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SYNTHESIS, CHARACTERIZATION OF NEW 1, 2, 4-TRIAZOLE DERIVATIVES BEARING QUINOLINE NUCLEUS AND THEIR ANTIMICROBIAL AND ANTITUBERCULAR EVALUATION

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Abstract:
A new series of quinoline based 1,2,4-triazole derivatives 8a-l synthesized by chloro-amine coupling of 3a-f and 7a-b using K_2CO_3 as a catalyst. In which substituted 1,2,4-triazole intermediates 7a–b were synthesized from 2-(un)substituted-N-phenylhydrazinecarbothioamide 6a-b using 2N NaOH in reflux condition. The imperative features of this method are easy experimental procedure, high yield, reduce reaction time. The newly synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR, FT-IR and Mass spectrometry. The synthesized compounds were evaluated for their antibacterial, antifungal and antitubercular activities.

Key words:β-Aryloxyquinoline, 1,2,4-Triazole, Chloro-amine coupling, Antibacterial, Antifungal and Antitubercular activities.

Introduction

The synthesis of nitrogen containing heterocyclic compounds has been increasing attention over the past decade. Inspired from current research on triazole derivatives hybrid molecules and our previous research on triazole incorporated heterocycles[I-II]. We have design the hybrid of quinoline based triazole derivatives. As the positions of nitrogen atoms present in the ring were responsible for the binding of enzymes and receptors in biological system and show major biological activity. From literature survey, 1, 2, 4 triazoles possess low toxicity and good versatile biological activities such as, antimicrobial activity[III-VIII], antioxidant[IX], antifungal activity[X], anti-inflammatory activity[XI], antibacterial activity[XII], antifungal activity[XIII], antioxidant[XIV].

The quinoline nucleus has gained vast attention among chemists as well as biologists as it is found in a large variety of naturally occurring compounds. Its derivatives are useful in various syntheses, pharmaceutical and are available as drugs today. The quinoline moiety has versatile biological activities such as, anti-tuberculosis[XV], anticancer[XVI], antimicrobial and antitubercular activity[XVII].

Therefore, need for new antimicrobial drugs with novel mode of action and a broad spectrum of activities is a major challenge. In the light of afore mentioned reports, we were encouraged

by potential clinical application of quinoline derivatives and various triazole derivatives. Our efforts are focused to design and synthesized such pharmaceutically active hybrid molecules having potential biological activities. An attempt has been through to undertake the quinoline based triazole derivatives catalyzed by K_2CO_3 and evaluated their antimicrobial and antitubercular activities.

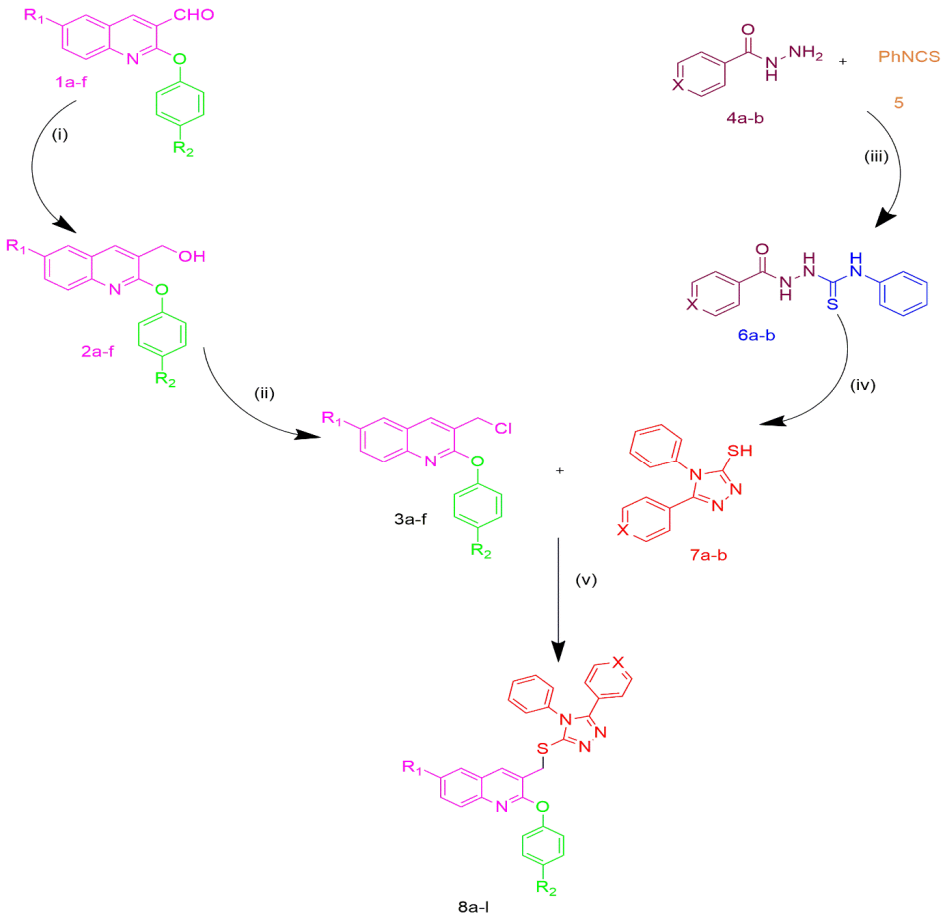
Results and Discussion

Chemistry

The synthesis of the target molecules is given in **Scheme 1**. From the literature procedure, the starting material 2-chloro-3-formyl quinoline **1a-f** was prepared by Vilsmeier-Haack reaction of acetanilide. The starting materials 3-(chloromethyl)-2-(4-(un)substituted phenoxy)-6-(un)substituted quinoline **3a-f** were prepared by reduction of 2(4(un)substitutedphenoxy)6(un)substitutedquinoline-3-carbaldehyde **1a-f**[XVIII] and then chlorination of (2-(4-(un)substituted phenoxy)-6-(un)substitutedquinolin-3-yl)methanol **2a-f** and another starting materials, 4-phenyl-5-(un)substitutedphenyl-4*H*-1,2,4-triazole-3-thiol **7a-b**[XIX], were prepared by mixing different hydrazides **4a-b** with phenylisocyanate **5,** and then refluxing with 2N NaOH. The final compounds 6-(un)substituted-2-(4(un)substitutedphenoxy)3(((4phenyl5(un)substitutedphenyl)-4*H*-1,2,4-triazol-3-yl)thio)methyl)quinoline **8a-l** were synthesized by chloro-amine coupling between **3a-f** and **7a-b** using K_2CO_3 as a catalyst.

The structures of all the synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR, and FT-IR spectrometry. In ^{1}H NMR of **8e** show signal for three protons of methyl at δ 2.44. For S-CH_2 protons (methylene protons at the quinoline ring) as a sharp singlet at around δ 4.61, so we can be confirmed that SH are attached to the CH_2 of this quinoline ring. The aromatic protons resonate as multiplets at δ 7.09-8.55 ppm. The ^{13}C spectra show signal at 21.3 for Ar-CH_3, the signal at around δ 32.5 ppm were assigned to the methylene carbon of quinoline at the 3-position attached to the sulphur of the 1,2,4-triazole. The signal at 121.8-159.1 for aromatic carbon atoms. Mass spectra of compound **8e** gave molecular ion peak at m/z 502 [M^+] corresponding molecular formula $C_{30}H_{23}N_5OS$. The IR spectra of **8e** showed the presence of characteristic absorption band 1642cm^{-1} which was attributed to the presence of C=N stretching and 1078 cm^{-1} band for the N-N starching for 1,2,4-triazole ring. From above data, we can be conformed the structure of **8e**. (See supplementary file)

Scheme 1. Synthetic route for the title compound **8a-l**



Where, (i) = Methanol, $NaBH_4$, RT, 10-15 min; (ii) = $SOCl_2$, DCM, 1.5-2 hr; (iii) = Ethanol, reflux, 1hr; (iv) = 2N NaOH, reflux, 2hr; (v) = DMF, K_2CO_3, 2hr. 85^oC

Table 1. Synthesis of new triazole based quinoline derivatives 8a-l at 85^{o}C using K_2CO_3

Compound	R_1	R_2	X	Yield (%)
3a	OCH_3	Cl	-	91
3b	H	H	-	89
3c	H	Cl	-	92
3d	CH_3	Cl	-	87
3e	CH_3	H	-	92
3f	H	H	-	92
7a	-	-	N	84
7b	-	-	CH	86
8a	OCH_3	Cl	N	76
8b	H	H	N	71
8c	H	Cl	N	69
8d	CH_3	Cl	N	93
8e	CH_3	H	N	79
8f	H	H	CH	75
8g	H	Cl	CH	72
8h	CH_3	Cl	CH	71
8i	OCH_3	Cl	CH	76

8j	OCH_3	H	N	73
8k	CH_3	H	CH	74
8l	OCH_3	H	CH	71

Biological activity

Antimicrobial activity

Gram positive bacteria

The values of the MIC against microorganisms tested are reported in Table II. The investigation showed that some of the compound showed excellent activity and some of them comparable activity against Gram-positive and Gram-negative strains. Among them compound 8f [MIC]=62.5 µg ml-1) show outstanding activity, compounds 8a, 8b, 8d, 8e, 8h (MIC=100 µg ml-1) displayed excellent activity, compounds 8g, 8i (MIC=125 µg ml-1) displayed good activity against Gram-positive bacteria B.subtillis as compared to standard drug Ampicillin (MIC=250 µg ml-1). Against C.tetani compound 8i (MIC=100 µg ml-1) displayed excellent activity, 8b, 8e, 8f (MIC=125 µg ml-1) show good activity, 8a, 8d, 8g (MIC=200 µg ml-1) exhibited moderate activity compare to ampicillin (MIC=250 µg ml-1).

Gram Negative bacteria

Against Gram-negative bacteria E.coli compounds 8a, 8e, 8f, 8h, 8i (MIC=100 µg ml-1) expressed comparable activity to ampicillin (MIC=100 µg ml-1). Against S.typhi compound 8e (MIC=62.52 µg ml-1) displayed excellent activity, compounds 8b, 8h (MIC=100 µg ml-1) displayed equivalent activity against ampicillin (MIC=100 µg ml-1). Moreover, against V.cholera compounds 8a, 8g (MIC=62.5 µg ml-1) showed outstanding activity, 8c, 8i (MIC=100 µg ml-1) found equipotent activity compare to ampicillin (MIC=100 µg ml-1).

Antifungal activity

Against fungal pathogen C.albicans, compounds 8b, 8d, 8f, 8h, 8i, 8j (MIC=500 µg ml-1) displayed equivalent activity compare to Griseofulvin (MIC=500 µg ml-1). Against T.rubrum compound 8g (MIC=500 µg ml-1) displayed equivalent activity compare to Griseofulvin (MIC=500 µg ml-1).

Table II. The in vitro antimicrobial activity of compounds 8a-l

Minimum inhibitory concentration in µg/Ml

Compound	**Gram positive bacteria**			**Gram negative bacteria**			**Fungi**	
	B.S. MTCC441	C.T. MTCC449	S.P. MTC1936	E.C. MTCC443	S.T. MTCC98	V.C. MTCC3906	C.A. MTCC227	T.R. MTCC296
8a	**100**	**200**	200	**100**	125	**62.5**	>1000	1000
8b	**100**	**125**	250	250	**100**	500	**500**	1000
8c	**250**	500	125	100	125	**100**	1000	>1000
8d	**100**	**200**	250	200	125	125	**500**	>1000
8e	**100**	**125**	125	**100**	**62.5**	125	1000	>1000
8f	**62.5**	**125**	125	**100**	125	250	**500**	1000
8g	**125**	**200**	250	250	250	**62.5**	1000	**500**
8h	**100**	**250**	200	**100**	**100**	250	**500**	1000
8i	**125**	**100**	200	**100**	200	**100**	**500**	>1000
8j	500	500	500	250	250	200	1000	1000
8k	**250**	**250**	250	250	500	250	**500**	1000
8l	500	500	250	500	250	200	1000	1000
Ampi.	250	250	100	100	100	100	-	-
Chlo.	50	50	50	50	50	50	-	-
Cipro.	50	100	50	25	25	25	-	-

Nyst.	-	-	-	-	-	-	100	500
Gre.	-	-	-	-	-	-	500	500

SP: *Streptococcus pneumoniae*, CT: *Clostridium tetani,* BS: *Bacillus subtilis*, ST: *Salmonella typhi*, VC: *Vibrio cholera*, EC: *Escherichia coli*, CA: *Candida albicans*, TR: Trichophytonrubrum, Ampi.: Ampicillin; Cipr.: Ciprofloxacin; Chlo.: Chloramphenicol; Gri.: Griseofulvin; Nyst.: Nystatin. MTCC: Microbial Type Culture Collection Bolt value indicates compounds are more or equal potent than standard drug, - not tested, [MIC]: minimum inhibitory concentration

Table III. Antituberculosis activity of compounds 8a-l

METHOD	**L.J.MEDIUM(CONVETIONAL METHOD)**		
BECTERIA	**$H_{37}RV$**		
CONCENTRATION	**250 µg/ml**		
STANDARD DRUG	**ISONIAZIDE**		
Compound	**% Inhibition**	**Compound**	**% Inhibition**
8a	54%	**8h**	63%
8b	58%	**8i**	45%
8c	30%	**8j**	74%
8d	24%	**8k**	45%
8e	**85%**	**8l**	56%
8f	**91**%	ISONIAZIDE	99%
8g	25%		

Antituberculosis activity

The screening results of the synthesized compounds and the standard drugs are reported in Table 3. The compound 8f displayed good activity against M. tuberculosis $H_{37}Rv$ with 91% inhibition and compound 8e displayed moderate activity against M. tuberculosis $H_{37}Rv$ with 85% inhibition. Unfortunately, the majority of compounds showed poor inhibition of M. tuberculosis growth.

Experimental

Chemistry

The chemicals were used without any further purification. All reactions were monitored by thin layer chromatography (TLC) on aluminium plates coated with silica gel 60 F254, of 0.25 mm thickness (Merck). Melting points were taken using the melting point apparatus ThermoCal10 (Analab Scientific Pvt. Ltd, India) and are uncorrected. Mass spectra were recorded using a Shimadzu LCMS 2010 spectrometer (Shimadzu, Tokyo, Japan) purchased under the PURSE program of DST at Sardar Patel University, Vallabh Vidyanagar, India. ^{1}H and ^{13}C Nuclear Magnetic Resonance spectra were recorded in DMSO-d_6 on a Bruker Avance 400F (MHz) spectrometer (Bruker Scientific Corporation Ltd, Switzerland) using the residual solvent signal as an internal standard at 400 MHz and 100 MHz, respectively. The IR spectra were recorded using a FTIR MB 3000 spectrometer (ABB Bomem Inc., Canada/Agaram Industries, Chennai) using Zn–Se optics (490–8500 cm^{-1}) and only the characteristic peaks are reported in cm^{-1}.

General procedure for the synthesis of targeted compound 6-(un)substituted-2-(4-(un)substitutedphenoxy)-3-(((4-phenyl-5-(un)substitutedphenyl)-4H-1,2,4-triazol-3-yl)thio)methyl)quinoline 8a-l

Take 50 mL round bottomed flask, fitted with a reflux condenser and was charged with a mixture of 3-(chloromethyl)-2-(4-(un)substituted phenoxy)-6-(un)substituted quinoline **3a–f** (1 mmol) and4-phenyl-5-(un)substitutedphenyl-4H-1,2,4-triazole-3-thiol **7a-b** (1 mmol) and

anhydrous K_2CO_3 (1.3 mmol) in dimethyl formamide (6 mL). The reaction mixture was heated at 85–90 °C for 1.5–2 h and the progress of the reaction was monitored by TLC. After completion of reaction cool the reaction mixture and then pour into crush ice with continuous stirring followed by neutralization with 1 N HCl to pH 7. Filter to give the crude product. The obtained product was recrystallized from ethanol. The physicochemical and spectroscopic characterization data of the synthesized compounds **8a–l**are given in supplementary.

Optimization reaction condition for the synthesis of 8d compound

In this research work, we examined the model reaction in absence and presence of catalyst at the different temperature. When the reaction was carried out without addition of catalyst, no product was obtained. When we were used acetic acid as a catalyst the product was obtained 58% with reflux condition. And if we used NaOH and p-TsOH than no product was found, starting material remains as same. The best result was obtained when K_2CO_3 was used and yield was 93%. Such results are shown in **Table IV**.

Table IV. Optimization Reaction condition for the synthesis of 8d compound

Entry[a]	Catalyst	Temperature	Time (min.)	Yield
1	CH_3COOH	Reflux	170	58
2	NaOH	Reflux	190	-
3	Piperidine	80	150	50
4	**K_2CO_3**	**85**	**120**	**93**
5	p-TsOH	80	140	-

2-(4-chlorophenoxy)-6-methoxy-3-(((4-phenyl-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)thio)methyl)quinoline (8a)

Creamy white solid; m.p. 210-214; IR (KBr) V_{max}: 1645 (C=N str.), 1072 (N-N str.), 746 (C-Cl str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.86 (s, 3H, Ar–OCH_3), 4.59 (s, 2H, S–CH_2), 7.13-7.50 (m, 14H), 8.27 (s, 1H), 8.55 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 32.5 (S-CH_2), 55.3 (Ar-OCH_3), 104.3, 121.6, 121.8 122.4, 125.8, 126.8, 128.0, 128.7, 129.5, 130.6, 132.5, 133.3, 134.3, 134.8, 139.4, 142.9, 143.6, 150.2, 151.5, 152.8, 154.3 159.6; LC-MS: 551$[M]^+$; anal. calcd (%) for $C_{30}H_{22}ClN_5O_2S$: C, 65.27; H, 4.02; N, 12.69. Found: C, 65.45; H, 4.12; N, 12.55

2-phenoxy-3-(((4-phenyl-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)thio)methyl)quinoline (8b)

Creamy white solid; m.p. 205-209; IR (KBr) V_{max}: 1656 (C=N str.), 1058 (N-N str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.62 (s, 2H, S-CH_2), 7.11-7.93 (m, 15H), 7.92 (d, 1H), 8.36 (s, 1H), 8.54 (d, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 32.4 (S-CH_2), 121.7, 121.8, 122.3, 124.8, 125.3, 126.7, 126.9, 127.1, 128.2, 129.6, 129.9, 130.5, 130.7, 132.8, 134.1, 134.7, 139.2, 143.6, 150.4, 152.6, 153.7, 159.5; LC-MS: 489$[M]^+$; anal. calcd (%) for $C_{29}H_{21}N_5OS$: C, 71.44; H, 4.34; N, 14.36. Found: C, 71.74; H, 4.29; N, 14.44

2-(4-chlorophenoxy)-3-(((4-phenyl-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)thio)methyl)quinoline (8c)

Creamy white solid; m.p. 212-218; IR (KBr) V_{max}: 1680 (C=N str.), 1065 (N-N str.), 845 (C-Cl str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.61 (s, 2H, S-CH_2), 7.15-7.63 (m, 14H), 7.93 (d, 1H), 8.38 (s, 1H), 8.54 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 32.5 (S-CH_2), 121.7, 122.1, 124.2, 124.6, 126.4, 127.0, 128.3, 129.4, 129.8, 130.4, 131.4, 132.6, 133.4, 139.6, 135.2, 139.5, 142.8, 150.4, 152.6, 152.9, 153.4, 159.2; LC-MS: 524[M+2]; anal. calcd (%) for $C_{29}H_{20}ClN_5OS$: C, 66.72; H, 3.86; N, 13.42. Found: C, 66.87; H, 3.68; N, 13.48

2-(4-chlorophenoxy)-6-methyl-3-(((4-phenyl-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)thio)methyl)quinoline (8d)

Creamy white solid; m.p. 210-214; IR (KBr) V_{max}: 1675 (C=N str.), 1062 (N-N str.), 762 (C-Cl str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.44 (s, 3H, Ar-CH_3), 4.59 (s, 2H, S-CH_2), 7.13-7.57 (m, 13H), 7.68 (s, 1H), 8.26 (s, 1H), 8.54 (d, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.3 (Ar–CH_3), 32.4 (S–CH_2), 121.8, 121.9, 124.1, 126.0, 126.9, 127.0, 128.0, 129.2, 129.8, 130.5, 130.8, 132.5, 133.8, 134.3, 135.1, 139.4, 143.6, 150.5, 152.6, 152.8, 152.9, 159.0; LC-MS: 537[M+2]; anal. calcd (%) For $C_{30}H_{22}ClN_5OS$: C, 67.22; H, 4.14; N, 13.06. Found: C, 67.43; H, 4.06; N, 13.42

6-methyl-2-phenoxy-3-(((4-phenyl-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)thio)methyl)quinoline (8e)

Creamy white solid; m.p. 225-230; IR (KBr) V_{max}: 1642 (C=N str.), 1078 (N-N str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.44 (s, 3H, Ar-CH_3), 4.61 (s, 2H, S-CH_2), 7.09-7.58 (m, 14H), 7.68 (s, 1H), 8.26 (s, 1H), 8.54 (d, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.3 (Ar–CH_3), 32.5 (S–CH_2), 121.8, 121.9, 122.1, 125.2, 125.9, 126.9, 126.9, 128.0, 129.9, 130.5, 130.8, 132.4, 133.8, 134.3, 134.9, 139.3, 143.8, 150.5, 152.8, 152.9, 153.8, 159.3; LC-MS: 502[M+2]; anal. calcd (%) For $C_{30}H_{23}N_5OS$: C, 71.83; H, 4.62; N, 13.96. Found: C, 71.65; H, 4.81; N, 13.94

3-(((4,5-diphenyl-4H-1,2,4-triazol-3-yl)thio)methyl)-2-phenoxyquinoline (8f)

Creamy white solid; m.p. 212-214; IR (KBr) V_{max}: 1655 (C=N str.), 1045 (N-N str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.59 (s, 2H, S-CH_2), 7.11-7.88 (m, 16H), 7.93 (d, 1H), 8.35 (s, 1H), 8.55 (d, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 32.4 (S-CH_2), 121.6, 121.8, 124.2, 126.3, 126.8, 127.1, 127.8, 128.3, 129.4, 129.8, 130.4, 130.8, 131.2, 132.6, 133.8, 134.4, 135.4, 139.2, 143.4, 150.5, 152.6, 152.8, 159.6; LC-MS: 487 $[M]^+$; anal. calcd (%) For $C_{30}H_{22}N_4OS$: C, 74.05; H, 4.56; N, 11.51. Found: C, 74.28; H, 4.35; N, 11.62

2-(4-chlorophenoxy)-3-(((4,5-diphenyl-4H-1,2,4-triazol-3-yl)thio)methyl)quinoline (8g)

Creamy white solid; m.p. 220-224; IR (KBr) V_{max}: 1682 (C=N str.), 1063 (N-N str.), 857 (C-Cl str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.60 (s, 2H, S-CH_2), 7.14-7.68 (m, 15H), 7.93 (d, 1H), 8.37 (s, 1H), 8.55 (d, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 32.4 (S-CH_2), 121.6, 121.7, 122.4, 126.4, 126.8, 127.1, 127.6, 128.4, 129.5, 129.7, 130.2, 130.4, 130.8, 131.2, 132.6, 133.6, 134.4, 135.3, 139.4, 142.8, 150.1, 151.8, 159.6; LC-MS: 522[M+2]; anal. calcd (%) For $C_{30}H_{21}ClN_4OS$: C, 69.16; H, 4.06; N, 10.75. Found: C, 69.34; H, 4.18; N, 10.52

2-(4-chlorophenoxy)-3-(((4,5-diphenyl-4H-1,2,4-triazol-3-yl)thio)methyl)-6-methylquinoline (8h)

Creamy white solid; m.p. 210-214; IR (KBr) V_{max}: 1665 (C=N str.), 1075 (N-N str.), 750 (C-Cl str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.44 (s, 3H, Ar-CH_3), 4.59 (s, 2H, S-CH_2), 7.11-7.60 (m, 14H), 7.67 (s, 1H), 8.26 (s, 1H), 8.54 (d, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.4 (Ar-CH_3), 32.5 (S-CH_2), 121.4, 121.8, 122.4, 126.2, 126.4, 126.9, 127.4, 128.6, 129.4, 129.9, 130.4, 130.6, 131.2, 131.8, 132.4, 132.9, 133.6, 133.8, 134.4, 135.4, 150.8, 151.4, 159.6; LC-MS: 536[M+2]; anal. calcd (%) For $C_{31}H_{23}ClN_4OS$: C, 69.59; H, 4.33; N, 10.47. Found: C, 69.45; H, 4.16; N, 10.62

2-(4-chlorophenoxy)-3-(((4,5-diphenyl-4H-1,2,4-triazol-3-yl)thio)methyl)-6-methoxyquinoline (8i)

Creamy white solid; m.p. 215-220; IR (KBr) V_{max}: 1670 (C=N str.), 1068 (N-N str.), 675 (C-Cl str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.87 (s, 3H, Ar-OCH_3), 4.59 (s, 2H, S-CH_2), 7.14-7.48 (m, 15H), 8.27 (s, 1H), 8.54 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 32.4 (S-CH_2), 55.4 (Ar-OCH3), 104.8, 121.3, 121.8, 123.9, 124.3, 125.9, 126.2, 126.8, 127.0, 128.0, 129.6, 130.4, 130.5, 132.4, 133.6, 134.5, 135.2, 139.3, 143.4, 150.4, 152.4, 152.6, 158.9; LC-MS: 552[M+2]; anal. calcd (%) For $C_{31}H_{23}ClN_4O_2S$: C, 67.57; H, 4.21; N, 10.17. Found: C, 67.36; H, 4.52; N, 10.22

6-methoxy-2-phenoxy-3-(((4-phenyl-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)thio)methyl)quinoline (8j)

Creamy white solid; m.p. 222-226; IR (KBr) V_{max}: 1652 (C=N str.), 1058 (N-N str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.86 (s, 3H, Ar-OCH_3), 4.60 (s, 2H, S-CH_2), 7.16-7.51 (m, 15H), 8.27 (s, 1H), 8.55 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 32.5 (S-CH_2), 55.6 (Ar-OCH_3), 104.6, 121.6, 122.0, 124.9, 125.8, 126.8, 126.9, 127.9, 129.6, 130.4, 130.6, 132.3, 133.7, 134.2, 134.8, 139.2, 143.6, 150.6, 152.8, 152.9, 153.6, 159.5; LC-MS: 517$[M]^+$; anal. calcd (%) For $C_{30}H_{23}N_5O_2S$: C, 69.61; H, 4.48; N, 13.53. Found: C, 69.42, H, 4.21; N, 13.85

3-(((4,5-diphenyl-4H-1,2,4-triazol-3-yl)thio)methyl)-6-methyl-2-phenoxyquinoline (8k)

Creamy white solid; m.p. 204-208; IR (KBr) V_{max}: 1673 (C=N str.), 1054 (N-N str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.44 (s, 3H, Ar-CH_3), 4.59 (s, 2H, S-CH_2), 7.12-7.60 (m, 15H), 7.67 (s, 1H), 8.26 (s, 1H), 8.54 (d, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.3 (Ar-CH_3), 32.4 (Ar-CH_2), 121.6, 121.8, 124.1, 125.8, 126.8, 127.0, 128.2, 129.3, 129.7, 130.4, 130.8, 132.3, 133.7, 133.9, 134.2, 135.5, 138.9, 143.4, 150.4, 151.7, 152.2, 152.8, 159.0; LC-MS: 500$[M]^+$; anal. calcd (%) For $C_{31}H_{24}N_4OS$: C, 74.38; H, 4.83; N, 11.19. Found: C, 74.31; H, 4.52; N, 11.10

3-(((4,5-diphenyl-4H-1,2,4-triazol-3-yl)thio)methyl)-6-methoxy-2-phenoxyquinoline (8l)

Creamy white solid; m.p. 225-230; IR (KBr) V_{max}: 1685 (C=N str.), 1078 (N-N str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.86 (s, 3H, Ar-OCH_3), 4.59 (s, 2H, S-CH_2), 7.14-7.50 (m, 16H), 8.26 (s, 1H), 8.55 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 32.4 (S-CH_2), 55.5 (Ar-OCH_3), 104.2, 120.9, 121.4, 123.3, 125.9, 126.4, 127.0, 128.3, 129.3, 129.5, 130.4, 132.6, 132.9, 134.4, 135.3, 139.2, 139.8, 142.8, 150.4, 151.8, 152.4, 152.6, 159.3; LC-MS: 516 $[M]^+$; anal. calcd (%) For $C_{31}H_{24}N_4O_2S$: C, 72.07; H, 4.68; N, 10.85. Found: C, 72.39; H, 4.52, N, 10.63

Biological Assay

Antimicrobial Assay

The in vitro antimicrobial activity of all the synthesized compounds was carried out by broth micro dilution method[XX]. Antibacterial activity of synthesized compound was screened against three Gram-positive (*Bacillus subtilis* MTCC441, *Clostridium tetani* MTCC449, *Streptococcus pneumonia* MTCC1936) and three Gram-negative (*Escherichia coli* MTCC443, *Salmonella typhi* MTCC98, *Vibrio cholera* MTCC3906), each synthesized compound was diluted with di methyl sulfoxide. The compounds found to be active in primary screening were further screened in a second set of dilution at concentrations of 200, 100, 62.5, and 50 µg ml^{-1}. 10µl suspensions from each well were further inoculated, and growth was noted after 24 and 48 h. Some compounds showed good to excellent antimicrobial and antifungal activity. In this study, Ampicillin, Ciprofloxacin, Chloramphenicol were used as standard antibacterial drugs, whereas Griseofulvin and Nystatin were used as standard antifungal drugs. The data are given in **Table II**

Antituberculosis screening

In vitro antituberculosis activity of all the compound against *M. tuberculosis* $H_{37}Rv$ strain was determined using Lowenstein-Jensen medium (conventional method) as described by Rattan (2000) [XXI]. The Culture of *M. tuberculosis* $H_{37}Rv$ growing on Lowenstein-Jensen medium was harvested in 0.85% saline in bijou bottles. All test compound make solution of 250 mg ml^{-1} concentration of compound was prepared in DMSO. These tubes were then incubated at 37°C for 24h followed by streaking of *M. tuberculosis* $H_{37}Rv$ (5 X 10^4 bacilli per tube). These tube were then incubated at 37°C. The growth of bacilli was seen after 12, 22, 28 days of incubation. Tubes having compounds were compared with control tubes where medium alone was incubated with *M. tuberculosis* $H_{37}Rv$. The screening results are summarized as % inhibition relative to standard drug isoniazid.

Conclusion

Here we have reported a conventional method for the synthesis of quinoline based triazole derivative using K_2CO_3 non-hazardous and biodegradable. This synthesis strategy allows the construction of quinoline based triazole derivative with thio as well as oxo linkage from the appraisal of antimicrobial activity. We can conclude that compounds **8f, 8e, 8a, 8g** having excellent antibacterial activity while compounds **8b, 8d, 8f, 8h, 8i, 8j** having equivalent antifungal activity, while compounds **8e, 8f** found to have more efficient antitubercular activity as compared to standard drugs.

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