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One-pot practical method for synthesis of functionalized 4*H*-chromen-5-one derivatives under catalyst and solvent-free conditions

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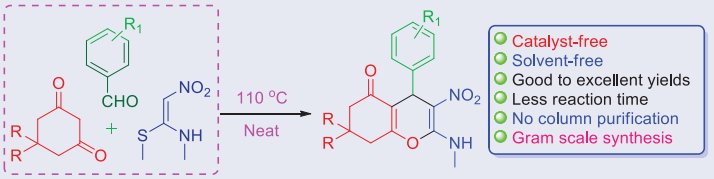
ABSTRACT

A facile and practical method was described for the synthesis of 4*H*-chromen-5-ones under catalyst- and solvent-free conditions by one-pot stirring of starting materials at 110 °C. The products were obtained by the reaction between cyclic 1,3-dicarbonyl compounds, aromatic aldehydes and *(E)*-N-methyl-1-(methylthio)-2-nitroethenamine (NMSM) in short duration with good to excellent yields. This simple and environmentally benign method eliminates the use of expensive, metallic and corrosive catalysts, hazardous organic solvents, and chromatographic separation.

GRAPHICAL ABSTRACT



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Catalyst-free; multicomponent reaction; solvent-free; 4H-Chromen-5-ones; (E)-N-methyl-1-(methylthio)-2-nitroethenamine (NMSM)

Introduction

In the mainstream of current research, green techniques or processes have recently gained significant economic and ecological interest, as they focused on approaches, which minimize the uses and generation of hazardous substances.[1,2] The main focus of green chemistry is to reshape the way and design different synthetic strategies to include the environment as a major concern. Therefore, the green chemistry provides modern synthetic pathways to architecting the molecules in a more economical and proficient manner. The replacement of either toxic solvent with eco-friendly solvent or catalyst- and solvent-free chemical processes have been a promising interest in academia and industry. Catalyst- and solvent-free multicomponent synthesis is particularly more

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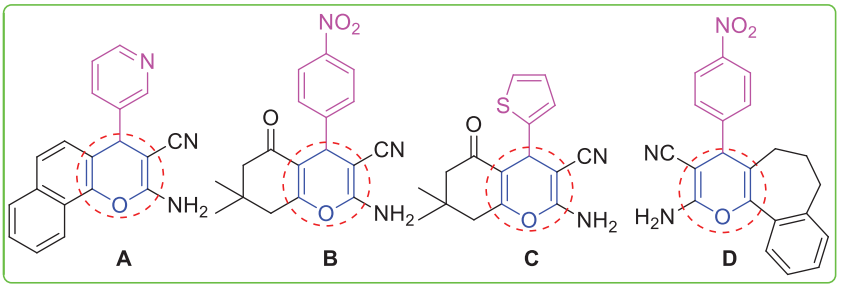


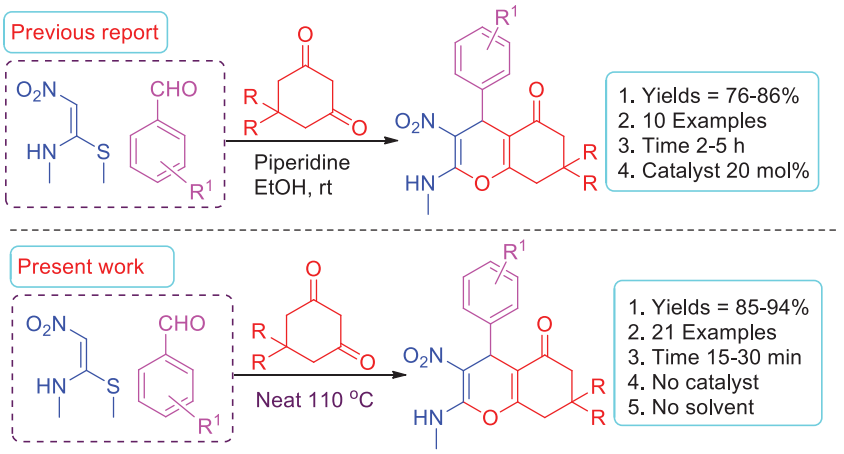
Figure 1. 4*H*-Chromenone and 4*H*-chromen containing biologically active compounds.

attractive because they incorporate many green chemistry principles.[3] In this specific circumstance, multicomponent reactions (MCRs) have emerged as a powerful strategy for the synthesis of biologically active compounds in green synthetic frameworks without isolation of unwanted intermediates,[4] which offered high atom economy, high selectivity, less waste production, and good yields.[5,6]

4*H*-Chromenone and its analogs exhibit a broad spectrum of biological and pharmacological activities such as anticancer,[7] anticoagulant,[8] antimicrobial,[9] anti-HIV, [10] antimalarial, [11] anti-tumour,[12] antidyslipidemic,[13] anticonvulsant,[14] and diuretic. [15] Compounds with 4*H*-chromenone framework are not only biologically and pharmacologically active, but also widely distributed as a key structural motif in many natural products and structure related to plant pigments.[16,17] In addition, these derivatives have also played promising roles in the field of agrochemicals and cosmetics industries.[18] Moreover, 4*H*-chromenone derivatives have also been applied for the treatment of human inflammatory TNFα-mediated diseases such as rheumatoid, psoriatic arthritis, as apoptosis inducers, and inhibitors for excitatory amino acid transport.[19] For example, compound **A** possesses antirheumatic activity[20] and compound **B** act as an antibacterial,[21] whereas anticancer activities shown by compounds **C** and **D**[22] (Figure 1). These diverse applications of 4*H*-chromenone derivatives in medicinal and pharmaceutical chemistry have dragged substantial interest among synthetic chemists to develop useful synthetic routes for their preparation. A number of synthetic methods for the construction of 2-aminochromenone and 4*H*-chromenone derivatives have been reported.[23]

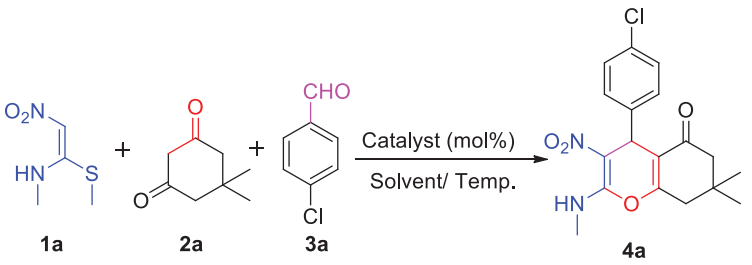
Recently, synthetic chemists explored *(E)*-N-methyl-1-(methylthio)-2-nitroethenamine (NMSM) and synthesized a variety of oxygen and nitrogen-containing heterocyclic compounds. [24] However, for the synthesis of substituted 4*H*-chromen-5-one derivatives by using NMSM, there were only two methods reported using 20 mol% piperidine and 1.5 mol% 6, 6′-thiobis(methylene)-β-cyclodextrin dimer as a catalyst.[25] Although this method is useful but associated with some demerits such as longer reaction time and use of catalysts as well as solvents. Therefore, it is need of time to develop an efficient and greener protocol for the synthesis of these important compounds, which might be a better alternative.

In continuation of our research work towards the synthesis of functionalized heterocycles by using green and sustainable approaches via MCRs,[26] herein, we wish to report a sustainable and efficient protocol for the synthesis of 4*H*-chromene-5-one



Scheme 1. Comparison of present work with reported method.

Table 1. Optimization of reaction conditions for the synthesis of compound **4a**[a].



1a **2a** **3a** **4a**

Entry	Catalyst (mol%)	Solvent	Temp.	Time	Yield[b] (%)
1	Nano ZnO (10)	EtOH	rt	3 h	40
2	Nano ZnO (10)	EtOH	78°C	2 h	65
3	Nano ZnO (10)	CH_3CN	80°C	2.5 h	60
4	Nano ZnO (10)	Neat	100°C	1 h	72
5	No Catalyst	Neat	100°C	40 min	84
6	**No Catalyst**	**Neat**	**110°C**	**20 min**	**90**
7	No Catalyst	Neat	115°C	20 min	90
6	No Catalyst	Neat	120°C	18 min	88
9	No Catalyst	Neat	130°C	15 min	86

[a]General reaction conditions: NMSM **1a** (1 mmol), dimedone **2a** (1 mmol) and 4-chlorobenzaldehyde **3a** (1 mmol).
[b]Isolated yields. Bold values in entry 6 signifies the optimized raction conditions.

derivatives in high yields by the reaction of cyclic-1,3-diketones and aromatic aldehydes with NMSM under neat conditions (Scheme 1).

Results and discussion

To optimize the reaction conditions, we first conducted a series of trial reactions with NMSM **1a** (1.0 mmol), dimedone **2a** (1.0 mmol), and 4-chlorobenzaldehyde **3a** (1.0 mmol) in the presence of recyclable heterogeneous nano ZnO (10 mol%) as a catalyst using ethanol at room temperature, ethanol at 78 °C, acetonitrile at 80 °C and without solvent at 100 °C, respectively (Table 1, entries 1–4). Again, the same reaction was

performed under catalyst- and solvent-free conditions at 100 °C (Table 1 entry 5). From the above preliminary experiments, we have noticed that catalyst- and solvent-free conditions at 100 °C afforded the comparably good result in terms of yield and time for exclusive formation of the desired product **4a**.

The product **4a** was characterized by the physical and spectral properties, which gives the good agreement with the reported data.[25] Encouraged by this result and in a quest to develop a green and sustainable method, we further commenced the same reaction at different temperature viz. 110 °C, 115 °C, 120 °C, and 130 °C at neat conditions and without a catalyst, which furnished the product in 90%, 90%, 88%, and 86% yields, respectively (Table 1, entries 6–9). The best result was achieved at 110 °C, which gives the desired product **4a** in 90% yield within 20 min of stirring. We have observed that there is no significant increase in yield while further increasing the temperature. From the above observations (Table 1, entry 6), the catalyst- and solvent-free conditions at 110 °C came out as the optimized reaction conditions in terms of best yield and time.

After optimizing the reaction conditions, we explored the scope of the synthetic protocol. For this, we started our reactions with benzaldehyde, dimedone, and NMSM under the same reaction conditions and it furnished the product **4 b** in 86% yields within 30 min. After getting these encouraging results, the reaction of various substituted aromatic aldehydes having electron donating groups such as 4-Et and 4-Me and withdrawing groups such as 4-Cl, 4-Br, 4-F, 4-NO_2, 4-OMe, 3-Cl, 3-Br, 3-OMe, 2-NO_2 and 2-F with dimedone and NMSM were performed under optimized conditions. The reaction proceeds effectively to afford a series of chromen-5-one derivative **4a–4q** in **85–94**% yields (Table 2). We have noticed that the aromatic aldehydes having electron withdrawing groups afforded the products with good to excellent yields. Electron donating substituted aromatic aldehydes also shows equal ease towards the product formation in good yields.

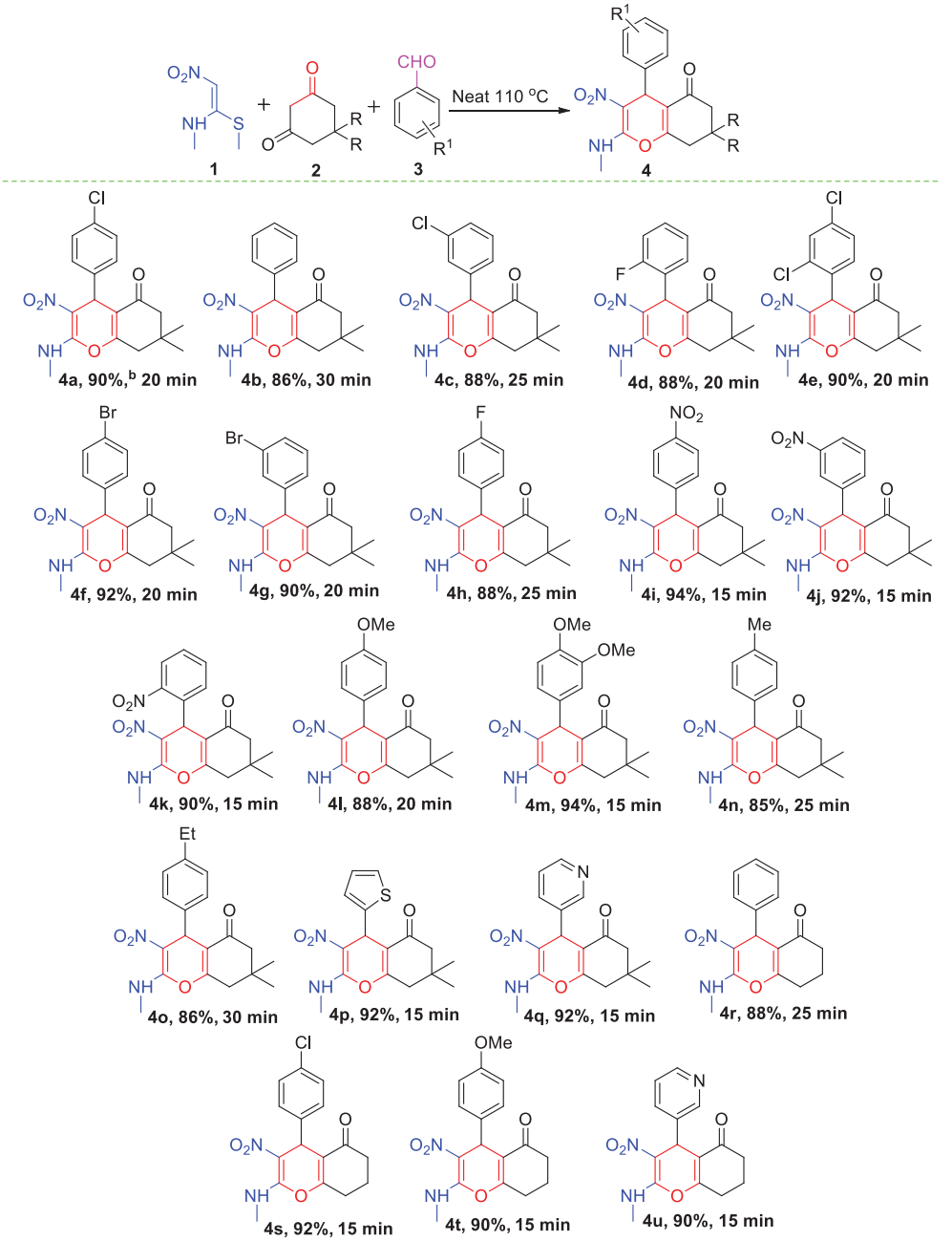
Further, the scope of this protocol was extended by the reaction of cyclohexane-1,3-dione with aromatic aldehydes and NMSM under optimized reaction conditions, which afforded the formation of desired products **4r–4u** in very good yields (Table 2). Subsequently, to create more complexity, we performed the reaction of terephthalaldehyde with cyclic-1,3-diketones and NMSM under optimized conditions, which furnished the corresponding novel bis 4*H*-chromen-5-one derivatives **6a** and **6b** as shown in Scheme 2.

Next, we moved to validate our protocol on gram-scale under the optimized conditions and compounds **4i** and **4q** were synthesized in gram scale by the reaction of NMSM, dimedone with corresponding aldehydes as depicted in Scheme 3.

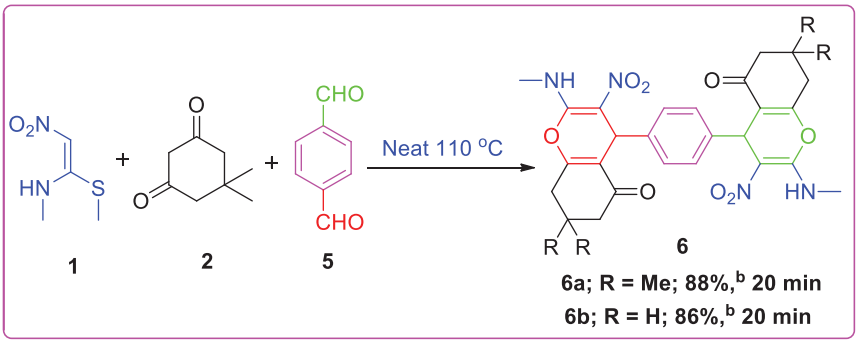
All the newly synthesized compounds were fully characterized by its melting point and spectroscopic techniques like IR, ^{1}H & ^{13}C NMR, HRMS and also by CHNS analysis. Reported compounds **4f**, **4i**, **4j**, **4l,** and **4n** were also fully characterized and the spectroscopic data are in good agreement with the proposed structure.[25] Moreover, the structure and configuration of one of the compound were confirmed by single crystal-XRD analysis and the ORTEP diagram of compound **4m** is shown in Figure 2.

Finally, a plausible reaction mechanism for the formation of 4*H*-chromene-5-ones was outlined in Scheme 4. The first step is Knoevenagel condensation of dimedone and

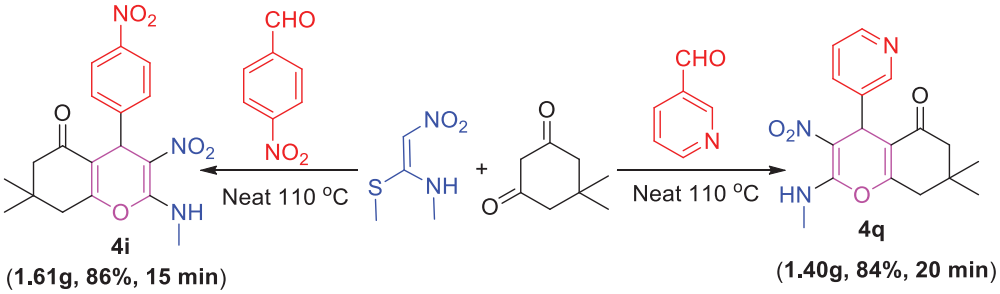
Table 2. Substrate scope for the synthesis of functionalized 4*H*-chromen-5-one derivtives[a].



[a]Reactions were performed with NMSM (1 mmol), cyclic-1,3-dikeone (1 mmol) and aromatic aldehydes (1 mmol) at 110 °C.
[b]Isolated yields.



Scheme 2. Synthesis of novel bis 4*H*-chromen-5-one derivtives.



Scheme 3. Gram scale synthesis of 4*H*-chromen-5-one **4i** and **4q**.

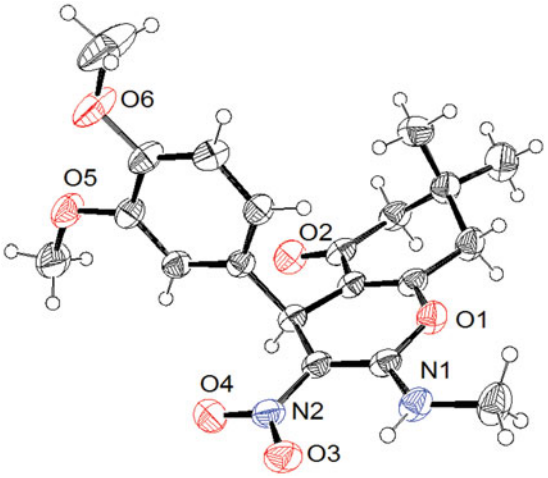
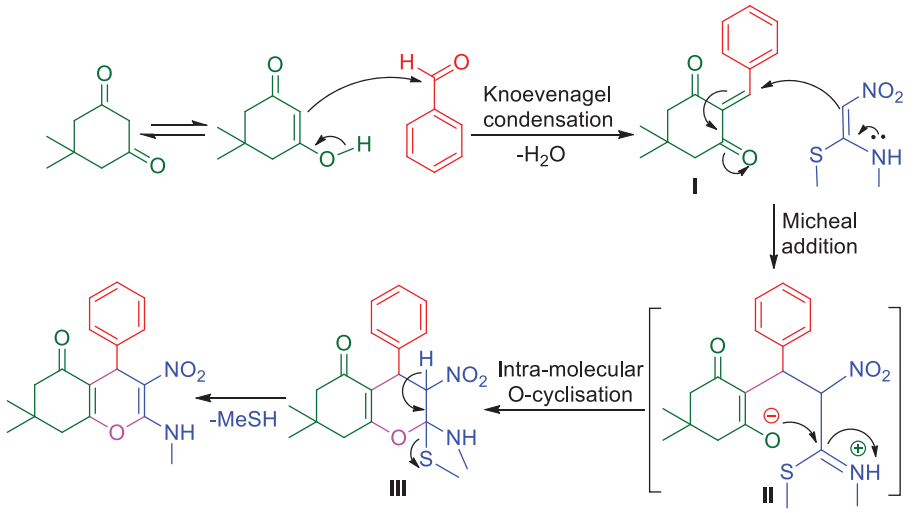


Figure 2. ORTEP diagram of compound **4m** (CCDC 1814849).

aromatic aldehyde to give an intermediate **I**, which undergoes Michael-type addition with NMSM to form species **II**. Then, the species **II** undergoes intra-molecular O-cyclization to afford the desired compound via species **III** by the elimination of –MeSH.



Scheme 4. Plausible reaction mechanism for the formation of 4*H*-chromen-5-ones.

Conclusion

In summary, we have developed an expedient and sustainable greener method for the synthesis of 4*H*-chromen-5-one derivatives from the reaction of cyclic-1,3-diketones, aromatic aldehydes, and NMSM in catalyst-free under neat conditions at 110 °C. The significant features of this presented method are simple, clean reaction profile, good to excellent yields, reduced reaction time, avoidance of toxic catalyst and no need of column chromatographic separation. We believe that these prominent features will facilitate this protocol to find wide applications in the field of synthetic organic chemistry and medicinal chemistry.

Experimental

Synthetic grade chemicals and all solvents were obtained from Sigma-Aldrich, Merck, Otto Chemie and used for carrying out this work as received. Infrared spectra were recorded in potassium bromide pellets in reflection mode on a Perkin-Elmer 10.4.00 IR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectral analysis were carried out on Bruker (Avance-II 400 MHz), Varian-AS400 NMR, and Bruker BioSpin GmbH spectrometers using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 or $CDCl_3$ as a solvent. Melting points were measured on a Labtronics apparatus and are uncorrected. Crystal data were collected with a SuperNova, single source at offset/far, HyPix3000 diffractometer (CCD) using graphite monochromated MoKα radiation ($\lambda = 0.71073$ Å) at 296 K. High-Resolution Mass Spectra (ESI) were obtained on ORBITRAP mass analyzer (Thermo Scientific, Q Exactive) by the ESI method, while the elemental analysis of the compounds was performed on a Perkin-Elmer-2400 CHN/S analyzer and Thermo Scientific (FLASH 2000) analyzer.

General procedure for the preparation of functionalized 4H-chromen-5-one derivatives (4a–4u)

In a dried 5 mL round-bottomed flask was charged with a mixture of aromatic aldehydes (1.0 mmol), cyclic-1,3-diketones (1.0 mmol) and NMSM (1.0 mmol) at 110°C. The resulting mixture was stirred for 15–30 min and the reaction progress was checked by TLC. After completion of the reaction as indicated by TLC, the resulting precipitate was cooled and added 2 ml of ethanol and stirred for 5 min. Then, the precipitate was filtered and washed with cold ethanol. Recrystallization was performed from hot acetonitrile to give the pure products.

4-(4-chlorophenyl)-7,7-dimethyl-2-(methylamino)-3-nitro-7,8-dihydro-4H-chromen-5(6H)-one (4a). Isolated as light yellow solid; Yield: 90%; m.p: 240–242°C; IR (KBr, cm^{-1}) 3285, 3021, 2963, 1678, 1638, 1560, 1487, 1469, 1254, 1195, 1086, 812; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.91 (s, 3H), 1.05 (s, 3H), 2.09 (d, $J = 16$ Hz, 1H), 2.27 (d, $J = 16.4$ Hz, 1H), 2.62 (dd, $J = 16.8$ Hz, 2H), 3.09 (d, $J = 5.2$ Hz, 3H), 4.87 (s, 1H), 7.23 (d, $J = 8$ Hz, 2H), 7.29 (d, $J = 8$ Hz 2H), 10.25 (t, $J = 4.8$ Hz, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 26.6, 28.3, 31.9, 35.2, 39.5, 49.7, 108.1, 114.8, 127.8, 129.9, 131.0, 141.4, 157.2, 161.1, 195.3; Anal. Calcd (%) for $C_{18}H_{19}ClN_2O_4$: C, 59.59; H, 5.28; N, 7.72 Found: C, 59.64; H, 5.20; N, 7.80; EI-HRMS: Anal. Calcd for $[C_{18}H_{19}ClN_2O_4 + H^+]$: Cacld: 363.1106, Found: 363.1103.

Typical procedure for the synthesis of bis 4H-chromen-5-one derivatives (6a and 6b)

In a dried 10 mL round-bottomed flask was charged with a mixture of terephthalaldehyde (1.0 mmol), cyclic-1,3-diketones (2.0 mmol) and NMSM (2.0 mmol) at 110 °C. The resulting mixture was stirred for 15–20 min and after completion of the reaction as indicated by TLC, the resulting precipitate was cooled and added 3 ml of ethanol and stirred for 5 min. Then, the precipitate was filtered and washed with cold ethanol. Recrystallization was performed from hot acetonitrile to give the pure products.

4,4'-(1,4-phenylene)bis(7,7-dimethyl-2-(methylamino)-3-nitro-7,8-dihydro-4H-chromen-5(6H)-one) (6a). Isolated as white solid; Yield: 88%; m.p: 290–292 °C; IR (KBr, cm^{-1}): 3278, 3223, 3024, 2958, 1671, 1634, 1564, 1472, 1368, 1236, 1163, 1052; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.89 (s, 3H) 0.90 (s, 3H), 1.02 (s, 3H), 1.05 (s, 3H), 2.10–2.15 (m, 2H), 2.18–2.28 (m, 2H), 2.58–2.64 (m, 4H), 3.06 (d, $J = 5.0$ Hz, 3H), 3.09 (d, $J = 5.0$ Hz, 3H), 4.84 (s, 1H), 4.86 (s, 1H) 7.05 (s, 2H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.78 (d, $J = 8.0$ Hz, 1H), 10.18 (s, 1H), 10.19 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.0, 27.6, 28.5, 28.7, 28.8, 28.9, 31.1, 32.4, 32.5, 35.3, 35.3, 36.7, 50.2, 50.3, 108.3, 108.9, 115.1, 115.9, 127.9 129.4, 129.7, 135.3, 141.1, 149.6, 1577, 158.0, 161.8, 161.9, 195.8, 195.9; Anal. Calcd (%) for $C_{30}H_{34}N_4O_8$: C, 62.27; H, 5.92; N, 9.68. Found: C, 62.20; H, 5.87; N, 9.58; EI-HRMS: Anal. Calcd for $[C_{30}H_{34}N_4O_8 + H^+]$: Cacld: 579.2449, Found: 579.2452.

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References

[1] Cioc, R. C.; Ruijter, E.; Orru, R. V. A. Multicomponent Reactions: Advanced Tools for Sustainable Organic Synthesis. *Green Chem*. **2014**, 16, 2958–2975. DOI: 10.1039/C4GC00013G. (b) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*. Oxford University Press: New York, **1998**. (c) Dunn, P. J. The Importance of Green Chemistry in Process Research and Development. *Chem. Soc. Rev*. **2012**, 41, 1452–1461. DOI: 10.1039/c1cs15041c.

[2] (a) Kirchhoff, M. M. Promoting Green Engineering through Green Chemistry. *Environ. Sci. Technol*. **2003**, 37, 5349–5353. DOI: 10.1021/es0346072. (b) Horvath, I. T.; Anastas, P. T. *Innovations and Green Chemistry*. *Chem. Rev*. **2007**, 107, 2169–2173. DOI: 10.1021/cr078380v.

[3] (a) Singh, M. S.; Chowdhury, S. Recent Developments in Solvent-Free Multicomponent Reactions: A Perfect Synergy for Eco-Compatible Organic Synthesis. *RSC Adv*. **2012**, 2, 4547–4592. DOI: 10.1039/C2RA01056A. (b) Kumar, A.; Sharma, S. A. Grinding-Induced Catalyst- and Solvent-Free Synthesis of Highly Functionalized 1,4-Dihydropyridines via a Domino Multicomponent Reaction. *Green Chem*. **2011**, 13, 2017–2020. DOI: 10.1039/C1GC15223H.

[4] (a) Khan, M. M.; Khan, S.; Saigal, Iqbal, S. Recent Developments in Multicomponent Synthesis of Structurally Diversified Tetrahydropyridines. *RSC Adv*. **2016**, 6, 42045–42061. DOI: 10.1039/C6RA06767K. (b) Khan, M. M.; Yousuf, R.; Khan, S.; Shafiullah. Recent Advances in Multicomponent Reactions Involving Carbohydrates. *RSC Adv*. **2015**, 5, 57883–57905. DOI: 10.1039/C5RA08059B. (c) Zhu, J.; Bienayme, H. *Multicomponent Reactions*, 1st ed.; Wiley-VCH: Weinheim, Germany, **2005**.

[5] (a) Metzger, J. O. Solvent-Free Organic Syntheses. *Angew. Chem. Int. Ed. Engl*. **1998**, 37, 2975–2978. DOI: 10.1002/(SICI)1521-3773(19981116)37:21<2975::AID-ANIE2975>3.0.CO;2-A. (b) Varma, R. S. Solvent-Free Organic Syntheses. *Green Chem*. **1999**, 1, 43–55. DOI: 10.1039/A808223E. (c) Tanaka, K.; Toda, F. Solvent-Free Organic Synthesis. *Chem. Rev*. **2000**, 100, 1025–1074. DOI: 10.1021/cr940089p

[6] (a) Haji, M. Multicomponent Reactions: A Simple and Efficient Route to Heterocyclic Phosphonates. *Beilstein J Org Chem*. **2016**, 12, 1269–1301. DOI: 10.3762/bjoc.12.121. (b) Carlone, A.; Cabrera, S.; Marigo, M.; Jorgensen, K. A. A New Approach for an Organocatalytic Multicomponent Domino Asymmetric Reaction. *Angew. Chem. Int. Ed*. **2007**, 46, 1101–1104. DOI: 10.1021/ol9024293.

[7] (a) Hatakeyama, S.; Ochi, N.; Numata, H.; Takano, S. A new route to substituted 3-methoxycarbonyldihydropyrans; enantioselective synthesis of (–)-methyl elenolate. *J. Chem. Soc. Chem. Commun*. **1988**, 1202–1204. DOI:10.1039/C39880001202. (b) Armesto, D.; Horspool, W. M.; Martin, N.; Ramos, A.; Seaone, C. Synthesis of cyclobutenes by the novel photochemical ring contraction of 4-substituted 2-amino-3,5-dicyano-6-phenyl-4H-pyrans. *J. Org. Chem*. **1989**, 54, 3069–3072. DOI: 10.1021/jo00274a021.

[8] Rajasekhar, M.; Rao, K. U. M.; Sundar, C. S.; Reddy, N. B.; Nayak, S. K.; Reddy, C. S. Green Synthesis and Bioactivity of 2-Amino-4H-Chromen-4-yl-Phosphonates. *Chem. Pharm. Bull*. **2012**, 60, 854–858. DOI: 10.1248/cpb.c12-00160.

[9] Wu, J. Y. C.; Fong, W. F.; Zhang, J. X.; Leung, C. H.; Kwong, H. L.; Yang, M. S.; Li, D.; Cheung, H. Y. Reversal of Multidrug Resistance in Cancer Cells by Pyranocoumarins Isolated from Radix Peucedani. *Eur. J. Pharmacol*. **2003**, 473, 9–17. DOI: 10.1016/S0014-2999(03)01946-0.

[10] (a) Flavin, M. T.; Rizzo, J. D.; Khilevich, A.; Kucherenko, A.; Sheinkman, A. K.; Vilaychack, V.; Lin, L.; Chen, W.; Greenwood, E. M.; Pengsuparp, T.; et al. Synthesis, Chromatographic Resolution, and anti-Human Immunodeficiency Virus Activity of (+/−)-Calanolide a and Its Enantiomers. *J. Med. Chem.* **1996**, 39, 1303–1313. DOI: 10.1021/jm950797i. (b) Rueping, M.; Sugiono, E.; Merino, E. Asymmetric Organocatalysis: An Efficient Enantioselective Access to Benzopyranes and Chromenes. *Chem. Eur. J.* **2008**, 14, 6329–6332. DOI: 10.1002/chem.200800836.

[11] Morgan, L. R.; Jursic, B. S.; Hooper, C. L.; Neumann, D. M.; Thangaraj, K.; LeBlanc, B. Anticancer Activity for 4,4'-Dihydroxybenzophenone-2,4-Dinitrophenylhydrazone (A-007) Analogues and Their Abilities to Interact with Lymphoendothelial Cell Surface Markers. *Bioorg. Med. Chem. Lett.* **2002**, 12, 3407–3411. DOI: 10.1016/S0960-894X(02)00725-4.

[12] Rueping, M.; Sugiono, E.; Merino, E. Asymmetric Organocatalysis: an Efficient Enantioselective Access to Benzopyranes and Chromenes. *Chemistry*. **2008**, 14, 6329–6332. DOI: 10.1002/chem.200800836.

[13] Elisa, P. S.; Ana, E. B.; Ravelo, A. G.; Yapu, D. J.; Turba, A. G. Antiplasmodial Activity of Naphthoquinones Related to Lapachol and Beta-Lapachone. *Chem. Biodivers.* **2005**, 2, 264–274. DOI: 10.1002/cbdv.200590009.

[14] Baraldi, P. G.; Manfredini, S.; Simoni, D.; Tabrizi, M. A.; Balzarini, J.; Clercq, E. D. Geiparvarin Analogues. 3. Synthesis and Cytostatic Activity of 3(2H)-Furanone and 4,5-Dihydro-3(2H)-Furanone Congeners of Geiparvarin, Containing a Geraniol-like Fragment in the Side Chain. *J. Med. Chem.* **1992**, 35, 1877–1882. DOI: 10.1021/jm00088a025.

[15] Kumar, A.; Maurya, R. A.; Sharma, S. A.; Ahmad, P.; Singh, A. B.; Bhatia, G.; Srivastava, A. K. Pyranocoumarins: A New Class of anti-Hyperglycemic and anti-Dyslipidemic Agents. *Bioorg. Med. Chem. Lett.* **2009**, 19, 6447–6451. DOI: 10.1016/j.bmcl.2009.09.031.

[16] Moon, D. O.; Kim, K. C.; Jin, C. Y.; Han, M. H.; Park, C.; Lee, K. J.; Park, Y. M.; Choi, Y. H.; Kim, G. Y. Inhibitory Effects of Eicosapentaenoic Acid on Lipopolysaccharide-Induced Activation in BV2 Microglia. *Int. Immunopharmacol.* **2007**, 7, 222–229. DOI: 10.1016/j.intimp.2006.10.001.

[17] (a) Elinson, M. N.; Dorofeev, A. S.; Miloserdov, F. M.; Ilovaisky, A. I.; Feducovich, S. K.; Belyakov, P. A.; Nikishin, G. I. Catalysis of Salicylaldehydes and Two Different C-H Acids with Electricity: First Example of an Efficient Multicomponent Approach to the Design of Functionalized Medicinally Privileged 2-Amino-4H-Chromene Scaffold. *Adv. Synth. Catal.* **2008**, 350, 591–601. DOI: 10.1002/adsc.200700493. (b) Atwal, K. S. Mycocardial protection with the ATP-sensitive potassium channel openers. *Curr. Med. Chem.* **1996**, 3, 227–238.

[18] Adbel Aziz Hafez, E.; Abdel Aziz Hafez, E.; Hilmy Elnagdi, M.; Ghani Ali Elagamey, A.; Mohamed Abdel Aziz El-Taweel, F. Nitriles in Heterocyclic Synthesis: Novel Synthesis of Benzo[c]Coumarin and of Benzo[c]Pyrano[3,2-c]Quinoline Derivatives. *Heterocycles*. **1987**, 26, 903–907. DOI: 10.3987/R-1987-04-0903.

[19] (a) Kemnitzer, W.; Kasibhatla, S.; Jiang, S.; Zhang, H.; Zhao, J.; Jia, S.; Xu, L.; Crogan-Grundy, C.; Denis, R.; Barriault, N.; et al. Discovery of 4-Aryl-4H-Chromenes as a New Series of Apoptosis Inducers Using a Cell- and Caspase-Based High-Throughput Screening Assay. 2. Structure-Activity Relationships of the 7- and 5-, 6-, 8-Positions. *Bioorg. Med. Chem. Lett.* **2005**, 15, 4745–4751. DOI: 10.1016/j.bmcl.2005.07.066. (b) Tian, D.; Das, S. G.; Doshi, J. M.; Peng, J.; Lin, J.; Xing, J. C. sHA14-1, a Stable and ROS-Free Antagonist against Anti-Apoptotic Bcl-2 Proteins, Bypasses Drug Resistances and Synergizes Cancer Therapies in Human Leukaemia Cell. *Cancer Lett.* **2008**, 259, 198–208. DOI: 10.1016/j.canlet.2007.10.012.

[20] Smith, C. W.; Bailey, J. M.; Billingham, M. E. J.; Chandrasekhar, S.; Dell, C. P.; Harvey, A. K.; Hicks, C. K.; Kingston, A. E.; Wishart, G. N. The anti-Rheumatic Potential of a Series of 2,4-di-Substituted-4H-Naphtho[1,2-b]Pyran-3-Carbonitriles. *Bioorg. Med. Chem.* **1995**, 5, 2783–2788. DOI: 10.1016/0960-894X(95)00487-E.

[21] Kumar, D.; Reddy, V. B.; Sharad, S.; Dube, U.; Kapur, S. A Facile One-Pot Green Synthesis and Antibacterial Activity of 2-Amino-4H-Pyrans and 2-Amino-5-Oxo-5,6,7,8-

Tetrahydro-4H-Chromenes. *Eur. J. Med. Chem.* **2009**, 44, 3805–3809. DOI: 10.1016/j.ejmech.2009.04.017.

[22] (a) Amr, A.-G. E.; Mohamed, A. M.; Mohamed, S. F.; Abdel-Hafez, N. A.; Hammam, A. E.-F. G. Anticancer Activities of Some Newly Synthesized Pyridine, Pyrane, and Pyrimidine Derivatives. *Bioorg. Med. Chem.* **2006**, 14, 5481–5488. DOI: 10.1016/j.bmc.2006.04.045. (b) Abdelrazeka, F. M.; Metza, P.; Farrag, E. K. Synthesis and Molluscicidal Activity of 5-oxo-5,6,7,8-Tetrahydro-4H-Chromene Derivatives. *Arch. Pharm. Pharm. Med. Chem.* **2004**, 337, 482–485. DOI: 10.1002/ardp.200400881.

[23] (a) Khan, A. T.; Lal, M.; Ali, S.; Khan, M. M. One-Pot Three-Component Reaction for the Synthesis of Pyran Annulated Heterocyclic Compounds Using DMAP as a Catalyst. *Tetrahedron lett.*, **2011**, 52, 5327–5332. DOI: 10.1016/j.tetlet.2011.08.019. (b) Shirini, F.; Daneshvar, N. Introduction of Taurine (2-Aminoethanesulfonic Acid) as a Green Bio-Organic Catalyst for the Promotion of Organic Reactions under Green Conditions. *RSC Adv.*, **2016**, 6, 110190–110205. DOI: 10.1039/C6RA15432H. (c) Maleki, B.; Nasiri, N.; Tayebee, R.; Khojastehnezhad, A.; Ali, H.; Akhlaghi. Green Synthesis of Tetrahydrobenzo[b]Pyrans, Pyrano[2,3-c]Pyrazoles and Spiro[Indoline-3,4,-Pyrano[2,3-c]Pyrazoles Catalyzed by Nano-Structured Diphosphate in Water. *RSC Adv.*, **2016**, 6, 79128–79134. DOI: 10.1039/C6RA15800E.

[24] (a) Kanchithalaivan, S.; Sivakumar, S.; Kumar, R. R.; Elumalai, P.; Ahmed; Q. N. Padala, A. K. K. Four-Component Domino Strategy for the Combinatorial Synthesis of Novel 1,4-Dihydropyrano[2,3-c]Pyrazol-6-Amines. *ACS Comb. Sci.*, **2013**, 15, 631–638. DOI: 10.1021/co4000997. (b) Gunasekaran, P.; Prasanna, P.; Perumal, S. L-Proline-Catalyzed Three-Component Domino Reactions for the Synthesis of Highly Functionalized Pyrazolo[3,4-b]Pyridines. *Tetrahedron Lett.*, **2014**, 55, 329–332. DOI: 10.1016/j.tetlet.2013.11.016. (c) Rao; H. S. P.; Parthiban, A. One-Pot Pseudo Three-Component Reaction of nitroketene-N,S-Acetals and Aldehydes for Synthesis of Highly Functionalized Hexa-Substituted 1,4-Dihydropyridines. *Org. Biomol. Chem.*, **2014**, 12, 6223–6238. DOI: 10.1039/C4OB00628C. (d) Gunasekaran, P.; Prasanna, P.; Perumal, S.; Almansour, A. I. ZnCl2-Catalyzed Three-Component Domino Reactions for the Synthesis of Pyrano[3,2-c]Quinolin-5(6H)-Ones. *Tetrahedron Lett.*, **2013**, 54, 3248–3252. DOI: 10.1016/j.tetlet.2013.04.022. (e) Reddy, M. V.; Reddy, G. D.; Kim; J. T.; Jeong, Y. T. An Efficient and Green Synthesis of Highly Functionalized N -Methyl-2-Nitro-Aryl-1 H -Benzo[f]Chromen-3-Amine Derivatives under Catalyst-Free Conditions. *Tetrahedron*, **2016**, *72*, 6484–6491. DOI: 10.3390/molecules23010235. (f) Mao, J.; Wang, J.; Zhang, W.; Li, Z.; Zhu, J.; Guo, C. Convenient multicomponent reaction synthesis of novel pyrano[4,3-b]pyran derivatives via a domino reaction under microwave irradiation. *Arkivoc*, **2016**, (iii), 171–186. DOI: 10.3998/ark.5550190.p009.398. (g) Sivakumar, S.; Kanchithalaivan, S.; Kumar, R. R. A One-Pot Three-Component Domino Protocol for the Synthesis of Penta-Substituted 4H-Pyrans. *RSC Adv.*, **2013**, 3, 13357–13364. DOI: 10.1039/C3RA41510D. (h) Poomathi, N.; Kamalraja, J.; Mayakrishnan, S.; Muralidharan; D.; and Perumal, P. T. Indium Trichloride Catalysed Domino Reactions of Isatin: A Facile Access to the Synthesis of Spiro(Indoline-3,4,-Pyrano[2,3-c]Pyrazol)-2-One Derivatives. *Synlett.* **2014**, 25, 0708–0712. DOI: 10.1055/s-0033-1340666. (i) Balachandra, B.; Shanmugam, S.; Muneewarahand, T.; Ramakritinan, M. Iodine Catalyzed One-Pot Synthesis of Highly Substituted N-Methyl Pyrroles via [3 + 2] Annulation and Their In Vitro Evaluation as Antibacterial Agents. *RSC Adv.*, **2015**, 5, 64781–64789. DOI: 10.1039/C5RA11094G. (j) Jadhav, A. M.; Krishnammagari, S. K.; Kim, J. T.; Jeong, Y. T. A Highly Efficient and Recyclable Silica-Supported Tungstic Acid (STA) Catalyst for the Synthesis of Pyrano[3,2- c]Chromen-5-Ones under Solvent Free Conditions. *Tetrahedron*, **2017**, 73, 5163–5169. DOI: 10.1016/j.tet.2017.07.008. (k) Jadhav, A. M.; Kim, Y. I.; Lim, K. T.; Jeong, Y. T. Application of p-TSA in the One Pot Synthesis of N -Methyl-3-Nitro-Aryl-Benzo[4,5]Imidazo[1,2-a]Pyrimidin-2-Amine. *Tetrahedron*, **2018**, 59, 554–557. DOI: 10.1002/cjoc.200890376. (l) Rahimi, F.; Hosseini, H.; Bayat, M.; Jeong, Y. T. A One-Pot Three-Component Approach to Synthesis of Novel

Dihydroxyoxoindeno[1,2-b]Pyrrole Derivatives. *Tetrahedron*, **2018**, 59, 818–822. DOI: /10.1016/j.tetlet.2018.01.050.

[25] (a) Kamalraja, J.; Muralidharan; D.; Perumal, P. T. An Efficient, One-Pot Regioselective Synthesis of Highly Functionalized Chromen-5-Ones and Pyrano[3,2-c]Chromen-5-Ones via a Tandem Knoevenagel–Michael–Cyclization Sequence. *Synlett*., **2012**, 23, 2894–2898. DOI: 10.1055/s-0032-1317543. (b) Shinde, V. V.; Jeong, D.; Cho, E.; Jung, S. 6,6,-Thiobis(Methylene)-β-Cyclodextrin Dimer as a Dimeric Host and Reusable Promoter for Synthesis of Chromenones in Water. *Tetrahedron*, **2018**, 74, 194–198. DOI: 10.1016/j.tet.2017.11.065.

[26] (a) Khan, M. M.; Saigal; Khan, S.; Shareef, S.; Hussain, S. *ChemistrySelect*, **2018**, *3*, 2261–2266. A Facile and Green Approach for One-Pot Synthesis of Functionalized Chromeno[3, 4-b]quinolines and Spiro Chromeno[3, 4-b]quinolines by Using Molecular Iodine as a Catalyst. DOI: 10.1002/slct.201702810. (b) Khan, M. M.; Khan, S.; Saigal; Sahoo, S. C. Organocatalyzed Synthesis and Antifungal Activity of Fully Substituted 1, 4-Dihydropyridines. *ChemistrySelect*, **2018**, 3, 1371–1380. DOI: 10.1002/slct.201800709. (c) Khan, M. M.; Khan, S.; Iqbal, S.; Saigal; Yousuf, R. *New J. Chem*., **2016**, *40*, 7504–7512. Synthesis of Functionalized Dihydro-2-Oxypyrroles and Tetrahydropyridines Using 2,6-Pyridinedicarboxylic Acid as an Efficient and Mild Organocatalyst. *New J. Chem*. **2016**, 40, 7504–7512. DOI: 10.1039/C6NJ01170E.