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GLYCEROL AS AN EFFICIENT RECYCLABLE GREEN PROMOTING MEDIA FOR A SINGLE-POT CATALYST FREE SYNTHESIS OF DENSELY FUNCTIONALIZED 4H-CHROMENES

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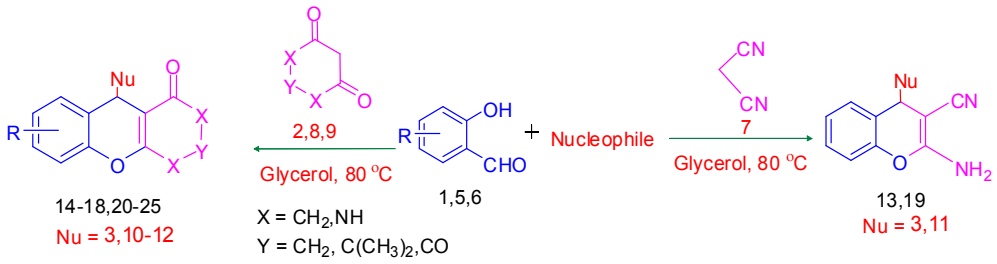
ABSTRACT :A clean and efficient, one pot, multicomponent strategy for the synthesis of 4H-chromenes in glycerol, a biodegradable and green promoting media, is reported. The present procedure eliminates the use of toxic transition metal catalysts, bases and volatile organic solvents, which adversely affect the environment and living beings. Other advantages of the present methodology include mild reaction conditions, broad substrate scope, operational simplicity, short reaction times, easy workup, high yields, 100% atom economy, cost effectivenessand recyclability of the solvent.



KEYWORDS: Green synthesis; 4H-chromenes; glycerol;one pot, multicomponent reaction; catalyst free.

INTRODUCTION

Multicomponent reactions have recently emerged as a useful new extension in synthetic organic chemistry and drug discovery.[I]MCRs allow assembly of complex molecules in one pot via a single operation with improved time and atom economy.[II]MCRs offers a wealth of products by the simultaneous formation of two or more bonds from simple substrates and provide unmatched opportunities for the expeditious increase in complexity of synthetic outcomes.[III]One major thrust area in green chemistry is the substitution of the harmful and toxic organic solvents with safe cheap and green solvents.[IV]In this backdrop, perfluorinated solvents,[V] water,[VI] ionic liquids,[VII] polyethylene glycol,[VIII] and supercritical fluids(particularly supercritical carbon dioxide - $scCO_2$)[IX] etc. have been used as the most probable alternatives to conventional organic solvents. But their use involves many drawbacks, compelling the scientific community to look for alternative green solvents. In this regard biomass-derived reaction media such as γ-valerolactone, 2-methyl-THF, lactic acid and glycerol are being explored as some of the attractive alternatives to conventional organic solvents.[X]Amongst them glycerol is considered the most promising. It possesses the benefits of both water and ionic liquids. In fact, as suggested by Jérôme and co-workers, glycerol can be considered as "organic water" since like water, it is abundant, biodegradable, inexpensive, non-toxic, highly polar, immiscible with hydrocarbons, able to form strong hydrogen-bond networks and dissolve a wide range of organic and inorganic compounds, including transition metal catalysts and like ionic liquid it has the advantage of higher boiling point, lower vapor pressure, reusability and ability to dissolve organic compounds usually immiscible with water.[XI,XII,XIII] Recently use of glycerol as a sustainable solvent for green chemistry has attracted even more attention.The peculiar properties of glycerol, such as high polarity, high boiling point, less toxicity, biodegradabilityand easy availability from renewable feedstocks, prompted us to further explore its use as a green solvent in organic synthesis.[XIV] Another area that has attracted much attention in green chemistry is the development of catalyst free reactions.[XV-XVII]The heterocyclic scaffold containing 4H-chromene moiety represent one of the most biologically and pharmaceutically active class of compounds. 4H-Chromenes have attracted great interest because they exhibit a wide spectrum of biological activities,[XVIII] such as antimicrobial and antifungal,[XIX]antioxidant,[XX] anti-leishmanial,[XXI]anticancer,[XXII,XXIII] antiviral,[XXIV] antitubercular,[XXV] antiproliferative,[XXVI] anti-HIV,[XXVII]anti-malarial,[XXVIII]anti-anaphylactic,[XXIX] andanticoagulant.[XXXI] They have also been usedas agrochemicals.[XXX]Substituted 4H-chromenes are also known to bind Bcl-2 protein (B-cell lymphoma 2) and induce apoptosis in tumor cells. Bcl-2 protein binding compounds provide a promising lead for the development of potential anticancer agents.[XXXII-XXXIV] It has been reported that substitution increases its biological activity due to synergistic effect of different nuclei in one molecule and such substituted 4H-chromenes arepresent in plenty of natural and medicinal scaffold.[XXXV]

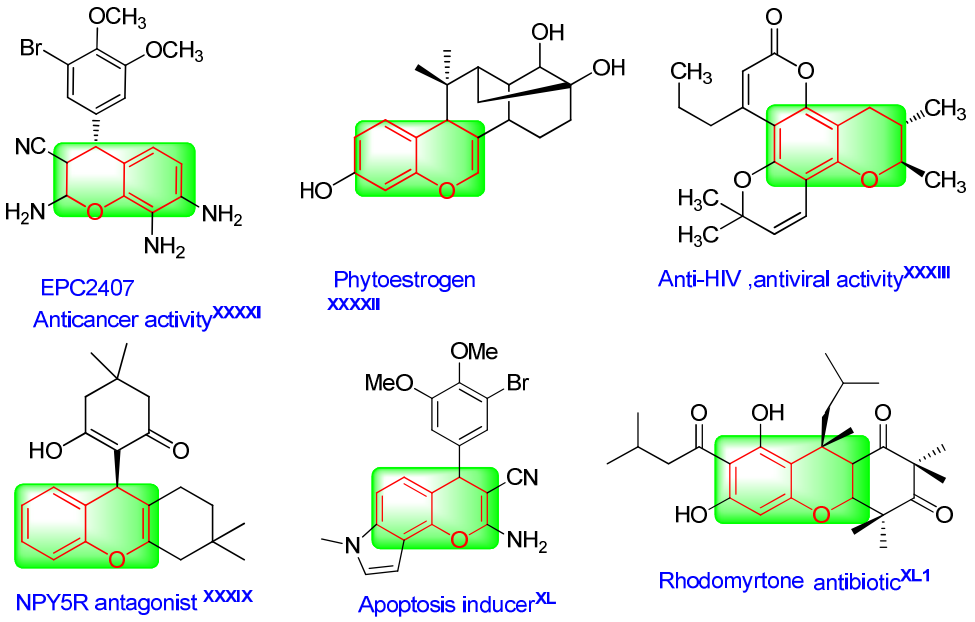
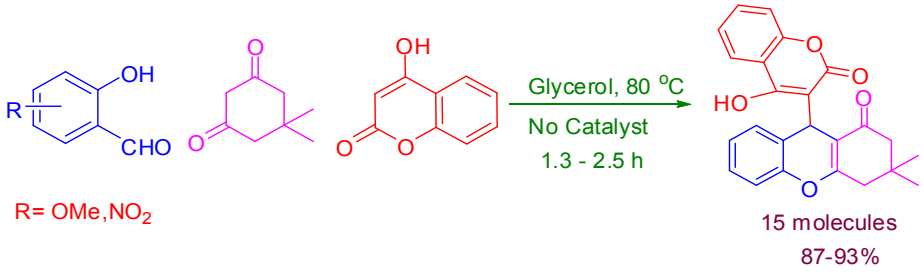


Figure 1.Some examples of biologically relevant compounds having 4H-chromenes skeleton.

For this reason, various methods have been developed for synthesizing 4H-chromenes. In spite of their potential usefulness, reported methods suffer from drawbacks such as utilization of hazardous chemicals, the use of environmentally harmful organic solvents, expensive catalysts, harsh reaction conditions, burdensome product isolation procedure, non-recyclability of solvents, commercial unavailability and low yields.

Also there are very few reports where chromene nucleus have been integrated with 4-hydroxycoumarin,[XLII,XLV] indole,[XLIIb,XLIII,XLV] pyrazolone,[XLIV,XLV]4-aminocoumarin,6-aminouracil, [XLV] and β-naphthol,[XLV] moieties. Therefore in continuation of our ongoing research program on the development of green synthetic routes to important heterocyclic molecules [XLVI] we herein report a new catalyst free and efficient, one-pot synthesis of a series of 4H-chromenes, linked with different moieties such as 4-hydroxycoumarin,indole, pyrazolone,4-aminocoumarin,6-aminouraciland β-naphthol, using glycerol as a promoting media.To the best of our knowledge, catalyst free glycerol promoted synthesis of 4H-chromenes substituted by a suitable nucleophile has not been reported so far.

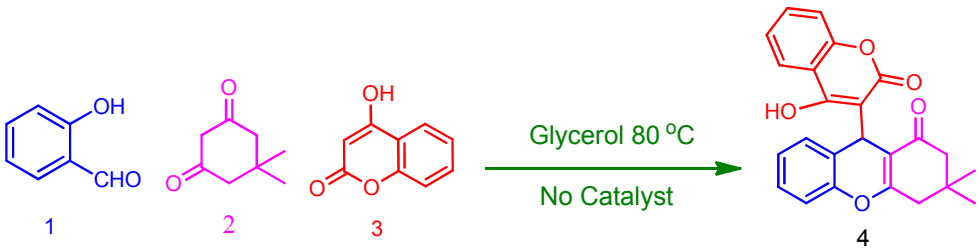


Scheme 1. General synthetic strategy

RESULTS AND DISCUSSION

In our initial endeavour we conducted a model reaction using salicylaldehyde (1, 1mmol), and dimedone (2, 1 mmol) in water at room temperature (RT). A white solution was obtained after 30 minutes with the disappearance of the starting material spots and formation of a new spot on TLC, indicating the formation of the intermediate. To the reaction mixture containing the intermediate was added 4-hydroxycoumarin (3, 1mmol). However, the reaction even after 24 h, failed to generate any product. Then the reaction was carried out in water in the presence of CTAB and SDS surfactant in these cases product was isolated in trace amount. Now in order to improve the yield we decided to screen different solvents. The reaction was first performed in ethanol at 60°C without using any catalyst. To our delight the reaction occurred in this case leading to the formation of solid product which turned out to be the desired product 4 in moderate yield (40 %), after about 5 h 30 min. The reaction was now re-conducted at reflux but no improvement in yield was observed though reaction time got marginally reduced (5 h). In our effort to further improve the yield, the experiment was carried out using PEG-400 at 75 °C but with little success as there was only a marginal increase in yield in this case (63 %). However use of glycerol in place of PEG led to a remarkable enhancement in yield (93%) and considerable reduction in reaction time (1.5 h). The experiment was now repeated at lower temperatures; 60 °C, 40 °C and RT (Table 1). However it was noticed that there was a decrease in yield and increase in reaction time with decreasing temperature. We now also put up the same reaction at a higher temperature (100 °C), but no increase in yield or reduction in reaction time was observed. From the above experiments it was inferred that use of glycerol at 80 °C gave the best result. An improvement in yield and shortening of reaction time was observed on increasing the reaction temperature, but raising the reaction temperature beyond 80 °C did not lead to any further increase in yield or rate of reaction.

Table 1. Effect of solvent and temperature on yield of 4H-chromenes†



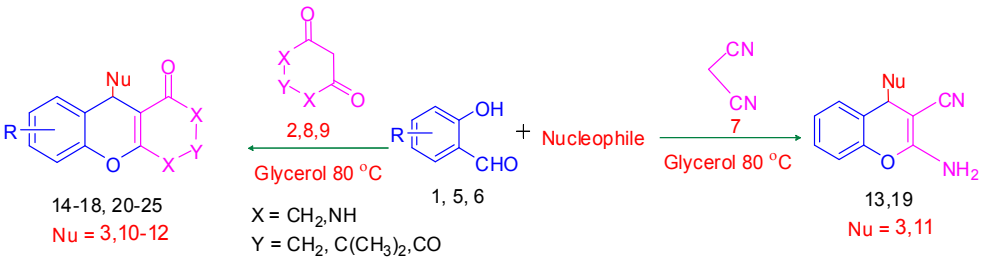
Entry	Solvent	Additive	Temperature	Time	Yield (%)‡
1	Water	None	RT	24 h	No reaction
2	Water	None	reflux	24 h	No reaction
3	Water	CTAB	RT	12 h	Trace amount
4	Water	CTAB	reflux	12 h	Trace amount
5	Water	SDS	RT	12 h	Trace amount
6	Water	SDS	reflux	12 h	Trace amount

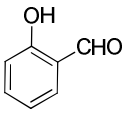
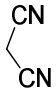
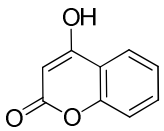
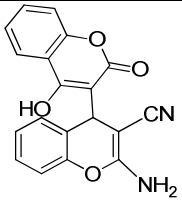
7	Ethanol	None	reflux	5 h	40
8	Ethanol	None	60 °C	6 h	40
9	PEG-400	None	75 °C	4 h	63
10.	Glycerol	None	80 °C	1.5 h	93
11.	Glycerol	None	60 °C	3h	86
12.	Glycerol	None	40 °C	4 h	80
13.	Glycerol	None	RT	6 h	76
14.	Glycerol	None	100 °C	1.5 h	93

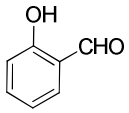
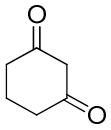
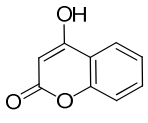
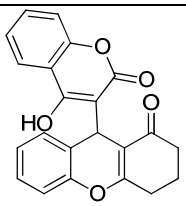
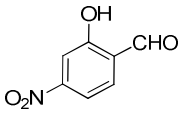
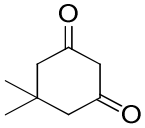
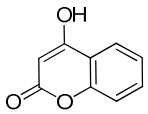
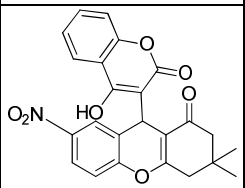
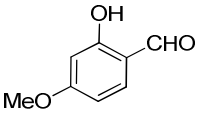
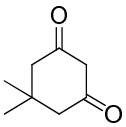
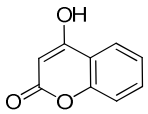
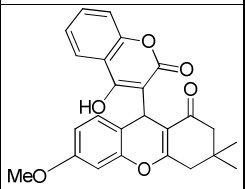
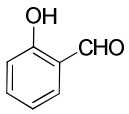
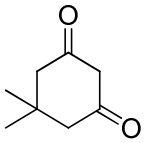
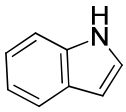
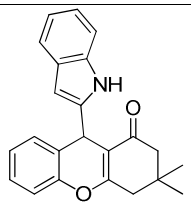
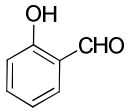
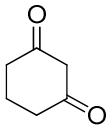
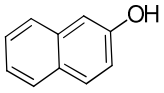
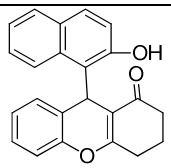
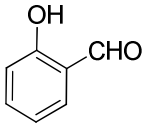
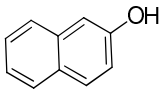
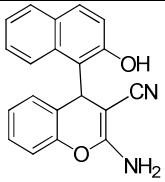
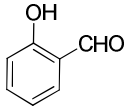
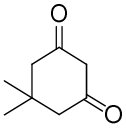
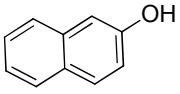
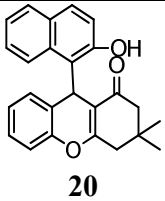
† All reactions were carried out with **1** (1 mmol), **2** (1mmol), **3** (1mmol) in 5 mL of solvent under air.‡Isolated yields.

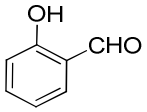
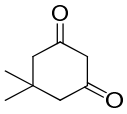
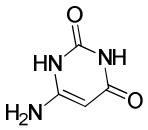
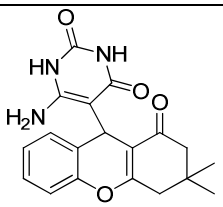
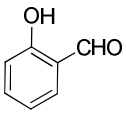
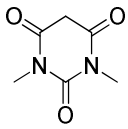
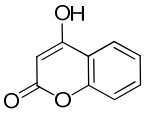
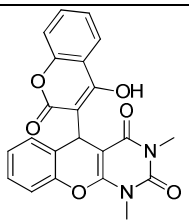
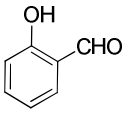
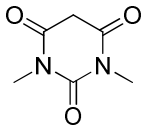
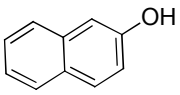
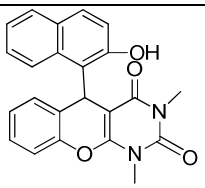
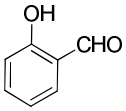
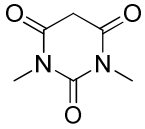
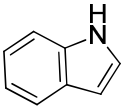
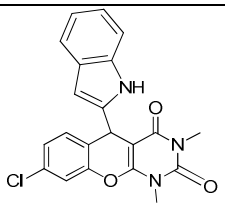
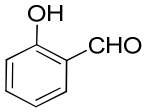
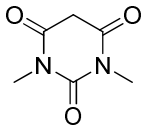
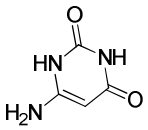
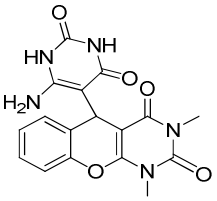
Once ideal conditions for conducting the reaction had been identified, the scope and limitations of the developed synthetic protocol was explored under the optimized reaction conditions with 2-hydroxy aromatic aldehydes, having both electron-withdrawing and electron-donating groups, active methylene compounds like dimedone, 1,3-cyclohexanedione, malononitrile and N,N-dimethylbarbituric acid and a carbon based nucleophile like 4-hydroxycoumarin, indole, 6-aminouracil, β-naphthol (Table 2). The reactions were consistently carried out at 1 mmol scale. No change in product yield was observed when the reaction was scaled up to 10 mmol scale.Since glycerol is often recovered easily by simple workup, they may be considered as promising safe and reusable solvent as well as being greener compared to traditional solvent.

Table 2. Substrate scope†



Entry	Salicylaldehyde	Active Methylene	Nucleophile	Product	Time (h)	Yield(%)‡
1	 **1**	 **7**	 **3**	 **13**	40	87

2	 **1**	 **8**	 **3**	 **14**	45	91
3	 **5**	 **2**	 **3**	 **15**	40	90
5	 **6**	 **8**	 **3**	 **16**	45	91
6	 **1**	 **8**	 **10**	 **17**	50	91
7	 **1**	 **8**	 **11**	 **18**	45	91
8	 **1**	 **7**	 **11**	 **19**	45	93
9	 **1**	 **2**	 **11**	 **20**	55	93

10	 **1**	 **2**	 **12**	 **21**	60	88
11	 **1**	 **9**	 **3**	 **22**	50	91
12	 **1**	 **9**	 **11**	 **23**	54	86
13	 **1**	 **9**	 **10**	 **24**	50	91
14`	 **1**	 **9**	 **12**	 **25**	65	85

†All reactions were carried out using2-hydroxybenzaldehyde (1mmol), active methylene compound (1mmol) and nucleophile (1mmol) in 5 mL of glycerol under air.‡Isolated yields.

A probable mechanistic pathway for the reaction has been presented in Scheme 2. Glycerol facilitates the knoevenagel-type coupling by hydrogen bonding to the oxygen of carbonyl groups of 2-hydroxybenzaldehyde. It is also presumed to activate the 1,3-diketone to act as a nucleophile due to keto-enol tautomerism. Subsequentlynucleophilic attack on the intermediate by the carbon-based nucleophile during the Michael addition step afforded the desired chromene derivative.

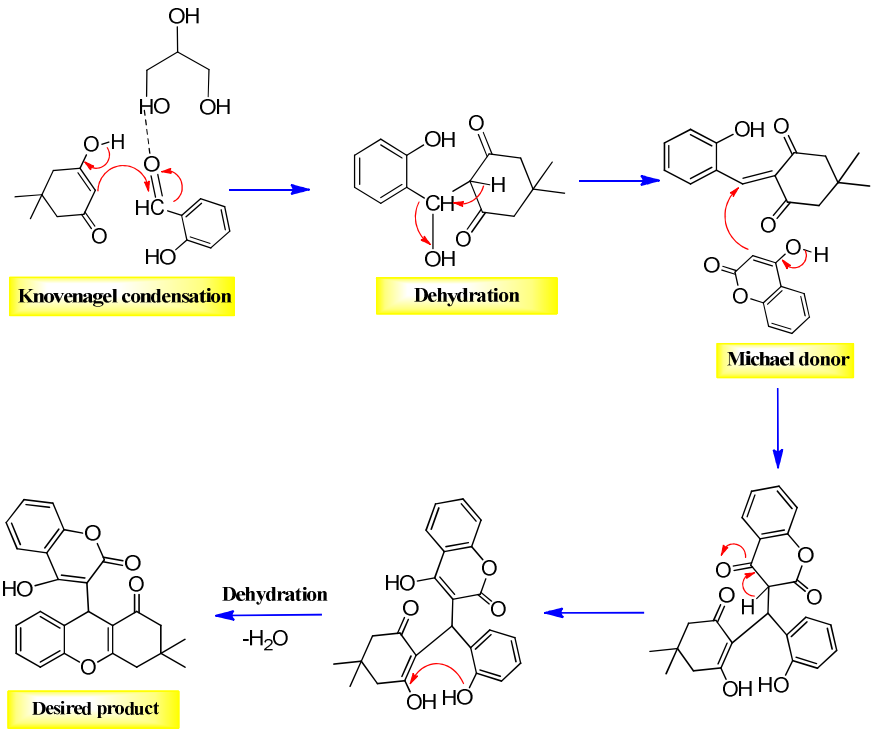


Figure2. Plausible mechanism

Once the methodology for the synthesis of 4H-chromenes had been perfected and its generality amply demonstrated we turned our attention towards examining the reusability of glycerol. Glycerol was dissolved in hot water while the product remained insoluble in water. The crude product was filtered, water evaporated in vacuo and the glycerol so obtained was again used for the reaction. It was observed that the products were obtained in good to excellent yields even after reusing the glycerol four times.

Experimental

General Remarks

All the chemicals were reagent grade and purchased from Alfa Aesar, Merck, Aldrich, Qualigensand Spectrochem, and were used as such. The reactions were examined using precoatedAluminium TLC plates of silica G/UV-254 of 0.25 mm thickness (Merck 60 F-254). Column chromatography was performed using silica gel (60-120) and (100-200). NMR spectra were recorded on a Bruker Avance-II 400FT spectrometer at 400 MHz (^{1}H) and 100 MHz (^{13}C) in DMSO or $CDCl_3$ using TMS as an internal reference. Mass spectra (ESIMS) were obtained on a Waters UPLC-TQD mass spectrometer. IR spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR spectrometer.Elemental analyses were carried out in a Perkin Elmer2400 CHN Elemental Analyser. Melting points were determined by open glass capillary method and were uncorrected.

General Experimental Procedure:

5 ml glycerol was added to a round bottom followed by the addition of the respective salicylaldehyde (1mmol) and dimedone (1mmol) under stirring and the temperature of the

reaction was fixed at 80 ºC. After formation of the intermediate, 4-hydroxycoumarin, (1mmol) was added to the reaction mixture and it was allowed to stir till completion of the reaction (TLC). Now warm water was added to the reaction mixture. Glycerol got dissolved in water and the insoluble solid crude products were separated by filtration and purified by column chromatography.The filtrate containing glycerol was extracted with methyl *t*-butyl ether to remove any organic compounds dissolved in the aqueous layer.The aqueous phase was evaporated *in vacuo* to give pure glycerol which was used for the next cycle.

9-(4-hydroxy-2-oxo-2H-chromen-3-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one(4) Yield: 90%, White solid; mp : 229−233°C; IR (KBr): 3418, 1709, 1625, 1158 cm−1; 1H NMR (300MHz DMSO-d6) (δ, ppm): 0.91 (s, 3H), 1.09(s, 3H), 2.11−2.24 (m, 2H), 2.38−2.50(m, 2H), 5.33(s, 1H), 6.80−6.98 (m, 5H), 7.21 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.4 Hz, 1H), 7.97 (d, J = 6.1 Hz, 1H); 13C NMR (DMSO-d6) (δ, ppm): 27.0, 27.1, 30.4, 40.1, 49.9, 114.2 114.5, 115.7, 117.4, 121.8, 122.5, 123.6, 124.6,125.5, 126.7, 127.5, 129.3, 152.1, 158.7, 166.2, 197.1 MS (ESI): m/z 389; found 390.11[M+H]+, Anal.Calcd for $C_{24}H_{20}O_5$;C, 74.21; H, 5.19; found C, 74.16; H, 4.47.

2'-amino-4-hydroxy-2-oxo-2H,4'H-[3,4'-bichromene]-3'-carbonitrile(13) Yield: 85%, White solid; mp : 202−204°C; IR (KBr): 3348, 2210, 1681, 1163 cm−1; 1H NMR (DMSO-d6) (δ, ppm): 5.26(s, 1H), 5.75 (s, 2H), 6.75−7.08 (m, 4H), 7.21−7.52 (m, 2H), 7.54−7.83 (m, 2H); 13C NMR (DMSO-d6) (δ, ppm): 31.1, 114.2, 115.3, 116.1, 116.7, 120.6, 121.5 123.1, 123.7, 124.4, 126.8, 127.9, 130.5, 132.5, 148.3, 150.1, 161.1; MS (ESI): m/z 333 ; found 334 [M+H]+, Anal.Calcd for $C_{19}H_{12}N_2O_4$, C, 68.67; H, 3.64; N, 8.43; found C, 68.71; H, 3.64; N, 8.40.

9-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2,3,4,9-tetrahydro-1H-xanthen-1-one(14) Yield: 90%, White solid; mp : 204−207 °C; IR (KBr): 3360, 3208, 1673, 1251 cm^{-1}; ^1H NMR (300 MHz; DMSO-d6) (δ, ppm): 1.56−1.81 (m, 2H), 2.36 (s, 2H), 2.68 (s, 2H), 5.56 (s, 1H), 6.59 (d, J = 6.5 Hz,1H), 7.01−7.14(m, 2H), 7.38−7.47 (m, 2H), 7.54 (d, J = 9.1Hz, 2H), 7.76 (d, J = 9.1 Hz, 1H); 13C NMR (DMSO-d_6) (δ, ppm): 26.9, 28.5, , 30.8, 51.0, 102.3, 108.2, 110.7, 111.6, 115.1, 123.6, 124.8, 126.3, 127.7, 128.3, 128.8, 129.8, 133.8, 150.8, 163.6, 194.9; MS (ESI): m/z 361 ; found 362 [M+H]+, Anal.calcd for $C_{22}H_{16}O_5$, C, 73.33 H, 4.48; found C, 73.35 H, 4.49.

9-(4-hydroxy-2-oxo-2H-chromen-3-yl)-3,3-dimethyl-7-nitro-2,3,4,9-tetrahydro-1H-xanthen-1-oneCompound(15) Yield: 90%, Pale yellow solid; mp : 219−223 °C; IR (KBr): 3322, 3198, 1663, 1289 cm^{-1}; ^1H NMR^1H NMR (300MHz DMSO-d6) (δ, ppm): 0.98 (s, 3H), 1.11 (s, 3H), 2.17−2.19 (m, 2H), 2.36−2.53 (m, 2H), 5.05 (s, 1H), 7.05−7.17 (m,2H), 7.39 (t, J = 7.5 Hz, 1H), 7.67 (s, 1H), 7.79−8.08 (m, 3H); 13C NMR (DMSO-d6) (δ, ppm) : 25.7, 28.7, 30.8, 31.9, 48.8, 101.1, 109.2, 114.6 115.9, 117.9, 118.4, 120.8, 122.3, 124.8, 126.9, 127.8, 129.8, 131.2, 138.1, 151.7, 166.8, 193.7; MS (ESI): m/z 434 ; found 435 [M+H]+, Anal. calcd for $C_{24}H_{19}NO_7$,C, 66.51; H, 4.42; N, 3.23; found C, 66.58; H, 4.46; N, 3.25

9-(4-hydroxy-2-oxo-2H-chromen-3-yl)-6-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (16) Yield: 90%,White solid; mp : 243−247 °C; IR (KBr) :3456, 3328 , 1671, , 1178, cm-^{11}H NMR (300MHz DMSO-d_6) (δ, ppm):: 0.94 (s, 3H), 1.08 (s, 3H), 1.98−2.21 (m, 2H), 2.33−2.52 (m, 2H), 3.66 (s, 3H), 5.37 (s, 1H), 6.31−7.45 (m, 6H), 7.89 (s, 1H); 13C NMR (DMSO-d6) (δ, ppm): 24.5, 26.5, 27.6, 28.9, 32.8, 48.3, 53.2, 55.3, 98.2, 107.3, 110.2, 115.1, 121.3, 122.9, 123.8, 128.1, 130.7, 131.4, 150.6, 157.1, 159.6, 161.5, 191.4; MS (ESI): m/z 419 ; found 420; [M+H]+, Anal.calcd for $C_{25}H_{22}O_6$, C, 71.76; H, 5.30; found C, 71.75; H, 5.16

9-(1H-indol-2-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (17) Yield: 88%, Pale yellow solid; mp.114−118oC; IR (KBr) : 3447, 3266 1636, 1197, cm^{-1};^{1}H NMR (300MHz DMSO-d6) (δ, ppm): 0.89 (s, 3H), 0.98 (s, 3H), 1.98−2.28 (m, 2H),2.39−2.48 (m, 2H), 5.06 (s, 1H), 6.28 (s, 1H), 6.48−7.38 (m, 8H),10.45 (s, 1H); 13C NMR (DMSO-d6) (δ, ppm): 25.2, 28.2, 31.1, 50.8, 110.7, 111.8, 113.3, 114.2, 117.7, 118.1, 119.2, 120.1, 122.1, 123.6, 124.4, 125.5, 135.8, 148.5, 153.4, 162.2, 194.3; MS (ESI): m/z 344 ; found 345; [M+H]+, Anal.calcd for $C_{23}H_{21}NO_2$, C, 80.44; H, 6.16; N, 4.08; found C, 79.91; H, 5.48; N, 4.01

9-(2-hydroxynaphthalen-1-yl)-2,3,4,9-tetrahydro-1H-xanthen-1-one (18) Yield: 92%, White solid; mp: 209−212 °C; IR (KBr) : 3396, 3233, 1622, 1159, cm^{-1}; ^{1}H NMR (300MHz DMSO-d6) (δ, ppm): 1.51−1.56 (m, 2H), 1.82−1.87 (m, 2H), 2.14 (d, J = 3 Hz, 2H), 5.66 (s, 1H), 7.16−7.29 (m, 2H), 7.27−7.45 (m, 2H), 7.39−7.47 (m, 2H),7.69−7.67 (d, J = 6.2 Hz, 2H), 7.72 (d, J = 7.5 Hz, 2H); 13C NMR (DMSO-d6)(δ, ppm): 28.1, 30.7, 31.3, 48.2, 100.1, 101.7, 110.1, 116.6, 120.7, 121.3, 123.6, 123.9, 128.6, 130.4, 131.9, 135.8, 138.7, 146.3, 151.2, 162.8, 163.1, 164.1, 196.4; MS (ESI): m/z 343; found 344 [M+H]+, Anal. calcd for $C_{23}H_{18}O_3$:C, 80.68; H, 5.30; found: C 80.61; H 5.24 %.

2-amino-4-(2-hydroxynaphthalen-1-yl)-4H-chromene-3-carbonitrile (19) Yield: 95%, White solid; mp. 211−213 °C; IR (KBr) : 3375, 3278, 2308, 1187 cm^{-1}; ^{1}H NMR (300MHz DMSO-d6) (δ, ppm):5.05 (s, 1H), 6.04 (s, 2H), 6.32 (s, 1H), 6.83 (s, 2H), 7.06 (s, 2H), 7.21−7.66 (m, 4H), 10.74 (s, 1H); 13C NMR (DMSO-d6) (δ, ppm): 30.4, 110.2, 118, 2, 119.1, 124.3, 124.7, 125.2, 125.7, 126.3, 126.8, 127.3, 127.9, 128.3, 129.8, 135.3, 139.8, 141.7, 14249, 151.8; MS (ESI): m/z 315; found 316[M + H]+, Anal. calcd for $C_{20}H_{14}N_2O_2$. C, 76.42; H, 4.49; N, 8.91; found: C, 76.47; H, 4.42; N, 8.94.

9-(2-hydroxynaphthalen-1-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one(20) Yield: 94%, White solid; mp: 233−237 °C; IR (KBr) : 3396, 3215, 1637, 1196, cm^{-1}; ^{1}H NMR (300MHz DMSO-d_6) (δ, ppm): 0.89 (s, 3H), 0.97 (s, 3H), 2.07−2.29 (m, 2H), 2.47−2.59 (m, 2H), 5.69 (s, 1H), 6.48−6.57 (m, 2H), 6.61−6.68 (m, 4H), 6.77 (t, J = 7.5 Hz, 1H), 7.18−7.37(d, J = 6 Hz, 1H) 7.67−7.69 (m, 2H), 8.07 (d, J = 6 Hz, 1H), 9.27 (s, 1H); 13C NMR (DMSO-d_6) (δ, ppm): 26.3, 28.1, 29.1, 32.8, 50.2, 113.7, 116.6, 117.9, 118.8, 120.7, 123.6, 125.9, 127.8, 128.8, 129.5, 131.6, 132.9,134.5, 136.8, 147.8, 153.7, 165.2, 197.7; MS

(ESI): m/z 371 ; found 372 [M+H]+, Anal.calcd for $C_{25}H_{22}O_3$, C, 81.06; H, 5.99; found C, 81.12; H, 5.92.

6-amino-5-(3,3-dimethyl-1-oxo-2,3,4,9-tetrahydro-1H-xanthen-9-yl)pyrimidine-2,4(1H,3H)-dione(21) Yield: 84%, White solid; mp >300 °C; IR (KBr) : 3364, 3209, 2996, 2915, 1714, 1646, 1206, cm^{-1}; ^{1}H NMR (300MHz DMSO-d_6) (δ, ppm): 0.97(s, 3H), 0.98 (s, 3H), 1.89− 2.08 (m, 2H), 2.39−2.48 (m, 2H), 4.57 (s, 1H), 6.18 (s, 2H), 6.76− 6.99 (m, 4H), 9.75 (s, 1H), 9.86 (s, 1H); 13C NMR (DMSO-d6) (δ, ppm): 25.2, 27.7, 29.9, 33.8, 106.7, 116.3, 115.7, 118.6, 120.5, 123.6, 126.8, 127.9, 128.8, 131.7, 135.8, 139.5, 151.4, 163.7, 197.5; MS (ESI): m/z 354 found 355 [M+H]+ Anal.Calcd for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89; found : C, 64.54; H, 5.37; N, 11.82.

5-(4-hydroxy-2-oxo-2H-chromen-3-yl)-1,3-dimethyl-1H-chromeno[2,3-d]pyrimidine-2,4(3H,5H)-dione(22) Yield: 92%, White solid; mp 266−268 °C; IR (KBr) : 3468, 3215, 1735,1645, 1226, cm^{-1}; ^{1}H NMR (300MHz DMSO-d_6) (δ, ppm): 3.45 (s,3H), 3.64 (s, 3H), 5.34 (s, 1H), 7.14−7.65 (m, 6H), 8.07−8.09 (m, 2H); 13C NMR(DMSO-d6) (δ, ppm): 28.7, 29.8, 30.5, 36.4, 87.1, 108.2, 115.6, 116.1, 116.8,121.6, 123.5, 124.5, 125.2, 125.9, 126.2, 128.3, 131.5, 149.7, 150.6, 161.4, 165.2, 186.4; MS (ESI): m/z 405 found 406 [M+H]+, Anal.calcd for $C_{22}H_{16}N_2O_6$ C, 65.34; H, 3.99; N, 6.93; found C, 65.18; H, 3.99; N, 6.96.

5-(2-hydroxynaphthalen-1-yl)-1,3-dimethyl-1H-chromeno[2,3-d]pyrimidine-2,4(3H,5H)-dione(23) Yield: 90%, White solid; mp 191−195°C; IR (KBr): 3486, 3315, ,1670, 1258, cm^{-1}; ^{1}H NMR (300MHz DMSO-d_6) (δ, ppm): 3.35 (s, 3H), 3.64 (s, 3H), 5.92(s, 1H), 6.73−7.15 (m, 5H), 7.14−7.36 (m, 2H), 7.53−7.65 (m, 3H), 9.85 (s, 1H); 13C NMR (DMSO-d6) (δ, ppm): 28.5, 30.7, 49.5, 109.4, 115.4, 117.6, 121.5, 122.9, 124.5, 125.6, 126.8, 127.7, 128.3, 129.1, 129.9, 130.5, 131.4, 134.3, 149.5, 150.7, 153.8, 153.6, 164.8; MS (ESI): m/z 387found 388[M+H]+, Anal.calcd for $C_{23}H_{18}N_2O_4$, : C, 71.49; H, 4.70; N, 7.25; found : C, 71.47; H, 4.76; N, 7.27.

8-chloro-5-(1H-indol-2-yl)-1,3-dimethyl-1H-chromeno[2,3-d]pyrimidine-2,4(3H,5H)-dione(24) Yield: 90%, White solid; mp 176−179 °C; IR (KBr) : 3437, 3346, 1687, 1145 cm^{-1}; ^{1}H NMR (300MHz DMSO-d_6) (δ, ppm): 3.05−3.18 (m, 3H), 3.36 (m, 3H), 5.29 (s,1H), 6.40−6.51 (m, 2H), 6.56−6.78 (m, 2H), 6.77−7.33 (m, 4H),10.77 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 28.6, 29.5, 30.7, 111.8, 116.6, 118.4, 118.9, 119.3, 119.9, 120.7, 122.3 123.8, 126.8, 127.2, 129.5, 131.7,133.4, 135.8, 137.6, 154.3, 163.1; MS (ESI): m/z 393 found 394 [M+H]+, Anal.calcd for $C_{21}H_{16}ClN_3O_3$ C, 64.05; H, 4.09; N, 10.67; found C, 64.11; H, 4.14; N, 10.68.

5-(6-amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3-dimethyl-1H-chromeno[2,3-d]pyrimidine-2,4(3H,5H)-dione(25) Yield: 84%, White solid; mp >300 °C IR(KBr) : 3368, 3245, 2996, 1685, 1286, cm^{-1}; ^{1}H NMR (300MHz DMSO-d_6) (δ, ppm): 3.26 (s, 3H), 3.45(s, 3H), 5.57 (s, 1H), 6.96−7.18 (m, 4H), 7.35 (t, J = 7.5 Hz, 1H),7.35−7.86 (m, 2H); 13C NMR (DMSO-d6) (δ, ppm): 20.6, 27.8, 29.3, 36.1, 114.2, 116.6, 118.8, 120.9, 123.3, 125.6, 127.7,

129.6, 135.5, 146.3, 151.2, 169.3, 198.5; MS (ESI): m/z 370; found 371 [M+H]+, Anal.calcd for $C_{17}H_{15}N_5O_5$, C, 55.28,H, 4.09; N, 18.96; found C, 55.25 ; H, 4.07; N, 18.94.

Conclusion

In conclusion, we have disclosed a rapid and an efficient one pot synthesis of 4H-chromenes - a biologically significant hybrid scaffold in compliance with green chemistry principles. Highlights of the present methodology are the use of non-hazardous reaction conditions, use of cheap starting materials, very high yields and 100% atom economy.One key feature of the present work is the use of glycerol as a recyclable promoting media, which clearly highlights the growing potential of glycerol in organic synthesis.

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