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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis, and biological evaluation of 4-*H* pyran derivatives as antimicrobial and anticancer agents

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Abstract A series of pyran derivatives (**5–27**) were synthesized in good yields by utilizing Baylis–Hillman chemistry and were further investigated for their in vitro anticancer, antibacterial, and antifungal activities. Most of the tested compounds exhibited promising antibacterial activity as compared to the standard towards Gram-positive bacterial strains. The compounds **5–7**, **11–13**, and **17–19** displayed two-fold higher activity whereas compound **21** showed four-fold higher antibacterial activity against *Staphylococcus aureus* MTCC 96 as compared to the standard Neomycin. Some of these compounds exhibited moderate antifungal activity against all the tested fungal strains. Two compounds **16** and **23** showed promising anticancer activity against selected four human cancer cell lines such as A549, DU145, HeLa, and MCF7.

Keywords 4-*H* pyran · Baylis–Hillman reaction · Antibacterial activity · Antifungal activity · Cytotoxicity

Introduction

The pyran core structure is a prominent heterocyclic framework, frequently found in both numerous natural products and bioisnpired synthetic compounds (Pettit et al. 1993; Smith et al. 1998; Hatakeyama et al. 1988; Uckun et al. 2000; Smith et al. 2002; Hu et al. 2012; Bensoussan et al. 2013; Armaly et al. 2015). From a medicinal chemistry perspective, it plays a significant functional role due to its diverse pharmacological activities (Green et al. 1995). Functionally, the substituted 4-H pyran scaffolds include chromenes which are more potential in exhibiting antibacterial (Kumar et al. 2009), antiviral (Wyatt et al. 2001), anti-coagulant (Zhang et al. 1982), anti-anaphylactic (Foye 1991), anti-cancer (Kemnitzer et al. 2008), and diuretic activities (Bonsignore et al. 1993). Furthermore, they are useful for the treatment of neurodegenerative disorders such as Parkinson's, Huntington's, and Alzheimer's diseases (Gourdeau et al. 2004; Kemnitzer et al. 2004). Recent studies revealed that 4-H pyran compounds, which structurally resemble 1,4-dihydropyridines also exhibit calcium channel antagonist activity (Atwal et al. 1990; Kappe 1998; Urbahns et al. 2003; Kang et al. 2013). In addition, some of the pyran derivatives find use in cosmetics, fluorescent materials, organic light-emitting diodes, agrochemicals and in large number of 2-amino 4-H pyran derivatives as photoactive

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materials (Armetso et al. 1989; Lee et al. 2010; Guo et al. 2012). Moreover, 4-H pyrans are privileged structural motifs for the synthesis of pharmaceutically relevant molecules such as 1,4-dihydropyridines, pyridines, 2-pyridones, pyrano-pyrimidines, and oxazins (Quintela et al. 1995; Bhattacharyya et al. 2012; Lin et al. 2012). Hence, the synthesis of 4-H pyran motifs has gained renewed interest among the synthetic organic chemists.

Over the past few decades, the Baylis–Hillman reaction has been a prevailing tool for making various functionalized scaffolds (Drewes and Roos 1988; Basavaiah et al. 1996 2003). In the recent years, our group has principally focussed on the synthesis of molecules based on Baylis–Hillman chemistry and its application towards the synthesis of new heterocyclic compounds (Narender et al. 2006; Ravinder et al. 2009, 2010). Some of our most promising constructs has displayed good biological profile (Narender et al. 2006; Pavan Kumar et al. 2011; Ravinder et al. 2012; Narendar Reddy et al. 2014; Bharath Kumar et al. 2014, Ramasatyaveni et al. 2016). In view of the widespread biological profile of pyran derivatives and in continuation to our efforts on Baylis–Hillman chemistry, herein we describe the synthesis of multi-substituted 4-*H*-pyran derivatives by using the Baylis–Hillman chemistry approach and further evaluation of their biological activities.

Experimental section

General

All commercially available chemicals were used without further purification. Melting points were determined on a Mel-Temp apparatus and were uncorrected. IR spectra were recorded using a Thermo Nicolet Nexus 670 FTIR spectrometer. The NMR spectra were recorded on Bruker Avance 300 spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively, using TMS as internal standard. The chemical shifts were expressed as δ values in parts per million (p.p.m.) and the coupling constants (*J*) were given in Hertz (Hz). ESI-MS were obtained on Thermo-Finnigan MAT-1020B instrument. Elemental analyzes were carried out using a Perkin Elmer 2400 Series II elemental analyzer. Column chromatography was performed using silica gel (60–120 mesh, Acme, India).

General procedure for the synthesis of Baylis–Hillman adducts (3a–3w)

Aromatic aldehydes **(1a–1w)** (10 mmol), acrylonitrile **(2)** (20 mmol) and 1,4-Diazabicyclo[2.2.2]octane (DABCO) (30 mol% with respect to aldehyde) were mixed and allowed to stir at room temperature until completion of the reaction (10–12 h). Upon completion, the reaction mixture was diluted with water (15 mL) and extracted with diethyl ether (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography using 10% EtOAc in hexane as eluent to afford pure Baylis–Hillman adducts **(3a–3w)** in 80–90% yield. The spectroscopic and analytical data of all the synthesized compounds were in good agreement with those reported in the literature (Singh and Batra 2008; Basavaiah et al. 2010; Narendar Reddy et al. 2014).

General procedure for the synthesis of [E]-α-cyanocinnamaldehydes (4a–4w)

A stirred solution of BH adduct (**3a–3w**) (1 mmol) and $NaNO_3$ (1 mmol) in 1 mL of [Hmim]HSO_4 was heated at 80 °C for 1–2 h. The reaction progress was monitored by TLC. Upon completion, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The resulting crude product was purified by column chromatography using 10% EtOAc in hexane as eluent to afford pure [E]-α-cyanocinnamaldehyde derivatives (**4a–4w**). The characterization data of the known compounds were in good agreement with the reported data (Basavaiah et al. 1999; Yadav et al. 2008; Narendar Reddy et al. 2014) and new compounds data were given below.

*(E)-2-formyl-3-(3-methoxyphenyl)acrylonitrile (**4h**)*

White solid; Yield: 71%; mp: 80–83 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.57 (s, 1H, CHO), 7.83 (s, 1H, C=CH), 7.69–7.67 (m, 1H, ArH), 7.50–7.40 (m, 2H, ArH), 7.16–7.12 (m, 1H, ArH), 3.89 (s, 3H, OCH_3); ESIMS (*m/z*) 188 $[M + H]^+$.

*(E)-3-(2-fluorophenyl)-2-formylacrylonitrile (**4l**)*

White solid; Yield: 65%; mp: 86–88 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.63 (s, 1H, CHO), 8.51–8.44 (m, 1H, ArH), 8.26 (s, 1H, C=CH), 7.69–7.57 (m, 1H, ArH), 7.35 (t, J = 7.5 Hz, 1H, ArH), 7.29–7.21 (m, 1H, ArH); ESIMS (*m/z*) 176 $[M + H]^+$.

*(E)-3-(2-bromophenyl)-2-formylacrylonitrile (**4o**)*

White solid; Yield: 68%; mp: 110–112 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.66 (s, 1H, CHO), 8.37 (s, 1H, C = CH), 8.33 (d, J = 7.6 Hz, 1H, ArH), 7.76 (d, J = 7.6 Hz, 1H, ArH), 7.51, (t, J = 7.6 Hz, 1H, ArH), 7.44 (t, J = 7.6 Hz, 1H, ArH); ESIMS (*m/z*) 254 $[M + NH_4]^+$.

*(E)-3-(3-chlorophenyl)-2-formylacrylonitrile (**4q**)*

White solid; Yield: 62%; mp: 92–94 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.60 (s, 1H, CHO), 8.00–7.95 (m, 2H, ArH), 7.85 (s, 1H, C=CH), 7.60 (d, $J = 7.7$ Hz, 1H, ArH), 7.51 (t, $J = 7.7$ Hz, 1H, ArH). ESIMS (*m/z*) 209 $[M + NH_4]^+$.

General procedure for the synthesis of pyran derivatives (5–27)

To a well stirred solution of cyanocinnamaldehyde (**4a–4w**, 1 mmol) in absolute ethanol propanedinitrile (1 mmol) and catalytic amount of piperidine (10 mol%) were added at room temperature and allowed to stir for 10–15 min. During the reaction in most cases precipitation of the product was observed. Upon completion, filtered the precipitated product and recrystallized from ethanol. In case if product was not precipitated in the reaction mixture then the solvent was removed under reduced pressure and recrystallized from ethanol. Compounds **5** and **8** are previously reported in the literature (Ciller et al. 1985). All the newly synthesized compounds were well characterized using spectral data (^{1}H NMR, ^{13}C NMR, mass, IR, and elemental analysis) are in full agreement with proposed structures. New compounds data were given below.

*2-amino-4-phenyl-4H-pyran-3,5-dicarbonitrile (**5**)*

White solid; Yield: 70%; mp: 206–208 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.68 (s, 1H, =CH–O), 7.41–7.28 (m, 5H, ArH), 6.57 (s, 2H, NH_2), 4.17 (s, 1H, CHAr); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.0, 150.1, 141.7, 128.8, 127.8, 127.6, 118.9 (CN), 116.2 (CN), 94.2, 55.59, 37.5; IR (KBr) ν_{max}: 3384, 3320, 3206, 2870, 2224, 2194, 1673, 1600, 1402, 1211, 1183 cm^{-1}; ESIMS (*m/z*) 246 $[M + Na]^+$; Anal. Calcd for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82; Found: C, 69.99; H, 4.09; N, 18.85.

*2-amino-4-(4-ethylphenyl)-4H-pyran-3,5-dicarbonitrile (**6**)*

White solid; Yield: 75%; mp: 136–138 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.36 (s, 1H, =CH–O), 7.22–7.15 (m, 4H, ArH), 6.74 (s, 2H, NH_2), 4.13 (s, 1H, CHAr), 2.69–2.62 (q, $J = 7.5$ Hz, 2H, CH_2), 1.25 (t, $J = 7.5$ Hz, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.0, 150.0, 143.3, 139.1, 128.2, 127.6, 119.0 (CN), 116.3 (CN), 94.2, 55.7, 37.3, 27.7, 15.3; IR (KBr) ν_{max}: 3413, 3321, 3206, 3096, 2966, 2931, 2207, 1674, 1597, 1398, 1203, 1116 cm^{-1}; ESIMS (*m/z*) 274 $[M + Na]^+$; Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72; Found: C, 71.77; H, 5.24; N, 16.76.

*2-amino-4-(4-isopropylphenyl)-4H-pyran-3,5-dicarbonitrile (**7**)*

White solid; Yield: 73%; mp: 151–153 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.34 (s, 1H, =CH-O), 7.23 (d, $J = 8.1$ Hz, 2H, ArH), 7.17 (d, $J = 8.1$ Hz, 2H, ArH), 6.69 (s, 2H, NH_2), 4.13 (s, 1H, CHAr), 2.96–2.87 (m, 1H, $CH(CH_3)_2$), 1.26 (d, $J = 6.9$ Hz, 6H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.0, 150.0, 147.8, 139.1, 127.5, 126.7, 119.0 (CN), 116.3 (CN), 94.3, 55.6, 37.2, 32.9, 23.7; IR (KBr) ν_{max}: 3432, 3338, 3216, 3094, 2962, 2228, 2199, 1680, 1634, 1597, 1400, 1208, 1174 cm^{-1}; ESIMS (*m/z*) 288 $[M + Na]^+$; Anal. Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84; Found: C, 72.46; H, 5.74; N, 15.89.

*2-amino-4-p-tolyl-4H-pyran-3,5-dicarbonitrile (**8**)*

White solid; Yield: 69%; mp: 185–188 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.70 (s, 1H, =CH–O), 7.22 (d, $J = 7.9$ Hz, 2H, ArH), 7.16 (d, $J = 7.9$ Hz, 2H, ArH), 7.12 (s, 2H, NH_2), 4.26 (s, 1H, CHAr), 2.31 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.0, 149.9, 138.6, 137.1, 129.39, 127.6, 118.9 (CN), 116.29 (CN), 94.39, 55.7, 37.2, 20.6; IR (KBr): 3377, 3325, 3194, 3092, 2208, 1675, 1603, 1509, 1399, 1201, 1174 cm^{-1}; ESIMS (*m/z*) 260 $[M + Na]^+$; Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71; Found: C, 70.86; H, 4.69; N, 17.68.

*2-amino-4-m-tolyl-4H-pyran-3,5-dicarbonitrile (**9**)*

White solid; Yield: 72%; mp: 182–184 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.71 (s, 1H, = CH-O), 7.42–7.27 (m, 1H, ArH), 7.13–7.07 (m, 5H, ArH, NH_2), 4.26 (s, 1H, CHAr), 2.33 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.0, 150.1, 141.7, 138.0, 128.7, 128.6, 128.5, 128.1, 124.9, 118.9 (CN), 116.2 (CN), 94.2, 55.6, 37.5, 20.9; IR (KBr) ν_{max}: 3405, 3329, 3213, 2924, 2224, 2196, 1673, 1597, 1407, 1203, 1173 cm^{-1}; ESIMS (*m/z*) 260 $[M + Na]^+$; Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71; Found: C, 70.83; H, 4.65; N, 17.75.

*2-amino-4-o-tolyl-4H-pyran-3, 5-dicarbonitrile (**10**)*

White solid; Yield: 82%; mp: 201–203 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.40 (s, 1H, =CH–O), 7.26–7.17 (m, 4H, ArH), 6.75 (s, 2H, NH_2), 4.52 (s, 1H, CHAr), 2.44 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.1, 150.2, 139.6, 135.4, 130.6, 128.7, 127.5, 126.8, 119.0 (CN), 116.3 (CN), 94.0, 55.4, 33.9, 18.7; IR (KBr) ν_{max}: 3399, 3324, 3210, 3106, 2220, 2198, 1673, 1640, 1601, 1401, 1210, 1180 cm^{-1}; ESIMS (*m/z*) 260 $[M + Na]^+$; Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71; Found: C, 70.81; H, 4.70; N, 17.69.

2-amino-4-(4-methoxyphenyl)-4H-pyran-3,5-dicarbonitrile ***(11)***

White solid; Yield: 71%; mp: 149–151 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.46 (s, 1H, =CH–O), 7.19 (d, J = 8.4 Hz, 2H, ArH), 6.91 (d, J = 8.4 Hz, 2H, ArH), 6.86 (s, 2H, NH_2), 4.13 (s, 1H, CHAr), 3.79 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.8, 157.9, 149.8, 133.8, 128.9, 119.0 (CN), 116.3 (CN), 114.1, 94.5, 55.0 (2), 36.8; IR (KBr) ν_{max}: 3406, 3329, 3210, 3104, 2923, 2204, 1673, 1600, 1513, 1401, 1262, 1176, 1027 cm^{-1}; ESIMS (*m/z*) 276 $[M + Na]^+$; Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59; Found: C, 66.44; H, 4.42; N, 16.60.

2-amino-4-(3-methoxyphenyl)-4H-pyran-3,5-dicarbonitrile ***(12)***

White solid; Yield: 70%; mp: 184–186 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.62 (s, 1H, =CH–O), 7.33–7.30 (t, J = 7.9 Hz, 1H, ArH), 7.04 (s, 2H, NH_2), 6.88 (d, J = 7.9 Hz, 1H, ArH), 6.84 (d, J = 7.9 Hz, 1H, ArH), 6.79 (s, 1H, ArH), 4.21 (s, 1H, CHAr), 3.78 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.4, 158.1, 150.2, 143.3, 130.0, 119.8 (CN), 118.9 (CN), 116.2, 113.7, 112.8, 94.1, 55.5, 55.0, 37.5; IR (KBr) ν_{max}: 3406, 3325, 3208, 3106, 2925, 2207, 1674, 1596, 1490, 1397, 1211, 1176 cm^{-1}; ESIMS (*m/z*) 254 $[M + H]^+$; Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59; Found: C, 66.43; H, 4.40; N, 16.62.

2-amino-4-(2-methoxyphenyl)-4H-pyran-3,5-dicarbonitrile ***(13)***

White solid; Yield: 80%; mp: 168–171 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.31–7.26 (m, 2H, =CH–O, ArH), 7.18 (d, J = 7.6 Hz, 1H, ArH), 7.00–6.94 (m, 2H, ArH), 6.62 (s, 2H, NH_2), 4.64 (s, 1H, CHAr), 3.86 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.8, 157.0, 150.5, 129.3, 129.09, 120.9 (2), 119.1 (CN), 116.4 (CN), 111.7, 93.6, 55.7, 54.7, 31.9; IR (KBr) ν_{max}: 3411, 3324, 3212, 3089, 3002, 2834, 2223, 2204, 1677, 1600, 1493, 1405, 1267, 1204, 1169 cm^{-1}; ESIMS (*m/z*) 254 $[M + H]^+$; Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59; Found: C, 66.47; H, 4.38; N, 16.62.

2-amino-4-(4-fluorophenyl)-4H-pyran-3,5-dicarbonitrile ***(14)***

White solid; Yield: 63%; mp: 171–173 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.30–7.26 (t, J = 8.3 Hz, 2H, ArH), 7.23 (s, 1H, =CH–O), 7.11–7.05 (t, J = 8.3 Hz, 2H, ArH), 6.45 (s, 2H, NH_2), 4.19 (s, 1H, CHAr); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.3, 157.7, 148.3, 136.2, 129.0, 128.9, 118 (CN).0, 115.3 (CN), 115.0, 94.7, 56.39, 37.4; IR (KBr) ν_{max}: 3384, 3328, 3213, 3105, 2222, 2199, 1676, 1603, 1510, 1401, 1210, 1184 cm^{-1}; ESIMS (*m/z*) 264 $[M + Na]^+$; Anal. Calcd for $C_{13}H_8FN_3O$: C, 64.73; H, 3.34; N, 17.42; Found: C, 64.74; H, 3.36; N, 17.44.

2-amino-4-(3-fluorophenyl)-4H-pyran-3,5-dicarbonitrile ***(15)***

White solid; Yield: 62%; mp: 170–172 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.75 (s, 1H, =CH–O), 7.50–7.43 (m, 1H, ArH), 7.26 (m, 2H, ArH), 7.21–7.13 (m, 3H, ArH, NH_2), 4.40 (s, 1H, CHAr); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.8, 160.6, 158.1, 150.5, 144.6 (d), 130.9 (d), 123.8 (d), 118.7 (CN), 116.0 (CN), 114.8, 114.6 (d), 114.3, 93.5, 55.0, 37.1; IR (KBr) ν_{max}: 3402, 3325, 3209, 3103, 2226, 2195, 1674, 1595, 1402, 1212, 1181 cm^{-1}; ESIMS (*m/z*) 264 $[M + Na]^+$; Anal. Calcd for $C_{13}H_8FN_3O$: C, 64.73; H, 3.34; N, 17.42; Found: C, 64.77; H, 3.33; N, 17.49.

2-amino-4-(2-fluorophenyl)-4H-pyran-3,5-dicarbonitrile ***(16)***

White solid; Yield: 83%; mp: 203–205 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.78 (s, 1H, =CH–O), 7.45–7.33 (m, 2H, ArH), 7.31–7.21 (m, 4H, ArH, NH_2), 4.59 (s, 1H, CHAr);^{13}C NMR (75 MHz, DMSO-d_6): δ 161.9, 158.4, 150.8, 130.1, 128.09, 127.9, 125.0, 118.7 (CN), 115.99 (CN), 115.7, 92.7, 54.1, 32.1; IR (KBr) ν_{max}: 3430, 3318, 3202, 2200, 2196, 1676, 1632, 1583, 1404, 1208, 1177 cm^{-1}; ESIMS (*m/z*) 264 $[M + Na]^+$; Anal. Calcd for $C_{13}H_8FN_3O$: C, 64.73; H, 3.34; N, 17.42; Found: C, 64.68; H, 3.34; N, 17.42.

2-amino-4-(4-bromophenyl)-4H-pyran-3,5-dicarbonitrile ***(17)***

White solid; Yield: 65%; mp: 110–113 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.53 (d, J = 8.0 Hz, 2H, ArH), 7.36 (s, 1H, =CH–O), 7.22 (d, J = 8.0 Hz, 2H, ArH), 6.76 (s, 2H, NH_2), 4.20 (s, 1H, CHAr); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.1, 150.4, 141.1, 131.7, 129.9, 121.0, 118.8 (CN), 116.0 (CN), 93.6, 55.0, 36.9; IR (KBr) ν_{max}: 3404, 3328, 3213, 3106, 2922, 2224, 2195, 1672, 1637, 1598, 1487, 1408, 1202, 1112 cm^{-1}; ESIMS (*m/z*) 303 $[M + H]^+$; Anal. Calcd for $C_{13}H_8BrN_3O$: C, 51.68; H, 2.67; N, 13.91; Found: C, 51.71; H, 2.69; N, 13.99.

2-amino-4-(3-bromophenyl)-4H-pyran-3,5-dicarbonitrile ***(18)***

White solid; Yield: 65%; mp: 128–130 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.76 (s, 1H, ArH), 7.55 (d, J = 7.9 Hz,

1H, ArH), 7.50 (s, 1H, =CH–O), 7.39 (t, $J = 7.4$ Hz, 1H, ArH), 7.33–7.29 (m, 3H, ArH, NH_2), 4.40 (s, 1H, CHAr); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.1, 150.5, 144.4, 131.0, 130.7, 130.3, 126.9, 122.0, 118.7 (CN), 116.0 (CN), 93.4, 54.9, 37.0; IR (KBr) ν_{max}: 3417, 3330, 3213, 3086, 2202, 1679, 1598, 1401, 1208, 1176 cm^{-1}; ESIMS (*m/z*) 303 $[M + H]^+$; Anal. Calcd for $C_{13}H_8BrN_3O$: C, 51.68; H, 2.67; N, 13.91; Found: C, 51.70; H, 2.69; N, 13.93.

2-amino-4-(2-bromophenyl)-4H-pyran-3,5-dicarbonitrile ***(19)***

White solid; Yield: 85%; mp: 189–191 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.78 (s, 1H, ArH), 7.66 (d, $J = 7.9$ Hz, 1H, ArH), 7.47 (t, $J = 7.3$, 7.7 Hz, 1H, ArH), 7.39 (s, 1H, =CH–O), 7.31–7.28 (m, 3H, ArH, NH_2), 4.79 (s, 1H, CHAr); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.39, 150.9, 139.79, 133.0, 131.0, 130.0, 128.7, 122.6, 118.5 (CN), 115.8 (CN), 92.7, 54.4, 37.4; IR (KBr) ν_{max}: 3401, 3326, 3213, 3109, 2220, 2196, 1674, 1600, 1403, 1211, 1180 cm^{-1}; ESIMS (*m/z*) 303 $[M + H]^+$; Anal. Calcd for $C_{13}H_8BrN_3O$: C, 51.68; H, 2.67; N, 13.91; Found: C, 51.69; H, 2.69; N, 13.93.

2-amino-4-(4-chlorophenyl)-4H-pyran-3,5-dicarbonitrile ***(20)***

White solid; Yield: 62%; mp: 168–171 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.39 (m, 3H, =CH–O, ArH), 7.28 (d, $J = 8.3$ Hz, 2H, ArH), 6.85 (s, 2H, NH_2), 4.21 (s, 1H, CHAr); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.0, 150.3, 140.7, 132.4, 129.6, 128.8, 118.7 (CN), 116.0 (CN), 93.7, 55.1, 36.9; IR (KBr): 3406, 3329, 3213, 2924, 2224, 2197, 1674, 1597, 1491, 1408, 1204, 1174, 1093 cm^{-1}; ESIMS (*m/z*) 280 $[M + Na]^+$; Anal. Calcd for $C_{13}H_8ClN_3O$: C, 60.60; H, 3.13; N, 16.31; Found: C, 60.72; H, 3.11; N, 16.39.

2-amino-4-(3-chlorophenyl)-4H-pyran-3,5-dicarbonitrile ***(21)***

White solid; Yield: 60%; mp: 171–173 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.75 (s, 1H, =CH–O), 7.46–7.40 (m, 2H, ArH), 7.36 (s, 1H, ArH), 7.29–7.26 (m, 3H, ArH, NH_2), 4.41 (s, 1H, CHAr); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.1, 150.6, 144.2, 133.4, 130.79, 127.9, 127.5, 126.5, 118.7 (CN), 116.0 (CN), 93.4, 54.9, 37.09; IR (KBr) ν_{max}: 3420, 3332, 3209, 3060, 2224, 2193, 1671, 1592, 1435, 1399, 1200, 1175 cm^{-1}; ESIMS (*m/z*) 280 $[M + Na]^+$; Anal. Calcd for $C_{13}H_8ClN_3O$: C, 60.60; H, 3.13; N, 16.31; Found: C, 60.65; H, 3.17; N, 16.34.

2-amino-4-(2-chlorophenyl)-4H-pyran-3,5-dicarbonitrile ***(22)***

White solid; Yield: 84%; mp: 206–209 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.78 (s, 1H, =CH–O), 7.50 (d, $J = 7.5$ Hz, 1H, ArH), 7.43–7.37 (m, 3H, ArH), 7.26 (s, 2H, NH_2), 4.80 (s, 1H, CHAr); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.4, 150.9, 138.0, 132.4, 130.9, 129.89, 129.7, 128.0, 118.6 (CN), 115.9 (CN), 92.6, 54.2, 35.2; IR (KBr) ν_{max}: 3398, 3325, 3213, 3107, 2222, 2199, 1674, 1601, 1468, 1403, 1213, 1181 cm^{-1}; ESIMS (*m/z*) 280 $[M + Na]^+$; Anal. Calcd for $C_{13}H_8ClN_3O$: C, 60.60; H, 3.13; N, 16.31; Found: C, 60.63; H, 3.16; N, 16.35.

2-amino-4-(furan-2-yl)-4H-pyran-3,5-dicarbonitrile ***(23)***

White solid; Yield: 68%; mp: 160–161 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.47 (s, 1H, =CH–O), 7.43–7.41 (m, 1H, ArH), 6.87 (s, 2H, NH_2), 6.37 (m, 1H, ArH), 6.30 (d, $J = 5.3$ Hz, 1H, Ar–H), 4.35 (s, 1H, CHAr); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.5, 152.9, 151.0, 143.39, 118.6 (CN), 115.8 (CN), 110.5, 107.5, 91.9, 53.1, 31.4; IR (KBr) ν_{max}: 3431, 3318, 3292, 3201, 3084, 2890, 2226, 2196, 1676, 1635, 1586, 1404, 1208, 1178, 1145 cm^{-1}; ESIMS (*m/z*) 236 $[M + Na]^+$: Anal. Calcd for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71; Found: C, 62.01; H, 3.28; N, 19.73.

2-amino-4-(thiophen-2-yl)-4H-pyran-3,5-dicarbonitrile ***(24)***

White solid; Yield: 69%; mp: 158–160 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.42 (s, 1H, =CH–O), 7.36 (d, $J = 4.3$ Hz, 1H, ArH), 7.02–6.97 (m, 2H, ArH), 6.92 (s, 2H, NH_2), 4.54 (s, 1H, CHAr); ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.9, 149.8, 146.5, 127.0, 126.4, 125.8, 118.7 (CN), 115.9 (CN), 94.5, 56.0, 32.8; IR (KBr) ν_{max}: 3371, 3323, 3206, 3083, 2925, 2230, 2198, 1673, 1597, 1408, 1208, 1180 cm^{-1}; ESIMS (*m/z*) 230 $[M + H]^+$; Anal. Calcd for $C_{11}H_7N_3OS$: C, 57.63; H, 3.08; N, 18.33; S, 13.99; Found: C, 57.60; H, 3.04; N, 18.34; S, 13.93.

2-amino-4-(naphthalen-1-yl)-4H-pyran-3,5-dicarbonitrile ***(25)***

White solid; Yield: 61%; mp: 97–100 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.32 (d, $J = 7.1$ Hz, 1H, ArH), 8.01–7.97 (m, 1H, ArH), 7.93 (d, $J = 8.1$ Hz, 1H, ArH), 7.81 (s, 1H, =CH–O), 7.61–7.53 (m, 3H, ArH), 7.49 (d, $J = 7.1$ Hz, 1H, ArH), 7.19 (s, 2H, NH_2), 5.30 (s, 1H, CHAr); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.1, 150.29, 133.4, 130.79, 128.6, 128.3, 127.1, 126.3, 125.8, 125.7, 122.8, 118.8 (CN), 116.1 (CN), 94.5, 59.6, 55.9; IR (KBr) ν_{max}:

3331, 3250, 3103, 2925, 2220, 2195, 1674, 1629, 1592, 1397, 1210, 1174 cm^{-1}; ESIMS (*m/z*) 296 $[M + Na]^+$; Anal. Calcd for $C_{17}H_{11}N_3O$: C, 74.71; H, 4.06; N, 15.38; Found: C, 74.73; H, 4.01; N, 15.35.

*2-amino-4-(naphthalen-2-yl)-4H-pyran-3,5-dicarbonitrile (**26**)*

White solid; Yield: 70%; mp: 171–173 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 7.99–7.92 (m, 3H, ArH), 7.82 (s, 1H, ArH), 7.80 (s, 1H, =CH–O), 7.56–7.53 (m, 2H, ArH), 7.45–7.42 (d, $J = 8.3$ Hz, 1H, ArH), 7.25 (s, 2H, NH_2), 4.51 (s, 1H, CHAr); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.0, 150.2, 139.0, 132.7, 132.4, 128.7, 127.7, 127.5, 126.4, 126.2, 125.3, 118.8 (CN), 116.19 (CN), 94.0, 55.5, 37.8; IR (KBr) ν_{max}: 3411, 3322, 3208, 3110, 3064, 2217, 2203, 1673, 1638, 1599, 1400, 1209, 1176, 1124 cm^{-1}; ESIMS (*m/z*) 274 $[M + H]^+$; Anal. Calcd for $C_{17}H_{11}N_3O$: C, 74.71; H, 4.06; N, 15.38; Found: C, 74.78; H, 4.09; N, 15.32.

*2-amino-4-(2,4-dichlorophenyl)-4H-pyran-3,5-dicarbonitrile (**27**)*

White solid; Yield: 78%; mp: 159–161 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 7.80 (s, 1H, =CH–O), 7.69 (d, $J = 2.2$ Hz, 1H, ArH), 7.52 (d, $J = 2.2$ Hz, 1H, ArH), 7.47 (s, 1H, ArH), 7.32 (s, 2H, NH_2), 4.82 (s, 1H, CHAr); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.4, 151.1, 137.1, 133.4, 133.39, 132.3, 129.29, 128.29, 118.4 (CN), 115.7 (CN), 92.1, 53.8, 34.8; IR (KBr) ν_{max}: 3394, 3326, 3211, 3071, 2226, 2204, 1677, 1596, 1470, 1403, 1206, 1178 cm^{-1}; ESIMS (*m/z*) 293 $[M + H]^+$; Anal. Calcd for $C_{13}H_7Cl_2N_3O$: C, 53.45; H, 2.42; N, 14.38; Found: C, 53.43; H, 2.38; N, 14.39.

Antimicrobial activity assay The antimicrobial activity of the synthesized compounds was determined using the well diffusion method (Amsterdam 1996) against different pathogenic reference bacterial and *Candida* strains were procured from Microbial Type Culture Collection and Gene Bank (MTCC), CSIR-Institute of Microbial Technology, Chandigarh, India. The pathogenic reference strains were seeded on the surface of the media Petri plates, containing Muller–Hinton agar with 0.1 ml of previously prepared microbial suspensions individually containing 1.5×10^8 cfu ml^{-1} (equal to 0.5 McFarland). Wells of 6.0 mm diameter were prepared in the media plates using a cork borer and the synthesized compounds at a dose range of 300–1.4 µg $well^{-1}$ were added in each well under sterile conditions in a laminar air flow chamber. Standard antibiotic solutions of Neomycin and Miconazole at a dose range of 300–1.4 µg $well^{-1}$ were used as positive controls and the well containing methanol served as a negative control. The plates were incubated for 24 h at 30 °C and the well containing the least concentration showing the inhibition zone is considered as the minimum inhibitory concentration. All experiments were carried out in duplicates and the mean values are represented.

Results and discussion

Chemistry

A series of pyran derivatives were synthesized as compiled in Scheme 1. Initially we synthesized various Baylis–Hillman (BH) adducts (**3a–3w**) by coupling the substituted aromatic aldehydes (**1a–1w**) with acrylonitrile using DABCO in catalytic amount at room temperature under solvent-free conditions (Singh and Batra 2008; Basavaiah et al. 2010; Narendar Reddy et al. 2014). Thus synthesized BH adducts were converted into corresponding substituted cinnamyl aldehydes (**4a–4w**) by treating them with ionic liquid (Yadav et al. 2008; Basavaiah et al. 1999) $[Hmim]HSO_4$ and $NaNO_3$ by the reported procedure (Scheme 1). Next, [*E*]-α-cyanocinnamaldehydes (**4a–4w**) were treated with malanonitrile in presence of piperidine to afford pyran derivatives (**5a–5w**) via a cascade of Michael addition followed by spontaneous intramolecular cyclization and the reaction was completed within 10–20 min (Scheme 1). The crude product was isolated as crystalline solids by recrystallization from ethanol to afford the desired product in good yields (Table 1).

To our delight, the electronic and steric effect of cyanocinnamaldehydes on this transformation was executed under the standard reaction conditions. The cyanocinnamaldehydes with electron-donating groups (methyl, methoxy, ethyl, and isopropyl) and electron-withdrawing groups (fluoro, chloro, and bromo) were well tolerated, and the corresponding products could be isolated successfully. Moreover, it was noted that phenyl group in cyanocinnamaldehyde having *ortho* substitution gave good yields as compared to the phenyl group possessing *para* and *meta* substitution, notwithstanding the electronic character of the substituents. In addition, cyanocinnamaldehyde bearing heteroaromatics such as 2-thienyl, 2-furyl and also extended aromatics such as 1-napthyl and 2-napthyl were smoothly tolerated resulting in desired constructs with satisfactory yields.

Biology

Antibacterial activity

All the synthesized compounds were screened for in vitro antibacterial activity towards six strains of bacteria, including four Gram-positive bacterial strains: *Staphylococcus aureus* MTCC 96, *S. aureus* MLS16 MTCC 2940, *Bacillus subtilis* MTCC 121, and *Micrococcus luteus* MTCC 2470,

Table 1 Synthesis of pyran derivatives

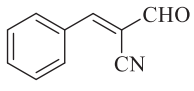
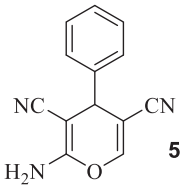
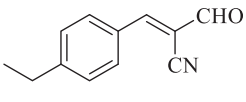
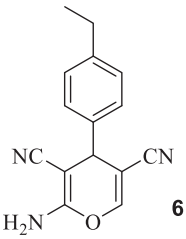
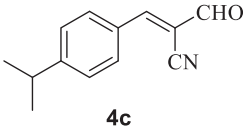
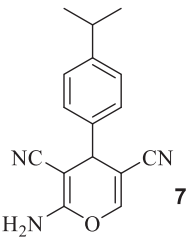
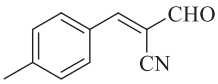
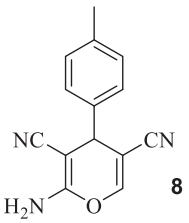
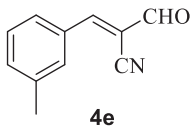
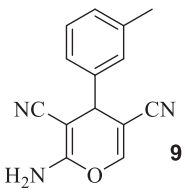
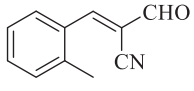
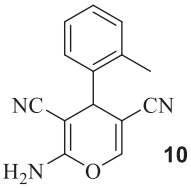
S.No	Aldehyde	Product	Isolated Yield (%)
1	 **4a**	 **5**	70
2	 **4b**	 **6**	75
3	 **4c**	 **7**	73
4	 **4d**	 **8**	69
5	 **4e**	 **9**	72
6	 **4f**	 **10**	82

Table 1 continued

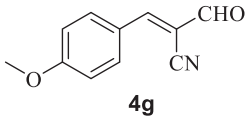
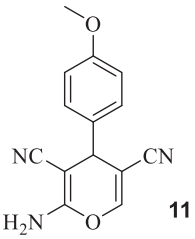
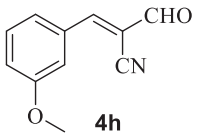
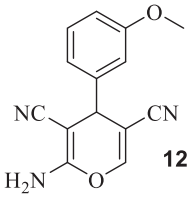
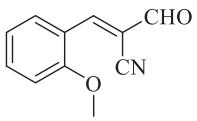
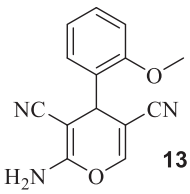
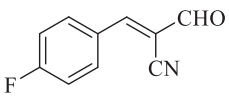
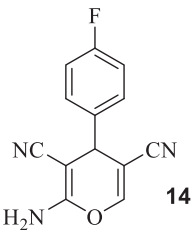
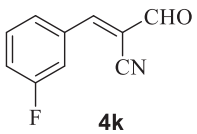
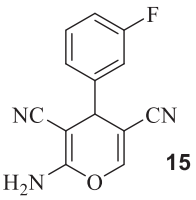
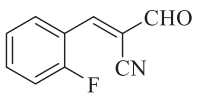
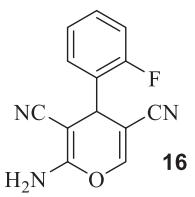
S.No	Aldehyde	Product	Isolated Yield (%)
7	 **4g**	 **11**	71
8	 **4h**	 **12**	70
9	 **4i**	 **13**	80
10	 **4j**	 **14**	63
11	 **4k**	 **15**	62
12	 **4l**	 **16**	83

Table 1 continued

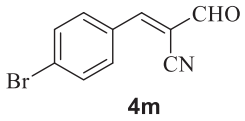
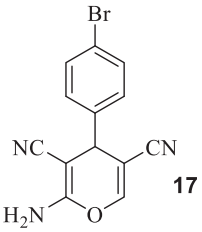
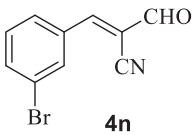
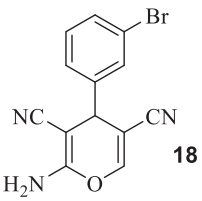
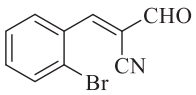
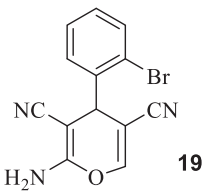
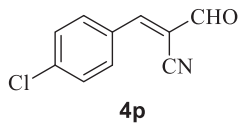
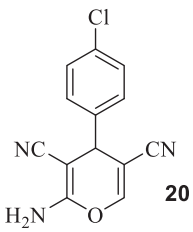
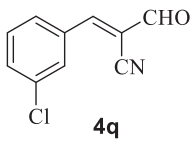
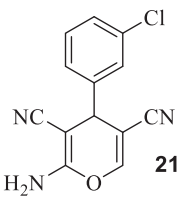
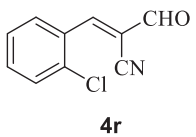
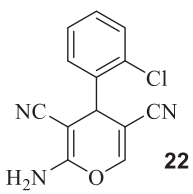
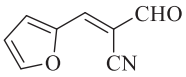
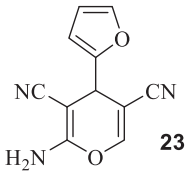
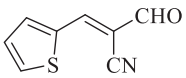
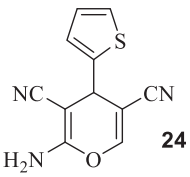
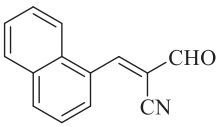
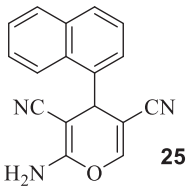
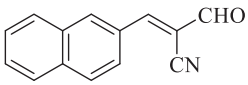
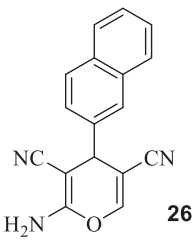
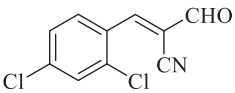
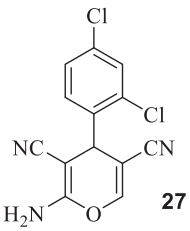
S.No	Aldehyde	Product	Isolated Yield (%)
13	 **4m**	 **17**	65
14	 **4n**	 **18**	65
15	 **4o**	 **19**	85
16	 **4p**	 **20**	62
17	 **4q**	 **21**	60
18	 **4r**	 **22**	84

Table 1 continued

S.No	Aldehyde	Product	Isolated Yield (%)
19	 **4s**	 **23**	68
20	 **4t**	 **24**	69
21	 **4u**	 **25**	61
22	 **4v**	 **26**	70
23	 **4w**	 **27**	78

and three Gram-negative bacterial strains: *Escherichia coli* MTCC 739, *Klebsiella planticola* MTCC 530, *and Pseudomonas aeruginosa* MTCC 2453 by well diffusion method (Amsterdam 1996) and Neomycin was used as a standard. The MIC (minimum inhibitory concentrations) values of these title compounds are depicted in Table 2.

The antibacterial data (Table 2) revealed that most of the tested compounds exhibited promising antibacterial activity towards Gram-positive bacterial strains and less effective towards Gram-negative bacterial strains as compared to the standard, Neomycin. The compounds **5, 6, 7, 11, 12, 13, 17, 18,** and **19** displayed 2-fold increase in activity (9.37 µg/mL), whereas compound **21** showed 4-fold higher activity (4.68 µg/mL) and compounds **25, 26,** and **27** showed equipotent (18.75 µg/mL) antibacterial activity, while the remaining compounds displayed no activity towards *S. aureus* MTCC 96 as compared to standard Neomycin (MIC value of 18.75 µg/mL).

Compounds **5, 6, 7, 17, 18, 19, 23, 24, 25, 26,** and **27** exhibited equipotent (18.75 µg/mL) activity against *B. subtilis* MTCC 121 as compared to standard Neomycin, while the remaining compounds showed no activity. However, compounds **5–22** showed no activity, while the compounds **23, 24, 25, 26,** and **27** displayed equipotent activity (18.75 µg/mL) against *S. aureus* MLS16 MTCC 2940 as compared to standard. In addition, compounds **5–18** and **24–27** were highly active (9.37 µg/mL), whereas the remaining compounds showed no activity towards *M. luteus* MTCC 2470. The compounds **22** and **23** were exhibited moderate activity (37.5 µg/mL) against *K. planticola* MTCC 530, while the remaining compounds showed either poor or no activity. None of the tested compounds showed promising antibacterial activity against *E. coli* MTCC 739 and *P. aeruginosa* MTCC 2453.

Antifungal activity

The synthesized compounds were screened for in vitro antifungal activity against 14 fungal strains, including *C. albicans* MTCC 183, *C. albicans* MTCC 227, *C. albicans* MTCC 854,

Table 2 Antibacterial activity of synthesized compounds

Compounds	Minimum inhibitory concentration (µg/mL)						
	Staphylococcus aureus MTCC 96	*Bacillus subtilis* MTCC 121	*Staphylococcus aureus* MLS16 MTCC 2940	*Micrococcus luteus* MTCC 2470	*Klebsiella planticola* MTCC 530	*Escherichia coli* MTCC 739	*Pseudomonas aeruginosa* MTCC 2453
5	9.37	18.75	–	9.37	–[a]	–	–
6	9.37	18.75	–	9.37	–	–	–
7	9.37	18.75	–	9.37	300	–	–
8	–	–	–	9.37	–	–	–
9	–	–	–	9.37	–	–	–
10	–	–	–	9.37	–	–	–
11	9.37	–	–	9.37	150	–	–
12	9.37	–	–	9.37	–	–	–
13	9.37	–	–	9.37	–	–	–
14	–		–	9.37	300	–	–
15	–	–	–	9.37	–	–	–
16	–	–	–	9.37	–	–	–
17	9.37	18.75	–	9.37	–	–	–
18	9.37	18.75	–	9.37	–	–	–
19	9.37	18.75	–	–	–	–	–
20	–	–	–	–	–	–	–
21	4.68	–	–	–	–	–	–
22	–	–	–	–	37.5	–	–
23	–	18.75	18.75	–	37.5	–	–
24	–	18.75	18.75	9.37	–	–	–
25	18.75	18.75	18.75	9.37	–	–	–
26	18.75	18.75	18.75	9.37	–	–	–
27	18.75	18.75	18.75	9.37	–	–	–
Neomycin	18.75	18.75	18.75	18.75	18.75	18.75	18.75

[a] No activity

Table 3 Antifungal activity of synthesized compounds

Minimum inhibitory concentration (MIC, μg/mL)														
Comp.no	*C.a* MTCC 183	*C.a* MTCC 854	*C.a* MTCC 1637	*C. p* MTCC 1744	*C.a* MTCC 3018	*I. o* MTCC 3020	*C.a* MTCC 3958	*C.a* MTCC 7315	*C.g* MTCC 3019	*C.a* MTCC 3017	*C.a* MTCC 4748	*Caaseri* MTCC 1962	*Ia. h* MTCC 4755	*C.a* MTCC 227
5	75	75	75	18.75	18.75	150	75	75	150	18.75	75	150	18.75	75
6	37.5	37.5	37.5	18.75	18.75	75	18.75	18.75	37.5	18.75	18.75	18.75	18.75	37.5
7	37.5	37.5	37.5	37.5	18.75	37.5	75	75	150	18.75	18.75	75	18.75	37.5
8	37.5	37.5	37.5	18.75	18.75	37.5	75	75	18.75	18.75	18.75	18.75	18.75	37.5
9	–[a]	–	–	37.5	18.75	150	–	–	150	18.75	75	150	75	–
10	18.75	18.75	18.75	18.75	18.75	37.5	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75
11	–	–	–	–	–	–	–	–	–	–	–	–	–	–
12	–	–	–	–	–	–	–	–	–	–	–	–	–	–
13	–	–	–	–	–	–	–	–	–	–	–	–	–	–
14	–	–	–	–	–	–	–	–	–	–	–	–	–	–
15	–	–	–	–	–	–	–	–	–	–	–	–	–	–
16	–	–	–	–	–	–	–	–	–	–	–	–	–	–
17	–	–	–	–	–	–	–	–	–	–	–	–	–	–
18	–	–	–	–	–	–	–	–	–	–	–	–	–	–
19	–	–	–	–	–	–	–	–	–	–	–	–	–	–
20	–	–	–	–	–	–	–	–	–	–	–	–	–	–
21	–	–	–	–	–	–	–	–	–	–	–	–	–	–
22	37.5	37.5	37.5	18.75	18.75	37.5	37.5	37.5	150	18.75	37.5	150	75	37.5
23	150	150	150	18.75	18.75	37.5	150	150	150	18.75	37.5	150	18.75	150
24	75	75	75	18.75	18.75	37.5	75	75	37.5	18.75	37.5	75	18.75	75
25	37.5	37.5	37.5	18.75	18.75	37.5	37.5	37.5	37.5	18.75	37.5	18.75	18.75	37.5
26	150	150	150	18.75	18.75	37.5	150	150	150	18.75	37.5	75	18.75	150
27	18.75	18.75	18.75	18.75	18.75	37.5	18.75	18.75	18.75	18.75	37.5	18.75	18.75	18.75
Miconazole	9.37	9.37	9.37	9.37	9.37	9.37	9.37	9.37	9.37	9.37	9.37	9.37	9.37	9.37

[a] No activity

C. albicans MTCC 1637, *C. albicans* MTCC 1962, *C. albicans* MTCC 3017, *C. albicans* MTCC 3018, *C. albicans* MTCC 3019, *C. albicans* MTCC 3958, *C. albicans* MTCC 4748, *C. albicans* MTCC 7315, *C. parapsilopsis* MTCC 1744, *Issatchenkia orientalis* MTCC 3020, and *I. hanoiensis* MTCC 4755 by well diffusion method (Amsterdam 1996) and Miconazole was used as a standard drug. The MIC (minimum inhibitory concentrations) values of these target compounds were compiled in Table 3.

The investigation of antifungal data (Table 3) revealed that compounds **5–10** and **21–27** showed moderate antifungal activity, with MIC values ranging between 18.75–150 µg/mL, while the remaining compounds showed no antifungal activity as compared with the standard Miconazole (9.37 µg/mL) towards all the tested fungal strains.

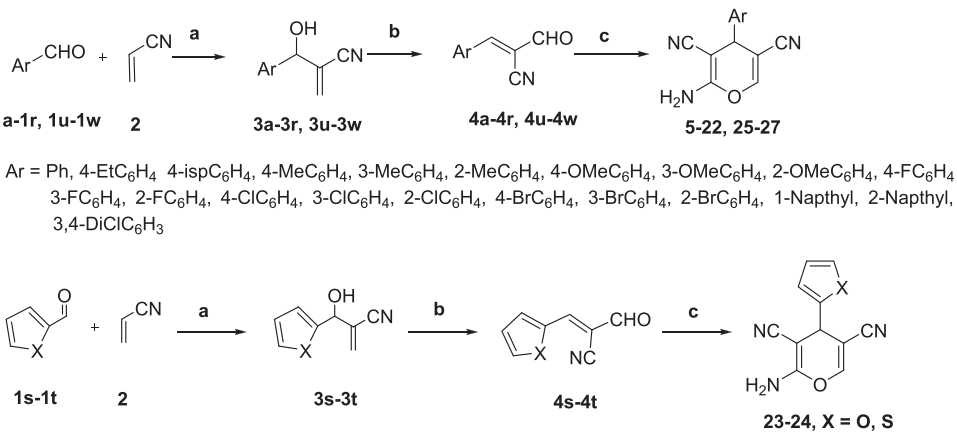
Table 4 In vitro cytotoxicity of synthesized compounds

Compound	IC_{50} values (in µM)			
	A549	DU145	HeLa	MCF7
5	–[a]	–	–	–
6	49.3	–	–	–
7	115.7	–	–	100.4
8	75.7	69.8	74.1	–
9	39.5	33.9	37.1	29.8
10	81.9	78.1	–	–
11	–	–	–	–
12	–	–	–	–
13	43.4	39.8	42.1	40.2
14	–	–	–	–
15	309.5	–	–	231.2
16	4.3	4.4	8.9	7.9
17	14.0	13.8	12.9	14.1
18	7.8	6.8	5.9	7.9
19	8.1	8.9	7.9	8.2
20	19.6	20.3	21.3	24.5
21	10.6	10.7	9.8	8.9
22	10.8	10.1	11.2	12.1
23	5.5	4.5	5.1	5.9
24	16.4	15.9	16.3	17.1
25	14.0	13.2	12.9	13.9
26	10.9	11.1	12.3	11.7
27	16.2	15.2	14.3	15.4
Doxorubicin	0.7	0.8	0.7	0.6

[a] No activity

Anti-cancer activity

All the title compounds were evaluated for their cytotoxic activity against a panel of four human cancer cell lines: A549 (Lung cancer, american type culture collection (ATCC) No. CCL-185), MCF7 (Breast cancer, ATCC No. HTB-22), DU145 (Prostate cancer, ATCC No. HTB-81), and HeLa (Cervical cancer, ATCC No. CCL-2) using the standard MTT assay (Mosmann 1983). The results of the assay are compiled in Table 4 (where the IC_{50} value is defined as the concentration of the compound that corresponds to 50% growth inhibition). The results of the cytotoxic study indicate that most of the tested compounds, with the exception of **5**, **11**, **12,** and **14** showed cytotoxic activity on all tested cell lines. Among them, compound **16** showed promising anticancer activity on both A549 (4.3 µM) and DU145 (4.4 µM) cell lines and moderate activity on HeLa (8.9 µM) and MCF7 (7.9 µM) cell lines as compared to the standard Doxorubicin. Compound **23** also showed promising activity against DU145 (4.5 µM) cell line and good activity on A549 (5.5 µM), HeLa (5.1 µM) and MCF7 (5.9 µM) cell lines. Compounds **17–22, 24–27** displayed good (5.9–8.9 µM) to moderate (10.1–24.5 µM) anticancer activity towards the four human cancer cell lines. From a structure-activity relationship (SAR) perspective, it can be noted that the phenyl moiety bearing *o*-fluoro functionality and as well 2-furyl motif exhibited more activity as compared to other compounds.



Scheme 1 Synthesis of pyran derivatives. Reagents and conditions: **a** DABCO (30 mol %), overnight; **b** $[Hmim]HSO_4$, $NaNO_3$, 80°C, **c** Malanonitrile, Piperidine, Etahnol, r.t

Conclusions

In conclusion, we have described efficient reaction conditions for the synthesis of pyran derivatives from Baylis–Hillman adducts and characterized by spectral analyzes. All the synthesized compounds were screened for their in vitro antibacterial, antifungal, and anti-cancer activities. The investigation of antibacterial data showed that compounds **5–7**, **11–13**, and **17–19** were two fold higher activity, whereas compound **21** was four fold higher antibacterial activity as compared to that of standard Neomycin against *S. aureus* MTCC 96. Some of these compounds had moderate antifungal activity against the tested fungal strains. Compounds bearing *o*-fluoro functionality (**16**) and 2-furyl motif (**23**) exhibited more anticancer activity against the tested cell lines. Based on these results, we understand that these compounds are promising leads with diverse biological activities and are new chemical entities.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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