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DOI: 10.1039/C7NJ01839H

Journal Name

ARTICLE

Synthesis of Novel Fused Chromone-Pyrimidine Hybrids and 2, 4, 5-Trisubstituted Pyrimidine Derivatives via the ANRORC Rearrangement

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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Abstract: A facile and versatile procedure for the synthesis of functionalized novel 2, 5-diphenyl-5H-chromeno [4, 3-d] pyrimidin-5-ol and (2, 4-diphenylpyrimidin-5-yl) (2-hydroxyphenyl) methanone has been described. The key step in the synthesis involves the ANRORC reaction of 3-benzoyl chromones with benzamidines

Introduction

Efficient synthesis of polycyclic aromatic hydrocarbons have attracted much attention due to their diverse biological activities[1] as well as electro-chemical and photochemical properties.[2] In this context pyrimidine derivatives are considered highly admired heterocyclic ring structure.[3] Pyrimidine derivatives usually existing in natural and unnatural products, play the crucial role in human life.[4] Pyrimidine activated sugars are also serve as essential functions in phospholipid and polysaccharide synthesis, glucuronidation in detoxification processes, glycosylation of proteins and lipids.[5] In addition, pyrimidines can be salvaged by human cells for the synthesis of deoxyribonucleotides that are used for DNA synthesis. Also, pyrimidine derivatives commonly display remarkable biological and pharmacological activity for human diseases, such as cancer,[6] varicella-zoster virus,[7] malaria,[8] tumor of L1210 and P388 leukemias.[9] Study indicates that the fusion of pyrimidine moiety with different heterocycle scaffolds gives rise to a new class of hybrid heterocycles with improved biological activity (**Fig 1**).[10]

Chemically, chromones (4H-chromene-4-ones) are heterocyclic compounds with the benzo-γ-pyrone framework. Molecules containing the chromone or benzopyrone ring have a wide range of biological activities.[11] They have been shown to be tyrosine and protein kinase inhibitors,[12-13] as well as anti-inflammatory,[14] antiviral,[15] antioxidant[16] and antihypertensive agents.[15] Chromone derivatives are also active at benzodiazepine receptors,[17] on lipooxygenase and cyclooxygenase.[18] In addition to this, they have shown to be anticancer agents.[19] Chromones may also have application in cystic fibrosis treatment, as they activate the cystic fibrosis trans-membrane conductance regulator.[20] The vast range of biological effects associated with this scaffold has resulted the chromone ring system being considered as a privilege structure.[21]

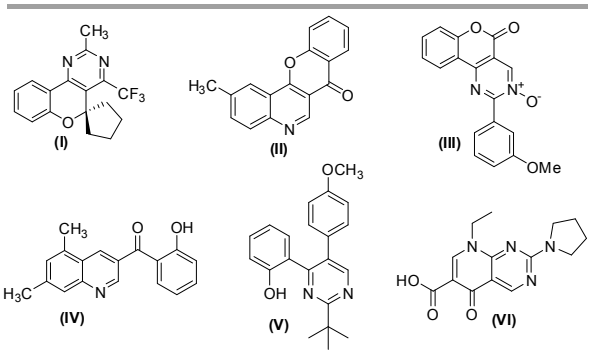

Fig 1: Some Biologically active Pyrimidines and Fused Chromone-Pyrimidine Hybrids

Synthesis of hybrid natural products has gained momentum in recent years.[22-24] It is expected that combining features of more than one biologically active natural segment in a single molecule may result in pronounced pharmacological activity while retaining high diversity and biological relevance.[25] Taking into consideration these two biologically significant structures (Chromone and Pyrimidine), we plan to develop a general method for the synthesis of chromone-pyrimidine hybrids and here in we report our initial result.

A major challenge in organic synthesis today is to devise reactions that can form several C-C and/or C-heteroatom bonds in one operation leading to the construction of target structures with proper chemo-, regio and stereo selectivity. In this context domino (also Known as tandem or cascade) reactions have proven to be a powerful shortcut for the assembly of complex ring systems minimizing the waste sub-products and synthetic efforts. During last three decades domino strategies were successfully applied in the synthesis of varies practically valuable cyclic compounds including heterocycles, pharmaceuticals and natural products. Owing to their special electronic properties the chemistry of heterocyclic systems like pyrones, chromones and their 3-acyl derivatives, have experienced a renaissance in recent years, namely they are often involved in domino transformations since the push-pull fragment in

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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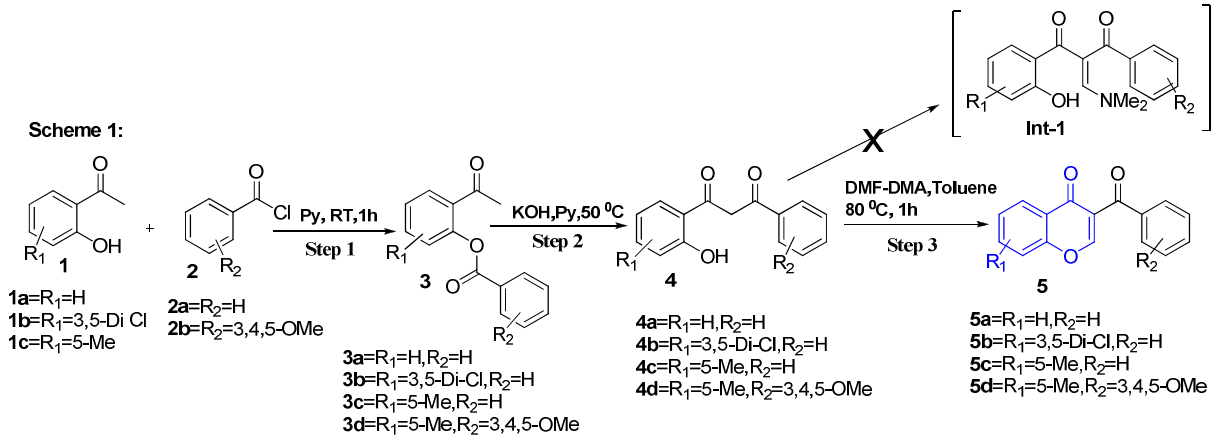
pyrone remains labile towards the external and internal nucleophiles.[26]

Considering the tendency of chromone framework to undergo an ANRORC (Addition of the Nucleophile, Ring Opening and Ring Closure) transformation with various nucleophiles leading to the synthesis of numerous valuable systems, we started exploring domino reaction of 3-benzoyl chromone with benzamidines (**Scheme 2**).[27] Herein we report an efficient and novel synthesis of functionalized novel 2, 5-diphenyl-5H-chromeno [4, 3-d] pyrimidin-5-ol and (2, 4-diphenylpyrimidin-5-yl) (2-hydroxyphenyl) methanone.

Scheme 1:



Results and discussion

Our synthesis started with the commercially available 2-hydroxy acetophenone **1a** (**Scheme 1**).Thus compound **1a** was treated with benzoyl chloride **2a** in pyridine at room temperature to give the O-benzoyl protected acetophenone **3a** in good yield.[28] The compound **3a** was converted to 1, 3-diketone derivative **4a** via the Baker Venkatraman rearrangement using KOH/ pyridine.[29] Compound **4a** was well characterized by 1H-NMR (keto-enol form) and LC-MS analysis. Initially, our aim was to treat compound **4a** with DMF-DMA (N,N-Dimethyformamide dimethyl acetal) to produce enaminone (**Int-1**) followed by cyclization to obtain the compound **5a**. But the treatment of compound **4a** with DMF-DMA/ toluene at 80 ^{0}C gave the compound **5a** directly instead of **Int-1**. Probably the intermediate (**Int-1)** was cyclized in situ in lieu of the hydroxyl group at the ortho position. This two-step condensation and cyclization reaction of 1, 3 diketo derivative **4a** was reported earlier with low yield.[30] By using this two-step method we have prepared a series of 3-benzoyl chromones (**5a-5d in Table1**) in very good yields.

Initially we tried the ANRORC reaction of compound **5a** with benzamidine **6a** using Et_3N as base and THF as solvent at RT. But even after 12 h we observe most of the SM was unreacted. We tried several reaction conditions to optimize the ANRORC reaction of compound **5a** with benzamidine **6a** and the results are summarized in **Table 2**. Finally treatment of compound **5a** with benzamidine **6a** in NaOMe/MeOH condition, we could able to isolate the two compounds by column chromatography. The major compound was found to be **7a** and the minor compound was assigned the structure as **8a** (**Figure 2**). The structure of the compounds **7a** and **8a** were supported by its IR, 1H- NMR, HMBC, LC-MS and HRMS analysis reports. GHMBC and HSQC experiments were performed to confirm the structure of compound **8a**. In HMBC experiment (**Fig 2**), the 7th position OH proton at 11.9 ppm giving correlation with C-3 at 118.5 ppm, C-4 at 163.1 ppm and C-5 at 119.4 ppm, 10th position carbonyl carbon at 200.6 ppm are giving correlation with H-6 at 7.25 ppm, H-8 at 8.88 ppm. All protons versus carbon connectivity's and 13C chemical shift values are supporting the structure of compound **8a**. The structure of the compound **7a** was confirmed by the NOE, HMBC, HSQC studies, as there was ambiguity in the structure of compound **7a**.[31] For the confirmation of compound **7a** (not **7B** in **Fig 3**) we have performed ^{15}N-NMR studies as it was difficult to differentiate between **7a** and **7B** in NOE, HMBC, HSQC studies. Finally ^{15}N-NMR studies confirm the structure of compound **7a** (**Figure 2**).[32] The mechanism was proposed for the formation of compound **7a** and **8a** based on the literature.[31] As proposed by Ghosh et al.[31] the reaction proceed through a Michael addition at the C-2 position of the chromone moiety with concomitant opening of the pyrone ring to form the intermediate **9**. The intermediate **9** thus formed undergoes recyclization with subsequent water elimination in two different pathways to give compound **7a** and compound **8a**. The pathway (**a**) which is energetically favoured, gives the predominant 2, 5-di-aryl-5-hydroxybenzopyrano-pyrimidine **7a** as major product through the intermediate **10**. The pathway (**b**) leads to minor product 2-aryl-5-(2-hydroxybenzoyl)-pyrimidine **8a**. The intermediate **10** can lose water molecule in two different modes (path **c** & path **d**). The pathway **d** relives steric crowding at the benzylic centre and creates a double bond in conjugation with the benzene ring to give compound **7a** which is energetically more favoured than the other pathway **c** that lead to 2, 5-di-aryl-10-hydroxy-dihydrobenzopyrimidine **7B.** The formation of pyrimidine ring in the compound **7a** by water elimination of compound **10** in the pathway **d** is probably the major reason for exclusive formation of compound **7a** not **7B.**

To prove the generality of this method various highly substituted aryl, hetero aryl, alkyl benzamidines as well as poly substituted 3-benzoyl chromones were examined and the results were given in **Table 3**. Similar yields were observed for the substrates having electron withdrawing groups (compounds **7e**, **8e** and **7f**, **8f**) as well as electron donating groups (compound **7c**, **8c**; **7j**, **8j**; **7n**, **8n**; **7s**, **8s** and **7t**, **8t**). More importantly previously inaccessible furan, pyrimidine and guanidine analogues were synthesized in very good yield (compound **7r**, **8r**; **7q**, **8q**; **7s**, **8s** and **7t**, **8t**). Alkyl amidines (acetamidine and guanidine) were also converted to their fused chromone-pyrimidines as well as tri substituted pyrimidines in good yield which are not reported in the literature.

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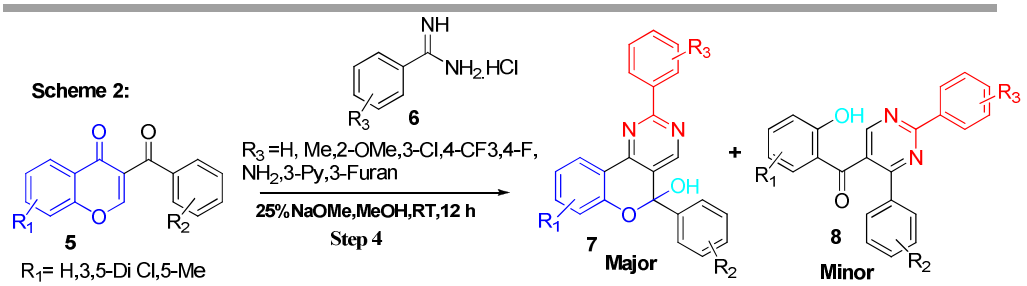
Scheme 2:



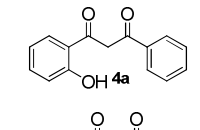
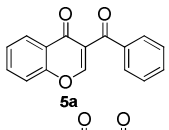
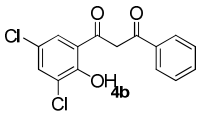
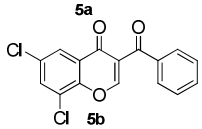
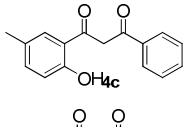
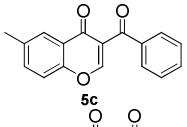
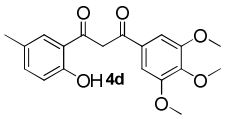
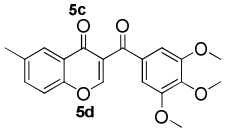
R1=H, 3,5-Di Cl,5-Me

R2=H, 3,4,5-OMe

R3=H, Me, 2-OMe, 3-Cl, 4-CF3, 4-F,NH_2,3-Py,3-Furan

Table : 1

List of Hydroxy 1,3-di ketones and 3-Benzoyl-chromones

S.No	Hydroxy 1,3-di Ketones	3-Benzoyl-4-Chromones	Yield (%)[a]
1			91
2			45
3			82
4			89

[a] isolated Yeild

Table 2

Entry	Base	Solvent	Result [b]
1	Et_3N	THF	72% of compound 7a, 20% of compound 8a & 7% of Compound 5a
2	DIPEA	THF	26% of compound 7a, 32% of compound 8a & 38% of Compound 5a
3	DBU	THF	70% of compound 7a, 18 % of compound 8a & 10% of compound 5a
4	$NaHCO_3$	DCM	9% of compound 7a, 21% of compound 8a & 69% of Compound 5a
5	KOtBu	THF	71% of compound 7a, 19% of compound 8a & 2% of Compound 5a
6	K_2CO_3	Dioxane	39% of compound 7a, 50 % of compound 8a & 4% of compound 5a
7	Cs_2CO_3	Dioxane	70% of compound 7a, 23 % of compound 8a & 6% of compound 5a
8	Na_2CO_3	EtOH	50% of compound 7a, 37 % of compound 8a & 11% of compound 5a
9	25%NaOMe	MeOH	64% of compound 7a & 34 % of compound 8a

[b] Results based on crude LC-MS

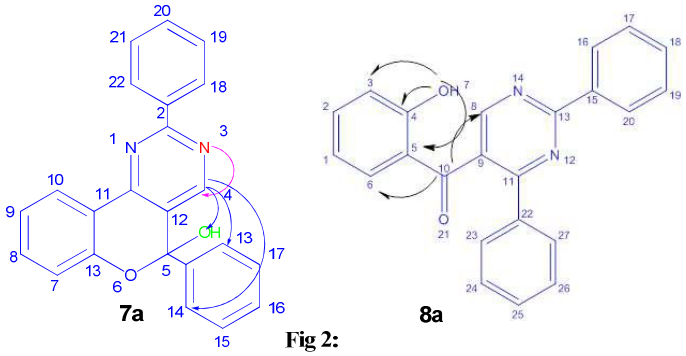


Fig 2:

NOE , HMBC and ^{15}N-HMBC Correlation studies of Compounds 7a and 8a

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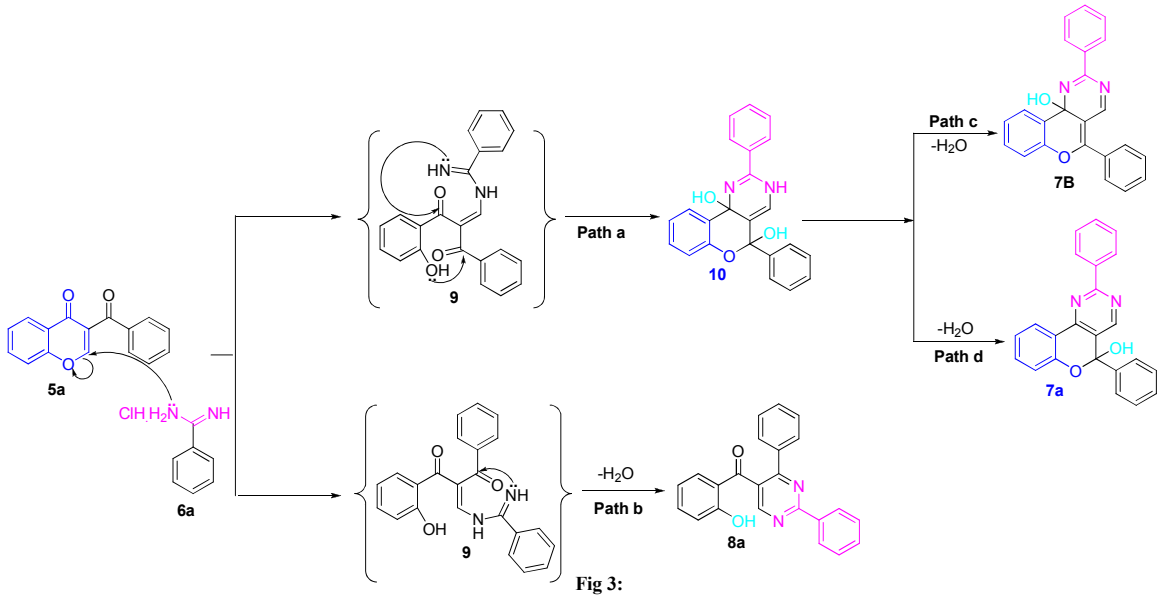

Fig 3:
Proposed Mechanism for the compounds 7a and 8a

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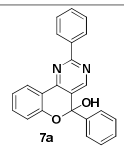
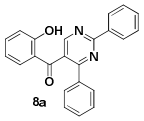
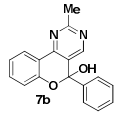
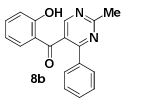
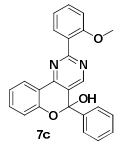
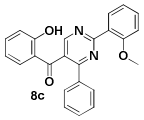
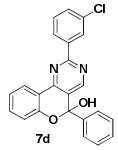
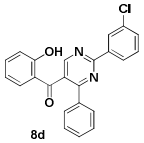
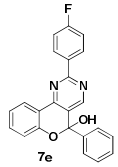
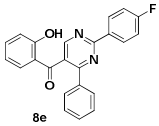
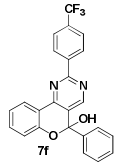
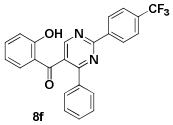
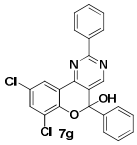
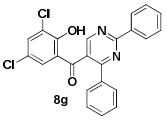
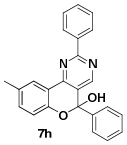
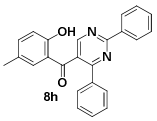
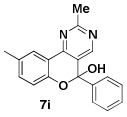
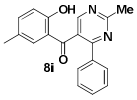
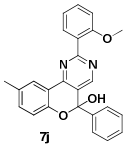
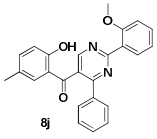
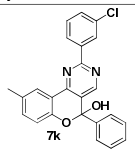
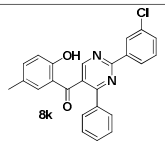
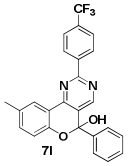
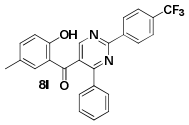
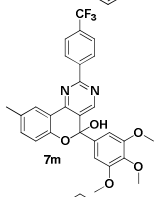
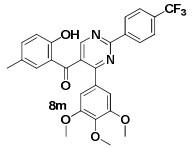
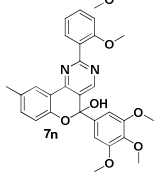
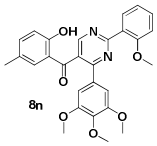
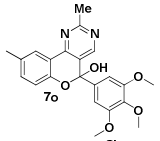
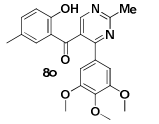
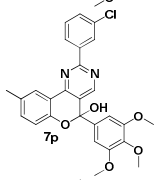
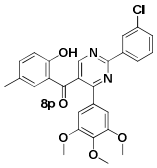
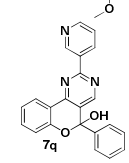
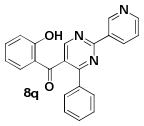
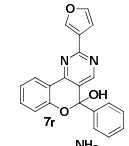
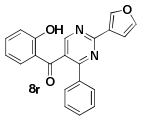
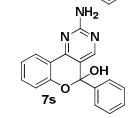
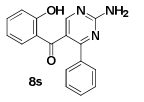
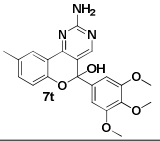
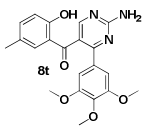
Table:3
List of Fused Chromone-Pyrimidine Hybrids and Trisubstituted Pyrimidines

S.No	Fused Chromone-Pyrimidine Hybrids	Yield [c]	2,4,5-Tri Substituted Pyrimidines	Yield [c]
1	 7a	57%	 8a	21%
2	 7b	72%	 8b	25%
3	 7c	65%	 8c	32%
4	 7d	70%	 8d	26%
5	 7e	61%	 8e	35%
6	 7f	72%	 8f	27%
7	 7g	65%	 8g	30%
8	 7h	60%	 8h	29%
9	 7i	58%	 8i	29%
10	 7j	66%	 8j	13%
11	 7k	77%	 8k	22%
12	 7l	75%	 8l	20%
13	 7m	67%	 8m	30%
14	 7n	55%	 8n	20%
15	 7o	70%	 8o	25%
16	 7p	60%	 8p	38%
17	 7q	65%	 8q	30%
18	 7r	77%	 8r	22%
19	 7s	50%	 8s	41%
20	 7t	59%	 8t	40%

[c] isolated yield

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Conclusions

In summary, we have developed a facile and versatile procedure for the synthesis of functionalized novel 2, 5-diphenyl-5H-chromeno [4, 3-d] pyrimidin-5-ol and (2, 4-diphenylpyrimidin-5-yl) (2-hydroxyphenyl) methanone. This is the first report of ANRORC reaction of 3-benzoyl chromone with benzamidines. These findings will significantly expand the value of chromones in the synthesis of heterocycles.

General Experimental Details. Dry solvents were purchased from chemical suppliers and used without further purification. Analytical thin-layer chromatography (TLC) was performed on commercially available Merck TLC Silica gel 60 F_{254}. Silica gel column chromatography was performed on silica gel 60 (spherical 100-200 μm). IR spectra were recorded on Perkin-Elmer FT/IR-4000 using ATR.^{1}H NMR spectra were recorded on Varian-400 (400 MHz) spectrometer. Chemical shifts of ^{1}H NMR spectra were reported relative to tetra methyl silane. ^{13}C NMR spectra were recorded on Varian-400 (100 MHz) spectrometer. Chemical shifts of ^{13}C NMR spectra were reported to relative to $CDCl_3$ (77.16) and DMSO-d_6 (39.5). Splitting patterns were reported as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Experimental Procedure for the Preparation of 2-acetylphenyl benzoate (3a): To a stirred solution of 2-hydoxy acetophenone (**1a)** (2 g, 14.68 mmol) in pyridine (3 ml) was added benzoyl chloride (**2a**) (2.9 g, 20.56 mmol) at 0 ^{0}C and the reaction mixture was stirred at RT for 1h. The progress of the reaction was monitored by TLC (5% Ethyl acetate in petroleum ether) showed completion of the reaction. After completion of the reaction; the reaction mixture was poured in to ice cold 1N HCl (70 ml) and stirred at RT for 2 h. The solid was filtered and washed with water and dried under vacuum to give the crude product. The crude product was washed with *n*-pentane to afford the pure compound **3a** (3 g, 85%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, 2H), 7.87 (d, 1H), 7.68 (m, 1H), 7.56 (m, 3H), 7.39 (t, 1H), 7.25 (m, 1H), 2.54 (s, 3H). MS (EI): *m/z* 240 (M+1,100).

1-(2-hydroxyphenyl)-3-phenylpropane-1, 3-dione (4a): To a stirred solution of compound **3a** (2.7g, 11.25mmol) in pyridine (10 ml) was added NaOH powder (675 mg, 16.87 mmol) at 50 ^{0}C and the reaction mixture was stirred at the same temperature for 1h. The reaction mixture became thick solid. The progress of the reaction was monitored by TLC (10% Ethyl acetate in petroleum ether) showed completion of the reaction. After completion of the reaction; the reaction mixture was acidified with 20 % acetic acid solution and stirred at RT for 3 h. The yellow coloured solid was filtered and washed with water and dried under vacuum to afford the pure compound **4a** (2.4 g, 90%) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.54 (s, 1H), 12.09 (s, 1H), 7.93 (m, 2H), 7.78 (dd, 1H), 7.75 (m, 1H), 7.50 (m, 3H), 7.01 (dd, 1H), 6.90 (t, 1H), 6.85 (s, 1H). MS (EI): *m/z* 240 (M+1,100).

3-benzoyl-4H- chromen-4-one (5a): To a stirred solution of compound **4a** (6 g, 25.00 mmol) in toluene (60 ml) was added DMF-DMA (17 ml, 75.00 mmol) at 5 ^{0}C and the reaction mixture was heated to 80 ^{0}C for 1h. The progress of the reaction was monitored by TLC (10% Ethyl acetate in petroleum ether) showed completion of the reaction. After completion of the reaction; the reaction mixture was evaporated to afford the crude compound which was purified by silica gel column chromatography (15 % EtOAc/petroleum ether) to gave the pure compound **5a** (5.5 g, 88%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (m, 2H), 7.87 (dd, 2H), 7.76 (t, 1H), 7.57 (m, 2H), 7.48 (m, 3H). MS (EI): *m/z* 250 (M+1,100).

2, 4-diphenylpyrimidin-5-yl)(2-hydroxyphenyl) methanone (8a) & 2, 5-diphenyl-5H-chromeno [4, 3-d] pyrimidin-5-ol (7a): 25 % NaOMe (0.8 ml, 3.6 mmol) in methanol was taken in methanol under N_2 atm, to this compound **6a** (0.313 g, 2.00 mmol) was added at RT and stirred for 5 min. Then compound **5a** was added and stirred the reaction mixture at RT for 16 h. The progress of the reaction was monitored by TLC (20% Ethyl acetate in petroleum ether) showed completion of the reaction. After completion of the reaction; the reaction mixture evaporated to afford the crude compound which was purified by silica gel column chromatography Elution of the column with 10% EtOAc/petroleum ether to gave the pure compound **7a** (0.400 g**,** 57%**)** as white solid. M.p. 171-175 °C. ^{1}H NMR (400 MHz, DMSO-d6): δ = 8.52 (m, 3H), 8.31 (d, 2H), 7.62 (m, 6H), 7.48 (m, 3H), 7.27 (t, 1H), 7.17 (d, 1H). IR (KBr, cm^{-1}): 3469, 3169, 1757, 1598, 1552, 1418, 1048, 957, 753, 692. ^{13}C NMR (100 MHz, CD_3COCD_3) = 164.8, 156.6, 155.8, 154.5, 142.5, 138.4, 131.7, 131.9, 134.5, 131.9, 129.8, 129.7, 129.5, 129.1, 127.9, 126.2, 125.8, 125.3, 123.2, 121.0, 120.8, 119.1, 99.9. MS (EI): *m/z* 352 (M+1,100), HRMS: (ESI): Calcd for: $C_{23}H_{16}N_2O_2$ [M+H]: 353.1212; Found: 353.1316.

Elution of the column with 5 % EtOAc/petroleum ether to gave the pure compound **8a** (0.150 g, 21%) as white solid. M.p. 129-133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.90 (s, 1H), 8.87 (s, 1H), 8.64 (m, 2H), 7.76 (dd, 2H), 7.56 (m, 3H), 7.39 (m, 4H), 7.36 (d, 1H), 7.01 (dd, 1H), 6.72 (t, 1H). IR (KBr, cm^{-1}): 3227, 3058, 1971, 1621, 1549, 1419, 1332, 1240, 922, 742, 692. ^{13}C NMR (100 MHz, DMSO-d6) = 196.34, 163.3, 159.3, 156.9, 136.86, 136.80, 136.5, 136.0, 131.4, 130.9, 130.27, 130.2, 129.05, 129.0, 128.8, 128.4, 128.41, 128.14, 128.10, 122.37, 122.3, 119.3, 117.3. MS (EI): *m/z* 352 (M+1,100), HRMS: (ESI): Calcd for: $C_{23}H_{16}N_2O_2$ [M+H]: 353.1212; Found: 353.1320.

Acknowledgements

Authors are grateful to GVK Biosciences Pvt. Ltd., for the financial support and encouragement. Help from the analytical department for the analytical data is appreciated. We thank Dr. Sudhir Kumar Singh for his invaluable support and motivation.

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32 See the supporting information

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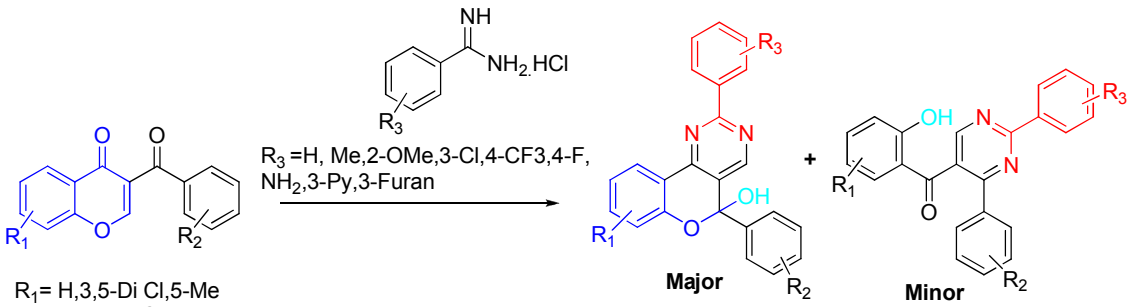
DOI: 10.1039/C7NJ01839H

Graphical Abstracts

Synthesis of Novel Fused Chromone-Pyrimidine Hybrids and 2, 4, 5-Trisubstituted Pyrimidine Derivatives via the ANRORC Rearrangement

M. Sambaiah[a,b], K. Raghavulu[a], K. Shiva Kumar[b], Satyanarayana Yennam[a] & Manoranjan Behera[*a]



R_1= H,3,5-Di Cl,5-Me
R_2= H, 3,4,5-OMe

R1=H, 3,5-Di Cl,5-Me
R2=H, 3,4,5-OMe
R3=H, Me, 2-OMe, 3-Cl, 4-CF3, 4-F,NH_2,3-Py,3-Furan

20 Examples