Thiazol-4-ones containing Azetidin-2-one

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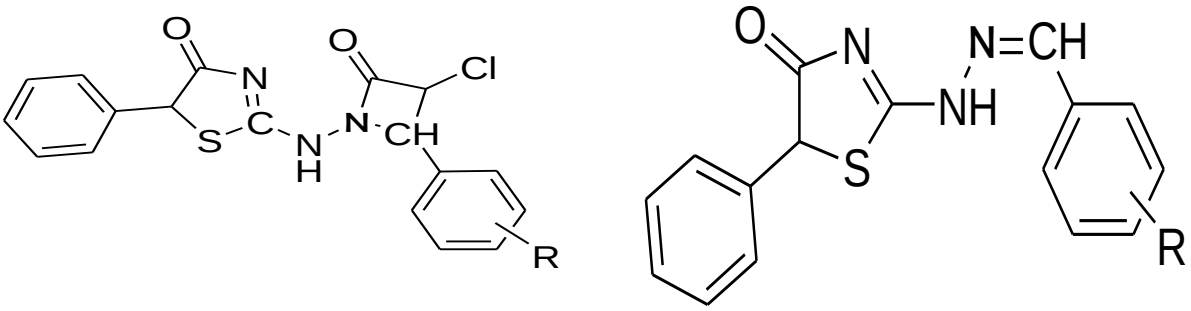


Abstract:

Ethyl-2-bromo-2-phenylethanoate and Thiosemicarbazide yielded 2-Hydrazine-5-phenylthiazol-4-one. The thiazol-4-one derivatives readily reacted with aromatic aldehyde to form Schiff base which on treatment with Chloroacetyl chloride in presence of triethyl amine yielded 2-[3-Chloro-2-(substituted)-phenyl-4-oxo-azetidin-1-yl]-5-phenyl-thiazol-4-one. These newly synthesized compounds were subjected to spectral techniques for their structural conformation. They were also tested for their anti-microbial activity.

Keywords: Thiosemicarbazide, Schiff Base, Chloroacetyl chloride.

Introduction:

The organic moiety having nitrogen and sulfur atom results towards higher efficiency against various diseases.[1]Sulfur is capable of forming both σ and π bonds therefore the studies of their binding interaction with receptor moiety was also an interesting field of research during last few years.[2] Thiazoles are applicable in anti-fire and hard PVC stabilizer compounds. However, their derivations are applicable in anti-wart [3], antiallergenic [4], anti-bacterial [5], anti-spasm [6], antiparoxysm[7] and anti-fungal[8-10]. Phenyl thiazole and their derivatives have possessed versatile biological activity [11-13]. Recently the applications of thiazoles were found in drug development for the treatment of allergies [14], hypertension [15], inflammation [16], schizophrenia [17], bacterial [18], HIV infections [19], hypnotics [20] and more recently for the treatment of pain [21], as ibrinogen receptor antagonists with antithrombotic activity [22] and as new inhibitors of bacterial DNA gyrase B. [23] Present work is an attempt to make new anti-microbial moieties.

Materials and methods

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The purity of the compounds was monitored by thin layer chromatography on silica gel coated aluminium plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer.

General Procedure:

Synthesis of 2-Bromo-2-phenylacetic acid (3):

In a round bottom flask mixture of Phenyl acetic acid**(1)** (0.1mole, 13.6g) and N-Bromosuccnimide**(2)** (0.15mole, 26.7g) were allowed to reflux for 8-10 hrs in CCl_4 (30ml) as a solvent and small quantity of benzoyl peroxide as a catalyst. The progress of the reaction was monitored on TLC. Upon completion, reaction mixture was quenched into the water and CCl_4 (10ml). Organic layer was separated and washed with water. CCl_4 was distilled out completely to yield crystals of compound **(3)**. Yield 70%, m.p. 81-83^{0}C.

Synthesis of Ethyl-2-bromo-2-phenylethanoate (4):

Compound **3** (0.1mole, 21.5g), $SOCl_2$ (0.15mole, 10.9ml), CCl_4 (10ml) as a solvent were refluxed for 2-3 hrs and ethanol (20ml) was then added. The reaction mixture was stirred further for 5-10 mins

and was washed using aqueous solution of Na_2CO_3 to remove traces of compound **3** if present. The organic layer so obtained was distilled off to obtain compound **4**. Yield 83%, b.p. 88-93^{0}C.

Synthesis of 2-Hydrazino-5-phenylthiazol-4-one (5):

Compound **4** (0.01mol, 2.43g) and thiosemicarbazide (0.01mol, 0.75g) were refluxed for 10 mins in presence of ethanol as a solvent and pyridine as a catalyst. The progress of the reaction was monitored on TLC. Upon completion, the reaction mixture was dumped on to crushed ice. The solid thus obtained was filtered, washed with water and recrystalized using hot and aqueous ethanol. Yield 73%, m.p. 255-256^{0}C**Spectral details of 2-Hydrazino-5-phenylthiazol-4-one (5):**

Anal. Calcd for $C_9H_9N_3OS$: C, 52.16; H, 4.38; N, 20.27; O, 5.42; S, 10.86%. Found C, 52.15; H, 4.39; N, 20.27; O, 5.24; S, 10.85%. IR(cm-1): 1688 (C=O), 3200(NH) 1H NMR(δ ppm): 3.31 (s,2H,NH_2), 4.52(s,1H,CH), 7.2-7.6(m,5H,Ar-H), 9.01(s,1H,NH) 13C NMR(δ ppm): 52.02(CH), 128.03-139.01(Ar-C), 160.10(C-N), 177.02(C=O).

Synthesis of 5H-2-(substituted-benzylidin)hydrazino-5-phenyl-4-oxo-1,3-thiazole (7a-g):

A mixture of compound **5** (0.01mole), Aromatic aldehyde**(6)** (0.01mole) and NaOH (0.02mole) in ethanol (10ml) were refluxed for 35 mins. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was poured onto ice. The solid product thus obtained was filtered, washed and recrystallized using ethanol to yield **7**. Thus compounds **7a-g** were synthesized.

5H-2-(benzylidin)hydrazino-5-phenyl-4-oxo-1,3-thiazole (7a)

Anal.Calcd for $C_{16}H_{13}N_3OS$: C, 65.06; H, 4.44; N, 14.23; O, 5.42; S, 10.86%. Found C, 65.08; H, 4.41; N, 14.24; O, 5.24; S, 10.85%. IR(cm-1): 1320 (C-S), 1600(C=N), 1650 (C=N), 1720(C=O), 3100(C-H) 1H NMR(δ ppm): 4.65(s,1H,CH), 7.8(s,1H,CH), 7.2-7.5(m,10H,Ar-H), 8.9(s,1H,NH) ^{13}C NMR(δ ppm): 54(CH), 128-140 (Ar-C), 152(C=N), 163(C=N), 188(C=O).

5H-2-(4'-Hydroxy-3'-methoxy--benzylidin)hydrazino-5-phenyl-4-oxo-1,3-thiazole (7b)

Anal.Calcd for C17H15N3O3S: C, 59.81; H, 4.43; N, 12.31; O, 14.06; S, 9.39%. Found C, 59.82; H, 4.39; N, 12.31; O, 14.07; S, 9.38%. IR(cm-1): 1320(C-S), 1600(C=N), 1650(C=N), 1720(C=O), 3100(CH), 3500(OH) 1H NMR(δ ppm): 3.75(s,3H,OCH_3), 4.7(s,1H,CH), 5.3(s,1H,OH), 7.8 (s,1H,CH), 7.62-7.75(m,8H,Ar-H), 8.95(s,1H,NH) ^{13}C NMR(δ ppm): 54(CH), 58(OCH_3), 128-140(Ar-C), 152 (C=N), 163(C=N), 188(C=O).

Synthesis of 2-[3-Chloro-2-(substituted)-phenyl-4-oxo-azetidin-1-yl]-5-phenyl-thiazol-4-one (8a-g):

A mixture of compound **7** (0.01mole) and triethylamine (0.1mole) was dissolved in 1,4-dioxane (10ml), kept in an ice bath, and stirred for 30 mins. To this, a cold solution of chloroacetyl chloride (0.01mole) was added slowly, further stirred for 3-4 hours at RT. The progress of the reaction was monitored on TLC. After completion of the reaction 1,4-dioxane was distilled off. Residue was poured on to cold water and the resulting solid was filtered, washed with n-hexane, and recrystallized from alcohol to obtain product **8a-g.**

2-[3-Chloro-2-phenyl-4-oxo-azetidin-1-yl]-5-phenyl-thiazol-4-one (8a)

Anal.Calcd for $C_{18}H_{14}ClN_3O_2S$: C, 58.14; H, 3.79; Cl, 9.53; N, 11.30; O, 8.61; S, 8.62%. Found C, 58.14; H, 3.77; Cl; 9.55; N, 11.30; O, 8.60; S, 8.61%. IR(cm^{-1}): 660 (C-Cl), 1320 (C-S), 1600 (C=N), 1720 (C=O), 1750 (C=O), 3100 (C-H), 3350 (NH) ^{1}H NMR(δ ppm): 4.7(s,1H,CH), 5.25(d,1H, CH), 5.4(d,1H,CH), 7.2-7.4(m,10H,Ar-H), 9.2(s,1H,NH) ^{13}C NMR(δ ppm): 54(CH), 58.2(CH), 64.0(C), 124-138(Ar-C), 162.2(C=N), 164.2(C=O), 188(C=O)

2-[3-Chloro-2-(4-hydroxy-3-methoxy-phenyl)-4-oxo-azetidin-1-yl]-5-phenyl-thiazol-4-one (8b)

Anal.Calcd for $C_{19}H_{16}ClN_3O_4S$: C, 54.61; H, 3.86; Cl, 8.48; N, 10.06; O, 15.32; S, 7.67%. Found C, 54.61; H, 3.83; Cl; 8.50; N, 10.05; O, 15.32; S, 7.66%. IR(cm^{-1}): 660(C-Cl), 1100(OCH_3), 1320(C-S), 1600(C=N), 1720(C=O), 1750(C=O), 3100(C-H), 3350(NH), 3580(OH) ^{1}H NMR(δ ppm): 3.8(s,3H,OCH_3), 4.65(s,1H,CH), 5.00(s,1H,OH), 5.28(d,1H,CH), 5.4(d,1H,CH), 7.0-7.5(m,8H,Ar-H), 9.2(s,1H,NH) ^{13}C NMR(δ ppm): 54 (CH), 56.4(OCH_3), 58.2(CH), 64(C), 124-138(Ar-C),162.2(C=N), 164.2(C=O), 188(C=O).

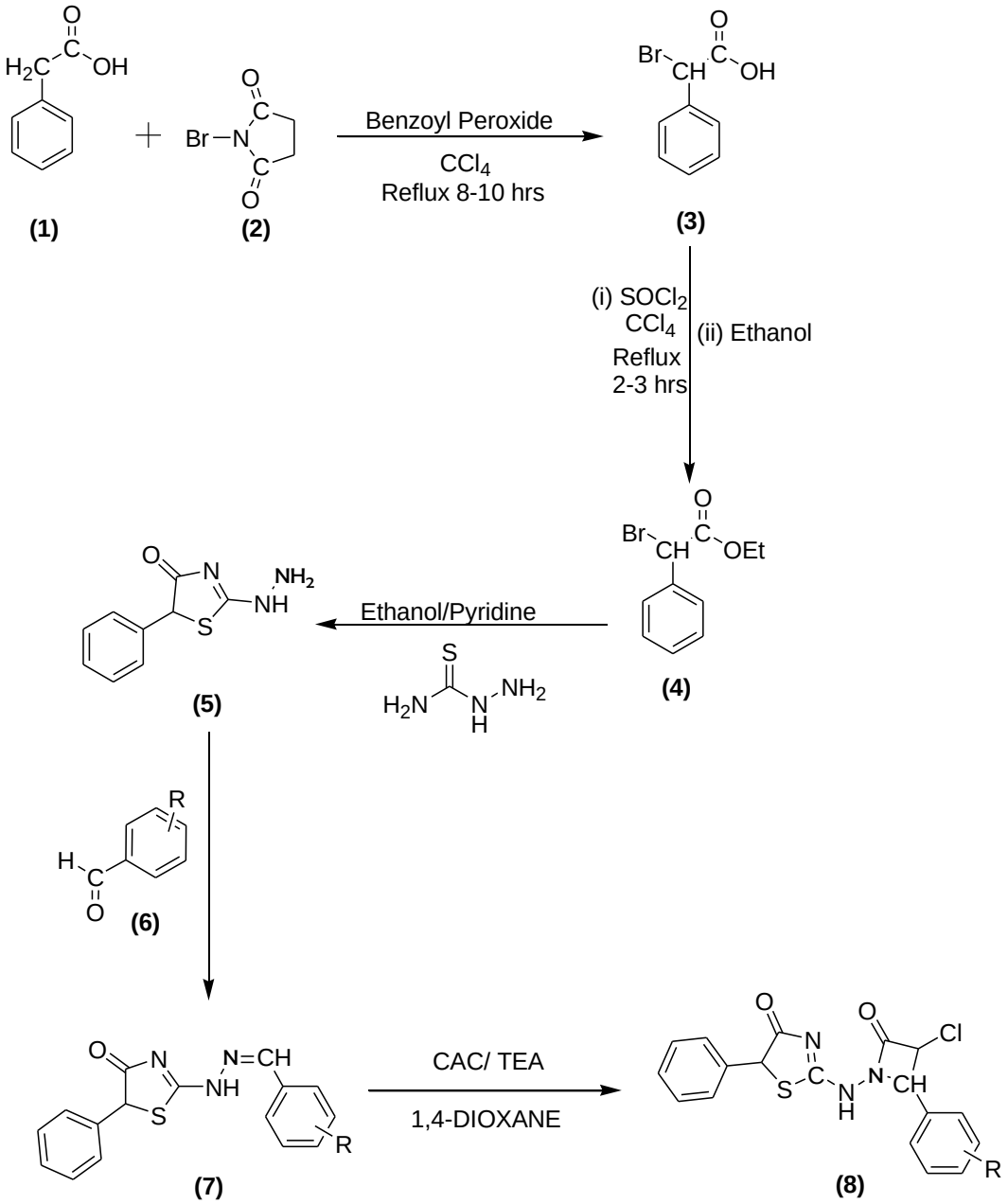
Table I: Characterization data of compounds 5 and 6

Compounds	R	Melting point ^0C	Yield %
7a	H	236-238	73
7b	4-OH, 3-OCH_3	225-227	71
7c	4-OCH_3	251-253	70
7d	4-OH	210-212	64
7e	2-OH	198-200	78
7f	4-Cl	159-161	75
7g	1-CH=CH-CHO	172-174	79
8a	H	281-283	68
8b	4-OH, 3-OCH_3	265-267	72
8c	4-OCH_3	270-272	73
8d	4-OH	250-252	66
8e	2-OH	278-280	78
8f	4-Cl	213-215	75
8g	1-CH=CH-CHO	221-223	81

Antibacterial Evaluation

The newly synthesized representative compounds were tested for their antimicrobial activity against the following microorganisms: (a) Gram-negative: Escherichia coli, P.aeruginosa;
(b) Gram-positive: S.aureus, C.diphtheria. The preliminary screening of the investigated compounds was performed using the filter paper disc-diffusion method. The compounds were tested at a concentration of 100 Kg/ml. The zone of inhibition was measured in mm and compared with reference standard ampicillin trihydrate (100 Kg/ml). The compounds tested displayed promising antimicrobial activity. The results of antibacterial screening studies are reported in **Table II**.

General Scheme



Results and Discussion

In the present study, a series of 1,3-thiazoles and azitidiones derivatives were designed and synthesized , it involves four steps , the compounds **3a-g** were synthesized in high yields by reacting substituted thiosemicarbazons with compound **2** in the presence of pyridine as a catalyst and ethanol as a solvent. Further, the various derivatives **(3a-g)** were treated with chloroacetyl chloride in the presence of triethylamine to yield desired azitidone derivatives **(4a-g)** The representative compounds were evaluated for their antifungal and antibacterial activity, which showed promising activity. The structures of all the synthesized compounds were characterized on the basis of the chemical and spectral techniques such as IR, ^{1}H NMR, ^{13}C NMR and elemental analysis techniques.

Table II. Antimicrobial activities of some newly synthesized compounds.

Compounds	Inhibition Zone (mm)			
	Gram-negative		Gram-positive	
	E.coli	P.aeruginosa	S.aureus	C.diphtheria
8a	11	15	16	14
8b	19	21	21	23
8c	12	16	20	18
8d	11	10	25	23
8e	15	14	21	16
8f	18	20	17	19
8g	17	18	24	22
Amphicilin trihydrate	21	24	26	28
DMSO	0	0	0	0

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