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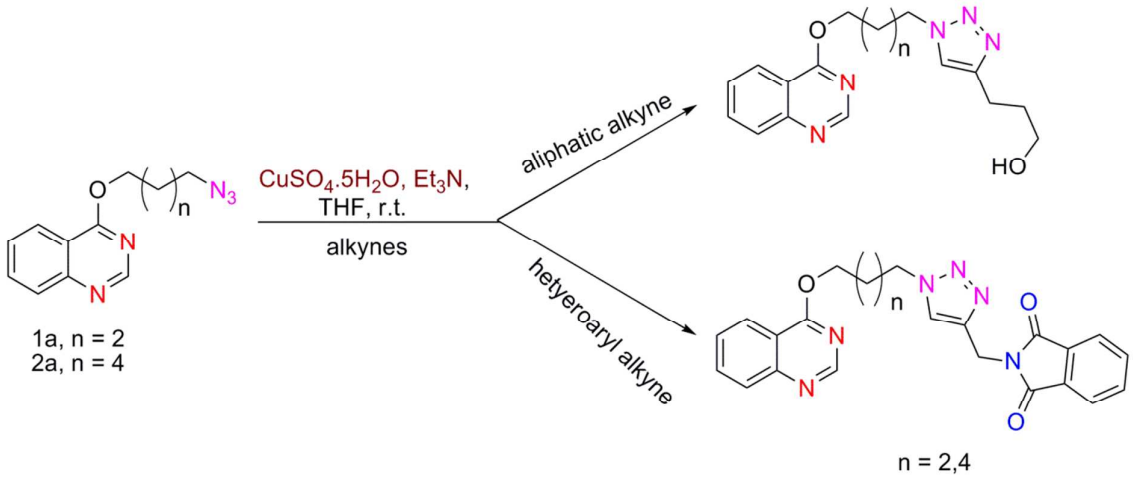

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ARTICLE TYPE

Synthesis of medicinally important quinazolines decorated with 1,4-disubstituted-1,2,3-triazoles using $CuSO_4.5H_2O$-Et_3N catalytic system

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The direct use of Cu(II) sulfate pentahydrate in presence of triethylamine has resulted into 1,4-disubstituted-1,2,3-triazoles *via* 1,3-dipolar cycloaddition of terminal alkyne(s) to azide(s) at room temperature. The study of additive effect of triethylamine in presence of Cu(II) sulfate pentahydrate revealed that it is essential for activation of copper catalyst and is responsible for the reaction between aliphatic/aromatic heterocyclic alkyne (s) and azide (s) which otherwise did not work under standard reaction conditions often used in click chemistry.

Introduction

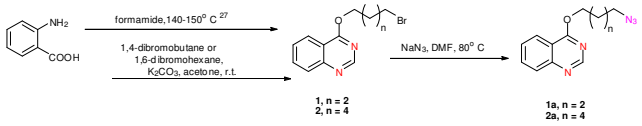
Click chemistry has recently drawn much attention as a powerful and efficient way to obtain 1,2,3-triazoles in sufficient yields *via* a simple and benign procedure[1] and is the fruit of re-evaluation of previously reported azide alkyne chemistry[2-5]. Copper catalyst in the form of Cu(I) and Cu(II) (e.g. CuI and $CuSO_4.5H_2O$) had been extensively used for attaining regio-selectivity[6,7] to obtain 1,4-disubstituted triazole over its 1,5-regioisomer. This reaction proceeds through a multistep mechanism[8] as compare to its original concerted nature involving azide-copper and alkyne-copper complexes.

1,2,3-Triazoles have a wide range of industrial applications in agrochemical and are used in addition as corrosion inhibitors, dyes and optical brighteners. As pharmaceuticals, triazole derivatives are fairly stable to metabolic degradation[9a-d] and are capable of participating in hydrogen bonding and dipole-dipole interactions and therefore provide potential advantages as target binding and cell permeability improvement.[9e-g] We, therefore, undertook the synthesis of some novel quinazoline based 1,2,3-triazole analogues where quinazoline scaffold was employed as the basic nucleus because it shows various biological activities such as anti-microbial,[10] anti-fungal,[11] anti-cancer[12] and act as anti-neoplastic[13] agent, phosphodiesterase 7 inhibitior[14] and c-Src inhibitors.[15] We have used a new methodology to construct 1,2,3-triazole moiety on quinazoline *via* a lipophilic linker so that both these biodynamic scaffolds are present in a single molecular frame in the target molecule.

Results and discussion

Earlier Cu(I) catalysts are either used directly or generated in situ from Cu(II) salts by using reducing agents such as sodium-ascorbate.[16] When sodium ascorbate can not be used in the reaction then an excess amount of a base, usually TEA or DIPEA is used in the presence of stoichiometric amount of copper(I) salts (CuI,[17] $Cu(CH_3CN)_4PF_6$,[18] $CuBr(PPh_3)_4$ or $CuIP(OEt)_3$[19, 20]) or in situ by oxidation of copper metal turnings.

We herein wish to report direct use of Cu(II) catalyst, $CuSO_4.5H_2O$ as a sole catalyst without using any additional reducing/oxidizing agents in the presence of an additive triethyl amine for the exclusive synthesis of 1,4-regioisomer of 1,2,3-triazoles in high yields. The products obtained did not require any further purification step except recrystalisation.

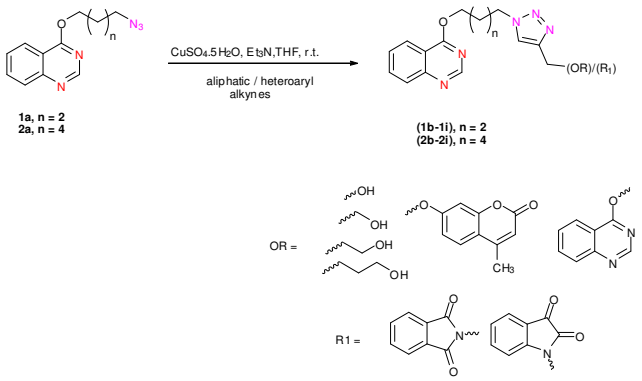


Scheme 1: Synthetic scheme illustrating synthesis of required azides (1a & 2a)

In majority of reported procedures, activation of terminal alkynes is achieved by the formation of Cu acetylide, with Cu(I) salts as the main catalyst precursor. However, there are some precedents in the literature where Cu(II) salts also effect the activation of terminal alkynes. For example, Reddy and co-workers[21] reported that $Cu(OAc)_2$ as well as a biopolymer supported Cu(II) catalyst ALG[22] (copper-alginates) catalyzed the synthesis of 1,4-regioisomer of 1,2,3-triazoles. Similarly Cu(II)-hydrotalcite[23] (heterogeneous catalyst), iron oxide nanoparticle[24] and $Cu(OTf)_2$ had also been mentioned[25] to catalyze the Huisgen [3+2] cycloaddition.

In order to synthesise the requisite triazole derivatives, initially template reaction between 4-(6-azidohexyloxy)quinazoline (**2a**) and 2-propyn-1-ol was tried under standard reaction conditions to obtain a model compound **2b,** using $CuSO_4.5H_2O$-Na-ascorbate in H_2O-tBuOH (2:1) in the absence of a base. Unfortunately our reaction did not proceed at all. Then different solvents such as THF, THF:H_2O (3:1), DMF, DCM, CH_3CN, H_2O were used in

the presence of stoichiometric amount of $CuSO_4.5H_2O$ along with



Scheme 2: Reaction conditions employed to obtain triazoles (1b-1i) and (2b-2i)

an excess of Na-ascorbate (Table I) at room temperature.

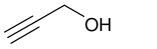
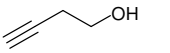
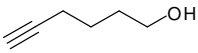
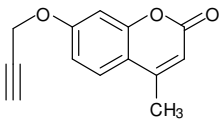
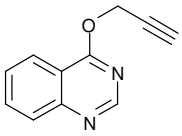
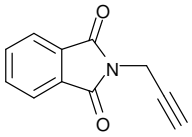
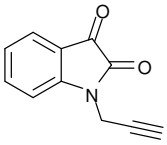
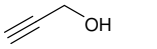
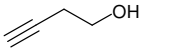
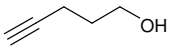
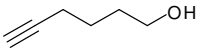
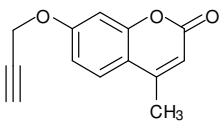
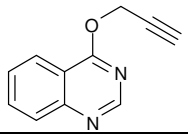
Table I: The effect of solvent and catalyst on the reaction[a-d] of 4-(6-azidohexyloxy) quinazoline (**2a**) and 2-propyn-1-ol.

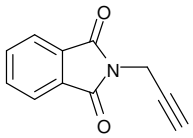
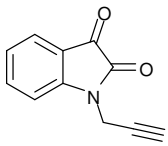
S.No.	Catalyst	Conditions	Solvent Used	Time (h)	Yield (%)
1	$CuSO_4.5H_2O$-Na ascorbate	r.t./Δ	H_2O-t-BuOH (1:1)	48	-[a]
2	$CuSO_4.5H_2O$-Na ascorbate	r.t./Δ	THF	48	-[a]
3	$CuSO_4.5H_2O$-Na ascorbate	r.t./Δ	THF-H_2O (3:1)	24	-[a]
4	$CuSO_4.5H_2O$-Na ascorbate	r.t./Δ	DMF	24	-[a]
5	$CuSO_4.5H_2O$-Na ascorbate	r.t./Δ	CH_3CN	24	-[a]
6	CuI-Et_3N	r.t./Δ	H_2O-t-BuOH (1:1)	16	52[b]
7	CuI-Et_3N	r.t./Δ	DMF	16	55[b]
8	CuI-Et_3N	r.t./Δ	THF	16	60[b]
9	$CuSO_4.5H_2O$-Et_3N	r.t.	THF	1/2	98[c]
10	$CuSO_4.5H_2O$	r.t./Δ	THF	12	-[d]
11	Et_3N	r.t./Δ	THF	12	-[d]

[a]all reactions were performed with stiochiometric amount of $CuSO_4.5H_2O$-Na ascorbate and reaction did not proceed [b]reaction was carried out with 10-20 mol % of catalyst and 1.2 mmol of Et_3N and reaction did not proceed to completion, product was isolated by chromatography [c]reaction was performed with 1.0 mmol of azide, 1 mmol of 2-propyn-1-ol, 1.2 mmol of Et_3N, 5 ml of solvent and 15 mol % catalyst [d]reaction was carried out with $CuSO_4.5H_2O$ and Et_3N separately.

The reaction even then did not occur in any of these reaction conditions. The above reaction was also carried out in presence of copper(I) salt (CuI) and excess of sodium ascorbate[26], but it again failed. The template reaction was not only carried out at room temperature but under heating conditions also, in both of the cases reaction was not proceeding at all (Table I, entry 1-5). Finally the reaction was carried out in presence of CuI/Et_3N, in different solvents and the results obtained are summarized in Table I. The reaction was proceeding with CuI/Et_3N at room temperature but was not going to completion, then heating conditions were also employed, but reaction did not go to completion even then (Table I, entry 6-8). THF can be illustrated as suitable solvent among others (H_2O-t-BuOH (1:1), DMF, THF) for the reaction (entry 8). Finally by optimizing the reaction conditions, a combination of $CuSO_4.5H_2O$ (15 mol %) and Et_3N (1.2 mmol) in THF at room temperature was found to be the most effective as it resulted **2b** in 98% yield in 30 minutes (Table I, entry 9). We also tried to carry out cycloaddition reaction of **2a** with 2-propyn-1-ol in the presence of catalytic amount of either $CuSO_4.5H_2O$ (15 mol%) or triethylamine (1.2 mmol) separately at room temperature as well as under heating condition using standardized reaction conditions, but unfortunately it did not give the desired product. It clearly demonstrated that the reaction did not proceed in the absence of either amine or $CuSO_4.5H_2O$ (Table I, entry 10 and 11) and hence the presence of both is must for the reaction to occur.

Table II: Formation of triazoles (1b-1i and 2b-2i) from different alkynes and azides (1a,2a).

Entry	Azide	Alkynes	Product	Yield (%)	Time (h)
1	1a		1b	90	2
2	1a		1c	92	6
3	1a		1d	91	8
4	1a		1e	92	9
5	1a		1f	90	9
6	1a		1g	92	9
7	1a		1h	90	8
8	1a		1i	91	6
9	2a		2b	98	½
10	2a		2c	95	1
11	2a		2d	93	3
12	2a		2e	94	5
13	2a		2f	92	8
14	2a		2g	93	7

15	**2a**		2h	91
16	**2a**		2i	93

The scope and generality of the reaction in the presence of $CuSO_4.5H_2O/Et_3N$ were therefore investigated by carrying out the reaction between two different azides (**1a** and **2a**) separately with various aliphatic/aromatic heterocyclic alkynes by using the standard reaction conditions (Table II). It was observed that the reaction time was less and yield was more in case of reaction between 4-(6-azidohexyloxy)quinazoline (**2a**) and alkynes as compare to the reaction between 4-(4-azidobutyloxy)quinazoline (**1a**) and various alkynes. Thus, it may be concluded that the azide with increased chain length is more stabilized under the present reaction conditions. The scope of the reaction with respect to various aliphatic alkynes was also examined. In contrast to results obtained in case of other azides (**1a** and **2a**), reaction was slow and results in decrease in yield, with increase in chain length of aliphatic alkynes.

These results prompted us to investigate further the effect of various aromatic heterocyclic alkynes as compare to aliphatic alkynes. Results revealed that reaction was also proceeding with heterocyclic alkynes under the standardized reaction conditions (Table I), moreover later ones reacted faster with the azides (**1a** and **2a**) with comparative more yield. Further the comparison between the *O*-alkylated and *N*-alkylated aromatic heterocyclic alkynes suggested a slow reaction in case of *O*-alkylated alkyne without any significant effect on the yields (Table II).

Conclusions

In conclusion, a combination of rather cheap copper sulfate pentahydrate with an additive triethylamine resulted not only in the initiation of 1,3-cycloaddition reaction but also yielded the requisite series of 1,4-regioisomer of novel 1,2,3-triazole analogues decorated with quinazolin-3H-4-alkoxy moiety. Products were obtained in high yields in short reaction time. It was found to be effective catalyst for the reactions between various azides and alkynes. Application of this methodology for the synthesis of various other hybrid targets is currently under investigation in our laboratory.

Experimental Section

All the starting materials were of GR (Guaranteed Reagent) quality of Merck and all solvents used were of HPLC/ AR grade. All spectroscopic measurements were done at room temperature, 25±1°C. Melting points were determined on a Tropical Lab equip apparatus and are uncorrected. IR (KBr) spectra were recorded on Perkin-Elmer FTIR spectrophotometer and the values are expressed as ν_{max} cm^{-1}. Mass spectral data were recorded on a Waters micromass LCT Mass Spectrometer. The ^1H NMR and ^{13}C NMR spectra were recorded on Jeol JNM ECX-400P at 400 MHz, respectively using TMS as an internal standard. The chemical shift values are recorded on δ scale and the coupling constants (*J*) are in Hertz.

General procedure for the synthesis of azides 1a and 2a

The respective starting bromo compounds 4-(4-bromobutyloxy)quinazoline (1g, 3.55 mmol) (1) and 4-(6-bromohexyloxy)quinazoline (0.81 g, 2.64 mmol) (2) were separately stirred with sodium azide (1x1.5 times) in DMF (5 ml) under heating condition (80° C) overnight. After completion of the reaction the reaction mixture was poured on crushed ice and content was then extracted with chloroform and the organic layer was dried over sodium sulfate. Then solvent was evaporated under vacuum to get the required compounds as yellow coloured oils which were further used without any additional purification. In turn the respective precursors bromo compounds 1 and 2 were synthesized by reacting quinazolin-3*H*-4-one with 1,4-dibromobutane and 1,6-dibromohexane respectively in acetone at room temperature. After completion of reaction the solution was filtered out and filtrate was concentrated under reduced pressure to obtain the crude product. This was then purified by silica gel column (petroleum ether-ethylacetate as eluent) to obtain the monobrominated products as the major compounds.

4-(4-Bromobutyloxy)quinazoline (1).

White solid; yield: 69 %; mp: 58-60 °C; IR (KBr): 2951, 2861, 1656, 1609, 1473, 1373, 1237, 1113, 1043, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, δ): 8.31(d, 1H, *J* = 8.0 Hz), 8.05 (s, 1H), 7.79-7.71 (m, 2H), 7.54-7.50 (m, 1H), 4.06 (t, 2H, *J* = 6.6 Hz, -OCH_2-), 3.46 (t, 2H, *J* = 5.8 Hz, -CH_2Br), 1.97 (brs, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 160.9, 147.9, 146.1, 134.1, 127.3, 127.2, 126.5, 121.9, 45.8 (-OCH_2), 32.4(-CH_2Br), 29.4, 28.0; TOF ES+ m/z: 281 (M^++1).

4-(6-Bromohexyloxy)quinazoline (2)

White solid; Yield: 77 %; mp 40-42 °C; IR (KBr): 2941, 2857, 1660, 1610, 1471, 1372, 1326, 1255, 1111, 961, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, δ): 8.32-8.30 (m, 1H), 8.03 (s, 1H), 7.78-7.70 (m, 2H), 7.53-7.49 (m, 1H), 4.01 (t, 2H, *J* = 7.3 Hz, -OCH_2-), 3.40 (t, 2H, *J* = 6.5 Hz, -CH_2Br), 1.90-1.79 (m, 6H), 1.55-1.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 160.8, 147.8, 134.0, 127.2, 127.1, 126.5, 121.9, 46.7 (-OCH_2-), 33.5 (-CH_2Br), 32.3, 29.0, 27.5, 25.6; TOF ES+ m/z: 309 (M^++1).

4-(4-Azidobutyloxy)quinazoline (1a)

yellow coloured oil; Yield: 93 %; IR (film): 2926, 2103, 1676, 1610, 1474, 1369, 1292, 1258, 1165, 1105, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, δ): 8.31-8.29 (m, 1H), 8.04 (s, 1H), 7.78-7.70 (m, 2H), 7.53-7.49 (m, 1H), 4.04 (t, 2H, *J* = 7.3 Hz, -OCH_2-), 3.36 (t, 2H, *J* = 6.6 Hz, - CH_2N_3), 1.94-1.86 (m, 2H), 1.71-1.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 161.0, 147.9, 146.2, 134.2, 127.3, 127.2, 126.5, 121.9, 50.8 (-OCH_2-), 46.2(-CH_2N_3), 26.5, 26.0; TOF ES+ m/z: 244 (M^++1).

4-(6-Azidohexyloxy)quinazoline (2a)

Yellow coloured oil; Yield: 91 %; IR (Film): 2936, 2860, 2096, 1674, 1610, 1564, 1473, 1373, 1258, 1179, 1091, 884 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, δ): 8.31 (d, 1H, J = 8.0 Hz), 8.03 (s, 1H), 7.78-7.70 (m, 2H), 7.53-7.49 (m, 1H), 4.01(t, 2H, *J* = 7.3 Hz, -OCH_2), 3.27 (t, 2H, *J* = 6.9 Hz, -CH_2N_3), 1.85-1.80 (m, 4H),

1.44-1.42 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 162.4, 160.9, 147.9, 146.4, 134.1, 127.2, 126.5, 122.0, 51.1 (-OCH_2-), 46.7(-CH_2N_3), 36.3, 29.1, 28.5; TOF ES+ m/z: 272 (M^++1).

General Procedure for the synthesis of compounds (1b-1i) and (2b-2i)

Alkynes (1 mmol) were stirred with $CuSO_4.5H_2O$ (15 mol %) and Et_3N (1.2 mmol) in THF at room temperature for 15 minutes then azide (1a or 2a) (1 mmol) dissolved in THF was added to reaction mixture and the progress of reaction was observed on TLC. After completion of the reaction (1/2-9 hours), solvent was evaporated under reduced pressure and crushed ice was poured in the reaction mixture, precipitated solid was filtered using vacuum pump. In case, solid was not precipitated then reaction mixture was extracted with ethyl acetate. The organic layer was dried on anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue obtained was washed with hot petroleum ether in order to prevent aliphatic impurities and then compounds were crystallized using chloroform/methanol or chloroform/acetone.

4-(4-(4-(1-Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)butyloxy)quinazoline (1b).

White solid; Yield: 90 %; mp 94-96 ^oC; IR (KBr): 3301, 2925, 2866, 1670, 1615,1460, 1380, 1294, 1215, 1123, 1034 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.22 (d, 1H, *J* = 8.0 Hz), 7.94 (s, 1H), 7.72-7.68 (m, 1H), 7.65-7.62 (m, 1H), 7.50 (s, 1H, triazole), 7.47-7.43 (m, 1H), 4.71 (s, 2H, -CH_2OH), 4.36 (t, 2H, *J* = 7.3 Hz, -OCH_2-), 3.95 (t, 2H, *J* = 7.3 Hz, >NCH_2-), 1.97-1.90 (m, 2H), 1.77-1.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 161.3, 147.9, 146.2, 134.4, 127.4, 126.6, 121.8, 56.3 (-CH_2OH), 49.4(-OCH_2-), 45.8(>NCH_2-), 27.2, 26.3; TOF ES+ m/z: 300 (M^++1).

4-(4-(4-(1-Hydroxyethyl)-1*H*-1,2,3-triazol-1-yl) butyloxy)quinazoline (1c).

Creamish solid; Yield: 92 %; mp 66-68 ^oC; IR (KBr): 3302, 2922, 2861, 1670, 1616, 1475, 1381, 1327, 1180, 1035, 1010, 778.cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.29 (d, 1H, *J* = 7.3 Hz), 7.96 (s, 1H), 7.79-7.75 (m, 1H), 7.72-7.70 (m, 1H), 7.54-7.50 (m, 1H), 7.44 (s, 1H, triazole), 4.42 (t, 2H, *J* = 7.3 Hz, -OCH_2-), 4.02 (t, 2H, *J* = 6.5 Hz, >NCH_2-), 3.95 (brs, 2H), 2.95 (t, 2H, *J* = 5.1 Hz), 2.83 (brs, 1H), 2.01-1.99 (m, 2H), 1.85-1.83 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.2, 148.0, 146.1, 134.4, 127.4, 126.6, 125.0, 123.7, 121.7, 61.6, 49.5, 45.7, 28.7, 27.2, 26.3; TOF ES+ m/z : 314 (M^++1).

4-(4-(4-(1-Hydroxyprop-3-yl)-1*H*-1,2,3-triazol-1-yl)butyloxy)quinazoline (1d).

Light yellow oil; Yield: 91 %; IR (film): 3370, 2925, 1670, 1611, 1459, 1375, 1217, 1057, 776 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.27 (d, 1H, *J* = 7.32 Hz), 8.02 (s, 1H), 7.75-7.69 (m, 2H), 7.52-7.50 (m, 1H), 7.33 (s, 1H, triazole), 5.95 (brs, 1H, -OH, D_2O exchangeable), 4.38 (t, 2H, *J* = 6.88 Hz, -OCH_2-), 4.02 (t, 2H, *J* = 7.32 Hz, >NCH_2-), 3.67 (t, 2H, *J* = 5.96 Hz), 2.81 (t, 2H, *J* = 7.32 Hz), 2.01-1.94 (m, 2H), 1.92-1.87 (m, 2H), 1.83-1.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 161.0, 147.7, 146.0, 134.4, 127.5, 127.3, 126.6, 121.9, 121.8, 121.1, 61.6, 50.8, 49.3, 45.9, 31.7, 27.2, 26.3, 21.9; TOF ES+ m/z : 327 (M^+).

4-(4-(4-(1-Hydroxybut-4-yl)-1*H*-1,2,3-triazol-1-yl)butyloxy)quinazoline (1e).

Creamish solid; Yield: 92 %; mp 48-50 ^oC; IR (KBr): 3340, 2943, 2873, 1688, 1612, 1475, 1323, 1180, 1064, 974 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.36 (s, 1H), 8.12 (d, 1H, *J* = 6.6 Hz), 7.82-7.79 (m, 2H), 7.66 (d, 1H, *J* = 8.0 Hz), 7.55-7.51 (m, 1H), 4.35-4.30 (m, 4H), 3.98 (t, 2H, *J* = 7.3 Hz, -OCH_2-), 3.39 (t, 2H, *J* = 5.8 Hz, >NCH_2-), 2.56 (t, 2H, *J* = 7.3 Hz), 1.84-1.76 (m, 2H), 1.68-1.63 (m, 2H), 1.59-1.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 160.2, 147.9, 146.9, 134.2, 127.1, 127.0, 126.0, 121.7, 121.5, 60.3, 48.6, 45.0, 31.9, 27.1, 25.7, 25.5, 24.8; TOF ES+ m/z : 342 (M^++1).

4-(4-(4-(4-Methylchromen-2H-on-7-yloxymethyl)-1H-1,2,3-triazol-1-yl)butyloxy)quinazoline (1f).

Creamish solid; Yield: 90 %; mp 94-96 ^oC; IR (KBr): 2940, 2869, 1708, 1683, 1609, 1439, 1398, 1102, 1087, 939, 773 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.41(s, 1H), 8.29-8.27 (m, 1H), 8.13 (d, 1H, *J* = 8.0 Hz), 7.82-7.79 (m, 1H), 7.65 (d, 2H, *J* = 8.0 Hz), 7.54-7.50 (m, 1H), 7.11 (s, 1H, triazole), 7.01-6.99 (m, 1H), 6.19 (s, 1H, alkenic proton), 5.23 (s, 2H, -CH_2O-C=), 4.41 (t, 2H, *J* = 6.6 Hz, -OCH_2-), 3.98 (t, 2H, *J* = 6.9 Hz, >NCH_2-), 2.36 (s, 3H, -CH_3), 1.85-1.78 (m, 2H), 1.68-1.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 160.9, 160.0, 154.5, 153.2, 147.8, 134.2, 127.1, 126.8, 125.9, 113.1, 112.4, 111.3, 101.4, 61.6, 48.9, 45.1, 26.8, 25.5, 18.0 (-CH_3); TOF ES+ m/z : 457 (M^+).

4-(4-(4-(Quinazolin-4-yloxymethyl)-1*H*-1,2,3-triazol-1-yl)butyloxy)quinazoline (1g)

White solid; Yield: 92 %; mp 88-90 ^oC; IR (KBr): 2949, 2871, 1664, 1610, 1473, 1363, 1293, 1161, 1051, 803 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.53 (s, 1H), 8.36 (s, 1H), 8.12-8.10 (m, 3H), 7.83-7.79 (m, 2H), 7.68-7.64 (m, 2H), 7.54-7.52 (m, 2H), 5.23 (s, 2H), 4.35 (t, 2H, *J* = 6.6 Hz, -OCH_2-), 3.96 (t, 2H, *J* = 6.9 Hz, >NCH_2-), 1.83-1.78 (m, 2H), 1.68-1.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 160.1, 159.8, 147.9, 134.4, 134.2, 127.2, 127.1, 127.0, 126.0, 123.7, 121.6, 48.8, 45.1, 41.0, 26.8, 25.7; TOF ES+ m/z : 427 (M^+).

4-(4-(4-(Isoindolin-1,3-dion-2-ylmethyl)-1*H*-1,2,3-triazol-1-yl)butyloxy)quinazoline (1h).

White solid; Yield: 90 %; mp 136-138 ^oC; IR (KBr): 2926, 2856, 1719, 1676, 1611, 1388, 1293, 1265, 1147, 1072, 1015, 844, 774 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.37 (s, 1H), 8.11-8.05 (m, 2H), 7.88-7.87 (m, 2H), 7.85-7.82 (m, 3H), 7.65 (d, 1H, *J* = 7.3 Hz), 7.54-7.50 (m, 1H), 4.80 (s, 2H, $CH_2N(CO)$), 4.34 (t, 2H, *J* = 6.6 Hz, -OCH_2-), 3.97 (t, 2H, *J* = 7.3 Hz, >NCH_2-), 1.83-1.75 (m, 2H), 1.67-1.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 167.3 (CO), 160.1, 147.9, 140.0, 134.5, 134.2, 131.5, 127.2, 127.0, 126.0, 123.2, 48.4, 45.4, 33.2, 27.0, 25.7; TOF ES+ m/z : 428 (M^+).

4-(4-(4-(Indolin-2,3-dion-1-ylmethyl)-1*H*-1,2,3-triazol-1-yl)butyloxy)quinazoline (1i).

Yellow solid; Yield: 91 %; mp 102-104 ^oC; IR (KBr): 2939, 2858, 1712, 1676, 1612, 1471, 1397, 1294, 1108, 941 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.29 (d, 1H, *J* = 8.0 Hz), 8.01 (s, 1H), 7.85-7.83 (m, 2H), 7.78-7.74 (m, 1H), 7.71-7.69 (m, 3H), 7.59 (s, 1H, triazole), 7.52-7.47 (m, 1H), 4.99 (s, 2H, -$CH_2N(CO)_2$), 4.30 (t, 2H, *J* = 7.3 Hz, -OCH_2-), 3.96 (t, 2H, *J* =

7.3 Hz, >NCH_2-), 1.89-1.70 (m, 4H), 1.38-1.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 167.6 (CO), 161.0, 160.8, 148.0, 146.4, 134.1, 134.0, 131.9, 127.4, 127.2, 123.4, 122.6, 50.1, 46.6, 33.0, 30.1, 29.0, 25.9; TOF ES+ m/z : 457 (M^++1).

4-(6-(4-(1-Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)hexyloxy)quinazoline (2b).

White solid; Yield: 98 %; mp 108-110 °C; IR (KBr): 3289, 2923, 2858, 1672, 1616, 1475, 1378, 1293, 1213, 1112, 1049, 778 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.29 (d, 1H, *J* = 7.3 Hz), 7.93 (s, 1H), 7.79-7.70 (m, 2H), 7.53 (s, 1H, triazole), 7.52-7.49 (m, 1H), 4.80 (s, 2H,-CH_2OH), 4.36 (t, 2H, *J* = 6.6 Hz, -OCH_2-), 3.96 (t, 2H, *J* = 7.3 Hz, >NCH_2-), 1.93-1.90 (m, 2H), 1.79-1.70 (m, 2H), 1.37-1.36 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 160.1, 147.7, 147.1, 133.6, 126.8, 126.5, 125.8, 121.8, 121.5, 55.2, 49.1, 48.7, 45.8, 29.4, 28.4, 25.3; TOF ES+ m/z : 328 (M^++1).

4-(6-(4-(1-Hydroxyethyl)-1*H*-1,2,3-triazol-1-yl)hexyloxy)quinazoline (2c).

White solid; Yield: 95 %; mp 47-49 °C; IR (KBr): 3400, 2928, 2857, 1693, 1669, 1475, 1377, 1222, 1050, 777 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.29 (d, 1H, *J* = 8.0 Hz), 8.00 (s, 1H), 7.78-7.74 (m, 1H), 7.71-7.69 (m, 1H), 7.53-7.49 (m, 1H), 7.41 (s, 1H, triazole), 4.32 (t, 2H, *J* = 7.3 Hz, -OCH_2-), 3.99-3.92 (m, 4H), 2.95 (t, 2H, *J* = 6.2 Hz), 1.93-1.86 (m, 2H), 1.81-1.75 (m, 2H), 1.40-1.33 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 161.0, 147.8, 146.4, 145.5, 134.2, 127.3, 126.5, 121.9, 121.4, 61.4, 49.9, 46.6, 29.8, 29.6, 28.9, 28.6, 25.8; TOF ES+ m/z : 341 (M^+).

4-(6-(4-(1-Hydroxyprop-3-yl)-1*H*-1,2,3-triazol-1-yl)hexyloxy)quinazoline (2d).

Light yellow oil; Yield: 93 %; IR (film): 3392, 2931, 2860, 1669, 1611, 1474, 1376, 1293, 1179, 1057, 776 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.30 (d, 1H, *J* = 8.0 Hz), 8.02 (s, 1H), 7.78-7.70 (m, 2H), 7.53-7.49 (m, 1H), 7.31 (s, 1H, triazole), 4.31 (t, 2H, *J* = 7.6 Hz, -OCH_2-), 3.98 (t, 2H, *J* = 7.3 Hz, >NCH_2-), 3.71 (t, 2H, *J* = 6.2 Hz), 2.83 (t, 2H, *J* = 6.6 Hz), 1.97-1.86 (m, 4H), 1.81-1.76 (m, 2H), 1.43-1.37 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 161.1, 148.0, 146.4, 134.2, 127.3, 126.6, 122.1, 120.7, 61.8, 49.9, 46.7, 31.8, 29.9, 29.0, 25.9, 22.0; TOF ES+ m/z : 356 (M^++1).

4-(6-(4-(1-Hydroxybut-4-yl)-1*H*-1,2,3-triazol-1-yl)hexyloxy)quinazoline (2e).

Light yellow oil; Yield: 94 %; IR (film): 3394, 2935, 2861, 1671, 1611, 1474, 1376, 1324, 1292, 1150, 1056, 776 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.30 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.4 Hz), 8.03 (s, 1H), 7.79-7.70 (m, 2H), 7.53-7.50 (m, 1H), 7.29 (s, 1H, triazole), 4.31 (t, 2H, *J* = 6.6 Hz, -OCH_2-), 3.98 (t, 2H, *J* = 7.3 Hz, >NCH_2-), 3.69-3.66 (m, 2H), 2.76-2.72 (m, 2H), 2.25-2.22 (m, 2H), 1.93-1.86 (m, 2H), 1.83-1.75 (m, 4H), 1.65-1.60 (m, 2H), 1.41-1.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 161.0, 147.9, 146.4, 134.2, 127.3, 127.2, 126.6, 122.1, 120.6, 77.0, 68.4, 62.1, 49.9, 46.7, 32.0, 29.0, 25.9, 25.5, 18.1; TOF ES+ m/z : 370 (M^++1).

4-(6-(4-(4-Methylchromen-2*H*-on-7-yloxymethyl)-1*H*-1,2,3-triazol-1-yl)hexyloxy)quinazoline (2f).

Creamish solid; Yield: 92 %; mp 100-102 °C; IR (KBr): 2935, 2839, 1719, 1681, 1610, 1387, 1266, 1201, 1158, 1067, 997, 783 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.36 (brs, 1H), 7.89 (brs, 1H), 7.75 (s, 1H), 7.52-7.47 (m, 3H), 7.27 (s, 1H), 6.96-6.90 (m, 2H), 6.13 (s, 1H, alkenic proton), 5.29 (s, 2H), 4.41 (brs, 2H), 3.99 (brs, 2H), 2.38 (s, 3H, -CH_3), 1.96 (brs, 2H), 1.80-1.76 (m, 4H), 1.41(brs, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 161.1, 161.0,155.0, 152.4, 150.0, 134.0, 127.2, 125.7, 125.5, 114.0, 112.3, 112.0, 102.7 (alkenic carbon), 61.3, 52.0, 50.5, 46.7, 29.8, 29.0, 25.9, 18.6 (-CH_3); TOF ES+ m/z : 485 (M^+).

4-(6-(4-(Quinazolin-4-yloxymethyl)-1*H*-1,2,3-triazol-1-yl) hexyloxy)quinazoline (2g).

Light pink solid; Yield: 93 %; mp 109-111 °C; IR (KBr): 2926, 2853, 1671, 1610, 1473, 1375, 1292, 1146, 1046, 774 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.36 (brs, 2H), 8.30-8.28 (m, 2H), 7.86 (brs, 1H), 7.75-7.73 (m, 4H), 7.52-7.47 (m, 2H), 5.28 (s, 2H), 4.32 (brs, 2H, -OCH_2-), 3.96 (t, 2H, *J* = 7.3 Hz, >NCH_2-), 1.92-1.85 (m, 2H), 1.79-1.76 (m, 2H), 1.38 (brs, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 163.0, 160.9, 134.3, 134.1, 127.6, 127.3, 126.8, 126.5, 62.9, 46.7, 29.8, 29.0, 25.9; TOF ES+ m/z : 455 (M^+).

4-(6-(4-(Isoindolin-1,3-dion-2-ylmethyl)-1*H*-1,2,3-triazol-1-yl)hexyloxy) quinazoline (2h).

White solid; Yield: 91 %; mp 102-104 °C; IR (KBr): 2939, 2858, 1712, 1676, 1612, 1471, 1397, 1294, 1108, 941 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.29 (d, 1H, *J* = 8.0 Hz), 8.01 (s, 1H), 7.85-7.83 (m, 2H), 7.78-7.74 (m, 1H), 7.71-7.69 (m, 3H), 7.59 (s, 1H, triazole), 7.52-7.47 (m, 1H), 4.99 (s, 2H, -$CH_2N(CO)_2$), 4.30 (t, 2H, *J* = 7.3 Hz, -OCH_2-), 3.96 (t, 2H, *J* = 7.3 Hz, >NCH_2-), 1.89-1.70 (m, 4H), 1.38-1.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 167.6 (CO), 161.0, 160.8, 148.0, 146.4, 134.1, 134.0, 131.9, 127.4, 127.2, 123.4, 122.6, 50.1, 46.6, 33.0, 30.1, 29.0, 25.9; TOF ES+ m/z : 457 (M^++1).

4-(6-(4-(Indolin-2,3-dion-1-ylmethyl)-1*H*-1,2,3-triazol-1-yl)hexyloxy)quinazoline (2i).

Yellow solid; Yield: 93 %; mp 60-62 °C; IR (KBr): 2928, 2857, 1740, 1670, 1610, 1471, 1369, 1324, 1291, 1176, 1095, 774 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.31 (d, 1H, *J* = 8.0 Hz), 7.75 (brs, 2H), 7.64 (s, 1H), 7.59-7.55 (m, 2H), 7.53-7.49 (m, 2H), 7.31 (d, 1H, *J* = 7.3 Hz), 7.11-7.08 (m, 1H), 5.02 (s, 2H, -$CH_2N(CO)$), 4.32 (t, 2H, *J* = 7.3 Hz, -OCH_2-), 3.95 (t, 2H, *J* = 7.3 Hz, >NCH_2-), 1.91-1.89 (m, 2H), 1.77-1.76 (m, 2H), 1.43-1.38 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 161.1, 158.0, 150.2, 138.6, 134.2, 127.4, 127.2, 126.5, 125.3, 124.1, 111.4, 50.2, 46.6, 35.4, 30.9, 29.8, 28.9, 25.8; TOF ES+ m/z : 456 (M^+).

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Notes and references

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