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 2021 Feb 22;26(4):1163. doi: 10.3390/molecules26041163Green synthetic protocol refers to the development of processes for the sustainable production of chemicals and materials. For the synthesis of various biologically active compounds, energy-efficient and environmentally benign processes are applied, such as microwave irradiation technology, ultrasound-mediated synthesis, photo-catalysis (ultraviolet, visible and infrared irradiation), molecular sieving, grinding and milling techniques, etc. Thesemethods are considered sustainable technology and become valuable green protocol to synthesize new drug molecules as theyprovidenumerous benefits over conventional synthetic methods.Based on this concept, oxadiazole derivatives are synthesized under microwave irradiation technique to reduce the formation of byproduct so that the product yield can be increased quantitatively in less reaction time. Hence, the synthesis of drug molecules under microwave irradiation follows a green chemistry approach that employs a set of principles to minimize or remove the utilization and production of hazardous toxic materials during the design, manufacture and application of chemical substances.This approach plays a major role in controlling environmental pollution by utilizing safer solvents, catalysts, suitable reaction conditions and thereby increases the atom economy and energy efficiency. Oxadiazole is a five-membered heterocyclic compound that possesses one oxygen and two nitrogen atoms in the ring system.Oxadiazole moiety is drawing considerable interest for the development of new drug candidates with potential therapeutic activities including antibacterial, antifungal, antiviral, anticonvulsant, anticancer, antimalarial, antitubercular, anti-asthmatic, antidepressant, antidiabetic, antioxidant, antiparkinsonian, analgesic and antiinflammatory, etc. This review focuses on different synthetic approaches of oxadiazole derivatives under microwave heating method and study of their various biological activities.Keywords: drug, green chemistry, microwave, oxadiazole, synthesis, biological activitiesThe green chemistry approach refers to the utilization of a set of principles that reduces the generation of chemical hazardous during the design, manufacture and use of chemical substances. This protocol plays a major role in controlling environmental pollution by using safer solvents, catalysts, suitable reaction conditions and thereby increases the atom economy and energy efficiency of the synthetic process. Hence, microwave-assisted synthesis followsthe green chemistry approach as it makes the synthetic process eco-friendly by reducing environmental pollution [1]. Microwave radiation energy offers significant benefits to carry out drug synthesis, including increased reaction rates, product yield enhancements, and cleaner reactions.The chemical transformations which take hours, or even days, to complete can now be completed in minutes with the help of microwave heating [2].Similarly, the ultrasonic irradiation method is applied to accelerate various chemical reactions, including both homogeneous and heterogeneous systems. The use of ultrasound in organic synthesis involves specific activation based on the physical phenomenon, i.e., acoustic cavitations.In contrast, photo-catalytic reactions involve the use of ultra-violet, visible light and infrared radiation to generate new medicinally active compounds with diverse molecular structures. To carry out a photochemical reaction, the UV-visible spectra of the photoactive compounds are recorded. The photoactive compound is the molecule that can be electronically excited and undergoes chemical reaction from its excited state [3].The grinding technique is also considered a green synthetic method to perform chemical reactions under solvent-free conditions with high product yield. Grinding of the recanting substances for a chemical reaction can be carried out by using mortar and pestle or by using a high-speed vibrating mill. Due to the collision between the reacting molecules, the chemical reaction is carried forward [4]. A milling technique like ball milling is considered to be one of the automated forms of mortar and pestle. In the case of theball mill, the reacting materials are placed in a reaction vessel equipped with grinding balls and covered with a lid. The vessel is allowed to shake at high-speed to carry out the chemical reactions [5].Based on these above facts, oxadiazole derivatives are synthesized to reduce the formation of byproducts so that the product yield can be increased in less reaction time. Further, the structural motif like oxadiazole is drawing considerable attention for the development of new drug candidates with potential therapeutic activities including antibacterial, antifungal, antiviral, anticonvulsant, anticancer, antimalarial, antitubercular, anti-asthmatic, antidepressant, antidiabetic, antioxidant, antiparkinsonian, analgesic and antiinflammatory, etc.Oxadiazole moiety is considered to be derived from furan ring by replacing two methane groups (-CH=) with two pyridine-type nitrogen (-N=).The aromaticity of oxadiazole is decreased due to the replacement of these groups in the furan ring so that it exhibits the property of conjugated diene. The oxadiazole ring is also recognized as furadiazole, furoxans, azoximes, oxybiazole, biozole and diazoxole. Oxadiazole derivatives are found to be a very weak base due to the inductive effect of the additional heteroatoms.Hence, there is the possibility of four isomers of oxadiazole, including 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole that depends on the position of nitrogen in the ring [6].The therapeuticpotentials of oxadiazole derivatives mainly depend on the effective binding interactions of drug molecules with different receptors or enzymes in the biological systems and thereby eliciting diverse bioactivities. This review provides new insights into the rational design to develop potential oxadiazole-based medicinal agents with less toxicity and improved pharmacokinetic properties.There are various green chemistry approaches to carry out different chemical reactions that include microwave irradiation (MWI), ultrasonication, photo-catalysis, grinding and milling methods (Figure 1). By applying these technologies, organic reactions become more efficient and economic by enhancing the rate of reaction with reduced reaction time and high product yield. Synthetic approaches like grinding or milling techniques involve the application of mechanochemistry for the rapid, clean, efficient and solvent-free synthesis of various biologically active compounds [7]. Green chemistry approaches.During the year 1991, the Environmental Protection Agency (EPA) and the National Science Foundation (NSF) initiated the Green Chemistry Program. P.T. Anastas and J.C. Warner have formulated twelve major principles of green chemistry to reduce or eliminate the risk of chemical hazards and environmental pollution [8,9,10,11].Prevention of waste or byproducts: It is essential to carry out the synthesis in such a way that the formation of waste or byproducts is less or absent.Atom economy: It represents the design of synthetic methods to maximize the incorporation of reactants (starting materials and reagents) to get the final products.Use of less hazardous and toxic chemicals: Various synthetic methods should be designed properly so that the use and generation of substances have less or no toxic effect on human health and the environment.Designing of Safer chemicals: The design of the chemical product should preserve efficacy while reducing toxicity.Selection of Safer solvents: Avoid the use of auxiliary materials (solvents, extractants) if possible, or otherwise, make them innocuous.Energy efficiency: Energy requirements should be minimized and conduct synthesis at ambient temperature and pressure.Renewable feedstock: Raw materials should be renewable.Reduce derivatives: Unnecessary derivatization should be avoided where possible.Smart catalysis: Selectively catalyzed processes are superior to stoichiometric processes.Biodegradable design: The design of chemical products should be in such a way that these can be degradable to innocuous products when disposed of.Real-time analysis for pollution prevention: Monitor the processes in real time to avoid excursions leading to the formation of hazardous substances.Prevention of hazards and accidents: Materials used in a chemical process should be selected to minimize hazardsand risk for chemical accidents.Oxadiazoles are five-membered heterocyclic compounds that possess one oxygen atom and two nitrogen atoms in the ring system [12]. Depending on the position of heteroatoms (oxygen or nitrogen), there are different isomeric forms of oxadiazole moiety such as 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole (Figure 2).These chemical compounds are of the azole family with the molecular formula C2H2N2O. Among these isomers, 1,2,3-oxadiazole is unstable and ring-opens to form the diazoketone tautomer. However, 1,3,4-oxadiazole is a thermally stable aromatic molecule and plays a major role in developing new drug candidates with diverse biological activities such as anticancer, antiparasitic, antifungal, antibacterial, antidepressant, antitubercular and antiinflammatory, etc. [13]. Chemical structures of oxadiazole isomers.The electrophilic-substitution reaction is very difficult at the carbon atom in the oxadiazole ring because of the relatively low electron density on the carbon atom. However, the electrophilic attack occurs at nitrogen if the oxadiazole ring is substituted with electron releasing groups. Similarly, the oxadiazole ring is usually resistant to nucleophilic attack. However, the halogen-substituted oxadiazole undergoes nucleophilic substitution with the replacement of halogen atom by nucleophiles [14]. Although 1,3,4-oxadiazole ring system was known in 1880, significant studies were carried out regarding its chemistry, structure, physical properties and application of its various derivatives from 1950 (Table 1). 1,3,4-oxadiazole is a liquid with a boiling point of 150 C. The percentage of C, H, N present in 1,3,4-oxadiazole is 34.29%, 2.88%, 40.00%, respectively [15].Bond angle and bond length of 1,3,4-oxadiazole moiety.AnglesBond Angle ()BondsBond Length (Pm)A105.6a139.9B113.4b129.7C102.0c134.8D113.4d134.8E105.6e129.7The first monosubstituted 1,3,4-oxadiazoles were reported in 1955 by two independent laboratories. Since 1955, other research groups have performed the reactions of 1,3,4-oxadiazole and reported that it is a liquid that boils at 150C. Ainsworth first prepared 1,3,4-oxadiazole (2) in 1965 by the thermolysis of ethylformate formyl hydrazone (1) at atmospheric pressure as depicted in Scheme 1 [16]. Synthesis of 1,3,4-oxadiazole.The 1,2,4-oxadiazole was synthesized first time in 1884 by Tiemann and Kruger. Most of the oxadiazole synthesis is based on heterocyclization of amidoxime and carboxylic acid derivatives or 1,3-dipolar cycloaddition of nitrile and nitrile oxide [17]. Microwave irradiation can also be applied in the heterocyclization of amidoximes and acyl chlorides/carboxylic acid esters in the presence of NH4F/Al2O3 or K2CO3 to produce corresponding oxadiazole derivatives [18]. Similarly, oxadiazole derivatives are produced by the reaction of aryl-nitrile with hydroxylamine hydrochloride to aryl-amidoxime inthe presence of a catalyst (MgO or CH3COOH or KF) under a microwave-assisted method. In the year 2017, Baykov et al. reported a study on the first one-pot synthetic procedure for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles (3) at room temperature from corresponding amidoximes (1) and carboxylic acids methyl or ethyl esters (2) in the presence of superbase medium NaOH/DMSOas presented in the Scheme 2 [19,20]. Synthesis of 1,2,4-oxadiazole analogs. R1 = 4-methylphenyl, R2 = methyl or phenyl, X = methoxy or ethoxy.Gorjizadeh et al. reported the efficient synthesis of a series of 1,3,4-oxadiazoles (3) from the cyclizationoxidation reaction of acyl hydrazones (1) with substituted aldehydes (2) by using 1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate (BTPPDS) as an oxidant in a solvent-free medium under microwave irradiation (Scheme 3). The reaction was found to proceed smoothly under microwave irradiation within 25 min, whereas 12 h were required to complete the reaction under reflux conditions [21]. Synthesis of a series of 1,3,4-oxadiazoles.Various medicinally active drug molecules containing oxadiazole moiety are used clinically for the treatment of different disease states (Figure 3).Oxolamine possesses a 1,2,4-oxadiazole ring and is used as a cough suppressant.Similarly, prenoxdiazine is a cough suppressant. Its IUPAC name is 3-(2,2-diphenylethyl)-5-(2-piperidin-1-ylethyl)-1,2,4-oxadiazole. Proxazole is chemically N,N-diethyl-2-[3-(1-phenylpropyl)-1,2,4-oxadiazol-5-yl]ethanamine. It is a drug used for functional gastrointestinal disorders. Butalamine is a vasodilator and is chemically known as N,N-dibutyl-N-(3-phenyl-1,2,4-oxadiazol-5-yl)ethane-1,2-diamine. Chemical structures of drugs based on a 1,2,4-oxadiazole moiety.Ataluren (PTC124) is a drug for the treatment of Duchenne muscular dystrophy. It was designed by PTC Therapeutics and is sold under the trade name Translarna in the European Union. Chemically, it is 3-[5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl]benzoic acid. Pleconaril is an antiviral drug. It exhibits its action by inhibiting viral replication. It was developed by Schering-Plough for the prevention of asthma exacerbations and common cold symptoms in patients exposed to picornavirus respiratory infections. Chemically, it is 3-[3,5-dimethyl-4-[3-(3-methyl-1,2-oxazol-5-yl)propoxy]phenyl]-5-(trifluoromethyl)-1,2,4-oxadiazole [22,23,24].Carbone M. et al. isolated two indole alkaloids, phidianidine-A and phidianidine-B (Figure 4), from sea slug opisthobranch Phidiana militaris. Chemically, phidianidine-B is 2-[5-[[5-(1H-indol-3-ylmethyl)-1,2,4-oxadiazol-3-yl]amino]pentyl]guanidine. Both phidianidines exhibit in vitro cytotoxic activity against tumor and non-tumor mammalian cell lines (rat glial-C6, human cervical-HeLa, colon adenocarcinoma-CaCo-2, mouse embryo-3T3-L1 and rat heart myoblast-H9c2) [25]. Similarly, quisqualic acid is a naturally occurring compound bearing 1,2,4-oxadiazole moiety. It is obtained from seeds of Quisqualis indica. It is usedfor the treatment of stroke, epilepsy and neurodegenerative disorders [26,27]. Structures of naturally occurring compounds containing 1,2,4-oxadiazole ring.Tiodazosin is a new antihypertensive drug, structurally resembles prazosin. It possesses alpha-adrenergic-blocking activity and exerts a direct vasodilation effect. Chemically, it is (4-(4-amino-6,7-dimethoxyquinolin-2-yl)piperazin-1-yl)(5-(methylthio)-1,3,4-oxadiazol-2-yl)-methanone [28]. Furamizole is a nitrofuran derivative and possesses antibacterial activity. Chemically, it is (E)-5-(1-(furan-2-yl)-2-(5-nitrofuran-2-yl)vinyl)-1,3,4-oxadiazol-2-amine.Raltegravir (MK-0518) is an antiretroviral drug produced by Merck and Co., Kenilworth, NJ, USA. It was approved by the U.S. Food and Drug Administration (USFDA) in October 2007. It is the new class of anti-HIV drug and acts as an integrase inhibitor. Chemically, it is N-(4-fluorobenzyl)-5-hydroxy-1-methyl-2-(2-(2-methyl-1,3,4-oxadiazole-5-carboxamido)propan-2-yl)-6-oxo-1,6-dihydropyrimidine-4-carboxamide. Nesapidilisacalcium channel blocker and exerts vasodilation effect. Its IUPAC name is1-(3-(1,3,4-oxadiazol-2-yl)phenoxy)-3-(4-(3-methoxyphenyl)piperazin-1-yl)propan-2-ol (Figure 5, Table 2) [29,30]. Structure of clinically useful drugs containing 1,3,4-oxadiazole scaffold.Therapeutic potentials oxadiazole derivatives.Type Oxadiazole DerivativesName of CompoundsTherapeutic Uses1,2,4-oxadiazolePhidianidine-A, BAntitumorQuisqualic acidAntiepilepticOxolamineCough suppressantPrenoxdiazineCough suppressantButalamineVasodilatorFasiplonAnxiolyticPleconarilAntiviralAtalurenTreatment of muscular dystrophyProxazoleTreatment of GI disorders1,3,4-oxadiazoleTiodazosinAntihypertensiveFuramizoleAntibacterialRaltegravirAntiretroviralNesapidilVasodilatorZibotentanAnticancerMicrowave-assisted drug synthesis is a Green technology that utilizes microwave radiation as a heating source to perform various synthetic reactions. The microwave radiation is used as an alternative energy source to complete various organic transformations in minutes instead of hours or even days. Microwaves are electromagnetic radiation with wavelengths ranging from one meter to one millimeter with frequencies between 300 MHz and 300 GHz [31]. These high-frequency electric fields of the microwave are applied to heat the reacting substances of an organic reaction with electric charges. In the case of the polar reaction medium, these are heated due to their dipolar rotation with the electric field and loose energy during collisions between reacting molecules. With the help of microwave heating technology, the rate of organic synthesis can be improved, and the drug products can be manufactured selectively by utilizing suitable microwave parameters. Thus, microwave technology provides several advantages such as instantaneous, rapid heating, homogeneity and selective heating as compared to conventional heating techniques like water bath, oil bath or sand batch, etc. [32].The synthesis of drug substances under microwave irradiation is primarily dependent on the ability of the reaction medium to absorb microwave energy efficiently and also depends on the selection of the solvent system to perform the synthetic reaction [33]. Due to the diverse polar and ionic properties of different solvents, they interact differently with microwave radiation. Hence, the ability of suitable solvents or reaction medium to convert microwave energy to heat is called as loss tangent (). Based on the value of tan , solvents can be categorized into high (tan > 0.5), medium (tan 0.10.5), and low microwave absorbing (tan < 0.1) type. Higher the value of tan represents that the solvent is suitable for absorption of microwave radiation so as to causes efficient heating [34].Polar solvents such as DMA, DMF, DMSO, NMP, methanol, ethanol, and acetic acid are selected for carrying out organic synthesis under microwaves due to their polarity. The solvents with low boiling points (e.g., methanol, dichloromethane and acetone) have lower reaction temperatures due to the pressure developed inside the reaction vessel. If a higher temperature is desirable to achieve a faster reaction, it is suggested to change the closely related solvent with a higher boiling point (e.g., dichloroethane instead of dichloromethane). Solvents can behave differently at elevated temperatures, and most of the solvents become less polar with an increase in temperature. For example, the bond angle in water widens at elevated temperatures, and its dielectric properties approach the organic solvents. Similarly, water at 250 C possesses similar dielectric properties like acetonitrile at room temperature. Hence, water can be used as a pseudo-organic solvent at elevated temperatures where organic compounds will dissolve, not only because of the temperature but also because of the change in dielectric properties. Nonpolar solvents (e.g., toluene, dioxane, THF) can only be heated if other components in the reaction mixture respond to microwave energy [35,36].However, ionic liquids (ILs) are reported as new, environmentally friendly, recyclable alternatives to dipolar aprotic solvents for organic synthesis. ILs are salts consisting of ions, which exist in the liquid state at ambient temperatures (