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A FACILE AND ONE-POT SYNTHESIS OF PYRONE DERIVATIVES VIA IONIC LIQUID CATALYSED KNOEVENAGEL REACTION AND THEIR BIOLOGICAL EVALUATION

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ABSTRACT A series of novel pyrone derivatives was synthesized by using a green chemistry approach i.e. by the use of an ionic liquid, 1-butyl-3-methylimidazolium bromide. The three component one-pot synthesis of pyrone involves the *Knoevenagel* condensation reaction of 4-hydroxy-6-methyl-pyrone, malononitrile and substituted aromatic aldehydes. The representative compounds were characterized by spectral data such as ^{1}H NMR, ^{13}C NMR and Mass analysis. All the synthesized pyrone derivatives were evaluated for their antimicrobial and anticancer potential. Among the compounds synthesized, **1d, 1f** and **1l** showed moderate antibacterial activity (Table 2) against *E. coli* strain. Against HCT-116 cells, **1a, 1c, 1d, 1e, 1k, 1l** and **1n** compounds and against MCF-7 cells, **1b, 1i, 1l** and **1n** compounds displayed anticancer activity. The common pyrone derivatives like **1d, 1f** and **1l** have both antimicrobial and anticancer properties.

KEYWORDS 4-Hydroxy-6-methylpyrone, Green Chemistry, 1-Butyl-3-methylimidazolium bromide, *Knoevenagel* condensation, anticancer activity

INTRODUCTION

Pyrone derivatives have attracted substantial attention from organic and medicinal chemists due to their useful biological and pharmacological properties such as spasmolytic, diuretic, anticoagulant, antimicrobial, anticancer and, anti-inflammatory, neurodegenerative diseases, AIDS associated dementia, Down's syndrome, Schizophrenia, myoclonus and anti-anaphylactic activity[1,2]. Pyrone derivatives can be synthesized by different methods using various catalysts[3], such as piperidine[4], KF-Alumina[5], phase transfer catalyst[6], $(NH_4)HPO_4$, and sodium selenite[7]. They can also be synthesized under microwave and ultrasound irradiations[8].

A highly efficient, convenient and facile method is employed for the synthesis of pyrone derivatives in the presence of ionic liquid, [bmim]Br as a catalyst and in aqueous ethanolic medium. The versatility of this ionic liquid encouraged us to study its utility for one-pot, three component synthesis of pyrones by green synthesis approach. The reaction between 4-hydroxy-6-methyl-pyrone, malononitrile, and aromatic aldehydes follows *Knoevenagel* condensation reaction[9] (Scheme 1). This reaction is catalysed by strong bases that often lead to undesirable side reactions. A variety of Lewis acids are found to catalyse this reaction, and these procedures are also not free from disadvantages. Thus, room temperature ionic liquids, particularly [bmim]Br, have been used as alternative green solvents to carry out the *Knoevenagel* condensation. The attractive features of this protocol are operational simplicity, mild reaction conditions, excellent yields of products, easy work up procedure[10-18].

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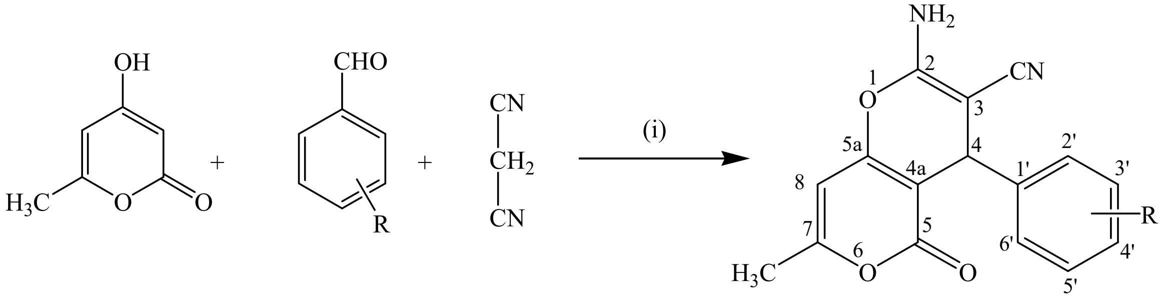

1a-p

Reagents and Conditions:- (i) 1-Butyl-3-methylimidazolium bromide, RT, 4-6 hr;

R:	1a	4-F	1g	4-OC_2H_5	1l	2-furan
	1b	3-phenylprop-2-en	1h	2,3,4-triOCH_3	1m	2-NO_2
	1c	4-NO_2	1i	4-pyridine	1n	4-OH-3-OCH_3
	1d	4-Cl-3-NO_2	1j	3-OH	1o	3-OH-4-OCH_3
	1e	4-Cl	1k	2-OCH_3	1p	2-NO_2
	1f	2,4-diCl				

SCHEME-1

Ionic liquids are liquids that consist exclusively of ions[19]. They exhibit ionic conductivity. They have low viscosities, low vapour pressures, melting points or glass-transition temperatures below 100^0 C and high thermal and chemical stabilities. They are non-flammable, have wider liquid ranges, electrochemical windows, readily recycled, exploited as solvents and new materials for wide-ranging applications spanning, for example, electrochemistry, organic chemistry, inorganic chemistry, biochemistry, materials science and pharmaceuticals[12, 20-30]. They contribute significantly to the development of green chemistry and green technology.

EXPERIMENTAL

Materials and methods

All the chemicals were procured from Sigma-Aldrich, SD Fine chemicals, Ranbaxy fine chemicals, Merck Pvt. Ltd. The Ionic liquid, 1-butyl-3-methylimidazolium chloride is procured from Sigma-Aldrich and all the remaining chemicals and reagents used were of analytical grade (AR). The progress of reactions was monitored by Merck TLC silica gel 60 F_{254} plates. Melting points were determined on shital melting point apparatus, which has an accuracy of ±1°C. Fourier transform infrared (FTIR) spectra was recorded on a schimadzu IR spectrometer and the values are given in cm^{-1}, ^1H &^{13}C NMR were obtained using 400 MHz Bruker NMR spectrometer in DMSO-d_6 as solvent and TMS as internal standard. Mass spectra of the compounds were obtained with schimadzu QP5050 GC-MS spectrometer.

General procedure for synthesis of 4-hydroxy-6-methylpyrone derivatives

To a solution of 4-hydroxy-6-methylpyrone (0.5g, 0.005 mol), aromatic aldehydes (0.005 mol), and malononitrile (0.25ml, 0.005 mol) in aqueous alcoholic solution (6 ml ethanol and 4 ml distilled water), catalytic amount of 1-butyl-3-methylimidazolium bromide ([bmim]Br), (0.25 mmol) was added and stirred for 4-6 h at room temperature. Progress of the reaction was monitored by TLC using petroleum ether:ethyl acetate (6:4) as the solvent system. After the completion of the reaction, the solid product separated was filtered off and washed with water. The crude product was purified by recrystallization using suitable solvents (toluene and methanol).

Spectral Data Analysis

1a: FTIR (KBr) cm^{-1}: 1707 (C=O stretching); 3393-3325 (NH_2, double band, moderate intensity), 2197 (-CN sharp intense peak), 3095 (=CH stretching), 2922-2881 (-C-H stretching), 1614-1446 (aryl C=C stretching pair bands), 1674 (aliphatic C=C stretching), 1039 (-C-O). ^1H NMR (400MHz, DMSO-d_6, ä ppm): 2.20 (s, 3H, -CH_3), 4.32 (s, 1H, -CH), 6.28 (s, 1H, =C-H), 7.25 (s, 2H, NH_2), 7.19-7.20 (m, 4H, C_2', C_3', C_5' and C_6'-H of phenyl), ^{13}C NMR (100MHz, DMSO-d_6, ä ppm): 19 (C-6, -CH_3), 36 (C-10), 58 (C-9), 98 (C-5), 101 (C-3), 115 (C-3', C-5'), 119 (C-9, CN), 129 (C-2', C-6'), 137 (C-1'), 158 (C-4'), 160 (C-8), 161 (C-6), 162 (C-4), 163 (C-2). APCI-MS, m/z : 299.08 (M^++1).

1c: FTIR (KBr) cm^{-1}: 1701 (C=O stretching), 3367-3313 (NH_2, double band, moderate intensity), 2194 (sharp intense peak of –CN), 3064 (=CH stretching), 2891-2862 (-CH stretching), 1608-1446 (aryl C=C stretching pair bands),1672 (aliphatic C=C stretching), 1039 (-C-O); ^{1}H NMR (400MHz, DMSO-d_6, ä ppm): 2.20 (s, 3H, $-CH_3$), 4.5 (s, 1H, -CH), 6.30 (s, 1H, =CH), 7.30 (s, 2H, NH_2), 7.10-7.50 (m, 4H, C_2', C_3', C_5' and C_6'-H of phenyl), ^{13}C NMR (100MHz, DMSO-d_6, ä ppm): 19 (C-6, $-CH_3$), 36 (C-10), 57 (C-9), 98 (C-5), 100 (C-3), 119 (C-9, CN), 124, 125 (C-3', C-5'), 129 (C-2', C-6'), 137 (C-1'), 151 (C-4'), 158 (C-8), 159 (C-6), 161 (C-4), 163 (C-2). APCI-MS, m/z : 326.08 (M+1)

1d: FTIR (KBr) cm^{-1}: 1703 (C=O stretching), 3410-3325 (NH_2, double band, moderate intensity), 2194 (sharp intense peak of –CN), 3068 (=CH stretching), 2899-2615 (-CH stretching), 1612-1477 (aryl C=C stretching pair bands), 1672 (aliphatic C=C stretching), 1041 (-C-O); ^{1}H NMR (400MHz, DMSO-d_6, ä ppm): 2.2 (s, 3H, $-CH_3$), 4.5 (s, 1H, -CH), 6.30 (s, 1H, =C-H), 7.40 (s, 2H, NH_2), 7.59-7.60 (d, 1H, J = 8.4 Hz, C-6' of phenyl-H), 7.70-7.80 (d, 1H, J =8 Hz, C-5' of phenyl-H), 7.96 (s, 1H, C-2' of phenyl-H). APCI-MS, m/z : 360.17 (M^++1).

1e: FTIR (KBr) cm^{-1}: 1707, (C=O stretching), 3381-3323, (NH_2, double band, moderate intensity), 2194 (sharp intense peak of –CN), 3093 (=CH stretching), 2887 (-CH stretching), 1612-1444 (aryl C=C stretching pair bands), 1672 (aliphatic C=C stretching), 1039 (-C-O); ^{1}H NMR (400MHz, DMSO-d_6, ä ppm): 2.23 (s, 3H, $-CH_3$), 4.31 (s, 1H, -CH), 6.28 (s, 1H, =C-H), 7.71-7.73 (d, 2H, J = 8.4 Hz, C-2', 6' of phenyl-H), 7.95-7.97 (d, 2H, J = 8.4 Hz, C-3',5' of phenyl-H), 8.55 (s, 2H, NH_2), ^{13}C NMR (100MHz, DMSO-d_6, ä ppm): 19 (C-6, $-CH_3$), 36 (C-10), 57 (C-9), 98 (C-5), 100 (C-3), 119 (C-9, -CN), 128 (C-3', C-5'), 132 (C-2', C-6'), 137 (C-1'), 143 (C-4'), 158 (C-8), 160 (C-6), 161 (C-4), 163 (C-2). APCI-MS, m/z : 315.08 (M^++1)

1i: FTIR (KBr) cm^{-1}: 1705 (C=O stretching), 3361-3331 (NH_2, double band, moderate intensity), 2196 (sharp intense peak of –CN), 3062 (=CH stretching), 2682-2360 (-CH stretching), 1622-1442 (aryl C=C stretching pair bands), 1672 (aliphatic C=C stretching), 1037 (-C-O); ^{1}H NMR (400MHz, DMSO-d_6, ä ppm): 2.23 (s, 3H, $-CH_3$), 4.34 (s, 1H, -CH), 6.31(s, 1H, =C-H), 7.23 (s, 2H, C-3', 5' of phenyl-H), 7.34 (s, 2H, C-2', C-6' of phenyl-H), 8.51 (s, 2H, NH_2); ^{13}C NMR (100MHz, DMSO-d_6, ä ppm): 19 (C-6, -CH3), 36 (C-10), 56 (C-9), 98 (C-5), 99 (C-3), 119 (C-9, -CN), 123 (C-4'), 150 (C-3', C-5'), 152 (C-2', C-6'), 158 (C-8), 159 (C-6), 161 (C-4), 163 (C-2). APCI-MS, m/z : 282.08 (M^++1)

1j: FTIR (KBr) cm^{-1}: 1707 (C=O stretching), 3313-3275 (NH_2, double band, moderate intensity), 2204 (sharp intense peak of –CN), 3109 (=CH stretching), 2872-2713 (-CH stretching), 1608-1479 (aryl C=C stretching pair bands), 1670 (aliphatic C=C stretching), 1033.85 (-C-O); ^{1}H NMR (400MHz, DMSO-d_6, ä ppm): 2.23 (s, 3H, $-CH_3$), 4.18 (s, 1H, -CH), 6.28(s, 1H, =C-H), 6.58 (s, 1H, C-2' of phenyl-H), 6.62 (s, 1H, C-6' of phenyl-H), 6.63 (s, 1H, C-4' of phenyl-H), 7.08-7.12 (d, 1H, J = 7.8 Hz, C-5' of phenyl-H), 7.19 (s, 2H, NH2), 9.38 (s, 1H, -OH); ^{13}C NMR (100MHz, DMSO-d_6, ä ppm): 19 (C-6, $-CH_3$), 36 (C-10), 58 (C-9), 98 (C-5), 101 (C-3), 114 (C-4', 5', 6'), 118 (C-2'), 119 (C-9, -CN), 129 (C-1'), 145(C-3'), 158 (C-6), 157 (C-8), 161 (C-4), 163 (C-2). APCI-MS, m/z : 295.17 (M^+-1).

1l: FTIR (KBr) cm^{-1}: 1708 (C=O stretching), 3392-3321 (NH_2, double band, moderate intensity), 2194 (sharp intense peak of –CN), 3091 (=CH stretching), 2906.-2798 (-CH stretching), 1614-1444 (aryl C=C stretching pair bands), 1674 (aliphatic C=C stretching), 1043 (-C-O); ^{1}H NMR (400MHz, DMSO-d_6, ä ppm): 2.23 (s, 3H, $-CH_3$), 4.44 (s, 1H, -CH), 6.19 (d, 1H, C-3' of phenyl-H), 6.27 (s, 1H, =C-H), 6.36 (t, 1H, C-4' of phenyl-H), 7.27 (s, 2H, NH2), 7.51 (d, 1H, C-5' of phenyl-H); ^{13}C NMR (100MHz, DMSO-d_6, ä ppm): 19 (C-6, -CH3), 30 (C-10), 55 (C-9), 98 (C-5, 3'), 106 (C-3), 110 (C-4'), 119 (C-9, -CN), 142(C-2', 5'), 154 (C-8), 159 (C-6), 161 (C-4), 163 (C-2). APCI-MS, m/z : 271.08 (M^++1).

Biological Screening

Cell culture and maintenance

HCT 116 human colon carcinoma and MCF-7 human breast cancer cell lines were procured from National Centre for Cell Science, Pune, India. The cells maintained in high glucose MDEM medium with 10% FBS and 1% penicillin-streptomycin, at 37^0C and in CO_2 incubator (NU-5510E, NuAire Inc., Plymouth, USA). To check the cell viability trypan blue dye exclusion method was used and more than 95% viable cells in culture were used for MTT assays. Three independent experiments in triplicates were done for MTT assay.

In vitro Cytotoxicity activity:

Cell viability test by MTT assay (Methodology)

Briefly, more than 70% confluent cultured flasks with $5x10^3$ cells/100 µl cells were plated in 96-well plates and allowed overnight in incubator to adhere. Cells were exposed to different concentration of compound for 48 h and further MTT reagent (50 µl/well, 1mg/ml solution in PBS) was added and cells incubated for 3 h. The formazan crystals formed due to MTT reagent by the viable cells are solubilised on addition of DMSO. Formed yellow colour was measured at 540 nm using microplate ELISA reader (ELx800, BioTek Instruments Inc., Winooski, USA).

IC_{50} for compounds was determined by using GraphPadPrism (5.03) demo version (GraphPad Prism Software Inc. La Jolla, USA).

Cell viability test by MTT assay (Results)

The lethal dose of **1b, 1c, 1f, 1i, 1l** and **1n** are much lower and comparable to doxorubicin. All the compounds tested on HCT 116 and MCF-7 have IC50 of = 100 µM concentration and IC50of doxorubicin is 1-2 µM. Few compounds like, 1b, 1c, 1f, 1i, 1l and 1n whose IC50 is = 100 but more than of doxorubicin (Table 1).

RESULTS AND DISCUSSIONS

The chemical entities are basically be cytotoxic to cancer cells if designed for anti-cancer activity which mostly evaluated by MTT assay in variety of cancer cell lines.

All the synthesized compounds were screened for their cytotoxic effect on HCT and MCF-7 cell lines by MTT method of assay. Among the tested compounds, compound **1b, 1f** and **1i** showed potent activity with IC_{50} value 62.8 µg/ml, 25 µg/ml and 2.93 µg/ml respectively against HCT cells. Among the tested compounds, compound **1c** showed potent activity with IC_{50} value 18.4 µg/ml, while **1b, 1i, 1l** and **1n** possess activity with IC_{50} value 55.8, 35.68, 10 and 33.5 µg/ml, respectively against MCF-7 cells.

All the synthesized compounds were screened for their antibacterial activity among which **1d, 1f** and **1l** were found to be active against *E. coli* strain with MIC in the range of 500-125 µg/ml and no drug was found to be active against *S. aureus* strain.

CONCLUSIONS

Having established the reaction conditions, various aldehydes were treated with 4-hydroxy-6-methyl-pyrone and malononitrile to investigate the reaction scope. Aromatic aldehydes underwent smooth transformation to the corresponding pyrone derivatives in excellent yields. An ionic liquid, [bmim]Br, is employed for the synthesis of pyrone derivatives. This method is applicable to a wide range of aldehydes. The attractive features of this procedure are high conversion, clean reaction profile, and the use of environmentally friendly catalyst. The products were characterized by ^{1}H NMR, ^{13}C NMR, IR, mass spectra.

The reaction conditions are mild (RT), accepting several functional groups, such as Cl, F, OMe, Me, NO_2 present in this reaction without any difficulty. The highly

Table 1: *In vitro* cytotoxic effect of synthesized compounds on HCT-116 and MCF-7 cells by MTT assay after 48 h of exposure.

Compound Code	HCT Cells IC_{50} Value (ig/ml)	MCF-7 Cells IC_{50} Value (ig/ml)
1a	>100	>100
1b	62.2	55.8
1c	>100	18.4
1d	>100	>100
1e	>100	>100
1f	25	>100
1i	2.93	35.68
1k	>100	>100
1l	>100	10
1n	>100	33.5
Doxorubicin	1-2	1-2

Table 2: Antibacterial activity of synthesized compounds by Microtiter plate method on *E. coli* and *S. aureus* bacterial strains

Compound Code	*E. coli* MIC (μg/ml)	*S. aureus* MIC (μg/ml)
1a	>500	>500
1b	>500	>500
1c	>500	>500
1d	250	>500
1e	>500	>500
1f	250	>500
1g	>500	>500
1h	>500	>500
1i	>500	>500
1j	>500	>500
1l	125	>500
Ciprofloxacin	10-20	10-20

Table 3: Physico-chemical data of synthesized compounds 1a-p

Compound No.	Molecular formula	Elemental Analysis Found (Calcd) %			M. P (^{0}C)	Yield (%)
		C	H	N		
1a	$C_{16}H_{11}FN_2O_3$	65.90	4.58	10.51	218-220	82
		(64.43)	(3.72)	(9.39)		
1b	$C_{18}H_{14}N_2O_3$	71.90	5.58	10.51	196-198	78.4
		(70.58)	(4.61)	(9.15)		
1c	$C_{16}H_{11}N_3O_5$	60.79	4.38	13.45	160-162	85
		(59.68)	(3.41)	(12.92)		
1d	$C_{16}H_{10}ClN_3O_5$	54.79	3.38	12.45	218-220	83.5
		(53.42)	(2.80)	(11.68)		
1e	$C_{16}H_{11}ClN_2O_3$	62.54	4.41	9.68	148-150	74
		(61.06)	(3.52)	(8.90)		
1f	$C_{16}H_{10}Cl_2N_2O_3$	56.62	3.41	9.68	141-143	72
		(55.04)	(2.89)	(8.02)		
1g	$C_{18}H_{16}N_2O_4$	67.56	5.48	9.86	130-132	69
		(66.66)	(4.97)	(8.64)		
1h	$C_{19}H_{18}N_2O_6$	62.56	5.48	8.56	220-222	68
		(61.62)	(4.90)	(7.56)		
1i	$C_{15}H_{11}N_3O_3$	65.26	4.38	16.10	216-218	71
		(64.05)	(3.94)	(14.94)		
1j	$C_{16}H_{12}N_2O_4$	65.96	4.38	10.66	230-232	78
		(64.86)	(4.08)	(9.46)		
1k	$C_{17}H_{14}N_2O_4$	67.06	5.38	10.66	226-228	77.4
		(65.80)	(4.55)	(9.03)		
1l	$C_{14}H_{10}N_2O_4$	63.06	4.08	11.66	215-217	76
		(62.22)	(3.73)	(10.37)		
1m	$C_{16}H_{11}N_3O_5$	60.36	4.08	13.26	240-242	80.4
		(59.08)	(3.41)	(12.92)		
1n	$C_{17}H_{14}N_2O_5$	63.06	4.88	9.86	230-232	83
		(62.57)	(4.32)	(8.59)		
1o	$C_{17}H_{14}N_2O_5$	63.06	4.88	9.86	238	89
		(62.57)	(4.32)	(8.59)		
1p	$C_{16}H_{11}N_3O_5$	60.86	3.88	13.86	230-232	83
		(59.08)	(3.41)	(12.92)		

sensitive molecules, furyl, pyridine and thienyl aldehydes participated in this reaction without any difficulty.

The compounds were tested for anti-cancer and anti-microbial activity. Against MCF-7 cell line, only 5 compounds (1b, 1c, 1i, 1l, 1n) showed activity with $IC_{50}<$ 100µg/ML. Against HCT-116 cell line, only 3 compounds (1b, 1f, 1i) showed activity with IC50< 100µg/ml. The active compounds were tested for acute toxicity against normal cell line (Vero) and they were found to exhibit low acute toxicity with $IC_{50}>$100µg/ml. The compounds were ineffective against *Staphylococcus aureus* strain against *Escherichiacoli* bacterial strain 3 compounds showed moderate activity with MIC values in the range of 500-125µg/ml.

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