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Synthesis and Biological Evaluation of Naphthopyranopyrimidines Derivatives as Potential Antifungal and Antibacterial Activities

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A new series of novel 8,10-dimethyl-12-aryl-12H-naphtho[1',2,5,6]pyrano[2,3-d]pyrimidine-9,11-diones derivatives synthesized from coupling (3CC) of aldehydes, β-naphthol and 1,3-dimethylbarbituric acid derivatives with using green condition through a simple, mild and efficient procedure utilizing cellulose sulfuric acid as a catalyst. Final compounds were evaluated for antibacterial and antifungal activity. Compounds **4a**, **4d**, **4h** display high potent antifungal activity against *Candida parapsilopsis,* compound **4d** show more potent activity (MIC 4.6 mg/mL) better than miconazole. While compound **4d** most effective on bacterial against *Micrococcus luteus, Staphylococcus aureus* MTCC 96 and *Staphylococcus aureus* MTCC 2940 with (MIC 2.3 mg/mL).

Keywords: Naphthopyranopyrimidines, Antifungal, Antibacterial activity, Green catalyst.

INTRODUCTION

The development of the new multi component reactions (MCRs) and improving the known multi component reactions are an area of significant current interest [1-3]. As opposed to the classical way to synthesize complex molecules by sequential synthesis, multi component reactions allow the assembly of complex molecules in one-pot and show a facile implementation, high atom-economy and high selectivity [4-7]. As a one-pot reaction, multi component reactions generally afford good yields and are essentially different from two-component and stepwise reactions in several aspects [8] and permitted a rapid access to combinatorial libraries of complex organic molecules for an efficient lead structure identification and optimization in drug discovery. Naphthopyranopyrimidine and its derivatives are important structural motifs in medicinal and pharmaceutical chemistry. They are known to exhibit potential biological properties such as antimicrobial [8,9] and antifungal activities [10].

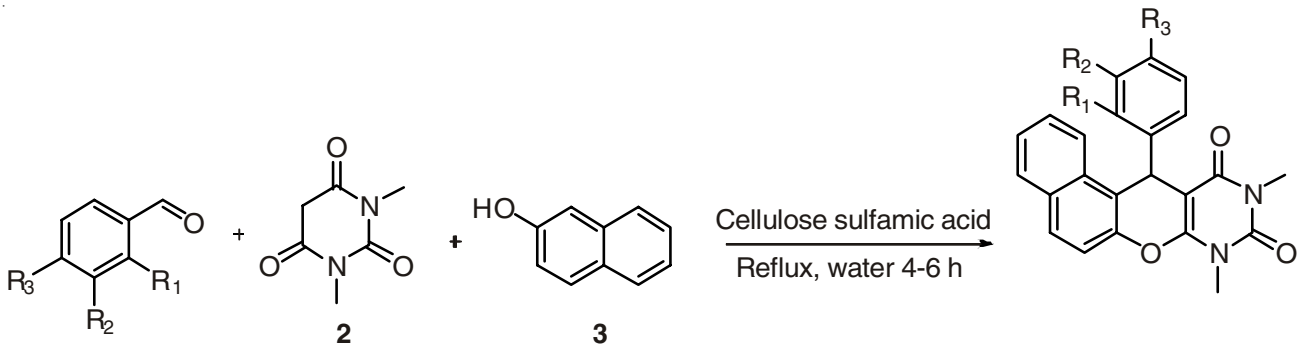
EXPERIMENTAL

All the chemicals employed in this study were procured from Sigma Aldrich. In present study, all the synthetic reactions were monitored by TLC. All the synthesized compounds were confirmed by different spectroscopic methods. The IR spectra were recorded using KBr pellets on a Perkin Elmer IR spectrophotometer. ^{1}H NMR spectra were recorded on Brucker 300 MHz Avance NMR spectrophotometer using $CdCl_3$ as solvent and TMS as internal standard (chemical shifts in δ ppm). The Mass spectra were recorded on Agilent 6300 series ion trap.

General procedure for the synthesis of naphthopyranopyrimidines derivatives

General procedure: A mixture of aldehyde (1.1 mmol), β-naphthol (1 mmol),1,3-dimethylbarbituric acid (1.0 mmol) and 10 mol % of cellulose sulfuric acid (0.05 g) was stirred at 100 °C for the appropriate time (**Scheme-I**). After completion of the reaction (TLC monitoring), the reaction mixture was cooled to ambient temperature, CH_2Cl_2 was added and the cellulose sulfuric acid was filtered off. The filtrate was concentrated to dryness and the crude solid product purified by column chromatography on silica gel (Acme, 60-120 mesh, ethyl acetate/*n*-hexane) to afford the pure product.

8,10-Dimethyl-12-phenyl-8,12-dihydro-9H-benzo[5,6]-chromeno[2,3-d]pyrimidine-9,11(10H)-dione (4a): White solid; m.p.: 223-225 °C. IR (KBr, ν_{max}, cm^{-1}): 2922, 2853,1706, 1666, 1644, 1593, 1486, 1232, 1176; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.3 Hz, 1H), 7.82-7.72 (m, 2H), 7.47-7.26 (m, 5H), 7.17 (t, *J* = 7.6 Hz, 2H), 7.11-7.08 (m, 1H), 5.75 (s, 1H), 3.57 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.8, 152.2, 150.4, 147.2, 143.7, 131.3, 130.6,



1a: R_1, R_2, R_3= H
1b: R_1, R_2 = H, R_3 = OCH_3
1c: R_1, R_2 = H, R_3 = Cl
1d: R_1, R_2 = H, R_3 = Br
1e: R_1, R_2 = H, R_3 = F
1f:R_1 = Br, R_2 = H, R_3 = Br
1g: R_1 = F, R_2 = H, R_3 = F
1h: R_1, R_2 = H, R_3 = NO_2
1i: R_1, R_2 = H, R_3 = CN
1j: R_1, R_2 = H, R_3 = CH_3

4a: R_1, R_2, R_3 = H, 4h, 85%
4b: R_1, R_2 = H, R_3 = OCH_3, 5h, 80%
4c: R_1, R_2 = H, R_3 = Cl, 4h, 90%
4d: R_1, R_2 = H, R_3 = Br, 6h, 87%
4e: R_1, R_2 = H, R_3 = F, 6h, 77%
4f:R_1 = Br, R_2 = H, R_3 = Br, 6h, 75%,
4g: R_1 = F, R_2 = H, R_3 = F, 5h,70%
4h: R_1, R_2 = H, R_3 = NO_2, 5h 75%
4i: R_1, R_2 = H, R_3 = CN, 4h, 78%
4j: R_1, R_2 = H, R_3 = CH_3, 5h 79%

Scheme-I

129.4, 129.0, 128.5, 128.2, 127.3, 126.6, 125.4, 123.8, 117.3, 116.2, 91.3, 35.8, 29.0, 28.1; MS-ESI: *m/z*: 371 (M+H); HRMS calcd. for $C_{23}H_{18}N_2O_3Na$: 393.1215, found: 393.1230.

12-(4-Methoxyphenyl)-8,10-dimethyl-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (4b): White solid; m.p.: 233-236 °C. IR (KBr, ν_{max}, cm^{-1}): 3050, 2921, 1715, 1642, 1598, 1488, 1230, 1168, 746, 721; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82-7.76 (m, 2H), 7.53-7.39 (m, 2H), 7.32-7.29 (m, 2H), 7.08 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.84-6.80 (m, 2H), 6.01 (s, 1H), 3.81 (s, 3H), 3.63 (s, 3H), 3.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.6, 152.4, 150.4, 146.8, 139.7, 133.7, 133.0, 130.9, 129.9, 129.6, 128.6, 127.6, 125.5, 123.7, 119.7, 116.2, 114.1, 114.4 89.9, 55.2, 33.7,29.0, 28.1; MS-ESI: *m/z*: 401 (M+H); HRMS calcd. for $C_{24}H_{20}N_2O_4$: 401.1432, found: 401.1439.

12-(4-Chlorophenyl)-8,10-dimethyl-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (4c): White solid; m.p.: 273-275 °C. IR (KBr, ν_{max}, cm^{-1}): 2923, 2852, 1704,1674, 1592, 1227, 1175, 1086, 750; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (d,*J* = 8.5 Hz, 1H), 7.86-7.77 (m, 2H), 7.48-7.41 (m, 2H), 7.36 (d, *J* = 9.1 Hz, 1H),7.25 (d, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 5.74 (s, 1H), 3.60 (s, 3H), 3.34 (s,3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.8, 152.1, 150.5, 147.2, 142.4, 132.5, 131.6, 130.7, 129.7, 129.5, 128.5, 127.4, 125.5, 123.4, 116.7, 116.5, 90.8, 35.4,29.0, 28.3; MS-ESI: *m/z*: 405 (M+H); HRMS calcd. for $C_{23}H_{18}N_2O_3Cl$: 405.1005, found: 405.1001.

12-(4-Bromophenyl)-8,10-dimethyl-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (4d): White solid; m.p.: 243-244 °C. IR (KBr, ν_{max}, cm^{-1}): 2922, 2852, 1706, 1669, 1645, 1594, 1482, 1226, 505; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84-7.76 (m, 3H), 7.42 (m, 2H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 8.8 Hz, 2H), 5.72 (s, 1H), 3.59 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.9, 152.1, 150.4, 147.2, 142.7, 131.4, 131.6, 130.6, 130.0, 129.8, 128.4, 127.6, 125.5, 123.6, 120.6, 116.4, 116.1, 90.8, 35.1, 29.0, 28.2; MS-ESI: *m/z*: 471 (M+Na); HRMS calcd. for $C_{23}H_{17}N_2O_3NaBr$: 471.0320, found: 471.0323.

12-(4-Fluorophenyl)-8,10-dimethyl-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (4e): White solid; m.p.: 305-307 °C. IR (KBr, ν_{max}, cm^{-1}): 3062, 2923,1706, 1671, 1646, 1595, 1484, 1451, 1228, 1166; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87-7.76 (m, 3H), 7.49-7.38 (m, 2H), 7.37-7.23 (m, 3H), 6.85 (t, *J* = 8.7 Hz, 2H), 5.76 (s, 1H), 3.62 (s, 3H), 3.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.8, 152.1, 150.8, 147.2, 139.7, 131.7, 130.5, 129.8, 129.6,128.6, 127.5, 125.6, 123.8, 117.0, 116.3, 115.4, 115.1, 91.2, 35.3, 29.1, 28.2; MSESI:*m/z*: 389 (M+H); HRMS calcd. for $C_{23}H_{18}N_2O_3F$: 389.1301, found: 389.1313.

12-(2,4-Dibromophenyl)-8,10-dimethyl-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (4f): White solid; m.p.: 219-221 °C. IR (KBr, ν_{max}, cm^{-1}): 3057, 2925, 1710, 1647, 1594, 1482, 1228, 1178, 749, 722; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.3 Hz, 1H), 7.82-7.76 (m, 3H), 7.53-7.39 (m, 2H), 7.32-7.29 (m, 2H), 7.08 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.01 (s, 1H), 3.63 (s, 3H), 3.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.6, 152.4, 150.4, 146.8, 139.7, 133.7, 133.0, 131.2, 136, 130.9, 129.9, 129.6, 128.6, 127.6, 125.5, 123.7, 119.7, 116.2, 89.9, 33.7,29.0, 28.1; MS-ESI: *m/z*: 527.9 (M+H); HRMS calcd. for $C_{23}H_{16}N_2O_3Br_2$: 527.9502, found: 527.9498.

12-(2,4-Difluorophenyl)-8,10-dimethyl-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (4g): White solid; m.p.: 219-221 °C. IR (KBr, ν_{max}, cm^{-1}): 3057, 2925, 1710, 1648, 1596, 1484, 1228, 1178, 765, 728; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82-7.76 (m, 2H), 7.53-7.39 (m, 2H), 7.32-7.29 (m, 2H), 7.08 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.98-6.95 (m, 2H), 6.01 (s, 1H), 3.63 (s, 3H), 3.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.6, 152.4, 150.4, 146.8, 139.7,

133.7, 133.0, 131.2, 136, 130.9, 129.9, 129.6, 128.6, 127.6, 125.5, 123.7, 119.7, 116.2, 89.9, 33.7,29.0, 28.1; MS-ESI: *m/z*: 407 (M+H); HRMS calcd. for $C_{23}H_{16}N_2O_3F_2$: 407.1127, found: 407.1130.

8,10-Dimethyl-12-(4-nitrophenyl)-8,12-dihydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (4h): White solid; m.p.: 291-293 °C. IR (KBr, ν_{max}, cm^{-1}): 2922, 1707, 1668, 1598, 1514, 1344, 1229, 1178; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.7 Hz, 2H), 7.87 (d, *J* = 8.9 Hz, 1H), 7.84-7.62 (m, 2H), 7.53 (d, *J* = 8.9 Hz, 2H), 7.47-7.42 (m, 2H), 7.42 (d, *J* = 8.9 Hz, 1H), 5.88 (s, 1H), 3.62 (s, 3H), 3.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.9, 152.3, 150.6, 150.4, 147.2, 146.5, 131.6, 130.4, 130.1, 129.2, 128.6, 127.7, 125.8, 123.6,123.2, 116.3, 115.6, 90.0, 36.0, 29.2, 28.3; MS (ESI): 416 (M+H).

4-(8,10-Dimethyl-9,11-dioxo-8,10,11,12-tetrahydro-9H-benzo[5,6]chromeno[2,3-d]pyrimidin-12-yl)benzonitrile (4i): White solid;m.p.: 277-280 °C. IR (KBr, ν_{max}, cm^{-1}): 2921, 2852, 2231, 1706, 1669, 1597, 1453, 1226, 1176; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88-7.76 (m, 3H), 7.51-7.42 (m, 6H),7.37 (d, *J* = 9.1 Hz, 1H), 5.83 (s, 1H), 3.62 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.6, 152.3, 150.2, 148.3, 147.2, 132.4, 131.6, 130.2, 130.1, 129.2, 128.6, 127.4, 125.8, 123.3, 118.8, 116.2, 115.7, 110.7, 90.2, 36.2, 29.3, 28.4; MSESI: *m/z*: 396 (M+H); HRMS calcd. for $C_{24}H_{18}N_3O_3$: 396.1348, found: 396.1340.

8,10-Dimethyl-12-(*p*-tolyl)-8,12-dihydro-9H-benzo-[5,6]chromeno[2,3-d]pyrimidine-9,11(10H)-dione (4j): White solid; m.p.: 200-202 °C. IR (KBr, ν_{max}, cm^{-1}): 2921, 2855, 1701, 1640, 14860, 1232, 1176; ^{1}H NMR (300 MHz, $CDCl_3$): 7.94 (d, *J* = 8.3 Hz, 1H), 7.82-7.74 (m, 2H), 7.46-7.33(m,3H), 7.21-7.18 (d, *J* = 8.3 Hz, 2H), 6.96 (d, *J* = 8.3 Hz, 2H), 5.72 (s, 1H), 3.58 (s,3H), 3.32 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 161.6, 151.9, 150.3,147.2, 140.8, 136.2, 131.8, 130.3, 129.4, 129.1, 128.3, 128.2, 127.3, 125.5, 124.2,117.6, 116.2, 91.5, 35.6, 28.9, 28.2, 21.2; MS-ESI: *m/z*: 407 (M+Na); HRMS calcd. for $C_{24}H_{20}N_2O_3Na$: 407.1371, found: 407.1388.

Antimicrobial activity: The antimicrobial activity of the synthesized compounds was determined using well diffusion method [11] against different pathogenic strains procured from Microbial Type Culture Collection and Gene Bank (MTCC), CSIR-Institute of Microbial Technology, Chandigarh, India. The pathogenic strains were seeded on the surface of the media petri plates, containing Mullere-Hinton agar with 0.1 mL of previously prepared microbial suspensions individually containing 1.5×10^8 CFU/mL (equal to 0.5 McFarland). Wells of 6 mm diameter were prepared in the media plates using a cork borer and the synthesized compounds at a dose range of 1.4-300 mg was added in each well under sterile conditions in a laminar air flow chamber. Standard antibiotic solutions of ciprofloxacin (bacterial strains), miconazole (*Candida* strains) at a dose range of 1.4-300 mg, served as positive controls, while the well containing DMSO served as negative control. The plates were incubated for 24 h at 30 °C and the well containing the least concentration showing the inhibition zone is considered as the minimum inhibitory concentration. All experiments were carried out in duplicates and mean values are represented.

RESULTS AND DISCUSSION

Several modifications for this classical method have been reported for the facile and efficient synthesis of important dibenzoxanthene derivatives. Other procedures comprise the use of BF_3–OEt_2, $Sr(OTf)_2$, TBAF, more recently with $InCl_3$ and I_2 [12], silica supported perchloric acid, these methods often involve long reaction times, harsh reaction conditions. To the best of our knowledge, the use of cellulose sulfuric acid [13] as a catalyst for the synthesis of naphthopyrano-pyrimidines derivatives previously has not been reported.

The present work was to design and synthesis of novel 8,10-dimethyl-12-aryl-12H-naphtho[10,2, 5,6]pyrano[2,3-d]pyrimidine-9,11-diones derivatives carrying biologically active pyrano-pyrimdiones moiety expected to have antifungal agents.

Cellulose sulfuric acid (CSA) is found to be a highly efficient catalyst for the three-component coupling (3CC) of aldehydes **1a-j**, 1,3-dimethylbarbituric acid **2** and β-naphthol **3** with using green condition cellulose sulfuric acid through a simple, mild and efficient procedure utilizing cellulose sulfuric acid (CSA) as a catalyst. in aqueous media to afford (**Scheme-I**). The corresponding 8,10-dimethyl-12-aryl-12H-naphtho-[10,205,6]pyrano[2,3-d]pyrimidine-9,11-diones in good yields with high selectivity. The reaction work-up is very simple and catalyst can be easily separated from reaction mixture and reused several times in subsequent reactions.

Biological activity

Antifungal activity: All the synthesize compounds of naphthopyranopyrimidines **4a-j** were evaluated for their antifungal activity by measuring Minimum inhibitory concentration (μg/mL). The results of preliminary antifungal activities (Table-1) indicated that most of the target compounds **4a**, **4d**, **4h** display very potent antifungal activity against *Candida parapsilopsis,* while compound **4d** show more potent activity (MIC 4.6 mg/mL) better than miconazole. Compound **4a** was

TABLE-1
BACTERIAL ACTIVITY

S. No.	Test compounds	Minimum inhibitory concentration (μg/mL)						
		Micrococcus luteus MTCC 2470	*Staphylococcus aureus* MTCC 96	*Staphylococcus aureus* MLS-16 MTCC 2940	*Bacillus subtilis* MTCC 121	*Escherichia coli* MTCC 739	*Pseudomonas aeruginosa* MTCC 2453	*Klebsiella planticola* MTCC 530
1	**4a**	9.37	9.37	9.37	18.75	>150	>150	18.75
3	**4d**	2.34	2.34	2.34	9.37	>150	>150	18.0
12	**4h**	>150	>150	>150	>150	18.75	>150	>150
Ciprofloxacin (Standard control)		0.58	0.58	0.58	0.58	0.58	0.58	0.58

TABLE-2
ANTIFUNGAL ACTIVITY

S. No.	Test compounds	Minimum inhibitory concentration (μg/mL)							
			Candida parapsilopsis MTC183	*Candida albican* MTCC3958	*Candida albican* MTCC962	*Issatechenkia orientail* MTCC3020	*Candida albicans* MTCC7315	*Candida albican* MTCC3018	*Candida albican* MTCC1637
1	**4a**	37.5	18.75	37.5	18.75	37.5	37.5	37.5	18.75
3	**4d**	>150	4.6	>150	>150	>150	>150	>150	>150
12	**4h**	>150	37.5	>150	>150	>150	>150	>150	>150
Micanzole (Standard control)		9.37	9.37	9.37	9.37	9.37	9.37	9.37	9.37

effective most of the all fungal strain (*Candida parapsilopsi* MTC183, *Candida albican* MTCC3958, *Candida albican* MTCC962, *Issatechenkia orientail* MTCC3020, *Candida albicans* MTCC7315, *Candida albican* MTCC3018 and *Candida albican* MTCC1637).

Antibacterial activity: Based on the antimicrobial results for all the synthesized naphthopyranopyrimidines compounds **4a-j** only compound **4a, 4d** exhibited good antibacterial activity (Table-2) against the various Gram-positive (*Micrococcus luteus* MTCC 2470, *Bacillus subtilis* MTCC 121, *Staphylococcus aureus* MTCC 96 and *S. aureus* MLS16MTCC 2940) and *Klebsiella planticola* MTCC 530, *Bacillus subtilis* MTCC 121 bacterial strains and the MIC values were comparable to those observed against the standard drug, ciprofloxacin, while compound **4h** was selectively active against *Escherichia coli* MTCC 739.

Conclusion

Cellulose sulfuric acid, an efficient, non-toxic, reusable and solid support biodegradable acid catalyst, has been prepared and utilized for the synthesis of naphthopyranopyrimidine *via* the three-component reaction with a wide range of aldehydes, β-naphthol and 1,3-dimethylbarbituric acid in aqueous media. Final compounds were evaluated for antibacterial and antifungal activity. Compounds **4a**, **4d**, **4h** display very high potent antifungal activity against *Candida parapsilopsis,* compound **4d** show more potent activity (MIC 4.6 mg/mL) better than miconazole. While compound **4d** most effective on bacterial against *Micrococcus luteus, Staphylococcus aureus* MTCC 96 and *Staphylococcus aureus* MTCC 2940 with (MIC 2.3 mg/mL).

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