A Platinum Open Access Journal for Organic Chemistry

Paper

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Design and synthesis of novel triclosan-linked-1,2,3-triazole scaffolds as antibacterial agents

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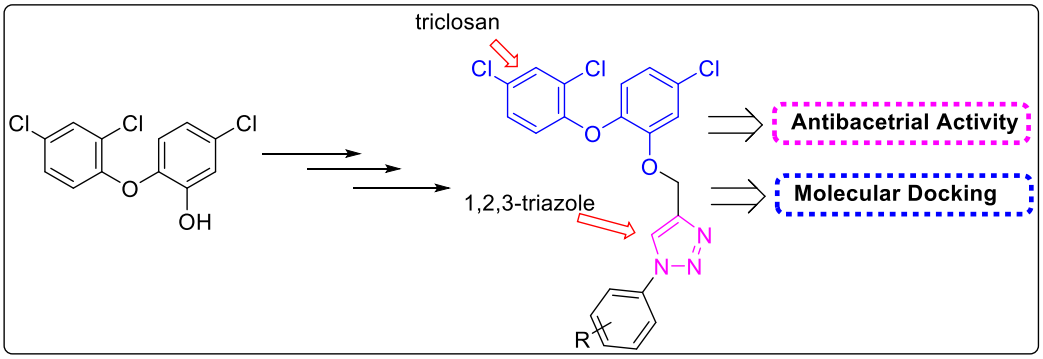
Received mm-dd-yyyy **Accepted** mm-dd-yyyy **Published on line** mm-dd-yyyy

Dates to be inserted by editorial office

Abstract

A series of new triclosan-linked-1,2,3-triazole derivatives was produced via a sequence of processes that included propargylation and a click reaction. The new scaffolds were evaluated for their in vitro antibacterial activity against two gram-positive and two gram-negative strains. All the analogues displayed prominent zones of inhibitions. A compound substituted with a meta-methoxy group presented the highest activity. Furthermore, a molecular-docking study of the best active compound against a crystalline structure of enoyl-acyl carrier protein reductase showed promising binding interactions.



Keywords: Antibacterial agent, molecular docking, triclosan, 1,2,3-triazole

Cite as *Arkivoc* **2025** (5) 202512351

DOI: https://doi.org/10.24820/ark.5550190.p012.351

Introduction

Triclosan, which is often referred to as irgasan, is a synthetic antimicrobial compound that is non-ionic and bis-aryl in nature. It has been demonstrated to possess antibacterial, antiviral and antifungal effects.[1] Although it does not pose a threat to human health, it possesses a wide range of antimicrobial activity which inhibits all infections that are typically encountered.[2] At higher concentrations, its antibacterial action is directed toward the cell wall; however, at lower concentrations, it inhibits the synthesis of fatty acids at the enoyl-acyl carrier protein reductase step.[3] This mechanism of action is responsible for its antibacterial activity. Inhibition of fatty-acid synthesis, which is important for the survival of bacteria, results in the disintegration of the cell membrane and the breakdown of the cell.[4] According to literature reports, the structural modification of triclosan has led to many biological effects and their enhancements.[5] The structure of triclosan was modified by attaching galactose to the OH function, and their antibacterial characteristics were investigated against gram-positive and gram-negative bacteria which yielded encouraging results.[6] Replacement of -Cl atoms on the structure of triclosan with various substituents such as alkyl, cyano or pyridyl groups, was found to have antitubercular properties.[7] Connecting the triazole moiety to the triclosan led to antimycobacterial activities.[8]

A 1,2,3-triazole scaffold is a powerful nitrogen-containing heterocyclic framework with extensive applications.[9,10] 1,2,3-Triazole is an unsaturated, π-rich, five-membered heterocycle featuring a 6π delocalized electron ring structure that imparts aromaticity. 1,2,3-Triazole consists of three nitrogen atoms and two carbon atoms.[11] Mubritinib and carboxyamidotriazole demonstrate significant anti-cancer efficacy.[12,13] Fluconazole, itraconazole and voriconazole are examples of pharmaceuticals that feature triazoles as their primary functional group and are recognized for their significant antifungal properties.[14,15] Trazodone is a triazole-derived medication frequently used as an antidepressant for the management of mental disorders, particularly major depressive disorder.[16] Ribavirin, a ribosyl triazole, is a commonly utilized antiviral agent.[17] The structural characteristics of these 1,2,3-triazoles permit the incorporation of various substituents (electrophiles and nucleophiles) around the core structure which facilitates the synthesis of numerous novel bioactive chemicals.[18–21] Sharpless and colleagues pioneered a novel paradigm shift by producing the inaugural examples of click reactions which facilitated the synthesis of 1,4-disubstituted-1,2,3-triazoles by a copper-catalysed alkyne-azide cycloaddition (CuAAC) reaction.[22,23] Numerous publications and reviews have been published in recent years about the synthesis of 1,4-disubstituted 1,2,3-triazoles due to their extensive application as possible pharmaceuticals for various diseases.[24–29]

The problem of antibiotic resistance is becoming increasingly concerning in modern times.[30] A recent investigation indicated that antibiotic resistance is a threat, and results in the deaths of around 700,000 individuals globally each year. By 2050, this number is projected to increase to 10 million, exceeding the mortality rate of cancer. The principal cause of antimicrobial resistance is the inappropriate use of medications, particularly their indiscriminate application without prior identification of the infection's source. Each of these factors adds to an increase in the count of recorded fatalities, healthcare costs for managing resistant diseases, hospitalization charges, and recovery durations.[31] Pharmaceutical companies are reluctant to pursue the synthesis of these essential new lead compounds for antibiotics, as antibiotic prescriptions are most often of short-term duration, in contrast to the treatment of chronic conditions, leading to diminished profit potential.[32–34] Nonetheless, the increasing resistance of microbes to these pharmaceuticals has necessitated the exploration of novel treatment alternatives in the present context.

Inspired by the concern about the lack of development of new antimicrobial agents, and the enormous properties of triclosan against bacterial infections and profound importance of 1,2,3-triazole in pharmaceuticals,

our aim was to design and synthesis a series of hybrids of triclosan-linked-1,2,3-triazole analogues (Figure 1) and evaluate their antibacterial properties.

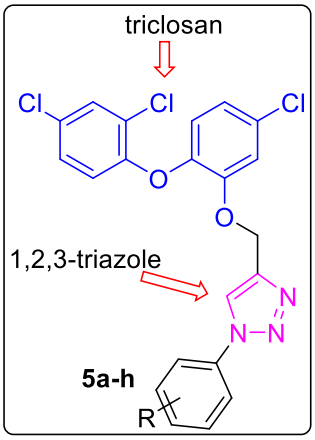
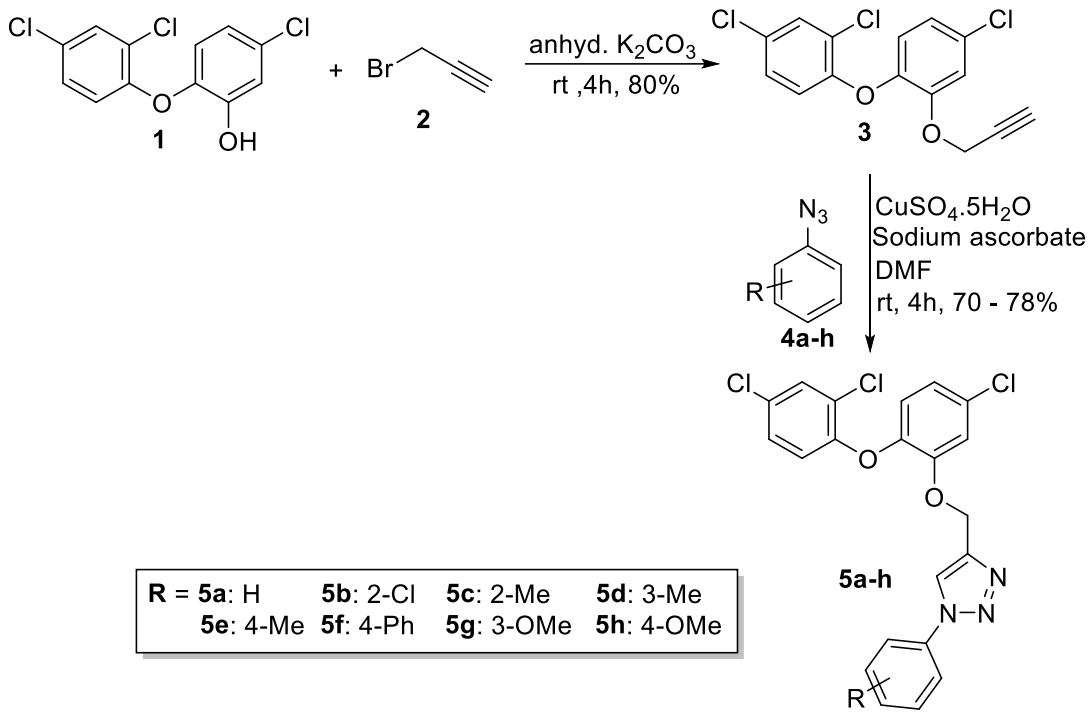


Figure 1 Design rational for triclosan-linked-1,2,3-triazole derivatives

Results and Discussion

The synthetic route for the accomplishment of novel triclosan-linked-1,2,3-triazole derivatives is outlined in Scheme 1. The initial reaction involved the propargylation of the free -OH group on 5-chloro-2-(2,4-dichlorophenoxy)phenol **1** with propargyl bromide **2** using anhydrous K_2CO_3, under stirring conditions at ambient temperature, to lead to the formation of 2,4-dichloro-1-(4-chloro-2-(prop-2-yn-1-yloxy)phenoxy)benzene **3** with a yield of 80%.[35–41] It was confirmed by the appearance of the propargyl group protons' signals as two singlets at δ 4.90 ppm and δ 3.37 ppm corresponding to -CH_2- and ≡CH in the ^{1}H NMR spectrum of intermediate **3**. The aromatic protons of the triclosan moiety appeared as a multiplet at δ 7.70 – 6.80 ppm. Additionally, in the ^{13}C NMR of compound **3**, the three carbons of the propargyl group appeared at δ 79.4, 78.7 and 56.9 ppm, respectively.

The alkyne group of intermediate compound **3** was subjected to copper-catalysed Huisgen's 1,3-dipolar cycloaddition reactions with various substituted aryl azides **4a-h** in the presence of catalytic amounts of copper sulphate (pentahydrate) and aqueous sodium ascorbate to achieve 4-((5-chloro-2-(2,4-dichlorophenoxy)phenoxy)methyl)-1-phenyl-1H-1,2,3-triazole derivatives **5a-h** in good yields. The characterizations of the compounds were confirmed by analysis of ^{1}H NMR, ^{13}C NMR and mass spectral data. As an example, using compound **5a**, formation of the triazole ring was confirmed by the appearance of a singlet at δ 8.07 ppm, corresponding to the triazole-ring proton and disappearance of the ≡CH proton at δ 3.37 ppm. The -CH_2- protons between triclosan and triazole appeared as a singlet at δ 5.31 ppm. There is also an additional number of five protons in the aromatic region corresponding to the phenyl ring linked to the triazole. The ^{13}C NMR of **5a** confirmed the disappearance of two carbon signals in the aliphatic region corresponding to the former alkyne function, and there appeared eighteen sets of aromatic carbon signals. The mass spectrum of compound **5a** shows a m/z 447.02 $[M+2H]^+$ peak.



Scheme 1 Synthesis of 4-((5-chloro-2-(2,4-dichlorophenoxy)phenoxy)methyl)-1-phenyl-1H-1,2,3-triazole derivatives (**5a-h)**.

Antibacterial activity

All the newly synthesized triclosan linked 1,2,3-triazole derivatives (**5a-h**) were screened for their in vitro antibacterial activity against two gram-positive (S. aureus, B. subtilis) and two gram-negative (E.coli, P. aeruginosa) strains of bacteria by employing triclosan as a standard reference. The results are presented in Table 1. All of the compounds displayed notable zones of inhibitions on par with triclosan. The structure-activity relationship (SAR) elucidates the influence of functional groups of each molecule on antibacterial efficacy. Compound **5g**, showcasing an electron-withdrawing methoxy group in the meta position, demonstrated the highest zone of inhibition. Moving the methoxy group to the para position of compound **5h** showed a slight change in its activity. Likewise, compound **5e** exhibited a comparable zone of inhibition due to the presence of the electron-donating methyl group in para position. The activity was maintained when the methyl group was moved into ortho (**5c**) or meta (**5d**) positions. The presence of an electron-withdrawing -Cl function in compound **5b** led to a small change in activity. The presence of the aromatic biphenyl ring in compound **5f** maintained the good activity, and absence of substituents in compound **5a** presented a little less zone of inhibition. The activity may be attributed to the presence of triclosan and 1,2,3-triazole moieties which have been demonstrated previously to have significant biological properties. Furthermore, the -Cl atoms on triclosan nuclei make it electron deficient which, in turn, enabled it to bind with electron-rich biological targets. The chlorine atoms also have the ability for H-bond acceptor interactions with biological targets.

Table 1. Zone of inhibition of target compounds **5a-h** against bacterial strains

Entry	Inhibition zone dia (mm), concentration (50 μg/ml)			
	Gram-negative bacteria		Gram-positive bacteria	
	E. coli	*P. aeruginosa*	*S. aureus*	*B. subtilis*
5a	15	15	14	15
5b	16	17	15	16
5c	19	19	16	17
5d	19	20	18	17
5e	20	19	18	18
5f	18	19	17	18
5g	22	20	20	19
5h	17	18	17	17
Triclosan	20	21	19	19

Molecular docking against Enoyl-[Acyl-Carrier-Protein] Reductase (ENR)

The enoyl-acyl carrier protein reductase (ENR) plays a part in bacterial fatty-acid production and operates as a target for antibacterial agents.[34] This was the reason the crystalline structure of ENR (PDB ID: 1QSG)[42] was chosen as an in silco target to study the binding interactions responsible for activity of the most potent compound, **5g**. We validated the docking results by re-docking the co-crystalized ligand triclosan onto the active site pocket of ENR which presented a root-mean-square deviation (RMSD) of 1.05 Å. The docking score of ligand **5g** was reported to be higher, with a binding energy value of -9.9 kcal/mol, than that of the reference ligand triclosan's value of -8.1 kcal/mol. The ligand **5g** displayed two key interactions with amino-acid sites Ile192 and Ala196 of ENR with a bond distance of 1.98 Å (strong) and 2.63 Å (moderate), respectively. Additionally, it showed two π-π T-shaped interactions with Tyr146 and Phe203, and a halogen-bond interaction with Ala189 of ENR, along with other hydrophobic interactions (Figure 2). The reference ligand triclosan had presented a H-bond interaction with Ile192 (2.29 Å), and hydrophobic interactions with Ile20, Tyr146 (π-π stacked), Tyr156, Ile200, and Met206 of ENR (Figure 3). Interestingly, the interactions of ligand **5g** coincided with interactions of triclosan. There were more interactions observed with ligand **5g**.

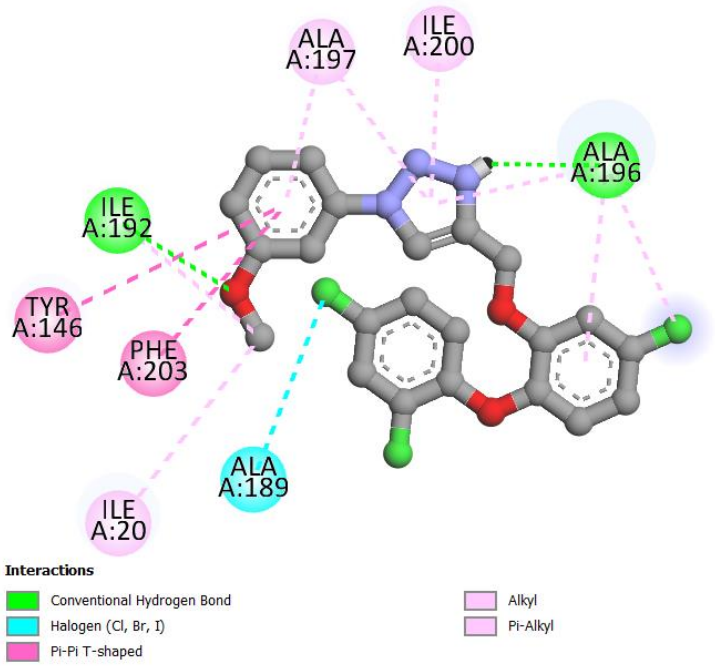


Figure 2. Binding interactions of ligand **5g** in cavity of ENR

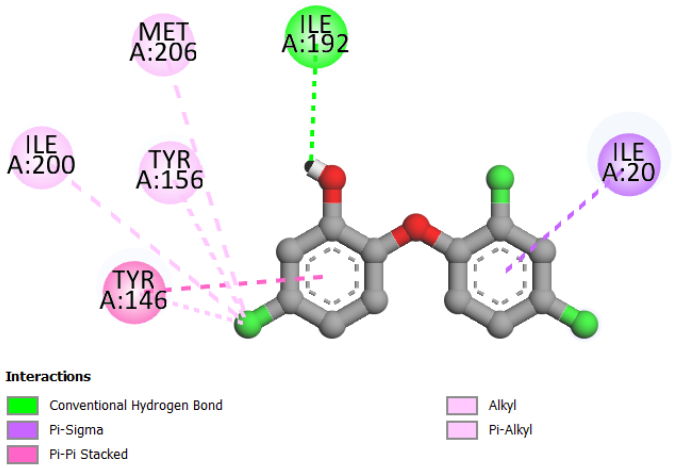


Figure 3. Binding interactions of triclosan in cavity of ENR

The docking image of ligand **5g** and triclosan (Figure 4) could explain their best fit into the active site pocket of ENR, leading to efficient inhibition.

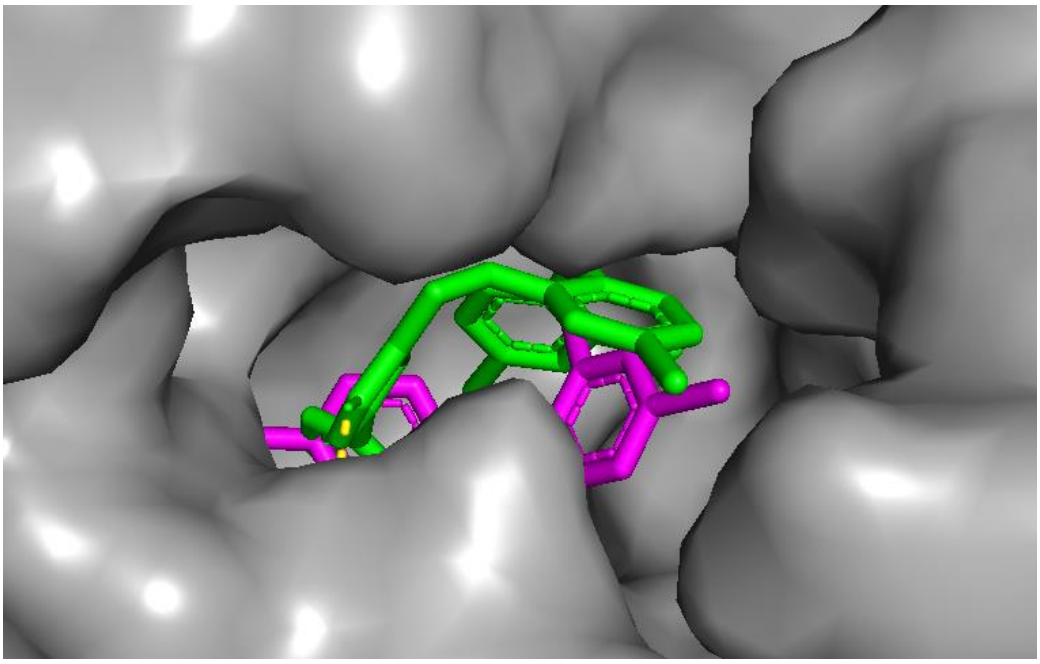


Figure 4. Dock pose image of ligand **5g** and triclosan in cavity of ENR

Conclusions

A series of novel triclosan-based-1,2,3-triazoles were synthesized and screened for their in vitro antibacterial activity against two gram positive (S. aureus, B. subtilis) and two gram negative strains (E.coli, P. aeruginosa) using triclosan as standard reference. All of the compounds displayed notable zones of inhibition on par with triclosan. The 3-methoxy compound presented the most potent activity, showing highest zone of inhibition. Compounds with 4-methoxy, 4-methyl, 2-methyl, 2-chloro, 4-phenyl and 3-methyl substitutions displayed comparable zones of inhibition. The compounds in which substituents were absent presented a little less zone of inhibition. The molecular docking study of the 3-methoxy-substituted ligand against crystal structure of ENR scored the best binding-affinity value, and presented important binding interactions such as H-bond and hydrophobic. Hence, these newly synthesized scaffolds could be considered for the development of antibacterial agents.

Experimental Section

General. ll chemicals were obtained from commercial sources and used without any further purification. Melting points were taken in glass capillary tubes on a Haake Bucher apparatus and are uncorrected. All proton NMR spectra were determined with a Varian 400 MHz spectrometer using deuterated-dimethylsulfoxide (DMSO-d_6) and are reported in δ (ppm) units. Thin-layer chromatography (TLC) was performed in E. Merck pre-soaked silica gel plates. Visualization was obtained by exposure to iodine vapors and/or under UV light (254 nm).

Procedure for synthesis of 2,4-dichloro-1-(4-chloro-2-(prop-2-yn-1-yloxy)phenoxy)benzene (3). To a solution of 4-chloro-2-(3,5-dichlorophenoxy)phenol **1** (0.001 mol) in DMF solvent (50 mL) was added propargyl bromide

2 (0.012 mol, 1.2 eq) and dry K_2CO_3 (0.012 mol, 1.2 eq). The reaction mixture was stirred for 4 hr at RT and progress was monitored by TLC. After completion, the reaction mixture was poured onto ice cold water, quenched with dilute HCl (5%) and obtained solid was purified via column chromatography using ethylacetate:n-hexane (1:9) as eluents to obtain the intermediate compound **3** as an off-white solid. Yield 81 %. m.p.: 115 – 117 °C. 1H NMR (400 MHz, DMSO) δ 7.70 – 6.80 (m, 6H), 4.90 (s, 2H), 3.37 (s, 1H). 13C NMR (101 MHz, DMSO) δ 152.1, 149.6, 143.2, 130.3, 129.8, 128.8, 127.6, 123.9, 122.5, 122.3, 119.0, 116.0, 79.4, 78.7, 56.9. M.F.: $C_{15}H_9Cl_3O_2$. ES-MS: m/z 328.00 $[M+2H]^+$.

General procedure for the synthesis triclosan-linked-1,2,3-triazole derivatives 5(a-h). To a solution of 4-chloro-2-(3,5-dichlorophenoxy)-1-(prop-2-yn-1-yloxy)benzene **3** (0.001 mol) in DMF (50 mL) was added various substituted aryl azides **4a-h** (0.001 mol, 1 eq), the reaction mixtures were stirred at room temperature for 4 h after addition of catalytic amounts of $CuSO_4.5H_2O$ and sodium ascorbate. The resulting reaction mass was poured onto crushed ice, the obtained solid was collected by filtration, and purified via column chromatography employing ethylacetate : n-hexane (3:7) as eluents.

4-((5-Chloro-2-(2,4-dichlorophenoxy)phenoxy)methyl)-1-phenyl-1H-1,2,3-triazole (5a) : White solid. Yield: 78% MP: 190 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.70 (s, 1H), 7.90 (m, 6H), 7.25 – 6.80 (s, 5H), 5.31 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 149.8, 143.3, 135.3, 134.7, 130.8, 130.2, 130.0, 128.1, 127.8, 124.4, 122.3, 122.1, 121.6, 120.7, 120.5, 118.2, 115.9, 63.5. M.F.: $C_{21}H_{14}Cl_3N_3O_2$. ESI-MS : m/z 447.02 $[M+2H]^+$.

4-((5-Chloro-2-(2,4-dichlorophenoxy)phenoxy)methyl)-1-(2-chlorophenyl)-1H-1,2,3-triazole (5b): White solid Yield 72%. MP : 185 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.38 (s,1H), 8.00 – 7.15 (s, 10H), 5.34 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2, 149.9, 143.5, 134.7, 131.7, 131.5, 130.9, 130.8, 130.6, 130.2, 128.5, 128.1, 128.0, 127.8, 124.9, 124.5, 122.3, 121.9, 118.2, 116.2, 63.6. M.F.: $C_{21}H_{13}Cl_4N_3O_2$. ESI-MS: m/z 480.98 $[M+H]^+$.

4-((5-Chloro-2-(2,4-dichlorophenoxy)phenoxy)methyl)-1-(o-tolyl)-1H-1,2,3-triazole (5c): Yellowish White solid. Yield 75%. MP : 170 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.59 (s, 1H), 7.65 – 7.58 (m, 2H), 7.27 – 7.06 (m, 6H), 6.79 (s, 1H), 5.27 (s, 2H), 3.83 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2, 149.9, 143.5, 136.3, 133.6, 131.6, 130.6, 130.1, 130.0, 128.1, 127.8, 126.9, 125.9, 124.4, 124.4, 124.3, 122.2, 121.9, 118.3, 116.2, 63.7, 17.8. M.F.: $C_{22}H_{16}Cl_3N_3O_2$. ESI-MS: m/z 460.74 $[M+H]^+$.

4-((5-Chloro-2-(2,4-dichlorophenoxy)phenoxy)methyl)-1-(m-tolyl)-1H-1,2,3-triazole (5d): Off-white solid. Yield : 77%. MP : 192 °C. ^{1}H NMR (400 MHz, DMSO) δ 9.67 (s, 1H), 8.51 (s, 1H), 7.72 (d, J = 6.4 Hz, 2H), 7.64 – 7.59 (m, 2H), 7.40 (d, J = 6.8 Hz, 2H), 7.27 (d, J = 8.0 Hz, 1H), 7.06 (s, 2H), 6.79 (d, J = 8.0 Hz, 1H), 5.29 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 147.5, 145.2, 139.4, 138.5, 138.1, 134.3, 130.0, 129.8, 129.2, 126.0, 125.5, 123.3, 123.2, 119.71, 117.3, 115.9, 115.5, 113.4, 111.7, 111.1, 58.8, 16.3. M.F.: $C_{22}H_{16}Cl_3N_3O_2$. ESI-MS: m/z 461.03 $[M+2H]^+$.

4-((5-Chloro-2-(2,4-dichlorophenoxy)phenoxy)methyl)-1-(p-tolyl)-1H-1,2,3-triazole (5e): Off-white solid. Yield : 73%. MP : 197 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.58 (s, 1H), 7.74 – 7.65 (m, 10H), 5.28 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 149.9, 143.4, 139.1, 134.6, 130.7, 130.3, 130.2, 128.1, 127.8, 124.5, 122.2, 122.0, 120.7, 120.6, 120.4, 118.2, 116.0, 63.7, 21.1. Chemical Formula: $C_{22}H_{16}Cl_3N_3O_2$. ESI-MS: m/z 461.03 $[M+2H]^+$.

1-([1,1'-Biphenyl]-4-yl)-4-((5-chloro-2-(2,4-dichlorophenoxy)phenoxy)methyl)-1H-1,2,3-triazole (5f): Off-white solid. Yield : 75%. MP : 202 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.73 (s, 1H), 7.94 (s, 2H), 7.76 – 7.43 (m, 7H), 7.28 (s, 1H), 7.07 (s, 2H), 6.80 (s, 1H), 5.33 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 149.9, 143.31, 141.9, 139.5, 135.9, 130.7, 130.2, 129.0, 128.4, 128.1, 128.0, 127.8, 127.1, 124.5, 122.2, 122.1, 120.7, 118.2, 115.9, 63.6. M.F.: $C_{27}H_{18}Cl_3N_3O_2$. ESI-MS: m/z 523.04 $[M+2H]^+$.

4-((5-Chloro-2-(2,4-dichlorophenoxy)phenoxy)methyl)-1-(3-methoxyphenyl)-1H-1,2,3-triazole (5g): Off-white solid. Yield : 72%. MP : 190 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.71 (s, 1H), 7.64 – 7.59 (m, 2H), 7.52 – 7.43 (m, 3H), 7.26 (d, J = 8.4 Hz, 1H), 7.06 (s, 3H), 6.78 (d, J = 8.4 Hz, 1H), 5.30 (s, 2H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 149.9, 143.3, 139.1, 134.6, 130.7, 130.3, 130.2, 130.1, 128.1, 127.8, 127.6, 124.5, 122.2, 122.0, 120.7, 120.6, 120.3, 118.2, 116.3, 63.6, 21.1. Chemical Formula: $C_{22}H_{16}Cl_3N_3O_2$. ESI-MS: m/z 477.02 $[M+2H]^+$.

4-((5-Chloro-2-(2,4-dichlorophenoxy)phenoxy)methyl)-1-(4-methoxyphenyl)-1H-1,2,3-triazole (5h): Off-white solid. Yield : 70%. MP : 193 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.66 (s, 1H), 7.91 (s, 2H), 7.64 – 7.59 (m, 2H), 7.47 (s, 2H), 7.27 – 7.25 (m, 1H), 7.06 (s, 2H), 6.79 – 6.77 (m, 1H), 5.30 (s, 2H), 3.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2, 149.6, 143.4, 136.3, 133.5, 131.5, 130.6, 130.1, 130.0, 128.1, 127.8, 126.9, 125.8, 124.4, 122.2, 121.9, 118.2, 116.1, 63.7, 17.8. Chemical Formula: $C_{22}H_{16}Cl_3N_3O_2$. ESI-MS: m/z 477.02 $[M+2H]^+$.

Acknowledgements

All authors thank the Head, Department of Chemistry, Osmania University for providing laboratory facilities.

Supplementary Material

Copies of the ^{1}H and ^{13}C NMR spectra of all products are provided in the Supplementary Material.

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