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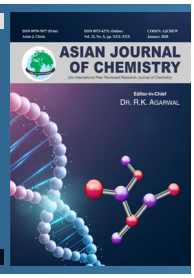

Design, Synthesis and Antimicrobial Evaluations of Novel 3,7-Disubstituted 2*H*-1-Benzopyran-2-ones

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In present study, a novel class of 3,7-disubstituted 2*H*-1-benzopyran-2-one derivatives (**3xa-3zc**) bearing a basic ether side chain at C-7 and a substituted phenyl ring at C-3 of the coumarin ring is synthesized. These compounds have been evaluated for antimicrobial (antibacterial/antifungal) activities. Some of the compounds *viz*. **3xc, 3xe**, **3xf**, **3yb, 3yc** and **3yf** have shown significant antifungal activities against selective strains. Compounds **3xe, 3yb** and **3yc** with the MIC values of 1.56 µg/mL displayed better antifungal activity than fluconazole against *Trichophyton mentagrophytes*.

Keywords: Coumarins, Benzopyrans, Antimicrobial agents.

INTRODUCTION

2*H*-1-Benzopyran-2-one (coumarin) is a privileged oxygen heterocyclic scaffold in the field of medicinal chemistry, widely distributed throughout the plant kingdom [1-3] and exhibited a wide range of biological activities [4] such as anticancer [5-8], anti-inflammatory [9,10], antioxidant [11], antitubercular [12], anti-hyperglycemic [13,14], MAO-B inhibitory anticoagulation [15-17], anti-microbial [18-23], *etc*. It has been reported that 7-amino substituted coumarins plays a significant role as biologically active comp-ounds in various diseases [2] and as substrates for P-450 isozymes [24]. 7-Amino 2*H*-1-benzopyran-2-one derivatives isolated from *Loeselia Mexicana*, *Petroselinum crispum*, *Ruta graveolens* and *Aesculus pavia* exhibited significant antimicrobial activity [25].

A series of 7-amino-and 7-hydroxy-substituted coumarins (Fig. 1), initially have been synthesized as potential zinc indicators were also possessed anti-inflammatory and antioxidant activities [26,27]. Recently, various analogues of 3,7-disubstituted coumarins were reported as antimicrobial agents and monoamine oxidase (MAO inhibitors) [28]. Therefore, coumarins and their derivatives have been the subject of extensive investigations in recent years. Furthermore, it has also been observed that by incorporating substituted phenyl ring at position C-3 of coumarin ring may increases many fold of their biological activities [29]. Based on the above facts that by incorporating a basic side chain at C-7 and a substituted phenyl ring at C-3 of coumarin ring may led to increases their biological activities. Therefore, it is worth to synthesize a compound bearing a substituted aminoethoxy chain at C-7 and a substituted phenyl ring at C-3 of coumarin ring of the designed prototype **V** (Fig. 2).

In continuation of our research work [30-34] on the design and synthesis/semi-synthesis of biologically potent scaffolds for exploring their different kinds of biological activities. In the present paper, we would like to report here the synthesis and biological activities of the designed prototype **V** (Fig. 2). To the best of our knowledge, 3,7-disubstituted-2*H*-1-benzopyran-2-ones bearing a basic ether side chain at position C-7 and a substituted aryl ring at position C-3 on the coumarin ring have not been studied so far.

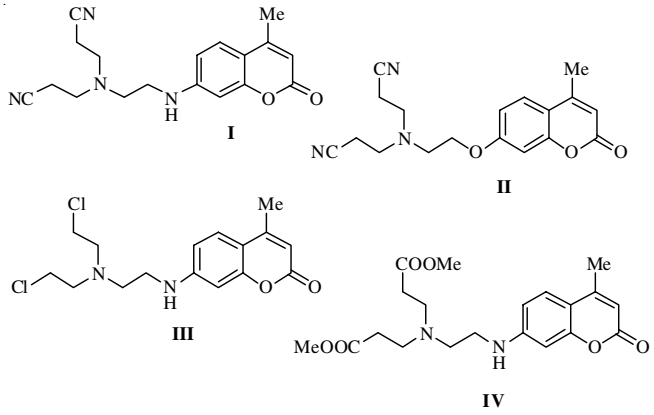


Fig. 1. Structures of some 7-substituted coumarins

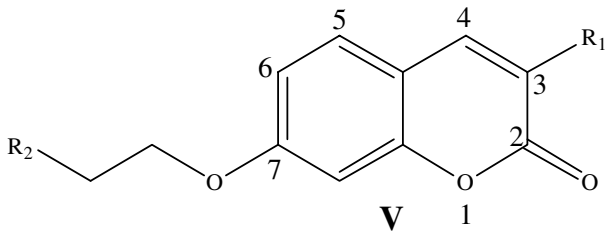


Fig. 2. Designed prototypes (**3xa-3zc**)

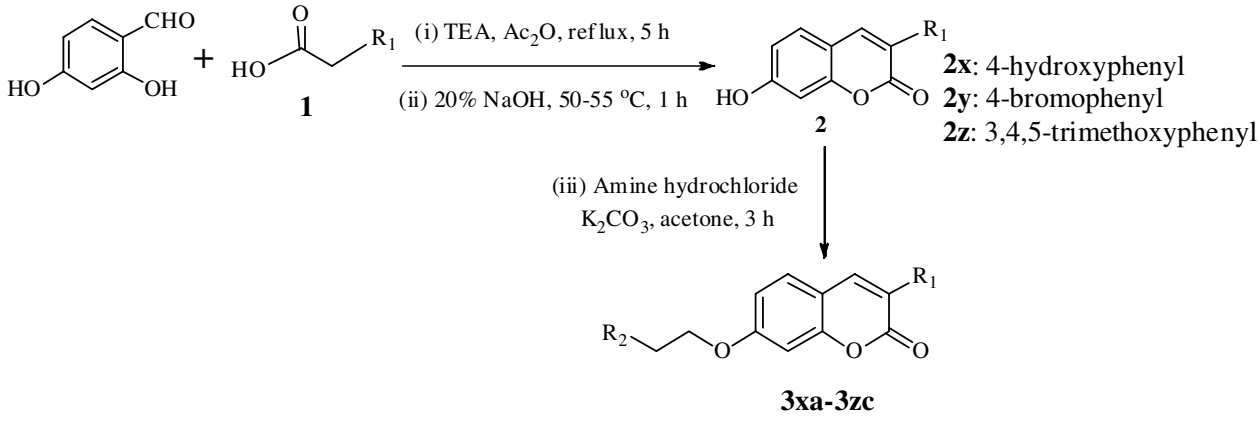
EXPERIMENTAL

The designed compounds **3xa-3zc** were synthesized from their corresponding 7-hydroxy-3-substituted 2*H*-1-benzopyran-2-one (**2x-z**), through the alkylation with different ammonium hydrochloride salts (**Scheme-I**). Compounds **2x-z** were prepared by the condensation of 2,4-dihydroxybenzaldehyde with various substituted phenyl acetic acids **(1)** in presence of triethylamine (TEA) and acetic anhydride, which was subsequently hydrolyzed with 20% NaOH afforded the 7-hydroxy derivatives (**2a-h**). The synthesized compounds **3xa-3zc** having different R_1 and R_2 substituents are depicted in Table-1.

Characterization: ^{1}H & ^{13}C NMR spectra were recorded on Bruker Supercon Magnet DPX-200 or DRX-300 spectrometers (operating at 200 and 300 MHz, respectively for ^{1}H; 50 and 75 MHz respectively, for ^{13}C) using $CDCl_3$ and DMSO-d_6 as solvent. Chemical shifts are expressed in parts per million (δ ppm); *J* values are given in Hertz. Tetramethylsilane (δ 0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (δ 77.23 ppm) in ^{13}C NMR. Reagents and solvents used were mostly AR grade. Reaction progress was monitored by TLC aluminum sheets silica gel 60 F_{254}. Detection of spots was done either by iodine vapors or spraying with 2% vanillin in H_2SO_4 followed by heating at 110 ºC. Melting points were taken in open capillaries on an electrically heated melting point apparatus Complab and were uncorrected. IR spectra were recorded on Perkin-Elmer RX-1 spectrophotometer using KBr pellets or in neat. High-resolution electron impact mass spectra (HREIMS) were obtained on JEOL MS route 600H instrument. Elemental analyses were performed on Vario EL-III C H N S analyzer. Column chromatography was performed over silica gel (particle size: 60-120 mesh) or flash silica gel (particle size: 230-400 mesh) procured from Qualigens (India).

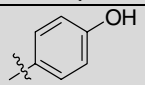
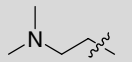
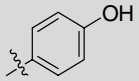
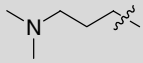
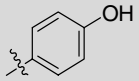
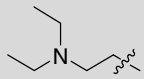
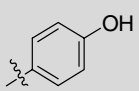
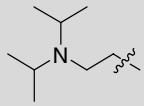
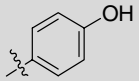
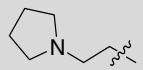
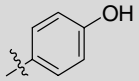
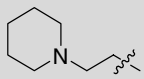
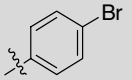
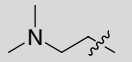
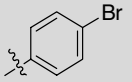
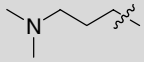
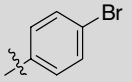
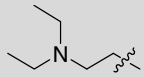
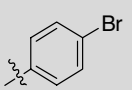
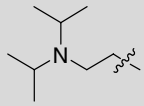
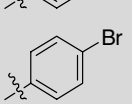
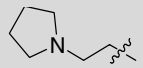
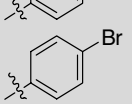
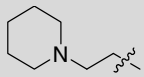
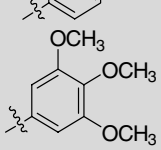
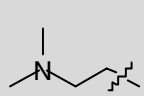
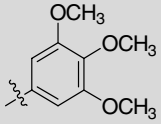
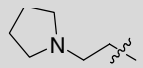
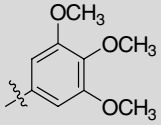
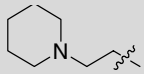
Synthesis of intermediate compounds 2*H*-1-benzopyran-2-ones (2x-z): A 250 mL round bottom flask was charged successively with phenyl acetic acid (**1**,1.1 mmol), 2,4-dihydroxybenzaldehyde (1 mmol) and acetic anhydride (2 mmol). After stirring for 5 min, triethylamine (1.4 mmol) was added dropwise over a period of 10 min. The mixture was refluxed at 130-135 ºC for 5 h. The reaction was monitored by TLC during the course of reaction. After completion of reaction, the reaction mixture was allowed to cool to 50-55 ºC and reaction was quenched by ice cooled water (200 mL) with continuous stirring for 15 min. The solid obtained was filtered and washed with ice cooled water (50 mL × 3). The wet solid product was placed in 250 mL flask and 15 mL of 20% NaOH solution was added. The mixture is stirred for 1 h at 50-55 ºC and then cooled to 15 ºC and acidified with 5 N HCl till acidic to litmus. The precipitated product was filtered, washed with ice cold water (50 mL × 3) and sucked dry. The product was further dried at 65 ºC under vacuum to afford the 3-substituted-7- hydroxyl-2*H*-1-benzopyran-2-one in 70-80% yield.

General procedure of the synthesis of compound (3xa-zc): To a solution of 2*H*-1-benzopyran-2-one (**2x-z**, 1 mmol) in 5 mL of dry acetone was added anhydrous potassium carbonate (3 mmol) and corresponding ammonium hydrochloride salt (1.2 mmol). The mixture was then refluxed for 3 h. The reaction



Scheme-I

TABLE-1
SYNTHESIZED COMPOUNDS **3xa-3zc**

Entry	Compd.	Substituents	
		R_1	R_2
1	**3xa**		
2	**3xb**		
3	**3xc**		
4	**3xd**		
5	**3xe**		
6	**3axf**		
7	**3ya**		
8	**3yb**		
9	**3yc**		
10	**3yd**		
11	**3ye**		
12	**3yf**		
13	**3za**		
14	**3zb**		
15	**3zc**		

mixture was cooled at room temperature and filtered through sintered funnel. The residue was washed with acetone (10 mL × 3). The filtrate was then concentrated to obtain a viscous liquid which was purified by silica gel column chromatography using 2-5% methanol-chloroform mixture as eluent.

Spectral data

7-Hydroxy-3-(4-hydroxyphenyl)-chromen-2-one (2x): Yield 65%; m.p.: 192-195 ºC; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ 6.46 (d, 1H, *J*=8.42), 6.58 (d, 1H, *J* = 2.3 Hz), 7.53-7.64 (m, 5H), 7.51-7.59 (m, 1H), 7.88 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 103.75, 112.41, 114.32, 124.74, 127.16, 130.42, 130.59, 131.88, 133.62, 134.67, 143.11, 156.22, 162.15; ES-MS (*m/z*) 255 $[M+H]^+$.

3-(4-Bromophenyl)-7-hydroxy-chromen-2-one (2y): Yield 69%; m.p.: 185-188 ºC; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ 5.96 (s, OH), 6. 52 (d, 1H, *J* = 8.4), 6.57 (d, 1H, *J* = 2.5 Hz), 7.31-7.47 (m, 5H), 7.54-7.58 (m, 1H), 7.92 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 104.69, 111.31, 113.74, 124.85, 127.74, 128.74, 129.10, 131.72, 132.64, 132.98, 133.85, 134.96, 143.92, 157.46, 162.23; ES-MS (*m/z*) 318 $[M+H]^+$.

7-Hydroxy-3-(3,4,5-trimethoxyphenyl)-chromen-2-one (2z): Yield 65%; m.p.: 191-194 ºC; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ 3.95 (s, 3H), 3.97 (s, 3H), 4.12 (s, 3H), 6.45 (d, 1H, *J* = 8.1 Hz), 6.53 (d, 1H, *J* = 7.9 Hz), 6.75-6.81 (m, 2H), 7.24 (d, 1H, *J* = 8.5 Hz), 7.86 (s, 1H), 8.54 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 56.74, 56.82, 57.14, 105.22, 106.14, 108. 74, 112.26, 120.71, 128.54, 129.30, 132.33, 133.14, 133.72, 134.52, 135.85, 144.36, 158.16, 161.92;ES-MS (*m/z*) 329 $[M+H]^+$.

7-(2-Dimethylaminoethoxy)-3-(4-hydroxyphenyl)-chromen-2-one (3xa): Yield 79%; m.p.: 95-78 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 6H), 2.81 (t, 2H, *J* = 5.4 Hz), 4.12 (t, 2H, *J* = 5.4 Hz), 5.12 (s, OH), 6.75-6.83 (m, 2H), 7.36-7.48 (m, 4H), 7.72-7.81 (m, 2H), 7.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.14 (NCH_3 × 2), 59.28 (NCH_2), 71.64 (OCH_2), 101.29 (CH), 113.48 (CH), 113.66 (C), 114.12 (CH), 115.23 (CH), 128.64 (CH × 3), 129.03 (CH), 135.28 (C), 143.24 (C), 156.52 (C), 160.18 (C), 162.12 (COH), 163.24 (CO); IR (KBr, ν_{max}, cm^{-1}): 3590, 1672, 1600, 1530, 1220, 765; ES-MS (*m/z*) 326 $[M+H]^+$. Elemental analysis calcd. (found) % of $C_{19}H_{19}NO_4$: C, 70.14 (70.82), H, 5.89 (6.09), N 4.31 (4.25); requires C 70.14%, H 5.89%, N 4.31%

7-(3-Dimethylaminopropoxy)-3-(4-hydroxyphenyl)-chromen-2-one (3xb): Yield 81%; m.p.: 92-93 °C ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 (quin, 2H, *J* = 7.1 Hz), 2.19 (s, 6H), 2.49 (t, 2H, *J* = 7.1 Hz), 4.12 (t, 2H, *J* = 6.3 Hz), 4.96 (s, OH), 6.67-6.94 (m, 2H), 7.45-7.58 (m, 4H), 7.46-7.82 (m, 2H), 7.65 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.68 (CH_2), 43.24 (NCH_3 × 2), 56.34 (NCH_2), 69.02 (OCH_2), 101.23 (CH), 113.30 (CH), 114.45 (CH), 115.52 (CH), 118.48 (C), 124.92 (C), 127.56 (CH), 128.61 (CH), 128.64 (CH), 129.02 (C), 134.37 (CH), 151.45 (C), 156.67 (C), 159.10 (C), 162.34 (CO); IR (KBr, ν_{max}, cm^{-1}): 3594, 1714, 1618, 1221, 1014 783; ES-MS (*m/z*) 340 $[M+H]^+$. Elemental analysis calcd. (found) % of $C_{20}H_{21}NO_4$: C, 70.78 (71.17); H, 6.24 (6.18); N 4.33 (4.82).

7-(2-Diethylaminoethoxy)-3-(4-hydroxyphenyl)chromen-2-one (3xc): Yield 84%; m.p.: 64-66 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 6H, *J* = 7.6 Hz), 2.45 (q, 4H, *J* = 6.9 Hz), 2.82 (t, 2H, *J* = 6.5 Hz), 4.05 (t, 2H, *J* = 5.9 Hz), 4.8 (s, OH), 6.86-6.92 (m, 2H), 7.54-7.68 (m, 4H), 7.86-7.94 (m, 2H), 7.32 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.88 (NCH_2-CH_3 × 2), 47.32 (NCH_2CH_3 × 2), 52.67 (NCH_2), 68.18 (OCH_2), 106.32 (CH), 112.69 (CH), 113.57 (CH), 115.86 (CH), 119.56 (C), 123.75 (C), 127.82 (CH), 127.98 (CH), 128.48 (CH), 128.86 (C),

129.24 (C), 136.56 (C), 141.36 (CH), 156.18 (C), 160.74 (C), 162.64 (CO); IR (KBr, ν_{max}, cm^{-1}): 3600, 1724, 1615, 1218, 770; ES-MS (*m/z*) 354 $[M+H]^+$. Elemental analysis calcd. (found) % of $C_{19}H_{18}NO_3Br$: C, 71.37 (71.86), H, 6.56 (6.94), N, 3.96 (3.98).

7-(2-Diisopropylaminoethoxy)-3-(4-hydroxyphenyl)-chromen-2-one (3xd): Yield 77%; m.p.: 85-87 6C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (d, 12H, *J* = 6.8 Hz), 2.67 (t, 2H, *J* = 6.9 Hz), 3.24 (t, 2H, *J* = 6.8 Hz), 4.22 (t, 2H, *J* = 6.8 Hz), 5.1 (s, OH), 6.76-6.82 (m, 2H), 7.62-7.78 (m, 5H), 7.84 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.62 ($NCHCH_3 \times 4$), 48.78 ($CH \times 2$), 49.12 (NCH_2), 71.31 (OCH_2), 106.45 (CH), 111.21 (CH), 114.52 (CH), 114.96 (CH), 119.78 (C), 125.42 (C), 127.94 (CH), 128.04 (CH), 128.12 (CH), 130.42 (C), 152.16 (C), 156.89 (C), 159.22 (C), 162.65 (CO); IR (KBr, ν_{max}, cm^{-1}): 3604, 1717, 1625, 1286, 1148, 786; ES-MS (*m/z*) 382 $[M+H]^+$. Elemental analysis calcd. (found) % of $C_{23}H_{27}NO_4$: C, 72.42 (72.12), H 7.13 (7.87), N, 3.67 (3.32).

3-(4-Hydroxyphenyl)-7-(2-pyrrolidin-1-yl-ethoxy)-chromen-2-one (3xe): Yield 82%; m.p.: 132-134 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.82-1.98 (m, 4H), 2.94-2.80 (m, 4H), 3.24 (t, 2H, *J* = 5.8 Hz), 4.65 (t, 2H, *J* = 5.8 Hz), 4.86 (s, OH), 6.66-6.72 (m, 2H), 7.46-7.58 (m, 3H), 7.82-7.90 (m, 2H), 8.16 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.85 ($NCH_2CH_2 \times 2$), 52.18 ($NCH_2 \times 3$), 70.15 (OCH_2), 106.34 (CH), 110.34 (CH), 114.45 (CH), 115.10 (CH), 118.23 (C), 126.90 (CH), 127.23 (C), 127.96 (CH), 129.42 (C), 151.42 (C), 157.05 (C), 158.42 (C), 162.08 (CO); IR (KBr, ν_{max}, cm^{-1}): 3596, 1718, 1608, 1265, 784; ES-MS (*m/z*) 336 $[M+H]^+$. Elemental analysis calcd. (found) % of $C_{21}H_{21}NO_4$: C, 71.78 (72.09), H, 6.02 (5.94), N, 3.99 (3.86).

3-(4-Hydroxyphenyl)-7-(2-piperidin-1-yl-ethoxy)-chromen-2-one (3xf): Yield 82%; m.p.: 104-106 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52-1.61 (m, 2H), 1.63-1.68 (m, 4H), 2.67-2.73 (m, 4H), 2.94 (t, 2H, *J* = 5.9 Hz), 4.43 (t, 2H, *J* = 5.9 Hz), 5.12 (s, OH), 6.66-6.78 (m, 2H), 7.54-7.67 (m, 3H), 7.80-7.86 (m, 2H), 7.96 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.25 ($NCH_2CH_2CH_2 \times 2$), 26.62 ($NCH_2CH_2CH_2$), 53.24 (NCH_2CH_2-$CH_2 \times 2$), 54.63 (NCH_2CH_2O), 71.43 (OCH_2CH_2N), 106.45 (CH), 111.24 (CH), 115.44 (CH), 115.56 (CH), 118.08 (C), 127.05 (CH), 127.86 (C), 128.63 (CH), 129.04 (CH), 130.05 (C), 134.24 (CH), 151.27 (C), 156.30 (C), 158.73 (C), 162.46 (CO); IR (KBr, ν_{max}, cm^{-1}): 3605, 1724, 1614, 1272, 785; ES-MS (*m/z*) 366 $[M+H]^+$. Elemental analysis calcd. (found) % of $C_{22}H_{23}NO_4$: C, 72.31 (72.89), H 6.34 (6.98), N, 3.83 (4.08).

3-(4-Bromophenyl)-7-(2-dimethylaminoethoxy)-chromen-2-one (3ya): Yield 76%; m.p.: 92-94 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 6H), 2.94 (t, 2H, *J* = 5.4 Hz), 4.25 (t, 2H, *J* = 5.4 Hz), 6.85-6.94 (m, 2H), 7.61-7.69 (m, 3H), 7.80-7.88 (m, 2H), 8.16 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.32 ($NCH_3 \times 2$), 59.65 (NCH_2), 72.55 (OCH_2), 106.11 (CH), 111.42 (CH), 116.68 (C), 118.23 (CH), 121.26 (CH), 123.23 (CBr), 128.11 (CH), 129.44 (CH×3), 134.38 (C), 144.68 (C), 157.32 (C), 160.18 (C), 162.56 (CO); IR (KBr, ν_{max}, cm^{-1}): 1690, 1596, 1524, 1222, 1045, 767; ES-MS (*m/z*) 388 $[M+H]^+$. Elemental analysis calcd. (found) % of $C_{19}H_{18}NO_3Br$: C, 58.78 (59.08), H, 4.67 (4.54), Br, (20.58) 20.11, N, 3.61 (3.02).

3-(4-Bromophenyl)-7-(3-dimethylamino-propoxy)-chromen-2-one (3yb): Yield 82%; m.p.: 96-98 ºC ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (quin, 2H, *J* =7.1 Hz), 2.46 (s, 6H), 2.51 (t, 2H, *J* = 7.1 Hz), 4.16 (t, 2H, *J* = 6.3 Hz), 6.91-6.98 (m, 2H), 7.45-7.56 (m, 3H), 7.82-7.91 (m, 2H), 8.06 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.17 ($CH_2CH_2CH_2$), 43.72 ($NCH_3 \times 2$), 55.43 (NCH_2), 69.88 (OCH_2), 105.33 (CH), 111.52 (CH), 118.81 (C), 123.04 (CBr), 128.12 (C), 128.64 (CH), 128.68 (CH), 129.13 (CH), 135.45 (C), 140.36 (CH), 155.23 (C), 160.89 (C), 162.65 (CO); IR (KBr, ν_{max}, cm^{-1}): 1716, 1621, 1224, 1012, 1063, 788; ES-MS (*m/z*) 403 $[M+H]^+$. Elemental analysis calcd. (found) % of $C_{20}H_{20}NO_3Br$: C, 59.71 (58.96), H 5.01 (5.24), Br 19.86 (20.06), N 3.48 (3.12).

3-(4-Bromophenyl)-7-(2-diethylaminoethoxy)chromen-2-one (3yc): Yield 84%; m.p.: 68-70 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (t, 6H, *J* = 7.1 Hz), 2.48 (q, 4H, *J* = 7.1 Hz), 2.81 (t, 2H, J=6.1 Hz), 4.16 (t, 2H, *J* = 6.1 Hz), 6.75-6.81 (m, 2H), 7.35-7.42 (m, 2H), 7.71-7.77 (m, 3H), 7.96 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.87 ($NCH_2CH_3 \times 2$), 47.31 ($NCH_2CH_3 \times 2$), 52.54 (NCH_2), 69.98 (OCH_2), 104.23 (CH), 111.95 (CH), 118.76 (C), 123.42 (CBr), 125.77 (C), 128.70 (CH), 129.93 (CH), 135.26 (C), 140.22 (CH), 155.47 (C), 161.10 (C), 162.15 (CO); IR (KBr, ν_{max}, cm^{-1}): 1727, 1618, 1221, 1058, 766; ES-MS (*m/z*) 417 $[M+H]^+$. Elemental analysis calcd. (found) % of $C_{21}H_{22}NO_3Br$: C, 60.59 (60.92), H 5.33 (5.54), Br 19.19 (18.98), N 3.36 (3.21).

3-(4-Bromophenyl)-7-(2-diisopropylaminoethoxy)-chromen-2-one (3yd): Yield 79%; m.p.: 82-84 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (d, 12H, *J* = 7.1 Hz), 2.93 (m, 2H), 3.14 (t, 2H, *J* = 6.9 Hz), 4.08 (t, 2H, *J* = 6.5 Hz), 6.76-6.82 (m, 2H), 7.62-7.78 (m, 5H), 7.84 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.84 ($NCHCH_3 \times 4$), 47.44 ($CH \times 2$), 48.56 (NCH_2), 73.78 (OCH_2), 107.15 (CH), 110.69 (CH), 113.12 (CH), 114.56 (CH), 119.93 (C), 124.62 (CBr), 126.31 (C), 128.10 (CH), 128.88 (CH), 128.96 (CH), 131.12 (C), 152.65 (C), 157.10 (C), 160.11 (C), 162.90 (CO); IR (KBr, ν_{max}, cm^{-1}): 1718, 1626, 1288, 1152, 1054,782; ES-MS (*m/z*) 445 $[M+H]^+$. Elemental analysis calcd. (found) % of $C_{23}H_{26}NO_3Br$: C, 72.42 (72.92), H 7.13 (6.95), N 3.67 (3.86).

3-(4-Bromophenyl)-7-(2-pyrrolidin-1-yl-ethoxy)-chromen-2-one (3ye): Yield 80%; m.p.: 129-132 ºC; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.91-1.97 (m, 4H), 2.83-2.91 (m, 4H), 3.32 (t, 2H, *J* = 5.3 Hz), 4.83 (t, 2H, *J* = 5.7 Hz), 6.55-6.67 (m, 2H), 7.67-7.80 (m, 3H), 7.88-7.97 (m, 2H), 8.35 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.15 ($NCH_2CH_2 \times 2$), 53.63 ($NCH_2 \times 3$), 71.19 (OCH_2), 107.14 (CH), 111.32 (CH), 115.66 (CH), 115.11 (CH), 117.96 (C), 127.10 (CH), 127.53 (C), 128.09 (CH), 129.82 (C), 152.55 (C), 157.43 (C), 159.11 (C), 162.78 (CO); IR (KBr, ν_{max}, cm^{-1}): 1723, 1604, 1270, 1045, 780; ES-MS (*m/z*) 415 $[M+H]^+$. Elemental analysis calcd. (found) % of $C_{21}H_{20}NO_3Br$: C, 60.88 (61.23), H 4.87 (4.18), Br 19.29 (19.09), N 3.38 (3.05).

3-(4-Bromophenyl)-7-(2-piperidin-1-yl-ethoxy)-chromen-2-one (3yf): Yield 79%; m.p.: 102-104 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52-1.61 (m, 2H), 1.63-1.68 (m, 4H), 2.67-2.73 (m, 4H), 2.94 (t, 2H, *J* = 5.9 Hz), 4.43 (t, 2H, *J* = 5.9 Hz), 6.71-6.83 (m, 2H), 7.69-7.78 (m, 3H), 7.95-8.06 (m, 2H), 8.12

(s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.25 ($NCH_2CH_2CH_2\times 2$), 26.62 ($NCH_2CH_2CH_2$), 53.32 ($NCH_2CH_2CH_2\times 2$), 55.12 (NCH_2CH_2O), 72.75 (OCH_2CH_2N), 107.26 (CH), 110.12 (CH), 116.04 (CH), 116.53 (CH), 118.31 (C), 124.24 (CBr), 126.94 (CH), 127.96 (C), 129.21 (CH), 129.86 (CH), 130.95 (C), 134.77 (CH), 151.45 (C), 156.73 (C), 159.03 (C), 162.84 (CO); IR (KBr, ν_{max}, cm^{-1}): 1727, 1610, 1274, 1048, 786; ES-MS (*m/z*) 429 $[M+H]^+$. Elemental analysis calcd. (found) % of $C_{22}H_{22}NO_3Br$: C, 61.69 (62.09), H 5.18 (5.45), Br 18.66 (18.88), N 3.27 (3.65).

7-(2-Dimethylaminoethoxy)-3-(3,4,5-trimethoxyphenyl)-chromen-2-one (3za): Yield 82%; m.p.: 118-120 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 6H), 2.86 (t, 2H, *J* = 5.9 Hz), 3.78 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 4.27 (t, 2H, *J* = 5.8 Hz), 6.82-6.97 (m, 3H), 7.30-7.43 (m, 2H), 7.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.74 ($NCH_3\times 2$), 56.36 (OCH_3), 56.41 (OCH_3), 56.70 (OCH_3), 58.63 (NCH_2), 67.18 (OCH_2), 102.46 (CH), 111.79 (CH), 112.13 (CH), 113.88 (CH), 114.16 (C), 121.78 (CH), 125.11 (C), 128.53 (C), 129.34 (CH), 139.96 (CH), 149.16 (C), 149.96 (C), 155.85 (C), 162.10 (C), 162.94 (CO); IR (KBr, ν_{max}, cm^{-1}): 1722, 1614, 1210, 1044, 765; ES-MS (*m/z*) 400 $[M+H]^+$. Elemental analysis calcd. (found) % of $C_{24}H_{27}NO_6$: C, 66.15 (66.82), H 6.31 (6.11), N 3.51 (3.76).

7-(2-Pyrrolidin-1-yl-ethoxy)-3-(3,4,5-trimethoxyphenyl)-chromen-2-one (3zb): Yield 76%; m.p.: 88-90 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88-1.92 (m, 4H), 2.41-2.53 (m, 4H), 2.86 (t, 2H, *J* = 5.8 Hz), 3.96 (s, 3H), 4.10 (s, 3H), 4.22 (t, 2H, *J* = 5.8 Hz), 6.91-7.12 (m, 3H), 7.27-7.35 (m, 2H), 7.48 (d, 1H, *J* = 8.7 Hz), 7.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.72 ($NCH_2CH_2\times 2$), 54.81 ($NCH_2\times 3$), 56.18 (OCH_3), 56.31 (OCH_3), 56.66 (OCH_3), 68.16 (OCH_2), 102.34 (CH), 111.52 (CH), 111.95 (CH), 114.10 (CH), 114.24(C), 121.86 (CH), 125.14 (C), 128.25 (C), 128.73 (CH), 139.94 (CH), 149.32 (C), 149.86 (C), 155.88 (C), 162.21 (C), 162.14 (CO); IR (KBr, ν_{max}, cm^{-1}): 1728, 1616, 1225, 1035, 746; ES-MS (*m/z*) 426 $[M+H]^+$. Elemental analysis calcd. (found) % of $C_{24}H_{27}NO_6$: C, 67.75 (68.14), H 6.40 (6.26), N 3.29 (3.74).

7-(2-Piperidin-1-yl-ethoxy)-3-(3,4,5-trimethoxyphenyl)-chromen-2-one (3zc): Yield 77%; m.p.: 97-99 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48-1.54 (m, 2H), 1.78-1.89 (m, 4H), 2.62-2.69 (m, 4H), 2.94 (t, 2H, *J* = 5.7 Hz), 3.95 (s, 3H), 3.98 (s, 3H), 4.10 (s, 3H), 4.21 (t, 2H, *J* = 5.5 Hz), 6.88-6.93 (m, 2H), 6.97 (d, 1H, *J* = 8.2 Hz), 7.43-7.51 (m, 2H), 7.73 (d, 1H, *J* = 8.3 Hz), 8.11 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.12 (NCH_2-CH_2CH_2), 26.54 ($NCH_2CH_2CH_2\times 2$), 54.12 ($NCH_2CH_2CH_2\times 2$), 56.10 (OCH_3), 56.35 (OCH_3), 56.64 (OCH_3), 57.87 (NCH_2), 67.26 (OCH_2), 102.22 (CH), 111.63 (CH), 112.48 (CH), 113.75 (CH), 113.86 (CH), 122.16 (CH), 125.18 (C), 128.64 (C), 128.96 (CH), 139.74 (CH), 149.12 (C), 150.14 (C), 155.89 (C), 161.74 (C), 162.13 (CO); IR (KBr, ν_{max}, cm^{-1}): 1727, 1620, 1245, 1038, 740; ES-MS (*m/z*) 440 $[M+H]^+$. Elemental analysis calcd. (found) % of $C_{25}H_{29}NO_6$: C, 68.32 (68.84), H 6.65 (6.71), N 3.19 (3.32).

Antimicrobial activity: All the synthesized compounds were screened for their antimicrobial activities. The bacterial and fungal strains were grown on nutrient agar at 37 ºC. After 24 h of incubation, bacterial cells were suspended in normal saline containing Tween 20 at 0.05% at a concentration of approximately 1.0-2.0 × 10^7 cells/mL by matching with 0.5 McFarland standards. The activity of compounds was determined as per CLSI protocol using Mueller Hinton broth (Becton Dickinson, USA) in 96-well tissue culture plates. Proper growth control, drug control and the negative control were adjusted onto the plate. Compounds were dissolved in DMSO at a concentration of 1 mg/mL and 20 µL of this was added to each well of 96-well tissue culture plate having 180 µL Mueller Hinton broth. From here, the solution was serially diluted resulting in two-fold dilution of the test compounds in subsequent wells. 100 µL of McFarland matched bacterial

TABLE-2
in vitro ANTIMICROBIAL ACTIVITIES OF 3-ARYL-7-ALKYLAMINOETHOXY-2*H*-1-BENZOPYRAN-2-ONE (**3xa-zc**)

Entry	Compound	MIC (µg/mL)									
		Bacteria				Fungi					
		1	2	3	4	5	6	7	8	9	10
1	**3xa**	–	50	–	–	50	25	25	12.5	25	50
2	**3xb**	–	–	–	–	12.5	6.25	25	12.5	50	50
3	**3xc**	–	–	50	–	1.56	1.56	50	6.25	50	50
4	**3xd**	–	–	–	–	–	–	50	25	–	–
5	**3xe**	50	–	25	25	12.5	6.25	25	1.56	12.5	25
6	**3xf**	50	50	–	–	3.12	12.5	3.12	6.25	25	25
7	**3ya**	–	–	–	–	–	–	12.5	25	–	–
8	**3yb**	–	50	50	–	25	50	25	1.56	25	50
9	**3yc**	–	–	–	–	3.12	12.5	12.5	1.56	25	–
10	**3yd**	50	–	–	–	25	25	–	50	–	–
11	**3ye**	–	50	–	–	25	–	6.25	25	–	–
12	**3yf**	–	50	–	–	3.12	25	3.12	25	–	50
13	**3za**	50	–	–	50	50	–	25	50	–	50
14	**3zb**	–	–	–	–	25	50	–	25	–	–
15	**3zc**	–	50	–	–	–	6.25	–	50	–	–
Flu*	NP	NP	NP	NP	NP	0.5	1.0	1.0	2.0	2.0	1.0

1. *E. coli* (ATCC 9637); 2. *Pseudomonas aeruginosa* (ATCC BAA-427); 3. *Staphyloccus aerus* (ATCC 25923); 4. *Klebsiella pneumoniae* (ATCC 27736); 5. *Candida albicans*; 6. *Cryptococcus neoformans*; 7. *Sporothrix schenckii*; 8. *Trichophyton mentagrophytes*; 9. *Aspergillus fumigatus*; **10**. *Candida parapsilosis* (ATCC- 22019); flu* = Fluconazole; '–' indicates MIC values above 50 µg/mL; NP: not performed.

suspension was diluted in 10 mL of media and then 100 µL of it was added in each well and kept for incubation. The maximum concentration of compounds tested was 50 µg/mL. The microtiter plates were incubated at 35 ºC in a moist, dark chamber and MICs were recorded spectrophotometrically after 24 h using SOFT max Pro 4.3 Software (Molecular Devices, Sunnyvale, USA).

RESULTS AND DISCUSSION

All the fifteen synthesized compounds **3xa-3zc** were screened for their antimicrobial activities against four pathogenic bacterias, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Klebsiella pneumonia*. The same compounds were also tested against six pathogenic fungi *Candida albicans*, *Cryptococcus neoformans*, *Sporothrix schenckii*, *Trichophyton mentagrophytes*, *Aspergillus fumigatus* and *Candida parapsilosis*. Biological studies of the compounds revealed that substitution at position 7 of 3-substituted coumarins by basic amino-ether side chain showed the MIC values at > 50 µg/mL against bacterial strains but have some significant results against antifungal strains. From the activity results it seems that compounds having diethyl amine, piperidine and pyrrolidine as the basic functionalities showed better activity against the antifungal strains. Three compounds **3xe, 3yb and 3yc** with the MIC values of 1.56 µg/mL are better than fluconazole against *Trichophyton mentagrophytes* (Table-2).

Conclusion

A novel class of 3,7-disubstituted 2*H*-1-benzopyran-2-one (**3xa-3zc**) were synthesized and evaluated for their antifungal and antibacterial activities. The compounds were found inactive against different strains of bacteria but some of these compounds **3xc, 3xe**, **3xf**, **3yb, 3yc** and **3yf** showed significant activity against selective fungal strains. Compounds **3xe, 3yb** and **3yc** with the MIC values of 1.56 µg/mL are better than the standard drug fluconazole against *Trichophyton mentagrophytes*.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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