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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME THIAZOLIDINONE-QUINOLINE DERIVATIVE

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ABSTRACT

N'-[2-(quinolin-8-yloxy) acetyl] benzohydrazide (2) obtained from 8-hydrozy quinoline (1) was converted to the corresponding 2-(quinolin-8-yloxy) acetohydrazide (3) by treatment with hydrazine hydrate. The basic treatment of (3) and substituted benzaldehyde yielded the corresponding schiff base derivatives (4a-e). The synthesis of N-(4-oxo-2- substituted phenyl-1, 3-thiazolidin-3-yl)-2-(quinolin-8-yloxy) acetamide (5a-e) was performed from the reaction of (4) with thioglycolic acid in basic media. The newly synthesized compounds were characterized by elemental analyses, IR, ^{1}H-NMR, and mass spectra. The antimicrobial activity study revealed that newly synthesized compounds dose not showed moderate activity against a variety of microorganisms (*E. coli, S. aureus, C. albicans*).

KEYWORDS: 8-hydroxy Quinoline, schiff base, 1,3-thiazolidin-3-yl, antimicrobial activity.

1.0 INTRODUCTION

The prevalence of heterocyclic ring among drugs and biological agents of mammalian origin can lead to the erroneous assumption that the presence of such rings in drugs means that this moiety necessarily constitutes a part of pharmacophore. Replacement of the particular ring system in such cases leads to loss of desirable biological activity. Recognition of pharmacophoric functions is still largely an empirical art.[1] The diversity of biological effects

is possessed by benzofused six membered heterocyclic rings. These range from antimicrobial property, CNS and inflammation influencing agents. It can be inferred that ring system itself is primarily a molecular scaffold, upon which the characteristic pharmacophore for the various receptor is involved. It is also interesting to note that range of bioactivities involved is different substantially from those seen with the benzofused five membered heterocycles.[2] Quinoline is used as a lead compound in which benzene ring is fused with pyridine ring on the 2-3 position. The heterocyclic ring of quinoline is a significant pharmacophore. Replacement of this ring leads to loss of pharmacological activity.

2.0 MATERIAL AND METHODS

All raw materials used in the synthesis have been obtained from M/s Fluka AG (Bachs-Switzerland) and M/s Sigma Aldrich chemicals and Co. Inc. (Milwoukee, WI, USA). 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-400 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, N Elemental Analyzer (Thermo-Finnigan Flash, EA 1112, Italy). Mass data have been recorded on Agilent GC-MS.

2.1 EXPERIMENTAL

2.1.1 Preparation of ethyl (quinolin-8-yloxy) acetate[3](2)

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%; white colour solid; mp; 95 °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

IR (KBr) cm^{-1}: 1096(-O-), 1732(-C=O), 767(Di-substituted Ar-H), 1613(-C=N)

MS (m/z): 231[M^+] ($C_{13}H_{13}NO_3^+$).

2.1.2 Preparation of 2-(quinolin-8-yloxy) acetohydrazide[4] (3)

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 °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

IR (KBr) cm^{-1}: 1082(-O-), 1693(-CONH), 763(Di substituted Ar-H), 1612(-C=N)

MS (m/z): 217 [M$^+$] ($C_{11}H_{11}N_3O_2^+$).

2.1.3.1 Preparation of *N*'-[(*E*)-(4-hydroxyphenyl)methylidene]-2-(quinolin-8-yloxy)acetohydrazide[5] (4a)

Compound 3 (0.01M, 2.17gm) in ethanol, substituted benzaldehyde (0.01M, 1.22) and 1 ml of glacial acetic acid was refluxed on water bath for 6 hours. Reaction was monitoring by TLC. After cooling, the solvent was removed under reduced pressure and the separated solid was washed, dried and recrystallized from ethanol. Further Derivatives 4a-e was synthesized in same manner.

Yield 90%; Pale yellow colour solid; mp; 235°C

^{1}H NMR (400 MHz- DMSO-d_6) δ (ppm) 4.2(s,2H, CH_2), 5.3(s,1H, NH), 8.3(s,1H, OH), 7.0-8.0(m,10H, Ar-H)

Anal. Calc. for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08;

found: C, 67.10; H, 4.50; N, 13

IR (KBr) cm^{-1}: 1629(-CONH), 1074(-O-), 3334(-OH)

MS (m/z): 321 [M$^+$] ($C_{18}H_{15}N_3O_3^+$).

2.1.3.2 Preparation of *N*'-[(*E*)-(3,4-dihydroxyphenyl)methylidene]-2-(quinolin-8-yloxy)acetohydrazide (4b)

^{1}H NMR (400 MHz- DMSO-d_6) δ (ppm) 4.4(s,2H, CH_2), 5.2(s,1H, NH), 8.2(s,1H, OH), 8.4(s,1H, OH), 7.0-8.0(m,10H, Ar-H)

Anal. Calc. for $C_{18}H_{15}N_3O_4$: C, 64.09; H, 4.48; N, 12.46;

found: C, 64; H, 4.16; N, 12.30;

IR (KBr) cm^{-1}: 1616(-CONH), 1074(-O-), 3325(-OH)

MS (m/z): 337 [M^+] ($C_{18}H_{15}N_3O_4^+$).

2.1.3.3 Preparation of *N*'-[(*E*)-(4-chlorophenyl)methylidene]-2-(quinolin-8-yloxy)acetohydrazide (4c)

^{1}H NMR (400 MHz- DMSO-d_6) δ (ppm) 4.2(s,2H, CH_2), 5.1(s,1H, NH), 7.0-8.0(m,10H, Ar-H)

Anal. Calc. for $C_{18}H_{14}N_3O_2Cl$: C, 63.63; H, 4.15; N, 12.37;

found: C, 63.50; H, 4.05; N, 12.10;

IR (KBr) cm^{-1}: 1674(-CONH), 1045(-O-), 721(-Cl)

MS (m/z): 339 [M^+] ($C_{18}H_{14}N_3O_2Cl^+$).

2.1.3.4 Preparation of N'-[(E)-(3,4-dimethoxyphenyl)methylidene]-2-(quinolin-8-yloxy)acetohydrazide (4d)

^{1}H NMR (400 MHz- DMSO-d_6) δ (ppm) 4.3(s,2H, CH_2), 3.2(s,3H, CH), 3.6(s,3H, CH), 5.4(s,1H, NH), 7.0-8.0(m,10H, Ar-H)

Anal. Calc. for $C_{20}H_{19}N_3O_4$: C, 65.74; H, 5.24; N, 11.50;

found: C, 65.57; H, 5.16; N, 11.30;

IR (KBr) cm^{-1}: 1649(-CONH), 1089(-O-), 2823(-OCH_3)

MS (m/z): 365 [M^+] ($C_{20}H_{19}N_3O_4^+$).

2.1.3.5 Preparation of *N*'-[(*E*)-(4-fluorophenyl)methylidene]-2-(quinolin-8-yloxy)acetohydrazide (4e)

^{1}H NMR (400 MHz- DMSO-d_6) δ (ppm) 4.3(s,2H, CH_2), 5.4(s,1H, NH), 7.0-8.0(m,10H, Ar-H)

Anal. Calc. for $C_{18}H_{14}N_3O_2F$: C, 66.87; H, 4.36; N, 13;

found: C, 66.57; H, 4.16; N, 12.90;

IR (KBr) cm^{-1}: 1639(-CONH), 1097(-O-), 2843(-OCH_3)

MS (m/z): 323 [M^+] ($C_{18}H_{14}N_3O_2F$).

2.1.4.1 Preparation of *N*-[2-(4-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-(quinolin-8-yloxy)acetamide[6] (5a)

Compound 4 (0.01M, 3.21gm) and thioglycolic acid (0.01M, 9.2gm) in dioxane with a pinch of anhydrous $ZnCl_2$ was refluxed for 12-14 hours on a water bath. The reaction mixture was

left to cool at room temperature. The solid product so formed was collected and recrystallized from ethanol to compound III-B.4. Further Derivatives III-B.4a-e is synthesized in same manner.

^{1}H NMR (400 MHz- DMSO-d_6) δ (ppm) 4.3(s, 2H, CH_2), 5.4(s, 1H, NH), 3.2(s, 2H, CH_2), 4.1(s, 1H, CH), 8.2(s, 1H, OH), 7.0-8.0(m, 10H, Ar-H)
Anal. Calc. for $C_{20}H_{17}N_3O_4S$: C, 60.75; H, 4.33; N, 10.63;
Found: C, 60.37; H, 4.16; N, 10.52
IR (KBr) cm^{-1}: 1131(-O-), 1622(-CONH), 3495(-OH), 1188(-C-N), 652(-CS)
MS (m/z): 395 [M^+] ($C_{20}H_{17}N_3O_4S^+$).

2.1.4.3 Preparation of *N*-[2-(3,4-dihydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-(quinolin-8-yloxy)acetamide (5b)

^{1}H NMR (400 MHz- DMSO-d_6) δ (ppm) 4.1(s,2H, CH_2), 5.7(s,1H, NH), 3.6(s,2H, CH_2), 4.5(s,1H, CH), 8.2(s,1H, OH), 7.0-8.0(m,10H, Ar-H)
Anal. Calc. for $C_{20}H_{17}N_3O_5S$: C, 58.38; H, 4.16; N, 10.21;
found: C, 58.37; H, 4.06; N, 10.12
IR (KBr) cm^{-1}: 1131(-O-), 1622(-CONH), 1188(-C-N), 652(-CS)
MS (m/z): 411 [M^+] ($C_{20}H_{17}N_3O_5S^+$).

2.1.4.3 Preparation of *N*-[2-(4-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-(quinolin-8-yloxy)acetamide (5c)

^{1}H NMR (400 MHz- DMSO-d_6) δ (ppm) 4.4(s,2H, CH_2), 5.1(s,1H, NH), 3.4(s,2H, CH_2), 4.6(s,1H, CH), 7.0-8.0(m,10H, Ar-H)
Anal. Calc. for $C_{20}H_{16}N_3O_3SCl$: C, 58.04; H, 3.90; N, 10.15;
found: C, 58.03; H, 3.76; N, 10.12
IR (KBr) cm^{-1}: 1086(-O-), 1634(-CONH), 789(-Cl), 1190(-CN), 620(-CS)
MS (m/z): 413 [M^+] ($C_{20}H_{17}N_3O_5S^+$).

2.1.4.4 Preparation of *N*-[2-(2,4-dimethoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-(quinolin-8-yloxy)acetamide (5d)

^{1}H NMR (400 MHz- DMSO-d_6) δ (ppm) 4.3(s,2H, CH_2), 5.2(s,1H, NH), 3.3(s,2H, CH_2), 4.2(s,1H, CH), 3.2(s,3H, CH), 3.6(s,3H, CH), 7.0-8.0(m,10H, Ar-H)
Anal. Calc. for $C_{22}H_{21}N_3O_5S$: C, 60.12; H, 4.82; N, 9.56;
found: C, 60.07; H, 4.88; N, 9.52

IR (KBr) cm^{-1}: 1089(-O-), 1921(-CONH), 2813(-C-H), 1157(-CN), 622(-CS)

MS (m/z): 439 $[M^+]$ ($C_{22}H_{21}N_3O_5S^+$).

2.1.4.5 Preparation of *N*-[2-(4-fluorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-(quinolin-8-yloxy)acetamide (5e)

^1H NMR (400 MHz- DMSO-d_6) δ (ppm) 4.4(s,2H, CH_2), 5.6(s,1H, NH), 3.3(s,2H, CH_2), 4.2(s,1H, CH), 7.0-8.0(m,10H, Ar-H)

Anal. Calc. for $C_{20}H_{16}N_3O_3F$:C, 60.44; H, 4.06; N, 10.57;

found: C, 60.41; H, 4.01; N, 10.50.

IR (KBr) cm^{-1}: 1073(-O-), 1614(-CONH), 1138(-F), 1198(-CN), 623(-CS)

MS (m/z): 397 $[M^+]$ ($C_{20}H_{16}N_3O_3F^+$).

2.2 Antimicrobial Activity[7]

The antimicrobial activity of all these compounds was screened by using cup-plate agar diffusion methods in DMF, using standard Ampicillin 10 µg/ml against gram positive and gram negative bacteria such as *E. coli, S. aureus, and C. albicans.* While all compounds were also screened for their antifungal activities by using standard Ketonazole 10 µg/ml against *C. albicans* in Tables no 2.

Table 1: - **Physical and analytical data of compound 5a-e.**

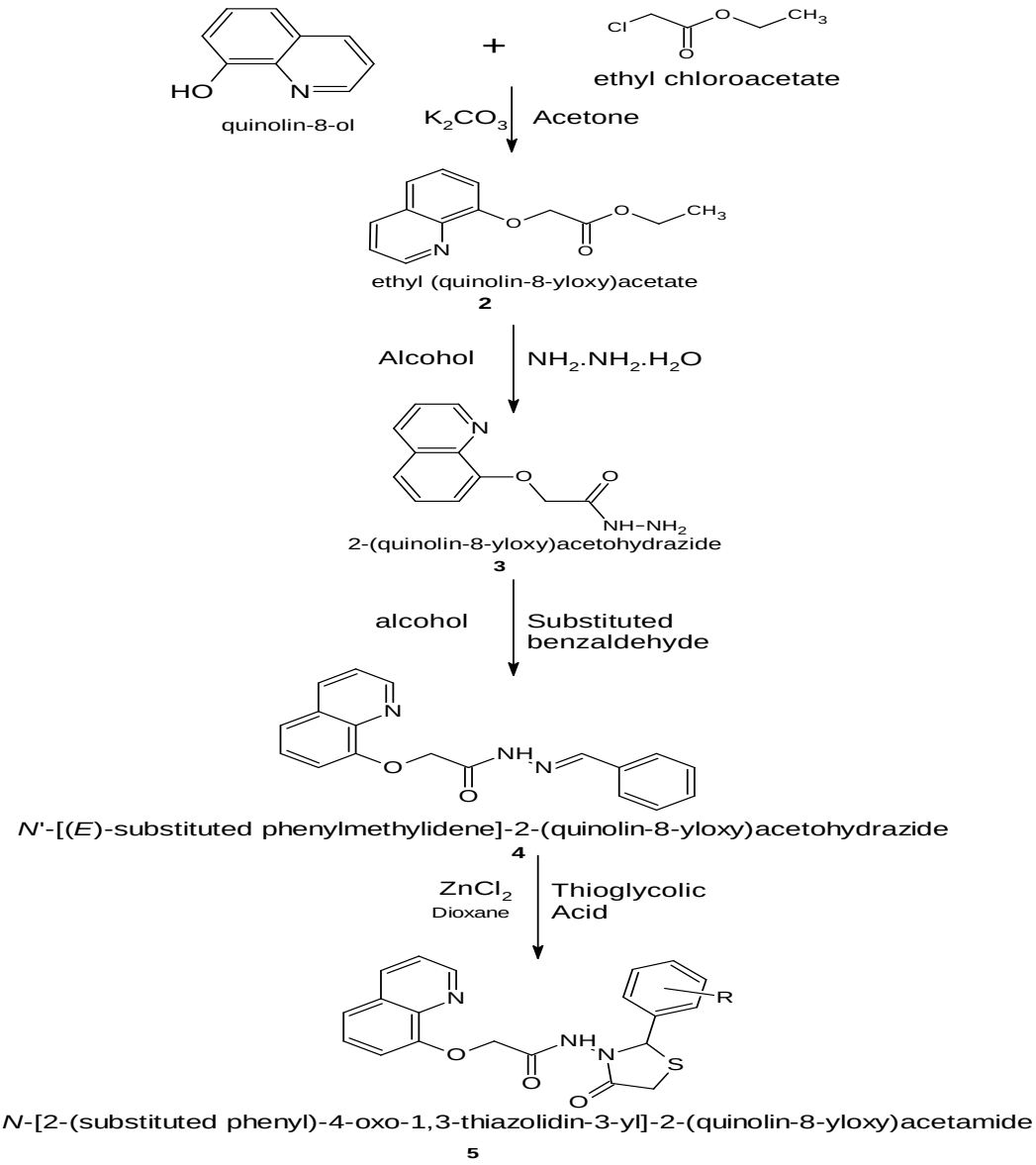
Sr No.	Comp.	R	mp (^0C)	Colour	Yield(%)
1	5a	-OH	255	Brown	69
2	5b	-diOH	248	Light brown	73
3	5c	-Cl	215	Green	58
4	5d	$-OCH_3$	218	Brown	62
5	5e	-F	203	Yellow	54

Table 2: - **Anti-microbial activity of Synthesized compound**.

Sr. No.	Comp.	Substituent's R	Anti-microbial Activity (µg/ml)		
			Anti-Bacterial Strain		Anti-Fungal Strain
			E. coli	*S. aureus*	*C. albicans*
1	5a	OH	-ve	-ve	-ve
2	5b	diOH	-ve	-ve	-ve
3	5c	Cl	-ve	-ve	-ve
4	5d	$diOCH_3$	-ve	-ve	-ve
5	5e	F	-ve	-ve	-ve

- Ampicillin (MIC-10 µg/ml) used as standard against *E. coli & S. aureus.*
- Kitonazole (MIC- 10 µg/ml) as standard against *C. albicans* and *A. niger.*

Table No 3: - SCHEMATIC REPRESENTATION



3.0 RESULTS AND DISCUSSION

Compounds (**5a-e)** were prepared according to reported procedures.[6] Target compounds 1,3-thiazolidin-3-yl derivatives **(5a-e)** were prepared by fusing compounds **(4a-e)** and thioglycolic acid. Structures of compounds were supported by IR, ^{1}H-NMR and MS in addition to elemental method of analyses. IR spectra of compounds (**5a-e)** were chacterized by the characteristic bands due to –CONH at 1680-1630 cm^{-1}. ^{1}H-NMR spectra of compounds **(5a-e)**, CH_2 and CH of thiazolidinone ring showing signal at 3.2 and 4.1ppm. CH_2 and NH which are present in between quinoline and thiazolidinone ring characterized signal at 4.3 and 5.4ppm. MS of compound **(5a-e)** revealed the molecular ion peaks M^+ corresponding to the molecular weight for compounds 5a, 5b, 5c, 5d, 5e.

4.0 CONCLUSION

A number of schiff base derivatives were prepared through 3 steps reaction. This protocol further involves the formation of 1,3-thiazolidin-3-yl done by the cyclization of schiff base derivative with thioglycolic acid. The structures of target compounds (5a-e) were elucidated depending upon different spectral data as well as the elemental methods of analyses. In addition, MS were carried out. The entire series of test compounds **(5a-e)** showed weak to moderate antibacterial and antifungal activity in comparison to ampicillin and ketonazole as a standard drug.

5.0 ACKNOWLEDGEMENT

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6.0 REFERENCE

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