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An expeditious regioselective synthesis of novel bioactive indole-substituted chromene derivatives via one-pot three-component reaction

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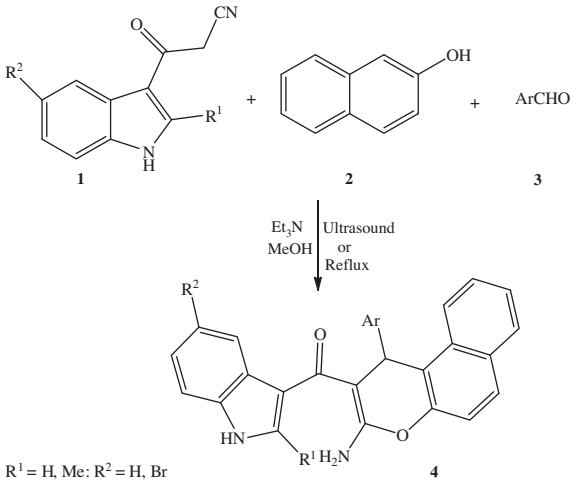
ABSTRACT

Novel fused 1*H*-benzo[*f*]chromen-indole derivatives were synthesized regioselectivly in good to high yields by triethyl amine catalyzed condensation of 3-cyanoacetylindoles, β-naphthol and aryl aldehydes in methanol under ultrasounic irradiations and conventional conditions. The easy work-up of the products, rapidity, and mild reaction conditions are notable features of this protocol. The antibacterial activity of the selected products was examined. Some products showed promising activities.

Functionalized nitrogen and oxygen containing heterocycles play a predominant role in medicinal chemistry and they have been intensively used as scaffolds for drug development. Chromene derivatives as an important class of compounds with diverse biological properties and therapeutic application have attracted many attentions.[1] They are prominent natural products, widely distributed among many plants.[2] Natural derivatives of chromene also exhibit a wide range of valuable physiological activities.[3] Substituted chromenes can bind to 5HT receptors, acting as antagonists[4] and were also reported as MAO and human β-secretase inhibitors.[5,6] They have considerable biological importance, especially as potentially useful pesticides,[7,8] for its antihypoxic, hypotensive and antiallergic properties,[9] and inhibitors of cell proliferation with potential anticancer effects.[10] Chromene compounds display high antifungal and antibacterial activities.[11–14] Furthermore, chromene derivatives have been found to possess anti-picornavirus properties, binding to virus capsids.[15] They have strong antioxidant activities[16] and also represent useful synthetic building blocks in organic and medicinal chemistry.[17–22] Thus, several synthetic pathways have been used to prepare chromene derivatives.[23]

On the other hand the indole nucleus is probably the most well-known heterocycle, being a common and important feature of a variety of natural products and medicinal agents.[24] Compounds carrying the indole moiety exhibit antibacterial and antifungal activities.[25]



R^1 = H, Me: R^2 = H, Br

Ar = 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 2,4-$Cl_2C_6H_3$, 3-$O_2NC_6H_4$, 3-$MeOC_6H_4$, 1,4-phenylene, 3-pyridyl, 2-naphthyl

Scheme 1. Synthesis of 1*H*-benzo[*f*]chromen-indole derivatives (**4a**–**m**).

Therefore, it would be beneficial to design a system which combines bio-labile nuclei such as indole and chromene in a molecular framework and to evaluate their additive microbial effects.

As a consequence of our recent interests aimed at developing new selective and environmentally benign methodologies for the synthesis of heterocyclic compounds,[26] and guided by the observation that the presence of two or more different heterocyclic moie-

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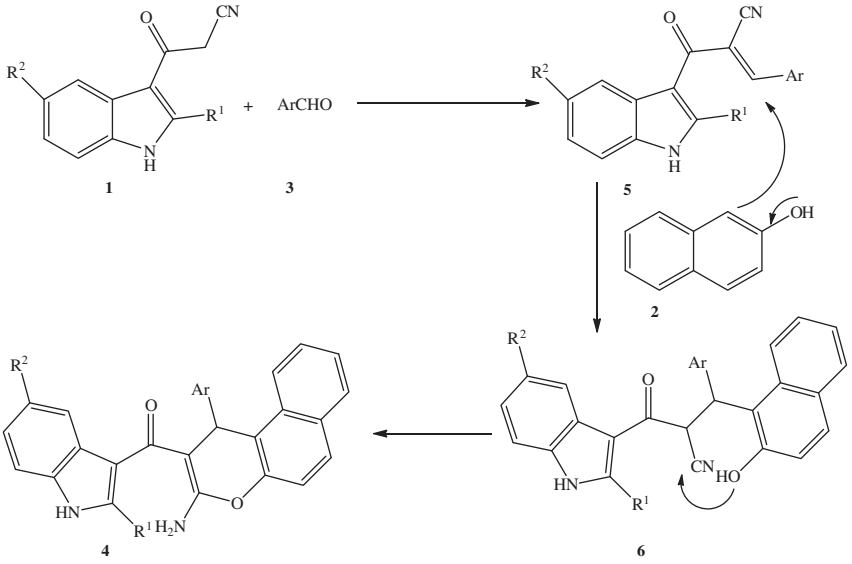
Table 1
Synthesis of products (**4a**–**m**) in conventional and Sonochemical methods

Entry	4	R^1	R^2	Ar	Conventional method		Sonochemical method	
					Time (min)	Yield[a] (%)	Time (min)	Yield[a] (%)
1	**4a**	H	H	4-FC_6H_4	60 (4)[b]	89 (15)[b]	4	90
2	**4b**	H	H	4-ClC_6H_4	60	85	5	90
3	**4c**	H	H	4-BrC_6H_4	90 (5)	75 (8)[b]	5	80
4	**4d**	H	H	2,4-$Cl_2C_6H_3$	50	90	4	90
5	**4e**	H	H	3-$O_2NC_6H_4$	45	91	5	95
6	**4f**	H	H	3-$MeOC_6H_4$	80	78	7	80
7	**4g**	H	H	1,4-Phenylene	90	72	7	70
8	**4h**	H	Br	4-ClC_6H_4	60	80	7	80
9	**4i**	H	Br	2,4-$Cl_2C_6H_3$	70	85	6	90
10	**4j**	H	Br	3-Pyridyl	40 (5)[b]	80 (10)[b]	5	93
11	**4k**	H	Br	2-Naphthyl	90 (12)[b]	68 (20)[b]	12	70
12	**4l**	H	Br	1,4-Phenylene	60	70	10	75
13	**4m**	Me	H	2,4-$Cl_2C_6H_3$	80 (5)[b]	88 (10)[b]	5	92

[a] Isolated yields.
[b] Isolated yields at the same time as sonochemical method.



Scheme 2. Mechanism of synthesis of products **4a**–**m**.

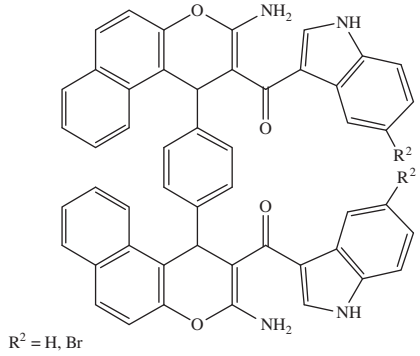


Figure 1. Structures of **4g** and **4l**.

ties in a single molecule often remarkably enhances the biocidal profile, we investigated one-pot, three-component reaction of 3-cyanoacetylindoles (**1**), β-naphthol (**2**), and various aryl aldehydes (**3**) to afford a series of 1*H*-benzo[*f*]chromen-2-yl)(1*H*-indol-3-yl)methanones (Scheme 1).

To optimize the reaction conditions, preparation of **4a** was performed as a model reaction. Therefore, the reaction of equimolar amount of premade 3-cyanoacetylindoles (**1**),[27] β-naphthol (**2**), and 4-fluorobezaldehyde (**3a**) in the presence of various catalysts (Et_3N, DBU, pipyridine, Fe^{3+}-montmorillonite, *p*-TSA, AcOH) and different solvents (MeOH, acetonitrile, 1,4-dioxane, CH_2Cl_2, DMF and EtOH) was studied at reflux condition. Excellent results, with high yield (89%), and lower reaction time (60 min) were obtained when triethyl amine (20 mol %) was used as catalyst in refluxing methanol. Various chromene derivatives were prepared under the optimized conditions. Under these conditions, the reaction proceeded smoothly providing a wide range of functionalized chromenes (Table 1). Varification of the results in Table 1 revealed that electron-releasing- groups provide products with lower yields, and electron-withdrawing substituents improved the efficiency of the reaction, providing the desired products with much higher yields.

Based on the above results, mechanistically the formation of the products (**4a**–**m**) can be visualized by initial Knoevenagel condensation of 3-cyanoacetylindoles (**1**) and aryl aldehydes (**3a–m**), followed by a Michael type nucleophilic addition of β- naphthol ring

Table 2
Antimicrobial activity of the compounds (**4a–m**)

Entry	Compound	Conc. of compound μg/well	Antimicrobial activity (zone of inhibition in mm)			
			Salmonella enterica	*Micrococcus luteus*	*Bacillus subtilis*	*Pseudomonas aeruginosa*
1	**4a**	12	6	33 (30)[a]	11	–
2	**4b**	12	17 (19)[a]	8	–	–
3	**4c**	12	–	10	–	–
4	**4e**	12	–	29 (31)[a]	8	–
5	**4f**	12	–	35 (37)[a]	–	17 (18)[a]
6	**4g**	12	–	7	–	–
7	**4h**	12	–	46 (45)[a] (45)[b]	6	–
8	**4i**	12	–	30 (32)[a] (31)[b]	–	–
9	**4j**	12	6	11	–	–
10	**4l**	12	–	30 (32)[a] (32)[b]	6	–
11	**4m**	12	17 (15)[a]	50 (50)[a] (50)[b]	–	16 (15)[a]
12	Erythromycin	15	8	10	12	10
13	Tetracycline	30	7	16	14	18

[a] Data of duplicated experiments.
[b] Data of triplicated experiments.

to the enone intermediate (**5**), and subsequent cyclodehydration to furnish regioselectively the desired compounds (Scheme 2).

The regioselectivity observed in this reaction may be rationalized by hard-soft-acid-base interaction in reaction intermediate **6** in which hydroxyl group prefer CN functionality rather than carbonyl group.

Interestingly this one-pot multicomponent approach also afforded an efficient protocol for the synthesis of bis-(chromen-indoles) **4g** and **4l** (Fig. 1) in good yields (70–72%) (Table 1).

Recently, there has been an increasing interest in using ultrasonic irradiations as a clean, green and environmentally benign source of energy for the preparation of organic compounds of synthetic and biological value.[28] Encouraged further by our recent findings in facilitating the synthesis of important heterocyclic compounds by exploiting ultrasound methodology,[26a,b] we investigated the effect of ultrasonic irradiation on the synthesis of novel 1*H*-benzo[*f*]chromen-2-yl)(1*H*-indol-3-yl)methanone (**4a–m**). Therefore an equimolar mixture of reactants **1**, **2** and **3** in the presence of triethyl amine (20 mol %) in methanol (5 mL) were placed in a Pyrex-glass open vessel and irradiated at 65 °C by ultrasonic irradiations (40 kHz) to furnish the desired products (**4a–m**) in very short reaction times (4–12 min) and good to excellent yields (70–95%) (Table 1).

The structures of all the products were fully characterized by spectroscopic (IR, ^{1}H NMR, ^{13}C NMR) and elemental analyses.[29]

The antibacterial activity of synthesized compounds **4a–m** was examined[30] using *Salmonella enterica* (SE), *Micrococcus luteus* (ML), *Bacillus subtillis* (BS) and *Pseudomonas aeruginosa* (PS). The results are tabulated in Table 2. For comparison, two routinely used antibiotics, tetracycline and erythromycin, were also included. The results revealed that most of compounds **4a–m** exhibit strong activities towards *Micrococcus luteus* (a Gram-negative bacterium). In addition, the results indicate that compounds **4a**, **4e**, **4h** and **4l** have moderate growth inhibitory activities against *B. subtilis* (a Gram-positive bacterium) as revealed by the diameters of their inhibition zones. Among these substances, **4f** and **4m** show moderate growth inhibitory effects on *Pseudomonas aeruginosa* (a Gram-negative bacterium). Also **4a**, **4b**, **4j** and **4m** have moderate activities against *Salmonella enterica*. All of the compounds listed in Table 2 exhibit weak antimicrobial activities against *B. subtilis*.

In conclusion, we have developed a simple, efficient and versatile one-pot three-component protocol for the synthesis of novel derivatives of functionalized indole-substituted chromene derivatives **4a–m** in a regiochemical manner by the reaction of 3-cyanoacetylindoles, β-naphthol, and arylaldehydes using triethyl amine under ultrasonic irradiations and conventional conditions. The reaction induced by ultrasound offered better yields and much lower reaction times than the conventional heating.

This method involves mild reaction conditions and easy work-up. These products were also evaluated for their antibacterial activities. Most of the compounds exhibited excellent antibacterial activity against *Micrococcus luteus*.

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References and notes

1. (a) Robert, S.; Bertolla, C.; Masereel, B.; Dogné, J.; Pochet, L. *J. Med. Chem.* **2008**, *51*, 3077; (b) Abrunhosa, L.; Costa, M.; Areias, F.; Venâncio, A.; Proença, F. *J. Ind. Microbiol. Biotechnol.* **2007**, *34*, 787; (c) Chimenti, F.; Bizzarri, B.; Bolasco, A.; Secci, D.; Chimenti, P.; Carradori, S.; Granese, A.; Rivanera, D.; Lilli, D.; Zicari, A.; Scaltrito, M.; Sisto, F. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3065; (d) Kostova, I. *Mini-Rev. Med. Chem.* **2006**, *6*, 365; (e) Nayyar, A.; Jain, R. *Curr. Med. Chem.* **2005**, *12*, 1873; (f) Fylaktakidou, K.; Hadjipavlou-Litina, K.; Litinas, K.; Nicolaides, D. *Curr. Pharm. Des.* **2004**, *10*, 3813; (g) Asres, K.; Seyoum, A.; Veeresham, C.; Bucar, F.; Gibbons, S.; Wilson, W.; Boykin, D. *Phytother Res.* **2005**, *19*, 557; (h) Jain, N.; Kanojia, R.; Xu, J.; Jian-Zhong, G.; Pacia, E.; Lai, M.; Du, F.; Musto, A.; Allan, G.; Hahn, D.; Lundeen, S.; Sui, Z. *J. Med. Chem.* **2006**, *49*, 3056; (i) Frédérick, R.; Robert, S.; Charlier, C.; Ruyck, J.; Wouters, J.; Pirotte, B.; Masereel, B.; Pochet, L. *J. Med. Chem.* **2005**, *48*, 7592.
2. Ellis, G. P. *The Chemistry of Heterocyclic Compounds*; Wiley, 1977. 31.
3. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.
4. Garino, C.; Tomita, T.; Pietrancosta, N.; Laras, Y.; Rosas, R.; Herbette, G.; Maigret, B.; Quéléver, G.; Iwatsubo, T.; Kraus, J. *J. Med. Chem.* **2006**, *49*, 4275; (b) Garino, C.; Tomita, T.; Pietrancosta, N.; Laras, Y.; Rosas, R.; Herbette, G.; Maigret, B.; Quéléver, G.; Iwatsubo, T.; Kraus, J. *Bioorg. Med. Chem.* **2006**, *16*, 1995.
5. (a) Santana, L.; Uriarte, E.; González-Díáz, H.; Zagotto, G.; Soto-Otero, R.; Médez-Álvarez, E. *J. Med. Chem.* **2006**, *49*, 1149; Catto, M.; Nicolotti, O.; Leonetti, F.; Carotti, A.; Favia, A.; Soto-Otero, R.; Méndez-Álvarez, E.; Carotti, A. *J. Med. Chem.* **2006**, *49*, 4912; (c) Bruhlmann, C.; Ooms, F.; Carrupt, P.; Testa, B.; Catto, M.; Leonetti, F.; Altomare, C.; Carotti, A. *J. Med. Chem.* **2001**, *44*, 3195; (d) Chimenti, F.; Secci, D.; Bolasco, A.; Chimenti, P.; Bizzarri, B.; Granese, A.; Carradori, S.; Yánez, M.; Orallo, F.; Ortuso, F.; Alcaro, S. *J. Med. Chem.* **2009**, *52*, 1935.
6. Maier, D.; Briner, C.; Ding, M.; Powell, M.; Jiang, Q.; Hill, G.; Heys, J.; Elmore, C.; Pierson, M.; Mrzljak, L. J. *Pharmacol. Exp. Ther.* **2009**, *330*, 342–351.
7. Bowers, W. S. Biochem Pharmacology; Gilbert, L. I., Kerkut, G. A., Eds.; Pergamon: Oxford, 1985; Vol. 8, p 551.
8. Bowers, W. S.; Ohta, T.; Cleere, J. S.; Marsella, P. A. *Science* **1976**, *193*, 542.
9. (a) Aggarwal, Bharat B. Chem. Abstr. 123,188,575 PCT Int. Appl. WO 9518606 A1, 1995.; (b) Chem. Abstr. 123,276,072 U.S.S.R. SU 1746675 A1, 1994.
10. William, K.; Shailaja, K.; Songchun, J.; Hong, Z.; Jianghong, Z.; Shaojuan, J.; Lifen, X.; Candace, C.; Réal, D.; Nancy, B.; Louis, V.; Sylvie, C.; Jennifer, D.; Giorgio, A.; Denis, L.; Serge, L.; Henriette, G.; Ben, T.; John, D.; Sui, X. C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4745.
11. Ahmed, M. M.; El-Saghier, M. B.; Naili, B. K.; Rammash, N. A.; Saleh Khaled, M. K. *Arkivoc* **2007**, *xvi*, 83.

12. Laurin, P.; Klich, M.; Dupis-Hamelin, C.; Mauvais, P.; Lassaigne, P.; Bonnefoy, A.; Musicki, B. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2079.
13. Tarik, E. A.; Salah, A. A. A.; Hafez, M. E.; Faten, I. H.; Ali, Z. E. *Turk. J. Chem.* **2008**, *32*, 365.
14. Tilak, R.; Richa, K. B.; Rakesh, K. S.; Vivek, G.; Deepak, S.; Mohan, P. S. I. *Eur. J. Med. Chem.* **2009**, *44*, 3209.
15. Cinzia, C.; Nicoletta, D. *Bioorg. Med. Chem.* **2010**, *18*, 6480.
16. Okram, M. S.; Nepram, S. D.; Dhanaraj, S. T.; Gurumayum, J. S. *Eur. J. Med. Chem.* **2010**, *45*, 2250.
17. Nohara, A.; Kuriki, H.; Saijo, T.; Sugihara, H.; Kanno, M.; Sanno, Y. *J. Med. Chem.* **1977**, *20*, 141.
18. Nohara, A.; Umetani, T.; Ukawa, K.; Sanno, Y. *Chem. Pharm. Bull.* **1974**, *22*, 2959.
19. Ukawa, K.; Ishiguro, T.; Wada, Y.; Nohara, A. *Heterocycles* **1931**, *1986*, 24.
20. Hsung, R. P. *J. Org. Chem.* **1997**, *62*, 7904.
21. Hsung, R. P.; Zificsak, C. A.; Wei, L.-L.; Zehnder, L. R.; Park, F.; Kim, M.; Tran, T. T. *J. Org. Chem.* **1999**, *64*, 8736.
22. Sosnovskikh, V. Ya.; Irgashev, R. A.; Levchenko, A. A. *Tetrahedron* **2008**, *64*, 6607.
23. (a) Puri, S.; Kaur, B.; Parmar, A.; Kumar, H. *Ultrason. Sonochem.* **2009**, *16*, 705; (b) Ullah, E.; Appel, B.; Fischerb, Ch.; Langera, P. *Tetrahedron* **2006**, *62*, 9694; (c) Adib, M.; Sheikhi, E.; Kavoosi, A.; Bijanzadeh, H. R. *Tetrahedron* **2010**, *66*, 9263; (d) Li, J.; Tang, W.; Lu, L.; Su, W. *Tetrahedron Lett.* **2008**, *49*, 7117; (e) Devi, I.; Bhuyan, P. J. *Tetrahedron Lett.* **2004**, *45*, 8625; (f) Abdolmohammadia, Sh.; Balalaieb, S. *Tetrahedron Lett.* **2007**, *48*, 3299.
24. Houlihan, W. J.; Remers, W. A.; Brown, R. K. *Indoles: Part I*; Wiley: New York, NY, 1992.
25. Sundberg, R. J. *The Chemistry of Indoles*; Academic: New York, NY, 1996.
26. Mamaghani, M.; Loghmanifar, A.; Taati, R. *Ultrason. Sonochem.* **2011**, *18*, 45; (b) Nikpassand, M.; Mamaghani, M.; Shirini, F.; Tabatabaeian, K. *Ultrason. Sonochem.* **2010**, *17*, 310; (c) Nikpassand, M.; Mamaghani, M.; Tabatabaeian, K. *Molecules* **2009**, *14*, 1468; (d) Samimi, H. A.; Mamaghani, M.; Tabatabaeian, K. *J. Heterocycl. Chem.* **2008**, *45*, 1765; (e) Samimi, H. A.; Mamaghani, M.; Tabatabaeian, K. *Heterocycles* **2008**, *75*, 2825.
27. Slätt, J.; Romero, I.; Bergman, J. *Synthesis* **2004**, *16*, 2760.
28. (a) Mantu, D.; Moldoveanu, C.; Nicolescu, A.; Deleanu, C.; Mangalagiu, I. I. *Ultrason. Sonochem.* **2009**, *16*, 452; (b) Li, J.-T.; Yin, Y.; Li, L.; Sun, M.-X. *Ultrason. Sonochem.* **2010**, *17*, 11; (c) Pizzuti, L.; Martins, P. L. G.; Ribeiro, B. A.; Quina, F. H.; Pinto, E. A.; Flores, F. C.; Venzke, D.; Pereira, C. M. P. *Ultrason. Sonochem.* **2010**, *17*, 34.
29. General: Melting points were measured on an electrothermal 9100 apparatus. IR spectra were determined on a Shimadzo IR-470 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz Bruker DRX-400 in DMSO-d6 as solvent and TMS as an internal standard. Chemical shifts on ^{1}H and ^{13}C NMR were expressed in ppm downfield from tetramethylsilane. Sonication was performed in Elmasonic S 40H ultrasonic cleaning unit. Elemental analyses were done on a Carlo-Erba EA1110CNNO-S analyser and agreed with the calculated values. All the chemicals were purchased from Merck and used without further purification. All solvents used were dried and distilled according to standard procedures.

General procedure for the synthesis of (4a–k): A mixture of equimolar amounts of 3-cyanoacetylindoles [27] (1 mmol), β-naphthol (1 mmol) and arylaldehydes (1 mmol) in absolute methanol (5 mL) containing triethylamine (20 mol %) was heated under reflux or by ultrasonic irradiations using Elmasonic S 40H ultrasonic cleaning unit. The progress of the reaction was monitored by TLC (EtOAc/hexane 3:2). After completion of the reaction, the reaction mixture was concentrated and cooled. The solid obtained was filtered off, washed with ethanol and recrystallized from appropriate solvent to furnish the desired pure product.

(3-Amino-1-(4-fluorophenyl)-1H-benzo[f]chromen-2-yl)(1H-indol-3-yl)methanone (4a). White solid; mp 198–201 °C; IR (KBr) (νmax/cm^{-1}); 3445, 3143, 1635, 1516, 1437, 1230, 1020, 803, 747; ^{1}H NMR (400 MHz, DMSO-d6): δH (ppm) 6.16 (s, 1H, CH), 6.74–6.78 (m, 2H, Ar-H), 6.89 (t, 2H, J = 8.8 Hz, Ar-H), 6.97 (t, 1H, J = 7.4 Hz, Ar-H), 7.18 (t, 1H, J = 7.4 Hz, Ar-H), 7.46 (m, 3H, Ar-H), 7.53 (d, 1H, J = 8.0 Hz, Ar-H), 7.60 (d, 1H, J = 7.6 Hz, Ar-H), 7.74 (m, 1H, Ar-H), 7.79 (d, 1H, J = 2.0 Hz, =CH-NH), 7.97 (d, 2H, J = 8.8 Hz, Ar-H), 8.77 (br. s, 2H, NH2), 11.67 (br., s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d6): δC (ppm) 37.0, 89.7, 112.6, 115.5, 115.7, 117.2, 118.0, 120.5, 120.7, 120.8, 122.4, 123.2, 125.8, 126.5 (d, ^{1}JCF = 224.0 Hz), 128.6 (d, ^{3}JC-F = 8.0 Hz), 128.8, 129.3 (d, ^{2}JC–F = 22.0 Hz), 130.5, 131.3, 136.4, 143.3 (d, ^{4}JC–F = 3.0 Hz), 147.6, 159.6, 162.1, 162.3, 188.0; Anal. Cald for $C_{28}H_{19}FN_2O_2$ (434.46): C, 77.41; H, 4.41; N, 6.45%. Found: C, 77.30; H, 4.28; N, 6.34%.

(3-Amino-1-(4-chlorophenyl)-1H-benzo[f]chromen-2-yl)(1H-indol-3-yl)methanone (4b). White solid; mp 220–222 °C; IR (KBr) (νmax/cm^{-1}); 3450, 3157, 1626, 1528, 14.81, 1437, 1193, 1092, 1014, 848, 744; ^{1}H NMR (400 MHz, DMSO-d6): δH (ppm) 6.16 (s, 1H, CH), 6.75 (s, 2H, Ar-H), 6.97 (s, 1H, Ar-H), 7.11–7.19 (m, 3H, Ar-H), 7.46–7.60 (m, 6H, Ar-H), 7.72–7.80 (m, 3H, Ar-H), 7.97 (br. s, 2H, NH2), 8.79 (br., s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d6): δC (ppm) 37.3, 89.4, 112.7, 117.2, 118.0, 120.2, 120.7, 120.8, 122.4, 123.2, 125.4, 125.7, 127.7, 128.8, 128.9, 129.2, 129.5, 130.5, 131.1, 131.3, 136.4, 146.0, 147.6, 162.3, 187.9; Anal. Cald for $C_{28}H_{19}ClN_2O_2$ (450.92): C, 74.58; H, 4.25; N, 6.21%. Found: C, 74.64; H, 4.30; N, 6.26%.

(3-Amino-1-(4-bromophenyl)-1H-benzo[f]chromen-2-yl)(1H-indol-3-yl)methanone (4c). White solid; mp 220–222 °C; IR (KBr) (νmax/cm^{-1}); 3448, 3221, 1639, 1518, 1236, 1095, 1011, 825, 748; ^{1}H NMR (400 MHz, DMSO-d6): δH (ppm) 6.15 (s, 1H, CH), 6.68 (d, J = 8.4 Hz, 2H, Ar-H), 6.97 (t, 1H, J = 7.4 Hz, Ar-H), 7.19 (t, 1H, J = 7.6 Hz, Ar-H), 7.24 (d, 2H, J = 8.4 Hz, Ar-H), 7.45 (m, 3H, Ar-H), 7.54 (d, 1H, J = 8.0 Hz, Ar-H), 7.60 (d, 1H, J = 8.0 Hz), 7.72 (m, 1H, Ar-H), 7.81 (d, 1H, J = 1.2 Hz, =CH-NH), 7.97 (d, 2H, J = 8.8 Hz, Ar-H), 8.79 (br., s, 2H, NH2), 11.68 (br., s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d6): δC (ppm) 37.4, 89.3, 112.7, 117.2, 118.0119.6, 120.1, 120.7, 120.8, 122.4, 123.2, 125.4, 125.7, 127.7, 128.9, 129.0, 129.2, 129.5, 130.5, 131.3, 131.8, 136.4, 146.5, 147.6, 162.3, 187.9; Anal. Cald for $C_{28}H_{19}BrN_2O_2$ (495.37): C, 67.89; H, 3.87; N, 5.66%. Found: C, 67.72; H, 3.80 N, 5.51%.

(3-Amino-1-(2,4-dichlorophenyl)-1H-benzo[f]chromen-2-yl)(1H-indol-3-yl)methanone (4d). White solid; mp 229–230 °C; IR (KBr) (νmax/cm^{-1}); 3443, 3166, 1629, 1523, 1437, 1236, 1188, 1094, 1019, 805, 744; ^{1}H NMR (400 MHz, DMSO-d6): δH (ppm) 6.44 (s, 1H, CH), 6.88 (t, J = 7.6 Hz, 1H, Ar-H), 6.94 (d, 1H, J = 8.8, Hz, Ar-H), 7.12–7.17 (m, 2H, Ar-H), 7.25 (d, 1H, J = 4.0 Hz, =CH-NH), 7.43–7.53 (m, 5H, Ar-H), 7.72–7.75 (m, 2H, Ar-H), 7.95–8.00 (m, 2H, Ar-H), 8.58 (br., s, 2H, NH2), 11.65 (br., s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d6): δC (ppm) 35.4, 89.1, 112.5, 117.4, 118.6, 119.8, 120.1, 120.7, 122.2, 123.0, 125.5, 125.9, 127.7, 128.5, 129.2, 129.3, 129.4, 129.8, 130.7, 131.2, 131.4, 131.8, 131.9, 136.5, 144.2, 147.7, 161.4, 188.4; Anal. Cald for $C_{28}H_{18}Cl_2N_2O_2$ (485.36): C, 69.29; H, 3.74; N, 5.77%. Found: C, 69.20; H, 3.75; N, 5.89%.

(3-Amino-1-(3-nitrophenyl)-1H-benzo[f]chromen-2-yl)(1H-indol-3-yl)methanone (4e). Yellow solid; mp 213–215 °C; IR (KBr) (νmax/cm^{-1}); 3434, 3138, 1632, 1524, 1438, 1344, 1195, 1086, 1024, 808, 757; ^{1}H NMR (400 MHz, DMSO-d6): δH (ppm) 6.13 (s, 1H, CH), 6.97 (t, 1H, J = 7.4 Hz, Ar-H), 7.15–7.27 (m, 2H, Ar-H), 7.34 (t, 1H, J = 7.8 Hz, Ar-H), 7.45–7.58 (m, 6H, Ar-H), 7.72 (d, 1H, J = 7.2 Hz, Ar-H), 7.83–7.87 (m, 2H, Ar-H), 7.97–8.27 (m, 2H, Ar-H), 8.84 (br., s, 2H, NH2), 11.74 (br., s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d6): δC (ppm) 37.7, 89.1, 112.7, 117.3, 118.0, 119.2, 120.4, 120.9, 121.3, 121.7, 122.5, 123.0, 125.6, 127.9, 128.8, 129.3, 130.0, 130.5, 131.3, 133.5, 136.5, 147.7, 148.1, 149.1, 162.2, 188.0; Anal. Cald for $C_{28}H_{19}N_3O_4$ (461.47): C, 72.88; H, 4.15; N, 9.11%. Found: C, 72.67; H, 4.10; N, 9.21%.

(3-Amino-1-(3-methoxyphenyl)-1H-benzo[f]chromen-2-yl)(1H-indol-3-yl) methanone (4f). White solid; mp 235–237 °C; IR (KBr) (νmax/cm^{-1}); 3444, 3150, 1626, 1529, 1434, 1261, 1193, 1094, 1036, 873, 748; ^{1}H NMR (400 MHz, DMSO-d6): δH (ppm) 3.45 (s, 3H, OCH3), 6.16 (s, 1H, CH), 6.25 (s, 1H, Ar-H), 6.34 (d, 1H, J = 7.6 Hz, Ar-H), 6.57 (d, 1H, J = 8.0 Hz, Ar-H), 6.95–7.00 (m, 2H, Ar-H), 7.19 (d, 1H, J = 7.6 Hz, Ar-H), 7.43–7.47 (m, 3H, Ar-H), 7.55 (d, 1H, J = 8.0 Hz, Ar-H), 7.62 (d, 1H, J = 8.0 Hz, Ar-H), 7.75 (d, 1H, J = 8.0 Hz, Ar-H), 7.82 (d, 1H, J = 2.0 Hz, =CH-NH), 7.97 (d, 2H, J = 8.8 Hz, Ar-H), 8.80 (br., s, 2H, NH2), 11.68 (br., s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d6): δC (ppm) 37.7, 55.0, 89.7, 111.4, 112.6, 113.0, 117.2, 118.1, 119.0, 120.5, 120.7, 120.8, 122.4, 123.4, 125.3, 125.8, 127.5, 128.7, 129.1, 129.3, 130.0, 130.7, 131.3, 136.4, 147.7, 148.7, 159.5, 162.4, 188.0; Anal. Cald for $C_{29}H_{22}N_2O_3$ (446.5): C, 78.01; H, 4.97; N, 6.27%. Found: C, 78.18; H, 4.85; N, 6.39%.

Bis-(3-amino-1-phenyl-1H-benzo[f]chromen-2-yl)(1H-indol-3-yl)methanone (4g). White solid; mp 228–230 °C; IR (KBr) (νmax/cm^{-1}); 3427, 1634, 1519, 1438,1232, 1186, 1092, 1022, 810, 747, 694; ^{1}H NMR (400 MHz, DMSO-d6): δH (ppm); 5.96 (s, 2H, CH), 6.48 (s, 4H, Ar-H), 6.86 (t, 2H, J = 7.4 Hz, Ar-H), 7.13 (t, 2H, J = 7.4 Hz, Ar-H), 7.35–7.45 (m, 6H, Ar- H), 7.47–7.50 (m, 4H, Ar-H), 7.63 (m, 4H, Ar-H), 7.91 (m, 4H, Ar-H), 8.64 (br., s, 4H, NH2), 11.54 (br., s, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d6): δC (ppm) 36.9, 89.7, 112.5, 117.2, 117.8, 120.7, 120.9, 122.3, 123.2, 125.3, 125.7, 126.8, 127.5, 128.8, 129.1, 130.5, 131.2, 136.3, 144.6, 147.8, 162.7, 187.6; Anal. Cald for $C_{50}H_{34}N_4O_4$ (754.83): C, 79.56; H, 4.54; N, 7.42%. Found: C, 79.43; H, 4.65; N, 7.28%.

(3-Amino-1-(4-chlorophenyl)-1H-benzo[f]chromen-2-yl)(5-bromo-1H-indol-3-yl) methanone (4h). White solid; mp 231–233 °C; IR (KBr) (νmax/cm^{-1}); 3426, 3242, 1635, 1519, 1481, 1440, 1231, 1185, 1091, 1013, 803, 745; ^{1}H NMR (400 MHz, DMSO-d6): δH (ppm) 6.12 (s, 1H, CH), 6.84 (d, 2H, J = 8.4 Hz, Ar-H), 7.14 (d, 2H, J = 8.4 Hz, Ar-H), 7.30 (dd, 1H, J = 8.8, 1.6 Hz, Ar-H), 7.40–7.55 (m, 4H, Ar-H), 7.78 (s, 1H, Ar-H), 7.89 (d, 1H, J = 8.0 Hz, Ar-H), 7.94–7.99 (m, 3H, Ar-H), 8.83 (br., s, 2H, NH2), 11.84 (br., s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d6): δC (ppm) 37.2, 89.2, 113.7, 114.6, 117.2, 120.2, 123.2, 125.0, 125.4, 126.4, 127.9, 128.0, 128.7, 128.9, 129.2, 129.5, 130.2, 130.5, 131.2, 131.3, 135.1, 145.8, 147.5, 162.6, 162.7, 187.1; Anal. Cald for $C_{28}H_{18}BrClN_2O_2$ (529.81): C, 63.48; H, 3.42; N, 5.29%. Found: C, 63.31; H, 3.28; N, 5.20%.

(3-Amino-1-(2,4-dichlorophenyl)-1H-benzo[f]chromen-2-yl)(5-bromo-1H-indol-3-yl) methanone (4i). white solid; mp 228–230 °C; IR (KBr) (νmax/cm^{-1}); 3450, 3252, 1635, 1520, 1438, 1231, 1185, 1096, 1016, 849, 804, 744, 688; ^{1}H NMR (400 MHz, DMSO-d6): δH (ppm) 6.40 (s, 1H, CH), 6.98 (d, J = 8.4 Hz, 1H, Ar-H), 7.16 (dd, 1H, J = 8.6, 2.2 Hz, Ar-H), 7.26 (dd, 2H, J = 8.6, 1.8 Hz, Ar-H), 7.45–7.51 (m, 4H, Ar-H), 7.55 (s, 1H, Ar-H), 7.79 (d, 1H, J = 8.0 Hz, Ar-H), 7.88 (d, 1H, J = 2.0 Hz, =CH-NH), 7.97–8.02 (m, 2H, Ar-H), 8.58 (br., s, 2H, NH2), 11.84 (br., s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d6): δC (ppm) 35.3, 89.0, 113.6, 114.5, 117.4, 117.8, 120.2, 122.3, 122.7, 124.8, 125.6, 127.9, 128.0, 128.7, 129.2, 129.9, 130.6, 130.9, 131.2, 131.8, 131.9, 135.2, 144.0, 147.7, 161.6, 161.7, 187.5; Anal. Cald for $C_{28}H_{17}BrCl_2N_2O_2$ (564.26): C, 59.60; H, 3.04; N, 4.96%. Found: C, 59.68; H, 3.24; N, 4.85%.

3-Amino-1-(pyridin-3-yl)-1H-benzo[f]chromen-2-yl)(5-bromo-1H-indol-3-yl) methanone (4j). White solid; mp 248–251 °C; IR (KBr) (νmax/cm^{-1}); 3426, 3149, 1642, 1583, 1517, 1432, 1226, 1186, 1082, 1021, 846, 801, 745; ^{1}H NMR (400 MHz, DMSO-d6): δH (ppm) 6.18 (s, 1H, CH), 7.09–7.12 (m, 1H, Ar-H), 7.21 (d, 1H, J = 8.0 Hz, Ar-H), 7.31 (dd, 1H, J = 8.4, 1.2 Hz, Ar-H), 7.45–7.56 (m, 4H, Ar-H), 7.79 (d, 1H, J = 1.2 Hz, =CH-NH), 7.92 (d, 1H, J = 8.4 Hz, Ar-H), 7.97–8.04 (m, 4H, Ar-H), 8.20–8.21 (m, 1H, Ar-H), 8.88 (br., s, 2H, NH2), 11.87 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d6): δC (ppm) 35.6, 88.8, 113.7, 114.6, 117.0, 117.2, 119.5, 123.0, 123.2, 124.3, 125.0, 125.5, 128.0, 128.1, 129.2, 129.8, 130.2, 131.3, 134.5, 135.1, 142.3, 147.6, 147.9, 148.0, 162.6, 162.7, 187.1; Anal. Cald for $C_{27}H_{18}BrN_3O_2$ (496.36): C, 65.34; H, 3.66; N, 8.46%. Found: C, 65.21; H, 3.48; N, 8.40%.

2-((5-Bromo-1H-indol-3-yl)methyl)-1-(naphthalen-2-yl)-1H-benzo[f]chromen-3-amine (4k). Pale brown solid; mp 256–258 °C; IR (KBr) (νmax/cm^{-1}); 3447, 1629, 1514, 1435, 1228, 1185, 1088, 1022, 880, 802, 742; ^{1}H NMR (400 MHz, DMSO-d6): δH (ppm) 6.29 (s, 1H, CH), 7.08 (d, 1H, J = 8.4 Hz, Ar-H), 7.17 (s, 1H, Ar-H), 7.29–7.37 (m, 3H, Ar-H), 7.43–7.53 (m, 5H, Ar-H), 7.64 (d, 1H, J = 8.8 Hz, Ar-H), 7.70 (m, 1H, Ar-H), 7.76 (d, 1H, J = 1.2 Hz, =CH-NH), 7.95–8.00 (m, 4H, Ar-H), 8.84 (br., s, 2H, NH2), 11.86 (br., s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d6): δC (ppm) 38.0, 89.5, 113.6, 114.6, 117.2, 117.4, 120.4, 123.2, 123.3, 124.7, 125.0, 125.4, 125.7, 126.1, 126.6, 127.8, 127.9, 128.1, 128.8, 129.2, 129.5, 130.1, 130.7, 131.3, 132.0, 133.1, 135.1, 144.3, 147.6, 162.6, 162.7, 187.3; Anal. Cald for $C_{32}H_{21}BrN_2O_2$ (545.44): C, 70.47; H, 3.88; N, 5.14%. Found: C, 70.22; H, 3.70; N, 5.03%.

Bis-2-((5-bromo-1H-indol-3-yl)methyl)-1-phenyl-1H-benzo[f]chromen-3-amine (4l). Pale brown solid; mp 290–293 °C; IR (KBr) (νmax/cm^{-1}); 3418, 1634, 1516, 1439, 1230, 1185, 1094, 1022, 885, 806, 745; ^{1}H NMR (400 MHz, DMSO-d6): δH (ppm) 5.94 (s, 2H, CH), 6.61 (d, 4H, J = 6.8 Hz, Ar-H), 7.26 (dd, 2H, J = 8.8, 1.6 Hz, Ar-H), 7.30–7.37 (m, 2H, Ar-H), 7.42–7.52 (m, 6H, Ar-H), 7.71 (d, 2H, J = 1.2, =CH-NH), 7.78 (d, 4H, J = 2.0 Hz, Ar-H), 7.88–8.00 (m, 4H, Ar-H), 8.70 (br., s, 4H, NH2), 11.74 (br., s, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d6): δC; 36.9, 89.6, 113.7, 114.4, 117.0, 117.1, 120.8, 121.0, 123.1, 123.2, 124.9, 125.3, 126.9, 127.8, 127.9, 128.0, 129.0, 129.1, 130.2, 130.5, 131.2, 135.0, 144.4, 144.5, 147.7, 163.0, 163.1, 186.6; Anal. Cald for $C_{50}H_{32}Br_2N_4O_4$ (912.62): C, 65.80; H, 3.53; N, 6.14%. Found: C, 65.75; H, 3.59; N, 6.10%.

(3-Amino-1-(2,4-dichlorophenyl)-1H-benzo[f]chromen-2-yl)(2-methyl-1H-indol-3-yl)methanone (4m). Pale brown solid; mp 271–273 °C; IR (KBr) (νmax/cm^{-1}); 3445, 3223, 1632, 1548, 1436, 1209, 1091, 1023, 805, 742; ^{1}H NMR (400 MHz, DMSO-d6): δH (ppm); 2.24 (s, 3H, CH3), 6.15 (s, 1H, CH), 6.67 (t, 1H, J = 7.2 Hz, Ar-H), 6.80 (d, 1H, J = 8.8 Hz, Ar-H), 7.05 (t, 1H, J = 7.6 Hz, Ar-H), 7.13–7.19 (m, 2H, Ar-H), 7.28–7.33 (m, 2H, Ar-H), 7.37–7.42 (m, 2H, Ar-H), 7.48 (d, 2H, J = 9.2 Hz, Ar-H), 7.93 (d,1H, J = 8.0 Hz, Ar-H), 7.97 (d, 1H, J = 8.0 Hz, Ar-H), 8.71 (br., s, 2H, NH2), 11.50 (br., s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d6): δC (ppm); 12.5, 35.3, 90.0, 111.6, 117.4, 118.0, 119.8, 120.4, 121.3, 122.9, 125.4, 126.1, 127.5, 128.3, 129.1, 129.2, 130.0, 130.7, 131.2, 131.5, 131.7, 132.0, 135.0, 139.6, 144.2, 147.6, 161.4, 161.5, 189.3; Anal. Cald for $C_{29}H_{20}Cl_2N_2O_2$ (499.39): C, 69.75; H, 4.04; N, 5.61%. Found: C, 69.61; H, 4.18; N, 5.54%.

30. *Determination of antimicrobial activity*: The antibacterial activity of the synthesized compounds (4a–m) was examined using Salmonella enterica (SE), Micrococcus luteus (ML), Bacillus subtilis (BS) and Pseudomonas aeruginosa (PS). All media were prepared according to manufacturers' instructions. A colony of each test organism was subcultured from nutrient agar plates into nutrient broth and incubated at 37 °C for 18 h. Mueller-Hinton agar plates were prepared and four plates were inoculated with bacteria from nutrient broth cultures. The antibacterial activity was performed by well diffusion technique. A concentration of 100 μg/ml of sample was prepared in DMSO. A sterilized glass tube (5 mm diameter) was used to aseptically scoop out the solid medium from the plate to create wells and 40 μL of the sample solution (12 μg/well) was aseptically added. The plates were incubated at 37 °C for 24 h. After incubation, zone of inhibition was measured.