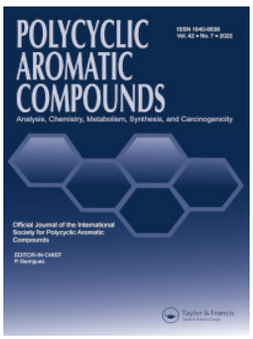


Polycyclic Aromatic Compounds

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/gpol20

Design, Synthesis, Biological Evaluation and Molecular Docking Studies of 1,4-Disubstituted 1,2,3-Triazoles: PEG-400:H_2O Mediated Click Reaction of Fluorescent Organic Probes under Ultrasonic Irradiation

Chenna Krishna Reddy Reddivari, Subba Rao Devineni, Bakthavatchala Reddy Nemallapudi, Gundala Sravya, Balakrishna Avula, Nayabrasool Shaik, Vishnu Nayak Badavath, Grigory V. Zyryanov, Rami Reddy YellalaVenkata & Naga Raju Chamarthi

To cite this article: Chenna Krishna Reddy Reddivari, Subba Rao Devineni, Bakthavatchala Reddy Nemallapudi, Gundala Sravya, Balakrishna Avula, Nayabrasool Shaik, Vishnu Nayak Badavath, Grigory V. Zyryanov, Rami Reddy YellalaVenkata & Naga Raju Chamarthi (2022) Design, Synthesis, Biological Evaluation and Molecular Docking Studies of 1,4-Disubstituted 1,2,3-Triazoles: PEG-400:H_2O Mediated Click Reaction of Fluorescent Organic Probes under Ultrasonic Irradiation, Polycyclic Aromatic Compounds, 42:7, 3953-3974, DOI: 10.1080/10406638.2021.1878246

To link to this article: https://doi.org/10.1080/10406638.2021.1878246

POLYCYCLIC AROMATIC COMPOUNDS
2022, VOL. 42, NO. 7, 3953–3974
https://doi.org/10.1080/10406638.2021.1878246

Taylor & Francis
Taylor & Francis Group

Design, Synthesis, Biological Evaluation and Molecular Docking Studies of 1,4-Disubstituted 1,2,3-Triazoles: PEG-400:H_2O Mediated Click Reaction of Fluorescent Organic Probes under Ultrasonic Irradiation

Chenna Krishna Reddy Reddivari[a], Subba Rao Devineni[a], Bakthavatchala Reddy Nemallapudi[c], Gundala Sravya[c], Balakrishna Avula[d], Nayabrasool Shaik[b], Vishnu Nayak Badavath[e], Grigory V. Zyryanov[c,f], Rami Reddy YellalaVenkata[a], and Naga Raju Chamarthi[a]

[a]Department of Chemistry, Sri Venkateswara University, Tirupati, Andhra Pradesh, India; [b]Department of Chemistry, Geethanjali Institute of Science and Technology, Nellore, India; [c]Chemical Engineering Institute, Ural Federal University, Yekaterinburg, Russian Federation; [d]Rajeev Gandhi Memorial College of Engineering and Technology (Autonomous), Nandyal, Andhra Pradesh, India; [e]Institute for Drug Research, School of Pharmacy, The Hebrew University, Jerusalem, Israel; [f]I. Ya, Postovskiy Institute of Organic Synthesis, Ural Division of the Russian Academy of Sciences, Yekaterinburg, Russian Federation

ABSTRACT

The perpetual demand of medicinally significant scaffolds has prompted the synthetic chemists to identify simple and efficient routes for flawless synthesis. A PEG-400:H_2O mediated highly versatile, efficacious and selective "Click reaction" of fluorescent organic Probes under ultrasonic irradiation is reported. 1,2,3-Triazole ring has also been revealed to play a crucial role in bioorthogonal methodologies, fragment-based drug design, and biomolecular mimetics. This methodology provides a rapid and efficient approach for the synthesis of 1,4-Disubstituted 1,2,3-triazoles under Copper (I)-Catalyzed Azide-Alkyne [3 + 2] Cycloaddition (CuAAC) conditions in good to excellent yields in less time. This synthetic protocol has been proven to endorse easy work-up under benign reaction conditions. The green solvent system employed has been efficaciously reused several times without any loss of its activity in an aqueous medium. All the title compounds were characterized by using elemental analysis, ^{1}HNMR, ^{13}CNMR, FTIR, and mass spectral data. The newly synthesized compounds were biologically evaluated for their antioxidant activity. The antioxidant activity results demonstrate that all compounds showed good to excellent antioxidant activity, particularly the compounds **5d, 8 b, 8c** and **8d** exhibited promising radical scavenging activity. Further, photophysical properties of the compounds were accomplished using spectrofluorimeter. By this method, compounds **5c, 5e, 5f, 8a, 8 b, 8c** and **8d** exhibited fluorescence in the visible region. Molecular docking studies suggested the antioxidant activity of synthesized compounds due to the inhibition of neuronal nitric oxide synthase (HnNOS).

ARTICLE HISTORY
Received 29 November 2020
Accepted 12 January 2021

KEYWORDS
Click reaction; ultrasonication; 123-triazole; antioxidant activity; photophysical properties; molecular docking studies

CONTACT Naga Raju Chamarthi rajuchamarthi10@gmail.com Department of Chemistry, Sri Venkateswara University, Tirupati, Andhra Pradesh, 517502, India.

Introduction

Heterocycles represent a fascinating class of molecules with unique properties, which have thrived on earth since time immemorial. These heterocyclic molecular components can introduce physical, chemical and biological properties to the overall assembled architectures in which they participate.[1] From the point of view of significance, heteroatoms constitute a very common fragment of a number of active pharmaceutical ingredients as well as excipients. Many heterocyclic scaffolds can be considered as privilege structures due to isosterically/bioisosterically replaced carbons/carbon substructures in aliphatic structures or real heterocycles.[2] They are also used as starting material in the synthesis of organic compounds. These are also used in sanitizers, developers, anti-ordinates, corrosion inhibitors *etc*. Heterocyclic compounds are widely found in nature, e.g., pyrimidine and purine are the parts of DNA, vitamins and enzymes. In medicinal chemistry, most frequently, nitrogen heterocycles or various positional combinations of nitrogen atoms, sulfur, and oxygen in five or six-membered rings make a lead in the invention, drug discovery, design, identification, and preparation of biologically active compounds, the study of metabolism, the interpretation of their mode of action at the molecular level and the construction of structure-activity relationships. According to statistics, more than 85% of all biologically-active chemical entities contain a heterocycle.[3] This fact reflects the central role of heterocycles in modern drug design. In fact, functionalized heterocycles can be found in a broad range of natural products like hematoporphyrin or chlorophyll, and also in non-natural molecules, with an increasing importance in medicinal chemistry, like tolmetin or atorvastatin, or fused ring junction heteroatoms with promising biological activities.[4] The manifestation of heterocycles enhances solubility, lipophilicity, polarity, and hydrogen bonding capacity of biologically active agents, which results in the optimization of the ADME/Tox properties of drugs or drug candidates.[5] The increasing presence of various heterocycles in drugs is related to advances in synthetic methodologies, such as metal-catalyzed cross-coupling and hetero-coupling reactions, that allow rapid access to a wide variety of functionalized heterocycles.[6] Thus, heterocycles have significant prominence for medicinal chemists to expand the available drug-like chemical space and drive more effective drug discovery programs. In an effort toward studying heterocyclic systems with surprisingly stable structure compared to other organic compounds, 1,2,3-Triazole have been appraised as an important class of heterocyclic compounds exhibiting a wide range of pharmacological activities. It is also known as pyrrodiazoles, and is a five-membered, diunsaturated ring system containing three nitrogen atoms in a heterocyclic core and occurs in two possible isomeric forms, 1,2,3 triazoles and 1,2,4 triazoles.

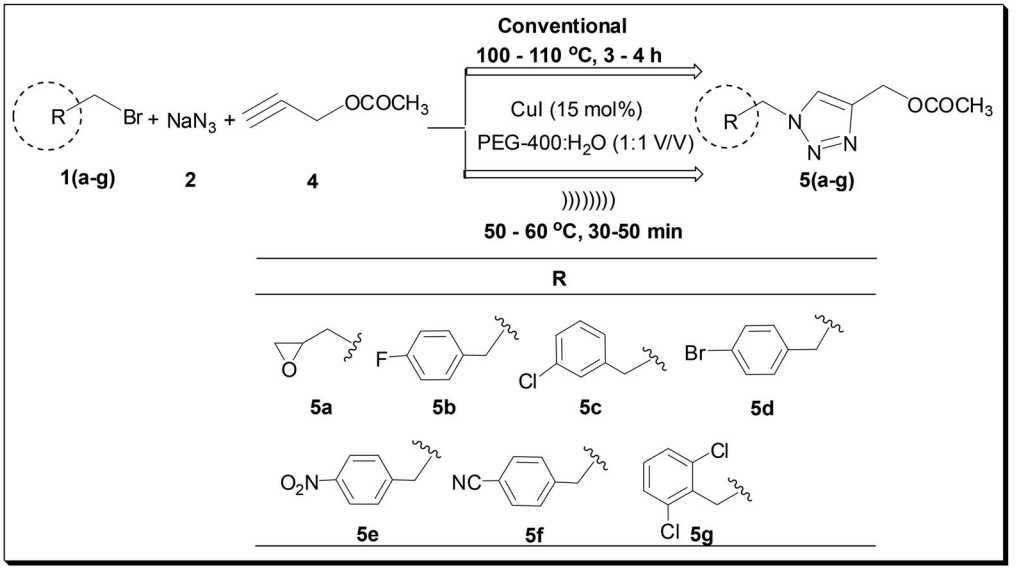
In recent years, 1,2,3-triazoles, the fragment of many marketed drugs have captivated renowned interest among the various azaheterocyclic systems by medicinal and organic chemists in modern drug discovery.[7] Among varied heterocycles, 1,2,3-triazole moiety can be prepared easily using 'click' chemistry with ruthenium or copper catalyzed azide-alkyne cycloaddition reactions that can act as the isostere of amide, ester, carboxylic acid and other heterocycles which is a common pharmacophore in many drugs and that can readily interact with diverse proteins, enzymes and receptors in organisms via weak bond interactions such as hydrophobic interactions, hydrogen bonds, and van der Waals forces.[8] 1,2,3-triazole-containing hybrids can be divided into two major categories: 1. type I, hybridization of 1,2,3-triazole moiety with other antibacterial pharmacophores with or without linker, 2. type II, two antibacterial pharmacophores tethered through 1,2,3-triazole.[9] 1,2,3-Triazole derivatives possess significant biological and pharmacological properties, inclusive of anti-Alzheimer's disease, anticancer, antimalarial, antitubercular, antiviral, and antibacterial activity. It is trustworthy that incorporation of 1,2,3-triazole moiety and other pharmacophores into one hybrid moiety can encompass the spectrum of biological activity, reduce side effects, overcome drug resistance, enhance the potency, and improve pharmacodynamics, pharmacokinetic as well as physicochemical profiles.[10] Moreover, some 1,2,3-triazole-containing hybrids such as cefatrizine, tazobactam and radezolid have already been

employed in clinics or under clinical evaluations for the treatment of infections caused by various bacteria including MRSA.[11] 1,2,3-Triazole-containing hybrids are potential inhibitors of bacterial DNA gyrase, topoisomerase IV, and efflux pump, so these compounds possess broad-spectrum activity against a panel of clinically important Gram-positive and Gram negative bacteria including drug-resistant pathogens such as MRSA, methicillin-resistant S. epidermidis (MRSE), vancomycin resistant S. aureus (VRSA), and vancomycin-resistant E. faecalis (VRE).[12] Thus, rational design of 1,2,3-triazole hybrids such as Suvorexant, Mubritinib (TAK-165) and Rufinamide containing multiple action mechanisms represents an attractive strategy to develop potential novel chemotherapeutic agents as first-line drugs.

In contrast, the derivatives of 1,2,3-triazoles possess profound applications in materials chemistry and industries such as light stabilizers, fluorescent whiteners, optical brightening agents, corrosion retardants.[13] Such 1,2,3-triazole derivatives are typically prepared by the Huisgen 1,3-dipolar cycloaddition of azides and alkynes. The reaction between an azide (1,3-dipole) and acetylenes (dipolarophiles) belonging to a concerted (one step),[14] $3+2$ cycloaddition reaction was studied methodically in early 1960s by Huisgen.[15] The Huisgen 1,3 dipolar cycloaddition reaction using azides and alkynes is an important method for the atom economic synthesis of 1,2,3-triazoles.[16] The copper(I)-catalyzed azide-alkyne cycloaddition reactions were discovered and successfully developed by Meldal and Sharpless research groups[17] and has grabbed much attention and has been popularized as 'click' chemistry concept.[18] The inertness of carbon azide and terminal alkyne reactants under favorable reaction conditions coupled with their high, specific thermodynamic reactivity toward each other creates them selective reaction partners.[19] Because Cu(I) (directly used or *in situ* generated) was found to greatly increases the reaction rates and governs the regioselectivity, favouring1,4-disubstituted 1,2,3-triazole formation.

In most recent times, fluorescence-based organic probes are being aided as a tool for in vitro imaging of biomolecules due to their prominence such as high sensitivity, convenient operation, low cost, no need for pretreatment and noninvasive detection and have attracted wide attention in various fields including life science, medicine, pharmacology and analytical chemistry. In biomedicine, these probes are used for the detection of a wide range of significant biomarkers and are essential for the diagnosis of critical diseases.[20] Selective and accurate determinations of specific enzymes, including β-galactosidase,[21] exoglycosidases,[22] cyclooxygenases,[23] and materials development and others,[24] have been achieved using the OFF–ON-type fluorogenic probes with fluorescence that can be turned on by enzymatic transformations. Several Fluorescence-based organic probes have been used in biomedical imaging for decades, in techniques such as positron emission tomography (PET), magnetic resonance imaging (MRI) or single-photon emission computerized tomography (SPECT). The Fluorescence-based organic probes are usually large because of presence of fused heterocyclic rings and these complexes are often named *theranostics*, due to their applications as both a therapy and a diagnostics tool. Herein, we report a "click reaction" as an effective approach for the development of fluorescent molecules and establishing their photophysical properties as shown in few advanced fluorogenic dyes like coumarin,[25] anthracene[26] and naphthalimide derivatives.[27]

In many pathophysiological conditions, the superfluous production of ROS overwhelms the natural antioxidant defense mechanisms. This imbalance is termed oxidative stress. Oxidative stress has been associated with the inflammation process. ROS, like superoxide radical anion, hydrogen peroxide, and hydroxyl radical, are produced during the inflammation process by phagocytic leukocytes (e.g., neutrophils, monocytes, macrophages, eosinophils) that invade the tissue. The formation of reactive oxygen species (ROS) is typical characteristic of aerobic organisms that can normally defend themselves against these highly reactive species using enzymes, like superoxide dismutase and glutathione peroxidase, and naturally occurring antioxidants, such as R-tocopherol (vitamin E), ascorbic acid (vitamin C), and $\hat{a}$-carotene. Moreover, these reactive species are involved in the biosynthesis of prostaglandins and in the cycloxygenase and

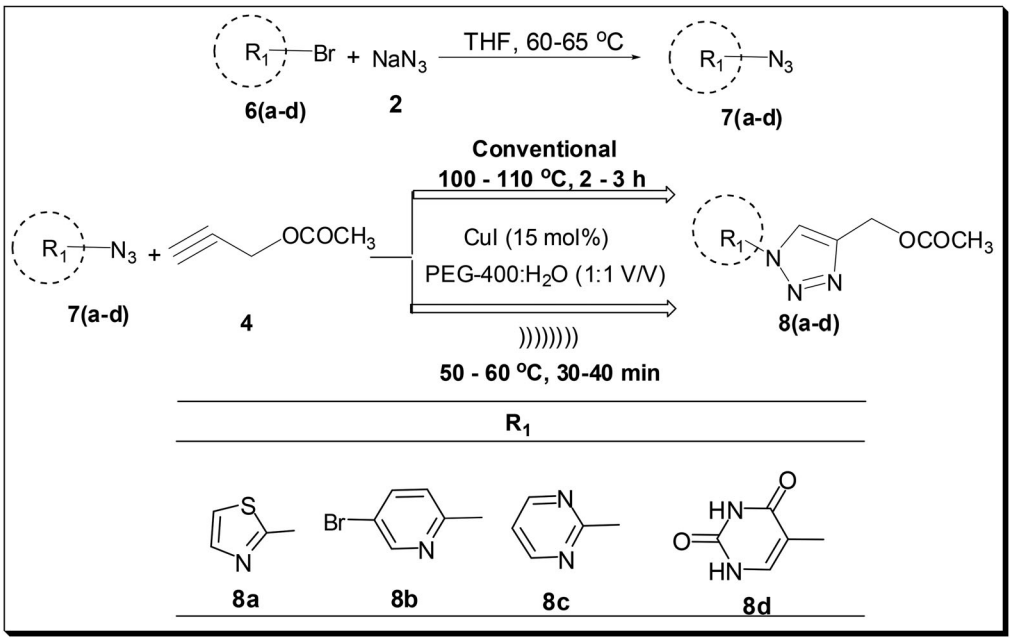


Scheme 1. Ultrasonicated three-component one-pot synthesis for triazoles.

lipoxygenase mediated conversion of arachidonic acid into proinflammatory intermediates. In addition, ROS may initiate inflammation via up regulating several different genes involved in this process by activating certain redox-sensitive transcription factors as the nuclear factor kB (NFkB) and activator protein-1 (AP-1). Many disease manifestations such as cancer, emphysema, cirrhosis, atherosclerosis and arthritis have been correlated with oxidative tissue damage.[28] Also, excessive generation of reactive oxygen species (ROS) induced by various stimuli leads to variety of pathophysiological abnormalities such as inflammation, diabetes, genotoxicity and osteoporosis.[29] Moreover, among several heterocycles, 1,2,3-triazoles,[30] 1,2,4-triazoles and benztriazole moiety possess a good antioxidant activity.[31]

With the recent development of green and sustainable chemistry, chemists are inspired to develop alternative protocols to minimize the drawbacks which are faced in conventional and industrialized methods. Based on recent investigations in organic synthesis, Ultrasonic irradiation represents a powerful synthetic protocol for accelerating the organic transformations proceeding with high yields, short reaction times and mild reaction conditions. Further, in order to overcome stringent environmental problems, employing polyethylene glycols (PEG) as reaction media has engrossed much attention in chemical and pharmaceutical industries as green solvent system. Because PEG is environmentally benign, economy, nontoxic, and its properties can be tuned by changing molecular weight. Different reactions in PEGs have been studied, such as polymerization, substitution reaction, oxidation reactions, and cross-coupling reactions, etc and its applications have been explored in various fields such as biotechnology and medicinal chemistry. With our continuous interest in the development of competent synthetic approaches, we have developed a highly efficient and rapid synthetic methodology of ultrasonic mediated synthesis of a new series of 1,4-disubstituted-1,2,3-triazoles in good to excellent yields in less reaction time (30-53 min) using co-solvent H_2O:PEG-400 (1:1 v/v) in the presence of CuI (15 mol%) as a catalyst. Antioxidant and photophysical properties of the newly synthesized compounds were evaluated (Scheme 1 and 2).

Nitric oxide (NO) is generated by nitric oxide synthases, which regulates the relaxation of smooth muscle and release of neurotransmitters and involved in neuronal communication. Over production of NO in the central nervous system has been reported to be associated with chronic



Scheme 2. Ultrasonicated two-component one-pot synthesis for triazoles.

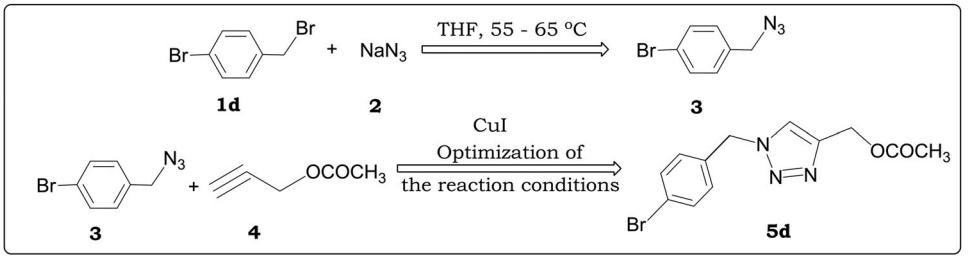
neurodegenerative pathogenesis, such as Alzheimer's disease, Parkinson's disease and Huntington's disease Therefore, inhibition of nNOS is a viable therapeutic strategy for treating neurodegenerative disorders. Peroxiredoxins regulate the levels of reactive oxygen species in cells leading to cell damage and necrotic or apoptotic cell death. Molecular docking studies carried out to understand the binding mode analysis of compound in to the active site of human neuronal nitric oxide synthase and peroxiredoxin 5.

Results and discussion

Chemistry

Our experiment commenced with the condensation of commercially available chemicals by employing a three-component reaction of sodium azide, aryl or alkyl halides (bromides) and prop-2-ynyl acetate for the synthesis of triazole derivatives in H_2O:PEG-400 (1:1 v/v) solvent system in the presence of CuI catalyst under ultrasonication conditions which were readily converted by using Huisgen 1,3 dipolar cycloaddition reaction. To optimize 1,3-dipolar cycloaddtion reaction, the synthesis of 1,4-disubstituted triazole derivatives, 1-(azidomethyl)-4-bromobenzene **(3)** and prop-2-ynyl acetate **(4)** were taken as substrates (Scheme 3). The former intermediate **(3)** could be generated from sodium azide **(2)** and 1-(bromomethyl)-4-bromobenzene **(1d)** in THF. Considering the anticipated role of copper catalysts for the construction of the triazoles, a catalytic proportion of copper(I) iodide was preferred as a catalyst.

To understand the role and efficacy of green solvent systems comparatively, various solvents were employed such as 1,4-dioxane, CH_3CN, DMF, H_2O, EtOH and PEG-400 under mild temperature conditions, we found that most befitting solvent system was PEG-400 and H_2O which favor the formation of the product, (1-(4-bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl acetate **(5d)** in good yields using 15 mol% of CuI catalyst under conventional conditions at 70–90 °C. After conducting the reaction with other solvents and solvent-free conditions very moderate yield was



Scheme 3. Optimization of the reaction conditions for the synthesis of triazole derivatives.

Table 1. Optimization of solvent for the synthesis of triazole(**5d**).[a]

Entry	Solvent	Condition	Temp (°C)	Time	Yield (%)
1.	1,4-Dioxane	Conventional	80	2.5 h	64
2.	CH_3CN	Conventional	80	2.5 h	53
3.	DMF	Conventional	90	2.5 h	67
4.	H_2O	Conventional	85	2.5 h	70
5.	EtOH	Conventional	65	3.0 h	65
6.	PEG-400	Conventional	90	2.5 h	81
7.	No solvent	Conventional	80	3.0 h	45
8.	PEG-400:H_2O (1:1 v/v)	Conventional	85	2.0 h	85
9.	PEG-400:H_2O (1:2 v/v)	Conventional	85	2.0 h	83
10.	PEG-400:H_2O (1:3 v/v)	Conventional	85	2.0 h	79
11.	PEG-400:H_2O (1:4 v/v)	Conventional	85	2.0 h	74
12.	PEG-400:H_2O (1:1 v/v)	Conventional[b]	75	2.0 h	87
13.	PEG-400:H_2O (1:1 v/v)	Ultrasonication	Rt	40 min	84
14.	PEG-400:H_2O (1:1 v/v)	Ultrasonication	40	30 min	89
15.	PEG-400:H_2O (1:1 v/v)	Ultrasonication	50	30 min	90
16.	PEG-400:H_2O (1:1 v/v)	Ultrasonication	60	30 min	88

(**a**)-1-(Azidomethyl)-4-bromobenzene **(3)** and prop-2-ynyl acetate **(4)** were taken as models to optimization for the synthesis of triazole derivative;
(**b**)-1-(Bromomethyl)-4-bromobenzene **(1d),** sodium azide**(2)** and prop-2-ynyl acetate **(4)** were selected as models to optimization for the synthesis of triazole derivative.

observed (entry 1-8, Table 1). The individual results in PEG-400 and H_2O for the synthesis of triazole derivatives encouraged to examine the model reaction in co-solvent system of them. The model reaction was examined in various ratio of combinations of PEG-400:H_2O (1:1, 1:2, 1:3 and 1:4 v/v) solvent systems. The experimental results (entry 9-12, Table 1) disclosed that the reaction was effectively carried out in 1:1 (v/v) ratio of PEG-400:H_2O solvent system as compared with other co-solvents system, and individual solvents. Slight decrease in the yield of the product was identified when increasing water content in the solvent system. Therefore, 1:1 (v/v) ratio of PEG-400:H_2O solvent system was optimized. To our delight, we have tried the reaction of the combination of three-components of 1-(bromomethyl)-4-bromobenzene **(1d),** sodium azide **(2)** and prop-2-ynyl acetate **(4)** in one-pot under this optimized reaction conditions (entry 15, Table 1). Remarkably, the desired product was obtained but no significant yield difference was observed as compared with two-component reaction.

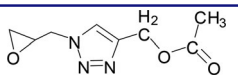
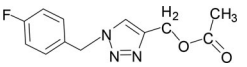
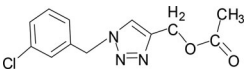
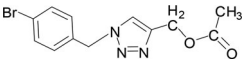
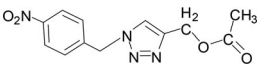
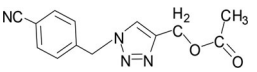
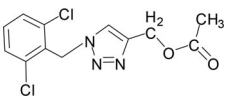
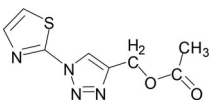
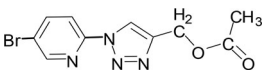
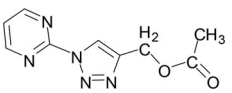
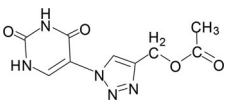
In complementary to our interest, virtuous outcomes have been noticed in employing sonication to obtain the products with high yields in less reaction time, the optimized reaction condition was examined in ultrasonication and also scrutinized the temperature effect on the reaction (entry 14-16, Table 1). The results revealed that in ultrasonication at 50 °C high yield of the product **5d** was obtained in less reaction time (30 min) over conventional conditions.

Further, the amount of catalytic effect on the model reaction was investigated by loading the catalyst in various mol% ratio (entry 1-5, Table 2). As can be seen in Table, 15 mol% of the catalyst, CuI was carried out the reaction promisingly. By enhancing the catalyst more than 15 mol%

Table 2. Amount of the catalyst effect for the synthesis of triazole **(5d)**.

Entry	Catalyst	Time[a/b]	Yield (%)[a/b]
1.	5 mol% of CuI	2.5 h/35 min	70/78
2.	10 mol% of CuI	2.5 h/35 min	82/89
3.	15 mol% of CuI	2.5 h/35 min	86/90
4.	20 mol% of CuI	2.5 h/35 min	89/94
5.	25 mol% of CuI	2.5 h/35 min	89/95

Table 3. Physical properties of the newly synthesized triazole compounds **5(a-g)** and **8(a-d)**.[32]

		Conventional conditions		Ultrasonication conditions	
Compd	Structure	Time	Yield (%)	Time	Yield (%)
5a		2.5 h	85	30 min	91
5b		2.0 h	88	30 min	91
5c		3.0 h	83	45 min	89
5d		2.5 h	86	35 min	90
5e		2.0 h	88	30 min	93
5f		2.5 h	84	30 min	91
5g		2.5 h	85	30 min	94
8a		3.0 h	83	40 min	90
8b		3.0 h	84	40 min	89
8c		3.0 h	85	40 min	91
8d		3.0 h	82	50 min	87

of the catalyst, CuI did not lead the reaction effectively. After optimization of the reaction conditions, generality was checked by altering aryl methyl bromides (Scheme 3) and the results are given in Table 3.This ultrasound sonication not only fetches formation of high yields of the products through the click reaction, but also promotes the activity of the catalytic species and completion of the reaction in short reaction times.

In the examination of generality, we have used some bromide entities in which bromide is directly attached to heteroaryl ring resulted in low yield of the desired product after a long reaction time under assigned reaction conditions. While using the corresponding heteroarylazides **7(a-d)** andprop-2-ynyl acetate **(4)** high yields of the products in less reaction times (Scheme 2) were obtained and the results are tabulated in Table 3. Hetero aryl azides were synthesized from the corresponding bromides and sodium azide in THF at refluxing conditions for 3–5 h.

Experimental

Apparatus and analysis

All chemicals, reagents and solvents used for the synthesis were commercially available, and AR grade and were used as such received from Sigma-Aldrich, Merck and Sd Fine Chem. Merck silica plates were used for the examination of progress of the reaction and spots were visualized with UV light. Column chromatography was used for the purification of the synthesized products. All melting points (m.p) were obtained with a digital Guna melting point apparatus and are uncorrected. IR spectra were recorded on a Alpha-T FTIR spectrophotometer. $^{1}H/^{13}C$ NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer operating at 400 MHz for ^{1}H in $CDCl_3$ and 100.25 MHz for ^{13}C in DMSO solvent and TMS was used as internal standard. Chemical shift values (δ) and coupling constants (J) are reported in ppm and Hz respectively.LC-MS was recorded on 2010 A (SHIMADZU) using positive mode and elemental analysis were performed on a Thermo Finnigan Instrument at University of Hyderabad, Hyderabad.

Sonication was performed using BANDELIN SONOREX® (Germany make) with a frequency of 35 kHz and a nominal power 200 W ultrasonic bath for ultrasonic irradiation with inbuilt heating 30-80 °C, which is thermostatically adjustable. The reaction vessel was placed inside the ultrasonic bath containing water.

Synthetic procedure for the synthesis of triazole derivatives

Conventional conditions

1-(Bromomethyl)-4-bromobenzene **(1d)** (1.0 mmol, 249 mg),sodium azide **(2)** (1.2 mmol, 78 mg), prop-2-ynyl acetate **(4)**(1.0 mmol, 98 mg) and CuI (15 mol%) were taken into 50 mL round bottomed flask containing 4 mL of PEG-400:H_2O (1:1 v/v) and stirred at 60–70 °C for 2.0 h. The progress of the reaction was monitored by TLC. After completion of the reaction as monitored by TLC, the reaction mass was diluted with water (15 mL) and the solid product, (1-(4-bromobenzyl)-1*H*-1,2,3-triazol-4-yl)methylacetate **(5d)** was filtered-off and then washed with brine water. The pure product, **5d**was dried under vacuum and characterized by spectroscopic data. The same procedure was employed for the synthesis of rest of 1,4-disubstituted-1*H*-1,2,3-triazole derivatives.

Some of the products were extracted with ethyl acetate (3 × 15 mL) from the reaction mass and the organic layer was washed with water and then dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure to obtain 1,4-disubstituted-1*H*-1,2,3-triazole derivatives.

Ultrasonication method

1-(Bromomethyl)-4-bromobenzene **(1d)**(1.0 mmol, 249 mg),sodium azide **(2)**(1.2 mmol, 78 mg), prop-2-ynyl acetate **(4)**(1.0 mmol, 98 mg) and CuI (15 mol%) were taken into 50 mL round bottomed flask containing 4 mL of PEG-400:H_2O (1:1 v/v). The reaction mass was stirred at 40 °C for 30 min under ultrasonication conditions. The progress of the reaction was monitored by TLC. After completion of the reaction as checked by TLC, the reaction mass was diluted with water (15 mL) and the solid product, (1-(4-bromobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl acetate **(5d)** was

filtered-off and then washed with brine water. The pure product, **5d**was dried under vacuum and characterized by spectroscopic data. The same procedure was adopted for the synthesis of remaining title triazole derivatives.

(1-(Oxiran-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl acetate (5a)

White solid,Yield: 91%, mp 85–87 °C.IR (KBr, υ cm^{-1}): 2950 (=C–H, str), 1715 (C–O, str), 1520 (N = N, str).^{1}H NMR ($CDCl_3$) δ 7.59 (s, 1H, CH, Triazole), 5.71 (s, 2H, CH_2), 3.99 (d, J = 6.0 Hz,2H, CH_2), 3.14-3.64 (m, 1H, CH (Oxirane)), 2.94 (d, J = 5.6 Hz, 2H, CH_2, Oxirane), 2.42 (s,3H,CH_3).^{13}C NMR (DMSO) δ 170.1, 141.5, 126.8, 62.1, 55.4, 46.5, 45.5, 20.9. MS (positive) m/z (%): 198 $[M+H]^+$ (100%).Anal.Calcd for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31; Found: C, 48.68; H, 5.58; N, 21.23.

(1-(4-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl acetate (5b)

Light brown solid, Yield: 91%, mp 93–95 °C.IR (KBr, υ cm^{-1}):2963 (=C–H, str), 1718 (C–O, str), 1508 (N = N, str).^{1}H NMR ($CDCl_3$) δ 7.53 (s, 1H,CH, Triazole) 7.27 (d, 2H, J = 8.4 Hz, Ar-H), 7.08 (d, 2H, J = 8.4 Hz, Ar-H) 5.50 (s, 2H, CH_2), 5.19 (s, 2H, CH_2), 2.11 (s, 3H, CH_3).^{13}C NMR (DMSO) δ 170.0, 160.7 (d, J = 148.6 Hz), 144.7, 132.1, 130.3, 124.6, 116.2, 57.0, 51.8, 20.5.MS (positive) m/z (%): 250 $[M+H]^+$ (100%).Anal.Calcd for $C_{12}H_{12}FN_3O_2$: C, 57.83; H, 4.85; N, 16.86; Found: C, 57.76; H, 4.82; N, 16.78.

(1-(3-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl acetate (5c)

White solid,Yield: 89%, mp 91–93 °C.IR (KBr, υ cm^{-1}): 2895 (=C–H, str), 1709 (C–O, str), 1482 (N = N, str).^{1}H NMR ($CDCl_3$) δ 7.69 (s, 1H,CH, Triazole) 7.56 (s, 1H, Ar-H), 7.32 (d, J = 8.0 Hz, 1H, Ar-H) 7.20-7.30 (m, 2H, Ar-H), 5.51 (s, 2H, CH_2), 5.21 (s, 2H, CH_2), 2.08 (s, 3H, CH_3).^{13}C NMR (DMSO) δ 170.70, 143.68, 138.19, 134.52, 132.05, 129.82, 126.67, 125.50, 123.08, 59.27, 54.53, 20.19. MS (positive) m/z (%): 268 $[M+2+H]^+$ (32.8%), 266 $[M+H]^+$ (100%). Anal. Calcd for $C_{12}H_{12}ClN_3O_2$: C, 54.25; H, 4.55; N, 15.82; Found: C, 54.17; H, 4.65; N, 15.76.

(1-(4-Bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl acetate (5d)

White amorphous solid,Yield: 90%,mp 92–94 °C.IR (KBr, υ cm^{-1}): 2964 (=C–H, str), 1730 (C–O, str), 1485 (N = N, str).^{1}H NMR ($CDCl_3$) δ 7.83 (d, 2H, J = 7.6 Hz, Ar-H), 7.55 (s, 1H, CH, Triazole), 7.26 (d, 2H, J = 8.0 Hz, Ar-H) 5.47 (s, 2H, CH_2), 5.18 (s, 2H, CH_2,) 2.06 (s, 3H, CH_3).^{13}C NMR (DMSO) δ 170.3, 142.9, 137.0, 133.0, 132.1, 123.8, 122.6, 60.4, 52.3, 20.5.MS (positive) m/z (%):310 $[M+H]^+$ (100%).Anal.Calcd for $C_{12}H_{12}BrN_3O_2$: C, 46.47; H, 3.90; N, 13.55; Found: C, 46.41; H, 3.85; N, 13.52.

(1-(4-Nitrobenzyl)-1H-1,2,3-triazol-4-yl)methyl acetate (5e)

Brown solid,Yield: 93%,mp 97–99 °C.IR (KBr, υ cm^{-1}): 2890 (=C–H, str), 1710 (C–O, str), 1526 (N = N, str).^{1}H NMR ($CDCl_3$) δ 8.16 (d, 2H, J = 7.6 Hz, Ar-H), 7.61 (s, 1H, CH, Triazole) 7.53 (d, 2H, J = 7.6 Hz, Ar-H), 5.50 (s, 2H, CH_2), 5.46 (s, 2H, CH_2), 2.20 (s, 3H, CH_3).^{13}C NMR (DMSO) δ 171.0, 145.5, 143.0, 142.6, 130.2, 124.6, 121.1, 61.4, 54.6, 20.9.MS (positive) m/z (%): 277 $[M+H]^+$ (100%).

(1-(4-Cyanobenzyl)-1H-1,2,3-triazol-4-yl)methyl acetate (5f)

Light brownsolid,Yield: 91%, mp 95–97 °C.IR (KBr, υ cm^{-1}): 2943 (=C–H, str), 1730 (C–O, str), 1505 (N = N, str). ^{1}H NMR ($CDCl_3$) δ 7.56 (s, 1H,CH, Triazole), 7.58 (d, 2H, J = 8.0 Hz, Ar-H),

7.40 (d, 2H, J = 8.0 Hz, Ar-H) 5.49 (s, 2H, CH_2), 5.36 (s, 2H, CH_2), 2.27 (s, 3H, CH_3).^{13}C NMR (DMSO) δ 170.0, 143.8, 141.2, 132.6, 128.7, 125.2, 118.4, 111.0, 57.0, 52.2, 20.5.MS (positive) m/z (%): 257 $[M+H]^+$ (100%).Anal. Calcd for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.86; Found: C, 60.87; H, 4.65; N, 21.80.

(1-(2,6-Dichlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl acetate (5g)

Light Yellow solid,Yield: 94%, mp 99–101 °C.IR (KBr, υ cm^{-1}): 2950 (=C–H, str), 1705 (C–O, str), 1560 (N = N, str).^{1}H NMR ($CDCl_3$) δ 7.64 (s, 1H, CH, Triazole) 7.51 (d, 2H, J = 7.2 Hz Ar-H), 7.42 (t, J = 7.6 Hz, 1H, Ar-H) 5.87 (s, 2H, CH_2), 5.18 (s, 2H, CH_2), 2.18 (s, 3H, CH_3).^{13}C NMR (DMSO) δ 170.0, 142.5, 139.0, 137.1, 129.3, 126.7, 126.1, 122.9, 60.5, 48.5, 20.4. MS (positive) m/z (%): 302 $[M+2+H]^+$ (63.62%), 300 $[M+H]^+$ (100%).

(1-(Thiazol-2-yl)-1H-1,2,3-triazol-4-yl)methyl acetate (8a)

Amorphous white solid,Yield: 90%, mp 81–83 °C.IR (KBr, υ cm^{-1}): 2935 (=C–H, str), 1720 (C–O, str), 1450 (N = N, str).^{1}H NMR ($CDCl_3$) δ 8.13 (s, 1H, CH, Triazole) 7.74 (d, J = 6.8 Hz, 1H, Thiazol), 7.61 (d, J = 6.8 Hz,Thiazol), 5.51 (s, 2H, CH_2), 2.23 (s, 3H, CH_3).^{13}C NMR (DMSO) δ 170.4, 155.6, 144.5, 140.3, 120.7, 118.8, 60.9, 21.3.MS (positive) m/z (%): 225$[M+H]^+$ (100%).Anal.Calcd for $C_8H_8N_4O_2S$: C, 42.85; H, 3.60; N, 24.99; Found: C, 42.78; H, 3.55; N, 24.91.

(1-(5-Bromopyridin-2-yl)-1H-1,2,3-triazol-4-yl)methyl acetate (8b)

White solid, Yield: 89%, mp 96–98 °C. IR (KBr, υ cm^{-1}): 2932 (=C–H, str), 1727 (C–O, str), 1557 (N = N, str). ^{1}H NMR ($CDCl_3$) δ 8.49 (d, J = 7.6 Hz, 1H, Ar-H) 8.28 (s, 1H, CH, Triazole) 8.14 (s, 1H, Ar-H), 7.45 (d, J = 8.0 Hz, 1H, Ar-H) 5.53 (s, 2H, CH_2), 2.08 (s, 3H, CH_3). ^{13}C NMR (DMSO) δ 170.4, 152.2, 143.3, 142.8, 141.6, 134.5, 130.4, 118.8, 60.8, 20.7. MS (positive) m/z (%): 297 $[M+H]^+$ (100%).

(1-(Pyrimidin-2-yl)-1H-1,2,3-triazol-4-yl)methyl acetate (8c)

Light yellow solid,Yield: 91%, mp 99–101 °C.IR (KBr, υ cm^{-1}): 2942 (=C–H, str), 1721 (C–O, str), 1506 (N = N, str).^{1}H NMR ($CDCl_3$) δ 8.37 (d, 2H, J = 7.6 Hz, Ar-H) 8.14 (s, 1H, CH, Triazole) 7.85 (t, J = 8.0 Hz, 1H, Ar-H), 5.38 (s, 2H, CH_2), 2.23 (s, 3H, CH_3).^{13}C NMR (DMSO) δ 170.4, 157.3, 146.1, 142.3, 122.2, 119.0, 60.2, 21.1.MS (positive) m/z (%): 220 $[M+H]^+$ (100%).Anal.Calcd for $C_9H_9N_5O_2$: C, 49.31; H, 4.14; N, 31.95; Found: C, 49.27; H, 4.11; N, 31.83.

(1-(2,4-Dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1H-1,2,3-triazol-4-yl)methyl acetate (8d)

Yellow solid, Yield: 82%, mp 97–99 °C.

IR (KBr, υ cm^{-1}): 2960 (=C–H, str), 1725 (C–O, str), 1450 (N = N, str).^{1}H NMR ($CDCl_3$) δ 11.10 (s, 1H, NH) 10.92 (s, 1H, NH), 7.87 (s, 1H, Pyrimidine), 7.81 (s, 1H, Triazole), 5.46 (s, 2H, CH_2) 2.25 (s, 3H, CH_3).^{13}C NMR (DMSO) δ 170.2, 168.9, 155.2, 144.0, 138.6, 120.8, 119.0, 60.6, 20.5.MS (positive) m/z (%): 252 $[M+H]^+$ (100%).Anal. Calcd for $C_9H_9N_5O_4$: C, 43.03; H, 3.61; N, 27.88; Found: C, 42.99; H, 3.58; N, 27.79.

Biological activity

The newly synthesized triazole derivatives **5(a-g)** and **8(a-d)** were evaluated for their antioxidant activity, molecular docking studies and photophysical properties.

Table 4. DPPH radical scavenging activity of the synthesized triazoles **5d**, **8b**, **8c** and **8d**.

		% of DPPH radical scavenging activity			
S. No	Compd.	25 μg/mL	50 μg/mL	75 μg/mL	100 μg/mL
1	**5d**	52.20 ± 2.52	61.33 ± 1.50	67.66 ± 1.24	76.04 ± 2.64
2	**8b**	50.26 ± 2.55	58.53 ± 1.11	62.66 ± 1.60	75.83 ± 2.91
3	**8c**	48.63 ± 2.05	55.50 ± 2.06	66.63 ± 1.59	73.13 ± 2.56
4	**8d**	46.03 ± 1.40	57.10 ± 2.55	64.53 ± 1.23	71.90 ± 2.02
5	**Std.**	54.56 ± 1.02	63.70 ± 1.70	69.00 ± 2.76	78.03 ± 2.90

Std.- Standard- Butylatedhydroxytoluene.

Antioxidant activity

1,1-Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging method

All the synthesized triazole derivatives **5(a-g)** and **8(a-d)** were evaluated for their antioxidant activity using DPPH method.[33] The tested samples were prepared in different concentrations (25, 50, 75, 100 μg/mL) in methanol (MeOH) and homogeneity of the test samples were attained using magnetic stirrer. DPPH solution was prepared in methanol and adjusted its concentration to 0.004% (w/v) by adding MeOH. The DPPH solution (4 mL, 0.004% (w/v)) was added to the aliquot of standard solution (BHT) and tested sample solutions (1 mL of each) of various concentrations in a set of test tubes, and shaken vigorously, and kept the solutions for 30 min. in the dark to complete the reaction. Then, the absorbance of the tested samples was measured by a UV/visible spectrophotometer against blank at 517 nm. The synthetic antioxidant, BHT was used as positive control. The scavenging capacity of DPPH radicals were calculated using the following equation. The experiment was repeated in triplicate and the average values are taken as final result (Table 4).

% of radical scavenging $= [A_{\text{control}} - A_{\text{sample}}/A_{\text{control}}] \times 100$where A_{control} is the absorbance of the control (DPPH solution without the test compound) and A_{sample} is the absorbance of the test sample (DPPH solution with the test compound solution).

Half maximal inhibitory concentration (IC_{50})

The compound concentration corresponding at which growth is inhibited by 50% with the control is IC Inhibitory concentration, IC_{50} of the test compound.This quantitative measure indicates how much of a particular drug or other substance is needed to inhibit a given biological process by half. The IC_{50} value was evaluated for the title compounds **5(a-g)** and **8(a-d)** using DPPH method. Different concentrations of the titled compounds were prepared based on the above tested results (with difference 1 mL of each). The DPPH solution (4 mL, 0.004% (w/v)) was added to aliquot of standard solution (BHT) and tested sample solutions (1 mL of each) of various concentrations in the set of the test tubes, and shaken vigorously, and kept the solutions for 30 min. in the dark to complete the reaction. Then the absorbance of the tested samples was measured against blank at 517 nm. The synthetic antioxidant, BHT was used as positive control. Concentration of the tested compound was recorded at which inhibited the given biological process by half (Table 5).

In the case of triazole derivatives **5(a-g)** and **8(a-d)**, **5d**, **8 b**, **8c** and **8d** showed the highest DPPH radical scavenging activity. The remaining compounds exhibited minimal activity when compared to the above derivatives. The DPPH radical scavenging activity with IC_{50} of **5d**, **8 b**, **8c** and **8d** exhibited in the following order: **5d** (IC_{50} 23.98 ± 1.17 μg/mL), **8 b** (IC_{50} 24.91 ± 1.28 μg/mL), **8c** (IC_{50} 25.73 ± 1.09 μg/mL), **8d** (IC_{50} 27.17 ± 0.82 μg/mL) and when compared with Butylated hydroxytoluene (IC_{50} 22.91 ± 0.43 μg/mL). This may be due to presence of a bromine atom on heterocyclic ring or a ∏-system adjacent to halogen atom increases lipophilicity can strongly polarize the parent molecule and seems to have profound effect on biological properties of title compounds.

Table 5. Half-maximal concentrations (IC_{50}) of the titled compounds **5(a-g)** and **8(a-d)**.

S. No	Compd.	Concentration (μg/mL)
1	**5d**	23.98 ± 1.17
2	**8b**	24.91 ± 1.28
3	**8c**	25.73 ± 1.09
4	**8d**	27.17 ± 0.82
5	**Std.**	22.91 ± 0.43

Std.- Standard- Butylated hydroxytoluene.

Table 6. NO radical scavenging activity of the synthesized compounds **5d, 8b, 8c** and **8d**.

		% of NO radical scavenging activity			
S. No	Compd.	25 μg/mL	50 μg/mL	75 μg/mL	100 μg/mL
1	**BHT**	32.80 ± 1.10	41.26 ± 1.70	46.33 ± 1.50	53.33 ± 1.50
2	**5d**	30.46 ± 2.15	39.50 ± 2.10	42.23 ± 1.90	50.56 ± 1.40
3	**8b**	28.10 ± 1.90	37.43 ± 2.20	41.03 ± 1.68	48.33 ± 2.00
4	**8c**	26.20 ± 1.85	31.03 ± 1.68	38.53 ± 2.11	45.13 ± 1.62
5	**8d**	24.10 ± 2.35	27.20 ± 1.92	34.26 ± 2.05	41.93 ± 1.75

Std.- Standard- Butylatedhydroxytoluene.

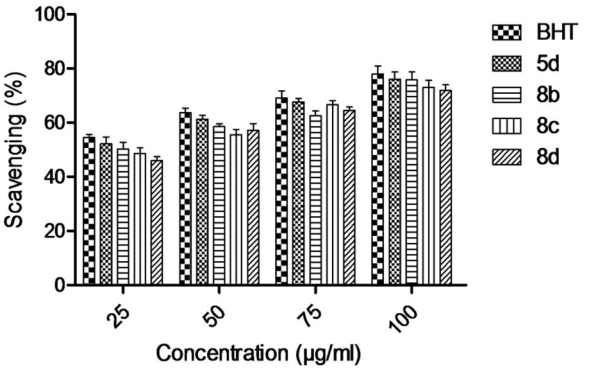
Nitric oxide (NO) radical scavenging method

Nitric oxide radical scavenging activity of the synthesized triazole derivatives **5(a-g)** and **8(a-d)** was screened using Green *et al.* and Marcocci *et al.* modified method.[34] The homogeneous tested samples, the title compounds and synthetic antioxidant, butylatedhydroxytoluene (BHT) in various concentrations (50 and 100 μg/mL) were prepared in methanol (MeOH). Nitric oxide radicals (NO) were generated from 1 mL of sodium nitroprusside (10 mM) and 1.5 mL of phosphate buffer saline (0.2 M, pH 7.4) were added to different concentrations of the test samples in a set of test tubes and incubated for 150 min. at 25 °C. 1 mL of the reaction mixture was treated with 1 mL of Griess reagent (1% sulfanilamide, 3% H_3PO_4 and 0.1% naphthyl ethylene diamine-dihydrochloride). The absorbance of the chromophore was measured at 546 nm. The scavenging capacity of NO radicals was calculated. The experiment was carried out in triplicate and the average value was taken as final result (Table 6).

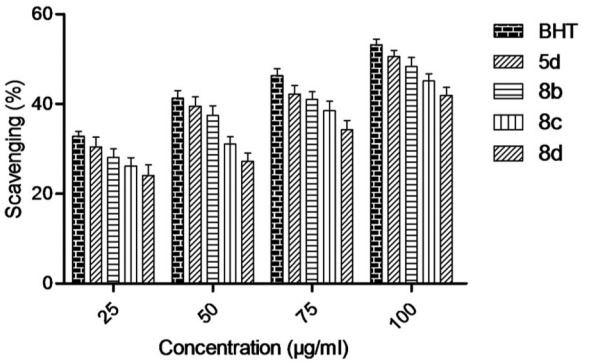
$$\% \text{ of radical scavenging} = [A_{\text{control}} - A_{\text{sample}}/A_{\text{control}}] \times 100$$

where $A_{control}$ is the absorbance of the control (NO solution without the test compound) and A_{sample} is the absorbance of the test sample (NO solution with the test compound solution). In the case of triazole derivatives **5(a-g)** and **8(a-d)**, **5d**, **8 b**, **8c** and **8d** showed the highest NO scavenging activity. The remaining compounds exhibited good to moderate activity. The reducing power activity with IC_{50} of **5d**, **8 b**, **8c** and **8d** exhibited in the following order: **5d** (IC_{50} 98.94 ± 3.23 μg/mL), **8b** (IC_{50} 103.72 ± 4.51 μg/mL), **8c** (IC_{50} 110.89 ± 4.25 μg/mL), **8d** (IC_{50} 119.38 ± 4.98 μg/mL) and when compared with Butylated hydroxytoluene (IC_{50} 93.79 ± 2.63 μg/mL).

The newly synthesized triazole derivatives **5(a-g)** and **8(a-d)** were evaluated for their antioxidant activity using DPPH, NO radical scavenging activity methods, and also examined for their half-maximal concentrations (IC_{50}). The experimental data (Table 4, Graph 1, Table 5, Table 6, Graph 2 and Table 7) displayed that the synthesized compounds have good to moderate radical scavenging activity in all the tested methods. Among the tested compounds, compound **5d** having 4-bromobenzylic entity (37.0 μg/mL), and **8 b** bearing 4-bromo-2-pyridine (43.0 μg/mL), **8c** substituted with pyrimidine-2-yl(44.5 μg/mL) and **8d** linked with 2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl (48.0 μg/mL) exhibited promising radical scavenging activity. In over all observation, brominated and nitrogen heterocycles linked derivatives exhibited good antioxidant activity.



Graph 1. DPPH radical scavenging activity.



Graph 2. NO radical scavenging activity.

Table 7. Half-maximal concentrations (IC_{50}) of the titled compounds **5d, 8b, 8c** and **8d**.

S. No	Compd.	Concentration (µg/mL)
1	**5d**	98.94 ± 3.23
2	**8b**	103.72 ± 4.51
3	**8c**	110.89 ± 4.25
4	**8d**	119.38 ± 4.98
5	**Std.**	93.79 ± 2.63

Molecular docking studies procedure

Docking studies were carried out against x-ray crystal structure of human neuronal nitric oxide synthase (PDB ID: 5FVP) and peroxiredoxin 5 (PDB ID: 1HD2), using AutoDock 4.2. Ligand structures were drawn using build panel and prepared using Ligprep module implemented Maestro-8.4 (Schrodinger LLC). Energy minimization is carried out using OPLS-2005 force field. Structures were saved in .pdb format and rewritten using open bable for AutoDock compatible atom type. For docking, grid parameter file (.gpf) and docking parameter files (.dpf) were written using MGL Tools-1.5.6. Receptor grids were generated using 100 × 100 × 100 Grid points in xyz with grid spacing of 0.37 Å. Grid box was generated by considering active residues.[35] Map types were generated using autogrid 4.2. Docking was carried out with following parameters with number of runs: 50, population size: 150, number of evaluations: 2,500,000 and number of generations: 27,000, using autodock 4.2. Analysis of docking results was done using MGL Tools-1.5.6. Top scoring molecule in the largest cluster was analyzed for its interaction with the protein.

Table 8. Estimated inhibition constant and free energy of binding of synthesized compounds.

	PDB: 5FVP		PDB: 1HD2	
Compound	Ki (uM)	Kcal/mole	Ki (uM)	Kcal/mole
5d	1.88	−7.81	235.98	−4.76
8b	3.51	−7.05	226.30	−4.97
8c	2.03	−7.77	385.73	−4.66
8d	4.03	−7.36	303.26	−4.80
BHT	2.62	−7.61	692.27	−4.31

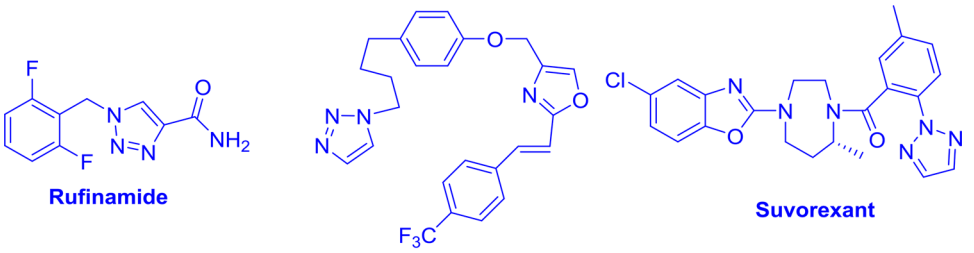


Figure 1. Clinically useful Triazole containing drugs.

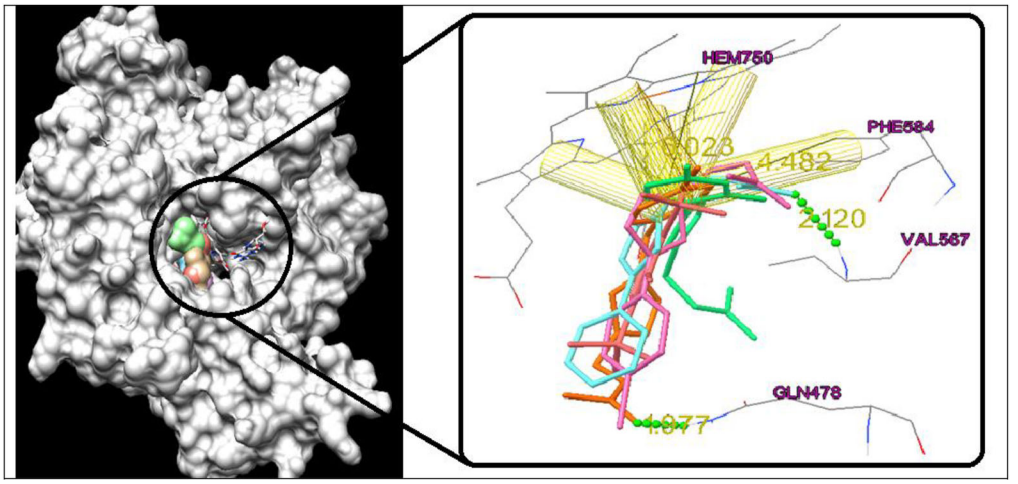


Figure 2. Binding mode of compounds (**5d**, **8b**, **8c**, **8d** and **BHT**) in the active site of human neuronal nitric oxide synthase.

Molecular docking studies

In order to understand the possible Docking studies were carried out against x-ray crystal structure of human neuronal nitric oxide synthase (PDB ID: 5FVP)[36] and peroxiredoxin 5 (PDB ID: 1HD2) using AutoDock 4.2.[37] All the synthesized compounds were completely occupied the active site cavity of human neuronal nitric oxide synthase (HnNOS) with overall minimum energy −7.05 to −8.1 Kcal/mole and with good inhibition constant (Figure 2), than x-ray crystal structure of peroxiredoxin 5 (PDB ID: 1HD2).Carboxyl oxygen of compounds (**8b** and **8c**) forms hydrogen bond (–C = O–H–N) with amino hydrogen of Val567 with bond distance of 2.18 Å and 2.12 Å, respectively (Figure 3), while the potent compound (**5d**) carboxyl oxygen form a hydrogen bond with amino hydrogen of Gln478 with bond distance of 1.97 Å, and also 4-Br attached ring

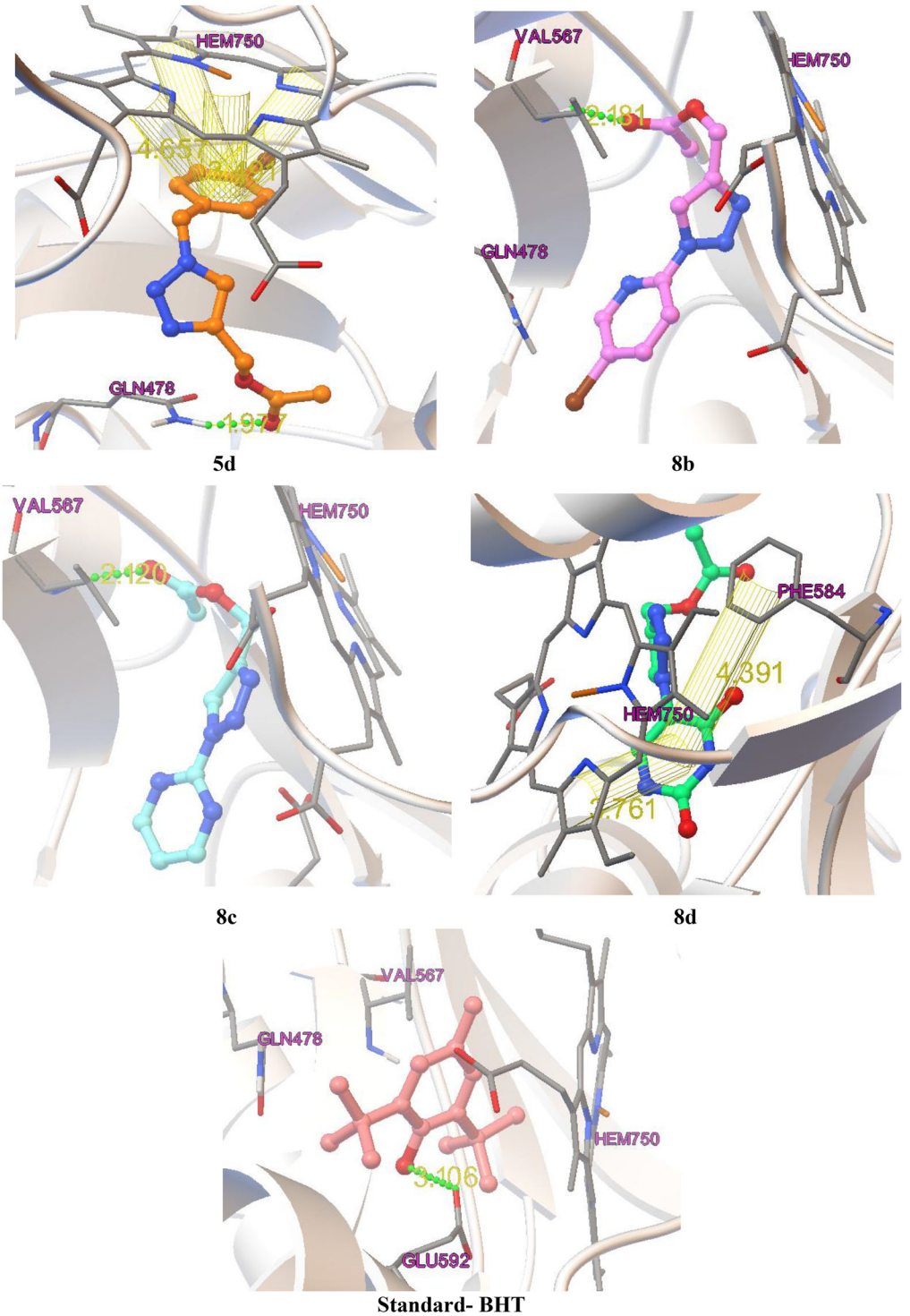


Figure 3. Interaction of compounds (**5d**, **8b**, **8c**, **8d** and **BHT**) in the active site of human neuronal nitric oxide synthase.

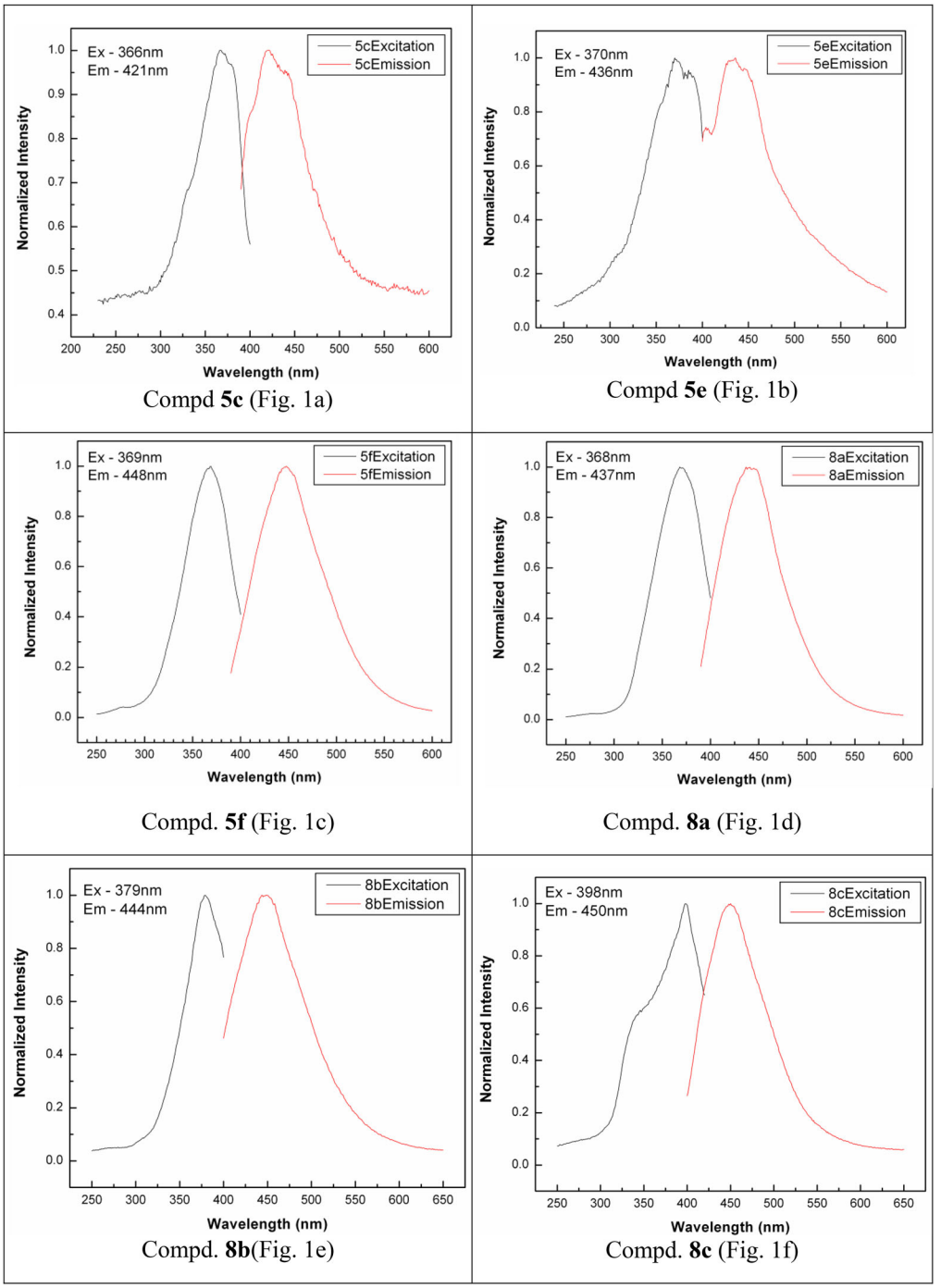


Figure 4. Excitation and emission spectra of triazole derivatives.
Excitation spectra of Compds.**5c, 5e, 5f, 8a, 8b, 8c and 8d** (Figure 1h)
Emission spectra of Compds. **5c, 5e, 5f, 8a, 8b, 8c and 8d** (Figure 1i)

to triazoles forms π–π interaction with three pyrrole ring of heme, this may be the reason for additional antioxidant activity of compound (**5d**) than other compounds in the series. Aromatic ring attached to triazoles compound (**5d** and **8d**) forms π-π interaction only with one pyrrole

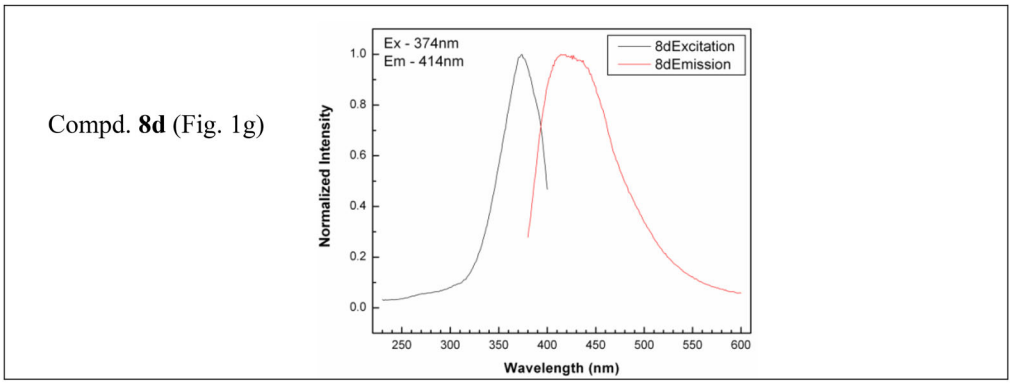


Figure 4. Continued.

ring of heme, additionally compound (**8d**) pyrimidine-2,4(1H,3H)-dione ring forms a π-π interaction with Phe584 (Figure 3). Standard butylated hydroxytoluene forms only one hydrogen bond with Glu592 with a bond distance of 3.106 Å.

Structural activity relationship

SAR study was established among the synthesized compounds to see the effect of substitution at N of triazole ring, rest of basic skeleton (1,2,3-triazol-4-yl)methyl acetate) is present in all the compounds. Compounds **5d** (4-bromobenzyl) and **8b** (4-bromo-2-pyridine) substitution at N of triazole were exhibited good radical scavenging activity than compounds **8c** (with pyrimidine-2-

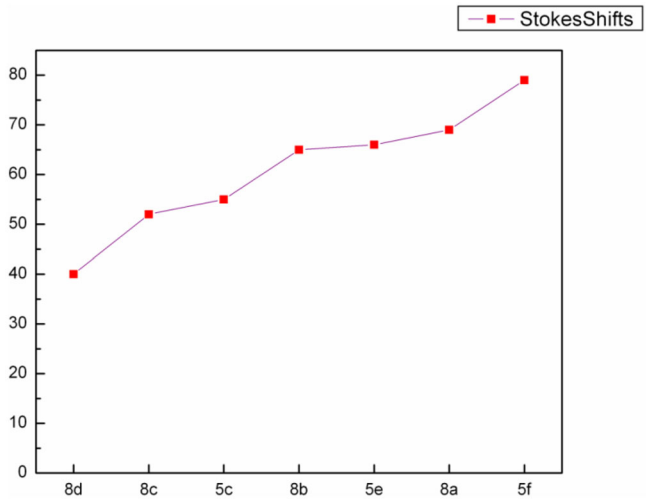


Figure 5. Stoke's shift of the test compounds.

yl) and **8d** (with 2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) in both methods (DPPH and NO). All other compounds **5a** (oxiran-2-ylmethyl), halogen substituted (**5 b**, **5c**, **5f** and **5 g**), **5e** (4-nitrobenzyl) and **8a** (thiazol-2-yl) substitutions (Table 3) were also showed significant antioxidant activity. The study suggested that the brominated and nitrogen heterocycles linked derivatives exhibited good antioxidant activity than other compounds. The additional antioxidant activity of compounds (**5d** and **8 b**) may be due to presence of a bromine atom on heterocyclic ring or a π-system adjacent to halogen atom increases lipophilicity can strongly polarize the parent molecule and seems to have profound effect on biological properties of title compounds, this obtained results were in good agreement with molecular docking studies (compound **5d with** 4-Br and **5d** with attached ring to triazoles forms π–π interaction with three pyrrole ring of heme of human neuronal nitric oxide synthase, this may be the reason for additional antioxidant activity than other compounds in the series (Figure 5). The study can be useful to rationale design novel compounds with improved antioxidant potential.

Photo physical properties

The newly synthesized triazoles were used to examine the excitation and emission spectra. The triazole derivatives **5(a-g)** and **8(a-d)** were dissolved in acetone to evaluate all the fluorescence profiles. The fluorescent spectra for all the title compounds were recorded in between 350-400 nm with the light path length of 1.0 cm. Excitation and emission spectra were recorded using JOBIN YVON Fluorolog-3 spectrofluorimeter (Department of Physics, Sri Venkateswara University, Tirupati) using xenon arc lamp (450 nm) as radiation source. All these measurements were carried out at room temperature.

The absorbance maximam (Abs_{max}), emission maximam (Em_{max}) and a large Stokes shift were examined for seven compounds and their values are tabulated in Table 9, which is important in view of the biomedical use of fluorescent compounds. The excitation and emission spectra for the clicked products **5c**, **5e**, **5f**, **8a**, **8 b**, **8c** and **8d** are given in Figure 1(a-i), and their Stokes shift values are presented in Figure 5. The test triazoles showed excitation maxima in the range of 366-398 nm, emission maxima in the range of 414–450 nm (visible range) and Stokes shift in the range of 40-79 nm. The lone pair electrons on nitrogen become part of the aromatic system and the main requisition to achieve the fluorescent property is that the newly formed double bonds inside of the triazole ring have to form conjugate double bonds with the parent molecule.

Table 9. Excitation maxima, emission maxima and Stoke's shifts of the test compounds.

Compd.	λ_{ex} max (nm)	λ_{em} max (nm)	λ_{ST} (nm)
5c	366	421	55
5e	370	436	66
5f	369	448	79
8a	368	437	69
8b	379	444	65
8c	398	450	52
8d	374	414	40

Table 10. Carcinogenic property values of the newly synthesized triazole compounds **5(b-g)** and **8(a-d)** calculated using OSIRIS server.

Compd	Mutagenic	Tumarogenic	Irritant	Reproductive effect	cLog*P*	Solubility	MW	TPSA	Drug likeness	Drug Score
5b	−	−	−	−	0.77	−1.79	249.0	57.01	−2.76	0.5
5c	−	−	−	−	1.27	−2.22	265.0	57.01	−2.73	0.49
5d	−	−	−	−	1.39	−2.31	309.0	57.01	−4.09	0.46
5e	−	−	−	−	−0.26	−1.94	276.0	102.8	−12.3	0.47
5f	−	−	−	−	0.5	−2.25	256.0	80.8	−7.17	0.47
5g	−	−	−	−	1.88	−2.95	299.0	57.01	−2.13	0.49
8a	−	+	−	−	0.09	−0.58	224.0	98.14	−2.47	0.31
8b	−	−	−	−	1.58	−0.81	296.0	69.9	−5.3	0.47
8c	−	−	−	−	−0.51	1.7	219.0	82.79	−2.74	0.52
8d	−	+	−	−	−1.61	−1.87	251.0	115.2	−0.94	0.49

Possibly the same principle could be extended to design other fluorescent molecules through CuAAC reaction. A substituent, which cannot participate in π-conjugation with triazole ring, had a minimum effect on λ_{em}max. A π-conjugating substituent on triazole ring shifted λ_{em}max to the higher wavelength; the extent of conjugation in the triazole compound plays a key role in determining λ_{em}max. The electron donating or electron withdrawing substituents present in the phenyl ring (phenyl substituted triazoles i.e., **5(b-g)** had a small effect on λ_{em}max but mainly is due to the extended π-conjugation. The lowest λ_{exci} and the lowest fluorescent intensity value was obtained for a non-conjugating alkyl substituent. The obtained Stokes shift values were unpredictable with respect to the substituents present at the triazole ring and increases linearly for compounds **8d**, **8c**, **5c**, **8 b**,**5e**, **8a** and **5f**, respectively.

Computational tool

Open source program like OSIRIS Property Explorer was employed to compute drug related properties of the newly synthesized compounds. This server predicts the molecule's Toxicity Risk Assessment, cLogP value, Molecular Weights, Solubility, Drug-Likeness prediction and overall Drug-Likeness score and is tabulated in Table 10.

Conclusion

Summarizing, we developed an efficient method for the direct synthesis of PEG-400:H_2O (1:1 v/v) mediated 1,4-disubstituted triazole derivatives in the presence of CuI (15 mol%) through a "click reaction" promoted by ultrasonic radiation. This sonication technique offers applicability of simple starting materials, efficiency, and greener solvent system, and it is one of the most classical approaches. The short reaction times, excellent chemoselectivity, high isolated yields, and easy workup procedure make this sonochemical methodology as one of the proficient protocol for the rapid synthesis of 1,4-disubstituted 1,2,3-triazoles, functioning as fluorescent organic Probes. Our

results showed that majority of the compounds exhibited promising antioxidant activity and seven compounds exhibited Abs_{max} in the range of 366-398 nm and Em_{max} in the range of 414-450 nm. The antioxidant activity of synthesized compounds may due to the inhibition of neuronal nitric oxide synthase (HnNOS).

Acknowledgements

The authors are grateful to the department of Chemistry and Biochemistry, Sri Venkateswara University, for providing necessary lab facility to carry out this research work.

References

1. B. Maleki, R. Nejat, H. Alinezhad, S. M. Mousavi, B. Mahdavi, and M. Delavari, "Nanostructural Cu-Doped ZnO Hollow Spheres as an Economical and Recyclable Catalyst in the Synthesis of 1*H* Pyrazolo[1,2-*b*]Phthalazine-5,10-Diones and Pyrazolo[1,2-*a*][1,2,4]Triazole-1,3-Diones,"*Organic Preparations and Procedures International* 52, no. 4 (2020): 328–39.
2. B. Maleki, F. B. Tabrizy, R. Tayebee, and M. Baghayeri, "Oxidative Aromatization of 1,3,5-Trisubstituted 2-Pyrazolines Using Oxalic Acid/Sodium Nitrite System,"*Polycyclic Aromatic Compounds* 39, no. 2 (2019): 93–8.
3. B. Maleki, H. Natheghi, R. Tayebee, H. Alinezhad, A. Amiri, S. A. Hossieni, and S. M. Mahdi Nouri, "Synthesis and Characterization of Nanorod Magnetic Co–Fe Mixed Oxides and Its Catalytic Behavior towards One-Pot Synthesis of Polysubstituted Pyridine Derivatives,"*Polycyclic Aromatic Compounds* 40, no. 3 (2020): 633–43.
4. H. Alinezhad, M. Tajbakhsh, B. Maleki, and F. P. Oushibi, "Acidic Ionic Liquid [H-NP]HSO_4 Promoted One-Pot Synthesis of Dihydro-1H-Indeno[1,2-b]Pyridines and Polysubstituted Imidazoles,"*Polycyclic Aromatic Compounds* 40, no. 5 (2020): 1485–500.
5. B. Maleki, O. Reiser, E. Esmaeilnezhad, and H. Jin. Choi, "SO_3H-Dendrimer Functionalized Magnetic Nanoparticles (Fe_3O_4@D-NH-$(CH_2)_4$-SO_3H): Synthesis, Characterization and Its Application as a Novel and Heterogeneous Catalyst for the One-Pot Synthesis of Polyfunctionalized Pyrans and Polyhydroquinolines," *Polyhedron* 162, (2019): 129–41.
6. F. Adibian, A. R. Pourali, B. Maleki, M. Baghayeri, and A. Amiri, "One-Pot Synthesis of Dihydro-1H-Indeno[1,2-b] Pyridines and Tetrahydrobenzo[b] Pyran Derivatives Using a New and Efficient Nanocomposite Catalyst Based on *N*-Butylsulfonate-Functionalized MMWCNTs-D-NH_2," *Polyhedron* 175, (2020): 114179.
7. F. Gao, T. Wang, J. Xiao, and G. Huang, "Antibacterial Activity Study of 1,2,4-Triazole Derivatives," *European Journal of Medicinal Chemistry* 173, (2019) : 274–81.
8. K. Bozorov, J. Zhao, H. A. Aisa. "1,2,3-Triazole-Containing Hybrids as Leads in Medicinal Chemistry: A Recent Overview," *Bioorganic & Medicinal Chemistry* 27, no. 16 (2019) : 3511–31.
9. Z. Xu, S. J. Zhao, Y. Liu. " 1,2,3-Triazole-containing Hybrids as Potential Anticancer Agents: Current Developments, Action Mechanisms and Structure-Activity Relationships ," *European Journal of Medicinal Chemistry* 183, (2019) : 111700.
10. L. S. Feng, Z. Xu, L. Chang, C. Li, X. F. Yan, C. Gao, C. Ding, F. Zhao, F. Shi, and X. Wu, "Hybrid Molecules with Potential in Vitro Antiplasmodial and in Vivo Antimalarial Activity against drug-resistant Plasmodium falciparum ," *Medical Research Review* 40, no. 3 (2020): 931–71.
11. C. P. Kaushik, J. Sangwan, R. Luxmi, K. Kumar, and A. Pahwa, "Synthetic Routes for 1,4-Disubstituted 1,2,3-Triazoles: A Review,"*Current Organic Chemistry* 23, no. 8 (2019): 860–900. no.
12. B. Zhang, "Comprehensive Review on the Anti-bacterial Activity of 1,2,3-triazole Hybrids ," *European Journal of Medicinal Chemistry* 168, (2019) : 357–72.
13. (a) S. T. Abu-Orabi, and 1. "3-Dipolar Cycloaddition Reactions of Substituted Benzyl Azides with Acetylenic Compounds,"*Molecules* 7, no. 2 (2002): 302–14. (b) W. Q. Fan, A. R. Katritzky, C. W. Rees and E. F. V. Scriven, In Comprehensive Heterocyclic Chemistry II, vol. 4. (Oxford: Elsevier Science, 1996): 1–126.
14. R. B. Woodward, and R. Hoffmann, "The Conservation of Orbital Symmetry,"*Angewandte Chemie International Edition in English* 8, no. 11 (1969): 781–53.
15. (a) R. Huisgen, and 1. "3-Dipolare Cycloaddition," Angewandte Chemie International Edition 75, (1963) : 604–37. (b) R. Huisgen, "1,3-Dipolar Cycloadditions. Past and Future,"*Angewandte Chemie International Edition in English* 2, no. 10 (1963): 565–98. (c) R. Huisgen, "Kinetics and Mechanism of 1,3-Dipolar Cycloadditions,"*Angewandte Chemie International Edition in English* 2, no. 11 (1963): 633–45.
16. R. Huisgen, In 1,3-Dipolar Cycloaddition Chemistry (Ed. A. Padwa), (New York: Wiley), 1 (1984): 1–176.

17. (a) C. W. Tornoe, C. Christensen, and M. Meldal, "Peptidotriazoles on Solid Phase:[1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cyclo Additions of Terminal Alkynes to Azides, *Journal of Organic,"Chemistry* 67, no. 2002 (2002): 3057–64. (b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, and K. B. Sharpless, "A Stepwise Huisgen Cycloaddition Process: Copper (I)-Catalyzed Regio Selective "Ligation" of Azides and Terminal Alkynes," *Angewandte Chemie International Edition* 41, (2002) : 2596–9.
18. H. C. Kolb, M. G. Finn, and K. B. Sharpless, "Click Chemistry: Diverse Chemical Function from a Few Good Reactions,"*Angewandte Chemie International Edition* 40, no. 11 (2001): 2004–21.
19. B. List, C. F. Barbas, and R. A. Lerner, "Aldol Sensors for the Rapid Generation of Tunable Fluorescence by Antibody Catalysis,"*Proceedings of the National Academy of Sciences of the United States of America* 95, no. 26 (1998): 15351–5.
20. (a) J. P. Goddard, and J. L. Reymond, "Recent Advances in Enzyme Assays,"*Trends in Biotechnology* 22, no. 7 (2004): 363–70. (b) R. P. Carlson, N. Jourdain, "Fluorogenic Polypropionate Fragments for Detecting Stereoselective Aldolases,"*Chemistry of Europian Journal* 6, (2000): 4154–62. (c) M. K. Froemming, and D. Sames, "Fluoromorphic Substrates for Fatty Acid Metabolism: Highly Sensitive Probes for Mammalian Medium-chain acyl-CoA Dehydrogenase,"*Angewandte Chemie (International ed. in English)* 45, no. 4 (2006): 637–42. (d) M. K. Froemming, "Harnessing Functional Plasticity of Enzymes: A Fluorogenic Probe for Imaging 17β-HSD10 Dehydrogenase, an Enzyme Involved in Alzheimer's and Parkinson's Diseases,"*Journal of the American Chemical Society* 129no. 46 (2007): 14518–22. (e) B. Xing, A. Khanamiryan, and J. Rao, "Cell-Permeable near-Infrared Fluorogenic Substrates for Imaging β-Lactamase Activity,"*Journal of the American Chemical Society* 127, no. 12 (2005): 4158–9. (f) H. M. Guo, M. Minakawa, and F. Tanaka, "Fluorogenic Imines for Fluorescent Detection of Mannich-Type Reactions of Phenols in Water,"*The Journal of Organic Chemistry* 73, no. 10 (2008): 3964–6. (g) F. Tanaka, "Development of Protein, Peptide, and Small Molecule Catalysts Using Catalysis-Based Selection Strategies,"*Chemical Record (New York, N.Y.)* 5, no. 5 (2005): 276–85. (h) J. Gildersleeve, A. Varvak, S. Atwell, D. Evans, and P. G. Schultz, "Development of a High-Throughput Screen for Protein Catalysts: Application to the Directed Evolution of Antibody Aldolases,"*Angewandte Chemie (International ed. in English)* 42, no. 48 (2003): 5971–3.
21. (a) F. Tanaka, R. Thayumanavan, N. Mase, and C. F. Barbas, "Rapid Analysis of Solvent Effects on Enamine Formation by Fluorescence: how Might Enzymes Facilitate Enamine Chemistry with Primary Amines,"*Tetrahedron Letters* 45, no. 2 (2004): 325–8. (b) N. Mase, F. Tanaka, "Rapid Fluorescent Screening for Bifunctional Amine-Acid Catalysts: Efficient Syntheses of Quaternary Carbon-Containing Aldols under Organocatalysis,"*Organic Letters* 5, no. 23 (2003): 4369–72. (c) N. Mase, F. Tanaka, "Synthesis of Beta-hydroxyaldehydes with Stereogenic Quaternary Carbon Centers by Direct Organocatalytic Asymmetric Aldol Reactions ,"*Angewandte Chemie (International ed. in English)* 43, no. 18 (2004): 2420–3.
22. D. J. Yee, V. Balsanek, and D. Sames, "New Tools for Molecular Imaging of Redox Metabolism: Development of a Fluorogenic Probe for 3 Alpha-Hydroxysteroid Dehydrogenases,"*Journal of the American Chemical Society* 126, no. 8 (2004): 2282–3.
23. K. E. Beatty, F. Xie, Q. Wang, and D. A. Tirrell, "Selective Dye-labeling of Newly Synthesized Proteins in Bacterial Cells ,"*Journal of the American Chemical Society* 127, no. 41 (2005): 14150–1.
24. (a) J. F. Lutz, and Z. Zarafshani, "Efficient Construction of Therapeutics, Bioconjugates, Biomaterials and Bioactive Surfaces Using Azide-Alkyne "Click" Chemistry,"*Advanced Drug Delivery Reviews* 60, no. 9 (2008): 958–70. (b) K. Sivakumar, F. Xie, B. M. Cash, S. Long, H. N. Barnhill, and Q. Wang, "A Fluorogenic 1,3-Dipolar Cycloaddition Reaction of 3-Azidocoumarins and Acetylenes,"*Organic Letters* 6, no. 24 (2004): 4603–6. (c) J. F. Lutz, "1,3-dipolar Cycloadditions of Azides and Alkynes: A Universal Ligation Tool in Polymer and Materials Science,"*Angewandte Chemie (International ed. in English)* 46, no. 7 (2007): 1018–25. (d) H. Nandivada, X. W. Jiang, and J. Lahann, "Click Chemistry: Versatility and Control in the Hands of Materials Scientists," *Advanced Materials* 19, (2007) : 2197–08.
25. Z. Zhou, and C. J. Fahrni, "A Fluorogenic Probe for the copper(I)-catalyzed Azide-alkyne Ligation Reaction: Modulation of the Fluorescence Emission via 3(n,pi)-1(pi,pi) Inversion,"*Journal of the American Chemical Society* 126, no. 29 (2004): 8862–3.
26. F. Xie, K. Sivakumar, Q. B. Zeng, M. A. Bruckman, B. Hodges, and Q. Wang, "A Fluorogenic Click Reaction of Azidoanthracene Derivatives,"*Tetrahedron* 64, no. 13 (2008): 2906–14.
27. M. Sawa, T. L. Hsu, T. Itoh, M. Sugiyama, S. R. Hanson, P. K. Vogt, and C. H. Wong, "Glycoproteomic Probes for Fluorescent Imaging of Fucosylated Glycans in Vivo,"*Proceedings of the National Academy of Sciences of the United States of America* 103, no. 33 (2006): 12371–6.
28. (a) M. L. Tiku, J. B. Liesch, and F. M. Robertson, "Production of Hydrogen Peroxide by Rabbit Articular Chondrocytes. Enhancement by Cytokines," *Journal of Immunology* 145, (1990) : 690–6. (b) B. E. Bax, A. S. Alam, B. Banerji, C. M. Bax, P. J. Bevis, C. R. Stevens, B. S. Moonga, D. R. Blake, and M. Zaidi, "Stimulation of Osteoclastic Bone Resorption by Hydrogen Peroxide,"*Biochemical and Biophysical Research Communications* 183, no. 3 (1992): 1153–8.

29. (a) J. E. Kinsella, E. Frankel, B. German, J. Kanner, "Possible Mechanisms for the Protective Role of Antioxidants in Wine and Plant Foods," *Food Technology*, 47 (1993) : 85–9. (b) N. Singh, and P. S. Rajini, "Free Radical Scavenging Activity of an Aqueous Extract of Potato Peel," *Food Chemistry* 85, no. 4 (2004): 611–6. (c) R. L. Prior, X. Wu, and K, Schaich, "Standardized Methods for the Determination of Antioxidant Capacity and Phenolics in Foods and Dietary Supplements,"*Journal of Agricultural and Food Chemistry* 53, no. 10 (2005): 4290–02.
30. S. Trakossas, E. Coutouli-Argyropoulou, and D. J. Hadjipavlou-Litina, "Synthesis of Modified Triazole Nucleosides Possessing One or Two Base Moieties via a Click Chemistry Approach,"*Tetrahedron Letters* 52, no. 14 (2011): 1673–6.
31. (a) C. Y. Lin, A. C. Ho, H. C. Chiang, J. S. Sun, S. Y. " Sheu, Reactive Oxygen Scavenger Effect of Pyrimidines, Benzotriazoles and Related Compounds," *Anticancer Research*, and 22. (2002) : 937–42. (b) O. Bekircan, T. Ozen, N. Gumrukcuoglu, and H. Bektas, "Synthesis and Antioxidant Properties of Some New 3-(4-Chlorophenyl)-5-(Pyridin-4-yl)-4H-1,2,4-Triazole Derivatives,"*Zeitschrift Fur Naturforschung* 63b, (2008) : 548–54. (c) G. Aktay, B. Tozkoparan, and M. Ertan, "Investigation of Antioxidant Properties of Some 6-(alpha-aminobenzyl)thiazolo[3,2-b]-1,2,4-triazole-5-ol Compounds,"*Journal of Enzyme Inhibition and Medicinal Chemistry* 24, no. 3 (2009): 898–02.
32. C. Juan-Carlos, B. Nestor-Fabian, T. Lenka-Victoria, M. Paula-Daniela, J. Hurtado, M. Macias, and J. Portilla, "Water-Compatible Synthesis of 1,2,3-Triazoles under Ultrasonic Conditions by a Cu(I) Complex-Mediated Click Reaction,"*ACS Omega* 5, no. 46 (2020): 30148–59.
33. C. W. Choi, S. C. Kim, S. S. Hwang, B. K. Choi, H. J. Ahn, M. Y. Lee, S. H. Park, and S. K. Kim, "Antioxidant Activity and Free Radical Scavenging Capacity between Korean Medicinal Plants and Flavonoids by Assay-Guided Comparison,"*Plant Science* 163, no. 6 (2002): 1161–8.
34. L. Marcocci, J. J. Maguire, M. T. Droy-Lefaix, and L. Packer, "The Nitric Oxide-Scavenging Properties of Ginkgo Biloba Extract EGb 761,"*Biochemical and Biophysical Research Communications* 201, no. 2 (1994): 748–55.
35. (a) H. Y. Wang, Y. Qin, H. Li, L. J. Roman, P. Martasek, T. L. Poulos, and R. B. Silverman, "Potent and Selective Human Neuronal Nitric Oxide Synthase Inhibition by Optimization of the 2-Aminopyridine-Based Scaffold with a Pyridine Linker,"*Journal of Medicinal Chemistry* 59, no. 10 (2016): 4913–25. (b) J. P. Declercq, C. Evrard, A. Clippe, D. V. Stricht, A. Bernard, and B. K. Declercq, "Crystal Structure of Human Peroxiredoxin 5, A Novel Type of Mammalian Peroxiredoxin at 1.5 Å Resolution,"*Journal of Molecular Biology* 311 (2001): 751–59.
36. J. M. Wang, C. Jun, K. Chai, K. Kwak, and Z. S. Quan, "Synthesis and Anticonvulsant Activity of 1-Substituted benzyl-N-Substituted-1,2,3-Triazole-4-Formamides," *Progress in Natural Science* 16, (2006) : 925–9.
37. (a) B. Vishnu Nayak, S. Ciftci-Yabanoglu, S. S. Jadav, M. Jagrat, B. N. Sinha, G. Ucar, and V. Jayaprakash, "Monoamine Oxidase Inhibitory Activity of 3, 5-Biaryl-4, 5-Dihydro-1H-Pyrazole-1-Carboxylate Derivatives, *Europian,"Journal of Medicinal Chemistry* 69 (2013) : 762–7. (b) B. Vishnu Nayak, I. Baysal, G. Ucar, B. N. Sinha, "Monoamine Oxidase Inhibitory Activity of Novel Pyrazoline Analogues: curcumin Based Design and Synthesis," *ACS Medicinal Chemistry Letters* 7, (2015): 56–61. (c) B. Vishnu Nayak, S. Ciftci-Yabanoglu, S. Bhakat, T. Ajay Kumar, B. N. Sinha, G. Ucar, M. E. S. Soliman, and V. Jayaprakash, " Monoamine Oxidase Inhibitory Activity of 2-Aryl-4H-Chromen-4-Ones," *Bioorganic Chemistry* 58, (2005) : 72–80.