SYNTHESIS OF SOME NEW THIAZOLIDINONE DERIVATIVES CONTAINING NAPHTHOFURAN MOIETY AND STUDY OF THEIR BIOLOGICAL ACTIVITY

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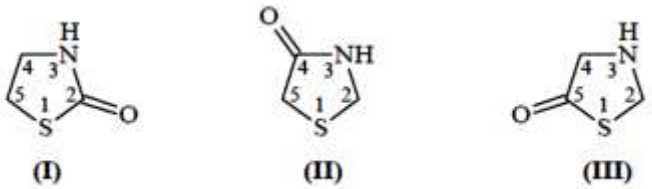
Abstract: *The titled compound were prepared from 2-acetylnaphtho [2, 1-b] furan as starting materials .The starting materials have been synthesized by literature (Stoermer and Schaffer) method. It is then converted in to a series of substituted chalcone* ***1a-e*** *by Claisen -Schmidt condensation with substituted aromatic aldehydes. These chalcones on reaction with thiourea in presence of ethanol and concentrated hydrochloric acid gave their corresponding thiopyrimidine derivatives* ***2a-e,*** *subsequent treatment with mono chloroacetic acid and anhydrous sodium acetate yields 5-(4-substitued aryl) -7 - (naphtho [2, 1-b] furan -2-yl) -2H – thiazole [3, 2-α] pyrimidine -3(5H)-one derivatives* ***3a-e.*** *The newly synthesized compounds are characterized by elemental analysis and spectral studies. Finally they have been evaluated for biological activity.*

Keywords: Naphthofuran, chalcone, chloroacetic acid, thiopyrimidine, thiazolidinone, sodium acetate.

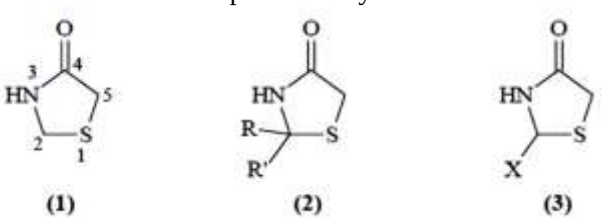
INTRODUCTION

Thiazole is well known five membered heterocyclic compounds with two hetero atoms, sulphur and nitrogen at position 1 and 3. This compound has well known character as aromatic which is widely reflected in its properties. The presence of thiazole moiety in the structure of severally occurring molecules with important antibiotic, immunosuppressive and antitumor activities have been known for several years [1-4].

Thiazolidinone is another heterocyclics have biological importance which contain sulphur atom at position 1, nitrogen atom at position 3, and a carbonyl group at the 1, 4 or 5 positions.The various derivatives:2-thiazolidinone (I) or 4-thiazolidinone (II) or 5-thiazolidinone(III) or 2-thioxo-4-thiazolidinone and thiazolidin -2,4 dione are associated with number of pharmacological properties.



Therefore, they have been considered as a moiety of choice. The aminothiazole ring system has found application in drug development for the treatment of HIV infection, hypertension and inflammation [5]. The several thiazole derivatives have been shown to exhibit excellent bactericidal [6], fungicidal [7,8] and antihelmintic [9] activity. Thiazole occurs widely in plant and specially in eggs, yeast and rice polishing. 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 nitrogen atom and the methylene carbon atom are possible for the structures represented by 2 and 3.



It is well known that a number of heterocyclic compounds containing nitrogen, oxygen and sulphur exhibit a wide variety of biological activity. 4-Thiazolidinones have reported to demonstrate a wide range of pharmacological activities which include anticonvulsant activity, anti–inflammatory activity, anti-tubercular activity, antihelminthic activity, antiviral

activity, antifungal activity, antibacterial activity, anticancer activity and anti-HIV activity[4-12] etc. In view of these reports and in continuation for search of pharmacologically potent naphtho [2, 1-b] furan derivatives [23-25]. We report in this paper the synthesis of some thiazolidinone derivatives of naphtho[2, 1-b] furan, other related compounds and biological activity of the newly synthesized compounds.

EXPERIMENTAL

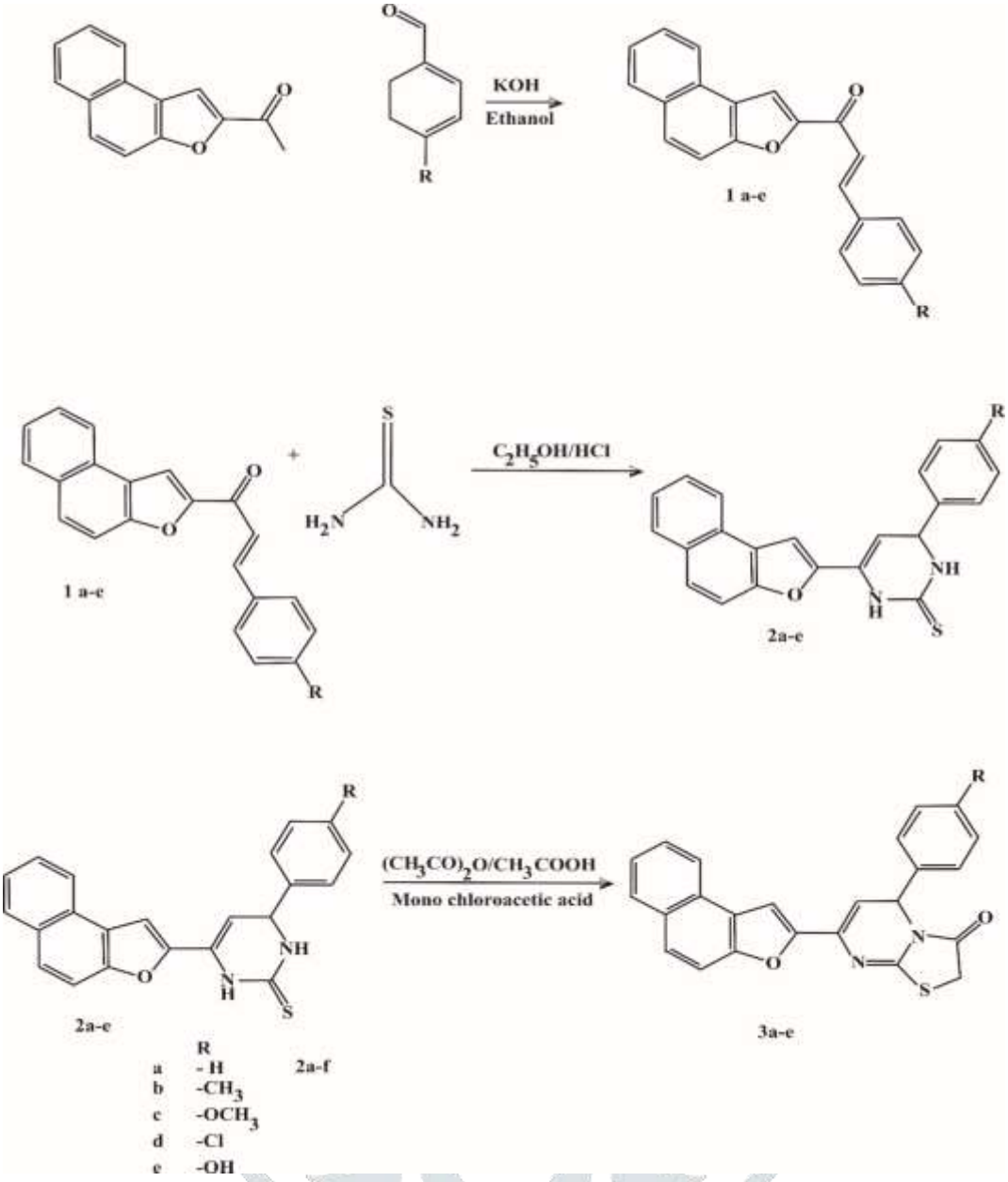
Melting points were determined in open capillary tubes and are uncorrected, IR spectra were recorded in KBr on Bruker FT-IR (Alpha-P),^{1}H NMR spectra on Brukner "AVANCE 400" MHz spectrometer using TMS as an standard. (Chemical shifts in δ ppm) and Mass spectra were performed on a Joel JMS-D 300 mass spectrometer operating at 70 eV. 2-acetylnaphtho [2, 1-b] furan[16] were synthesized by standard method. Progress of reaction was monitored by TLC, Naphthaldehyde, chloroacetone, thiourea, p-substituted aromatic aldehydes, mono chloroacetic acid, silica gel were purchased from Market.

Synthesis of 3-(4-hydroxyphenyl)-1-(naphtho 2, 1-b] furan-2yl) prop-2-en-1-one. 1c

A mixture of 2-acetylnaphtho [2,1-b] furan (4.22 gm,0.01 mole) and p-hydroxy benzaldehyde (2.66 gm,0.021 mole) was stirred in ethanol (50 mL) and then aqueous solution of potassium hydroxide (50%) (10mL) was added to it portion wise, keeping the temperature below 10^{o}C throughout the addition. The mixture was kept for 36 hr and it was acidified with conc. HCl. The reaction mixture was poured into crushed ice and the solid obtained was filtered under vacuum. It was washed with sodium carbonate solution and then with water, dried and the product was recrystallized from ethanol. **1c**. same procedure is extended for other compounds of this series **1a-e** was synthesized by using appropriate aromaticaldehydes.

IR(KBr, λmax):3311 cm^{-1} (Ar-O-H Str), 3059 cm^{-1}(-CH Str. of Ar), 1644 cm^{-1}(C=0 str. of ketone), 1585 cm^{-1}(C=C of chalcone), 1516 cm^{-1}(C = C str. of Ar), 1444 & 1358 cm^{-1}(CH_3 def), 1154 & 1166 cm^{-1}(C – O – C str), 831 cm^{-1}(-CHstr.),748cm^{-1}(Ar-Hopb.);^{1}**HNMR**($CDCl_3$inδppm):6.35(d,1H,-CO-CH=),6.95(d,1H,C=CH)7.21 – 8.24(complexm,11H,Arproton),10.31(s,1H,phenolic–OH);**Mass**(m/z):314[M^+]221,195,147,119,118, 91, 69, 65, 43.

Scheme



Synthesis of 3, 4-dihydro-6-(naphtho[2, 1-b] furan 4-phenyl pyrimidine -2[1H] thione. 2a.

A 250 mL four necked round bottom flask fitted with overhead mechanical stirrer, was charged with 1-(naphtho[2, 1-b] furan-2-yl)-3-phenylprop- 2-en-1-one **1a** (2.99 gm, 0.01 mole) and thiourea (1.51 gm, 0.02 mole) were dissolved in dry ethanol (50 mL) and 10 mL of conc.HCl was added, further it was refluxed for 18 hr. The reaction was monitored by TLC,on completion of reaction, contents were filtered in hot condition and allowed to cool. Then it was neutralized by 5N sodium hydroxide solution. The resulting solid was washed well with water and recrystallized from acetic acid. Compound **2b-e** were prepared in same manner from **1b-e. T**he physical data of the thiopyrimidine derivatives are given in **Table I**.

IR (KBr, λmax) :3425 cm^{-1}(N-H str.), 3061 cm^{-1}(C-H str.ofAr), 2921 cm^{-1}(CH str.of -CH_2), 2432 cm^{-1}(S-H str. of C=S). 1629 cm^{-1}(C=N str.), 1381 cm^{-1}(C = S str.) [27], 1073-1109 cm^{-1}(C-O -C); **^{1}H NMR** ($CDCl_3$ in δppm): 3.98 (s, 1H, N-H Proton of –CH=C-NH-), 3.41 (d, 1H, N-H proton of –CH-CH-NH-Ar) 3.86 (d, 1H, C-4 proton), 5.82(d, 1H,C-5proton),6.90-8.30(m,12H,Arprotons);**Mass**(m/z):356[M^+]195,194,115,105,103,94,91,77,70,66,
65, 55, 44.

Synthesis of 5-(4-hydroxyphenyl)-7(naphtho[2,1-b]furan-2-yl)-2H-thiazole [3,2-α] pyrimidines -3(5H)-one. 3e
A mixture of 3,4-dihydro-4-(4-hydroxy phenyl)-6-(naphtho[2,1-b] furan -2-yl) pyrimidin-2[1H] thione**2e**(4.08 gm, 0.012 mole) and mono-chloroacetic acid (0.95 gm, 0.02 mole) and anhydrous sodium acetate (0.90 gm, 0.011 mole) were dissolved in 25 mL glacial acetic acid and few drops of acetic anhydride was added. This reaction mixture was refluxed for 6 hr. The progress of reaction was monitored by TLC. After completion of reaction, reaction mixture was cooled and poured on crushed ice. The solid formed was filtered, washed, dried and recrystallised from acetic acid **3e**. Compounds **3a-d** was prepared similarly from **2a-d**. The physical and analytical data of the newly synthesized compounds is presented in TableII.

IR (KBr, λmax):, 3351-3200 cm^{-1}(-OH str.), 3087 cm^{-1}(C-H str. in Ar), 1661 cm^{-1}(C = O str. in thiazolidinone), 1581 cm^{-1}(C = N str. in thiazolidinone), 1230 – 1191 cm^{-1}(C – O – C str.) 716 cm^{-1} (C –S – C str. in thiazolidinone); **^{1}H NMR** ($CDCl_3$ in δppm): 3.71 (s, 2H, S-CH_2-C=O), 5.41(d, 1H, C-5 proton) 6.11(d, 1H, C-6 proton),6.71-8.41(m,11H,Arproton);**Mass**(m/z):412$[M]^+$220,194,192,148,127,120,119,100,91,88,77, 69, 65, 51

Antimicrobial activity

All the newly synthesized compounds were studied for antibacterial activity against gram positive, *staphylococcus aureus* and gram negative *Salmonella typhi*, and antifungal activity against *Aspergillus nigar*and *Candida albicans* according to cup plate [26] and poison plate method at concentration of 0.005 mol/ml. Penicillin were used as standard for antibacterial activity and Griseofulvin wereusedasantifungalactivityrespectively.TheresultsaresummarizedinTableII.

The results revealed that compound **3a-e** were exhibit well antibacterial activity against *staphylocus aureus* but inactive against *Salmonella typhi* whereas compound **3a, 3b, 3e** shows significant activity when compared with standard drug.

Table I: Physical and analytical data of synthesized compounds

Comp. code	Molecular formula	Molecular weight	Yield %	M.P. ^oC	Element % cal (found)			
					C	H	N	Cl
2a	$C_{22}H_{16}N_2OS$	365.44	53	273	74.08	4.48	7.86	-
					(74.09)	(4.50)	(7.80)	-
2b	$C_{23}H_{18}N_2OS$	370.49	64	280	74.49	4.85	7.55	-
					(74.51)	(4.86)	(7.59)	-
2c	$C_{23}H_{18}N_2O_2S$	386.49	66	294	71.41	4.65	7.24	-
					(71.41)	(4.66)	(7.21)	-
2d	$C_{22}H_{15}ClN_2OS$	390.89	59	290	67.53	3.83	7.16	9.08
					(67.52)	(3.85)	(7.19)	(9.12)
2e	$C_{22}H_{16}N_2O_2S$	372.44	60	>300	70.88	4.29	7.59	-
					(70.91)	(4.28)	(7.54)	-
3a	$C_{24}H_{16}N_2O_2S$	396.09	54	277	72.70	4.07	7.07	-
					(72.68)	(4.10)	(7.08)	-
3b	$C_{25}H_{18}N_2O_2S$	410.52	60	290	73.15	4.42	6.82	-
					(73.17)	(4.40)	(6.84)	-
3c	$C_{25}H_{18}N_2O_3S$	426.15	51	>300	70.41	4.25	6.79	-
					(70.44)	(2.28)	(6.81)	-
3d	$C_{24}H_{15}ClN_2O_2S$	430.90	58	>300	66.90	3.57	6.57	8.23
					(66.93)	(3.54)	(6.55)	8.20
3e	$C_{24}H_{16}N_2O_3S$	412.46	62	>300	69.89	3.91	6.50	-
					(69.90)	(3.90)	(6.52)	-

Table II: Antimicrobial activity of the Compound 3a-e

Comp. code	Antibacterial activity Zone of inhibition (in mm)		Antifungal activity	
	Salmonella typhi	*Staphylococcus aureus*	*Aspergillus nigar*	*Candida albicans*
3a	15	27	+ ve	-ve
3b	15	28	+ ve	+ve
3c	17	30	+ve	-ve
3d	14	25	-ve	-ve
3e	19	30	+ve	+ve
Penicillin	20	32	-	–
Griseofulvin	–	–	+ ve	+ ve

Control (DMSO), (– ve) – No activity

RESULTS AND DISCUSSION

The reaction of 2-hydroxy 1-naphthaldehyde and chloroacetone in acetone gave 2- acetylnaphtho [2,1-b] furan. The reaction of 2-acetylnaphtho [2, 1-b] furan with substituted aromatic aldehyde and aqueous solution of potassium hydroxide in ethanol gives the compounds **1a-e** and well characterized using its spectral and analytical data. The reaction of **1a-e** with thiourea and conc. HCl in ethanol gaves **2a-e** and characterized by using its Spectral and analytical data. Further the reaction of **2a-e** with mono chloro acetic acid in presence of anhydrous sodium acetate glacial acetic acid and few drop of acetic anhydride gave titled compound **3a-e**. It is characterized using spectral and analytical data and elemental analysis. Microbial screening of compounds showed good to moderate activity against the organismtested.

CONCULISION

The present study reports the synthesis of a new series of 5-(4-substituted aryl)-7(naphtho[2, 1-b] furan -2-yl)-2H-thiazole [3,2-α] pyrimidines -3(5H)-one **3a-e**. Antibacterial and antifungal activity of the new synthesized compounds bearing naphthofuran moiety, revealed that all tested compounds showedmoderate to good activities against selected microbialstrains.

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