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Original article

Synthesis and antimicrobial activities of novel quinoline derivatives carrying 1,2,4-triazole moiety

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ABSTRACT

A new class of quinoline derivatives containing 1,2,4-triazole moiety were synthesized from derivatives of 4-hydroxy-8-(trifluoromethyl)quinoline-3-carbohydrazide **4** through multi-step reactions. The compound **4**, on treatment with substituted Isothiocyanates yielded quinoline-thiosemicarbazides **5a–c**, which were conveniently cyclized to (5-mercapto-4*H*-triazol-3-yl)-quinolin-4-ols **6a–c** in basic medium. These intermediates were then transformed to their respective chloro derivatives **7a–c** by treatment with phosphorus oxychloride, which on further reaction with different biologically active rare amines yielded the target compounds **8a–g**, **9a–h** and **10a–h** in good yield. The ultimate step, involving nucleophilic substitution reaction was achieved by microwave-induced technique, which has reduced the reaction time drastically as well as improved the yield when compared to conventional heating. The newly synthesized final compounds were evaluated for their in vitro antibacterial and antifungal activities against four strains each. Preliminary results indicated that most of the compounds demonstrated very good antimicrobial activity, comparable to the first line standard drugs. The most effective compounds have exhibited activity at MIC of 6.25 μg/mL.

1. Introduction

Quinoline moiety is of great importance to chemists as well as biologists as it is found in a large variety of naturally occurring compounds and also chemically useful molecules having diverse biological activities. A large variety of quinoline derivatives have been used as antimalarial [1], anti-inflammatory [2], anticancer [3], antibiotic [4], antihypertensive [5], tyrokinase PDGF-RTK inhibiting agents [6], and anti HIV [7,8]. In addition to the medicinal importance, multi-substituted quinolines are valuable synthons used for the preparation of nano- and mesostructures with enhanced electronic and photonic properties [9–11].

It has been well established that fluorinated, in particular, CF_3 substituted heterocycles have got a significant place in modern medicinal chemistry [12]. Their biological studies clearly indicate that the presence of trifluoromethyl group in position **8** of the quinoline ring gives useful biological activity and are the subject of considerable growing interest [13]. These effective derivatives are ideally suited for further modifications to obtain more efficacious antibacterial compounds.

On the other hand, it has been reported that 1,2,4-triazole derivatives possess a wide spectrum of chemotherapeutic activities including anti-inflammatory [14], anticancer [15], anti depressant [16], antibacterial [17], antifungal [18] and anticonvulsant properties [19]. In fact, some of their derivatives are active constituents of currently used drugs. Further, various amino derivatives of quinolines as well as 1,2,4-triazoles were shown to possess excellent pharmacological properties such as antimicrobial, analgesic and anti-inflammatory activities. On the basis of these observations, it was thought of synthesizing a new class of heterocyclics, wherein potent 1,2,4-triazole moiety is linked to position **3** while biologically active rare amines attached to position **4** of 8-trifluoromethyl quinoline. These structures have been designed on the basis of combinatorial synthesis, which is the current trend being practiced in most of the drug discoveries. This communication reports the synthesis of hitherto unknown **8a–g**, **9a–h** and **10a–h** starting from 2-trifluoro aniline **1** and evaluation of their in vitro antimicrobial properties. In the present synthesis, the ultimate step was achieved using microwave technique. This has brought about drastic reduction in reaction time and moreover, it has enhanced the yields of target compounds (Table 1).

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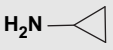
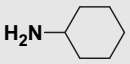
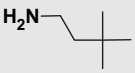
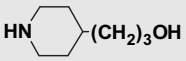
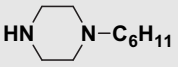
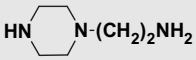
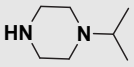
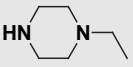
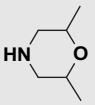
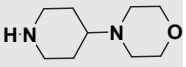
Table 1
4-Subsituted-5-[4-(substituted amino)-8-(trifluoromethyl)quinolin-3-yl]-4*H*-1,2,4-triazole-3-thiols.

R1	R2					
					
$-CH_2Ph$	**8a**	**8b**	**8c**	**8d**	**8e**
$-Ph$	**9a**	**9b**	**9c**	**9d**	**9e**
$-CH_2CH_2OMe$	**10a**	**10b**	**10c**	**10d**	**10e**

R1	R2					
						
$-CH_2Ph$	**8f**	**8g**	–	–	–	–
$-Ph$	**9f**	–	**9g**	–	–	**9h**
$-CH_2CH_2OMe$	**10f**	–	–	**10g**	**10h**	–

2. Results and discussion

2.1. Chemistry

The reaction sequences employed for synthesis of title compounds are shown in Scheme 1. Following the procedure described by Price and Roberts [20], the starting material 2-(trifluoromethyl) aniline **1** was conveniently converted to diethyl ({[2-(trifluoromethyl) phenyl] amino} methylidene) propanedioate **2**, by condensing it with diethyl ethoxymethylene malonate. The diester **2**, on heating at 250 °C in Dowtherm medium, readily cyclized to ethyl 4-hydroxy-8-(trifluoromethyl)quinoline-3-carboxylate **3**, which on condensation with hydrazine hydrate in alcoholic medium gave 8-(trifluoromethyl)-4-hydroxyquinoline-3-carbohydrazide **4** in good yield. Further, the key intermediates, thiosemicarbazides **5a–c** were synthesized by refluxing the carbohydrazide **4** with different isothiocyanates in alcoholic medium using the procedure described by Silber and Cosma [21]. The compounds **5a–c** were then conveniently cyclized in basic medium to give (5-mercapto-4*H*-triazol-3-yl)-8-(trifluoromethyl) quinolin-4-ol **6a–c**, which on refluxing with phosphorus oxychloride yielded the corresponding 4-chloro derivatives, **7a–c**. Interestingly, an unusual product, with a yield of 20–30%, was isolated during the reaction, which was found to be a dimer of type **7d–f** on analysis. Finally, the target compounds, viz. 5-(4-amino substituted-8-(trifluoromethyl)quinolin-3-yl)-4-(un) substituted phenyl-4*H*-1,2,4-triazole-3-thiols (**8a–g**, **9a–h** and **10a–h**) were synthesized from their precursors **7a–c** by acetonitrile assisted microwave-induced reaction using different rare and bio-active amines. This reaction went on very fast and their yields were excellent. The structures of all the newly synthesized compounds were confirmed by FTIR, ^1H and ^{13}C NMR and mass spectral (ESI) studies and elemental analysis.

The formation of ester **2** from 2-(trifluoromethyl) aniline **1** was evidenced by its IR, ^1H NMR and mass spectra. Its IR spectrum showed strong bands at 1709, 1657 and 3467 cm^{-1} indicating the presence of ester >C═O, >C═C< and –NH– groups respectively, while its ^1H NMR spectrum showed two triplets and two quartets at δ 1.33, 1.38 and δ 4.26, 4.45 respectively, due to two $-CH_2-$ and $-CH_3$ protons, indicating the presence of two $-COOC_2H_5$ groups. The presence of a sharp doublet at δ 8.45 clearly reveal the presence of >C═CH– proton and a broad doublet at δ 11.45 (which disappeared on D_2O exchange) manifest the presence of –NH–C. The mass spectrum of **2** showed a molecular ion peak at *m*/*z* 332.3 (100%), which matches with its molecular formula $C_{15}H_{16}F_3NO_4$.

The cyclization of diethyl ester **2** to 4-hydroxyquinoline-3-carboxylate **3** was evidenced by its ^1H NMR spectrum; the disappearance of one triplet and one quartet of $-CH_2-$ and $-CH_3$ protons from δ 1.38 and δ 4.45 clearly evidences the smooth cyclization, also disappearance of a sharp doublet from δ 8.45 of >C═CH– proton indicates the aromatization of quinoline ring. Appearance of a broad singlet at δ 11.69 (which disappeared on D_2O exchange) confirms the presence of –OH proton at the 4th position of quinoline. The entire aromatic proton shift towards downfield also gives a strong indication of quinoline aromatization. In the FTIR spectrum, compound **3** exhibited a broad band at 3519 cm^{-1} due to –OH stretching. The mass spectrum of it showed a molecular ion peak at *m*/*z* 285.96 (100%), which matches with its molecular formula $C_{13}H_{10}F_3NO_3$.

The formation of 4-hydroxy-8-(trifluoromethyl)quinoline-3-carbohydrazide **4** from ester **3** was confirmed by its FTIR, ^1H NMR and LC/MS spectra. FTIR spectrum of **4** showed strong bands at 3256 and 3293 cm^{-1} indicating the presence of $-NHNH_2$ group, while the disappearance of triplet and quartet of $-CH_2-$ and $-CH_3$ protons in ^1H NMR spectrum clearly confirms the formation of **4**. Further the mass spectrum of **4** showed a molecular ion peak at *m*/*z* 271.9 (98%), which tallies with its molecular formula $C_{11}H_8F_3N_3O_2$.

The structures of compounds **5a–c** were elucidated by its FTIR, NMR and LC/MS. FTIR spectrum of **5a** reveals the presence of both –NH groups due to absorbance bands at 3442 and 3491 cm^{-1} while that of >C═O and >C═S were observed at 1671 and 1269 cm^{-1} respectively. The ^1H NMR spectrum was in accordance with its structure while the mass spectrum of it showed a molecular ion peak at 421 (52%), which matches with its molecular formula $C_{19}H_{15}F_3N_4O_2S$.

The cyclization of **5a–c** to form **6a–c** was established by recording its FTIR, NMR and MS spectra. In FTIR spectrum of **6a** absorbance band of >C═S appeared at 1204 cm^{-1} while that of >C═O disappeared, this gives a strong indication of cyclization of **5a**. Also, the spectrum showed strong bands at 1623 and 3529 cm^{-1} indicating the presence of >C═N– and –OH group respectively. The mass spectrum of **6a** displayed a molecular ion peak at *m*/*z* 403 (100%), which confirms to its molecular formula $C_{19}H_{13}F_3N_4OS$. In the ^1H NMR spectrum of **6a**, it appeared a singlet at δ 14.08 integrating for one proton of triazole ring. The smooth cyclization of **5a** was further

confirmed by the fact that the doublet peak of benzylic proton at δ 4.73 in **5a** was shifted towards downfield to a singlet at δ 5.28.

The structure of 4-benzyl-5-[4-chloro-8-(trifluoromethyl)quinolin-3-yl]-4*H*-1,2,4-triazole-3-thiol **7a** was determined by FTIR, MS, ^{1}H and ^{13}C NMR spectral studies. In FTIR spectrum of **7a** the appearance of medium band at 780 cm^{-1} and disappearance of strong O–H stretching band clearly indicates the replacement of O–H with Cl group. In the ^{1}H NMR shifting of δ from 7.95 to 8.54 due to aromatic –CH– group adjacent to quinoline N clearly indicates the formation of **7a**. Further, ^{13}C NMR showed signals at δ: 47.24 due to benzylic C, peak at δ 120.57 due to CF_3, δ 127.58, 128.18, 130.09, 135.46 due to benzene ring C, peaks at δ 125.81, 126.86, 127.25, 128.79, 131.51, 131.58, 146.78, 151.26, 168.47 due to quinoline ring C and δ 144.37 and 145.37 due to triazole C_2 and C_5. Further, its mass spectrum showed molecular ion peak at *m*/*z* 421.0 (100%), which corresponds to its molecular formula $C_{19}H_{12}ClF_3N_4S$.

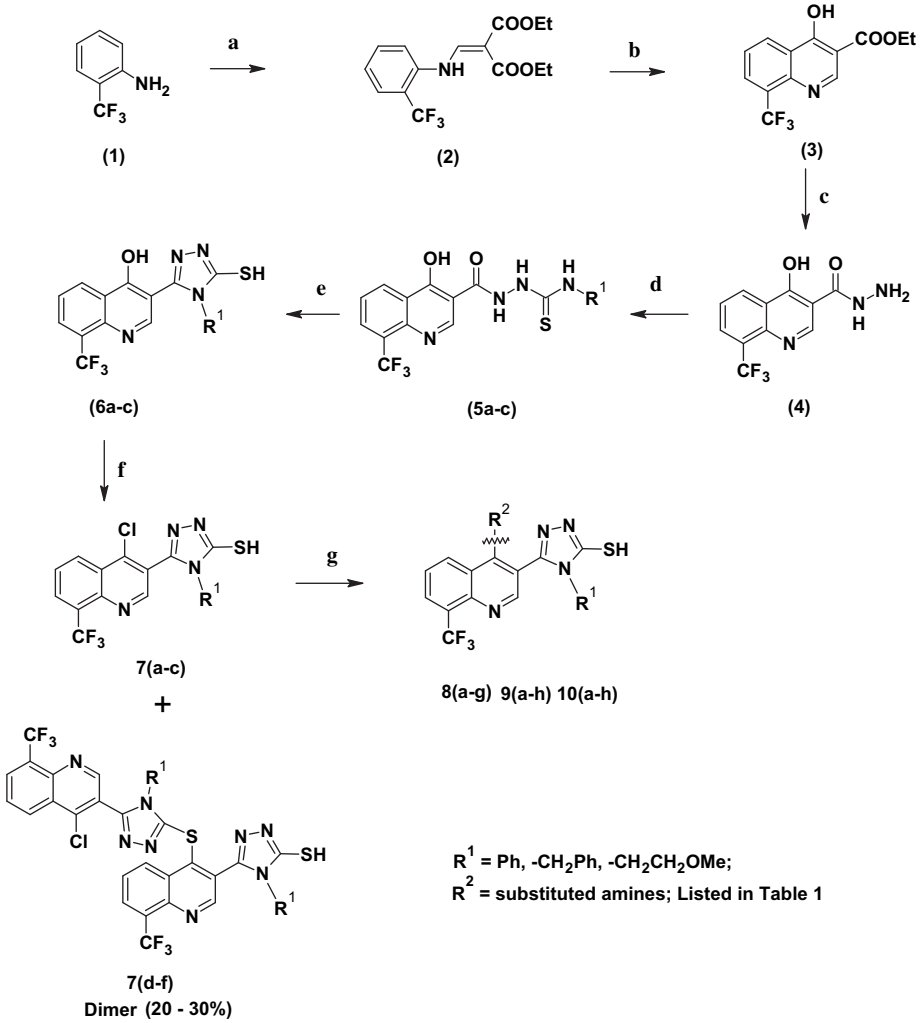
The formation of unusual product **7d** was confirmed by LC/MS and ^{1}H NMR and was in accordance with its structure as shown in Scheme 1.

The formation of the title compound **8a** by microwave-assisted reaction with cyclopropyl amine with the corresponding chloro compound **7a** was evidenced by IR, ^{1}H NMR and mass spectral data. The IR spectrum of **8a** showed a broad band at 3345 cm^{-1} due to –NH– stretching, also the disappearance of C–Cl stretching band indicates the chloro amine coupling at the 4th position of quinoline ring. Its ^{1}H NMR spectrum indicates the presence of two multiplet due to two $-CH_2-$ groups at δ 0.41 and 0.55 and one multiplet due to –CH– group at δ 2.21 of cyclopropyl ring, and a broad singlet at δ 7.86 clearly reveals the coupling of cyclopropyl amine with **7a**. Finally, the structure of the compound **8a** was confirmed by its mass spectrum, which showed molecular ion peak at *m*/*z* 442.1 (100%). This conforms to its molecular formula $C_{22}H_{18}F_3N_5S$. Similarly, the structure of 5-(4-(4-(2-aminoethyl)piperazin-1-yl)-8-(trifluoromethyl)quinolin-3-yl)-4-benzyl-4*H*-1,2,4-triazole-3-thiol (**8g**) was evidenced by its mass spectrum. It displayed the molecular ion peak at *m*/*z* 515 (45%), which is in agreement with the molecular formula $C_{25}H_{26}F_3N_7S$. The major peaks at *m*/*z* 515 (M + 2, 45%), 496 (19%), 470 (18%), 438 (37%), 395 (37%), 353 (37%), 351 (100%) and 239 (18%) were due to the fragmentation of molecular ion leading to formation of important species with complex structures, as shown in Scheme 2. Further, the mass spectral data of compounds **9b** and **10d** confirmed their structures (Table 2).

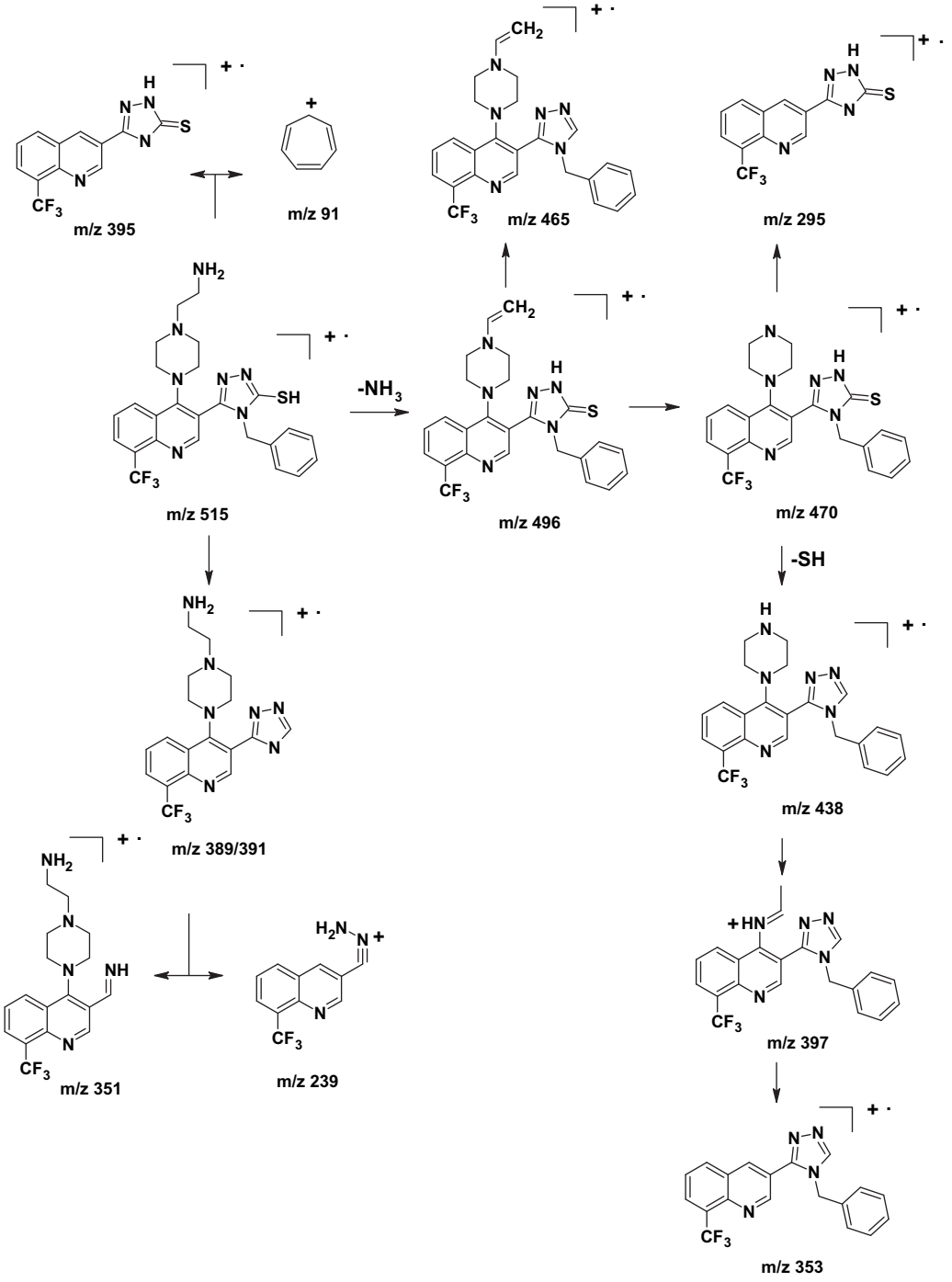
2.2. Biological activities

2.2.1. Antibacterial studies

The newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25923), *Pseudomonas aeruginosa* (ATCC-27853) and



Scheme 1. (a) 2-CF_3 aniline, $(COOEt)_2C{=}C{-}OEt$, 110 °C, 4 h (b) Diphenylether, 250 °C, 4 h (c) NH_2NH_2, 80 °C, 6 h. (d) R^1NCS, EtOH, 82 °C. (e) KOH, 110 °C, 2 h (f) $POCl_3$, 60 °C, 2 h (g) NR^2, K_2CO_3, ACN, 120 °C, μW, 10 min.



Scheme 2. Mass fragmentation pattern of compound **8g**.

Klebsiella pneumoniae (recultured) bacterial stains by serial plate dilution method [22,23]. Serial dilutions of the drug in Mueller–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 an hour. 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 [24,25]. Zone of inhibition was determined for **6a–c**, **7a–c**, **8a–g**, **9a–h** and **10a–h** and the results are summarized in Table 3.

Table 2
Characterization data of compounds **6a–c, 7a–c, 8a–g, 9a–h** and **10a–h**.

Compound	R1	R2	Molecular formula/Mol. weight	M.P (°C)	Yield[a]%	Analysis % found. Found (Calc.)		
						C	H	N
6a	CH_2–Ph	OH	$C_{19}H_{13}F_3N_4OS$/402	280	86	56.72 (56.71)	3.25 (3.26)	13.94 (13.92)
6b	Ph	OH	$C_{18}H_{11}F_3N_4OS$/388	303	88	55.71 (55.67)	2.89 (2.85)	14.47 (14.43)
6c	CH_2CH_2OMe	OH	$C_{15}H_{13}F_3N_4O_2S$/370	152	95	48.69 (48.65)	3.58 (3.54)	15.11 (15.13)
7a	CH_2–Ph	Cl	$C_{19}H_{12}$ ClF_3N_4S/420	192	65	54.26 (54.23)	2.89 (2.87)	13.27 (13.31)
7b	Ph	Cl	$C_{18}H_{10}$ ClF_3N_4S/406	203	73	53.18 (53.14)	2.52 (2.48)	13.84 (13.77)
7c	CH_2CH_2OMe	Cl	$C_{15}H_{12}$ ClF_3N_4OS/388	173	71	46.39 (46.34)	3.17 (3.11)	14.45 (14.41)
8a	CH_2–Ph	Cyclopropyl amine	$C_{22}H_{18}F_3N_5S$/441	210	83	59.89 (59.85)	4.14 (4.11)	15.82 (15.86)
8b	CH_2–Ph	Cyclohexyl amine	$C_{25}H_{24}F_3N_5S$/483	253	86	62.13 (62.10)	4.98 (5.00)	14.50 (14.48)
8c	CH_2–Ph	3,3 Dimethyl butylamine	$C_{25}H_{26}F_3N_5S$/485	219	88	61.82 (61.84)	5.49 (5.40)	14.46 (14.42)
8d	CH_2–Ph	Piperidine-4-propanol	$C_{27}H_{28}F_3N_4OS$/527	245	86	61.48 (61.46)	5.38 (5.35)	13.24 (13.27)
8e	CH_2–Ph	Morpholine	$C_{23}H_{20}F_3N_5OS$/471	240	86	58.52 (58.59)	4.24 (4.28)	14.81 (14.85)
8f	CH_2–Ph	1-Cyclohexyl piperazine	$C_{29}H_{31}F_3N_6S$/552	294	90	63.06 (63.02)	5.67 (5.65)	15.24 (15.21)
8g	CH_2–Ph	2-Piperazine ethyl amine	$C_{25}H_{26}F_3N_7S$/513	237	80	58.40 (58.47)	5.18 (5.10)	19.04 (19.09)
9a	Ph	Cyclopropyl amine	$C_{21}H_{16}F_3N_5S$/427	223	88	59.12 (59.01)	3.83 (3.77)	16.29 (16.38)
9b	Ph	Cyclohexyl amine	$C_{24}H_{22}F_3N_5S$/469	250	91	61.45 (61.39)	4.77 (4.72)	14.98 (14.92)
9c	Ph	3,3 Dimethyl butylamine	$C_{24}H_{24}F_3N_5S$/471	242	90	61.17 (61.13)	5.16 (5.13)	14.89 (14.85)
9d	Ph	Piperidine-4-propanol	$C_{26}H_{26}F_3N_5OS$/513	219	91	60.83 (60.80)	5.15 (5.10)	13.68 (13.64)
9e	Ph	Morpholine	$C_{22}H_{18}F_3N_5OS$/457	246	86	57.80 (57.76)	4.01 (3.97)	15.39 (15.31)
9f	Ph	1-Cyclohexyl piperazine	$C_{28}H_{29}F_3N_6S$/538	226	86	62.50 (62.44)	5.49 (5.43)	15.69 (15.60)
9g	Ph	2-Piperazine ethyl amine	$C_{25}H_{25}F_3N_6S$/498	209	86	60.29 (60.23)	5.08 (5.05)	16.89 (16.86)
9h	Ph	4-Piperidine morpholine	$C_{27}H_{27}F_3N_6OS$/540	234	78	60.05 (59.99)	5.09 (5.03)	15.60 (15.55)
10a	CH_2CH_2OMe	Cyclopropyl amine	$C_{18}H_{18}F_3N_5OS$/409	238	92	52.84 (52.80)	4.47 (4.43)	17.14 (17.11)
10b	CH_2CH_2OMe	Cyclohexyl amine	$C_{21}H_{24}F_3N_5OS$/451	235	92	55.89 (55.86)	5.39 (5.36)	15.56 (15.51)
10c	CH_2CH_2OMe	3,3 Dimethyl butylamine	$C_{21}H_{26}F_3N_5OS$/453	210	96	55.69 (55.61)	5.83 (5.78)	15.50 (15.44)
10d	CH_2CH_2OMe	Piperidine-4-propanol	$C_{23}H_{28}F_3N_5O_2S$/495	191	89	55.76 (55.74)	5.73 (5.70)	14.14 (14.13)
10e	CH_2CH_2OMe	Morpholine	$C_{19}H_{20}F_3N_5O_2S$/439	256	92	51.98 (51.93)	4.65 (4.59)	15.98 (15.94)
10f	CH_2CH_2OMe	1-Cyclohexyl piperazine	$C_{25}H_{31}F_3N_6OS$/520	246	77	57.61 (57.68)	6.09 (6.00)	16.19 (16.14)
10g	CH_2CH_2OMe	4-Ethyl piperazine	$C_{21}H_{25}F_3N_6OS$/466	213	87	53.12 (53.09)	5.14 (5.12)	18.60 (18.57)
10h	CH_2CH_2OMe	3,5 Dimethyl morpholine	$C_{21}H_{24}F_3N_5O_2S$/467	266	86	53.98 (53.95)	5.19 (5.17)	14.93 (14.98)

[a] After column purification.

2.2.2. Antifungal studies

Newly prepared compounds were screened for their antifungal activity against *Aspergillus flavus* (NCIM No. 524), *Aspergillus fumigatus* (NCIM No. 902), *Penicillium marneffei* (recultured) and *Trichophyton mentagrophytes* (recultured) in DMSO by serial plate dilution method [26,27]. 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. Zones of inhibition were determined for **6a–c**, **7a–c**, **8a–g**, **9a–h** and **10a–h** and the results are summarized in Table 4.

2.2.3. Biological results

The investigation of antibacterial and antifungal screening data revealed that all the tested compounds **6a–c**, **7a–c**, **8a–g**, **9a–h** and **10a–h** showed moderate to good inhibition at 6.25–12.5 μg/mL in DMSO. The compounds **6b**, **6c**, **7b**, **8a**, **9a**, **9b**, **9c**, **9e**, **9h**, **10a**, **10b**, **10e** and **10h** showed comparatively very good activity against all the bacterial strains. The good activity is attributed to the presence of pharmacologically active rare amine at position **4** of quinoline, –SH, $-CH_2CH_2OCH_3$ and –Ph groups attached to triazole moiety at position **3** of the quinoline ring. Introduction of aryl group such as phenyl and alkyl group $-CH_2CH_2OCH_3$ to the triazole ring at position **3** of quinoline caused enhanced activity. The presence of $-CF_3$ groups at position **8** of quinoline ring caused good antibacterial activity while introduction of benzylic group at triazole caused decrease in activity against most of the strains. The compounds **7c**, **8b**, **8c** and **8d** exhibited moderate activity compared to that of standard against all the bacterial strains. Compounds **9f**, **9g**, **10f** and **10g** showed very good activity against *E. coli*, while compounds **8e**, **8f**, **8g**, **9d** and **10d** showed very good activity against *S. aureus*. The compounds **6b**, **6c**, **7b**, **8a**, **9a**, **9b**, **9c**, **9e**, **9h**, **10a**, **10b**, **10c**, **10e** and **10h** showed comparatively very good activity against all the fungal strains. The structures of these compounds contain biologically active –SH, $-CH_2CH_2OCH_3$ and –Ph groups attached to triazole ring in position **3** of the quinoline ring and aryl group such as phenyl and alkyl group $-CH_2CH_2OCH_3$ to the triazole ring at position **3** of quinoline ring. The compounds **7c**, **8b**, **8c**, **8d** and **8e** exhibited moderate activity against all fungal strains. Results showed that combination of quinoline with triazole ring gave an enhanced biological effect against all the bacterial strains.

3. Conclusion

The research study reports the successful synthesis and antimicrobial activity of new 5-(4-amino substituted-8-(trifluoromethyl)quinolin-3-yl)-4-(un)substituted phenyl-4*H*-1,2,4-triazole-3-thiols carrying biologically active groups. Their antimicrobial activity study revealed that all the compounds tested showed moderate to very good antibacterial and antifungal activities against pathogenic strains. Structure–biological activity relationship of title compounds showed that the presence of $-CF_3$ at position **8** and biologically active amines at position **4** of quinoline ring and bioactive moieties such as –SH, $-CH_2CH_2OCH_3$ and –Ph groups at triazole ring of title compounds are responsible for increased antimicrobial activity in newly synthesized title

Table 3
Antibacterial activity of the title compounds **6a–c**, **7a–c**, **8a–g**, **9a–h** and **10a–h**.

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)
6a	50 (<10)	50 (<10)	50 (<10)	50 (<10)
6b	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16– 20)
6c	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16– 20)
7a	50 (<10)	50 (<10)	50 (<10)	50 (<10)
7b	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
7c	12.5 (10–15)	6.25 (16–20)	12.5 (10–15)	12.5 (12–16)
8a	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
8b	12.5 (10–15)	12.5 (16–20)	12.5 (10–15)	12.5 (12–16)
8c	12.5 (10–15)	12.5 (16–20)	12.5 (10–15)	12.5 (12–16)
8d	12.5 (10–15)	12.5 (16–20)	12.5 (10–15)	12.5 (12–16)
8e	6.25 (16–20)	12.5 (16–20)	50 (<10)	50 (<10)
8f	6.25 (16–20)	50 (<10)	50 (<10)	50 (<10)
8g	50 (<10)	6.25 (20–24)	50 (<10)	50 (<10)
9a	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
9b	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
9c	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
9d	6.25 (16–20)	12.5 (16–20)	50 (<10)	50 (<10)
9e	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
9f	50 (<10)	6.25 (20–24)	50 (<10)	50 (<10)
9g	50 (<10)	6.25 (20–24)	50 (<10)	50 (<10)
9h	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
10a	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
10b	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16– 20)
10c	50 (<10)	50 (<10)	50 (<10)	50 (<10)
10d	6.25 (16–20)	6.25 (20–24)	50 (<10)	50 (<10)
10e	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
10f	50 (<10)	6.25 (20–24)	50 (<10)	50 (<10)
10g	50 (<10)	6.25 (20–24)	50 (<10)	50 (<10)
10h	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
Ciprofloxacin (standard)	6.25 (22–30)	6.25 (30–40)	6.25 (25–33)	6.25 (23–27)

Note: The MIC values where evaluated at concentration range, 6.25–50 μg/mL. The figures in the table show the MIC values in μg/mL and the corresponding zone of inhibition in mm.

Table 4
Antifungal activity of title compounds **6a–c**, **7a–c**, **8a–g**, **9a–h** and **10a–h**.

Compound	MIC in μg/mL and zone of inhibition in mm			
	P. marneffei (recultured)	*T. mentagrophytes* (recultured)	*A. flavus* (NCIM No. 524)	*A. fumigatus* (NCIM No. 902)
6a	50 (<10)	50 (<10)	50 (<10)	50 (<10)
6b	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
6c	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
7a	50 (<10)	50 (<10)	50 (<10)	50 (<10)
7b	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
7c	12.5 (10–15)	12.5 (10–15)	12.5 (10–15)	12.5 (10–15)
8a	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
8b	12.5 (10–15)	12.5 (16–20)	12.5 (10–15)	12.5 (10–15)
8c	12.5 (10–15)	12.5 (16–20)	12.5 (10–15)	12.5 (10–15)
8d	12.5 (10–15)	12.5 (16–20)	12.5 (10–15)	12.5 (10–15)
8e	12.5 (10–15)	12.5 (16–20)	12.5 (10–15)	12.5 (10–15)
8f	50 (<10)	50 (<10)	50 (<10)	50 (<10)
8g	50 (<10)	50 (<10)	50 (<10)	50 (<10)
9a	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
9b	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
9c	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
9d	50 (<10)	50 (<10)	50 (<10)	50 (<10)
9e	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
9f	50 (<10)	50 (<10)	50 (<10)	50 (<10)
9g	50 (<10)	50 (<10)	50 (<10)	50 (<10)
9h	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
10a	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
10b	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
10c	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
10d	50 (<10)	50 (<10)	50 (<10)	50 (<10)
10e	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
10f	50 (<10)	6.25 (20–24)	50 (<10)	50 (<10)
10g	50 (<10)	6.25 (20–24)	50 (<10)	50 (<10)
10h	6.25 (16–20)	6.25 (20–24)	6.25 (16–20)	6.25 (16–20)
Ciclopirox olamine (standard)	6.25 (20–27)	3.125 (27–33)	3.125 (25–30)	6.25 (25–30)

Note: The MIC values where evaluated at concentration range, 6.25–50 μg/mL. The figures in the table show the MIC values in μg/mL and the corresponding zone of inhibition in mm.

compounds. In the final step of synthesis we made use of microwave initiator, which not only made reaction time less but also gave very good yields. It can be concluded that a combination of two different heterocyclic systems namely quinoline and triazole has enhanced the pharmacological effect and hence they are ideally suited for further modifications to obtain more efficacious antibacterial compounds.

4. Experimental section

4.1. General

All reagents were purchased from Aldrich. Some of the amines which were used for final coupling were synthesized in the laboratory. Solvents used were extra dried. Final purifications were carried out using Quad biotage Flash purifier (A Dyax Corp. Company). Microwave-assisted syntheses were performed in Biotage initiator. TLC experiments were performed on alumina-backed silica gel 40 F254 plates (Merck, Darmstadt, Germany). The plates were illuminated under UV (254 nm) and molybidinic acid. Melting points were determined using Buchi B-540 and are uncorrected. Elemental analyses were carried out on an automatic Flash EA 1112 Series, CHNSO Analyzer (Thermo). All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 (300.12 MHz) and AM-400 (400.13 MHz), Bruker BioSpin Corp., Germany. Molecular weights of unknown compounds were checked by LCMS 6200 series Agilent Technology. The mass spectra of a few were recorded on a 410 Prostar binary PDA detector (Varian Inc, USA). Chemical shifts are reported in ppm (δ) with reference to internal standard TMS. The signals are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet; brs, broad singlet, brt, broad triplet.

The microwave reaction was carried out in a 5 mL vial type. The absorption level was kept high with a pre-stirring of 30 s and stirring rate at 600 rpm. Initially the power was kept zero, followed by a gradual increase to 175 W, the reaction proceeded at a constant power of 35 W with temperature 120 °C and 2-bar pressure. The microwave irradiation was continued at 35 W for 10 min wherein the reaction was completed. Fig. 1 show graphs A, B and C which summarize variation of power, temperature and pressure against time during the reaction.

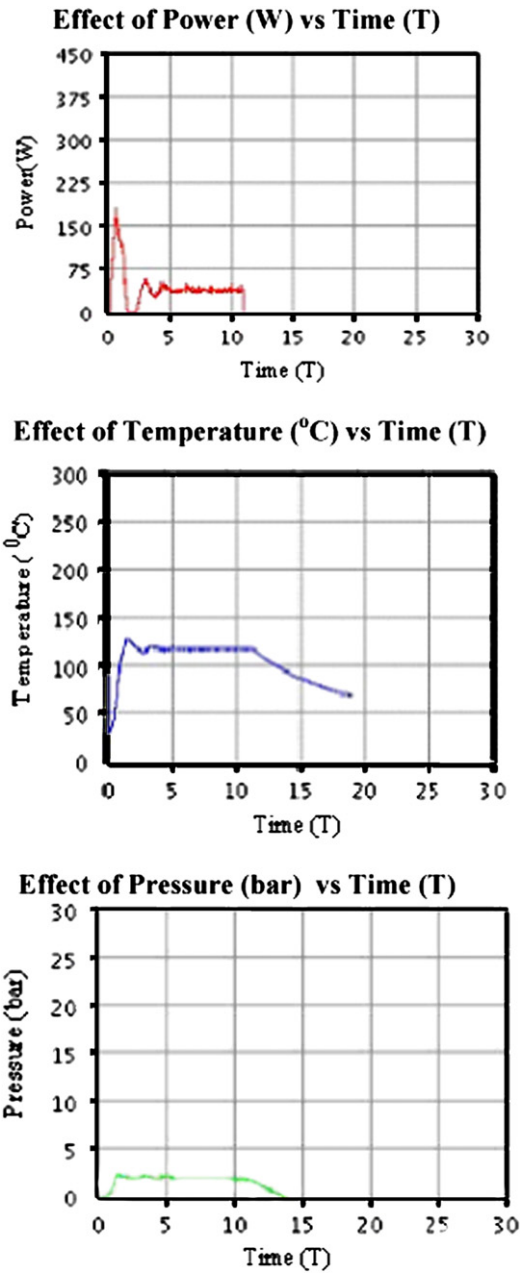


Fig. 1. Graphs A, B and C which summarize variation of power, temperature and pressure against time respectively during the reaction.

4.2. Preparation of diethyl({[2-(trifluoromethyl)phenyl]amino}methylene)malonate (**2**)

A suspension of 2-(trifluoromethyl)aniline 5 g (31 mmol) and diethyl ethoxymethylene malonate 8 g (37.2 mmol) was heated to 110 °C for 4 h. The reaction mixture was cooled to room temperature, the solid thus formed was taken in pet ether and stirred for 15 min and filtered to get compound **2** as a white crystalline solid 9.7 g (95% yield).

IR (KBr, cm^{-1}) υ: 3467 (>NH), 1709 (>C═O), 1657 (>C═C<), 1164 (>C–F). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm; 1.35 (t, $-CH_3$, 3H, $J = 5.3$ Hz), 1.38 (t, $-CH_3$, 3H, $J = 5.3$ Hz), 4.25 (q, $-CH_2$, 2H), 4.34 (q, $-CH_2$, 2H), 7.25 (m, –CH, 1H), 7.36 (d, –CH, 1H, $J = 6.1$ Hz), 7.62 (m, –CH, 2H), 8.45 (d, –NCH═, 1H, $J = 9.6$ Hz). Anal. Calcd for $C_{15}H_{16}F_3NO_4$; C, 54.38; H, 4.87; N, 4.23; found; C, 54.31; H, 4.79; N, 4.17.

4.3. Preparation of ethyl 8-(trifluoromethyl)-4-hydroxyquinoline-3-carboxylate (**3**)

Compound **2**, 9 g (27 mmol) was heated at 250 °C for 4 h in Dowtherm medium. The reaction mixture was cooled to room temperature and added hexane and stirred for 15 min, the solid thus precipitated was filtered and dried to get compound **3** as a white solid 3.5 g (45% yield).

IR (KBr, cm^{-1}) υ: 3519 (O–H), 3449 (>NH), 1709 (>C═O), 1164 (>C–F). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm; 1.29 (t, $-CH_3$, 3H, $J = 7.2$ Hz), 4.23 (q, $-CH_2$, 2H), 7.59 (t, –CH, 1H, $J = 6.9$ Hz), 8.13 (d, –CH, 1H, $J = 7.5$ Hz), 8.47 (m, –CH, 2H), 11.69 (brs, –OH, 1H, disappeared on D_2O exchange). LC/MS: (ESI) m/z 286 (M + 1). Anal. Calcd for $C_{13}H_{10}F_3NO_3$; C, 54.74; H, 3.53; N, 4.91; found; C, 54.71; H, 3.43; N, 4.97.

4.4. Synthesis of 4-hydroxy-8-(trifluoromethyl)quinoline-3-carbohydrazide (**4**)

A mixture of 10 g (35 mmol) ethyl 4-hydroxy-8-(trifluoromethyl)quinoline-3-carboxylate and 5.2 g (105 mmol)of

hydrazine hydrate 60% in 50 mL of ethanol was heated under reflux for 2.5 h. Completion of the reaction was monitored by TLC. The reaction mixture was concentrated and allowed to cool. The solid product obtained was filtered, washed with water and recrystallized from ethanol: diethyl ether (1:3) to give product **4** as white solid 8 g (85% yield).

IR (KBr, cm^{-1}) υ: 3519 (O–H), 3256 & 3293 (>NH), 1653 (>C═O), 1164 (>C–F). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm; 7.61 (t, –CH, 1H, $J = 7.8$ Hz), 8.16 (d, –CH, 1H, $J = 7.5$ Hz), 8.55 (d, –CH, 1H, $J = 7.8$ Hz), 8.65 (s, –CH, 1H), 10.52 (brs, –OH, 1H disappeared on D_2O exchange). LC/MS: (ESI) m/z 271.9 (M + 1). Anal. Calcd for $C_{11}H_8F_3N_3O_2$; C, 48.72; H, 2.97; N, 15.49; found; C, 48.78; H, 2.93; N, 15.55.

4.5. General procedure for the synthesis of 4-hydroxy-8-(trifluoromethyl)quinoline thiosemicarbazide (**5a–c**)

A suspension of **4** (1 mmol), isothiocyanate (1.5 mmol) and a catalytic amount of pyridine (0.2 mmol) in ethanol (10 mL) was heated under reflux on oil bath for 3 h. Reaction completion was monitored by TLC. The solvent was concentrated and the solid thus obtained was taken in minimum quantity of ethanol, stirred for 10 min and filtered. The compounds were recrystallized from ethanol to afford products **5a–c** as white crystalline solid (85–90% yield). Purity of all the quinoline-thiosemicarbazide derivatives obtained were judged through TLC and MS and were taken as such for the next step without any further purification.

4.6. General procedure for the synthesis of (5-mercapto-4H-triazol-3-yl)-8-(trifluoromethyl)quinolin-4-ol (**6a–c**)

A suspension of **5a–c** (1 mmol) in 50 mL of aqueous potassium hydroxide (4 mmol) was gently heated to 105 °C for 2 h. The reaction mixture was cooled to room temperature, was added 10 mL of water and aqueous layer was extracted with diethyl ether (2 times with 100 mL). Then the aqueous layer was cooled to 0 °C, acidified to pH ≈ 4, the precipitate thus obtained was filtered, dried and finally recrystallized from diethyl ether to get the desired product as white fluffy solid. Characterization data of **6a–c** are given below.

4.6.1. 3-(4-Benzyl-5-mercapto-4H-1,2,4-triazol-3-yl)-8-(trifluoromethyl)quinolin-4-ol (**6a**)

Compound **6a** was obtained as a white solid. Yield 91%. IR (KBr, cm^{-1}) υ: 3529 (O–H), 3345 (>NH), 1623 (>C═N), 1204 (>C═S), 1164 (>C–F). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm; 5.28 (s, $–CH_2$, 2H), 6.98 (m, –CH, 2H), 7.00 (m, –CH, 3H), 7.62 (t, –CH, 1H, $J = 7.8$ Hz), 7.95 (s, –CH, 1H), 8.18 (d, –CH, 1H, $J = 7.8$ Hz), 8.53 (d, –CH, 1H, $J = 8.7$ Hz), 11.82 (s, –SH, 1H), 14.08 (s, –OH, 1H, disappeared on D_2O exchange). LC/MS: (ESI) m/z 403 (M + 1).

4.6.2. 8-(Trifluoromethyl)-3-(5-mercapto-4-phenyl-4H-1,2,4-triazol-3-yl)quinolin-4-ol (**6b**)

Compound **6b** was obtained as an off white solid. Yield 93%. IR (KBr, cm^{-1}) υ: 3525 (O–H), 3345 (>NH), 1623 (>C═N), 1204 (>C═S), 1164 (>C–F). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm; 7.31–7.37 (m, –CH, 5H), 7.43 (t, –CH, 1H, $J = 7.8$ Hz), 8.12 (d, –CH, 1H, $J = 7.5$ Hz), 8.24 (d, –CH, 1H, $J = 6.3$ Hz), 8.28 (s, –CH, 1H), 11.73 (d, –SH, 1H, $J = 6.6$ Hz), 14.08 (s, –OH, 1H, disappeared on D_2O exchange). LC/MS: (ESI) m/z 389 (M + 1).

4.6.3. 8-(Trifluoromethyl)-3-(5-mercapto-4-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl) quinolin-4-ol (**6c**)

Compound **6c** was obtained as white solid. Yield 92%. IR (KBr, cm^{-1}) υ: 3529 (O–H), 3345 (>NH), 1623 (>C═N), 1204 (>C═S), 1164 (>C–F), 1121 (>C–O–). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm; 3.03 (s, –OMe, 3H), 3.51 (t, $–CH_2$, 2H, $J = 5.4$ Hz), 4.07 (t, $–CH_2$, 2H, $J = 5.4$ Hz), 7.59 (t, –CH, 1H, $J = 7.8$ Hz), 8.12 (s, –CH, 1H), 8.19 (d, –CH, 1H, $J = 7.5$ Hz), 8.51 (d, –CH, 1H, $J = 7.8$ Hz), 11.90 (s, –SH, 1H), 14.06 (s, –OH, 1H, disappeared on D_2O exchange). LC/MS: (ESI) m/z 371 (M + 1).

4.7. General procedure for the synthesis of 4-chloro-8-(trifluoromethyl) quinolin-3-yl triazole-3-thiole (**7a–c**)

Compound **6a–c** (1 mmol) was taken in 10 mL of distilled $POCl_3$ and heated for 3 h at 60 °C. Reaction completion was monitored by TLC. Excess of $POCl_3$ was distilled off and to the distillate was added crushed ice. After stirring for 15 min, the aqueous layer was extracted with ethyl acetate (2 times with 100 mL). Combined organic extract was washed with brine, dried over Na_2SO_4, filtered and concentrated. Crude product thus obtained was purified by column chromatography on silica gel eluting with ethyl acetate/pet ether (1:9) to get product as a yellow crystalline solid. Characterization data of **7a–c** are given below.

4.7.1. 4-Benzyl-5-(4-chloro-8-(trifluoromethyl)quinolin-3-yl)-4H-1,2,4-triazole-3-thiol (**7a**)

Compound **7a** was obtained as a pale yellow solid. Yield 65%. IR (KBr, cm^{-1}) υ: 3335 (>NH), 1623 (>C═N), 1204 (>C═S), 1164 (>C–F), 780 (C–Cl). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm; 5.27 (s, $–CH_2$, 2H), 6.87 (d, –CH, 2H, $J = 7.8$ Hz), 7.07 (t, –CH, 2H, $J = 6.9$ Hz), 7.17 (m, –CH, 1H), 7.85 (t, –CH, 1H, $J = 7.8$ Hz), 8.27 (d, –CH, 1H, $J = 7.5$ Hz), 8.51 (d, –CH, 1H, $J = 9$ Hz), 8.54 (s, –CH, 1H), 12.25 (brs, –SH, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 47.24, 120.57, 125.81, 126.86, 127.25, 127.58, 128.18, 128.79, 130.09, 131.51, 131.58, 135.46, 144.37, 145.37, 146.78, 151.26, 168.47. LC/MS: (ESI) m/z 421 (M + 1).

4.7.2. 5-(4-Chloro-8-(trifluoromethyl)quinolin-3-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol (**7b**)

Compound **7b** was obtained as a yellow solid. Yield 73%. IR (KBr, cm^{-1}) υ: 3335 (>NH), 1623 (>C═N), 1204 (>C═S), 1164 (>C–F), 780 (C–Cl). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm; 7.32–7.45 (m, –CH, 5H), 7.77 (t, –CH, 1H, $J = 7.8$ Hz), 8.22 (d, –CH, 1H, $J = 7.2$ Hz), 8.44 (d, –CH, 1H, $J = 8.4$ Hz), 8.92 (s, –CH, 1H), 12.34 (brs, –SH, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm; 120.66, 125.51, 126.84, 127.23, 128.48, 128.88, 129.61, 129.96, 131.6, 133.79, 143.71, 145.21, 146.69, 152.08, 168.98. LC/MS: (ESI) m/z 407 (M + 1).

4.7.3. 5-(4-Chloro-8-(trifluoromethyl)quinolin-3-yl)-4-(2-methoxyethyl)-4H-1,2,4-triazole-3-thiol (**7c**)

Compound **7c** was obtained as a white solid. Yield 71%. IR (KBr, cm^{-1}) υ: 3335 (>NH), 1623 (>C═N), 1204 (>C═S), 1164 (>C–F), 1124 (>C–O–), 780 (C–Cl). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm; 3.12 (s, $–CH_3$, 3H), 3.61 (t, $–CH_2$, 2H, $J = 4.8$ Hz), 4.17 (t, $–CH_2$, 2H, $J = 4.8$ Hz), 7.84 (t, –CH, 1H), 8.27 (d, –CH, 1H, $J = 7.2$ Hz), 8.56 (d, –CH, 1H, $J = 8.7$ Hz), 8.97 (s, –CH, 1H), 11.88 (brs, –SH, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 44.48, 58.40, 68.37, 121.06, 125.97, 126.89, 128.74, 130.19, 131.41, 144.11, 145.32, 147.56, 152.11, 167.52. LC/MS: (ESI) m/z 389 (M + 1).

4.8. General procedure for the synthesis of title compounds (**8a–g**, **9a–h** and **10a–h**)

To a suspension of compound **7a–c** (1 mmol) in dry acetonitrile, taken in a 5 mL microwave vial was added dry potassium carbonate (2 mmol). The reaction mixture was purged with argon gas for 1 min and was added substituted amine (1 mmol). The vial was irradiated with microwave for 10 min at 35 W constant power and 120 °C temperature. Reaction was monitored by TLC. Reaction mixture was then added to water followed by neutralized with 1.5 N HCl, then extracted with ethyl acetate (75 mL × 2). Combined organic layer was dried over magnesium sulphate, concentrated

and the solvent was evaporated under reduced pressure. The crude compound thus obtained was purified by biotage column. The compound comes out with 60–80% of pet ether/ethyl acetate.

*4.8.1. 4-Benzyl-5-[4-(cyclopropylamino)-8-(trifluoromethyl)quinolin-3-yl]-4H-1,2,4-triazole-3-thiol (**8a**)*

Compound **8a** was obtained as a white solid. IR (KBr, cm^{-1}) υ: 3345 (>NH), 1623 (>C═N), 1204 (>C═S), 1164 (>C–F). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm; 0.41 (m, –CH_2, 2H of cyclopropyl ring), 0.55 (m, –CH_2, 2H of cyclopropyl ring), 2.21 (m, –CH, 1H of cyclopropyl ring) 5.15 (s, CH_2, 2H of benzylic moiety), 6.97 (d, –CH, 2H, $J = 7.5$ Hz), 7.18 (m, –CH, 3H), 7.63 (t, –CH, 1H, $J = 7.8$ Hz), 7.86 (brs, NH, 1H), 8.04 (s, –CH, 1H), 8.11 (d, –CH, 1H, $J = 7.2$ Hz), 8.72 (d, –CH, 1H, $J = 9$ Hz), 14.09 (brs, –SH, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 8.42, 29.54, 47.24, 120.57, 125.81, 126.86, 127.25, 127.58, 128.18, 128.79, 130.09, 131.51, 131.58, 135.46, 144.37, 145.37, 146.78, 151.26, 168.47. LC/MS: (ESI) *m*/*z* 442.1 (M + 1).

*4.8.2. 4-Benzyl-5-[4-(cyclohexylamino)-8-(trifluoromethyl)quinolin-3-yl]-4H-1,2,4-triazole-3-thiol (**8b**)*

Compound **8b** was obtained as a white solid. IR (KBr, cm^{-1}) υ: 3345 (>NH), 1623 (>C═N), 1204 (>C═S), 1164 (>C–F). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 0.82–1.25 (m, –CH, 5H of cyclohexane), 1.46–1.6 (m, –CH, 5H of cyclohexane), 2.29 (m, –CH, 1H of cyclohexane), 5.08 (s, CH_2, 2H of benzylic moiety), 6.97 (m, –CH, 2H and –NH, 1H), 7.16 (m, –CH, 3H), 7.63 (t, –CH, 1H, $J = 8$ Hz), 8.13 (d, –CH, 1H, $J = 7.2$ Hz), 8.22 (s, –CH, 1H), 8.70 (d, –CH, 1H, $J = 8.5$ Hz), 14.18 (brs, –SH, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 25.42, 28.66, 34.54, 47.24, 51.8, 120.57, 125.81, 126.86, 127.25, 127.58, 128.18, 128.79, 130.09, 131.51, 131.58, 135.46, 144.37, 145.37, 146.78, 151.26, 168.47. LC/MS: (ESI) *m*/*z* 484.1 (M + 1).

*4.8.3. 5-(4-(3,3-Dimethylbutylamino)-8-(trifluoromethyl)quinolin-3-yl)-4-benzyl-4H-1,2,4-triazole-3-thiol (**8c**)*

Compound **8c** was obtained as an off white solid. IR (KBr, cm^{-1}) υ: 3340 (>NH), 1623 (>C═N), 1204 (>C═S), 1164 (>C–F). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm; 0.73 (s, –$C(CH_3)_3$, 9H of tert butyl), 1.31 (t, –CH_2, 2H of isobutyl moiety, $J = 8.4$ Hz), 2.54 (m, –N–CH_2, 2H of isobutyl moiety), 5.12 (s, CH_2, 2H of benzylic moiety), 6.97 (d, –CH, 2H, $J = 7.2$ Hz), 7.15 (m, –CH, 3H), 7.19 (brs, –NH, 1H), 7.64 (t, –CH, 1H, $J = 7.8$ Hz), 8.12 (d, –CH, 1H, $J = 7.2$ Hz), 8.19 (s, –CH, 1H), 8.65 (d, –CH, 1H, $J = 8.7$ Hz), 14.18 (brs, –SH, 1H). LC/MS: (ESI) *m*/*z* 486.1 (M + 1).

*4.8.4. 2-(1-(3-(4-Benzyl-5-mercapto-4H-1,2,4-triazol-3-yl)-8-(trifluoromethyl)quinolin-4-yl)piperidin-4-yl) propan-1-ol (**8d**)*

Compound **8d** was obtained as yellow solid. IR (KBr, cm^{-1}) υ: 3495 (O-H), 1623 (>C═N), 1204 (>C═S), 1164 (>C–F). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 1.39–1.45 (m, $(CH_2)_4$ and –CH, 9H), 1.57 (m, –OCH_2, 2H of propanol moiety), 2.74 (m, N–CH_2, 2H, CH_2 of piperidine moiety), 3.33 (m, –NCH_2, 2H of piperidine moiety), 4.37 (t, –OH, 1H of propanol moiety, $J = 5.1$ Hz), 5.25 (s, CH_2, 2H of benzylic moiety), 7.00 (d, –CH, 2H, $J = 6.8$ Hz), 7.18 (m, –CH, 3H), 7.73 (t, –CH, 1H, $J = 7.8$ Hz), 8.12 (d, –CH, 1H, $J = 7.2$ Hz), 8.29 (d, –CH, 1H, $J = 8.4$ Hz), 8.58 (s, –CH, 1H), 14.26 (brs, –SH, 1H). LC/MS: (ESI) *m*/*z* 528.1 (M + 1).

*4.8.5. 4-Benzyl-5-(8-(trifluoromethyl)-4-morpholinoquinolin-3-yl)-4H-1,2,4-triazole-3-thiol (**8e**)*

Compound **8e** was obtained as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm; 2.68 (brt, –$N(CH_2)_2$, 4H of morpholine ring), 3.62 (brt, –$O(CH_2)_2$, 4H of morpholine ring), 5.29 (s, –CH_2, 2H of benzylic moiety), 7.02 (d, –CH, 2H, $J = 6$ Hz), 7.17 (m, –CH, 3H), 7.77 (t, –CH, 1H, $J = 7.8$ Hz), 8.26 (d, –CH, 1H, $J = 6.9$ Hz), 8.42 (d, –CH, 1H, $J = 8.4$ Hz), 8.66 (s, –CH, 1H), 14.34 (brs, –SH, 1H). LC/MS: (ESI) *m*/*z* 472.1 (M + 1).

*4.8.6. 4-Benzyl-5-(4-(4-cyclohexylpiperazin-1-yl)-8-(trifluoromethyl)quinolin-3-yl)-4H-1,2,4-triazole-3-thiol (**8f**)*

Compound **8f** was obtained as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 1.06–1.28 (m, –$C(CH_2)_3$, 6H of cyclohexyl moiety), 1.73 (m, –$C(CH_2)_2$, 4H of cyclohexyl moiety), 2.24 (m, –N–CH, 1H, junction proton of cyclohexyl moiety), 2.79 (brs, –$N(CH_2)_2$, 4H of piperazine moiety), 3.34 (m, –$N(CH_2)_2$, 4H of piperazine moiety), 5.26 (brs, –CH_2, 2H of benzylic moiety), 6.99 (d, –CH, 2H, $J = 7.2$ Hz), 7.19 (m, –CH, 3H), 7.74 (t, –CH, 1H, $J = 8$), 8.23 (d, –CH, 1H, $J = 7.2$ Hz), 8.36 (d, –CH, 1H, $J = 8.6$ Hz), 8.60 (s, –CH, 1H), 14.30 (brs, –SH, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 25.76, 26.33, 28.77, 47.13, 49.05, 52.69, 63.19, 120.15, 126.06, 128.15, 128.43, 128.95, 130.38, 135.62, 146.37, 148.57, 152.50, 156.58, 168.28. LC/MS: (ESI) *m*/*z* 553.2 (M + 1).

*4.8.7. 5-(4-(4-(2-Aminoethyl)piperazin-1-yl)-8-(trifluoromethyl)quinolin-3-yl)-4-benzyl-4H-1,2,4-triazole-3-thiol (**8g**)*

Compound **8g** was obtained as a pale yellow solid. IR (KBr, cm^{-1}) υ: 1623 (>C═N), 1204 (>C═S), 1164 (>C–F). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm; 2.12 (brs, –NH_2, 2H), 2.20 (brt, –$N(CH_2)_2$, 4H of piperazine ring), 2.32 (t, N–CH_2, 2H, attached to piperazine ring, $J = 6.6$ Hz), 2.74 (t, N–CH_2, 2H, attached to NH_2 group, $J = 6$ Hz), 3.48 (brt, –$N(CH_2)_2$, 4H of piperazine ring attached to quinoline ring) 5.16 (s, –CH_2, 2H of benzylic moiety), 6.93 (d, –CH, 2H, $J = 6.9$ Hz), 7.15 (m, –CH, 3H), 7.68 (t, –CH, 1H, $J = 7.8$ Hz), 8.14 (d, –CH, 1H, $J = 7.2$ Hz), 8.27 (s, –CH, 1H), 8.52 (d, –CH, 1H, $J = 8.7$ Hz), 14.22 (brs, –SH, 1H). MS: (ESI) (*m*/*z*, %): 515 (M + 2, 45), 496 (19), 470 (18), 438 (37), 395 (37), 353 (37), 351 (100), 239 (18).

*4.8.8. 5-(4-(Cyclopropylamino)-8-(trifluoromethyl)quinolin-3-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol (**9a**)*

Compound **9a** was obtained as off white solid. IR (KBr, cm^{-1}) υ: 3345 (>NH), 1630 (>C═N), 1210 (>C═S), 1164 (>C–F). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm; 0.62 (m, –CH_2, 2H of cyclopropyl ring), 0.63 (m, –CH_2, 2H of cyclopropyl ring), 1.26 (m, –CH, 1H of cyclopropyl ring), 4.46 (brs, –NH, 1H), 7.33 (d, –CH, 2H, $J = 7$ Hz), 7.39 (m, –CH, 3H), 7.64 (m, –CH, 1H), 8.05 (d, –CH, 1H, $J = 7.2$ Hz), 8.51 (s, –CH, 1H), 8.57 (d, –CH, 1H, $J = 8.7$ Hz), 14.15 (brs, –SH, 1H). LC/MS: (ESI) *m*/*z* 428.2 (M + 1).

*4.8.9. 5-(4-(Cyclohexylamino)-8-(trifluoromethyl)quinolin-3-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol (**9b**)*

Compound **9b** was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 0.92–1.4 (m, –CH, 5H of cyclohexane), 1.73–1.83 (m, –CH, 5H of cyclohexane), 2.82 (m, –CH, 1H of cyclohexane), 6.90 (brs, –NH, 1H), 7.27–7.42 (m, –CH, 5H), 7.56 (t, –CH, 1H, $J = 7.8$ Hz), 8.07 (d, –CH, 1H, $J = 7.2$ Hz), 8.56 (s, –CH, 1H), 8.58 (d, –CH, 1H, $J = 8.6$ Hz), 14.25 (brs, –SH, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 25.55, 32.98, 39.77, 54.29, 99.47, 115.99, 120.21, 124.19, 128.28, 129.37, 129.60, 129.70, 129.81, 134.15, 145.59, 149.65, 149.89, 153.80, 168.30. MS: (ESI) (*m*/*z*, %): 470.3 (M + 1, 9), 469.3 (18), 468.4 (100).

*4.8.10. 5-(4-(3,3-Dimethylbutylamino)-8-(trifluoromethyl)quinolin-3-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol (**9c**)*

Compound **9c** was obtained as off white solid. IR (KBr, cm^{-1}) υ: 3340 (>NH), 1630 (>C═N), 1210 (>C═S), 1164 (>C–F).^{1}H NMR (300 MHz, DMSO-d_6) δ ppm; 0.82 (s, –$C(CH_3)_3$, 9H of tert butyl), 1.49 (t, –CH_2, 2H of isobutyl moiety, $J = 5.4$), 3.05 (m, –N–CH_2, 2H of isobutyl moiety), 7.19 (brs, –NH, 1H), 7.38 (m, –CH, 5H, benzene ring), 7.52 (t, –CH, 1H, $J = 7.8$ Hz), 8.07 (d, –CH, 1H, $J = 7.5$ Hz), 8.47 (s, –CH, 1H), 8.53 (d, –CH, 1H, $J = 9$ Hz), 14.25 (brs, –SH, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 29.66, 32.46, 41.20, 46.35, 120.66, 125.51, 126.84, 127.23, 128.48, 128.88, 129.61, 129.96, 131.6, 133.79,

143.71, 145.21, 146.69, 152.08, 168.98. LC/MS: (ESI) *m/z* 472.2 (M + 1).

*4.8.11. 3-(1-(8-(Trifluoromethyl)-3-(5-mercapto-4-phenyl-4H-1,2,4-triazol-3-yl)quinolin-4-yl)piperidin-4-yl)propan-1-ol (**9d**)*

Compound **9d** was obtained as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 1.43–1.48 (m, $(CH_2)_4$ and –CH, 9H), 1.74 (m, $–OCH_2$, 2H of propanol moiety), 2.61 (m, $N–CH_2$, 2H, CH_2 of piperidine moiety), 3.40 (m, $–NCH_2$, 2H of piperidine moiety), 4.40 (t, –OH, 1H of propanol moiety, $J = 5.1$ Hz), 7.43 (m, –CH, 5H, benzene ring), 7.69 (t, –CH, 1H, $J = 7.8$ Hz), 8.16 (d, –CH, 1H, $J = 7.2$ Hz), 8.29 (d, –CH, 1H, $J = 8.5$ Hz), 8.74 (s, –CH, 1H), 14.34 (brs, –SH, 1H). LC/MS: (ESI) *m/z* 514.2 (M + 1).

*4.8.12. 5-(8-(Trifluoromethyl)-4-morpholinoquinolin-3-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol (**9e**)*

Compound **9e** was obtained as a off white solid. IR (KBr, cm^{-1}) υ: 1630 (>C=N), 1210 (>C=S), 1164 (>C–F). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 2.95 (brt, $–N(CH_2)_2$, 4H of morpholine ring), 3.80 (brt, $–O(CH_2)_2$, 4H of morpholine ring), 7.46 (m, –CH, 5H, benzene ring), 7.70 (t, –CH, 1H, $J = 7.8$ Hz), 8.19 (d, –CH, 1H, $J = 7.2$ Hz), 8.39 (d, –CH, 1H, $J = 8.4$ Hz), 8.76 (s, –CH, 1H), 14.42 (brs, –SH, 1H). LC/MS: (ESI) *m/z* 458.1 (M + 1).

*4.8.13. 5-(4-(4-Cyclohexylpiperazin-1-yl)-8-(trifluoromethyl)quinolin-3-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol (**9f**)*

Compound **9f** was obtained as a off white solid. IR (KBr, cm^{-1}) υ: 1630 (>C=N), 1210 (>C=S), 1164 (>C–F). LC/MS: (ESI) *m/z* 539.2 (M + 1).

*4.8.14. 5-(8-(Trifluoromethyl)-4-(4-isopropylpiperazin-1-yl)quinolin-3-yl)-4-phenyl-4 H-1,2,4-triazole-3-thiol (**9g**)*

Compound **9g** was obtained as a pale yellow solid. IR (KBr, cm^{-1}) υ: 1630 (>C=N), 1210 (>C=S), 1164 (>C–F). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm; 1.15 (d, $–C(CH_3)_2$, 6H, $J = 6.6$ Hz), 2.62 (m, $–N(CH_2)_2$, 4H of piperazine ring), 2.96 (m, N–CH, 1H, junction proton of isopropyl group), 3.09 (brs, $N–(CH_2)_2$, 4H of piperazine ring connected to quinoline ring), 7.45 (m, –CH, 5H, benzene ring), 7.73 (t, –CH, 1H, $J = 7.9$ Hz), 8.18 (d, –CH, 1H, $J = 7.5$ Hz), 8.36 (d, –CH, 1H, $J = 8.1$ Hz), 8.79 (s, –CH, 1H), 14.23 (brs, –SH, 1H). LC/MS: (ESI) *m/z* 499.2 (M + 1).

*4.8.15. 5-(8-Trifluoromethyl-4-(4-morpholinopiperidin-1-yl)quinolin-3-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol (**9h**)*

Compound **9h** was obtained as a off white solid. IR (KBr, cm^{-1}) υ: 1630 (>C=N), 1210 (>C=S), 1164 (>C–F). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 1.24 (m, $–C(CH_2)_2$, 4H of piperidine), 1.67–1.87 (m, $–N(CH_2)_2$, 4H of morpholine ring), 2.65 (m, $N–(CH_2)_2$, N–CH junction proton of piperidine, 5H), 3.60 (brs, $O(CH_2)_2$, 4H of morpholine ring), 7.45 (m, –CH, 5H, benzene ring), 7.71 (t, –CH, 1H, $J = 7.8$ Hz), 8.18 (d, –CH, 1H, $J = 7.3$ Hz), 8.26 (d, –CH, 1H, $J = 8.6$ Hz), 8.76 (s, –CH, 1H), 14.37 (brs, –SH, 1H). MS: (ESI) *m/z* 541.2 (M + 1).

*4.8.16. 5-[4-(Cyclopropylamino)-8-(trifluoromethyl)quinolin-3-yl]-4-(2-methoxyethyl)-4H-1,2,4-triazole-3-thiol (**10a**)*

Compound **10a** was obtained as an off white solid. IR (KBr, cm^{-1}) υ: 3345 (>NH), 1623 (>C=N), 1204 (>C=S), 1164 (>C–F), 1120 (>C–O–). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm; 0.45 (m, $–CH_2$, 2H of cyclopropyl ring), 0.57 (m, $–CH_2$, 2H of cyclopropyl ring), 1.25 (m, –CH, 1H of cyclopropyl ring), 3.01 (s, $–OCH_3$, 3H), 3.59 (m, $–OCH_2$, 2H of methoxyethyl moiety), 3.98 (t, $–NCH_2$, 2H of methoxyethyl moiety, $J = 5.1$ Hz), 4.22 (brt, –NH, 1H), 7.63 (m, –CH, 1H), 8.15 (d, –CH, 1H, $J = 7.2$ Hz), 8.43 (s, –CH, 1H), 8.71 (d, –CH, 1H, $J = 8.4$ Hz), 13.96 (brs, –SH, 1H). LC/MS: (ESI) *m/z* 410.1 (M + 1).

*4.8.17. 5-(4-(Cyclohexylamino)-8-(trifluoromethyl)quinolin-3-yl)-4-(2-methoxyethyl)-4H-1,2,4-triazole-3-thiol (**10b**)*

Compound **10b** was obtained as a white solid. IR (KBr, cm^{-1}) υ: 3345 (>NH), 1623 (>C=N), 1204 (>C=S), 1164 (>C–F), 1122 (>C–O–). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm; 0.83 (m, –CH, 2H of cyclohexane), 1.28–1.73 (m, $–(CH_2)_4$, 8H of cyclohexane), 2.82 (m, N–CH, 1H of cyclohexane), 3.00 (s, $–OCH_3$, 3H), 3.53 (m, $–OCH_2$, 2H of methoxyethyl moiety), 3.98 (t, $–NCH_2$, 2H of methoxyethyl moiety, $J = 4.8$ Hz), 7.75 (t, –CH, 1H, $J = 8.1$ Hz), 8.12 (brs, –NH, 1H), 8.24 (d, –CH, 1H, $J = 7.5$ Hz), 8.42 (s, –CH, 1H), 8.97 (d, –CH, 1H, $J = 8.4$ Hz), 14.21 (brs, –SH, 1H). LC/MS: (ESI) *m/z* 452.1 (M + 1).

*4.8.18. 5-(4-(3,3-Dimethylbutylamino)-8-(trifluoromethyl)quinolin-3-yl)-4-(2-methoxy ethyl)-4H-1,2,4-triazole-3-thiol (**10c**)*

Compound **10c** was obtained as a white solid. IR (KBr, cm^{-1}) υ: 3345 (>NH), 1623 (>C=N), 1204 (>C=S), 1164 (>C–F), 1124 (>C–O–). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm; 0.80 (s, $–C(CH_3)_3$, 9H of tert butyl), 1.47 (brt, $–CH_2$, 2H of isobutyl moiety), 2.87 (brt, $–N–CH_2$, 2H of isobutyl moiety), 2.98 (s, $–OCH_3$, 3H), 3.53 (m, $–OCH_2$, 2H of methoxyethyl moiety), 3.99 (t, $–NCH_2$, 2H of methoxyethyl moiety, $J = 4.6$ Hz), 4.25 (t, –NH, 1H, $J = 4.5$ Hz), 7.71 (t, –CH, 1H, $J = 8$ Hz), 8.19 (d, –CH, 1H, $J = 7.2$ Hz), 8.40 (s, –CH, 1H), 8.80 (d, –CH, 1H, $J = 8.4$ Hz), 14.13 (brs, –SH, 1H). LC/MS: (ESI) *m/z* 454.2 (M + 1).

*4.8.19. 3-(1-(8-(Trifluoromethyl)-3-(5-mercapto-4-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl) quinolin-4-yl)piperidin-4-yl)propan-1-ol (**10d**)*

Compound **10d** was obtained as off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 1.45–1.48 (m, $(CH_2)_4$ and –CH, 9H), 1.74 (m, $–OCH_2$, 2H of propanol moiety), 2.74 (m, $N–CH_2$, 2H of piperidine moiety), 3.01 (s, $–OCH_3$, 3H), 3.36 (m, $–NCH_2$, 2H of piperidine moiety), 3.61 (m, $–OCH_2$, 2H of methoxyethyl moiety), 4.06 (m, $–NCH_2$, 2H of methoxyethyl moiety), 4.39 (t, –OH, 1H of propanol moiety, $J = 5.1$ Hz), 7.77 (t, –CH, 1H, $J = 7.8$ Hz), 8.24 (d, –CH, 1H, $J = 7.2$ Hz), 8.39 (d, –CH, 1H, $J = 8.5$ Hz), 8.73 (s, –CH, 1H), 14.16 (brs, –SH, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 29.99, 30.22, 32.84, 32.99, 35.36, 44.64, 58.27, 61.38, 63.42, 68.29, 111.77, 125.41, 125.78, 128.82, 129.67, 129.77, 130.45, 146.43, 149.47, 153.34, 157.11, 167.23. MS: (ESI) (*m/z*, %): 496.2 (M + 1, 12), 495.3 (31), 494.4 (100).

*4.8.20. 5-(8-(Trifluoromethyl)-4-morpholinoquinolin-3-yl)-4-(2-methoxyethyl)-4H-1,2,4-triazole-3-thiol (**10e**)*

Compound **10e** was obtained as an off white solid. IR (KBr, cm^{-1}) υ: 1623 (>C=N), 1204 (>C=S), 1164 (>C–F), 1124 (>C–O–). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm; 2.35 (brt, $–N(CH_2)_2$, 4H of morpholine ring), 3.00 (s, $–OCH_3$, 3H), 3.31 (brt, $–O(CH_2)_2$, 4H of morpholine ring), 3.58 (m, $–OCH_2$, 2H of methoxyethyl moiety), 4.00 (m, $–N–CH_2$, 2H of methoxyethyl moiety attached to triazole ring), 7.77 (t, –CH, 1H, $J = 8.1$ Hz), 8.25 (d, –CH, 1H, $J = 6.9$ Hz), 8.45 (d, –CH, 1H, $J = 7.8$ Hz) , 8.76 (s, –CH, 1H), 14.16 (brs, –SH, 1H). LC/MS: (ESI) *m/z* 440.1 (M + 1).

*4.8.21. 5-(4-(4-Cyclohexylpiperazin-1-yl)-8-(trifluoromethyl)quinolin-3-yl)-4-(2-methoxy ethyl)-4H-1,2,4-triazole-3-thiol (**10f**)*

Compound **10f** was obtained as a pale green solid. IR (KBr, cm^{-1}) υ: 1623 (>C=N), 1204 (>C=S), 1164 (>C–F), 1124 (>C–O–). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm; 1.06–1.30 (m, $–C(CH_2)_3$, 6H of cyclohexyl moiety), 1.79–1.75 (m, $–C(CH_2)_2$, 4H of cyclohexyl moiety), 2.30 (m, –N–CH, 1H, junction proton of cyclohexyl moiety), 2.68 (brs, $–N(CH_2)_2$, 4H of piperazine moiety), 3.01(s, $–OCH_3$, 3H), 3.06 (m, $–N(CH_2)_2$, 4H of piperazine moiety), 3.61 (m, $–OCH_2$, 2H of methoxyethyl moiety), 4.06 (m, $–N–CH_2$, 2H of methoxyethyl moiety attached to triazole ring), 7.77 (t, –CH, 1H, $J = 8.1$ Hz), 8.25

(d, –CH, 1H, $J = 6.9$ Hz), 8.45 (d, –CH, 1H, $J = 7.8$ Hz) , 8.76 (s, –CH, 1H), 14.20 (brs, –SH, 1H). LC/MS: (ESI) m/z 521.2 (M + 1).

*4.8.22. 5-(8-(Trifluoromethyl)-4-(4-ethylpiperazin-1-yl)quinolin-3-yl)-4-(2-methoxy ethyl)-4*H*-1,2,4-triazole-3-thiol (**10g**)*

Compound **10g** was obtained as an off white solid. IR (KBr, cm^{-1}) υ: 1623 (>C═N), 1204 (>C═S), 1164 (>C–F), 1120 (>C–O–). MS: (ESI) m/z 467.1 (M + 1).

*4.8.23. 5-(8-(Trifluoromethyl)-4-(2,6-dimethylmorpholino)quinolin-3-yl)-4-(2-methoxy ethyl)-4*H*-1,2,4-triazole-3-thiol (**10h**)*

Compound **10h** was obtained as a off white solid. IR (KBr, cm^{-1}) υ: 3345 (>NH), 1623 (>C═N), 1204 (>C═S), 1164 (>C–F), 1122 (>C–O–). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm; 1.25 (m, $(CH_3)_2$, 6H of morpholine), 2.40 (brt, $-N(CH_2)_2$, 4H of morpholine ring), 3.00 (s, $-OCH_3$, 3H), 3.61–3.82 (m, $-OCH_2$, 2H of methoxyethyl moiety and 3,5–CH, 2H of morpholine), 4.20 (m, $-N-CH_2$, 2H of methoxyethyl moiety attached to triazole ring), 7.83 (t, –CH, 1H, $J = 8$ Hz), 8.26 (d, –CH, 1H, $J = 6.9$ Hz), 8.48 (d, –CH, 1H, $J = 7.8$ Hz) , 8.81 (s, –CH, 1H), 14.21 (brs, –SH, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 35.36, 44.64, 60.22, 66.56, 68.29, 120.19, 124.43, 124.732 128.82, 129.34, 129.45, 130.45, 150.43, 152.47, 154.34, 157.11, 161.23. LC/MS: (ESI) m/z 468.1 (M + 1).

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