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Synthesis and Antimicrobial Activity of 6,7,8,9-Tetrahydro-5(*H*)-5-nitrophenylthiazolo[2,3-b]-quinazoline-3(2*H*)-one Derivatives

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6,7,8,9-Tetrahydro-5(*H*)-5-nitrophenylthiazolo[2,3-b]-quinazolin-3-(2*H*)-one (**2**) has been synthesized as intermediate from 3,4,5,6,7,8-hexahydro-4-nitro phenyl quinazolin-2-thione (**1**) with chloro acetic acid. The treatment of intermediate with various aldehyde afforded respective benzylidine derivatives (**3a-c**). This on further treatment with phenyl hydrazine yielded hydrazine derivatives (**4a-c**). The structures of the compounds were supported by spectral data. The synthesized compounds have been screened for antimicrobial activity.

Key Words: Synthesis, Antimicrobial activity, Phenyl hydrazine, Quinazolines.

INTRODUCTION

The bridge-head nitrogen containing compounds are emerging an important medicinal agent and have been reported[1] to posses wide range of biological accessibility and known to exhibit potent antimicrobial activity, analgesic and antiinflammatory activity, *etc*. Several reports are available regarding the antimicrobial, analgesic and antiinflammatory activity of quinazoline derivatives and the importance of benzylidine and hydrazine in antimicrobial, analgesic and antiinflammatory effect. Hence, the present work has been directed on designing of benzylidine and hydrazine derivatives of quinazoline.

In present work, 6,7,8,9-tetrahydro-5(*H*)-5-nitro phenyl thiazolo[2,3-b]-quinazolin-3(2*H*)-one (**2**) has been synthesized by treating 3,4,5,6,7,8-hexahydro-4-nitro phenylquinazolin-2-thione[2,3] (**1**) with chloro acetic acid followed by thermal cyclization gives intermediate **2** compound. The treatment of

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intermediate **2** with different aldehyde afforded benzylidine derivatives **3a-c**, respectively. The yielded derivatives of benzylidine, on treatment with phenyl hydrazine yielded **4a-c**.

EXPERIMENTAL

Melting points of all the synthesized compounds were determined by using open capillary method and are uncorrected. The precoated alumina plates with silica gel GF_{254} (E.Merck) were used for purity determination and pet.ether:ethyl acetate (1:2) was employed as irrigant. IR spectra were recorded (cm^{-1}) on ABB BOMEM FT-IR spectrometer using KBr pellet technique, ^1H NMR was recorded (δ ppm) on BUKER AV 400 using TMS as internal standard and Mass spectra (EI) were recorded on GCMS QP 5000 Shimadzu.

Synthesis of 3a-c: An equimolar quantities of compound **2** (0.015 mol) and respective aldehydes (0.015 mol) and anhydrous sodium acetate (6 g) in glacial acetic acid was taken in 500 mL round bottomed flask fitted with double surface condenser with a guard tube and was heated under reflux for 8-10 h. The reaction mixture was kept overnight for crystallization. The formed crystals were filtered and recrystallized to give **3a-c**. The purity of the all synthesized compounds were established on TLC plate. The physical data were presented in Table-1.

TABLE-1
PHYSICAL DATA OF THE SYNTHESIZED COMPOUNDS (**3a-c**)

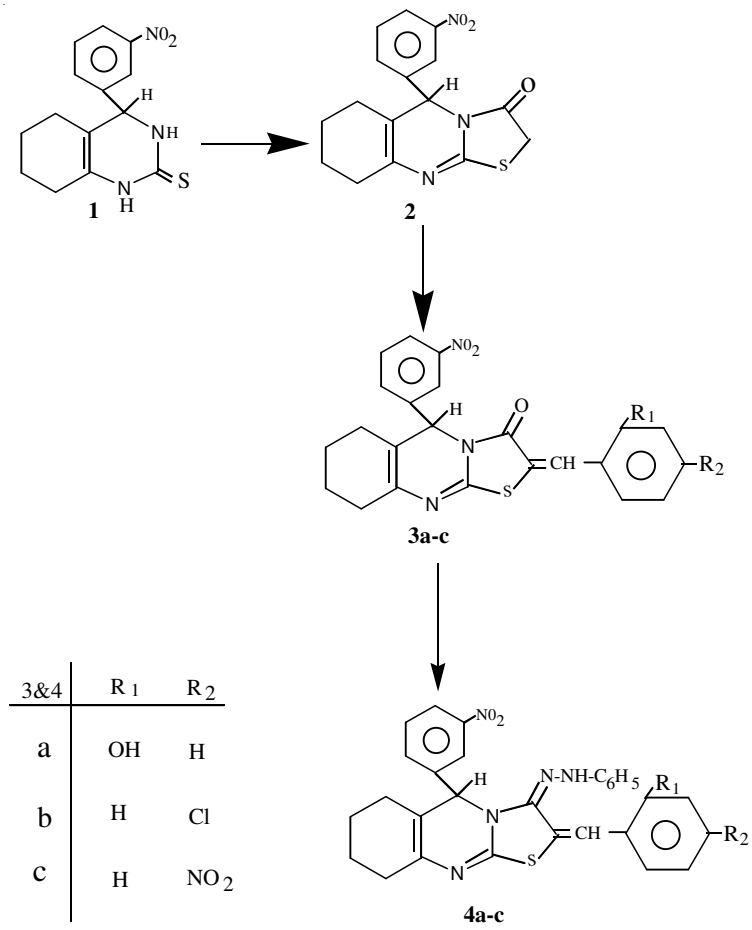
Compd.	m.p. (ºC)	Yield (%)
3a	116-118	42.55
3b	143-145	50.00
3c	216-218	47.22

Compound 3a: 2-(*o*-Hydroxy benzylidine)-5(*H*)-5-nitro phenyl-6,7,8,9-tetrahydro thiazolo[2,3-b]quinazolin-3-one, yield-42.55 %, m.p. 116-118 ºC; IR (KBr, ν_{max}, cm^{-1}): 1715 (C=O), 1644, 1525, 1580 (C=N & C=C), 3650 (-OH), 1486 (N=O); ^1H NMR ($CDCl_3$): 5.471 (1H, S, C-H), 2.032-2.321 (8H, m, $-CH_2-CH_2-CH_2-CH_2$), 6.879-7.759 (8H, m, Ar) 8.131 (1H, S, =CH), 4.112 (1H, S, OH); Mass (EI): m/e 433 (2 %, M^+) m/e 95 (100 % base peak).

Compound 3b: 2-(*p*-Chloro benzylidine)-5(*H*)-5-nitro phenyl-6,7,8,9-tetrahydro thiazolo[2,3-b]quinazolin-3-one, yield - 42.55 %, m.p. 116-118 ºC; IR (KBr, ν_{max}, cm^{-1}): 1716 (C=O), 1604, 1526 (C=N & C=C), 807 (C-Cl), 1489 (N=O); ^1H NMR ($CDCl_3$): 5.567 (1H, S, C-H), 2.019-2.394 (8H, m, $-CH_2-CH_2-CH_2-CH_2$), 7.516-7.983 (8H, m, Ar), 8.142 (1H, S, =CH) ; Mass (EI): m/e 433 (2 %, M^+) m/e 95 (100 % base peak).

Compound 3c: 2-(*p*-Nitro benzylidine)-5(*H*)-5-nitro phenyl-6,7,8,9-tetrahydro thiazolo[2,3-b]quinazolin-3-one, yield-42.55 %, m.p. 116-118 ºC; IR (KBr, ν_{max}, cm^{-1}): 1715, (C=O), 1669, 1528 (C=N & C=C), 1486 (N=O); ^1H NMR ($CDCl_3$): 3.995 (1H, S, C-H), 1.995-2.283 (8H, m, $-CH_2-CH_2-CH_2-CH_2$), 7.287-7.810 (8H, m, Ar), 8.208 (1H, S, =CH); Mass (EI): m/e 433 (2 %, M^+) m/e 95 (100 % base peak).

Synthesis of 4a-c: A mixture of compound **3a-c** (0.00517 mol), phenyl hydrazine and anhydrous sodium acetate in glacial acetic acid was taken in 500 mL round bottomed flask fitted with condenser with a guard tube and was refluxed for 14-22 h. The volume was concentrated to its half and the mixture was kept for 48 h at room temperature for crystallization. The separated product was filtered and recrystallized to yielded **4a-c** (**Scheme-I**). The purity of the all synthesized compounds were established on TLC plate. The physical data were presented in Table-2.



3&4	R_1	R_2
a	OH	H
b	H	Cl
c	H	NO_2

Scheme-I

TABLE-2
PHYSICAL DATA OF THE SYNTHESIZED COMPOUNDS (**4a-c**)

Compd.	m.p. (ºC)	Yield (%)
4a	95-97	62.22
4b	155-157	60.00
4c	185-187	59.50

Compound 4a: 2-(*o*-Hydroxy benzylidine)-3-phenylhydrazine-5(*H*) -5-nitro phenyl-6,7,8,9-tetrahydro thiazolo[2,3-b]quinazoline, yield-42.55 %, m.p.116-118 ºC; IR (KBr, ν_{max}, cm^{-1}): 1654, 1525 (C=N & C=C), 3649 (-OH), 1489 (N= O); ^{1}H NMR ($CDCl_3$): 4.276 (1H, S, C-H), 1.608-2.330 (8H, m, $-CH_2-CH_2-CH_2-CH_2$), 7.134-7.410 (8H, m, Ar), 7.575 (1H, S, =CH), 1.253 (1H, S, =N-NH), 4.210 (1H, S, OH); Mass (EI): m/e 433 (2 %, M^+) m/e 95 (100 % base peak).

Compound 4b: 2-(*p*-Chloro benzyl indene)-3-phenyl hydrazine-5(*H*)-5-nitro phenyl-6,7,8,9-tetra hydro thiazolo[2,3-b]quinazoline, yield-42.55 %, m.p. 116-118 ºC; IR (KBr, ν_{max}, cm^{-1}): 1654, 1525 (C=N & C=C), 810 (C-Cl), 1489 (N=O); ^{1}H NMR ($CDCl_3$): 5.471 (1H, S, C-H), 2.019-2.381 (8H, m, $-CH_2-CH_2-CH_2-CH_2$), 6.989-7.542 (8H, m, Ar), 8.210 (1H, S, =CH), 1.283 (1H, S, =N-NH); Mass (EI): m/e 433 (2 %, M^+) m/e 95 (100 % base peak).

Compound 4c: 2-(*p*-Nitro benzylidine)-3-phenylhydrazine-5(*H*)-5-nitro phenyl-6,7,8,9-tetrahydro thiazolo[2,3-b]quinazoline, yield-42.55 %, m.p. 116-118 ºC; IR (KBr, ν_{max}, cm^{-1}): 1669, 1525 (C=N & C=C), 1490 (N=O); ^{1}H NMR ($CDCl_3$): 1.817 (1H, S, C-H), 2.091-2.228 (8H, m, $-CH_2-CH_2-CH_2-CH_2$), 7.642-7.865 (8H, m, Ar), 1.743 (1H, S, =N-NH); Mass (EI): m/e 433 (2 %, M^+) m/e 95 (100 % base peak).

Antimicrobial activity: The synthesized compounds were screened for antibacterial activity against *E. coli*, *Klebsiella pneumonia*, *Staphylococcus aureus* and *Staphylococcus epidermis* and antifungal activity against *Aspergillus niger* and *Candida albicans*. Neat samples and serial tube dilution method[4] in DMF were used to determine minimum inhibitory concentration (MIC). The MIC was measured in µg/mL and the activity was compared with ciprofloxacin and ketoconazole[5] as standard for antibacterial and antifungal activity, respectively.

RESULTS AND DISCUSSION

In this study six new 6,7,8,9-tetrahydro-5*H*-5-nitrophenylthiazolo quinazoline-3-one derivatives having aromatic aldehyde and phenyl hydrazine substitution on 6,7,8,9-tetrahydro-5*H*-5-nitrophenylthiazolo quinazoline-3-one ring were synthesized to evaluate antimicrobial activity. An examination of result reveals that all the compounds showed antimicrobial activity ranging from 50 to 200 µg/mL. The synthesized compounds antimicrobial data showed in Table-3.

TABLE-3
BIOLOGICAL SCREENING DATA OF SYNTHESIZED COMPOUNDS **3a-c**, **4a-c** AT A CONCENTRATION OF 200 µg/mL

Compd.	Antibacterial activity				Antifungal activity	
	EC	KP	SA	SE	AN	CA
3a	16	17	18	20	18	16
3b	15	18	17	18	17	18
3c	16	17	19	18	16	17
4a	24	23	21	25	21	21
4b	23	21	19	20	19	18
4c	24	22	21	24	21	20
Standard (100 µg/mL)	28	25	24	27	24	24
Blank	–	–	–	–	–	–

EC = *E. coli*; KP = *K. pneumonia*; SA = *S. aureus*; SE = *S. epidermis*; AN = *A. niger*; CA = *C. albicans*.

These results clearly demonstrated that the presence of phenyl hydrazine group at 6,7,8,9-tetrahydro-5*H*-5-nitrophenylthiazolo quinazoline-3-one ring cause improvement in antimicrobial activity.

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