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Original article

Design, synthesis and antimicrobial activities of some new quinoline derivatives carrying 1,2,3-triazole moiety

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ABSTRACT

A new series of [1-(6-methoxy-2-methylquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl] methanamine derivatives were synthesized starting from 4-methoxyaniline through multi-step reactions. The title compounds **5a**–**y** were prepared by treating the azide intermediate **4** with propargyl bromide and different alkyl/heterocyclic amines in a sequential three component synthesis. All the new compounds were characterized by spectral and elemental analyses. The newly synthesized final compounds were evaluated for their *in vitro* antibacterial and antifungal activities against pathogenic strains. The preliminary screening results indicated that most of the compounds demonstrated moderate to very good antibacterial and antifungal activities, comparable to the first-line drugs.

1. Introduction

Currently, resistance to first-line antibiotic agents is a severe problem. Infections caused by these resistant microbes fail to respond to treatment resulting in prolonged illness and greater risk of death. The alarming rates of emerging and reemerging microbial threats coupled with increasing antibacterial resistance, particularly in regard to multi drug-resistant Gram-positive bacteria [1–4], are major concerns to the public health as well as scientific communities worldwide. These trends have emphasized the pressing need for new, more effective and safe antibacterial agents and which in turn has opened up a new area of research for the scientists.

At present, the role of heterocyclic compounds has become increasingly important in designing new class of structural entities of medicinal importance. Among pharmacologically important heterocyclic compounds, quinoline and its derivatives have been well known in pharmaceutical chemistry because of their wide spectrum of biological activities and their presence in naturally occurring compounds. They have been shown to possess antimalarial [5–7], antibiotic [8,9], anticancer [10], anti-inflammatory [11], antihypertensive [12], tyrokinase PDGF-RTK inhibition [13] and anti-HIV [14,15] properties. In addition, 1,2,3-Triazoles are an important class of heterocyclic compounds due to their wide range of applications as pharmaceutical agents [16]. They have attracted continued interest to organic and medicinal scientists over the years because of their varied biological activities such as anti-allergic [17–19], antibacterial [20], antifungal [21], anti-HIV [22], anticonvulsant [23], anti-inflammatory [24,25] and β-lactamase inhibition properties [26]. It is quite evident that the favorable properties of 1,2,3-triazole ring like moderate dipole character, hydrogen bonding capability, rigidity and stability under *in vivo* conditions are responsible for their enhanced biological activities [27].

A thorough literature review reveals that more efficacious antibacterial compounds can be designed by joining two or more biologically active heterocyclic systems together in a single molecular framework [28]. Against this background and as a part of our general program in the continued research for new antibactierials, it has been planned to introduce active 1,2,3-triazole ring at position 4 of potent 6-methoxy substituted quinoline moiety and to derivatize the resulting biheterocyclic system with different pharmaceutically accepted amines having active groups like methoxy, fluoro etc at position 4 of 1,2,3-triazole ring. It has been hoped that combination of these active groups in the new molecular design would lead to better antimicrobial agents. In this communication, we report the synthesis of newly designed [1-(6-methoxy-2-methylquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl]

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methanamine derivatives **5a**–**y** starting from 4-methoxyaniline and evaluated these compounds for antibacterial and antifungal activities.

2. Results and discussion

2.1. Chemistry

The title compounds were synthesized by a series of reactions as shown in Scheme 1. The intermediate, 3-(4-methoxy-phenylamino)-but-2-enoic acid ethyl ester (**1**) was synthesized from corresponding 4-methoxyaniline by treating it with ethylacetoacetate in presence of magnesium sulfate in ethanol at 90 °C. The intermediate **1** was then converted to 6-methoxy-2-methylquinolin-4-ol (**2**) by heating it at 270 °C using Dowtherm for 20 min. The required key intermediate 4-azido-6-methoxy-2-methylquinoline (**4**) was obtained by heating the compound **2** with phosphorous oxychloride, followed by treating the chloro derivative **3** with sodium azide in presence of 1:1 aqueous ethanol as solvent. The conversion of chloro intermediate **3** to an azide compound **4** was carried out in an autoclave by heating to 100 °C and maintaining the reaction for 12 h. The title compounds **5a**–**y** were then synthesized by sequential one pot reaction of intermediate **4** with propargyl bromide and different primary and secondary amines in presence of triethylamine and copper iodide [29].

The newly synthesized compounds were characterized by FTIR, ^{1}H NMR, ^{13}C NMR, LCMS and elemental analysis. The formation of 6-methoxy-2-methylquinolin-4-ol (**2**) was indicated by its FTIR spectrum. In its FTIR spectrum, the compound **2** exhibited a broad band at 3528 cm^{-1} due to OH stretching. The structure of the compound **2** was further confirmed by its ^{1}H NMR spectrum, wherein the appearance of a broad peak at δ 11.45 ppm indicated the presence of –OH group which disappeared on D_2O exchange. The formation of chloro derivative **3** was confirmed by its ^{1}H NMR spectrum. In its spectrum, the disappearance of a broad peak at 11.45 ppm and the appearance of a singlet at higher δ value, i.e. at δ 7.65 ppm are due to chloro substituent. This confirms the conversion of hydroxyl derivative to its corresponding chloro derivative and is also evidenced by LCMS and IR spectral data. The formation of intermediate **4** was confirmed by its spectral studies. In its ^{1}H NMR spectrum, δ values of the aromatic protons and the proton on the C3 and C5 position next to the azide group were shifted to lower δ values due to the substitution of chloro group by azide functionality.

The cyclization of azide derivative **4** to title compounds, viz., N-{[1-(6-methoxy-2-ethylquinolin-4-yl)-1H-1,2,3-triazol-4-yl] methylamines (**5a**–**y**) was confirmed by their ^{1}H NMR. The ^{1}H NMR spectrum of **5a** showed a singlet at δ 8.01ppm clearly indicating the cyclization. Further, appearance of a broad peak at δ 6.71ppm shows the presence of –NH group of cyclopropyl ring of **5a**. The cyclization was further confirmed by its ^{13}C NMR and LCMS spectral data. The spectral data is discussed in experimental section. The characterization data of compounds **5a**–**y** are tabulated in Table 1.

2.2. Biological activities

All the title compounds were subjected to *in vitro* antibacterial and antifungal screening against pathogenic strains using ciprofloxacin and ciclopirox olamine as standards, respectively. Their MIC values were determined (Tables 2 and 3).

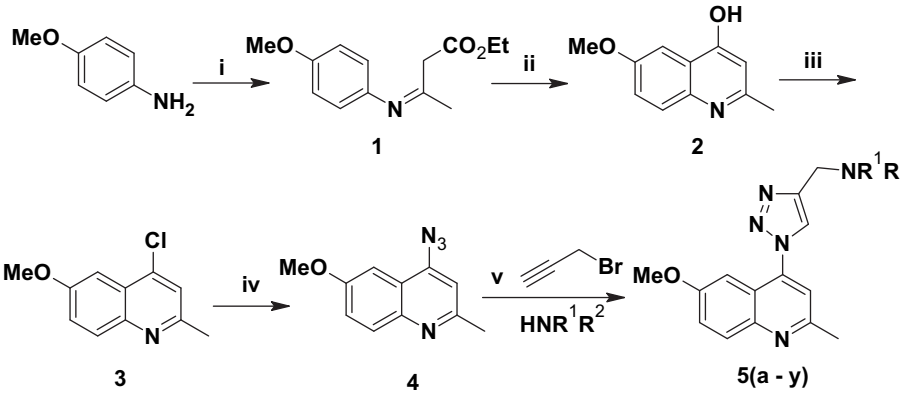
2.3. Biological results

The *in vitro* preliminary antimicrobial screening of newly synthesized compounds against antibacterial and antifungal strains exhibited moderate to very good activity at MIC of 6.25–12.5 μg/mL in DMSO. The amine derivatives **5a**, **5c**, **5h**, **5i**, **5j**, **5n**, **5p**, **5q**, **5r**, **5t** and **5x** showed comparatively good activity against all the bacterial strains. The enhanced antibacterial activity can be attributed to the presence of active piperazine moiety in their structures. It was also observed that methyl, ethyl, isopropyl and acetyl substituted piperazine contributed significantly in increasing antibacterial activity in them. Further, the compounds **5b**, **5e**, **5f**, **5g**, **5l**, **5m** and **5o** displayed moderate antibacterial activity.

As seen from the results of antifungal testing of title compounds, the compounds **5a**, **5c**, **5h**, **5i**, **5j**, **5n**, **5p**, **5q**, **5r**, **5t** and **5x** were found to be active against all the strains. The presences of active groups like cyclopropyl, substituted piperazines, methoxy and fluoro has contributed significantly in enhancing the activity. It is interesting to note that these compounds displayed good antibacterial as well as antifungal activities.

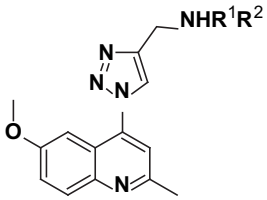
3. Conclusion

We herein report the successful synthesis of twenty five newly designed derivatives of 1-[1-(6-methoxy-2-methylquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl]methanamine. The required cyclization has been effectively carried out using the sequential one pot synthesis. All the title compounds have been investigated for their antimicrobial activities. Interestingly, the majority of them showed moderate to very good activity against all the pathogenic strains. The compounds **5a**, **5c**, **5h**, **5i**, **5j**, **5n**, **5p**, **5q**, **5r**, **5t** and **5x** have been shown to be active antibacterial and antifungal agents. The enhanced activity is due to the presence of active piperazine and its



Scheme 1. 1-[1-(6-Methoxy-2-methylquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl] methanamine derivatives. (i) Ethylacetoacetate, EtOH, $MgSO_4$, 90 °C, 5 h (ii) Dowtherm, 270 °C, 20 min (iii) $POCl_3$, 105 °C, 2 h (iv) sodium azide, EtOH/Water, 100 °C, 12 h. (v) Propargyl bromide, CuI, substituted amines, THF/Water (1:1), reflux, 2h.

Table 1
Characterization data of compounds **5a**–**y**.



Compd	R^1R^2 (Amines)	Mol. formula	Mol. wt	m.p (°C)	Yield[a] (%)
5a	Cyclopropyl	$C_{17}H_{19}N_5O$	309.36	88–89.7	70
5b	Cyclopentyl	$C_{19}H_{23}N_5O$	337.41	94.5–95.1	68
5c	$HN(CH_3)_2$	$C_{16}H_{19}N_5O$	297.35	89–90.6	82
5d	$HN(C_2H_5)_2$	$C_{18}H_{23}N_5O$	325.40	97.4–98.9	85
5e	Pyrolidine	$C_{18}H_{21}N_5O$	323.39	74.6–75.7	80
5f	Piperidine	$C_{19}H_{23}N_5O$	337.41	115.4–116.1	63
5g	4-phenyl-piperidine	$C_{25}H_{27}N_5O$	413.51	148.8–149.2	57
5h	1-methyl piperazine	$C_{19}H_{24}N_6O$	352.43	118–119.1	78
5i	1-ethyl piperazine	$C_{20}H_{26}N_6O$	366.46	115.5–116.2	83
5j	1-acetyl piperazine	$C_{20}H_{24}N_6O_2$	380.44	ND	76
5k	1-cyclohexylpiperazine	$C_{24}H_{32}N_6O$	420.55	121–121.9	65
5l	1-(2-(Fluoro)-phenyl piperazine	$C_{24}H_{25}FN_6O$	432.49	190.7–191.4	67
5m	1-(4-(Fluoro)-phenyl) piperazine	$C_{24}H_{25}FN_6O$	432.49	192–193.7	65
5n	1-(4-(methoxy)-phenyl) piperazine	$C_{25}H_{28}N_6O_2$	444.52	142.1–142.9	84
5o	1-(4-(methyl)-phenyl) piperazine	$C_{25}H_{28}N_6O$	428.52	136.6–137.5	62
5p	1-(4-(methoxy)-2-(methyl) -phenyl) piperazine	$C_{26}H_{30}N_6O_2$	458.55	ND	71
5q	N,N,N′-trimethylethane-1,2-diamine	$C_{19}H_{26}N_6O$	354.44	89.4–90.2	60
5r	N,N-dimethylpropane-1,3-diamine	$C_{19}H_{26}N_6O$	354.44	100.2–101.6	51
5s	Cyclohexylamine	$C_{20}H_{25}N_5O$	351.44	84.2–84.8	67
5t	Morpholine	$C_{18}H_{21}N_5O_2$	339.39	126.3–127.5	78
5u	N-methylcyclohexyl amine	$C_{21}H_{27}N_5O$	365.47	111.6–112.3	61
5v	1-phenyl-piperazine	$C_{24}H_{26}N_6O$	414.50	177.2–178	70
5w	4-(piperidin-4-yl) Morpholine	$C_{23}H_{30}N_6O_2$	422.52	ND	61
5x	1-(propan-2-yl)piperazine	$C_{21}H_{28}N_6O$	381.47	ND	67
5y	Butan-2-amine	$C_{18}H_{23}N_5O$	325.40	ND	58

ND – Not detected.
[a] Isolated yield after column purification.

derivatives in their structures. The scaffolds synthesized in the research work can be taken for further derivatization in order to find the lead in these series.

4. Experimental

4.1. General

Melting points were determined using Buchi B-540 by open capillary and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FTIR 157 spectrophotometer. Final compound purifications were carried out using Quad biotage Flash purifier (A Dyax Corp. Company). All ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 (300.12 MHz), Bruker BioSpin Corp., Germany, using TMS (tetra methyl silane) as an internal standard. All chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane. The mass spectra were recorded either on Single quadrapole mass or XCT Ion trap spectrometer operating at 70 eV. The mass spectra of a few were recorded on a 410 Prostar binary PDA detector (Varian Inc, USA). Elemental analysis was performed on Flash EA 1112 Thermo Electron Corporation CHNSO analyzer. The homogeneity of the compounds was monitored by thin layer chromatography (TLC) on silica gel 40 F254 (Merck, Darmstadt, Germany) (Merck) coated on aluminum plates, visualized by UV light and $KMnO_4$ solution. Starting materials were purchased from Aldrich Chemical Company or Spectrochem chemical company and used without further purification. All the solvents were of analytical grade and freshly distilled prior to use.

4.2. Procedure for the preparation of ethyl-3-[(4-methoxyphenyl) imino] butanoate (*1*)

A mixture of 4-methoxyaniline (30 g, 0.243 mol), ethylacetoacetate (34.87 g, 0.267 mol), anhydrous magnesium sulfate (35.09 g, 0.291 mol), and acetic acid (2 mL) in ethanol (250 mL) was heated to 90 °C for 5 h. Reaction completion was monitored by TLC. Reaction was complete. The reaction mass was filtered and ethanol

Table 2
Antibacterial activity data of the title compounds **5a**–**y**.

Compound	MIC in μg/mL and zone of inhibition in mm				
	S. aureus (ATCC 25923)	*E. coli* (ATCC 25922)	*P. aeruginosa* (ATCC 27853)	*K.pneumoniae* (recultured)	*S.Pyogenes*
5a	6.25(16–20)	6.25(16–20)	6.25(12–16)	6.25(18–22)	6.25(12–14)
5b	6.25(12–16)	6.25(12–16)	6.25(12–14)	6.25(14–18)	6.25(12–14)
5c	6.25(16–18)	6.25(14–18)	6.25(14–18)	6.25(16–20)	6.25(14–18)
5d	6.25(12–16)	6.25(14–16)	6.25(12–14)	6.25(12–14)	6.25(14–18)
5e	12.5(10–11)	12.5(10–14)	12.5(12)	12.5(11–12)	12.5(11)
5f	50(<10)	12.5(10–14)	50(<10)	50(<10)	12.5(10–12)
5g	12.5(10–11)	12.5(10–14)	12.5(12)	12.5(11–12)	12.5(11)
5h	6.25(16–22)	6.25(20–24)	6.25(14–16)	6.25(14–18)	6.25(16–20)
5i	6.25(18–22)	6.25(18–22)	6.25(12–14)	6.25(16–20)	6.25(12–16)
5j	6.25(20–22)	6.25(18–22)	6.25(14–16)	6.25(12–14)	6.25(16–20)
5k	12.5(10–12)	12.5(10–12)	12.5(10–12)	12.5(10–11)	12.5(10–12)
5l	12.5(10–12)	12.5(10–12)	6.25(10–12)	6.25(10–12)	6.25(14–16)
5m	12.5(11–12)	6.25(12–14)	6.25(10–12)	6.25(12–14)	12.5(<10)
5n	6.25(16–20)	6.25(20–24)	6.25(14–16)	6.25(16–20)	6.25(14–16)
5o	50(<10)	50(<10)	50(<10)	50(<10)	50(<10)
5p	12.5(14–16)	12.5(14–18)	12.5(10–14)	6.25(16–20)	6.25(16–20)
5q	6.25(14–16)	6.25(14–16)	6.25(14–16)	6.25(14–16)	6.25(16–18)
5r	6.25(14–18)	6.25(10–14)	6.25(12–14)	6.25(12–14)	6.25(14–18)
5s	25(<10)	12.5(10–14)	12.5(11)	12.5(10–11)	12.5(12)
5t	6.25(16–20)	6.25(16–20)	6.25(14–16)	6.25(14–18)	6.25(16–20)
5u	50(<10)	50(<10)	50(<10)	50(<10)	50(<10)
5v	6.25(10–14)	12.5(12–16)	12.5(12–16)	12.5(12–16)	12.5(10–15)
5w	12.5(10–14)	12.5(11)	12.5(10–12)	12.5(11)	12.5(12)
5x	6.25(18–20)	6.25(20–22)	6.25(14–16)	6.25(16–20)	6.25(16–20)
5y	12.5(10–14)	6.25(14–16)	12.5(10–12)	12.5(11)	12.5(12)
Ciprofloxacin (Standard)	6.25(22–30)	6.25(30–40)	6.25(16–20)	6.25(23–27)	6.25(25)

Note: MIC values were evaluated at concentration ranging between 6.25 and 100 μg/mL. The figures in the table show the MIC values in μg/mL and the corresponding zone of inhibition in mm inside the bracket. MIC (μg/mL) = minimum inhibitory concentration, i.e., lowest concentration to completely inhibit bacterial growth.

layer was concentrated under reduced pressure to give a pale brown liquid. The crude product was purified by flash chromatography on a silica gel (230–400 mesh) using ethyl acetate (20–40%) in petroleum ether as eluant to afford **1** as a pale yellow liquid (34.76 g, 75%). ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 1.28 (t, 3H, J = 7.1 Hz), 1.88 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.14 (q, 2H, J = 7.1 Hz, CH_2), 4.65 (s, 1H), 6.84–6.86 (d, 2H, J = 8.6 Hz, ArH), 7.01–7.04 (d, 2H, J = 8.5 Hz, ArH); LCMS (ESI-MS) m/z = 236.18 (M + 1).

Table 3
Antifungal activity data of the title compounds **5a**–**y**.

Compd	MIC in μg/mL and zone of inhibition in mm				
	A.flavus (NCIM No. 524)	*A. fumigatus* (NCIM No. 902)	*P.marneffei* (recultured)	*T.mentagrophytes* (recultured)	*Candida albicans*
5a	6.25(14–18)	6.25(18–20)	6.25(18–20)	6.25(15–18)	6.25(13–15)
5b	6.25(10–12)	6.25(14–16)	6.25(10–14)	6.25(10–14)	6.25(10–12)
5c	6.25(12–14)	6.25(16–20)	6.25(18–22)	6.25(10–12)	6.25(10–14)
5d	12.5(11)	12.5(10–12)	25(<10)	12.5(10–12)	12.5(11)
5e	12.5(11)	12.5(10–12)	12.5(10–14)	12.5(12)	12.5(10–11)
5f	12.5(10–12)	12.5(10–14)	12.5(12–14)	12.5(10–14)	12.5(10–12)
5g	50(<10)	50(<10)	50(<10)	50(<10)	50(<10)
5h	6.25(16–20)	6.25(18–22)	6.25(16–20)	6.25(14–16)	6.25(14–16)
5i	6.25(16–20)	6.25(14–16)	6.25(18–22)	6.25(12–14)	6.25(12–14)
5j	6.25(14–18)	6.25(16–20)	6.25(16–20)	6.25(14–18)	6.25(10–14)
5k	50(<10)	50(<10)	50(<10)	50(<10)	50(<10)
5l	6.25(10–14)	6.25(12–14)	6.25(12–16)	6.25(10–12)	6.25(10–14)
5m	12.5(10–11)	6.25(14–16)	6.25(12–14)	6.25(10–12)	6.25(12–14)
5n	6.25(14–18)	6.25(16–20)	6.25(18–20)	6.25(16–20)	6.25(14–16)
5o	12.5(12–14)	12.5(10–14)	25(<10)	12.5(12–14)	12.5(12–14)
5p	6.25(14–16)	6.25(16–20)	6.25(14–18)	6.25(14–18)	6.25(10–14)
5q	6.25(16–20)	6.25(14–18)	6.25(16–20)	6.25(14–16)	6.25(12–14)
5r	6.25(14–18)	6.25(16–20)	6.25(14–18)	6.25(12–14)	6.25(14–18)
5s	12.5(12)	25(<10)	12.5(10–12)	25(<10)	12.5(11)
5t	6.25(16–20)	6.25(18–22)	6.25(12–14)	6.25(12–14)	6.25(14–17)
5u	50(<10)	50(<10)	50(<10)	50(<10)	50(<10)
5v	6.25(14–18)	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(12–15)
5w	12.5(11)	50(<10)	50(<10)	50(<10)	50(<10)
5x	6.25(16–20)	6.25(18–22)	6.25(14–18)	6.25(16–20)	6.25(14–16)
5y	12.5(11–12)	25(<10)	12.5(10–14)	25(<10)	12.5(11–12)
Ciclopirox olamine (Standard)	3.125(25–30)	6.25(25–30)	6.25(20–27)	3.125(27–33)	6.25(20)

Note: MIC values were evaluated at concentration ranging between 6.25 and 100 μg/mL. The figures in the table show the MIC values in μg/mL and the corresponding zone of inhibition in mm inside the bracket. MIC (μg/mL) = minimum inhibitory concentration, i.e., lowest concentration to completely inhibit bacterial growth.

4.3. Procedure for the preparation of 6-methoxy-2-methylquinolin-4-ol (**2**)

A solution of ethyl-3-[(4-methoxyphenyl) imino] butanoate (**1**) (34 g) in 50 mL Dowtherm was heated to 270 °C for 20 min. The reaction mass was cooled to 25 °C, diluted with ethyl acetate and the solid was filtered to afford **2** (21.34 g, 78%) as an off white solid (Yield-78%). m.p = 298–299 °C; IR (KBr, cm^{-1}) ν_{max}: 3528 (O–H), 2878 (C–H), 1498 (C–H), 1210 (C–O); ^{1}H NMR (DMSO-300 MHz) δ ppm = 2.32 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 5.86 (s, 1H, ArH), 6.96–6.99 (m, 1H, ArH), 7.43–7.46 (m, 2H, ArH), 11.45 (brs, 1H, OH); LC/MS(ESI-MS) m/z = 190.08 (M + 1). Anal. Calcd for $C_{11}H_{11}NO_2$; C, 69.83; H, 5.86; N, 16.91; Found; C, 69.97; H, 5.92; N, 17.01.

4.4. Procedure for the preparation of 4-chloro-6-methoxy-2-methylquinoline (**3**)

The intermediate 6-methoxy-2-methylquinolin-4-ol (**2**) (20 g, 0.105 mol) in phosphorous oxycholoride (60 mL) was heated to 105 °C for 2h. The excess of phosphorous oxychloride was removed under reduced pressure. The residue was quenched into crushed ice. The reaction mixture was neutralized using saturated solution of sodium bicarbonate. The solid obtained was filtered and vacuum dried to afford **3** as a off white solid (21.16 g, 92%). m.p = 99–100 °C; IR (KBr, cm^{-1}) ν_{max}: 2878 (C–H), 1210 (C–O), 770 (C–Cl); ^{1}H NMR (DMSO-d_6-300 MHz) δ ppm = 2.61 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 7.38 (d, 1H, J = 2.7 Hz, ArH), 7.46 (dd, 1H, J = 9 Hz, ArH), 7.65 (s, 1H, ArH) 7.91 (d, 1H, J = 9.0 Hz, ArH), LC/MS (ESI-MS) m/z = 208.05 (M + 1). Anal. Calcd for $C_{11}H_{10}ClNO$; C, 63.62; H, 4.85; N, 17.07; Found; C, 63.56; H, 4.97; N, 17.01.

4.5. Procedure for the preparation of 4-azido-6-methoxy-2-methylquinoline (**4**)

To a solution of 4-chloro-6-methoxy-2-methylquinoline (**3**) (19 g, 0.091 mol) in EtOH/water mixture (20 vol), sodium azide (29.57 g, 0.455 mol) was added and the reaction mass was heated to 100 °C in an autoclave for 12 h (Caution-Pressurized reaction condition). The reaction mass was cooled to 25 °C. The reaction mass quenched with ice water. The solid obtained was filtered, washed with water and vacuum dried to afford **4** (18.62 g, 95%) as an off white solid. m.p = 108–110 °C; IR(KBr, cm^{-1}) ν_{max}: 2878 (C–H), 1498 (C–H), 1210 (C–O), 1080 (C–N); ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 2.71 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 6.99 (s, 1H, ArH), 7.21 (d, 1H, J = 3 Hz, ArH), 7.36 (dd, 1H, J = 9.3 Hz, ArH), 7.89 (d, 1H, J = 9.3 Hz, ArH); LC/MS(ESI-MS) m/z = 215.09(M + 1). Anal. Calcd for $C_{11}H_{10}N_4O$; C, 61.67; H, 4.71; N, 26.15; Found; C, 61.59; H, 4.75; N, 26.29.

4.6. General procedure for the preparation of N-{[1-(6-methoxy-2-ethylquinolin-4-yl)-1H-1,2,3-triazol-4-yl]methylamine derivatives (**5a**–**y**)

A mixture of 4 mL of water, 4 mL of THF, triethylamine (0.26 mL, 1.85 mmol), primary/secondary amines (1.11 mmol), and propargyl bromide (0.13 g, 1.1 mmol) was stirred vigorously for 1 h at 25 °C. Then, 4-azido-6-methoxy-2-methylquinoline (**4**) (0.2 g, 0.93 mmol) followed by CuI (10 mol%) was added slowly. The reaction mass was heated at 70 °C for 2 h. The reaction completion was monitored by TLC. Reaction was complete. The reaction mass was concentrated under reduced pressure, diluted with ethyl acetate, washed with water, brine solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified on a Biotage parallel column purifier using ethyl acetate: petroleum ether (4:1) as eluant to methanol: methylene chloride (2–6%). The spectral data of compounds **5a**–**y** are given below:

4.6.1. N-{[1-(6-Methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl] methyl} cyclopropanamine (**5a**)

Appearance – white solid; IR (KBr, cm^{-1}) ν_{max}: 3410 (N–H), 2925 (C–H), 1498 (C–H), 1210 (C–O), 1140 (C–N); ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 0.98 (m, 2H, CH_2), 1.01 (m, 2H, CH_2), 1.6 (m, 1H, CH), 2.77 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.69 (d, 2H, J = 5.7 Hz, CH_3), 6.71 (b, 1H, NH) 7.15 (d, 1H, J = 2.7 Hz, ArH), 7.34 (s, 1H, ArH), 7.43 (dd, 1H, J = 9.3 Hz, ArH), 8.01 (s, 1H, ArH), 8.04 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 9.20, 23.48, 28.60, 41.9, 56.60, 107.17, 107.18, 112.10,117.12, 121.30, 129.35, 134.95, 136.40, 141.10, 156.12, 162.13; LC/MS (ESI-MS) m/z = 310.16(M + 1). Anal. Calcd for $C_{17}H_{19}N_5O$; C, 66.00; H, 6.19; N, 22.64; Found; C, 66.09; H, 6.12; N, 22.73.

4.6.2. N-((1-(6-methoxy-2-methylquinolin-4-yl)-1H-imidazol-4-yl) methyl)cyclopentanamine (**5b**)

Appearance – white solid; IR (KBr, cm^{-1}) ν_{max}: 3410 (N–H), 2925 (–C–H), 1498 (C–H), 1210 (C–O), 1140 (C–N); ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 1.37–1.42 (m, 4H, CH_2), 1.78–1.82 (m, 4H, CH_2), 2.60 (m, 1H, CH), 2.78 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.12 (s, 2H, CH_2), 7.21(d, 1H, J = 2.7 Hz, ArH), 7.33 (s, 1H, ArH), 7.43 (dd, 1H, J = 9.3 Hz, ArH), 7.98 (s, 1H, ArH), 8.02 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 23.48, 23.50, 33.94, 43.09, 56.60, 61.73, 107.18, 112.13, 117.02, 118.33, 121.03, 129.75, 134.27, 141.10, 143.05, 156.12, 162.73; LC/MS (ESI-MS) m/z = 338.19 (M + 1). Anal. Calcd for $C_{19}H_{23}N_5O$; C, 67.63; H, 6.87; N, 20.76; Found; C, 67.58; H, 6.95; N, 20.62.

4.6.3. 1-[1-(6-Methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl]-N,N-dimethyl methanamine (**5c**)

Appearance – off white solid; IR (KBr, cm^{-1}) ν_{max}: 2925 (C–H), 1498 (C–H), 1210 (C–O), 1140 (C–N); ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 2.39 (s, 6H, NCH_3), 2.79 (s, 1H, CH_3), 3.86 (s, 3H, OCH_3), 3.95 (d, 2H, J = 5.7 Hz, CH_2), 7.22 (d, 1H, J = 2.7 Hz, ArH), 7.37 (s, 1H, ArH), 7.43 (dd, 1H, J = 9.3 Hz, ArH), 7.97 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 23.48, 44.63, 52.32, 56.60, 107.18, 112.10, 117.02, 118.34, 121.30, 129.75, 134.27, 141.07, 141.10, 156.12, 162.73; LC/MS (ESI-MS) m/z = 298.16 (M + 1). Anal. Calcd for $C_{16}H_{19}N_5O$; C, 64.63; H, 6.44; N, 23.55; Found; C, 64.71; H, 6.49; N, 23.43.

4.6.4. N-Ethyl-N-((1-(6-methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methyl) ethanamine (**5d**)

Appearance – pale yellow solid; IR (KBr, cm^{-1}) ν_{max}: 2925 (C–H), 1498 (C–H), 1210 (C–O), 1140 (C–N); ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 1.11 (t, 3H, J = 7.2 Hz, CH_3), 2.45 (q, 2H, J = 7.2 Hz, CH_2), 2.79 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 3.95 (s, 2H, CH_2), 7.22 (d, 1H, J = 2.7 Hz, ArH), 7.37 (s, 1H, ArH), 7.43 (dd, 1H, J = 9.3 Hz, ArH), 7.97 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 11.49, 23.48, 48.64, 51.90, 56.60, 107.18, 112.10, 117.02, 118.34, 121.30, 129.75, 134.27, 141.07, 141.10, 156.12, 162.73; LC/MS (ESI-MS) m/z = 326.19 (M + 1). Anal. Calcd for $C_{18}H_{23}N_5O$; C, 66.44; H, 7.12; N, 21.52; Found; C, 66.56; H, 7.05; N, 21.48.

4.6.5. 6-Methoxy-2-methyl-4-(4-((pyrrolidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)quinoline (**5e**)

Appearance – white solid; IR(KBr, cm^{-1}) ν_{max}: 2925 (C–H), 1498 (C–H), 1210 (C–O), 1140 (C–N); ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 1.27–1.30 (m, 2H, CH_2), 1.49–1.51 (m, 2H, CH_2), 2.58 (m, 4H, NCH_2), 2.80 (s, 3H, CH_3), 3.83 (s, 2H, CH_2), 3.86 (s, 1H, OCH_3), 7.20 (d, 1H, J = 2.7 Hz, ArH), 7.38 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3 Hz, ArH), 7.99 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3 Hz, ArH); LC/MS (ESI-MS) m/z = 324.18 (M + 1).

*4.6.6. 6-Methoxy-2-methyl-4-(4-((piperidin-1-yl)methyl)-1H-1,2,3-triazol-1-yl) quinoline (**5f**)*

Appearance – off white solid; IR(KBr,cm^{-1}) ν_{max}: 2925 (C–H), 1498 (C–H), 1210 (C–O), 1140 (C–N); ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 1.27–1.30 (m, 2H, CH_2), 1.4–1.52 (m, 4H, CH_2), 3.1 (m, 4H, NCH_2), 2.80 (s, 3H, CH_3), 3.83 (s, 2H, CH_2), 3.86 (s, 1H, OCH_3), 7.20 (d, 1H, J = 2.7 Hz, ArH), 7.38 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3 Hz, ArH), 7.99 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm = 22.76, 23.48, 26.18, 49.06, 55.98, 56.61, 107.18, 112.10, 117.02, 118.34, 121.30, 129.75, 134.27, 141.07, 141.10, 156.12, 162.73; LC/MS (ESI-MS) m/z = 338.19 (M + 1).

*4.6.7. 6-Methoxy-2-methyl-4-{4-[(4-methylpiperazin-1-yl) methyl]-1H-1,2,3-triazol-1-yl}quinoline (**5g**)*

Appearance – pale brown solid; IR (KBr, cm^{-1}) ν_{max}: 3090 (C–H), 1450 (C=C), 1498 (C–H), 1210 (C–O), 1140 (C–N); ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 2.33 (s, 3H, CH_3), 2.53 (m, 4H, NCH_2), 2.58 (m, 4H, NCH_2), 2.68 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 3.88 (s, 3H, CH_2), 7.10–7.18 (m, 5H, ArH) 7.21 (d, 1H, J = 2.7 Hz, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3 Hz, ArH), 8.03 (s, 1H, ArH), 8.05 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 23.48, 34.26, 40.04, 49.06, 56.60, 57.20, 107.18, 112.10, 117.02, 118.34, 121.30, 126.74, 127.29,128.21, 129.75, 134.27, 141.10, 142.25, 144.77, 156.12, 162.73; LC/MS (ESI-MS) m/z = 414.22 (M + 1).

*4.6.8. 6-Methoxy-2-methyl-4-(4-((4-methylpiperazin-1-yl) methyl)-1H-1,2,3-triazol-1-yl)quinoline (**5h**)*

Appearance – white solid; ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 2.33 (s, 3H, CH_3), 2.53–2.56 (m, 4H, NCH_2), 2.58–2.60 (m, 4H, NCH_2), 2.79 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 3.88 (s, 2H, CH_2), 7.20 (d, 1H, J = 2.7 Hz, ArH), 7.38 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3 Hz, ArH), 7.99 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 23.48, 42.90, 48.98, 54.94, 55.04, 56.60, 107.18, 112.10, 117.02, 118.34, 121.30, 129.75, 134.27, 141.07, 141.10, 156.12, 162.73; LC/MS (ESI-MS) m/z = 353.20 (M + 1). Anal. Calcd for $C_{19}H_{24}N_6O$; C, 64.75; H, 6.86; N, 23.85; Found; C, 64.68; H, 6.89; N, 23.98.

*4.6.9. 4-(4-((4-Ethylpiperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-6-methoxy-2-methyl quinoline (**5i**)*

Appearance – off white solid; ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 1.11 (t, 3H, J = 7.2 Hz, CH_3), 2.45 (q, 2H, J = 7.2 Hz, CH_2), 2.55–2.58 (m, 4H, NCH_2), 2.69–2.71 (m, 4H, NCH_2), 2.79 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 3.88 (s, 2H, CH_2) 6.86–6.97 (m, 5H, ArH), 7.21 (d, 1H, J = 2.7 Hz, ArH), 7.38 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3 Hz, ArH), 7.96 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 9.69, 23.48, 47.44, 48.98, 53.55, 55.44, 56.60, 107.18, 112.10, 117.02, 118.34, 121.30, 129.75, 134.27, 141.07, 141.10, 156.12, 162.73; LC/MS (ESI-MS) m/z = 367.22 (M + 1). Anal. Calcd for $C_{20}H_{26}N_6O$; C, 65.55; H, 7.15; N, 22.93; Found; C, 65.67; H, 7.20; N, 22.86.

*4.6.10. 1-(4-((1-(6-Methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methyl) piperazin-1-yl)ethanone (**5j**)*

Appearance – viscous liquid; IR (KBr, cm^{-1}) ν_{max}: 2925 (C–H), 1645 (C=O), 1498 (C–H), 1210 (C–O), 1140 (C–N); ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 2.20 (s, 3H, CH_3), 2.55–2.58 (m, 4H, NCH_2), 2.69–2.71 (m, 4H, NCH_2), 2.79 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 3.88 (s, 2H, CH_2) 6.86–6.97 (m, 5H, ArH), 7.21 (d, 1H, J = 2.7 Hz, ArH), 7.38 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3 Hz, ArH), 7.96 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 21.09, 23.48, 44.67, 46.61, 48.98, 56.01, 56.60, 107.18, 112.10, 117.02, 118.34, 121.30, 129.75, 134.27, 141.07, 141.10, 156.12, 162.73, 169.73; LC/MS (ESI-MS) m/z = 381.2 (M + 1).

*4.6.11. 4-(4-((4-Cyclohexylpiperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-6-methoxy-2-methylquinoline (**5k**)*

Appearance – white solid; ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 1.27–1.37 (m, 6H, CH_2), 1.67 (m, 2H, CH_2), 1.83–2.03 (m, 2H, CH_2), 2.55–2.58 (m, 1H, NCH_2), 2.69–2.71 (m, 4H, NCH_2), 2.69 (m, 4H, NCH_2), 2.79 (s, 1H, CH_3), 3.86 (s, 3H, OCH_3), 3.95 (s, 2H, CH_2), 7.22 (d, 1H, J = 2.7 Hz, ArH), 7.37 (s, 1H, ArH), 7.43 (dd, 1H, J = 9.3 Hz, ArH), 7.97 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 23.48, 25.95, 26.40, 28.89, 48.98, 52.03, 56.06, 56.60, 63.90, 107.18, 112.10, 117.02, 118.34, 121.30, 129.75, 134.27, 141.07, 141.10, 156.12, 162.73 LC/MS (ESI-MS) m/z = 421.27 (M + 1).

*4.6.12. 4-(4-((4-(2-Fluorophenyl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-6-methoxy-2-methylquinoline (**5l**)*

Appearance – yellow solid; ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 2.55–2.58 (m, 1H, NCH_2), 2.69–2.71 (m, 4H, NCH_2), 2.79 (s, 1H, CH_3), 3.86 (s, 3H, OCH_3), 3.95 (s, 2H, CH_2), 7.0–7.16 (m, 4H, ArH), 7.22 (d, 1H, J = 2.7 Hz, ArH), 7.37 (s, 1H, ArH), 7.43 (dd, 1H, J = 9.3 Hz, ArH), 7.97 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 23.48, 48.98, 51.27, 56.60, 56.71, 107.18, 112.10, 114.18, 114.88, 117.02, 118.34, 121.30, 122.83, 125.05, 125.22, 126.24, 129.75, 134.27, 141.10, 141.77, 151.28, 156.12, 157.78, 162.73; LC/MS (ESI-MS) m/z = 433.21 (M + 1).

*4.6.13. 4-(4-((4-(4-Fluorophenyl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-6-methoxy-2-methylquinoline (**5m**)*

Appearance- brown solid; IR (KBr, cm^{-1}) ν_{max}: 3090 (C–H), 1450 (C=C), 1498 (C–H), 1210 (C–O), 1174 (C–F), 1140 (C–N); ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 2.55–2.58 (m, 1H, NCH_2), 2.69–2.71 (m, 4H, NCH_2), 2.79 (s, 1H, CH_3), 3.86 (s, 3H, OCH_3), 3.95 (s, 2H, CH_2), 6.80–6.95 (m, 4H, ArH), 7.22 (d, 1H, J = 2.7 Hz, ArH), 7.37 (s, 1H, ArH), 7.43 (dd, 1H, J = 9.3 Hz, ArH), 7.97 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 23.48, 48.98, 49.45, 56.60, 56.71, 107.18, 112.10, 114.27, 114.97, 117.02, 118.34, 121.30, 124.11, 124.29, 129.75, 134.27, 141.10, 141.77, 143.16, 143.23, 156.09, 156.12, 162.59, 162.73; LC/MS (ESI-MS) m/z = 433.21 (M + 1).

*4.6.14. 6-Methoxy-4-(4-((4-(4-methoxyphenyl) piperazin-1-yl) methyl)-1H-1,2,3-triazol-1-yl)-2-methylquinoline (**5n**)*

Appearance – off white solid; ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 2.55–2.58 (m, 4H, NCH_2), 2.69–2.71 (m, 4H, NCH_2), 2.79 (s, 1H, CH_3), 3.72 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.95 (s, 2H, CH_2), 6.77 (d, 2H, J = 8.5 Hz, ArH), 7.09 (d, 2H, J = 8.5 Hz, ArH), 7.22 (d, 1H, J = 2.7 Hz, ArH), 7.37 (s, 1H, ArH), 7.43 (dd, 1H, J = 9.3 Hz, ArH), 7.97 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 23.48, 48.98, 49.45, 55.20, 56.60, 56.71, 107.18, 112.10, 112.82, 117.02, 118.34, 121.30, 124.0, 129.75, 134.27, 139.97, 141.10, 141.77, 156.12, 157.24, 162.73; LC/MS (ESI-MS) m/z = 445.23 (M + 1). Anal. Calcd for $C_{25}H_{28}N_6O_2$; C, 67.55; H, 6.35; N, 18.91; Found; C, 67.61; H, 6.47; N, 18.85.

*4.6.15. 6-Methoxy-2-methyl-4-(4-((4-p-tolylpiperazin-1-yl) methyl)-1H-1,2,3-triazol-1-yl)quinoline (**5o**)*

Appearance – pale yellow solid; IR (KBr, cm^{-1}) ν_{max}: 3090 (C–H), 1450 (C=C), 1498 (C–H), 1210 (C–O), 1140 (C–N); ^{1}H NMR ($CDCl_3$-300 MHz), δ ppm = 2.25 (s, 3H, CH_3), 2.55–2.58 (m, 1H, NCH_2), 2.69–2.71 (m, 4H, NCH_2), 2.79 (s, 1H, CH_3), 3.86 (s, 3H, OCH_3), 3.95 (s, 2H, CH_2), 6.82 (d, 2H, J = 8.6 Hz), 7.05 (d, 2H, J = 8.6 Hz, ArH), 7.22 (d, 1H, J = 2.7 Hz, ArH), 7.37 (s, 1H, ArH), 7.43 (dd, 1H, J = 9.3 Hz, ArH), 7.97 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 20.60, 23.48, 48.98, 49.45, 56.60, 56.71, 107.18, 112.10, 112.84, 117.02, 118.34, 121.30, 128.52, 129.75, 134.27, 139.97, 141.10, 141.77, 144.14, 156.12, 162.73; LC/MS (ESI-MS) m/z = 429.23 (M + 1).

*4.6.16. 6-Methoxy-4-(4-((4-(4-methoxy-2-methylphenyl) piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-2-methylquinoline (**5p**)*

Appearance – yellow gummy solid; ^{1}H NMR ($CDCl_3$-300 MHz), δ ppm = 2.30 (s, 3H, CH_3), 2.55–2.58 (m, 1H, NCH_2), 2.69–2.71 (m, 4H, NCH_2), 2.79 (s, 1H, CH_3), 3.72 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.95 (s, 2H, CH_2), 6.75 (d, 1H, J = 9.0 Hz), 6.82 (d, 1H, J = 9.0 Hz), 7.10 (s, 1H, ArH), 7.22 (d, 1H, J = 2.7 Hz, ArH), 7.37 (s, 1H, ArH), 7.43 (dd, 1H, J = 9.3 Hz, ArH), 7.97 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 18.14, 23.48, 48.98, 49.86, 55.18, 56.60, 56.71, 107.18, 112.10, 113.73, 116.92, 118.34, 119.13, 121.30, 129.09, 129.75, 134.27, 141.10, 141.77, 142.50, 153.52, 156.12, 162.73; LC/MS (ESI-MS) m/z = 459.25 (M + 1).

*4.6.17. N1-((1-(6-Methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)-N1,N2,N2-trimethylethane-1,2-diamine (**5q**)*

Appearance – white solid; ^{1}H NMR ($CDCl_3$-300 MHz), δ ppm = 2.30 (s, 6H, NCH_3), 2.52 (s, 3H, NCH_3), 2.59 (t, 2H, J = 6.0 Hz, NCH_2), 2.70 (t, 2H, J = 5.3 Hz, NCH_2), 2.79 (s, 1H, CH_3), 3.86 (s, 3H, OCH_3), 3.95 (s, 2H, CH_2), 7.22 (d, 1H, J = 2.7 Hz, ArH), 7.37 (s, 1H, ArH), 7.43 (dd, 1H, J = 9.3 Hz, ArH), 7.97 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 23.48, 40.06, 45.60, 50.21, 52.12, 56.12, 56.60, 107.18, 112.10, 117.02, 118.34, 121.30, 129.09, 129.75, 134.27, 141.10, 141.16, 156.12, 162.73; LC/MS (ESI-MS) m/z = 355.22 (M + 1).

*4.6.18. N1-((1-(6-Methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)-N3,N3- dimethylpropane-1,3-diamine (**5r**)*

Appearance – off white solid; ^{1}H NMR ($CDCl_3$-300 MHz), δ ppm = 1.3 (m, 2H, CH_2), 2.20 (t, 2H, J = 5.3 Hz, NCH_2), 2.30 (s, 6H, NCH_3), 2.59 (m, 2H, NCH_2), 2.79 (s, 1H, CH_3), 3.86 (s, 3H, OCH_3), 3.95 (d, 2H, J = 5.7 Hz, CH_2), 7.22 (d, 1H, J = 2.7 Hz, ArH), 7.37 (s, 1H, ArH), 7.43 (dd, 1H, J = 9.3 Hz, ArH), 7.97 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 23.48, 27.71, 44.52, 45.40, 49.01, 56.60, 57.90, 107.18, 112.10, 117.02, 118.34, 121.30, 129.09, 129.75, 134.27, 141.10, 141.16, 156.12, 162.73; LC/MS (ESI-MS) m/z = 355.22 (M + 1).

*4.6.19. N-((1-(6-Methoxy-2-methylquinolin-4-yl)-1H-imidazol-4-yl)methyl)cyclohexanamine (**5s**)*

Appearance – white solid; IR (KBr, cm^{-1}) ν_{max}: 2925 (C–H), 1210 (C–O), 1140 (C–N); ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 1.64–2.03 (m, 10H, CH_2), 2.88 (s, 3H, CH_3), 3.25 (m, 1H, CH), 3.84 (s, 3H, OCH_3), 7.20 (d, 1H, J = 2.7 Hz, ArH), 7.36 (s, 1H, ArH), 7.48 (dd, 1H, J = 9.3 Hz, ArH), 7.98 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 23.48, 25.22, 25.54, 32.96, 43.09, 56.60, 60.53, 107.18, 112.10, 117.02, 118.34, 121.30, 129.09, 129.75, 134.27, 141.10, 141.16, 156.12, 162.73; LC/MS (ESI-MS) m/z = 352.21 (M + 1).

*4.6.20. 4-(4-((4-Ethylpiperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-6-methoxy-2-methylquinoline (**5t**)*

Appearance – pale yellow solid; IR (KBr, cm^{-1}) ν_{max}: 2925 (C–H), 1210 (C–O), 1140 (C–N); ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 2.64 (m, 4H, CH_2), 2.79 (s, 3H, CH_3), 3.75 (m, 4H, CH_2), 3.86 (s, 3H, OCH_3), 7.20 (d, 1H, J = 2.7 Hz, ArH), 7.36 (s, 1H, ArH), 7.48 (dd, 1H, J = 9.3 Hz, ArH), 7.98 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 23.48, 48.87, 56.60, 61.64, 66.61, 107.18, 112.10, 117.02, 118.34, 121.30, 129.09, 129.75, 134.27, 141.10, 141.16, 156.12, 162.73; LC/MS (ESI-MS) m/z = 340.17 (M + 1).

*4.6.21. N-((1-(6-Methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)-N-methylcyclohexanamine (**5u**)*

Appearance – off white colour solid; ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 1.27–1.37 (m, 6H, CH_2), 1.67 (m, 2H, CH_2), 1.83–2.03 (m, 2H, CH_2), 2.39 (s, 3H, NCH_3), 2.52 (m, 1H, CH), 2.79 (s, 1H, CH_3), 3.86 (s, 3H, OCH_3), 3.95 (s, 2H, CH_2), 7.22 (d, 1H, J = 2.7 Hz, ArH), 7.37 (s, 1H, ArH), 7.43 (dd, 1H, J = 9.3 Hz, ArH), 7.97 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3 Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ ppm = 23.48, 25.95, 26.40, 30.28, 42.72, 47.80, 56.60, 66.99, 107.18, 112.10, 117.02, 118.34, 121.30, 129.09, 129.75, 134.27, 141.10, 141.16, 156.12, 162.73; LC/MS (ESI-MS) m/z = 366.2 (M + 1).

*4.6.22. 6-Methoxy-2-methyl-4-(4-((4-phenylpiperazin-1-yl) methyl)-1H-1,2,3-triazol-1-yl)quinoline (**5v**)*

Appearance – off white solid; ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 2.74 (s, 3H, CH_3), 2.82 (m, 4H, NCH_2), 3.86 (s, 3H, CH_3), 3.94 (s, 2H, CH_2), 6.86–6.97 (m, 5H, ArH), 7.21 (d, 1H, J = 2.7 Hz, ArH), 7.38 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3 Hz, ArH), 8.01 (s, 1H, ArH), 8.05 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 23.48, 48.98, 49.45, 56.60, 56.71, 107.18, 112.10, 115.91, 117.02, 118.34, 120.30, 121.30, 129.10, 129.75, 134.27, 141.10, 141.77, 149.54, 156.12, 162.73; LC/MS (ESI-MS) m/z = 415.22 (M + 1).

*4.6.23. 6-Methoxy-2-methyl-4-(4-((4-morpholinopiperidin-1-yl) methyl)-1H-1,2,3-triazol-1-yl)quinoline (**5w**)*

Appearance – yellow gummy solid; ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 1.24 (m, 4H, CH_2), 1.67–1.87 (m, 4H, NCH_2), 2.65–2.68 (m, 5H), 3.60 (br, 4H, OCH_2), 2.80 (s, 3H, CH_3), 3.83 (s, 2H, CH_2), 3.86 (s, 1H, OCH_3), 7.20 (d, 1H, J = 2.7 Hz, ArH), 7.38 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3 Hz, ArH), 7.99 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm = 23.48, 29.13, 48.79, 51.91, 55.64, 56.60, 60.44, 67.04, 107.18, 112.10, 117.02, 118.34, 121.30, 129.75, 134.27, 141.07, 141.10, 156.12, 162.73; LC/MS (ESI-MS) m/z = 423.25 (M + 1).

*4.6.24. 4-(4-((4-Isopropylpiperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-6-methoxy-2-methylquinoline (**5x**)*

Appearance – tan viscous liquid; ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 1.15 (d, 6H, J = 6.6 Hz), 2.53–2.56 (m, 4H, NCH_2), 2.58–2.60 (m, 4H, NCH_2), 2.79 (s, 3H, CH_3), 2.96 (m, 1H, CH), 3.86 (s, 3H, OCH_3), 3.88 (s, 2H, CH_2), 7.20 (d, 1H, J = 2.7 Hz, ArH), 7.38(s, 1H, ArH), 7.44 (dd, 1H, J = 9.3 Hz, ArH), 7.99 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 18.30, 23.48, 48.98, 51.01, 54.70, 56.29, 56.60, 107.18, 112.10, 117.02, 118.34, 121.30, 129.75, 134.27, 141.07, 141.10, 156.12, 162.73; LC/MS (ESI-MS) m/z = 382.23 (M + 1).

*4.6.25. N-((1-(6-Methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)butan-2-amine (**5y**)*

Appearance – brown gummy solid; ^{1}H NMR ($CDCl_3$-300 MHz) δ ppm = 0.90 (t, J = 7.6 Hz, 3H), 1.16 (d, J = 6.8 Hz, 3H), 1.45–1.58 (m, 2H), 3.06 (m, 1H), 2.79 (s, 1H, CH_3), 3.86 (s, 3H, OCH_3), 3.95 (s, 2H, CH_2), 7.22 (d, 1H, J = 2.7 Hz, ArH), 7.37 (s, 1H, ArH), 7.43 (dd, 1H, J = 9.3 Hz, ArH), 7.97 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3 Hz, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 9.97, 20.47, 23.48, 31.10, 42.47, 56.60, 58.96, 107.18, 112.10, 117.02, 118.34, 121.30, 129.75, 134.27, 141.07, 141.10, 156.12, 162.73; LC/MS (ESI-MS) m/z = 326.19 (M + 1).

4.7. Antibacterial studies

The newly synthesized final compounds were evaluated for their antibacterial activity against *Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25923), *Pseudomonas aeruginosa* (ATCC-27853), *Klebsiella pneumoniae* (recultured) and *S. Pyogenes* bacterial strains by serial plate dilution method [30,31]. Serial dilutions of the drug in Muller-Hinton broth were taken in tubes and their pH was adjusted to 5.0 using phosphate buffer. A standardized suspension of the test bacterium was inoculated and incubated for 16–18 h at 37 °C. The minimum inhibitory concentration (MIC) was noted by seeing the lowest concentration of the drug at which there was no visible growth. A number of antimicrobial discs are placed on the agar for the sole purpose of producing zones of inhibition in the bacterial lawn. Twenty

milliliters of agar media was poured into each Petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37 °C for 1 h. Using an agar punch, wells were made on these seeded agar plates and minimum inhibitory concentrations of the test compounds in dimethylsulfoxide (DMSO) were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at 37 °C for 3–4 days. Antibacterial activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with ciprofloxacin as standard [32,33]. MIC (μg/mL) and zone of inhibition (mm) were determined for **5a**–**y** and the corresponding results are summarized in Table 2.

4.8. Antifungal studies

Newly prepared title compounds were screened for their antifungal activity against *Aspergilus flavus* (NCIM No. 524), *Aspergilus fumigatus* (NCIM No. 902), *Penicillium marneffei* (recultured), *Trichophyton mentagrophytes* (recultured) and *Candida albicans* in DMSO by serial plate dilution method [34,35]. Sabourands agar media was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 mL) and adjusting the pH to 5.7. Normal saline was used to make a suspension of spore of fungal strains for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species. Twenty milliliters of agar media was poured into each petri dish. Excess of suspension was decanted and plates were dried by placing in incubator at 37 °C for 1 h. Using a punch, wells were made on these seeded agar plates minimum inhibitory concentrations of the test compounds in DMSO were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at 37 °C for 3–4 days. Antifungal activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with Ciclopirox olamine as standard. MIC (μg/mL) and zone of inhibition (mm) were determined for **5a**–**y** and their corresponding results are given in Table 3.

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