IOSR Journal of Applied Chemistry (IOSR-JAC)
e-ISSN: 2278-5736.Volume 8, Issue 5 Ver. II (May. 2015), PP 01-03
www.iosrjournals.org

Synthesis of Quinoline Analogues as Anti-microbial Agents

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Abstract : *Various substituted Quinoline containing different functional group have been synthesized by conventional method. The quinoline derivative is synthesized by using 8-hydroxy quinoline) was first treated with ethyl chloroacetate to form ester intermediate which was subsequently treated with Hydrazine Hydrate result into formation of Hydrazone derivative then this intermediate was made to react with substituted benzoic acid. The final structures have been established on the basis of their chemical analysis and spectral data. Final compounds were further evaluated for in-vitro anti-microbial activity using standards.*

Keywords - *Anti-Microbial activity, Quinoline, Hydrazone*

I. Introduction

In the recent time, quinoline nucleus has gathered an immense attention among chemists as well as biologists as it is one of the key building elements for many naturally occurring compounds [1]. While 8-hydroxyquinolines have been explored as a viable drug discovery platform in many instances. The numbering in quinoline commences from the nitrogen atom which is assigned position-1.Quinoline ring structure is obtained by ortho-condensation of benzene ring with pyridine. It is also called l-azanapthalene or benzo pyridine. Quinoline moiety is of great interest to synthetic and medicinal chemists due to their unique chemical and biological properties**[2]**. 8-Hydroxyquinoline (oxine) is a bicyclic aromatic and is toxic if injected. Quinoline and their derivatives are receive increasing importance due to their wide range of biological and pharmacological activities However its derivatives have long been used for their antiallergic[2], antimalarial[3], antibacterial[4], antiproliferative[5], anticancer[6] and antiparasitic[7] activities.

II. Materials And Methods

All commercial solvents used in the experimental work were redistilled and dried before use. Melting points were recorded on a Thermonik Melting point Apparatus (Campbell Electronics, Mumbai, India) and are uncorrected. IR spectra were recorded on an IR-Affinity, Shimadzu using DRS system. ^{1}H-NMR spectra have been recorded on a JEOL AL-300 FT-NMR spectrometer (400 MHz, JEOL Ltd., Tokyo, Japan), using TMS as internal standard in solvent DMSO. Elemental analysis has been carried out on a C, H, and N Elemental Analyzer (Thermo-Finnigan Flash EA 1112, Italy). Mass data have been recorded on Agilent GC-MS.

III. Experimental

3.1 Preparation of ethyl (quinolin-8-yloxy)acetate (Compound 2)[8]

A mixture of 8-hydroxyquinoline (0.01M, 1.45gm), ethylchloroacetate (0.01M, 1.22gm) and anhydrous K_2CO_3 (0.005M, 0.69gm) in dry acetone was refluxed on water bath for 18 hours. Reaction was monitored by TLC. The mixture was then filtered and solvent was removed under reduced pressure. The resulting solid was recrystallized from ethanol. Yield 95%; colourless crystalline solid; mp;95^{0}C. ^{1}H NMR(400 MHz, DMSO-δ6) δ (ppm) 2.30 (t, 3H), 3.18 (q, 2H), 4.13 (s, 2H), 7.18-8.26 (m, 6H, Ar-H) Anal. calcd for $C_{13}H_{13}NO_3$:C, 62.90; H, 4.87; Found: C, 67.52; H, 5.67.N, 6.06 MS (m/z): 231[M^+] ($C_{13}H_{13}NO_3^+$), 186 ($C_{11}H_8O_2N$), 158($C_{10}H_8ON$), 128(C_9H_6N).

3.2 Preparation of 2-(quinolin-8-yloxy)acetohydrazide (Compound 3)[9]

Compound 2 (0.01M, 2.31gm) and hydrazine hydrate (0.01M, 1.36gm) in ethanol was refluxed on a water bath for 6 hours. Reaction was monitored by TLC. After completion of reaction keep the reaction mixture on cooling, the solid that separated was washed with water, dried and recrystallized from ethanol. Yield 85%; White colour solid; mp;162^{0}C; ^{1}H NMR(400 MHz, DMSO-δ6) δ (ppm) 6.98-7.65 (m, 5H Ar-H), 3.13 (s, 1H), 5.89 (s, 2H), 4.12 (s, 2H) Anal. calcd for $C_{11}H_{15}N_5O_2$:C, 53.00; H, 6.07; N, 28.10 Found: C, 53.37; H, 6.16; N, 28.40; MS (m/z): 217 [M^+] ($C_{11}H_{11}N_3O_2^+$), 201 ($C_{11}H_9O_2N_2$),186 ($C_{11}H_8O_2N$), 158 ($C_{10}H_8ON$), 128 (C_9H_6N).

3.3 Preparation of N'-[2-(quinolin-8-yloxy)acetyl]benzohydrazide (Compound 4)[10]

Compound 3 (0.01M, 2.17gm) and substituted benzoic acid (0.01M, 1.22gm) in ethanol refluxed on water bath for 6 hours. Completion of reaction was monitored by TLC. After cooling, the solvent was removed under reduced pressure and the separated solid was recrystallized from ethanol to yield compound 4. The further derivatives III-A.3a-e were synthesizes in similar manner; white Colour Solid; mp; 228^0C ^{1}H NMR(400 MHz, DMSO-δ6) δ(ppm) 7.0-8.0 (m,10H, Ar-H), 4.5 (s,2H, CH), 5.6 (s,3H, NH), 8.6 (s,2H, NH). Anal. calcd for $C_{18}H_{14}BrN_3O_3$:C, 54; H, 35; N, 10.5. Found: C, 53.80; H, 34.90; N, 10.40; MS (m/z): 400 [M^+] ($C_{18}H_{14}BrN_3O_3^+$).

Table 1: Schematic Representation of Titled Compounds

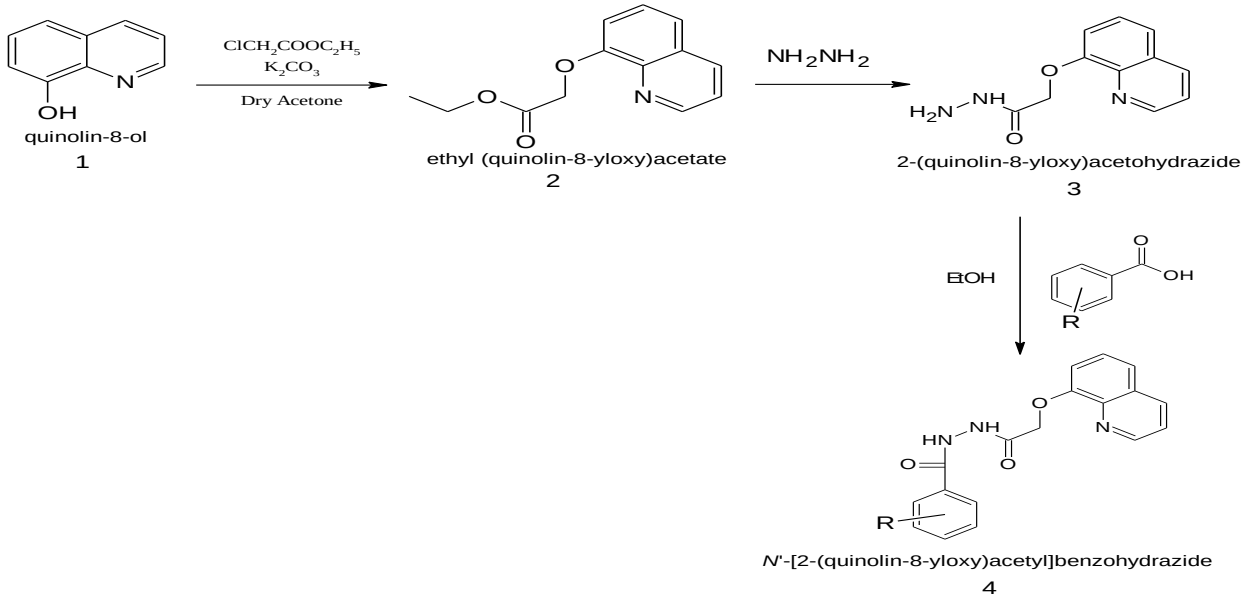

Table 2: Physical and Analytical data of compounds synthesized as per the scheme (4a-e)

Compounds	Molecular Formula	Mp [^{0}c]	Yield [%]	IR (KBr)/ cm^{-1}	C,H,N Analysis		Mass spectrometer
					Found	Calculated	
4a	$C_{18}H_{14}BrN_3O_3$	228	76	-O- 1101 -CONH 1616 -Br 632 -C=N 1583	C:53.80% H:34.90% N:10.40%	C:54% H:35% N:10.5%	402 ($C_{18}H_{14}BrN_3O_3^{2+-}$)
4b	$C_{19}H_{14}F_3N_3O_4$	218	71	-O- 1086 -CONH 1667 -F 1122 -C=N 1612 -CH 2836	C:56.20% H:3.39% N:10.30%	C:56.29% H:3.45% N:10.37%	405 ($C_{19}H_{14}F_3N_3O_4^+$)
4c	$C_{18}H_{14}FN_3O_3$	206	68	-O- 1089 -CONH 1618 -F 1123 -C=N 1559	C:63.65% H:4.03% N:12.25%	C:63.71% H:4.12% N:12.38%	339 ($C_{18}H_{14}FN_3O_3^+$)
4d	$C_{19}H_{13}F_4N_3O_3$	230	81	-O- 1085 -CONH 1622 -F 1131	C:55.90% H:3.02% N:10.20%	C:56.01% H:3.19% N:10.31%	407 ($C_{19}H_{13}F_4N_3O_3^+$)
4e	$C_{19}H_{14}F_3N_3O_4$	218	66	-O- 1088 -CONH 1620 -F 1175 -C=N 1529	C:56.15 H:3.36% N:10.20%	C:56.29 H:3.45% N:10.37%	405 ($C_{19}H_{14}F_3N_3O_4^+$)

Table 3: Anti-microbial activity of compounds (4a-e)

Compounds	R	Anti-Microbial Activity(µg/ml)		
		Bacterial strains		Fungal strains
		E. coli	S. aureus	C. albicans
4a	-Br	-ve	-ve	-ve
4b	2,4,5-tri F -3-OCH_3	-ve	-ve	-ve
4c	-F	-ve	-ve	-ve
4d	2-F-4-CF_3	-ve	-ve	-ve
4e	4-OCF_3	-ve	-ve	-ve

IV. Result And Conclusion

In summary, we have described the synthesis and biological screening of Substituted N'-[2-(quinolin-8-yloxy) acetyl] benzohydrazide derivatives. New compounds (4a-e) have been synthesized by the reaction of 2-(quinolin-8-yloxy)acetohydrazide with various substituted benzoic acid in 60 to 80% yield. The structures of compounds are confirmed by IR, NMR and Mass spectral data and are further supported by correct elemental analysis. The antimicrobial screening results revealed that synthesized compounds does not showing any kind of potency against microbial strains.

Acknowledgements

The authors are thankful to SAIF, IIT Powai, Mumbai for carrying out the elemental analysis (CHN) and also thankful to SAIF, Punjab University, chandigarh for recording the NMR spectra.

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