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Synthesis of 1,2,3-triazole-bound-1,2,4-triazoles containing N-phenylmorpholine structure: antibacterial, antifungal, and antioxidant properties, and AChE-inhibition analysis

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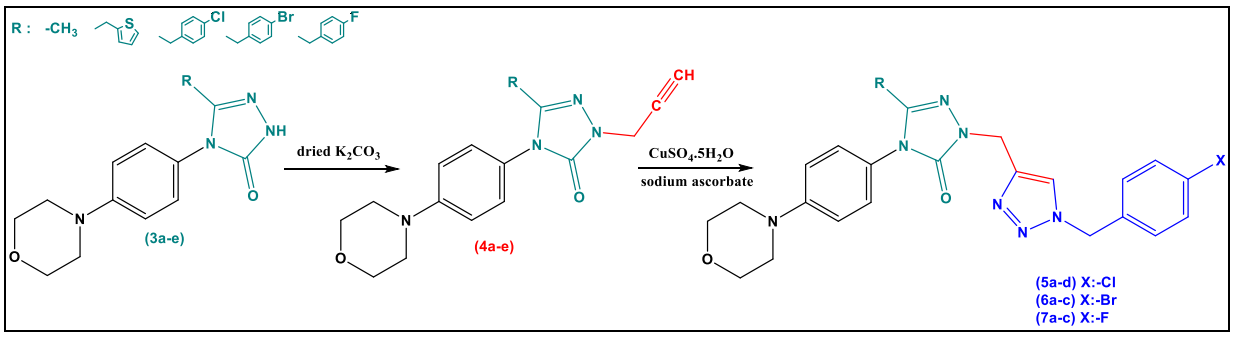
Abstract

Azole compounds are the most common antifungals in clinical use; however, their clinical efficacy has been reduced due to drug resistance following prolonged use. Hybrid triazole derivatives with different heterocyclic rings are gaining interest in this field. In this study, different triazole rings are combined by click reaction. In vitro antibacterial, antifungal and antioxidant properties for all compounds were determined. The ability of the compounds to inhibit acetylcholinesterase (AChE) enzyme activity was also investigated.



Keywords: Triazoles, phenylmorpholines, click reaction, antioxidant activity, AChE inhibition

Introduction

Antifungal drugs generally consist of four basic classes of molecules: fluoroptopyrimidines, polyenes, azoles and echinocandins. Among these molecular classes, azoles are considered to be the most commonly used antifungals in clinical use. They are the nucleus of drugs such as itraconazole and fluconazole. Whilst interesting pharmacological activities have been observed in many compounds containing a five-membered triazole-ring nucleus, their effects and efficacy have been significantly reduced due to the drug resistance that develops after long-term use.

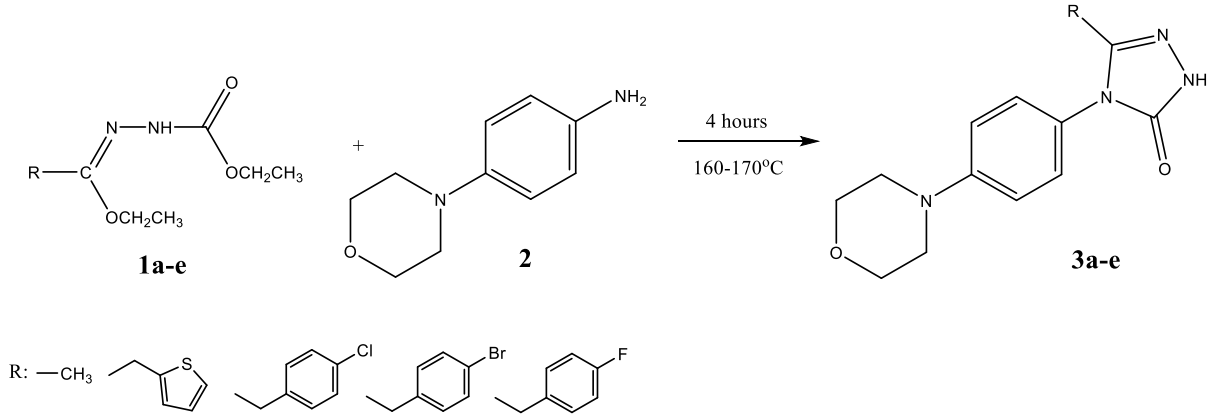
Due to the drug resistance resulting from the prolonged use of antifungal drugs, the preparation of new hybrid triazole derivatives, modified with different heterocyclic rings, has gained importance in this field. 1,2,3- and 1,2,4-Triazole derivatives have been the most interesting ring systems in terms of their heterocyclic chemistry and pharmacological properties. In several recent studies, the syntheses of molecules containing 1,2,4-triazole and 1,2,3-triazole rings were performed, and their antifungal effects investigated[1-3] Based on the analysis of structure-functional characterization of fungal CYP51, it was recently shown that azole drugs act as competitive fungal CYP51 inhibitors, occupying the active site of Cyp51 protein, preventing substrate binding and oxidation. This effect is reported to occur when the nitrogen atom in the N-4 position in the triazole ring binds to the heme-iron in its structure.[4-7]

It has been demonstrated through in vitro testing that newly synthesized morpholine-containing 1,2,3-triazoles have significant antibacterial effects.[8] Morpholine-containing triazoles and sugar compounds containing morpholine-fused triazoles were synthesized for a study investigating the effects of protein efficacy on enzymatic inhibition of carbohydrate-coupled heterocyclic compounds.[9] It has also been demonstrated that morpholine-containing triazole derivatives, e.g., 1,2,4- and 1,2,3-triazoles , act as neurokinin-1 receptor antagonists in the human body, and can form a new class in this field.[10] In this purposeful study, coumarin-derivative-1,2,3-triazoles and coumarin-derivative-1,2,4-triazoles were synthesized together.[11] It has been determined that 1,2,3-triazole- and 1,2,4-triazole-related compounds that bind to methylene bridges in morpholine- and piperazine-containing coumarin triazoles have anti-cancer effects against five cancer-cell systems.[12] In a study of the determination of the biochemical behavior of triazoles, a study of the 1,2,3-triazole-containing tacrine compound revealed that such compounds were effective on the inhibition of the acetylcholine esterase (AchE) enzyme which plays a key role in neurotransmitter hydrolysis in the central nervous system.[13] In another study for a new AChE-inhibitor design, compounds containing the acridone derivative 1,2,4-oxadiazole and 1,2,3-triazole ring system were synthesized; promising inhibition results were obtained.[14] As is known, tacrine compounds, which are phenanthridinium and aminoacridine derivatives, used as AchE enzyme inhibitors, are still the main drugs used in the treatment of Alzheimer's disease.[15] The resistance of many different types of pathogens to antimicrobial drugs raises new problems in treatments. Therefore, new antimicrobial drugs must be designed and synthesized. In the light of the important information presented above, in this study, the synthesis of morpholino-functional-bi-heteroazole derivatives containing 1,2,4-triazole-3-(5)-one and 1,2,3-triazole heterocycles were performed. Structural characterizations of the related compounds were made by various spectroscopic methods. By studying their antifungal activities and antioxidant properties, the relationship of these compounds with the inhibition of choline esterase (acetylcholine and butyrylcholine esterase) was investigated.

Results and Discussion

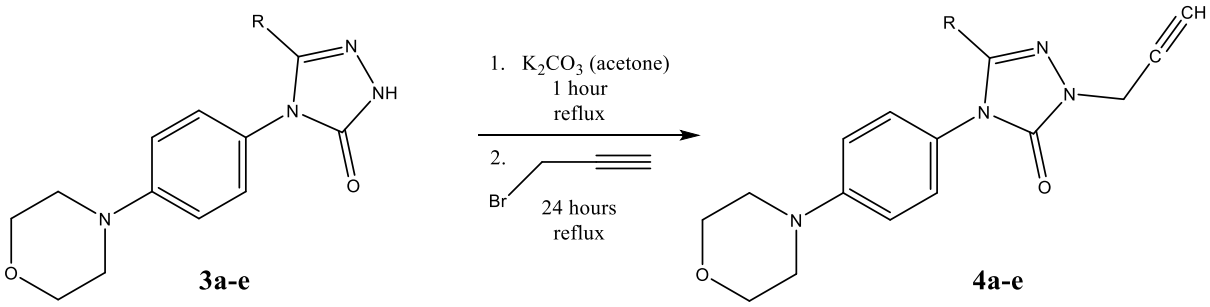
Chemistry

In the first step of the study, 5-alkyl/arylalkyl-4-(4-morpholinophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (3a-e) was obtained from the reaction of ethyl-2-(1-ethoxyethylidene)hydrazine-1-carboxylate (**1a-e**), which was obtained according to the literature methods[16,17], with 4-morpholinoaniline (**2**) as shown in Scheme 1.



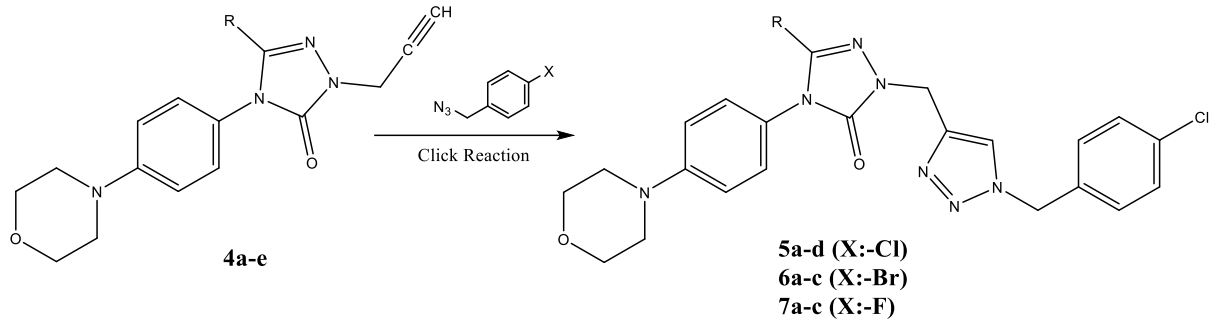
Scheme 1. The synthesis of type **3** compounds.

In the next step, the triazole potassium salt, formed by the removal of the triazol-3-one ring acidic NH proton with K_2CO_3, was converted into acetylenic triazole compounds (**4a-e**) by nucleophilic substitution with propargyl bromide as shown in Scheme 2.



Scheme 2. The synthesis of type **4** compounds.

In the last step, 1,2,3-triazole (**5a-d**), (**6a-c**), (**7a-c**) target compounds with 1,2,4-triazole content were obtained by reacting the key morpholine-containing acetylenic-unit-carrying triazole compounds (**4a-e**) with chlorobenzy lazide, bromobenzyl azide and fluorobenzyl azide, ascorbic acid and copper sulfate catalyst, as required by the click reaction shown in Scheme 3.



Scheme 3. The synthesis of types **5, 6** and **7** compounds

As is known, there is a probability of 1,4- and 1,5- disubstituted regioisomers likely to occur in click reactions.[18,19] On the other hand, it was reported that only 1,4-isomers were formed when copper salt catalyst was used. Similar results were obtained in our study, meaning that only 1,4-disubstituted-1,2,3-triazole target compounds were obtained in high yields (62-95%). When IR data related to type **3** compounds synthesized in the first step are evaluated, it was observed that the vibration at the 1,2,4-triazole ring N-1 position occurs at 3157-3346 cm^{-1}; these values are significantly lower in 4-halogenobenzyl derivatives. This is thought to be the result of the inductive effects of the halogen atoms. In the same region, aromatic C=CH stretching bands occur in the range of 3071-3078 cm^{-1}, and aliphatic CH tension bands appear in the range of 2960-2971 cm^{-1}, respectively. While the C=N group tension bands related to the triazole ring are observed in the range of 1584-1586 cm^{-1}, the C=O stretching bands are observed in the range of 1700-1765 cm^{-1}. Also, the COC group tension band in the morpholine ring is observed to form a tension vibration band at 1224-1237 cm^{-1} as an obvious peak. In the 4-halogenobenzyl derivatives, C-H deformation bands in the 1,4-substituted benzene rings attached at the 3-position to the triazole ring, with the aromatic ring directly attached to the morpholine ring, were also observed at 800-832 cm^{-1}. The most important band in the IR spectra of the acetylenic 1,2,4-triazole compounds (**4a-e**), obtained from the reaction of 1,2,4-triazole compounds (**3a-e**) with propargyl bromide and sodium ethoxide, is the C≡C group observed in the range of 2119-2130 cm^{-1}. On the other hand, the -C≡C-H stretching band of the acetylenic fragment appears in the range of approximately 3230-3270 cm^{-1}. The FT-IR spectra of all synthesized compounds are presented in the Supplementary Material in addition to the most prominent FT-IR values presented here.

The -NH group proton signals at the 1,2,4-triazole-ring N1 position of compounds **3a**, **3b**, **3c**, **3d** and **3e** in ^{1}H-NMR spectra were observed as a singlet peak corresponding to one proton in the range of 11.51-11.79 ppm. It was observed that the protons belonging to the NH group in the spectrum disappeared in a proton-deuterium exchange with D_2O.

In the ^{13}C-NMR spectral data of the type 3 compounds, the equivalent aromatic =CH carbons at the 2,6-position of the phenyl ring connected from the 3-position of the 1,2,4-triazole ring were observed at 115.24-115.45 ppm, higher than all other sp^2 hybridized carbons. The two-equivalent aromatic =CH carbons at position 3,5 of the same ring are seen at 128.13-128.66 ppm as a single signal in the lower field.

The most prominent IR spectral band is the stretching band of the C≡C group of the additional acetylenic group in type **4** compounds was observed in the range 2119-2130 cm^{-1}. The N-H stretching band present in type **3** compounds is observed to have disappeared in type **4** compounds. C=O Voltage bands of compounds of type **3** were compared with type **4** compounds; C=O voltage bands were observed at 1700-1765 cm^{-1} in compounds of type **3** and 1695-1708 cm^{-1} in acetylenic **4**-type compounds. Between the two groups of compounds, the C=O group has a significant difference in terms of wave numbers. The reason for the

significant difference is that, as expected, in acetylenic-1,2,4-triazole compounds, the electron density in the ring is significantly higher than that of the acetylene group.

When the ^{1}H-NMR spectral data of **4**-type acetylenic triazole compounds were examined, it was observed that the NH-proton signal completely disappears in the transition from compounds of type **3** to compounds of type **4**. In addition, the CH_2-proton signal of the acetylenic group at the N-1 position of the triazole ring appears at approximately 4.55 ppm in the downfield.

As a matter of fact, in the APT spectra of the C≡CH group, while both carbon signals were expected to form resonances with different phase sign, it was observed that both peaks of the ≡C and ≡CH carbons at approximately 75 ppm and 79 ppm formed resonances with the same phase sign. Such actions have been reported to be encountered in 13C-NMR applications of acetylenic groups such as DEPT, INEPT, HETCOR, SEFT and APT. [20]

When the synthesized compounds of type **5** were examined, it was observed that the C≡C-H stretching vibrations at approximately 3230-3270 cm^{-1} and 2119-2130 cm^{-1}, which were present in the IR data of compounds of type **4**, had disappeared.

There are detailed data on the formation of type **5** 1,2,3-triazole ring by the "click" reaction of benzylic azides with acetylenic 1,2,4-triazole compounds of type **4**. The C=C-H proton signal at the C-5 position of the aromatic 1,2,3-triazole ring provides very valuable structural data.[21] The peak in question appears as a singlet spectral line at approximately 8.12-8.15 ppm in the lowest region of the spectrum. On the other hand, because of the formation of the 1,2,3-triazole ring, it is observed that the CH_2 protons in the 1,2,4-triazole-N1-CH_2-1,2,3-triazole position connecting the 1,2,4-triazole ring and the 1,2,3-triazole ring are clearly shifteddownfield. In fact, in the acetylenic 1,2,4-triazoles of type **4**, similar 1,2,4-triazole-N1-CH_2-C≡CH group protons at the equivalent position appear at 4.51-4.55 ppm, while, in the 1,2,3-triazole derivatives of type **5**, this peak appears at 4.92-4.99 ppm , providing evidence of cyclization. Similarly, Ph-CH_2 group protons from the azide group, and linked to the N-1 position of the 1,2,3-triazole ring by cyclization, are observed to appear much farther downfield at 5.57-5.61 ppm.

^{13}C-NMR spectral data of type **5** compounds show that the two peaks belonging to acetylenic carbons (-C≡CH) disappeared during the transition from type **4** to type **5** compounds. Because of the click reaction, the most important data on the formation of the 1,2,3-triazole ring is the CH carbon signal from the acetylenic group at the 5-position of this ring, which occurs at approximately 124.25-124.30 ppm. In the synthesized compounds of type **5**, the C=O and C=N group carbons in the lowest region generate signals in the range of 153.03-153.38 ppm and 151.38-151.53 ppm, respectively.

Chemical-shift values of attached to the triazole ring at 5-position C-4 quaternary carbon peaks of compounds **3c** and **3d**, which are 4-chloro- and 4-bromobenzyl derivatives, respectively, show remarkable spectral data. Peak appears at 131.76 ppm in the 4-chlorobenzylderivative compound **3c**, while it appears at 120.17 ppm in the 4-bromobenzylderivative compound **3d**. The significant difference in the chemical shifts of the carbons at the 4-position of the chlorine and bromine derivatives revealed the strong inductive-electron attraction of chlorine relative to bromine. This explanation is strongly confirmed by the shift of the 4-fluorine-bonded quaternary carbon at the same position in compound **3e** to the lowest region of the spectrum. Thus, in compound **3e**, the quaternary C-4 forms two distinct peaks at 160.31 and 162.72 ppm, respectively, involving a carbon-fluorine interaction (coupling constant, ^{4}J C-F 241 Hz). In compounds 3c and 3d, which are 4-chloro, and 4-bromo benzyl 1,2,4-triazole derivatives, the $C_{3',5'}$-H and $C_{2',6'}$-H carbon peaks in the phenyl rings are observed to be equivalent. Whereas, in compound 3e, it is observed that the equivalent carbon atoms in the same position differ as a result of the interaction of the fluorine atom with carbon in the 4-fluoro benzyl group.

As a result of the C-F interaction in compound **3e**, $C_{3',5'}$-H peaks at 115.49 and 115.28 ppm (matching constant, ^{3}J C-F 21 Hz) and $C_{2',6'}$-H carbon peaks at 130.91 and 130.84 ppm (matching constant, ^{2}J C-F 7.6 Hz) form four different peaks in pairs. Similarly, the quaternary C-1 carbon peak of the same compound appeared at 131.78 ppm, differing approximately 4 ppm from the equivalent carbon peaks in other similar derivatives, without forming a pairing. The coupling constants obtained in compound **3e** demonstrate complete compatibility data for the 4-fluorophenyl ring.

Antioxidative activity results

The antioxidant properties of the synthesized compounds were determined according to DPPH and superoxide-dismutase methods. Considering the results obtained from the antioxidant-activity investigations of the synthesized compounds, the DPPH free-radical-scavenging activity of compound **6b**, which is a 1,2,4-triazol-5-one consisting of a 1,2,3-triazole compound with thiophene and bromobenzyl substituents, shows a very high inhibition of 97%. 1,2,4-Triazol-5-one **3b**, which also carries a thiophene substituent, also shows a very high inhibition of 96%. The acetylenic derivative of the same compound, **4b**, exhibited almost the same level of free-radical scavenging activity at 95%.

To determine the antioxidant properties of the same compounds, superoxide-dismutase activities were determined. This activity, which can also be defined as the potential to inhibit free-radical formation, revealed that the synthesized compounds have certain antioxidant potential. As a matter of fact, **3a**, **4a**, **3e** and **3b** exhibited high oxidation-inhibition rates of 89%, 79%, 76% and 71%, respectively. In terms of antioxidant character, it is seen that the synthesized compounds have both radical-scavenging and radical-formation-inhibitory potential. Comparative antioxidant-activity results obtained by both methods are presented in the Supplementary Material.

Acetylcholinesterase inhibitory activity results

It has been revealed previously that azole-class compounds in general, and 1,2,3-triazole compounds as a special class, are effective in the inhibition of the acetyl choline esterase (AChE) enzyme, which plays a key role in neurotransmitter hydrolysis in the central nervous system. To determine these properties, AChE inhibition data of synthesized compounds **3**, **4**, **5** and **6** were obtained and compared. Accordingly, the results were in good agreement with the literature data. In particular, very significant inhibition results, e.g., 75% in 1,2,3-triazole-containing compound **5d**, and 69% in compound **6b**, were obtained. Thus, these compounds were found to be suitable as AChE inhibitors. Other data are presented graphically in the Supplementary Material. Based on recent studies, the high cholinesterase inhibition of 1,2,3-triazole and 1,2,4-triazole heterocycles are leading them to becoming candidate drug molecules for the treatment of Alzheimer's.[22,23] In this respect, our new generation triazole compounds **5d** and **6b** could constitute an important role.

Antibacterial and antifungal activity results

The compounds obtained were subjected to antimicrobial testing against 13 micro-organisms. The results showed that the solutions obtained from **6b**, **4d**, **5d**, **4c** and **3e** showed significant antibacterial and antifungal activity against all tested fungi and bacteria, if specifically indicated by sample number and compound of interest. Compounds **4d**, **5d** and **4c**, containing 1,2,4-triazole and 1,2,3-triazole together with a morpholine ring, showed very high antifungal activity against *A. niger*, while they showed very high antimicrobial activity against *C. albicans*. On the other hand, compounds **4d**, **5d**, **4c** and **3e** showed high antibacterial and antifungal activities against all tested fungi and bacteria. The most effective example of the compounds synthesized in

the study was found to be the compound containing 4-fluorobenzyl-substituted-1,2,4-triazole (**3e**). Antifungal inhibition-zone values are presented in the Supplementary Material.

The biggest inhibition zones among the screened original-compound samples were observed for solutions of **4d** and **5d** (23 mm), containing 1,2,4-triazole and 1,2,3-triazole with a morpholine ring, against *Micrococcus luteus* bacteria and *Candida albicans* fungi, respectively. It is noteworthy that all of the compounds tested were found to be selectively more effective against *Gram negative bacteria* than *Gram positive* ones.

Determination and optimization of the crystal structure

XRD analysis was performed to determine the crystal-structural parameters of the compounds and reveal their crystallographic-structure information. Using compound **7b**, analysis revealed that the crystallization system of the compounds exhibited an orthorhombic structure with the space group P21 21 21 (Figure 1). There are two triazole rings in the main skeletal structure of the 2-((1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(4-morpholinophenyl)-5-(thiophen-2-ylmethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one compound (**7b**). The 1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl group has a methylene group (-CH_2) attached to it, while 4-(4-morpholinophenyl) refers to a phenyl group containing a morpholine ring at the 4th position. The 5-(thiophen-2-ylmethyl) has a methyl group (-CH_2) attached to the 5th position of the thiophene ring (C_4H_4S), while the designation 2,4-dihydro-3H-1,2,4-triazol-3-one refers to the 1,2,4-triazol-3-one ring and the partial saturation of hydrogen in this ring (dihydro).

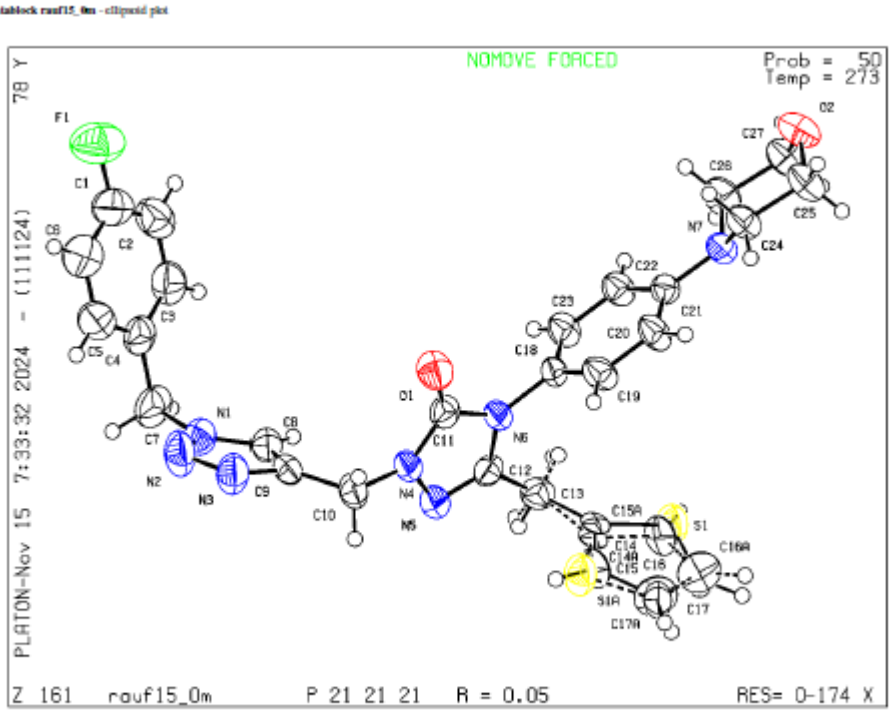


Figure 1. X-ray structure of (**7b**)

The unit cell dimensions are a = 5.8401(7) Å, b = 17.074(2) Å and c = 25.685(3) Å, while the interaxial angles are α = β = γ = 90°. The unit cell volume is 2561.2 (5) Å^3, and the number of molecules per unit cell is Z = 4. The X-ray structure was refined using a multi-scan absorption correction, with temperature limits Tmin = 0.652 and Tmax = 0.745 (Figure 2).

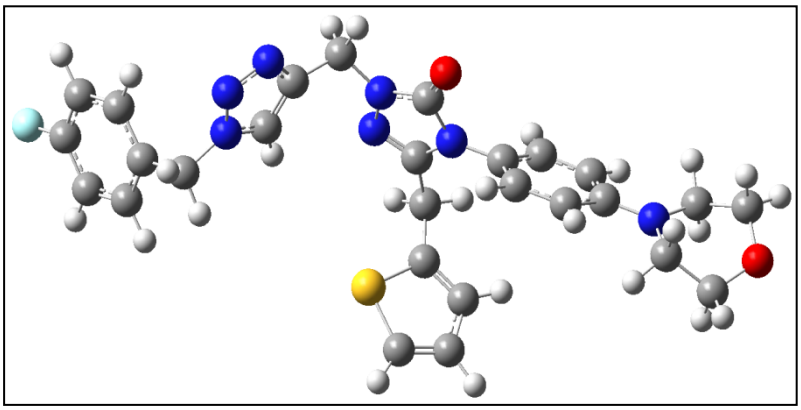


Figure 2. Optimized X-ray structure of **7b**

The final R-squared values obtained for the observed data were R1 = 0.0500 and wR2 = 0.1065. The R-squared coefficient-of-determination (goodness-of-fit) value of 1.013 demonstrated that the crystallographic model is of high quality. The crystallographic data are presented in detail in the Table 4, S7-Supplementary Material. A comparison of the geometric parameters between the X-ray data and the DFT theoretical values for the crystal structure is also provided in the Table 2, S4-Supplementary Material.

In the structural solution, a disorder structure was detected in the thiophene ring attached to the 1,2,4-triazole ring. The carbon and sulfur atoms in this structure are shown as A and B (SA, SB and CA, CB). When performing the DFT calculation, the disorder state in this ring was excluded for clarity, as shown in the Supplementary Material, which shows the optimized molecule image. The XRD,DFT and literature bond lengths (Å) for some selected single bonds between atoms in the molecular structure of the studied compound are : C1 - F1 (1.374, 1.349, 1.358[24]), S1A - C14A (1.680, 1749, 1.746[25]), C4 - C7 (1.510, 1.516, 1.512[26]), N1 - C7 (1.465, 1.460, 1.461[27]), N1 - C8 (1.330, 1.379, 1.376[28]), N6 - C12 (1.383, 1.383,1.373[29]), N4 - N5 (1.389, 1.380,1.388[30]), N7 - C26 (1.457, 1.458, 1.340[31]), O2 - C25 (1.418, 1.424, 1.452[32]). Some selected double bonds between atoms in the molecular structure of the compound are: C8 = C9 (1.299, 1.302, 1.369[27]), N5 = C12 (1.299, 1.302, 1.300[28]) O1 = C11 (1.218, 1.219, 1.220[33]), C14A =C15A (1.400, 1.368, 1.419[28]). The XRD experimental and DFT theoretical values show good agreement when compared to the geometric parameters reported in the literature.

In the crystal structure, two phenyl rings (R1: C1/C6), (R4: C18/C23) and two triazole rings (R2: N1/C8), (R3: N4/C11) exhibit a planar conformation; the other rings do not. X-ray diffraction measurements showed that the dihedral angles between the rings R1 - R2, R1 - R3, R1 - R4, R2 - R3, R2 - R4, R3 - R4 were 71.56º, 34.65º, 84.88º, 76.97º, 42.57º and 70.03º, respectively. The visualization is also shown in Figure 3d.

Additionally, a strong correlation was observed between the theoretical structural geometry and the experimental structural parameters obtained through X-ray diffraction analysis. As illustrated in Figure 3, the experimental and calculated parameters of the molecule exhibit a high degree of agreement. Specifically, the bond lengths show a strong correlation with an R^2 = 0.977 (SI 5a), indicating that the values from both data sets are very close. Similarly, the bond angles and dihedral angles display excellent correlations of R^2 = 0.932 (SI 5b) and R^2 = 0.939 (SI 5c), respectively, confirming their close agreement.

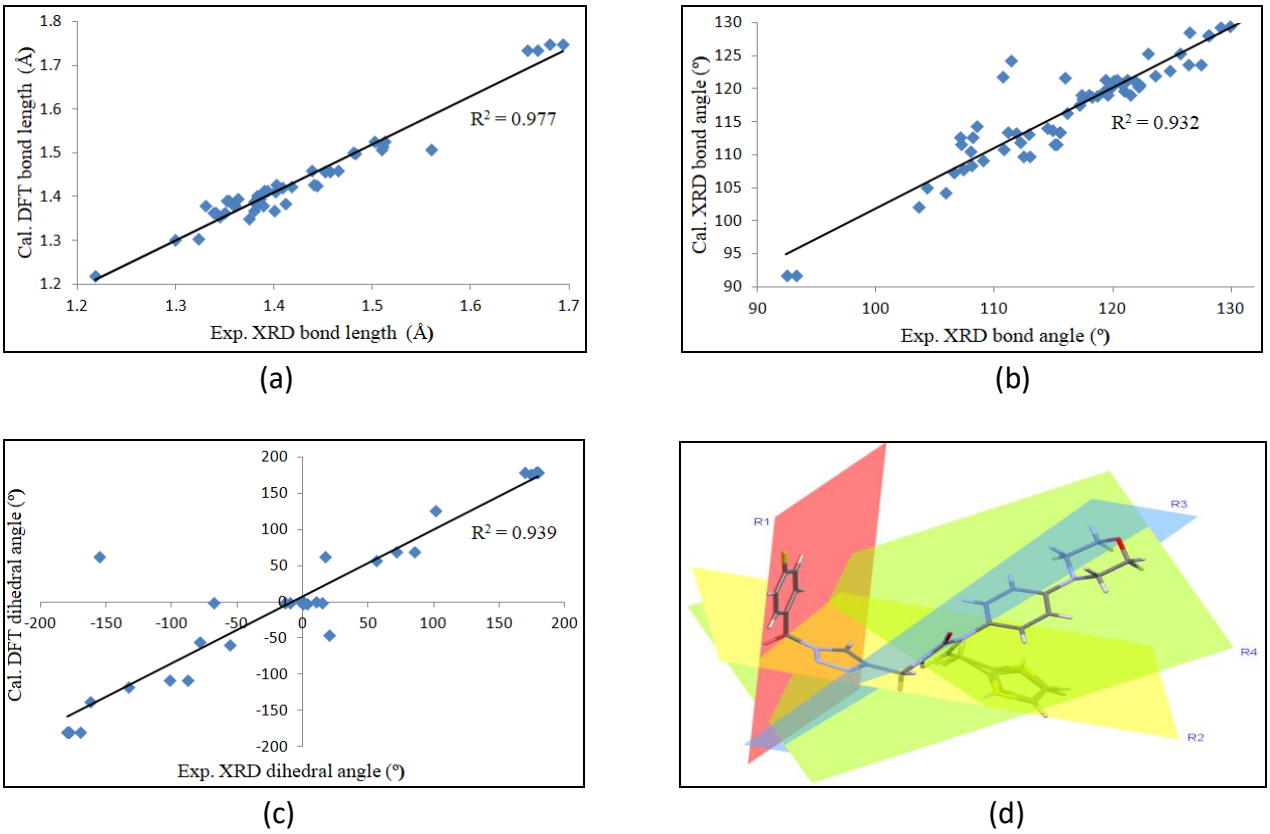


Figure 3. Graphical correlation XRD experimental and DFT theoretical correlation versus (a) bond lengths (b) bond angles (c) torsion angles, (d) Dihedral angles between ring planes in the molecule.

The structural stability of a compound largely depends on intramolecular and intermolecular interactions.[34]. in the Table 3, Supplementary Material (S6) presents the lengths and angles of the identified hydrogen bonds in the compound, detailing the interactions between donor and acceptor atoms. The distances of the hydrogen bonds (D—H, H···A, and D···A) and their angles indicate the presence of strong, and stable, interactions. The central molecule is connected to other neighboring molecules by hydrogen bonds at 12 points in 6 types, but in pairs, thus providing crystal packing. These intermolecular hydrogen bonds are shown in the S5-Supplementary Material. The participation of O, N and F atoms in hydrogen bonds in the molecule increases the structural stability of the compound. Anionic and cationic interactions occur through C—H···O, N—H···O, and C—H···N hydrogen bonds, with distances ranging from 2.379 Å to 2.740 Å. According to Table 3 in the Supplementary Material (S6) most of the C—H···O hydrogen bonds exhibit favorable distances (H···A < 2.7 Å), and large angles (150° and above), which contribute to the stability of the molecular structures. The C10—H10A···O2 hydrogen bond especially shows that both short distances and large angles (168.28°) reflect strong hydrogen bonds. The bond is very close to linear geometry. In addition, the C—H···N nitrogen hydrogen bonds in the triazole ring appear to provide intermolecular interactions that increase the overall stability of the molecule. The π-π interactions of the phenyl rings in the crystal structure were analyzed with the OLEX2-1.5 program. As a result of the analysis, no π-π interactions were found between the rings. Therefore, these interactions did not contribute to crystal packing. The crystal-packing diagram with intermolecular hydrogen bond interactions is shown in Figure 4.

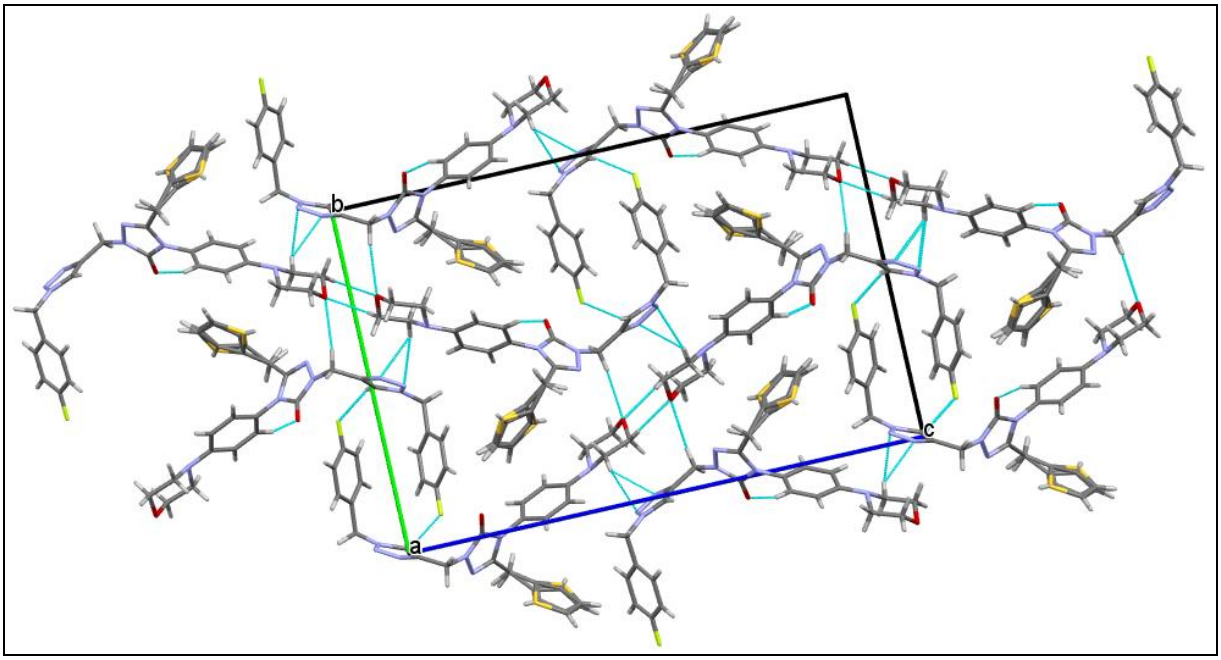


Figure 4. Crystal-packing diagram with intermolecular hydrogen-bond interactions along the a-axis in the unit cell.

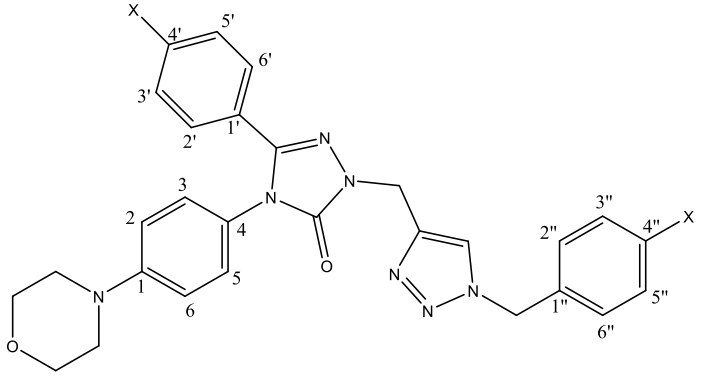
Conclusions

This study has investigated the synthesis and biochemical evaluation of compounds containing different triazole isomeric structures via the click reaction. Our research focuses on exploring the antimicrobial, antioxidant, and acetylcholinesterase (AChE) inhibition properties of these compounds, particularly those with 1,2,4-triazole and 1,2,3-triazole rings. The synthesis of various derivatives, including fluorine-substituted compounds, led to the identification of highly effective antimicrobial agents and promising AChE inhibitors. The 1,2,4-triazole derivative (**3e**) exhibited particularly strong antimicrobial activity, while compounds containing 1,2,3-triazole rings showed significant enzyme inhibition. High levels of AChE enzyme-inhibition results were observed in the **5-** and **6**-type 1,2,3-triazole compounds. These findings underscore the potential of triazole-based compounds in pharmaceutical applications, especially for treating infections and neurodegenerative diseases. Further investigation of these compounds, particularly through medical and clinical studies, is essential to confirm their therapeutic potential.

Experimental Section

General. In this study, all solvents used in the syntheses were used after purification and drying. The chemicals used in all the experimental studies were supplied by companies such as Sigma-Aldrich, Merck, Fluka and Carlo Erba. All the experimental studies were conducted at the Karadeniz Technical University, Faculty of Science, Department of Chemistry, Organic Chemistry Research Laboratories. NMR spectra of the synthesized compounds were taken in DMSO-d6 solvent. NMR spectra: Karadeniz Technical University, Department of Chemistry, Varian Mercury (200 MHz); Recep Tayyip Erdogan University, Agilent Technologies, (400 MHz), and

Giresun University, Bruker AVANCE III, (400 MHz). IR Spectra were taken in a Perkin Elmer Spectrum FT-IR spectrophotometer at Karadeniz Technical University, Department of Chemistry. Mass spectra was taken in absolute ethanol using a Quattro LC 4.0 micromass spectrophotometer in Karadeniz Technical University, Department of Chemistry. Melting points were determined using a Schmezpunktbestimmer SMP II digital device. Reaction times of all reactions were determined by TLC using aluminum plates.



General procedure for the synthesis of 5-alkyl/arylalkyl-4-(4-morpholinophenyl)-2,4-dihydro-*3H*-1,2,4-triazol-3-one (3a-e)

Compounds **3a-e** were synthesized according to a method given in the literature.[35]

5-Methyl-4-(4-morpholinophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (3a). Ethyl-2-(1-ethoxyethylidene)-1-methyl hydrazine -1-carboxylate (**1a**) (0.01 mol) with 4-morpholinoaniline (0.01 mol) extension tube fitted in a 50 ml bottom round flask was refluxed at 160-170°C for 2 hours. The progress of the reaction was monitored by TLC at appropriate time intervals. After cooling the flask, the precipitated purple solid was removed by dissolving with hot ethyl acetate and filtered. The filtered solution was recrystallized from ethyl acetate-petroleum ether (1:1). White crystals, yield (67%), mp: 238-240°CIR (ATR, cm^{-1}): 3301 (-NH), 3073(Ar-CH), 2965 (Aliph.CH), 1700(C=O), 1588 (C=N), 1237(C-O), 800 (Ar-CH def.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.01 (s, 3H, CH_3), 3.16-3.18 (t, 4H, morp. N-CH_2 *J* 4 Hz), 3.73-3.75 (t, 4H, morp. O-CH_2 *J* 4 Hz), 7.04-7.05 (d, 2H, morp. phenyl-$H_{2,6}$ *J* 4 Hz), 7.20-7.21 (d, 2H, morp. phenyl-$H_{3,5}$ *J* 4 Hz), 11.51 (s, 1H, -NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 12.7 (CH_3), 48.6 (N-CH_2 morp.), 66.2 (O-CH_2 morp.), 115.6 (phenyl-$C_{2,6}$), 124.5 (phenyl-C_4), 128.3 (phenyl-$C_{3,5}$), 144.8 (phenyl-C1), 150.8 (C=N), 154.9 (C=O). Anal. Calcd. For $C_{13}H_{16}N_4O_2$ Ma: 260.30 g/mol, $[M]^+$ (m/z): 261 (27%) [M+1]

4-(4-Morpholinophenyl)-5-(thiophene-2-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-one (3b). Ethyl 2-(1-ethoxy-2-(thiophen-2-yl)ethylidene)hydrazine-1-carboxylate (**1b**) (0.01 mol) with 4-morpholinoaniline (0.01 mol) extension tube fitted in a 50 ml bottom round flask was refluxed at 160-170°C for 2 hours. The progress of the reaction was monitored by TLC at appropriate time intervals. After cooling the flask, the precipitated purple solid was removed by dissolving with hot ethyl acetate and filtered. The filtered solution was recrystallized from ethyl acetate-petroleum ether (1:1). Light-brown crystals, yield (78.9%), mp:221-223°C. IR (ATR, cm-1): 3346 (-NH), 3071 (Ar-CH), 2960 (Aliph.CH), 1741 (C=O), 1585 (C=N), 1229 (C-O), 822 (Ar-CH def.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.16 (bs,4H, morpholine (morp.) N-CH_2), 3.74 (bs, 4H, morp. O-CH_2), 3.99 (s, 2H, CH_2), 6.65 (s, 1H, thiophene (thiop.) CH), 6.84 (s, 1H, thiop. CH.), 6.98-6.99 (d, 2H, phenyl-$H_{2,6}$ *J* 4 Hz), 7.12 (bs, 2H, phenyl-$H_{3,5}$), 7.33-7.34 (d, 1H, thiop. CH *J* 4 Hz), 11.70 (s, 1H, -NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 27.0 (CH_2), 48.5 (morp. N-CH_2), 66.5 (O-CH_2 morp.), 115.2 (phenyl-$C_{2,6}$), 124.1 (phenyl-C_4), 125.8 (thiop. -C_5), 127.1 (thiop. -C_4), 127.3 (thiop. -C_3), 128.1 (phenyl-$C_{3,5}$), 137 (thiop. C_q), 146.2 (phenyl-C1), 151.4 (C=N), 155.1 (C=O). Anal. Calcd. For $C_{17}H_{18}N_4O_2S$ Ma: 342.42 g/mol, $[M]^+$ (m/z): 365 (50%) [M+Na]

5-(4-Chlorobenzyl)-4-(4-morpholinophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (3c). Ethyl 2-(2-(2-(4-chlorophenyl)-1-ethoxyethylidene)hydrazine-1-carboxylate (**1c**) (0.01 mol) with 4-morpholinoaniline (0.01 mol) extension tube fitted in a 50 ml bottom round flask was refluxed at 160-170°C for 2 hours. The progress of the reaction was monitored by TLC at appropriate time intervals. After cooling the flask, the precipitated purple solid was removed by dissolving with hot ethyl acetate and filtered. The filtered solution was recrystallized from ethyl acetate-petroleum ether (1:2). White crystals, yield (60%), mp: 195-196°C. IR (ATR, cm^{-1}): 3357 (-NH), 3074 (Ar-CH), 2962 (Aliph.CH), 1736 (C=O), 1584 (C=N), 1235 (C-O), 827 (Ar-CH def.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.13-3.15 (t, 4H, morp. N-CH_2 *J* 4 Hz), 3.73-3.74 (t, 4H, morp. O-CH_2 *J* 4 Hz), 3.76 (s, 2H, Ph-CH_2), 6.98 (bs, 2H, phenyl-$H_{2,6}$), 7.03 (bs, 2H, phenyl-$H_{3,5}$), 7.08 (bs, 2H, 4-Cl-phenyl-$H_{2',6'}$), 7.42 (bs, 2H, 4-Cl-phenyl-$H_{3',5'}$), 11.68 (s, 1H, -NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 31.7 (Ph-CH_2), 48.6 (N-CH_2morp.), 66.0 (O-CH_2morp.), 115.5 (morp. phenyl-$CH_{2,6}$), 124.1 (morp. phenyl-C_4), 128.7 (morp. phenyl-$CH_{3,5}$), 128.7 (4-Cl-phenyl-$CH_{3',5'}$), 131.0 (4-Cl-phenyl-$CH_{2',6'}$), 131.8 (4-Cl-phenyl-$C_{4'}$), 134.6 (4-Cl-phenyl-$C_{1'}$), 146.3 (morp. phenyl C_1), 151.2 (C=N), 155.1 (C=O). Anal. Calcd. For $C_{19}H_{19}ClN_4O_2$ Ma: 370.84 g/mol, $[M]^+$ (m/z): 371 (41%) [M+1]

5-(4-Bromobenzyl)-4-(4-morpholinophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (3d). Ethyl 2-(2-(2-(4-bromophenyl)-1-ethoxyethylidene)hydrazine-1-carboxylate (**1d**) (0.01 mol) with 4-morpholinoaniline (0.01 mol) with an extension tube fitted in a 50 ml bottom round flask was refluxed at 160-170°C for 2 hours. The progress of the reaction was monitored by TLC at appropriate time intervals. After cooling the flask, the precipitated purple solid was removed by dissolving with hot ethyl acetate and filtered. The filtered solution was recrystallized from ethyl acetate-petroleum ether (1:1). White crystals, yield (73%), mp: 180°C. IR (ATR, cm^{-1}): 3163 (-NH), 3078 (Ar-CH), 2961 (Aliph. CH), 1735 (C=O), 1585 (C=N), 1234 (C-O), 828 (Ar-CH def.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.16 (bs,4H, morp. N-CH_2), 3.75 (bs, 4H, morp. O-CH_2), 3.76 (s, 2H, Ph-CH_2), 6.96 (bs, 2H, phenyl-$H_{2,6}$), 6.96 (bs, 2H, phenyl-$H_{3,5}$), 7.08 (bs, 2H, 4-Br-phenyl-$H_{2',6'}$), 7.42 (bs, 2H, 4-Br-phenyl-$H_{3',5'}$), 11.68 (s, 1H, -NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 31.7 (Ph-CH_2), 48.5 (N-CH_2morp.), 66.4 (O-CH_2morp.), 115.4 (morp. phenyl-$CH_{2,6}$), 124.0 (morp. phenyl-C_4), 128.7 (morp. phenyl-$CH_{3,5}$), 131.6 (4-Br-phenyl-$CH_{3',5'}$), 131.3 (4-Br-phenyl-$CH_{2',6'}$), 120.2 (4-Br-phenyl-$C_{4'}$), 135.6 (4-Br-phenyl-$C_{1'}$), 146.3 (morp. phenyl C_1), 151.5 (C=N), 155.1 (C=O). Anal. Calcd. For $C_{19}H_{19}BrN_4O_2$ Ma: 415,29 g/mol, $[M]^+$ (m/z): 415 (21%) [M+]

5-(4-Fluorobenzyl)-4-(4-morpholinophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (3e). Ethyl 2-(2-(2-(4-fluorophenyl)-1-ethoxyethylidene)hydrazine-1-carboxylate (**1e**) (0.01 mol) with 4-morpholinoaniline (0.01 mol), an extension tube fitted in a 50 ml bottom round flask was refluxed at 160-170°C for 2 hours. The progress of the reaction was monitored by TLC at appropriate time intervals. After cooling the flask, the precipitated purple solid was removed by dissolving with hot ethyl acetate and filtered. The filtered solution was recrystallized from ethyl acetate-petroleum ether (1:1). White crystals, yield (75%), mp: 200°C. IR (ATR, cm^{-1}): 3167 (-NH), 3072 (Ar-CH), 2971 (Aliph.CH), 1765 (C=O), 1586 (C=N), 1224 (C-O), 830 (Ar-CH def.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.08 (bs,4H, morp. N-CH_2), 3.72 (bs, 4H, morp. O-CH_2), 3.75 (s, 2H, Ph-CH_2), 6.93 (bs, 2H, phenyl-$H_{2,6}$), 6.93 (bs, 2H, phenyl-$H_{3,5}$), 7.00 (bs, 2H, 4-F-phenyl-$H_{2',6'}$), 7.07 (bs, 2H, 4-F-phenyl-$H_{3',5'}$), 11.79 (s, 1H, -NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 31.6 (Ph-CH_2), 48.4 (morp. N-CH2), 66.4 (morp. O-CH_2), 115.4 (morp. phenyl-$CH_{2,6}$), 128.6 (morp. phenyl-$CH_{3,5}$), 124.1 (morp. phenyl-C_4), 115.3-115.5 (4-F-phenyl -$CH_{3',5'}$), 130.8-130.9 (4-F-phenyl -$CH_{2',6'}$), 131.8 (4-F-phenyl-$C_{1'}$), 146.8 (morp. phenyl-C_1), 151.4 (C=N), 155.3 (C=O), 162.7 (4-F-phenyl-$C_{4'}$). Anal. Calcd. For $C_{19}H_{19}FN_4O_2$ Ma: 354.39 g/mol, $[M]^+$ (m/z): 355 (18%) [M+1]

5-Methyl-4-(4-morpholinophenyl)-2-(prop-2-yn-1-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (4a). 5-Methyl-4-(4-morpholinophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**3a**) (0.01 mol) was dissolved in 100 ml of dry acetone in a 2-neck flask fitted with reflux condenser and drying tube, anhydrous K_2CO_3 1.39 g (0.01 mol) was added

and refluxed for 1 hour. At the end of this period, 1.18 g (0.01 mol; d=1.34 g/mol 80%) propargyl bromide was added to the cooled solution which was then refluxed for 24 hours. The cooled solution was filtered and evaporated. An ice-water mixture was added to the solid residue formed. The white solid product was filtered, washed several times with water and crystallized from acetone-petroleum ether (1:1). White crystals, yield (92%), mp: 150°C. IR (ATR, cm^{-1}): 3276 (Alkynyl C-H), 3125(Ar-CH), 2981 (Aliph.CH), 2130 (C≡C), 1695 (C=O), 1589 (C=N), 1231 (C-O), 835 (Ar-CH def.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.98 (s, 3H, -CH_3), 3.14 (bs, 4H, morp. N-CH_2), 3.29 (bs, 1H, C≡C-H+H_2O) 3.72 (bs, 4H, morp. O-CH_2), 4.51 (s, 2H, Alkyn-CH_2), 7.01-7.02 (d, 2H, phenyl-$H_{2,6}$ *J* 4 Hz), 7.18-7.21 (d, 2H, phenyl-$H_{3,5}$ *J* 4 Hz). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 12.5 (CH_3), 34.7 (Alkynyl-CH_2), 48.5 (morp. N-CH_2), 66.5 (morp. O-CH_2), 75.3 (C≡CH), 79.0 (C≡CH), 115.6 (morp. phenyl-$CH_{2,6}$), 124.1 (4–morp. phenyl-C_4), 128.3 (morp. phenyl-$CH_{3,5}$), 14.3 (morp. phenyl-C_1), 151.5 (C=N), 152.7 (C=O). Anal. Calcd. For $C_{16}H_{18}N_4O_2$ Ma: 298.35 g/mol, $[M]^+$ (m/z): 299 (86%) [M+1].

4-(4-Morpholinophenyl)-2-(prop-2-yn-1-yl)-5-(thiophen-2-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (4b). 4-(4-morpholinophenyl)-5-(thiophene-2-ylmethyl)-2,4-dihydro-3H-1,2,4-triazole-3-one (**3b**) (0.01 mol) was dissolved in 100 ml of dry acetone in a 2-neck flask fitted with a reflux condenser and drying tube, anhydrous K_2CO_3 1.39 g (0.01 mol) was added and refluxed for 1 hour. At the end of this period, 1.18 g (0.01 mol; d=1.34 g/mol 80%) propargyl bromide was added to the cooled solution which was then refluxed for 24 hours. The cooled solution was filtered and evaporated. An ice-water mixture was added to the solid residue formed. The white solid product was filtered, washed several times with water and crystallized from dimethylformamide-ethyl alcohol (1:1). White crystals, yield (64%), mp: 197-199°C. IR (ATR, cm^{-1}): 3228 (Alkynyl C-H), 3086 (Ar-CH), 2961 (Aliph.CH), 2124 (C≡C), 1706 (C=O), 1585 (C=N), 1230 (C-O), 825 (Ar-CH def.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.14 (bs, 4H, morp. N-CH_2), 3.34 (bs, 1H, C≡C-H) 3.72, (bs, 4H, morp. O-CH_2), 4.01 (s, 2H, thiop. -CH_2), 4.55 (s, 2H, Alkyn-CH_2), 6.65 (s, 1H, thiop. -CH), 6.85, (s, 1H, thiop.-CH.), 6.96-6.98 (d, 2H, phenyl-$H_{2,6}$ *J* 8 Hz), 7.10-7.12 (d, 2H, phenyl-$H_{3,5}$ *J* 8 Hz), 7.31-7.32 (d, 1H, thiop. -CH *J* 4 Hz). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 26.8 (thiop. -CH_2), 34.9 (Alkynyl-CH_2), 48.4 (morp. N-CH_2), 66.4 (morp. O-CH_2), 75.5 (C≡CH), 78.9 (C≡CH), 115.4 (morp. phenyl-$CH_{2,6}$), 123.6 (morp. phenyl-C_4), 125.8 (thiop. -C_5), 127.0 (thiop. -C_4), 127.3 (thiop. -C_3), 128.5 (morp. Ph-$CH_{3,5}$), 136.9 (thiop. -C_q), 145.7 (morp. phenyl-C_1), 151.6 (C=N), 152.8 (C=O). Anal. Calcd. For $C_{20}H_{20}N_4O_2S$ Ma: 380.47 g/mol, $[M]^+$ (m/z): 419 (53%) [M+K].

5-(4-Chlorobenzyl)-4-(4-morpholinophenyl)-2-(prop-2-yn-1-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (4c). 5-(4-chlorobenzyl)-4-(4-morpholinophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**3c**) (0.01 mol) was dissolved in 100 ml of dry acetone in a 2-neck flask fitted with a reflux condenser and drying tube, anhydrous K_2CO_3 1.39 g (0.01 mol) was added and refluxed for 1 hour. At the end of this period, 1.18 g (0.01 mol; d=1.34 g/mol 80%) propargyl bromide was added to the cooled solution and refluxed for 24 hours. The cooled solution was filtered and evaporated. An ice-water mixture was added to the solid residue formed. The white solid product was filtered, washed several times with water and crystallized from acetone-petroleum ether (1:1). White crystals, yield (60%), mp: 144-145°C. IR (ATR, cm^{-1}): 3243 (Alkynyl C-H), 3054 (Ar-CH), 2975 (Aliph.CH), 2119 (C≡C), 1704 (C=O), 1582 (C=N), 1229 (C-O), 832 (Ar-CH def.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.16 (t, 4H, morp. N-CH_2 *J* 8 Hz), 3.36 (s, 1H, C≡C-H), 3.73-375 (t, 4H, morp. O-CH_2 *J* 8 Hz), 3.76 (s, 2H, Ph-CH_2), 4.57 (s, 2H, Alkyn-CH_2), 6.97-6.99 (d, 2H, phenyl-$H_{2,6}$ *J* 8 Hz), 7.05-7.07 (d, 2H, phenyl-$H_{3,5}$ *J* 8 Hz), 7.11-7.13 (d, 2H, 4-Cl-phenyl-$H_{2',6'}$ *J* 8 Hz), 7.29-7.31 (d, 2H, 4-Cl-phenyl-$H_{3',5'}$ *J* 8 Hz). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 31.2 (Ph-CH_2), 34.7 (Alkynyl-CH_2), 48.4 (morp. N-CH_2), 66.2 (morp. O-CH_2), 75.0 (C≡CH), 78.7 (C≡CH), 115.3 (morp.phenyl-$CH_{2,6}$), 123.4 (morp.phenyl-C_4), 128.7 (morp.phenyl-$CH_{3,5}$), 131.0 (4-Cl-phenyl-$CH_{3',5'}$), 131.6 (4-Cl-phenyl-$CH_{2',6'}$), 132.0 (4-Cl-phenyl-$C_{4'}$), 134.1 (4-Cl-phenyl-$C_{1'}$), 146.3 (morp.phenyl-C_1), 151.5 (C=N), 153.0 (C=O). Anal. Calcd. For $C_{22}H_{21}ClN_4O_2$ Ma: 408.89 g/mol, $[M]^+$ (m/z): 409 (35%) [M+1].

5-(4-Bromobenzyl)-4-(4-morpholinophenyl)-2-(prop-2-yn-1-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (4d). 5-(4-bromobenzyl)-4-(4-morpholinophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**3d**) (0.01 mol) was dissolved in 100 ml of dry acetone in a 2-neck flask fitted with reflux condenser and drying tube, anhydrous K_2CO_3 1.39 g (0.01 mol) was added and refluxed for 1 hour. At the end of this period, 1.18 g (0.01 mol; d=1.34 g/mol 80%) propargyl bromide was added to the cooled solution which was then refluxed for 24 hours. The cooled solution was filtered and evaporated. An ice-water mixture was added to the solid residue formed. The white solid product was filtered, washed several times with water and crystallized from ethyl acetate-petroleum ether (1:1). White crystals, yield (59%), mp: 98-100°C. IR (ATR, cm^{-1}): 3236 (Alkynyl C-H), 3093 (Ar-CH), 2968 (Aliph.CH), 2122 (C≡C), 1708 (C=O), 1581 (C=N), 1234 (C-O), 824 (Ar-CH def.). ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 3.12 (bs, 4H, morp. N-CH_2), 3.34 (bs, 1H, C≡C-H) 3.73-3.76 (bs, 4H, morp. O-CH_2), 3.71 (s, 2H, Ph-CH_2), 4.55 (s, 2H ,Alkyn-CH_2), 6.96-6.98 (d, 2H, phenyl-$H_{2,6}$ *J* 8 Hz + 2H, phenyl-$H_{3,5}$ *J* 8 Hz), 7.08-7.10 (d, 2H, 4-Br-phenyl-$H_{2',6'}$ *J* 8 Hz), 7.38-7.40 (d, 2H, 4-Br-phenyl-$H_{3',5'}$ *J* 8 Hz). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 31.5 (Ph-CH_2), 34.9 (Alkynyl-CH_2), 48.3 (morp. N-CH_2), 66.4 (morp. O-CH_2), 75.5 (C≡CH), 79.0 (C≡CH), 115.4 (morp. phenyl-$CH_{2,6}$), 120.4 (4-Br-phenyl-$C_{4'}$), 123.7 (morp. phenyl-C_4), 128.6 (morp. phenyl-$CH_{3,5}$), 131.4 (4-Br-phenyl-$CH_{3',5'}$), 131.6 (4-Br-phenyl-$CH_{2',6'}$), 134.7 (4-Br-phenyl-$C_{1'}$), 146.0 (morp. phenyl-C_1), 151.6 (C=N), 152.9 (C=O). Anal. Calcd. For $C_{22}H_{21}BrN_4O_2$ Ma: 453.34 g/mol, $[M]^+$ (m/z): 454 (5%) [M+1].

5-(4-Fluorobenzyl)-4-(4-morpholinophenyl)-2-(prop-2-yn-1-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one(4e). 5-(4-fluorobenzyl)-4-(4-morpholinophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**3e**): (0.01 mol) was dissolved in 100 ml of dry acetone in a 2-neck flask fitted with a reflux condenser and drying tube, anhydrous K_2CO_3 1.39 g (0.01 mol) was added and refluxed for 1 hour. At the end of this period, 1.18 g (0.01 mol; d=1.34 g/mol 80%) propargyl bromide was added to the cooled solution and refluxed for 24 hours. The cooled solution was filtered and evaporated. An ice-water mixture was added to the solid residue formed. The white solid product was filtered, washed several times with water and crystallized from ethyl acetate-petroleum ether (1:1). White crystals, yield (54%), mp: 189-190°C. IR (ATR, cm^{-1}): 3237 (Alkynyl C-H), 3066 (Ar-CH), 2977 (Aliph.CH), 2118 (C≡C), 1705 (C=O), 1583 (C=N), 1230 (C-O), 829 (Ar-CH def.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.09-3.12 (t, 4H, morp. N-CH_2 *J* 8 Hz), 3.37 (s, 1H, C≡C-H), 3.73-3.78 (t, 4H, morp. O-CH_2 *J* Hz), 3.83 (s, 2H, Ph-CH_2), 4.53 (s, 2H, Alkyn-CH_2), 6.98-7.01 (d, 2H, phenyl-$H_{2,6}$ *J* 8 Hz), 7.05-7.08 (d, 4H, 4-F-phenyl-$H_{3',5}$ *J* 8 Hz′ + 4F-phenyl-$H_{2',6'}$ *J* 8 Hz), 7.10-7.13 (d, 2H, phenyl-$H_{3,5}$ *J* 8 Hz). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 31.3 (Ph-CH_2), 34.9 (Alkynyl-CH_2), 39.5 (morp. N-CH_2), 40.4 (morp. O-CH_2), 75.5 (C≡CH), 79.0 (C≡CH), 115.5 (morp.phenyl-$CH_{2,6}$), 115.7 (4F-phenyl-$CH_{3',5'}$), 123.3 (morp.phenyl-C_4), 128.7 (morp.phenyl-$CH_{3,5}$), 131.1 (4F-phenyl-$CH_{2',6'}$), 131.2 (4F-phenyl-$C_{4'}$), 146.3 (morp.phenyl-C_1), 151.5 (C=N), 152.9 (C=O), 162.7 (4F-phenyl-$C_{1'}$). Anal. Calcd. For $C_{22}H_{21}FN_4O_2$ Ma: 392.43 g/mol, $[M]^+$ (m/z): 393.17 (24%) [M+1].

General procedure for the synthesis of type 5 compounds. Compounds **5a-d** were synthesized according to a method given in the literature.[36]

2-((1-(4-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-5-methyl-4-(4-morpholinophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (5a). 5-methyl-4-(4-morpholinophenyl)-2-(prop-2-yn-1-yl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**4a**) (0.01 mol) was dissolved in 100 ml acetone-water (1:1) mixture in a round bottom flask. 1-(azidomethyl)-4-chlorobenzene (0.01 mole) was added to this solution and stirred for 10 minutes. After this time, to the solution mixture was added 0.1 g of $CuSO_4.5H_2O$ and 0.1 g of sodium ascorbate as catalyst, the reaction mixture was refluxed for 24 hours. The solution was cooled and evaporated; the oily solid residue was precipitated from the ethyl alcohol-water mixture. The resulting solid was filtered, dried, and crystallized from ethyl alcohol-water (1:1). The crystals were filtered and dried in a desiccator over $CaCl_2$ under vacuum. White crystals, yield (58%), mp: 188-190°C. IR (ATR, cm^{-1}): 3055 (Ar-CH), 2951 (Aliph.CH), 1701 (C=O), 1587 (C=N),

1235 (C-O), 823 (Ar-CH def.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.98 (s, 3H, -CH_3), 3.14 (bs, 4H, morp. N-CH_2), 3.71-372 (d, 4H, morp. O-CH_2 *J* 4 Hz), 4.92 (s, 2H, 1,2,3-triazoyl.-CH_2), 5.57 (s, 2H, 1,2,3- triazole N_1-CH_2-), 7.01-7.02 (d, 2H, morph. phenyl-$H_{2,6}$ *J* 4 Hz), 7.20-7.21 (d, 2H, morph. phenyl-$H_{3,5}$ *J* 4 Hz), 7.33-7.35 (bs, 2H, 4-Cl-phenyl-$H_{2'',6''}$), 7.41-7.43 (bs, 2H, 4-Cl-phenyl-$H_{3'',5''}$), 8.14 (s, 1H, 1,2,3-triazole =CH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 12.5 (CH_3), 40.6 (1,2,4 triazole-N_1-CH_2), 48.4 morp. N-CH_2), 52.4 (1,2,3-triazole-N_1-CH_2), 66.4 (morp. O-CH_2), 115.5 (morp. phenyl-$CH_{2,6}$), 124.2 (morp. phenyl C_q), 124.3 (1,2,3 triazole C_5-H), 128.3 (morp. phenyl-$CH_{3,5}$), 129.2 (4Cl-phenyl-$CH_{2'',6''}$), 130.5 (4Cl-phenyl-$CH_{3'',5''}$), 133.4 (1,2,3 triazole C4-quat.), 135.4 (4-Cl-phenyl-$C_{4''}$), 143.3 (4-Cl-phenyl-$C_{1''}$), 143.9 (morp. phenyl-C_1), 151.4 (C=N), 153.0 (C=O). Anal. Calcd. For $C_{23}H_{24}ClN_7O_2$ Ma: 465.94 g/mol, $[M]^+$ (m/z): 466 (41%) [M+1].

2-((1-(4-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(4-morpholinophenyl)-5-(thiophen-2-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (5b). 4-(4-morpholinophenyl)-2-(prop-2-yn-1-yl)-5-(thiophen-2-ylmethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**4b**) (0.01 mol) was dissolved in 100 ml acetone-water (1:1) mixture in a round bottom flask. 1-(azidomethyl)-4-chlorobenzene (0.01 mole) was added to this solution and stirred for 10 minutes. After this time, the solution mixture was added 0.1 g of $CuSO_4.5H_2O$ and 0.1 g of sodium ascorbate as catalyst, the reaction mixture was refluxed for 24 hours. The solution was cooled and evaporated; the oily solid residue was precipitated from the ethyl alcohol-water mixture. The resulting solid was filtered, dried, and crystallized from acetone-petroleum ether (1:1). The crystals were filtered and dried in a desiccator over $CaCl_2$ under vacuum. White crystals, yield (95%), mp:157-159°C. IR (ATR, cm^{-1}): 3068 (Ar-CH), 2957 (Aliph.CH), 1705 (C=O), 1584 (C=N), 1230 (C-O), 825 (Ar-CH def.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.17(bs, 4H, morp. N-CH_2), 3.75 (bs, 4H, morp. O-CH_2), 3.99 (s, 2H, thiop.-CH_2), 4.99 (s,2H, 1,2,3-triazoyl.-CH_2), 5.61 (s, 2H, 1,2,3-triazoyl.-CH_2), 6.63 (s, 1H, thiop.-CH), 6.85 (s, 1H, thiop.-CH.), 7.00 (bs, 2H, phenyl-$H_{2,6}$), 7.13 (bs, 2H, phenyl-$H_{3,5}$), 7.38-7.42 (d, 2H, 4-Cl-phenyl-$H_{2'',6''}$ +1H, thiop.-CH), 7.43-7.45 (bs, 2H, 4-Cl-phenyl-$H_{3'',5''}$), 8.15 (s,1H, 1,2,3-triazole=CH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 26.8 (thiop.-CH_2), 40.7 (1,2,4 triazole-N_1-CH_2), 48.4 (morp. N-CH_2), 52.5 (1,2,3-triazole-N_1-CH_2), 66.4 (morp. O-CH_2), 115.3 (morp.phenyl-$CH_{2,6}$), 123.8 (morp. phenyl C_q), 124.3 (1,2,3 triazole C_5-H), 125.7 (thiop.-C_5) 126.9 (thiop.-C_4), 127.3 (thiop.-C_3), 128.5 (morp.phenyl-$CH_{3,5}$), 129.2 (4Cl-phenyl -$CH_{2'',6''}$), 130.5 (4Cl-phenyl -$CH_{3'',5''}$), 133.4 (1,2,3 triazole C_q), 135.5 (4-Cl-phenyl $C_{4''}$), 137.2 (thiop.-C_2) 143.2 (4-Cl-phenyl $C_{1''}$), 145.3 (morp.phenyl C_1), 151.5 (C=N), 153.1 (C=O). Anal. Calcd. For $C_{27}H_{26}ClN_7O_2S$ Ma: 548.06 g/mol, $[M]^+$ (m/z): 548 (5%) [M].

5-(4-Chlorobenzyl)-2-((1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4-(4-morpholinophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (5c). 5-(4-chlorobenzyl)-4-(4-morpholinophenyl)-2-(prop-2-yn-1-yl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**4c**) (0.01 mol) was dissolved in 100 ml acetone-water (1:1) mixture in a round bottom flask. 1-(azidomethyl)-4-chlorobenzene (0.01 mole) was added to this solution and stirred for 10 minutes. After this time, the solution mixture was added 0.1 g of $CuSO_4.5H_2O$ and 0.1 g of sodium ascorbate as catalyst, the reaction mixture was refluxed for 24 hours. The solution was cooled and evaporated; the oily solid residue was precipitated from the ethyl alcohol-water mixture. The resulting solid was filtered, dried, and crystallized from dimethylformamide-water (1:1). The crystals were filtered and dried in a desiccator over $CaCl_2$ under vacuum. White crystals, yield (71%), mp: 186-187°C. IR (ATR, cm^{-1}): 2972 (Ar-CH), 2944 (Aliph.CH), 1696 (C=O), 1580 (C=N), 1234 (C-O), 827 (Ar-CH def.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.11 (s, 4H, morp. N-CH_2), 3.72 (bs, 4H, morp. O-CH_2+ 2H, Ph-CH_2), 5.00 (s, 2H, 1,2,3-triazoyl.-CH_2), 5.58 (s, 2H, 1,2,3-triazoyl.-CH_2), 6.92-6.94 (m, 2H, morp.phenyl-$H_{2,6}$ +2H, morp.phenyl-$H_{3,5}$), 7.24-7.27 (m, 2H, 4-Cl-phenyl-$H_{2'',6''}$ + 2H, 4-Cl-phenyl-$H_{3'',5''}$), 7.32-7.41 (m, 2H, 4-Cl-phenyl-$H_{2',6'}$ + 2H, 4-Cl-phenyl-$H_{3',5'}$), 8.12 (s, 1H, 1,2,3-triazole=CH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 31.6 (Ph-CH_2), 40.7 (1,2,4 triazole-N_1-CH_2), 48.3 (morp.N-CH_2), 52.5 (1,2,3-triazole-N_1-CH_2), 66.4 (morp.O-CH_2), 115.4 (morp.phenyl-$CH_{2,6}$), 124.0 (morp.phenyl C_4-quat.), 124.3 (1,2,3 triazole C_5), 128.6 (morp.phenyl-$CH_{3,5}$), 129.2 (4-Cl-phenyl-$CH_{2'',6''}$), 130.4 (4-Cl-phenyl-$CH_{3'',5''}$), 130.9 (4Cl-

phenyl-$CH_{2',6'}$), 130.9 (4Cl- phenyl-$CH_{3',5'}$), 131.8 (4-Cl-phenyl-$C_{4'}$), 131.8 (4-Cl-phenyl-$C_{1'}$), 133.4 (1,2,3 triazole C4-quat.), 135.4 (4-Cl-phenyl $C_{4''}$), 143.2 (4-Cl-phenyl $C_{1''}$), 145.6 (4–morp.phenyl C_1), 151.4 (C=N), 153.2 (C=O). Anal. Calcd. For $C_{29}H_{27}Cl_2N_7O_2$ Ma: 576.48 g/mol, $[M]^+$ (m/z): 614 (5%) [M+K].

5-(4-Bromobenzyl)-2-((1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4-(4-morpholinophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (5d). 5-(4-bromobenzyl)-4-(4-morpholinophenyl)-2-(prop-2-yn-1-yl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**4d**) (0.01 mol) was dissolved in 100 ml acetone-water (1:1) mixture in a round bottom flask. 1-(azidomethyl)-4-chlorobenzene (0.01 mole) was added to this solution and stirred for 10 minutes. After this time, the solution mixture was added 0.1 g of $CuSO_4.5H_2O$ and 0.1 g of sodium ascorbate as catalyst, the reaction mixture was refluxed for 24 hours. The solution was cooled and evaporated; the oily solid residue was precipitated from the ethyl alcohol-water mixture. The resulting solid was filtered, dried, and crystallized from acetone-petroleum ether (1:1). The crystals were filtered and dried in a desiccator over $CaCl_2$ under vacuum. Light-brown crystals, yield (62%), mp: 140-142°C. IR (ATR, cm^{-1}): 3048 (Ar-CH), 2956 (Aliph.CH), 1706 (C=O), 1578 (C=N), 1235 (C-O), 824 (Ar-CH def.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.15 (bs, 4H, morp. N-CH_2), 3.75 (bs, 4H, morp. O-CH_2+ 2H, Ph-CH_2), 4.98 (s,2H, 1,2,3-triazoyl.-CH_2), 5.61 (s,2H, 1,2,3-triazoyl.-CH_2), 6.93-7.02 (t, 2H, morp.phenyl-$H_{2,6}$ +2H, morp.phenyl-$H_{3,5}$), 7.10 (bs, 2H, 4-Cl-phenyl-$H_{2'',6''}$), 7.35 (bs, 2H, 4-Cl-phenyl-$H_{3'',5''}$ + 2H,4-Br-phenyl-$H_{2',6'}$), 7.44 (bs, 2H, 4-Br-phenyl-$H_{3',5'}$), 8.15 (s, 1H, 1,2,3-triazole=CH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 31.7 (Ph-CH_2), 40.6 (1,2,4 triazole-N_1-CH_2), 48.0 (morp. N-CH_2), 52.0 (1,2,3-triazole-N_1-CH_2), 65.6 (morp. O-CH_2), 115.4 (Ph-$CH_{2,6}$), 120.4 (4-Br-phenyl-C_4), 123.8 (4–morp. phenyl C_4), 124.3 (1,2,3 triazole C_5), 128.6 (morp.phenyl-$CH_{3,5}$), 129.2 (4-Br-phenyl-$CH_{2',6'}$), 130.4 (4-Br-phenyl-$CH_{3',5'}$), 130.3 (4Cl-phenyl-$CH_{2'',6''}$), 131.6 (4Cl-phenyl-$CH_{3'',5''}$), 133.3 (1,2,3 triazole C4-quat.), 134.9 (4-Br-phenyl $C_{1'}$), 135.5 (4-Cl-phenyl $C_{4''}$), 142.9 (4-Cl-phenyl $C_{1''}$), 145.0 (morp. phenyl C_1), 151.4 (C=N), 153.4 (C=O). Anal. Calcd. For $C_{29}H_{27}BrClN_7O_2$ Ma: 620.94 g/mol, $[M]^+$ (m/z): 621 (11%) [M+1].

General procedure for the synthesis of type 6 compounds. Compounds **6a-c** were obtained from the reaction of compounds **4a-e** with 1-(azidomethyl)-4-bromobenzene, similar to the syntheses for compounds **5a-d**.

2-((1-(4-Bromobenzyl)-*1H*-1,2,3-triazol-4-yl) methyl)-5-methyl-4-(4-morpholinophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (6a). 5-methyl-4-(4-morpholinophenyl)-2-(prop-2-yn-1-yl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**4a**) (0.01 mol) was dissolved in 100 ml acetone-water (1:1) mixture in a round bottom flask. 1-(azidomethyl)-4-bromobenzene (0.01 mole) was added to this solution and stirred for 10 minutes. After this time, the solution mixture was added 0.1 g of $CuSO_4.5H_2O$ and 0.1 g of sodium ascorbate as catalyst, the reaction mixture was refluxed for 24 hours. The solution was cooled and evaporated; the oily solid residue was precipitated from the ethyl alcohol-water mixture. The resulting solid was filtered, dried, and crystallized from acetone-petroleum ether (1:1). The crystals were filtered and dried in a desiccator over $CaCl_2$ under vacuum.
Light-brown crystals, yield (64%), mp: 183-185°C. IR (ATR, cm^{-1}): 3054 (Ar-CH), 2953 (Aliph.CH), 1702 (C=O), 1587 (C=N), 1236 (C-O), 823 (Ar-CH def.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.01 (s, 3H, CH_3), 3.19 (s, 4H, morp. N-CH_2), 3.75 (s, 4H, morp. O-CH_2), 4.94 (s, 2H, 1,2,3-triazole C_4-CH_2), 5.58 (s, 2H, 1,2,3-triaz.N_1-CH_2), 7.06 (s, 2H, morp.phenyl-$CH_{2,6}$), 7.23 (s, 2H, morp.phenyl-$CH_{3,5}$), 7.29-7.31 (d, 2H, 4-Br-phenyl-$CH_{2'',6''}$ *J* 8 Hz), 7.58 (s, 2H, 4-Br-phenyl-$CH_{3'',5''}$), 8.17 (s, 1H, C=CH-N 1,2,3-triazole). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 12.5 (CH_3), 40.6 (1,2,4 triazole-N_1-CH_2), 48.4 (morp.N-CH_2), 66.5 (morp.O-CH_2), 52.5 (1,2,3-triazole-N_1-CH_2), 115.5 (morp.phenyl-$CH_{2,6}$), 121.9 (4-Br-phenyl $C_{4''}$), 124.2 (morp.phenyl C_4-quat.), 124.3 (1,2,3 triazole C_5), 128.3 (morp.phenyl-$CH_{3,5}$), 130.8 (4-Br-phenyl-$CH_{2'',6''}$), 132.2 (4-Br-phenyl-$CH_{3'',5''}$), 135.9 (1,2,3 triazole C_4-quat.), 143.3 (4-Br-phenyl $C_{1''}$), 143.9 (morp.phenyl C_1), 151.4 (C=N), 153.0 (C=O). Anal. Calcd. For $C_{23}H_{24}BrN_7O_2$ Ma: 510.40 g/mol, $[M]^+$ (m/z): 511 (4%) [M+1].

2-((1-(4-Bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(4-morpholinophenyl)-5-(thiophen-2-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (6b). 4-(4-morpholinophenyl)-2-(prop-2-yn-1-yl)-5-(thiophen-2-ylmethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**4b**) (0.01 mol) was dissolved in 100 ml acetone-water (1:1) mixture in a round bottom flask. 1-(azidomethyl)-4-bromobenzene (0.01 mole) was added to this solution and stirred for 10 minutes. After this time, the solution mixture was added 0.1 g of $CuSO_4.5H_2O$ and 0.1 g of sodium ascorbate as catalyst, the reaction mixture was refluxed for 24 hours. The solution was cooled and evaporated; the oily solid residue was precipitated from the ethyl alcohol-water mixture. The resulting solid was filtered, dried, and crystallized from ethyl alcohol-water (1:1). The crystals were filtered and dried in a desiccator over $CaCl_2$ under vacuum. Light-brown crystals, yield (87%), mp: 166-168°C. IR (ATR, cm^{-1}): 3067 (Ar-CH), 2957 (Aliph.CH), 1705 (C=O), 1585 (C=N), 1231 (C-O), 824 (Ar-CH def.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.15 (s, 4H, morp. N-CH_2), 3.73 (s, 4H, morp. O-CH_2), 3.99 (s, 2H, thiop.-CH_2), 4.98 (s, 2H, 1,2,3-triazole C_4-CH_2), 5.59 (s, 2H, 1,2,3-triaz.N_1-CH_2), 6.62 (s, 1H, thiop.-CH), 6.86 (s, 1H, thiop.-CH), 6.98 (s, 2H, morp.phenyl-$CH_{2,6}$), 7.11 (s, 2H, morp.phenyl-$CH_{3,5}$), 7.31 (s, 1H, thiop.-CH + s, 2H, 4Br-phenyl-$CH_{2'',6''}$), 7.60 (s, 2H, 4Br-phenyl-$CH_{3'',5''}$), 8.14 (s, 1H, C=CH-N 1,2,3-triazole). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 26.8 (thiop.-CH_2), 40.6 (1,2,4 triazole-N_1-CH_2), 48.4 (morp.N-CH_2), 52.5 (1,2,3-triazole-N_1-CH_2), 66.4 (morp.O-CH_2), 115.4 (morp.phenyl-$CH_{2,6}$), 121.9 (4-Br-phenyl $C_{4''}$), 123.8 (morp.phenyl C_4-quat.), 124.3 (1,2,3 triazole C_5-H), 125.7 (thiop.-C_5), 126.9 (thiop.-C_4), 127.3 (thiop.-C_3), 128.5 (morp.phenyl-$CH_{3,5}$), 130.8 (4-Br-phenyl-$CH_{2'',6''}$), 132.2 (4-Br-phenyl-$CH_{3'',5''}$), 135.9 (1,2,3 triazole C_4-quat.), 137.2 (thiop.-C_2 qua.), 143.2 (4-Br-phenyl $C_{1''}$), 145.3 (morp.phenyl C_1), 151.5 (C=N), 153.1 (C=O). Anal. Calcd. For $C_{27}H_{26}BrN_7O_2S$ Ma: 592.52 g/mol, $[M]^+$ (m/z): 593 (5%) [M+1].

2-((1-(4-Bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-5-(4-chlorobenzyl)-4-(4-morpholinophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (6c). 5-(4-chlorobenzyl)-4-(4-morpholinophenyl)-2-(prop-2-yn-1-yl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**4c**) (0.01 mol) was dissolved in 100 ml acetone-water (1:1) mixture in a round bottom flask. 1-(azidomethyl)-4-bromobenzene (0.01 mole) was added to this solution and stirred for 10 minutes. After this time, the solution mixture was added 0.1 g of $CuSO_4.5H_2O$ and 0.1 g of sodium ascorbate as catalyst, the reaction mixture was refluxed for 24 hours. The solution was cooled and evaporated; the oily solid residue was precipitated from the ethyl alcohol-water mixture. The resulting solid was filtered, dried, and crystallized from dimethylformamide-water (1:1). The crystals were filtered and dried in a desiccator over $CaCl_2$ under vacuum. Light-brown crystals, yield (66%), mp: 164-166°C. IR (ATR, cm^{-1}): 3066 (Ar-CH), 2944 (Aliph.CH), 1697 (C=O), 1580 (C=N), 1235 (C-O), 817 (Ar-CH def.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.12 (s, 4H, morp. N-CH_2), 3.71-3.75 (d, 4H, morp. O-CH_2 + d, 2H, 4-Cl-phenyl-CH_2), 4.96 (s, 2H, 1,2,3-triazole C_4-CH_2), 5.57 (s, 2H, 1,2,3-triaz.N_1-CH_2), 6.95-7.05 (d, 2H, morp.phenyl-$CH_{2,6}$ + d, 2H, morp.phenyl-$CH_{3,5}$ + d, 2H, 4-Cl-phenyl-$CH_{2',6'}$), 7.21-7.27 (d, 2H, 4-Cl-phenyl-$CH_{3',5'}$ + d, 2H, 4-Br-phenyl-$CH_{2'',6''}$), 7.54 (s, 2H, 4-Br-phenyl-$CH_{3'',5''}$), 8.13 (s, 1H, C=CH-N 1,2,3-triazole). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 31.4 (Ph-CH_2), 40.7 (1,2,4 Triazole-N_1-CH_2), 48.3 (morp.N-CH_2), 52.5 (1,2,3-triazole-N_1-CH_2), 66.4 (morp.O-CH_2), 115.4 (morp.phenyl-$CH_{2,6}$), 121.9 (4-Br-phenyl $C_{4''}$), 123.8 (morp.phenyl C_4-quat.), 124.3 (1,2,3 triazole C_5), 128.6 (morp.phenyl-$CH_{3,5}$), 128.7 (4-Cl-phenyl-$CH_{2',6'}$), 130.7 (4-Cl-phenyl-$CH_{3',5'}$), 130.9 (4-Br-phenyl-$CH_{2'',6''}$), 131.8 (4-Cl-phenyl-$C_{4'}$), 132.1 (4-Br-phenyl-$CH_{3'',5''}$), 134.4 (4-Cl-phenyl-$C_{1'}$), 135.8 (1,2,3 triazole C_4-quat.), 143.3 (4-Br-phenyl $C_{1''}$), 145.6 (morp.phenyl C_1), 151.5 (C=N), 153.2 (C=O). Anal. Calcd. For $C_{29}H_{27}BrClN_7O_2$ Ma: 620.94 g/mol, $[M]^+$ (m/z): 623 (11%) [M+2], 646 (20%) [M+2+Na].

General procedure for the synthesis of type 7 compounds. Compounds **7a-c** were obtained from the reaction of compounds **4a-e** with 1-(azidomethyl)-4-florobenzene, similar to the syntheses methods for compounds **5a-d**.

2-((1-(4-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-5-methyl-4-(4-morpholinophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (7a). 5-methyl-4-(4-morpholinophenyl)-2-(prop-2-yn-1-yl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**4a**) (0.01 mol) was dissolved in 100 ml acetone-water (1:1) mixture in a round bottom flask. 1-(azidomethyl)-4-florobenzene (0.01 mole) was added to this solution and stirred for 10 minutes. After this time, the solution mixture was added 0.1 g of $CuSO_4.5H_2O$ and 0.1 g of sodium ascorbate as catalyst, the reaction mixture was refluxed for 24 hours. The solution was cooled and evaporated; the oily solid residue was precipitated from the ethyl alcohol-water mixture. The resulting solid was filtered, dried, and crystallized from ethyl acetate-petroleum ether (1:1). The crystals were filtered and dried in a desiccator over $CaCl_2$ under vacuum. White crystals, yield (64%), mp: 171-173°C. IR (ATR, cm^{-1}): 3056 (Ar-CH), 2967 (Aliph.CH), 1707 (C=O), 1579 (C=N), 1239 (C-O), 824 (Ar-CH def.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.01 (s, 3H, CH_3), 3.15-3.18 (t, 4H, morp. N-CH_2), 3.73-3.75 (t, 4H, morp. O-CH_2 *J* 8 Hz), 4.95 (s, 2H, 1,2,3-triazole C_4-CH_2), 5.59 (s, 2H, 1,2,3-triaz.N_1-CH_2), 7.03-7.05 (d, 2H, morp.phenyl-$CH_{2,6}$ *J* 8 Hz), 7.19-7.25 (dd, 4H, morp.phenyl-$CH_{3,5}$ + 4-F-phenyl-$CH_{2'',6''}$), 7.41-7.44 (q, 2H, 4-F-phenyl-$CH_{3'',5''}$), 8.19 (s, 1H, C=CH-N 1,2,3-triazole). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 12.5 (CH_3), 40.4 (1,2,4 Triazole-N_1-CH_2), 48.4 (morp.N-CH_2), 52.5 (1,2,3-triazole-N_1-CH_2), 66.5 (morp.O-CH_2), 115.5 (morp.phenyl-$CH_{2,6}$), 116.0-116.2 (4-F-phenyl-$CH_{3'',5''}$), 124.1 (1,2,3 triazole C_5-H), 124.3 (morp.phenyl C_4-quat.), 128.3 (morp.phenyl-$CH_{3,5}$), 130.8-130.9 (4-F-phenyl-$CH_{2'',6''}$), 132.7-132.8 (4-F-phenyl $C_{4'}$), 143.3 (1,2,3 triazole C_4-quat.), 143.9 (morp.phenyl C_1), 151.4 (C=N), 153.0 (C=O), 161.2-163.6 (4-F-phenyl $C_{1'}$). Anal. Calcd. For $C_{23}H_{24}FN_7O_2$ Ma: 449.49 g/mol, $[M]^+$ (m/z): 450 (25%) [M+1].

2-((1-(4-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4-(4-morpholinophenyl)-5-(thiophen-2-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (7b). 4-(4-morpholinophenyl)-2-(prop-2-yn-1-yl)-5-(thiophen-2-ylmethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**4b**) (0.01 mol) was dissolved in 100 ml acetone-water (1:1) mixture in a round bottom flask. 1-(azidomethyl)-4-florobenzene (0.01 mole) was added to this solution and stirred for 10 minutes. After this time, the solution mixture was added 0.1 g of $CuSO_4.5H_2O$ and 0.1 g of sodium ascorbate as catalyst, the reaction mixture was refluxed for 24 hours. The solution was cooled and evaporated; the oily solid residue was precipitated from the ethyl alcohol-water mixture. The resulting solid was filtered, dried, and crystallized from ethyl acetate-petroleum ether (1:1). The crystals were filtered and dried in a desiccator over $CaCl_2$ under vacuum. White crystals, yield (88%), mp: 168-170°C. IR (ATR, cm^{-1}): 3046 (Ar-CH), 2974 (Aliph.CH), 1698 (C=O), 1574 (C=N), 1225 (C-O), 824 (Ar-CH def.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.14-3.17 (t, 4H, morp. N-CH_2), 3.37-3.75 (t, 4H, morp. O-CH_2), 3.99 (thiop.-CH_2), 4.98 (s, 2H, 1,2,3-triazole C_4-CH_2), 5.59 (s, 2H, 1,2,3-triaz.N_1-CH_2), 6.61-6.62 (q, 1H, thiop.-CH), 6.84-6.86 (q, 1H, thiop.-CH), 6.98-7.00 (d, 2H, Morp.Ph-$CH_{2,6}$ *J* 8 Hz), 7.11-7.13 (d, 2H, morp.phenyl-$CH_{3,5}$ *J* 8 Hz), 7.20-7.24 (m, 2H, 4-F-phenyl-$CH_{2'',6''}$), 7.32-7.33 (q, 1H, thiop.CH), 7.40-7.43 (m, 2H, 4-F-phenyl-$CH_{3'',5''}$), 8.14 (s, 1H, C=CH-N 1,2,3-triazole). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 26.8 (thiop.-CH_2), 40.6 (1,2,4 triazole-N_1-CH_2), 48.3 (morp.N-CH_2), 52.5 (1,2,3-triazole-N_1-CH_2), 66.4 (morp.O-CH_2), 115.4 (morp.phenyl-$CH_{2,6}$), 116.0-116.2 (4-F-phenyl-$CH_{3'',5''}$), 123.8 (morp.phenyl C_4-quat.), 124.2 (1,2,3 triazole C_5-H), 125.6 (thiop.-C_5), 126.9 (thiop.-C_4), 127.3 (thiop.-C_3), 128.5 (morp.phenyl-$CH_{3,5}$), 130.8-130.9 (4-F-phenyl-$CH_{2'',6''}$), 132.7 (4-F-phenyl $C_{4'}$), 137.2 (thiop.-C-quat.), 143.2 (1,2,3 triazole C_4-quat.), 145.3 (morp.phenyl C_1), 151.5 (C=N), 153.1 (C=O), 161.2-163.6 (4-F-phenyl $C_{1''}$). Anal. Calcd. For $C_{27}H_{26}FN_7O_2S$ Ma: 531.61g/mol, $[M]^+$ (m/z): 532 (29%) [M+1].

5-(4-Fluorobenzyl)-2-((1-(4-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4-(4-morpholinophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (7c). 5-(4-fluorobenzyl)-4-(4-morpholinophenyl)-2-(prop-2-yn-1-yl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**4e**) (0.01 mol) was dissolved in 100 ml acetone-water (1:1) mixture in a round bottom flask. 1-(azidomethyl)-4-florobenzene (0.01 mole) was added to this solution and stirred for 10 minutes. After this time, the solution mixture was added 0.1 g of $CuSO_4.5H_2O$ and 0.1 g of sodium ascorbate as catalyst, the reaction mixture was refluxed for 24 hours. The solution was cooled and evaporated; the oily solid residue was

precipitated from the ethyl alcohol-water mixture. The resulting solid was filtered, dried, and crystallized from ethyl acetate-petroleum ether (1:1). The crystals were filtered and dried in a desiccator over $CaCl_2$ under vacuum. White crystals, yield (59%), mp: 118-120°C. IR (ATR, cm^{-1}): 3056 (Ar-CH), 2961 (Aliph.CH), 1702 (C=O), 1586 (C=N), 1238 (C-O), 824 (Ar-CH def.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.13-3.15 (t, 4H, morp. N-CH_2 *J* 8 Hz), 3.73-3.75 (t, 4H, morp. O-CH_2 *J* 8 Hz), 4.96 (s, 2H, 1,2,3-triazole C_4-CH_2), 5.59 (s, 2H, 1,2,3-triaz.N_1-CH_2), 6.95-6.97 (m, 8H, morp.phenyl-$CH_{2,6}$ + 4-F-phenyl-$CH_{3',5'}$ + 4-F-phenyl-$CH_{2',6'}$ + 4-F-phenyl-$CH_{3'',5''}$), 7.02-7.08 (m, 2H, morp.phenyl-$CH_{3,5}$), 7.19-7.43 (m, 2H, 4-F-phenyl-$CH_{2'',6''}$), 8.14 (s, 1H, C=CH-N 1,2,3-triazole). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 31.3 (Ph-CH_2), 40.6 (1,2,4 triazole-N_1-CH_2), 48.4 (morp.N-CH_2), 52.5 (1,2,3-triazole-N_1-CH_2), 66.4 (morp.O-CH_2), 115.4 (morp.phenyl-$CH_{2,6}$), 115.4-115.6 (4-F-phenyl-$CH_{3',5'}$), 116.0-116.2 (4-F-phenyl-$CH_{3'',5''}$), 124.1 (1,2,3 triazole C_5-H), 124.2 (morp.phenyl C_4-quat.), 128.6 (morp.phenyl-$CH_{3,5}$ + 4-F-phenyl $C_{4'}$), 130.8 (4-F- phenyl-$C_{4''}$), 130.9 (4-F-phenyl-$C_{1'}$), 130.8 (4-F-phenyl-$CH_{2',6'}$), 130.9 (4-F-phenyl-$CH_{2'',6''}$), 143.2 (1,2,3 triazole C_4-quat.), 145.9 (4–morp. phenyl C_1), 151.5 (C=N), 153.3 (C=O), 162.7-163.6 (4-F-phenyl-$C_{1''}$). Anal. Calcd. For $C_{29}H_{27}F_2N_7O_2$ Ma: 543.58g/mol, $[M]^+$ (m/z): 544 (31%) [M+1].

Antioxidative activity

The antioxidant activities of the synthesized compounds were determined according to DPPH and superoxide dismutase methods.[37]

DPPH radical-scavenging activity

To measure the DPPH free radical scavenging activity of the investigated molecules, the absorbance of 1 mL of 0.4 mM DPPH solvent in methanol was measured at 517 nm (as a control). Various concentrations of compound solutions were added to the DPPH solution. After an incubation period of 30 min at room temperature (in the dark), the absorbance was measured against the blank control. The concentration that scavenged 50% of the free radicals in the medium was calculated using the SC50 values found for scavenging activities as a function of molecule concentrations.

Superoxide dismutase radical scavenging

The nitro blue tetrazolium (NBT) photoreduction method was used to determine superoxide-dismutase radical-scavenging activity. Superoxide radicals were generated in 50 mM phosphate buffer (pH 7.8) containing 0.1 M EDTA, 2 uM riboflavin, 13 mM L-methionine and 75 uM NBT. Solutions of different concentrations of molecules or native enzyme were added to each radical-generating mixture. Each reaction mixture was incubated in the presence of a fluorescent light for 5 min and absorbances were measured at 560 nm.

Acetylcholinesterase inhibitory activity

The acetylcholinesterase-inhibition activities of the molecules were determined by the Ellman et al. modified spectrophotometric method. Acid thiochloroiodide was used as the substrate for the reaction and Elekroel acetylcholinesterase (Type-VI-S, EC 3.1.1.7, Sigma) was used as the enzyme source. 5,5-Dithio-bis(2-nitrobenzoic) acid (DTNB) was used for the measurement of cholinesterase activity. The procedure was as follows; 140 uL of 0.1 mM sodium phosphate buffer (pH 8.0), 20 µL of 0.2 M DTNB, 20 µL of sample solution and 20 µL of 0.2 M acetylcholinesterase solution were added and incubated at 25℃ for 15 min. The reaction was then initiated by the addition of 10 µL of 0.2 M acetylthiocholine iodide. The hydrolysis of acetylthiocholine iodide was catalyzed by enzymes and monitored at a wavelength of 412 nm, with the formation of the yellow 5-thio-2-nitrobenzoate anion by the reaction of DTNB with the thiocolines.

Galanthamine, an anticholinesterase alkaloid drug isolated from cardamom bulbs (Galanthus sp.), was used as a reference.[38] The acetylcholinesterase enzyme inhibition rate was calculated as 91.18% in the presence of galanthamine at a concentration of 8 µg/mL.

Antibacterial and antifungal activity

Bacterial strains and growth conditions

The antimicrobial activity of the compound samples was evaluated against ten bacteria (six gram-neg and five gram-pos): Pseudomonas aeruginosa ATCC27853 Gram (-), Proteus vulgaris ATCC®7829 Gram (-), Escherichia coli ATCC®25922 Gram (-), Klebsiella pneumoniae ATCC®13883 Gram (-), Listeria monocytogenes ATCC®7677 Gram (+), Clostridium perfringens ATCC 313124 Gram (-), Salmonella enteric ATCC 14028, Gram (-), Bacillus subtilis B209, Gram (+), Streptococcus mutans RSHE 676, Gram (+), Micrococcus luteus B1018,Gram (+), Staphylococcus aureus ATCC 6538 Gram (+), Mueller Hinton Agar (MHA, Merck) and or Mueller Hinton Broth (MHB, Merck) Aspergillus niger ATCC®9642 and Candida albicans ATCC®10231 and Sabouraud Dextrose Broth (SDB, Difco) and or Sabouraud Dextrose Agar (SDA, Oxoid) were used for the growth of bacterial and yeast or fungal cells, respectively.

Disk diffusion test

Antimicrobial activity was measured by the method followed by Ronald.[39] MHA medium (Merck, 40 mL) for bacteria and SDA medium (Oxoid, 40 mL) for fungi and yeast were poured into each petri dish. All bacterial strains were grown in MHB (Merck) for 24 h at 37°C. Yeast and fungal strains were grown in SDB (Difco) for 48 h at 27°C. Shortly, thereafter, the bacteria were diluted with water and the final bacterial and yeast/fungal cell concentrations were adjusted to 108 and 107cells/mL, respectively, and measured spectrophotometrically at A600 nm. 100 uL of each diluted suspension was then placed on agar in petri dishes and dispersed. Sterile paper disks (6 mm diameter) were then placed on agar to load 25 µL of each compound sample (20 mg/mL). For fungi and yeasts, Nystatin, and for bacteria, Ampicillin and Cefazolin, were used as positive controls. Alcohol and acetone were also used as negative controls. The inhibition zones formed on the respective media were measured in millimeters (mm) after incubation for 24 h at 37°C for antibacterial activity, and at 27°C for antifungal activity, respectively. All tests were performed three times

Statistical analysis

Statistical analyses were performed with SPSS for Windows (Ver. 13.0) software. Differences between means of inhibition sites were tested by one-way analysis of variance followed by Tukey HSD test. Results were evaluated at a confidence limit of 0.05.

X-ray analysis

Structural X-ray analysis of compound 7b

The crystallographic analysis of a single crystal of **7b** was conducted using a Bruker APEX-II CCD diffractometer with Mo Kα radiation (λ = 0.71073 Å). Data collection was carried out at a temperature of 273° K, utilizing both ϕ- and ω-scan techniques. The crystal structure of **7b** was resolved and refined using the SHELXT and SHELXL programs from the WinGX-2014.1 software [40] Visual representations were generated with Mercury 4.0[41] and ORTEP-3.[42] Non-hydrogen atoms were initially refined anisotropically, while hydrogen atoms were positioned based on geometric calculations, and refined using the riding model. π-π Interactions of phenyl rings within the crystal structure were analyzed with OLEX2-1.5[43] The crystallographic data and final refinement

parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under the accession number 2403655.

Computational structural X-ray analysis of compound 7b

In this study, theoretical DFT calculations were conducted using Gaussian 09W.[44] The optimization process was carried out at the B3LYP theory level with the 6-31G(d,p) basis set in the gas phase. The optimized structure and geometric parameters were visualized using GaussView 6.0.16.[45]

Acknowledgements

Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra, IR and mass spectra, and X-ray crystallographic related data of new compounds, along with data sets and graphical plots of antifungal-inhibition-zone values, comparative antioxidant activity, and acetylcholinesterase-inhibition results are contained in the Supplementary Material associated with this manuscript.

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