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Efficient synthesis of novel 1, 2, 3-triazole-based diazepam derivatives by click CuAAC reaction: Spectroscopic characterizations and DFT studies

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ABSTRACT

A new family of 1, 2, 3-triazole-based benzodiazepines have been synthesized by the Huisgen [3+2] dipolar cycloaddition reaction of diazepam with *O*-propargyl salicylaldehydes in the aqueous medium. Mild reaction conditions, excellent yields (70–98%), environment-friendly method and easily prepared starting materials are the key features of the protocol. Density functional theory calculations were also conducted using the B3LYP functional and 6-31++G(d, p) basis set on the structure of the characterized structure **6a**. Structural, electronic and thermodynamic data such as electrophilicity index, APT charge distribution and electrostatic potential map were calculated by the computational method and interpreted.

1. Introduction

Nitrogen containing seven-membered heterocyclic compounds like 1, 4-benzodiazepines with various substituents show a wide range of pharmacological activities such as analgesic, sedative, antidepressive, anticonvulsant, antianxiety, anticancer, antimicrobial, anti-HIV, muscle relaxant, antitumor antibiotics agents, *etc.* [1-5]. Also, the 1, 4-benzodiazepine cores such as Diazepam (Valium) (Fig. 1) are found in numerous psychoactive pharmaceutical agents [6].

Among the triazoles, 1, 2, 3-triazoles are excellent heterocyclic structures willing in various natural products and synthetic pharmaceuticals [7]. Moreover, some studies display 1, 4-benzodiazepines linked to 1, 2, 3-triazole core are considerable skeletons have interesting biological properties such as antimicrobial, antifungal, anti-tubercular, anti-inflammatory, anticancer, analgesic, anticonvulsant and anti-tyrosinase activities [8-10].

One of the multicomponent reactions for the synthesis 1, 2, 3-triazoles is the click 1,3-dipolar cycloaddition between azides and terminal alkynes [11-15]. The best known method for synthesis 1,4-disubstituted 1,2,3-triazoles is via the copper-catalyzed azide alkyne cycloaddition reaction (CuAAC) [16-18]. A two-step synthesis of fused triazole derivatives has recently been reported through Ugi reaction (Scheme 1, A) [19]. Novel fused-triazole benzodiazepines have been synthesized by the Ma group (Scheme 1, B) [20]. Zhang and co-workers illustrated a one pot-economy synthesis involving sequential [3+2] cycloaddition of azomethine ylides, *N*-propargylation, to synthesis triazole-based benzodiazepines [21]. This one-pot and three-step reaction has only two operation steps, including the initial [3+2] cycloaddition of an azomethine ylide and then followed by the addition of propargyl bromide. The propargylated compound spontaneously undergoes the click reaction at elevated temperature to form the final product.

Recently, our research group synthesized the β-hydroxy-1,4-disubstituted-1,2,3-triazole-based benzodiazepinediones and 1,5-bis(*N*-substituted 1,2,3–triazole) benzodiazepinediones by the Huisgen [3+2] dipolar cycloaddition reaction under mild conditions [22, 23]. Based on the background of the research group in the synthesis of the 1,4-disubstituted 1,2,3-triazole derivatives [24-32] and inspired by the promising therapeutic activities of 1,4-benzodiazepines and 1, 2, 3-triazoles, we wish to design the synthesis of a new category of 1,4-benzodiazepine-triazole compounds based on diazepam scaffold, through a highly efficient click reaction (Scheme 2). In the final section of this study, physicochemical properties of the characterized structure of **6a** were studied by us-

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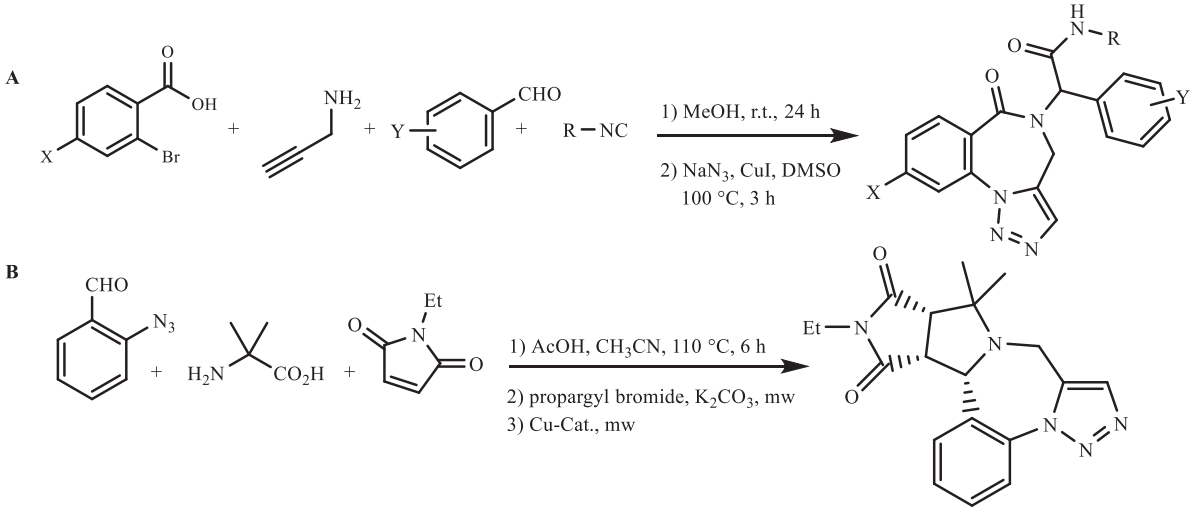


Scheme 1. Synthesis of some 1, 2, 3-triazole-based benzodiazepine derivatives.

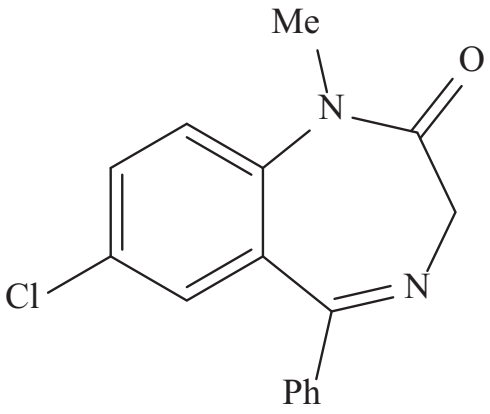


Fig. 1. Chemical structure of Diazepam (Valium).

ing the density functional theory (DFT) calculations in conjunction with B3LYP/6-31++G (d, p) method.

2. Experimental

2.1. General information

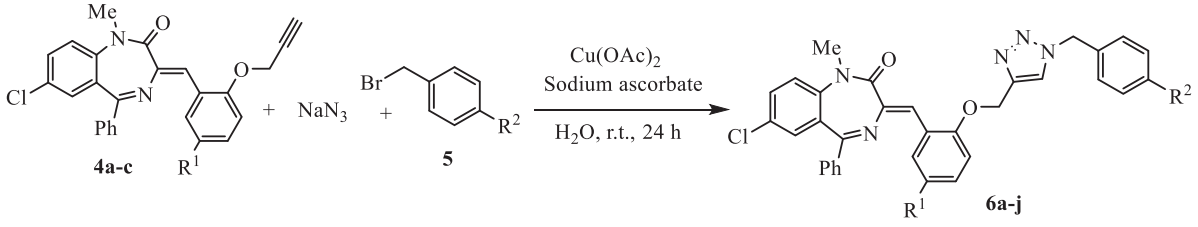
Diazepam was obtained from Hakim Pharmaceutical Co. and all of the other commercially available reagents and solvents purchased from Sigma–Aldrich and Merck and were used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and. IR spectra were recorded with a Shimadzu IR-21 prestige spectrometer. ^{1}H and $^{13}CNMR$ spectra were recorded on a Bruker DRX-500-Avance spectrometer in $CDCl_3$. LC-MS analysis was performed on an Agilent 1200 LC system. Elemental analyses were carried out by a CHN-O Rapid Heraeus elemental analyzer (Wellesley, MA). Silica gel 60 (0.040–0.063 mm) were used for column chromatography. Thin layer chromatography (TLC) was performed using silica gel 60/Kieselguhr F254 precoated on Aluminum sheets (thickness 0.2 mm), commercially available from Merck. Visualization of spots on the TLC plate was accomplished with UV light.

2.2. Computational details

The geometry of the structure **6a** was optimized at the DFT/B3LYP level with 6-31++G(d, p) basis set using the Gaussian 09 software [33]. In addition, the frequency calculations were performed using the mentioned computational method to obtain the thermodynamic data of enthalpy and Gibbs free energy of the molecule **6a** at a temperature of 298 K. Molecular electrostatic potential (MEP) maps for **6a** was calculated by applying B3LYP/6-31++G(d, p) computational methods. Optimized Cartesian coordinates and energies of all proposed structures are inserted into electronic supplementary material.

2.3. General procedure for the synthesis of O-propargyl salicylaldehyde derivatives *2a-c*

The *O*-propargyl salicylaldehydes **2a-c** were prepared according to the literature [34]. A solution of salicylaldehydes **1** (2.0 mmol) and propargyl bromide (2.4 mmol, 286 mg) in DMF (15 mL) was reacted in the presence of K_2CO_3 (2.0 mmol, 276 mg) at room temperature for 12 h. TLC followed the progress of the reaction. After completion, the water was added, and the precipitated solid was filtered and washed with water to give **2a-c**.



Scheme 2. General synthetic protocol for novel 1,2,3-triazole-based diazepam derivatives **6a-j**.

2.4. General procedure for the synthesis of **4a-d**

A mixture of diazepam **3** (1 mmol) and *O*-propargyl salicylaldehyde **2a-c** (1 mmol) in *t*-BuOH (5 mL) was heated and treated slowly with KO*t*-Bu/*t*-BuOH (1 mmol/ 5 mL). The reaction mixture was refluxed for 3–6 h. The reaction was monitored by TLC. The solvent was then removed under reduced pressure, and the mixture was purified by silica gel column chromatography (*n*-hexane-EtOAc, 3/1) to give the desired pure products **4a-d**.

2.5. General procedure for the synthesis of 1,2,3-triazole-based diazepam **6a-j**

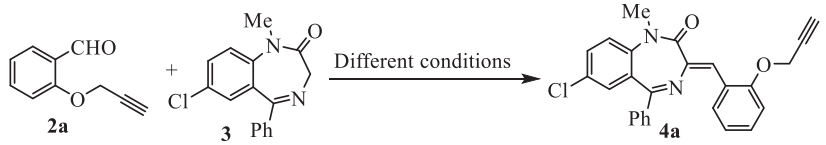
NaN_3 is toxic and potentially explosive material and therefore the reaction should be carried out only by a trained professional in an efficient chemical hood [35].

In a tube equipped with a magnetic stirring bar, **4a-d** (1 mmol) and benzyl bromide **5** (1 mmol) were added in water (15 mL). Then sodium azide (1 mmol), $Cu(OAc)_2$ (0.2 mmol), sodium ascorbate (0.2 mmol) were added to the reaction mixture, which was stirred for 24 h at room temperature and subsequently extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, and the solvent was evaporated. Finally, the crude product was purified by silica gel column chromatography ((*n*-hexane-EtOAc, 4/1) to afford the desired pure products **6a-j** as yellow powders.

2.6. Spectral data of 1,2,3-triazole-based diazepam **6a-j**

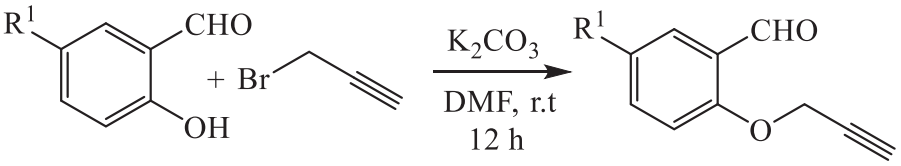
3-(2-((1-benzyl-1H-1, 2, 3-triazol-4-yl) methoxy) benzylidene)-7-chloro-1-methyl-5-phenyl-1, 3-dihydro-2H-benzo[e] [1, 4] diazepin-2-one **6a**: yellow powder; m.p.: 136-138°C; FT-IR (KBr): 3441, 3165, 3024, 2920, 2850, 1660, 1601, 754, 698 cm^{-1}; ^{1}HNMR: δ = 3.53 (3H, s, Me), 5.34 (2H, dd, ^3J =12.0, 8.0, NCH_2), 5.63 (2H, s, OCH_2), 7.02 (1H, s, CH), 7.31-7.40 (5H, m, 5CH), 7.42 (1H, d, ^3J =2.5, CH), 7.44-7.61 (9H, m, 9CH), 7.77 (1H, s, CH), 7.94-7.96 (2H, m, 2CH); ^{13}CNMR: δ = 35.6 (Me), 53.3 (NCH_2), 62.0 (OCH_2), 112.6 (CH), 113.0 (CH), 121.3 (C), 123.8 (CH), 124.6 (C), 125.3 (CH), 128.4 (CH), 128.5 (CH), 128.6 (2CH), 128.9 (CH), 129.2 (2CH), 129.3 (2CH), 129.8 (CH), 129.9 (2CH), 131.0 (CH), 131.1 (C), 131.9 (CH), 132.1 (CH), 136.4 (C), 137.2 (C), 140.6 (C), 142.1 (C), 142.2 (C), 156.3 (C), 164.6 (C=O), 170.4 (C=N). Anal. Calcd. for $C_{33}H_{26}ClN_5O_2$: C, 70.77; H, 4.68; N, 12.51, Found: C, 70.65; H, 4.87; N, 12.41. *3-(2-((1-(4-bromobenzyl)-1H-1, 2, 3-triazol-4-yl) methoxy) benzylidene)-7-chloro-1-methyl-5-phenyl-1, 3-dihydro-2H-benzo[e] [1, 4] diazepin-2-one* **6b***:* yellow powder, m.p.: 137-139°C; FT-IR (KBr): 3443, 3138, 3065, 2924, 2859, 1661, 1599, 752, 696 cm^{-1}; ^{1}HNMR: δ = 3.35 (3H, s, Me), 5.17 (2H, dd, ^3J = 24, 6.5, NCH_2), 5.41 (2H, s, OCH_2), 6.84 (1H, s, CH), 6.91-6.94 (2H, m, 2CH), 7.07-7.19 (5H, m, 5CH), 7.37-7.47 (6H, m, 6CH), 7.56 (1H, dd ^3J = 3.5, 13, CH), 7.62 (1H, s, CH), 7.75-7.79 (2H, m, 2CH); ^{13}CNMR: δ = 35.6 (Me), 53.3 (NCH_2), 63.2 (OCH2), 112.7 (CH), 114.6 (CH), 121.2 (C), 122.7 (C), 122.8 (CH), 122.9 (C), 124.6 (CH), 128.6 (CH), 129.1 (CH), 129.2 (2CH), 129.3 (CH), 129.7 (2CH), 131.2 (CH), 131.4 (C), 132.3 (CH), 133.6 (2CH), 137.2 (CH), 139.9 (2CH), 141.9 (C), 142.5 (C), 144.9 (C), 151.4 (C), 151.5 (C), 156.3 (C), 163.9 (C=O), 171.1 (C=N). Anal. Calcd for $C_{33}H_{25}BrClN_5O_2$: C, 62.03; H, 3.94; N, 10.96, Found: C, 62.14; H, 3.86; N, 10.90. *7-chloro-1-methyl-3-(2-((1-(4-nitrobenzyl)-1H-1, 2, 3-triazol-4 yl) methoxy) benzylidene)-5-phenyl-1, 3-dihydro-2H-benzo[e] [1, 4] diazepin-2-one* **6c**: yellow powder, m.p.: 142.145°C; FT-IR (KBr): 3426, 3138, 3069, 2928, 2862, 1661, 1601, 746, 700 cm^{-1}. ^{1}HNMR: δ = 3.41 (3H, s, Me), 5.26 (2H, dd, ^3J = 17.5, 12, NCH_2), 5.64 (2H, s, OCH_2), 6.89 (1H, s, CH), 6.99- 7.01 (2H, m, 2CH), 7.27-7.32 (1H, m, CH), 7.39-7.49 (6H, m, 6CH), 7.54- 7.57 (1H, m, CH), 7.68- 7.71 (4H, m, 4CH), 7.81-7.83 (3H, m, 3CH); ^{13}CNMR: δ = 35.1 (Me), 52.7 (NCH_2), 67.7 (OCH_2), 112.6 (CH), 114.4 (CH), 120.9 (C), 122.3 (C), 122.8 (CH), 123.8 (C), 127.0 (CH), 128.2 (CH), 128.3 (CH), 128.7 (2CH), 128.8 (CH), 128.9 (2CH), 129.3 (CH), 130.3 (C), 130.8 (CH), 130.9 (2CH), 131.3 (CH), 132.0 (2CH), 136.7 (C), 138.1 (C), 139.4 (C), 141.1 (C), 141.4 (C), 163.7 (C), 167.2 (C=O), 170.7 (C=N). Anal. Calcd for $C_{33}H_{25}ClN_6O_4$: C, 65.51; H, 4.16; N, 13.89, Found: C, 65.57; H, 4.20; N, 13.80. *3-(2-((1-benzyl-1H-1, 2, 3-triazol-4-yl) methoxy)-5-bromobenzylidene)-7-chloro-1-methyl-5-phenyl-1, 3-dihydro-2H-benzo[e] [1, 4] diazepin-2-one* **6d**: yellow powder, m.p.: 140-144°C; FT-IR (KBr): 3441, 3129, 3067, 2922, 2855, 1661, 1609, 741, 694 cm^{-1}; ^{1}HNMR: δ = 3.36 (3H, s, Me), 5.12 (2H, d, ^3J = 4.5, NCH_2), 5.45 (2H, s, OCH_2), 6.71 (1H, s, CH), 7.19-7.22 (6H, m, 6CH), 7.27-7.31 (3H, m, 3CH), 7.38-7.47 (4H, m, 4CH), 7.53 (1H, s, CH), 7.76-7.80 (2H, m, 2CH), 7.92 (H, d, ^3J = 4.5, CH); ^{13}CNMR: δ = 35.7 (Me), 51.3 (NCH_2), 61.6 (OCH_2), 106.9 (C), 112.9 (CH), 114.2 (C), 122.3 (C), 122.4 (C), 122.9 (CH), 123.9 (CH), 124.0 (CH), 125.2 (2CH), 126.5 (2CH), 128.1 (2CH), 128.6 (2CH), 128.7 (CH), 129.1 (C), 129.9 (CH), 131.3 (CH), 131.4 (CH), 131.6 (CH), 133.3 (C), 134.1 (C), 137.0 (C), 140.8 (C), 149.5 (C), 150.3 (C), 161.3 (C=O), 166.4 (C=N); MS (ESI): 640 $[M+H]^+$; Anal. Calcd for $C_{33}H_{25}BrClN_5O_2$: C, 62.03; H, 3.94; N, 10.96, Found: C, 62.00; H, 3.98; N, 10.93. *3-(5-bromo-2-((1-(4-bromobenzyl)-1H-1, 2, 3-triazol-4-yl) methoxy) benzylidene)-7-chloro-1-methyl-5-phenyl-1, 3-dihydro-2H-benzo[e] [1, 4] diazepin-2-one* **6e**: yellow powder, m.p.; 139-143°C; FT-IR (KBr): 3437, 3129, 3069, 2922, 2864, 1659, 1605, 779, 691 cm^{-1}; ^{1}HNMR: δ = 3.36 (3H, s, Me), 5.13 (2H, dd, ^3J = 24.0, 7.0, NCH_2), 5.40 (2H, s, OCH_2), 6.72 (1H, s, CH), 6.80 (2H, dd, ^3J = 12.5, 6.0, CH), 7.06-7.11 (2H, m, 2CH), 7.19-7.22 (2H, m, 2CH), 7.25 (1H, s, CH), 7.25 (1H, d, ^3J= 2.0, CH), 7.38-7.49 (4H, m, 4CH), 7.57 (1H, s, CH), 7.76-7.80 (2H, m, 2CH), 7.89 (1H, d, ^3J = 5.0, CH); ^{13}CNMR: δ = 35.7 (Me), 53.5 (NCH_2), 63.2 (OCH_2), 113.1 (CH), 113.6 (C), 114.3 (CH), 122.7 (CH), 122.9 (CH), 123.0 (C), 126.6 (C), 128.7 (2CH), 129.4 (C), 129.5 (CH), 129.8 (CH), 129.9 (2CH), 131.1 (C), 131.4 (CH), 131.5 (2CH), 131.6 (CH), 132.3 (2CH), 133.4 (C), 134.1 (CH), 137.2 (C), 140.8 (C), 141.7 (C), 144.3 (C), 155.2 (C), 164.4 (C=O), 170.8 (C=N); Anal. Calcd for $C_{33}H_{24}Br_2ClN_5O_2$: C, 55.22; H, 3.37; N, 9.76, Found: C, 55.13; H, 3.42; N, 9.81. *3-(5-bromo-2-((1-(4-nitrobenzyl)-1H-1, 2, 3-triazol-4-yl) methoxy) benzylidene)-7-chloro-1-methyl-5-phenyl-1, 3-dihydro-2H-benzo[e] [1, 4] diazepin-2-one* **6f**: yellow powder, m.p.: 147-150°C; FT-IR (KBr): 3437, 3138, 3075, 2924, 2859, 1650, 1607, 754, 694 cm^{-1}. ^{1}HNMR: δ = 3.41 (3H, s, Me), 5.18-5.27 (2H, dd, ^3J = 19.0, 12.0, NCH_2), 5.63 (2H, s, OCH_2), 6.78 (1H, s, CH), 6.87-6.89 (1H, d, ^3J = 8.5, CH), 7.31 (2H, s, 2CH), 7.40-7.42 (2H, m, 2CH), 7.48-7.55 (4H, m, 4CH), 7.76 (1H, s, CH), 7.82-7.89 (4H, m, 4CH), 8.21-8.22 (2H, m, 2CH); ^{13}CNMR: δ = 35.2 (Me), 52.8 (NCH_2), 63.0 (OCH_2), 112.8 (CH), 114.0 (C), 114.1 (CH), 122.3 (CH), 122.7 (CH), 122.9 (C), 123.9 (C), 125.7 (2CH), 126.1 (C), 126.3 (CH), 128.3 (CH), 129.1 (2CH), 129.4 (C), 130.0 (CH), 130.9 (2CH), 131.1 (CH), 131.2 (2CH), 133.7 (C), 134.8 (C), 137.9 (C), 141.2 (C), 142.9 (C), 146.3 (C), 159.9 (C), 166.8 (C=O), 170.3 (C=N); Anal. Calcd for $C_{33}H_{24}BrClN_6O_4$: C, 57.95; H, 3.54; N, 12.29, Found: C, 58.01; H, 3.59; N, 12.27. *3-(2-((1-benzyl-1H-1, 2, 3-triazol-4-yl) methoxy)-5-methoxybenzylidene)-7-chloro-1-methyl-5-phenyl-1, 3-dihydro-2H-benzo[e] [1, 4] diazepin-2-one* **6g**: yellow powder, m.p.: 137-139°C; FT- IR (KBr): 3447, 3136, 3069, 2926, 2857, 1661, 1605, 754, 702 cm^{-1}. ^{1}HNMR: δ = 3.36 (3H, s, Me), 3.77 (3H, s, OMe), 5.13 (2H, dd, ^3J = 25.0, 58.0, NCH_2), 5.46 (2H, s, OCH_2), 6.77-6.80 (2H, m, 2CH), 6.94-7.09 (2H, m, 2CH), 7.16-7.23 (6H, m, 6CH), 7.25-7.27 (1H, m, 1 CH), 7.37-7.48 (4H, m, 4CH), 7.74-7.78 (2H, m, 2CH), 7.97 (1H, s, CH); ^{13}CNMR: δ = 33.1 (Me), 55.8 (OMe), 57.6 (NCH_2), 67.2 (OCH_2), 108.4 (C), 111.5 (CH), 115.2 (CH), 118.3 (CH), 122.8 (C), 123.8 (C), 123.9 (CH), 125.3 (CH), 125.4 (CH), 126.1 (2CH), 128.2 (2CH), 128.4 (2CH), 128.6 (2CH), 128.9 (CH), 129.2 (C), 129.8 (CH), 130.4 (CH), 131.4 (2CH), 132.2 (C), 132.9 (C), 137.2 (C), 140.5 (C), 144.9 (C), 152.6 (C=O), 158.8 (C=N); MS (ESI): 590 $[M+H]^+$; Anal. Calcd for $C_{34}H_{28}ClN_5O_3$: C, 69.21; H, 4.78; N, 11.87, Found: C, 69.11; H, 4.73; N, 11.91. *3-(2-((1-(4-bromobenzyl)-*

Table 1
Solvent, temperature and time efficacy in the synthesis of **4a**[a]



Entry	Base	Solvent	T (°C)	Time (h)	Yield [b] (%)
1	KOH	EtOH	r.t	3	10
2	KOH	EtOH	reflux	24	25
3	KOH	THF	reflux	24	45
4	KOH	Toluene	reflux	24	23
5	KOH	DMSO	120	24	-
6	TEA	CH_3CN	reflux	24	-
7	NaOAc	Ac_2O	reflux	24	-
8	KO*t*-Bu	*t*-BuOH	reflux	5	85

[a] Diazepam **3** (1 equiv.); *O*-propargyl salicylaldehyde **2a** (1 equiv.); base (1 equiv.); solvent (10 ml)
[b] Isolated yield.



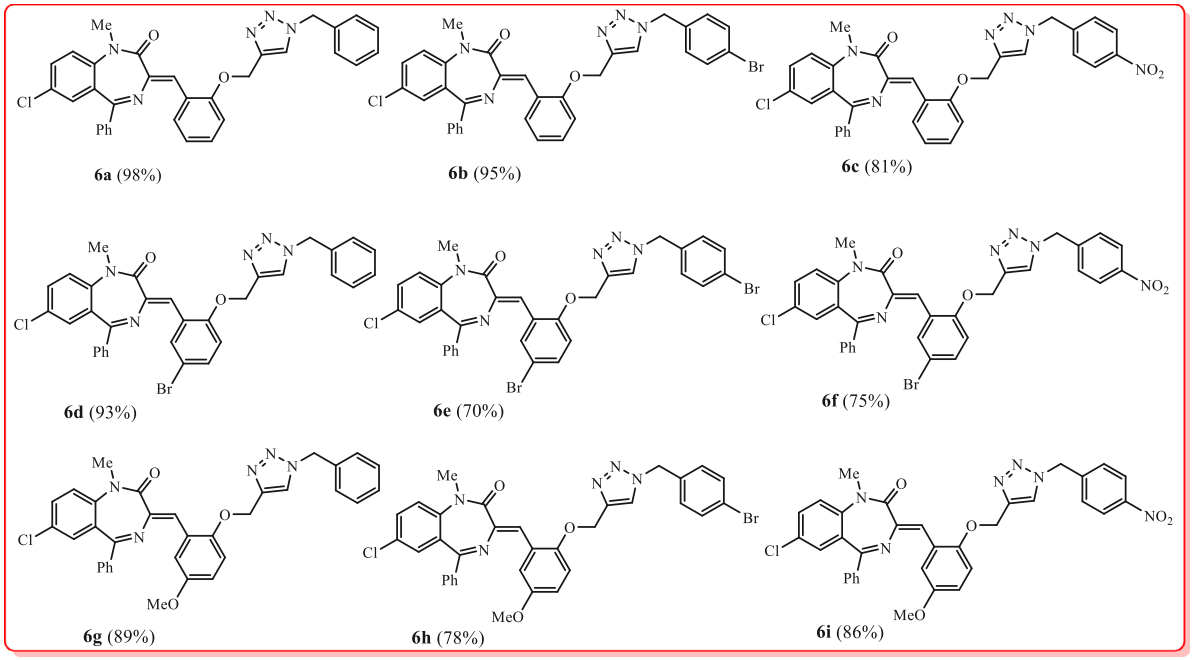
1

R^1 = H, Br, OMe

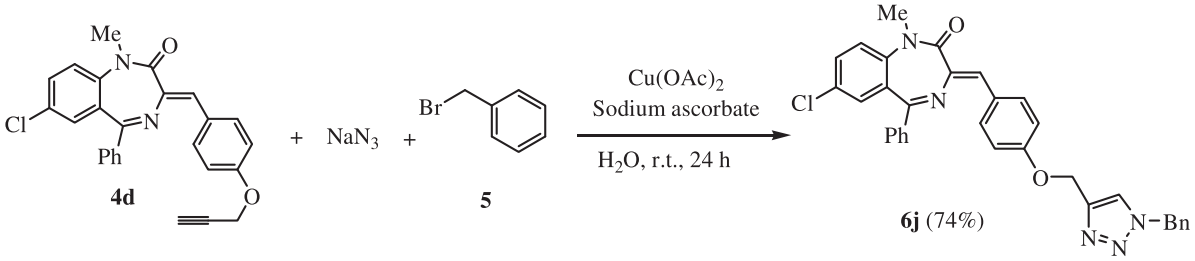
2a-c

	R^1	Yield (%)
2a	H	98
2b	Br	86
2c	OMe	70

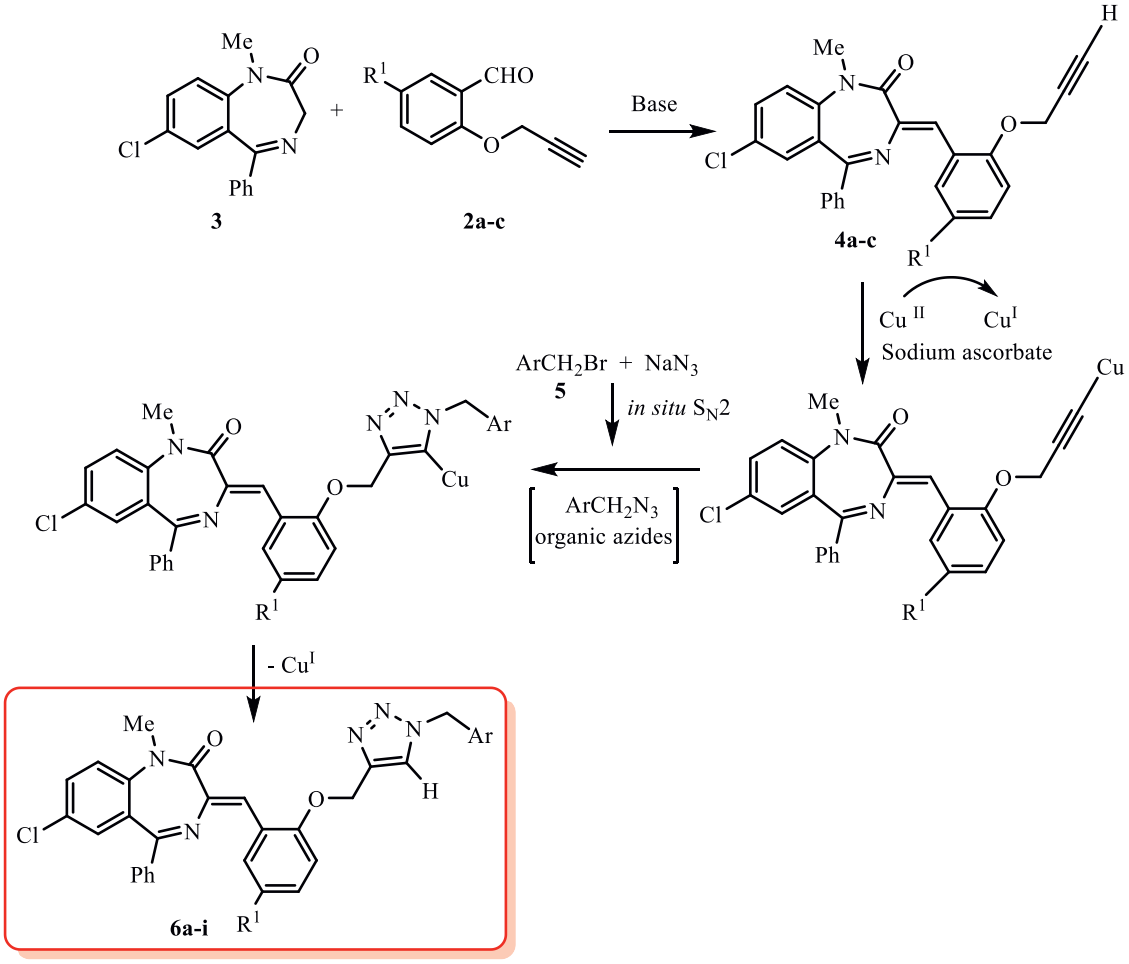
Scheme 3. Synthesis of *O*-propargyl salicylaldehydes **2a-c**.



Scheme 4. Chemical structures of the synthesized 1,4-disubstituted-1,2,3-triazole-based diazepam **6a-i**.



Scheme 5. Synthesis of 1,2,3-triazole-based diazepam **6j**.



Scheme 6. Proposed mechanism for the synthesis of **6a-i**.

1H-1, 2, 3-triazol-4-yl) methoxy)-5-methoxybenzylidene)-7-chloro-1-methyl-5-phenyl-1, 3-dihydro-2H-benzo[e] [1, 4] diazepin-2-one **6h**: yellow powder, m.p.: 144–148°C; FT-IR (KBr): 3441, 3136, 3069, 2926, 2857, 1659, 1605, 752, 694 cm^{-1}; ^{1}HNMR: δ = 3.35 (3H, s, Me), 3.79 (3H, s, OMe), 5.18 (2H, dd, ^3J = 25.5, 58.5, NCH_2), 5.41 (2H, s, OCH_2), 6.78 (1H, s, CH), 6.93-7.20 (6H, m, 6CH), 7.25 (1H, m, 1CH), 7.34-7.48 (6H, m, 6CH), 7.74-7.78 (2H, m, 2CH), 8.07 (1H, s, CH); ^{13}CNMR: δ = 35.5 (Me), 53.4 (NCH_2), 55.8 (OMe), 67.0 (OCH_2), 112.3 (CH), 115.5 (C), 116.6 (CH), 122.8 (CH), 123.0 (CH), 123.9 (C), 128.7 (C), 129.2 (2CH), 129.3 (C), 129.8 (CH), 131.2 (CH), 131.3 (2CH), 131.5 (C), 132.1 (CH), 133.9 (2CH), 134.8 (CH), 135.1 (2CH), 137.2 (C), 140.3 (CH), 141.8 (C), 143.2 (C), 146.0 (C), 152.6 (C), 161.3 (C), 164.2 (C=O), 164.6 (C=N); MS (ESI): 670 $[M+H]^+$; Anal. Calcd for $C_{34}H_{27}BrClN_5O_3$: C, 61.04; H, 4.07; N, 10.47, Found: C, 61.09; H, 4.02; N, 10.44. *7-chloro-3-(5-methoxy-2-((1-(4-nitrobenzyl)-1H-1, 2, 3-triazol-4-yl) methoxy) benzylidene)-1-methyl-5-phenyl-1, 3-dihydro-2H-benzo[e] [1, 4] diazepin-2-one* **6i**: yellow powder, m.p.: 118-121°C; FT-IR (KBr): 3433, 3204, 3075, 2926, 2857, 1661, 1605, 752, 696 cm^{-1}. ^{1}HNMR: δ = 3.38 (3H, s, Me), 3.87 (3H, s, OMe), 5.31 (2H, dd, ^3J = 12.5, 62.5, NCH_2), 5.62 (2H, s, OCH_2), 6.83-6.86 (2H, m, 2CH), 7.02 (2H, m, 2CH), 7.27-7.30 (1H, m, 1CH), 7.40 - 7.59 (7H, m, 7CH), 7.79-7.81 (2H, m, 2CH), 8.10 (2H, m, 2CH), 8.21 (1H, s, CH); ^{13}CNMR: δ = 34.9 (Me), 52.6 (NCH_2), 55.4 (OMe), 66.4 (OCH_2), 111.9 (CH), 115.1 (C), 122.3 (CH), 122.5 (CH), 123.4 (CH), 123.6 (C), 127.9 (C), 128.2 (2CH), 128.4 (C), 128.7 (CH), 128.9 (CH), 129.0 (2CH), 129.3 (C), 130.8 (CH), 130.9 (2CH), 131.0 (CH), 136.6 (2CH), 139.6 (C), 141.3 (CH), 141.5 (C), 144.8 (C), 145.4 (C), 147.4 (C), 152.1 (C), 163.9 (C=O), 170.7 (C=N); Anal. Calcd for $C_{34}H_{27}ClN_6O_5$: C, 64.30; H, 4.29; N, 13.23, Found: C, 64.18; H, 5.64; N, 13.33. *3-(4-((1-benzyl-1H-1, 2, 3-triazol-4-yl) methoxy) benzylidene)-7-chloro-1-methyl-5-phenyl-1, 3-dihydro-2H-benzo[e] [1, 4] diazepin-2-one* **6j**: yellow powder, m.p.: 131-136°C; ^{1}HNMR: δ = 3.14 (3H, s, Me),

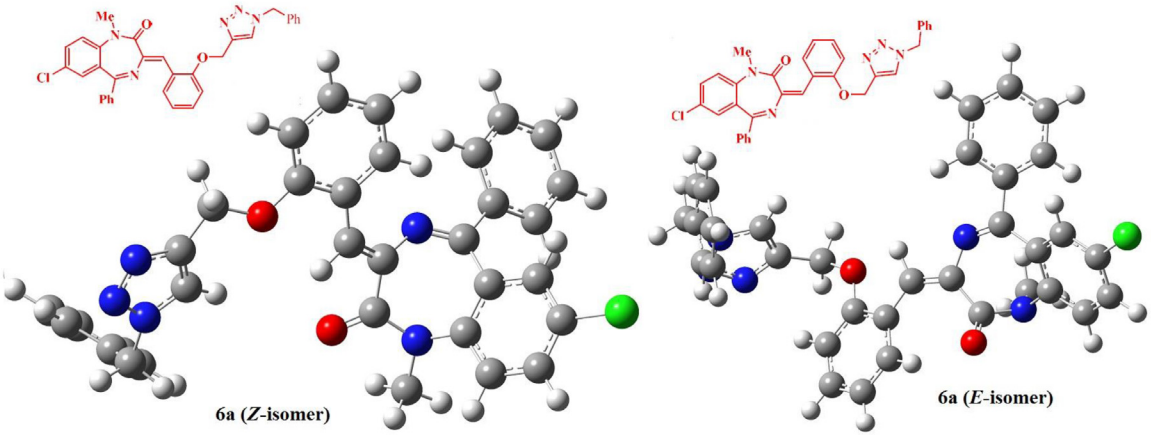


Fig. 2. The B3LYP/6-31++G(d, p) optimized geometry of **6a** and **6a′**.

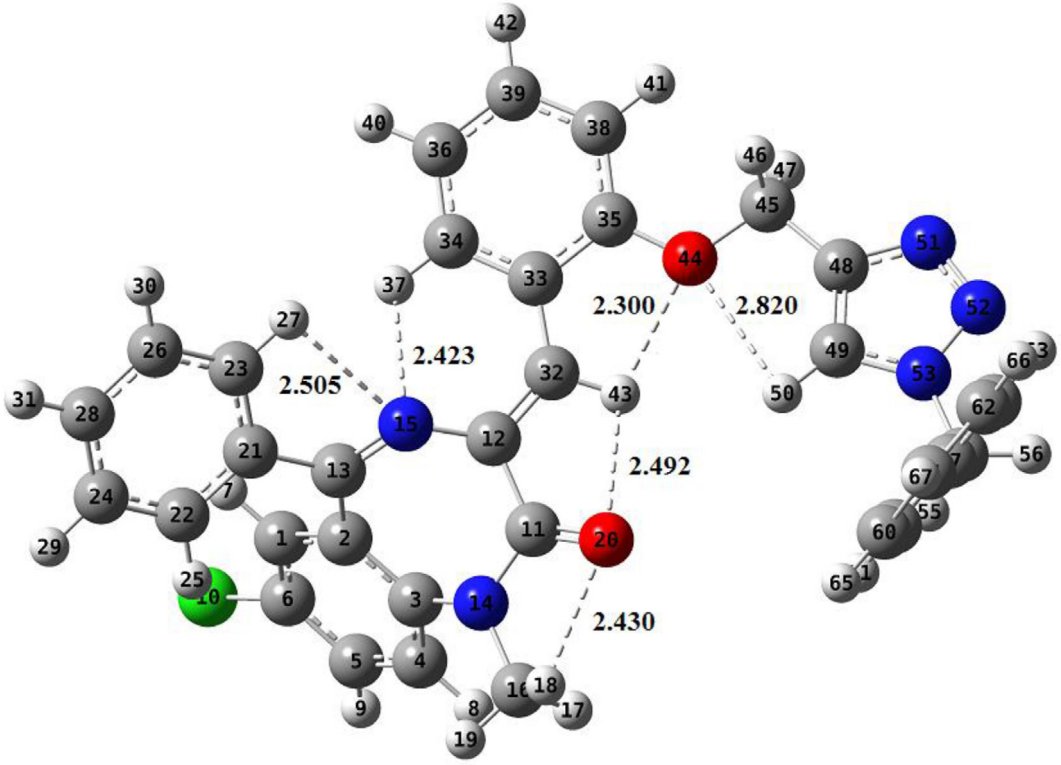


Fig. 3. Possible intramolecular C-H...N and C-H...O hydrogen bond interactions in the optimized structure **6a**. Dashed lines represent hydrogen bonds. The bond distances are in (Å).

Table 2
The representative B3LYP/6-31++G(d, p) calculated bond lengths and bond angles for **6a.**

Atom groups[a]	Bond lengths (Å)	Atom groups	Bond angles (°)
O^{20}-C^{11}	1.226	N^{14}-C^{11}-C^{12}	117.6
N^{15}-C^{13}	1.289	C^{45}-O^{44}-C^{35}	120.0
N^{51}-N^{52}	1.308	H^{17}-C^{15}-H^{19}	109.7
C^{6}-Cl^{10}	1.756	C^{38}-C^{39}-C^{36}	120.4
C^{1}-C^{2}	1.405	O^{20}-C^{11}-C^{12}	121.9
C^{49}-H^{50}	1.078	H^{27}-O^{23}-H^{26}	120.6
C^{45}-O^{44}	1.4275	C^{33}-C^{32}-H^{43}	115.7
C^{34}-H^{37}	1.082	H^{46}-C^{45}-H^{47}	108.2

[a] For numbering of atoms refer Fig. 3.

5.17 (2H, dd, ^{3}J= 24.0, 6.5, NCH_2), 5.40 (2H, s, OCH_2), 6.84 (1H, s, CH), 6.90-6.95 (2H, m, 2CH), 7.07-7.19 (5H, m, 5CH), 7.37-7.49 (6H, m, 6CH), 7.54-7.58 (1H, m, CH), 7.63 (1H, s, CH), 7.75-7.80 (2H, m, 2CH), 7.98 (1H, s, CH); ^{13}CNMR: δ = 35.5 (Me), 54.9 (NCH_2), 66.0 (OCH_2), 113.6 (CH), 114.8 (CH), 119.9 (C), 121.3 (2CH), 123.9 (CH), 126.2 (CH), 127.6 (C), 127.8 (2CH), 128.1 (2CH), 128.3 (2CH), 129.4 (CH), 129.7 (2CH), 129.8 (C), 130.7 (2CH), 131.5 (CH), 132.4 (CH), 132.9 (C), 134.5 (C), 134.9 (C), 135.8 (C), 140.9 (C), 148.9 (C), 162.4 (C=O), 165.2 (C=N); Anal. Calcd for $C_{33}H_{26}ClN_5O_2$: C, 70.77; H, 4.68; N, 12.51, Found: C, 70.70; H, 4.61; N, 12.55.

3. Results and discussion

*3.1. Synthesis and spectroscopic characterization of 1,2,3-triazole-based diazepam **6a-j***

The starting compounds 3-(2-(prop-2-yn-1-yloxy) benzylidene)-1, 3-dihydro-2H-benzo[e] [1, 4] diazepin-2-one **4a-c** are readily

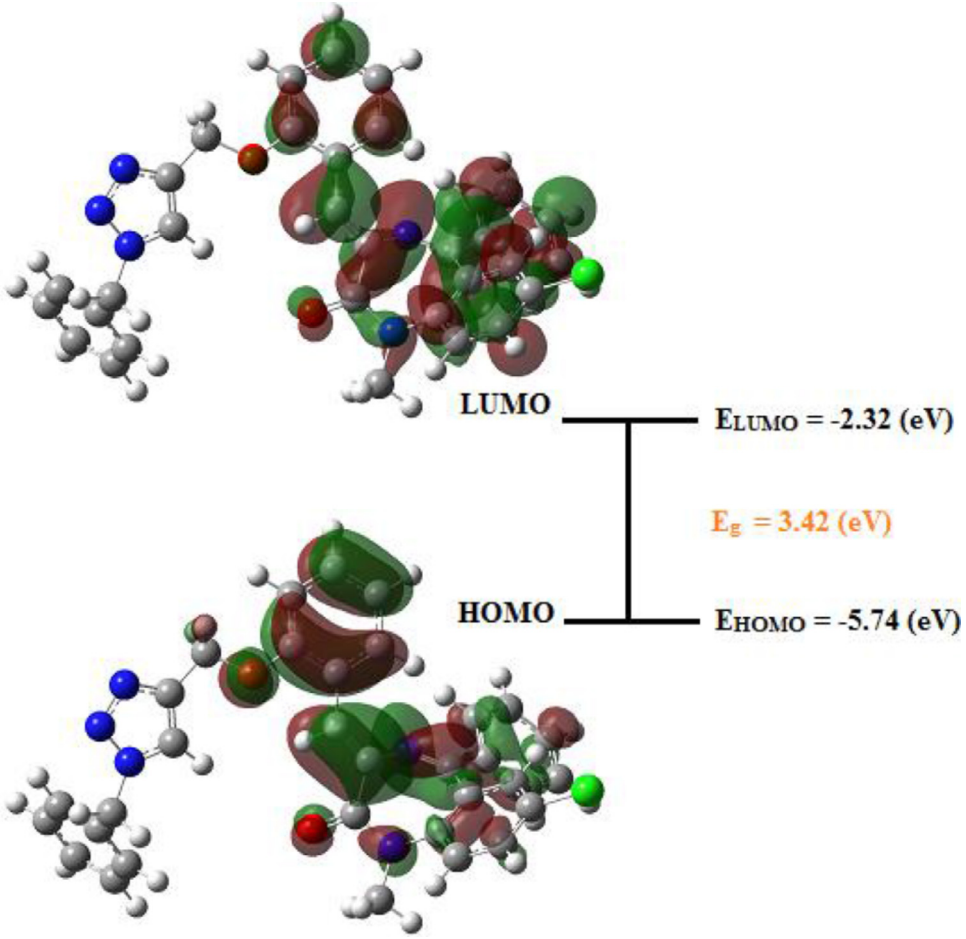


Fig. 4. Frontier orbitals (HOMO and LUMO) and E_g for **6a** resulted from the B3LYP/6-31++G(d, p) method.

Table 3
The calculated electronic data of **6a** by B3LYP/6-31++G(d, p) method.

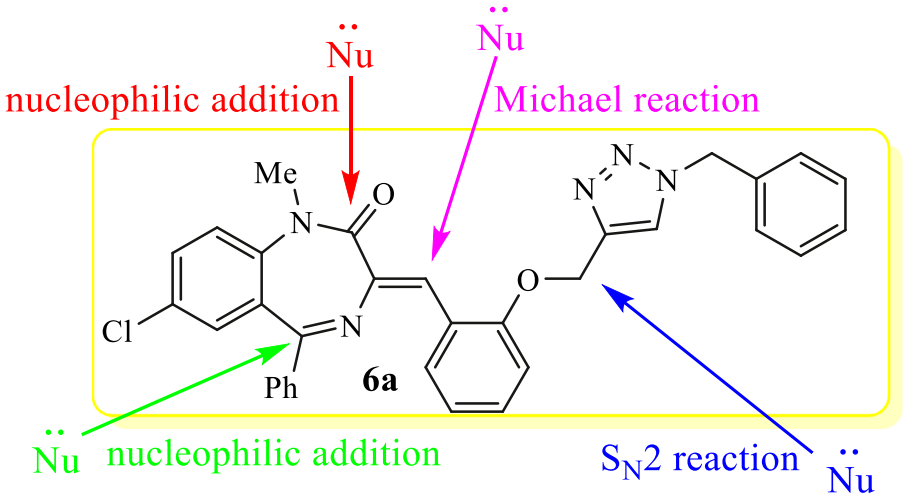
Parameter	Value	derivation
Energy (Hartree)	2157.6	-
μ_D (Debye)	5.52	-
E_{HOMO} (eV)	−5.74	-
E_{LUMO} (eV)	−2.32	-
E_g (eV)	3.42	$E_{LUMO} - E_{HOMO}$
Chemical potential (μ) (eV)	−4.03	$(E_{LUMO}+E_{HOMO})/2$
Chemical hardness (η) (eV)	1.71	$(E_{LUMO}-E_{HOMO})/2$
Electrophilicity (ω) (eV)	4.75	$\omega = \mu^2/2\eta$ [45]

synthesized from the commercially available materials in high yield and excellent purity in house. *O*-propargyl salicylaldehyde derivatives **2a-c** were prepared from the corresponding substituted salicylaldehydes **1**. Treatment of salicylaldehydes **1** with propargyl bromide in the presence of K_2CO_3 in DMF at room temperature for 12 h gave *O*-propargylbenzaldehyde **2a-c** in 70–98% yields (Scheme 3) [34].

In the next step, diazepam **3** was subjected to condensation with *O*-propargyl salicylaldehyde derivatives **2a-c** under different conditions (Table 1). The results showed that the best condition and yield (85%) was obtained in the presence of KOt-Bu as a base in refluxing t-BuOH for 5 h. Using the optimization condition, the Knoevenagel adducts **4b, 4c** and **4d** (Scheme 4) were also synthesized with high yields 87%, 81% and 90%, respectively.

With the propargyl benzodiazepine derivatives **4a-c** in hand, attention was focused on copper (I)-catalyzed azide-alkyne cycloaddition reaction **4a-c** to the synthesis of 1,4-disubstituted-1,2,3-triazole-based diazepam **6a-j**. The desired 1,2,3-triazole **6a-j** were prepared by treatment of **4** (1 equiv.), benzyl bromide derivatives **5** (1 equiv.), NaN_3 (1 equiv.), $Cu(OAc)_2$ (0.2 equiv.) and sodium ascorbate (0.2 equiv.) in water. The crude product was purified using silica gel column chromatography to afford the desired products **6a-j** in pure form. As shown in Scheme 4, using copper (II) acetate in the presence of sodium ascorbate for an *in situ* reduction, the desired products **6a-j** were formed under mild condition. A diverse range of benzyl bromide derivatives **5** reacted successfully with the propargyl benzodiazepine derivatives **4a-c**, and the corresponding desired 1,2,3-triazole-based diazepam **6a-j** were obtained in excellent yields (70-98%). Structures of all the synthesized compounds **6a-j** were fully characterized by FT-IR, ^{1}HNMR, ^{13}CNMR, MS (ESI) and CHN analysis (Experimental section and electronic supplementary information). As a representative example, the spectral analysis of **6a** is discussed below.

The experimental ^{1}HNMR spectrum of **6a** in $CDCl_3$ revealed a singlet peak at δ = 3.53 ppm for CH_3 and a doublet of doublet resonance at δ = 5.34 ppm for the NCH_2 group (electronic supplementary material). The vinylic proton was observed at δ = 5.40 ppm as a distinct singlet signal. The methylene protons of OCH_2 group in **6a** appeared at δ = 5.63 ppm as a singlet line. The protons on aromatic rings were appeared at δ = 7.02–7.96 ppm. The characteristic triazole proton was observed at δ = 7.77 ppm as a singlet resonance. The ^{1}H–decoupled ^{13}CNMR spectrum of **6a** showed 29 signals, which is in accord with the proposed structure that the corresponding signals of Me, NCH_2 and OCH_2 groups appeared at 35.6, 53.3 and 62.0 ppm, respectively. The sp^2 carbon



Scheme 7. Possible nucleophilic carbon centers in **6a**, based on APT charge analysis and electrophilicity index.

atoms were observed at 112.6–170.4 ppm, with the amide carbon appearing at δ = 164.6 ppm and imine carbon (C=N) at δ = 170.4 ppm.

The method's applicability is further extended by performing the [3 + 2] cycloaddition reaction of 4-*O*-propargyl benzaldehyde derivative of **4d** (1 mmol) with benzyl bromide **5** (1 mmol) and NaN_3 (1 mmol) (Scheme 5). The reaction was performed well, and the desired product **6j** is synthesized in good yield (74%).

A proposed mechanism for the domino condensation-click reaction is illustrated in Scheme 6. The first step is condensation between diazepam and *O*-propargyl salicylaldehyde 2a–c. Next, a Cu (II) ion is enhanced to the reaction that in the presence of sodium ascorbate reduced to the Cu (I). The triple bond is activated with Cu (I) through the formation of a copper acetylide complex, afterward coordination of organic azides to the acetylide, initiates an azide-alkyne 1,3-dipolar cycloaddition to form the desired products 6a-j. In the end, the Cu (I) is separated from the reaction medium [36, 37].

*3.2. Theoretical studies on the characterized 1,2,3-triazole-based diazepam **6a***

Quantum computational modelling methods such as DFT can be utilized in chemistry to get the structural/electronic properties of chemical systems. With the encouraging experimental data of **6a-i**, our attention was turned on DFT calculations to investigate physicochemical properties of the synthesized compounds such as structural parameters (bond lengths and bond angles) and electronic data (electrophilicity and nucleophilicity index, APT charge distribution, and molecular electrostatic potential analysis). It should be mentioned that nowadays, the DFT method in connection with the hybrid functional B3LYP (DFT-B3LYP) is utilized by chemists as a robust method for a variety of chemical quantum calculations [38-42]. The DFT-B3LYP computational method supplies a good balance between placed and localized bond structures. This method has been used here for performing the related computations. It should be noted that structure **6a** can exist in two geometric forms of *Z*- and *E*-isomers, due to C=C. The B3LYP/6-31++G(d, p) optimized structures of **6a** (*Z*-isomer) and **6a′** (*E*-isomer) are shown in Fig. 2. The *Z*-isomer is 93.48 kJ mol^{-1} more stable than the corresponding *E*-configuration. In this study, attention was focused on *Z*-isomer (**6a**). It should be mentioned that the *Z*-isomer (**6a**) can be stabilized by some favorable intramolecular interactions between acid and base groups (Fig. 3). As shown in Fig. 3, the stabilization of **6a** is due to intramolecular C–H...N and C–H...O hydrogen bond interactions. Strong intramolecular hydrogen bonding was observed in **6a** [H^{43}...O^{44}, 2.300 Å] with the hydrogen atom (H^{43}) as a donor and the oxygen atom (O^{44}) as an acceptor site. Analogous type of these interactions has been discussed in the literature [43, 44].

The representative calculated bond lengths and bond angles of **6a** are tabulated in Table 2. All bond lengths and bond angles are in the normal range. The bond between C=O and C=N were found to be 1.226 and 1.289 Å, respectively. Carbonyl group in **6a** has a resonance structure that emphasizes the pi-donor properties of the amine group. This bonding arrangement is confirmed by a short C^{10}–N^{31} distance (1.394 Å) and the planarity of the O^{20}-C^{11}-C^{14} core (120.3°). Thus, the molecule **6a** has two planar $N^{14}C^{11}$=O^{20} and $C^{13}N^{15}$=C^{12} groups lying in the plane with C(sp^2)-H and C(sp^3)-H bonds. The noncovalent intramolecular hydrogen bonds stabilize such arrangement (Fig. 3).

The calculated total energy, dipolar moment (μ_D) and electronic data such as electrophilicity and nucleophilicity index of **6a** are inserted in Table 3. The all electronic data are reactivity descriptors, which obtained from the HOMO and LUMO energies of **6a**. The dipole moment is an important physical parameter of the electronic distribution in a molecule, which can be related to the interaction strength of the molecule with metal ions. The calculated dipole moment value of **6a** is 5.52 D, which reveals high dipolar properties. The presence of polar functional groups such as amide moiety and the asymmetric chemical structure of **6a** are the main reasons for this high dipolar moment value.

The gap between the highest occupied molecular orbital (HOMO, π donor) and lowest unoccupied molecular orbital (LUMO, π acceptor) energy levels (E_g) is a helpful hint to determine the chemical reactivity of an organic compound. As the E_g value decreases, the reactivity of the compound increases [45]. Fig. 4 shows the graphical sketches of HOMO and LUMO orbitals for **6a**. The HOMO and LUMO orbitals are mainly localized on the diazepam framework.

Electrophilicity index (ω, eV) as a trustable and valuable descriptor for quantitative classification of the electrophilic nature of the organic molecules is calculated as 4.75 (eV). Electrophilicity can be categorized based on Domingo' scale [46]. Based on this scale, electrophiles are divided into three groups based on the electrophilic index: strong, mild and weak. When the electrophilic index ω is more than 1.5 eV, the electrophile is strong; in the range of 0.8 to 1.5 eV, it is mild and less than 0.8 eV the electrophile is weak. Based on this scale, compound **6a** is strong electrophile and can easily interact with a nucleophile. The atomic polar tensor (APT) charge distribution for the structure of **6a** is

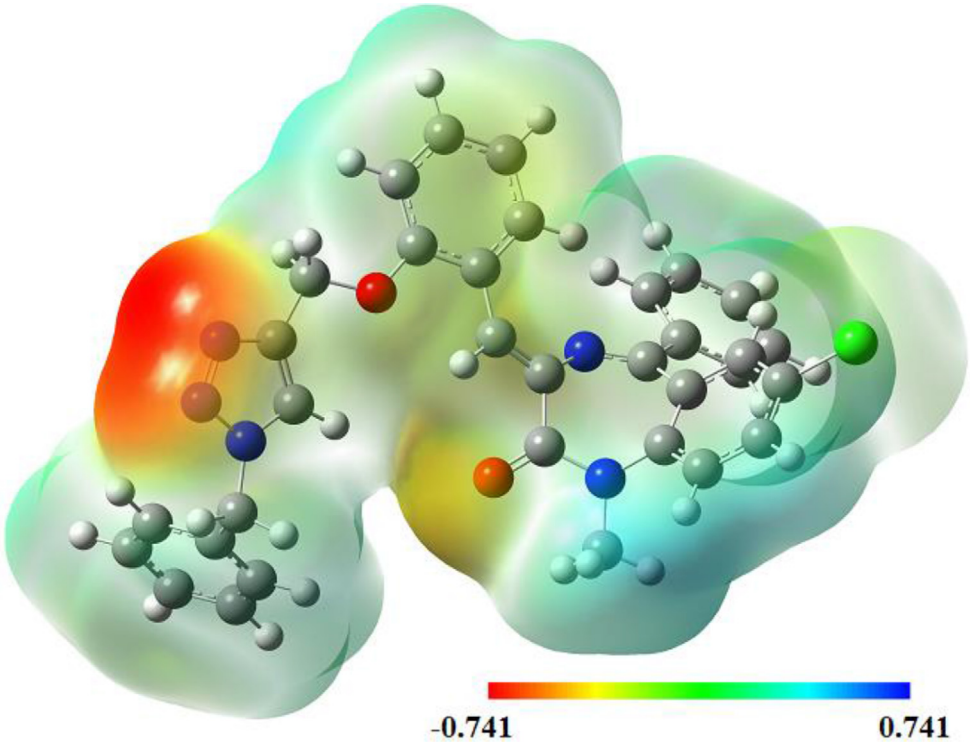


Fig. 5. Molecular electrostatic potential map for **6a**.

shown in Fig. 33S (electronic supplementary material). According to APT charge distribution analysis there is a remarkable excess of positive charge (1.230e) on the carbon atom of the carbonyl group (C^{11}=O^{20}). The study also indicates that the carbon atom of the imine unit (N^{15}=C^{13}), C^{32} and C^{45} bear a positive charge 0.670, 0.145 and 0.735e, respectively. APT charge analysis and electrophilicity index of **6a** show that a nucleophile can attack to these positive carbon centers (Scheme 7).

The molecular electrostatic potential (MEP) maps can also be used to identify the sites for the electrophilic and nucleophilic attack in **6a** [47]. The MEP map for **6a** is represented in Fig. 5. In the MEP map, red shows areas of most negative electrostatic potential, the minimum electrostatic potential and act as electrophilic attack, while blue corresponds to areas of most positive electrostatic potential, the maximum of electrostatic potential and act as nucleophilic attack. As shown in Fig. 5, the most negative charge on the MEP map of **6a** is associated with the nitrogen atoms of triazole ring. The MEP pattern also shows negative region (yellow) around the oxygen of the carbonyl unit (C=O). Oxygen and nitrogen atoms can interact through hydrogen bonding with amino and hydroxyl groups on a biological molecule and electron-deficient sites. The C^{11}, C^{13}, C^{32} and C^{45} atoms in MEP maps of **6a** are positive (pale blue region), and a nucleophile can be approached these sites more readily than other atoms, according to the above explanations (Scheme 7).

4. Conclusion

In summary, we have successfully shown that a library of novel 1, 2, 3-triazoles based diazepam has been synthesized by employing a domino condensation-copper catalyzed click reaction from commercially available materials. The facility of the synthetic method and the wide scope of the reaction make it advantageous in synthetic and medicinal chemistry. In the second section of the study, structural and electronic data such as bond lengths and bond angles, APT charge distribution, band gaps (HOMO and LUMO energies) and molecular electrostatic potential map for the synthesized compound **6a** were also calculated by applying DFT-B3LYP/6-31++G(d, p) method.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2021.131206.

CRediT authorship contribution statement

Zohreh Esmaeeli: Formal analysis, Investigation, Resources, Software, Validation, Visualization. **Mohammad Reza Khodabakhshi:** Conceptualization, Formal analysis, Investigation, Resources, Software, Validation, Visualization, Writing – review & editing. **Zohreh Mirjafary:** Writing – review & editing. **Hamid Saeidian:** Conceptualization, Formal analysis, Investigation, Resources, Software, Validation, Visualization, Writing – review & editing.

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