© 2019 IJSRST | Volume 6 | Issue 4 | Print ISSN: 2395-6011 | Online ISSN: 2395-602X
Themed Section: Science and Technology
DOI : https://doi.org/10.32628/IJSRST

Synthesis and Antimicrobial Evaluation of Novel Hexahydroquinolines

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ABSTRACT

A series of diversely substituted hexahydroquinolines have been synthesized using a one pot multi-component approach. All the newly synthesized hexahydroquinolines were characterized by different spectroscopic techniques and elemental analyses. All the compounds were evaluated for their antibacterial and antifungal activity against selected bacterial and fungal strains.

Keywords: Polyhydroquinolines, Hexahydroquinolines, Multi-component reaction; Antibacterial activity; Antifungal activity.

I. INTRODUCTION

Microbial resistance to antimicrobial agents is of grave concern in the medical community. Hence, the development of novel, potent, and unique antimicrobial agents which can fight the resistant microbes and also posess less toxicity is the need of time. The discovery of new compounds with higher antimicrobial activity and unique new mechanisms of action to combat resistant microbes is possible through designing and developing new scaffolds.

Polyhydroquinoline derivatives including hexahydroquinolines, tetrahydroquinolines, dihydroquinolines etc. have drawn much more attention of organic chemists for the development of active compounds in the medicinal field.

Among polyhydroquinolines, hexahydroquinolines have been found to display wide-spectrum of biological activities viz., anti-cancer [1], anti-hypertensive [2-5], anti-inflammatory [6], calcium-channel modulatory [7], anti-oxidant [8], spasmolytic [9] activity etc. Number of literature reports have assessed potential of hexahydroquinoline derivatives in the development of novel antibacterial and antifungal agents [10-12].

Keeping in view these observations, it was thought worthwhile to synthesize a series of novel hexahydroquinolines and assess their antibacterial and antifungal activity.

II. METHODS AND MATERIAL

Open capillary tubes were used to determine melting points and they are uncorrected. TLC on silica gel-G plates was used to monitor the progress of the reaction and formation of the products. Shimadzu FT-IR-8400 instrument was used for recording IR spectra using the KBr pellet method. Shimadzu GC-MS-QP-2010 mass spectrometer was used to record mass spectra using Direct Injection Probe technique. Bruker Ac 400 MHz spectrometer was used to record ^{1}H NMR spectra using DMSO-d_6 solution of the compounds. The results are in agreements with the structures assigned.

General procedure for the synthesis of ethyl 4-(substituted 2-chloroquinolin-3-yl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (4a-f):

In a stoppered flask, 5,5-Dimethylcyclohexane-1,3-dione (0.01 mol), ethyl acetoacetate (0.01 mol) and substituted 2-chloro-quinoline-3-carbaldehyde (0.01 mol) were dissolved in ethanol. To this reaction mixture, ammonium acetate (0.01 mol) was added portion-wise with stirring. Catalytic amount of L-proline was added. The resulting reaction mixture was stirred at ambient temperature. Progress of the reaction was monitored by TLC. After completion of the reaction, the separated solid product was filtered to give **(4a-f)**, which was recrystallized from ethanol.

Representative analysis data:

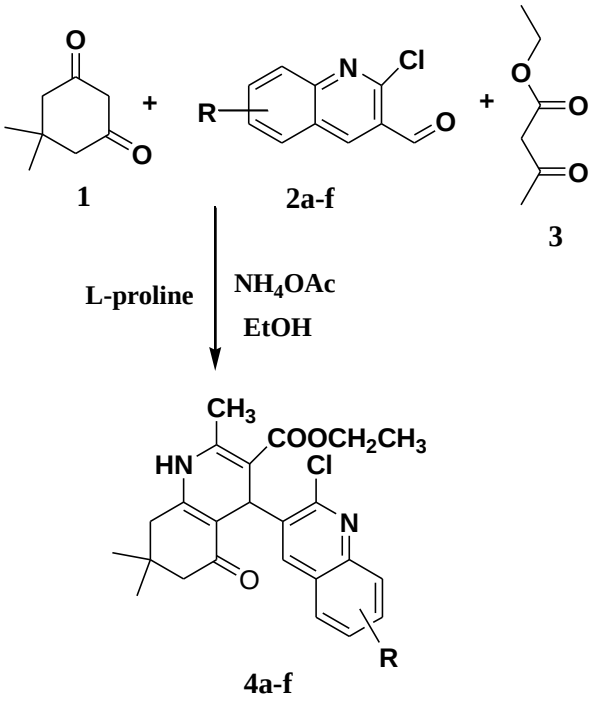
Ethyl 4-(2-chloroquinolin-3-yl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (4f)

Mass: *m/z* 424. IR (cm^{-1}): 3287, 3066, 2956, 2872, 1690, 1615, 1420, 1361, 1068; ^1H NMR, δ (ppm) 0.92 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.11-1.13 (t, 3H, CH_3), 2.11-2.34 (m, 4H, CH_2), 2.39 (s, 3H, CH_3), 4.01-4.03 (q, 2H, CH_2), 4.97 (s, 1H, CH), 7.07-7.61 (m, 5H, Ar-H), 8.11 (s, 1H, -NH). Anal. Calcd. for $C_{24}H_{25}ClN_2O_3$: C, 67.84; H, 5.93; N, 6.59, Found: C, 67.81; H, 5.91; N, 6.56.

III. RESULTS & DISCUSSION

Chemistry

The synthesis of ethyl 4-(substituted 2-chloroquinolin-3-yl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate **(4a-f)** was accomplished by reacting 5,5-Dimethylcyclohexane-1,3-dione **(1)**, ethyl acetoacetate **(2)**, substituted 2-chloro-quinoline-3-carbaldehyde **(3)** and ammonium acetate in presence of catalytic amount of L-proline using ethanol as a solvent **(Scheme 1)**.



Scheme 1. Synthesis of hexahydroquinolines (4a-f)

The reaction protocol successfully furnished the hexahydroquinolines **(4a-f)** in excellent yields during shorter reaction time which shows that L-proline has a good catalytic efficiency for the reaction protocol.

Table-1. Physical constants and other data for hexahydroquinolines (4a-f)

	R	M.F.	Mol. Wt.	M.P. ºC	Yield %
4a	**4-F**	$C_{24}H_{24}ClFN_2O_3$	442	165-167	71
4b	**3-Cl**	$C_{24}H_{24}Cl_2N_2O_3$	458	162-164	70
4c	**3-NO_2**	$C_{24}H_{24}ClN_3O_5$	469	154-156	68
4d	**4-CH_3**	$C_{25}H_{27}ClN_2O_3$	438	158-160	62
4e	**4-Br**	$C_{24}H_{24}ClBrN_2O_3$	442	144-146	76
4f	**H**	$C_{24}H_{25}ClN_2O_3$	424	158-161	73

Spectral Discussion

All the newly synthesized hexahydroquinolines **(4a-f)** were characterized by IR, ^{1}H NMR, mass spectroscopic techniques and elemental analyses.

For hexahydroquinolines **(4a-f),** characteristic multiplets were observed for methylene groups of cyclohexanone ring in the range of 2.1-2.5 δ ppm.

Confirmatory signal of methine proton was observed in the range of 4.8-5.0 δ ppm.

The aromatic ring protons were observed in the range of 7.1-8.2 δ ppm and J values were found to be in accordance with substitution pattern on phenyl ring.

The singlet for secondary amine (-NH) proton was observed in the range of 8.1-8.3 δ ppm.

The spectral data of all the newly synthesized compounds were in full agreement with the proposed structures.

Biological screening

The title compounds **(4a-f)** were evaluated for their antibacterial activity against Escherichia coli, Staphylococcus aureus and antifungal activity against Candida albicans using the broth-dilution method[15]. The activities of hexahydroquinolines **(4a-f)** were compared with those of some known drugs, viz. Ampicillin, Ciprofloxacin and Nystatin.

The results are summarized in **Table 2**.

Table-2. Antimicrobial Evaluation of hexahydroquinolines (4a-f)

	Minimum inhibition		
Compound	**Antibacterial**		**Antifungal**
	E. coli	S.	C. albicans
4a	62.5	62.5	100
4b	500	250	500
4c	62.5	62.5	62.5
4d	1000	500	1000
4e	62.5	62.5	100
4f	100	250	500
Ampicillin	100	250	-
Ciprofloxacin	25	50	-
Nystatin	-	-	100

Antimicrobial screening results have revealed that hexahydroquinolines bearing electron-withdrawing groups viz. fluoro, bromo at the 4th position on the aryl substituent were found to be the most active against most of the bacterial and fungal strains used in the screening, i.e. they displayed broad-spectrum activity. However, presence of electron-withdrawing groups on the 3rd position of the aryl substituent did not result in good activity in all the cases except for the nitro group. Further structural modifications of this series of compounds in future may provide more potent antimicrobial agents.

IV. CONCLUSION

To summarize, a simple and facile protocol has been successfully developed to synthesize a series of novel diversely substituted hexahydroquinolines. Some of the newly synthesized hexahydroquinolines have shown promising broad-spectrum antimicrobial activities. These results have demonstrated that the newly developed hexahydroquinolines can serve as

interesting lead molecules for further synthesis of related heterocycles and their biological evaluation.

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Cite this article as :

Dipti Dodiya, "Synthesis and Antimicrobial Evaluation of Novel Hexahydroquinolines ", International Journal of Scientific Research in Science and Technology (IJSRST), Online ISSN : 2395-602X, Print ISSN : 2395-6011, Volume 6 Issue 4, pp. 469-472, July-August 2019.

Journal URL : https://ijsrst.com/IJSRST229514