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Synthesis Characterization and Biological Evaluation of Substituted Some Novel Quinoline Derivatives Baring Hydrazone Moiety

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ABSTRACT

We recently present a series of substituted quinolines linked as hydrazones with core structural component 1,2,3-triazole compound as discriminative antimicrobial inhibitors. A wide range of research has been conducted on quinolines and triazole derivatives which have proved a large significance of heterocyclic nucleons. The present report is an attempt to discover the Safety profile of the in-vitro antimicrobial activity in five micro bacterial stains disclosed in this description.Characterizations of all hydrazones were conducted by Maas, IR, ^{1}HNMR and ^{13}C CMR spectrometers.

Keywords: 1-2-3-triazole, quinolines, hydrazones, high amount of purity and yield, antimicrobial activity, antifungal, *E. coli, P. aeruginosa, Kl. pneumoniae, S. aureus, P. marneffei*

1. INTRODUCTION

One of the leading diseases are microbial infections spread by bacteria and fungi, which causes millions of deaths every year worldwide due to the lack of effective antimicrobial therapy and more resistance captured by microorganisms against conventional antibiotics[1]. Evolution of resistance to actual drugs is a constant growing phenomenon that has concerned researchers all over the world, and now has attained alarming levels for certain infections. This

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combined with the current decline in the development of new drugs to combat them, which can be anticipated to margin to infections lacking ready treatments. A quinoline scaffold possess unique physico-chemical properties and so that it is present in many classes of biologically-active compounds [2] as HIV inhibitor[3] antimicrobial [3-8], anti-tuberculosis [9-12], antimalarial [13], antifungal [14-15], anti-inflammatory [16], anti-oxidants [17-18].

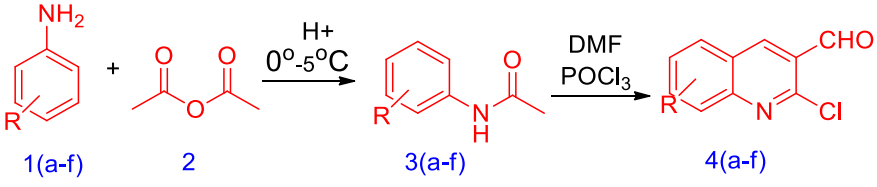
On other hand, the recent antifungal drugs are immensely toxic for example, amphotericin B, or are being ineffective due to presence of resistant stain for example- flucytosine and azoles. In treatment of fungal infection azoles remains the mainstay of therapy [19-20]. Triazoles are also described as an important family of heterocyclic compounds used in drug synthesis with various biological activities. Among them 1,2,4-triazole shows admirable safety profile immune kinetic characteristics for candida-albicans and Cryptococcus-neoformans due to its resistant activity [21]. Where 1,2,3-Triazole moieties are stable to metabolic degradation and are potent for hydrogen bonding, which can be supportive binding of bio-molecular targets and ligands with high solubility [22]. Additionally, hydrazone derivatives also exhibit potent and broad spectrum of biological activities as anti-microbial, analgesic-anti-inflammatory [23-36].

In present work we have evaluated the antimicrobial impact of (E)-1-(4-chlorophenyl)-N'-((2-chloroquinolin-3-yl)methylene)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide with excellent yield. These were synthesized using simple conventional method without heating source consuming less time (Table 2).

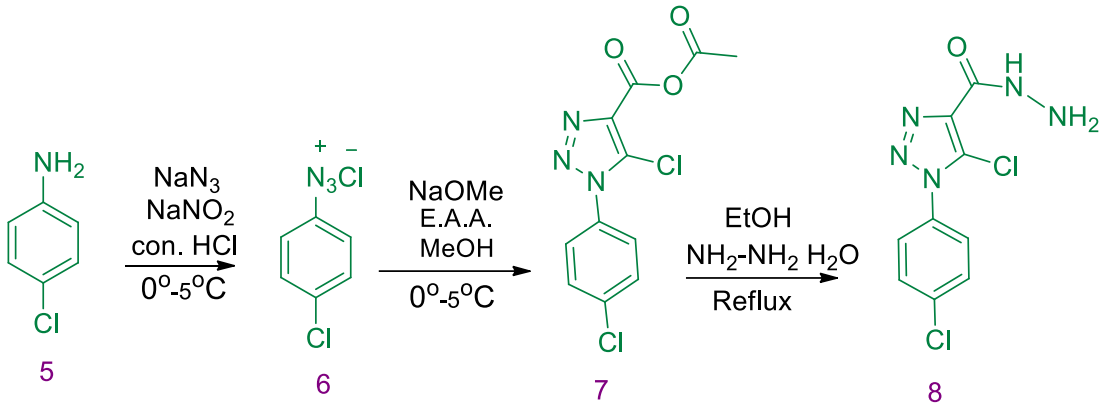
2. RESULTS AND DISCUSSION

We initially examine the synthesis of title compounds were prepared in presence of acidic media by conventional methods at room temperature (RT) adding dimethylformamide (DMF) as solvent. In earlier reports many methods taking place using various bases. The synthetic route used to synthesize the proposed scaffolds was outlined in Scheme 1. Aniline (1) was taken as starting material from which we have synthesized intermediates (4a-f) as per the reported process named Vilsmeier-Haack reaction and the synthesized intermediates were confirmed with the reported data. In the next Scheme 2, 4-chloroaniline (5) were diazotized by the treatment with $NaNO_2$ in the presence of hydrochloric acid followed by the reaction with sodium azide to afford desired azido benzene (6). azido benzene was reacted with ethylacetoacetate (E.A.A). in presence of sodium methoxide in methanol to afford the desired Intermediates (7). Further prepared intermediates reacted with hydrazine hydrate at reflux temperature to give corresponding Intermediates (8). Intermediates (4) and (8) were mixed in DMF in acidic media to give conjugated hydrazones as final Products (9a-f).

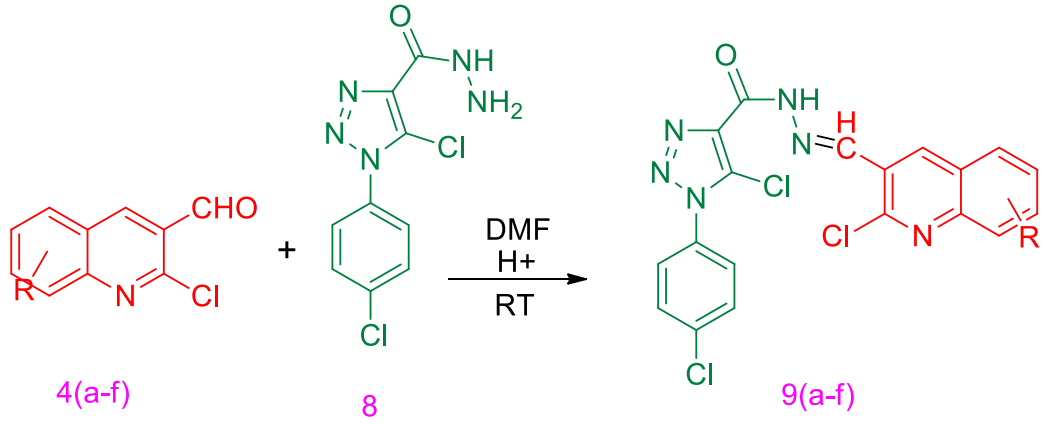
Table 1 and 2 represent list of optimization of yield produced by conventional method of synthesis of 9(a-f) using different solvent, time and % of yield. All the compounds were screened for their antimicrobial activity in 2 gram positive and 2 gram negative microbes along with one fungal stain. Table 3 represents biological evolution of all target molecules.



Scheme 1. Route of synthesis of compounds 4(a-f)



Scheme 2. Route of synthesis for compound 8



Scheme 3. Route of synthesis for compounds 9a-j

Table 1. Optimization of yield for the conventional method of synthesis of 9(a-j) using different solvents

Sr. No	Solvent	Time (min)	% yield
1	Hexane	60	10
2	Diethyl ether	40	10
3	Dichloromethane	35	60
4	Methanol	30	70
5	Ethanol	30	75
6	Dimethylformamide	≤15	≤ 80

Table 2. List of substituted Hydrazones (9 a-j) with Time, %yield and MP

Sr. No	Compound	substitutions	Time (min)	% yield	MP (°C)
1	9a	H	10	88	152
2	9b	6,7-dimethyl	15	84	183
3	9c	6-bromo	12	80	198
4	9d	6-methyl	15	82	176
5	9e	6,8-dimethyl	17	82	201
6	9f	5,8-dimethyl	15	80	187

Table 3. Antibacterial/Antifungal Activity Table[microgram/ml]. Minimum Inhibition Concentration

Sr. No	Code	*E. coli*	*P. aeruginosa*	*Kl. pneumoniae*	*S. aureus*	*P. marneffei*
		MTCC 443	MTCC 1688	MTCC 109	MTCC 96	WILD STAIN
1	9a	12.5	25	25	100	100
2	9b	25	50	100	50	500
3	9c	100	25	50	50	100
4	9d	50	50	100	25	250
5	9e	12.5	50	25	100	50
6	9f	25	50	100	25	50
7	Furacin	25	25	50	50	-
8	Itraconozole	-	-	-	-	100

Antibacterial activity of (E)-N'-((2-chloroquinolin-3-yl) methylene)-5-methyl-1-phenyl-1H-1,2,3-triazole-4-carbohydrazide derivatives **(9a,b,d,e)** was appraised against *E. coli, P. aeruginosa, Kl. pneumoniae, S. aureus, P. marneffei* (antifungal bacteria) using Furacin and itraconazole's standard drugs. Minimum bacterial inhibitory concentration (MIC) values were resolved by Broth dilution technique. Dimethylsulfoxide was used as diluent. MIC values of the appraised compounds are recorded in (Table 3). Majority of the prepared compounds displayed less activity than standard drug Furacin and ltraconozole against *E. coli, P. aeruginosa, Kl. pneumoniae, S. aureus, P. marneffei.*

3. MATERIALS AND METHODS

All starting materials and solvents used were pro analysis grade originated from Spectrochem, Sigma-Aldrich, Lobachemie. And Merck without further purification, i.e., substituted aniline, E.A.A, DMF, ethanol, methanol, sodium hydroxide, dichloromethane, hexane, ethylacetate, hydrochloric acid, chloroform, and dimethylsulfoxide. Thin layer chromatography (TLC) was conducted by using aluminum plates 20×20 cm coated by silica gel 60 F254 (Merck).

4. EXPERIMENTAL

4. 1. General information

All Final compounds (9a-f) were confirmed by mean of ^{1}H NMR, ^{13}C NMR and Mass and IR analysis. All melting points were recorded by melting point apparatus (uncorrected) using open capillary method. For all these conversions, progress of reaction was carried out by TLC plate. Visualization was made with ultra-violet (UV) light (254-365 nm) or with an iodine vapor. Solvents were evaporated with a BUCHI rotary evaporator. Mass spectra of the products were achieved from Mass spectrometer by Shimadzu GCMS-QP-2010 model using Direct Injection Probe technique.IR spectra were recorded on FTIR-8400 spectrometer using DRS prob. ^{1}H and ^{13}C NMR spectra were collected on a Bruker AVANCE II 400 MHz. 400 MHz (^{1}H) and 100 MHz (^{13}C) using $CDCl_3$ and DMSO as solvents, chemical shift are expressed in δ ppm down filed from TMS as standard internal.

4. 2. General procedure for the hydrozone synthesis from 1,2,3-triazol and quinoline intermediates

4. 2. 1. Synthesis of various N-phenylacetamide (3)

Aniline (1) (5.0g,0.038 mol) was taken in round bottom flask (RBF) at 0oC-5oC in ice bath acetic anhydride (4.7g,0.046 mol) was added drop wise into it with continuous stirring. After completion of addition, catalytic amount of sulfuric acid (H_2SO_4) is added to generate acidic media. Reaction progress was observed by TLC. After completion of the reaction pour the soluble content in to ice water to get precipitates (white solid product). Filter and dry it. (5.7g, 80.02%).

4. 2. 2. Synthesis of various 2-chloroquinoline-3-carbaldehyde (4a-f)

Phosphorus oxychloride ($POCl_3$) (67.91g, 0,4439 mol) was taken in RBF at 0 °C - 5 °C, DMF (6.32g, 0.1109) is added drop wise into $POCl_3$ by help of addition funnel very slowly at 0 °C - 5 °C. After completion of addition, yellow colored salt was prepared after that calculated amount of N-phenylacetamide (3) (5.0g, 0.0369 mol) is added in to it & RBF placed in oil bath at 80 °C for 16-24 hours. After completion of reaction pour the reaction mass in to crushed ice to get solid precipitate. (Yellow solid product) (5.9g, 83.76%).

4. 2. 3. Synthesis of azide salt derivatives of 4-chloroaniline (6)

To Form 1-azido-4-chlorobenzenechloride salt, addition of mixture of HCl (6 ml) and water (20 ml) were taken in RBF and cooled in ice bath at 0 °C - 5 °C. 4-chloroaniline (5.0g,

0.053 mol) was added slowly in to the solution while temperature kept constant between 0 °C - 5 °C then solution of sodium nitrite (3.65g,0.053mol) and sodium azide (3.44g,0.053 mol) were added drop wise at 0 °C - 5 °C. This reaction mass was stirred for 30 min. After completion of the reaction extraction of the residue using chloroform was taken place to give1-azido-4-chlorobenzene, chloride salt (4.2g, 70.42%).

4. 2. 4. Synthesis of ethyl 1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazole-4-carboxylate (7)

To lead the formation of ethyl1-(4-chlorophenyl)-5-methyl-1-phenyl-1H-1,2,3-triazole-4-carboxylate derivatives azide (4.2g ,0.035 mol) substance treated with E.A.A. (9.1g, 0.07 mol) then reaction mixture cooled at 0 °C - 5 °C and then sodium methoxide (3.78g, 0.07 mol) was added under inert atmosphere where methanol taken as a solvent. The reaction mixture was stirred at RT. After the completion of reaction content was poured in to the crushed ice, the obtained residue were filtered, dried and recrystallized from ethanol to give component (7) (6.5g, 80.39%)

4. 2. 5. Synthesis of 1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide (8)

The carbohydrazide derivative can be prepared by dissolving ethyl1-(4-chlorophenyl)-5-methyl-1-phenyl-1H-1,2,3-triazole-4-carboxylate (6g, 0.0259 mol) in to ethanol (30 ml) and then hydrazine hydrate (14 ml) was added drop wise and this reaction mass was refluxed for 6 hr at 80 ºC. After the completion of reaction, the reaction mass was cooled, residue was separated were filtered and washed with water to give product (5g, 88.80%).

4. 2. 6. Synthesis of (E)-1-(4-chlorophenyl)-N'-(1-(2-chloroquinolin-3-yl) ethylidene)-5-methyl-1-phenyl-1H-1,2,3-triazole-4-carbohydrazide (9a-f)

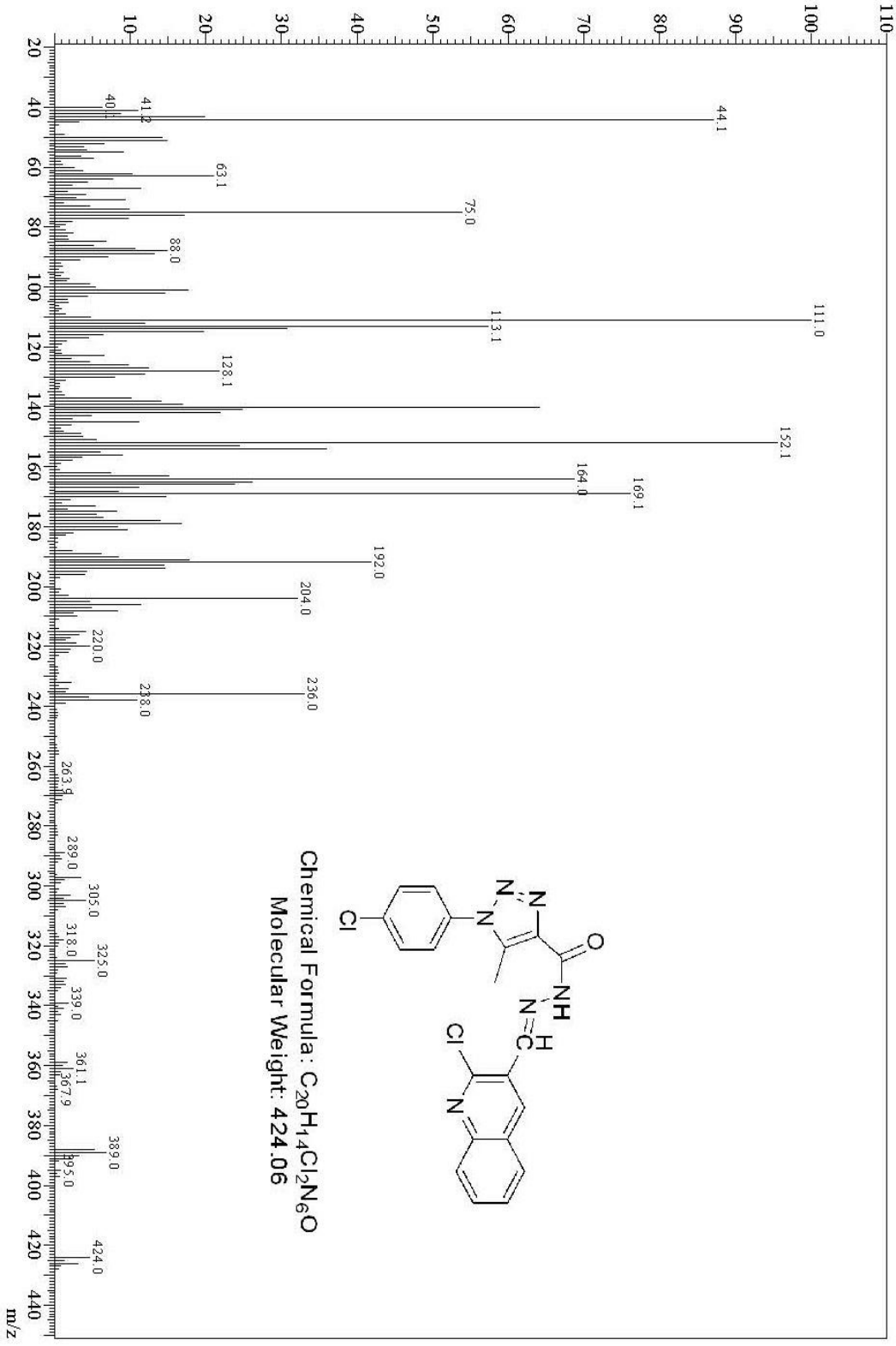
Hydrazones were prepared by dissolving 2-chloroquinoline-3-carbaldehyde(0.5g, 0.0026 mol) in to DMF and then added catalytic amount of H_2SO_4 to generate acidic medium at RT with continuous stirring, 1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide (0.650g, 0.0026 mol) was added into the reaction mass. Reaction mass was Stir for 11-15 min. after precipitation filter the mass and wash it with ice cold water and recrystallized from ethanol.

4. 3. Spectral data

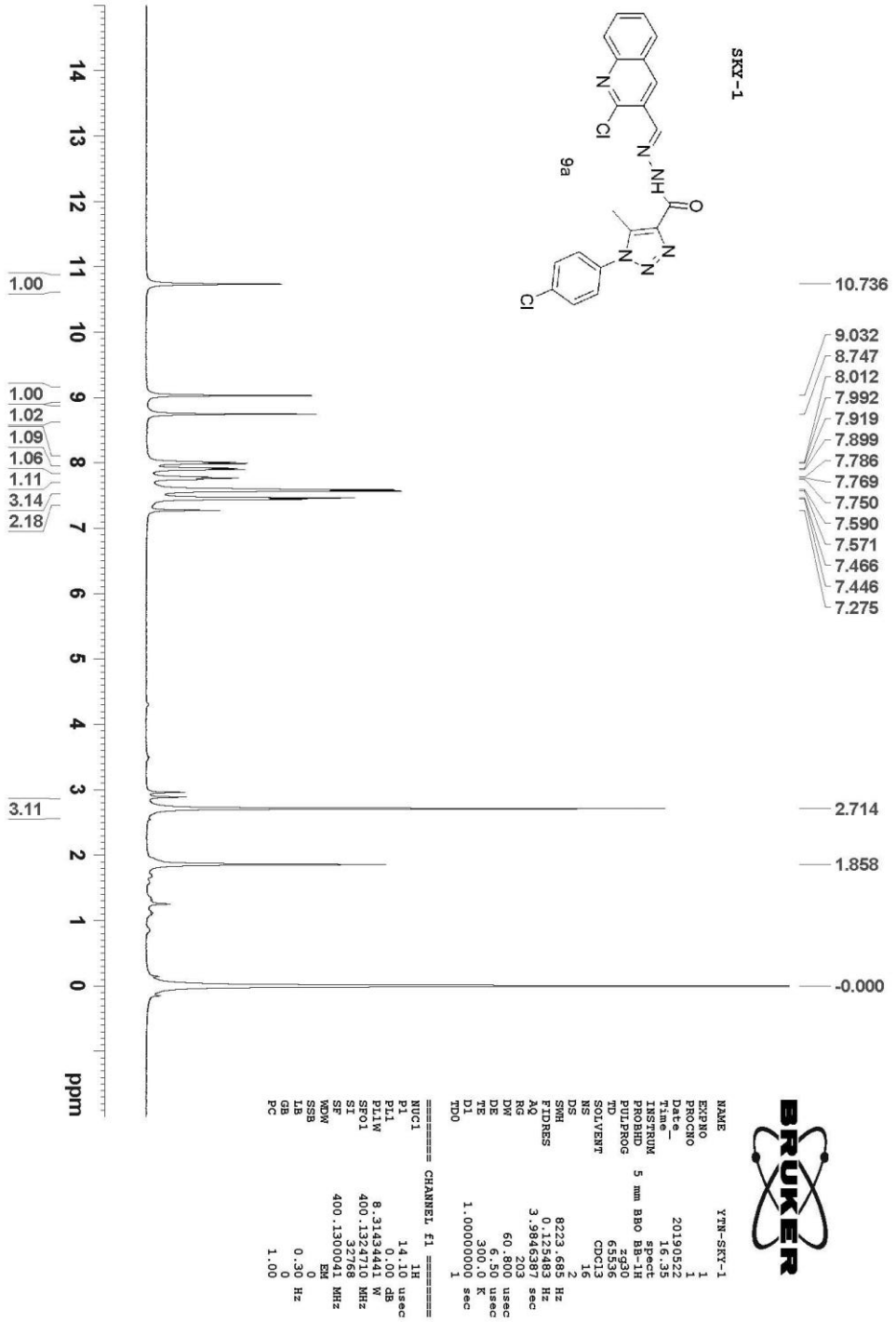
4. 3. 1. (E)-1-(4-chlorophenyl)-N'-((2-chloroquinolin-3-yl)methylene)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide (9a)

White colored solid yield: 88%,; m.p.:152 °C.; Chemical Formula: $C_{20}H_{14}Cl_2N_6O$; ^{1}H NMR (400 MHz, $CDCl_3$), δ 9.032 (s, 1H,), 8.747 (s, 1H), 8.745 (S, 1H), 8.012-7.275 (M, 8H), 2.714 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$. d), δ 156 (s), 153 (s), 150 (s), 146(s), 140 (s), 134(s), 133 (s), 131 (s), 130(s), 129.67 (s), 129.24 – 129.03 (m), 128.12 (s), 127.90 (d, J = 3.2 Hz), 126 (s), 126(s), 126 – 126 (m), 11(s). IR (KBr, cm^{-1}) 3500, 3300, 3200, 2800, 1600, 1560, 1500, 1400, 1250 cm^{-1} Elemental Analysis: C, 56.48; H, 3.32; Cl, 16.67; N, 19.76; O, 3.76, LCMS (m/z): 424.06.

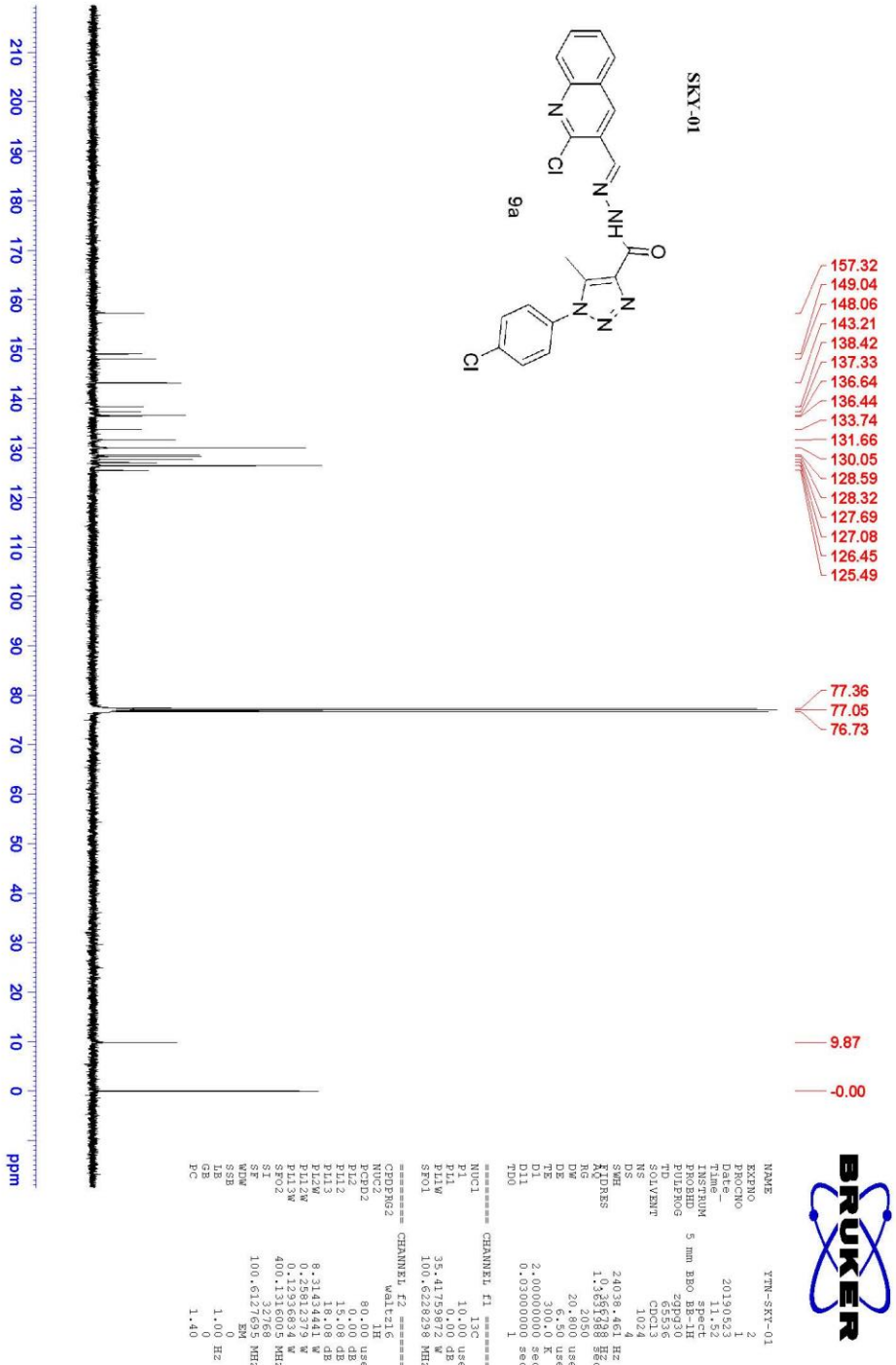
Mass Spectra of Compound 9a



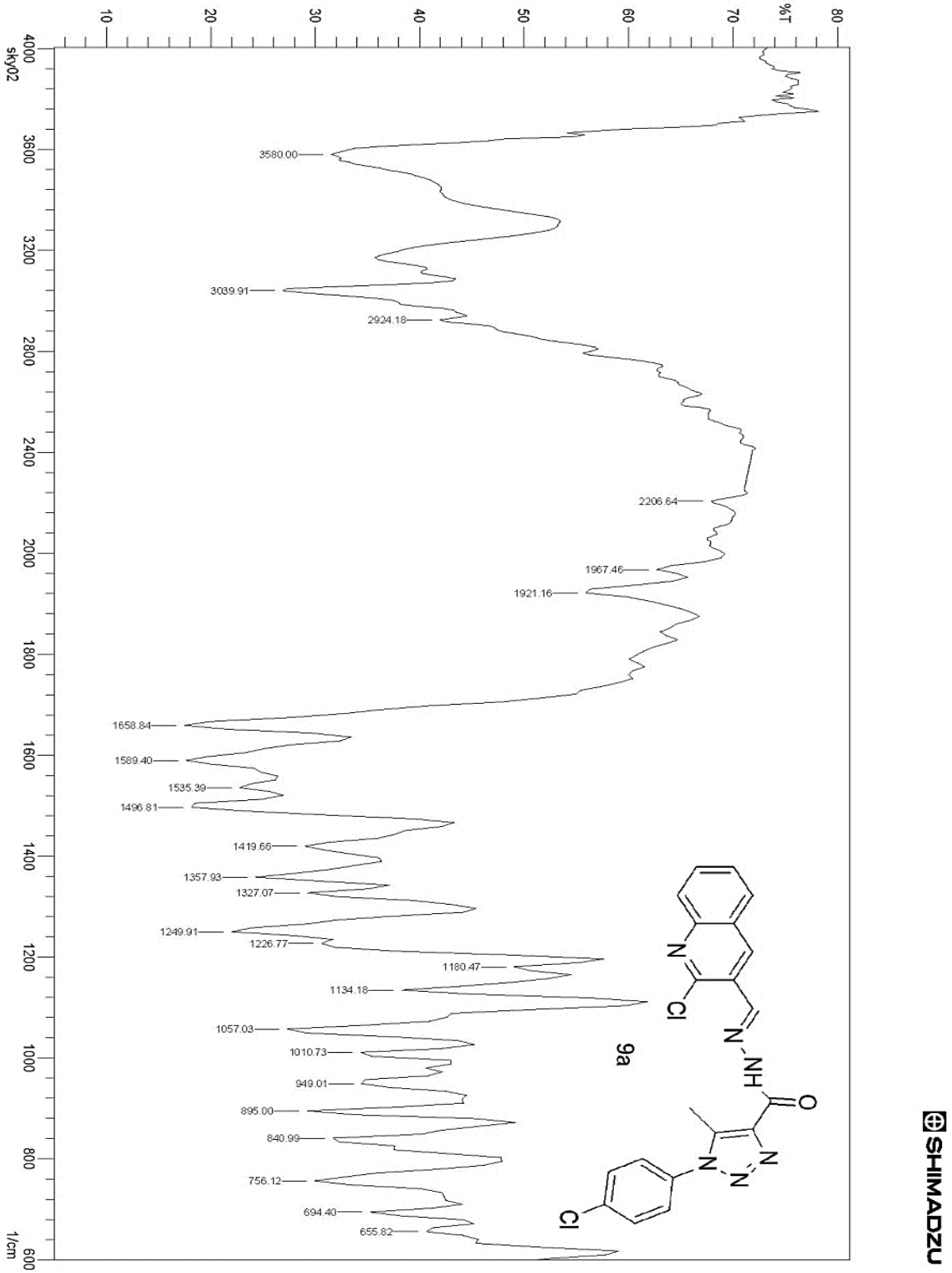
^{1}H NMR Spectra of Compound 9a



^{13}C NMR Spectra of Compound 9a



IR spectra of compound 9a



4. 3. 2. (E)-N'-((2-chloro-6,8-dimethylquinolin-3-yl)methylene)-1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide (9b)

White colored yield: 84%.; m.p.: 183 °C; Chemical Formula: $C_{22}H_{18}Cl_2N_6O$ ^{1}HNMR (400 MHz, $CDCl_3$-d), δ 10.591 (s, 1H,), 8.895 (s,1H), 8.720 (s, 1H), 7.600-7.257 (m, 6H), 2.721 (s, 6H), 2.490 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, d), δ 152 (s), 141 (s), 140 (s), 138 (s), 133 (s), 132.13 - 128.51 (m), 124.78 (s), 121.97-119.70 (m), 72.13-71.49 (t), 16.35 (s), 12.40 (s). IR (KBr, cm^{-1}) 3406, 3100, 3000, 1400, 1570, 1450, 750, Elemental Analysis: C, 58.29; H, 4.00; Cl, 15.64; N, 18.54; O, 3.53, LCMS (m/z): 452.06.

4. 3. 3. (E)-N'-((6-bromo-2-chloroquinolin-3-yl)methylene)-1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide (9c)

Yellow colored yield: 80%.; m.p.: 198 °C; Chemical Formula: $C_{20}H_{13}BrCl_2N_6O$; ^{1}HNMR (400 MHz, $CDCl_3$. d), δ 10.542 (s, 1H), 8.927 (s, 1H), 8.729 (s, 1H), 8.043-7.266 (m, 7H), 2.722(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$-d), δ 156.32 (s), 153.82 (s), 150.47 (s), 146.78 (s), 140.81 (s), 134.52 (s), 133.90 (s), 132.90 (s), 130.84 (s), 130.33 (s), 129.15 (t, J = 2.8 Hz), 127.17 (s), 126.92 (s), 126.45 – 126.07 (m), 126.04 (s), 117.75 (s), 11.06 (s). IR (KBr, cm^{-1}) 3420, 3030, 1620, 1550, 1430, 1230, 730,650. Elemental Analysis: C, 47.65; H, 2.60; Br, 15.85; Cl, 14.06; N, 16.67; O, 3.17; LCMS (m/z): 501.9.

4. 3. 4. (E)-N'-((2-chloro-6-methylquinolin-3-yl)methylene)-1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide (9d)

White colored yield: 82%; m.p. 176 °C; Chemical Formula: $C_{21}H_{16}Cl_2N_6O$; ^{1}H NMR (400 MHz, $CDCl_3$ d), δ 10.681 (s,1H), 8.836 (s, 1H), 8.741 (s, 1H), 7.905-7.273 (m,7H), 2.717 (s, 3H) 2.540 (s, 3H). IR (KBr, cm^{-1}) 3450, 3120, 3080, 2890, 1600, 1530, 1430, 1370. Elemental Analysis: C, 57.42; H, 3.67; Cl, 16.14; N, 19.13; O, 3.64; LCMS (m/z): 438.08.

4. 3. 5. (E)-N'-((2-chloro-5,8-dimethylquinolin-3-yl) methylene)-1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide (9e)

Yellow colored yield: 82%; m.p. 201 °C; Chemical Formula: $C_{22}H_{18}Cl_2N_6O$; ^{1}HNMR (400 MHz, $CDCl_3$ d), δ 10.599 (s, 1H), 8.895 (s, 1H), 8.720 (s, 1H), 7.600-7.267 (m, 6H), 2.721 (s, 6H), 2.490 (s, 3H). IR (KBr, cm^{-1}) 3400, 3130, 3120, 1600, 1570, 1450, 740. Elemental Analysis: C, 58.29; H, 4.00; Cl, 15.64; N, 18.54; O, 3.53, LCMS (m/z): 452.06.

4. 3. 6. (E)-5-chloro-N'-((2-chloro-6,7-dimethylquinolin-3-yl)methylene)-1-(4chlorophenyl)-1H-1,2,3-triazole-4-carbohydrazide (9f)

Yellow colored solid yield: 80%; m.p. 187 °C; Chemical Formula: $C_{22}H_{18}Cl_2N_6O$; ^{1}HNMR (400MHz, $CDCl_3$-d)δ 10.664 (s, 1H), 8.899 – 7.275 (m, 8H), 2.962 – 2.441 (m, 9H). IR (KBr, cm^{-1}) 3410, 3120, 3050, 1610, 1550, 1420, 770. Elemental Analysis: C, 53.24; H, 3.19; Cl, 22.45; N, 17.74; O, 3.38; LCMS (m/z): 452.04.

5. CONCLUSION

The final series of hydrazones 9(a-f) were successfully synthesized via shorter reaction time at RT with using acidic media by the conventional method and purified by Column

chromatography and characterized by different spectroscopic techniques like ^{1}H NMR, ^{13}C NMR and Mass analysis,all the compounds were carried out for their antibacterial and antifungal activity using 2 gram positive and 2 gram negative bacteria's as well as one fungal stain. From this study we came to know that all the compounds emerged out as potent antibacterial and antifungal agents expect 9a, 9b, 9e and 9f.

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