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Synthesis and characterization of 3, 4-dihydro-4(4-substituted aryl)-6-(naphtho [2, 1-b] furan-2-yl) pyrimidine-2[1H] thiones as potential antimicrobial agents

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ABSTRACT

2-Acetylnaphtho [2, 1-b] furan **(1)** has been synthesized from 2-hydroxy-1-naphthaldehyde by reacting with chloroacetone, anhydrous potassium carbonate and dry acetone through Stoermer and Schaffer method. It was then converted to a series of substituted chalcones **(2a-e)** by Claisen-Schmidt condensation with substituted aromatic aldehydes in presence of aqueous potassium hydroxide solution. The resulting compound **(2a-e)** was treated with thiourea in presence of ethanol and concentrated hydrochloric acid yields the title compound. The structure of the compounds has been confirmed by elemental analysis and spectral studies and was screened for their antibacterial and antifungal activities.

KEYWORDS

Naphthofuran;
Chalcones;
Thiopyrimidine;
Antimicrobial activity.

INTRODUCTION

Nitrogen, Oxygen and sulphur containing heterocyclic compounds have received considerable attention due to their wide range of pharmacological activity. Pyrimidine based heterocyclic compounds are of interest as potential bioactive molecules and exhibit analgesic[1], antiviral[2,3], anticancer[4,5], antipyretic[6], antihypertensive[7,8] and anti-inflammatory[9,10] activities. Many of the pyrimidine derivatives are reported to possess potential CNS depressant properties[11]. The naphthofuran derivatives have been shown to exhibit cytotoxic activity[12], keeping these reports in view and in continuation of our search for more potent naphtho furan derivatives[13-16], recently two PCT international applications have been found for 2-thiopyrimidine derivatives possessing potent activity against inflammation and immune disorders[17-22]. It was thought worthwhile to synthesize new derivatives of naphtho [2, 1-b] thiopyrimidine by simple method and investigate them for biological activities.

EXPERIMENTAL

Melting points were determined by open capillary method and are uncorrected. Reaction was monitored

Full Paper

by TLC using silica gel (Merck India). Naphthaldehyde, chloroacetone, thiourea and p-substituted aromatic aldehydes were purchased from Merck India. IR spectra were recorded in KBr, on Thermo Nicolet USA FTIR, ^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker 'AVANCE 400' MH_Z Spectrometer using TMS as an internal standard. Mass spectrum on Shimadzu GCMS QP 5050 A Japan mode DI mass Spectrophotometer. All the compounds have been recrystallized from ethanol.

Synthesis of 2-Acetyl naphtho [2, 1-b] furan (1)[16]

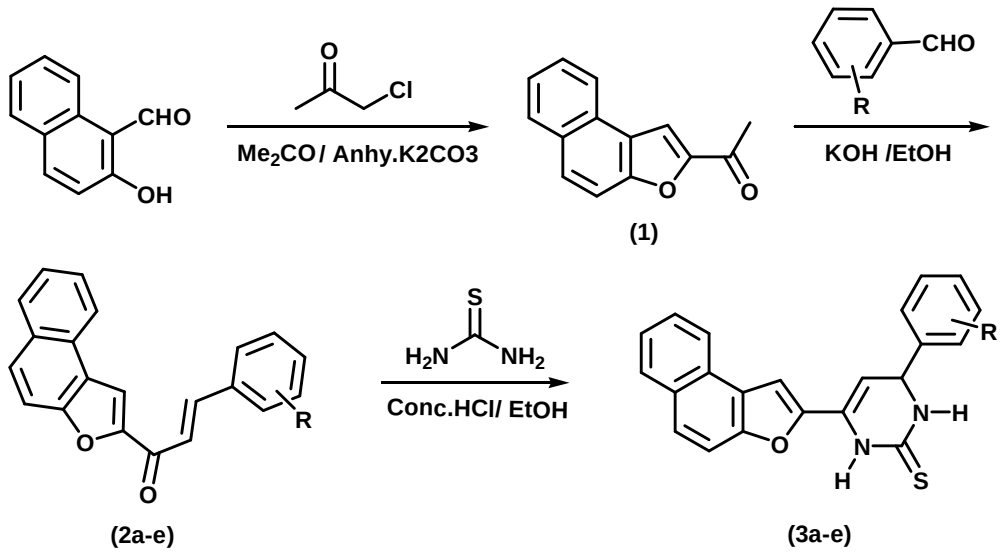
A 250 mL 4-necked round bottom flask fitted with over head mechanical stirrer, a dropping funnel, and a thermometer and reflux condenser with child water circulation. Flask was charged with 2-hydroxy -1-naphthaldehyde (17.80 gm, 0.10 mol), chlorocacetone (10.75gm, 0.11 mol) and anhydrous potassium carbonate (15gm, 0.11mol) were refluxed in dry acetone. (75 mL) for 12 h. Potassium salt were filtered off and the filtrate on removed of solvent and on trituration with ethanol gave the pale yellow crystals of 2-acetyl naphtho [2, 1-b] furan (1). The sample was purified by absolute ethanol. m.p. 96°C yield 60%.

Typical experimental procedure for synthesis of 3-(4-hydroxyphenyl)-1-(naphtho [2, 1-b] furan -2yl) prop-2-en-one (2a-e)

Flask was charged with mixture of 2-acetylnaphtho [2,1-b] furan (4.20gm,0.02 mole) **(1)** and p-hydroxy benzaldehyde (2.68gm,0.022 mol). It was stirred in ethanol (50 mL) and then potassium hydroxide (50%) (10mL) was added portion wise, keeping the temperature below 10^0C throughout the addition. The mixture was kept for 36 h. After completion of reaction, 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 to afford the pure product in 60-70 % yield **(2c)**. Same procedure is extended for other compound of this series. The physical and characterization data of the chalcones are shown in TABLE 1

Synthesis of 3, 4-dihydro-6-(naphtho [2,1-b] furan -2-yl) -4-phenyl pyrimidin -2(1H) thione (3a-e)

A mixture of 1-(naphtho [2, 1-b] furan -2-yl) -3-phenyl prop - 2- en-one (2.98gm,0.01 mole) **(2a)** and thiourea (1.52gm,0.02 mole) were dissolved in dry ethanol (50 mL) and concentrated HCl (10 mL) was added and refluxed for 18 h with constant stirring. The progress of the reaction was monitored by TLC. After completion of reaction, it was filtered while hot and allowed to cool then neutralized with 5N sodium hydroxide solution. The resulting solid was washed well with water (25 mL × 3) dried and the product was recrystallized from acetic acid to obtain **(3a)**. Compounds **(3b-e)** were prepared similarly from **(2b-e)**. The physical data of the thiopyrimidine are shown in TABLE 1.



R = a = 4-H, b = 4-CH_3, c = 4-OH, d = 4-OCH_3, e = 4-Cl.

Scheme 1

Purification

Crude product was dissolved in 10 mL absolute ethanol and heated up to 70°C to get clear solution and cooled slowly up to 10°C, filtered, sucked and dried in vacuum to offered pure compound. Under similar conditions synthesis of compounds of the series was carried out. Results are summarized in TABLE 1. Good to excellent yields with perfect selectivity was obtained in all the cases

RESULTS AND DISCUSSION

TABLE 1 : Physical and characterization data of the synthesized compound.

Comp.	Molecular Formula	Mol. Weight	Yield %	M.P. °C	Elements %							
					C		H		N		Cl	
					Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
2a	$C_{21}H_{14}O_2$	298.1	60	132	84.53	84.55	4.69	4.70	-	-	-	-
2b	$C_{22}H_{16}O_2$	312.1	66	151	84.58	84.59	5.12	5.16	-	-	-	-
2c	$C_{21}H_{14}O_3$	314.0	65	172	80.25	80.23	4.45	4.43	-	-	-	-
2d	$C_{23}H_{16}O_3$	340.0	72	135	81.17	81.19	4.70	4.71	-	-	-	-
2e	$C_{21}H_{13}ClO_3$	332.7	57	143	75.74	75.75	3.90	3.94	-	-	10.67	10.61
3a	$C_{22}H_{16}N_2OS$	356.4	59	273	74.07	74.09	4.48	4.50	7.86	7.80	-	-
3b	$C_{23}H_{18}N_2OS$	370.4	55	280	74.49	74.51	4.85	4.86	7.55	7.57	-	-
3c	$C_{22}H_{16}N_2O_2S$	372.4	52	>300	70.88	70.91	4.29	4.28	7.59	7.54	-	-
3d	$C_{23}H_{18}N_2O_2S$	386.4	58	294	71.41	71.40	4.65	4.66	7.24	7.21	-	-
3e	$C_{22}H_{15}ClN_2OS$	390.8	51	290	67.53	67.52	3.83	3.85	7.16	7.19	9.08	9.12

SPECTRAL INTERPRETATION

Compound (2c)

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

Compound (3a)

IR: (KBr, νmax), cm^{-1}) 3426 (N-H str.), 3062 (C-H) 2922 (C-H str.in– CH_2) 2431 (S-H str.). 1628 (C=Nstr.), 1380 (C=S str.)[23], 1074-1109 (-C-O-C str.). ^{1}H NMR: ($CDCl_3$ in δ ppm): 3.98 (d, 1H, Protons of position 1), 3.41 (d, 1H, proton of position 3), 3.86 (d, 1H, proton of position 4), 5.81 (d, 1H, proton of position 5), 6.90 – 8.30 (m, 12 H, Ar-protons). Mass: (m/z) 356 (M^+) 195, 194, 115, 105, 103, 94, 91, 77, 70, 66, 65, 55, 44.

ANTIMICROBIAL ACTIVITY

In the present study, filter paper disc diffusion plate method was employed to evaluate the antimicrobial activity[24]. The zone of inhibition was compared with the standard drug. (Penicillin for bacteria and Griseofulvin for fungi. Results are summarized in TABLE 2.

TABLE 2 : Antimicrobial activity of synthesized compound.

Compound	Antibacterial activity (Zone of inhibition in mm)				Antifungal activity			
	E.coli	*S.thypi*	*S.aureus*	*B.substillis*	*A.niger*	*P.chrysogenum*	*F.moneliforme*	*C.albicans*
3a	11	12	22	18	- ve	+ ve	- ve	+ ve
3b	13	15	27	22	+ve	- ve	+ ve	- ve
3c	17	18	30	26	+ ve	+ ve	+ ve	+ ve
3d	15	16	28	24	+ ve	+ ve	- ve	+ ve
3e	10	11	20	16	- ve	+ ve	- ve	- ve
Penicillin	18	20	32	28	-	-	-	-
Griseofulvin	-	-	-	-	+ ve	+ ve	+ ve	+ ve

Control (DMSO), – ve No activity.

Investigation of antimicrobial activity revealed that the compounds **(3a-e)** showed significant antibacterial activity when compared with standard drug Penicillin. However the compounds **(3c)**, **(3d)** and **(3b)** were found to be more potent on all the bacterial strains. Compounds **(3a-e)** showed significant antifungal activity when compared with standard drug Griseofulvin. Compound 3c,3d and 3b showed good antifungal activities.

The results clearly revealed the contribution of electron releasing groups on the aromatic ring in enhancing the microbial activity.

CONCLUSION

We believe that these synthesized and characterization compounds of 3, 4-dihydro-4(4-substituted aryl)-6-(naphtho [2, 1-b] furan-2-yl) pyrimidine-2[1H] thione will help in the modern development of hetrocyclic chemistry as antimicrobial activities.

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