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Indium(III) chloride catalyzed three-component coupling reaction: A novel synthesis of 2-substituted aryl(indolyl)kojic acid derivatives as potent antifungal and antibacterial agents

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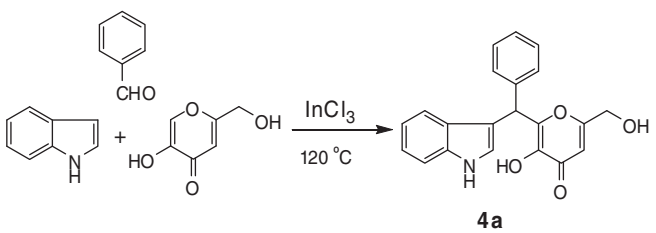
ABSTRACT

Three-component coupling of aldehyde, indole and kojic acid has been achieved using a catalytic amount of $InCl_3$ under solvent free conditions to produce a novel series of 2-substituted aryl(indolyl)kojic acid derivatives in good yields and with high selectivity. These compounds are found to exhibit potent antifungal properties.

Multi-component, one-pot syntheses have received considerable attention because of their wide range of applications in pharmaceutical chemistry for generation of structural diversity and combinatorial libraries for drug discovery.[1] The indole nucleus is an important structural motif in medicinal chemistry.[2–4] Substituted indoles have been referred to as privileged structures as they are capable of binding to many receptors with high affinity.[5–8] Therefore, the synthesis and selective functionalization of indoles have been the focus of active research over the years.[9–16] Recently, $InCl_3$ has emerged as a mild Lewis acid catalyst for a variety of organic transformations.[17–24] However, to the best of our knowledge, there are no reports on the coupling of indole, aldehyde and kojic acid by means of a three-component reaction to produce a novel class of 2-substituted aryl(indolyl)kojic acid derivatives.

Following our interest on catalytic application of indium(III) chloride,[25–29] we herein disclose a novel three-component reaction for the one-pot synthesis of 2-substituted aryl(indolyl)kojic acid derivatives from kojic acid, aryl aldehydes and indoles. Thus treatment of benzaldehyde with indole and kojic acid in presence of 10 mol % of $InCl_3$ at 120 °C under solvent free conditions gave the 2-((1*H*-indol-3-yl)(phenyl)methyl)-3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one **4a** in 85% yield (Scheme 1).

This result provided the incentive for further study of reactions with various substituted indoles such as 2-methyl, 2-phenyl, 5-bromo, 5-chloro derivatives. Aromatic aldehydes such as *p*-methoxy, *m*-phenoxy, *o*-chloro, 2,4,6-trimethylbenzaldehydes and 2-naphthaldehyde reacted well with kojic acid to afford 2-substituted aryl(indolyl)kojic acid derivatives in good yields (Table 1). Aliphatic aldehyde, for example, *n*-propanaldehyde also participated well in this reaction under similar conditions (entry l, Table 1). Both aromatic aldehydes and aliphatic aldehyde worked well in this reaction. Interestingly, bromo and chloro substituted indoles were also effective for this three-component reaction (entries i and j, Table 1). In the absence of $InCl_3$, the products were obtained in low yield (20–35%) after long reaction times (8–12 h). Mechanistically, we assume that the reaction proceeds via the formation of enone from kojic acid and aldehyde. The resulting enone may undergo conjugate addition with indole to give the desired product as depicted in Scheme 2.



Scheme 1. 3CC reaction of indole, benzaldehyde and kojic acid.

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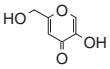
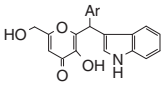
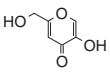
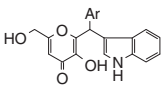
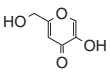
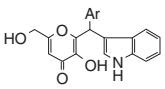
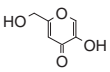
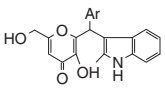
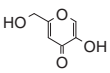
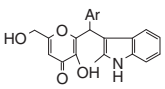
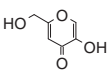
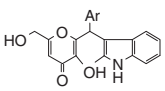
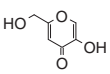
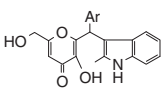
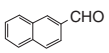
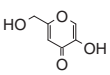
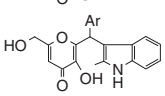
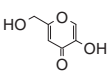
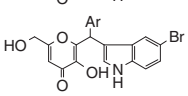
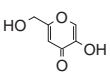
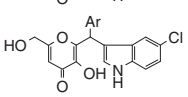
Table 1
$InCl_3$-catalyzed one-pot synthesis of 2-substituted alkyl and aryl(indolyl)kojic acid derivatives

Entry	Indole (**1**)	Aldehyde (**2**)	Koijc acid (**3**)	Product (**4**)[a]	Time (min)	Yield[b] (%)
a					65	85
b					70	80
c					55	87
d					60	85
e					55	85
f					75	80
g					75	80
h					65	85
i					75	90
j					75	90
k					85	75
l					80	80
m					75	85

[a] All products were characterized by ^1H NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.

Scheme 2. A plausible reaction mechanism.

The scope and generality of this process is illustrated with respect to various indoles and aldehydes and the results are presented in Table 1.[30]

The minimum inhibitory concentrations (MIC) of various synthetic compounds were tested against three representative Gram positive organisms viz. *Bacillus subtilis* (MTCC 441), *Staphylococcus*

Table 2
Antibacterial activity of compounds **4d–4l**

	MIC (μg/mL)					
Compd code	*B. Subtilis*	*S. aureus*	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*
4a	150	150	150	150	150	75
4b	150	37.5	18.75	150	75	75
4c	150	37.5	18.75	75	75	75
4d	150	150	150	150	150	150
4e	150	18.75	150	75	75	75
4f	150	150	150	150	150	150
4g	150	37.5	18.75	18.75	18.75	75
4h	150	150	150	150	150	150
4i	150	18.75	18.75	37.5	37.5	75
4j	150	2.34	150	4.68	4.68	18.75
4k	150	37.5	150	75	75	150
4l	18.75	9.375	18.75	9.375	37.5	75
4m	150	4.68	150	37.5	18.75	75
Penicillin	1.562	1.562	3.125	12.5	12.5	6.25
Streptomycin	6.25	6.25	3.125	6.25	1.562	3.125

Table 3
Antifungal activity of compounds **4d–4l**

	Zone of Inhibition (mm)									
Compound code	*R. oryzae*		*A. niger*		*C. rugosa*		*C. albicans*		*S. cerevisiae*	
	100 μg	150 μg	100 μg	150 μg	100 μg	150 μg	100 μg	150 μg	100 μg	150 μg
4a	0	0	10	14	6	9	0	0	0	0
4b	0	0	0	0	6	9	0	0	0	0
4c	7	10	11	16	13	18	14	19	14	19
4d	0	0	0	0	0	0	0	0	0	0
4e	0	0	9	14	11	16	9	14	10	14
4f	0	0	0	0	0	0	0	0	0	0
4g	7	10	8	12	0	0	0	0	0	0
4h	0	0	0	0	0	0	0	0	0	0
4i	0	0	12	18	13	19	13	18	10	16
4j	0	0	14	20	0	0	11	16	16	21
4k	0	0	10	14	10	14	9	12	9	14
4l	0	0	0	0	0	0	0	0	14	20
4m	0	0	0	0	0	0	10	14	12	16
Ampotericin B	24		25		22		23.5		22	

aureus (MTCC 96), *Staphylococcus epidermidis* (MTCC 2639) and Gram-negative organisms viz *Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 741), and *Klebsiella pneumoniae* (MTCC 618) by broth dilution method recommended by National Committee for Clinical Laboratory (NCCL) standards (1).[31] Standard Antibacterial agents like Penicillin and Streptomycin were also screened under identical conditions for comparison. The minimum inhibitory concentration (MIC) values are presented in Table 2.

The minimum inhibitory concentration (MIC) was determined for each compound against with Penicillin and Streptomycin as standard controls and the results are presented in Table 2. The MIC values of indolyl kojic acid derivatives against tested organisms displayed significant activity with a high degree of variation. Only compound **4l** showed substantial activity against all the tested organisms. Moderate activity was shown by the compounds **4g, 4j, 4m** and **4i** against all the tested organisms except for *B. subtilis*. Among them, **4j** was more effective especially against *S. aureus*, *E. coli* and *P. aeruginosa*. Compounds **4b** and **4c** were showed similar activity against all tested strains. The compounds **4d, 4h, 4f** and **4a** have not been shown any notable activity compared to other compounds and **4e, 4k** showed some activity against *S. aureus*.

In vitro antifungal activity of the newly synthesized compounds was studied against the fungal strains, *Candida albicans* (MTCC 227), *Candida rugosa* (NCIM 3462), *Saccharomyces cerevisiae* (MTCC 36), *Rhizopus oryzae* (MTCC 262), *Aspergillus niger* (MTCC 282) by Agar Well Diffusion Method (2). The ready-made Potato Dextrose Agar (PDA) medium (Hi-media, 39 g) was suspended in distilled water (1000 mL) and heated to boiling until it dissolved completely, the medium and Petri dishes were autoclaved at pressure of 15 lb/inc[32] for 20 min. Agar well bioassay was employed for testing antifungal activity in Table 3.

The medium was poured into sterile Petri dishes under aseptic conditions in a laminar air flow chamber. When the medium in the plates solidified, 0.5 mL of (week old) culture of test organism was inoculated and uniformly spread over the agar surface with a sterile L-shaped rod. Solutions were prepared by dissolving the compound in DMSO and different concentrations were made. After inoculation, wells were scooped out with 6 mm sterile cork borer and the lids of the dishes were replaced. To each well different concentrations of test solutions were added. Controls were maintained. The treated and the controls were kept at 27 °C for 48 h. Inhibition zones were measured and the diameter was calculated in millimeter. Three to four replicates were maintained for each treatment.

The antifungal screening data of **4a–4m** revealed that all the tested compounds showed moderate to good antifungal activities against the tested fungal strains. The compounds **4b, 4d, 4h, 4b, 4f** are showing no activity against the tested organisms. The compound **4c** showed better antifungal activity against all fungal strains. The compounds **4e, 4j, 4i** and **4k** displayed antifungal activity except on *R. oryzae*. Compound **4e** and **4k** exhibited almost

similar activity. The compounds **4j** and **4c** were observed as most active with a zone of inhibition values in the range of 11–21 mm at the concentration of 150 μg/mL. Narrow spectrum of activity was observed with **4m** against *C. albicans* and *S. cerevisiae* and **4l** against *S. cerevisiae*.

In summary, we have developed a novel method for the synthesis of 2-substituted aryl(indolyl)kojic acid derivatives by means of a three-component reaction between kojic acid, aldehyde and indole using a catalytic amount of $InCl_3$ under neat conditions. This method is simple and convenient to prepare a wide range of kojic acid derivatives in a single-step operation which are found to possess interesting antibacterial and antifungal properties.

Acknowledgement

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References and notes

1. Zhu, J.; Bienayme, H. *Multi-Component Reactions*; Wiley: Weinheim, 2005.
2. Sundberg, R. J. *Indoles*; Academic Press, 1996.
3. Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1.
4. Ninomiya, I. *J. Nat. Prod.* **1992**, *55*, 541.
5. Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Bird, C. W., Eds.; Pergamon Press: Oxford, 1996; Vol. 2,. p 207.
6. Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491.
7. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.
8. Tois, J.; Franzen, R.; Koskinen, A. *Tetrahedron* **2003**, *59*, 5395.
9. (a) Cacchi, S.; Fabrici, G. *Chem. Rev.* **2005**, *105*, 2873; (b) Nair, N. V.; Vidya, N.; Abhilash, K. G. *Tetrahedron Lett.* **2006**, *47*, 2871.
10. (a) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199; (b) Deb, L. M.; Bhuyan, J. P. *Tetrahedron Lett.* **2007**, *48*, 2159.
11. Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875.
12. (a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550; (b) Zhao, X.; Yu, Z.; Xu, T.; Wu, P.; Yu, H. *Org. Lett.* **2007**, *9*, 5263.
13. (a) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172; (b) Yadav, J. S.; Reddy, B. V. S.; Rao, K. V. R.; Kumar, G. G. K. S. N. *Tetrahedron Lett.* **2007**, *48*, 5573.
14. (a) Jensen, K. B.; Thorhange, J.; Hazel, R. G.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160; (b) Jana, U.; Maiti, S.; Biswas, S. *Tetrahedron Lett.* **2007**, *48*, 7160.
15. (a) Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109; (b) Yadav, J. S.; Reddy, B. V. S.; Narasimhulu, G.; Reddy, N. S.; Reddy, P. N.; Purnima, K. V.; Naresh, P.; Jagadeesh, B. *Tetrahedron Lett.* **2010**, *51*, 244.
16. Bartoli, G.; Bartolacci, M.; Bosco, M.; Foglia, G.; Giuliani, A.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2003**, *68*, 4594.
17. Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149.
18. Babu, G.; Perumal, P. T. *Aldrichimica Acta* **2000**, *33*, 16.
19. Ghosh, R. *Indian J. Chem.* **2001**, *40B*, 550.
20. Clarke, P. A.; Zaytzev, A. V.; Whitwood, A. C. *Tetrahedron Lett.* **2007**, *48*, 5209.
21. Shanthi, G.; Perumal, P. T. *Tetrahedron Lett.* **2009**, *50*, 3959.
22. Shanthi, G.; Perumal, T. P. *Tetrahedron Lett.* **2008**, *49*, 7139.
23. Yadav, J. S.; Reddy, B. V. S.; Satheesh, G.; Narasimhulu, G.; Portier, Y.; Madhavi, C.; Kunwar, A. C. *Tetrahedron Lett.* **2008**, *49*, 3341.
24. Kumar, R.; Nandi, G. C.; Verma, R. K.; Singh, M. S. *Tetrahedron Lett.* **2010**, *51*, 442.
25. Yadav, J. S.; Sunny, A.; Reddy, B. V. S.; Sabitha, G. *Tetrahedron Lett.* **2001**, *42*, 8063.
26. Yadav, J. S.; Reddy, B. V. S.; Kumar, G. M. *Synlett* **2001**, 1781.
27. Yadav, J. S.; Reddy, B. V. S.; Sabitha, G.; Prabhakar, A.; Kunwar, A. C. *Tetrahedron Lett.* **2003**, *44*, 2221.
28. Yadav, J. S.; Reddy, B. V. S.; Reddy, Ch. S. *Tetrahedron Lett.* **2004**, *45*, 4583.
29. Yadav, J. S.; Reddy, B. V. S.; Madan, Ch. *New J. Chem.* **2000**, *24*, 853.
30. *General procedure:* A mixture of aldehyde (1 mmol), kojic acid (1 mmol), indole (1 mmol) and $InCl_3$ (10 mol %) was stirred at 120 °C for a specified time as required to complete the reaction (Table 1). After complete conversion, as indicated by TLC, the reaction mixture was diluted with water and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 60–120 mesh, ethyl acetate/hexane, 3:7) to afford the pure substituted aryl(Indolyl)kojic acid derivative.
2-((1H-Indol-3-yl)(phenyl)methyl)-3-hydroxy-6-(hydroxymethyl)-4H-pyran-4-one (**4a**): solid, mp 78–80 °C; ^{1}H NMR(500 MHz, DMSO + $CDCl_3$, 1:4): δ 10.86 (s, 1H), 8.77 (s, 1H), 6.9–7.31 (m, 10H), 6.31 (s, 1H), 5.98 (s, 1H), 5.28 (s, 1H), 4.22 (s, 2H); ^{13}C NMR(75 MHz, DMSO): δ 173.5, 167.1, 150.4, 141.4, 138.8, 135.1, 133.4, 129.5, 130.9, 128.1, 127.1, 120.1, 118.7, 118.4, 110.5, 108.8, 107.7, 59.3, 38.2, 11.7; IR (KBr): *ν* 3327, 2923, 2855, 1715, 1619, 1456, 1203, 748 cm^{-1}; ESI-MS: *m*/*z* [M+1] 347.
2-((1H-Indol-3-yl)(4-methoxyphenyl)methyl)-3-hydroxy-6-(hydroxymethyl)-4H-pyran-4-one (**4b**): solid, mp 97–99 °C; ^{1}H NMR (300 MHz, DMSO + $CDCl_3$, 1:4): δ 10.21 (s, 1H), 7.47 (s, 1H), 6.72–7.35 (m, 9H), 6.38 (s, 1H), 5.95 (s, 1H), 4.27 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (75 MHz, DMSO): δ 173.2, 167.0, 157.9, 151.3, 140.6, 136.1, 132.3, 129.2, 126.3, 123.8, 121.1, 118.5, 118.4, 111.5, 108.9; IR (KBr): *ν* 3288, 2929, 1652, 1618, 1580, 1511, 1456, 1309, 1255, 1095, 998, 765, 738 cm^{-1}; ESI-MS: *m*/*z* [M+1] 378.
2-((1H-Indol-3-yl)(3-phenoxyphenyl)methyl)-3-hydroxy-6-(hydroxymethyl)-4H-pyran-4-one (**4c**): solid, mp 94–95 °C; ^{1}H NMR (500 MHz, DMSO + $CDCl_3$, 1:4): δ 10.35 (s, 1H), 7.99 (s, 1H), 6.80–7.34 (m, 14H), 6.37 (s, 1H), 6.02 (s, 1H), 5.30 (s, 1H), 4.25 (s, 2H); ^{13}C NMR (75 MHz, DMSO): δ 173.7, 167.2, 156.6, 156.4, 150.6, 142.6, 141.0, 136.1, 129.9, 126.2, 124.0, 123.4, 121.3, 118.7, 118.5, 116.8, 112.4, 111.6, 108.9, 59.5, 48.5, 30.1, 29.0, 17.2; IR (KBr): *ν* 3408, 2923, 1621, 1581, 1484, 1451, 1235, 1008, 746 cm^{-1}; ESI-MS: *m*/*z* [M+1] 440.
3-Hydroxy-6-(hydroxymethyl)-2-((4-methoxy-phenyl)(2-methyl-1H-indol-3-yl)methyl)-4H-pyran-4-one (**4d**): solid, mp 90–92 °C; ^{1}H NMR (500 MHz, DMSO + $CDCl_3$, 1:4): δ 10.42 (s, 1H), 8.13 (s, 1H), 6.72–7.20 (m, 8H), 6.36 (s, 1H), 6.04 (s, 1H), 5.25 (s, 1H), 4.10–4.27 (m, 2H), 3.74 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, DMSO): δ 173.6, 170.4, 167.1, 157.6, 151.5, 141.3, 135.2, 133.4, 131.7, 128.7, 127.4, 120.0, 118.9, 113.6, 110.5, 108.8, 59.7, 59.4, 54.9, 20.7, 14.07, 11.8; IR (KBr): *ν* 3391, 2924, 1713, 1618, 1576, 1509, 1456, 1302, 1245, 1179, 1030, 860, 828, 745 cm^{-1}; ESI-MS: *m*/*z* [M+1] 392.
3-Hydroxy-6-(hydroxymethyl)-2-((2-methyl-1H-indol-3-yl)(3-phenoxyphenyl)methyl)-4H-pyran-4-one (**4e**): solid, mp 85–87 °C; ^{1}H NMR (500 MHz, DMSO + $CDCl_3$, 1:4): δ 10.55 (s, 1H), 8.35 (s, 1H), 7.20–7.25 (m, 5H), 6.78–7.02 (m, 8H), 6.33 (s, 1H), 6.06 (s, 1H), 5.31 (s, 1H), 4.09–4.26 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, DMSO): δ 173.5, 167.1, 156.4, 156.4, 150.6, 142.1, 141.4, 135.1, 133.6, 129.8, 127.2, 122.8, 123.2, 120.0, 118.8, 118.3, 118.2, 118.1, 116.6, 110.5, 108.5, 108.7, 107.8, 59.3, 11.7; IR (KBr): *ν* 3393, 2924, 2854, 1620, 1580, 4184, 1455, 1238, 1161, 1081, 746 cm^{-1}; ESI-MS: *m*/*z* [M+1] 454.
3-Hydroxy-2-((4-hydroxy-3-methoxyphenyl) (2-methyl-1H-indol-3-yl)methyl)-6-(hydroxymethyl)-4H-pyran-4-one (**4f**): solid, mp 80–82 °C; ^{1}H NMR (300 MHz, DMSO + $CDCl_3$, 1:4): δ 10.41 (s, 1H), 8.13 (s, 1H), 6.55–7.29 (m, 7H), 6.33 (s, 1H), 5.97 (s, 1H), 5.10 (s, 1H), 4.14–4.27 (m, 2H), 3.65 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, DMSO): δ 173.6, 168.1, 167.0, 151.1, 147.4, 145.0, 141.1, 139.2, 138.16, 133.4, 130.6, 127.5, 120.2, 118.9, 118.3, 115.2, 112.3, 110.5, 109.8, 108.9, 59.5, 55.6, 11.8; IR (KBr): *ν* 3388, 2952, 2855, 1651, 1617, 1573, 1512, 1456, 1198, 1029, 859, 744 cm^{-1}; ESI-MS: *m*/*z* [M+1] 408.
2-((4-Chlorophenyl)(2-methyl-1H-indol-3-yl) methyl)-3-hydroxy-6-(hydroxymethyl)-4H-pyran-4-one (**4g**): solid, mp 92–94 °C; ^{1}H NMR (500 MHz, DMSO + $CDCl_3$, 1:4): δ 10.64 (s, 1H), 8.45 (s, 1H), 7.12–7.25 (m, 6H), 6.94 (t, 1H, *J* = 7.3 Hz), 6.82 (t, 1H, *J* = 7.3 Hz), 6.33 (s, 1H), 6.03 (s, 1H), 5.33 (s, 1H), 4.09–4.25 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, DMSO): δ 173.5, 167.1, 150.4, 141.4, 138.8, 135.2, 133.7, 130.9, 129.5, 128.1, 127.1, 120.1, 118.7, 118.4, 110.5, 108.8, 107.7, 59.3, 38.2, 11.7; IR (KBr): *ν* 3391, 2922, 1650, 1621, 1576, 1457, 1304, 1201, 1089, 1013, 860, 821, 747 cm^{-1}; ESI-MS: *m*/*z* [M+1] 396.
3-Hydroxy-6-(hydroxymethyl)-2-((2-methyl-1H-indol-3-yl)(naphthalen-2-yl)methyl)-4H-pyran-4-one (**4h**): solid, mp 87–89 °C; ^{1}H NMR (500 MHz, DMSO + $CDCl_3$, 1:4): δ 10.19 (s, 1H), 7.24–7.74 (m, 9H), 6.95 (t, 1H, *J* = 7.3 Hz), 6.82 (t, 1H, *J* = 7.3 Hz), 6.42 (s, 1H), 6.23 (s, 1H), 5.07 (s, 1H), 4.13–4.27 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, DMSO): δ 173.6, 167.2, 150.9, 141.5, 137.6, 135.6, 135.1, 133.7, 132.8, 131.6, 127.4, 127.7, 126.5, 126.0, 125.5, 125.5, 120.0, 118.7, 118.3, 110.5, 108.8, 108.1, 59.4, 59.7, 20.6, 11.8, 14.0; IR (KBr): *ν* 3484, 3265, 2908, 1713, 1626, 1583, 1457, 1372, 1244, 1194, 1159, 1159, 1094, 983, 858, 827, 751 cm^{-1}; ESI-MS: *m*/*z* [M+1] 412.
2-((5-Bromo-1H-indol-3-yl)(4-methoxyphenyl) methyl)-3-hydroxy-6-(hydroxymethyl)-4H-pyran-4-one (**4i**): viscous liquid; ^{1}H NMR (300 MHz, DMSO + $CDCl_3$, 1:4): δ 10.98 (s, 1H), 8.60 (s, 1H), 7.39–6.76 (m, 8H), 6.32 (s, 1H), 5.90 (s, 1H), 4.26 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, DMSO): δ 182.1, 172.3, 156.6, 149.2, 139.3, 133.5, 130.3, 127.6, 126.7, 123.8, 122.1, 112.1, 111.7, 111.4, 110.0, 107.2, 94.2, 58.3, 53.3, 27.8; IR (KBr): *ν* 3330, 2929, 1618, 1510, 1457, 1249, 1031, 797, 762 cm^{-1}; ESI-MS: *m*/*z* [M+1] 457.
2-((5-Chloro-1H-indol-3-yl)(4-methoxyphenyl) methyl)-3-hydroxy-6-(hydroxymethyl)-4H-pyran-4-one (**4j**): viscous liquid; ^{1}H NMR (500 MHz, DMSO + $CDCl_3$, 1:4): δ 10.37 (s, 1H), 6.73–7.42 (m, 8H), 6.39 (s, 1H), 5.90 (s, 1H), 5.22 (s, 1H), 4.30 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, DMSO): δ 173.6, 167.0, 158.0, 150.8, 140.7, 134.6, 131.9, 129.1, 127.3, 125.7, 123.2, 121.1, 117.6, 113.7, 113.1, 108.9, 59.4, 54.9, 48.4, 45.6, 30.0, 28.9, 17.1; IR (KBr): *ν* 3355, 2930, 1621, 1578, 1510, 1459, 1249, 1181, 1030, 799, 763 cm^{-1}; ESI-MS: *m*/*z* [M+1] 412.
3-Hydroxy-6-(hydroxymethyl)-2-((4-methoxy- phenyl)(2-phenyl-1H-indol-3-yl)methyl)-4H-pyran-4-one (**4k**): solid, mp 96–98 °C; ^{1}H NMR (300 MHz, DMSO + $CDCl_3$, 1:4): δ 11.12 (s, 1H), 7.82 (s, 1H), 7.62–6.63 (m, 13H), 6.37 (s, 1H), 6.09 (s, 1H), 4.28–4.05 (m, 2H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, DMSO): δ 173.7, 167.4, 157.7, 151.0, 141.4, 136.7, 136.3, 132.0, 128.8, 128.6, 128.4, 127.9, 127.4, 121.3, 118.7, 113.7, 111.7, 111.3, 109.2, 108.8, 59.7, 59.4, 54.9, 48.4, 30.1, 29.0, 20.7, 17.1, 14.0; IR (KBr): *ν* 3325, 3060, 2923, 2855, 1715, 1619, 1455, 1313, 1093, 859, 748 cm^{-1}; ESI-MS: *m*/*z* [M+1] 454.
3-Hydroxy-6-(hydroxymethyl)-2-(1-(2-phenyl-1H-indol-3-yl)propyl)-4H-pyran-4-one (**4l**): solid, mp 85–87 °C; ^{1}H NMR (300 MHz, DMSO + $CDCl_3$, 1:4): δ 10.58 (s, 1H), 7.8–6.9 (m, 9H), 6.4 (s, 1H), 4.59 (t, 1H, *J* = 7.9 Hz), 4.45–4.26 (m, 2H), 2.28–2.10 (m, 2H), 0.79 (t, 3H, *J* = 7.9 Hz); ^{13}C NMR (75 MHz, DMSO): δ 174.1, 167.6, 152.9, 141.2, 136.7, 136.5, 133.1, 131.2, 129.6, 128.9, 128.1, 127.6, 121.7, 121.2, 119.2, 111.7, 110.5, 109.0, 60.2, 30.0, 18.9, 14.5, 12.7; IR (KBr): *ν* 3301, 2965, 2871, 1621, 1572, 1454, 1203, 1092, 986, 857, 746 cm^{-1}; ESI-MS: *m*/*z* [M+1] 376.
3-Hydroxy-6-(hydroxymethyl)-2-((2-hydroxy- phenyl)(2-phenyl-1H-indol-3-

yl)methyl)-4H-pyran-4-one (**4m**): solid, mp 97–99 °C; ^{1}H NMR (300 MHz, DMSO + $CDCl_3$, 1:4): δ 11.03 (s, 1H), 9.08 (s, 1H), 7.6–6.6 (m, 13H), 6.30 (s, 1H), 6.20 (s, 1H), 4.16 (s, 2H); ^{13}C NMR (75 MHz, DMSO): δ 173.9, 167.0, 155.2, 152.1, 141.6, 136.5, 133.3, 129.8, 128.9, 128.1, 128.0, 126.9, 121.5, 120.4, 119.4, 119.0, 115.2, 111.7, 109.5, 109.3, 59.9, 36.1, 14.5; IR (KBr): ν 3388, 2920, 1651, 1616, 1570, 1510, 1455, 1370, 1198, 1083, 1029, 859, 740 cm^{-1}; ESI-MS: *m*/*z* [M+1] 440.

31. National Committee for Clinical Laboratory (NCCL). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria, which Grows Aerobically*, 5th ed.; Approved Standard M7-A5, NCCLS: Villanova, PA, 2000.
32. Linday, M. E. *Practical Introduction to Microbiology*; E and F. N. Spon Ltd: United Kingdom, 1962.