of 3-(1,1-dicyanoethenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole (DNCP) dye was studied [58] (See Scheme 14). The photo-stability of the same dye was investigated. The lowest amplified spontaneous emission (ASE) threshold and highest gain coefficient was obtained for the poly (*N*-vinyl carbazole) (PVK) matrix with DCNP dye. The slowest photo-degradation process of DCNP was observed for the polymethyl methacrylate (PMMA) matrix.



Scheme 14

Pyrazole derivatives may show hydrogen bonding ability [60]. Based on that blends of pyrazole derivatives with hydrogen bonding and biodegradable poly (vinyl alcohol) (PVA) were studied. The diffusion coefficients of pyrazole derivatives changed in blends with PVA with respect to their pure state. In addition, the UV bands of the derivatives depicted changes in the blends with PVA [59] (See Scheme 15). Thus, a model system for drug delivery purposes was developed.

Finding new applications of pyrazole derivatives is related to detailed characterization. The challenges of the detailed characterization need to be solved so that new applications of pyrazole derivatives might be investigated. In addition, the pyrazole unit is a core structure in some natural products [61]. The extraction of natural products having pyrazole as the central core will be helpful in finding new applications of pyrazole derivatives. The nitrogen-containing heterocycles have good coordination capability with metal ions [62]. For instance, pyrazole derivatives have strong chelation capability and large extraction capacity for Th(IV) ions, a radioactive element [61, 63]. These examples of metal extraction indicate that pyrazole based organic compounds or even polymer molecules will have important applications in other areas in addition to drug development in pharmacy.



Scheme 15

Conclusion

Synthesis of pyrazole derivatives and even their complexes with various metals is well established. Mostly, the bioactivity of the pyrazole derivatives was studied in detail. There are recent attempts in understanding different properties of the pyrazole derivatives. In addition, there are some challenges to overcome. These challenges include efficiency for high yields in synthesis, generating novel pyrazole derivatives with bioactivity in the sub-micro molar range, and characterizing the properties of the derivatives accurately. For this reason, we believe there is a need for investigating new synthetic routes, studying different properties and seeking new applications of novel derivatives especially in blends with polymers. Therefore, the new trend in pyrazole derivatives will be towards new applications in various areas.

Acknowledgment

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