Recent developments in synthetic chemistry and biological activities of pyrazole derivatives

MUHAMMAD FAISAL*, AAMER SAEED*, SARWAT HUSSAIN, PARSA DAR and
FAYAZ ALI LARIK

Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan

E-mail: mfaisal4646@gmail.com; aamersaeed@yahoo.com

MS received 10 January 2019; revised 13 March 2019; accepted 18 May 2019

Abstract. Pyrazole, a five-membered heterocycle containing two nitrogen atoms, is extensively found as a core framework in a huge library of heterocyclic compounds that envelops promising agro-chemical, fluorescent and biological potencies. Attributed to its several potential applications, there is a rise in the significance of designing novel pyrazoles, disclosing innovative routes for synthesizing pyrazoles, examining different potencies of pyrazoles, and seeking for potential applications of pyrazoles. This review consists of two parts. The first part provides an overview on the recent developments in synthetic approaches to pyrazoles, which is related to the new or advanced catalysts and other 'environment-friendly' procedures, including heterogeneous catalytic systems, ligand-free systems, ultrasound and microwave-assisted reactions. The second part focuses on the recently reported novel biological affinities of pyrazoles. This systematic review covers the published studies from 1990 to date. It is expected that this review will be helpful in future research and for new thoughts in the quest for rational designs for developing more promising pyrazoles.

Keywords. Pyrazole; pharmaceutical activities; biological activities; synthesis; green chemistry; polycondensed compounds.

1. Introduction

Heterocyclic compounds are a highly valuable and unique class of compounds. These compounds demonstrate a broad spectrum of physical, chemical and biological characteristics.^{1,2} In nature, heterocyclic compounds are widely distributed and display an important part in metabolism owing to their structural nucleus occurring in various natural products, including hormones, antibiotics, alkaloids, vitamins and many others.^{3–5}

Amongst heterocyclic compounds, nitrogen-containing heterocycles are extensively found as a core framework in a huge library of heterocycles and show several employments in natural science and other areas of science.⁶ Additionally, nitrogen-containing heterocycles have striking structural features and they are widely observed in natural products, for instance, vitamins, hormones and alkaloids.^{7,8} Pyrazole **1** is known to be one of the most potential families of nitrogen-containing compounds. Pyrazole derivatives exhibit a broad spectrum of biological profiles, for instance, anti-tubercular,⁹ anti-AIDS,¹⁰ anti-malarial,⁸

anti-microbial,¹¹ antitumor,^{12,13} anticancer¹⁴ and anti-fungal.⁶ In addition, pyrazoles have also been found as promising anti-hyperglycemic,¹⁵ anti-depressant,¹⁶ anti-convulsant,¹⁷ anti-pyretic,¹⁸ anti-anxiety^{19,20} and insecticidal agents.²¹ Bipyrazole shows diuretic, cytotoxic and cardiovascular efficacy.¹⁹ It has achieved great attention since the privileged framework is frequently observed as a bioactive component in commercially available medicines, for example, Floxan **2** (anti-inflammatory medicine), pyrazomycin **3** (anti-cancer), difenamizole **4** (anti-inflammatory drug), and deramaxx **5** (NSAID) (Figure 1).^{22,23} It is also utilized in paint and photographic industries and in the development of heat resistant resins.²⁴ The corresponding 3-oxygenated derivative, pyrazolone **6**, which has an additional keto-group, is the basic component in drugs such as metamizole sodium and phenylbutazone (both are non-steroidal anti-inflammatory medicines, generally used as powerful painkillers and fever reducers) (Figure 1).¹⁹ Also, the benzo-fused derivative of pyrazole (*i.e.*, tetrahydroindazole **7**) is well-known to be biologically active, and used against cancer²⁵ and inflammation.²⁶ Indole **8**, which is an isostere of indazole, is perhaps the most commonly found heterocyclic system

*For correspondence

Figure 1. Structures of important pyrazole derivatives.

in nature. For instance, the essential neurotransmitters in the central nervous system, serotonin and the crucial amino acid, tryptophan are two out of several important indole derivatives (Figure 1).²⁷

Chemically, in the basic structure, pyrazole **1** has two nitrogen atoms at adjacent positions in the five-membered ring. The molecular formula of pyrazole **1** is $C_3H_4N_2$ which has 6 π electrons delocalized over the ring forming an aromatic system. Pyrazole is closely linked to several of its reduced or oxidized forms such as pyrazoline (**11**, **12** and **13**), pyrazolidine **9**, and pyrazolone **10**. Unlike pyrazole, pyrazoline, and pyrazolidine are not aromatic compounds due to the lack of conjugation and delocalization of π electrons (Figures 1 and 2).²⁸

In synthetic chemistry, the development of novel and productive approaches for the synthesis of pyrazole derivatives along with their bioactivities examination is known to be an important and continuing challenge. This review provides an extensive summary of progress over the last decade for the formation of pyrazoles as well as their biological profile. We hope that this review will be useful for scientists working in the area of synthetic and medicinal chemistry.

2. Aromaticity, chemical reactivity and physical properties of pyrazole

2.1 Aromatic character of pyrazole

Pyrazole **1** is a five-membered aromatic heterocyclic compound. Pyrazole is a π -excessive heterocyclic system, which contains two nitrogen atoms; one is pyrrole type at position-1; while, other is pyridine type at

Figure 2. Structures of pyrazolines.

position-2. Among the two nitrogens, one is basic and the other is neutral in nature. The aromatic nature in pyrazole systems appears from the unshared pair of electrons on the $-NH$ nitrogen and the four π -electrons. Pyrazole exists in three partially reduced forms, *i.e.*, 1-pyrazoline **11**, 2-pyrazoline **12** and 3-pyrazoline **13** (Figure 2).²⁹

These are also aromatic systems attributed to their conjugated planar ring frameworks with six highly delocalized π -electrons. It is found from various experimental investigations that the bond length between atoms at position 3 and 4 has a high value.³⁰ 2-Pyrazolines **12** are observed to be the most commonly examined pyrazoline-type heterocyclic systems (Figure 2).³¹

2.2 Chemical reactivity of pyrazole

The chemical reactivity of pyrazole **1** can be described by the effect of individual atoms. The nitrogen atom at position-2 with lone pair of electrons is moderately basic in nature and thus reacts with electrophilic centers of reagents. The nitrogen atom at position-1 is not reactive but gives up its H^+ in the existence of the base. The combined effect of two nitrogen atoms reduces the charge density at carbon-3 and carbon-5, making them vacant for attack by electrophilic reagents. Removal of H^+ at carbon-3 can take place in the existence of a strong base, ending in the opening of the ring. Addition of H^+ ions to pyrazoles results in the formation of pyrazolium ions which are less likely to experience electrophilic

Figure 3. Three tautomeric structures of pyrazole.

Figure 4. Tautomeric forms of 16.

attack at carbon-4, but an electrophilic attack at carbon-3 is facilitated. The anions of pyrazole are much less reactive toward nucleophilic attack, but the reactivity toward electrophiles is enhanced.³² Owing to their planar conjugated ring skeletons with 6 highly delocalized *pi*-electrons, pyrazole molecules are aromatic heterocycles. Hence, various significant properties of pyrazoles have been investigated by matching with the properties of benzene analogues.³³ Like other nitrogen atom(s) involving heterocyclic compounds, different tautomeric forms (14 and 15) can also be written for pyrazole heterocycles. Unsubstituted pyrazole 1 can be illustrated in three tautomeric structures (Figure 3).³⁴

5-Amino-3-(cyanomethyl)-1H-pyrazol-4-yl cyanide 16 is a *pi*-excessive aromatic monocyclic heterocyclic compound having two N-atoms in a 5-membered 1,2-diazole ring, there are three sites for electrophilic attack in pyrazole moiety 16 which is in tautomeric equilibrium with 17, the active methylene group and the amino group, whereas two such sites are also available for nucleophilic attack, the carbon atom of the conjugated nitrile group and the carbon atom of the non-conjugated nitrile group (Figure 4).³⁵

2.3 Chemical and physical properties of pyrazole

Unsubstituted pyrazole 1 is a colorless solid with a melting point in the range of 69–70 °C. The boiling point of unsubstituted pyrazole is in the range of 186–188 °C that is attributed to intermolecular H-bonding. The ionization potential of this molecule is 9.15 eV. It follows from a comparison with an azole (having ionization potential of 8.231 eV) that pyridine-like nitrogen-atom reduces the energy of the HOMO (highest occupied molecular orbital), indeed even more so than in the case of 1,3-diaza-2,4-cyclopentadiene (with ionization potential of 8.782 eV) (Table 1). The dipole moment (μ) of pyrazole 1 in benzene is estimated to be 1.921 D (Debye). The value of μ relies on the concentration of pyrazole 1 because cyclic dimers of pyrazole 1 develop at higher concentrations in compound 1. The μ is directed from

Table 1. Physical properties of pyrazole.

Property name	Property value
Molecular formula	C ₃ H ₄ N ₂
Formula weight	68.07726
Composition	C (52.93%), H (5.92%), N (41.15%)
Molar refractivity	18.17 ± 0.3 cm ³
Molar volume	60.9 ± 3.0 cm ³
Parachor	161 ± 4.0 cm ³
Index of refraction	1.528 ± 0.02
Surface tension	48.6 ± 3.0 dyne/cm
Dielectric constant	Not available
Polarizability	7.44 ± 0.5 × 10 ^{−24} cm ³
Monoisotopic mass	68.037448 Da
Nominal mass	68 Da
Average mass	68.078461 Da

Figure 5. Acidic behavior of pyrazole.

the center of the pyrazole to the bond between atoms 2 and 3. In most pyrazole reactions, a similarity with 1,3-diaza-2,4-cyclopentadienes is evident, and contrasts are also possible.^{36,37}

2.4 Acid-base reactions

Unsubstituted pyrazole 1 displays acidity due to –NH group present at position-1. The pK_a value of pyrazole 1 is experimentally calculated to be 14.211, which is equal to the pK_a value of 1,3-diaza-2,4-cyclopentadiene (Figure 5). Pyrazolines (11, 12 and 13) are basic in nature. It is reported that in the excited state of Pyrazoline, an intermolecular conjugated charge transfer process exists. In the conjugated part (–C3–N2–N1–) of the ring of 1, the N-atom at the position-3 has, respectively electron withdrawing and donating capabilities. The carbon atoms at position-4 and position-5 are not conjugated intermolecularly with the remaining part of the ring of 1.³⁷

3. Nomenclature of pyrazoles and related systems

Pyrazoles and related ring systems can be designated as 1H, 2H, 3H and 4H-pyrazoles. The 2H and 3H-pyrazoles (12 and 11) are called pyrazolines (2-pyrazoline 12 and 1-pyrazoline 11) and dihydropyrazoles. The designations 1H, 2H, 3H and 4H prior to the term ‘pyrazole’ show the position of the hydrogen atom, which resembles the lowest numbering system for the nitrogen

Figure 6. The naming system for pyrazoles and related systems.

or the location for saturation (Figure 6). The word 'dihydro' indicates the location of a formally reduced double bond. For dihydro 2H or 3H pyrazole, the entity must contain one double bond. In order to be named as 4H-pyrazole **14**, which is *aka.* isopyrazole or cyclic azine, the entity must contain one tetrahedral carbon and two double bonds.³⁸

4. Methodologies for the synthesis of pyrazoles

The pyrazole entity is a significant pharmacophore displaying a multitude of pharmacological and biological activities. Naturally, these broad biological activities render this class of compounds synthetically interesting. Consequently, new approaches for the development of this heterocyclic skeleton have attracted significant consideration during recent years. The development of methods for efficient construction of several pyrazole derivatives is the focus of this book chapter, which also includes the development of a new eco-friendly synthetic pathway to the construction of pyrazole derivatives. Also, benzo-fused and dihydropyrazolone analogues of pyrazole (*i.e.* indazoles and tetrahydroindazoles) are of interest in this context.

4.1 Recent green methodologies to construct the skeleton of pyrazole analogues

4.1a Microwave-mediated solvent-free approach:

An innovative solvent-less microwave-based methodology to the construction of pyrazoles **22** from tosyl hydrazones **21** (generated *in situ*) of α,β -unsaturated

carbonyls **19** having a beta-hydrogen in the presence of K_2CO_3 and *p*-toluenesulfonyl hydrazide **20** is recently disclosed by Anna Corradi *et al.* (Scheme 1). In this approach, activation was brought about with microwave irradiation (MWI). With the proposed microwave based solvent-less procedure, good results in terms of yields and reaction speed were observed, which indicate that this process is the eco-friendly, fast and simple synthetic route to attain pyrazoles **22** from α,β -unsaturated ketones **19** having beta-hydrogen.³⁹

4.1b One-pot deep eutectic solvent-based synthesis of polysubstituted pyrazoles: Polysubstituted pyrazoles **25** were efficiently synthesized by Beyzaei *et al.*, through two-step one-pot procedure. In this technique, the reaction of 2,4-dinitrophenylhydrazine **25**, malononitrile **23**, and different aldehydes **24** in deep eutectic solvent (DES) were carried out.⁴⁰ In order to obtain optimized results and investigate the effectiveness of DES towards the synthesis of pyrazoles, some deep eutectic solvents having different molar ratios of potassium carbonate to glycerol were prepared and employed as reaction bath and catalyst in this synthetic approach. The finest results in terms of product yields and reaction times were achieved in molar ratios 1:4:14 of K_2CO_3 /glycerol/ H_2O (Scheme 2). In the existence of DES, the reaction times and productivity of reactions were improved considerably.

4.1c Catalyst-free and eco-friendly formation of phthalide-fused pyrazole derivatives: A promising catalyst-free and eco-friendly procedure for the

Scheme 2. Synthesis of polysubstituted pyrazoles using deep eutectic solvent.

Scheme 3. Development of phthalide-fused pyrazole derivatives.

Scheme 4. Formation of 1,4-dihydropyrano[2,3-c]pyrazoles using maltobiose.

formation of phthalide-fused pyrazole derivatives **30** through condensation of acetylenic ester **27**, hydrazine monohydrate **28** and phthalaldehydic acid **29** in water at 100 °C for one day is disclosed by A. Bazgir and co-workers.⁴¹ The course of work-up of these eco-friendly reactions required only filtration and subsequent washing with excess methanol (Scheme 3). Further, this method shows remarkable characteristics, for instance, application of H₂O as a solvent, uncomplicated workup of products, and reduced waste formation without employing any catalyst or additive.

4.1d Eco-friendly formation of 1,4-dihydropyrano[2,3-c]pyrazoles through biodegradable catalyst maltobiose: A novel and highly effective technique for four-component one-pot preparation of highly derivatized 1,4-dihydropyrano[2,3-c]pyrazoles **33** using phenylhydrazine or hydrazine monohydrate **32**, acetoacetic ester **31**, malononitrile **23** and aldehydes **24** under thermal and solvent-less conditions with maltobiose as a

catalyst has been unveiled by Kangani *et al.*⁴² The reaction efficiently proceeded to produce the respective products **33** (Scheme 4). Use of inexpensive and non-toxic materials, short reaction times, simple and clean work-up, non-hazardous catalyst, minimum pollution of the environment, operational simplicity and excellent yields of the pyrazoles are the benefits of this technique.

4.1e Eco-friendly TBAB-based formation of pyrazoles under solvent-less conditions: Soltanzadeh *et al.*, disclosed a green, environment-friendly, novel and inexpensive technique for the production of a library of pyrazoles **37**.⁴³ The reaction took place in the existence of *N*'-benzoylbenzohydrazide **34**, **35**, isocyanide **36** and tetrabutylammonium bromide (TBAB; a commercially available organic ionic salt) at r.t. under solvent-less conditions for 0.5–12 h (Scheme 5). Operational simplicity, excellent yields of the pyrazoles (75–86%) and short times of reaction are the merits of this technique.

Scheme 5. Development of pyrazole cores using TBAB.

Scheme 6. Construction of 4H-pyrano[2,3-c]pyrazoles using [bmim]OH.

Scheme 7. Construction of pyrazole frameworks using NIL as catalyst.

4.1f Eco-friendly development of pyrazole frameworks using IL [bmim]OH: A unique and appropriate technique for the preparation of 4H-pyrano[2,3-c]pyrazole derivatives **39** by three-component condensation reaction of malononitrile **23**, aryl-aldehydes **24** and pyrazolone **38** or four-component condensation reaction of malononitrile **23**, hydrazine monohydrate, aromatic aldehydes **24** and acetoacetic ester **31** using [bmim]OH **40** as ionic liquid (IL) at 50–60 °C has been disclosed by Khurana *et al.*⁴⁴ The procedure was expressed to be environmentally benign and efficient in terms of excellent yields, ease of recovery, low reaction times and recyclability of reaction medium (Scheme 6).

4.1g Synthesis of pyrazole derivatives by 1-methylimidazolium trinitromethanide: a nano-IL: In the report of Zolfigol *et al.*, an effective and green NIL catalyst viz., 1-methylimidazolium trinitromethanide {[HMIM]C(NO₂)₃} **42** was employed in the formation of 5-amino-pyrazole-4-carbonitriles **44** by the three-component condensation reaction of malononitrile **23**, aryl aldehydes **24**, and phenyl hydrazine **41** under solventless conditions at r.t. (Scheme 7). 1,4-Dihydropyrano[2,3-c]-pyrazoles **43** were also prepared via four-component condensation reaction of malononitrile **23**, aryl aldehydes **24**, ethyl acetoacetate **39** and phenyl hydrazine **41** under similar reaction conditions.⁴⁵

The disclosed reactions by Zolfigol *et al.*, were in fair agreement with the disciplines of green synthesis and their key benefits are ease of separation, cleaner reaction profile, reasonably high productivity, short times of reaction and recyclability of NIL.

4.1h Copper(II) IL for chemoselective green preparation of highly functionalized pyrazoles: A chemoselective, eco-friendly, novel and effective technique for the production of highly substituted pyrazoles **48** by the one-pot reaction of aldehydes **45**, aryl-hydrazine **46** and dimethyl 2-butynedioate **47** in the presence of Lewis acidic IL $[n\text{-Bu}_4\text{P}][\text{CuBr}_3]$ as a reusable catalyst has been described by Safaei *et al.*⁴⁶ This catalytic system is chemoselective and simple with excellent yields (Scheme 8). Short times of reaction, straightforward operation, eco-friendliness and elimination of the application of toxic reagents, as well as organic solvents, are remarkable benefits of the present technique.

4.1i Green formation of fluorinated pyrazolines by means of ultrasonic irradiation: A library of fluorinated pyrazoles **52** were constructed by Shelke *et al.*,⁴⁷ in reasonable yields (65–82%) from the respective fluorinated-chalcones **51** by using ultrasonic irradiation and the reaction took place in the presence of hydrazine monohydrate, ethanol and AcOH (Scheme 9). The fluorinated-chalcones **51** were obtained through the reaction of aldehydes **49** and aromatic ketones **50** in the existence of 40% KOH in ethanol under ultrasonic irradiation. Owing to higher yields, shorter reaction times, lower temperatures and ease of operation, the ultrasonic irradiation approach is an eco-friendly alternative process to the conventional formation of pyrazoline analogues.

4.1j Pyrazole-4-carbonitriles formation in aqueous bath with copper(II) oxide in zirconium dioxide: Maddila *et al.*, reported an eco-friendly and well-organized one-pot three-component process for the formation of pyrazole-4-carbonitrile analogues **54** via reaction of

Scheme 11. Formation of pyrido[2,3-*d*]pyrimidine-dione derivatives.

Scheme 12. Synthesis of pyrazoles using $\text{NaHSO}_4\text{-SiO}_2$.

malononitrile **23**, aldehydes **24** and phenyl hydrazine **53** in the presence of copper(II) oxide in zirconium dioxide (CuO/ZrO_2) as a catalyst in water as reaction medium (Scheme 10). The catalyst is recyclable for over five runs, without affecting its outstanding potency. This recyclable and simple heterogeneous catalytic system, CuO in ZrO_2 , displayed an extraordinary catalytic affinity for MCR approach. The existing methodology deals with numerous benefits, for instance, short reaction times, good to high yields, purity of products, simple workup, cost-effectiveness, need of environmentally benign green solvents and a small amount of inexpensive catalysts. This technique reveals to be a favorable environmentally benign method for the preparation of a series of pyrazole analogues.⁴⁸

4.1k A multi-component aqueous preparation of pyrido[2,3-*d*]pyrimidine-dione derivatives: A unique one-pot preparation of pyrazolo[41,31:5,6]pyrido[2,3-*d*]pyrimidine-diones **59** (pyrazole-based pyrido[2,3-*d*]pyrimidine-dione derivatives) via a five-component aqueous reaction has been disclosed by Heravi *et*

*al.*⁴⁹ The aqueous reaction of acetoacetic ester **55** and hydrazine monohydrate **56** was rapidly and smoothly proceeded to furnish 3-methyl-5-hydrazolone **57**, nearly in quantitative yield. Next, in the same flask, the synthesized 3-methyl-5-hydrazolone **57** was reacted with other three components (ammonium acetate, aryl aldehydes **24** and 1,3-dimethyl barbituric acid **58**) to furnish a five-component reaction and affords pyrazole derivatives **59** (Scheme 11). The whole process was catalyzed by nano ZnO catalyst in water. The notable advantages of this method are short times of reaction, good yields, simple workup, and environmental benignancy.

4.11 Utilization of silica supported sodium bisulfate for pyrazoles synthesis: An effective and useful process for the preparation of library of pyrazole analogues **63** under solvent-free thermal conditions via heterocyclic-enaminones using $\text{SiO}_2\text{-NaHSO}_4$ (sodium bisulfate supported on silica) as an efficient catalyst has been described by Siddiqui *et al.*⁵⁰ This approach demonstrates very striking features such as economic

viability, simple work-up and reasonable yields of the pyrazoles (Scheme 12). The catalyst can be reused various times without important loss of its catalytic potency.

4.1m Four-component one-pot reaction in aqueous media for pyrazole cores formation: A green, four-component, catalyst-free and one-pot formation of methyl 6-amino-5-cyano-4-aryl-2,4-dihydropyrano [2,3-*c*]pyrazole-3-carboxylate derivatives **64** in aqueous media is described by Adeleh Moshtaghi Zonouz *et al.*⁵¹ The four-component were aldehyde, malononitrile, hydrazine and dimethyl but-2-ynedioate (Scheme 13). The technique does not include any tedious purification or work-up and is atom-economical, catalyst-free and affords the target pyrazoles in reasonable yields.

4.1n One-pot eco-friendly solvent-less procedure for pyrano[2,3-*c*]-pyrazoles synthesis: Convenient multi-component synthesis of pyrazoles is disclosed by Al-Matar *et al.*⁵² In this approach, synthesis of pyrano[2,3-*c*]pyrazole derivatives **69** were accomplished through

the mixing of hydrazine monohydrate, malononitrile **23**, ethyl acetoacetate **31**, and ketones or aldehydes **65** in the solvent-free conditions (Scheme 14). Alternatively, the reaction of aminopyrazolones **66** with arylidene-malononitrile **67** afforded pyrano[2,3-*c*]pyrazoles **69**. The yields in multi-component synthetic approach were observed to be nearly identical to those of previously reported synthetic methodologies in this book chapter but they are highly greener, avoiding the utilization of solvent, purification and separation steps. Chitosan could be employed as a catalyst for the reaction by replacing the use of homogeneous catalyst. The mild conditions applied as well as the high yields obtained are significant features of the reaction. This method avoids the use of tedious workup and column chromatographic purification of products, making the method expedient and superior.

4.1o Organo-nanocatalyst: magnetically retrievable iron oxide-anchored GSH for MW-mediated pyrazoles synthesis: Polshettiwar *et al.*, developed a unique

Scheme 15. Organo-nanocatalyst microwave-assisted pyrazoles synthesis.

Scheme 16. Scandium triflate-catalyzed formation of functionalized pyrazoles.

concept of organo-nanocatalyst, by supporting totally benign and environmentally abundant glutathione (GSH) on magnetic nanocatalyst.⁵³ Post-synthetic modification of magnetic NPs surface by GSH imparts required chemical functionality and allows the catalytic site's formation on the exteriors of ensuing organocatalysts. The catalyst displayed an outstanding affinity for microwave (MW)-assisted pyrazoles synthesis. The reaction of **70** with **53** in the existence of organo-nanocatalyst in aqueous medium under MWI afforded pyrazoles **71** in 78–98% (Scheme 15). This innovative organo-nanocatalyst bridges the gap between heterogeneous and homogeneous catalysis; therefore, preserving the required attributes of both the synthetic systems.

Their paramagnetic nature coupled with an insoluble character allows easy isolation of these nanoparticles from the reaction contents using bar magnet, which minimizes the prerequisite catalyst separation by filtration.

4.1p Scandium triflate-catalytic system for pyrazoles synthesis under MWI: An eco-friendly, rapid and effective formation of functionalized pyrazole derivatives **72** under solvent-less conditions by the treatment of aldehydes **24** with acetoacetic ester **31** and phenyl hydrazine **53** has been reported by Kumari *et al.*⁵⁴ This methodology exploits the synthetic potential of MWI and scandium(III) triflate $\text{Sc}(\text{OTf})_3$ combination and illustrates numerous benefits such as easy isolation of

Scheme 17. Development of poly-substituted amino-pyrazole systems.

Scheme 18. Application of zirconium dioxide NPs as a nanocatalyst for construction pyrazoles.

products, shorter reaction times, eco-friendly reaction conditions and excellent product yields (Scheme 16).

4.1q Multi-component green media formation of 5-amino-1,3-aryl-1H-pyrazole-4-carbonitriles: Hasani-nejad *et al.*, disclosed a convenient and novel three-component one-pot approach for the preparation of poly-substituted amino-pyrazoles **73** via a tandem cyclo-Knoevenagel condensation of malononitrile **23**, aryl-aldehydes **24**, and phenyl hydrazine **53** in H₂O and EtOH at r.t.⁵⁵ This multi-component catalyst-free methodology smoothly proceeded in reasonable yields and illustrates numerous other benefits *i.e.*, no toxic by-products, simple work-up experimental procedures and short reaction times (Scheme 17). The method also eliminates the application of anhydrous conditions, toxic organic solvents and catalysts. This procedure signifies a promising eco-friendly pathway for the construction of poly-substituted amino-pyrazole systems **73**.

4.1r Benzylpyrazolyl coumarins and pyrano[2,3-*c*]pyrazoles synthesis using zirconium dioxide NPs:

A one-pot novel multi-component procedure for the development of bio-active benzylpyrazolyl coumarin derivatives **75** and pyrano[2,3-*c*]pyrazole derivatives **76** has been reported by Saha *et al.*, using ZrO₂ (zirconium dioxide) nanoparticles (NPs) as a nanocatalyst at r.t.⁵⁶ The reactions were high yielding and very fast

(Scheme 18). The tetragonal plane of the zirconium dioxide NPs and catalytic potency remained unaffected after the tenth recycle. The process by Saha *et al.*, is eco-friendly as the nanocatalyst is reusable and non-toxic, reactions were accomplished at 25 °C in a green solvent (ethanol-water); pyrazoles were decontaminated through recrystallization from EtOH, and chromatographic purification was not desired by this scheme; hence, the application of hazardous and volatile solvents has also been circumvented.

4.1s Polyfunctionalized pyrano[2,3-*c*]pyrazole systems synthesis through BMIMBF₄ ILs: A rapid, eco-friendly and highly effective production of 4*H*-pyrano [2,3-*c*]pyrazoles **77** using multi-component cyclocondensation of phenyl hydrazine/hydrazine monohydrate, malononitrile **23**, aryl-aldehydes **24** and acetoacetic ester **31** in the presence of IL 1-butyl-3-methylimidazolium tetrafluoroborate and L-proline at r.t. has been disclosed by Khurana *et al.*⁵⁷ Reusability of the IL without important loss of potency was a chief benefit (Scheme 19).

4.1t Grinding induced formation of highly substituted pyrazoles: Grinding induced formation of highly substituted pyrazoles **80** by application of malononitrile **23**, phenylhydrazine **53** and functionalized aldehydes **78** has been disclosed by Madhulika Srivastava *et al.*⁵⁸ In this process, IL **79** is utilized as a catalyst with H₂O

Scheme 19. IL-based multi-component preparation of pyrano[2,3-c]pyrazoles.

Scheme 20. IL mediated formation of highly substituted pyrazoles.

Scheme 21. Synthesis of pyrazoles by application of the IL [BMIM][BF₄].

and no byproducts were formed (Scheme 20). Most importantly, simple handling and attainment of high yield up to 97% are the advantages of this methodology.

4.1u Synthesis of tert-butylpyrazoles by using ionic liquid: This approach is reported by Clarissa P. Frizzo *et al.* In his report, investigations on different ionic liquids, ([HMIM][CF₃CO₂], [HMIM][HSO₄], [BMIM][SCN], [BMIM][OH], [DBMIM][BF₄], [DBMIM][Br], [BMIM][PF₆], [OMIM][BF₄], [BMIM][Br] and [BMIM][BF₄]) were performed. The results of the investigation revealed that ionic liquid [BMIM][BF₄] provides the highest efficiency for cyclocondensation reactions. The cyclocondensation reaction between 4-dimethylamino-1-phenyl-3-alken-2-one derivatives **81** and *tert*-butylhydrazine **82** in the existence of ionic liquid [BMIM][BF₄] afforded *tert*-butylpyrazoles **83** in excellent yields.⁵⁹ [BMIM][BF₄] IL was also observed to be an efficient, fast and mild approach for the regioselective preparation of *tert*-butylpyrazoles **83**

Scheme 22. Synthesis of 3,5-diaminopyrazole.

(Scheme 21). This technique permitted the formation of a series of new pyrazole derivatives that are problematic to prepare by other techniques.

4.2 Well-known classical approaches to construct important pyrazole derivatives

4.2a Synthesis of 5-amino-3-(cyanomethyl)-1H-pyrazol-4-yl cyanide: Using the 1st attempt in 1894, Rothenburg suggested that malononitrile **23** can be treated with hydrazine monohydrate to afford 1H-pyrazole-3,5-diamines **84** (Scheme 22). Von Rothenburg failed to observe that the formation 1H-pyrazole-3,5-diamine **84** was completed through the release of ammonia.^{60,61}

Scheme 23. Formation of malononitrile dimer.

Scheme 24. Synthesis of 5-amino-3-(cyanomethyl)-1H-pyrazol-4-yl cyanide.

After some years, co-workers have demonstrated that the product was already **87** produced through the process of malononitrile **23** dimerisation to furnish dimer of malononitrile (2-aminoprop-1-ene-1,1,3-tricarbonitrile) **86** (Scheme 23).⁶² The mechanism of reaction proposed that the elimination of a H^+ from the activated methylene moiety in malononitrile **23** and subsequent nucleophilic addition of this anion to the unsaturated carbon of a 2nd malononitrile entity **23** affords a 2-iminopropane-1,1,3-tricarbonitrile **85** which would readily rearrange to the more stabilized form **86**.⁶³ Compound **86** appears as one of the numerous zwitterionic structures stabilized by electron delocalization (Scheme 23).

The reaction of malononitrile dimer **86** or malononitrile **23** with hydrazine hydrate provided 5-amino-3-(cyanomethyl)-1H-pyrazol-4-yl cyanide **87** (Scheme 24).^{64,65}

The product was synthesized from one mole of hydrazine monohydrate and two moles of malononitrile **23** with the elimination of one mole of NH_3 to produce **87** in 40% yields. The best method was the reaction of a dimer of malononitrile **86** with hydrazine monohydrate to provide **87** in 71.5% (Scheme 24). The mechanism

of the reaction for the synthesis of pyrazoles involves Michael addition in which hydrazine hydrate attacks the α,β -unsaturated system of malononitrile dimer as intermediate and cyclizes to give pyrazole **87**.

4.2b Synthesis of azo dyes of pyrazole: Azo dyes are prepared through two-step reactions, *i.e.*, diazotization and coupling reactions. Diazotization involves treatment of a primary aromatic amino group of pyrazole analogues with nitrous acid to afford an aromatic diazonium ion; the next step is the coupling of the diazonium salt of pyrazole analogues with a nucleophilic compound in baseline conditions. Active methylene compounds are very beneficial because they act as intermediates in organic synthesis; they show different reactions, for example, Knoevenagel condensation and synthesis of azo dyes, on account of the acidic hydrogens in the active methylene group that could copulate with a number of aminoaromatic compounds to configure numerous hydrazones. Diazonium salts of pyrazole analogues couple with active hydrogen-containing reagents mainly ethyl acetoacetate, ethyl cyanoacetate, malononitrile, acetylacetone, pyrazole derivatives and pyrazolones and yield the corresponding azo derivatives

Scheme 25. Formation of pyrazolo[5,1-c]-1,2,4-triazines. **Scheme 26.** Formation of pyrazolo[5,1-c]1,2,4-triazines. **Scheme 27.** Synthesis of hydrazone derivatives.

or lead to the development of the pyrazolo[1,5-c]as-triazines,^{66,67} through cyclocondensation reaction, that takes place by nucleophilic attack of nitrogen atom of pyrazole on the electrophilic group in active hydrogen reagents.

In 1989, triazine analogues were formed directly under the same reaction conditions by coupling 5-amino-3-phenyl-4-nitropyrazole **88** with malononitrile and benzoylacetone reagents, the resulting compound was readily cyclized to yield pyrazolo[5,1-c]-1,2,4-triazines **90a-b**, respectively (Scheme 25).⁶⁸

Also, malononitrile and benzoylacetone could easily be coupled with the amino compound **91**, the resulting compound can readily be cyclized *via* stirring under the same conditions of coupling reaction to afford **92a-b**, respectively (Scheme 26).⁶⁹ The coupling of Diazonium salt of arylazopyrazole **94** with malononitrile and ethyl acetoacetate yielded directly the pyrazolo[5,1-c]1,2,4-triazines **93** and **95** (Scheme 26).⁷⁰

Diazotization of 4-(ethoxycarbonyl)-3-methyl-1H-pyrazole-5-diazonium chloride **97**,⁷¹ on reaction with mono and 1,3-disubstituted pyrazolones **98** produced

Scheme 28. Synthesis of triazine dye, pyrazolone dye and hydrazone derivative.

Scheme 29. Formation of pyridazinimine derivatives.

three tautomeric forms of compound **99a–c**, as well as cyclization possibilities in good yields of 85% (Scheme 27). Hydrazone derivative **101** was formed through the conversion of 3-aminopyrazole **100** into diazonium salts, followed by coupling with 3-amino-1H-pyrazol-5(4*H*)-one in pyridine as solvent (Scheme 27).⁷²

Fati and Fikret⁷³ reported the ten unique dyes viz., pyrazolo[5,1-*c*][1,2,4]triazines **103a–b**, prepared by refluxing ethyl pyrazolylazo cyanoacetate **102b** and pyrazolylazo malononitrile **102a** in glacial AcOH. Whereas, coupling reaction of 5-amino-3-methyl-4-

heterylazo-1H-pyrazole **104** with 3-methyl-1H-pyrazol-5(4*H*)-one produced pyrazolone dye **105**, without cyclization attempt/step (Scheme 28).⁷⁴ Pyrazolyl diazonium chloride **106** has been coupled with the active methylene group of cyanoacetanilide and affords the corresponding hydrazone derivative **107**.⁷⁵

Also, the cyclocondensation reaction was completed when compound **108** was refluxed with acetic acid. The reaction mechanism occurs *via* nucleophilic attack of the ring nitrogen atom on the electrophilic cyano group in the compound to yield **109** (Scheme 29).⁷⁶ Malononitrile dimer reacts with different aryldiazonium chlorides

Figure 7. Structures of pyrazole-based potent anti-bacterial compounds.

Table 2. Antimicrobial activity-sensitivity testing of compounds (113a–113f and 114–114e).

Compound	Zone of inhibition in mm						
	Antibacterial activity					Antifungal activity	
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>Salmonella typhi</i>	<i>C. albicans</i>	<i>A. niger</i>
113a	10	11	8	8	N.R	22	24
113b	13	15	9	9	N.R	23	26
113c	10	12	8	9	N.R	19	22
113d	12	13	9	9	N.R	26	22
113e	11	10	9	9	N.R	17	20
113f	10	9	8	8	N.R	17	20
114a	14	12	9	N.R	11	N.R	N.R
114b	26	17	14	N.R	18	N.R	N.R
114c	28	19	15	N.R	20	N.R	N.R
114d	23	13	11	N.R	14	N.R	N.R
114e	19	15	10	N.R	11	N.R	N.R

N.R = not reported.

to give pyridazine derivatives that are found to be good intermediates for the formation of fused heterocycles.⁵⁵ The reaction of MND with diazonium chloride salts of aniline derivatives yields intermediate substituted arylhydrazones **110a–b**, that readily cyclizes in basic medium providing pyridazinimine derivatives **111a–b** (Scheme 29).⁷⁷

5. Overview of biological potency of pyrazole containing compounds

Pyrazoles are known to be one of the most prominent types of N-containing heterocycles exhibiting large spectrum of biological potencies such as anti-inflammatory, anti-cancer, anti-bacterial, anti-microbial, anti-analgesic, anti-tubercular, anti-viral, anthelmintic, antifungal, hypotensive, anti-nociceptive, insecticidal, MAO inhibitory, anti-mycobacterial, antihelmintic, anti-HIV, antitumor, anti-oxidant, ACE-inhibitory, anti-convulsant and antidepressant activities.^{78–118} The following section describes in brief, the biological activities elucidated by the presence of pyrazole moiety in various compounds.

5.1 Anti-bacterial potency of pyrazole derivatives

Nada M. Abunada and co-workers prepared 1,3,4,5-tetraaryl-2-pyrazoline, pyrrolo[3,4-c]pyrazole-4,6-dione and 1,3-diaryl-5-(cyanoaminocarbonyl and ethoxycarbonyl)-2-pyrazoline analogues of pyrazole.⁷⁸ The synthesized derivatives were subjected to investigation for anti-bacterial potency. The compound **112** viz., 1-((4*R*,5*S*)-1,3-bis(4-fluorophenyl)-4-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-7-chlorohepta-2,4,6-triyn-1-one was observed to be active against *S. aureus* and *E. coli*. R. Antimicrobial screening results of the compound **112** shows that inhibition zones were 12 mm, 12 mm, 0.0 mm and 10 mm for *E. coli*, *S. aureus*, *A. flavus* and *C. albicans*, respectively. Chawla and co-workers prepared 3,5-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide derivatives **113a–113f** by making the use of MWI technology (Figure 7). All the prepared pyrazole derivatives were investigated for anti-microbial potency against two Grampositive strains (*Bacillus subtilis* and *Staphylococcus aureus*) and two Gram-negative strains (*Pseudomonas aeruginosa* and *Escherichia coli*).⁷⁹ The investigation revealed that derivatives **113a–113f** of synthesized compounds

Figure 8. Structures of pyrazole-mediated anti-cancer agents.

Table 3. SAR of the urea and carbamate groups.

Compound	R ₂	X	mTOR ^a	PI3K α ^a	Selectivity ^b	LNCap ^a	Micros ^c
119a	CH ₃	O	4.3 $\pm$ 0.6	1026 $\pm$ 434	239	355 $\pm$ 45	> 30
119b	CH ₂ CH ₂ OH	O	1.0 $\pm$ 0.2	681 $\pm$ 124	681	28 $\pm$ 1	> 30
119c	Et	NH	0.32 $\pm$ 0.06	490 $\pm$ 198	1153	55	> 30
119d	CH ₂ CH ₂ F	NH	0.61 $\pm$ 0.03	505 $\pm$ 225	828	52 $\pm$ 13	> 30
119e	CH(CH ₂) ₂	NH	0.45 $\pm$ 0.04	661 $\pm$ 156	1469	42 $\pm$ 3	> 30
119f	3-Pyr	NH	0.20 $\pm$ 0.01	35 $\pm$ 6	175	31 $\pm$ 4	24
119g	Ph-4-Pip-CH ₃	NH	0.30 $\pm$ 0.02	18	60	60 $\pm$ 15	9

^aAverage IC₅₀ (nM) $\pm$ SEM. ^bPI3K α /mTOR. ^cNude mouse microsomes T_{1/2} (min).

show reasonable anti-bacterial efficacy and noteworthy anti-fungal activity (Table 2). S. B. Jadhav and co-workers synthesized a new library of 5-(6-methoxynaphthalen-1-yl)-3-phenyl-4,5-dihydro-1H-pyrazole analogues **114a–114e** (Figure 7).⁸⁰ All the constructed pyrazole derivatives were inspected for their anti-microbial power. All the derivatives demonstrated significant to modest anti-microbial capacity (Table 2). A. Kumar and co-workers synthesized a variety of pyrazole derivatives.⁸¹ All the newly developed derivatives were evaluated for their anti-bacterial potency against *B. subtilis*, *E. coli*, *S. aureus* and *K. pneumoniae*. All the results were compared with that of ciprofloxacin, which is a standard drug. The most potent anti-bacterial derivative of the series was **115** (Figure 7). In detail, zone of inhibition were 28, 24, 27 and 22 mm against *K. pneumoniae*, *S. aureus*, *E. coli*, and *B. subtilis*, respectively) than standard drug ciprofloxacin.

5.2 Role of pyrazole derivatives as anti-cancer agents

Faidallah and co-workers⁸² synthesized some poly-substituted fused pyrazole-based ring systems viz., pyrazolo[4,3-c] pyridines and pyrano[4,3-c]pyrazoles **116** (Figure 8). All the prepared pyrazole derivatives were investigated for anti-microbial and anti-cancer potencies. All the derivatives demonstrated considerable to modest anti-cancer capacity. Dean *et al.*,⁸³

synthesized pyrazolo[1,5-a]pyrimidine derived compounds. Among all the derivatives, the compounds **117** and **118** were found to be potent. However, the best results were demonstrated by **117**. It was selective CDK inhibitor and significantly inhibit the activities of CDK9, CDK7, CDK5, CDK1 and CDK2 (IC₅₀ = 90, 250, 30, 30 and 3 nmol/L, respectively). Cell-based studies showed inhibition of the phosphorylation of CDK substrates, Rb and the RNA polymerase II C-terminal domain, down-regulation of cyclins A, E, and D1, and cell cycle block in the S and G₂/M phases. Consistent with these findings, **117** demonstrated potent antiproliferative activity in 60 cancer cell lines tested (mean GI₅₀ = 280 nmol/L). Zask *et al.*,⁸⁴ reported the mammalian target of rapamycin pyrazolopyrimidine pyrazole derivatives **119** which were highly potent in anti-cancer activity (Table 3).^{85,86}

5.3 Application of pyrazoles in anti-inflammatory activity

V. H. Bhaskar and co-workers⁸⁷ prepared various derivatives of 5-phenyl-4-(5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-4H-1,2,3-triazoles **120** through the reaction of hydrazine monohydrate with chalcones in presence of AcOH. All the prepared derivatives **120** were investigated for anti-inflammatory affinity (Figure 9). The detected increase in anti-inflammatory affinity was

Figure 9. Structures of novel anti-inflammatory agents based on pyrazoles.

Table 4. Antibacterial and antifungal data of compounds **120a–120h**.

Compound	R ₁	R ₂	Zone of inhibition in mm							
			<i>S. aureus</i>		<i>E. coli</i>		<i>C. albicans</i>		<i>A. niger</i>	
			50 ug	100 ug	50 ug	100 ug	50 ug	100 ug	50 ug	100 ug
120a	H	H	13	15	10	12	12	15	10	12
120b	Cl	H	15	16	15	17	18	20	15	17
120c	H	Cl	15	16	14	15	18	20	13	15
120d	H	Br	11	14	10	12	16	18	11	13
120e	H	OCH ₃	12	17	8	10	9	22	20	22
120f	H	OH	15	12	8	11	12	15	11	15
120g	H	NO ₂	15	13	10	11	13	15	10	12
120h	H	N(CH ₃) ₂	12	13	10	12	15	17	9	11

owing to the presence of 4-Cl, 4-OH and 4-NO₂ in phenyl ring at five-position of pyrazoline ring of prepared derivatives. In some cases, their potencies were equal or more potent as compared to standard drugs (Table 4). Venkataraman and co-workers⁸⁸ designed and developed pyrazoline analogues. All the prepared derivatives were characterized by their anti-inflammatory potency. Some of the evaluated derivatives showed excellent anti-inflammatory potency. The **121** was found to be the most potent. Antibacterial screening results of the compound **121** show that inhibition zones were 8 mm, 6 mm, 0.0 mm and 2 mm for *S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa*, respectively. Sridevi *et al.*,⁸⁹ disclosed a library of 1,3,5-trifunctionalized-2-pyrazolines. All the constructed products were screened for their anti-depressant potency. The examined pyrazoline-benzimidazole **122** and pyrazoline-benzoxazole **123** analogues in the library were shown to have important anti-depressant properties in improved forced swimming tests (Table 5).

5.4 Pyrazole derivatives of anti-microbial potential

Halogenated derivatives of pyrazole, 1,5-diphenyl-4-(phenyl(1H-pyrazol-1-yl)methyl)-1H-pyrazoles **124**

Table 5. Anti-inflammatory activity of phenyl pyrazolo indoloquinoxaline derivatives.

Compound	Dose, mg/kg	Mean edema volume ± S.E	% Reduction
122	200	0.24 ± 0.145a	40.0
123	200	0.26 ± 0.14a	35.0

a = P < 0.05 (Vs) control.

were constructed by Menozzi and co-workers.⁹⁰ These compounds were screened for anti-microbial potential. Anti-microbial screening results of the compound **124** show that inhibition zones were 11 mm and 2 mm for *Bacillus pumilus* and *Staphylococcus aureus*, respectively (Figure 10). All the derivatives demonstrated significant anti-microbial capacity. Ayoob Bazgir and his colleagues⁹¹ synthesized pyrazolo[4',3':5,6]pyrido [2,3-d]pyrimidine-diones **125**. These compound were investigated *in vitro* for their anti-bacterial and anti-microbial properties (Table 6). Rakesh *et al.*,⁹² synthesized new derivatives of pyrazole **126** by Hantzsch cyclization and modified Bignelli's reaction and all the derivatives exhibited better to moderate activity (Figure 10).

Figure 10. Structures of novel pyrazole derivatives as anti-microbial agents.

5.5 Analgesic and anti-tubercular capability of pyrazoles

S. K. Sahu and co-workers⁹³ prepared a variety of pyrazole analogues and evaluated them for their analgesic affinity. Compounds **127** and **128** demonstrated highly potent analgesic activity against herpes simplex virus type-1 (HSV-1) and hepatitis-A virus (HAV) (Figure 11). K.K. Sivakumar and co-workers⁹⁴ constructed a library of coumarin-mediated pyrazole analogues. All the compounds were investigated for anti-inflammatory and analgesic activities. Compound **129** was observed to have the most powerful analgesic activity. Dias and Salvado⁹⁵ prepared and exposed (4-methylthiophen-3-yl)(1H-pyrazol-1-yl)methanone **130**, which has an excellent analgesic affinity (Figure 11). A variety of unique 1-(5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl)-1H-pyrazole-4-carbaldehyde derivatives **131** were disclosed by Prathapa *et al.* Their anti-tubercular and anti-oxidant properties were also scrutinized. All the prepared derivatives revealed significant anti-tubercular affinity.⁹⁶

5.6 Pyrazoles as anti-viral, anthelmintic and anti-fungal agents

Osama and co-workers⁹⁷ synthesized 1-(5-(4-(benzyl-oxy)phenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl) ethanone analogues. The analogue having R=Cl, *i.e.*, **132** displayed powerful anti-viral action against a broad panel of viruses in various cell cultures (HEL Cell cultures) (Table 7). Aymn and co-workers⁹⁸ prepared functionalized pyrazole analogues **133**. These analogues displayed excellent anti-viral potency against Herpes Simplex virus type-1 and hepatitis A virus using plaque infective assay (Figure 12). El Badwi and co-workers⁹⁹ disclosed that pyrazole-based alkaloids screened from *ashwagandha* possess significant anthelmintic property. Priyadersini and co-workers¹⁰⁰ synthesized 2-(5-(4-chlorostyryl)-1-(penta-1,3-dien-2-yl)-1H-pyrazol-3-yl)phenol **134** and 2-(5-(4-chlorosty-

Table 6. MIC ($\mu\text{g/mL}$) values of compounds (**125a–125e**).

Compound	X	Z	Bacillus subtilis	Bacillus pumilus	Micrococcus luteus	Staphylococcus aureus	Staphylococcus epidermidis	Sterptococcus mutans	Escherichia coli
125a	C ₆ H ₅	H	2	< 2	< 2	2	2	< 2	< 2
125b	4-Cl-C ₆ H ₄	H	4	2	< 2	64	4	< 2	< 2
125c	4-Br-C ₆ H ₄	H	2	2	2	58	2	< 2	< 2
125d	4-Me-C ₆ H ₄	H	2	2	< 2	2	2	< 2	< 2
125e	3-NO ₂ -C ₆ H ₅	H	2	2	2	2	2	< 2	< 2

Figure 11. Structures of analgesic and anti-tubercular compounds.

Table 7. Cytotoxicity and antiviral activity of compound 132 in HEL cell cultures, Vero cell cultures and HeLa cell cultures.

Compound	Minimum cytotoxic concentration ^a (mg/mL)	EC ₅₀ ^b (mg/mL)				
132 in HEL cell cultures	100	Herpes simplex virus-1 (KOS)	Herpes simplex virus-2 (G)	Vaccinia virus	Vesicular stomatitis virus	Herpes simplex virus-1 TK KOS ACV ^r
132 in Vero cell cultures	20	> 20	> 20	7 ± 3	> 20	> 20
		Parainfluenza-3 virus	Reovirus-1	Sindbis virus	Coxsackie virus B4	Punta toro virus
132 in HeLa cell cultures	> 20	> 4	> 4	> 4	> 4	> 4
		Vesicular stomatitis virus	Coxsackie virus B4	Respiratory syncytial virus		
		> 20	> 20	> 20		

^aRequired to cause a microscopically detectable alteration of normal cell morphology. ^bRequired to reduce virus-induced cytopathogenicity by 50%.

ryl)-1H-pyrazol-3-yl)phenol **135** and observed them possessing moderate potency against *black mold*. Hassan¹⁰¹ observed that compound **135** enclosed excellent efficacy against *C. albicans* (Figure 12).

5.7 Usefulness of pyrazole-based hypotensive and insecticidal agents

Kevser Erol and co-workers¹⁰² constructed some analogues of 2-(2-(3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-5-methoxyphenol (**137a** and **137b**) and evaluated their hypotensive capability by a tail-cuff approach using catapres as the reference standard (Figure 13). All the inspected analogues illustrated considerable hypotensive capacities (Table 8). Silver and Soderlund¹⁰³ prepared pyrazole-based insecticides (**138** and **139**) and studied the mechanism of action of prepared entities mediated on available toxicological, pharmacological and electrophysiological information and observed these entities to act at neuronal target sites (Figure 13).

5.8 Anti-nociceptive capacity of pyrazole derivatives

Carlos F. Mello and co-workers¹⁰⁴ examined the participation of spinal noradrenergic and serotonergic systems in anti-nociception prompted by potent pyrazolines PPCA **140** and MPCA **141** (Figure 14). The results revealed that spinal α 2-adrenoreceptors and 5-HT receptors are involved and prompted by PPCA **140** and MPCA **141**, but not elicited by dipyrone.

5.9 MAO and ACE-inhibiting activity of pyrazoles

B. Bizzarri and co-workers¹⁰⁵ prepared a library of 1-(but-1-en-2-yl)-5-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole analogues **142** and examined them as inhibitors of monoamine oxidase B (MAO-B) and monoamine oxidase A (MAO-A) isoforms (Figure 15). The synthesized compounds displayed inhibiting action with micromolar (μ M) values against MAO-selectivity and observed to be beneficial as adjuvants in the medication of Alzheimer's disease and Parkinson's

Figure 12. Some potent anti-viral, anthelmintic and anti-fungal agents.

Figure 13. Structures of pyrazole-based hypotensive and insecticidal agents.

Table 8. Hypotensive activity of compounds (**137a** and **137b**).

Compound	Reduction of arterial blood pressure (mm Hg) ($X \pm SEM$)
137a	13.80 ± 3.45
137b	12.29 ± 3.41

disease (PD) (Table 9). U. Salgin-Goksen and co-workers¹⁰⁶ constructed a variety of pyrazole derivatives and these derivatives were observed to be inhibitors of human MAO-selectivity. M. Bonesi and co-workers disclosed a series of pyrazoles **143** and examined them as an angiotensin-I-converting enzyme (ACE)-inhibitory agents by carrying out different assays (Figure 15).¹⁰⁷ These analogues of pyrazole presented efficient ACE-inhibitory potency with an IC_{50} value of 0.123 mM. A new molecular series of COX-2 inhibitors have been recently disclosed by Qi-Huang Zheng and co-workers. The products were tested for their inhibitory property. The investigation revealed that **144a** and

Figure 14. Structures of unique pyrazolines, MPCA and PPCA.

144b demonstrate powerful inhibitory efficiency in the MDA-MB-435 human cancer cell line as compared to stranded entity celecoxib.¹⁰⁸

5.10 Anti-mycobacterial, anti-helminthic and anti-HIV activity of pyrazoles

Mamolo and co-workers¹⁰⁹ synthesized pyridine-based pyrazole analogues and screened them for their *in vitro*

Figure 15. Structures of MAO and ACE inhibitors of pyrazole.

Table 9. Minimal inhibitory concentration (MIC) of compounds **142** and metronidazole (M) against *H. pylori* strains.

Compound	R	R ₁	R ₂	MIC (μg/mL)		
				Range	MIC ₅₀	MIC ₉₀
142a	H	–C(O)CH ₃	4-Cl	2–8	4	8
142b	2-OH	–C(O)CH ₃	4-Cl	2–8	4	8
142c	2-OH	–C(O)CH ₃	3,4-OCH ₃	2–16	8	16
142d	4-OH	–C(O)CH ₃	2-Cl	1–8	2	8
142e	4-OH	–C(O)CH ₃	4-Cl	0.25–16	8	16
142f	4-OH	–C(O)CH ₃	2-OCH ₃	4–32	8	16
142g	4-OH	–C(O)CH ₃	4-OCH ₃	2–16	4	8

Figure 16. Structures of novel anti-mycobacterial, anti-helminthic and anti-HIV agents.

anti-mycobacterial potency. Compound **145** confirmed potent anti-mycobacterial capacity. Ozdemir and co-workers¹¹⁰ reported novel thiophene-based pyrazole analogues and tested them for *in vitro* anti-mycobacterial capacity against *Mycobacterium tuberculosis* H37Rv (Figure 16). The activity of the **145** against *M. tuberculosis* H₃₇Rv and *M. tuberculosis* H4 clinical isolate was observed to be 8 and 8, respectively. Compound **146** possessed the potent anti-mycobacterial capacity. M. G. Mamolo and co-workers¹¹¹ disclosed several imidazole-based pyrazole analogues and screened them for their *in vitro* anti-mycobacterial and anti-fungal potencies. The pyrazole analogue **147** exhibited a remarkable anti-tubercular affinity against *Mycobacterium tuberculosis* strain H37Rv and an outstanding anti-fungal capacity against the clinical strain of *Candida albicans*.¹¹² Sreenivara and co-workers¹¹³ prepared a library of

pyrazole derivatives **148** and estimated their anti-helminthic efficacy against earthworms. All the derivatives demonstrated significant to modest anti-helminthic capacity (Figure 16). Charles and co-workers^{114–116} constructed 3-cyanophenoxypyrazoles **149** and investigated it *in vitro* against HIV. The compounds illustrated excellent anti-HIV affinity (Table 10).

5.11 Role of pyrazoles as anti-tumor and anti-oxidant

A variety of 5-(1H-indol-3-yl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide derivatives **150** were prepared by Nassar and his colleagues and the derivatives were also screened against tumors¹¹⁷ and microbes (Figure 17).¹¹⁸ Activity of the **150** against a human breast carcinoma cell line (MCF7) and a liver carcinoma cell line (HEPG2) was observed to be 2.62 and 2.48,

Table 10. Profiles of 3-cyanophenoxypyrazole derivatives.

Compound	X	R	RT IC ₅₀ ^a (μM)	AV ₅₀ ^a (nM)	AV ₉₀ ^a (nM)	CC ₃₀ ^a (μM)	HLM T _{1/2} ^a (min)	Predicted CL _u (mL/min/kg) ^a	Dofetilide binding ^a
149a	H	CH ₂ CH ₂ OH	0.35	N.R	N.R	N.R	27	50	N.R
149b	F	CH ₂ CH ₂ OH	0.081	5.7	25	> 30	44	< 30	0% @ 25IM
149c	CN	CH ₂ CH ₂ OH	0.119	4.0	25	> 30	73	8	0% @ 25IM
149d	Cl	CH ₂ CH ₂ OH	0.034	4.0	5.4	> 30	67	109	N.R
149e	Me	CH ₂ CH ₂ OH	0.042	0.30	3.0	> 30	17	N.R	N.R

^aAV₅₀ and AV₉₀ are anti-viral IC₅₀ and IC₉₀, respectively, in cell culture in SupT1 cells infected with the RF strain of HIV. CC₃₀ = the 30% cytotoxic concentration of the compound in cell culture in SupT1 cells. HLM = human liver microsome preparation. CL_u = unbound clearance from human hepatocyte experiments. N.R. = not reported.

Figure 17. Structures of potent anti-tumor and anti-oxidant compounds.

respectively. C.F. Mello and co-workers¹¹⁹ prepared a library of pyrazoles **151** and tested them for anti-oxidant activity. All pyrazoles displayed reasonable potency.

5.12 Pyrazole-mediated anti-convulsants and anti-depressants

Adriana Bolasco and co-workers synthesized a new variety of pyrazole analogues and examined their selectively inhibiting capability against monoamine (MAO) oxidase A and B. The synthesized compounds **152a** and **152b** were shown to be more potent (Figure 18), reversible and selective inhibitors of MAO-A as compared to MAO-B (Table 11).¹²⁰ Abdel-Aziz and co-workers disclosed a novel variety of pyrazole analogues (**153a**, **153b** and **153c**).¹²¹ These compounds showed anti-depressant potency using tail suspension behavioral despair test and anti-convulsant potency against pentylenetetrazol (PTZ)-induced seizures in mice (Figure 18). Analogues **153a**, **153b** and **153c** showed a protective effect against tonic-clonic seizure induced by intraperitoneal (I.P) injection of PTZ at a dose amount of 20 mg/kg (Table 12).¹²²

5.13 Angiogenic and nematocidal activities of functionalized pyrazoles

Kumar *et al.*, synthesized functionalized pyrazoles **54** and screened them for their antiangiogenic activity by the chorioallantoic membrane (CAM) assay (Figure 19).¹²³ Investigation reveals that functionalized pyrazoles **54** exhibit excellent cytotoxic and angiogenic properties (Table 13). Cheng *et al.*, developed novel pyrazole carboxamides and investigated their nematocidal activity.¹²⁴ The preliminary insecticidal activity showed that some of them possessed good insecticidal activities against *Meloidogyne incognita*. Avermectin was used as control. The nematocidal activity decreased when the methyl group was replaced by ethyl group on the *N*-position of the amide group (Table 14). Likewise, Fei *et al.*, synthesized a series of novel thioether bridged

Figure 18. Structures of pyrazole-mediated anti-convulsants and anti-depressants.

Table 11. Monoamine oxidase inhibitory activity of compound (**152a** and **153b**).

Compound	MAO IC ₅₀	MAO-A IC ₅₀	MAO-B IC ₅₀	SI selectivity ^a
152a	$3.0 \times 10^{-5} \pm 0.05$	$8.8 \times 10^{-9} \pm 0.01$	$1.0 \times 10^{-4} \pm 0.06$	11363
152b	$4.0 \times 10^{-5} \pm 0.02$	$8.0 \times 10^{-9} \pm 0.01$	$1.3 \times 10^{-4} \pm 0.03$	16250

^aSI: selectivity index = IC₅₀ (MAO-B)/IC₅₀ (MAO-A).

Table 12. Antidepressant activities of the compounds **153a–153c** as compared to imipramine.

Compound ^a	Duration of immobility (s) (mean $\pm$ S.E.M.)	Change from control (%)
153a	183.90 $\pm$ 9.30	−24.41
153b	198.70 $\pm$ 6.80	−18.33
153c	153.30 $\pm$ 4.60	−36.99
Imipramine	132.00 $\pm$ 2.60	−45.75

Values represent the mean $\pm$ S.E.M. (n = 6); ^aCompounds and imipramine were tested at 10 mg/kg dose level, ip.

N-phenylpyrazole derivatives and insecticidal activities (Figure 19).¹²⁵ **56a**, **56b** and **56c** with sulfur-containing heterocycle substituents possessing good insecticidal activity against *Musca domestica* L. among the series (LC₅₀ = 0.67–1.30 μ g/g).

5.14 Anti-metastatic activities of hybrids based on coumarin/pyrazole oximes

A series of hybrids based on coumarin/pyrazole oxime have been synthesized by Dai *et al.* The formed compounds were screened for their metastatic activities (Figure 20).¹²⁶ Metastatic activities reveal that **157**

154a: R=H, R₁=H, R₂=H, R₃=H, R₄=H, R₅=H

154b: R=H; R₁=H, R₂=F, R₃=H, R₄=H, R₅=H

154c: R=H, R₁=H, R₂=H, R₃=H, R₄=Cl, R₅=H

154d: R=H, R₁=H, R₂=CH₃, R₃=H, R₄=H, R₅=H

154e: R=H, R₁=H, R₂=CH₃, R₃=H, R₄=Cl, R₅=H

154f: R=H, R₁=H, R₂=Cl, R₃=H, R₄=CH₃, R₅=H

Figure 19. Structure of pyrazole carboxamides.

Table 13. IC₅₀ values of compounds **54a–54g** on trypan blue and MTT assay at 48 h in MCF-7 cells.

Compound	Trypan blue assay IC ₅₀ value (μM)	MTT assay IC ₅₀ value (μM)
54a	19 ± 0.27	21 ± 0.18
54b	7.9 ± 0.07	7.6 ± 0.08
54c	17 ± 0.17	16 ± 0.22
54e	44 ± 0.12	49 ± 0.16
54f	71 ± 0.19	65 ± 0.13
54g	10.6 ± 0.07	10.4 ± 0.08

Table 14. Control efficacy of compounds **55** against *Meloidogyne incognita* at 40 mg/L.

Compound	R ₆	R ₇	Inhibitory (%)
55a	CH ₃	2,4-F ₂	80
55b	Et	4-Cl	64
55c	CH ₃	4-Cl	80
55d	CH ₃	3,4-Cl ₂	94.5
55e	CH ₃	4-Br	90
55f	CH ₃	4-CH ₃	91.8
55g	CH ₃	4-COOMe	80
55h	CH ₃	4-OCF ₃	90.9
55i	CH ₃	3-CF ₃	60
Avermectin			100

Figure 20. Structure of hybrids based on coumarin/pyrazole oxime.

displays significant anti-metastasis effects through inhibiting cell migration and invasion in highly metastatic SMMC-7721 cell line, and dose-dependently reverses TGF-β1-induced epithelial-mesenchymal transition (EMT) procedure

6. Conclusions

Numerous biological activities of pyrazoles and various synthetic protocols to construct pyrazoles have been highlighted in this review article. In the recent past, a lot of research has been carried out for the

development of pyrazole scaffolds. In the case of green approaches, BMIMBF₄ IL, zirconium dioxide NPs, organo-nanocatalyst, ultrasonic irradiation, copper(II) IL and [bmim]OH IL are the most novel approaches; while, in the case of classical approaches, synthesis of pyrazoles from methylene ketones, alkanyl bromides and propargylic alcohols are some novel approaches. However, currently, there are some important challenges that need to be dealt with in order to further develop the chemistry of pyrazoles. These challenges deal with proficiency for quantitative chemical yields in the formation of pyrazoles, precisely characterizing the inhibiting affinity of the pyrazoles and generating novel pyrazoles with a biological profile in the submicromolar range. It is expected that this review will be helpful in future research and for new and novel ideas in the quest of rational designs for syntheses of more promising pyrazoles.

7. Future prospective

The aim of this review is to summarize recent synthetic developments and biological activities of pyrazole derivatives. This review will inspire the scientists to plan and construct a new and potent series of bioactive pyrazole derivatives using highly efficient synthetic protocols. Further, the review will be cooperative to achieve structural-modifications intended to understand and enhance the inhibitory efficiency of pyrazoles. For future research, authors have listed a number of recommendations. Following are these recommendations: (i) it is suggested to couple other molecular frameworks, such as isatin, carbazole, benzothiophene, thiophene and terpyridine derivatives, with pyrazoles in order to enhance the bioactivity of pyrazole-based drugs; (ii) to replace current commercial bioactive drugs or to construct commercial-level pyrazoles-based drugs; it is important to produce drugs that contain inexpensive and commercially available starting chemicals, milder reaction conditions and one-pot synthetic approach. Further, construction must include properties of quantitative yield and eco-friendly procedures, *i.e.*, MW-assisted approaches and IL-mediated methods; (iii) in order to further enhance the yield of pyrazoles, it is recommended to investigate nano-catalytic systems and sono-mediated approaches; (iv) nowadays, cytotoxicity is the main issue of drugs; therefore, the researcher should focus on cytotoxic properties of pyrazoles. Further, solubility of pyrazoles is also required to be improved; (iv) dimer, trimer, tetramer and star-type polymeric pyrazoles should also be synthesized and investigated for anti-cancer activity; (v) to design and

develop extremely bio-operative pyrazole derivatives for the selective and sensitive inhibiting the target cells it is important to understand the structure-activity relationship and develop computational models; and (vi) in order to make pyrazoles highly soluble in H₂O, pyrazoles must be containing in the association of a hydrophobic region. It is hoped that this review will assist to increase knowledge and will be supportive of new thoughts in scheming more operative synthetic protocols for pyrazoles and in developing more potent drugs.

References

- Eftekhari-Sis B, Zirak M and Akbari A 2013 Arylglyoxals in Synthesis of Heterocyclic Compounds *Chem. Rev.* **113** 2958
- Ansari A, Ali A and Asif M 2017 Biologically active pyrazole derivatives *New J. Chem.* **41** 16
- Ju Y and Varma R S 2006 Aqueous N-Heterocyclization of Primary Amines and Hydrazines with Dihalides: Microwave-Assisted Syntheses of N-Azacycloalkanes, Isoindole, Pyrazole, Pyrazolidine, and Phthalazine Derivatives *J. Org. Chem.* **71** 135
- Zárate-Zárate D, Aguilar R, Hernández-Benitez R I, Labarrios E M, Delgado F and Tamariz J 2015 Synthesis of α -ketols by functionalization of captodative alkenes and divergent preparation of heterocycles and natural products *Tetrahedron* **71** 6961
- Gordon E M, Barrett R W, Dower W J, Fodor S P A and Gordon M A 1994 Gallop Applications of Combinatorial Technologies to Drug Discovery. 1. Background and Peptide Combinatorial Libraries *J. Med. Chem.* **37** 1385
- Ardiansah B 2017 Recent reports on pyrazole-based bioactive compounds as candidate for anticancer agents *Asian J. Pharm. Clin. Res.* **12** 45
- Srivastava M, Singh J, Singh S B, Tiwari K, Pathak K V and Singh J 2012 Synthesis of novel fused heterocycle-oxa-aza-phenanthrene and anthracene derivatives via sequential one-pot synthesis in aqueous micellar system *Green Chem.* **14** 901
- Pai G and Chattopadhyay A P 2016 N-arylation of nitrogen containing heterocycles with aryl halides using copper nanoparticle catalytic system *Tetrahedron Lett.* **57** 3140
- Bekhit A A, Hassan A M, Abd El Razik H A, El-Miligy M M, El-Agroudy E J and Bekhit Ael-D 2015 New heterocyclic hybrids of pyrazole and its bioisosteres: Design, synthesis and biological evaluation as dual acting antimalarial-antileishmanial agents *Eur. J. Med. Chem.* **94** 30
- Sony J K and Ganguly S 2016 A battle against AIDS: New pyrazole key to an older lock-reverse transcriptase *Int. J. Pharm. Sci.* **8** 75
- Surendra Kumar R, Arif I A, Ahamed A and Idhayadhulla A 2016 Antiinflammatory and antimicrobial activities of novel pyrazole analogues *Saudi J. Biol. Sci.* **23** 614
- Alam R, Wahi D, Singh R, Sinha D, Tandon V, Grover A and Rahisuddin 2016 Design, synthesis, cytotoxicity, Hu TopoII α inhibitory activity and molecular docking studies of pyrazole derivatives as anticancer agents *Bioorg. Chem.* **69** 77
- Shamsuzzaman S, Siddiqui T, Alam M G and Dar A M 2015 Synthesis, characterization and anticancer studies of new steroidal oxadiazole, pyrrole and pyrazole derivatives *J. Saudi Chem. Soc.* **19** 387
- Faisal M, Hussain S, Haider A, Saeed A and Larik F A 2018 Assessing the effectiveness of oxidative approaches for the synthesis of aldehydes and ketones from oxidation of iodomethyl group *Chem. Pap.* **73** 1053
- Kees K L, Fitzgerald J J, Steiner K E, Mattes, Mihan B, Tosi T, Mondoro D and McCaleb M L 1996 New potent antihyperglycemic agents in db/db mice: synthesis and structure-activity relationship studies of (4-substituted benzyl) (trifluoromethyl)pyrazoles and -pyrazolones *J. Med. Chem.* **39** 3920
- Bailey D M, Hansen P E, Hlavac A G, Baizman E R, Pearl J, Defelice A F and Feigenson M E 1985 3,4-Diphenyl-1H-pyrazole-1-propanamine antidepressants *J. Med. Chem.* **28** 256
- Michon V, Penhoat C H D, Tombret F, Gillardin J M, Lepage F and Berthon L 1995 Preparation, structural analysis and anticonvulsant activity of 3- and 5-aminopyrazole N-benzoyl derivatives *Eur. J. Med. Chem.* **30** 147
- Wiley R H and Wiley P 1964 *Pyrazolones, Pyrazolidones and Derivatives* (New York: Wiley) p. 102
- Jamwal A, Javed A and Bhardwaj V 2013 A review on pyrazole derivatives of pharmacological potential *J. Pharm. BioSci.* **3** 114
- Haufel J, Breitmaier E 1974 Synthesis of Pyrazolo Heteroaromatic Compounds by Means of 5-Amino-3-methyl-1-phenylpyrazole-4-carbaldehyde *Angew. Chem.* **13** 604
- Heller S T and Natarajan S R 2006 1,3-Diketones from Acid Chlorides and Ketones: A Rapid and General One-Pot Synthesis of Pyrazoles *Org. Lett.* **8** 2675
- Faisal M, Saeed A, Larik F A, Ghumro S A, Rasheed S and Channar P A 2018 WOS Sol-Gel Based Synthesis and Structural, Morphological, Electrical and Magnetic Characterization of Co-Sm Doped M-Type Barium Hexaferrite Materials *J. Electron. Mater.* **47** 7011
- Wyde P R, Gilbert B E and Ambrose M W 1989 Comparison of the anti-respiratory syncytial virus activity and toxicity of papaverine hydrochloride and pyrazofurin *in vitro* and *in vivo* *Antiviral Res.* **11** 15
- Bakr F A W and Kamal M D 2012 Synthesis and applications of bipyrazole systems *ARKIVOC* **1** 491
- Xia M, Zhang T, Wang Y and Xing G 2006 "Tetrahydroindole derivatives and tetrahydroindazole derivatives, and use thereof" WO 2006133634
- Rosati O, Curini M, Marcotullio M C, Macchiarulo A, Perfumi M, Mattioli L, Rismondo F and Cravotto G 2007 Synthesis, docking studies and anti-inflammatory

- activity of 4,5,6,7-tetrahydro-2H-indazole derivatives *Bioorg. Med. Chem.* **15** 3463
27. Nakhai A 2009 In *Synthetic studies of Nitrogen containing heterocycles, particularly pyrazole and benzotriazine derivatives* (Biovetenskaper och näringslära/Biosciences and Nutrition) (Stockholm: Karolinska Institutet) p. 111
 28. Ansari A, Ali A and Asif M 2017 biologically active pyrazole derivatives *New J. Chem.* **41** 16
 29. Md J A, Ozair A, Perwaiz A and Mohammad J N 2015 A Review on Pyrazole chemical entity and Biological Activity International *J. Pharm. Sci. Res.* **6** 1433
 30. Dewangan D, Kumar T, Alexander A, Nagori K and Tripathi D K 2003 Pyrazole: Their Chemistry and Pharmacological Potentials: A Review *Curr. Pharmac. Res. Sat.* **4** 369
 31. Arunachalam S, Gowrishankar N L, Krishnan A, Prakash M, Muhsin T, Naseena U and Poornima G 2018 A brief review on pyrazole derivatives possessing various pharmacological and biological evaluation *World J. Pharm. Pharma. Sci.* **5** 1496
 32. Raj K B 2007 *Heterocyclic Chemistry* 4th edn. (New International Publishers)
 33. Krygowski T M, Anulewicz R, Cyrafski M K, Puchala A, Rasata D 1998 Separation of the energetic and geometric contribution to the aromaticity. Part IX. Aromaticity of pyrazoles in dependence on the kind of substitution *Tetrahedron* **54** 12295
 34. Behr L C, Fusco R and Jarboe C H 1967 *The Chemistry of Heterocyclic Chemistry: Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings* (Wiley & Sons: London) p. 113
 35. Ragab E A, Metwally N H and Mohamed M S 2017 Synthesis of some novel pyrazolo [1, 5-a] quinazolines and their fused derivatives *Synth. Commun.* **2** 148
 36. Arunachalam S, Gowrishankar N L, Krishnan A, Prakash M, Muhsin T, Naseena U and Poornima G 2018 A brief review on pyrazole derivatives possessing various pharmacological and biological evaluation *World J. Pharm. Pharma. Sci.* **5** 1496
 37. Ciccolini C, Mari M, Lucarini S, Mantellini F, Pier-santi G and Favi G 2018 Polycyclic Indolines by an Acid-Mediated Intramolecular Dearomative Strategy: Reversing Indole Reactivity in the Pictet-Spengler-Type Reaction *Adv. Synth. Cat.* **360** 4060
 38. Desalegn N 2005 *Kinetic Studies of The Thermolysis of 3-Halogenated-4, 5-Dihydro-3h-Pyrazoles* (Georgia State University: Atlanta, Georgia) p. 84
 39. Corradi A, Leonelli C, Rizzuti A, Rosa R, Veronesi P, Grandi R, Baldassari S and Villa C 2007 New “green” approaches to the synthesis of pyrazole derivatives *Molecules* **7** 1482
 40. Beyzaei H, Motraghi Z, Aryan R, Zahedi M M and Samzadeh-Kermani A 2017 Green One-pot Synthesis of Novel Polysubstituted Pyrazole Derivatives as Potential Antimicrobial Agents *Acta Chim. Slov.* **64** 4 911
 41. Motamedi A, Sattari E, Mirzaei P, Armaghan M and Bazgir A 2014 An efficient and green synthesis of phthalide-fused pyrazole and pyrimidine derivatives *Tetrahedron Lett.* **55** 2366
 42. Kangani M, Hazeri N, Mghsoodlou M T, Habibi-khorasani S M and Salahi S 2015 Green synthesis of 1, 4-dihydropyrano [2, 3-c] pyrazole derivatives using maltose as biodegradable catalyst *Res. Chem. Inter.* **4** 2513
 43. Soltanzadeh Z, Imanzadeh G, Noroozi-Pesyan N and Şahin E 2017 Green synthesis of pyrazole systems under solvent-free conditions *Green Chem. Lett. Rev.* **3** 148
 44. Khurana J M and Chaudhary A 2012 Efficient and Green Synthesis of 4 H-pyrans and 4 H-pyrano [2, 3-c] Pyrazoles Catalyzed by Task-specific Ionic Liquid [bmim] OH under Solvent-free Conditions *Green Chem. Lett. Rev.* **4** 633
 45. Zolfigol M A, Afsharnadery F, Bagheri S, Salehzadeh S and Maleki F 2015 Catalytic applications of [HMIM] C (NO 2) 3: as a nano ionic liquid for the synthesis of pyrazole derivatives under green conditions and a mechanistic investigation with a new approach *RSC Adv.* **92** 75555
 46. Safaei S, Mohammadpoor-Baltork I, Khosropour A R, Moghadam M, Tangestaninejad S and Mirkhani V 2013 Copper (II) ionic liquid catalyzed cyclization–aromatization of hydrazones with dimethyl acetylenedicarboxylate: a green synthesis of fully substituted pyrazoles *New J. Chem.* **7** 2037
 47. Shelke S N, Mhaske G R, Bonifácio V D and Gawande M B 2012 Green synthesis and anti-infective activities of fluorinated pyrazoline derivatives *Bioorg. Med. Chem. Lett.* **22** 5727
 48. Maddila S, Rana S, Pagadala R, Kankala S, Maddila S and Jonnalagadda S B 2015 Synthesis of pyrazole-4-carbonitrile derivatives in aqueous media with CuO/ZrO₂ as recyclable catalyst *Cat. Comm.* **61** 26
 49. Heravi M M and Daraie M 2016 A novel and efficient five-component synthesis of pyrazole based pyrido [2, 3-d] pyrimidine-diones in water: a triply green synthesis *Molecules* **4** 441
 50. Siddiqui Z N and Farooq F 2012 Silica supported sodium hydrogen sulfate (NaHSO₄–SiO₂): A novel, green catalyst for synthesis of pyrazole and pyranil pyridine derivatives under solvent-free condition via heterocyclic β-enaminones *J. Mol. Cat. A: Chem.* **363** 451
 51. Zonouz A M., Eskandari I and Khavasi H R 2012 A green and convenient approach for the synthesis of methyl 6-amino-5-cyano-4-aryl-2, 4-dihydropyrano [2, 3-c] pyrazole-3-carboxylates via a one-pot, multi-component reaction in water *Tetrahedron Lett.* **41** 5519
 52. Al-Matar, H M, Khalil K D, Adam A Y and Elnagdi M H 2010 Green one pot solvent-free synthesis of pyrano [2, 3-c]-pyrazoles and pyrazolo [1, 5-a] pyrimidines *Molecules* **9** 6619
 53. Polshettiwar V and Varma R S 2010 Nano-organocatalyst: magnetically retrievable ferrite-anchored glutathione for microwave-assisted Paal–Knorr reaction, aza-Michael addition, and pyrazole synthesis *Tetrahedron* **5** 1091
 54. Kumari K, Raghuvanshi D S, Jouikov V and Singh K N 2012 Sc (OTf)₃-catalyzed, solvent-free domino synthesis of functionalized pyrazoles under controlled microwave irradiation *Tetrahedron Lett.* **9** 1130

55. Hasaninejad A and Firoozi S 2013 Catalyst-free, one-pot, three-component synthesis of 5-amino-1, 3-aryl-1H-pyrazole-4-carbonitriles in green media *Mol. Div.* **3** 459
56. Saha A, Payra S and Banerjee S 2015 One-pot multicomponent synthesis of highly functionalized bioactive pyrano [2, 3-c] pyrazole and benzylpyrazolyl coumarin derivatives using ZrO₂ nanoparticles as a reusable catalyst *Green Chem.* **5** 2859
57. Khurana J M, Nand B and Kumar S 2011 Rapid synthesis of polyfunctionalized pyrano [2, 3-c] pyrazoles via multicomponent condensation in room-temperature ionic liquids *Synth. Comm.* **3** 405
58. Srivastava M, Rai P, Singh J and Singh J 2013 An environmentally friendlier approach—ionic liquid catalysed, water promoted and grinding induced synthesis of highly functionalised pyrazole derivatives *RSC Adv.* **3** 16994
59. Frizzo C P, Marzari M R, Buriol L, Moreira D N, Rosa F A, Vargas P S, Zanatta N, Bonacorso H G and Martins M A 2009 Ionic liquid effects on the reaction of β -enaminones and tert-butylhydrazine and applications for the synthesis of pyrazoles *Cat. Comm.* **15** 1967
60. Hany F A and Mohamed H E 2009 Recent developments in aminopyrazole chemistry *ARKIVOC* **1** 198
61. Von R 1849 Pyrrole reaction *R. Chem. Ber.* **27** 685
62. Taylor E C and Hartke K S J 1959 The Reaction of Malononitrile with Substituted Hydrazines: New Routes to 4-Aminopyrazolo[3,4-d]pyrimidines *Am. Chem. Soc.* **81** 2456
63. Eberts F S 1961 1, 1, 3-Tricyano-2-amino-1-propene (U-9189), a Biologically active component of aqueous solutions of malononitrile *Arch. Biochem. Biophys.* **95** 305
64. Shruti K, Krunal P, Nilesh D, Palak S, Parita S and Shruti Kushwah 2012 Synthesis of pyrazole azo dyes *Ijprbs* **2** 287
65. Barry H M, Mark H, Bury and Roy M 2001 "Pyrrole synthesis" *U.S. Patent* 6200371 B1
66. Hamid M H, Nada M A and Huwaida M H 2010 Synthesis of pyrazole *Nat. Sci.* **2** 1349
67. Sabir H, Deepika K and Mukta S 2010 Synthesis and Biological Evaluation of Some New 1-substituted-3,5-dimethyl-4-[(Substituted Phenyl) Diazenyl] Pyrazole Derivatives *Am.-Eur. J. Sci. Res.* **4** 257
68. Ibrahim M K A, Ramiz M M M and El-Ghandour A H H 1989 Synthesis of n-(azolyl)-alpha-ketohydrazidoyl chlorides, azolotriazole and azolotriazine derivatives *J. Chem. Soc. Pak.* **11** 291
69. Swelam S A, El-Said N S, Aly A S and Abdel-Fatth A M 2009 Production of pyrans, pyridazines, pyrimidines, pyrazines and triazine compounds using benzoylacetoneitriles as a precursor *Inter. J. Pharm. Tech. Res.* **1** 445
70. Ahmed E, Fadda A A, Khalil A M, Ameen T A E and Farid A B 2009 Synthesis, antitumor evaluation, molecular modeling and quantitative structure-activity relationship (QSAR) of some novel arylazopyrazolodiazine and triazine analogs *Bioorg. Med. Chem.* **17** 5096
71. Nițu S V, Bercean V N, Badea V and Csunderlik C 2008 Azoic Compounds Obtained from 1H-4-ethoxycarbonyl-3-methyl-5-aminopyrazole and 1, 3-disubstituted 1H-pyrazol-5-ones *Chem. Bull.* **53** 1
72. Metwally M A, Gouda M A, Ammar N H and Khalil A M 2012 *Inter. J. Mod. Org. Chem.* **1** 96
73. Fati K and Fikret K 2008 Synthesis of some novel pyrazolo [5, 1-c][1, 2, 4] triazine derivatives and investigation of their absorption spectra *Dye Pig.* **76** 97
74. Fati K and Fikret K 2008 Synthesis and absorption spectra of some novel heterocyclic disazo dyes derived from pyridone and pyrazolone derivatives *Dye Pig.* **76** 147
75. Ahmed A F, Samir B, Ramy R and Hassan A 2008 Cyanoacetamide Derivatives as Synthons in Heterocyclic Synthesis *Turk. J. Chem.* **32** 259
76. Abu-Shanab F A, Mousa S A, Eshak E A, Sayed A Z and Al-Harrasi A 2011 Dimethylformamide dimethyl acetal (DMFDMA) in heterocyclic synthesis: Synthesis of polysubstituted pyridines, pyrimidines, pyridazine and their fused derivatives *Int. J. Org. Chem.* **1** 207
77. Abdel-Zaher A E, H H D, Nouria A A and Elnagdia M H 2007 Chemistry of carbofunctionally substituted hydrazones *ARKIVOC* **2** 272
78. Abunada N M, Hassaneen, Kandile N G and Miqdad O A 2008 Synthesis and biological activity of some new pyrazoline and pyrrolo [3,4-c]pyrazole-4,6-dione derivatives: reaction of nitrilimines with some dipolarophiles *Molecules* **13** 1011
79. Chawla R, Sahoo U, Arora A, Sharma P C and Radhakrishnan V 2010 Microwave assisted synthesis of some novel 2-pyrazoline derivatives as possible antimicrobial agents *Acta Pol. Pharm.* **67** 1 55
80. Jadhav S B, Shastri R A, Gaikwad K V and Gaikwad S V 2009 Synthesis and antimicrobial studies of some novel pyrazoline and isoxazoline derivatives *Eur. J. Chem.* **6** 83
81. Kaur H, Kumar S, Singh I and Kumar A 2010 Synthesis, characterization and antibacterial activity of various substituted oxadiazolylpyrazolinyl/isoxazolinylicoumarin derivatives *Int. J. Pharm. Sci. Res.* **1** 58
82. Faidallah H M, Rostom S A and Al-Saadi M S 2010 Synthesis and biological evaluation of some new substituted fused pyrazole ring systems as possible anticancer and antimicrobial agents *JKAU Sci* **22** 177
83. Dean A, Heathcote, Hetal P, Sebastian H B K, Pascale H, Manikandan P, Mary A, Seshu K K, Ashutosh S J, Bodo S, Marion B, Andreas B, Jan B and Alekasandra S 2010 A novel pyrazolo [1, 5-a] pyrimidine is a potent inhibitor of cyclin-dependent protein kinases 1, 2, and 9, which demonstrates antitumor effects in human tumor xenografts following oral administration *J. Med. Chem.* **53** 8508
84. Zask A, Verheijen J C, Curran K, Kaplan J, Richard D J, Nowak P, Malwitz D J, Brooijmans N, Bard J, Svenson K and Lucas J 2009 ATP-competitive inhibitors of the mammalian target of rapamycin: design and synthesis of highly potent and selective pyrazolopyrimidines *J. Med. Chem.* **52** 5013
85. Guertin D A and Sabatini D M 2007 Defining the Role of mTOR in Cancer *Cancer Cell* **12** 9

86. Chiang G G and Abraham R T 2007 Targeting the mTOR signaling network in cancer *Trends Mol. Med.* **13** 433
87. Bhaskar V H and Mohitea P B 2011 Synthesis analgesic, anti-inflammatory and antimicrobial activities of some 1-[5-(substituted phenyl)-4,5-dihydro-1H-pyrazol-3-yl]-5-phenyl-1H-tetrazole *J. Optoelectron. Biomed. Mat.* **3** 7
88. Venkataraman S, Jain S, Shah K and Upmanyu N 2010 Synthesis and biological activity of some novel pyrazolines *Acta Pol. Pharm.* **67** 361
89. Sridevi C, Balaji K and Naidu A 2011 Synthesis and pharmacological evaluation of some phenylpyrazolo indoquinoline derivatives *E-J. Chem.* **8** 924
90. Menozzi G, Merello L, Fossa P, Silvia S, Angelo R, Luisa M, Francesco B, Roberta L, Chiara M, Valeria M, Paolo L, C and Elena T 2009 Synthesis and evaluation of electron-rich curcumin analogues *Bioorg. Med. Chem. Lett.* **1** 360
91. Ayoob B, Maryam M K and Ali A S 2008 One-pot synthesis and antibacterial activities of pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidine-dione derivatives *Bioorg. Med. Chem. Lett.* **21** 5800
92. Kumar R, Malik S and Chandra R 2009 Synthesis and antimicrobial activity of 4-[5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl]-dihydropyridines and 4-[5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl]-3,4-dihydropyrimidin-2-ones *Indian J. Chem. B* **49** 718
93. Sahu S K, Banerjee M, Samantray A, Behera C and Azam M A 2008 Synthesis and antiviral evaluation of some new pyrazole and pyrazolopyrimidine derivatives *Trop J. Pharm. Res.* **7** 961
94. Sivakumar K K, Rajasekaran A, Ponnilaravasan I, Somasundaram A and Kamalaveni S 2010 Synthesis and evaluation of anti-microbial analgesic activity of some (4Z)-3-methyl-1-[(2-oxo-2H-chromen-4-yl) carbonyl]-1H-pyrazole-4,5-dione-4-[(substitutedphenyl) hydrazone] *Der Pharm. Lett.* **2** 211
95. Dias L R and Salvador R R S 2012 Pyrazole Carbohydrazone Derivatives of Pharmaceutical Interest *Pharmaceuticals* **5** 317
96. Prathap K J, Himaja M, Mali S V, Karigar A A and Sikarwar M S 2011 Synthesis of New 3-Aryl-1-(5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl)-1H-pyrazole-4-carbaldehydes as Antitubercular Agents *Drug Inv.* **3** 10
97. El-Sabbagh O I, Baraka M M, Ibrahim S M, Pan-necouque P, Andrei G, Snoeck R, Balzarini J and Rashad A 2009 Synthesis and antiviral activity of new pyrazole and thiazole derivatives *Eur. J. Med. Chem.* **44** 3746
98. Rashad A E, Hegab M I, Abdel-Megeid R E, Micky J A and Abdel-Megeid F M E 2008 Synthesis and antiviral evaluation of some new pyrazole and fused pyrazolopyrimidine derivatives *Bioorg. Med. Chem.* **16** 7102
99. El-Badawi S M A and Bakhiet A O 2012 Chemotherapeutic and economic potentials of some lactiferous plants *J. Med. Plant Res.* **6** 3278
100. Priyadarsini P, Ujwala, B, Venkata R C and Madhava R V 2012 Synthesis and antimicrobial activity of some novel pyrazoles *Der Pharm. Lett.* **4** 1123
101. Hassan S Y 2013 Synthesis, Antibacterial and antifungal activity of some new pyrazoline and pyrazole derivatives *Molecules* **18** 2683
102. Turan Z G, Chevallet P, Kilic T S and Erolic K 2000 Synthesis of some thiazolyl-pyrazoline derivatives and preliminary investigation of their hypotensive activity *Eur. J. Med. Chem.* **35** 635
103. Silver K S and Soderlund D M 2005 Action of pyrazoline type insecticides at neuronal target side *Pestic. Biochem. Physiol.* **81** 136
104. Godey M C M, Figuera M R, Souza F R, Rubin M A, Oliveira M R, Zennata N and Mello C F 2004 α 2-Adrenoceptors and 5-HT receptors mediate the antinociceptive effect of new pyrazolines, but not of dipyrone *Eur. J. Pharma.* **496** 93
105. Chimenti P, Granese A, Rivanera D, Lilli D, Scaltrito M M and Brenciaglia M I 2005 Synthesis and *in vitro* selective anti-*Helicobacter pylori* activity of pyrazoline derivatives *Bioorg. Med. Chem. Lett.* **15** 603
106. Salgin-Goksen U, Yabanoglu-Ciftci S, Ercan A, Yelekci K, Ucar G and Gokhan-Kelekci N 2013 Evaluation of selective human MAO inhibitory activities of some novel pyrazoline derivatives *J. Neural. Transm.* **120** 863
107. Bonesi M, Loizzo M R, Statti G A, Michel S, Tilleguin F and Menichini 2010 The synthesis and angiotensin converting enzyme (ACE) inhibitory activity of chalcones and their pyrazole derivatives *Bioorg. Med. Chem. Lett.* **20** 1990
108. Gao M, Wang M, Miller K D and Zheng Q H 2001 Synthesis and preliminary *in vitro* biological evaluation of new carbon-11-labeled celecoxib derivatives as candidate PET tracers for imaging of COX-2 expression in cancer *Eur. J. Med. Chem.* **46** 4760
109. Mumolo M, Zumieri D, Fulgani V, Vio L and Bunfi E 2001 Synthesis and antimycobacterial activity of 5-aryl-1-isonicotinyl-3-(pyridyl-2-yl)-4,5-dihydro-1H-pyrazole derivatives *Frmaco* **56** 593
110. Ozdamir A and Zitouni G T 2008 Novel analogues of 2-pyrazoline: Synthesis, characterization and antimycobacterial evaluation *Turk. J. Chem.* **32** 529
111. Zampieri D, Mamolo M G, Lourini E, Sciolino G, Bunfi E and Vio L 2008 Antifungal and antimycobacterial activity of 1-(3,5-diaryl-4,5-dihydro-1H-pyrazol-4-yl)-1H-imidazole derivatives *Bioorg. Med. Chem.* **16** 4516
112. Sreenivasa G M, Jaychandran E, Shivkumar B, Kumar K J and Vijay K V 2009 Synthesis of bioactive molecule fluoro benzothiazole comprising potent heterocyclic moieties for anthelmintic activity *Arch. Pharm. Sci. Res.* **1** 150
113. Faisal M, Larik F A and Saeed A 2018 A highly promising approach for the one-pot synthesis of biscoumarins using HY zeolite as recyclable and green catalyst *J. Porous Mater.* **26** 455
114. Charles E M, Catherine B, Romuald C, Simon G, Michael H, Manos P, Isabelle T, David A P, Faye J Q, Matthew D S, Paul A S and Rob W 2009 Pyrazole NNRTIs 4: selection of UK-453,061 (Iersivirine) as a development candidate *Bioorg. Med. Chem. Lett.* **19** 5857
115. Kasralikar H M, Jadhavar S C, Goswami S V, Kam-inwar N S and Bhusare S R 2019 Design, Synthesis

- and Molecular Docking of Pyrazolo [3, 4d] thiazole hybrids as Potential Anti-HIV-1 NNRT Inhibitors *Bioorg. Chem.* **86** 437
116. Vekariya M K, Vekariya R H, Patel K D, Raval N P, Shah P U, Rajani D P and Shah N K 2018 Pyrimidine-Pyrazole Hybrids as Morpholinopyrimidine-Based Pyrazole Carboxamides: Synthesis, Characterisation, Docking, ADMET Study and Biological Evaluation *Chem. Select.* **3** 6998
117. Nassar E 2010 Synthesis, (in vitro) Antitumor and Antimicrobial Activity of some Pyrazoline, Pyridine, and Pyrimidine Derivatives Linked to Indole Moiety *J. Am. Sci.* **6** 8
118. Feng J, Qi H, Sun X, Feng S, Liu Z, Song Y and Qiao X 2018 Synthesis of novel pyrazole derivatives as promising DNA-binding agents and evaluation of antitumor and antitopoisomerase I/II activities *Chem. Pharm. Bull.* **c18** 546
119. Pasin J S M, Ferreria A P O, Saraiva A L L, Ratzlaff V, Andrighetto R, Machado P, Marchesam S, Zanette R A and Martins M A P 2010 Antipyretic and antioxidant activities of 5- trifluoromethyl-4,5-dihydro-1H-pyrazoles in rats *Braz. J. Med. Biol. Res.* **43** 1193
120. Chimenti F, Bolasco A, Manna F, Secci D, Chimenti P, Befani O, Turini P, Giovannini V, Mondovì B, Cirilli R and Torre F L 2004 Synthesis and selective inhibitory activity of 1-acetyl-3, 5-diphenyl-4, 5-dihydro-(1 H)-pyrazole derivatives against monoamine oxidase *J. Med. Chem.* **47** 2071
121. Abdel-Aziz M, Abuo-Rahman G E A and Hassan A A 2009 Synthesis of novel pyrazole derivatives and evaluation of their antidepressant and anticonvulsant activities *Eur. J. Med. Chem.* **44** 3480
122. Wu Y, Huang Y P, Zhou S C, Tan Y Q, Xu B G, Liang Z and Deng X Q 2018 Synthesis of 1, 3-Diaryl Pyrazole Derivatives and Evaluation of Anticonvulsant and Antimicrobial Activities *Lat. Am. J. Pharm.* **37** 1017
123. Dileep Kumar A, Bharath S, Dharmappa R N, Naveen S, Lokanath N K and Ajay Kumar K 2018 Design, synthesis and spectroscopic and crystallographic characterisation of novel functionalized pyrazole derivatives: biological evaluation for their cytotoxic, angiogenic and antioxidant activities *Res. Chem. Intermediat.* **44** 5635
124. Cheng L, Shen Z H, Xu T M, Tan C X, Weng J Q, Han L, Peng W L and Liu X H 2018 Synthesis and Nematocidal Activity of N-Substituted 3-Methyl-1H-pyrazole-4-carboxamide Derivatives Against *Meloidogyne incognita* *J. Heterocycl. Chem.* **55** 946
125. Fei C, Chen Y, Jiang Z and Jiang D 2018 Thioether-bridged arylalkyl-linked N-phenylpyrazole derivatives: Design, synthesis, insecticidal activities, structure-activity relationship and molecular-modeling studies *Bioorg. Med. Chem. Lett.* **28** 1792
126. Dai H, Huang M, Qian J, Liu J, Meng C, Li Y, Ming G, Zhang T, Wang S, Shi Y and Yao Y 2019 Excellent antitumor and antimetastatic activities based on novel coumarin/pyrazole oxime hybrids *Eur. J. Med. Chem.* **166** 470