Efficient Synthesis of Novel Coumarin-3-carboxamides (=2-Oxo-2*H*-1-benzopyran-3-carboxamides) Containing Lipophilic Spacers

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Dedicated to Prof. *Rolf Gleiter* on the occasion of his 75th birthday

The novel coumarin-3-carboxamides (=2-oxo-2*H*-1-benzopyran-3-carboxamides) **5a**–**5g** containing lipophilic spacers were synthesized through the *Ugi*-four-component reaction (*Scheme 1*). The reactions of aromatic aldehydes **1**, 4,4′-oxybis[benzenamine] or 4,4′-methylenebis[benzenamine] as diamine **2**, coumarin-3-carboxylic acid (=2-oxo-2*H*-benzopyran-3-carboxylic acid; **3**), and alkyl isocyanides **4** lead to the desired substituted coumarin-3-carboxamides **5a**–**5g** at room temperature with high bond-forming efficiency. These novel coumarin derivatives exhibit brilliant fluorescence at 544 nm in $CHCl_3$.

Introduction. – Coumarins (=2*H*-1-benzopyran-2-ones), and their analogs have attracted considerable attention in organic and medicinal chemistry [1]. They have wide applications in food, pharmaceutical, and optical chemistry [2–4]. Natural coumarins and their synthetic structural analogs show broad biological activities [5], such as antimicrobial [6], antitumor [7], and antiviral activities [8]. Meanwhile, some coumarin derivatives could affect human immunodeficiency virus integrase inhibitors [9]. Some coumarins have inhibitory activity against some serine proteases and matrix metalloproteases (MMPs) [10], and also act as a selective antiproliferative agent [11–14].

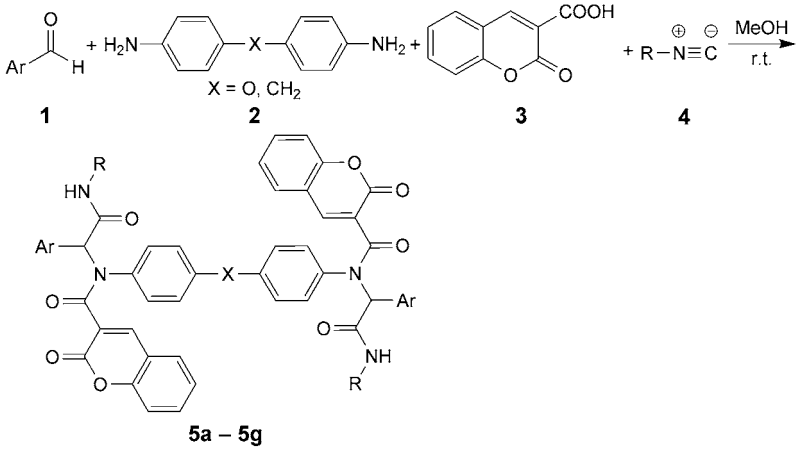
It was shown that the existence of the amide group in coumarin-3-carboxamides (=2-oxo-2*H*-1-benzopyran-3-carboxamides) improve the biological activity of these compounds [15–18]. The presence of some nonpolar spacers could affect their ability to penetrate the blood–brain barrier [19][20]. These compounds showed anti-*Helicobacter pylori* activity and also inhibition of breast cancer growth. Recently, some novel coumarin-3-carboxamides with effective anticoagulant activity [21] and also inhibitory activity against human monoamine oxidase (MAO) were synthesized [22].

In continuation of our research work [23] to design novel one-pot reactions, we wish herein to report an approach to the synthesis of some new amidated coumarins which contain a lipophilic moiety and several amide bonds *via* the *Ugi*-four-component reaction (*Ugi*-4CR). Recently, *Che*, *Yang* and co-workers reported sequential *Ugi*-4CR

and intramolecular *Michael* addition with coumarin-3-carboxylic acid to construct chromeno[3,4-*c*]pyrrole-3,4-diones (= [1]benzopyrans[3,4-*c*]pyrrol-3,4-diones) [24].

Results and Discussion. – The *Ugi*-4CR of an aromatic aldehyde **1**, 4,4′-oxybis[benzenamine] (**2a**) or 4,4′-methylenebis[benzenamine] (**2b**), coumarin-3-carboxylic acid (=2-oxo-2*H*-1-benzopyran-3-carboxylic acid; **3**), and alkyl isocyanides **4** led to functionalized bis-coumarins **5a**–**5g** in good to high yields.

Scheme 1. *Synthesis of Coumarin-3-carboxamides* **5a**–**5g** *through an* Ugi-*4CR.* See *Table* for Ar an R.



Coumarin-3-carboxylic acid (**3**) was obtained from the reaction of salicylaldehyde (=2-hydroxybenzaldehyde) and *Meldrum*'s acid (=2,2-dimethyl-1,3-dioxane-4,6-dione) in H_2O [25]. Then, treatment of **3**, 2,4-dimethoxybenzaldehyde (**1b**), bis-amine **2b**, and cyclohexyl isocyanide (**4a**, R = Chx) was selected as a model reaction in MeOH at room temperature. The desired product **5f** was isolated in 68% yield (*Table*, *Entry 6*). Encouraged by this result, we turned our attention to other substituted benzaldehydes and bis-amines. Thus, all aromatic aldehydes **1**, bis-amines **2**, coumarin-3-carboxylic acid (**3**), and alkyl isocyanides **4** in MeOH at room temperature (*Scheme 1*) underwent a smooth 2:1:2:2 condensation reaction, to give amidated coumarins **5a**–**5g** in 68–76% yields (*Table*).

The structures of compounds **5a**–**5g** were deduced from their spectroscopic data and high-resolution mass spectra (HR-ESI-MS). The distinguished peak at δ(H) 6.10–6.42 in the ^{1}H-NMR spectra of the products arose from the Ar–C*H*N protons. For instance, the ^{1}H-NMR spectra of **5d** displayed a *s* at δ(H) 6.10, and the NH-protons resonated at δ(H) 7.26. The ^{13}C-NMR spectrum revealed two distinct peaks at δ(C) 165.3 and 168.2 for the amide C=O groups, and the lactone C=O groups appeared at δ(C) 157.9.

According to the commonly accepted *Ugi*-4CR mechanism, the amine, the aldehyde, and the acid are in equilibrium with the iminium carboxylate **6** in the reaction medium. The addition of the carbenoid C-atom of the isocyanide onto the iminium group (*a*) in *Scheme 2* followed by the addition of the carboxylate ion onto the

Table. *Synthesis of Coumarin-3-carboxamides* **5a**–**5g** *through an* Ugi-*4CR of Aldehyde* **1**, *Diamine* **2**, *Acid* **3**, *and Isocyanide* **4**[a])

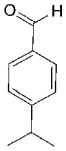
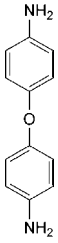
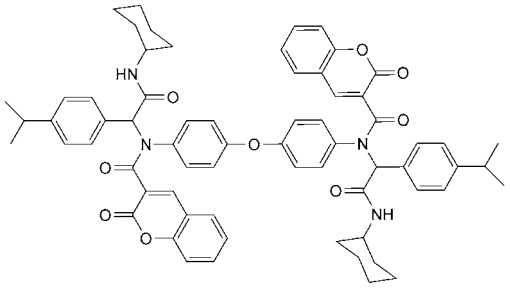
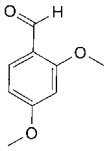
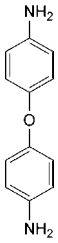
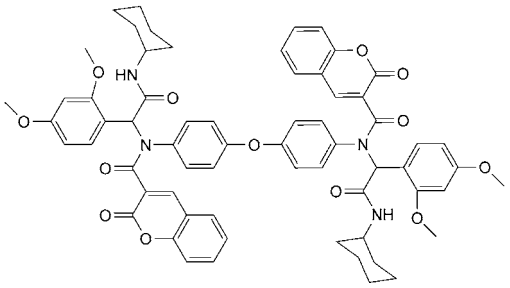
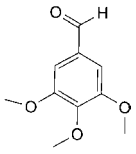
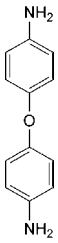
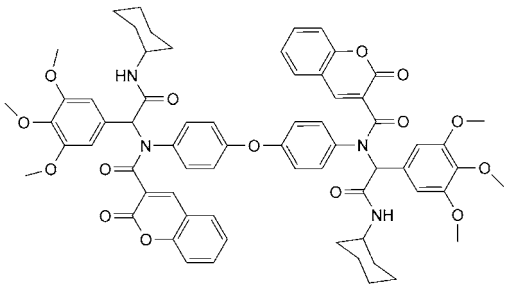
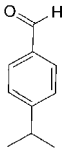
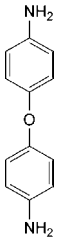
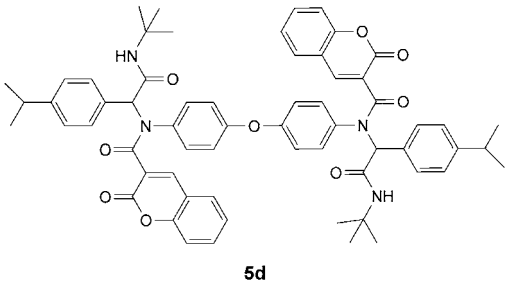
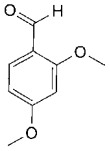
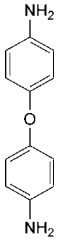
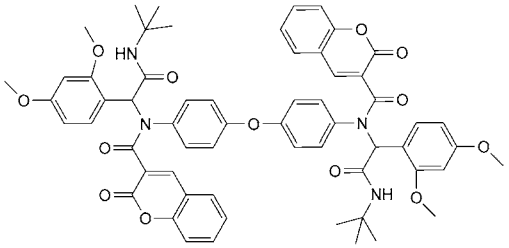
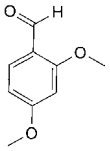
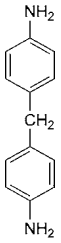
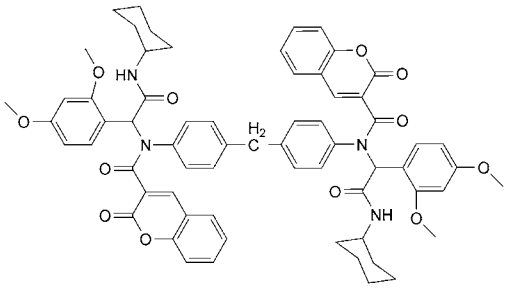
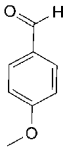
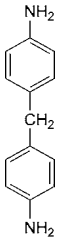
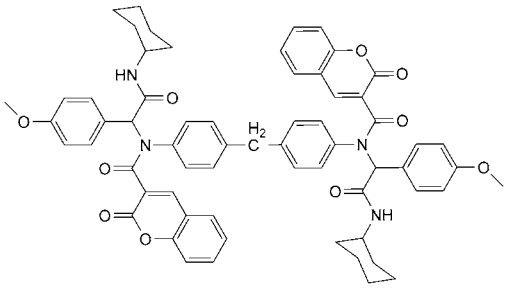
Entry	**1**	**2**	**4** (R)[b])	*Ugi* product **5**	Yield [%]
1	 **1a**	 **2a**	**4a** (Chx)	 **5a**	70
2	 **1b**	 **2a**	**4a** (Chx)	 **5b**	75
3	 **1c**	 **2a**	**4a** (Chx)	 **5c**	76
4	 **1a**	 **2a**	**4b** (*t*Bu)	 **5d**	70

Table (cont.)

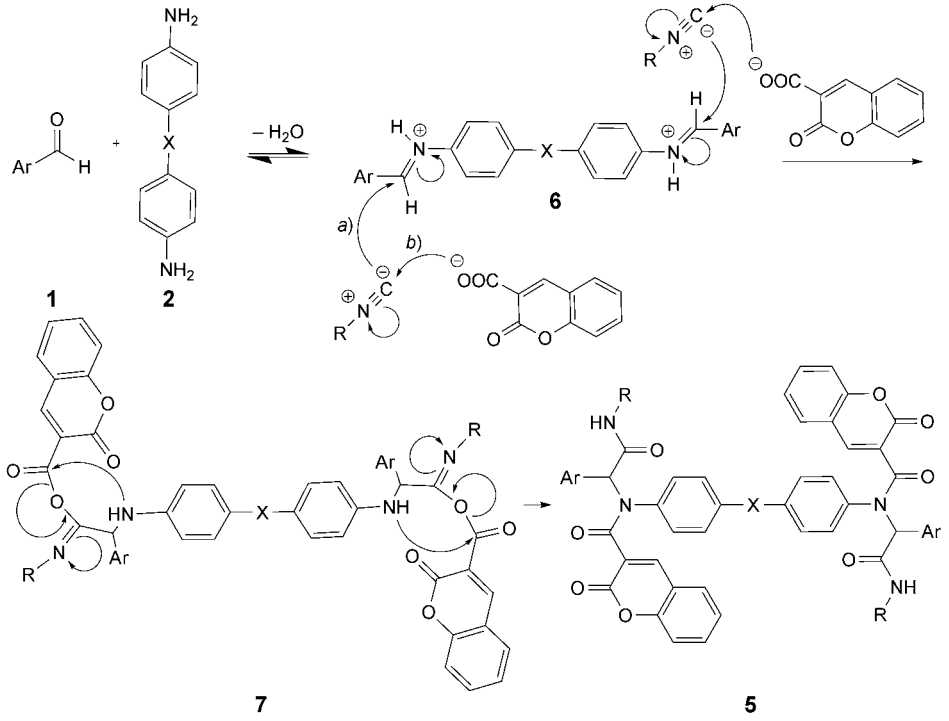
Entry	**1**	**2**	**4** (R)[b])	*Ugi* product **5**	Yield [%]
5	 **1b**	 **2a**	**4b** (^{t}Bu)	 **5e**	70
6	 **1b**	 **2b**	**4a** (Chx)	 **5f**	68
7	 **1d**	 **2b**	**4a** (Chx)	 **5g**	70

[a]) In all cases, coumarin-3-carboxylic acid (**3**) was used. [b]) Chx = cyclohexyl.

C-atom of the nitrilium ion (*b*) in *Scheme 2* leads to the formation of the primary four-component adduct **7**, which undergoes an intramolecular acylation known as *Mumm* rearrangement to give the stable *Ugi* adduct **5**.

Since some coumarin derivatives could be used as fluorophors [26][27], we were interested in the fluorescence property of the synthesized compounds. The fluorescence property of our novel coumarin-3-carboxamides **5a**, **5e**, and **5g** were investigated in $CHCl_3$, MeCN, and DMF. Excitations were carried out with the four different wavelengths 200, 210, 220, and 230 nm, and the emission was investigated in the range

Scheme 2. *Proposed Mechanism for the Synthesis of Coumarin-3-carboxamides* **5a**–**5g** *through an* Ugi-*4CR*



300–700 nm. In the case of **5a**, the maximum emission occurred at the excitation wavelength 200 nm, and the maximum emissions were observed at 442, 486, and 544 nm, respectively. The fluorescence study of **5a**, **5e**, and **5g** revealed that all three bis-coumarins possess similar excitation and emission maxima (*Fig.*).

Conclusion. – We reported an efficient approach for the synthesis of functionalized bis[coumarin-3-carboxamides] of the type **5**. The simplicity of the synthetic protocol and availability of diverse starting materials make this an attractive strategy for obtaining functionalized coumarins. The method offers several advantages such as high yields of products, mild reaction conditions, cleaner reaction profiles, operational simplicity, and also chemical library. Some of the products had maximum emission at 544 nm.

S. B. would like to thank the *Iran National Science Foundation* (*INSF*) for financial support.

Experimental Part

General. Commercially available materials were used without further purification. TLC: silica gel *60* F_{254} (SiO_2; *Merck*). M.p.: *Electrothermal-9100* apparatus; uncorrected. Fluorescence spectra (*Fig.*): *Photon-Technology-International-MP1* steady-state fluorimeter; at r.t. in *NSG Precision Cells Inc.*

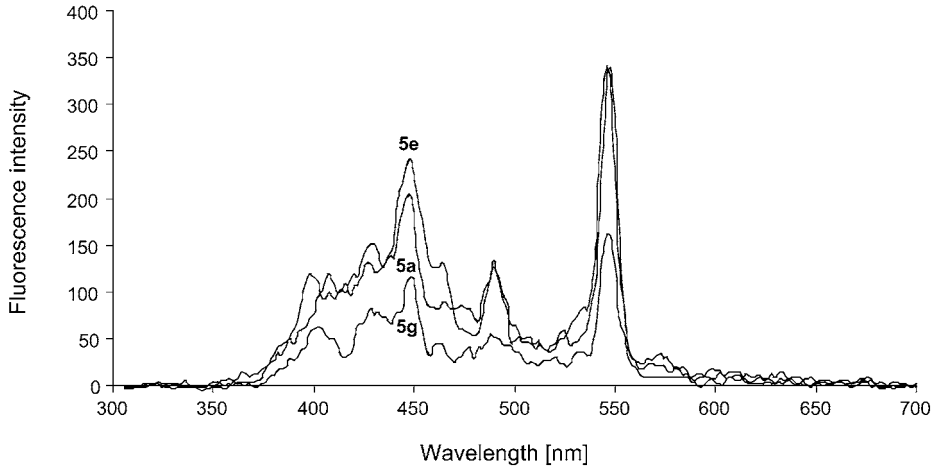


Figure. *Emission spectra of compounds* **5a**, **5e**, *and* **5g** *in* $CHCl_3$

(Farmingdale, NY) *ES* (*Extrasil*) quartz cuvettes (190–2000 nm). IR Spectra: *ABB-FT-IR FTLA-2000* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker* spectrometers; at 300 MHz (^1H) and 75 MHz (^{13}C); $CDCl_3$ and (D_6)DMSO as solvent; δ in ppm rel. to Me_4Si as internal standard, J in Hz. HR-MS: *Mass-ESI-POS* (*Apex-Qe-FT-ICR* instrument) spectrometer; in *m*/*z*.

Coumarin-3-carboxylic Acid (=*2-Oxo-2*H-*1-benzopyran-3-carboxylic Acid*; **3**) [25]. A mixture of salicylaldehyde (10 mmol, 1.22 g) and *Meldrum*'s acid (12 mmol, 1.73 g) in H_2O (20 ml) was heated under reflux and stirring for 10 h. The mixture was cooled and filtered through a *Büchner* funnel. Further purification was achieved by crystallization from MeOH: **3** (1.805 g, 95%).

Chromene-3-carboxamides **5a**–**5g**: *General Procedure.* Primary bis-amine **2** (0.5 mmol) was added to a soln. of aldehyde **1** (1 mmol) in MeOH (5 ml), and the mixture was stirred at r.t. for 1 h. Then, **3** (1 mmol) was added, and stirring was continued for 15 min, followed by addition of alkyl isocyanide **4** (1 mmol). The resulting soln. was stirred at r.t. for 18–24 h. After completion of the reaction (TLC monitoring), the solvent was evaporated, and the product was precipitated by addition of H_2O. Further purification was achieved by CC (SiO_2, AcOEt/petroleum ether 1:3).

N,N′-*[4,4′-Oxybis(4,1-phenylene)]bis[*N-*{2-(cyclohexylamino)-1-[4-(1-methylethyl)phenyl]-2-oxoethyl}-2-oxo-2*H-*1-benzopyran-3-carboxamide]* (**5a**): Yield 741 mg (70%). M.p. 233–237°. IR (KBr): 3278, 1719, 1651, 1608. ^1H-NMR (300 MHz, (D_6)DMSO): 1.07 (*d*, *J* = 6.5, 4 Me); 1.07–1.78 (*m*, 10 CH_2); 2.75 (*m*, 2 Me_2CH); 3.61–3.63 (*m*, 2 C*H*NH); 6.11 (br. *s*, 4 arom. H, 2 C*H*N); 6.43 (br. *s*, 2 NH); 6.81–7.00 (*m*, 10 arom. H); 7.27–7.34 (*m*, 4 arom. H); 7.57–7.67 (*m*, 4 arom. H); 7.98 (*s*, 2 =CH); 8.08 (*d*, *J* = 7.2, 2 arom. H). ^{13}C NMR (75 MHz, (D_6)DMSO): 23.6; 23.8; 24.5; 24.6; 25.2; 32.2; 32.3; 33.0; 48.0; 63.3; 116.1; 117.2; 117.6; 124.9; 125.3; 125.8; 128.9; 129.9; 132.2; 132.4; 132.7; 134.1; 142.0; 148.1; 152.9; 155.1; 157.1; 164.3; 167.9. HR-ESI-MS: 1059.49135 ($[M+H]^+$, $C_{66}H_{67}N_4O_9^+$; calc. 1059.49146), 1097.44649 ($[M+K]^+$, $C_{66}H_{66}KN_4O_9^+$; calc. 1097.44653).

N,N′-*[4,4′-Oxybis(4,1-phenylene)]bis[*N-*[2-(cyclohexylamino)-1-(2,4-dimethoxyphenyl)-2-oxoethyl]-2-oxo-2*H-*1-benzopyran-3-carboxamide]* (**5b**): Yield 821 mg (75%). M.p. 172–174°. IR (KBr): 3427, 1721, 1638, 1607. ^1H-NMR (300 MHz, $CDCl_3$): 1.14–2.04 (*m*, 10 CH_2); 3.70 (*s*, 2 MeO); 3.71 (*s*, 2 MeO); 3.91–3.93 (*m*, 2 C*H*NH); 6.22–6.29 (*m*, 8 arom. H); 6.42 (*s*, 2 CHN); 6.65 (br. *s*, 2 NH); 6.94–6.97 (*d*, *J* = 8.0, 4 arom. H); 7.19–7.27 (*m*, 6 arom. H); 7.41 (*d*, *J* = 7.5, 2 arom. H); 7.51 (*t*, *J* = 7.6, 2 arom. H); 7.78 (*s*, 2 =CH). ^{13}C NMR (75 MHz, $CDCl_3$): 24.8; 25.0; 25.5; 32.7; 33.1; 48.8; 55.2; 55.3; 60.0; 97.9; 104.0; 114.7; 116.6; 117.9; 118.0; 124.8; 126.3; 128.4; 131.3; 132.0; 132.5; 134.2; 141.9; 153.6; 155.7; 158.2; 158.5; 161.2; 165.3 168.6. HR-ESI-MS: 1095.43941 ($[M+H]^+$, $C_{64}H_{62}N_4O_{13}^+$; calc. 1095.43920), 1117.41916 ($[M+Na]^+$, $C_{64}H_{61}N_4NaO_{13}^+$; calc. 1117.41900), 1133.39223 ($[M+K]^+$, $C_{64}H_{61}KN_4O_{13}^+$; calc. 1133.39205).

N,N′-*[4,4′-Oxybis(4,1-phenylene)]bis[*N-*[2-(cyclohexylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl]-2-oxo-2*H-*1-benzopyran-3-carboxamide]* (**5c**): Yield 877 mg (76%). M.p. 262–266°. IR (KBr): 3293, 1721, 1656, 1607. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.14–2.03 (*m*, 10 CH_2); 3.69 (*s*, 3 MeO); 3.80 (*s*, 3 MeO); 3.89–3.94 (*m*, 2 C*H*NH); 6.12 (br. *s*, 2 CHN); 6.39–6.44 (*m*, 10 arom. H); 7.04 (br. *s*, 2 NH); 7.20–7.28 (*m*, 6 arom. H); 7.43 (*d*, *J* = 7.4, 2 arom. H); 7.52 (*t*, *J* = 7.4, 2 arom. H); 7.78 (*s*, 2 =CH). ^{13}C-NMR (75 MHz, $CDCl_3$): 24.8; 24.9; 25.4; 32.7; 32.8; 49.0; 56.0; 60.7; 65.9; 107.4; 116.7; 117.8; 118.4; 124.9; 125.7; 128.5; 129.2; 131.6; 132.7; 134.4; 137.9; 142.3; 152.9; 153.6; 155.9; 158.1; 165.4; 167.7. HR-ESI-MS: 1177.44235 ($[M+Na]^+$, $C_{66}H_{66}N_4NaO_{15}^+$; calc. 1177.44242), 119346653 ($[M+K]^+$, $C_{66}H_{66}KN_4O_{15}^+$; calc 1193.46662).

N,N′-*[4,4′-Oxybis(4,1-phenylene)]bis[*N-*[2-[(1,1-dimethylethyl)amino]-1-[4-(1-methylethyl)phenyl]-2-oxoethyl]-2-oxo-2*H-*1-benzopyran-3-carboxamide]* (**5d**): Yield 705 mg (70%). M.p. 175–178°. IR (KBr): 3346, 1728, 1652, 1606. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.10 (*d*, *J* = 6.8, 4 Me); 1.14 (*s*, 2 ^{t}Bu); 2.80 (*m*, 2 $(Me)_2CH$); 6.10 (*s*, 2 CHN); 6.19 (br. *s*, 2 NH); 6.34 (*d*, *J* = 8.3, 4 arom. H); 7.01–7.14 (*m*, 12 arom. H); 7.18–7.24 (*m*, 4 arom. H); 7.39 (*d*, *J* = 7.2, 2 arom. H); 7.50 (*t*, *J* = 7.3, 2 arom. H); 7.26 (*s*, 2 =CH). ^{13}C-NMR (75 MHz, $CDCl_3$): 23.8; 28.6; 33.7; 51.8; 65.9; 116.6; 117.9; 118.2; 124.8; 125.8; 126.3; 128.3; 130.3; 131.2; 131.4; 132.5; 134.3; 142.0; 149.1; 153.6; 155.7; 157.9; 165.3; 168.2. HR-ESI-MS: 1007.46022 ($[M+H]^+$, $C_{62}H_{63}N_4O_9^+$; calc. 1007.46033), 1029.44189 ($[M+Na]^+$, $C_{62}H_{62}N_4NaO_9^+$; calc. 1029.44199), 1045.45771($[M+K]^+$, $C_{62}H_{62}KN_4O_9^+$; calc. 1045.45860).

N,N′-*[4,4′-Oxybis(4,1-phenylene)]bis[1-[2,4-dimethoxyphenyl]-*N-*{2-[(1,1-dimethylethyl)amino]-2-oxoethyl}-2-oxo-2*H-*1-benzopyran-3-carboxamide]* (**5e**): Yield 730 mg (70%). M.p. 168–172°. IR (KBr): 3366, 1730, 1653, 1608. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.42 (*s*, 2 ^{t}Bu); 3.70 (*s*, MeO); 3.71 (*s*, MeO); 3.72 (*s*, 2 MeO); 6.23–6.31 (*m*, 2 CHN, 2 NH, 8 arom. H); 6.99–7.02 (*d*, *J* = 8.0, 6 arom. H); 7.19–7.26 (*m*, 4 arom. H); 7.39 (*d*, *J* = 7.3, 2 arom. H); 7.53 (*t*, *J* = 7.2, 2 arom. H); 7.72 (*s*, 2 = CH). ^{13}C-NMR (75 MHz, $CDCl_3$): 28.6; 51.7; 55.1; 55.2; 55.3; 60.2; 97.8; 97.9; 104.0; 104.1; 114.8; 116.6; 117.9; 124.7; 126.1; 128.3; 131.2; 131.8; 132.4; 134.3; 141.7; 153.5; 155.8; 158.0; 158.4; 161.1; 165.2; 168.8. HR-ESI-MS: 1043.48821 ($[M+H]^+$, $C_{60}H_{59}N_4O_{13}^+$; calc. 1043.48830), 1065.38955 ($[M+Na]^+$, $C_{60}H_{58}N_4NaO_{13}^+$; calc 1065.38958), 1081.36386 ($[M+K]^+$, $C_{60}H_{58}KN_4O_{13}^+$; calc.1081.36393).

N,N′-*[4,4′-Methylenebis(4,1-phenylene)]bis[*N-*[2-(cyclohexylamino)-1-(2,4-dimethoxyphenyl)-2-oxoethyl]-2-oxo-2*H-*1-benzopyran-3-carboxamide]* (**5f**): Yield 0.743 mg (68%). M.p. 120° (dec.). IR (KBr): 3352, 1730, 1658, 1608. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.16–2.02 (*m*, 10 CH_2); 3.49 (*s*, $ArCH_2Ar$); 3.59 (*s*, MeO); 3.61 (*s*, MeO); 3.71 (*s*, 2 MeO); 3.85–3.88 (*m*, 2 C*H*NH); 6.14–6.16 (*m*, 2 arom. H); 6.20–6.25 (*m*, 2 arom. H); 6.38 (br. *s*, 2 CHN); 6.42 (*d*, *J* = 7.5, 4 arom. H); 6.74 (br. *s*, 2 NH); 6.90 (*d*, *J* = 6.3, 4 arom. H); 6.99 (*dd*, *J* = 6.0, 1.5, 2 arom. H); 7.16 (*d*, *J* = 7.8, 2 arom. H); 7.24 (*d*, *J* = 6.6, 2 arom. H); 7.39 (*d*, *J* = 7.7, 2 arom. H); 7.49 (*td*, *J* = 7.8, 1.4, 2 arom. H); 7.74 (*s*, 2 =CH). ^{13}C NMR (75 MHz, $CDCl_3$): 24.8; 25.0; 25.4; 32.7; 33.1; 40.1; 48.8; 55.0; 55.3; 60.3; 97.8; 97.9; 104.0; 104.1; 114.8; 116.6; 118.0; 124.7; 126.3; 128.4; 128.5; 129.5; 131.9; 132.0; 132.4; 137.1; 139.9; 141.8; 153.5; 158.2; 158.4; 161.0; 165.2; 168.5. HR-ESI-MS: 1093.45788 ($[M+H]^+$, $C_{65}H_{65}N_4O_{12}^+$; calc. 1093.45773), 1115.43901 ($[M+Na]^+$, $C_{65}H_{64}N_4NaO_{12}^+$; calc.1115.43901), 1131.41427 ($[M+K]^+$, $C_{65}H_{64}KN_4O_{12}^+$; calc. 1131.41417).

N,N′-*[4,4′-Methylenebis(4,1-phenylene)]bis[*N-*[2-(cyclohexylamino)-1-(4-methoxyphenyl)-2-oxoethyl]-2-oxo-2*H-*1-benzopyran-3-carboxamide]* (**5g**): Yield 723 mg (70%). M.p. 130° (dec.). IR (KBr): 3351, 1730, 1653, 1607. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.15–2.05 (*m*, 10 CH_2); 3.55 (*s*, $ArCH_2Ar$); 3.72 (*s*, MeO); 3.73 (*s*, MeO); 3.86–3.89 (*m*, 2 C*H*NH); 6.18 (*s*, 2 CHN); 6.52 (*d*, *J* = 8.6, 4 arom. H); 6.61 (br. *s*, 2 NH); 6.67 (*dd*, *J* = 8.6, 1.5, 4 arom. H); 6.90–6.92 (*m*, 4 arom. H); 7.06 (*d*, *J* = 8.6, 4 arom. H); 7.19–7.27 (*m*, 4 arom. H); 7.40 (*d*, *J* = 6.7, 2 arom. H); 7.53 (*td*, *J* = 7.8, 1.4, 2 arom. H); 7.74 (*s*, 2 =CH). ^{13}C NMR (75 MHz, $CDCl_3$): 24.8; 24.9; 25.7; 32.7; 32.9; 40.1; 49.0; 55.2; 65.3; 113.6; 116.6; 117.9; 120.8; 124.8; 125.7; 126.0; 128.4; 128.9; 129.2; 129.9; 130.4; 131.7; 132.5; 137.1; 140.1; 142.1; 158.1; 159.3; 165.2; 168.1. HR-ESI-MS: 1033.43883 ($[M+H]^+$, $C_{63}H_{61}N_4O_{10}^+$; calc. 1033.43889), 1055.42022 ($[M+Na]^+$, $C_{63}H_{60}N_4NaO_{10}^+$; calc. 1055.42023), 1071.39403 ($[M+K]^+$, $C_{63}H_{60}KN_4O_{10}^+$; calc.1071.39402).

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