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Condensation reactions of various nucleophiles with 3-formylchromone

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3-Formylchromones **1** are condensed with 1-(2,4-difluorophenyl-2-[1,2,4]triazol-4-yl)ethanone in acetic anhydride to afford 3-[3-(2,4-difluoro-phenyl)-3-oxo-2-[1,2,4]triazol-4-yl)propenyl]chromon-4-ones **2**. 3-Formylchromone **1** when heated with benzo[d]isoxazol-3-yl-acetic acid in dry pyridine yield 3-(2-benzo[d]isoxazol-3-yl-vinyl)chromon-4-ones **3**. Further, 3-formylchromone **1** on heating with N-methylpiperizine in ethanol give 1-(2-hydroxyphenyl)-3-(4-methyl-piperazin-1-yl)propenones **4**.

Keywords: Formylchromones, styrylchromone, condensation, nucleophiles

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Hormothamnione is the first naturally occurring styrylchromone isolated from the blue green algae Hormothamnione enteramorphoides[1]. It has potent cytotoxicity to P-388 lymphocytic leukemia and HL-60 human promyelocytic leukemia cells.

Condensation reactions of active methylene group with aldehyde function of 3-formylchromone has been studied by different workers[2-10]. Condensation products of these reactions showed significant biological activities. Benzisoxazoles and triazoles also have been found to be associated with important biological activities.

Fluorine containing amino acids are potential enzyme inhibitors and therapeutic agents[11]. Fluorinated analogs are accepted by enzymes as substrates, as fluorine is comparable in steric demand to hydrogen, but often are not substrates for normal enzymatic reactions. Fluorinated analogs of naturally occurring nucleic acids are found to be associated with antiviral[12], antitumor[13,14] and antifungal activities. Fluorinated aromatic compounds have been widely used as antibiotics, sedatives, agrochemicals, etc.

Due to activities associated with chromones, styrylchromones and enamine compounds it was thought worthwhile to synthesize some new derivatives of these compounds and test them for biological activities.

In present investigation, 3-formylchromones 1 were condensed with 1-(2,4-difluorophenyl-2-[1,2,4]triazol-4-yl)ethanone in acetic anhydride to afford 3-[3-(2, 4-difluorophenyl)-3-oxo-2-[1,2,4] triazol-4-yl)propenyl]chromon-4-ones **2**. Also, 3-formylchromones **1** on heating with benzo[d]isoxazol-3-yl-acetic acid in dry pyridine gave 3-(2-benzo[d]isoxazol-3-yl-vinyl)-chromon-4-ones **3**. Further, 3-formylchromones **1** when heated with N-methylpiperizine in ethanol furnished 1-(2-hydroxyphenyl)-3-(4-methylpiperazin-1-yl)propenones **4** (**Scheme I**, **Table I**).

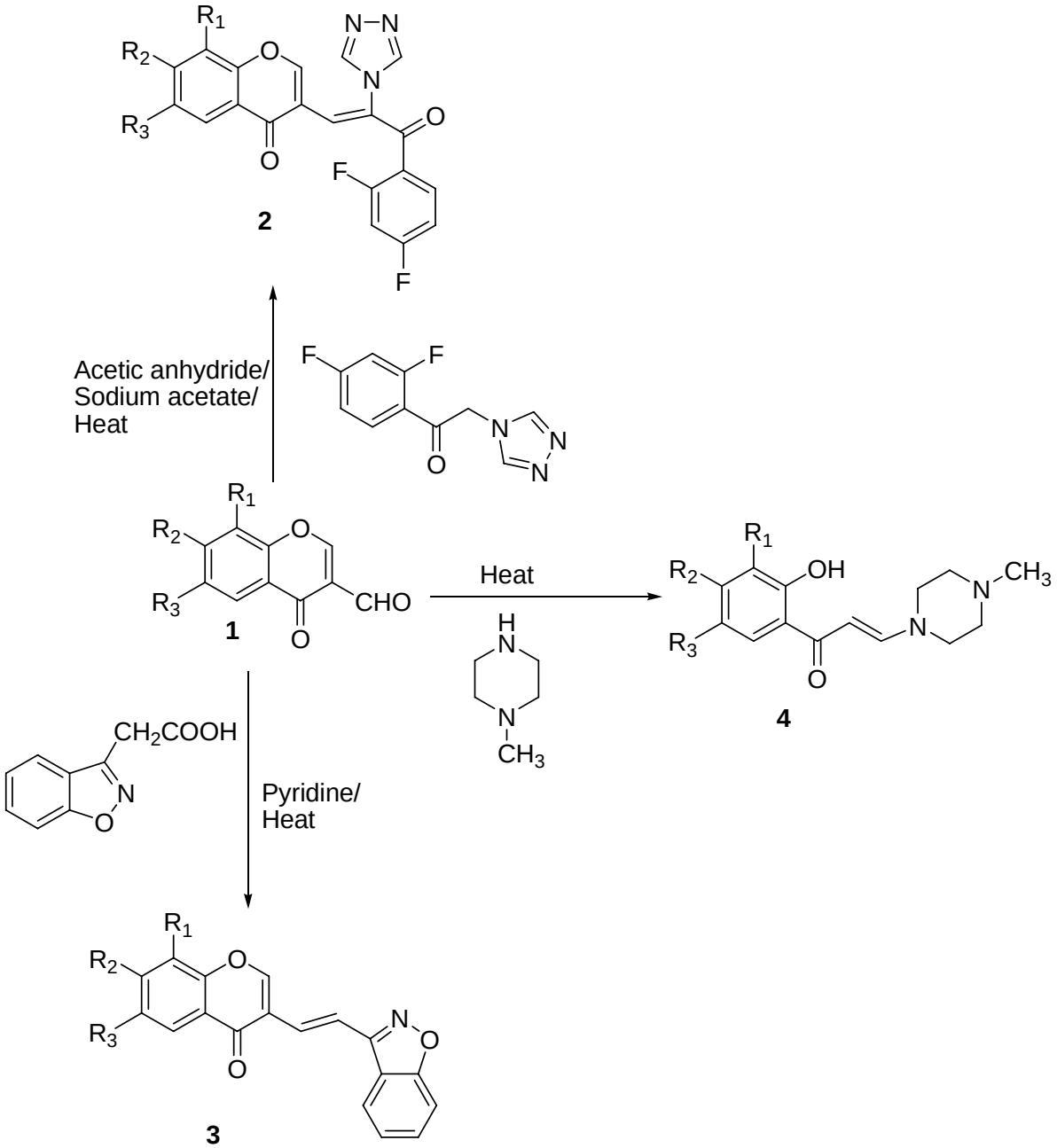
Antimicrobial screening

Compounds listed in **Table I** were screened (doses of 100 μg) for their antibacterial activity against gram –ve bacteria *E.coli* and gram+ve bacteria *S.albus* using filter paper disc method. Plates were incubated for *E.coli* at 48 hr and for *S.albus* 24 hr respectively at room temperature. Streptomycin sulphate was used as a standard. Inhibition zones were measured in mm and results obtained are shown in **Table II**.

All these compounds were also screened (doses of 100 μg) for their antifungal activities against *A.niger* using greseofulvin as a standard. The results are shown in **Table II**.

Experimental Section

All the melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT spectrophotometer in KBr disc; ^{1}H NMR spectra on a Varian 300 MHz spectrophotometer using DMSO-d_6 as a solvent and TMS as an internal standard (chemical shifts in δ,



Scheme I

ppm); and mass spectra on a Finnegan mass spectrometer.

3-[3-(2,4-Difluorophenyl)-3-oxo-2-[1,2,4]triazol-4-yl)propenyl]chromon-4-one 2. 3-Formylchromone **1** (0.001 mole), 1-(2,4-difluorophenyl-2-[1,2,4]triazol-4-yl)ethanone (0.001 mole) and sodium acetate (1.5 g) were taken in RBF with 15 mL acetic anhydride as a solvent. Reaction mixture was heated under reflux for 5 hr. The contents were cooled to room temperature and poured onto crushed ice with vigorous stirring. Solid product thus obtained was separated by filtration and crystallized from acetic acid to get **2a**; IR: 3009, 1670, 1652, 1609, 1069, 734 cm^{-1}; ^1H NMR: δ 8.82 (s, 1H), 8.18 (s, 1H), 8.10 (s, 1H), 7.29 to 7.83 (m, 7H); Mass: M^+ at 413.

Compounds **2b-h** were prepared similarly. The physical data of **2a-h** are given in **Table I**.

3-(2-Benzo[*d*]isoxazol-3-yl-vinyl)chromon-4-one 3. 3-Formylchromone **1** (0.001 mole), benzo[*d*]isoxazol-3-yl-acetic acid (0.001 mole) were taken in RBF with 15 mL dry pyridine. Reaction mixture was heated under reflux for 4 hr. The contents were then

Table I — Physical data of compounds **2a-h**, **3a-h** and **4a-h**

Compd	R_1	R_2	R_3	R_4	N (%) Found	N (%) Calcd	m.p. °C	Yield (%)
2a	H	H	Cl	H	10.10	10.16	320	56
2b	H	H	CH_3	H	10.55	10.68	218	58
2c	CH_3	H	CH_3	H	10.25	10.31	224	61
2d	H	CH_3	H	CH_3	10.26	10.31	211	46
2e	H	CH_3	H	H	10.65	10.68	216	55
2f	Cl	H	H	H	10.15	10.16	254	63
2g	Cl	H	Cl	H	09.35	09.38	240	65
2h	H	CH_3	Cl	H	09.80	09.82	236	64
3a	H	H	Cl	H	09.95	09.98	224	62
3b	H	H	CH_3	H	10.75	10.76	205	56
3c	CH_3	H	CH_3	H	10.20	10.21	214	53
3d	H	CH_3	H	CH_3	10.15	10.21	209	55
3e	H	CH_3	H	H	10.75	10.76	198	59
3f	Cl	H	H	H	09.93	09.98	211	51
3g	Cl	H	Cl	H	08.85	08.89	233	58
3h	H	CH_3	Cl	H	09.45	09.50	238	61
4a	H	H	Cl	H	04.30	04.33	124	42
4b	H	H	CH_3	H	04.60	04.62	129	45
4c	CH_3	H	CH_3	H	04.35	04.41	140	40
4d	H	CH_3	H	CH_3	04.40	04.41	132	44
4e	H	CH_3	H	H	04.55	04.62	137	43
4f	Cl	H	H	H	04.31	04.33	126	41
4g	Cl	H	Cl	H	03.90	03.91	138	46
4h	H	CH_3	Cl	H	04.10	04.15	142	45

cooled to room temperature and poured onto crushed ice. Solid product thus obtained was separated by filtration and crystallized from acetic acid to get **3a**; IR: 3056, 1651, 1610, 735 cm^{-1}; ^1H NMR: δ 9.00 (s, 1H), 8.22 (d, *J*=17.1Hz, 1H), 7.66 (d, *J*=17.1Hz, 1H), 7.49 to 8.30 (m, 7H); Mass: M^+ at 323.

Compounds **3b-h** were prepared similarly. The physical data of **3a-h** are given in **Table I**.

1-(2-Hydroxyphenyl)-3-(4-methylpiperazin-1-yl) propenone 4. 3-Formylchromone **1** (0.001 mole), *N*-methylpiperizine (0.003 mole) were taken in RBF with 15 mL dry ethanol. Reaction mixture was heated under reflux for 5 hr. The contents were then cooled to room temperature and poured onto crushed ice. Solid product thus obtained was separated by filtration and crystallized from ethanol to get **4a**; IR: 3438, 1625, 1577, 1535, 736 cm^{-1}; ^1H NMR: δ 2.20 (s, 3H), 2.40 (s, 4H), 3.65 (s, 4H), 6.2 (d, *J*=12Hz, 1H), 7.89 (d, *J*=12Hz, 1H), 6.82 to 8.06 (m, 3H), 14.62 (s, 1H,exchangeable with D_2O); Mass: M^+ at 280.

Compounds **4b-h** were prepared similarly. The physical data of **4a-h** are given in **Table I**.

Table II — Antimicrobial activities of the synthesized compounds

Compd	Zone of inhibition in mm		
	E.coli	*S.albus*	*A.niger*
2a	18	16	12
2b	14	16	10
2c	14	14	12
2d	16	14	10
2e	18	14	12
3a	12	12	08
3b	12	10	08
3c	14	12	10
3d	14	10	08
3e	12	12	08
4a	10	10	08
4b	12	12	06
4c	10	10	08
4d	12	10	08
4e	10	12	06
Sreptomycin *sulphate*	20	18	not tested
Greseofulvin	not tested	not tested	14

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