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L-Proline catalyzed multicomponent one-pot synthesis of *gem*-diheteroarylmethane derivatives using facile grinding operation under solvent-free conditions at room temperature

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An efficient and straightforward L-proline catalyzed one-pot synthesis of a series of biologically relevant *gem*-(β-dicarbonyl)arylmethanes has been developed *via* a three-component reaction between indoles, aldehydes and C–H activated acids by grinding them together under solvent-free conditions at room temperature. Mild reaction conditions, high atom-economy, good yields, and eco-friendliness are some of the salient features of the present protocol.

Introduction

Both 1,1-dihomoaryl- and 1,1-diheteroaryl-methane scaffolds, particularly involving indolyl and coumarolyl moieties represent "privileged" structural motifs in pharmaceutical drugs and numerous potentially bioactive natural products.[1–5] Fig. 1 offers a glimpse of such naturally occurring pharmaceutically potent molecules: 3,3′-diindolylmethane (DIM; **I**; anticancer),[6,7] 1,1-bis(3′-indolyl)ethane (BIE; **II**; antibacterial),[8] 5-bromo-1-ethyl-3-((4-fluorophenyl)(1*H*-imidazol-1-yl) methyl)-1*H*-indole (**III**; aromatase inhibitor),[9] arzanol (**IV**; anti-inflammatory, antibiotic, anti-oxidant),[10] carbochromen (**V**; a potent drug for estimation of coronary dilatory capacity),[11] warfarin (**VI**; anticoagulant normally used in the prevention of thrombosis and thromboembolism)[12] and bromadiolone (**VII**; anticoagulant functioning as a vitamin K antagonist).[13] In spite of their natural prevalence and wide range of biological activities, *gem*-diheteroarylmethanes have indeed gained little attention to the synthetic chemists; one such method is reported earlier for the synthesis of *gem*-(β-dicarbonyl)arylmethanes by Minassi and co-workers.[14] However, this method suffers from using chlorinated solvent, long reaction time (24–72 h) and poor yields in many occasions.[14] Hence, the development of a simple and high-yielding environmentally benign protocol for the one-pot synthesis of such biologically relevant *gem*-(β-dicarbonyl)arylmethane scaffolds is of great challenge. Inspired by successful completion of one of our recent works in developing an efficient method to synthesize 3-aminoalkylated indoles,[15] we thus have been motivated to explore our vision for a more facile and environmentally benign route to the title compounds. As part of our continuing efforts to develop green synthetic methodologies for useful organic transformations,[15,16] herein we wish to report a convenient, clean and highly efficient protocol for the synthesis of *gem*-(β-dicarbonyl)arylmethanes *via* multicomponent reaction (MCR) simply by grinding the mixture of indoles, C–H activated acids (4-hydroxycoumarin, 4-hydroxy-6-methyl-2*H*-pyran-2-one, dimedone, *N*,*N*-dimethylbarbituric acid, Meldrum's acid) and aldehydes in the absence of solvent under L-proline catalysis at room temperature (Scheme 1).

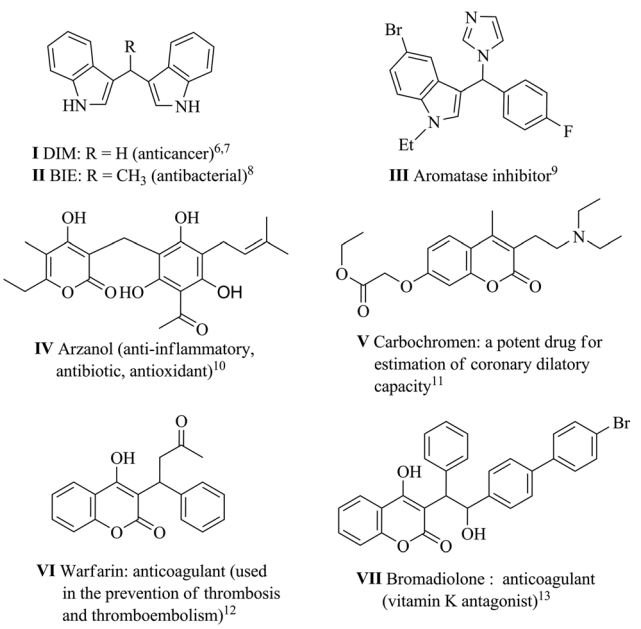

Fig. 1 Representative examples of few bioactive *gem*-dihomoaryl- and diheteroarylmethanes.[6–13]

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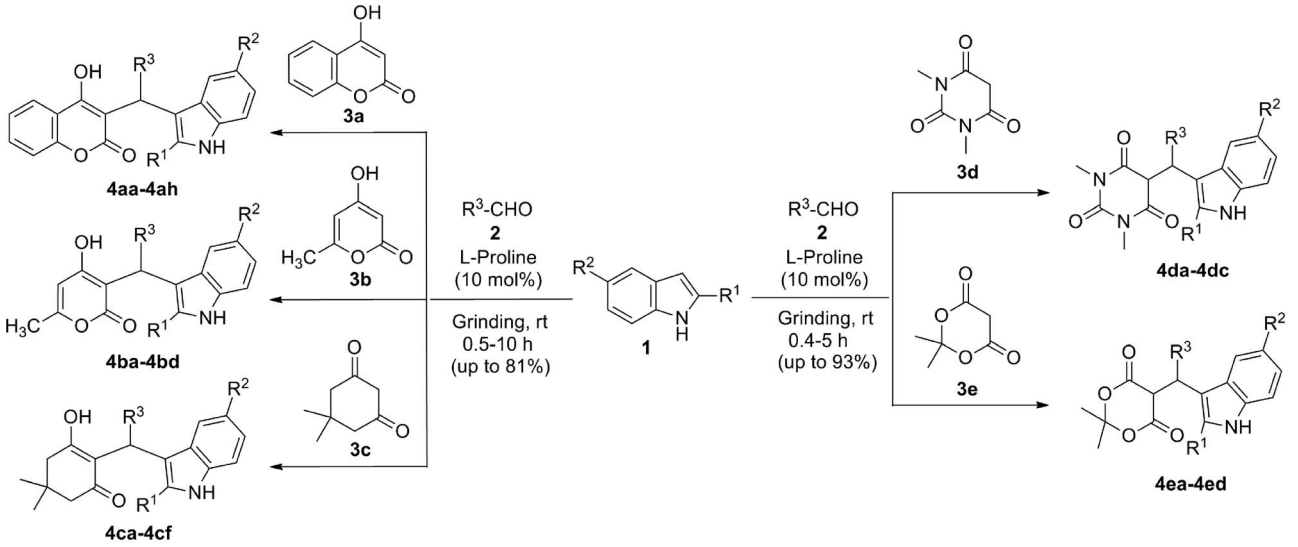


Scheme 1 L-Proline catalyzed three-component one-pot synthesis of *gem*-(β-dicarbonyl)arylmethanes.

A striking advantage of using amino acids as organocatalysts is their amphoteric nature, possessing both amine and carboxylic acid moieties—the amino group could catalyze the reaction *via* electrophilic imine formation and the carboxylic group might stabilize the charge generated on the nitrogen.[17] Furthermore, MCR technique is now-a-days a well accepted strategy to the synthetic chemists at large for the construction of novel and complex molecular structures due to its several benefits including shorter reaction times, high atom-economy, lower costs, and avoidance of time consuming expensive purification processes.[18,19]

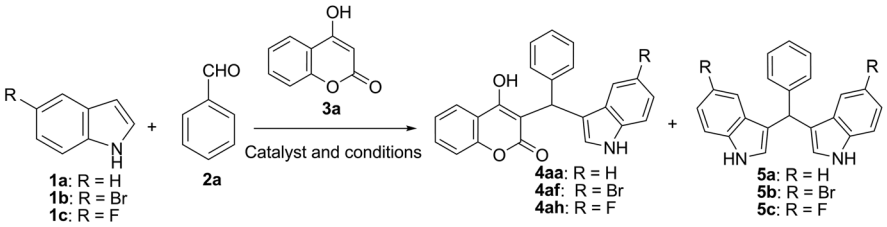
In addition, implementation of several transformations in a single manipulation in MCR strategy is highly compatible with the goals of sustainable and "green" chemistry.[20,21] With increasing public concern over environmental degradation, the use of environmentally benign solvents like water[22] and solvent-free reactions[23] offers very powerful green chemical protocols from both the economic and synthetic point of view with several advantages like reduced pollution, lower cost, and simplicity in processing, which are beneficial to the industry as well as to the environment. In recent years, mechanochemistry, *i.e.* reactions conducted by grinding solid reactants together, has attracted much attention because it allows promotion of reactions under solvent-free conditions.[24] Mechanochemical synthesis affords many advantages, such as greater efficiency with regard to time, materials, and energy usage, as well as the discovery of new or improved reactivity and products, as an alternative approach to synthesis.[24a]

Results and discussion

Preliminary studies were mainly focused on optimization of the reaction conditions, and for this purpose a series of trial reactions of indole (**1a**), 5-bromoindole (**1b**) and 5-fluoroindole (**1c**) with benzaldehyde (**2a**) and 4-hydroxycoumarin (**3a**) were performed in 1 mmol scale in the absence and presence of different catalysts at room temperature (Table 1), and also checked the effects of varying amounts of catalyst-loading and solvents (Table 2). It was much astonishing to observe that the reaction pathway is directed towards the formation of bis-indole derivatives **5a–5c** rather than the desired products **4aa**, **4af** and **4ah** in presence of all the Lewis acid catalysts and the ionic liquid except sodium formate and L-proline, whereas the latter exhibited better performance. It was also observed that although simple indole **1a** underwent the reaction affording the desired product **4aa** with moderately good yield of 63% under catalyst- and solvent-free conditions, the substituted indoles **1b** and **1c** gave the corresponding desired product **4af** and **4ah** with poor yields (36% and 31%, respectively) under the same reaction conditions (Table 1; entry 11). To our delight that use of catalytic amount of L-proline was sufficient enough to enhance the reaction rate remarkably for these reactions (Table 1; entry 9). A variety of solvent systems and proportion of aldehydes were also screened for this particular reaction using L-proline as catalyst (Table 2); however, the best result was obtained when the reaction was carried out using 1.2 equivalent of aldehyde, by grinding the reactants together under solvent-free conditions (Table 2; entry 3).

To explore the scope and generality of the present MCR protocol for the synthesis of *gem*-(β-dicarbonyl)arylmethanes under the optimized conditions, a variety of aromatic aldehydes (**2**) containing electron donating or electron withdrawing substituents in the aromatic ring such as –Me, $-OCH_2O-$, –F, –Cl, and $-NO_2$ were reacted with 4-hydroxycoumarin (**3a**) and substituted indoles **1** (1*H*-indole, 5-bromo-1*H*-indole, 5-fluoro-1*H*-indole, and 2-methyl-1*H*-indole) to furnish diverse *gem*-(β-dicarbonyl)arylmethanes; butyraldehyde, an aliphatic aldehyde, was also found to undergo the reaction giving rise to the desired products **4ad** and **4bd** (Table 3) in 65% and 44% yields, respectively.

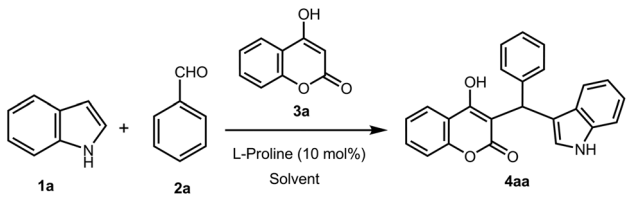
Table 1 Screening of catalyst for one-pot synthesis of *gem*-(β-dicarbonyl)arylmethanes[a]



Entry	Catalyst	Loading (mol%)	Indole (R = H) Time (h)	% Yield[b] (**4aa**)	% Yield[b] (**5a**)	5-Bromoindole (R = Br) Time (h)	% Yield[b] (**4af**)	% Yield[b] (**5b**)	5-Fluoroindole (R = F) Time (h)	% Yield[b] (**4ah**)	% Yield[b] (**5c**)
1	Anhyd·$AlCl_3$	10	0.25	20	67	2	Trace	74	1	Trace	77
2	$ZrOCl_2 \cdot 8H_2O$	10	0.33	27	60	2	Trace	72		nd[c]	
3	$Bi(NO_3)_3 \cdot 5H_2O$	10	0.33	25	58	2	Trace	69		nd[c]	
4	[HMIM][HSO_4] (IL)	10	0.33	30	59	2	Trace	71	1.5	Trace	63
5	Sodium formate	5	1	58	Trace	4	38	21		nd[c]	
6	Sodium formate	10	1	61	Trace	4	38	23	2.5	41	29
7	Sodium formate	20	1	61	Trace	4	40	23	2.5	45	31
8	L-Proline	5	1	68	Trace	4	45	20		nd[c]	
9	L-Proline	10	1	75	Trace	4	53	24	2	61	20
10	L-Proline	20	1	78	Trace	4	53	24	2	62	20
11	No catalyst	–	1	63	Trace	8	36	51	5	31	57

[a] Experimental conditions: 4-hydroxycoumarin (**3a**; 1 mmol), benzaldehyde (**2a**; 1.2 mmol), indole (**1a**; 1 mmol)/5-bromoindole (**1b**; 1 mmol)/5-fluoroindole (**1c**; 1 mmol) and catalyst on grinding under solvent-free conditions at room temperature. [b] Isolated yield. [c] Not done.

Table 2 Screening of the reactants-ratio and checking of solvent system for one-pot synthesis of *gem*-(β-dicarbonyl)arylmethanes[a]



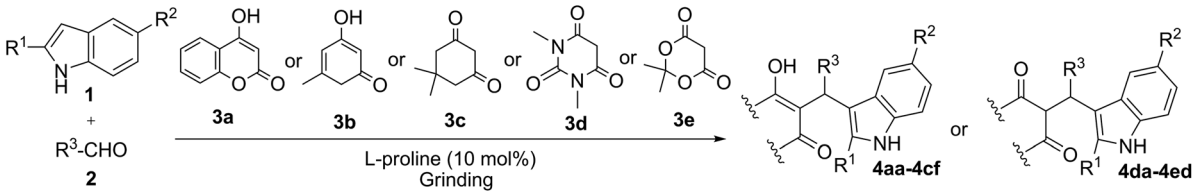
Entry	Condition	Reactants (in equiv.) (**1a** : **2a** : **3a**)	Time (h)	% Yield[b]
1	Grinding	1 : 1 : 1	1	67
2	Grinding	1 : 1.1 : 1	1	69
3	Grinding	1 : 1.2 : 1	1	75
4	Grinding	1 : 1.3 : 1	1	75
5	Stirred in EtOH	1 : 1.2 : 1	24	39
6	Stirred in H_2O	1 : 1.2 : 1	24	Trace
7	Stirred in THF	1 : 1.2 : 1	24	Trace

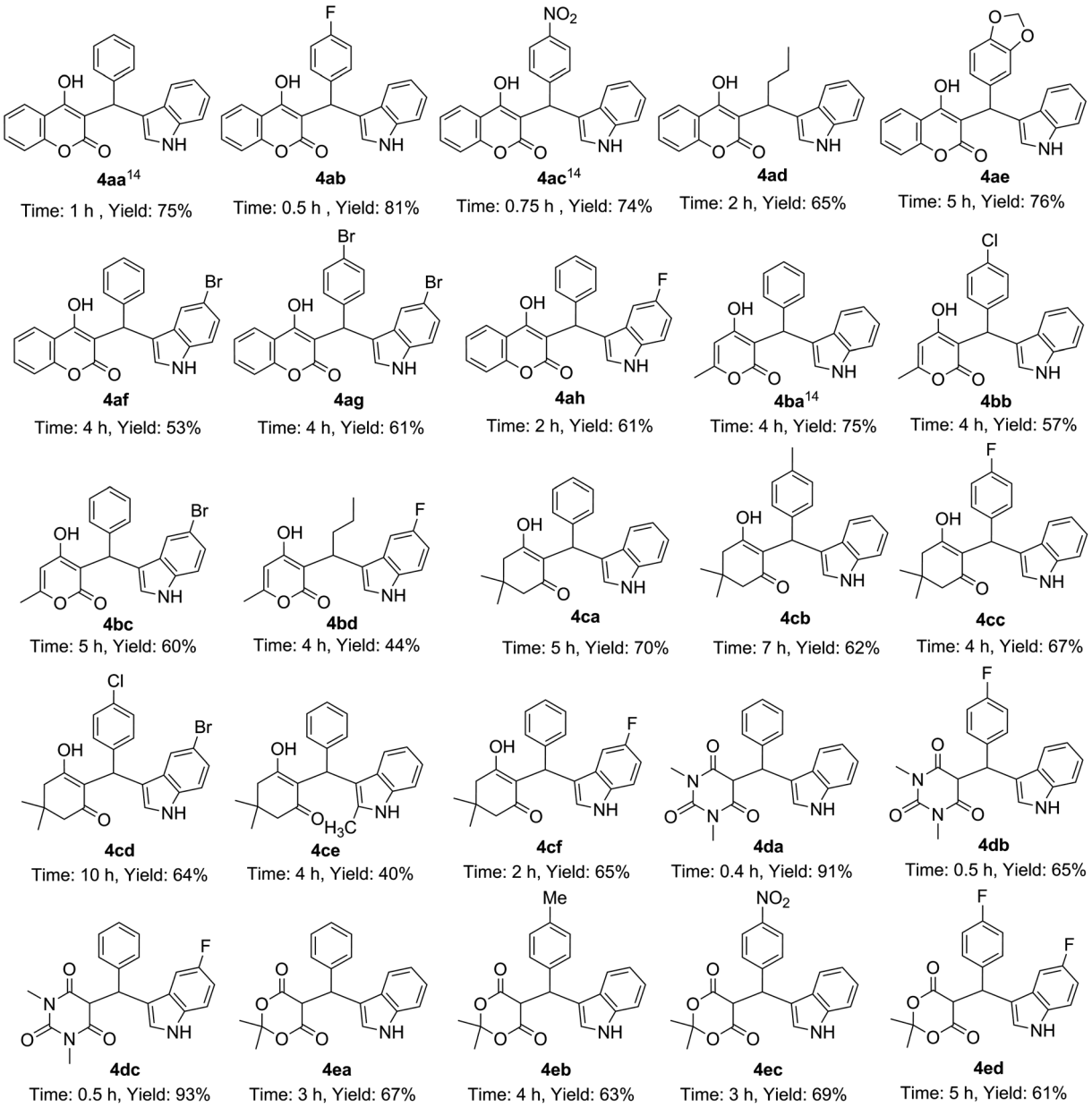
[a] Experimental conditions: indole (**1a**), benzaldehyde (**2a**), 4-hydroxycoumarin (**3a**), and L-proline (10 mol%) under various conditions at room temperature. [b] Isolated yields.

The present protocol was successfully extended for the other four C–H activated acids *viz.* 4-hydroxy-6-methyl-2*H*-pyran-2-one (**3b**), dimedone (**3c**), *N*,*N*-dimethylbarbituric acid (**3d**), and Meldrum's acid (**3e**) for which the desired *gem*-(β-dicarbonyl)-arylmethanes (**4ba–4ed**; Table 3) were obtained in moderate to good yields. In case of 2-methylindole, the isolated yield of the product **4ce** is only 40%; it is supposed that the introduction of the electron-donating methyl group into the indole nucleus enhances its reactivity prior to the C–H activated acids leading to the rapid formation of bis-indole derivative. The overall results are summarized in Table 3. In this connection it is to be mentioned that the products **4** are non-racemic in nature as expected from the use of L-proline as a catalyst. All the entries were found to exhibit optical rotations with a varying degree of $[\alpha]_D$; however, enantiomeric ratio (er) of the isomers for the respective products **4** are not reported in this present communication. It is also to note that the products **4da–4dc** and **4ea–4ed** arising out of the reaction of *N*,*N*-dimethylbarbituric acid (**3d**) and Meldrum's acid (**3e**), respectively are expected to be of diastereoisomeric mixtures (*syn* and *anti* with respect to the α-H), and this has been observed in case of **4ea–4ed**, whereas **4da–4dc** were obtained with complete *syn*-diastereoselectivity.

We suggest herein a plausible mechanism for the L-proline catalyzed synthesis of the *gem*-(β-dicarbonyl)arylmethanes **4** (Scheme 2). It is well-reported in literature that L-proline can effectively participate in the formation of iminium salt[17] and also can act as an efficient catalyst both in Mannich[17b,25] and Michael[17a,b,26] reactions. Thus the initially formed iminium salt (**5**) arising out of the reaction between aldehyde (**2**) and L-proline, undergoes Mannich reaction with C–H

Table 3 L-Proline catalyzed one-pot synthesis of *gem*-(β-dicarbonyl)arylmethanes *via* three-component reaction[a]



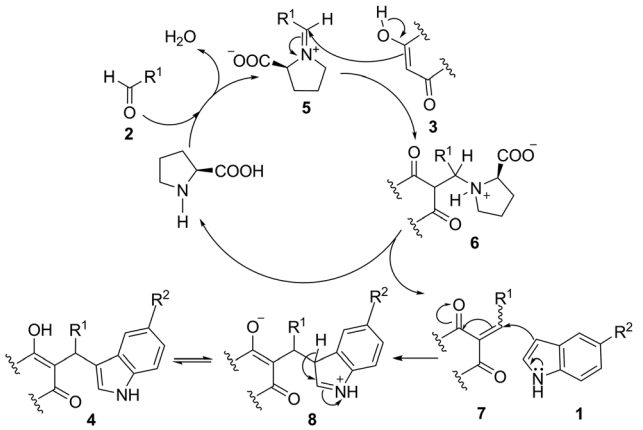


[a] Experimental conditions: C–H activated acid (1 mmol), aldehyde (1.2 mmol), indole (1 mmol) and L-proline (10 mol%) by grinding under solvent free conditions at room temperature.

activated acid (**3**) to generate intermediate **7** which immediately takes part in Michael addition with the indole moiety (**1**) affording the desired product **4**. L-Proline releases out for the next cycle.

Conclusions

In conclusion, we have developed a green and efficient organocatalysed multicomponent reaction of C–H activated acids,



Scheme 2 Plausible mechanism for the L-proline catalyzed multi-component synthesis of the *gem*-(β-dicarbonyl)arylmethanes (**4**).

aldehydes, and indoles for the synthesis of a series of biologically interesting *gem*-(β-dicarbonyl)arylmethane derivatives under solvent-free conditions at room temperature. L-Proline is a very useful and environmentally friendly organo-catalyst to validate this useful transformation in a facile manner. In addition to other notable outcomes such as mild and solvent-free reaction conditions, operational simplicity and good yields, the major advantage of our present protocol is an improved conditions for the synthesis of *gem*-(β-dicarbonyl)-arylmethane derivatives instead of the formation of usual bis-indoles. It is to be mentioned herein that all the synthesized entries are non-racemic in nature; the effect of L-proline on imparting the degree of stereoselectivity of this reaction is under study.

Experimental

General

Infrared spectra were recorded using a Shimadzu (FT-IR 8400S) FT-IR spectrophotometer using KBr disc. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained at 400 and 100 MHz, respectively, using Bruker DRX spectrometer (Bruker Instruments, Billerica, MA, USA) and DMSO-d_6 as the solvent. Mass spectra (TOF-MS) were measured on a QtofMicro™ mass spectrometer. Elemental analyses were performed with an Elementar Vario EL III Carlo Erba 1108 micro-analyzer instrument (Carlo Erba Reagenti SpA, Rodano, Italy), and optical rotation was measured on a polarimeter manufactured by Bellingham Stanley Ltd. (Model ADP410). Melting points were recorded on a Chemiline CL725 melting point apparatus and are uncorrected. Column chromatography was carried out over silica gel (Merck 60–120 mesh) and TLC was performed using silica gel 60 F_{254} (Merck) plates.

General procedure for preparation of *gem*-diheteroaryl methane derivatives (4aa–4ed)

In an oven-dried watch-glass, C–H activated acid (4-hydroxycoumarine **3a** or 4-hydroxy-6-methyl-2*H*-pyran-2-one **3b** or dimedone **3c** or *N*,*N*-dimethylbarbituric acid **3d** or Meldrum's acid **3e**; 1 mmol), aldehyde (**2**; 1.2 mmol), indole (**1**; 1 mmol), and L-proline (10 mol%) were taken together, and instantly started to grind the mixture by a spatula. After few minutes of scratching/grinding, when the solid reaction mixture liquefied followed by semi-solidification, it was left for stipulated time (Table 3) with occasional grinding till it solidified again. After completion of the reaction (as monitored by TLC), the solid reaction mixture was subjected to column chromatography using silica gel (60–120 mesh) and petrol ether-ethyl acetate mixture to furnish the pure products (**4aa–4ed**), characterized by conventional spectroscopic methods and elemental analyses. It was also possible to isolate pure products of **4aa–4af** and **4da–4dc** without using column chromatographic resolution just by washing the crude products in ethanol—however, with ~5–7% lower yields in comparison to the generalized method, possibly due to partial solubility of these compounds in ethanol.

Characterization data of selected entries

3-((4-Fluorophenyl)(1*H*-indol-3-yl)methyl)-4-hydroxy-2*H*-chromen-2-one (4ab). Pinkish white solid (0.312 g, 81%); mp 195–197 °C; $[\alpha]_D^{25}$ = +31.5 (acetone, *c* 1.0); e.r. could not be evaluated at this time. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.11 (s, 1H, –CH), 6.92 (t, J = 7.2 Hz, 1H, ArH), 7.06 (t, 3H, J = 8.8, 8.4 Hz, ArH), 7.13 (s, 1H, ArH), 7.36 (t, J = 7.6, 10.4 Hz, 6H, ArH), 7.60 (t, J = 7.6, 7.2 Hz, 1H, ArH), 8.04 (d, J = 7.6 Hz, 1H, ArH), 10.95 (s, 1H, –NH), 11.69 (s, 1H, –OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 36.94, 108.82, 111.96, 114.52, 114.66, 114.87, 116.66, 116.71, 118.83, 118.91, 121.33, 123.95, 124.26, 124.74, 127.57, 130.38, 130.46, 132.38, 136.50, 139.24, 152.66, 159.79, 160.81, 162.20. IR ν_{max} (KBr): 3437, 3317, 3284, 3095, 3043, 2901, 2850, 1687, 1612, 1534, 1497, 1336, 1159, 1099, 1036, 945, 854, 758 cm^{-1}. TOF-MS: calcd for $C_{24}H_{16}FNO_3Na$ [M + Na]$^+$: 408.1012; found: 408.1015. Anal. calcd for $C_{24}H_{16}FNO_3$: C, 74.80; H, 4.18; N, 3.63; found: C, 74.82; H, 4.16; N, 3.66.

3-(1-(1*H*-Indol-3-yl)butyl)-4-hydroxy-2*H*-chromen-2-one (4ad). White solid (0.217 g, 65%); mp 139–140 °C; $[\alpha]_D^{25}$ = +42.3 (acetone, *c* 1.0); e.r. could not be evaluated at this time. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.95 (s, 3H, –CH_3), 1.35 (s, 2H, –CH_2), 2.09 (br s, 1H, –CH), 2.40 (br s, 1H, –CH) 4.73 (s, 1H, –CH), 6.90 (s, 1H, ArH), 7.00 (s, 1H, ArH), 7.30 (d, J = 4 Hz, 4H, ArH), 7.53 (d, J = 5.6 Hz, 2H, ArH), 8.03 (d, J = 5.2 Hz, 1H, ArH), 10.79 (s, 1H, –NH), 11.40 (br s, 1H, –OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.14, 20.87, 31.21, 33.40, 108.27, 111.29, 116.03, 116.16, 116.21, 118.08, 118.31, 120.56, 122.87, 123.28, 123.66, 127.11, 131.50, 135.82, 152.01, 159.65, 161.35. IR ν_{max} (KBr): 3412, 3217, 3176, 3149, 2955, 2930, 2858, 1677, 1612, 1564, 1497, 1448, 1340, 1207, 1157, 1105, 1040, 879, 752 cm^{-1}. TOF-MS: calcd for $C_{21}H_{19}NO_3Na$ [M + Na]$^+$: 356.1263; found: 356.1269. Anal. calcd for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20; found: C, 75.69; H, 5.73; N, 4.21.

3-(Benzo[*d*][1,3]dioxol-5-yl(1*H*-indol-3-yl)methyl)-4-hydroxy-2*H*-chromen-2-one (4ae). Brownish white solid (0.313 g, 76%); mp 242–244 °C; $[\alpha]_D^{25}$ = −33.2 (acetone, *c* 1.0); e.r. could not be evaluated at this time. ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.95 (s, 2H, –CH_2), 6.26 (s, 1H, –CH), 6.62 (d, J = 8 Hz, 1H, ArH), 6.71 (s, 1H, ArH), 6.76 (d, J = 8.4, 1H, ArH), 7.31–7.37 (m, 5H, ArH), 7.59 (t, J = 7.2, 8 Hz, 2H, ArH), 7.91 (d, J = 7.6 Hz, 2H, ArH), 10.81

(s {weak}, 1H, –NH), 10.89 (s {weak}, 1H, –OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.79, 100.68, 104.33, 107.50, 107.72, 115.93 (2C), 118.00, 119.49 (2C), 123.68 (2C), 123.89 (2C), 128.66, 131.57, 131.83 (2C), 133.91, 145.16, 147.27, 152.23 (2C), 164.70, 165.29. IR ν_{max} (KBr): 3409, 3295, 3119, 3084, 3049, 2893, 1655, 1636, 1607, 1560, 1491, 1232, 1184, 1040, 933, 764 cm^{-1}. TOF-MS: calcd for $C_{25}H_{17}NO_5Na$ [M + Na]$^+$: 434.1004; found: 434.1001. Anal. calcd for $C_{25}H_{17}NO_5$: C, 72.99; H, 4.16; N, 3.40; found: C, 72.95; H, 4.16; N, 3.39.

3-((5-Bromo-1*H*-indol-3-yl)(phenyl)methyl)-4-hydroxy-2*H*-chromen-2-one (4af). Brownish white solid (0.237 g, 53%); mp 138–140 °C; $[\alpha]_D^{25}$ = +12.8 (acetone, *c* 1.0); e.r. could not be evaluated at this time. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.09 (s, 1H, –CH), 7.15–7.19 (m, 2H, ArH), 7.23–7.29 (m, 5H, ArH), 7.35–7.38 (m, 3H, ArH), 7.48 (d, J = 1.6 Hz, 1H, ArH), 7.59–7.63 (m, 1H, ArH), 8.05 (dd, J = 1.6, 0.8, 8.2 Hz, 1H, ArH), 11.17 (d, J = 1.2 Hz, 1H, –NH), 11.75 (br s, 1H, –OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 37.18, 108.63, 111.45, 114.00, 114.38, 116.67, 121.16, 123.37, 123.69, 123.99, 124.29, 126.23, 126.68, 128.24 (2C), 128.46 (2C), 129.59, 132.41, 135.08, 142.80, 152.65, 160.82, 162.15. IR ν_{max} (KBr): 3398, 3265, 3242, 3074, 3022, 2895, 2860, 1687, 1616, 1566, 1489, 1452, 1415, 1326, 1248, 1169, 1105, 1041, 939, 887, 758 cm^{-1}. TOF-MS: calcd for $C_{24}H_{16}BrNO_3Na$ [M + Na]$^+$: 468.0211; found: 468.0218. Anal. calcd for $C_{24}H_{16}BrNO_3$: C, 64.59; H, 3.61; N, 3.14; found: C, 64.63; H, 3.60; N, 3.17.

3-((5-Fluoro-1*H*-indol-3-yl)(phenyl)methyl)-4-hydroxy-2*H*-chromen-2-one (4ah). Reddish white solid (0.235 g, 61%); mp 178–179 °C; $[\alpha]_D^{25}$ = +23.2 (acetone, *c* 1.0); e.r. could not be evaluated at this time. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.06 (s, 1H, –CH), 6.88–6.92 (m, 1H, ArH), 7.01 (d, J = 10 Hz, 1H, ArH), 7.15–7.18 (m, 1H, ArH), 7.23–7.29 (m, 5H, ArH), 7.34–7.38 (m, 3H, ArH), 7.61 (t, J = 8, 7.6 Hz, 1H, ArH), 8.03 (d, J = 7.6 Hz, 1H, ArH), 11.06 (s, 1H, –NH), 11.80 (br s, 1H, –OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 37.34, 103.42, 103.65, 108.62, 109.22, 109.47, 112.85, 112.95, 114.79, 116.67, 123.95, 124.30, 126.21, 127.03, 127.86, 127.95, 128.24, 128.48, 132.41, 133.05, 142.77, 152.63, 160.84, 162.17. IR ν_{max} (KBr): 3480, 3328, 3278, 3107, 1686, 1614, 1564, 1494, 1219, 1161, 1061, 897, 847, 760 cm^{-1}. TOF-MS: calcd for $C_{24}H_{16}FNO_3Na$ [M + Na]$^+$: 408.1012; found: 408.1015. Anal. calcd for $C_{24}H_{16}FNO_3$: C, 74.80; H, 4.18; N, 3.63; found: C, 74.88; H, 4.15; N, 3.61.

3-((4-Chlorophenyl)(1*H*-indol-3-yl)methyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (4bb). Brown solid (0.209 g, 57%); mp 107–109 °C; $[\alpha]_D^{25}$ = +23.6 (acetone, *c* 1.0); e.r. could not be evaluated at this time. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.15 (s, 3H, –CH_3), 5.78 (s, 1H, –CH), 6.02 (s, 1H, –CH), 6.90 (t, J = 7.6 Hz, 1H, ArH), 7.03–7.06 (m, 2H, ArH), 7.22–7.27 (m, 5H, ArH), 7.35 (d, J = 8 Hz, 1H, ArH), 10.86 (s, 1H, –NH), 11.51 (br s, 1H, –OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.35, 35.63, 100.02, 103.78, 111.49, 114.23, 118.38, 120.86 (2C), 124.13, 127.11, 127.57 (2C), 130.06 (2C), 130.10, 136.03, 142.26, 161.03, 163.90, 165.52. IR ν_{max} (KBr): 3402, 3261, 3042, 2945, 2920, 1670, 1634, 1576, 1489, 1444, 1404, 1279, 1094, 968, 831, 742 cm^{-1}. TOF-MS: calcd for $C_{21}H_{16}ClNO_3Na$ [M + Na]$^+$: 388.0716; found: 388.0721. Anal. calcd for $C_{21}H_{16}ClNO_3$: C, 68.95; H, 4.41; N, 3.83; found: C, 68.97; H, 4.39; N, 3.85.

3-((5-Bromo-1*H*-indol-3-yl)(phenyl)methyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (4bc). Deep brown solid (0.246 g, 60%); mp 110–112 °C; $[\alpha]_D^{25}$ = +35.3 (acetone, *c* 1.0); e.r. could not be evaluated at this time. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.15 (s, 3H, –CH_3), 5.76 (s, 1H, –CH), 6.03 (s, 1H, –CH), 7.09 (d, J = 2 Hz, 1H, ArH), 7.12–7.15 (m, 2H, ArH), 7.23–7.24 (m, 4H, ArH), 7.32 (s, 1H, ArH), 7.34–7.37 (m, 1H, ArH), 11.07 (s, 1H, –NH), 11.46 (s, 1H, –OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.28, 35.91, 101.55, 103.65, 110.84, 113.46, 114.64, 120.56, 123.10, 125.65, 125.90, 126.53, 127.70, 127.96, 128.06, 129.04, 134.62, 142.63, 163.75, 165.38, 166.32. IR ν_{max} (KBr): 3398, 3362, 3317, 3076, 3006, 2922, 2851, 1668, 1570, 1556, 1447, 1275, 1099, 1033, 987, 878, 702 cm^{-1}. TOF-MS: calcd for $C_{21}H_{16}BrNO_3Na$ [M + Na]$^+$: 432.0211; found: 432.0218. Anal. calcd for $C_{21}H_{16}BrNO_3$: C, 61.48; H, 3.93; N, 3.41; found: C, 61.46; H, 3.95; N, 3.43.

2-((1*H*-Indol-3-yl)(phenyl)methyl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (4ca). Brownish white solid (0.242 g, 70%); mp 164–168 °C; $[\alpha]_D^{25}$ = +22.7 (acetone, *c* 1.0); e.r. could not be evaluated at this time. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.01 (s, 6H, 2CH_3), 2.28 (s, 4H, 2CH_2), 5.83 (s, 1H, –CH), 6.86–6.92 (m, 2H, ArH), 7.02 (t, J = 7.6, 7.2 Hz, 1H, ArH), 7.08 (d, J = 4 Hz, 1H, ArH), 7.17–7.22 (m, 5H, ArH), 7.34 (d, J = 8 Hz, 1H, ArH), 10.37 (br s, 1H, –NH), 10.73 (s, 1H, –OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.42 (2C), 32.07, 35.42, 46.50, 49.38, 111.69, 116.39, 117.15, 118.41, 119.04, 120.96, 124.54, 125.32, 127.77, 127.94 (2C), 128.61 (2C), 136.43, 145.14, 165.41, 195.54. IR ν_{max} (KBr): 3443, 3394, 3325, 3269, 3240, 3045, 2949, 2862, 1676, 1601, 1581, 1564, 1495, 1448, 1265, 1225, 1148, 1105, 1016, 863, 949, 741 cm^{-1}. TOF-MS: calcd for $C_{23}H_{23}NO_2Na$ [M + Na]$^+$: 368.1626; found: 368.1630. Anal. calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05; found: C, 79.95; H, 6.69; N, 4.09.

2-((1*H*-Indol-3-yl)(*p*-tolyl)methyl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (4cb). Reddish white solid (0.223 g, 62%); mp 88–92 °C; $[\alpha]_D^{25}$ = +23.8 (acetone, *c* 1.0); e.r. could not be evaluated at this time. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.00 (s, 6H, 2CH_3), 2.16 (d, J = 8 Hz, 2H, –CH_2), 2.21 (s, 3H, CH_3), 2.37–2.39 (m, 2H, –CH_2), 5.78 (s, 1H, –CH), 6.85–6.90 (m, 2H, ArH), 6.96–7.07 (m, 5H, ArH), 7.19 (d, J = 7.6 Hz, 1H, ArH), 7.33 (d, J = 8 Hz, 1H, ArH), 10.30 (s, 1H, –NH), 10.71 (s, 1H, –OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.60, 27.97, 31.63 (2C), 34.62, 43.32, 50.45, 111.23, 116.07, 116.86, 117.94, 118.64, 120.49, 124.03, 127.49, 127.95 (2C), 128.11 (2C), 133.60, 136.01, 141.62, 170.29, 196.05. IR ν_{max} (KBr): 3406, 3396, 3317, 3108, 2951, 2920, 2856, 1650, 1602, 1591, 1573, 1454, 1255, 1225, 1094, 1012, 742 cm^{-1}. TOF-MS: calcd for $C_{24}H_{25}NO_2Na$ [M + Na]$^+$: 382.1783; found: 382.1788. Anal. calcd for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.01; N, 3.90; found: C, 80.21; H, 6.99; N, 3.91.

2-((4-Fluorophenyl)(1*H*-indol-3-yl)methyl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (4cc). Reddish brown white solid (0.244 g, 67%); mp 105–107 °C; $[\alpha]_D^{25}$ = +35.1 (acetone, *c* 1.0); e.r. could not be evaluated at this time. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.00 (s, 6H, 2CH_3), 2.17 (br s, 2H, –CH_2), 2.40 (br s, 2H, –CH_2), 5.80 (s, 1H, –CH), 6.88 (dd, J = 7.6, 8 Hz, 2H, ArH), 6.96–7.04 (m, 3H, ArH), 7.15–7.20 (m, 3H, ArH), 7.34 (d, J = 8 Hz, 1H, ArH), 10.44 (s, 1H, –NH), 10.75 (s, 1H, –OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.39 (2C), 32.06, 34.84, 43.65, 50.84, 111.73,

114.23, 114.44, 116.21, 117.01, 118.48, 118.98, 121.02, 124.48, 127.75, 130.17, 130.25, 136.48, 141.17, 159.34, 161.73, 196.45. IR ν_{max} (KBr): 3398, 3278, 3052, 2947, 2864, 1709, 1585, 1500, 1223, 1149, 1085, 1014, 746 cm^{-1}. TOF-MS: calcd for $C_{23}H_{22}FNO_2Na$ $[M + Na]^+$: 386.1532; found: 386.1537. Anal. calcd for $C_{23}H_{22}FNO_2$: C, 76.01; H, 6.10; N, 3.85; found: C, 76.05; H, 6.11; N, 3.83.

2-((5-Fluoro-1*H*-indol-3-yl)(phenyl)methyl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (4cf). Brownish white solid (0.236 g, 65%); mp 169–171 °C; $[\alpha]_D^{25}$ = +44.3 (acetone, *c* 1.0); e.r. could not be evaluated at this time. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.92 (s, 6H, $2CH_3$), 2.20 (br s, 4H, $2CH_2$), 5.68 (s, 1H, –CH), 6.77–6.80 (m, 2H, ArH), 6.92 (s, 1H, ArH), 7.01–7.03 (m, 1H, ArH), 7.09–7.13 (m, 4H, ArH), 7.25 (q, J = 4.4, 4.8, 9.4 Hz, 1H, ArH), 10.49 (br s, 1H, –NH), 10.79 (s, 1H, –OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.37 (2C), 32.08 (2C), 35.38, 44.61, 103.45, 103.68, 108.86, 109.12, 112.57, 112.67, 116.70, 125.45, 126.71, 127.87, 127.99, 128.53, 135.06, 144.63, 155.68, 157.97, 195.23. IR ν_{max} (KBr): 3487, 3366, 2949, 1682, 1548, 1473, 1253, 1163, 1084, 1024, 842, 783 cm^{-1}. TOF-MS: Calcd for $C_{23}H_{22}FNO_2Na$ $[M + Na]^+$: 386.1532; found: 386.1529. Anal. calcd for $C_{23}H_{22}FNO_2$: C, 76.01; H, 6.10; N, 3.85; found: C, 76.03; H, 6.08; N, 3.87.

5-((1*H*-Indol-3-yl)(phenyl)methyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4da). White solid (0.329 g, 91%); mp 172–174 °C; $[\alpha]_D^{25}$ = +34.8 (acetone, *c* 1.0); e.r. could not be evaluated at this time. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.76 (s, 3H, $-CH_3$), 2.89 (s, 3H, $-CH_3$), 4.89 (d, J = 2.8 Hz, 1H, –CH), 4.96 (d, J = 2.8 Hz, 1H, –CH), 6.81 (t, J = 7.2, 7.6 Hz, 1H, ArH), 6.97 (t, J = 7.2, 7.6 Hz, 1H, ArH), 7.05 (d, J = 8 Hz, 1H, ArH), 7.09–7.20 (m, 5H, ArH), 7.29 (d, J = 8 Hz, 1H, ArH), 7.40 (br s, 1H, ArH), 10.98 (s, 1H, –NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.19, 28.32, 47.19, 55.11, 112.00, 118.80, 118.97, 121.64, 124.85 (2C), 126.75 (2C), 127.59 (2C), 128.52 (2C), 136.47, 139.96, 151.51, 168.35, 169.15. IR ν_{max} (KBr): 3144, 3063, 3034, 2955, 1738, 1680, 1672, 1444, 1286, 1136, 1107, 1008, 927, 837, 762 cm^{-1}. TOF-MS: calcd for $C_{21}H_{19}N_3O_3Na$ $[M + Na]^+$: 384.1324; found: 384.1328. Anal. calcd for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63; found: C, 69.82; H, 5.28; N, 11.59.

5-((5-Fluoro-1H-indol-3-yl)(phenyl)methyl)-1,3-dimethyl pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4dc). White solid (0.353 g, 93%); mp 174–176 °C; $[\alpha]_D^{25}$ = +31.9 (acetone, *c* 1.0); e.r. could not be evaluated at this time. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.84 (s, 3H, $-CH_3$), 2.96 (s, 3H, $-CH_3$), 4.38 (d, J = 3.2 Hz, 1H, –CH), 5.00 (d, J = 2.8 Hz, 1H, –CH), 6.79–6.92 (m, 2H, ArH), 7.20–7.28 (m, 5H, ArH), 7.36 (q, J = 4.4 Hz, 1H, ArH), 7.58 (s, 1H, ArH), 11.18 (s, 1H, –NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.20, 28.31, 46.91, 54.93, 103.45, 103.68, 109.63, 109.89, 112.97, 113.07, 113.45, 127.00, 127.64, 128.54, 133.12, 139.73, 151.51, 155.83, 158.13, 168.32, 169.04. IR ν_{max} (KBr): 3388, 3122, 2951, 1747, 1668, 1467, 1288, 1170, 1105, 925, 806, 761 cm^{-1}. TOF-MS: calcd for $C_{21}H_{18}FN_3O_3Na$ $[M + Na]^+$: 402.1230; found: 402.1233. Anal. calcd for $C_{21}H_{18}FN_3O_3$: C, 66.48; H, 4.78; N, 11.08; found: C, 66.46; H, 4.75; N, 11.03.

5-((1*H*-Indol-3-yl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4ea). White solid (0.234 g, 67%); mp 129–131 °C; $[\alpha]_D^{25}$ = +41.6 (acetone, *c* 1.0 for *syn*-isomer); e.r. could not be evaluated at this time. ^{1}H NMR (400 MHz, DMSO-d_6): for *syn* isomer: δ 1.45 (s, 3H, $-CH_3$), 1.74 (s, 3H, $-CH_3$), 5.17 (d, J = 2.8 Hz, 1H, –CH), 5.35 (d, J = 2.4 Hz, 1H, –CH), 6.79–6.86 (m, 1H, ArH), 6.92–7.02 (m, 2H, ArH), 7.07–7.19 (m, 4H, ArH), 7.22–7.25 (m, 2H, ArH), 7.36 (dd, J = 1.6, 2.4, 4.8 Hz, 1H, ArH), 10.95 (s, 1H, –NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.19, 28.14, 31.14, 52.14, 105.46, 111.90, 113.67, 119.01, 121.62, 124.38, 126.47, 126.79, 128.22, 128.42, 128.66, 129.32, 136.25, 141.66, 143.37, 165.52, 166.05. IR ν_{max} (KBr): 3398, 2970, 2941, 1761, 1745, 1604, 1307, 1215, 1081, 1012, 904, 829, 756 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): for *anti* isomer: δ 1.99 (s, 6H, $2CH_3$), 4.27 (d, J = 12.4 Hz, 1H, –CH), 4.74 (d, J = 12.4 Hz, 1H, –CH), 6.79–6.86 (m, 1H, ArH), 6.92–7.02 (m, 2H, ArH), 7.07–7.19 (m, 4H, ArH), 7.30 (d, J = 8.4 Hz, 2H, ArH), 7.46 (d, J = 8 Hz, 1H, ArH), 10.82 (s, 1H, –NH). TOF-MS: calcd for $C_{21}H_{19}NO_4Na$ $[M + Na]^+$: 372.1212; found: 372.1218. Anal. calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01; found: C, 72.26; H, 5.45; N, 3.99.

5-((1*H*-Indol-3-yl)(*p*-tolyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4eb). White solid (0.182 g, 63%); mp 128–130 °C; $[\alpha]_D^{25}$ = +68.2 (acetone, *c* 1.0 for *syn*-isomer); e.r. could not be evaluated at this time. ^{1}H NMR (400 MHz, DMSO-d_6): for *syn* isomer: δ 1.45 (s, 3H, $-CH_3$), 1.73 (s, 3H, $-CH_3$), 2.21 (s, 3H, $-CH_3$), 5.12 (s, 1H, –CH), 5.31 (s, 1H, –CH), 6.92–6.97 (m, 3H, ArH), 7.09–7.14 (m, 2H, ArH), 6.82 (q, J = 8.4, 7.6, 7.2, 15.4 Hz, 2H, ArH), 7.19–7.24 (m, 1H, ArH), 7.28–7.39 (m, 1H, ArH), 10.93 (s, 1H, –NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.20, 28.14, 31.14, 21.02, 52.13, 105.13, 111.87, 113.88, 117.07, 118.92, 119.03, 121.57, 124.36, 127.45, 128.81, 128.98, 129.24, 135.79, 136.26, 138.55, 165.48, 166.10. IR ν_{max} (KBr): 3425, 3181, 2997, 2850, 1776, 1734, 1577, 1504, 1298, 1193, 1063, 902, 850, 740 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): for *anti* isomer: δ 2.00 (s, 6H, $2CH_3$), 2.10 (s, 3H, $-CH_3$), 4.22 (d, J = 12 Hz, 1H, –CH), 4.69 (d, J = 12.4 Hz, 1H, –CH), 6.92–6.97 (m, 3H, ArH), 7.09–7.14 (m, 3H, ArH), 7.19–7.24 (m, 1H, ArH), 7.28–7.33 (m, 1H, ArH), 7.43 (d, J = 7.6 Hz, 1H, ArH), 10.79 (s, 1H, –NH). TOF-MS: calcd for $C_{22}H_{21}NO_4Na$ $[M + Na]^+$: 386.1368; found: 386.1372. Anal. calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85; found: C, 72.68; H, 5.80; N, 3.89.

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References

1 (*a*) Atta-ur-Rahman and A. Basha, *Indole Alkaloids*, Harwood Academic Publishers, Chichester, UK, 1998; (*b*) M. Somai and F. Yamada, *Nat. Prod. Rep.*, 2005, **22**, 73; (*c*) *Indoles*, ed. R. J. Sundberg, Academic Press, London, 1996; (*d*) H. C. Zhang, L. V. R. Bonaga, H. Ye, C. K. Derian, B. P. Damiano and B. E. Maryanoff, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 2863; (*e*) B. Jiang,

C. G. Yang and J. Wang, *J. Org. Chem.*, 2001, **66**, 4865; (*f*) H. Zhang and R. C. Larock, *Org. Lett.*, 2001, **3**, 3083; (*g*) M. Sakagami, H. Muratake and M. Natsume, *Chem. Pharm. Bull.*, 1994, **42**, 1393; (*h*) T. Fukuyama and X. Chen, *J. Am. Chem. Soc.*, 1994, **116**, 3125; (*i*) R. J. Sundberg, *The Chemistry of Indoles*, Academic Press, New York, 1970.

2 (*a*) B. Bao, Q. Sun, X. Yao, J. Hong, C. O. Lee, C. J. Sim, K. S. Im and J. H. Jung, *J. Nat. Prod.*, 2005, **68**, 711; (*b*) S. Hibino and T. Chozi, *Nat. Prod. Rep.*, 2001, **18**, 66; (*c*) A. Casapullo, G. Bifulco, I. Bruno and R. Riccio, *J. Nat. Prod.*, 2000, **63**, 447; (*d*) T. R. Garbe, M. Kobayashi, N. Shimizu, N. Takesue, M. Ozawa and H. Yukawa, *J. Nat. Prod.*, 2000, **63**, 596.

3 (*a*) M. P. Leze, M. L. Borgne, P. Marchand, D. Loquet, M. Kogler, G. L. Baut, A. Palusczak and R. W. Hartmann, *J. Enzyme Inhib. Med. Chem.*, 2004, **19**, 549; (*b*) M. L. Borgne, P. Marchand, B. Delevoye- Seiller, J. M. Robert, G. L. Baut, R. W. Hartmann and M. Palzer, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 333.

4 (*a*) R. D. H. Murray, *Nat. Prod. Rep.*, 1995, **12**, 477; (*b*) A. Estévez-Braun and A. G. González, *Nat. Prod. Rep.*, 1997, **14**, 465; (*c*) A. Lacy and R. O'Kennedy, *Curr. Pharm. Des.*, 2004, **10**, 3797.

5 (*a*) A. D. Patil, A. J. Freyer, D. S. Eggleston, R. C. Haltiwanger, M. F. Bean, P. B. Taylor, M. J. Caranfa, A. L. Breen, H. R. Bartus, R. K. Johnson, R. P. Hertzberg and J. W. Westley, *J. Med. Chem.*, 1993, **36**, 4131; (*b*) D. Guilet, J.-J. Hélesbeux, D. Séraphin, T. Sévenet, P. Richomme and J. Bruneton, *J. Nat. Prod.*, 2001, **64**, 563.

6 (*a*) C. A. Bradfield and L. F. Bjeldanes, *J. Agric. Food Chem.*, 1987, **35**, 46; (*b*) T. A. Broadbent and H. S. Broadbent, *Curr. Med. Chem.*, 1998, **5**, 337; (*c*) T. A. Broadbent and H. S. Broadbent, *Curr. Med. Chem.*, 1998, **5**, 469; (*d*) For a review, see: S. Safe, S. Papineni and S. Chintharlapalli, *Cancer Lett.*, 2008, **269**, 326.

7 L. Xue, J. J. Pestka, M. Li, G. L. Firestone and L. F. Bjeldanes, *J. Nutr. Biochem.*, 2008, **19**, 336.

8 T. O. Watsuji, S. Yamada, T. Yamabe, Y. Watanabe, T. Kato, T. Saito, K. Ueda and T. Beppu, *Appl. Environ. Microbiol.*, 2007, **73**, 6159.

9 M. L. Borgne, P. Marchand, B. Delevoye-Seiller, J. M. Robert, G. L. Baut, R. W. Hartmann and M. Palzer, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 333.

10 (*a*) G. Appendino, M. Ottino, N. Marquez, F. Bianchi, A. Giana, M. Ballero, O. Sterner, B. L. Fiebich and E. Muñoz, *J. Nat. Prod.*, 2007, **70**, 608; (*b*) A. Rosa, M. Deiana, A. Atzeri, G. Corona, M. P. Melis, G. Appendino and M. A. Dessì, *Chem.–Biol. Interact.*, 2007, **165**, 117; (*c*) P. S. Kothevade, D. M. Nagnoti, V. D. Bulani and A. R. Juvekar, *Sci. World J.*, 2013, 986429; (*d*) J. Bauer, A. Koeberle, F. Behm, F. Pollastro, G. Appendino, H. Northoff, A. Rossi, L. Sautebin and O. Werz, *Biochem. Pharmacol.*, 2011, **81**, 259.

11 (*a*) D. Opherk, G. Schuler, W. Waas, R. Dietz and W. Kübler, *Eur. Heart J.*, 1990, **11**, 342; (*b*) J. Grayson, M. Irvine and J. R. Parratt, *Br. J. Pharmacol.*, 1969, **37**, 523P.

12 (*a*) J. Ansell, J. Hirsh, E. Hylek, A. Jacobson, M. Crowther and G. Palareti, *Chest*, 2008, **133**, 160S; (*b*) A. M. Holbrook, J. A. Pereira, R. Labiris, H. McDonald, J. D. Douketis, M. Crowther and P. S. Wells, *Arch. Intern. Med.*, 2005, **165**, 1095; (*c*) J. Hirsh, V. Fuster, J. Ansell and J. L. Halperin, *J. Am. Coll. Cardiol.*, 2003, **41**, 1633.

13 (*a*) F. R. Rowe, C. J. Plant and A. Bradfield, *J. Hyg. Comb.*, 1981, **87**, 171; (*b*) M. A. Stahmann, C. F. Huebner and K. P. Link, *J. Biol. Chem.*, 1941, **138**, 513.

14 G. Appendino, L. Cicione and A. Minassi, *Tetrahedron Lett.*, 2009, **50**, 5559.

15 G. Brahmachari and S. Das, *J. Heterocycl. Chem.*, 2013, DOI: 10.1002/jhet.1909, in press.

16 (*a*) G. Brahmachari and S. Laskar, *Tetrahedron Lett.*, 2010, **51**, 2319; (*b*) G. Brahmachari, S. Laskar and S. Sarkar, *J. Chem. Res.*, 2010, **34**, 288; (*c*) G. Brahmachari, S. Laskar and S. Sarkar, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2010, **49**, 1274; (*d*) G. Brahmachari and S. Das, *Tetrahedron Lett.*, 2012, **53**, 1479; (*e*) G. Brahmachari and B. Banerjee, *Asian J. Org. Chem.*, 2012, **1**, 251; (*f*) G. Brahmachari and S. Das, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2013, **52B**, 387; (*g*) S. Das and G. Brahmachari, *SOA J.Org. Biomol. Chem.*, 2013, **1**, 33; (*h*) G. Brahmachari, S. Laskar and P. Barik, *RSC Adv.*, 2013, **3**, 14245; (*i*) G. Brahmachari and B. Banerjee, *Org. Med. Chem. Lett.*, 2013, **1**, 1, DOI: 10.1186/2191-2858-3-1; (*j*) G. Brahmachari, S. Laskar and B. Banerjee, *J. Heterocycl. Chem.*, 2013, DOI: 10.1002/jhet.1974, in press; (*k*) G. Brahmachari and S. Das, *J. Heterocycl. Chem.*, 2013, DOI: 10.1002/jhet.2123, in press; (*l*) G. Brahmachari and B. Banerjee, *ACS Sustainable Chem. Eng.*, 2013, DOI: 10.1021/sc400312n.

17 (*a*) B. List, *Tetrahedron*, 2002, **58**, 5573; (*b*) W. Notz, F. Tanaka and C. F. Barbas, *Acc. Chem. Res.*, 2004, **37**, 580; (*c*) S. Abdolmohammadia and S. Balalaie, *Tetrahedron Lett.*, 2007, **48**, 3299; (*d*) P. Renzi, J. Overgaard and M. Bella, *Org. Biomol. Chem.*, 2010, **8**, 980; (*e*) A. Kumar, M. K. Gupta and M. Kumar, *Green Chem.*, 2012, **14**, 290.

18 (*a*) N. Elders, D. van der Born, L. J. D. Hendrickx, B. J. J. Timmer, A. Krause, E. Janssen, F. J. J. de Kanter, E. Ruijter and R. V. A. Orru, *Angew. Chem., Int. Ed.*, 2009, **48**, 5856; (*b*) A. Dömling, *Chem. Rev.*, 2006, **106**, 17.

19 (*a*) R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown and T. A. Keating, *Acc. Chem. Res.*, 1996, **29**, 123; (*b*) K. Kumaravel and G. Vasuki, *Curr. Org. Chem.*, 2009, **13**, 1820; (*c*) S. Brauch, L. Gabriel and B. Westermann, *Chem. Commun.*, 2010, **46**, 3387.

20 B. M. Trost, *Science*, 1991, **254**, 1471.

21 R. A. Sheldon, *Pure Appl. Chem.*, 2000, **72**, 1233.

22 (*a*) W. Wang, J. Wu, C. Xiaa and F. Li, *Green Chem.*, 2011, **13**, 3440; (*b*) R. B. N. Baig and R. S. Varma, *Green Chem.*, 2012, **14**, 625; (*c*) K. Arya, D. S. Rawata and H. Sasaib, *Green Chem.*, 2012, **14**, 1956; (*d*) T. R. Reddy, L. S. Reddy, G. R. Reddy, K. Yarbagi, Y. Lingappa, D. Rambabu, G. R. Krishna, C. M. Reddy, K. S. Kumar and M. Pal, *Green Chem.*, 2012, **14**, 1870; (*e*) Z. N. Tisseh, M. Dabiri, M. Nobahar, H. R. Khavasi and A. Bazgir, *Tetrahedron*,

2012, **68**, 1769; (*f*) B. S. P. A. Kumar, K. H. V. Reddy, B. Madhav, K. Ramesh and Y. V. D. Nageswar, *Tetrahedron Lett.*, 2012, **53**, 4595; (*g*) Y. Gu, *Green Chem.*, 2012, **14**, 2091; (*h*) Z.-J. Quan, Q. Xu, Z. Zhang, Y.-X. Da and X.-C. Wang, *Tetrahedron*, 2013, **69**, 881.

23 (*a*) M. A. P. Martins, C. P. Frizzo, D. N. Moreira, L. Buriol and P. Machado, *Chem. Rev.*, 2009, **109**, 4140; (*b*) V. Polshettiwar and R. S. Varma, *Acc. Chem. Res.*, 2008, **41**, 629; (*c*) A. L. Garay, A. Pichona and S. L. James, *Chem. Soc. Rev.*, 2007, **36**, 846; (*d*) K. Tanaka and F. Toda, *Chem. Rev.*, 2000, **100**, 1025; (*e*) B. Rodríguez, A. Bruckmann, T. Rantanen and C. Bolm, *Adv. Synth. Catal.*, 2007, **349**, 2213; (*f*) L. Basolo, A. Bernasconi, E. Borsini, G. Broggini and E. M. Beccalli, *ChemSusChem*, 2011, **4**, 1637; (*g*) A. Stolle and B. Ondruschka, *Pure Appl. Chem.*, 2011, **83**, 1343; (*h*) H. M. Marvaniya, K. N. Modi and D. J. Sen, *Int. J. Drug Dev. Res.*, 2011, **3**, 34; (*i*) M. Gupta, S. Paul and R. Gupta, *Acta Chim. Slov.*, 2009, **56**, 749.

24 (*a*) S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friscic, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. Ch. Shearouse, J. W. Steed and D. C. Waddell, *Chem. Soc. Rev.*, 2012, **41**, 413; (*b*) T. Friscic, *Chem. Soc. Rev.*, 2012, **41**, 3493.

25 (*a*) B. List, P. Polariley, W. T. Biller and H. J. Martin, *J. Am. Chem. Soc.*, 2002, **124**, 823; (*b*) Y. Hayashi, T. Urushima, W. Tsuboi and M. Shoji, *Nat. Protoc.*, 2007, **2**, 113; (*c*) E. Veverková, L. Liptáková, M. Veverka and R. Šebesta, *Tetrahedron: Asymmetry*, 2013, **24**, 548.

26 (*a*) P. Kotrusz and Š. Toma, *ARKIVOC*, 2006, 100; (*b*) P. Kotrusz and Š. Toma, *Molecules*, 2006, **11**, 197; (*c*) N. Moirangthem, B. Thingom, S. D. Moirangthem and W. S. Laitonjam, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2013, **52**, 937; (*d*) K. Xu, S. Zhang, Y. Hu, Z. Zha and Z. Wang, *Chem. – Eur. J.*, 2013, **19**, 3573.

