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Original article

Click chemistry approach: Regioselective one-pot synthesis of some new 8-trifluoromethylquinoline based 1,2,3-triazoles as potent antimicrobial agents

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ABSTRACT

Three series of 8-trifluoromethylquinoline based 1,2,3-triazoles derivatives (**5a**–**c**, **6a**–**d** and **7a**–**c**) were synthesized by multi-step reactions by click chemistry approach. Synthesized compounds were characterized by spectral studies and X-ray analysis. The final compounds were screened for their *in-vitro* antimicrobial activity by well plate method (zone of inhibition). Compounds **5c**, **6b**, **8b**, **11** and **12** were found to be active against tested microbial strains. The results are summarized in Tables 5 and 6.

1. Introduction

In recent years, the mounting threat of bacterial resistance has heightened the urgency to discover and develop new anti-infective agents with novel mechanism of action and enhanced activity profile [1–3]. The fluorinated compounds have been very important in the pharmaceutical field because of their multiple pharmacological action. Incorporation of trifluoromethyl group instead of hydrogen atom can alter the biological activities [4,5]. Introduction of trifluoromethyl group provides better electronic effect at neighboring carbon centers, as well as having a substantial effect on the molecule's dipole moment, acidity and basicity of neighboring groups [6]. Fluorine is much more lipophilic than hydrogen, so incorporation of fluorine atoms in a molecule will make it more fat soluble and as a hydrogen bond acceptor [7].

Quinoline derivatives are well-known heterocycles, play an important role in developing new antimicrobial agents (Eg. Ciprofloxacin, Grepafloxacin). A large variety of quinoline derivatives are found in plant alkaloids, which are used in the treatment of Malaria, bacterial infection and tuberculosis [8–11]. Recent observations suggested that, substitution of trifluoromethyl group at C-8 position of the quinoline have a profound effect on biological activity [12,13]. Trifluoromethyl quinolines and its derivatives have wide range of applications in the field of pharmaceuticals as antimalarial [14], antibacterial, antifungal [12], antituberculosis [15], anticancer agents [16]. Mefloquine and Tafenoquine are some of the drugs which contain trifluoromethyl group and quinoline as a core moiety (Figs. 1 and 2).

Synthesis of 1,2,3-triazoles and their derivatives form an important class of heterocycles with various pharmacological activities. 1,2,3-Triazole derivatives have been reported as antibacterial, antifungal, antitubercular, anticancer, antiviral, antihypertensive, anticholinergic and anti-inflammatory agents [17–20]. Literature review revealed that, insertion of pharmacophore at position four of quinoline with heterocyclic derivatives enhances its antimicrobial [21] and antituberculosis activity [15]. The substitution of trifluoromethyl functional group at eighth position showed good pharmacological properties like antimicrobial,

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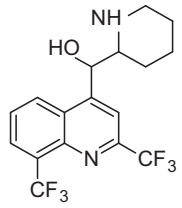


Fig. 1. Structure of Mefloquine.

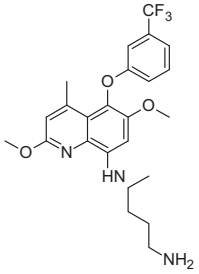


Fig. 2. Structure of Tafenoquine.

antifungal and antitumor activities [12,22]. In recent years, regioselective click chemistry has wide application in the synthetic organic chemistry and biomedicinal chemistry. Click chemistry has been explored as a new approach to synthesis regioselective 1,2,3-triazole derivatives for the new drugs development. Prompted by these observations and in continuation of our research on biologically active heterocycles [23–26], we hereby report the synthesis of some new 1,2,3-triazole derivatives containing 8-trifluoromethyquinoline nucleus by the click chemistry approach. The synthesized compounds were screened for their antimicrobial properties.

2. Results and discussion

2.1. Chemistry

Gould-Jacobs method was utilized to synthesize the intermediate (**3**). The selective O-alkylation of **3** was carried out by treating it with propargylbromide in acetone media [27–29] (Scheme 1). The targeted regioselective 1,4 substituted 1,2,3-triazole derivatives (**5a**–**c**, **6a**–**d** and **7a**–**c**) were synthesized by multicomponent one pot click chemistry approach, reacting 4-prop-2-ynyloxy-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (**4**) with various benzyl bromides, phenacyl bromides and alkyl bromides (Scheme 2). 6-Trifluoromethyl-furo[3,2-*c*]quinoline derivatives (**8a**,**b**) were synthesized by treating ethyl chloroacetate and 4-hydroxy-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (**3**) in dimethylformamide using potassium carbonate base followed by the hydrolysis of ester using LiOH (Scheme 3). The versatile Suzuki reaction was employed to synthesize 4-ethoxy-3-(1-methyl-1*H*-indol-5-yl)-8-trifluoromethyl-quinoline (**12**) in satisfactory good yields by reacting *N*-methylindole-5-boronic acid with **11** (Scheme 4). The crude products were purified by column chromatography. The reaction pathway has been summarized in Schemes 1–4. Newly synthesized compounds were characterized by IR, NMR, mass spectral and C, H, N elemental analyses.

The formation of 4-prop-2-ynyloxy-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (**4**) was conformed by the peaks at 3261 cm^{-1}, 2120 cm^{-1} in IR spectrum which is due to the (C≡C–H-str) stretching of propargyl chain. Bands at 1700 cm^{-1} and 1103 cm^{-1} are due to C=O stretch of carboxylic ester and phenolic ether respectively. The ^{1}H NMR spectrum of **4** showed triplet and a quartet at δ 1.35, δ 4.38 corresponding to carboxylic ethyl ester. The acetylene CH proton appeared as singlet at δ 3.66. The CH_2 proton appeared as a singlet at δ 5.08. The triplet at δ 7.82 is due to sixth proton of quinoline ring. Doublets appeared at δ 8.28 and δ 8.55 are due to quinoline fifth and seventh protons respectively. The quinoline third proton appeared as a singlet at δ 9.24.

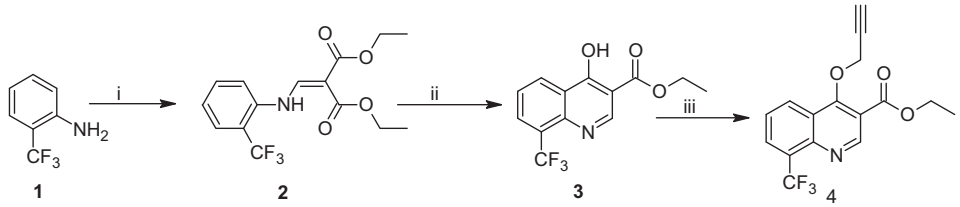
Formation of 1,2,3-triazol-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester derivatives (**5a**–**c**, **6a**–**d** and **7a**–**c**) were confirmed by the presence of absorption peak at 1724–1582 cm^{-1} in IR spectra which are due to (C=O) stretching of carboxylic esters. Absorption band at 1254–1131 cm^{-1} are due to N=N of the 1,2,3-triazoles. The ^{1}H NMR spectra of compounds **5a**–**c**, **6a**–**d** and **7a**–**c** showed triplet at δ 1.36–1.40 and a quartet at δ 4.40–4.49 are due to the carboxylic ethyl esters. CH_2 protons appeared as singlets at δ 31–5.54 and 4.42–6.19. A singlet at δ 8.19–8.27 are due to proton of 1,2,3-triazole moiety. All other aromatic protons appeared in δ 7.06 to 9.26 regions. The mass spectra of all the final derivatives showed comparable molecular ion peak with respect to molecular formula. Three dimensional structures of **5c**, **6c** and **8a** were evidenced by X-ray crystallographic study. Similarly the spectral values for all the compounds and C, H, N analyses are presented in the experimental part and the characterization data are provided in Table 1.

2.2. X-ray crystallographic study of compound *5c*, *6c* and *8a*

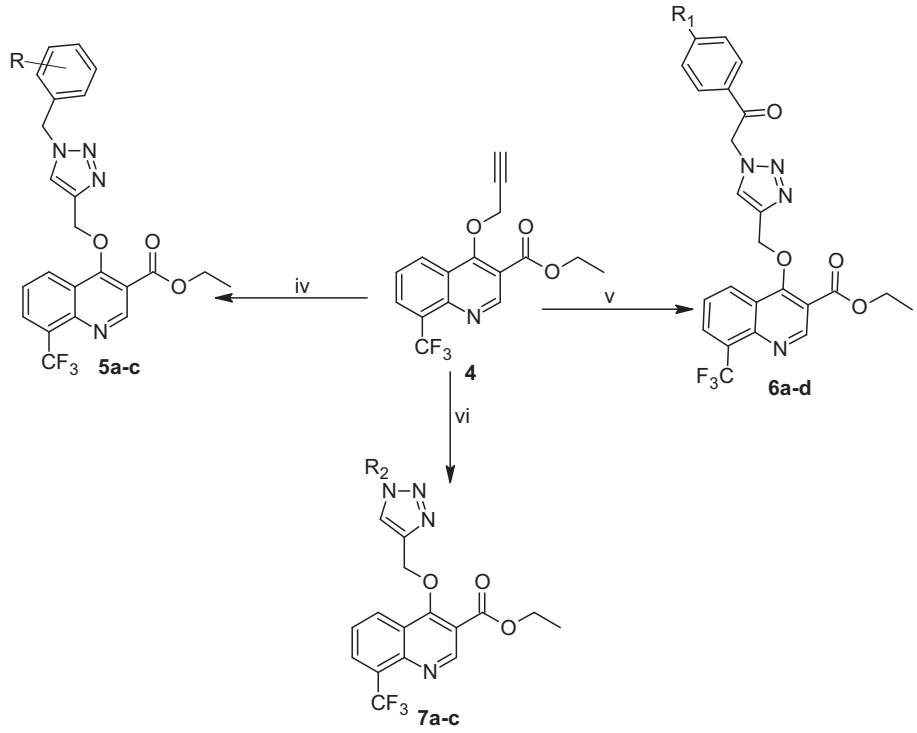
The X-ray crystallographic analysis of the compounds **5c**, **6c** and **8a** were carried out by fine-focus sealed tube graphite. The crystal structure solution was worked out by Bruker SMART APEXII DUO CCD diffractometer. All the atoms were located in different Fourier maps and refined isotropically, using a riding model and all the projections were generated using ORTEP. The details of the crystal data and refinement are shown in Tables 2–4. Also the single crystal image for compounds **5c**, **6c** and **8a** are given in Figs. 3–5 [30–32].

2.3. Antimicrobial studies

The newly synthesized compounds (**5a**–**c**, **6a**–**d**, **7a**–**c**, **8a**,**b**, **11** and **12**) were screened for their *in-vitro* antibacterial activity against *Escherichia coli*, *Bacillus subtilis* and *Pseudomonas aeruginosa*

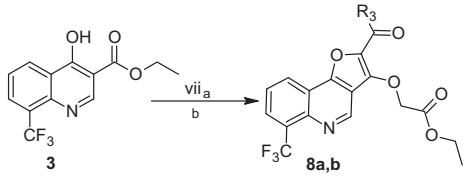


Scheme 1. Synthetic route for 4-prop-2-ynyloxy-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (**4**): (i) diethyl ethoxymethylene malonate, 110 °C, 6 h; (ii) Dowtherm, 250 °C, 5 h; (iii) propargylbromide, K_2CO_3, acetone, 50 °C, 12 h.



Where R = H, 4-NO_2, 2,4-Cl_2; R_1 = F, Cl, Br, OCH_3; R_2 = CH_2CH_3, $CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$.

Scheme 2. Synthetic route for 1,2,3-triazol-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester derivatives (**5a**–**c**, **6a**–**d** and **7a**–**c**): (iv, v and vi) alkyl bromide (aromatic, phenacyl and aliphatic), NaN_3, aqueous PEG 400 (5 mL, 1:1, v/v), sodium ascorbate, 10 mol % of Copper sulfate.

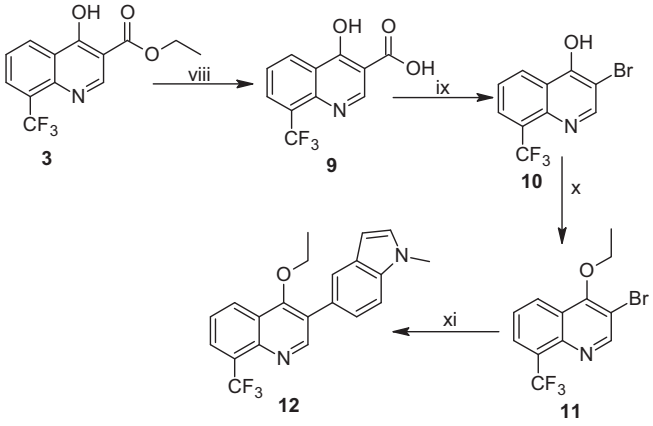


Where R = OCH_2CH_3, OH.

Scheme 3. Synthetic route for 3-ethoxycarbonylmethoxy-6-trifluoromethyl-furo[3,2-*c*]quinoline-2-carboxylic acid ethyl ester (**8a**) and 3-ethoxycarbonylmethoxy-6-trifluoromethyl-furo[3,2-*c*]quinoline-2-carboxylic acid (**8b**): (vii) a: ethyl chloroacetate, K_2CO_3, DMF, RT, 6 h; (vii) b: LiOH, MeOH, 2 h.

using Ciprofloxacin as standard by well plate method (zone of inhibition) [33,34]. The test compounds were dissolved in dimethylsulfoxide (DMSO) at concentrations of 0.5 mg/mL and 1.0 mg/mL.

The antibacterial screening revealed that, all the tested compounds showed good inhibition against various tested microbial strains compared to the standard drug. Among the synthesized compounds **5c**, **6b**, **8b**, **11** and **12** were found to be more active against tested bacterial strains as compared to the standard. The enhanced antibacterial activity of **5c** and **6b** were due to presence of chlorine in the 4-benzyl-[1,2,3]-triazole at the fourth position of 8-trifluoromethylquinoline-3-carboxylic ester. The compounds **8b**, **11** and **12** contains furan ring (**8b**), bromo (**11**) and *N*-methylindole (**12**) groups at third position of 8-trifluoromethylquinoline ring which accounts for the enhanced antibacterial activity. Compounds **5b**, **6c** and **8a** exhibited moderate antibacterial activity against all tested bacterial stains. In general, increase of electron donating strength on the 1,2,3-triazole (alkyl chain and methoxy substitution) decreases antibacterial activity. On the other hand, introducing halogen or electron withdrawing phenyl ring on 1,2,3-triazole with triflurometh quinoline increases the antibacterial activity. The activity exhibited by the synthesized compounds were due to both 1,2,3-triazole and quinoline core rings. Since the presence of active functional group on both the rings (quinoline and 1,2,3-triazole), no definite SAR could be established in this series of compounds. General structure of final derivatives are given in Fig 6.



Scheme 4. Synthetic route for 4-ethoxy-3-(1-methyl-1*H*-indol-5-yl)-8-trifluorometh yl-quinoline (**12**): (vii) LiOH, MeOH, 2 h; (ix) NBS, THF, RT, 12 h; (x) EtI, K_2CO_3, DMF, RT, 2 h; (xi) *N*-methylindole-5-boronic acid, toluene, EtOH, K_2CO_3, palladium acetate, 80 °C, 2 h.

Table 1
Characterization data of the compounds (**5a**–**c**, **6a**–**d**, **7a**–**c**, **8a**,**b**, **11** and **12**).

Compounds	$R/R_1/R_2/R_3$	Molecular formula (mol. wt.)	M.p. (°C)	Yield (%)
5a	H	$C_{23}H_{19}F_3N_4O_3$ (456.4)	93–95	76
5b	4-NO_2	$C_{23}H_{18}F_3N_5O_5$ (501.4)	152–154	89
5c	2,4-Cl_2	$C_{23}H_{17}Cl_2F_3N_4O_3$ (525.3)	150–152	79
6a	F	$C_{24}H_{18}F_4N_4O_4$ (502.4)	125–127	80
6b	Cl	$C_{24}H_{18}ClF_3N_4O_4$ (518.8)	120–122	72
6c	Br	$C_{24}H_{18}BrF_3N_4O_4$ (563.3)	105–107	72
6d	OCH_3	$C_{25}H_{21}F_3N_4O_5$ (514.4)	134–136	53
7a	CH_2CH_3	$C_{18}H_{17}F_3N_4O_3$ (394.3)	100–102	55
7b	$CH_2CH_2CH_3$	$C_{19}H_{19}F_3N_4O_3$ (408.3)	71–73	49
7c	$CH_2CH_2CH_2CH_3$	$C_{20}H_{21}F_3N_4O_3$ (422.4)	63–65	42
8a	OCH_2CH_3	$C_{19}H_{16}F_3NO_6$ (411.3)	125–127	92
8b	OH	$C_{17}H_{12}F_3NO_6$ (383.2)	133–135	90
11	–	$C_{12}H_9BrF_3NO$ (320.1)	106–108	85
12	–	$C_{21}H_{17}F_3N_2O$ (370.3)	60–62	67

The *in-vitro* antifungal activities of newly synthesized compounds (**5a**–**c**, **6a**–**d**, **7a**–**c**, **8a**,**b**, **11** and **12**) were determined by well plate method [35,36]. The results indicate that, among the tested compounds **8b** and **12** were active against all tested fungal strains. The enhanced activities of compounds are due to heterocyclic moieties (furan, *N*-methylindole) attached to the 8-trifluoromethylquinoline ring. All other compounds such as, 1,2,3-triazole with alkyl, aryl and phenacyl substitution with trifluoromethylquinoline showed lesser antifungal activity as compared with that of trifluoromethylquinoline core moiety with heterocyclic attachment at third position. Probably in this case, direct substitution of heterocyclic moieties at third position of trifluoromethylquinoline is more suited compared with 1,2,3-triazole with ether linkage to enhance the antifungal activity. Tables 5 and 6 depict the antimicrobial screening results of the final compounds.

Table 2
Crystal data and measurement details for compound **5c**.

Crystal data	
Empirical formula	$C_{23}H_{17}Cl_2F_3N_4O_3$
Formula weight	525.31
Crystal system	Monoclinic
Crystal dimension	0.32 mm × 0.31 mm × 0.17 mm
Space group	P21/c
a (Å)	10.0414 (6)
b (Å)	18.3997 (11)
c (Å)	15.5456 (7)
Volume (Å^3)	2246.0 (2)
Angle α, β, γ	90, 128.559, 90
Z	4
F_{000}	1072
μ (mm^{-1})	0.35
Temperature (*T*)	100 K
Radiation wavelength (Å)	0.71073
Radiation type	Mo Kα
Radiation source	Fine-focus sealed tube
Radiation monochromator	Graphite

Table 3
Crystal data and measurement details for compound **6c**.

Crystal data	
Empirical formula	$C_{24}H_{18}BrF_3N_4O_4$
Formula weight	563.33
Crystal system	Monoclinic
Crystal dimension	0.58 mm × 0.16 mm × 0.07 mm
Space group	P21/c
a (Å)	5.2809 (2)
b (Å)	24.5131 (10)
c (Å)	18.3517 (7)
Volume (Å^3)	2342.08 (16)
Angle α, β, γ	90, 99.643, 90
Z	4
F_{000}	1136
μ (mm^{-1})	1.82
Temperature (*T*)	200 K
Radiation wavelength (Å)	0.71073
Radiation type	Mo Kα
Radiation source	Fine-focus sealed tube
Radiation monochromator	Graphite

Table 4
Crystal data and measurement details for compound **8a**.

Crystal data	
Empirical formula	$C_{19}H_{16}F_3NO_6$
Formula weight	411.33
Crystal system	Triclinic
Crystal dimension	0.56 mm × 0.38 mm × 0.15 mm
Space group	$P\bar{1}$
a (Å)	8.9167 (3)
b (Å)	8.9223 (3)
c (Å)	13.4125 (5)
Volume (Å^3)	904.22 (5)
Angle α, β, γ	102.895, 97.098, 16.035
Z	2
F_{000}	424
μ (mm^{-1})	0.13
Temperature (*T*)	200 K
Radiation wavelength (Å)	0.71073
Radiation type	Mo Kα
Radiation source	Fine-focus sealed tube
Radiation monochromator	Graphite

3. Conclusion

Three series of 8-trifluoromethylquinoline based 1,2,3-triazoles derivatives (**5a**–**c**, **6a**–**d**, **7a**–**c**, **8a**,**b**, **11** and **12**) were synthesized by multi-step reactions. Compounds with an electron withdrawing group in 1,2,3-triazole ring are shown better yield compared with an electron donating group. The synthesized compounds were characterized by spectral studies, single crystal X-ray analysis and screened for their antimicrobial activities.

Among the screened samples **5c**, **6b**, **8b**, **11** and **12** showed moderate to good inhibition against all tested bacterial strains. The enhanced antibacterial activity of **5c** and **6b** are due to chlorine

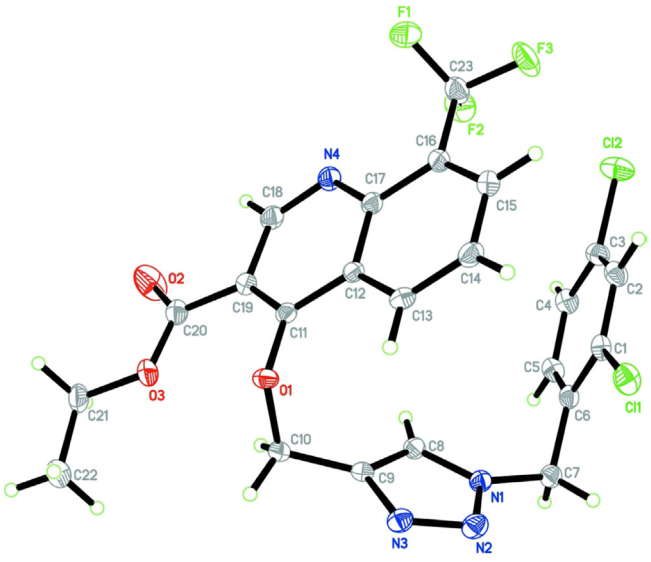


Fig. 3. ORTEP diagram showing the X-ray crystal structure of compound **5c**.

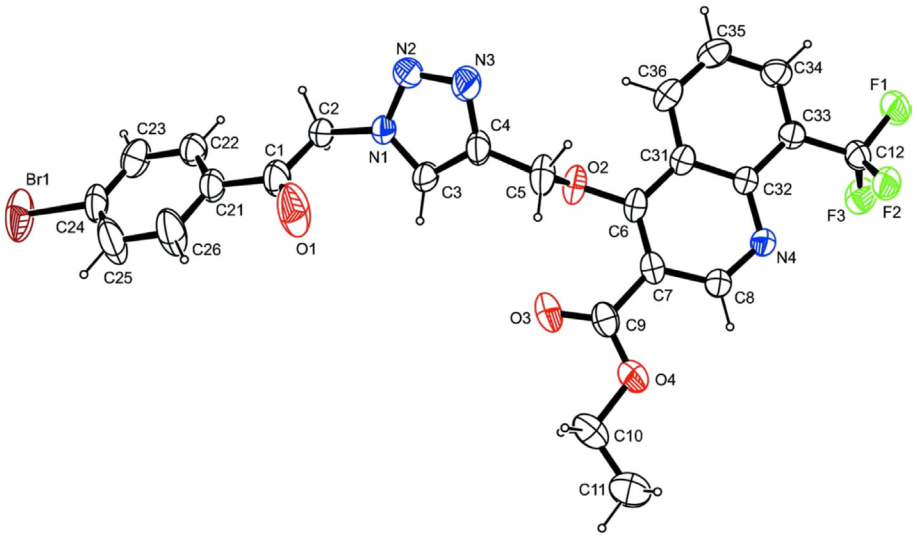


Fig. 4. ORTEP diagram showing the X-ray crystal structure of compound **6c**.

substitution on the phenyl ring of 1,2,3-triazole and ethyl 8-(trifluoromethyl)quinoline-3-carboxylate. Substitution of heterocyclic fused rings (**8b**) at 3rd position and derivatization at 3rd position of 8-trifluoromethylquinoline may be the reasons for the enhanced activity of compounds **11** and **12**. Compound **8b** and **11** showed significant inhibition against fungal strains as compared with standard drugs, this may be due to the substitution of oxygen derivative at 4th position of 8-trifluoromethylquinoline. On the other hand, heterocyclic (furan, *N*-methylindole) substituted 8-trifluoromethylquinoline derivatives were found to good antimicrobial agents compared with the standard drugs. In conclusion, electron donating character or increase of alkyl chain in the 1,2,3-triazole ring at 4th position of 8-trifluoromethylquinoline reduces antimicrobial activity. The presence of electron withdrawing group (NO_2) and halogen (chloro and dichloro) substitution on the phenyl ring of 1,2,3-triazole at 4th position of the 8-trifluoromethylquinoline derivatives increase the antimicrobial activity of the final derivatives.

In our study we have incorporated 1,2,3-triazole at fourth position of quinoline ring with ether linkage. Probably in this case 1,2,3-triazole is not so important for antimicrobial activity. Moreover, the presence of active pharmacophore on phenyl ring cause certain change of activity. As regards the relationships between the structure of the heterocyclic scaffold and detected antimicrobial properties, it showed that benzyl-[1,2,3]-triazole with electron withdrawing group at the 4th position of the 8-trifluoromethylquinoline and heterocyclic (furan, *N*-methylindole) at 3rd position of 8-trifluoromethyl ring are ideally suited for obtaining more efficient antimicrobial compounds.

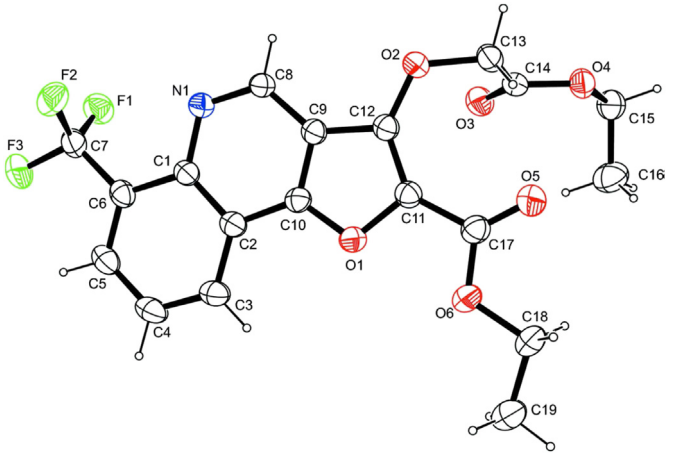
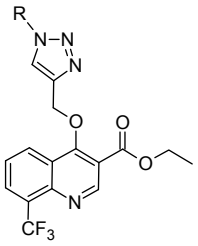


Fig. 5. ORTEP diagram showing the X-ray crystal structure of compound **8a**.

4. Experimental

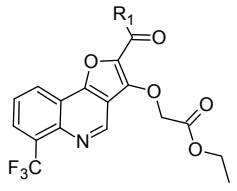
4.1. Analysis and instruments

All the chemicals were purchased from Sigma Aldrich, Merck and S. D. Fine chemicals-India. Commercial grade solvents were used and were distilled before use. Melting points were determined by open capillary method and were uncorrected. The IR spectra (neat) were recorded on a Nicolet Avatar 5700 FTIR spectrophotometer and Bruker, Varian (400 MHz) spectrometer was used to



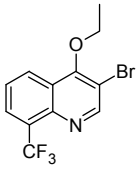
5a-c, 6a-d and **7a-c**

Where R = Benzyl, 4-nitrobenzyl, 2,4-dichlorobenzyl, 4-fluorophenacyl, 4-chlorophenacy, 4-bromophenacyl, 4-methoxyphenacyl, ethyl, propyl, butyl.



8a,b

Where $R_1 = OCH_2CH_3$, OH.



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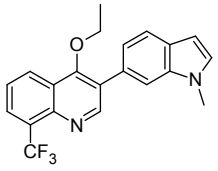

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Fig. 6. Structure of final derivatives.

Table 5
Antibacterial activity of the compounds (**5a**–**c**, **6a**–**d**, **7a**–**c**, **8a**,**b**, **11** and **12**).

Compound no.	Zone of inhibition in mm (mean ± S.D.) $n = 3$					
	Escherichia coli		*Bacillus subtilis*		*Pseudomonas aeruginosa*	
Concentration mg/mL						
Standard	0.5	1	0.5	1	0.5	1
Ciprofloxacin	22 ± 0.5	24 ± 0.9	22 ± 0.5	25 ± 0.7	24 ± 0.4	28 ± 0.5
Control	00	00	00	00	00	00
5a	02 ± 0.1	04 ± 0.2	03 ± 0.4	05 ± 0.6	04 ± 0.2	06 ± 0.3
5b	08 ± 0.9	10 ± 0.3	07 ± 0.3	10 ± 0.4	06 ± 0.7	09 ± 0.5
5c	13 ± 0.6	15 ± 0.7	11 ± 0.4	13 ± 0.1	13 ± 0.9	16 ± 0.8
6a	02 ± 0.1	04 ± 0.2	03 ± 0.2	06 ± 0.4	04 ± 0.4	05 ± 0.8
6b	14 ± 0.6	15 ± 0.4	08 ± 0.7	11 ± 0.3	10 ± 0.3	13 ± 0.6
6c	07 ± 0.6	10 ± 0.8	04 ± 0.3	06 ± 0.8	06 ± 0.3	08 ± 0.7
6d	04 ± 0.2	06 ± 0.3	03 ± 0.4	05 ± 0.7	05 ± 0.7	06 ± 0.3
7a	08 ± 0.4	12 ± 0.7	06 ± 0.7	08 ± 0.4	05 ± 0.3	08 ± 0.3
7b	05 ± 0.8	08 ± 0.6	07 ± 0.7	08 ± 0.6	04 ± 0.3	06 ± 0.2
7c	04 ± 0.4	07 ± 0.6	06 ± 0.4	09 ± 0.3	06 ± 0.5	07 ± 0.7
8a	08 ± 0.7	10 ± 0.8	04 ± 0.2	06 ± 0.3	08 ± 0.3	11 ± 0.9
8b	10 ± 0.8	12 ± 0.9	07 ± 0.5	10 ± 0.7	09 ± 0.4	12 ± 0.9
11	04 ± 0.8	16 ± 0.4	13 ± 0.5	15 ± 0.4	15 ± 0.6	17 ± 0.7
12	17 ± 0.4	18 ± 0.2	15 ± 0.8	16 ± 0.5	15 ± 0.9	17 ± 0.5

record ^{1}H NMR and ^{13}C NMR spectra (DMSO-d_6, $CDCl_3$) using TMS as internal standard. Chemical shift values were given in δ (ppm) scales. The mass spectra were recorded on LC-MS-Agilent 1100 series and elemental analysis was performed on a Flash EA 1112 series CHNS-O Analyzer. The completion of the reactions was monitored by silica gel coated aluminum sheets (silica gel 60 F254). The names of the structures were given as per chemdraw and chemsketch.

4.2. Syntheses of diethyl 2-[(2-trifluoromethyl-phenylamino)-methylene]-malonic acid diethyl ester (**2**)

2-(Trifluoromethyl)aniline (**1**) (10.0 g, 0.062 mol) and diethyl ethoxymethylene malonate (20.10 g, 0.093 mol) were heated to 110 °C for 6 h. The reaction mixture was cooled to room temperature, the solid thus formed was taken in pet ether and stirred for 20 min. Further it was filtered to get white crystalline solid.

Yield: (19.1 g, 92.8%). M.p: 84–86 °C (84–86). IR (neat ν_{max}/cm^{-1}): 3278 (N–H), 3176, 2986 (C–H-str), 1706 and 1654 (C=O). Anal. calcd. for $C_{15}H_{16}F_3NO_4$; Calcd: C, 54.38; H, 4.80; N, 4.23; found: C, 54.38; H, 4.80; N, 4.20 [27].

4.3. Syntheses of 4-hydroxy-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (**3**)

Diethyl 2-[(2-trifluoromethyl-phenylamino)-methylene]-malonic acid diethyl ester (**2**) (10.0 g, 0.030 mol) and Dowtherm (100 mL) were heated to 250 °C for 5 h. The reaction mixture was then cooled to 25 °C and stirred in 150 mL of hexane for 10 min. The solid product obtained was filtered and dried. The crude product was purified by column chromatography using pet ether and ethyl acetate (5:5) as the eluent to get white solids.

Yield: (8.1 g, 94.1%). M.p: 295–297 °C. IR (neat ν_{max}/cm^{-1}): 3352 (–OH), 3118, 2979 (C–H-str), 1708 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 1.23 (t. 3H, J = 8.0 Hz, $-CH_3$), 4.16 (q, 2H, $-CH_2$), 7.53 (t, 1H, ArH, J = 8.0 Hz), 8.07 (d, 1H, ArH, 7.8 Hz), 8.41 (d, 2H, ArH, J = 8.0 Hz), 11.62 (s, 1H, –OH, D_2O-exchangeble). ^{13}C NMR: δ ppm 14.70, 60.49, 111.39, 119.07, 122.60, 124.00, 124.61, 125.35,

Table 6
Antifungal activity of the compounds (**5a**–**c**, **6a**–**d**, **7a**–**c**, **8a**,**b**, **11** and **12**).

Compound no.	Zone of inhibition in mm (mean ± S.D.) $n = 3$					
	Aspergillus flavus		*Chrysosporium keratinophilum*		*Candida albicans*	
Concentration mg/mL						
Standard	0.5	1	0.5	1	0.5	1
Fluconazole	13 ± 0.2	10 ± 0.1	17 ± 0.2	15 ± 0.2	22 ± 0.2	20 ± 0.2
Control	00	00	00	00	00	00
5a	*	*	*	*	*	*
5b	02 ± 0.1	04 ± 0.2	03 ± 0.5	04 ± 0.6	04 ± 0.1	06 ± 0.3
5c	05 ± 0.3	07 ± 0.4	04 ± 0.5	06 ± 0.5	04 ± 0.6	06 ± 0.4
6a	–	–	–	–	–	–
6b	04 ± 0.2	06 ± 0.7	04 ± 0.4	05 ± 0.2	04 ± 0.3	06 ± 0.3
6c	*	*	*	*	*	*
6d	*	*	*	*	*	*
7a	*	*	*	*	*	*
7b	*	03 ± 0.3	02 ± 0.3	04 ± 0.2	02 ± 0.4	05 ± 0.3
7c	02 ± 0.3	04 ± 0.2	03 ± 0.5	05 ± 0.3	04 ± 0.4	05 ± 0.2
8a	06 ± 0.3	08 ± 0.5	06 ± 0.7	09 ± 0.6	05 ± 0.7	07 ± 0.3
8b	07 ± 0.5	10 ± 0.4	08 ± 0.6	10 ± 0.6	07 ± 0.8	10 ± 0.4
11	04 ± 0.7	06 ± 0.6	02 ± 0.3	04 ± 0.3	03 ± 0.3	05 ± 0.2
12	09 ± 0.7	12 ± 0.6	08 ± 0.5	11 ± 0.5	09 ± 0.5	11 ± 0.7

*Not detected inhibition.

130.99, 131.04, 131.55, 146.43, 164.50. MS: $m/z = 286$ (M + 1). Anal. calcd. for $C_{13}H_{10}F_3NO_3$; Calcd: C, 54.74; H, 3.53; N, 4.91; found: C, 54.75; H, 3.54; N, 4.95.

4.4. Syntheses of 4-prop-2-ynyloxy-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (**4**)

A mixture of 4-hydroxy-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (**3**) (5.0 g, 0.017 mol), potassium carbonate (2.66 g, 0.019 mol) and propargylbromide (2.02 g, 0.17 mol) in dry acetone (25 mL) was stirred at 50 °C for 12 h. The completion of reaction was monitored by TLC. After completion of reaction, reaction mixture was concentrated under vacuum and poured into ice-cold water. The solid product obtained was purified by column chromatography using pet ether and ethyl acetate as eluent to get white solids.

Yield: (3.89 g, 68.72%). M.p: 50–52 °C. IR (neat ν_{max}/cm^{-1}): 3261 (C≡C–H-str), 2990, 2948 (C–H-str), 2120 (C≡C), 1700 (C=O), 1103 (C–O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.35 (t, 3H, CH_3, $J = 7.10$ Hz), 3.66 (s, 1H, CH), 4.38 (q, 2H, CH_2, $J = 14.22$ Hz, $J = 7.10$ Hz), 5.08 (s, 2H, CH_2), 7.82 (t, 1H, ArH, $J = 7.88$ Hz), 8.28 (d, 1H, ArH, $J = 7.20$ Hz), 8.55 (d, 1H, ArH, $J = 7.80$), 9.24 (s, 1H, ArH). Anal. calcd. for $C_{16}H_{12}F_3NO_3$; Calcd: C, 59.45; H, 3.74; N, 4.33; found: C, 59.47; H, 3.73; N, 4.34.

4.5. General procedure for the syntheses of 1,2,3-triazol-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester derivatives (**5a–c**, **6a–d** and **7a–c**)

To a stirred solution of alkyl bromide (aromatic, phenacyl and aliphatic) (0.50 g, 0.0017 mol), sodium azide (0.117 g, 0.0018 mol) in aqueous PEG 400 (polyethylene glycol) (5 mL, 1:1, v/v), 4-prop-2-ynyloxy-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (0.58 g, 0.0018 mol), sodium ascorbate (0.356 g, 0.0018 mol), 10 mol % of Copper sulfate were added. The heterogeneous mixture was stirred vigorously overnight (12 h). Completion of the reaction was monitored by the TLC. The product was then extracted in ethyl acetate and concentrated. The crude product was purified by column chromatography using pet ether and ethyl acetate as the eluent.

4.5.1. 4-(1-Benzyl-1H-[1,2,3]triazol-4-ylmethoxy)-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (**5a**)

IR (neat ν_{max}/cm^{-1}): 3031, 2974 (C–H-str), 1724 (C=O), 1206 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.36 (t, 3H, CH_3, $J = 7.10$ Hz), 4.40 (q, 2H, CH_2, $J = 14.2$ Hz, $J = 7.12$ Hz), 5.44 (s, 2H, CH_2), 5.58 (s, 2H, CH_2), 7.16–7.18 (m, 2H, ArH), 7.31–7.32 (m, 3H, ArH), 7.70 (t, 1H, ArH, $J = 7.88$ Hz), 8.25 (s, 1H, ArH), 8.27 (s, 1H, ArH), 8.35 (d, 1H, ArH, $J = 8.24$ Hz), 9.24 (s, 1H, ArH). Anal. calcd. for $C_{23}H_{19}F_3N_4O_3$; Calcd: C, 60.52; H, 4.20; N, 12.28; found: C, 60.55; H, 4.21; N, 12.24.

4.5.2. 4-[1-(4-Nitro-benzyl)-1H-[1,2,3]triazol-4-ylmethoxy]-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (**5b**)

IR (neat ν_{max}/cm^{-1}): 3082, 2976 (C–H-str), 1705 (C=O), 1525 (NO_2), 1220 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.37 (t, 3H, CH_3, $J = 7.10$ Hz), 4.41 (q, 2H, CH_2, $J = 14.2$ Hz, $J = 7.10$ Hz), 5.46 (s, 2H, CH_2), 5.76 (s, 2H, CH_2), 7.38 (d, 2H, ArH, $J = 8.76$ Hz), 7.72 (t, 1H, ArH, $J = 7.88$ Hz), 8.17 (d, 2H, ArH, $J = 8.80$ Hz), 8.24 (d, 1H, ArH, $J = 7.48$ Hz), 8.33 (s, 1H, ArH), 8.36 (d, 1H, ArH, $J = 7.64$ Hz), 9.24 (s, 1H, ArH); ^{13}C NMR: 14.44, 52.35, 62.17, 69.08, 116.17, 124.30, 124.71, 126.25, 126.76, 129.02, 129.30, 130.86, 142.66, 143.72, 146.85, 147.69, 153.13, 162.78, 164.44. Anal. calcd. for $C_{23}H_{18}F_3N_5O_5$; Calcd: C, 55.09; H, 3.62; N, 13.97; found: C, 55.10; H, 3.60; N, 13.98.

4.5.3. 4-[1-(2,4-Dichloro-benzyl)-1H-[1,2,3]triazol-4-ylmethoxy]-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (**5c**)

IR (neat ν_{max}/cm^{-1}): 3078, 2977 (C–H-str), 1690 (C=O), 1218 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.37 (t, 3H, CH_3, $J = 7.10$ Hz), 4.41 (q, 2H, CH_2, $J = 14.2$ Hz, $J = 7.12$ Hz), 5.45 (s, 2H, CH_2), 5.66 (s, 2H, CH_2), 7.11 (d, 1H, ArH, $J = 8.32$ Hz), 7.40 (dd, 1H, ArH, $J = 8.32$ Hz, $J = 2.12$ Hz), 7.65–7.72 (m, 2H, ArH), 8.23 (s, 1H, ArH), 8.25 (d, 1H, ArH, $J = 7.16$ Hz), 8.35 (d, 1H, ArH, $J = 7.80$ Hz), 9.24 (s, 1H, ArH); ^{13}C NMR: 14.43, 50.55, 62.16, 69.05, 116.28, 124.72, 126.22, 126.70, 128.27, 129.03, 129.61, 130.85, 132.19, 132.76, 134.16, 134.46, 142.39, 146.86, 153.13, 162.86, 164.54. MS: $m/z = 525$. Anal. calcd. for $C_{23}H_{17}Cl_2F_3N_4O_3$; Calcd: C, 52.59; H, 3.26; N, 10.67; found: C, 52.58; H, 3.26; N, 10.66 [30].

4.5.4. 4-{1-[2-(4-Fluoro-phenyl)-2-oxo-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (**6a**)

IR (neat ν_{max}/cm^{-1}): 3069, 2976 (C–H-str), 1710, 1590 (C=O), 1222 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.40 (t, 3H, CH_3, $J = 7.10$ Hz), 4.45 (q, 2H, CH_2, $J = 14.22$ Hz, $J = 7.10$ Hz), 5.49 (s, 2H, CH_2), 6.19 (s, 2H, CH_2), 7.44 (t, 2H, ArH, $J = 8.84$ Hz), 7.78 (t, 1H, ArH, $J = 7.88$ Hz), 8.13–8.16 (m, 2H, ArH), 8.24 (s, 1H, ArH), 8.28 (d, 1H, ArH, $J = 7.60$ Hz), 8.43 (d, 1H, ArH, $J = 7.76$ Hz), 9.26 (s, 1H, ArH). Anal. calcd. for $C_{24}H_{18}F_4N_4O_4$; Calcd: C, 57.37; H, 3.61; N, 11.15; found: C, 57.39; H, 3.62; N, 11.14.

4.5.5. 4-{1-[2-(4-Chloro-phenyl)-2-oxo-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (**6b**)

IR (neat ν_{max}/cm^{-1}): 3040, 2990 (C–H-str), 1710, 1582 (C=O), 1212 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.36 (t, 3H, CH_3, $J = 8.00$ Hz), 4.40 (q, 2H, CH_2, $J = 12.00$ Hz, $J = 4.00$ Hz), 5.44 (s, 2H, CH_2), 6.15 (s, 2H, CH_2), 7.63 (d, 2H, ArH, $J = 8.00$ Hz), 7.74 (t, 1H, ArH, $J = 8.00$ Hz), 8.02 (d, 2H, ArH, $J = 8.00$ Hz), 8.21 (s, 1H, ArH), 8.24 (d, 1H, ArH, $J = 8.00$ Hz), 8.39 (d, 1H, ArH, $J = 8.00$ Hz), 9.22 (s, 1H, ArH); ^{13}C NMR: 14.48, 56.40, 62.22, 69.30, 115.98, 124.65, 126.85, 127.34, 129.06, 129.59, 130.58, 133.30, 139.62, 142.35, 146.92, 153.14, 163.03, 164.65, 191.66. Anal. calcd. for $C_{24}H_{18}ClF_3N_4O_4$; Calcd: C, 55.55; H, 3.50; N, 10.80; found: C, 55.58; H, 3.51; N, 10.75.

4.5.6. 4-{1-[2-(4-Bromo-phenyl)-2-oxo-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (**6c**)

IR (neat ν_{max}/cm^{-1}): 3085, 2974 (C–H-str), 1706, 1582 (C=O), 1132 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.36 (t, 3H, CH_3, $J = 8.00$ Hz), 4.40 (q, 2H, CH_2, $J = 8.00$ Hz), 5.44 (s, 2H, CH_2), 6.15 (s, 2H, CH_2), 7.74–7.79 (m, 3H, ArH), 7.93 (d, 2H, ArH, $J = 8.00$ Hz), 8.21 (s, 1H, ArH), 8.24 (d, 1H, ArH, $J = 8.00$ Hz), 8.39 (d, 1H, ArH, $J = 8.00$ Hz), 9.22 (s, 1H, ArH); ^{13}C NMR: 14.48, 56.38, 62.22, 69.30, 115.97, 124.65, 126.85, 127.33, 128.87, 129.06, 130.63, 130.95, 132.54, 133.62, 142.34, 146.93, 153.15, 163.04, 164.65. MS: $m/z = 563$. Anal. calcd. for $C_{24}H_{18}BrF_3N_4O_4$; Calcd: C, 51.17; H, 3.22; N, 9.95; found: C, 51.17; H, 3.21; N, 9.94 [31].

4.5.7. 4-{1-[2-(4-Methoxy-phenyl)-2-oxo-ethyl]-1H-[1,2,3]triazol-4-ylmethoxy}-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (**6d**)

IR (neat ν_{max}/cm^{-1}): 2979, 2937 (C–H-str), 1707, 1588 (C=O), 1231 (N=N), 1130 (C–O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.36 (t, 3H, CH_3, $J = 8.00$ Hz), 4.00 (s, 3H, CH_3), 4.49 (q, 2H, CH_2, $J = 12.00$ Hz, $J = 4.00$ Hz), 65.44 (s, 2H, CH_2), 6.09 (s, 2H, CH_2), 7.06 (d, 2H, ArH, $J = 8.00$ Hz), 7.74 (t, 1H, ArH, $J = 8.00$ Hz), 7.99 (d, 2H, ArH, $J = 8.00$ Hz), 8.22 (s, 1H, ArH), 8.24 (d, 1H, ArH, $J = 8.00$ Hz), 8.39 (d, 1H, ArH, $J = 8.00$ Hz), 9.22 (s, 1H, ArH); ^{13}C NMR: 14.49, 56.04, 56.18, 62.23, 69.32, 114.71, 126.86, 127.39, 129.08, 131.06,

142.24, 153.15, 163.04, 164.41. Anal. calcd. for $C_{25}H_{21}F_3N_4O_5$; Calcd: C, 58.37; H, 4.11; N, 10.89; found: C, 58.39; H, 4.21; N, 10.88.

4.5.8. 4-(1-Ethyl-1H-[1,2,3]triazol-4-ylmethoxy)-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (**7a**)

IR (neat ν_{max}/cm^{-1}): 2984, 2940 (C–H-str), 1699 (C=O), 1251 (N=N); ^1H NMR (400 MHz, DMSO-d_6): δ 1.33–1.41 (m, 6H, $2CH_3$), 4.31–4.45 (m, 4H, $2CH_2$), 5.39 (s, 2H, CH_2), 7.74 (t, 1H, ArH, $J = 7.86$ Hz), 8.23 (s, 1H, ArH), 8.24 (d, 1H, ArH, $J = 7.44$ Hz), 8.38 (d, 1H, ArH, $J = 8.32$), 9.21 (s, 1H, ArH); ^{13}C NMR: 14.44, 15.86, 45.08, 62.18, 69.30, 116.11, 124.62, 125.01, 126.78, 129.03, 130.86, 142.25, 146.89, 153.09, 162.89, 164.63. Anal. calcd. for $C_{18}H_{17}F_3N_4O_3$; Calcd: C, 54.82; H, 4.35; N, 14.21; found: C, 54.82; H, 4.36; N, 14.20.

4.5.9. 4-(1-Propyl-1H-[1,2,3]triazol-4-ylmethoxy)-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (**7b**)

IR (neat ν_{max}/cm^{-1}): 2975, 2939 (C–H-str), 1704 (C=O), 1252 (N=N); ^1H NMR (400 MHz, DMSO-d_6): δ 0.71 (t, 3H, CH_3, $J = 7.38$ Hz), 1.38 (t, 3H, CH_3, $J = 7.10$ Hz), 1.70–1.79 (m, 2H, CH_2), 2.48–2.49 (m, 2H, CH_2), 4.42 (q, 2H, CH_2, $J = 14.22$ Hz, $J = 7.10$ Hz), 5.43 (s, 2H, CH_2), 7.75 (t, 1H, ArH, $J = 7.86$ Hz), 8.21 (s, 1H, ArH), 8.26 (d, 1H, ArH, $J = 7.16$ Hz), 8.38 (d, 1H, ArH, $J = 7.76$), 9.24 (s, 1H, ArH); ^{13}C NMR: 11.04, 14.57, 23.57, 51.38, 62.11, 69.24, 116.14, 124.65, 125.52, 126.75, 129.06, 130.91, 142.10, 146.82, 153.11, 162.85, 164.54. Anal. calcd. for $C_{19}H_{19}F_3N_4O_3$; Calcd: C, 55.88; H, 4.69; N, 13.72; found: C55.87; H, 4.69; N, 13.73.

4.5.10. 4-(1-Butyl-1H-[1,2,3]triazol-4-ylmethoxy)-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (**7c**)

IR (neat ν_{max}/cm^{-1}): 2964, 2930 (C–H-str), 1702 (C=O), 1254 (N=N); ^1H NMR (400 MHz, DMSO-d_6): δ 0.80 (t, 3H, CH_3, $J = 7.36$ Hz), 1.02–1.12 (m, 2H, CH_2), 1.38 (t, 3H, CH_3, $J = 7.10$ Hz), 1.65–1.72 (m, 2H, CH_2), 4.31 (t, 2H, CH_2, $J = 6.94$ Hz), 4.42 (q, 2H, CH_2, $J = 14.22$ Hz, $J = 7.10$ Hz), 5.43 (s, 2H, CH_2), 7.73 (t, 1H, ArH, $J = 7.88$ Hz), 8.19 (s, 1H, ArH), 8.25 (d, 1H, ArH, $J = 7.08$ Hz), 8.37 (d, 1H, ArH, $J = 8.44$ Hz), 9.24 (s, 1H, ArH). ^{13}C NMR: 13.65, 14.43, 19.32, 31.99, 49.50, 62.16, 69.21, 116.14, 123.00, 124.75, 125.49, 126.69, 129.06, 130.88, 142.06, 146.87, 153.10, 162.87, 164.57. Anal. calcd. for $C_{20}H_{21}F_3N_4O_3$; Calcd: C, 56.87; H, 5.01; N, 13.26; found: C, 56.88; H, 5.00; N, 13.24.

4.6. Synthesis of 3-ethoxycarbonylmethoxy-6-trifluoromethyl-furo [3,2-c]quinoline-2-carboxylic acid ethyl ester (**8a**)

To a suspension of 4-hydroxy-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (2.0 g, 0.0070 mol), potassium carbonate (1.06 g, 0.0077 mol) in dimethylformamide (20 mL) was added ethyl 4-chloroacetoacetate (2.53 g, 0.0154 mol). The mixture was allowed to stir for 6 h at 80 °C and was quenched by the slow addition water (25 mL), The precipitated solids were collected by filtration and recrystallized from ethanol.

IR (neat ν_{max}/cm^{-1}): 2989, 2958 (C–H-str), 1748, 1711 (C=O), 1134 (C–O); ^1H NMR (400 MHz, DMSO-d_6): δ 1.14 (t, 3H, CH_3, $J = 8.0$ Hz), 1.32 (t, 3H, CH_3, $J = 8.0$ Hz), 4.12 (q, 2H, CH_2, $J = 8.0$ Hz), 4.30 (q, 2H, CH_2, $J = 8.0$ Hz), 4.98 (s, 2H, CH_2), 7.80 (t, 1H, ArH, $J = 8.0$ Hz), 8.26 (d, 1H, ArH, $J = 8.0$ Hz), 8.72 (d, 1H, ArH, $J = 8.0$ Hz), 9.19 (s, 1H, ArH); ^{13}C NMR: 14.42, 61.46, 62.23, 70.68, 71.95, 114.71, 116.11, 124.23, 126.76, 127.80, 129.43, 131.06, 132.08, 146.79, 153.14, 162.94, 164.37, 168.47, 168.86. Anal. calcd. for $C_{19}H_{16}F_3NO_6$; Calcd: C, 55.48; H, 3.92; N, 3.41; found: C 55.51; H, 3.92; N, 3.40 [32].

4.7. Synthesis of 3-ethoxycarbonylmethoxy-6-trifluoromethyl-furo [3,2-c]quinoline-2-carboxylic acid (**8b**)

To a suspension of 3-ethoxycarbonylmethoxy-6-trifluoromet hyl-furo[3,2-*c*]quinoline-2-carboxylic acid ethyl ester (1.0 g, 0.0024 mol) in methanol (10 mL) at 0 °C was added lithium hydroxide (0.06 g, 0.0026 mol) for 5 min. The mixture was allowed to stir for 2 h and was quenched by the slow addition water (25 mL), acidified using dilute HCl. The precipitated solids were collected by filtration and recrystallized by ethanol.

IR (neat ν_{max}/cm^{-1}): 3236 (–OH), 3095, 2981 (C–H-str), 1736 (C=O), 1130 (C–O); ^1H NMR (400 MHz, DMSO-d_6): δ 1.17 (t, 3H, CH_3, $J = 8.0$ Hz), 4.10 (q, 2H, CH_2, $J = 8.0$ Hz), 5.02 (s, 2H, CH_2), 7.54 (t, 1H, ArH, $J = 8.0$ Hz), 8.09 (d, 1H, ArH, $J = 8.0$ Hz), 8.43 (d, 1H, ArH, $J = 8.0$ Hz), 8.49 (s, 1H, ArH), 11.72 (s, 1H, OH, D_2O-exchangeble). Anal. calcd. for $C_{17}H_{12}F_3NO_6$; Calcd: C, 53.27; H, 3.16; N, 3.65; found: C 53.26; H, 3.19; N, 3.65.

4.8. Synthesis of 4-hydroxy-8-trifluoromethyl-quinoline-3-carboxylic acid (**9**)

To a suspension of 4-hydroxy-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (**3**) (5 g, 0.017 mol) in methanol (50 mL) at 0 °C was added lithium hydroxide (0.45 g, 0.019 mol) for 10 min. The mixture was allowed to stir for 2 h and was quenched by the slow addition water (100 mL), acidified using dilute HCl. The precipitated solids were collected by filtration and recrystallized by ethanol.

Yield: (4.3 g, 95.5%). M.p: 258–260 °C. IR (neat ν_{max}/cm^{-1}): 3440 (–OH), 3113, 3061 (C–H-str), 1720 (C=O). Anal. calcd. for $C_{11}H_6F_3NO_3$; Calcd: C, 51.37; H, 2.35; N, 5.45; found: C, 51.39; H, 2.33; N, 5.46.

4.9. Synthesis of 3-bromo-8-trifluoromethyl-quinolin-4-ol (**10**)

The 4-hydroxy-8-trifluoromethyl-quinoline-3-carboxylic acid (5.0 g, 0.019 mol) was taken up in THF (50 mL). NBS (3.73 g, 0.021 mol) was added, and the reaction mixture was allowed to stir at room temperature overnight. After completion of the reaction, the reaction mixture was concentrated under vacuum, poured into ice-cold water. The solid product obtained was filtered, washed with water and recrystallized from ethanol to get white solids.

IR (neat ν_{max}/cm^{-1}): 3165, 3015 (C–H-str), 1607 (C=C); ^1H NMR (400 MHz, DMSO-d_6): δ 7.28 (t, 1H, ArH, $J = 8.00$ Hz), 7.86 (d, 1H, ArH, $J = 8.00$ Hz), 8.19 (s, 1H, ArH), 8.61 (d, 1H, ArH, $J = 8.00$ Hz), 11.73 (s, 1H, OH, D_2O-exchangeble); ^{13}C NMR: 105.83, 122.67, 125.38, 130.94, 131.54, 135.49, 141.38, 171.46, 194.17. Anal. calcd. for $C_{10}H_5BrF_3NO$; Calcd: C, 41.13; H, 1.73; N, 4.80; found: C 41.13; H, 1.71; N, 4.82.

4.10. Synthesis of 3-bromo-4-ethoxy-8-trifluoromethyl-quinoline (**11**)

The mixture of 3-Bromo-8-trifluoromethyl-quinolin-4-ol (3.0 g, 0.010 mol) potassium carbonate (1.52 g, 0.011 mol) and ethyliodide (2.40 g, 0.015 mol) in dimethylformamide (30 mL) was stirred at room temperature for 2 h. After completion of reaction, the reaction mixture was poured into ice-cold water. The solid product obtained was filtered. The crude product obtained was purified by column chromatography using pet ether and ethyl acetate (9:1) as the eluent to get white solids.

IR (neat ν_{max}/cm^{-1}): 3015, 2954 (C–H-str), 1573 (C=C), 1128 (C–O); ^1H NMR (400 MHz, DMSO-d_6): δ 1.50 (t, 3H, CH_3, $J = 7.0$ Hz), 4.33 (q, 2H, CH_2, $J = 7.0$ Hz, $J = 13.8$ Hz), 7.82 (t, 1H, ArH, $J = 7.8$ Hz), 8.25 (d, 1H, ArH, $J = 7.2$ Hz), 8.45 (d, 1H, $J = 8.8$ Hz), 9.14 (s, 1H, ArH). MS: $m/z = 320.1$ (M + 1). Anal. calcd. for $C_{12}H_9BrF_3NO$; Calcd: C, 45.03; H, 2.83; N, 4.38; found: C 45.05; H, 2.83; N, 4.37.

4.11. Synthesis of 4-ethoxy-3-(1-methyl-1H-indol-5-yl)-8-trifluoromethyl-quinoline (**12**)

3-Bromo-4-ethoxy-8-(trifluoromethyl)quinoline (0.5 g, 0.0015 mol), *N*-methylindole-5-boronic acid (0.29 g, 0.0017 mol) were dissolved in a mixture of toluene and ethanol (5:5, 10 mL). The solution was subsequently stirred for 10 min under nitrogen atmosphere. Potassium carbonate (0.234 g, 0.0017 mol) and palladium acetate (0.050 g, 0.00022 mol) were then added to the reaction mass and refluxed for 2 h under nitrogen atmosphere. After completion of the reaction, the reaction mixture was filtered through celite bed. The crude product obtained was purified by column chromatography using pet ether and ethyl acetate (9:1) as the eluent.

IR (neat ν_{max}/cm^{-1}): 2975, 2942 (C–H-str); ^1H NMR (400 MHz, DMSO-d_6): δ 1.13 (t, 3H, CH_3, J = 7.00 Hz), 3.73 (q, 2H, CH_2, J = 13.74 Hz, J = 7.00 Hz), 3.85 (s, 3H, CH_3), 6.52 (d, 1H, ArH, J = 2.96 Hz), 7.40 (d, 1H, ArH, J = 3.04 Hz), 7.46 (dd, 1H, ArH, J = 8.48 Hz, J = 1.44 Hz), 7.58 (d, 1H, ArH, J = 8.52 Hz), 7.76 (t, 1H, ArH, J = 7.84 Hz), 7.86 (s, 1H, ArH), 8.16 (d, 1H, ArH, J = 7.2 Hz), 8.55 (d, 1H, ArH, J = 8.24 Hz), 9.02 (s, 1H, ArH). MS: m/z = 371. Anal. calcd. for $C_{21}H_{17}F_3N_2O$; Calcd: C, 68.10; H, 4.63; N, 7.56; found: C, 68.10; H, 4.61; N, 7.57.

5. Antibacterial studies

The *in-vitro* antibacterial activity of the synthesized compounds was done using *Escherichia coli*, *Bacillus subtilis* and *Pseudomonas aeruginosa* bacterial strains by well plate method. The above activity was examined qualitatively and quantitatively by the presence or absence of inhibition zones and zone diameter. A number of antimicrobial discs were placed on the agar for the purpose of producing zones of inhibition in the bacterial lawn. 15–20 mL of agar media were poured into each petri dish. Agar containing plates were dried by placing in a laminar air flow at 37 ± 2 °C for an hour. Using an agar punch, wells were made on the seeded agar plates and minimum inhibitory concentrations of the test compounds in dimethylsulfoxide (DMSO) were added into each labeled wells. 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 ± 2 °C for 24–48 h. Activities were determined by measuring the diameter of inhibition zone (mm). Ciprofloxacin was used as standard. Experiments were triplicates and standard deviation was calculated.

6. Antifungal studies

Antifungal studies of newly synthesized compounds (**5a**–**c**, **6a**–**d**, **7a**–**c**, **8a**,**b**, **11** and **12**) were carried out against *Aspergillus flavus*, *Chrysosporium keratinophilum* and *Candida albicans*. The required amounts of each fungal strain were suspended in 5 mL of distilled water with 2 drops of Tween 80. This suspension was uniformly spread on Petri plates containing malt extract agar media using sterile swabs. After applying the samples into the wells, the plates were incubated at 25 °C for 72 h. The plates were then examined for the presence of zones of inhibition and the results were recorded. Fluconazole was used as the positive control at a concentration of 1 mg/mL, 0.5 mg/mL and dimethylsulfoxide (DMSO) was used as negative control.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.01.008.

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