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Research Article

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Synthesis and biological study of some new thiazolidinone derivatives containing naphthofuran moiety

Sajeevan Gaikwad*[1], Venkat Suryawanshi[2], Yogiraj Vijapure[1] and Vishnu Shinde[2]

[1]Dept. of Chemistry, S. K. Mahavidyalaya, Gunjoti, Osmanabad (M.S.), India
[2]Dept. of Chemistry, P. G. and Research Centre, S. C. S. College, Omerga, Osmanabad (M.S.), India

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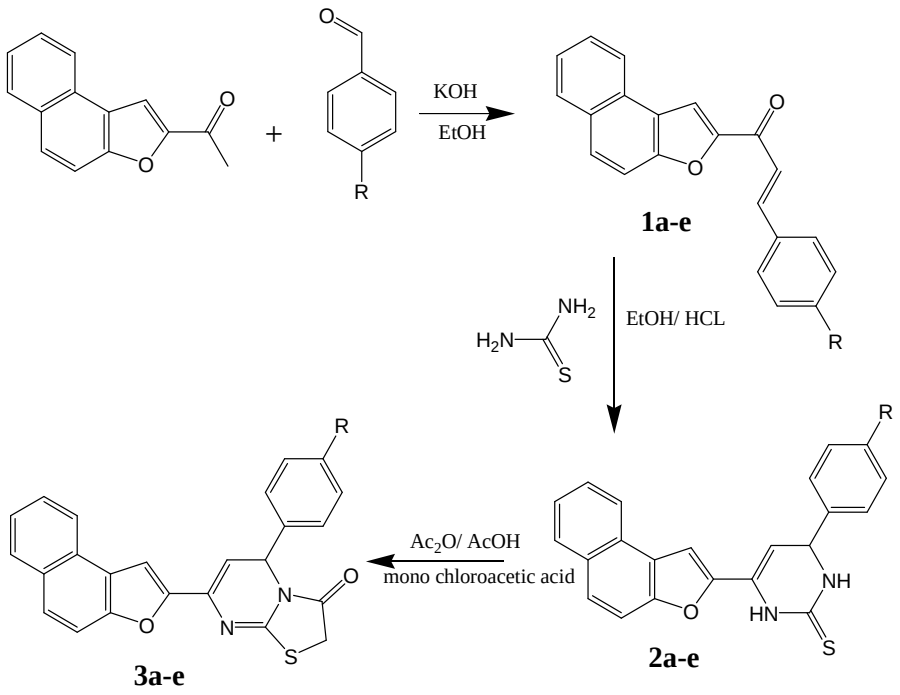
ABSTRACT

*The starting materials 2-acetylnaphtho [2, 1-b] furan have been synthesized by literature (Stoermer and Schaffer) method. It is then converted in to a series of substituted chalcone **1a-e** were prepared 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, spectral studies and have been evaluated for biological activity.*

Keywords: Napthofuran, chalcone, thiopyrimidine, thiazolidinone, biological activity.

INTRODUCTION

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]. 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 anthelmintic [9] activity.Thiazole occurs widely in plant and specially in eggs, yeast and rice polishing. The deficiency of thiamine in diet causes diseases beriberi. Literature survey reveals that 4-thiazolidinones are usually synthesized starting from thiourea[9-11], thiosemicarbazides [12] and azomethines [13].Thiazolidinones have been synthesized and screened for possible antimicrobial activity [14-18] moreover, thiazolidinones have a broad spectrum of pharmacological properties like anti HIV [19], antipsychotic [20] , anticonvulsant [21] and antitubercular [22] activity. 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.



Where, R =a = -H, b = -CH_3, c = -OH, d = -OCH_3, e = -Cl

Scheme I

Table I: Physical and analytical data of synthesized compounds

Comp.	Molecular formula	Molecular weight	Yield %	M.P. °C	Element % cal (found)			
					C	H	N	Cl
2a	$C_{22}H_{16}N_2OS$	365.44	53	273	74.07	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	$C_{22}H_{16}N_2O_2S$	372.44	60	>300	70.88	4.29	7.59	-
					(70.91)	(4.28)	(7.54)	-
2d	$C_{23}H_{18}N_2O_2S$	386.49	66	294	71.41	4.65	7.24	-
					(71.40)	(4.66)	(7.21)	-
2e	$C_{22}H_{15}ClN_2OS$	390.89	59	290	67.53	3.83	7.16	9.08
					(67.52)	(3.85)	(7.19)	(9.12)
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	$C_{24}H_{16}N_2O_3S$	412.46	62	>300	69.89	3.91	6.79	-
					(69.90)	(3.90)	(6.81)	-
3d	$C_{25}H_{18}N_2O_3S$	426.15	51	>300	70.40	4.25	6.57	-
					(70.44)	(2.28)	(6.55)	-
3e	$C_{24}H_{15}ClN_2O_2S$	430.90	58	>300	66.90	3.57	6.50	8.23
					(66.93)	(3.54)	(6.52)	(8.20)

Antimicrobial activity

All the newly synthesized compounds were screened 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 and Griseofulvin were used as standards for antibacterial and antifungal activity respectively. The results are summarized in Table II

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 II: Antimicrobial activity of the Compound 3a-e

Comp.	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	19	30	+ve	+ve
3d	17	30	+ ve	-ve
3e	14	25	-ve	- ve
Penicillin	20	32	-	–
Griseofulvin	–	–	+ ve	+ ve

Control (DMSO), (– ve) – No activity

EXPERIMENTAL SECTION

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 Bruker "AVANCE 400" MHz spectrometer using TMS as an standard. (Chemical shifts in δ ppm) and mass spectrum on shimadzu GCMS QP 5050 A, Japan Mode-DI. Mass spectrometer, operating at 70 eV. 2-acetylnaphtho [2, 1-b] furan[16] were synthesized by literature method. Progress of reaction was monitored by TLC, Naphthaldehyde, chloroacetone, thiourea, p-substituted aromatic aldehydes, mono chloroacetic acid, silica gel were purchased from Merk, India.

Typical 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 (4.20 gm,0.02 mole) and p-hydroxy benzaldehyde (2.68 gm,0.022 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 firstly 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 aromatic aldehydes.

IR(KBr, λmax):3310 cm^{-1} (Ar-O-H Str), 3058 cm^{-1}(-CH Str. of Ar), 1644 cm^{-1}(C=0 str. of ketone), 1586 cm^{-1}(C=C of chalcone), 1515 cm^{-1}(C = C str. of Ar), 1443 & 1359 cm^{-1}(CH_3 def), 1153 & 1167 cm^{-1}(C – O – C str), 830 cm^{-1}(- CH str.), 747 cm^{-1}(Ar-H opb.); **^{1}H NMR** ($CDCl_3$ in δppm): 6.35 (d, 1H, -CO-CH =), 6.95 (d, 1H, C = CH) 7.21 – 8.24 (complex m, 11H, Ar proton), 10.32 (s, 1H, phenolic – OH); **Mass** (m/z) :314[M^+] 221, 195, 147, 119, 118, 91, 69, 65, 43.

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, a dropping funnel, a thermometer and condenser with chilled water circulation. Flask was charged with 1-(naphtho[2, 1-b] furan-2-yl)-3-phenylprop-2-en-1-one **1a** (2.98 gm, 0.01 mole) and thiourea (1.52 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) :3426 cm^{-1}(N-H str.), 3062 cm^{-1}(C-H str.of Ar), 2922 cm^{-1}(CH str.of -CH_2), 2431 cm^{-1}(S-H str. of C=S). 1628 cm^{-1}(C=N str.), 1380 cm^{-1}(C = S str.) [27], 1074-1109 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), 5.81(d, 1H, C-5 proton), 6.90-8.30 (m, 12H, Ar protons); **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. 3c

A mixture of 3,4-dihydro-4-(4-hydroxy phenyl)-6-(naphtho[2,1-b] furan -2-yl) pyrimidin-2[1H] thione **2c** (4.09 gm, 0.011 mole) and mono-chloroacetic acid (0.94 gm, 0.01 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 **3c**. Compounds **3a-e** was prepared similarly from **2a-e**. The physical and analytical data of the newly synthesized compounds is presented in Table II.

IR (KBr, λmax):, 3350-3200 cm^{-1}(-OH str.), 3086 cm^{-1}(C-H str. in Ar), 1660 cm^{-1}(C = O str. in thiazolidinone), 1580 cm^{-1}(C = N str. in thiazolidinone), 1230 – 1190 cm^{-1}(C – O – C str.) 715 cm^{-1}(C –S – C str. in thiazolidinone); **^{1}H NMR** ($CDCl_3$ in δppm): 3.70 (s, 2H, S-CH_2-C=O), 5.40(d, 1H, C-5 proton) 6.10(d, 1H, C-6 proton), 6.70-8.40 (m, 11H, Ar proton); **Mass** (m/z) :412 [$M]^+$ 220, 194, 192, 148, 127, 120, 119, 100, 91, 88, 77, 69, 65, 51

RESULTS AND DISCUSSION

The reaction of 2-hydroxy 1-naphthaldehyde and chloroacetone in acetone gave 2- acetylnaphtho [2,1-b] furan. The compounds **1a-e** was obtained by reaction of 2-acetylnaphtho [2, 1-b] furan with substituted aromatic aldehyde and aqueous solution of potassium hydroxide in ethanol 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 organism tested.

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 moity, revealed that all tested compounds showed moderate to good activities against selected microbial strains.

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