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Synthesis and Biological Activity of Some 3,4-Dihydro-4-(4-substituted aryl)-6-(naptho [2,1-b]furan-2-yl pyrimidine-2(1*H*)-one Derivatives

SANJEEVAN S. GAIKWAD, VENKAT S. SURYAWANSHI[§*],
KISHAN S. LOHAR, DHANAJI V. JADHAV[#] and NARAYAN D. SHINDE[§]

Dept. of Chemistry, Shrikrishna College, Gunjoti
Tal-Omerga, Dist-Osmanabad, Maharashtra-413613, India
[§]Dept. of Chemistry, PG studies and Research Center
Shri Chattrapati Shivaji College, Omerga, Maharashtra-413 606, India
[#]Dept. of Chemistry, Y. C. Arts & Science College, Mangrulpir
Dist-Washim, Maharashtra-444 403, India
venkatesh1@sify.com

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Abstract: A series of new oxopyrimidine were prepared by cyclocondensation route with various substituted chalcones in presence of alcoholic solution of potassium hydroxide at reflux temperature. The synthesized oxopyrimidine derivatives were characterized by means of their IR, ^{1}H NMR, mass spectral data and elemental analysis. The synthesized oxopyrimidines derivatives were evaluated for antibacterial and antifungal activities, some of them were found to possess significant activity.

Keywords: Naphthofuran, Chalcone, Oxopyrimidines, Synthesis, Biological activities

Introduction

The search for new potent anti-microbial agents with reduced toxicity and lower side effects is of continuous process. One of the most frequently encountered groups of organic compound in medicinal chemistry is oxopyrimidine and their derivatives. Pyrimidines[1] have occupied unique place in the field of medicinal chemistry. Some antibacterial[2-7] and antimalerial[8-10] drug is constituted by pyrimidine derivatives. Certain pyrimidine derivatives are known to display as analgesic[11], anthelmintic[12- 13], antitumor[14], antifungal[15], antiviral[16-18], anticancer[19], insecticidal[20] and diuretic & anti-inflammatory[21-22] activities. Keeping in view of the biological importance[23] and chemotherapeutic properties of oxopyrimidine and naphthofuran derivatives, attempts has been made to synthesize some new oxopyrimidine derivatives linked with naphthofuran and aryl group with the hope that they might display antimicrobial activity.

Experimental

Melting points were determined on an open capillary melting point apparatus and are uncorrected. IR spectra were recorded on Brucker FT-IR (Alpha-P) spectrometer, ^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker "AVANCE 400" MHz spectrometer using TMS as an internal standard and Mass spectrum on Shimadzu GCMS QP 5050A,mode-DI,operating at 70eV. Progress of reaction was monitored by TLC. Naphthaldehyde, chloroacetone, Urea, aromatic aldehydes were purchased from Merk, India. All compounds have been recrystallized in ethanol.

*Synthesis of 2-acetylnaphtho [2, 1-b] furan **(1)***

In a 250 mL four necked round bottom flask fitted with overhead mechanical stirrer, a dropping funnel, a thermometer and condenser with child water circulation, 2-hydroxy-1-naphthaldehyde (0.1 mole), chloroacetone (0.11 mole) and anhydrous potassium carbonate (15gm) were refluxed in dry acetone (75 mL) for 12 h. Potassium salts were filtered off, the filtrate on removal of solvent and on trituration with ethanol gave the pale yellow crystals of 2-acetylnaphtho [2, 1-b] furan (1). The sample was purified by recrystallized from absolute ethanol. MP = 96 °C, Yield = 60%

*Typical synthesis of 3-(4-hydroxyphenyl)-1 (naphtho [2,1-b]furan-2 yl) prop-2-en-1-one **(2c)***

A mixture of 2-acetylnaphtho [2,1-b] furan **(1)** (0.02 mole) and *p*-hydroxy benzaldehyde (0.022 mole) was stirred in ethanol (50 mL) and then in aqueous solution of potassium hydroxide (50%) (10 mL) was added to it portion wise, keeping the temperature below 10 °C throughout the addition. The mixture was kept for 36 h and it was acidified with conc. HCl. The reaction mixture was poured into crushed ice and the solid obtained was filtered under vaccum. It was washed firstly with sodium carbonate solution and then with water, dried and the product was recrystalized from ethanol. Same procedure is extended for other compounds of this series. **(2a-e)** were synthesized by using appropriate aldehyde. The physical data of chalcones were shown in Table 1.

Table 1. Physical data of the synthesized compounds

Compound No.	Molecular Formula	Molecular Weight	Yield %	M.P. ^{0}C	Elements %			
					C	H	N	Cl
					Calcd. Found	Calcd Found	Calcd Found	Calcd Found
2a	$C_{21}H_{14}O_2$	298.1	60	132	84.53 84.55	4.69 4.7	- -	- -
2b	$C_{22}H_{16}O_2$	312.1	66	151	84.58 84.57	5.12 5.10	- -	- -
2c	$C_{21}H_{14}O_3$	314.0	65	172	80.25 80.24	4.45 4.44	- -	- -
2d	$C_{23}H_{16}O_3$	340.0	72	135	81.17 81.11	4.70 4.69	- -	- -
2e	$C_{21}H_{13}ClO_2$	332.7	55	143	75.74 75.73	3.90 4.00	- -	10.67 10.61

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

A mixture of 1-(naphtho [2, 1-b] furan-2-yl)-3-phenyl prop-2-en-1-one **(2a)** (0.01 mole) and urea (0.02 mole) dissolved in ethanol (50 mL) under stirring. To this an alcoholic potassium hydroxide 50% (10 mL) was added and refluxed for 10 h. After completion of reaction, it was cooled and poured in ice cold water and neutralized by acetic acid. The solid product was filtered washed with water and recrystallized from absolute ethanol. Compounds **(3b-e)** were prepared similarly from **(2b-e).** The physical data of oxopyrimidine derivatives are given in Table 2.

Table 2. Physical data of the synthesized compounds

Compound	Molecular Formula	Molecular Weight	Yield %	M.P. ^{0}C	Elements %			
					C	H	N	Cl
					Calcd. Found	Calcd Found	Calcd Found	Calcd Found
3a	$C_{22}H_{16}N_2O_2$	340.3	52	235	77.57 77.56	4.7 4.7	8.22 8.21	- -
3b	$C_{23}H_{18}N_2O_2$	354.4	55	247	77.87 77.81	5.07 5.00	7.90 7.89	- -
3c	$C_{22}H_{16}N_2O_3$	356.12	56	297	74.13 74.19	4.49 4.48	7.86 7.86	- -
3d	$C_{23}H_{18}N_2O_3$	370.1	52	260	74.57 74.49	4.86 4.85	7.56 7.55	- -
3e	$C_{22}H_{15}ClN_2O_2$	374.08	50	258	70.43 70.10	4.0 4.04	7.47 7.46	9.47 9.49

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 condition, a compound of this series has been carried out. Results are summarized in Table 1 & 2. Good to excellent yields and perfect selectivity was obtained in all cases.

Spectral Discussion

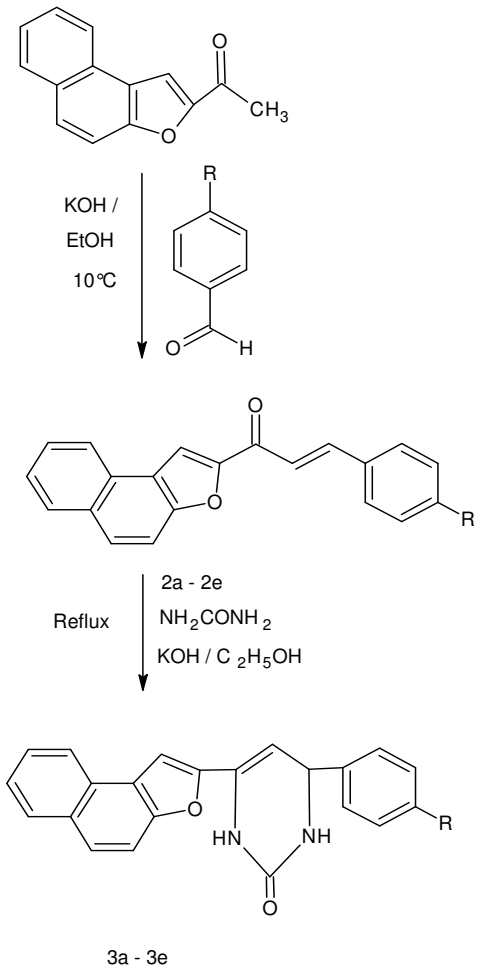
*Compound **2c***

IR (KBr, λ_{max}): 3310 cm^{-1} (Ar-O- H str.), 3058 cm^{-1} (-CH str. of Ar), 1644 cm^{-1} (C=O str. in ketone), 1586 cm^{-1} (C=C), 1515 cm^{-1} (C=C str. in 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, Ar. Proton 11H), 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, λ_{max}.): 3300-3400 cm^{-1} (C-H str. in Ar), 1659 cm^{-1} (C=O str. in N-CO-N), 1541 cm^{-1} (-C-O-C- in Ar), 1262 cm^{-1} (C-O-C str.) ^{1}H NMR ($CDCl_3$ in δppm) 5.46 (d, 1H, H-4), 5.68 (s, 1H, N-H-3), 5.84(d, 1H, H-5), 6.01(s, 1H, N-H-1), 6.71-7.80 (m, 12H, Ar-H) Mass (*m/z*): 340[M]$^+$, 297, 296, 220, 198, 197, 194, 105, 104, 103, 102, 101, 91, 77, 70.

Reaction Scheme



Scheme 1

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

Antimicrobial activity

The antimicrobial activity was determined by cup-plate method[24-25]. *In vitro* antimicrobial activity was carried out against 24 h. culture of four bacteria and four fungi. The bacteria used were *Escherichia coli, Salmonua typhi, Staphylococcus aureus* and *Bacillus substilis.* While the fungi used were *Aspergillus niger, Penicillium chrysogenum, Fusirium moneliforme* and *Candida albicans.* The compounds were tested at a (20 mg) dissolved in dimethyl sulphoxide (5 mL) against all organisms. Penicillin and griseofulvin were used as standards for comparison of antibacterial and antifungal activities respectively. The zone of inhibition was compared with the standard drug after 24 h. incubation at 37 °C for antibacterial activity & 48 h. at 28-30 °C for antifungal activity. The results are reported in Table 3.

Table 3. Antimicrobial activity of synthesized compounds

Compound	Antibacterial activity zone of inhibition				Antifungal activity			
	E.coli	*S.typi*	*S.aureus*	*B.sub stilis*	*A.niger*	*P. Chrysogen.*	*F. Moneli*	*C. Albicans*
3a	-ve	-ve	13	-ve	-ve	-ve	**+ve**	-ve
3b	-ve	-ve	14	11	+ve	-ve	-ve	**+ve**
3c	-ve	-ve	13	11	-ve	**+ve**	**+ve**	-ve
3d	-ve	-ve	12	-ve	**+ve**	**+ve**	-ve	-ve
3e	-ve	-ve	15	15	-ve	**+ve**	-ve	**+ve**
penicillin	18	20	32	28	-	-	-	-
Griseofulvin	-	-	-	-	**+ve**	**+ve**	**+ve**	**+ve**

Penicillin & Griseofulvin were used as standards for antibacterial & antifungal activities respectively. Control (DMSO) –ve no activity

Results and Discussion

Compounds (**3a-e**) showed significant antibacterial activity at 0.02 mL (20 mg) concentration level when compared with standard drug penicillin. However the oxopyrimidine **3b, 3c & 3e** were found to be more potent on all the bacteria strains. Compounds (**3a-e**) also showed significant antifungal activity at 0.02 mL (20 mg) concentration levels when compared with standard drug griseofulvin compound **3a, 3b, 3c, 3d & 3e** showed maximum antifungal activity.

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