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Microwave Assisted One-Pot Synthesis of Amino Substituted Tetrahydroquinolines

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ABSTRACT

Microwave assisted one pot synthesis of novel amino substituted tetrahydroquinoline-3-carbonitriles has been reported by the reaction of cyclohexanone and arylidene malononitriles. The newly synthesized amino substituted tetrahydroquinoline-3-carbonitriles were characterized using different spectroscopic techniques and elemental analyses. The tetrahydroquinoline-3-carbonitriles were screened for their antibacterial and antifungal activity against different strains of bacteria and fungi respectively.

Keywords: Tetrahydroquinolines, Multi-Component Reaction, Antibacterial Activity, Antifungal Activity.

I. INTRODUCTION

It is a matter of concern for the medicinal experts that pathogenic microorganisms are showing resistance towards clinical drugs. So, search for new and efficient drugs with antimicrobial potency which can fight the resistant microbes and also possess 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 pinched higher attention of organic chemists for the advancement of active compounds in the medicinal field.

Polyhydroquinolines have been found to display wide-spectrum of biological activities viz., anti-hypertensive[1], anti-cancer[2-4], anti-oxidant[5], anti-inflammatory[6] activity etc. Number of literature reports have assessed potential of polyhydroquinoline derivatives in the development of novel antibacterial and antifungal agents[7,8].

Keeping in view these observations, it was thought worthwhile to synthesize a series of novel tetrahydroquinolines and assess their antibacterial and antifungal activity. The biological activity of the synthesized compounds was compared with reference standard drugs.

II. METHODS AND MATERIAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on SHIMADZU-FT-IR-8400 [Fourier transform–infrared (FT-IR)]. The IR spectra were taken using KBr pellets. ^{1}H NMR were recorded on Bruker AMX spectrometer. All the chemicals were commercial products and were used without further purification.

General procedure for the synthesis of 2-Amino-5,6,7,8-tetrahydro-4quinoline-3-carbonitriles (3a-e):

A mixture of the cyclohexanone (0.01 mol), 2-((2-chloro-substituted quinolin-3-yl) methylene) malononitrile (0.01 mol) and ammonium acetate (0.08 mol) in ethanol (5 mL) was irradiated under microwave irradiation at 80 °C for 5-7 min. The microwave irradiation was operated in 30-second cycles. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the separated solid was filtered, dried and crystallized from ethanol.

Representative analysis data:

Yield: 78%; m.p. 196-198 ºC; IR (cm^{-1}): 3391 and 3296 (N-H stretching of primary amine), 3043 (C-H stretching of aromatic ring), 2922 (C-H stretching of CH_2 group of cyclohexanone ring), 2214 (C≡N stretching of nitrile group), 1645 (N-H deformation of NH_2 group), 1587, 1558 and 1446 (C=C stretching of aromatic ring), 1222 (C-N stretching of primary amine), 1062 (C-H out of plane bending for aromatic ring), 756 (C-Cl stretching); ^{1}H NMR (DMSO-d6) δ ppm: 1.56-1.62 (m, 2H), 1.69-1.79 (m, 2H), 2.76-2.81 (m, 2H), 2.06-2.14 (m, 1H), 2.36-2.41 (m, 1H), 6.34 (s, 1H), 7.75-7.77 (m, 1H), 7.32-7.39 (m, 1H), 7.47-7.49 (d, 1H), 7.90 (s, 1H); MS: m/z 352; Anal. Calcd. for $C_{19}H_{14}ClFN_4$: C, 64.68; H, 4.00; N, 15.88. Found: C, 64.62; H, 3.93; N, 15.81%.

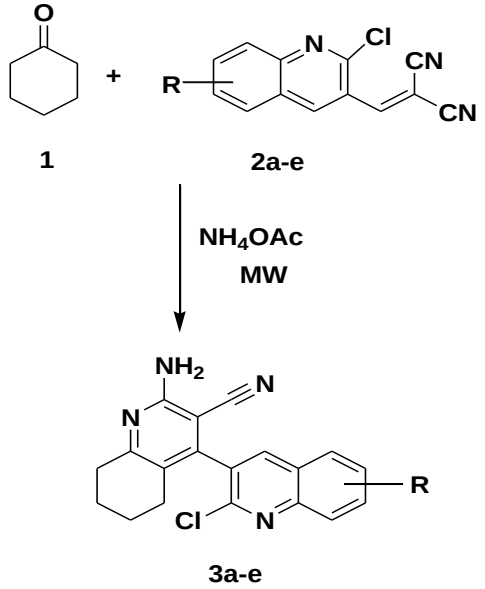
III.RESULTS AND DISCUSSION

Chemistry

The microwave assisted synthesis of novel amino-substituted tetrahydroquinoline-3-carbonitriles furnished the desired products in excellent yield and purity.

Treatment of cyclohexanone **1** with arylidene malononitriles **2** and ammonium acetate in ethanol under microwave irradiation at 300 W afforded the amino-substituted 5,6,7,8-tetrahydroquinoline-3-carbonitriles **(3a-e) (Scheme 1).**

The microwave assisted reactions were characterized by excellent yields (71-81%) and shorter reaction times as compared to the conventional heating producing lower yields after long reaction times (9-15 h).



Scheme 1. Synthesis of 5,6,7,8-tetrahydroquinoline-3-carbonitriles (3a-e)

Code	R	Time (min.)	Yield %
3a	4-F	7	78
3b	4-Cl	8	80
3c	3-OCH_3	11	71
3d	4-OCH_3	9	80
3e	4-CH_3	8	81

Spectral Discussion

All the newly synthesized amino-substituted 5,6,7,8-tetrahydroquinoline-3-carbonitriles **(3a-e)** were characterized by IR, ^{1}H NMR, mass spectroscopic techniques and elemental analyses.

For amino-substituted 5,6,7,8-tetrahydroquinoline-3-carbonitriles **(3a-e),** characteristic multiplets were

observed for methylene groups of cyclohexane ring in the range of 1.4-2.9 δ ppm.

The aromatic ring protons were observed in the range of 7.1-8.3 δ ppm and J value were found to be in accordance with substitution pattern on phenyl ring. The singlet for primary amine (-NH_2) protons was observed in the range of 6.3-6.4 δ ppm.

Biological screening

The compounds **(3a-e)** were evaluated for their antibacterial activity against Escherichia coli, Staphylococcus aureus and antifungal activity against Candida albicans using the broth-dilution method[9].

After 24 h of incubation at 37 °C, the zones of inhibition were measured in mm. The activities were compared with those of some known drugs, viz. Ampicillin, Ciprofloxacin and Nystatin.

The results are summarized in **Table 1**.

TABLE-1. ANTIMICROBIAL EVALUATION OF (3A-E)

	Minimum inhibition concentration (ug mL^{-1})		
Compound	**Antibacterial Activity**		**Antifungal Activity**
	E. coli	S. aureus	C. albicans
3a	100	1000	250
3b	1000	500	1000
3c	250	100	1000
3d	500	500	1000
3e	250	500	>1000
Ampicillin	100	250	-
Ciprofloxacin	25	50	-
Nystatin	-	-	100

Moderate to good antimicrobial activity was observed. Compound **3c** exhibited good antimicrobial activity against Gram +ve as well as Gram –ve bacterial strains, however it was not active against the fungal strain C. albicans as compared to the reference drugs. Compound **3a** showed highest antifungal activity among all the newly synthesized amino-substituted 5,6,7,8-tetrahydroquinoline-3-carbonitriles **(3a-e)**.

IV. CONCLUSION

The newly synthesized amino-substituted 5,6,7,8-tetrahydroquinoline-3-carbonitriles **(3a-e)** exhibited moderate to good antimicrobial activity, which makes them suitable as leads for further structural modification in order to develop new classes of antimicrobial compounds.

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