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SYNTHESIS OF 6 , 7 , 8 , 9 - TETRAHYDRO- 5 - (CHLOROPHENYL / NITROPHENYL) THIAZOLO [2,3-B] QUINAZOLINES AS POTENTIAL ANTIMICROBIAL AGENTS

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ABSTRACT

In the present study, a novel series of 6,7,8,9-tetrahydro-5H-5-(substituted phenyl)- thiazolo [2,3-b]- quinazolin – 3(2H)-ones were synthesized and characterized by means of IR, ^{1}H-NMR,Mass spectral and elemental analysis. The compounds were screened for antibacterial (S*taphylococcus aureus* ATCC 9144 , *Staphylococcus epidermidis* ATCC 155 , *Klebsiella pneumoniae* ATCC 29665 and *Escherichia coli* ATCC 25922) and antifungal (*Candida albicans* ATCC 2091 and *Aspergillus niger* ATCC 9029) activities. The Minimum Inhibitory Concentrations (MIC) of the compounds were also ascertained by agar streak dilution method. 2-(4'- nitrobenzylidene)-5H-5-(2"-chlorophenyl)- 6, 7, 8, 9 - tetrahydrothiazolo [2,3-b]quinazolin-3-(2H)–ylidene)-3-phenylhydrazine (8) was found to exhibit the most potent *in vitro* antimicrobial activity with MIC of 8,10,11,13,22 and 24µg/ml against *E .coli, K. pneumoniae, S. aureus, S. epidermidis, C. albicans* and *A. niger* respectively. All the other compounds exhibited moderate activity against the bacterial and fungal organisms tested.

Key words: Quinazoline; Phenyl hydrazine; Antibacterial; Antifungal

INTRODUCTION

The substituted quinazolinones were reported to possess anticancer[1], antiviral[2], antiparkinsonian[3], antiasthma and antiallegy and antihypertensive[4], anti-inflammatory and analgesic[5,6] and antimicrobial properties[7-10]. The thiazole ring[11] bearing compounds show varied biological activities. For example, compounds like Tigemonam and Tenonitrozole[12] reported to possess antibacterial and antifungal activity respectively. The wide range of therapeutic value of these nucleus prompted us to synthesize compounds comprised of these fused ring system with substitution at 2,3 & 5th positions would possess potential antimicrobial properties. In the present study, a novel series of 6, 7, 8, 9 - tetrahydro - 5H - 5 - (chlorophenyl / nitrophenyl) thiazolo [2, 3 - b] quinazolines, were synthesized and characterized by IR, ^{1}H-NMR,^{13}C-NMR, Mass spectral data and elemental analysis. The compounds were screened for antibacterial and antifungal activities. The minimum inhibitory concentrations were also determined by agar streak dilution method.

Chemistry

In the present study, substituted benzylidene cyclohexanone refluxed with thiourea in the presence of potassium hydroxide formed 4- substituted phenyl 3,4,5,6,7,8- hexahydro-4-(2"-chloro/nitrophenyl)quinazoline-2-thione 1 which was treated with chloro acetic acid formed 6,7,8,9-tetrahydro-5H-5-substituted phenyl thiazoloquinazoline-3(2H)-ones(2). The resulting intermediate by treatment with various substituted benzaldehyde gives 2-substituted benzylidene - 5H - 5 - (5'' –

chlorophenyl / 5'' - nitrophenyl) 6, 7, 8, 9 tetrahydrothiazolo quinazolinones 3-8. The intermediate so formed by treatment with phenyl hydrazine to obtain the derived products, 2-(substituted benzylidene) -3-phenyl hydrazinyl-5H,5-(5''-chlorophenyl/5''-nitrophenyl) - 6,7,8,9-tetrahydro thiazolo- [2,3-b]quinazolin-3(2H)-ylidene-3-phenylhydrazine9-14.

Biological investigation

The *invitro* antibacterial (*Staphylococcus aureus* ATCC 9144, *Staphylococcus epidermidis* ATCC 155, *Klebsiella pneumoniae* ATCC 29665 and *Escherichia coli* ATCC 25922) and antifungal (*Candida albicans* ATCC 2091 and *Aspergillus niger* ATCC 9029) activities of the compounds were evaluated by paper disc diffusion method. The Minimum Inhibitory Concentrations of the compounds were also determined by agar streak dilution method.

EXPERIMENTAL

Chemistry

The melting points were taken in open capillary tube and are uncorrected. The IR spectra of the compounds were recorded on ABB Bomem FTIR spectrometer MB104 with KBr pellets. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on 300 MHz-Bruker DPX 200. The chemical shifts are reported as parts per million downfield from tetra methyl silane. Mass spectra were recorded on Finnigan MAT 8230. Microanalyses for C, H, N were performed in Heraeus CHN Rapid Analyzer.

Synthesis of 3,4,5,6,7,8- hexahydro- 4- (2"-chloro/nitro phenyl quinazolin - 2 - thione [1]

Equimolar quantities (0.75 mol) of 2- chloro/nitro benzylidene cyclohexanone (0.75 mol), thio urea (0.75 mol) in ethanol was refluxed for 3 h. The reaction mixture concentrated to half of its volume, then acidified with dilute acetic acid and kept overnight. The solid thus obtained was filtered, washed with water and recrystallized using absolute ethanol

Synthesis of 6,7,8,9 – tetrahydro- 5H – 5- substituted phenylthiazolo [2,3-b] – quinazolin – 3(2H) – one [2].

Chloroacetic acid (0.096 mol) was melted on a water bath and thione 1 (0.009 mol) added to it portion wise to maintain its homogeneity. The homogenous melt was further heated on a water bath for 30 min and kept overnight. The solid thus obtained was washed with water until neutral and recrystallized from absolute ethanol. Yield = 89%, mp: 160-161˚C.

General method of synthesis [3-8].

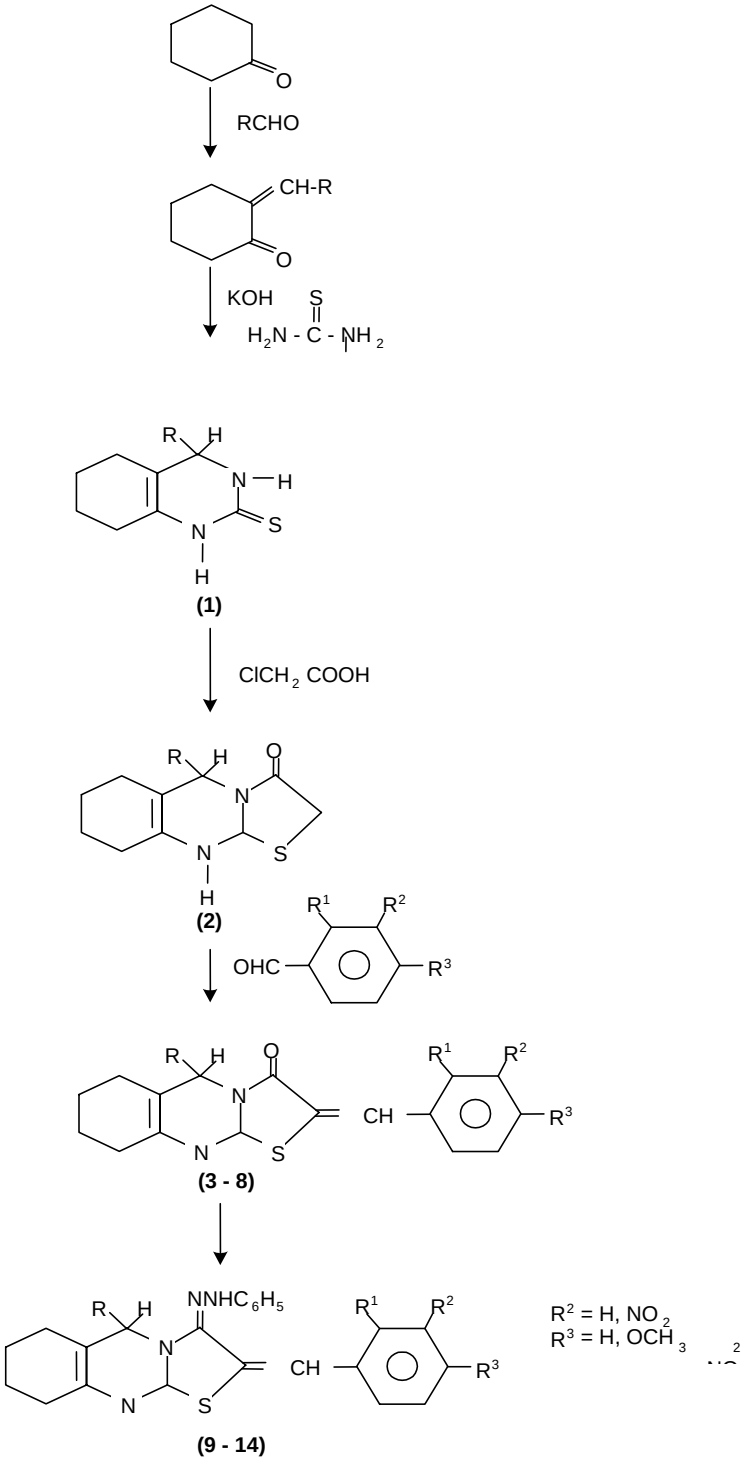
Equimolar quantities of compound 2 (0.0015 mol) and various substituted aromatic aldehyde in presence of anhydrous sodium acetate in glacial acetic acid refluxed under anhydrous condition for 4 h. The reaction mixture kept overnight and yellow color crystals thus separated, filtered and recrystallized using absolute ethanol.

General method of synthesis [9-14]

Compound 2 (0.005 mol) individually treated with phenyl hydrazine (0.02 mol) and in presence of anhydrous sodium acetate in glacial acetic acid refluxed under anhydrous condition for 20 h. The yellow colored crystals thus obtained, filtered, washed with water and recrystallised from methanol..

RESULTS AND DISCUSSION

All the synthesized compounds exhibited significant antibacterial and moderate antifungal activity. 2 - (4' - nitro benzylidene) - 5H - 5 - (2" - chlorophenyl) - 6, 7, 8, 9 - tetrahydrothiazolo [2,3-b]quinazolin-3-(2H)–ylidene)-3-phenylhydrazine 8 was found to exhibit most potent antimicrobial activity against all the microbial strains tested. All the compounds were active against all tested microorganism with a range of MIC values for *S. aureus* (9–23 μg/ml), *S. epidermidis* (10–22 μg/ml), *K. pneumoniae* (10–24 μg/ml), *E. coli* (8–28 μg/ml), *C. albicans* (19–45 μg/ml) and *A. niger* (23–38 μg/ml).



The MIC of the compounds 3-7 against *A. niger* was >100 µg/ml. Compounds 8,11 and 14 exhibited significant activity against *E.coli* (MIC : 8 µg/ml) *k. Pneumonia* (MIC : 11 µg/ml) and *A. niger* (MIC :

23 µg/ml). Compounds 4, 6, 7, 9 and 13 exhibited moderate activity against all the bacteria and fungi tested. The results revealed that most of the synthesized compounds exhibited significant antibacterial activity but they showed moderate antifungal activity.

Table-1:Physicochemical parameters of synthesized compounds

Compd.	IR (KBr) cm^{-1}	^{1}H- NMR ($CDCl_3$) δ	Mass m/z (M^+)	Yield %	M. P. (°C)
1	1600 (C=O), 830 (C-Cl), 1488 (C=N), 3580 (OH).	12.8 7.75 - 7.16 5.41 2.12 – 2.01 1.92 – 1.81 1.58 – 1.47 1.22 – 1.11 .	422	76	110– 111
2	1598 (C=O), 802 (C-Cl), 1488 (C=N), 1090(OCH_3).	: 8.03, 7.75 - 7.24 , 3.79, 2.12 – 2.01, 1.90- 1.81, 1.61 – 1.46, 1.20 – 1.11	436	59	95 – 96
3	1608 (C=O), 1486 (C-NO_2), 1525 (C=N), 3650 (OH).	8.12, 7.71 – 7.04 , 5.68, 4.35, 2.11 – 2.01, 1.61-1.44, 1.22 – 1.23	433	42	116-118
4	1604 (C=O), 1489 (C-NO_2), 1526 (C=N), 807 (Cl).	: 8.03 7.71-7.43 5.73 5. 2.11 – 2.01 1.90- 1.80 1.61-1.55 1.22 – 1.12.	451	50	143-145
5	804 (C-Cl), 1489 (C=N), 1091 (OCH_3), 3418 (N-N).	8.14 – 7.02, 6.94, 5.81, 3.74, 2.34 – 2.23, 1.54-1.44, 1.22 – 1.12	527	77	60-62
6	(C-Cl), 1489 (C=N), 3580 (OH), 3418 (N-N-N)	8.15 – 6.85 7.12 6.10 ,5.91 ,1.91-1.73,1.53-1.43,1.23 – 1.13	513	80	70-71
7	804 (C-Cl), 1489 (C=N), 1091 (OCH_3), 3418 (N-N).	8.14 – 7.02, 7.78 . 6.94, 5. 81, 3.74, 2.34 – 2.23, 1.81-1.74, 1.54-1.44, 1.22 – 1.12	527	77	60-62
8	801 (C-Cl), 1489 (C=N), 1091 (OCH_3), 3418 (N-N), 1.53-1.44,	8.71 – 7.13, 7.81, 7.04, 6.01, 2.34 – 2.12, 1.53-1.44, 1.22 – 1.12, 1.91-1.83, 1.22 – 1.12,	542	78	102-104
9	1594 (C=O), 1488 (C-NO_2), 1528 (C=N).	8.03, 8.31-7.32, 5.73, 2.11 – 2.01,1.90- 1.80	462	47	216-218
10	1489 (C-NO_2), 1524 (C=N), 3649 (OH), 3325 (N-N)	8.22- 6.91, 7.12, 6.04, 2.41 – 2.31, 1.92 -1.81, 1.54 – 1.44, 1.22 – 1.12	523	62	95-97
11	1489 (C-NO_2), 1524 (C=N), 810 (Cl), 3366 (N-N).	8-12- 7.03, 7.01, 1.90-1.81, 1.54-1.44, 1.22-1.12	542	60	155-157
12	1490 (C-NO_2), 1525 (C=N), 3364 (N-N)	8-21- 7.04, 7.80, 7.03, 2.42- 2.31, 1.91-1.82, 1.54-1.44, 1.22-1.1, 1.81- 1.74	552	59	185-187

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Table-2:Antimicrobial activity of the synthesized compounds

Compd.	Invitro activity – Zone of inhibition (MIC)					
	E .coli	*K. pneumonia*	*S. aureus*	*S. epidermidis*	*C. albicans*	A.*niger*
3.	18 (21)	19 (20)	23 (18)	20 (19)	15 (35)	12 (>100)
4.	19 (18)	21 (16)	17 (20)	20 (15)	16 (33)	13 (>100)
5.	16 (22)	18 (20)	20 (18)	17 (22)	17 (31)	12 (>100)
6	22 (11)	23 (12)	25 (9)	21 (12)	14 (37)	15 (>100)
7.	23 (12)	21 (13)	19 (15)	16 (17)	12 (45)	14 (>100)
8.	25 (8)	22 (10)	21 (11)	24 (13)	18 (22)	20 (24)
9.	16 (19)	17 (18)	21 (16)	20 (17)	15 (36)	18 (26)
10.	15 (28)	18 (22)	17 (23)	19 (21)	18 (26)	14 (>100)
11	24 (9)	23 (11)	21 (13)	24 (11)	20 (19)	19 (27)
12.	16 (25)	17 (24)	19 (18)	18 (20)	19 (20)	17 (38)
13.	23 (16)	21 (18)	19 (20)	20 (17)	17 (33)	18 (29)
14.	24 (10)	22 (11)	21 (11)	24 (10)	19 (25)	20 (23)
Ciprofloxacin (100 µg/disc)	28	25	24	27	_	_
Ketoconazole	_	_	_	_	21	23
Synthetic scheme	_	_	_	_	_22	_24

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