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Design, Synthesis and Biological Evaluation of 8-Aminoquinoline Derivatives Drug

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ABSTRACT

The synthesis, antibacterial activities of new quinoline analogs were carried out with the aim to find possible hits/leads that can be taken up for future drug development. A series of 2-amino-N'-((2-chloroquinolin-3-yl)methylene) acetohydrazide derivatives (3a-h) have been synthesized. The characterization was achieved by FT-IR, 1H NMR, 13C NMR, and mass spectral analysis. The in silico ADMET studies of the synthesized molecules were analyzed for their drug likeliness and toxic properties. The ADMET study indicates that the synthesized compounds were found to be possessing reliable ADME properties and are nontoxic. The antimicrobial properties were tested against bacterial and fungal species with amoxicillin and fluconazole as standard drugs. The compounds 3c, 3e, and 3g exhibited good antibacterial potency against P. aeruginosa, and the compounds 3a, 3f, and 3h have shown good activity against E. coli with 1000 µg/mL. The possible hits generated from biological activity could be taken for the generation of lead molecules for the drug discovery of antimicrobial and antioxidant entities from quinoline.

KEYWORD Quinoline, 8-aminoquinoline, antibacterial, Characterization, Molecular docking

INTRODUCTION

The reports from the World Health Organization (WHO) indicate that public health has a major concern due to population explosion and an increase in widespread epidemic diseases. Genomic studies on various microorganisms have shown that prolonged use of antibiotics makes these micro-organisms more resistant against them. Literature surveys indicate that quinoline derivatives possess diverse pharmacological activities, including antimicrobial (1), antimalarial (2), antiviral (3), antitumor (4), immunomodulatory (5), caspase-3 inhibition (6), antileishmanial (7), local anesthetic (8), antiarrhythmic (8) and anti-inflammatory activities (9). Also, thiosemicarbazones constitute one of the most versatile classes of compounds possessing a wide spectrum of activities.

It has been reported that thiosemicarbazone derivatives possess antimicrobial (1, 10), antimalarial (11), antiamoebic (12) and antitumor (13) activities. They have been in the focus of interest of medicinal chemists in the past decades because of the outstanding biological activities exhibited by several derivatives incorporating the heterocyclic moiety. Structures of the new compounds were verified on the basis of spectral and elemental analyses. Eight new compounds were tested for their possible antimicrobial activities. Most of the tested compounds showed weak to moderate antibacterial activity against most of the bacterial strains used in comparison with ciprofloxacin as a reference drug.

MATERIALS AND METHODS

Materials: Solvents of the analytical grade were employed in this experiment. TLC plates were used to check the products' purity, and melting point equipment was used to figure out what they were. For monitoring reactions on TLC plates, n-hexane and ethyl acetate were often utilised as the solvent medium. Thin layer chromatography was used to keep an eye on the reaction's progress. A UV light was employed as a visualisation tool. The entire process was carried out in clean glassware under specified catalyst conditions that may be either basic or acidic. Different spectroscopic methods, including lH NMR and 13C NMR, were used to describe all produced molecules. On the Advance Bruker AM 300, 400, and 500 MHz, lH NMR investigations were conducted. On pre-coated silica gel aluminium plates of 3x8 cm, thin layer chromatography (TLC) was carried out (Kieselgel 60, 254, E. Merck, Germany). Dual wavelength UV visualisation of the chromatogram was performed at 254 and 365 nm. The melting point of the Gallon Kemp device was discovered.

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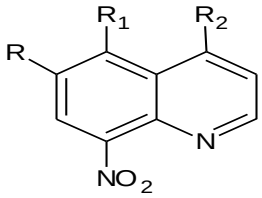
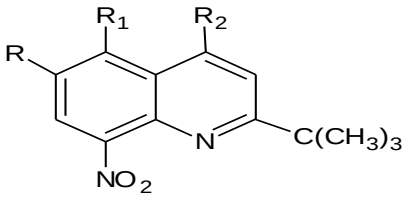


5-SUBSTITIUTED-6-SUBSTITUTED
8-nitroquinolines [1.0mmol]

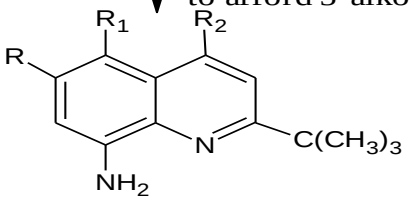
1. Dissolve derivatives of compound 1 in methyl cyanide(5ml)
2. Heated the reaction mixture at 80 °C
3. Then added silver nitrate(0.6mmol), trimethyl acetic acid(3.0mmol) and 10% H_2SO_4(10ml)
4. Added then freshly prepared solution of ammonium persulfate(3.0mmol) in water(10ml) dropwise to preheated mixture(80 °C) during 10 minutes
5. Removed the heat source and allowed the reaction to carried out with the evolution of CO_2
6. After 15 min., the reaction mixture was poured onto ice and made alkaline byadding NH_4OH.
7. The reaction mixture was then extracted with ethyl acetate (4x50ml), and combined extracts were washed with brine(2x10ml) solution and dried over Na_2SO_4, and the solvent was removed under vacuum to afford oil, whichupon column chromatography over silica gel(230-400mesh)afforded products. Elution was done in EtOAc/Hexane(1:99) and(3:97)



5-Substituted-2-tert-butyl-6-methoxy-8-nitroquinolines

1. 5.0 mmol of compound 2 in 95% absolute alcohol
2. hydrogenated over Raney nickel (T1 grade) at 45 psi in a Parr hydrogenator for 45 min.
3. The catalyst was removed by filtration, and the filtrate was evaporated under vaccum

to afford 5-alkoxy-2-tert-butyl-6-methoxy-8-quinolinamines.



5-alkoxy-2-tert-butyl-6-methoxy-8-quinolinamines
3. Final Product

Scheme 1: Synthesis of 8-aminoquinoline derivatives (13, 14)

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Table 1: List of Compounds Synthesized

Derivatives	R	R_1	R_2
3a	OCH_3	OC_4H_9	OCH_3
3b	OCH_3	OC_4H_9	OC_2H_5
3c	OCH_3	O-Ph(3,4-Cl_2)	OCH_3
3d	OCH_3	O-Ph(3,4-Cl_2)	OC_2H_5
3e	OC_2H_5	OC_4H_9	OCH_3
3f	OC_2H_5	OC_4H_9	OC_2H_5
3g	OC_2H_5	O-Ph(3,4-Cl_2)	OCH_3
3h	OC_2H_5	O-Ph(3,4-Cl_2)	OC_2H_5

4.5 ANTI BACTERIAL ACTIVITY

i) Methods Used for Screening

- The test chemicals were first dissolved in sterile Dimetylformamide (DMF), which inhibited E. coli, and then sterile water was added.

- Because its boiling point is below 121 °C and it is thermo-instable, 1,4–Dioxane was utilised to dissolve the test compounds, which was then filter sterilised using a membrane filter of 0.2u.

- Antibacterial activity of compounds was investigated at concentrations of 50-100 µg/ml. The standard was ciprofloxacin, which was dissolved in sterile water.

- Water and 1, 4-dioxane were also used as controls. (16-20)

RESULTS AND DISCUSSION

2-tert-Butyl-4 methoxy,5-butoxy-6-methoxy-8-quinolinamines (3a):- Brown solid, Yield: 55.20%; mp 118°C; Rf 0.56; IR (cm-1): 3245 (–NH of amide), 3215 (–NH), 2225 (C,,N), 1674 (C,O), 1165(C,S); 1H NMR (d, ppm): 3.83 (s, 3H, OCH3), 6.87 (d, 2H,J= 8.4 Hz, H-3,5, Phenyl), 7.86 (d, 2H, J= 8.4 Hz, H-2,6,Phenyl), 9.60 (s, 1H, NH), 12.06 (br s, 1H, NH–C,O). Element Analyzed calculated $C_{19}H_{28}N_2O_3$:- C, 68.65; H, 8.49; N, 8.43; O, 14.44.

2-tert-Butyl-4 ethoxy,5-butoxy-6-methoxy-8-quinolinamines (3b):- Brown solid, Yield: 48.30%; mp 122°C; Rf 0.49; IR (cm-1): 3285(–NH of amide), 3218 (–NHNH2), 2210 (C,,N), 1680(C,O), 1065 (C–O–C); 1H NMR (d, ppm): 3.84 (s, 3H, OCH3), 3.97 (br s, 3H, NHNH2), 6.93 (d, 2H, J =8.4 Hz,H-3,5, phenyl), 7.77 (d, 2H, J= 8.4 Hz, H-2,6, phenyl),11.71 (br s, 1H, NH–C,O). Element Analyzed calculated $C_{20}H_{30}N_2O_3$:- C, 69.33; H, 8.73; N, 8.09; O, 13.85.

2-tert-Butyl-4 methoxy,5-[3,4-dichloro phenyl]-6-methoxy-8-quinolinamines (3c):- Yellowish brown solid; Yield: 57.60%; mp 116°C; Rf 0.43; IR (cm-1):648.08(C-Cl),1697.36(C=O), 3371.57(–NH of amide),1465(C=N),2854.65(C-N),3100(Ar-CH); 13C NMR (d, ppm): 90.38 (s,1C,-CH), 115.08 (s,1C,-CN), 122.15-160.59 (m,13C , Ar-C), 176.93 (s, 1C, -HC=O). Element Analyzed calculated $C_{21}H_{22}N_2O_2Cl_2$:- C, 62.23; H, 5.47; N, 6.91; O, 7.89; Cl, 17.49.

2-tert-Butyl-4 ethoxy,5-[3,4-dichloro phenyl]-6-methoxy-8-quinolinamines (3d):- Yellowish solid, Yield: 49.70%; mp 109°C; Rf 0.46; IR (cm-1):3371.57(C-OH),1620.21(C=O), 3371.57(–NH of amide),1411.89(C=N),2368.59(C-N),3100(Ar-CH); 13C NMR (d, ppm): 90.38 (s,1C,-CH), 115.08 (s,1C,-CN), 122.15-160.59 (m,13C , Ar-C), 176.93 (s, 1C, -HC=O). Element Analyzed calculated $C_{22}H_{24}Cl_2N_2O_2$:- C, 63.01; H, 5.77; N, 6.68; O, 7.63; Cl, 16.91.

2-tert-Butyl-4 methoxy,5-butoxy-6-ethoxy-8-quinolinamines (3e):- Pale brown solid, Yield: 56.20%; mp 128°C; Rf 0.57; IR (cm-1):717.52(C-Br),1651.07(C=O), 3379.29(–NH of amide),1404.18(C=N),2137.13(C-N),3100(Ar-CH); 13C NMR (d, ppm): 90.38 (s,1C,-CH), 115.08 (s,1C,-CN), 122.15-160.59 (m,13C , Ar-C), 176.93 (s, 1C, -HC=O). Element Analyzed calculated $C_{20}H_{30}N_2O_3$:- C, 69.33; H, 8.73; N, 8.09; O, 13.85; Cl, 16.91.

2-tert-Butyl-4 ethoxy,5-butoxy-6-ethoxy-8-quinolinamines (3f):- Pale yellow solid, Yield: 58.65%; mp 124°C; Rf 0.46; IR (cm-1): 1070 (C–O–C),1658.78(C=O), 3371.57(–NH of amide),1404.18(C=N),2214.28(C-N),3100(Ar-CH); 13C NMR (d, ppm): 90.38

(s,1C,-CH), 115.08 (s,1C,-CN), 122.15-160.59 (m,13C , Ar-C), 176.93 (s, 1C, -HC=O). Element Analyzed calculated $C_{21}H_{32}N_2O_3$:- C, 69.97; H, 8.95; N, 7.77; O, 13.31.

2-tert-Butyl-4 methoxy,5-[3,4-dichloro phenyl]-6-ethoxy-8-quinolinamines (3g):- Yellow solid, Yield: 51.05%; mp 121°C; Rf 0.58; IR (cm-1):2638.62(C-N),1604.77(C=O), 3371.57(–NH of amide),1404.18(C=N),2854.65(C-N),3100(Ar-CH); 13C NMR (d, ppm): 90.38 (s,1C,-CH), 115.08 (s,1C,-CN), 122.15-160.59 (m,13C , Ar-C), 176.93 (s, 1C, -HC=O). Element Analyzed calculated $C_{22}H_{24}N_2O_2Cl_2$:- C, 63.01; H, 5.77; N, 6.68; O, 7.63; Cl, 16.91.

2-tert-Butyl-4 ethoxy,5-[3,4-dichloro phenyl]-6-ethoxy-8-quinolinamines (3h):- Yellowish White solid, Yield: 48.60%; mp 114°C; Rf 0.44; IR (cm-1):1658.78(C=O), 3379.29(–NH of amide),1404.18(C=N),2600.04(C-N),3100(Ar-CH); 13C NMR (d, ppm): 90.38 (s,1C,-CH), 115.08 (s,1C,-CN), 122.15-160.59 (m,13C , Ar-C), 176.93 (s, 1C, -HC=O). Element Analyzed calculated $C_{23}H_{26}N_2O_2Cl_2$:- C, 63.74; H, 6.05; N, 6.46; O, 7.38; Cl, 16.36.

Molecular Docking

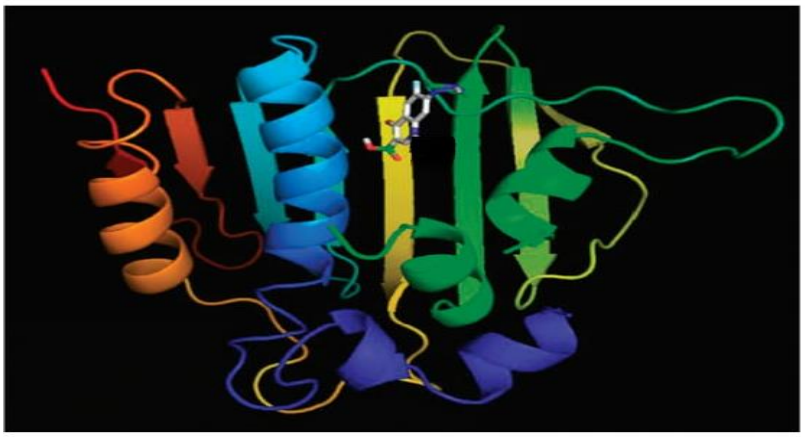

Fig 1:- Molecular docking of comp 3c

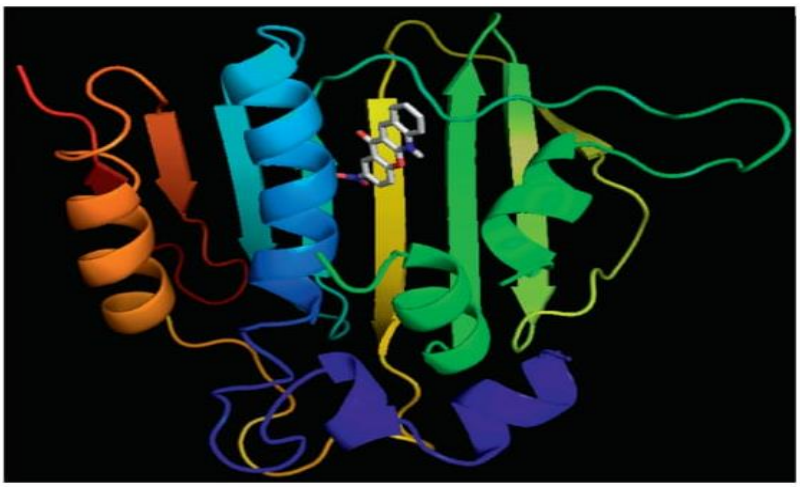

Fig 2:- Molecular docking of comp 3d

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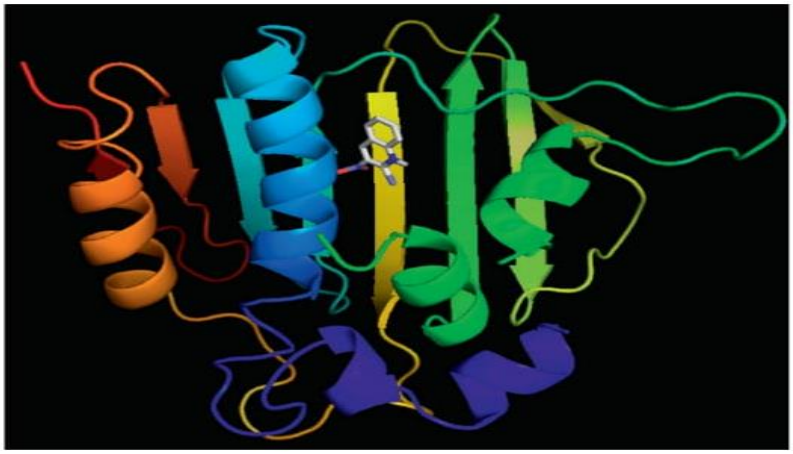

Fig 3:- Molecular docking of comp-3f

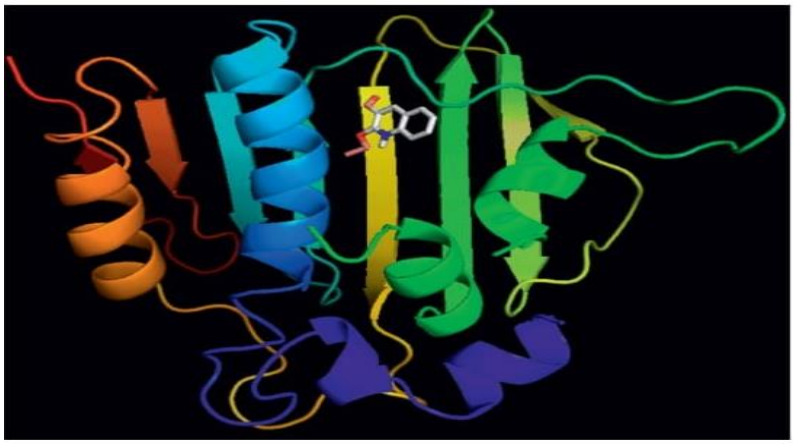

Fig 4:- Molecular docking of comp-3g

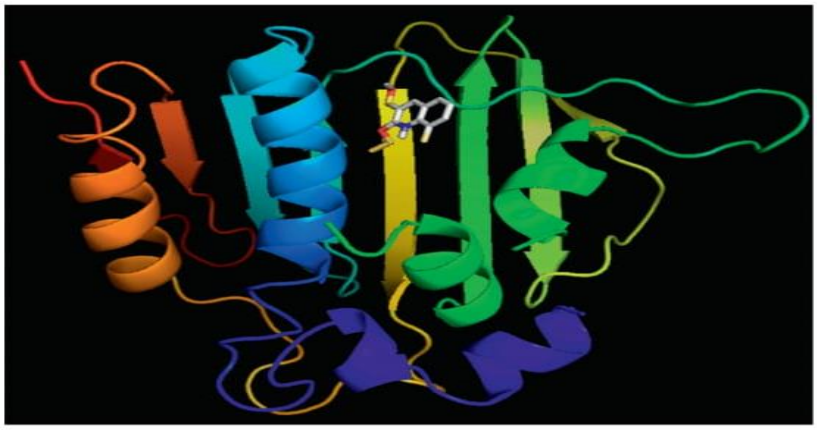

Fig 5:- Molecular docking of comp-3h

Methods Used For Screening: -

- The test chemicals were first dissolved in sterile Dimetylformamide (DMF), which inhibited E. coli, and then sterile water was added.

- Because its boiling point is below 121 °C and it is thermo-instable, 1,4–Dioxane was utilised to dissolve the test compounds, which was then filter sterilised using a membrane filter of 0.2u.

- Antibacterial activity of compounds was investigated at concentrations of 50-100 ug/ml. The standard was ciprofloxacin, which was dissolved in sterile water.

- Water and 1, 4-dioxane were also used as controls.

Table 2: Anti-Bacterial activity data of synthesized quinoline derivatives

Sr. No.	Compound	Zone of inhibition (diameter in MM)	
		E. coli	S. aureus
1	3a	22	16
2	3b	20	14
3	3c	18	17
4	3d	21	10
5	3e	28	29
6	3f	30	27
7	3g	15	12
8	3h	19	14
9	S	32	31
10	C	-	-

Note:- 0 to 25 is poor to moderate activity

More than 25 is good activity

S for Standard = Ciprofloxacin

C for Control = 1,4-Dioxane

Discussion: TLC was used to monitor all processes, and physical constant and FTIR spectrum analyses were used to evaluate the structure and purity of the predicted compounds, which were then followed by NMR and Mass spectroscopy. We made care to pronounce the reaction complete based on the TLC. Iodine vapours or viewing in a UV chamber were used to visualize the TLC plates. All reaction products were purified using various workup techniques to eliminate any unreacted starting material and recrystallization using appropriate solvents.

According to the literature review, quinoline has been reported for a variety of pharmacological properties, with certain molecules showing high activity and others showing moderate to excellent activity. All of the synthesised quinoline derivatives were tested for antibacterial activity against S. aureus and E. coli using DMF as a solvent. Candida albicans was used to test antifungal activity. On nutritional agar media, using the disc diffusion technique. Ciprofloxacin was employed as the antibacterial standard.

According to the antimicrobial screening results indicated in the table above, compounds Comp-1, Comp-2, and Comp-3e, had poor activity at 50 g/ml, but medium activity at l00 g/ml against S. aureus and medium activity against E. coli. When compared to the standard antibiotic Ciprofloxacin, Comp-3c, Comp-3d, Comp-3f, Comp-3g, and Comp-3h showed extremely strong action against S. aureus at l00 g/ml.

All of the substances examined, however, showed lower levels of activity than the benchmark. The major focus of the discussion section is on the antibacterial and activities of produced drugs. Because of the presence of the electron donating group OCH_3, OH, Cl linked to the phenyl ring, the Comp-3c, Comp-3d, Comp-3e, Comp-3f, Comp-3g, and Comp-3h" have showed strong antibacterial action. "Comp-3c, Comp-3d, Comp-3f, Comp-3g, and Comp-3h" have showed strong antifungal activity, which might be owing to the presence of electron donating groups OCH_3, OH, CH_3, and Cl, which are connected to the phenyl ring system.

CONCLUSION

According to the screening results, the compounds in the scheme have demonstrated antibacterial activity comparable to that of mainstream medications. This is due to the presence of groups such as -OCH_3, -NO_2, -Br, and -N-CH_3 at various places on the

phenyl nucleus and the heterocyclic system connected to the quinoline nucleus. The foregoing findings indicate that synthesised substituted quinoline can be a valuable source for investigation. As a result, in the quest for novel active compounds, it may be beneficial to look into this area, or to make or introduce various functional groups to secondary amines, or to use cyclization as a replacement, which might lead to better pharmacological agents.

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Conflict of Interest Statement: All authors have nothing else to disclose.