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Synthesis and Antimicrobial Activity of Some Thiazolidinone Derivatives from 2-Methyl, 8-hydroxy Quinoline

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A series of thiazolidinone derivatives were synthesized from 2-methyl, 8-hydroxy quinoline. Schiff bases were prepared by condensation of hydrazide of quinoline moiety with different aromatic aldehydes (**3a-3i**). Cyclocondensation of Schiff bases with thioglycollic acid in presence of anhydrous zinc chloride yielded a series of thiazolidinones (**4a-4i**). The structures of the synthesized compounds have been established by IR, ^{1}H NMR and mass spectra.The compounds have been screened for their antibacterial and antifungal activities.

Key Words: Thiazolidinones, Schiff bases, Antibacterial, Antifungal activity.

INTRODUCTION

4-Thiazolidinone derivatives are associated with various biological properties such as antibacterial, antifungal[1], antimicrobial[2,3], pesticidal[4], nematicidal[5], hypoglycemic and hypolipidemic[6], antitubercular[7] activities. Similarly quinoline moiety was also reported to possess diversified pharmacological activities like antibacterial[8], antitubercular[9] and antiviral activities. So it was thought that quinoline moiety if coupled to 4-thiazolidinones, might exert enhanced activity.

By considering the above factors, it was thought to synthesize some 4-thiazolidinone derivatives from 2-methyl, 8-hydroxy quinoline and screen them for their antibacterial and antifungal activities. 2-Methyl, 8-hydroxy quinoline was treated with ethylchloroacetate yielded 2-methyl,8-oxy quinolinyl ethyl acetate, which on treatment with hydrazine hydrate yielded 2-methyl,8-oxy quinolinyl acetyl hydrazide. The hydrazide derivative of the parent compound yielded Schiff base on condensation with different aromatic aldehydes which on cyclocondensation with thioglycollic acid yielded substituted thiazolidinone derivatives.

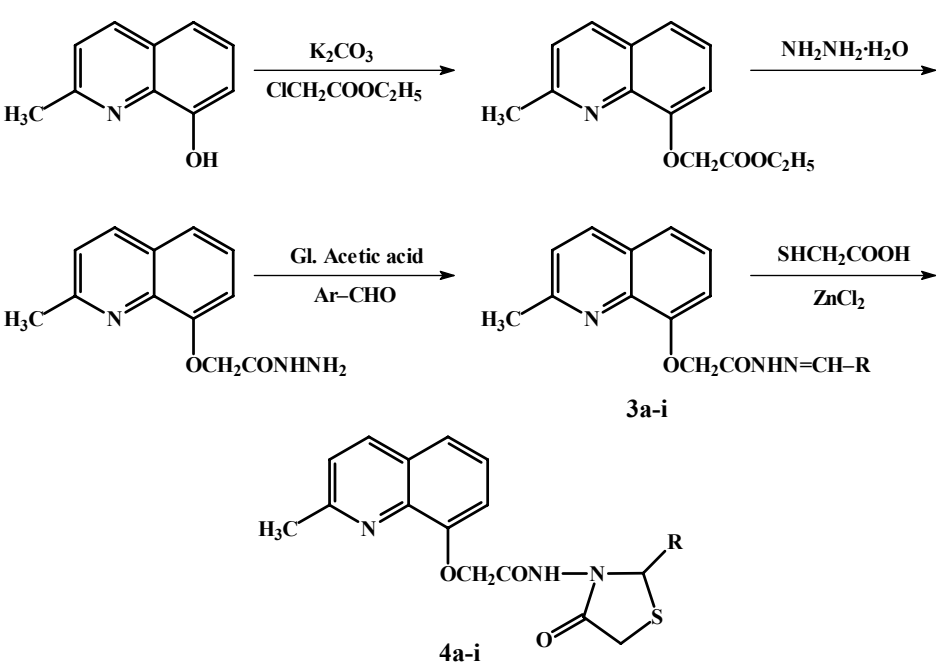
EXPERIMENTAL

Melting points of the newly synthesized compounds were determined by open capillary method and were uncorrected. Purity of the compounds were checked by TLC on silica gel G. The IR spectrum was recorded on Perkin-Elmer spectropho-

tometer using KBR, ^{1}H NMR spectrum were recorded on Bruker DRX-500 using TMS as internal standard, mass spectrum was recorded on Jeol SX102/DA-6000 mass spectrometer using Ar/Xe as FAB gas.

Synthesis of 2-methyl-8-oxyquinolinyl ethyl acetate (1): A mixture of 2-methyl-8-hydroxy quinoline (0.05 mol), ethyl chloroacetate (0.05 mol) and anhydrous potassium carbonate in dry acetone was refluxed for 24 h at 70 °C. The resultant reaction mixture was cooled and filtered. The excess solvent was distilled off and the reaction mixture was dissolved in an ice cold water. Further extracted with ether and the ethereal layer was washed with cold water and dried over anhydrous sodium sulphate. The ether portion was concentrated to get the corresponding ester. b.p.: 116-118 °C. R_f 0.84, I.R (KBr, ν_{max}, cm^{-1}): 3053 (Ar-CH), 1755 (C=O of ester), 1249 (C-O-C), ^{1}H NMR (DMSO) δ: 7.30-6.87 (5H, m, Ar), 4.86 (2H, s, OCH_2), 4.20 (2H, m, CH_2 of ethyl), 2.67 (3H, S, Ar CH_3), 1.23 (3H, m, CH_3-ethyl).

Synthesis of 2-methyl-8-oxyquinolinyl acetyl hydrazide (2): A mixture of **1** (0.05) and hydrazine hydrate 99 % (0.07 mol) was refluxed in ethanol for 6 h. The excess of ethanol was distilled off. On cooling the reaction mixture yielded white needle like crystals of 2-methyl-8-oxyquinolinyl acetyl hydrazide, which were separated and recrystallized from ethanol. m.p. 147-149 °C, R_f 0.76, IR (KBr, ν_{max}, cm^{-1}): 3042 (Ar-CH), 3273 (NH), 1664 (C=O of amide), 1432 (C-N), ^{1}H NMR (DMSO) δ: 10.64 (1H, s, NH), 8.07-7.12 (6H, m, Ar), 4.82 (2H, s, OCH_2), 3.73, (2H, m, NH_2), 2.80 (3H, s, CH_3).



Scheme

Synthesis of 2-{2-(methyl-8-hydroxy)quinoline}-N-{(4-hydroxy)benzylidine}-acetohyrazide (3a): A mixture of **2** (0.05 mol) and *p*-hydroxy benzaldehyde was refluxed along with a few drops of glacial acetic acid for 6 h. The reaction mixture was cooled and then poured on to crushed ice and stirred well. The separated solid was filtered and recrystallized from ethanol. m.p. 160-162 °C, R_f 0.78. IR (KBr, ν_{max}, cm^{-1}): 3387 (-OH), 3193 (-NH), 2987 (CH),1687 (C=O of amide), ^1H NMR (DMSO) δ: 11.43 (1H, s, NH), 9.43 (IH, s, OH), 8.1 (1H, s, -N=CH), 8.52-6.85 (9H, Ar), 4.82 (2H, s, OCH_2), 2.80 (3H, s, CH_3). All other Schiff bases are synthesized by similar method.The physical data of all the Schiff bases are given in Table-1.

TABLE-1
PHYSICAL DATA OF SCHIFF BASES

Compd.	R	m.f.	m.w.	m.p. (ºC)	R_f value	Yield (%)
3a	C_6H_4-4-OH	$C_{19}H_{16}N_3O_3$	334	142-144	0.78	83
3b	C_6H_4-4-$N(CH_3)_2$	$C_{21}H_{22}N_4O_2$	362	110-112	0.71	84
3c	C_6H_4-3-OH	$C_{19}H_{16}N_3O_3$	334	156-158	0.85	78
3d	C_6H_4-3-NO_2	$C_{19}H_{16}N_4O_4$	370	147-148	0.91	73
3e	C_6H_4-4-Cl	$C_{19}H_{16}N_3O_2Cl$	352	132-134	0.51	88
3f	C_6H_3-3,4-$(OCH_3)_2$	$C_{21}H_{21}N_3O_4$	379	160-162	0.78	91
3g	Furfuryl	$C_{21}H_{21}N_3O_3$	334	130-132	0.56	66
3h	C_6H_4-4-OCH_3	$C_{20}H_{18}N_3O_3$	335	152-154	0.68	68
3i	C_6H_4-4-NO_2	$C_{19}H_{16}N_3O_3$	370	158-160	0.80	82

Synthesis of N-[-4-{(4-hydroxy)phenyl}-4-thiazolidin-1-yl]-(2-methyl-8-hydroxy)quinoline acetamide (4a): A mixture of **3a** (0.01 mol) and thioglycollic acid (0.01 mol) in DMF was refluxed for 8 h in presence of anhydrous zinc chloride. The resultant reaction mixture was cooled and then poured on to crushed ice and stirred well. The separated solid was filtered and recrystallized from DMF. m.p. 160-162 °C, R_f 0.88, IR (KBr, ν_{max}, cm^{-1}): 3451 (-OH), 3366 (-NH), 1710 (C=O of thiazolidinone), 1656 (C=O of amide), 1437 (-C-N), 697 (C-S-C). ^1H NMR (DMSO) δ: 11.39 (1H, s, NH), 9.8 (1H, s, OH), 8.18-6.81 9H, m, Ar), 4.88 (2H, s, OCH_2), 5.39, (2H, s, CH_2 of thiazolidinone), 3.59 (1H, s, CH of thiazolidinone). FAB Mass $[M^+]$ -410, 365, 172. All other thiazolidinone derivatives have been synthesized by similar method.The physical data of all the thiazolidinone derivatives are presented in Table-2.

Spectral data

3d: {(2-Methyl-8-hydroxy)quinolin}-N-{(3-nitro)bezylidine} acetohydrazide: IR (KBr, ν_{max}, cm^{-1}): 3243 (-NH), 3087 (-CH), 1665 (C=O of amide). ^1H NMR (DMSO) δ: 11.06 (1H, s, NH), 8.21 (1H, s, N=CH), 8.71-6.85 (9H, Ar), 4.82(1H, s, OCH_2).

3f: {(2-Methyl-8-hydroxy)quinolin}-N-{(3,4-dimethoxy)bezylidine}aceto-hydrazide: IR (KBr, ν_{max}, cm^{-1}): 3133 (-NH), 3047 (-CH), 1675 (C=O of amide). ^1H NMR (DMSO) δ: 11.03 (H, s, NH), 7.93 (1H, s, N=CH), 8.41-6.85 9H, Ar), 4.83 (1H, s, OCH_2), 3.67 (3H, s, OCH_3).

TABLE-2
PHYSICAL DATA OF THIAZOLIDINONE DERIVATIVES

Compd.	R	m.f.	m.w.	m.p. (ºC)	R_f value	Yield (%)
4a	C_6H_4-4-OH	$C_{21}H_{19}N_3O_4S$	409	160-162	0.88	74
4b	C_6H_4-4-$N(CH_3)_2$	$C_{23}H_{24}N_4O_3S$	434	126-128	0.93	62
4c	C_6H_4-3-OH	$C_{21}H_{19}N_3O_4S$	409	182-184	0.81	71
4d	C_6H_4-3-NO_2	$C_{21}H_{16}N_4O_5S$	436	172-174	0.63	64
4e	C_6H_4-4-Cl	$C_{21}H_{18}N_3O_3SCl$	437	156-158	0.65	68
4f	C_6H_3-3,4-$(OCH_3)_2$	$C_{23}H_{23}N_3O_5S$	453	202-205	0.68	74
4g	Furfuryl	$C_{21}H_{21}N_3O_3S$	409	146-148	0.72	53
4h	C_6H_4-4-OCH_3	$C_{22}H_{21}N_3O_4S$	423	192-194	0.58	56
4i	C_6H_4-4-NO_2	$C_{21}H_{16}N_3O_4S$	436	188-190	0.88	62

4d: N-[-4-{(3-Nitro)phenyl}-4-thiazolidin-1-yl]-(2-methyl-8-hydroxy)-quinoline acetamide: IR (KBr, ν_{max}, cm^{-1}): 3207 (NH), 1711 (C=O of thiazolidinone), 1603 (C=O of amide), 1429 (C-N), 692 (C-S-C). ^{1}H NMR (DMSO) δ: 11.53 (1H, s, NH), 8.26-6.97 (6H, m, Ar), 4.90 (2H, s, CH_2), 5.41 (2H, s, CH_2 of thiazolidinone), 3.53 (1H, s, CH of thiazolidinone). FAB Mass [M^+] -410, 365, 172.

4f: N-[-4-{(3,4-Dimethoxy)phenyl}-4-thiazolidin-1-yl]-(2-methyl-8-hydroxy)-quinoline acetamide: IR (KBr, ν_{max}, cm^{-1}): 3241 (NH), 1911 (C=O of thiazolidinone), 1622 (C=O of amide), 1421 (C-N), 651 (C-S-C). ^{1}H NMR (DMSO) δ: 11.53 (1H, s, NH), 8.58-6.97 (6H, m, Ar), 4.91 (2H, s, OCH_2), 5.39 (2H, s, CH_2 of thiazolidinone), 3.81(6H, s, 2XOCH_3). FAB Mass [M^+] -410, 365, 172.

Antibacterial and antifungal activity: The newly synthesized thiazolidinone derivatives were screened for their anti bacterial activity against *S. aureus, B. subtilis, E. coli, P. aeruginosa* using modified Kirby-Bauer method[10]. The compounds were tested at 50 µg level. The results were compared with norfloxacin (10 µg level). All the compounds showed moderate to good antibacterial activity (Table-3).

TABLE-3
ANTIMICROBIAL AND ANTIFUNGAL ACTIVITY DATA OF THIAZOLIDINONE DERIVATIVES

Compound	Diameter of zone of inhibition				
	B. subtilis	*S. aureus*	*E. coli*	*P. aueruginosa*	*C. albicans*
4a	12	14	16	15	9
4b	13	15	14	13	–
4c	11	12	13	12	8
4d	13	15	16	16	11
4e	14	17	17	18	12
4f	12	16	13	–	–
4g	10	13	–	–	–
4h	11	14	13	–	8
4i	13	16	16	17	10
Norfloxacin	15	20	18	19	–
Griseofulvin	–	–	–	–	14

The antifungal activities of the synthesized compounds were evaluated at 50 µg level against *Candida albicans* using modified Kirby-Bauer method[10] and the results were compared with griseofulvin (Table-3).

RESULTS AND DISCUSSION

Various thiazolidinone derivatives prepared from 2-methyl-8-hydroxy quinoline with a view of enhanced activity. The synthesis of the tittle compounds by the above mentioned method resulted in products with good yield. The structures of the newly synthesized compounds were confirmed by IR, ^{1}H NMR and mass spectral analysis.

The compounds **4a**, **4b**, **4d** and **4e** have shown significant antibacterial activity and the other compounds have shown moderate activity. Compounds **4a**, **4d**, **4e** and **4i** have shown significant antifungal activity.

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