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4-THIAZOLIDINONE DERIVATIVES : SYNTHESIS AND BIOLOGICAL STUDY

S. V. GAIKWAD[*], A. B. BHAKE[a] and S. E. BHANDARKAR[b]

Department of Applied Chemistry, Dr. Babasaheb Ambedkar College of Engineering & Research, NAGPUR (M.S.) INDIA
[a]Department of Applied Chemistry, Yeshwantrao Chavan College of Engineering, NAGPUR (M.S.) INDIA
[b]Department of Chemistry, Govt. Vidarbha Institute of Science and Humanities, AMRAVATI (M.S.) INDIA

ABSTRACT

Synthesis of 2-acetyl-substituted-1-naphthol was first carried out by the acetylation of substituted-1-napthol in presence of glacial acetic acid and zinc chloride. This compound on treatment with KCNS and Br_2 yielded 2-(2-amino-1,3-thiazol-4-yl)-substituted-naphthalen-1-ol, which on facile condensation with aromatic aldehyde gave Schiff Bases. These on cyclo-condensation reaction with mercaptoacetic acid yields 4-thiazolidinone derivatives. The synthesized compounds were characterized by elemental analysis, ^1H NMR, IR spectroscopy. Newly synthesized compound were also studied for their antimicrobial activities.

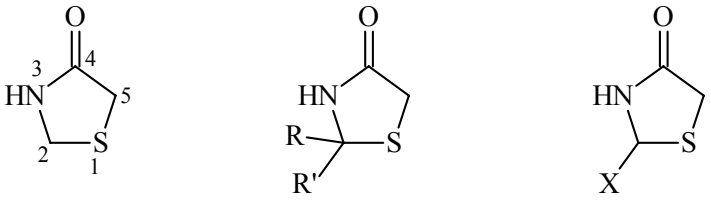
Key words: Synthesis, Thiazolidinone derivatives, Antimicrobial, Biological study.

INTRODUCTION

Thiazolidinone, a saturated form of thiazoles with carbonyl group on fourth carbon, has been considered as a moiety of choice as it possesses a broad spectrum of pharmacological activities against several targets. This array of biological response profile has attracted the attention of scientists' the world over to further investigate the potential of this organic motif. 4-Thiazolidinones are derivatives of thiazolidine with a carbonyl group at the 4-position (1). Substituents in the 2-, 3- and 5-positions may be varied, but the greatest difference in structure and properties is exerted by the group attached to the carbon atom in the 2-position (R and R' in 2 or X in 3). Variations in the substituents attached to the

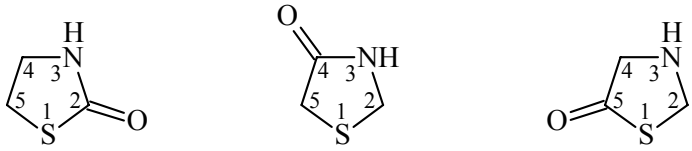
[*]Author for correspondence; E-mail: swatigaikwad71@gmail.com, avinashbhake9@gmail.com, subodhb@rediffmail.com

nitrogen atom and the methylene carbon atom are possible for the structures represented by 2 and 3.



(1) **(2)** **(3)**

Thiazolidinones, which belong to an important group of heterocyclic compounds have been extensively explored for their application in the field of medicine. Thiazolidinones, with a carbonyl group at position 2 (I), 4 (II) or 5 (III), have been subjects of extensive study in the recent past. Numerous reports have appeared in the literature, which highlight their chemistry and use.



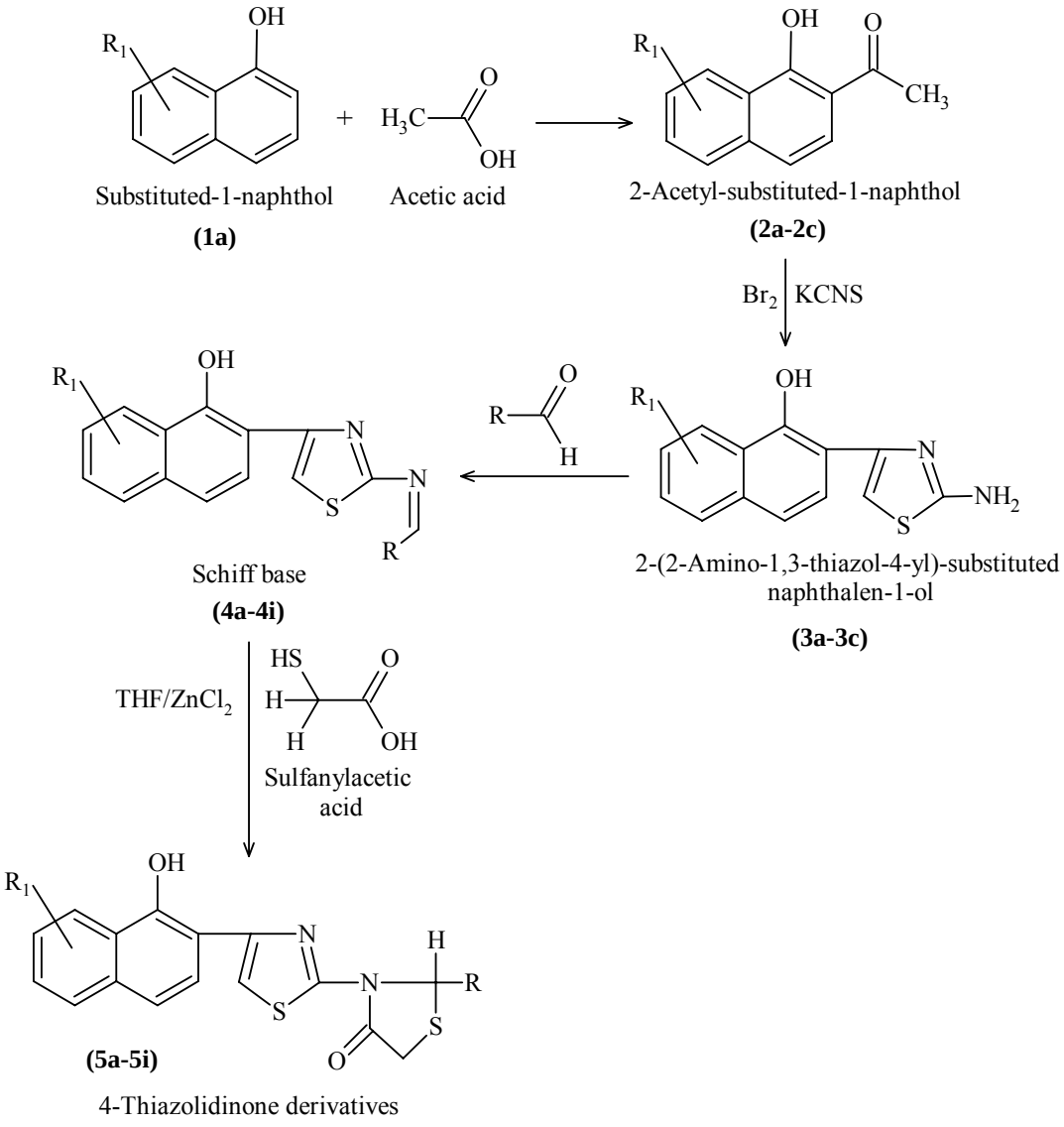
(I) **(II)** **(III)**

The chemistry of heterocycles lies at the heart of drug discovery[1]. 4-Thiazolidinone is one of the most intensively investigated classes of five member heterocycles[2,3]. 4-Thiazolidinones are the heterocyclic compounds having nitrogen and sulfur atoms and are known for a long time for their wide range of interesting biological activities namely anticonvulsant activity, anti–inflammatory activity, anti-tubercular activity, anthelmintic activity, antiviral activity, antifungal activity, antibacterial activity, anticancer activity and anti-HIV activity[4-12] etc. There are many protocols for the synthesis of 4-thiazolidinone[13-22]. Present work deals with the synthesis of thiazolidinone derivatives and their characterization by spectral analysis (IR, ^{1}H NMR).

EXPERIMENTAL

All the melting points were taken in silicon oil bath with open capillary tubes and are uncorrected. IR spectra were recorded on a Nicolet-Impact 400 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Brucker AC 300 FNMR spectrometer (300 MHz),

using TMS as an internal standard. Microanalysis of nitrogen was obtained by Kjeldahal's method. Thin layer chromatography on silica gel-G, was used to check the purity of the compounds.



R_1 = H, OH, OCH_3

R = phenyl, 4-hydroxy phenyl, 4-methoxy phenyl

Scheme

Synthesis 2-acetyl-substituted-1-naphthol

In hot glacial acetic acid, fused $ZnCl_2$ was added and refluxed till dissolved, then powdered substituted-1-naphthol was added and the mixture was refluxed for about 8 hrs then cooled & poured in acidulated water. The solid obtained was filtered, washed, dried and recrystallized from rectified spirit to obtain titled compound.

Synthesis of 2-(2-amino-1,3-thiazol-4-yl)-substituted-naphthalen-1-ol

In a three necked flask, a solution of 2-acetyl-substituted-1-naphthol in 1,4-dioxane was placed. Then the flask was kept in an ice-bath. The mechanical stirrer was fitted. The KCNS was added gradually into the solution with constant stirring. Finally Br_2 (16 mL) in acetic acid (100 mL) was added slowly with constant stirring. The whole assembly with stirrer was kept in an ice-bath for 6 hrs. The resultant mixture was kept aside until reached room temperature. The product was poured into ice-water, filtered and washed with 1,4-dioxane. The product thus was recrystallized by 1,4-dioxane-ethanol mixture and checked on TLC. Finally, the product was purified by column chromatography over silica gel using ethyl acetate: benzene (30:70) as an eluent.

Preparation of Schiff base

A mixture of equimolar amount of 2-(2-amino-1,3-thiazol-4-yl)-substituted-naphthalen-1-ol, benzaldehyde derivative (benzaldehye, p-hydroxybenzaldehyde and 4-methoxybenzaldehyde) in ethanol : 1,4-dioxane (50 : 50) and piperidine was refluxed for 5 hrs on water bath. The reaction mixture was concentrated, cooled and poured in water; the solid obtained was filtered and recrystallised from ethanol to give Schiff base.

Synthesis of 4-thiazolidinone derivatives

A mixture of Schiff base in THF and mercapto acetic acid with a pinch of anhydrous $ZnCl_2$ was then refluxed to get a residue, which was dissolved in 1,4-dioxane-ethanol mixture passed through a column of silica gel using benzene : chloroform (8:2) mixture as an eluent. The eluent was concentrated and the product recrystallized 4-thiazolidinone derivatives from ethanol: 1,4-dioxane (1:1).

Spectral interpretation

IR (KBr) cm^{-1}: (C=O) 1760, (OH) 3320, (N-H) 1580; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ : 3.83 (s, 3H, OCH_3), 7.125-7.532 (m, 11H, Ar – H), 11.71 (s, 1H, OH).

Table 1: Physical and analytical characterization data of newly synthesized compounds

Compd.	R	R_1	Molecular formula	Melting point (^oC)	Yield (%)	% Nitrogen		R.F. Value
						Found	Calculated	
2a	-	H	$C_{12}H_{10}O_2$	76	68	-	-	-
2b	-	OH	$C_{12}H_{10}O_3$	85	75	-	-	-
2c	-	OCH_3	$C_{13}H_{12}O_3$	90	60	-	-	-
3a	-	H	$C_{13}H_{10}N_2OS$	145	68	-	-	-
3b	-	OH	$C_{13}H_{10}N_2O_2S$	140	67	-	-	-
3c	-	OCH_3	$C_{14}H_{12}N_2O_2S$	155	63	-	-	-
4a	C_6H_5	H	$C_{20}H_{14}N_2OS$	150	62	-	-	-
4b	C_6H_5	OH	$C_{20}H_{14}N_2O_2S$	165	59	-	-	-
4c	C_6H_5	OCH_3	$C_{21}H_{16}N_2O_2S$	161	53	-	-	-
4d	C_6H_4OH	H	$C_{20}H_{14}N_2O_2S$	140	57	-	-	-
4e	C_6H_4OH	OH	$C_{20}H_{14}N_2O_3S$	145	51	-	-	-
4f	C_6H_4OH	OCH_3	$C_{21}H_{16}N_2O_3S$	155	56	-	-	-
4g	$C_6H_4OCH_3$	H	$C_{21}H_{16}N_2O_2S$	170	58	-	-	-
4h	$C_6H_4OCH_3$	OH	$C_{21}H_{16}N_2O_3S$	166	53	-	-	-
4i	$C_6H_4OCH_3$	OCH_3	$C_{22}H_{18}N_2O_3S$	152	58	-	-	-
5a	C_6H_5	H	$C_{22}H_{16}N_2O_2S_2$	213	42	6.91	6.93	0.55
5b	C_6H_5	OH	$C_{22}H_{16}N_2O_3S_2$	223	44	6.63	6.67	0.58
5c	C_6H_5	OCH_3	$C_{23}H_{18}N_2O_3S_2$	198	43	6.41	6.45	0.52
5d	C_6H_4OH	H	$C_{22}H_{16}N_2O_3S_2$	263	41	6.66	6.67	0.62
5e	C_6H_4OH	OH	$C_{22}H_{16}N_2O_4S_2$	254	46	6.40	6.42	0.64
5f	C_6H_4OH	OCH_3	$C_{23}H_{18}N_2O_4S_2$	217	43	6.21	6.22	0.52
5g	$C_6H_4OCH_3$	H	$C_{23}H_{18}N_2O_3S_2$	241	45	6.42	6.45	0.58
5h	$C_6H_4OCH_3$	OH	$C_{23}H_{18}N_2O_4S_2$	223	42	6.21	6.22	0.56
5i	$C_6H_4OCH_3$	OCH_3	$C_{24}H_{20}N_2O_4S_2$	199	41	5.99	6.03	0.62

Antimicrobial studies

All above thiazolidinone derivatives have been studied for their antimicrobial activity against *Escherichia coli*, *Proteus mirabilis*, *Staphylococcus aureas*, *Pseudomonas aeruginosa*. The culture of each species was incubated at 37^{o}C and the zone of inhibition was measured after 24 hr. Most of these compounds were found active.

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