Isoquinoline-substituted hybrid compounds: Synthesis and computational studies

Ayşegül GÜMÜŞ*, Selçuk GÜMÜŞ and Duygu YENİDEDE

Yuzuncu Yıl University, Department of Chemistry, Van, 65080, Turkey

*Corresponding author.

Ayşegül Gümüş

Yuzuncu Yil University, Department of Chemistry, *Van, 65080, Turkey*

Tel: 90 432 2251024 / 22248

email: gumusa@gmail.com

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Yuzuncu Yıl University, Department of Chemistry, Van, 65080, Turkey

Abstract

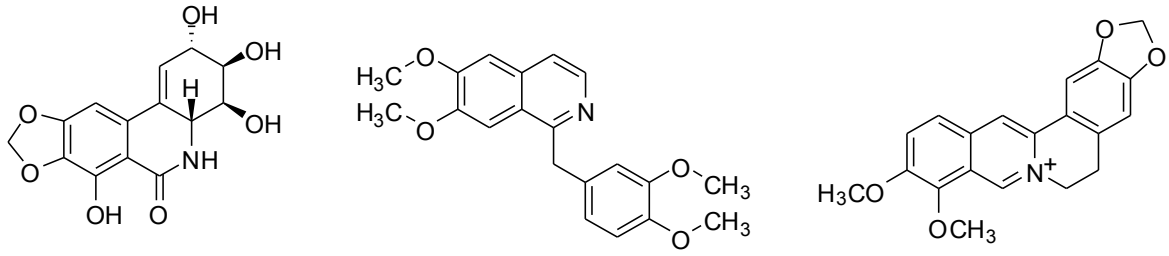
The one-pot synthesis of novel 1,4-disubstituted 1,2,3-triazoles from isoquinoline-substituted homopropargyl alcohol backbone is described (42-88% yields). A ring closing metathesis (RCM) reaction and an intramolecular Pauson-Khand reaction (PKR) of enyne system derived from a homopropargyl alcohol backbone to afford the corresponding isoquinoline-substituted dihydropyran and cyclopentenone-pyran, respectively, are also described (54% and 78% yields). Information about the structural, electronic and physico-chemical properties of the novel compounds, obtained by density functional theory application, is also reported.

Keywords: isoquinoline, 1,2,3-triazoles, ring closing metathesis reaction, Pauson-Khand reaction

1. Introduction

Heterocycles are important scaffolds for organic synthesis, natural bioactive compounds and advanced materials.[1-7] Isoquinoline is an important heterocyclic template playing an important role in organic chemistry, not only as key structural units in many natural products[8] but also as building blocks in important pharmaceuticals.[9-12] For example, narciclasine is a powerful antitumor agent inhibiting eukaryotic protein

synthesis at the ribosomal level.[13] Papaverine is a well-known drug mainly used in the treatment of visceral spasm and vasospasm.[14] Berberine is widely distributed in the



Narciclasine Papaverine Berberine

plant kingdom. It has been used as an antibacterial drug in China since the 1950s and was identified as a good hypolipidemic drug in 2004.[15-16]

Figure 1. Important isoquinoline derivatives

Isoquinoline derivatives are also utilized as chiral ligands for transition metal catalysts[17-20] and their iridium complexes are used in organic light-emitting diodes.[21-23] For these reasons, the efficient synthesis of complex and biologically active isoquinoline derivatives continues to attract interest of synthetic chemists.

In addition, compounds containing 1,2,3-triazole nucleus have been reported to possess a wide-range spectrum of chemotherapeutic activities including anti-inflammatory, anticancer, antidepressant, anti-bacterial and antifungal activities.[24-28] In recent years, some studies have been reported incorporating quinoline and triazole skeleton in the same molecular scaffold.[29-36] However, there is still limited number of

papers on the synthesis of hybrid compounds combining these heterocycles and investigation of their antimicrobial activities.

Bicyclic fused cyclopentenone derivatives are important structural units in natural product synthesis. Therefore, these types of bicyclic compounds have attracted attention of synthetic organic chemists over decades.[37-40] The Pauson-Khand reaction[41-46] has been established as a powerful method for the construction of bicyclic cyclopentenone structures. The intramolecular version of the reaction has gained much popularity, because it can afford complex cyclopentenone-fused ring systems.[47-52]

Herein, we report the synthesis of novel isoquinoline-substituted 1,2,3-triazole derivatives through one-pot synthesis method and also isoquinoline-substituted dihydropyran and cyclopentenone pyran derivatives by ring closing metathesis and Pauson-Khand reactions, separately.

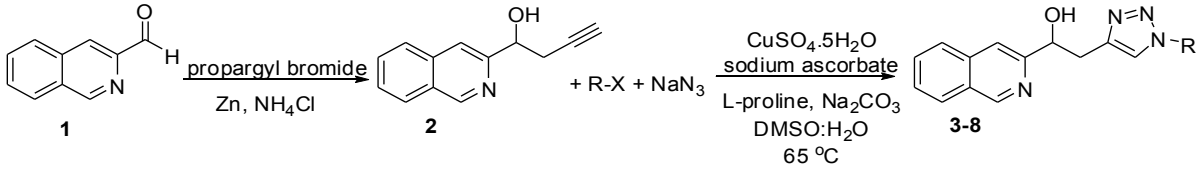
2. Results and Discussion

Isoquinoline-substituted homopropargyl alcohol **2** was used as template for the construction of triazole scaffolds. In addition, it was an important precursor for preparing enyne system because of its oxygen-anchoring site. The target isoquinolinyl homopropargyl alcohol **2** was synthesized by the addition of propargyl bromide to the commercially available isoquinoline-3-carbaldehyde **1** using Zn as depicted in Scheme 1.

2.1. One-pot triazole synthesis

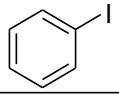
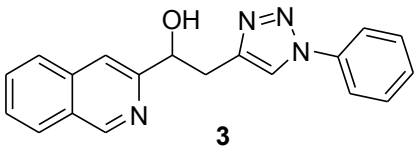
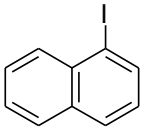
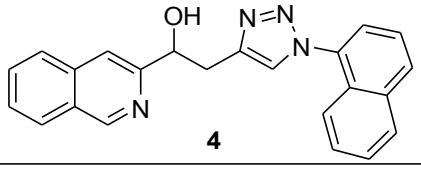
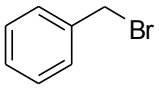
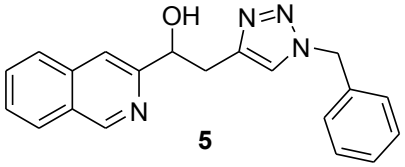
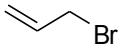
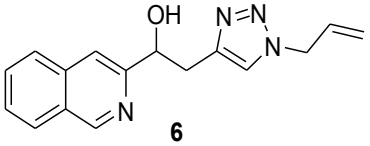
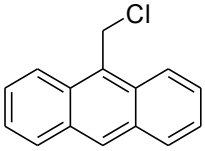
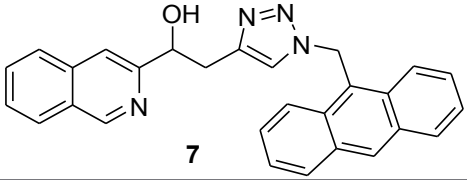
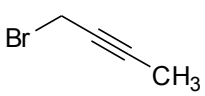
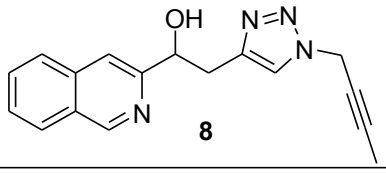
The terminal acetylene unit on homopropargyl alcohol derivative **2** makes it a valuable candidate for one-pot synthesis of target triazole structures.[53-54] Aliphatic and aromatic azides can be generated easily from the corresponding halides as intermediates

via a one-pot synthesis method[55] and converted into the desired triazole derivatives without isolation. The operational simplicity of this method makes it adorable for a wide-spectrum of applications. Isoquinoline homopropargyl alcohol **2** was subjected to one-pot two-step procedure by reaction with sodium azide and a halide (Scheme 1).



Scheme 1. One-pot synthesis of isoquinoline-substituted 1,2,3-triazole derivatives, **3-8**.

Table 1. Isoquinoline-substituted 1,2,3-triazole derivatives.

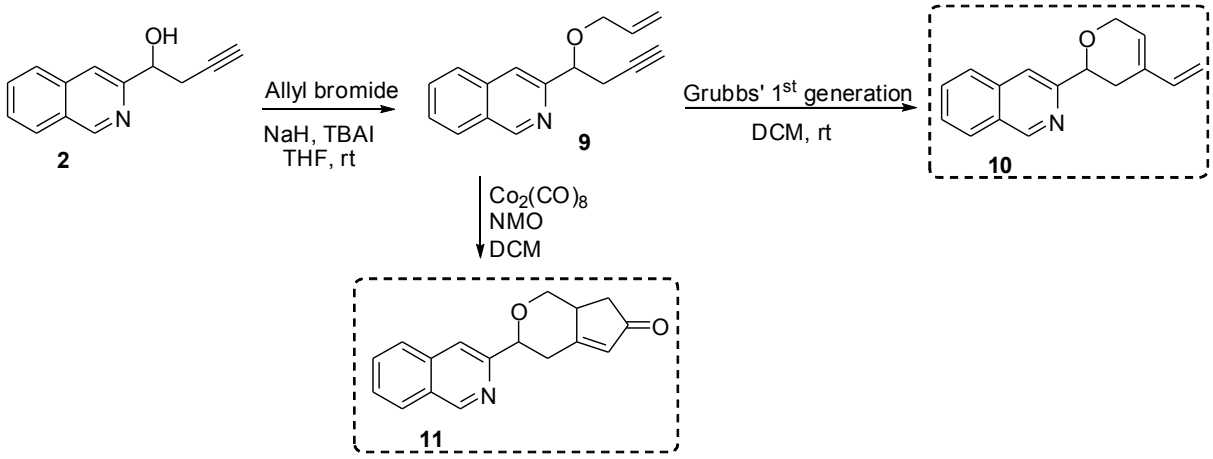
entry	*halide*	*product*	*Yield (%)*
1		 **3**	67
2		 **4**	42
3		 **5**	47
4		 **6**	88
5		 **7**	80
6		 **8**	55

Both aromatic and allylic halides were employed under the optimized conditions and finally, novel isoquinoline-substituted 1,2,3-triazole derivatives **3-8** were achieved in moderate to good yields (Table 1).

2.2. Synthesis of pyran derivatives

The acyclic unsaturated moiety on homopropargylic alcohol **2**, together with the alcohol unit subsequent second acyclic unsaturated motif could make it valuable candiate for the construction of pyran rings. In our synthetic strategy, we chose ring closing metathesis (RCM) and intramolecular Pauson-Khand reaction (PKR) as methods to construct isoquinoline-substituted pyran skeletons.

Initially, required enyne system for the cyclization was built on homopropargylic alcohol **2** backbone by O-allylation using allyl bromide with NaH and tetrabutyl-ammonium iodide (TBAI) in THF (Scheme 2).



The enyne scaffold **9** was subjected to ring closing metathesis with Grubbs' first jeneration catalyst in DCM and isoquinoline-substituted dihydropyran **10** was afforded in 54% chemical yield (Scheme 2).

Scheme 2. Synthesis of isoquinoline-substituted pyran derivatives, **10-11**.

We also planned to evaluate the applicability of intramolecular Pauson-Khand reaction to enyne anchored to isoquinoline-substituted carbinol to build up cyclopentenone-pyran ring system. The enyne tethered to isoquinoline ring was subjected to the most common conditions for PKR. In this protocol, cobalt-alkyne complex was prepared using enyne-dicobalt octacarbonyl in a molar ratio of 1:2 in DCM, and then N-methyl-morpholine N-oxide was added as a promoter. The reaction was monitored by thin layer chromatograhy (TLC). Single diastereomer of target cyclopentenone-pyran derivative **11** was obtained in 78% chemical yield (Scheme 2).

2.3. Computational Investigation

In order to obtain structural information about the compounds under study, density functional theory application at B3LYP/6-31G(d,p) level was performed. The geometry optimized structures and three-dimensional electrostatic potential maps of the present compounds are given in Figure 2. The substituents are responsible for the difference in structural properties and charge distribution throughout the molecules. These molecules showing potential biological activity might show different properties from one to the other.

The position of the OH group makes intramolecular hydrogen bonding possible between; i) OH and nitrogen of the triazole ring, and ii) OH and nitrogen of the isoquinoline. Hydrogen bonding for the former case is six centered while it is five centered for the latter. Conformational analysis was performed to find the more stable conformation supported by hydrogen bond formation. The analysis resulted in two minima on the two dimensional potential energy surface. The bond length of hydrogen bonding interactions for each case are shown in Figure 3. The hydrogen bond lengths

for OH-triazole interaction vary between 1.94-2.00 Å. However, that of OH with isoquinoline nitrogen is not sufficiently close except of the compound **8**. This long range weak interaction could not decrease the energy of the system. Therefore, for all cases the ground state geometry contains the type i interaction.

The theoretical observation of intramolecular hydrogen bonding is well supported with the experimental data, such that OH stretching frequency signal in FTIR and OH peak in H-NMR broadened and dwarfed.

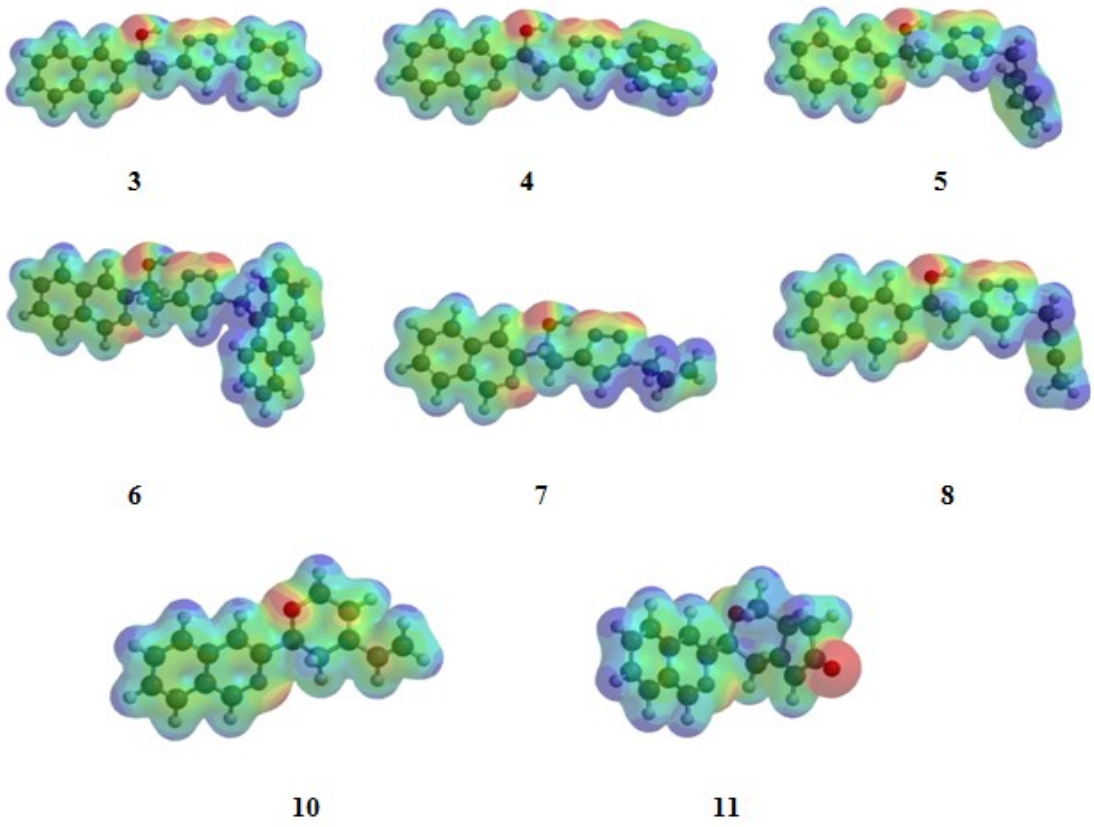


Figure 2. Geometry optimized structures with three-dimensional electrostatic potential

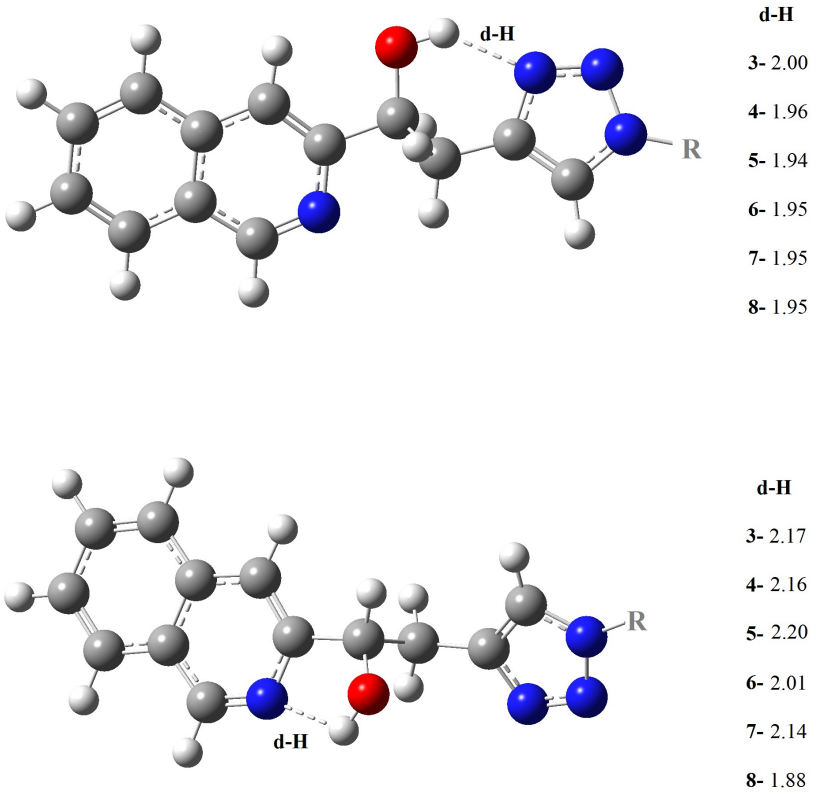


Figure 3. Hydrogen bonding lengths for two possible types.

Figure 4 shows a representative frontier molecular orbital (HOMO-LUMO) schemes for compound **3**. HOMO of the structure is located on isoquinoline part but the LUMO is on triazole and benzene moiety. The HOMO-LUMO energy gap is big due to lact of conjugation through the structure. All the compounds under present consideration have similar molecular orbital energy profiles, except for anthracene derivative **7** whose HOMO is higher and LUMO is lower in energy, resulting in a narrower interfrontier energy gap (Table 2).

Some computed physico-chemical parameters for **3-11** are given in Table 3. The hydrophobic constant (logP) is used to rationalize interactions of small ligands and molecules with various macromolecules in the fields of biochemistry, medicinal chemistry, and environmental sciences. Molecular polarizability is another important

property related to electron movements. Many research groups have investigated the effective polarizability effects on the properties of organic compounds in gas phase (such as protonic acidities and basicities).[56-58] Heat capacity or thermal capacity (Cv) is a physical quantity equal to the ratio of the heat added to (or removed from) an object to the resulting temperature change.

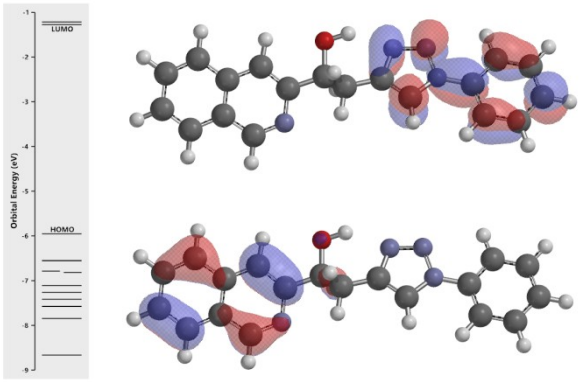


Figure 4. A representative HOMO and LUMO orbital schemes of **3**.

These data of molecules represent their physico-chemical behaviour. The molecules having the same or close physico-chemical properties show similar behaviour. Thus, according to the data in Table 3, **1** and **3** might possess almost the same physico-chemical behaviours. The data reported herein may be useful for future QSAR and QSPR studies.

Table 2. Frontier molecular orbital energies (eV)

Compound	HOMO	LUMO	Δε
3	-5.95	-1.27	4.68
4	-5.94	-1.56	4.38
5	-5.90	-1.17	4.73
6	-5.60	-2.09	3.51
7	-5.91	-1.18	4.73
8	-5.90	-1.17	4.73
10	-6.02	-1.31	4.71
11	-6.22	-1.60	4.62

Table 3. Computed physico-chemical parameters for **3-11** (Dipole: Debye, Density: g/mL, Solvation Energy: kJ/mol, Cv: J/mol)

Compound	Dipole	Density	Polarizability	logP	Solvation Energy	Cv
3	3.93	0.98	66.57	1.65	-66.74	239.
4	4.02	0.97	70.83	2.64	-68.10	275.
5	4.41	0.96	68.10	1.72	-72.73	252.
6	4.60	0.97	76.65	3.71	-78.04	326.
7	4.25	0.96	63.95	0.68	-72.65	218.
8	4.95	0.95	65.10	0.80	-76.36	227.
10	1.07	0.91	61.41	0.77	-16.76	189.
11	4.29	0.97	62.50	0.20	-35.51	202.

3. Experimental

3.1. General

All experiments were carried out in pre-dried glassware in inert atmosphere of argon. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Spectrospin Avance DPX-400 spectrometer. ^{1}H (400 MHz) and ^{13}C NMR were recorded in $CDCl_3$ and the

chemical shifts are expressed in ppm relative to $CDCl_3$ (d 7.26 and 77.0 for ^1H and ^{13}C NMR, respectively) as the internal standard. H/D exchange experiments in ^1H NMR were performed by the addition of D_2O in order to proof OH units in products. FTIR spectra were recorded on Shimadzu IRAffinity-1 spectrometer with KBr pellets. HRMS spectra were recorded on an Agilent Technologies 6224 Accurate-Mass TOF LC/MS at the National Nanotechnology Research Center of Bilkent University (UNAM). Melting points were measured by Stuart SMP3 instrument. Flash column chromatography was performed bu using thick-walled glass columns and silica gel (60-mesh; Merck). The reactions were monitored by thin-layer chromatography (TLC) using Merck 0.2-mm silica gel 60 F254 analytical aluminum plates, visualized by UV light and polymolybden phosphoric acid in ethanol. All extracts were dried over anhydrous magnesium sulfate and solutions were concentrated under reduced pressure by using a rotary evaporator.

3.2. Synthesis of 1-(isoquinolin-3-yl)but-3-yn-1-ol, 2.

A solution of saturated aqueous ammonium chloride (10 mL) was added dropwise to a stirring suspension of isoquinoline-3-carbaldehyde **1** (1.57 g, 10 mmol), propargyl bromide (80% in toluene, 2.23 g, 15 mmol) and zinc dust (3.27 g, 50 mmol) in THF (20 mL) at 0 °C (ice bath) over 1 h. The mixture was allowed to warm to room temperature and stirred at this temperature for 24 h, with monitoring by TLC. The mixture was filtered and the filter cake was washed with ethyl acetate. The combined filtrates were washed with saturated $NaHCO_3$ (50 mL), then brine (50 mL) and dried over magnesium sulfate. The residue was purified by flash chromatography on silica gel to afford homopropargylic alcohol, **2** as a light yellow solid product (750 mg, 38% yield). mp 94-

96 °C ; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.17 (s, 1H), 7.92 (d, *J*=8.2 Hz, 1H), 7.80 (d, *J*=8.2 Hz, 1H), 7.75 (s, 1H), 7.69-7.65 (m, 1H), 7.58-7.54 (m, 1H), 5.08-5.05 (m, 1H), 4.41 (bs, OH), 2.90-2.77 (m, 2H), 2.02-2.00 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 153.6, 151.8, 136.2, 130.7, 128.1, 127.6, 127.2, 126.8, 116.9, 80.8, 71.9, 70.8, 28.4. HRMS (ESI-TOF). Anal. Calcd for $C_{13}H_{11}NO$: *m/z* 197.0841. Found $[M+H]^+$: *m/z* 198.0910.

3.3. General procedure for one-pot 1,2,3-triazole synthesis

A mixture of an aromatic or aliphatic halide (0.25 mmol), homopropargyl alcohol, **2** (50 mg, 0.25 mmol), L-proline (6 mg, 0.05 mmol), Na_2CO_3 (6 mg, 0.05 mmol), NaN_3 (16 mg, 0.25 mmol), sodium ascorbate (5 mg, 0.025 mmol), DMSO/H_2O (1.8:0.2, 2.0 mL), and $CuSO_4{\cdot}5H_2O$ solution (1 M, 0.02 mL) in a 20 mL scintillation vial was stirred overnight at 65°C. The crude mixture was poured into cold dilute NH_4OH solution (10 mL) and extracted with ethyl acetate (4 × 10 mL). The collected organic layer was washed with brine, dried over $MgSO_4$, and concentrated in *vacuo*. The crude product was purified by flash column chromatography using mixtures of ethylacetate and hexane.

3.3.1. 1-(isoquinolin-3-yl)-2-(1-phenyl-1H-1,2,3-triazol-4-yl)ethanol, 3.

White solid (53 mg, 67% yield); mp 157-159 °C. IR ν_{max} (neat cm^{-1}): 3325, 3132, 2958, 2924, 2855, 1732, 1504, 1230, 1053, 964, 756. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.23 (s, 1H), 8.00-7.98 (m, 1H), 7.87-7.85 (m, 1H), 7.83-7.82 (m, 1H), 7.74-7.68 (m, 3H), 7.63-7.59 (m, 1H), 7.54-7.47 (m, 2H), 7.43-7.39 (m, 1H), 5.32 (dd, *J*=8.2 and 3.7 Hz, 1H), 4.57 (bs, OH), 3.53 (dd, *J*=15.1 and 3.7 Hz, 1H), 3.32 (dd, *J*=15.1 and 8.0 Hz, 1H); ^{13}C

NMR ($CDCl_3$, 400 MHz): δ 154.2, 151.4, 145.4, 137.1, 136.5, 130.9, 129.7, 128.8, 128.6, 127.9, 127.7, 127.3, 126.9, 120.4, 116.9, 72.6, 34.3. HRMS (ESI-TOF). Anal. Calcd for $C_{19}H_{16}N_4O$: *m/z* 316.1324. Found $[M+H]^+$: *m/z* 317.1400.

3.3.2. 1-(isoquinolin-3-yl)-2-(1-(naphthalen-1-yl)-1H-1,2,3-triazol-4-yl)ethanol, 4.

Yellow solid (38 mg, 42% yield); mp 143-145 °C. IR ν_{max} (neat cm^{-1}): 3421, 3055, 2955, 2924, 2854, 1740, 1627, 1458, 1041, 802, 771. ^1H NMR ($CDCl_3$, 400 MHz): δ 9.24 (s, 1H), 8.01-7.96 (m, 2H), 7.94-7.92 (m, 1H), 7.82-7.81 (m, 1H), 7.74-7.70 (m, 2H), 7.64-7.60 (m, 1H), 7.57-7.51 (m, 3H), 7.35-7.34 (m, 2H), 5.39 (dd, *J*=7.6 and 4.0 Hz, 1H), 4.57 (bs, OH), 3.59 (ddd, *J*=15.0, 4.1 and 0.4 Hz, 1H), 3.43 (ddd, *J*=14.9, 7.7 and 0.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 154.6, 151.7, 144.5, 136.3, 134.0, 133.7, 130.8, 130.3, 128.5, 128.2, 127.9, 127.7, 127.6, 127.2, 126.9, 126.8, 125.0, 124.9, 123.5, 122.1, 116.8, 72.9, 34.3. HRMS (ESI-TOF). Anal. Calcd for $C_{23}H_{18}N_4O$: *m/z* 366.1481. Found $[M+H]^+$: *m/z* 367.1549.

3.3.3. 2-(1-benzyl-1H-1,2,3-triazol-4-yl)-1-(isoquinolin-3-yl)ethanol, 5.

Light yellow solid (39 mg, 47% yield); mp 95-97 °C. IR ν_{max} (neat cm^{-1}): 3314, 3120, 3063, 2924, 2854, 1753, 1589, 1458, 1307, 1076, 740, 702. ^1H NMR ($CDCl_3$, 400 MHz): δ 9.15 (s, 1H), 7.95-7.93 (m, 1H), 7.79-7.77 (m, 1H), 7.70-7.66 (m, 2H), 7.60-7.55 (m, 1H), 7.28-7.23 (m, 4H), 7.14-7.13 (m, 2H), 5.44 (s, 2H), 5.23-5.21 (m, 1H), 4.49 (bs, OH), 3.42-3.37 (m, 1H), 3.24-3.18 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 154.7, 151.6, 145.2, 136.3, 134.7, 130.6, 129.0, 128.6, 127.8, 127.5, 126.8, 122.1, 116.6, 72.9, 54.0, 34.2. Anal. Calcd for $C_{20}H_{18}N_4O$ $[M+H]^+$: *m/z* 330.1481. Found: *m/z* 331.1549.

3.3.4. 2-(1-allyl-1H-1,2,3-triazol-4-yl)-1-(isoquinolin-3-yl)ethanol. 6.

Light yellow solid (48 mg, 88% yield); mp 73-75 °C. IR ν_{max} (neat cm^{-1}): 3306, 3132, 2924, 2854, 1685, 1550, 1392, 1215, 1060, 894, 756, 675. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.17 (s, 1H), 7.95-7.92 (m, 1H), 7.79-7.77 (m, 1H), 7.73 (s, 1H), 7.68-7.64 (m, 1H), 7.58-7.54 (m, 1H), 7.34 (s, 1H), 5.98-5.88 (m, 1H), 5.70 (bs, OH), 5.26-5.21 (m, 2H), 5.19-5.14 (m, 1H), 4.89-4.87 (m, 2H), 3.41 (dd, *J*=15.0 and 3.9 Hz, 1H), 3.22 (dd, *J*=15.0 and 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 154.9, 151.6, 145.0, 136.3, 131.3, 130.6, 127.8, 127.5, 127.1, 126.7, 122.1, 119.7, 116.6, 72.9, 52.5, 34.2. Anal. Calcd for $C_{16}H_{16}N_4O$: *m/z* 280.1324. Found $[M+H]^+$: *m/z* 281.1399.

3.3.5. 2-(1-(anthracen-9-ylmethyl)-1H-1,2,3-triazol-4-yl)-1-(isoquinolin-3-yl)ethanol, 7.

Light yellow solid (86 mg, 80% yield); mp 195-198 °C. IR ν_{max} (neat cm^{-1}): 3225, 2955, 2924, 2854, 1736, 1462, 1365, 1273, 1084, 1056, 976. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.98 (s, 1H), 8.51 (s, 1H), 8.21 (d, *J*=8.1 Hz, 1H), 8.03-8.01 (m, 2H), 7.85 (d, *J*=8.1 Hz, 1H), 7.64 (s, 1H), 7.59 (s, 1H), 7.55-7.45 (m, 4H), 7.28 (s, 1H), 6.97 (s, 1H), 6.88 (s, 1H), 6.43 (s, 2H), 5.10-5.07 (m, 1H), 4.30 (s, OH), 3.20 (dd, *J*=15.0 and 3.6 Hz, 1H), 3.02 (dd, *J*=15.0 and 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 156.4, 151.4, 144.7, 136.0, 131.3, 130.6, 130.5, 129.5, 129.3, 127.5, 127.4, 126.9, 126.6, 125.4, 124.7, 123.3, 122.0, 116.2, 114.3, 72.8, 45.9, 34.2. Anal. Calcd for $C_{28}H_{22}N_4O$: *m/z* 430.1794. Found $[M+H]^+$: *m/z* 431.1865.

3.3.6. 2-(1-(but-2-ynyl)-1H-1,2,3-triazol-4-yl)-1-(isoquinolin-3-yl)ethanol, 8.

Light yellow solid (40 mg, 55% yield); mp 118-120 °C. IR ν_{max} (neat cm^{-1}): 3398, 3069, 2955, 2924, 2854, 1754, 1632, 1462, 1361, 1188, 1080, 968, 817. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.19 (s, 1H), 7.97-7.94 (m, 1H), 7.82-7.80 (m, 1H), 7.76 (s, 1H), 7.70-7.66 (m, 1H), 7.60-7.56 (m, 2H), 5.23 (dd, *J*=8.2 and 3.7 Hz, 1H), 5.03 (dq, *J*=2.5 and 0.7 Hz, 2H), 4.64 (bs, OH), 3.43 (dd, *J*=15.1 and 3.6 Hz, 1H), 3.22 (dd, *J*=15.1 and 8.3 Hz, 1H), 1.82 (t, *J*=2.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 154.6, 151.6, 144.9, 136.4, 130.7, 127.9, 127.6, 127.1, 126.8, 121.9, 116.8, 83.6, 72.9, 70.7, 40.3, 34.3, 3.5. Anal. Calcd for $C_{17}H_{16}N_4O$: *m/z* 292.1324. Found $[M+H]^+$: *m/z* 293.1395.

3.4. Synthesis of 3-(1-(allyloxy)but-3-ynyl)isoquinoline, 9.

To a solution of 2 (0.2 g, 1.0 mmol) in dry THF (10 mL) was added NaH (0.64 g, 60% dispersion in oil, 1.6 mmol). The solution was mixed for 30 min. and cooled to 0 °C. Then, allil bromide (0.18 g, 1.5 mmol) was added dropwise followed by tetrabutylammonium iodide (0.11 g, 0.3 mmol). The mixture was stirred for 2 h at rt and hydrolyzed by the cautious addition of water (10 mL). The aqueous layer was extracted with ether (3 x 20 mL). The combined organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by flash column chromatography using ethylacetate/hexane (1:6) solvent as eluent and enyne , **9** was obtained.

Light yellow oil (160 mg, 67% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.24 (s, 1H), 7.97 (d, *J*=8.2 Hz, 1H), 7.85 (d, *J*=8.2 Hz, 1H), 7.80 (s, 1H), 7.72-7.68 (m, 1H), 7.62-7.58 (m, 1H), 6.02-5.92 (m, 1H), 5.31 (qd, *J*=17.2 and 1.6 Hz, 1H), 5.20 (qd, *J*=10.4 and 1.4 Hz, 1H), 4.80 (t, *J*=6.0 Hz), 4.14 (tdd, *J*=12.9, 5.2 and 1.4 Hz, 1H), 4.03 (tdd, *J*=12.9, 6.0 and 1.4 Hz, 1H), 2.94 (ddd, *J*=16.8, 5.7 and 2.6 Hz, 1H), 2.82 (ddd, *J*=16.8, 6.3 and 2.6 Hz, 1H), 1.93 (t, *J*=2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 153.1, 152.4,

136.1, 134.5, 130.5, 128.1, 127.6, 127.2, 126.8, 117.6, 117.4, 80.7, 79.8, 70.5, 70.0, 26.2. Anal. Calcd for $C_{16}H_{15}NO$: *m/z* 237.1154. Found $[M+H]^+$: *m/z* 238.1225.

3.5. Ring closing metathesis reaction.

O-Allyl anchored substrate **9** (37 mg, 0.15 mmol) was dissolved in DCM (3 mL) and Grubbs' first generation catalyst (5 mol %) was added to the solution. The reaction was monitored by TLC. The crude product was concentrated and purified by flash column chromatography.

3-(4-vinyl-3,6-dihydro-2H-pyran-2-yl)isoquinoline, 10.

Light yellow solid (20 mg, 54% yield); mp 80-82 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.25 (s, 1H), 7.99-7.97 (m, 1H), 7.85-7.83 (m, 2H), 7.71-7.67 (m, 1H), 7.61-7.57 (m, 1H), 6.44 (dd, *J*=17.5 and 10.7 Hz, 1H), 5.86-5.84 (m, 1H), 5.20 (d, *J*=17.5 Hz, 1H), 5.03 (d, *J*=10.7 Hz, 1H), 4.86 (dd, *J*=10.3 and 3.0 Hz, 1H), 4.56-4.55 (m, 2H), 2.84-2.78 (m, 1H), 2.51-2.42 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 154.8, 152.0, 137.8, 136.4, 134.0, 130.5, 127.9, 127.5, 127.0, 126.8, 126.0, 116.3, 111.8, 76.3, 66.5, 31.6. Anal. Calcd for $C_{16}H_{15}NO$: *m/z* 237.1154. Found $[M+H]^+$: *m/z* 238.12283.

3.6. Pauson-Khand reaction.

To a solution of **9** (37 mg, 0.15 mmol) in CH_2Cl_2 (5 mL) was added $Co_2(CO)_8$ (102 mg, 0.30 mmol) and stirred for 2 h (TLC monitoring). Then, NMO (158 mg 1.35 mmol) was added at 0 °C and stirred for 24 h at room temperature. The crude product was filtered through celite and purified by flash column chromatography using ethylacetate/hexane solvent as eluent (1:2) system.

3-(isoquinolin-3-yl)-3,4,7,7a-tetrahydrocyclopenta[c]pyran-6(1H)-one, 11.

Yellow solid (32 mg, 78% yield); mp 147-149 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.24 (s, 1H), 7.99 (d, *J*=8.1 Hz, 1H), 7.86-7.82 (m, 2H), 7.73-7.70 (m, 1H), 7.64-7.60 (m, 1H), 6.07 (bs, 1H), 4.68-4.65 (m, 1H), 4.56 (dd, *J*=10.6 and 6.5 Hz, 1H), 3.42-3.33 (m, 2H), 3.17-3.11 (m, 1H), 2.78 (t, *J*=12.3 Hz, 1H), 2.55 (dd, *J*=18.7 and 6.7 Hz, 1H), 2.00 (bd, *J*=18.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 207.6, 179.5, 152.8, 152.3, 136.3, 130.7, 128.1, 127.9, 127.6, 127.4, 126.8, 116.8, 80.6, 73.7, 41.0, 38.0, 37.1. Anal. Calcd for $C_{17}H_{15}NO_2$: *m/z* 265.1103. Found $[M+H]^+$: *m/z* 266.1177.

3.7. Computational Method.

The geometry optimizations of all the structures leading to energy minima were performed by the application of the density functional theory (DFT)[59,60] at the level of B3LYP/6-31G(d,p) with no symmetry restrictions. The exchange term of B3LYP consists of hybrid Hartree–Fock and local spin density (LSD) exchange functions with Becke's gradient correlation to LSD exchange.[61] The correlation term of B3LYP consists of the Vosko, Wilk, Nusair (VWN3) local correlation functional[62] and Lee, Yang, Parr (LYP) correlation correction functional. After geometry optimizations, single point calculations at the same level were performed to obtain accurate frontier molecular orbital energy values. All the bond lengths were thoroughly searched in order to find out whether any bond cleavage occurred or not during the geometry optimization process. All these computations were performed by using the Gaussian 09 package program.[63] Frequency analysis for each compound did not yield any imaginary frequencies, indicating that the structure of each molecule corresponds to at least a local minimum on the potential energy surface. The normal mode analysis was performed for 3N-6

vibrational degrees of freedom, N is the number of atoms forming the corresponding molecule.

The physico-chemical properties of the compounds have been calculated using Spartan 14 package program.[64]

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