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Synthesis and Antimicrobial Activity of Novel 3,7-Disubstituted 2*H*-1-Benzopyran-2-Ones

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Abstract

2*H*-1-benzopyran-2-one (Coumarin), an important oxygen heterocyclic scaffold, widely distributed throughout the plant kingdom, displayed a wide range of potential biological activities such as anti-microbial, anti-inflammatory and antioxidant activities. In this paper, we have synthesized a novel class of 3,7-disubstituted 2*H*-1-benzopyran-2-one derivatives **(3aa-3hb)** bearing a basic ether side chain at C-7 and a substituted phenyl ring at C-3 of the coumarin ring. These compounds have been evaluated for anti-microbial (antibacterial/antifungal) activities. Some of the compounds **3ac, 3ae**, **3bb**, **3bc** have shown significant anti-fungal activities against selective strains. Compound **3ae** and **3bc** 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 an important oxygen heterocyclic scaffold, widely distributed throughout the plant kingdom [1-3] and exhibited a wide range of biological activities [4] such as anticancer [5,6], anti-inflammatory [7], antioxidant [8], anti-tubercular [9], antihyperglycemic [10,11], MAO-B inhibitory anticoagulation [12,13] antimicrobial [14-17], (antifungal and antimicrobial) etc. It has been reported that 7-amino substituted coumarins plays a significant role as biologically active compounds in various diseases and as substrates for P-450 isozymes [18] and 7-amino 2*H*-1-benzopyran-2-one derivatives isolated from *Loeselia Mexicana*, *Petroselinum crispum*, *Ruta graveolens* and *Aesculus pavia* exhibited significant antimicrobial activity [19]. A series of 7-amino-and 7-hydroxy-substituted coumarins (Figure 1, Compound **I-IV**), initially have been synthesized as potential zinc indicators were also possessed anti-inflammatory and antioxidant activities [20,21]. In recent years, various analogues of 3,7-disubstituted coumarins were reported as antimicrobial agents and monoamine oxidase (MAO inhibitors) [22,23]. Therefore, coumarins and their derivatives has been the subject of extensive investigations in recent years. Furthermore, it has also been realized that by incorporating substituted phenyl ring at position C-3 of the coumarin ring may increases many fold their biological activities [24]. 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, we became interested 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** (Figure 2).

Our group [25-31] has been working since several years on the design and synthesis/semisynthesis 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** (Figure 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 till now.

Chemistry

The designed compounds **3aa-hb** were synthesized from their corresponding 7-hydroxy-3-substituted 2*H*-1-benzopyran-2-one **2a-h,** through their alkylation with different ammonium hydrochloride salts (Scheme 1). Compounds **2a-h** 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**. Various kinds of the synthesized compounds **3aa-3hb** having different R^1 and R^2 substituents are depicted in Tables 1 and 2.

Experimental

^{1}H NMR and ^{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. Splitting patterns are described as singlet (s), broad singlet (br s), broad multiplet (br m), doublet (d), triplet (t), quintet (q), septet (sep), td (doublet of triplet) and multiplet (m). 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°C. 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

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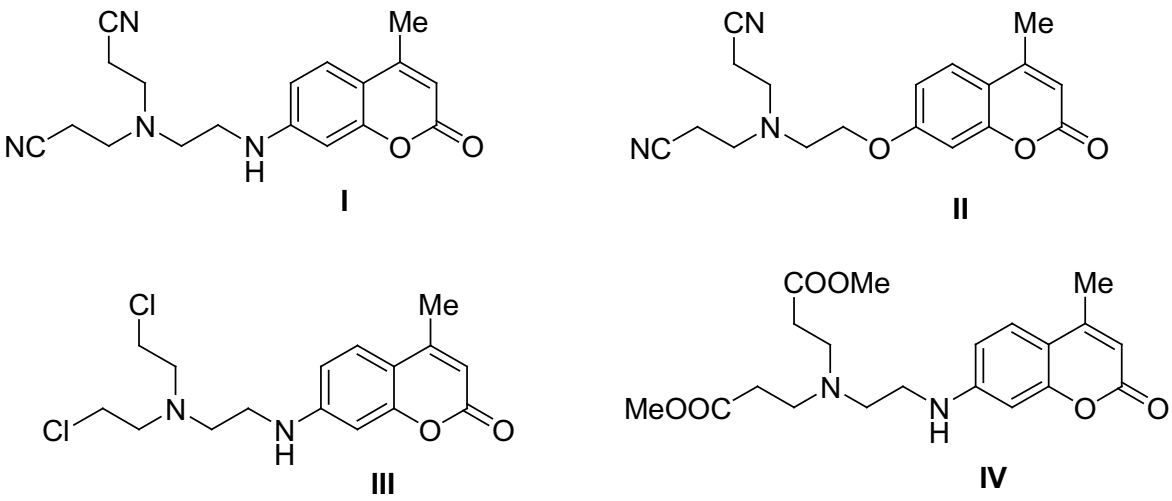


Figure 1: Structures of some 7-substituted coumarins.

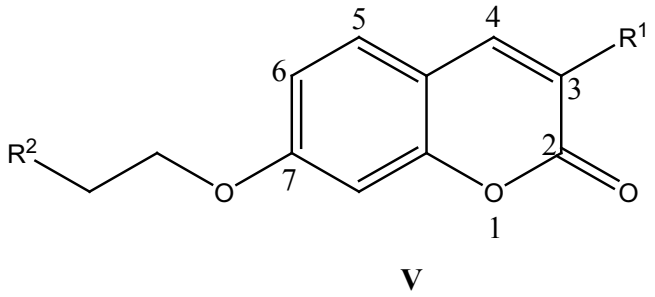


Figure 2: Designed Prototypes (**3aa-3hb**).

silica gel (particle size: 60-120 Mesh) or flash silica gel (particle size: 230-400 Mesh) procured from Qualigens (India).

General procedure of preparation of intermediate compounds 2H-1-benzopyran-2-ones (2a-h)

In a 250 mL round bottom flask was charged successively 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°C 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°C 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°C and then cooled to 15°C, and acidified with 5N 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°C under vacuum to afford the 3-substituted-7- hydroxyl-2*H*-1-benzopyran-2-one in 70-80% yield.

7-Hydroxy-3-phenyl- 2H-1-benzopyran-2-one (2a): Yield 68%; mp 195-197°C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 6.84 (dd, 1H, *J*=8.5, 2.3 Hz), 6.87 (d, 1H, *J*=2.0 Hz), 7.31-7.42 (m, 5H), 7.46-7.49 (m, 1H), 7.67 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 102.53, 111.35, 113.51, 121.87, 126.56, 129.06, 129.41, 131.30, 133.42, 134.09, 142.99, 155.51, 161.52; ES-MS (*m/z*) 239 $[M+H]^+$.

7-Hydroxy-3-(2-methoxy-phenyl)- 2H-1-benzopyran-2-one (2c): Yield 70%; mp 180-182°C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 3.82 (s, 3H), 6.80-6.84 (m, 2H), 6.97-7.03 (m, 2H), 7.33-7.38 (m, 3H), 7.68 (s, 1H), 9.95 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 55.58, 102.57, 111.13, 112.03, 113.30, 120.36, 121.47, 124.40, 128.82, 129.61, 130.73, 140.72, 142.27, 155.32, 157.09, 160.98; ES-MS (*m/z*) 269 $[M+H]^+$.

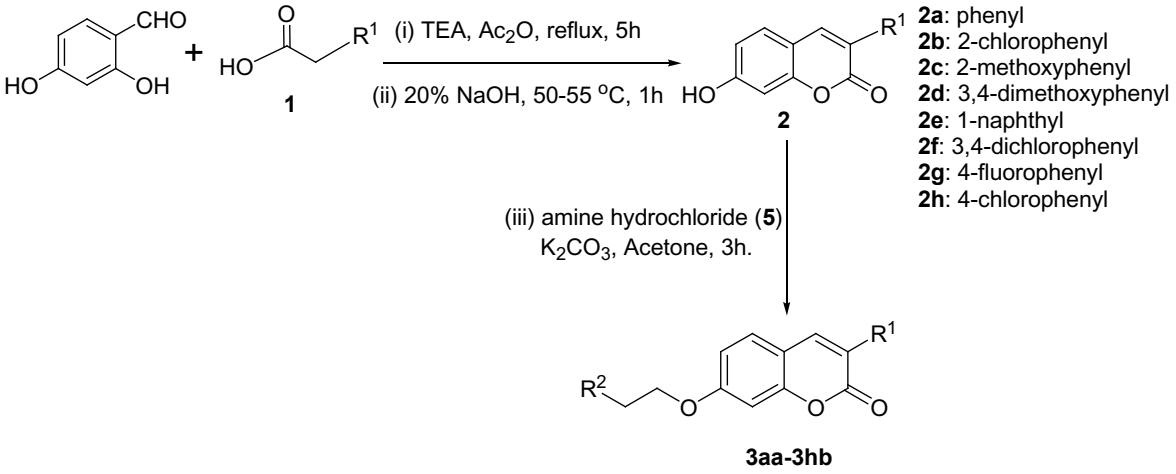
3-(3,4-Dimethoxy-phenyl)-7-hydroxy- 2H-1-benzopyran-2-one (2d): Yield 67%; mp 193-195°C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 3.92 (s, 3H), 3.94 (s, 3H), 6.81-6.86 (m, 2H), 6.93 (d, 1H, *J*=8.3 Hz), 7.24-7.29 (m, 3H), 7.36 (d, 1H, *J*=8.4 Hz), 7.71 (s, 1H), 9.57 (s, 1H, OH); ES-MS (*m/z*) 299 $[M+H]^+$.

7-Hydroxy-3-naphthalen-1-yl-2H-1-benzopyran-2-one (2e): Yield 70%; mp 183-185°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (dd, 1H, *J*=8.5, 2.3 Hz), 6.94 (d, 1H, *J*=2.0 Hz), 7.36 (d, 1H, *J*=8.5 Hz), 7.44-7.55 (m, 4H), 7.74 (s, 1H), 7.78-7.81 (m, 1H), 7.88-7.91 (m, 2H), 9.86 (s, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 103.01, 112.14, 113.85, 123.45, 125.39, 126.04, 126.38, 127.78, 128.53, 129.02, 129.16, 131.82, 133.36, 133.73, 143.54, 155.90, 161.55; ES-MS (*m/z*) 289 $[M+H]^+$.

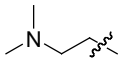
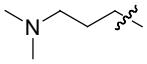
3-(4-Fluoro-phenyl)-7-hydroxy-2H-1-benzopyran-2-one (2g): Yield 64%; mp 243-245°C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 6.81-6.86 (m, 2H), 7.08-7.14 (m, 2H), 7.33-7.38 (m, 1H), 7.64-7.69 (m, 2H), 7.73 (s, 1H), 9.86 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 101.77, 111.50, 113.12, 114.36, 114.64, 121.45, 128.65, 129.50, 129.61, 130.76, 140.03, 154.62, 160.88; ES-MS (*m/z*) 257 $[M+H]^+$.

General procedure of preparation of compound (3aa-hb)

To a solution of 2*H*-1-benzopyran-2-one **2a-h** (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 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.



Scheme 1: Synthesized compounds 3aa-hb.

Entry	Compounds	Substituents	
		R^1	R^2
1	**3aa**		
2	**3ab**		
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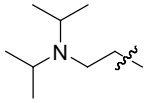
4	**3ad**		
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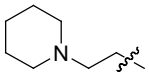
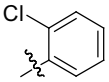
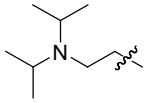
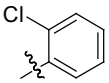
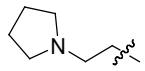
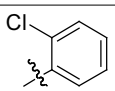
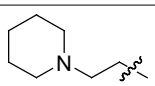
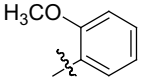
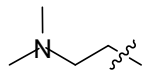
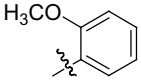
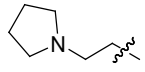
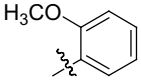
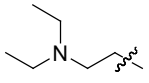
6	**3af**		
7	**3ba**		
8	**3bb**		
9	**3bc**		
10	**3ca**		
11	**3cb**		
12	**3cc**		

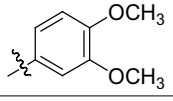
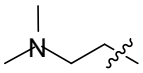
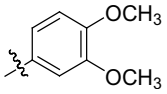
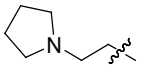
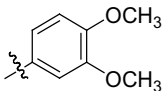
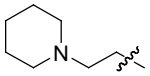
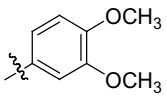
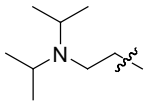
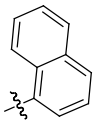
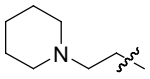
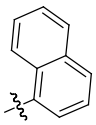
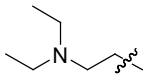
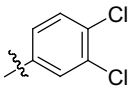
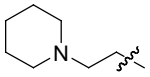
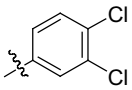
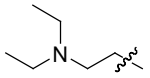
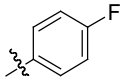
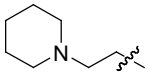
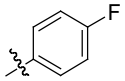
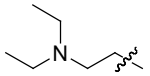
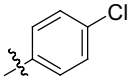
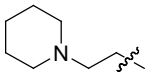
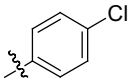
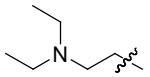
13	**3da**		
14	**3db**		
15	**3dc**		
16	**3dd**		
17	**3ea**		
18	**3eb**		
19	**3fa**		
20	**3fb**		
21	**3ga**		
22	**3gb**		
23	**3ha**		
24	**3hb**		

Table 1: Synthesized compounds **3aa-3hb**.

Entry	Compound	MIC (µg/mL)									
		Bacteria				Fungi					
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
1	**3aa**	-	-	-	-	50	25	25	12.5	50	50
2	**3ab**	-	-	-	-	12.5	12.5	25	12.5	50	50
3	**3ac**	-	-	-	-	**1.56**	**1.56**	50	12.5	50	50
4	**3ad**	-	-	-	-	-	-	50	25	-	-
5	**3ae**	-	-	25	50	12.5	12.5	25	**1.56**	12.5	25
6	**3af**	50	50	-	-	6.25	12.5	6.25	6.25	25	25
7	**3ba**	-	-	-	-	-	-	12.5	25	-	-
8	**3bb**	-	50	-	-	50	50	25	**3.12**	20	50
9	**3bc**	-	-	-	-	50	50	12.5	**1.56**	25	-
10	**3ca**	-	-	-	-	-	-	-	50	-	-
11	**3cb**	-	50	-	-	-	-	-	25	-	-
12	**3cc**	-	-	-	-	-	-	-	50	-	-

13	**3da**	50	50	-	50	50	-	50	50	-	50
14	**3db**	-	-	-	-	50	50	-	25	-	-
15	**3dc**	-	-	-	-	-	-	-	50	-	-
16	**3dd**	-	-	-	-	-	50	-	50	-	-
17	**3ea**	50	50	50	50	6.25	25	12.5	12.5	25	12.5
18	**3eb**	-	50	-	-	12.5	-	6.25	12.5	25	25
19	**3fa**	-	-	-	50	12.5	25	12.5	6.25	12.5	6.25
20	**3fb**	50	50	-	50	12.5	25	12.5	6.25	25	25
21	**3ga**	50	50	-	-	50	50	50	12.5	-	12.5
22	**3gb**	-	-	-	-	**3.12**	-	12.5	12.5	50	6.25
23	**3ha**	50	50	-	-	**3.12**	-	12.5	12.5	-	12.5
24	**3hb**	-	50	-	-	**3.12**	-	6.25	6.25	25	50
flu*	ND	ND	ND	ND	ND	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; ND: Not done.

Table 2: *In-vitro* antimicrobial activities of 3-aryl-7-alkylaminoethoxy 2*H*-1-benzopyran-2-one (**3aa-hb**).

7-(2-Dimethylamino ethoxy)-3-phenyl 2H-1-benzopyran-2-one (3aa): Yield 81%; mp 96-98°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 6H), 2.78 (t, 2H, *J*=5.6 Hz), 4.14 (t, 2H, *J*=5.6 Hz), 6.87-6.93 (m, 2H), 7.38-7.47 (m, 4H), 7.67-7.71 (m, 2H), 7.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.11 (NCH_3×2), 58.24 (NCH_2), 66.89 (OCH_2), 101.29 (CH), 113.48 (CH), 113.66 (C), 128.64 (CH×3), 129.03 (CH), 135.28 (C), 140.19 (CH), 144.51 (C), 155.50 (C), 161.09 (C), 162.09 (CO); ν_{max} (KBr, cm^{-1}) 1670, 1598, 1527, 1216 761; ES-MS (*m/z*) 310 $[M+H]^+$. Found C 73.87%, H 6.21%, N 4.55%; $C_{19}H_{19}NO_3$ requires C 73.80%, H 6.19%, N 4.53%.

7-(3-Dimethylaminopropoxy)-3-phenyl-2H-1-benzopyran-2-one (3ab): Yield 83%; mp 94-96°C ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (quin, 2H, *J*=7.1 Hz), 2.27 (s, 6H), 2.48 (t, 2H, *J*=7.1 Hz), 4.09 (t, 2H, *J*=6.3 Hz), 6.86-6.89 (m, 2H), 7.35-7.47 (m, 4H), 7.68-7.71 (m, 2H), 7.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.47 ($CH_2CH_2CH_2$), 45.72 (NCH_3×2), 56.34 (NCH_2), 67.02 (OCH_2), 101.23 (CH), 113.30 (CH), 113.48 (C), 124.92 (C), 128.61 (CH), 128.64 (CH), 129.02 (CH), 135.27 (C), 140.31 (CH), 155.50 (C), 161.20 (C), 162.28 (CO); ν_{max} (KBr, cm^{-1}) 1711, 1611, 1217, 1008 780; ES-MS (*m/z*) 324 $[M+H]^+$. Found C 74.37%, H 6.49%, N 4.32%; $C_{20}H_{21}NO_3$ requires C 74.28%, H 6.55%, N 4.33%.

7-(2-Diethylaminoethoxy)-3-phenyl -2H-1-benzopyran-2-one (3ac): Yield 82%; mp 66-68°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (t, 6H, *J*=7.1 Hz), 2.65 (q, 4H, *J*=7.1 Hz), 2.90 (t, 2H, *J*=6.1 Hz), 4.11 (t, 2H, *J*=6.1 Hz), 6.86-6.89 (m, 2H), 7.34-7.46 (m, 4H), 7.67-7.70 (m, 2H), 7.75 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.07 (NCH_2CH_3×2), 48.12 (NCH_2CH_3×2), 51.74 (NCH_2), 67.60 (OCH_2), 101.26 (CH), 113.39 (CH), 113.54 (C), 124.97 (C), 128.60 (CH), 128.99 (CH), 135.26 (C), 140.22 (CH), 155.47 (C), 161.10 (C), 162.15 (CO); ν_{max} (KBr, cm^{-1}) 1721, 1613, 1215, 768; ES-MS (*m/z*) 338 $[M+H]^+$. Found C 74.80%, H 6.84%, N 4.18%; $C_{21}H_{23}NO_3$ requires C 74.75%, H 6.87%, N 4.15%.

7-(2-Diisopropylaminoethoxy)-3-phenyl- 2H-1-benzopyran-2-one (3ad): Yield 79%; mp 87-89°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (d, 12H, *J*=6.5 Hz), 2.86 (t, 2H, *J*=7.2 Hz), 3.06 (sep, 2H, *J*=6.5 Hz), 3.97 (t, 2H, *J*=7.2 Hz), 6.85-6.88 (m, 2H), 7.35-7.47 (m, 4H), 7.67-7.70 (m, 2H), 7.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.10 ($NCHCH_3$×4), 44.36 (NCH_2×2), 49.88 (CH×2), 70.11 (OCH_2), 101.35 (CH), 113.27 (CH), 113.44 (C), 124.86 (C), 128.60 (CH), 129.01 (CH), 135.31 (C), 140.26 (CH), 155.53 (C), 161.15 (C), 162.31 (CO); ν_{max} (KBr, cm^{-1}) 1715, 1622, 1283, 1144, 784; ES-MS (*m/z*) 366 $[M+H]^+$. Found C 75.68%, H 7.35%, N 3.87%; $C_{23}H_{27}NO_3$ requires C 75.59%, H 7.45%, N 3.83%.

3-Phenyl-7-(2-pyrrolidin-1-yl-ethoxy)- 2H-1-benzopyran-2-one (3ae): Yield 85%; mp 130-132°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.76-1.92 (m, 4H), 2.61-2.70 (m, 4H), 2.95 (t, 2H, *J*=5.8 Hz), 4.18 (t, 2H, *J*=5.8 Hz), 6.86-6.92 (m, 2H), 7.37-7.48 (m, 4H), 7.66-7.71 (m, 2H), 7.76 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.72 (NCH_2CH_2×2), 54.98 (NCH_2×3), 67.95 (OCH_2), 101.29 (CH), 113.43 (CH), 113.59 (C), 125.03 (C), 128.61 (CH), 129.02 (CH), 135.25 (C), 140.22 (CH), 155.46 (C), 161.12 (C), 162.08 (CO); ν_{max} (KBr, cm^{-1}) 1719, 1598, 1267, 780; ES-MS (*m/z*) 336 $[M+H]^+$. Found C 75.29%, H 6.29%, N 4.2%; $C_{21}H_{21}NO_3$ requires C 75.20%, H 6.31%, N 4.18%.

3-Phenyl-7-(2-piperidin-1-yl-ethoxy)-2H-1-benzopyran-2-one (3af): Yield 86%; mp 101-103°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46-1.49 (m, 2H), 1.59-1.66 (m, 4H), 2.53 (br m 4H), 2.81 (t, 2H, *J*=5.9 Hz), 4.18 (t, 2H, *J*=5.9 Hz), 6.87-6.90 (m, 2H), 7.36-7.47 (m, 4H), 7.67-7.71 (m, 2H), 7.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.36 ($NCH_2CH_2CH_2$), 26.15 ($NCH_2CH_2CH_2$×2), 55.34 ($NCH_2CH_2CH_2$×2), 57.86 (NCH_2CH_2O), 66.94 (OCH_2CH_2N), 101.34 (CH), 113.44 (CH), 113.59 (C), 125.05 (C), 128.63 (CH), 129.01 (CH), 135.27 (C), 140.22 (CH), 155.50 (C), 161.12 (C), 162.11 (CO); ν_{max} (KBr, cm^{-1}) 1721, 1609, 1268, 783; ES-MS (*m/z*) 350 $[M+H]^+$. Found C 75.69%, H 6.60%, N 4.04%; $C_{22}H_{23}NO_3$ requires C 75.62%, H 6.63%, N 4.01%.

3-(2-Chlorophenyl)-7-(2-diisopropylaminoethoxy) -2H-1-benzopyran-2-one (3ba): Yield 81%; mp 133-135°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (d, 12H, *J*=6.5 Hz), 2.88 (t, 2H, *J*=7.5 Hz), 3.07 (sep, 2H, *J*=6.5 Hz), 3.99 (t, 2H, *J*=6.6 Hz), 6.85-6.89 (m, 2H), 7.32-7.36 (m, 2H), 7.39-7.43 (m, 2H), 7.47-7.50 (m, 1H), 7.69 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.08 ($CHCH_3$×4), 44.38 (NCH_2), 49.97 (CH_3CH×2), 70.12 (OCH_2), 101.63 (CH), 112.80 (C), 113.33 (CH), 123.55 (C), 127.01 (CH), 129.21 (CH), 129.98 (CH), 130.11 (CH), 131.75 (CH), 134.01 (C), 134.33 (C), 143.02 (CH), 156.03 (C), 160.45 (C), 162.65 (CO); ν_{max} (KBr, cm^{-1}) 1724, 1612, 1214, 761; ES-MS (*m/z*) 400 $[M+H]^+$. Found C 69.15%, H 6.46%, N 3.48% ;$C_{23}H_{26}ClNO_3$ requires C 69.08%, H 6.55%, N 3.50%.

3-(2-Chlorophenyl)-7-(2-pyrrolidin-1-yl-ethoxy)- 2H-1-benzopyran-2-one (3bb): Yield 78%; mp 95-97°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 -1.85 (m, 4H), 2.66 (br m, 4H), 2.96 (t, 2H, *J*=5.6 Hz), 4.19 (t, 2H, *J*=5.6 Hz), 6.89-6.93 (m, 2H), 7.31-7.34 (m, 2H), 7.39-7.43 (m, 2H), 7.47-7.49 (m, 1H), 7.68 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.72 (NCH_2CH_2×2), 54.95 (NCH_2×3), 67.94 (OCH_2), 101.54 (CH), 111.93 (C), 113.46 (CH), 123.69 (C), 127.00 (CH), 129.21 (CH), 129.99 (CH), 130.08 (CH), 131.71 (CH), 133.96 (C), 134.25 (C), 142.97 (CH), 155.94 (C), 160.39 (C), 162.40 (CO); ν_{max} (KBr, cm^{-1}) 1725, 1613, 1216,

761; ES-MS (*m/z*) 370 $[M+H]^+$. Found C 68.31%, H 5.40%, N 3.77%; $C_{21}H_{20}ClNO_3$ requires C 68.20%, H 5.45%, N 3.79%.

3-(2-Chlorophenyl)-7-(2-piperidin-1-yl-ethoxy)-2H-1-benzopyran-2-one (3bc): Yield 75%; mp 105-107°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46-1.47 (m, 2H), 1.61-1.62 (m, 4H), 2.51-2.52 (m, 4H), 2.81 (t, 2H, *J*=5.9 Hz), 4.18 (t, 2H, *J*=6.0 Hz), 6.88-6.90 (m, 2H), 7.31-7.36 (m, 2H), 7.39-7.42 (m, 2H), 7.46-7.49 (m, 1H), 7.68 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.35 ($NCH_2CH_2CH_2$), 26.13 ($NCH_2CH_2CH_2\times2$), 53.33 ($NCH_2CH_2CH_2\times2$), 57.83 (NCH_2), 66.96 (OCH_2), 101.57 (CH), 112.91 (C), 113.48 (CH), 123.6 (C), 127.00 (CH), 129.20 (CH), 129.99 (CH), 130.10 (CH), 131.72 (CH), 133.98 (C), 134.27 (C), 142.97 (CH), 155.97 (C), 160.40 (C), 162.44 (CO); ν_{max} (KBr, cm^{-1}) 1721, 1609, 1122, 777; ES-MS (*m/z*) 384 $[M+H]^+$. Found C 68.91%, H 5.64%, N 3.63%; $C_{22}H_{22}ClNO_3$ requires C 68.83%, H 5.78%, N 3.65%.

7-(2-Dimethylaminoethoxy)-3-(2-methoxy phenyl)-2H-1-benzopyran-2-one (3ca): Yield 70%; viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 6H), 2.77 (t, 2H, *J*=5.6 Hz), 3.82 (s, 3H), 4.13 (t, 2H, *J*=5.6 Hz), 6.86-6.89 (m, 2H), 6.96-7.04 (m, 2H), 7.34-7.39 (m, 3H), 7.67 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.01 ($NCH_3\times2$), 55.91 (OCH_3), 58.13 (NCH_2), 66.72 (OCH_2), 101.29 (CH), 111.51 (CH), 113.07 (CH), 113.41 (C), 120.73 (CH), 123.14 (C), 124.56 (C), 128.85 (CH), 130.06 (CH), 131.01 (CH), 141.98 (CH), 155.55 (C), 157.44 (C), 160.72 (C), 161.79 (CO); ν_{max} (KBr, cm^{-1}) 1727, 1614, 1266, 738; ES-MS (*m/z*) 340 $[M+H]^+$. Found C 70.86%, H 6.19%, N 4.12%; $C_{20}H_{21}NO_4$ requires C 70.78%, H 6.25%, N 4.13%.

3-(2-Methoxyphenyl)-7-(2-pyrrolidin-1-yl-ethoxy)-2H-1-benzopyran-2-one (3cb): Yield 72%; viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84-1.86 (m, 4H), 2.64-2.68 (m, 4H), 2.96 (t, 2H, *J*=5.8 Hz), 3.83 (s, 3H), 4.19 (t, 2H, *J*=5.8 Hz), 6.87-6.89 (m, 2H), 6.97-7.04 (m, 2H), 7.34-7.39 (m, 3H), 7.67 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.72, ($NCH_2CH_2\times2$), 54.97 ($NCH_2\times3$), 55.99 (OCH3), 67.84 (OCH2), 101.44 (CH), 111,58 (CH), 113.12 (CH), 113.48 (C), 120.82 (CH), 123.24 (C), 124.64 (C), 128.91 (CH), 130.14 (CH), 131.09 (CH), 142.04 (CH), 155.65 (C), 157.52 (C),160.83 (C), 161.86 (CO); ν_{max} (KBr, cm^{-1}) 2361, 1723, 1613, 1216, 761; ES-MS (*m/z*) 366 $[M+H]^+$. Found C 72.45%, H 6.24%, N 3.85%; $C_{22}H_{23}NO_4$ requires C 72.31%, H 6.34%, N 3.83%.

7-(2-Diethylaminoethoxy)-3-(2-methoxyphenyl) -2H-1-benzopyran-2-one (3cc): Yield 76%; mp 113-115°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, 6H, *J*=7.2 Hz), 2.66 (q, 4H, *J*=7.2 Hz), 2.91 (t, 2H, *J*=6.1 Hz), 3.83 (s, 3H), 4.12 (t, 2H, *J*=6.1 Hz), 6.84-6.88 (m, 2H), 6.97-7.04 (m, 2H), 7.34-7.39 (m, 3H), 7.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.99 ($NCH_2CH_3\times2$), 48.07 ($NCH_2\times3$), 55.96 (OCH_3), 67.45 (OCH_2), 101.36 (CH), 111.55 (CH), 113.09 (CH), 113.39 (C), 120.79 (CH), 123.19 (C), 124.62 (C), 128.89 (CH), 130.12 (CH), 131.07 (CH), 142.05 (CH), 155.62 (C), 157.50 (C), 160.83 (C), 161.92 (CO); ν_{max} (KBr, cm^{-1}) 2361, 1726, 1610, 1265, 740; ES-MS (*m/z*) 368 $[M+H]^+$. Found C 72.05%, H 6.69%, N 3.84%; $C_{22}H_{25}NO_4$ requires C 71.91%, H 6.86%, N 3.81%.

3-(3,4-Dimethoxyphenyl)-7-(2-dimethylaminoethoxy) 2H-1-benzopyran-2-one (3da): Yield 80%; mp 120-121°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 6H), 2.78 (t, 2H, *J*=5.6 Hz), 3.92 (s, 3H), 3.94 (s, 3H), 4.14 (t, 2H, *J*=5.6 Hz), 6.87-6.94 (m, 3H), 7.24-7.29 (m, 2H), 7.42 (d, 1H, *J*=8.6 Hz), 7.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.09 ($NCH_3\times2$), 56.15 (OCH_3), 56.21 (OCH_3), 58.21 (NCH_2), 66.82 (OCH_2), 101.17 (CH), 111.26 (CH), 111.99 (CH), 113.40 (CH), 113.67 (C), 121.21 (CH), 124.65 (C), 127.98 (C), 128.80 (CH), 139.13 (CH), 148.90 (C), 149.61 (C), 155.19 (C), 161.20 (C), 161.83 (CO); ν_{max} (KBr, cm^{-1}) 2361, 1720, 1611, 1216, 1027, 761; ES-MS (*m/z*) 370 $[M+H]^+$. Found C 68.37%, H 6.30%, N 3.82%; $C_{21}H_{23}NO_5$ requires C 68.28%, H 6.28%, N 3.79%.

3-(3,4-Dimethoxyphenyl)-7-(2-pyrrolidin-1-yl-ethoxy)-2H-1-benzopyran-2-one (3db): Yield 78%; mp 90-91°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.81 -1.86 (m, 4H), 2.61-2.68 (m, 4H), 2.95 (t, 2H, *J*=5.8 Hz), 3.92 (s, 3H), 3.94 (s, 3H), 4.19 (t, 2H, *J*=5.8 Hz), 6.87-6.95 (m, 3H), 7.24-7.29 (m, 2H), 7.42 (d, 1H, *J*=8.4 Hz), 7.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.67 ($NCH_2CH_2\times2$), 54.94 ($NCH_2\times3$), 56.13 (OCH_3), 56.17 (OCH_3), 67.86 (OCH_2), 101.20 (CH), 111.16 (CH), 111.88 (CH), 113.35 (CH), 113.63 (C), 121.17 (CH), 124.59 (C), 127.94 (C), 128.81 (CH), 139.17 (CH), 148.83 (C), 149.54 (C), 155.16 (C), 161.24 (C), 161.81 (CO); ν_{max} (KBr, cm^{-1}) 2359, 1724, 1612, 1210, 1012 740; ES-MS (*m/z*) 396 $[M+H]^+$. Found C 69.97%, H 6.29%, N 3.52%; $C_{23}H_{25}NO_5$ requires C 69.86%, H 6.37%, N 3.54%.

3-(3,4-Dimethoxyphenyl)-7-(2-piperidin-1-yl-ethoxy)-2H-1-benzopyran-2-one (3dc): Yield 78%; mp 96-98°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45-1.49 (m, 2H), 1.60-1.66 (m, 4H), 2.51-2.54 (m, 4H), 2.81 (t, 2H, *J*=5.9 Hz), 3.92 (s, 3H), 3.94 (s, 3H), 4.18 (t, 2H, *J*=5.9 Hz), 6.86-6.89 (m, 2H), 6.93 (d, 1H, *J*=8.3 Hz), 7.24-7.29 (m, 2H), 7.42 (d, 1H, *J*=8.4 Hz), 7.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.33 ($NCH_2CH_2CH_2$), 26.09 ($NCH_2CH_2CH_2\times2$), 53.31($NCH_2CH_2CH_2\times2$), 56.19 (OCH_3), 56.24 (OCH_3), 57.84 (NCH_2), 66.87 (OCH_2), 101.33 (CH), 111.29 (CH), 112.03 (CH), 113.39 (CH), 113.69 (CH), 121.23 (CH), 124.68 (C), 128.03 (C), 128.82 (CH), 139.16 (CH), 148.94 (C), 149.65 (C), 155.25 (C), 161.26 (C), 161.86 (CO); ν_{max} (KBr, cm^{-1}) 1723, 1610, 1210, 1009 738; ES-MS (*m/z*) 410 $[M+H]^+$. Found C 70.52%, H 6.69%, N 3.46%; $C_{24}H_{27}NO_5$ requires C 70.40%, H 6.65%, N 3.42%.

7-(2-Diisopropylaminoethoxy)-3-(3,4-dimethoxy-phenyl) -2H-1-benzopyran-2-one (3dd): Yield 88%; mp 113-115°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (d, 12H, *J*=6.5 Hz), 2.86 (t, 2H, *J*=7.3 Hz), 3.06 (sep, 2H, *J*=6.5 Hz), 3.92 (s, 3H), 3.95 (s, 3H), 3.97 (t, 2H, *J*=7.2 Hz), 6.84-6.87 (m, 2H), 6.93 (d, 1H, *J*=8.4 Hz), 7.24-7.29 (m, 2H), 7.42 (d, 1H, *J*=9.3 Hz), 7.72 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.09 ($CHCH_3\times4$), 44.37 (NCH_2), 49.90 ($CH_3CH\times2$), 56.18 (OCH_3), 56.24 (OCH_3), 70.09 (OCH_2), 101.33 (CH), 111.29 (CH), 112.04 (CH), 113.24 (CH), 113.53 (C), 121.22 (CH), 124.52 (C), 128.08 (C), 128.82 (CH), 139.22 (CH), 148.93 (C), 149.61 (C), 155.30 (C), 161.31 (C), 162.09 (CO); ν_{max} (KBr, cm^{-1}) 2361, 1716, 1612, 1216, 1025 761; ES-MS (*m/z*) 426 $[M+H]^+$; HRMS-EI: found 425.2234, calcuated 425.2202. Found C 70.69%, H 7.23%, N 3.24%; $C_{25}H_{31}NO_5$ requires C 70.57%, H 7.34%, N 3.29%.

3-Naphthalen-1-yl-7-(2-piperidin-1-yl-ethoxy) 2H-1-benzopyran-2-one (3ea): Yield 87%; mp 86-88°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41-1.51 (m, 2H), 1.60-1.68 (m, 4H), 2.53-2.56 (m, 4H), 2.83 (t, 2H, *J*=5.9 Hz), 4.21 (t, 2H, *J*=5.9 Hz), 6.89-6.93 (m, 2H), 7.42 (d, 1H, *J*=8.5 Hz), 7.46-7.53 (m, 4H), 7.75 (s, 1H), 7.78-7.81 (m, 1H), 7.88-7.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.32 ($NCH_2CH_2CH_2$), 26.09 ($NCH_2CH_2CH_2\times2$), 55.32 ($NCH_2CH_2CH_2\times2$), 57.82 (NCH_2CH_2O), 66.90 (OCH_2CH_2N), 101.53 (CH), 113.20 (C), 113.43 (CH), 124.85 (C), 125.43 (CH), 125.48 (CH), 126.21 (CH), 126.58 (CH), 127.91 (CH), 128.71 (CH), 129.04 (CH), 129.33 (CH), 131.87 (C), 133.20 (C), 133.89 (C), 143.12 (CH), 155.94 (C), 161.35 (C), 162.24 (C); ν_{max} (KBr, cm^{-1}) 1710, 1612, 1215, 1010 777; ES-MS (*m/z*) 400 $[M+H]^+$. Found C 78.30%, H 6.24%, N 3.48%; $C_{26}H_{25}NO_3$ requires C 78.18%, H 6.31%, N 3.51%.

7-(2-Diethylaminoethoxy)-3-naphthalen-1-yl-2H-1-benzopyran-2-one (3eb): Yield 89%; mp 78-80°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, 6H, *J*=7.1 Hz), 2.67 (quart, 4H, *J*=7.1 Hz), 2.93 (t,

2H, *J*=6.1 Hz), 4.15 (t, 2H, *J*=6.1 Hz), 6.89-6.93 (m, 2H), 7.41-7.54 (m, 5H), 7.75-7.81 (m, 2H), 7.89-7.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.89 (NCH_2CH_3×2), 48.08 (NCH_2CH_3×2), 51.67 (NCH_2CH_2O), 67.42 (OCH_2CH_2N), 101.52 (CH), 113.24 (C), 113.39 (CH), 124.88 (C), 125.45 (CH), 125.51 (CH), 126.23 (CH), 126.61 (CH), 127.93 (CH), 128.73 (CH), 129.07 (CH), 129.35 (CH), 131.88 (C), 133.21 (C), 133.91 (C), 143.16 (CH), 155.95 (C), 161.38 (C), 162.24 (C); ν_{max} (KBr, cm^{-1}) 1710, 1614, 1216, 1009 780; ES-MS (*m/z*) 388 $[M+H]^+$. Found C 77.61%, H 6.46%, N 3.58%; $C_{25}H_{25}NO_3$ requires C 77.49%, H 6.50%, N 3.61%.

3-(3,4-Dichlorophenyl)-7-(2-piperidin-1-yl-ethoxy) 2H-1-benzopyran-2-one (3fa): Yield 84%; mp 110-112°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49-1.53 (m, 2H), 1.63-1.70 (m, 4H), 2.57-2.59 (m, 4H), 2.86 (t, 2H, *J*=5.8 Hz), 4.21 (t, 2H, *J*=5.8 Hz), 6.87-6.90 (m, 2H), 7.33-7.36 (m, 2H), 7.40-7.43 (m, 1H), 7.52 (d, 1H, *J*=1.7 Hz), 7.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.24 ($NCH_2CH_2CH_2$), 25.89 ($NCH_2CH_2CH_2$×2), 55.28 ($NCH_2CH_2CH_2$×2), 57.77 (NCH_2CH_2O), 66.67 (OCH_2CH_2N), 101.56 (CH), 112.77 (C), 113.59 (CH), 122.49 (C), 127.39 (CH), 129.30 (CH), 129.99 (CH), 132.54 (CH), 132.73 (C), 134.77 (C), 135.27 (C), 143.29 (CH), 155.97 (C), 160.28 (C), 162.53 (C); ν_{max} (KBr, cm^{-1})1724, 1613, 1216, 761; ES-MS (*m/z*) 418 $[M+H]^+$. Found C 63.28%, H 5.02%, N 3.34%; $C_{22}H_{21}Cl_2NO_3$ requires C 63.17%, H 5.06%, N 3.35%.

3-(3,4-Dichlorophenyl)-7-(2-diethylaminoethoxy) -2H-1-benzopyran-2-one (3fb): Yield 78%; mp 66-68°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (t, 6H, *J*=7.1 Hz), 2.65 (quart, 4H, *J*=7.1 Hz), 2.91 (t, 2H, *J*=6.1 Hz), 4.12 (t, 2H, *J*=6.1 Hz), 6.88-6.92 (m, 2H), 7.29-7.38 (m, 2H), 7.40-7.43 (m, 1H), 7.50 (d, 1H, *J*= 1.8 Hz), 7.68 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.98 (NCH_2CH_3×2), 48.08 (NCH_2CH_3×2), 51.72 (NCH_2), 67.62 (OCH_2), 101.52 (CH), 112.70 (C), 113.59 (CH), 122.42 (C), 127.37 (CH), 129.29 (CH), 129.96 (CH), 132.54 (CH), 132.77 (C), 134.77 (C), 135.22 (C), 143.28 (CH), 156.00 (C), 160.23 (C), 162.68 (C); ν_{max} (KBr, cm^{-1}) 1723, 1614, 1216, 1026 763; ES-MS (*m/z*) 406 $[M+H]^+$. Found C 62.20%, H 5.27%, N 3.47%; $C_{21}H_{21}Cl_2NO_3$ requires C 62.08%, H 5.21%, N 3.45%.

3-(4-Fluorophenyl)-7-(2-piperidin-1-yl-ethoxy)- 2H-1-benzopyran-2-one (3ga): Yield 79%; mp 124-126°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44-1.49 (m, 2H), 1.59-1.67 (m, 4H), 2.51-2.54 (m, 4H), 2.81 (t, 2H, *J*=5.9 Hz), 4.18 (t, 2H, *J*=5.9 Hz), 6.86-6.91 (m, 2H), 7.09-7.15 (m, 2H), 7.43 (d, 1H, *J*=8.6 Hz), 7.65-7.69 (m, 2H), 7.73 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.34 ($NCH_2CH_2CH_2$), 26.11 ($NCH_2CH_2CH_2$×2), 55.33 ($NCH_2CH_2CH_2$×2), 57.84 (NCH_2), 66.93 (OCH_2), 101.38 (CH), 113.48 (C), 113.54 (CH), 115.40 (CH), 115.83 (CH), 124.02 (C), 129.01 (CH), 130.36 (CH), 130.53 (CH), 131.31 (C), 140.07 (CH), 155.47 (C), 162.18 (C); ν_{max} (KBr, cm^{-1}) 1723, 1616, 1210, 768; ES-MS (*m/z*) 368 $[M+H]^+$. Found C 72.03%, H 6.03%, N 3.86% ;$C_{22}H_{22}FNO_3$ requires C 71.92%, H 6.04%, N 3.81%.

7-(2-Diethylaminoethoxy)-3-(4-fluorophenyl)- 2H-1-benzopyran-2-one (3gb): Yield 81%; mp 95-97°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, 6H, *J*=7.1 Hz), 2.66 (q, 4H, J=7.1 Hz), 2.91 (t, 2H, *J*=6.1 Hz), 4.12 (t, 2H, *J*=6.1 Hz), 6.86-6.90 (m, 2H), 7.09-7.15 (m, 2H), 7.42 (d, 1H, *J*=8.3 Hz), 7.65-7.69 (m, 2H), 7.73 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.04 (NCH_2CH_3×2), 48.13 (NCH_2CH_3×2), 51.75 (NCH_2), 67.62 (OCH_2), 101.31 (CH), 113.44 (C), 113.51 (CH), 115.46 (CH), 115.74 (CH), 123.97 (C), 129.00 (CH), 130.38 (CH), 130.48 (CH), 131.25 (C), 140.07 (CH), 155.47 (C), 161.10 (C), 162.23 (CO); ν_{max} (KBr, cm^{-1}) 1723, 1614, 1210, 770; ES-MS (*m/z*) 356 $[M+H]^+$. Found C 71.02%, H 6.29%, N 3.89% ;$C_{21}H_{22}FNO_3$ requires C 70.97%, H 6.24%, N 3.94%.

3-(4-Chlorophenyl)-7-(2-piperidin-1-yl-ethoxy)-2H-1-benzopyran-2-one (3ha): Yield 68%; mp 118-120°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46-1.48 (m, 2H), 1.61-1.63 (m, 4H), 2.53 (br m, 4H), 2.81 (t, 2H, *J*=5.9 Hz), 4.18 (t, 2H, *J*=5.9 Hz), 6.86-6.90 (m, 2H), 7.39-7.44 (m, 3H), 7.63-7.66 (m, 2H), 7.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.31 ($NCH_2CH_2CH_2$), 26.08 ($NCH_2CH_2CH_2$×2), 55.32 ($NCH_2CH_2CH_2$×2), 57.81 (NCH_2CH_2O), 66.88 (OCH_2CH_2N), 101.33 (CH), 113.38 (CH), 113.59 (CH), 123.74 (C), 128.83 (CH), 129.10 (CH), 129.89 (CH), 133.64 (C), 134.63 (C), 140.31 (CH), 155.52 (C), 160.91 (C), 162.28 (C); ν_{max} (KBr, cm^{-1}) 1721, 1612, 1198, 763; ES-MS (*m/z*) 384 $[M+H]^+$. Found C 68.92%, H 5.72%, N 3.63% ;$C_{22}H_{22}ClNO_3$ requires C 68.83%, H 5.78%, N 3.65%.

3-(4-Chlorophenyl)-7-(2-diethylaminoethoxy)- 2H-1-benzopyran-2-one (3hb): Yield 65%; mp 138-140°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.09 (t, 6H, *J*=7.1 Hz), 2.66 (quart, 4H, J=7.1 Hz), 2.92 (t, 2H, *J*=6.0 Hz), 4.14 (t, 2H, *J*=6.0 Hz), 6.86-6.94 (m, 2H), 7.37-7.44 (m, 3H), 7.64-7.69 (m, 2H), 7.83 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.89 (NCH_2CH_3×2), 47.92 (NCH_2CH_3×2), 50.97 (NCH_2), 66.87 (OCH_2), 101.36 (CH), 113.36 (C), 113.58 (CH), 123.73 (C), 128.83 (CH), 129.10 (CH), 129.86 (CH), 133.56 (C), 134.61 (C), 140.32 (CH), 155.50 (C), 161.01 (C), 162.30 (CO); ν_{max} (KBr, cm^{-1}) 1722, 1614, 1201, 770; ES-MS (*m/z*) 372 $[M+H]^+$. Found C 67.91%, H 5.91%, N 3.72%; $C_{21}H_{22}ClNO_3$ requires C 67.83%, H 5.96%, N 3.77%.

Biological activity

Antimicrobial activity: All the synthesized compounds were screened for their antimicrobial activities. The bacterial and fungal strains were grown on nutrient agar at 37°C. 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 Mc Farland matched bacterial 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 micro-titer plates were incubated at 35°C 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 twenty four synthesized compounds **3aa-hb** were screened for their antimicrobial activities against four pathogenic bacterias, *E. coli* (Ec), *Pseudomonas aeruginosa* (Pa), *Staphyloccus aerus* (Sa) and *Klebsiella pneumonia* (Kp). The same compounds were also tested against six pathogenic fungi *Candida albicans* (Ca), *Cryptococcus neoformans* (Cn), *Sporothrix schenckii* (Ss), *Trichophyton mentagrophytes* (Tm), *Aspergillus fumigatus* (Af) and *Candida parapsilosis* (Cp). 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. Two compounds **3ae** and **3bc** with the MIC values of 1.56 µg/mL are better than Fluconazole against *Trichophyton mentagrophytes*.

Conclusions

A novel class of 3,7-disubstituted 2*H*-1-benzopyran-2-one were synthesized and evaluated for their anti-fungal and anti-bacterial activities for the first time. The compounds were found inactive against different strains of bacteria but some of these compounds **3ac, 3ae**, **3bb**, **3bc** showed significant activity against selective fungal strains. Compound **3ae** and **3bc** with the MIC values of 1.56 µg/mL are better than the standard drug Fluconazole against *Trichophyton mentagrophytes*.

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