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$InCl_3$ mediated one-pot multicomponent synthesis, anti-microbial, antioxidant and anticancer evaluation of 3-pyranyl indole derivatives

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ABSTRACT

A simple and convenient method for the one-pot three-component synthesis of 3-pyranyl indoles has been accomplished by tandem Knoevenagel–Michael reaction of 3-cyanoacetyl indole, various aromatic aldehydes and malononitrile catalyzed by $InCl_3$ in ethanol under reflux conditions. The newly synthesized 3-pyranyl indoles were evaluated for anti-microbial, antioxidant, and anticancer activities. Some of the compounds showed good anticancer activity against MCF-7 breast cancer cell lines on comparison with of standard drug.

The structural diversity and biological importance of nitrogen containing heterocycles have made them attractive targets for synthesis over many years. They are found in various natural products and have been identified as products of chemical and biological importance. Multicomponent reactions (MCR) have emerged as a powerful tool for delivering the molecular diversity needed in the combinatorial approaches for the preparation of bioactive heterocyclic compounds.[1,2]

Multifunctionalized 4*H*-pyrans are important class of compounds present in several natural or synthetic compounds with important biological or pharmacological activities such as anticoagulant, anticancer, antioxidant, spasmolytic, diuretic, and anti-anaphylactic activities. A number of 2-amino-4*H*-pyran derivatives are used as photoactive materials, cosmetics, and pigments.[3] Hence, the synthesis of 4*H*-pyrans has received a great attention of the researchers.

Interest in synthesizing new indole derivatives continue due to their biological properties such as anti-inflammatory, anticonvulsant, cardiovascular, antibacterial, and also their presence in various natural products such as alkaloids.[4] In particular, 3-substituted indole derivatives play a key role in the synthesis of biologically active compounds especially with anticancer, antitumor, hypoglycemic, anti-inflammatory, analgesic and antipyretic activities.[5] Some of the biologically active 3-substituted indole representatives are shown in Figure 1.[6]

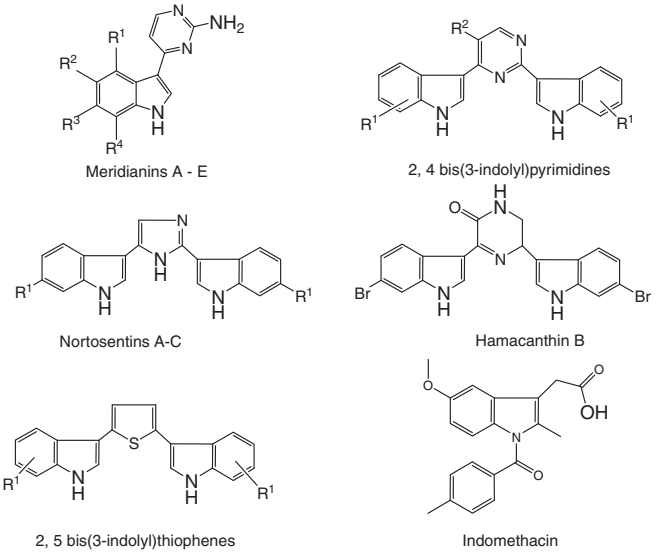
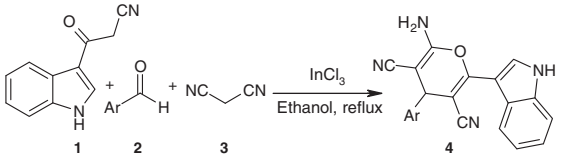


Figure 1. Representatives of 3-substituted indoles.



Scheme 1. Synthesis of 3-pyranyl indole derivatives.

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Table 1
Screening of various Lewis acids and bases in ethanol

Entry	Lewis acids and bases	Yield[a,b] (%)
1	$SnCl_2{\cdot}2H_2O$	52
2	$AlCl_3$	26
3	$InCl_3$	85
4	K_2CO_3	38
5	NaOH	21
6	Pyridine	74
7	NEt_3	83

[a] Isolated yield.
[b] All reactions were carried out with 20 mol % of Lewis acids and bases for 40 min at reflux temperature.

The wide-ranging biological activity associated with 3-substituted indole and pyran derivatives, both naturally occurring and synthetic, ensures that the synthesis of these important ring systems remains a topic of current interest. Various methods for the preparation of these compounds have been reported. However, these methods suffer from tedious synthetic routes, longer reaction time, drastic reaction conditions, as well as narrow substrate scope.[7–9]

Recently, the utility of indium(III) Lewis acids[10] in organic synthesis has received a great attention due to their relatively low toxicity, stability in air and water and recyclability. To the best of our knowledge, there have been no reports for the synthesis of indol-3-yl derivatives including pyranyl moieties using 3-cyanoacetyl indole. In continuation of our research on the development of new synthetic methods for 3-substituted indoles,[11–13] use of green chemical techniques,[14–16] and the application of $InCl_3$[11,17] in organic synthesis, herein, we report a simple and facile one pot procedure for the synthesis of 3-pyranyl indole derivatives in ethanol under reflux condition.

In our initial endeavor, we have investigated a three component reaction of 3-cyanoacetyl indole **1**, benzaldehyde **2a**, and malononitrile **3** in different solvent systems like methanol, ethanol, toluene, and acetonitrile and in presence of various Lewis acids and bases under reflux condition to afford polyfunctionalized 3-pyranyl indoles **4** (Scheme 1).

Among the Lewis acids (Table 1, entry 1, 2, and 3) tried by us, $InCl_3$ has catalyzed the reaction in shorter reaction time with high yield. Among the bases (Table 1, entry 4, 5, 6, and 7) triethyl amine has catalyzed the reaction with high yield. The best results were obtained by refluxing the reaction mixture in ethanol in presence of 20 mol % of $InCl_3$.

The scope and limitations of the reaction were further studied with various substituted aldehyde derivatives. Under optimized conditions, the reaction proceeded smoothly with various aldehydes, including those containing electron withdrawing and electron releasing groups to provide 3-pyranyl indoles **4a–q** in good yields (68–87%). The results are given in Table 2.

Based on the above results, a plausible mechanism is proposed (Scheme 2). Initially malononitrile **3** undergoes tautomerisation to give **3a**. 3-Cyanoacetyl indole **1** undergoes Knoevenagel condensation with aromatic aldehyde **2** to give **1a** in presence of $InCl_3$. The intermediate **1a** can be isolated and its formation was proved by NMR.[24] Compound **1a** undergoes Michael addition with the tautomer of malononitrile **3a** to give **3b**. Compound **3b** enolises to afford the intermediate **3c** which gives **3d** via the nucleophilic addition of hydroxyl group to the cyano group. Finally **3d** rearranges via proton transfer to yield 3-pyranyl indole **4**.

The structures of 3-pyranyl indole derivatives **4a–q** were confirmed by spectroscopic studies and elemental analysis. IR spectrum of **4b** showed peaks at 3423, 3332, and 2198 for $-NH_2$ and –CN groups, respectively.[25] The ^{1}H NMR spectrum of compound **4b** exhibited two singlets at δ 5.38 and 11.97 for benzylic proton and –NH proton of indole ring, respectively, which proved the incorporation of indole ring in the structure. The benzylic characteristic carbon was resonated at δ 56.8 in the ^{13}C NMR spectrum. The aromatic protons were appeared in the region of δ 112.9-159.3. Moreover, the presence of a molecular ion peak at m/z 388.4 (M^+) in the mass spectrum of **4b** confirmed the structure of **4b**. The relative stereochemistry of the product **4b** was established through single-crystal X-ray analysis (Fig. 2).[18]

The characteristic peaks of $-NH_2$ and –CN groups were appeared at 3433, 3316, and 2200, respectively, in the IR spectrum of **4q**.[26] In the ^{1}H NMR spectrum of **4q**, the benzylic proton resonated as a singlet at δ 4.82. A singlet at δ 6.07 appeared for $-OCH_2O-$ protons in ^{1}H NMR spectrum. The signal at δ 11.95 corresponds to –NH proton of indole ring. The benzylic carbon signal was appeared at δ 55.2 ppm in ^{13}C NMR spectrum of **4q**. The aromatic carbons were resonated in the region of δ 112.8–159.4 in the ^{13}C NMR spectrum. The mass spectrum displayed the (M^+) peak at m/z 461.2. The stereochemistry of the product was assigned by analogy of compound **4b**.

The newly synthesized compounds have indole and pyran nuclei in their structures which possess antibacterial, antioxidant and anticancer properties.[3–5] Hence, we have decided to study antibacterial, antioxidant and anticancer activities for all the newly synthesized compounds.

All compounds **4a–q** were screened for their antibacterial activity by paper disc diffusion method[19] against two Gram-positive bacteria (*Staphylococcus aureus* ATCC 9144, *Bacillus cereus* ATCC 11778), and two Gram-negative bacteria (*Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 11298). Ciprofloxacin is used as reference compound. In this technique, the filter paper (Whatmann No. 1) sterile disks of 6 mm diameter impregnated with the test compounds (100 μg/ml of dimethyl formamide) were placed in the nutrient agar plates[20] and the plates were pre-incubated for 1 h at room temperature and incubated at 37 °C for 24 h for antibacterial activity. The inhibition zones around the dried disks were measured after 24 h. MIC of the compound was determined by agar streak dilution method.[20] A stock solution of the synthesized compound (100 μg ml^{-1}) in dimethyl formamide was prepared and graded quantities of the test compounds were incorporated in specified quantity of molten sterile agar (nutrient agar for antibacterial activity). A specified quantity of the medium (40–50 °C) containing the compound was poured into a petridish to give a depth of 3–4 mm and allowed to solidify. Suspension of the micro-organism were prepared to contain approximately 10^5 CFU ml^{-1} (colony forming unit/ml) and applied to plates with serially diluted compounds in dimethyl formamide to be tested and incubated at 37 °C for 24 h for bacteria. The MIC was considered to be the lowest concentration of the test substance exhibiting no visible growth of bacteria on the plate. The observed zone of inhibition and MIC are presented in Table 3 which shows the observed antibacterial activities of 3-pyranyl indoles. The diameter of zone of inhibition was measured in mm. 2-Amino-4-(2-chlorophenyl)-6-(1*H*-indol-3-yl)-4*H*-pyran-3,5-dicarbonitrile **4e** was found to exhibit the more potent invitro antibacterial activity with the MIC of 12.4, 16.4, 16.5, and 16.1 against *S. aureus*, *B. cereus*, *E. coli*, *K. pneumoniae*, respectively. The compounds **4a**, **4d**, **4h**, and **4m** exhibited significant antibacterial activity when compared to standard drug ciprofloxacin due to the presence of the substituents such as –Cl, –F, –OMe groups in the benzene ring. Other compounds showed moderate antibacterial activity.

The newly synthesized compounds **4a–q** were also tested for antioxidant activity by observing their interaction with the stable free radicals DPPH[21] and ABTS[22] using the standard drug ascorbic acid (Tables 4 and 5). The antioxidant activity of the test compounds and standard were assessed on the basis of the radical scavenging effect of the stable DPPH free radical. To a 50, 100, 200, and 400 μg/ml

Table 2
Synthesis of 3-pyranyl indole derivatives

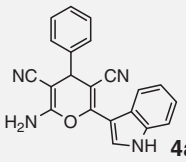
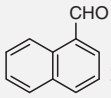
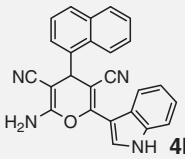
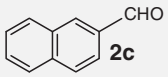
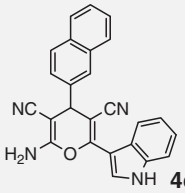
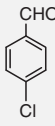
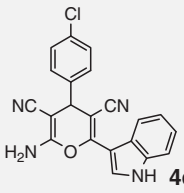
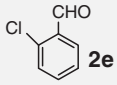
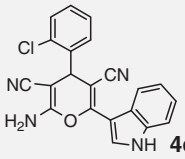
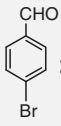
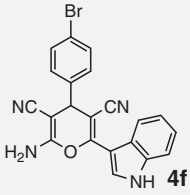
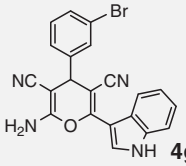
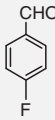
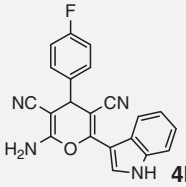
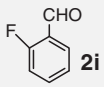
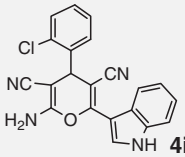
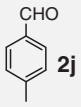
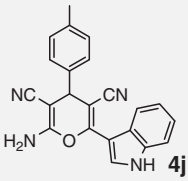
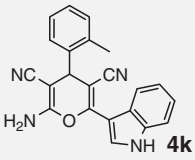
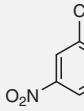
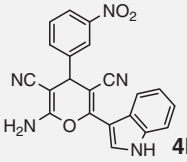
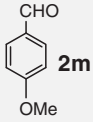
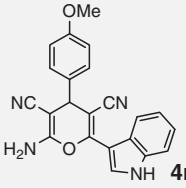
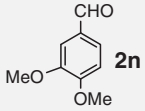
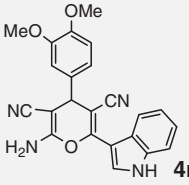
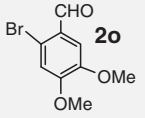
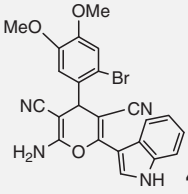
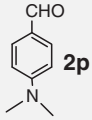
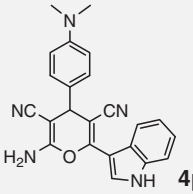
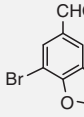
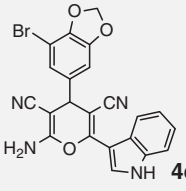
Entry	Aldehyde	Product[a]	Time (min)	Yield[b] (%)
1	 **2a**	 **4a**	30	87
2	 **2b**	 **4b**	40	81
3	 **2c**	 **4c**	45	76
4	 **2d**	 **4d**	30	82
5	 **2e**	 **4e**	45	72
6	 **2f**	 **4f**	30	88
7	 **2g**	 **4g**	45	71
8	 **2h**	 **4h**	35	82
9	 **2i**	 **4i**	50	68

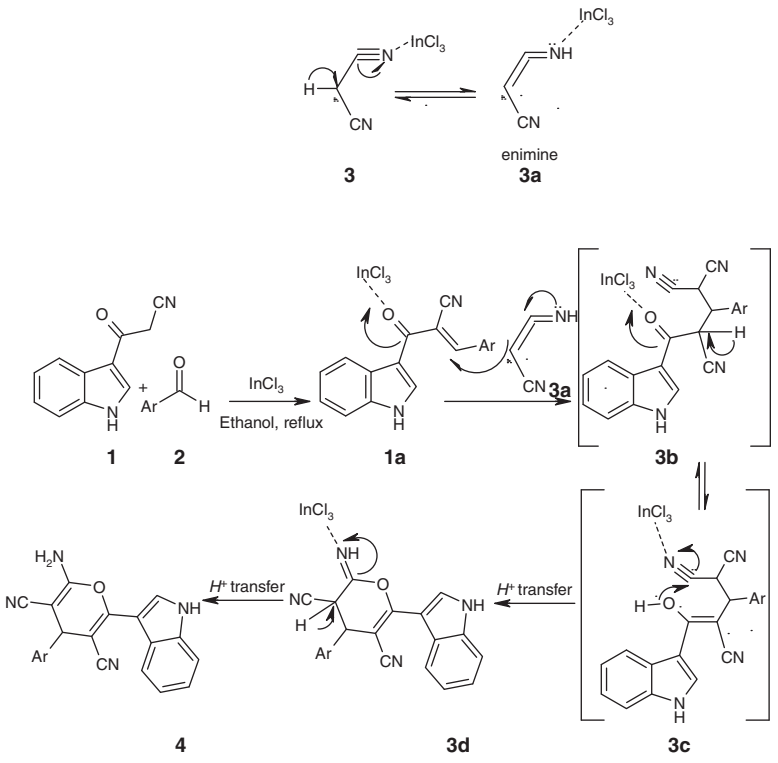
Table 2 (*continued*)

Entry	Aldehyde	Product[a]	Time (min)	Yield[b] (%)
10	 **2j**	 **4j**	30	83
11	 **2k**	 **4k**	40	71
12	 **2l**	 **4l**	45	68
13	 **2m**	 **4m**	45	81
14	 **2n**	 **4n**	40	71
15	 **2o**	 **4o**	45	68
16	 **2p**	 **4p**	35	76
17	 **2q**	 **4q**	40	72

[a] The products were characterized by NMR, IR, mass and elemental analysis.
[b] Isolated yield.

of each test compounds and standard, 1 ml of DPPH and methanol (0.33%) were added in a test tube. After incubation at 37 °C for 30 min, the absorbance of each solution was determined at 517 nm using spectrophotometer. The corresponding blank reading was also taken and the results in percentage were expressed as the ratio of absorbance decrease at 517 nm and the absorbance of DPPH solution in the absence of 3-pyranylindoles.

[***]The antioxidant activity of the test compounds and standard were assessed on the basis of the radical scavenging effect of the stable ABTS free radical. The $ABTS^{\cdot+}$ solution was prepared by mixing 0.02 mol of ABTS salt with 0.01 mol of potassium persulfate in 25 ml of distilled water. The solution was held at room temperature in the dark for 16 h before use. Then the $ABTS^{\cdot+}$ solution was diluted with methanol in order to obtain an absorbance between



Scheme 2. Plausible mechanism for the synthesis of 3-pyranyl indoles **4**.

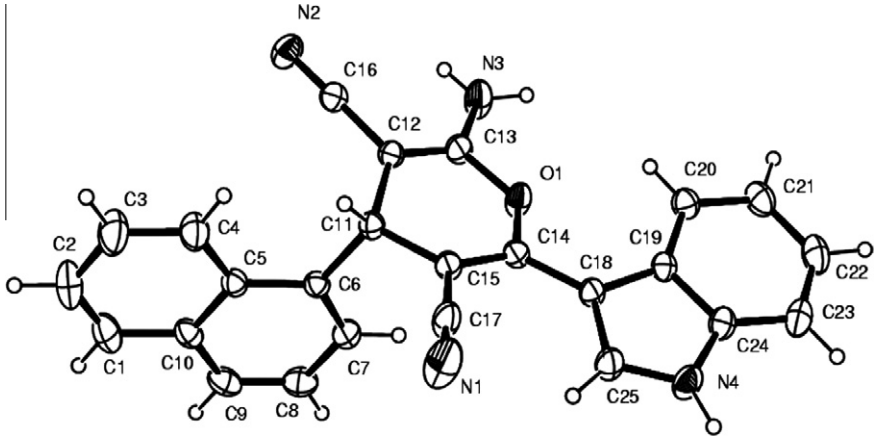


Figure 2. ORTEP diagram of compound **4b**.

0.7 and 0.9 at 734 nm using the spectrophotometer. Fresh $ABTS^{\cdot+}$ solutions were prepared for each assay. To a 50, 100, 200, and 400 μg/ml of each test compounds and standard, 1 ml of $ABTS^{\cdot+}$ solution was added and allowed to react for 2 h in dark condition. Then the absorbance was taken at 734 nm using the spectrophotometer. The corresponding blank reading was also taken and the results in percentage were expressed as the ratio of absorbance decrease at 734 nm and the absorbance of $ABTS^{\cdot+}$ solution in the absence of 3-pyranylindoles.

The compounds **4m**, **4n**, **4o**, and **4p** showed good radical scavenging activity in both DPPH and ABTS method due to the presence of electron donating groups such as –OMe and $-N(CH_3)_2$ in the benzene ring when compared with the standard drug ascorbic acid in both DPPH and ABTS method. Other compounds except **4c**, **4d**, **4g**, **4i**, and **4l** showed moderate antioxidant activity. IC_{50} values of the compounds **4m**, **4n**, **4o**, and **4p** were found to be less than 50 μg/ml in DPPH method. The IC_{50} value of the standard ascorbic acid in DPPH method is found to be less than 50 μg/ml. The IC_{50} values of the compounds in ABTS method **4m**, **4n**, **4o**, and **4p** were found to be 900, 858.69, 867.28, and 880.30 μg/ml, respectively. IC_{50} value of the standard ascorbic acid in ABTS method is found to be 650 μg/ml. The analysis of Tables 4 and 5 leads us to conclude that radical scavenging activity of 3-pyranyl indoles in both DPPH and ABTS method increases with increase in the concentration (Figs. 3, 4 and 5).

The compounds **4b**, **4c**, **4f**, **4h**, **4i**, and **4n** were evaluated for anticancer activity against MCF-7 breast cancer cell lines using the standard drug doxorubicin (Table 6). In vitro cytotoxicity was determined using a standard MTT assay[23] with protocol appropriate for the individual test system. MTT [(3-(4,5-dimethylthiazol-2yl)-2,5-diphenyltetrazoliumbromide] measures the metabolic activity of the viable cells. During incubation period, viable cells convert MTT to a water-insoluble formazan dye. In brief, exponentially growing cells were plated in 96-well plates (10^4 cells/wells in

Table 3
Antibacterial activity of the synthesized compounds—in vitro activity—zone of inhibition in mm (MIC 100 μg/ml)

Compounds	Gram-positive bacteria		Gram-negative bacteria	
	S. aureus	*B. cereus*	*E. coli*	*K. pneumoniae*
4a	22 (15.2)	16 (18.5)	18 (19.6)	18 (20.2)
4b	15 (28.6)	16 (26.2)	16 (28.0)	15 (33.2)
4c	14 (32.4)	15 (23.3)	16 (29.4)	15 (30.5)
4d	23 (13.4)	18 (19.0)	19 (21.5)	18 (17.5)
4e	24 (12.4)	17 (16.4)	21 (16.5)	20 (16.1)
4f	20 (21.3)	14 (28.0)	15 (25.4)	16 (26.3)
4g	16 (27.5)	14 (24.0)	14 (30.2)	14 (26.3)
4h	21 (16.8)	16 (20.3)	18 (26.2)	17 (20.1)
4i	19 (23.4)	14 (22.6)	15 (27.4)	15 (30.2)
4j	20 (22.3)	14 (25.8)	15 (36.3)	17 (25.1)
4k	16 (25.0)	15 (27.8)	16 (26.0)	15 (27.2)
4l	19 (24.0)	13 (35.4)	16 (27.5)	15 (25.5)
4m	21 (15.4)	16 (24.5)	18 (23.4)	19 (19.6)
4n	15 (31.8)	16 (25.4)	17 (26.7)	17 (21.2)
4o	20 (21.0)	14 (24.5)	16 (29.5)	19 (33.4)
4p	18 (23.8)	15 (25.6)	17 (26.7)	16 (25.2)
4q	19 (23.5)	13 (28.7)	17 (27.3)	16 (24.8)
Ciprofloxacin	26 (0.2)	25 (0.3)	27 (0.2)	26 (0.1)
Blank	–	–	–	–

(–) Showed no antibacterial activity.

Table 4
Antioxidant activities of the test compounds and standard using DPPH scavenging method—% DPPH radical scavenging activity

Compounds	Concentration				
	50 μg/ml (%)	100 μg/ml (%)	200 μg/ml (%)	400 μg/ml (%)	IC_{50} (μg/ml)
4a	38	46	49.7	51.2	308.2
4b	18.78	21.82	22.84	26.39	1599.62
4c	–	–	–	–	–
4d	–	–	–	–	–
4e	27.9	34.01	39.59	45.68	467.49
4f	46.7	49.7	54.3	57.8	117.8
4g	–	–	–	–	–
4h	26.9	28.9	31.4	36.5	901.11
4i	–	–	–	–	–
4j	24.8	25.8	28.9	30.4	1590.74
4k	25.8	27.42	28.32	32.46	1371.65
4l	–	–	–	–	–
4m	53.6	56.88	59.89	60.25	<50
4n	55.8	57.86	59.09	62.90	<50
4o	51.7	53.8	57.3	64.4	<50
4p	72.1	73.12	74.64	75.66	<50
4q	20.3	23.8	25.8	22.84	1779.24
Ascorbic acid	77.15	79.69	82.30	85.34	<50
Blank	–	–	–	–	–

(–) Showed no scavenging activity.

100 μl of medium) and incubated for attachment. Test compounds and standard drug doxorubicin were prepared prior to the experiment by dissolving in 0.1% DMSO and diluted with medium. The cells were then exposed to different concentrations of the drugs (1–100 μm) in the volume of the 100 μl/well. Cells in the control wells were received the same volume of the medium containing 0.1% DMSO. After 24 h, the same volume of the medium was removed and cell cultures were incubated with 100 μl MTT reagent (1 mg/ml) for 4 h at 37 °C. The formazan produced by the viable cells was soluble by the addition of 100 μl DMSO.

The suspension was placed on a micro-vibrator for 5 min and the absorbance was recorded at 540 nm by the ELISA reader. The experiment was performed in triplicate. The percentage cytotoxicity was calculated using the formula.

Table 5
Antioxidant activities of the test compounds and standard using ABTS scavenging method—% ABTS radical scavenging activity

Compounds	Concentration				
	50 μg/ml (%)	100 μg/ml (%)	200 μg/ml (%)	400 μg/ml (%)	IC_{50} (μg/ml)
4a	14.4	19.28	24.5	26.7	993.66
4b	4.7	6.8	7.7	10.4	>1000
4c	–	–	–	–	–
4d	–	–	–	–	–
4e	8.5	10.4	14.5	21.4	>1000
4f	14.2	14.57	10.57	22.7	947.09
4g	–	–	–	–	–
4h	8.4	16.2	22.4	26.7	960.00
4i	–	–	–	–	–
4j	5.2	5.5	6.2	8.5	>1000
4k	10.4	17.23	21.43	25.7	>1000
4l	–	–	–	–	–
4m	12.4	20.0	26.4	28.7	858.69
4n	14.5	19.1	26.1	28.1	867.28
4o	18.5	20.5	24.2	26.7	880.30
4p	14.4	18.5	20.5	26.7	900.00
4q	5.7	6.4	10.0	12.5	>1000
Ascorbic acid	28.8	29.7	31.5	33.4	650.00
Blank	–	–	–	–	–

(–) Showed no scavenging activity.

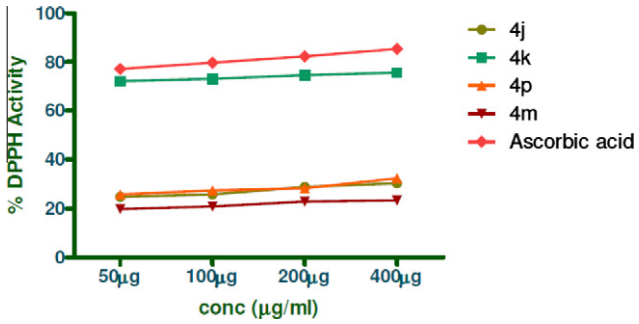


Figure 3. Free radical scavenging activity of compounds **4j**, **4k**, **4p**, and **4m**.

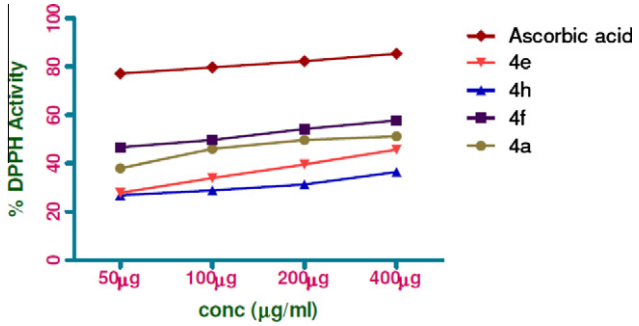


Figure 4. Free radical scavenging activity of compounds **4e**, **4h**, **4f**, and **4a**.

$$\text{Cytotoxicity } \% = \{[(\text{control abs} - \text{blank abs}) - (\text{test abs} - \text{blank abs})]/(\text{control abs} - \text{blank abs})\} * 100$$

The compounds **4b** and **4c** exhibited good cytotoxicity due to the presence of naphthalene ring and other compounds showed moderate activity when compared with the standard drug doxorubicin. The growth inhibition GI_{50} of the compounds **4b** and **4c** were found to be 18.2, 15.5 μm, respectively, and for the standard it was found to be 0.02 μm.

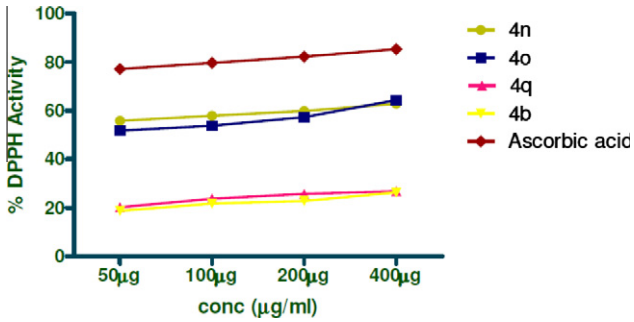


Figure 5. Free radical scavenging activity of compounds **4n**, **4o**, **4q**, and **4b**.

Table 6
Report of cytotoxicity against MCF-7 breast cancer cell lines

Compounds	MCF-7		
	GI_{50} (µm)	TGI (µm)	LC_{50} (µm)
4b	18.2	33.9	80.2
4c	15.5	46.6	91.5
4f	21.8	48.1	>100
4h	28	52.4	>100
4i	22.8	48.2	>100
4n	20.6	37.4	72.1
Doxorubicin	0.02	0.21	0.74
Blank	—	—	—

(—) Showed no cytotoxic activity.

The lethal concentration (LC_{50}) of the compounds **4b** and **4c** were found to be 80.2 and 91.5 µm, respectively, and for the standard it was found to be 0.74 µm. Lethal concentration of the above title compounds are more when compared to standard drug doxorubicin (Table 6). Thus, the compounds **4b** and **4c** are much more safety than the standard drug and showed significant anticancer activity.

In conclusion, we have developed an $InCl_3$ mediated simple and efficient one-pot synthesis of 3-pyranyl indole derivatives. A privileged medicinal scaffold was synthesized through a three-component reaction of 3-cyanoacetyl indole, benzaldehyde and malononitrile. The synthesized compounds showed good to moderate antibacterial, antioxidant and anticancer activities. Further studies to delineate the scope and limitations of the present methodology are underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.07.039.

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18. Crystallographic data of compound **4b** in this paper have been deposited with the Cambridge Crystallographic Data centre as supplemental publication no. CCDC-767159. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 01223 336033 or email: deposit@ccdc.cam.ac.uk).
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24. Compound **2a**: ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.41(s, 1H), 7.23–7.27 (m, 2H), 7.53–7.56 (m, 3H), 8.0–8.02 (m, 2H), 8.18–8.22 (m, 2H), 8.45 (s, 1H), 12.31 (s, 1H, -N*H*, D_2O exchangeable); ^{13}C NMR (125 MHz, DMSO-d_6): δ 112.1, 113.1, 114.1, 118.2, 121.9, 123.0, 124.2, 126.7, 129.7, 130.8, 132.8, 132.9, 136.7, 137.3, 152.7, 181.9.
25. Typical experimental procedure for **4b**: A mixture of 3-cyanoacetyl indole **1**, naphthaldehyde **2b** (1 mmol) and malononitrile **3** (1.0 mmol) was refluxed in ethanol in presence of 20 mol % of $InCl_3$. The reaction mixture was refluxed for futher 40 min and cooled to room temperature. The solid formed in the reaction mixture was filtered, dried and recrystallized in ethanol to obtain the

pure product in good yield (81%). *2-Amino-6-(1H-indol-3-yl)-4-(naphthalen-1-yl)4H-pyran-3,5-dicarbonitrile* (Table 1, entry 2): White solid mp 242–244 °C; R_f 0.25 (50% AcOEt/Petroleum ether); IR (KBr): 3423, 3332, 2198, 1667, 1527, 1399, 1140, 778, 747 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 5.38 (s, 1H, -CH), 7.15 (t, 1H, J = 6.85 Hz, Ar-H), 7.22 (t, 1H, J = 7.65 Hz, Ar-H), 7.29 (s, 2H, –NH_2, D_2o exchangeable), 7.48–7.56 (m, 5H, Ar-H), 7.89–7.98 (m, 3H, Ar-H), 8.10 (d, 1H, J = 7.25 Hz, Ar-H), 8.38 (d, 1H, J = 7.65 Hz, Ar-H), 11.97 (br s, 1H, –N*H*, –D_2O exchangeable); ^{13}C NMR (125 MHz, DMSO-d_6): δ 56.8, 84.9, 105.9, 112.6, 119.4, 119.8, 121.5, 122.1, 123.2, 123.6, 125.1, 126.5, 126.9, 128.9, 129.4, 129.8, 131.5, 134.2, 136.5, 156.4, 159.3; MS (EI): m/z 388.42 [M^+]; Anal. Calcd for $C_{25}H_{16}N_4O$: C, 77.30; H, 4.15; N, 14.42. Found: C, 77.50; H, 4.14; N, 14.39.

26. Typical experimental procedure for **4q**: A mixture of 3-cyanoacetyl indole **1**, and 7-bromobenzo[*d*[1,3dioxole-5-carbaldehyde **2q** (1 mmol) and malononitrile **3** (1.0 mmol) was refluxed in ethanol in presence of $InCl_3$. The reaction mixture was refluxed for 40 min and cooled to room temperature. The solid formed in the reaction mixture was filtered, dried and recrystallized in ethanol to obtain the pure product in good yield (72%). *2-Amino-4-(7-bromo-3a,4-dihydrobenzo[d][1,3]dioxol-5-yl)-6-(1H-indol-3-yl)-4H-pyran-3,5-dicarbonitrile* (Table 1, entry 17): Yellow solid; mp 258–260 °C; R_f 0.25 (40% AcOEt/Petroleum ether); IR (KBr): 3433, 3316, 2200, 1670, 1480, 1150, 742 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 4.82 (s, 1H, –CH), 6.07 (s, 2H, –CH_2), 6.96 (s, 1H, Ar-H), 7.12 (t, 1H, J = 6.85 Hz, Ar-H), 7.18–7.20 (m, 2H, Ar-H), 7.29 (s, 2H, –NH_2, –D_2O exchangeable), 7.47 (d, 1H, J = 7.65 Hz, Ar-H), 7.93 (d, 1H, J = 8.4 Hz, Ar-H), 8.10 (d, 1H, J = 6.55 Hz, Ar-H), 11.95 (br s, 1H, –N*H*, D_2O exchangeable); ^{13}C NMR (125 MHz, DMSO-d_6): δ 31.2, 55.2, 83.2, 102.9, 105.9, 112.8, 112.9, 113.7, 119.1, 119.4, 121.4, 122.2, 123.2, 125.0, 129.9, 136.4, 148.5, 156.6, 159.4; MS (EI): m/z 461.20 [M^+], 463.20 [M^++2]; Anal. Calcd for $C_{22}H_{13}BrN_4O_3$: C, 57.28; H, 2.84; N, 12.15. Found: C, 57.43; H, 2.87; N, 12.11.