Med Chem Res
DOI 10.1007/s00044-012-0288-3

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Green approach towards the facile synthesis of dihydropyrano(*c*)chromene and pyrano[2,3-*d*]pyrimidine derivatives and their biological evaluation

Pradeep K. Paliwal · Srinivasa Rao Jetti · Shubha Jain

Received: 8 April 2012 / Accepted: 20 October 2012

Abstract A simple and efficient one-pot synthesis of heteroaryl-substituted dihydropyrano(*c*)chromenes and pyrano[2,3-*d*]pyrimidines has been developed. Reaction proceeds via initial Knoevenagel, subsequent Michael and final heterocyclization reactions of heteroaryl aldehyde, malononitrile, and barbituric acid/dimedone. Triethylammonium acetate acts as a green catalyst as well as reusable solvents for this reaction. Short reaction time, environment friendly procedure, reusability, and excellent yields are the main advantages of this procedure. All synthesized compounds have shown good antibacterial activity against different microbial stains but not active against cancer cell lines.

Keywords Multi-component · Green · Triethylammonium acetate (TEAA) · Dihydropyrano(*c*)chromene · Pyrano[2,3-*d*]pyrimidine · Antibacterial and anticancer activity

Introduction

Multi-component reactions (MCRs) have attracted considerable interest because of their exceptional synthetic and practical efficiency (Dömling, 2000). MCRs involve three or more starting materials reacting in a single flask to form a new product, where basically all the atoms contribute to the newly formed product. Chromenes, pyridines, and pyrimidinones, etc., are some examples of multi-component synthesis (Sharanin and Klokol, 1984; Jin *et al*., 2005). Pyran derivatives are of considerable interest as they possess a wide range of biological properties such as spasmolytic, diuretic, antiallergic, anticoagulant, anticancer, and anti-anaphylactic activity, etc. (Zhang *et al*., 1982; Atwal *et al*., 1992; Hiroshi *et al*., 1993). Polyfuctionalized pyran derivatives are common structural subunits in variety of important natural products (Katritzky *et al*., 1984; Bonsignore *et al*., 1993). In addition, they can be used as cognitive enhancers, for the treatment of neurodegenerative diseases (Riley and Rankin, 1976). A number of 2-amino-2*H* pyrans are useful as photoactive substances also (Armesto *et al*., 1989).

There are some methods reported in the literature for the synthesis of polyfuctionalized pyran derivatives (Wang *et al*., 2003; Singh *et al*., 1996). Unfortunately, many of these processes suffer from limitations such as long reaction times, hazardous by-products, microwave irradiations, use of stoichiometric, or even excess amount of base, and use of metal triflates (Abd El-Rahman *et al*., 2007; Mobinikhaledi *et al*., 2010; Balalaie *et al*., 2009). The search for a non-volatile and recyclable alternative is thus holding a key role in this field of research. The development of cleaner technologies is a major emphasis in green chemistry. Among the several aspects of green chemistry, the reduction/replacement of volatile organic solvents from the reaction medium is of utmost importance. So we tried to explore the new catalyst that has certain properties such as good thermal and mechanical stabilities of supported reagents, easy to handle, of low toxicity, non-corrosive, easy to separate from reaction mixture through filtration, and feasible for reuse.

Ionic liquids as new reaction media and catalyst have been experimentally and theoretically recognized and accepted (Holbrey *et al*., 2000). A great deal of attention has been given to imidazolium ionic liquid in the past several years (Martyn and Kenneth, 2000; Louie and Meade, 1999). However, industrial application of these

P. K. Paliwal (✉) · S. R. Jetti · S. Jain
School of Studies in Chemistry & Biochemistry,
Vikram University, Ujjain 456010, MP, India
e-mail: paliwalchemi@gmail.com

Published online: 09 November 2012

ionic liquids is limiting because of the high price imidazolium ionic liquids and also due to low reusability (Namboodiri and Varma, 2002). Triethylammonium acetate (TEAA) is an inexpensive and easily synthesized ionic liquid that can be used in laboratory without special precautions, and it has not been used much in heterocyclic synthesis, only a few reports are there in the literature (Wang *et al*., 2006; Balaskar *et al*., 2010; Sandhu, 2009; Da-Zhen *et al*., 2010). Therefore, in this article, we wish to report triethylammonium ionic liquid-mediated one-pot synthesis of heteroaryl-substituted pyran derivatives. The antibacterial and anticancer activities were also tested.

Experimental

Melting points were determined by open capillary method and are uncorrected. ^{1}H NMR and ^{13}C NMR analysis were carried out on a Bruker AM-400 spectrometer in $CDCl_3$/DMSO-d_6. Chemical shift values are reported as δ values (in ppm) relative to tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer. Reactions were monitored by thin layer chromatography on 0.2 mm silica gel F-252 (Merck) plates. All chemicals were obtained from Aldrich Chemical Co. and CDH Chemical Co. and were used without further purification. Antibacterial activity was tested by the disk diffusion assay and anticancer activity by using sulforhodamine B assay against human breast cancer, prostate cancer, and ovarian cancer cell lines (Grivsky *et al*., 1980; Midolo *et al*., 1995; Drew *et al*., 1972; Monks *et al*., 1990).

Procedure of triethylammonium ionic liquid TEAA synthesis (Wang *et al*., 2006; Weng *et al*., 2006): The synthesis of ionic liquid was carried out in a 250-mL round-bottomed flask, which was immersed in a water-bath and fitted with a reflux condenser. Acetic acid (1.5 mol, 90.1 g, and 86.03 mL) was dropped into 101.2 g triethylamine (1 mol, 139.4 mL) at 70 °C within 1 h. After the addition, the reaction mixture was stirred for 2 h at 80 °C to ensure that the reaction had proceeded to completion. The reaction mixture was then dried at 80 °C in high vacuum (5 mmHg) until the weight of the residue remained constant. The yield of TEAA was 98 %. ^{1}H NMR (DMSO-d_6): δ = 1.18 (t, 9H, CH_3), 2.10 (s, 3H, CH_3), 3.10 (m, 6H, CH_2), 9.0 (s, 1H, NH) ppm.

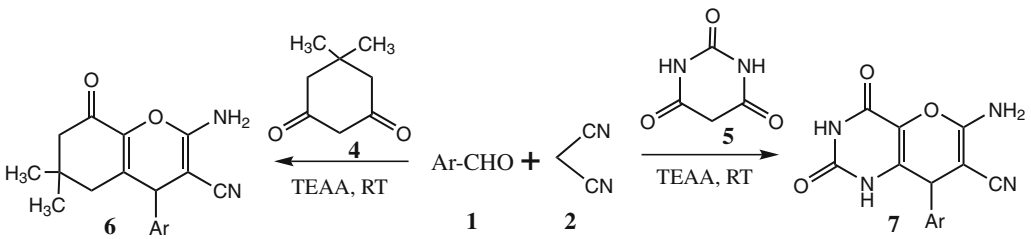
General procedure for the synthesis of heteroaryl-substituted pyrano(c)chromene/pyrano[2,3-*d*] *pyrimidine*: 5-Memberd heteroaryl aldehyde (2 mmol), malononitrile (2 mmol), 5,5′-dimethyl-cyclohexane-1,3-dione/barbituric acid (2 mmol), and TEAA (5 mL) were added to a round bottom flask. The reaction mixture was stirred at room temperature for appropriate time (Scheme 1; Table 1). The completion of the reaction was monitored by TLC. After completion of the reaction, water (5–10 mL) was added in reaction mixture, precipitation of product is occurred. The pure product (**6/7**) was obtained by recrystallization from ethanol:water (9:1). Products (**6/7**) thus obtained were in high yields.

Antimicrobial activity measurements

All test micro organisms were obtained from Microbiology Department, Lokmanya Tilak College Ujjain and were as follows: *Citrobactor freundii*, *Klebsiella pneumoniae*, *Bacillus megaterium*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Salmonella typhi*. Antibacterial activity of the prepared compounds **6a**–**6f** and **7a**–**7f** was tested by the disk diffusion method. Whatman No. 1 filter paper disks were sterilized by autoclaving for 1 h at 140 °C. All the synthesized compounds were dissolved in DMSO for dilution to prepare stock solutions of 20 mg/mL for antimicrobial assay. Agar plates were uniformly surface inoculated with fresh broth culture of *C. freundii*, *K. pneumoniae*, *B. megaterium*, *E. coli*, *P. aeruginosa*, and *S. typhi*. The impregnated disks were placed on the medium suitably spaced apart and the plates were incubated at 30 °C for 1 h to permit good diffusion and were then transferred to an incubator at 37 ± 2 °C for 24 h. The zones of inhibition were measured on mm scale. Streptomycin was used as standard antimicrobial drug. Dimethylsulphoxide was used as solvent control.

Anticancer activity measurement

All test cancer cell lines were obtained from NCI, USA and were as follows: human breast cancer cell line MDA-MB-435, human prostate cancer cell line PC3, and human ovarian



Scheme 1 TEAA promoted synthesis of pyrano(*c*)chromene and pyrano[2,3-*d*]pyrimidine

Table 1 TEAA promoted synthesis of pyrano(*c*)chromene and pyrano[2,3-*d*]pyrimidine

Entry	Aldehyde (2 mmol)	AMC (2 mmol)	Time (min)	Product	Yield[a] (%)	M.P. (°C)
1	**1a**	Dimedone	40	**6a**	90	216–218 [217–219]
2	**1b**	Dimedone	40	**6b**	94	205–207 [204–205]
3	**1c**	Dimedone	50	**6c**	84	178–180
4	**1d**	Dimedone	40	**6d**	95	208–210 [209–211]
5	**1e**	Dimedone	50	**6e**	95	214–215
6	**1f**	Dimedone	40	**6f**	97	217–219
7	**1a**	Barbituric acid	30	**7a**	92	280–282
8	**1b**	Barbituric acid	30	**7b**	94	284–286
9	**1c**	Barbituric acid	50	**7c**	86	191–193
10	**1d**	Barbituric acid	40	**7d**	95	274–275
11	**1e**	Barbituric acid	50	**7e**	96	289–291
12	**1f**	Barbituric acid	50	**7f**	97	>320

AMC active methylene compound

[a] Isolated yields

cancer cell line Ovkar-3. DMSO was used as vehicle for anticancer activity and adriamycin (ADR) as a positive control drug. GI50, TGI, and LC50 parameters were studied using sulforhodamine B assay method.

Spectroscopic data

*2-Amino-7,7-dimethyl-4-(furan-2-yl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6a**)*

White solid, m.p. 216–218 °C (lit. m.p. 217–219 °C, Bhosale *et al*., 2003). IR (KBr): 3355, 3208 (NH_2), 2941 (C–H), 2202 (CN), 1680 (C=O), 1652 (C=C) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6), δ 0.99 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.17 (m, 2H, CH_2), 2.48 (m, 2H, CH_2), 4.33 (s, 1H, CH), 6.05 (s, 1H), 6.32 (s, 1H), 7.07 (s, 2H), 7.48 (s, 1H) ppm; EI-MS (*m*/*z*): 284 (M^+). $C_{16}H_{16}N_2O_3$: % calcd. C, 67.59; H, 5.67; N, 9.85. Found: C, 67.88; H, 5.56; N, 9.63.

*2-Amino-7,7-dimethyl-4-(5-methyl-furan-2-yl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6b**)*

Yellow solid, m.p. 205–207 (lit. m.p. 204–205 °C, Shestopalov *et al*., 2003). IR (KBr) cm^{-1} 3396, 3210 (NH_2), 2966 (C–H), 2196 (CN), 1680 (C=O), 1660 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6), 2.17 (s, 3H, CH_3), 6.32–6.33 (dd, 1H, Ar–H), 6.05 (d, 1H, Ar–H), 7.08 (s, 2H, NH_2), 4.33 (s, 1H), 2.50 (s, 2H, CH_2), 2.30 (d, 1H, CH_2), 2.15 (d, 1H), 1.04 (s, 3H, CH_3), 0.99 (s, 3H, CH_3) ppm; EI-MS (*m*/*z*): 298 (M^+) $C_{17}H_{18}N_2O_3$ (298.34): % calcd. C, 68.44; H, 6.08; N, 9.39. Found: C, 68.40; H, 6.10; N, 9.41.

*2-Amino-7,7-dimethyl-5-oxo-4-(1H-pyrrol-2-yl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6c**)*

White solid, m.p. 178–180 °C. IR (KBr): 3355, 3208 (NH_2), 2941 (C–H), 2212 (CN), 1675 (C=O), 1658 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6), δ 0.99 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 2.22 (m, 2H), 2.42 (m, 2H), 4.31 (s, 1H), 5.21 (s, 1H, NH), 6.05 (s, 1H, Ar–H), 5.91 (s, Ar–H), 6.32 (s, Ar–H), 7.07 (s, 2H, NH_2); EI-MS (*m*/*z*): 283 (M^+) $C_{16}H_{17}N_3O_2$ (283.33): calcd. C, 67.83; H, 6.05; N, 14.83. Found: C, 67.88; H, 5.99; N, 14.84.

*2-Amino-7,7-dimethyl-4-(thiophen-2-yl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6d**)*

Yellow solid, m.p. 208–210 °C (lit. m.p. 209–211 °C, Tu *et al*., 2002). IR (KBr) 3402, 3212 (NH_2), 2977 (C–H), 2206 (CN), 1678 (C=O), 1662 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6), δ 6.32–6.33 (dd, 1H, Ar–H), 6.15 (d, 1H, Ar–H), 6.05 (d, 1H, Ar–H), 7.08 (s, 2H, NH_2), 4.33 (s, 1H, CH), 2.50 (m, 2H, CH_2), 2.30 (m, 2H, CH_2), 1.04 (s, 3H, CH_3), 0.99 (s, 3H, CH_3); EI-MS (*m*/*z*): 300 (M^+) $C_{16}H_{16}N_2O_2S$ (300.09): calcd. C, 63.98; H, 5.37; N, 9.33. Found: C, 63.92; H, 5.34; N, 9.42.

*2-Amino-7,7-dimethyl-4-(3-methyl-thiophen-2-yl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6e**)*

Light yellow, m.p. 214–215 °C. IR (KBr) 3396, 3209 (NH_2), 2966 (C–H), 2196 (CN), 1680 (C=O), 1660 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6), δ 2.29 (s, 3H, CH_3), 6.32–6.33 (dd, 1H, Ar–H), 6.05 (d, 1H, Ar–H), 7.08 (s, 2H, NH_2), 4.33 (s, 1H, CH), 2.50 (s, 2H, CH_2), 2.35 (s, 2H, CH_2), 1.04 (s, 3H, CH_3), 0.99 (s, 3H, CH_3); EI-MS (*m*/*z*): 314 (M^+) $C_{17}H_{18}N_2O_2S$ (314.11): calcd. C, 64.94; H, 5.77; N, 8.91. Found: C, 64.98; H, 5.73; N, 8.89.

*2-Amino-7,7-dimethyl-4-(5-methyl-thiophen-2-yl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6f**)*

Yellow solid, m.p. 217–219 °C. IR (KBr) 3386, 3219 (NH_2), 2976 (C–H), 2189 (CN), 1679 (C=O), 1661 (C=C)

cm^{-1}; ^1H NMR (DMSO-d_6), δ 2.19 (s, 3H, CH_3), 6.32–6.33 (dd, Ar–H), 6.05 (d, Ar–H), 7.08 (s, 2H, NH_2), 4.33 (s, CH), 2.50 (s, 2H, CH_2), 2.30 (d, 2H, CH_2), 1.04 (s, 3H, CH_3), 0.99 (s, 3H, CH_3); EI-MS (*m/z*): 314 (M^+) $C_{17}H_{18}N_2O_2S$ (314.11): calcd. C, 64.94; H, 5.77; N, 8.91. Found: C, 64.92; H, 5.75; N, 8.86.

*7-Amino-5-furan-2-yl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (**7a**)*

Dark yellow solid, m.p. 280–282 °C. IR (KBr): 3391, 3302 (NH_2), 3188 (NH), 3072 (C–H), 2197 (CN), 1718 (C=O), 1665 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6) δH: 4.26 (s, CH), 7.20 (br s, 2H, NH_2), 7.22 (1H, d, H–Ar), 6.59 (1H, m, H–Ar), 6.51 (1H, d, H–Ar), 11.12 (1H, br s, NH), 12.14 (1H, br s, NH); EI-MS (*m/z*): 272 (M^+); $C_{12}H_8N_4O_4$ (272.22): calcd. C, 52.95; H, 2.96; N, 20.58. Found: C, 52.94; H, 2.93; N, 20.47.

*7-Amino-5-(5-methyl-furan-2-yl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d] pyrimidine-6-carbonitrile (**7b**)*

Dark yellow solid, m.p. 284–286 °C. IR (KBr): 3402, 3299 (NH_2), 3178 (NH), 2989 (C–H), 2202 (CN), 1715 (C=O), 1460 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6) δH: 4.12 (1H, s, CH), 7.16 (2H, br s, NH_2), 2.15 (3H, s, CH_3), 6.59 (1H, m, H–Ar), 6.51 (1H, d, H–Ar), 11.12 (1H, br s, NH), 12.14 (1H, br s, NH); EI-MS (*m/z*): 286 (M^+) $C_{13}H_{10}N_4O_4$ (286.24): calcd. C, 54.55; H, 3.52; N, 19.57. Found: C, 54.46; H, 3.56; N, 19.59.

*7-Amino-2,4-dioxo-5-(1H-pyrrol-2-yl)-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (**7c**)*

Pale-yellow solid, m.p. 191–193 °C. IR (KBr): 3402, 3299 (NH_2), 3168 (NH), 2989 (C–H), 2202 (CN), 1708 (C=O), 1460 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6) δH: 4.19 (1H, s, CH), 7.10 (2H, br s, NH_2), 6.97 (1H, d, H–Ar), 6.59 (1H, m, H–Ar), 6.51 (1H, d, H–Ar), 11.12 (1H, br s, NH), 12.14 (1H, br s, NH); EI-MS (*m/z*): 271 (M^+) $C_{12}H_9N_5O_3$ (271.23): calcd. C, 53.14; H, 3.34; N, 25.82. Found: C, 53.07; H, 3.28; N, 25.89.

*7-Amino-5-(thiophen-2-yl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (**7d**)*

Dark yellow solid, m.p. 274–275 °C. IR (KBr): 3390, 3306 (NH_2), 3188 (NH), 3072 (C–H), 2197 (CN), 1708 (C=O), 1459 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6) δH: 4.21 (1H, s), 7.38 (2H, br s, NH_2), 7.02 (1H, d, H–Ar), 6.57 (1H, m, H–Ar), 6.49 (1H, d, H–Ar), 11.42 (1H, br s, NH), 12.09 (1H, br s, NH); EI-MS (*m/z*): 288 (M^+) $C_{12}H_8N_4O_3S$ (288.28): calcd. C, 50.00; H, 2.80; N, 19.43. Found: C, 49.89; H, 2.84; N, 19.46.

*7-Amino-5-(3-methyl-thiophen-2-yl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d] pyrimidine-6-carbonitrile (**7e**)*

m.p. 289–291 °C. IR (KBr): 3399, 3281 (NH_2), 3174 (NH), 2981 (C–H), 2200 (CN), 1707 (C=O), 1463 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6) δH: 3.99 (1H, s, CH), 7.26 (2H, br s, NH_2), 2.20 (3H, s, CH_3), 6.62 (1H, m, H–Ar), 6.48 (1H, d, H–Ar), 11.02 (1H, br s, NH), 12.04 (1H, br s, NH); EI-MS (*m/z*): 302 (M^+) $C_{13}H_{10}N_4O_3S$ (302.5): calcd. C, 51.65; H, 3.33; N, 18.53. Found: C, 51.62; H, 3.36; N, 18.57.

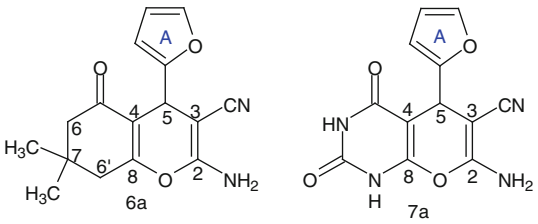
*7-Amino-5-(5-methyl-thiophen-2-yl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d] pyrimidine-6-carbonitrile (**7f**)*

m.p. >320 °C. IR (KBr): 3402, 3299 (NH_2), 3178 (NH), 2989 (C–H), 2202 (CN), 1715 (C=O), 1460 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6) δH: 4.02 (1H, s, CH), 7.16 (2H, br s, NH_2), 2.26 (3H, s, CH_3), 6.59 (1H, m, H–Ar), 6.51 (1H, d, H–Ar), 11.12 (1H, br s, NH), 12.14 (1H, br s, NH); EI-MS (*m/z*): 302 (M^+) $C_{13}H_{10}N_4O_3S$ (302.05): calcd. C, 51.65; H, 3.33; N, 18.53. Found: C, 51.62; H, 3.38; N, 18.51.

Results and discussion

We found TEAA as an efficient organic catalyst as well as reaction medium for one-pot multi-component synthesis with high yields. TEAA is air and water stable ionic liquid which is easy to synthesize by just neutralizing triethylamine and acetic acid, which are relatively inexpensive. It is needless to say that the synthesis of this unconventional triethylammonium ionic liquid is direct, simple, and eco-friendly. This method offers an alternative route for the synthesis of dihydropyrano(*c*)chromenes and pyrano[2,3-*d*] pyrimidines in reasonable yields. Structures of the products **6** and **7** have been deduced from their spectral data and melting points. It is expected that the synthesis of **6/7** follows initial arylidinemalonontrile formation followed by Michael addition of **4/5**–**3** which on heterocyclization with **4/5** gives intermediate **8**. Intermediate **8** on tautomerization (proton transfer) gives **6** or **7** (Scheme 2). This mechanism has been supported by synthesizing **3** in separate single step.

We investigated the reusability of the ionic liquid TEAA without any catalyst. For this purpose, after the completion of the reaction TEAA was separated from the reaction mixture, washed with water and dried at high vacuum. As shown in Fig. 1 TEAA could be reused for six times without apparent loss of catalytic activity.



The IR spectrum of 2-amino-3-cyano-4-(furan-2-yl)-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo-[*b*]pyran has a series of stretching absorption bands of the amino group (3,355 and 3,208) and a bending band of this group (1,675–1,650 cm^{-1}). The high intensity of the absorption band at 2,202 and 1,680 cm^{-1} confirm the presence of the cyano and carbonyl group, respectively, and in ^1H NMR presence of new signal at δ: 0.99 (s, 3H, H7′), 1.05 (s, 3H, H7″), 2.17 (m, 2H, H6), 2.48 (m, 2H, H6′), 4.33 (s, 1H, H5), 7.07 (s, 2H) confirms the structure **6a**.

The IR spectrum of 7-amino-5-furan-2-yl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitr-ile has a series of stretching absorption bands of the –NH at (3,188), amino group (3,391 and 3,302), and a bending band of this group (1,675–1,650 cm^{-1}). The high intensity of the absorption band at 2,197 and 1,718 cm^{-1} confirm the presence of the cyano and carbonyl group, respectively, and in ^1H NMR presence of new peak at δ: 11.12 (1H, br s, NH), 12.14 (1H, br s, NH, 4.26 (s, 1H, H5), 7.20 (s, 2H, NH_2) confirms the structure **7a**.

The EI-MS gave M^+ at *m*/*z* 284 (100) for **6a**, and at *m*/*z* 272 (100) for **7a** which were consistent with the molecular formula to be $C_{16}H_{16}N_2O_3$ for **6a** and $C_{12}H_8N_4O_4$ for **7a** requiring structure. $C_{16}H_{16}N_2O_3$ **6a**: % calcd. C, 67.59; H, 5.67; N, 9.85. Found: C, 67.88; H, 5.56; N, 9.63. $C_{12}H_8N_4O_4$ (272.22) **7a**: calcd. C, 52.95; H, 2.96; N, 20.58. Found: C, 52.94; H, 2.93; N, 20.47.

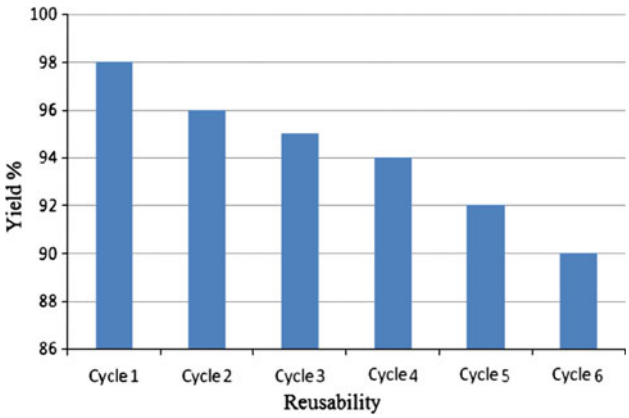
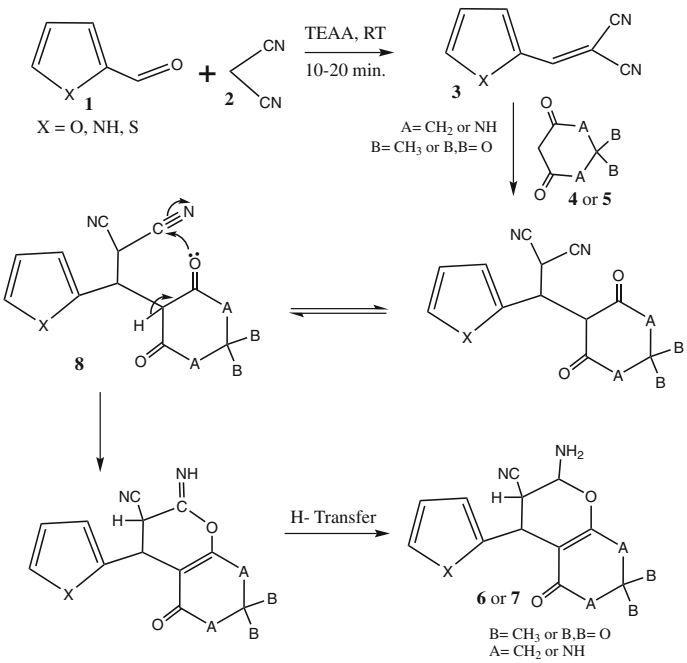


Fig. 1 Reusability of ionic liquid TEAA

Antimicrobial activity measurements

Antimicrobial activity: the antimicrobial strains reveal that the heteroaryl-substituted products (**6** and **7**) showed differential activities (Fig. 1). The presence of heteroaryl ring and cyano and amino groups on pyran ring make these more basic which increases its penetrating power on bacterial cell wall (protein) and the compounds becomes more active. In these cases, heteroaryl part is associated with the bacterial cell wall which makes them more active. The comparative antibacterial activities of the products are summarized in Tables 2 and 3.



Scheme 2 A plausible mechanism for the synthesis of pyrano(*c*)chromene and pyrano[2,3-*d*] pyrimidine

Table 2 Comparative antibacterial activity of dihydropyrano(*c*)chromenes (μg)

S. no.	Bacteria	Diameter of zone of inhibition in mm					
		6a	**6b**	**6c**	**6d**	**6e**	**6f**
1.	*Citrobacter freundii* ATCC 8090	10	10	10	10	10	10
2.	*Klebsiella pneumoniae* ATCC 15380	15	15	19	19	20	21
3.	*Bacillus megaterium* ATCC 12872	12	12	12	10	12	10
4.	*Escherichia coli* ATCC 25922	16	17	20	20	21	22
5.	*Salmonella typhi* ATCC 19430	15	16	22	22	19	19
6.	*Pseudomonas aeruginosa* ATCC 27853	14	15	20	20	22	22

MIC value is 10 μg for each bacterial species

Table 3 Comparative antibacterial activity of pyrano[2,3-*d*]pyrimidines (μg)

S. no.	Bacteria	Diameter of zone of inhibition in mm					
		7a	**7b**	**7c**	**7d**	**7e**	**7f**
1.	*Citrobacter freundii* ATCC 8090	10	10	12	12	12	12
2.	*Klebsiella pneumoniae* ATCC 15380	16	17	20	20	22	22
3.	*Bacillus megaterium* ATCC 12872	14	14	12	12	10	10
4.	*Escherichia coli* ATCC 25922	12	12	14	15	16	16
5.	*Salmonella typhi* ATCC 19430	18	18	22	22	21	20
6.	*Pseudomonas aeruginosa* ATCC 27853	14	15	18	18	20	22

MIC value is 10 μg for each bacterial species

Table 4 Anticancer activity of dihydropyrano(*c*)chromenes and pyrano[2,3-*d*] pyrimidines

S. no.	Cell lines	Compound[a]/ parameters	**6a**	**7a**	ADR[b]
1.	Breast cancer cell line MDA-MB-435	LC50	>100	>100	91.8
		TGI	>100	>100	5.5
		GI50	>100	>100	<0.1
2.	Prostate cancer cell line PC-3	LC50	>100	>100	>100
		TGI	>100	>100	76.7
		GI50	>100	98.8	<0.1
3.	Ovarian cancer cell line Ovkar-3	LC50	>100	>100	>100
		TGI	>100	>100	56.3
		GI50	>100	>100	<0.1

[a] Molar drug conc. used are 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}

[b] Adriamycin (positive control drug)

The compounds **6e**, **6f** exhibit highest activity towards *K. pneumoniae*, **6c–6f** against *E. coli*, **6c**, **6d** against *S. typhi* and compound **6c**, **6d** exhibit moderate activity against *K. pneumoniae*, **6a**, **6b** against *E. coli*, **6c**, **6e**, **6f** against *S. typhi*, and rest of the compounds have least activity towards all the rest of the bacteria. The compounds **7c–7f** exhibit highest activity towards *K. pneumoniae* and *S. typhi* and **7a**, **7b** exhibit moderate activity against *K. pneumoniae* and *S. typhi*, **7c–7f** and **7e**, **7f** against *E. coli* and *P. aeruginosa*, respectively, and rest of the compounds have least activity towards all the bacteria. All the synthesized compounds may act as good pharmaceuticals template in organic synthesis, as they possess good biological activities. Compounds **6a** and **7a** were also tested for anticancer activity test by using SRB assay method. But, both the compounds did not give the satisfactory results in between 10^{-7} and 10^{-4} molar concentrations in comparison with ADR (doxorubicin) as a positive control drugs (Table 4).

Acknowledgments Author is thankful to SAIF-CDRI, Lucknow for providing spectral and elemental analysis data and Mr. Kapilesh Jadhav, Lok Manya Tilak College, Ujjain for providing microbiological facilities and Tata Memorial Centre ACTREC for carrying out cancer activity test.

References

Abd El-Rahman NM, El-Kateb AA, Mohamed FM (2007) Simplified approach to the uncatalyzed Knoevenagel condensation and Michael addition reactions in water using microwave irradiation. Synth Commun 37:3961–3970

Armesto D, Horspool WM, Martin NR, Ramos A, Seaone C (1989) Synthesis of cyclobutenes by the novel photochemical ring contraction of 4-substituted 2-amino-3,5-cyano-6-phienyl-4 *H*-pyrans. J Org Chem 54:3069–3072

Atwal KS, Moreland S, McCullough JR, O'Reilly BC, Syed ZA, Diane EN (1992) Aryl cyanoguanidine potassium channel openers. Bioorg Med Chem Lett 2(1):83–86

Balalaie S, Bararjanian M, Movassagh B, Amani AM (2009) One-pot synthesis of pyrano[2,3-*d*]pyrimidinone derivatives catalyzed by L-proline in aqueous media. J Iran Chem Soc 6(2):436–442

Balaskar RS, Gavande SN, Mane MS, Shingate BB, Shingare MS, Mane DV (2010) Greener approach towards the facile synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazol-5-yl cyanide derivatives at room temperature. Chin Chem Lett 21(10):1175–1179

Bhosale RS, Magar CV, Solanke KS, Mane SB, Choudhary SS, Pawar RP (2003) Convenient synthesis of 5-oxo-5,6,7,8-tetrahydro-4

H-benzo-[*b*]-pyran derivatives catalyzed by KF-alumina. Synth Commun 33:119–126

Bonsignore L, Loy G, Secci D, Calignano A (1993) Synthesis and pharmacological activity of 2-oxo-(2*H*)-1-benzopyran-3-carboxamide derivatives. Eur J Med Chem 28:517–520

Da-Zhen X, Liu Y, Shi S, Wang Y (2010) A simple, efficient and green procedure for Knoevenagel condensation catalyzed by $[C_4dabco][BF_4]$ ionic liquid in water. Green Chem 12:514–517

Dömling A (2000) Multicomponent reactions with isocyanides. Angew Chem Int Ed 39(18):3168–3210

Drew WL, Barry AL, O'Toole R, Sherris JC (1972) Reliability of the Kirby–Bauer disc diffusion method for detecting methicillin-resistant strains of *Staphylococcus aureus*. Appl Microbiol 24:240–247

Grivsky EM, Lee S, Sigel CW, Duch DS, Nichol CA (1980) Synthesis and antitumor activity of 2,4-diamino-6-(2,5-dimethoxybenzyl)-5-methylpyrido[2,3-d]pyrimidine. J Med Chem 23:327–329

Hiroshi K, Haruhiko S, Imagawa J, Takenori I, Shohshin Y, Izumi S, Naoki T, Takahashi T, Hiroyuki N (1993) Synthesis and antihypertensive activity of KC-399, a benzopyran K^+ channel opener with long duration of action and less tachycardia. Bioorg Med Chem Lett 3(10):2005–2010

Holbrey JD, Seddon KR, Lau RM, Rantwijk FV, Sheldon RA (2000) Lipase-catalyzed reactions in ionic liquids. Org Lett 2(26): 4189–4191

Jin TS, Liu LB, Tu SJ, Zhao Y, Li TS (2005) A clean one-pot synthesis of 7-amino-5-aryl-6-cyano-1,5-dihydro-2*H*-pyrano [2,3-d]pyrimidine-2,4(3*H*)-diones in aqueous media under ultrasonic irradiation. J Chem Res 3:162–163

Katritzky ARC, Rees W, Neunhoeffer H (1984) Comprehensive heterocyclic chemistry, vol 3. Pergamon Press, Oxford, p 385

Louie AY, Meade TJ (1999) Metal complexes as enzyme inhibitors. Chem Rev 99:2711–2736

Martyn JE, Kenneth RS (2000) Ionic liquids: green solvents for the future. Pure Appl Chem 72(7):1391–1398

Midolo PD, Turnidge J, Lambert JR, Bell JM (1995) Validation of a modified Kirby–Bauer disk diffusion method for metronidazole susceptibility testing of helicobacter pylori. Diagn Microbiol Infect Dis 21(3):135–140

Mobinikhaledi A, Foroughifar N, Fard MAB (2010) Ecofriendly and efficient synthesis of pyrano[2,3-*d*]pyrimidinone and tetrahydrobenzo[b]pyran derivatives in water. Synth React Inorg Met Org Nano Met Chem 40:179–185

Monks A, Skehan P, Storeng R, Scudiero D, McMohan J, Vistica D, Warren JT, Bokesch H, Kenny S, Boyd MR (1990) New colorimetric cytotoxicity assay for anticancer-drug screening. J Natl Cancer Inst 82(13):1107–1112

Namboodiri VV, Varma RS (2002) An improved preparation of 1, 3-dialkylimidazolium tetrafluoroborate ionic liquids using microwaves. Tetrahedron Lett 43(31):5381–5383

Riley TN, Rankin GO (1976) Synthesis and pharmacological evaluation of some 3-substituted octahydropyrido[2,1-*c*][1,4] oxazines. J Med Chem 19(2):334–336

Sandhu JS (2009) An efficient green protocol for the production of 1,8-dioxooctahydro xanthenes in TEAA a recyclable inexpensive ionic liquid. Rasayan J Chem 2(4):937–940

Sharanin YA, Klokol GV (1984) Nitrile cyclization reactions. XVI. Reaction of arylidene derivatives of malononitrile and ethyl cyanoacetate with barbituric acid. Zh Org Khim 20:2448–2452

Shestopalov AM, Yu M, Emelianova VNN (2003) One-pot synthesis of substituted 2-amino-5,6,7,8-tetrahydro-4*H*-benzo[b]pyrans. Russ Chem Bull 52(5):1164–1171

Singh K, Singh J, Singh H (1996) A synthetic entry into fused pyran derivatives through carbon transfer reactions of 1,3-oxazinanes and oxazolidines with carbon nucleophiles. Tetrahedron 52: 14273–14280

Tu SJ, Gao Y, Guo C, Shi D, Lu Z (2002) 2-Amino-4-aryl-3-cyano-4*H*-pyrans from arylidenemalononitriles under microwave irradiation in the absence of solvent. Synth Commun 32(14): 2137–2141

Wang XS, Shi DQ, Tu SJ, Yao CS (2003) A convenient synthesis of 5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[b]pyran derivatives catalyzed by KF-alumina. Synth Commun 33(1):119–126

Wang C, Guo L, Li H, Wang Y, Weng J, Wu L (2006) Preparation of simple ammonium ionic liquids and their application in the cracking of dialkoxypropanes. Green Chem 8:603–607

Weng J, Wang C, Li H, Wang Y (2006) Novel quaternary ammonium ionic liquids and their use as dual solvent-catalysts in the hydrolytic reaction. Green Chem 8:96–99

Zhang YL, Chen BZ, Zheng KQ, Xu ML, Lei XH, Yao X, Xue B (1982) Chemotherapeutic studies on schistosomiasis. Chem Abstr 96:135383e