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Synthesis and Tautomerization of Hydroxylated Isoflavones Bearing Heterocyclic Hemi-Aminals

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Abstract

The aminomethylation of hydroxylated isoflavones with 2-aminoethanol, 3-amino-1-propanol, 4-amino-1-butanol, and 5-amino-1-pentanol in the presence of excess formaldehyde led principally to 9-(2-hydroalkyl)-9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]-oxazin-4-ones **4** and/or the tautomeric 7-hydroxy-8-(1,3-oxazepan-3-ylmethyl)-4*H*-chromen-4-ones **5**. The ratio of these tautomers was dependent on solvent polarity, electronic effects of aryl substituents in the isoflavone and the structure of the amino alcohol. NMR studies confirmed the interconversion of tautomeric forms.

Introduction

In connection with our interest in developing antineoplastic agents targeting cyclin-dependent kinases (CDKs), we sought antagonists that mimicked natural products in the chromone-based alkaloid family such as rohitukine (**1a**) and chrotacumines A-D¹ (**1b–d** and **2**) (Fig. 1). These natural products inhibit CDKs^{1–4} and possess a skeleton that couples two, different structural subunits: a 5,7-dihydroxy-2-methylchromone characteristic of the isoflavonoids and a 3-hydroxypiperidine ring found in various alkaloids. Chrotacumine A (**2**) possesses an interesting hemi-aminal (O/N-acetal) linkage connecting the chromone and piperidine rings. Our interest in developing hydroxylated isoflavones with O/N-acetal subunits, as in chrotacumine A (**2**), led to an investigation of synthetic pathways to these

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targets and led to questions regarding tautomerization of hydroxylated isoflavones bearing hemi-aminals.

We required the hemi-aminal functionality as a mimic of the basic heterocycles found in 2, and we required the hydroxyl group as a functional handle to which we would ultimately attach D-(+)-biotin. These biotinylated chromones would provide a means of identifying the biological targets of these analogs, just as we have recently done in other systems.⁵ We now report the synthesis of various hydroxylated isoflavones bearing heterocyclic hemi-aminals in which we address this tautomerization issue as a necessary prelude to biological studies.

Results and discussion

The Mannich reaction affects the aminomethylation of carbonyl and activated aromatic compounds^{6,7} and accommodates a range of amines including amino alcohols, N-benzylamino alcohols,^{8,9} N,N-dibenzylamino alcohols,^{10–12} 3,4-dihydro-2H-1,3-benzoxazines,^{13–15} (1,3-oxazolidin-3-yl)methylphenols and (1,3-morpholin-3-yl)methyl phenols.^{15,16} Despite this precedent and our understanding of the Mannich reaction, we could not predict the outcome and preference for tautomeric forms in Mannich reactions using isoflavones and various ω -amino-1-alcohols. As carbonyl components for our study, we selected isoflavones that included natural products, such as formononetin (**3a**) and cladrin (**3b**), and that also included synthetic isoflavones **3c–3i** (Fig. 2) as starting materials for synthesis of aminoalkylated isoflavone derivatives. Since many recent drugs contain one or more fluorine atoms,^{17–19} we included isoflavones bearing either fluoroaryl rings as in **3c** and **3f** and/or trifluoromethyl groups as in **3g–3i**.

The synthesis of the required 7-hydroxyisoflavones **3** utilized 2,4-hydroxylated deoxybenzoins under Vilsmeier-Haack conditions using boron trifluoride in N,N-dimethylformamide to afford the desired isoflavones **3a–3c**. The use of N,N-dimethylacetamide in place of N,N-dimethylformamide led to the formation of 7-hydroxy-2-methylisoflavones **3d–3f**. A similar condensation of deoxybenzoins with trifluoroacetic anhydride in pyridine led to the 7-hydroxy-2-trifluoromethylisoflavones **3g–3i**. With this range of isoflavones available to us, we were in a position to evaluate the influence of different C-2 substituents (*e.g.*, hydrogen, methyl and trifluoromethyl) in isoflavones on the outcome of Mannich reactions using ω -amino-1-alcohols. In the absence of a specific procedure for the synthesis of chromones^{20–25} bearing heterocyclic substituents, we evaluated published options including the reductive amination of formyl-substituted chromones^{26–29} or the N-alkylation of amines with chloromethyl-substituted chromones.^{30–36} These reports, although encouraging, were limited in scope and led us to develop an alternate, general procedure.

The aminomethylation of isoflavones **3a–f** using ω -amino-1-alcohols and an excess of aqueous formaldehyde in isopropanol (Method A) gave mixtures of 3-aryl-9,10-dihydro-4*H*, 8*H*-chromeno[8,7-*e*][1,3]oxazin-4-ones²⁵ **4a–4f** as well as the tautomeric isomer, 7-hydroxy-3-aryl-8-(1,3-oxazinan-3-ylmethyl)-4*H*-chromen-4-one **5a–5f** (Scheme 1).

These latter isomers **5a–5f** were minor products relative to **4a–4f** (Table 1). Schmidt¹⁵ recently demonstrated a similar outcome with resorcarene condensations with formaldehyde and ω -amino-1-alcohols but did not report the equilibration of the tautomeric forms. Mass spectral and ¹H NMR data for **4** and **5** unambiguously supported these structural assignments in which the following features were most important: [1] an ion with m/z [MH-12]⁺, which resulted from the loss of the hemi-aminal methylene group from either tautomer **4** or **5**; [2] ³J(H,H) values of 8.3–9.2 Hz within the isoflavone ring that confirmed the aminomethylation at position C-8 and excluded aminomethylation at C-5 or C-6; and [3] a singlet at 4.99–5.03 ppm that was assigned to the hemi-aminal methylene group of **4a–4f** or a singlet at 4.43–4.49 ppm that was assigned to the hemi-aminal methylene group of **5a–5f**. Because 1,3-oxazolidines are chemically equivalent to a mixture of 2-aminoethanol and formaldehyde and useful for the aminomethylation of heterocycles,^{37–40} we also utilized either 3-butoxymethyl-1,3-oxazolidine (Method B, Table 1, entries 3, 9) or bis(oxazolidin-3-yl)methane (Method C, Table 1, entries 5, 7, 10, 12) in the aminomethylation of isoflavones. In all cases using Methods B and C, we observed the formation of a mixture of **4** and **5** in a ratio comparable to that seen with 2-aminoethanol and formaldehyde under conditions described in Method A.

In addition to the mass spectral and NMR data in support of the structural assignments of these tautomers, acid-catalyzed hydrolysis of these isomers afforded the amino diols **6** (Scheme 2). The amino diols **6** were a presumed intermediate in route from the isoflavones **3** to the tautomers **4** and **5**. A combination of solvent polarity and acidity of the C-7 phenolic group in **3** dictated the balance between the formation of the tautomers **4** and **5** versus the amino diols **6**. For example, the isoflavones **3g** and **3i** possessed an electron-withdrawing trifluoromethyl group that increased the acidity of the C-7 phenolic hydroxyl group. Condensation of these isoflavones with formaldehyde and 2-aminoethanol (Method A) provided exclusively the amino diols **6g** and **6i** ($n=1$), respectively. Introduction of two electron-donating methoxy groups, as in isoflavone **3h**, counterbalanced the effect of the trifluoromethyl group and led to the formation of oxazolidinyl-substituted isoflavone **4h**. Solvent also had a dramatic effect on outcomes. For example, aminomethylation of isoflavone **3g** with formaldehyde and 3-amino-1-propanol in ethanol led to the amino diol **6g** but this same combination of reagents in isopropanol led to the isoflavone **5g** bearing the 2-(1,3-oxazinanyl)methyl group. Finally, the aminomethylation of isoflavones **3** with 4-amino-1-butanol or 5-amino-1-pentanol gave predominately the fused tautomer **4** and little or none of the isomeric **5**.

Unlike the cases where we used either 2-aminoethanol or 3-amino-1-propanol, the trifluoromethyl groups in isoflavones **3g–3i** had no influence on the outcome, and these isoflavones led to the oxazines **4** as the principal product. In general, we concluded that polar solvents and electron-withdrawing substituents on the isoflavone led to the formation of the amino diols **6** whereas less polar solvents and electron-donating groups on the isoflavone led to the tautomeric isomers **4** and **5**.

NMR techniques allowed us to confirm the equilibration of the isomers **4** and **5** in a manner similar to related tautomerizations reported for 1,3-oxazolidines and 1,3-terahydrooxazines

that contain NH proton and could exhibit ring-chain isomerization involving Schiff's base.^{41–48} For example, the ratio of **4b** to **5b** was 9:1 in CDCl₃ (Fig. 3, Panel B), but this ratio changed to 19:1 in either DMSO-d₆ (Fig. 3, Panel C) or CD₃OD (Fig. 3, Panel D). The addition of DMSO-d₆ to a CDCl₃ solution of containing a 9:1 ratio of **4b** and **5b** also led to an increase in **4b**. This increase was best followed by monitoring the hemi-aminal methylene protons (labeled A in Fig. 3, Panel A). On the other hand, if CCl₄ were added to a CDCl₃ solution of **4b** and **5b** in DMSO-d₆, the ratio changed in favor of **5b**. These outcomes were consistent with a hydrogen-bonded complex between the amino group and the C-7 phenolic group in **5b** in non-polar solvents such as CCl₄ and the disruption of this hydrogen bonding and an equilibrium shift toward **4b** in polar solvents such as DMSO-d₆ or CD₃OD. Preference for the formation N-AlkOH-Solv (for **4**) with ArOH-Solv (for **5**) was best explained by Pearson's acid base concepts. Additional confirmation of this point was obtained using a non-polar NMR solvent, C₆D₆, which showed a similar ratio of **4b** to **5b** found using CDCl₃. Applying polar base solvent Py-d₅ showed increased amounts of **4b** form, consistent with the expected shift of equilibrium toward **5b** due to interaction with ArOH as stronger acid than AlkOH. It should also be noted that the equilibrium between tautomers was rapidly established and remained unchanged after 24 hours.

The 2D NOESY spectrum of tautomers **4b** and **5b** displayed chemical exchange cross-peaks between pairs of methylene groups, the hemi-aminal methylene groups and the 2-aminoethanol fragments. These chemical exchange cross-peaks had the same phase as the diagonal peaks in contrast to the opposite-phased normal cross-peaks of aromatic protons and methylene groups of the amine fragment for **4b** and **5b** (Fig. 4). These correlations are the unambiguous evidence of dynamic reversible conversion of tautomers, which is intermediate or slow on the NMR time scale, and these cross-peaks confirm the equilibration between **4b** and **5b**.

Similar results were obtained for tautomers using 3-aminopropan-1-ol and 4-aminobutan-1-ol. It was unexpected that this tautomerism was observed for 4-aminobutan-1-ol derivatives **4**, **n=3** and was not observed for 5-aminopentan-1-ol derivatives **4**, **n=4** despite the expected, increased stability of 1,3-benzoxazine ring for **4**, **n=3** or **4** in comparison with 1,3-axazepane (**5**, **n=3**) or 1,3-oxazocane (**5**, **n=4**) rings. Probably, ring-ring tautomerism of **4**, **n=1...3** and **5**, **n=1...3** is possible due to steric proximity of AlkO-H...N and ArO-H...N fragments together with ring-chain tautomerism in 1,3-diaza and 1,3-oxaza heterocycles.⁴⁹ We also observed that the ¹H NMR spectra of either **4b** or **5g** in DMSO-d₆ did not change when either of these compounds was heated. Finally, we noted that the interconversion of tautomeric forms occurred rapidly in presence of trifluoroacetic acid (TFA) at 20°C (Fig. 5, Panels A and B). Addition of TFA at room temperature and heating to 60°C led to minimal change other than the sharpening of some peaks (Fig. 5, Panel C). Cooling below 20°C led, as expected, to the broadening of signals for aliphatic protons linked to nitrogen.

In summary, a combination of chemical and spectroscopic studies established that isoflavones **3** underwent Mannich reactions with amino alcohols and an excess of formaldehyde to afford principally two tautomeric isomers **4** and **5** that incorporate two molecules of formaldehyde for each amino alcohol. A combination of solvent polarity, electronic effects dictated by aryl substituents in the isoflavone, and the structure of the

amino alcohol determined the ratio of these tautomers. In some circumstances, such as in the presence of polar solvents and electron-withdrawing groups on the isoflavone **3**, the reaction provided an amino diol **6**, a presumed intermediate in the conversion of isoflavones **3** to the tautomers **4** and **5**. Spectroscopic studies established the dynamic nature of the equilibrium between these tautomeric forms which presumably occurs through a transitory immonium salt as well as the steric interactions of $\text{AlkO(H)}\cdots\text{N}\cdots\text{(H)OAr}$ fragments.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker 500 (500 MHz/125 MHz), Bruker 400 (400 MHz/100 MHz) spectrometer in CDCl_3 , DMSO-d_6 , and D_2O . ^{19}F NMR spectra were recorded on a Bruker 400 (376 MHz) relative to CFCl_3 . CDCl_3 was stored over K_2CO_3 to prevent possible formation of HCl . Chemical shifts of compounds **4**, $n=1,3,4$ and **5**, $n=2$ are given for the major tautomeric form in the solvents in which the content of the major form was the highest. IR spectra were recorded on a Nicolet Nexus 470 ESP FT/IR spectrometer. Melting points were determined in open capillarity tubes with an Buchi B-535 apparatus and uncorrected. Mass spectra were obtained with an Agilent 1100 using chemical ionization. TLC was conducted on Merck silica gel 60 F254 plates.

General procedure for synthesis of 7-hydroxyisoflavones **3a–3f**

To a solution of benzoin (0.1 mol) in 70 mL of *N,N*-dimethylformamide or *N,N*-dimethylacetamide at 30–40 °C was added boron trifluoride (38 mL, 0.3 mol). The mixture was stirred for 0.5 h and phosphorous oxytrichloride (18.6 mL, 0.2 mol) was added at the same temperature. The mixture was heated at 55–60 °C for 2 h (in the case of **3a–3c**) or 6–8 h (in the case of **3d–3f**). The mixture was poured into 500 mL of hot water with vigorous stirring and then cooled. A precipitate was collected and washed with water. Recrystallization from methanol gave isoflavones **3a–3f** as white or pale yellow powders.

7-Hydroxy-3-(4-methoxyphenyl)-4H-chromen-4-one (3a)—Pale yellow solid (20.9 g, 78%); mp 259–261 °C (lit.⁵⁰ mp 256–258 °C); ^1H NMR (400 MHz, DMSO-d_6): δ 3.79 (s, 3H, 4'-OCH₃), 6.87 (d, 1H, $^4J=2.2$ Hz, 8-H), 6.94 (dd, 1H, $^3J=9$ Hz, $^4J=2.2$ Hz, 6-H), 6.99 (d, 2H, $^3J=8.8$ Hz, 3', 5'-H), 7.52 (d, 2H, $^3J=8.8$ Hz, 2', 6'-H), 7.98 (d, 1H, $^3J=9$ Hz, 5-H), 8.31 (s, 1H, 2-H), 10.73 ppm (s, 1H, 7-OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.09 (4'-OCH₃), 102.09 (8-C), 113.55 (3', 5'-C), 115.13 (6-C), 116.61 (4a-C), 123.14 (1'-C), 124.23 (3-C), 127.24 (5-C), 130.02 (2', 6'-C), 153.03 (2-C), 157.41 (8a-C), 158.92 (4'-C), 162.53 (7-C), 174.56 ppm (4-C); IR (KBr): ν_{max} 3131, 2979, 1639, 1624, 1568, 1513, 1453, 1246 cm^{-1} ; MS (CI): m/z (%) 269.1 (100, MH^+). Anal. Calcd for $\text{C}_{16}\text{H}_{12}\text{O}_4$: C, 71.64; H, 4.51. Found: C, 71.71; H, 4.56.

3-(3,4-Dimethoxyphenyl)-7-hydroxy-4H-chromen-4-one (3b)—White solid (24.8 g, 83%); mp 254–256 °C (lit.⁵¹ mp 233–234 °C); ^1H NMR (400 MHz, DMSO-d_6): δ 3.79 (s, 6H, 3', 4'-OCH₃), 6.88 (d, 1H, $^4J=2.4$ Hz, 8-H), 6.96 (dd, 1H, $^3J=8.8$ Hz, $^4J=2.4$ Hz, 6-H), 7.01 (d, 1H, $^3J=8.3$ Hz, 5'-H), 7.13 (dd, 1H, $^3J=8.3$ Hz, $^4J=2.0$ Hz, 6'-H), 7.20 (d, 1H, $^4J=2.0$ Hz, 2'-H), 7.99 (d, 1H, $^3J=8.8$ Hz, 5-H), 8.38 (s, 1H, 2-H), 10.82 ppm (s, 1H, 7-OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.52 (3', 4'-OCH₃), 102.16 (8-C), 111.48 (5'-

C), 112.79 (2'-C), 115.21 (6-C), 116.68 (4a-C), 121.24 (6'-C), 123.30 (1'-C), 124.60 (3-C), 127.33 (5-C), 148.29, 148.61 (3', 4'-C), 153.31 (2-C), 157.42 (8a-C), 162.60 (7-C), 174.62 ppm (4-C); IR (KBr): $\nu_{\max}$ 3200, 3066, 2951, 1625, 1586, 1515, 1214, 1175, 1136 cm^{-1} ; MS (CI): m/z (%) 299.2 (100, MH^+). Anal. Calcd for $\text{C}_{17}\text{H}_{14}\text{O}_5$: C, 68.45; H, 4.73. Found: C, 68.32; H, 5.01.

3-(4-Fluorophenyl)-7-hydroxy-4H-chromen-4-one (3c)—Pale yellow solid (18.5 g, 72%); mp 233–235°C (lit. mp ⁵² 202–203°C; lit. ⁵³ 235–236°C); ¹H NMR (400 MHz, DMSO- d_6): δ 6.88 (d, 1H, ⁴ J = 2.2 Hz, 8-H), 6.95 (dd, 1H, ³ J = 8.8 Hz, ⁴ J = 2.2 Hz, 6-H), 7.25 (t, 2H, ³ J (H,H) = 8.8 Hz, ³ J (C,F) = 8.8 Hz, 3', 5'-H), 7.61 (dd, 2H, ³ J (H,H) = 8.8 Hz, ⁴ J (C,F) = 5.6 Hz, 2', 6'-H), 7.98 (d, 1H, ³ J = 8.8 Hz, 5-H), 8.39 (s, 1H, 2-H), 10.81 ppm (s, 1H, 7-OH); ¹³C NMR (100 MHz, DMSO- d_6): δ 102.22 (8-C), 114.99 (d, ² J (C,F) = 21.1 Hz, 3', 5'-C), 115.31 (6-C), 116.58 (4a-C), 122.59 (3-C), 127.32 (5-C), 128.46 (d, ⁴ J (C,F) = 3.5 Hz, 1'-C), 130.96 (d, ³ J (C,F) = 8.1 Hz, 2', 6'-C), 153.80 (2-C), 157.50 (8a-C), 161.85 (d, ¹ J (C,F) = 244.6 Hz, 4'-C), 162.74 (7-C), 174.38 ppm (4-C); ¹⁹F NMR (376 MHz, DMSO- d_6): δ -114.73 ppm; IR (KBr): $\nu_{\max}$ 3421, 3072, 2906, 1635, 1595, 1510, 1332, 1227, 1145, 795 cm^{-1} ; MS (CI): m/z (%) 257.1 (100, MH^+). Anal. Calcd for $\text{C}_{15}\text{H}_9\text{FO}_3$: C, 70.31; H, 3.54. Found: C, 70.60; H, 3.68.

7-Hydroxy-3-(4-methoxyphenyl)-2-methyl-4H-chromen-4-one (3d)—White solid (19.2 g, 68%); mp 286–288 °C; ¹H NMR (400 MHz, DMSO- d_6): δ 2.23 (s, 3H, 2-CH₃), 3.79 (s, 3H, 4'-OCH₃), 6.82 (d, 1H, ⁴ J = 2 Hz, 8-H), 6.90 (dd, 1H, ³ J = 8.8 Hz, ⁴ J = 2 Hz, 6-H), 6.98 (d, 2H, ³ J = 8.8 Hz, 3', 5'-H), 7.19 (d, 2H, ³ J = 8.8 Hz, 2', 6'-H), 7.87 (d, 1H, ³ J = 8.8 Hz, 5-H), 10.74 ppm (s, 1H, 7-OH); ¹³C NMR (100 MHz, DMSO- d_6): δ 19.17 (2-CH₃), 55.05 (4'-OCH₃), 101.90 (8-C), 113.45 (3', 5'-C), 114.72 (6-C), 115.79 (4a-C), 121.70 (1'-C), 125.34 (3-C), 127.12 (5-C), 131.71 (2', 6'-C), 157.05 (2-C), 158.51 (8a-C), 162.42, 162.44 (7, 4'-C), 174.99 ppm (4-C); IR (KBr): $\nu_{\max}$ 3249, 2962, 1624, 1608, 1511, 1450, 1291, 1159 cm^{-1} ; MS (CI): m/z (%) 283.1 (100, MH^+). Anal. Calcd for $\text{C}_{17}\text{H}_{14}\text{O}_4$: C, 72.33; H, 5.00. Found: C, 72.54; H, 4.86.

3-(3,4-Dimethoxyphenyl)-7-hydroxy-2-methyl-4H-chromen-4-one (3e)—White solid (20 g, 64%); mp 227–228°C (lit. ⁵⁴ mp 226–228°C); ¹H NMR (400 MHz, DMSO- d_6): δ 2.25 (s, 3H, 2-CH₃), 3.74 (s, 3H, 3'-OCH₃), 3.79 (s, 3H, 4'-OCH₃), 6.78 (dd, 1H, ³ J = 7.8 Hz, ⁴ J = 1.5 Hz, 6'-H), 6.83 (d, 1H, ⁴ J = 2.4 Hz, 8-H), 6.85 (d, 1H, ⁴ J = 1.5 Hz, 2'-H), 6.90 (dd, 1H, ³ J = 8.8 Hz, ⁴ J = 2.4 Hz, 6-H), 6.99 (d, 1H, ³ J = 7.8 Hz, 5'-H), 7.87 (d, 1H, ³ J = 8.8 Hz, 5-H), 10.74 ppm (s, 1H, 7-OH); ¹³C NMR (100 MHz, DMSO- d_6): δ 19.20 (2-CH₃), 55.46, 55.52 (3', 4'-OCH₃), 101.89 (8-C), 111.38 (5'-C), 114.35 (2'-C), 114.72 (6-C), 115.62 (4a-C), 122.00 (1'-C), 122.84 (6'-C), 125.74 (3-C), 127.11 (5-C), 148.14, 148.26 (3', 4'-C), 157.03 (8a-C), 162.40 (2-C), 162.57 (7-C), 174.95 ppm (4-C); IR (KBr): $\nu_{\max}$ 3151, 2953, 1630, 1593, 1516, 1453, 1269, 1160 cm^{-1} ; MS (CI): m/z (%) 313.1 (100, MH^+). Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{O}_5$: C, 69.22; H, 5.16. Found: C, 68.95; H, 5.27.

3-(4-Fluorophenyl)-7-hydroxy-2-methyl-4H-chromen-4-one (3f)—Pale yellow solid (19.5 g, 72%); mp 284–285°C; ¹H NMR (400 MHz, DMSO- d_6): δ 2.23 (s, 3H, 2-CH₃), 6.83 (d, 1H, ⁴ J = 1.7 Hz, 8-H), 6.90 (dd, 1H, ³ J = 8.8 Hz, ⁴ J = 1.7 Hz, 6-H), 7.24 (t,

2H, $^3J(\text{H,H}) = 8.8 \text{ Hz}$, $^3J(\text{C,F}) = 8.8 \text{ Hz}$, 3', 5'-H), 7.31 (dd, 2H, $^3J(\text{H,H}) = 8.8 \text{ Hz}$, $^4J(\text{C,F}) = 5.8 \text{ Hz}$, 2', 6'-H), 7.87 (d, 1H, $^3J = 8.8 \text{ Hz}$, 5-H), 10.75 ppm (s, 1H, 7-OH); ^{13}C NMR (100 MHz, DMSO- d_6): δ 19.16 (2-CH₃), 101.93 (8-C), 114.84 (6-C), 114.90 (d, $^2J(\text{C,F}) = 21.5 \text{ Hz}$, 3', 5'-C), 115.48 (4a-C), 121.16 (3-C), 127.10 (5-C), 129.61 (d, $^4J(\text{C,F}) = 3.5 \text{ Hz}$, 1'-C), 132.61 (d, $^3J(\text{C,F}) = 8.8 \text{ Hz}$, 2', 6'-C), 157.07 (8a-C), 161.51 (d, $^1J(\text{C,F}) = 244.2 \text{ Hz}$, 4'-C), 162.54 (7-C), 162.73 (2-C), 174.75 ppm (4-C); ^{19}F NMR (376 MHz, DMSO- d_6): δ -115.24 ppm; IR (KBr): ν_{max} 3272, 3074, 1632, 1585, 1511, 1452, 1227, 1159 cm^{-1} ; MS (CI): m/z (%) 271.1 (100, $\text{MH}^+ - 12$). Anal. Calcd for C₁₆H₁₁FO₃: C, 71.11; H, 4.10. Found: C, 71.02; H, 4.39.

General procedure for synthesis of 7-hydroxy-2-(trifluoromethyl)isoflavones 3g–3i

To a solution of 10 mmol of the appropriate deoxybenzoin in 20 mL of pyridine was added 30 mmol of trifluoroacetic anhydride dropwise with cooling in an ice bath. After standing at 25°C for 48 h, the mixture was poured into 100 mL of ice water, and the precipitate was collected and recrystallized from methanol.

7-Hydroxy-3-(4-methoxyphenyl)-2-(trifluoromethyl)-4H-chromen-4-one (3g)—

Pale yellow solid (2.8 g, 67%); mp 149–151°C; ^1H NMR (400 MHz, DMSO- d_6): δ 3.81 (s, 3H, 4'-OCH₃), 6.93 (d, 1H, $^4J = 2.2 \text{ Hz}$, 8-H), 6.97–7.04 (m, 3H, 6, 3', 5'-H), 7.19 (d, 2H, $^3J = 8.8 \text{ Hz}$, 2', 6'-H), 7.93 (d, 1H, $^3J = 9.0 \text{ Hz}$, 5-H), 11.06 ppm (s, 1H, 7-OH); ^{13}C NMR (100 MHz, DMSO- d_6): δ 55.10 (4'-OCH₃), 102.18 (8-C), 113.39 (3', 5'-C), 115.41 (4a-C), 116.26 (6-C), 119.45 (q, $^1J(\text{C,F}) = 276.0 \text{ Hz}$, 2-CF₃), 121.32 (1'-C), 124.71 (3-C), 127.46 (5-C), 131.20 (2', 6'-C), 146.49 (q, $^2J(\text{C,F}) = 34.8 \text{ Hz}$, 2-C), 156.44 (8a-C), 159.43 (4'-C), 163.84 (7-C), 175.21 ppm (4-C); ^{19}F NMR (376 MHz, DMSO- d_6): δ -63.07 ppm; IR (KBr): ν_{max} 3296, 2971, 1638, 1604, 1455, 1274, 1191 cm^{-1} ; MS (CI): m/z (%) 337.2 (100, MH^+). Anal. Calcd for C₁₇H₁₁F₃O₄: C, 60.72; H, 3.30. Found: C, 60.95; H, 3.48.

3-(3,4-Dimethoxyphenyl)-7-hydroxy-2-(trifluoromethyl)-4H-chromen-4-one (3h)—

Pale yellow solid (2.6 g, 71%); mp 232–233°C; ^1H NMR (400 MHz, DMSO- d_6): δ 3.72 (s, 3H, 3'-OCH₃), 3.80 (s, 3H, 4'-OCH₃), 6.79 (dd, 1H, $^3J = 8.3 \text{ Hz}$, $^4J = 2 \text{ Hz}$, 6'-H), 6.88 (d, 1H, $^4J = 2 \text{ Hz}$, 2'-H), 6.94 (d, 1H, $^4J = 2 \text{ Hz}$, 8-H), 6.99–7.04 (m, 2H, 6, 5'-H), 7.94 (d, 1H, $^3J = 8.3 \text{ Hz}$, 5-H), 11.13 ppm (s, 1H, 7-OH); ^{13}C NMR (100 MHz, DMSO- d_6): δ 55.44 (3'-OCH₃), 55.54 (4'-OCH₃), 102.18 (8-C), 111.12 (5'-C), 113.71 (2'-C), 115.42 (4a-C), 116.29 (6-C), 119.44 (q, $^1J(\text{C,F}) = 276.0 \text{ Hz}$, 2-CF₃), 121.55 (1'-C), 122.41 (6'-C), 124.89 (3-C), 127.49 (5-C), 146.49 (q, $^2J(\text{C,F}) = 34.9 \text{ Hz}$, 2-C), 148.08, 148.98 (3', 4'-C), 156.40 (8a-C), 163.78 (7-C), 175.17 ppm (4-C); ^{19}F NMR (376 MHz, DMSO- d_6): δ -63.07 ppm; IR (KBr): ν_{max} 3378, 2942, 1650, 1611, 1516, 1270, 1214, 1140 cm^{-1} ; MS (CI): m/z (%) 367.2 (100, MH^+). Anal. Calcd for C₁₈H₁₃F₃O₅: C, 59.02; H, 3.58. Found: C, 58.76; H, 3.45.

3-(4-Fluorophenyl)-7-hydroxy-2-(trifluoromethyl)-4H-chromen-4-one (3i)—

Pale yellow solid (2.4 g, 75%); mp 212–213°C; ^1H NMR (400 MHz, DMSO- d_6): δ 6.94 (d, 1H, $^4J = 2 \text{ Hz}$, 8-H), 7.02 (dd, 1H, $^3J = 8.8 \text{ Hz}$, $^4J = 2 \text{ Hz}$, 6-H), 7.21–7.36 (m, 4H, 3-C₆H₄F), 7.92 (d, 1H, $^3J = 8.8 \text{ Hz}$, 5-H), 11.07 ppm (s, 1H, 7-OH); ^{13}C NMR (100 MHz, DMSO- d_6): δ 102.24 (8-C), 114.95 (d, $^2J(\text{C,F}) = 21.1 \text{ Hz}$, 3', 5'-C), 115.38 (4a-C), 116.37

(6-C), 119.33 (q, $^1J(\text{C},\text{F}) = 276.2$ Hz, 2-CF₃), 124.05 (3-C), 125.82 (d, $^4J(\text{C},\text{F}) = 3.5$ Hz, 1'-C), 127.48 (5-C), 132.12 (d, $^3J(\text{C},\text{F}) = 8.4$ Hz, 2', 6'-C), 146.64 (q, $^2J(\text{C},\text{F}) = 35.2$ Hz, 2-C), 156.47 (8a-C), 162.27 (d, $^1J(\text{C},\text{F}) = 245.8$ Hz, 4'-C), 163.92 (7-C), 175.02 ppm (4-C); ^{19}F NMR (376 MHz, DMSO-d₆): δ -113.83, -63.24 ppm; IR (KBr): ν_{max} 3185, 1639, 1602, 1459, 1272, 1197, 1151 cm⁻¹; MS (CI): m/z (%): 325.1 (100, MH⁺). Anal. Calcd for C₁₆H₈F₄O₃: C, 59.27; H, 2.49. Found: C, 59.53; H, 2.30.

General procedures for the aminomethylation of 7-hydroxyisoflavones **3** with 2-aminoethanol

Method A—A solution of 2.5 mmol of isoflavones **3a–3i**, 3 mmol of 2-aminoethanol, 6 mmol of aqueous 37% formaldehyde, and 1–2 mg of 4-(N,N-dimethylamino)pyridine in 10 mL of solvent (see Table 1) was refluxed for 4–6 h. The mixture was cooled, and the precipitate was collected. If precipitation did not occur, the mixture was diluted with 10 mL of hexane or the solution was concentrated. The products were recrystallized from a mixture of isopropanol and hexane.

9-(2-Hydroxyethyl)-3-(4-methoxyphenyl)-9,10-dihydro-4H,8H-chromeno[8,7-e]

[1,3]oxazin-4-one (4a, n=1): White solid (480 mg, 68%); mp 114–116°C; ^1H NMR (400 MHz, CDCl₃): δ 2.98 (t, 2H, $^3J = 5.2$ Hz, 1''-CH₂), 3.77 (t, 2H, $^3J = 5.2$ Hz, 2''-CH₂), 3.85 (s, 3H, 4'-OCH₃), 4.23 (s, 2H, 10-CH₂), 5.00 (s, 2H, 8-CH₂), 6.89 (d, 1H, $^3J = 8.9$ Hz, 6-H), 6.98 (d, 2H, $^3J = 9$ Hz, 3', 5'-H), 7.49 (d, 2H, $^3J = 9$ Hz, 2', 6'-H), 7.93 (s, 1H, 2-H), 8.10 ppm (d, 1H, $^3J = 8.9$ Hz, 5-H); ^{13}C NMR (125 MHz, CDCl₃): δ 44.83 (1''-C), 53.70 (10-C), 55.23 (4'-OCH₃), 59.35 (2''-C), 83.38 (8-C), 107.32 (10a-C), 113.85 (3', 5'-C), 115.17 (6-C), 117.93 (4a-C), 123.94 (1'-C), 124.83 (3-C), 125.30 (5-C), 130.00 (2', 6'-C), 151.53 (2-C), 154.45 (10b-C), 158.31 (4'-C), 159.50 (6a-C), 175.76 ppm (4-C); IR (KBr): ν_{max} 3410, 2958, 2846, 1632, 1592, 1434, 1250 cm⁻¹; MS (CI): m/z (%) 342.2 (100, MH⁺-12). Anal. Calcd for C₂₀H₁₉NO₅: C, 67.98; H, 5.42; N, 3.96. Found: C, 68.25; H, 5.31; N, 4.15.

3-(3,4-Dimethoxyphenyl)-9-(2-hydroxyethyl)-9,10-dihydro-4H,8H-chromeno[8,7-e]

[1,3]oxazin-4-one (4b, n=1): White solid (375 mg, 49%); mp 126–128°C; ^1H NMR (400 MHz, CDCl₃): δ 2.98 (t, 2H, $^3J = 5.2$ Hz, 1''-CH₂), 3.77 (t, 2H, $^3J = 5.2$ Hz, 2''-CH₂), 3.92 (s, 3H, 3'-OCH₃), 3.94 (s, 3H, 4'-OCH₃), 4.23 (s, 2H, 10-CH₂), 5.00 (s, 2H, 8-CH₂), 6.90 (d, 1H, $^3J = 9$ Hz, 6-H), 6.93 (d, 1H, $^3J = 8.3$ Hz, 5'-H), 7.05 (dd, 1H, $^4J = 2.1$ Hz, $^3J = 8.3$ Hz, 6'-H), 7.21 (d, 1H, $^4J = 2.1$ Hz, 2'-H), 7.96 (s, 1H, 2-H), 8.10 ppm (d, 1H, $^3J = 9$ Hz, 5-H); ^{13}C NMR (125 MHz, CDCl₃): δ 44.89 (1''-C), 53.78 (10-C), 55.94 (3'-OCH₃), 55.96 (4'-OCH₃), 59.33 (2''-C), 83.42 (8-C), 107.31 (10a-C), 111.19 (5'-C), 112.54 (2'-C), 115.35 (6-C), 118.09 (4a-C), 121.03 (6'-C), 124.46 (1'-C), 125.07 (3-C), 125.48 (5-C), 148.79, 149.18 (3', 4'-C), 151.74 (2-C), 154.52 (10b-C), 158.41 (6a-C), 175.86 ppm (4-C); IR (KBr): ν_{max} 3264, 2980, 2880, 1644, 1602, 1442, 1284, 1156 cm⁻¹; MS (CI): m/z (%) 372.2 (100, MH⁺-12). Anal. Calcd for C₂₁H₂₁NO₆: C, 65.79; H, 5.52; N, 3.65. Found: C, 65.49; H, 5.41; N, 3.88.

3-(4-Fluorophenyl)-9-(2-hydroxyethyl)-9,10-dihydro-4H,8H-chromeno[8,7-e]

[1,3]oxazin-4-one (4c, n=1): White solid (550 mg, 81%); mp 149–151°C; ^1H NMR (400 MHz, CDCl₃): δ 2.98 (t, 2H, $^3J = 5.1$ Hz, 1''-CH₂), 3.77 (t, 2H, $^3J = 5.1$ Hz, 2''-CH₂), 4.23

(s, 2H, 10-CH₂), 5.01 (s, 2H, 8-CH₂), 6.91 (d, 1H, ³J = 8.8 Hz, 6-H), 7.13 (t, 2H, ³J(H,H) = 8.8 Hz, ³J(H,F) = 8.8 Hz, 3', 5'-H), 7.53 (dd, 2H, ³J(H,H) = 8.8 Hz, ⁴J(H,F) = 5.5 Hz, 2', 6'-H), 7.94 (s, 1H, 2-H), 8.10 ppm (d, 1H, ³J = 8.8 Hz, 5-H); ¹³C NMR (125 MHz, CDCl₃): δ 44.89 (1''-C), 53.77 (10-C), 59.38 (2''-C), 83.45 (8-C), 107.40 (10a-C), 115.38 (d, ²J(C,F) = 21.9 Hz, 3', 5'-C), 115.43 (6-C), 117.96 (4a-C), 124.48 (3-C), 125.41 (5-C), 127.68 (d, ⁴J(C,F) = 3.5 Hz, 1'-C), 130.64 (d, ³J(C,F) = 8.0 Hz, 2', 6'-C), 151.93 (2-C), 154.54 (10b-C), 158.55 (6a-C), 162.70 (d, ¹J(C,F) = 247.8 Hz, 4'-C), 175.50 ppm (4-C); ¹⁹F NMR (376 MHz, CDCl₃): δ -114.14 ppm; IR (KBr): ν_{max} 3434, 2950, 2860, 1632, 1600, 1442, 1250 cm⁻¹; MS (CI): *m/z* (%) 330.2 (100, MH⁺-12). Anal. Calcd for C₁₉H₁₆FNO₄: C, 66.86; H, 4.72; N, 4.10. Found: C, 67.03; H, 4.61; N, 4.12.

9-(2-Hydroxyethyl)-3-(4-methoxyphenyl)-2-methyl-9,10-dihydro-4H,8H-chromeno[8,7-*e*][1,3]oxazin-4-one (4d, n=1): White solid (342 mg, 47%); mp 151–153°C; ¹H NMR (400 MHz, CDCl₃): δ 2.31 (s, 3H, 2-CH₃), 2.99 (t, 2H, ³J = 5.2 Hz, 1''-CH₂), 3.77 (t, 2H, ³J = 5.2 Hz, 2''-CH₂), 3.85 (s, 3H, 4'-OCH₃), 4.23 (s, 2H, 10-CH₂), 4.99 (s, 2H, 8-CH₂), 6.85 (d, 1H, ³J = 8.9 Hz, 6-H), 6.97 (d, 2H, ³J = 8.7 Hz, 3', 5'-H), 7.20 (d, 2H, ³J = 8.7 Hz, 2', 6'-H), 8.02 ppm (d, 1H, ³J = 8.9 Hz, 5-H); ¹³C NMR (125 MHz, CDCl₃): δ 19.36 (2-CH₃), 44.97 (1''-C), 53.75 (10-C), 55.25 (4'-OCH₃), 59.30 (2''-C), 83.32 (8-C), 106.95 (10a-C), 113.87 (3', 5'-C), 114.82 (6-C), 116.99 (4a-C), 123.08 (1'-C), 125.10 (3-C), 125.40 (5-C), 131.49 (2', 6'-C), 154.17 (10b-C), 158.16 (2-C), 159.10 (4'-C), 162.23 (6a-C), 176.48 ppm (4-C); IR (KBr): ν_{max} 3434, 2925, 2833, 1630, 1606, 1437, 1246 cm⁻¹; MS (CI): *m/z* (%) 356.3 (100, MH⁺-12). Anal. Calcd for C₂₁H₂₁NO₅: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.77; H, 5.51; N, 3.94.

3-(3,4-Dimethoxyphenyl)-9-(2-hydroxyethyl)-2-methyl-9,10-dihydro-4H,8H-chromeno[8,7-*e*][1,3]oxazin-4-one (4e, n=1): White solid (431 mg, 54%); mp 168–170°C (decomp); ¹H NMR (400 MHz, CDCl₃): δ 2.31 (s, 3H, 2-CH₃), 2.98 (t, 2H, ³J = 5.2 Hz, 1''-CH₂), 3.76 (t, 2H, ³J = 5.2 Hz, 2''-CH₂), 3.88 (s, 3H, 3'-OCH₃), 3.91 (s, 3H, 4'-OCH₃), 4.22 (s, 2H, 10-CH₂), 4.99 (s, 2H, 8-CH₂), 6.78–6.83 (m, 2H, 2', 5'-H), 6.85 (d, 1H, ³J = 8.8 Hz, 6-H), 6.91–6.69 (m, 1H, 6'-H), 8.01 ppm (d, 1H, ³J = 8.8 Hz, 5-H); ¹³C NMR (125 MHz, CDCl₃): δ 19.34 (2-CH₃), 44.92 (1''-C), 53.69 (10-C), 55.81 (3', 4'-OCH₃), 59.30 (2''-C), 83.29 (8-CH₂), 106.95 (10a-C), 111.13 (5'-C), 113.60 (2'-C), 114.78 (6-C), 116.88 (4a-C), 122.70 (6'-C), 123.19 (1'-C), 125.25 (5-C), 125.48 (3-C), 148.55, 148.70 (3', 4'-C), 154.09 (10b-C), 158.15 (2-C), 162.34 (6a-C), 176.37 ppm (4-C); IR (KBr): ν_{max} 3474, 2964, 2930, 2834, 1634, 1620, 1434, 1252 cm⁻¹; MS (CI): *m/z* (%) 386.1 (100, MH⁺-12). Anal. Calcd for C₂₂H₂₃NO₆: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.65; H, 5.91; N, 3.37.

3-(4-Fluorophenyl)-9-(2-hydroxyethyl)-2-methyl-9,10-dihydro-4H,8H-chromeno[8,7-*e*][1,3]oxazin-4-one (4f, n=1): White solid (465 mg, 65%); mp 112–114 °C; ¹H NMR (400 MHz, CDCl₃): δ 2.30 (s, 3H, 2-CH₃), 2.98 (t, 2H, ³J = 5.2 Hz, 1''-CH₂), 3.77 (t, 2H, ³J = 5.2 Hz, 2''-CH₂), 4.23 (s, 2H, 10-CH₂), 4.99 (s, 2H, 8-CH₂), 6.85 (d, 1H, ³J = 9.2 Hz, 6-H), 7.12 (t, 2H, ³J(H,H) = 8.5 Hz, ³J(H,F) = 8.5 Hz, 3', 5'-H), 7.25 (dd, 2H, ³J(H,H) = 8.5 Hz, ⁴J(H,F) = 5.6 Hz, 2', 6'-H), 8.01 ppm (d, 1H, ³J = 9.2 Hz, 5-H); ¹³C NMR (125 MHz, CDCl₃): δ 19.38 (2-CH₃), 45.05 (1''-C), 53.82 (10-C), 59.43 (2''-C), 83.44 (8-C), 107.13 (10a-C), 115.03 (6-C), 115.39 (d, ²J(C,F) = 21.9 Hz, 3', 5'-C), 116.92 (4a-C), 124.64 (3-C),

125.36 (5-C), 128.93 (d, $^4J(\text{C},\text{F}) = 3.5$ Hz, 1'-C), 132.17 (d, $^3J(\text{C},\text{F}) = 8.0$ Hz, 2', 6'-C), 154.23 (10b-C), 158.41 (2-C), 162.37 (d, $^1J(\text{C},\text{F}) = 246.8$ Hz, 4'-C), 162.38 (6a-C), 176.22 ppm (4-C); ^{19}F NMR (376 MHz, CDCl_3): δ -114.83 ppm; IR (KBr): ν_{max} 3436, 2946, 2844, 1634, 1604, 1510, 1436, 1248 cm^{-1} ; MS (CI): m/z (%) 344.1 (100, $\text{MH}^+ - 12$). Anal. Calcd for $\text{C}_{20}\text{H}_{18}\text{FNO}_4$: C, 67.60; H, 5.11; N, 3.94. Found: C, 67.51; H, 4.88; N, 3.79.

3-(3,4-Dimethoxyphenyl)-9-(2-hydroxyethyl)-2-(trifluoromethyl)-9,10-dihydro-4H,8H-

chromeno[8,7-e][1,3]oxazin-4-one (4h, n=1): White solid (540 mg, 60%); mp 168–170°C; ^1H NMR (400 MHz, CDCl_3): δ 2.99 (t, 2H, $^3J = 5.1$ Hz, 1''-CH₂), 3.78 (t, 2H, $^3J = 5.1$ Hz, 2''-CH₂), 3.88 (s, 3H, 3'-OCH₃), 3.93 (s, 3H, 4'-OCH₃), 4.26 (s, 2H, 10-CH₂), 5.03 (s, 2H, 8-CH₂), 6.76–6.86 (m, 2H, 2', 6'-H), 6.92–6.96 (m, 2H, 6, 5'-H), 8.03 ppm (d, 1H, $^3J = 9$ Hz, 5-H); ^{13}C NMR (125 MHz, CDCl_3): δ 44.70 (1''-C), 53.80 (10-C), 55.81 (3'-OCH₃), 55.84 (4'-OCH₃), 59.33 (2''-C), 83.67 (8-C), 107.57 (10a-C), 110.84 (5'-C), 113.07 (2'-C), 116.36 (6-C), 116.78 (4a-C), 119.44 (q, $^1J(\text{C},\text{F}) = 277.8$ Hz, 2-CF₃), 121.09 (6'-C), 122.50 (1'-C), 125.57 (5-C), 127.78 (3-C), 148.02 (q, $^2J(\text{C},\text{F}) = 35.9$ Hz, 2-C), 148.59, 149.49 (3', 4'-C), 153.37 (10b-C), 159.51 (6a-C), 176.25 ppm (4-C); ^{19}F NMR (376 MHz, CDCl_3): δ -63.95 ppm; IR (KBr): ν_{max} 3527, 2940, 2913, 2839, 1651, 1608, 1435, 1216, 1144, 1134 cm^{-1} ; MS (CI): m/z (%) 440.1 (100, $\text{MH}^+ - 12$). Anal. Calcd for $\text{C}_{22}\text{H}_{20}\text{F}_3\text{NO}_6$: C, 58.54; H, 4.47; N, 3.10. Found: C, 58.30; H, 4.66; N, 2.83.

7-Hydroxy-8-[(2-hydroxyethyl)amino]methyl]-3-(4-methoxyphenyl)-2-

(trifluoromethyl)-4H-chromen-4-one (6g, n=1): White solid (600 mg, 73%); mp 207–208°C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 2.86 (t, 2H, $^3J = 5.4$ Hz, 1''-CH₂), 3.60 (t, 2H, $^3J = 5.4$ Hz, 2''-CH₂), 3.80 (s, 3H, 4'-OCH₃), 4.19 (s, 2H, 8-CH₂), 6.63 (d, 1H, $^3J = 9$ Hz, 6-H), 6.99 (d, 2H, $^3J = 8.5$ Hz, 3', 5'-H), 7.16 (d, 2H, $^3J = 8.5$ Hz, 2', 6'-H), 7.71 ppm (d, 1H, $^3J = 9$ Hz, 5-H); ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$): δ 42.74 (1''-C), 49.04 (8-CH₂), 55.04 (4'-OCH₃), 57.92 (2''-C), 105.58 (8-C), 110.73 (4a-C), 113.17 (3', 5'-C), 118.96 (6-C), 119.93 (q, $^1J(\text{C},\text{F}) = 276.0$ Hz, 2-CF₃), 121.60 (3-C), 124.01 (1'-C), 125.65 (5-C), 131.01 (2', 6'-C), 145.05 (q, $^2J(\text{C},\text{F}) = 34.8$ Hz, 2-C), 154.48 (8a-C), 159.07 (4-C), 171.42 (7-C), 174.12 ppm (4'-C); ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$): δ -61.96 ppm; IR (KBr): ν_{max} 3427, 2912, 1639, 1608, 1396, 1286, 1180 cm^{-1} ; MS (CI): m/z (%) 410.1 (100, MH^+). Anal. Calcd for $\text{C}_{20}\text{H}_{18}\text{F}_3\text{NO}_5$: C, 58.68; H, 4.43; N, 3.42. Found: C, 58.81; H, 4.21; N, 3.58.

3-(3,4-Dimethoxyphenyl)-7-hydroxy-8-[(2-hydroxyethyl)amino]methyl]-2-

(trifluoromethyl)-4H-chromen-4-one (6h, n=1): White solid (595 mg, 63%); mp 230–232°C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 2.96–3.13 (m, 2H, 1''-CH₂), 3.68–3.90 (m, 8H, 3', 4'-OCH₃, 2''-CH₂), 4.32 (s, 2H, 8-CH₂), 5.20–5.40 (br. s, 1H, OH), 6.76–6.86 (m, 2H, 2', 6'-H), 7.04 (d, 1H, $^3J = 8.1$ Hz, 5'-H), 7.31 (d, 1H, $^3J = 9$ Hz, 6-H), 8.01 (d, 1H, $^3J = 9$ Hz, 5-H), 8.70–9.28 (br. s, 2H, NH_2^+), 11.91–12.52 ppm (br. s, 1H, 7-OH); ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$): δ 38.46 (1''-C), 49.33 (8-CH₂), 55.44 (3'-OCH₃), 55.53 (4'-OCH₃), 56.17 (2''-C), 105.56 (8-C), 111.18 (5'-C), 113.58 (2'-C), 115.14 (6-C), 115.48 (4a-C), 119.27 (q, $^1J(\text{C},\text{F}) = 276.3$ Hz, 2-CF₃), 121.05 (6'-C), 122.33 (1'-C), 124.71 (3-C), 127.88 (5-C), 146.55 (q, $^2J(\text{C},\text{F}) = 35.9$ Hz, 2-C), 147.99, 148.97 (3', 4'-C), 154.75 (8a-C), 162.74 (7-C), 175.08 ppm (4-C); ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$): δ -60.72 ppm; IR (KBr): ν_{max}

3400, 3126, 2962, 1655, 1612, 1454, 1272 cm^{-1} ; MS (CI): m/z (%) 440.1 (100, MH^+). Anal. Calcd for $\text{C}_{21}\text{H}_{20}\text{F}_3\text{NO}_6\text{-HCl}$: C, 53.01; H, 4.45; N, 2.94. Found: C, 52.83; H, 4.20; N, 3.28.

3-(4-Fluorophenyl)-7-hydroxy-8-[(2-hydroxyethyl)amino]methyl]-2-(trifluoromethyl)-4H-chromen-4-one (6i, n=1): White solid (639 mg, 80%); mp 216–218°C (decomp); ^1H NMR (400 MHz, DMSO-d_6): δ 2.87 (t, 2H, $^3J = 5.4$ Hz, 1''- CH_2), 3.60 (t, 2H, $^3J = 5.4$ Hz, 2''- CH_2), 4.18 (s, 2H, 8- CH_2), 6.60 (d, 1H, $^3J = 9$ Hz, 6-H), 7.23–7.33 (m, 4H, 3- $\text{C}_6\text{H}_4\text{F}$), 7.69 ppm (d, 1H, $^3J = 9$ Hz, 5-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 42.56 (1''-C), 49.00 (8- CH_2), 57.82 (2''-C), 105.46 (8-C), 110.27 (4a-C), 114.69 (d, $^2J(\text{C},\text{F}) = 21.5$ Hz, 3', 5'-C), 119.39 (6-C), 119.44 (q, $^1J(\text{C},\text{F}) = 276.1$ Hz, 2- CF_3), 123.34 (3-C), 125.66 (5-C), 126.17 (d, $^4J(\text{C},\text{F}) = 3.0$ Hz, 1'-C), 131.98 (d, $^3J(\text{C},\text{F}) = 8.0$ Hz, 2', 6'-C), 145.14 (q, $^2J(\text{C},\text{F}) = 35.0$ Hz, 2-C), 154.69 (8a-C), 161.97 (d, $^1J(\text{C},\text{F}) = 244.7$ Hz, 4'-C), 172.27 (7-C), 173.77 ppm (4-C); ^{19}F NMR (376 MHz, DMSO-d_6): δ -112.03, -61.00 ppm; IR (KBr): ν_{max} 3425, 2913, 1639, 1601, 1450, 1286, 1143 cm^{-1} ; MS (CI): m/z (%) 398.1 (100, MH^+). Anal. Calcd for $\text{C}_{19}\text{H}_{15}\text{F}_4\text{NO}_4$: C, 57.44; H 3.81; N, 3.53. Found: C, 57.41; H, 3.98; N, 3.76

Method B—A solution of 2.5 mmol of isoflavone **3a** or **3d**, 3 mmol of bis(1,3-oxazolidin-3-yl)methane^{55,56} in 10 mL of 1,4-dioxane was refluxed for 2–4 h. The mixture was cooled; the solvent was evaporated; and the product was treated with hexane to obtain a precipitate that was recrystallized from a mixture of isopropanol and hexane to afford **3a** or **3d**. Compounds **3a** and **3d** were identical to material synthesized by Method A.

Method C—A solution of 2.5 mmol of isoflavone **3b–3e** and 3 mmol of 3-butoxymethyl-1,3-oxazolidine⁵⁷ in 10 mL of 1,4-dioxane was refluxed for 2–4 h. The mixture was cooled; the solvent was evaporated; and the product was isolated in the same fashion as described in Method A.

Synthesis of 8-(2-hydroxyethylaminomethyl)-7-hydroxyisoflavone hydrochlorides **6a–6f** where n=1

A solution of 2.5 mmol of isoflavone **3a–3f**, 3 mmol of 2-aminoethanol, 6 mmol of aqueous 37% formaldehyde, and 1–2 mg of 4-(N,N-dimethylamino)pyridine in 10 mL of ethanol was refluxed for 4–6 h. To this mixture was added 0.2 mL of concentrated hydrochloric acid, and the mixture was refluxed for 10–15 min. The product was cooled to afford precipitated hydrochlorides that were collected and recrystallized from a mixture of methanol and acetonitrile.

7-Hydroxy-8-[(2-hydroxyethyl)amino]methyl]-3-(4-methoxyphenyl)-4H-chromen-4-one hydrochloride (6a, n=1)—White solid (591 mg, 78%); mp 187–191°C; ^1H NMR (400 MHz, DMSO-d_6): δ 2.99–3.10 (m, 2H, 1''- CH_2), 3.66–3.74 (m, 2H, 2''- CH_2), 3.80 (s, 3H, 4'- OCH_3), 4.28–4.37 (m, 2H, 8- CH_2), 7.01 (d, 2H, $^3J = 8.7$ Hz, 3', 5'-H), 7.20 (d, 1H, $^3J = 8.9$ Hz, 6-H), 7.51 (d, 2H, $^3J = 8.7$ Hz, 2', 6'-H), 8.05 (d, 1H, $^3J = 8.9$ Hz, 5-H), 8.43 (s, 1H, 2-H), 8.88–8.98 (m, 2H, NH_2^+), 11.84 ppm (br. s, 1H, 7-OH); ^{13}C NMR (125 MHz, D_2O): δ 39.56 (1''-C), 49.23 (8- CH_2), 55.81 (4'- OCH_3), 56.96 (2''-C), 105.02 (8-C), 114.30 (3', 5'-C), 115.26 (6-C), 116.95 (4a-C), 123.79, 123.82 (3, 1'-C),

129.10 (5-C), 130.37 (2', 6'-C), 154.43 (2-C), 156.36 (8a-C), 159.25 (4'-C), 162.02 (7-C), 177.76 ppm (4-C); IR (KBr): $\nu_{\max}$ 3388, 2958, 2834, 1626, 1512, 1448, 1294 cm^{-1} ; MS (CI): m/z (%) 342.2 (100, MH^+). Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_5\cdot\text{HCl}$: C, 60.40; H, 5.34; N, 3.71. Found: C, 60.16; H, 5.48; N, 4.25.

3-(3,4-Dimethoxyphenyl)-7-hydroxy-8-[(2-hydroxyethyl)amino]methyl-4H-chromen-4-one hydrochloride (6b, n=1)—White solid (565 mg, 69%); mp 221–223°C; ^1H NMR (400 MHz, DMSO-d_6): δ 3.01–3.09 (m, 2H, 1''-CH₂), 3.69–3.75 (m, 2H, 2''-CH₂), 3.79 (s, 6H, 3', 4'-OCH₃), 4.30–4.37 (m, 2H, 8-CH₂), 7.02 (d, 1H, $^3J = 8.5$ Hz, 5'-H), 7.13 (dd, 1H, $^3J = 8.5$ Hz, $^4J = 1.7$ Hz, 6'-H), 7.18 (d, 1H, $^4J = 1.7$ Hz, 2'-H), 7.23 (d, 1H, $^3J = 9$ Hz, 6-H), 8.05 (d, 1H, $^3J = 9$ Hz, 5-H), 8.46 (s, 1H, 2-H), 8.92–9.05 (m 2H, NH_2^+), 11.85 ppm (br. s, 1H, 7-OH); ^{13}C NMR (125 MHz, D_2O): δ 39.63 (1''-C), 49.35 (8-CH₂), 55.84 (3'-OCH₃), 56.06 (4'-OCH₃), 59.99 (2''-C), 104.96 (8-C), 111.60 (5'-C), 112.09 (2'-C), 115.15 (6-C), 116.90 (4a-C), 121.60 (6'-C), 123.36 (1'-C), 124.04 (3-C), 129.05 (5-C), 147.82, 148.32 (3', 4'-C), 154.49 (2-C), 156.06 (8a-C), 161.91 (7-C), 177.47 ppm (4-C); IR (KBr): $\nu_{\max}$ 3427, 3247, 3016, 1645, 1622, 1516, 1450, 1286 cm^{-1} ; MS (CI): m/z (%) 372.2 (100, MH^+). Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_6\cdot\text{HCl}$: C, 58.90; H, 5.44; N, 3.43. Found: C, 58.61; H, 5.72; N, 3.38.

3-(4-Fluorophenyl)-7-hydroxy-8-[(2-hydroxyethyl)amino]methyl-4H-chromen-4-one hydrochloride (6c, n=1)—White solid (551 mg, 75%); mp 238–240°C; ^1H NMR (400 MHz, DMSO-d_6): δ 2.99–3.91 (m, 2H, 1''-CH₂), 3.68–3.75 (m, 2H, 2''-CH₂), 4.33 (s, 2H, 8-CH₂), 7.24 (d, 1H, $^3J = 8.8$ Hz, 6-H), 7.29 (t, 2H, $^3J(\text{H,H}) = 7.8$ Hz, $^3J(\text{H,F}) = 7.8$ Hz, 3', 5'-H), 7.61 (dd, 2H, $^3J(\text{H,H}) = 7.8$ Hz, $^4J(\text{H,F}) = 5.9$ Hz, 2', 6'-H), 8.05 (d, 1H, $^3J = 8.8$ Hz, 5-H), 8.49 (s, 1H, 2-H), 8.96–9.06 (br. s, 2H, NH_2^+), 11.92 ppm (s, 1H, 7-OH); ^{13}C NMR (125 MHz, D_2O): δ 39.61, (1''-C), 49.29 (8-CH₂), 56.96 (2''-C), 105.29 (8-C), 115.48 (6-C), 116.01 (d, $^2J(\text{C,F}) = 21.4$ Hz, 3', 5'-C), 117.00 (4a-C), 124.04 (3-C), 127.43 (d, $^4J(\text{C,F}) = 3.5$ Hz, 1'-C), 129.14 (5-C), 131.38 (d, $^3J(\text{C,F}) = 8.5$ Hz, 2', 6'-C), 155.01 (2-C), 156.68 (8a-C), 162.25 (7-C), 163.15 (d, $^1J(\text{C,F}) = 245.3$ Hz, 4'-C), 178.08 ppm (4-C); ^{19}F NMR (376 MHz, D_2O): δ -113.50 ppm; IR (KBr): $\nu_{\max}$ 3423, 2964, 1635, 1623, 1508, 1442, 1267 cm^{-1} ; MS (CI): m/z (%) 330.2 (100, MH^+). Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{FNO}_4\cdot\text{HCl}$: C, 59.10; H, 4.68; N, 3.83. Found: C, 58.78; H, 4.91; N, 3.15.

7-Hydroxy-8-[(2-hydroxyethyl)amino]methyl-3-(4-methoxyphenyl)-2-methyl-4H-chromen-4-one hydrochloride (6d, n=1)—White solid (538 mg, 69%); mp 207–209°C; ^1H NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 3H, 2-CH₃), 3.02–3.10 (m, 2H, 1''-CH₂), 3.72–3.77 (m, 2H, 2''-CH₂), 3.79 (s, 3H, 4'-OCH₃), 4.30–4.37 (m, 2H, 8-CH₂), 6.99 (d, 2H, $^3J = 8.8$ Hz, 3', 5'-H), 7.16–7.22 (m, 3H, 6, 2', 6'-H), 7.94 (d, 1H, $^3J = 8.8$ Hz, 5-H), 8.97–9.05 (m, 2H, NH_2^+), 11.78 ppm (br. s, 1H, 7-OH); ^{13}C NMR (125 MHz, D_2O): δ 19.51 (2-CH₃), 39.64 (1''-C), 49.27 (8-CH₂), 56.05 (4'-OCH₃), 56.97 (2''-C), 105.02 (8-C), 114.67 (3', 5'-C), 114.94 (6-C), 116.02 (4a-C), 122.46 (1'-C), 125.30 (3-C), 128.95 (5-C), 132.26 (2', 6'-C), 156.23 (8a-C), 159.26 (4'-C), 161.89 (2-C), 166.19 (7-C), 178.73 ppm (4-C); IR (KBr): $\nu_{\max}$ 3392, 2962, 1641, 1631, 1513, 1450, 1267 cm^{-1} ; MS (CI): m/z (%) 356.3 (100, MH^+). Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_5\cdot\text{HCl}$: C, 61.30; H, 5.66; N, 3.57. Found: C, 61.58; H, 5.93; N, 3.84.

3-(3,4-Dimethoxyphenyl)-7-hydroxy-8-(((2-hydroxyethyl)amino)methyl)-2-methyl-4H-chromen-4-one hydrochloride (6e, n=1)—White solid (540 mg, 64%); mp 234–236°C; ^1H NMR (400 MHz, DMSO- d_6): δ 2.33 (s, 3H, 2-CH₃), 3.01–3.09 (m, 2H, 1''-CH₂), 3.68–3.82 (m, 8H, 3', 4'-OCH₃, 2''-CH₂), 4.29–4.37 (m, 2H, 8-CH₂), 5.29–5.38 (br. s, 1H, CH₂OH), 6.78 (dd, 1H, 4J = 1.7 Hz, 3J = 8.3 Hz, 6'-H), 6.82 (d, 1H, 4J = 1.7 Hz, 2'-H), 7.01 (d, 1H, 3J = 8.3 Hz, 5'-H), 7.18 (d, 1H, 3J = 8.8 Hz, 6-H), 7.94 (d, 1H, 3J = 8.8 Hz, 5-H), 8.91–9.05 (br. s, 2H, NH₂⁺), 11.77 ppm (s, 1H, 7-OH); ^{13}C NMR (125 MHz, D₂O): δ 19.49 (2-CH₃), 39.61 (1''-C), 49.31 (8-CH₂), 56.32 (3'-OCH₃), 56.36 (4'-OCH₃), 56.97 (2''-C), 105.02 (8-C), 112.30 (5'-C), 114.70 (6-C), 114.90 (2'-C), 116.01 (4a-C), 122.57 (1'-C), 124.04 (6'-C), 125.69 (3-C), 128.91 (5-C), 148.59, 148.62 (3', 4'-C), 156.17 (8a-C), 161.86 (2-C), 166.22 (7-C), 178.56 ppm (4-C); IR (KBr): ν_{max} 3436, 2996, 1637, 1608, 1518, 1446, 1265 cm⁻¹; MS (CI): m/z (%) 386.1 (100, MH⁺). Anal. Calcd for C₂₁H₂₃NO₆·HCl: C, 59.79; H, 5.73; N, 3.32. Found: C, 60.02; H, 6.00; N, 3.13.

3-(4-Fluorophenyl)-7-hydroxy-8-(((2-hydroxyethyl)amino)methyl)-2-methyl-4H-chromen-4-one hydrochloride (6f, n=1)—White solid (465 mg, 61%); mp 140–142°C; ^1H NMR (400 MHz, DMSO- d_6): δ 2.32 (s, 3H, 2-CH₃), 3.03–3.11 (m, 2H, 1''-CH₂), 3.70–3.77 (m, 2H, 2''-CH₂), 4.34 (s, 2H, 8-CH₂), 5.32 (br. s, 1H, OH), 7.17 (d, 1H, 3J = 8.5 Hz, 6-H), 7.24–7.34 (m, 4H, 3-C₆H₄F), 7.95 (d, 1H, 3J = 8.5 Hz, 5-H), 8.89–9.08 (br. s, 2H, NH₂⁺), 11.79 ppm (s, 1H, 7-OH); ^{13}C NMR (125 MHz, D₂O): δ 19.45 (2-CH₃), 39.61 (1''-C), 49.27 (8-CH₂), 56.96 (2''-C), 105.09 (8-C), 115.03 (6-C), 115.94 (4a-C), 116.18 (d, $^2J(\text{C},\text{F})$ = 21.9 Hz, 3', 5'-C), 122.25 (3-C), 128.82 (d, $^4J(\text{C},\text{F})$ = 3.0 Hz, 1'-C), 128.94 (5-C), 132.85 (d, $^3J(\text{C},\text{F})$ = 8.5 Hz, 2', 6'-C), 156.36 (8a-C), 162.07 (2-C), 162.98 (d, $^1J(\text{C},\text{F})$ = 247.8 Hz, 4'-C), 166.55 (7-C), 178.88 ppm (4-C); ^{19}F NMR (376 MHz, D₂O): δ -113.79 ppm; IR (KBr): ν_{max} 3403, 2962, 1637, 1601, 1508, 1448, 1211 cm⁻¹; MS (CI): m/z (%) 344.1 (100, MH⁺). Anal. Calcd for C₁₉H₁₈FNO₄·HCl: C, 60.08; H, 5.04; N, 3.69. Found: C, 59.86; H, 5.25; N, 3.98.

General procedure for the aminomethylation of 7-hydroxyisoflavones **3** with 3-amino-1-propanol

A solution of 2.5 mmol of isoflavone **3a–3i**, 3 mmol of 3-amino-1-propanol, 6 mmol of aqueous 37% formaldehyde, and 1–2 mg of 4-(N,N-dimethylamino)pyridine in 10 mL of isopropanol was refluxed for 4–6 h. The mixture was cooled and the precipitate was collected. If precipitation did not occur, the mixture was concentrated, and the residue was treated with hexane. The precipitated material was recrystallized from a mixture of isopropanol and hexane.

7-Hydroxy-3-(4-methoxyphenyl)-8-(1,3-oxazinan-3-ylmethyl)-4H-chromen-4-one (5a, n=2)—White solid (550 mg, 75%); mp 129–131°C; ^1H NMR (500 MHz, CDCl₃): δ 1.77–19.91 (m, 2H, 5''-CH₂), 2.97–3.05 (m, 2H, 4''-CH₂), 3.83 (s, 3H, 4'-OCH₃), 3.86–3.93 (m, 2H, 6''-CH₂), 4.28 (s, 2H, 8-CH₂), 4.38 (s, 2H, 2''-CH₂), 6.89 (d, 1H, 3J = 8.7 Hz, 6-H), 6.96 (d, 2H, 3J = 8.7 Hz, 3', 5'-H), 7.48 (d, 2H, 3J = 8.7 Hz, 2', 6'-H), 7.90 (s, 1H, 2-H), 8.13 ppm (d, 1H, 3J = 8.7 Hz, 5-H); ^{13}C NMR (125 MHz, CDCl₃): δ 22.11 (5''-C), 47.08 (4''-C), 49.48 (8-CH₂), 55.26 (4'-OCH₃), 67.71 (6''-C), 83.59 (2''-C), 106.68 (8-C), 113.88 (3', 5'-C), 115.59 (6-C), 117.30 (4a-C), 124.15 (1'-C), 124.48 (3-C), 126.95 (5-C),

130.05 (2', 6'-C), 151.38 (2-C), 155.25 (8a-C), 159.52 (4'-C), 163.39 (7-C), 175.78 ppm (4-C); IR (KBr): $\nu_{\max}$ 3425, 2964, 1633, 1601, 1405, 1255 cm^{-1} ; MS (CI): m/z (%) 356.3 (100, MH^+ -12). Anal. Calcd for $\text{C}_{21}\text{H}_{21}\text{NO}_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.39; H, 5.55; N, 4.11.

3-(3,4-Dimethoxyphenyl)-7-hydroxy-8-(1,3-oxazinan-3-ylmethyl)-4H-chromen-4-one (5b, n=2)—White solid (623 mg, 78%); mp 261–263°C; ^1H NMR (500 MHz, CDCl_3): δ 1.78–1.90 (m, 2H, 5''-CH₂), 3.00–3.08 (m, 2H, 4''-CH₂), 3.87–3.98 (m, 8H, 3', 4'-OCH₃, 6''-CH₂), 4.30 (s, 2H, 8-CH₂), 4.38 (s, 2H, 2''-CH₂), 6.89–6.96 (m, 2H, 6-H, 5'-H), 7.05 (dd, 1H, 3J = 8.4 Hz, 4J = 2.0 Hz, 6'-H), 7.22 (d, 1H, 4J = 2.0 Hz, 2'-H), 7.94 (s, 1H, 2-H), 8.14 ppm (d, 1H, 3J = 8.9 Hz, 5-H); ^{13}C NMR (125 MHz, CDCl_3): δ 22.15 (5''-C), 47.28 (4''-C), 49.54 (8-CH₂), 55.95 (3'-OCH₃), 55.96 (4'-OCH₃), 67.80 (6''-C), 83.65 (2''-C), 106.95 (8-C), 111.25 (5'-C), 112.64 (2'-C), 115.69 (6-C), 117.35 (4a-C), 120.99 (6'-C), 124.58 (3-C), 124.71 (1'-C), 126.87 (5-C), 148.81, 149.12 (3', 4'-C), 151.53 (2-C), 155.20 (4a-C), 163.52 (7-C), 175.82 ppm (4-C); IR (KBr): $\nu_{\max}$ 3427, 1632, 1603, 1411, 1267 cm^{-1} ; MS (CI): m/z (%) 386.3 (100, MH^+ -12). Anal. Calcd for $\text{C}_{22}\text{H}_{23}\text{NO}_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.58; H, 5.99; N, 3.67.

3-(4-Fluorophenyl)-7-hydroxy-8-(1,3-oxazinan-3-ylmethyl)-4H-chromen-4-one (5c, n=2)—White solid (461 mg, 65%); mp 116–118°C; ^1H NMR (400 MHz, CDCl_3): δ 1.78–1.92 (m, 2H, 5''-CH₂), 2.97–3.07 (m, 2H, 4''-CH₂), 3.86–3.97 (m, 2H, 6''-CH₂), 4.29 (s, 2H, 8-CH₂), 4.38 (s, 2H, 2''-CH₂), 6.91 (d, 1H, 3J = 9 Hz, 6-H), 7.12 (t, 2H, $^3J(\text{H,H})$ = 8.5 Hz, $^3J(\text{H,F})$ = 8.5 Hz, 3', 5'-H), 7.53 (dd, 2H, $^3J(\text{H,H})$ = 8.5 Hz, $^4J(\text{H,F})$ = 5.6 Hz, 2', 6'-H), 7.91 (s, 1H, 2-H), 8.13 ppm (d, 1H, 3J = 9 Hz, 5-H); ^{13}C NMR (125 MHz, CDCl_3): δ 22.12 (5''-C), 47.28 (4''-C), 49.53 (8-CH₂), 67.81 (6''-C), 83.63 (2''-C), 106.99 (8-C), 115.38 (d, $^2J(\text{C,F})$ = 21.4 Hz, 3', 5'-C), 115.81 (6-C), 117.27 (4a-C), 124.09 (3-C), 126.91 (5-C), 127.89 (d, $^4J(\text{C,F})$ = 3.0 Hz, 1'-C), 130.65 (d, $^3J(\text{C,F})$ = 7.5 Hz, 2', 6'-C), 151.73 (2-C), 155.25 (8a-C), 162.69 (d, $^1J(\text{C,F})$ = 246.3 Hz, 4'-C), 163.66 (7-C), 175.52 ppm (4-C); ^{19}F NMR (376 MHz, CDCl_3): δ -114.37 ppm; IR (KBr): $\nu_{\max}$ 3427, 2850, 1632, 1597, 1510, 1414, 1232 cm^{-1} ; MS (CI): m/z (%) 344.3 (100, MH^+ -12). Anal. Calcd for $\text{C}_{20}\text{H}_{18}\text{FNO}_4$: C, 67.60; H, 5.11; N, 3.94. Found: C, 67.38; H, 5.34; N, 4.17.

7-Hydroxy-3-(4-methoxyphenyl)-2-methyl-8-(1,3-oxazinan-3-ylmethyl)-4H-chromen-4-one (5d, n=2)—White solid (444 mg, 58%); mp 258–260°C; ^1H NMR (500 MHz, CDCl_3): δ 1.79–1.91 (m, 2H, 5''-CH₂), 2.31 (s, 2H, 2-CH₃), 2.96–3.06 (m, 2H, 4''-CH₂), 3.84 (s, 3H, 4'-OCH₃), 3.88–3.96 (m, 2H, 6''-CH₂), 4.28 (s, 2H, 8-CH₂), 4.40 (s, 2H, 2''-CH₂), 6.86 (d, 1H, 3J = 8.8 Hz, 6-H), 6.96 (d, 2H, 3J = 8.3 Hz, 3', 5'-H), 7.20 (d, 2H, 3J = 8.3 Hz, 2', 6'-H), 8.05 ppm (d, 1H, 3J = 8.8 Hz, 5-H); ^{13}C NMR (125 MHz, CDCl_3): δ 19.41 (2-CH₃), 22.31 (5''-C), 47.48 (4''-C), 49.43 (8-CH₂), 55.29 (4'-OCH₃), 67.84 (6''-C), 83.98 (2''-C), 106.59 (8-C), 113.88 (3', 5'-C), 115.17 (6-C), 116.33 (4a-C), 122.68 (1'-C), 125.38 (3-C), 126.84 (5-C), 131.58 (2', 6'-C), 154.89 (8a-C), 159.09 (2-C), 161.81 (4'-C), 163.23 (7-C), 176.44 ppm (4-C); IR (KBr): $\nu_{\max}$ 3432, 2958, 1651, 1606, 1400, 1261, 1213, 1140 cm^{-1} ; MS (CI): m/z (%) 412.1 (100, MH^+ -12). Anal. Calcd for $\text{C}_{22}\text{H}_{23}\text{NO}_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 68.99; H, 6.22; N, 3.89.

3-(3,4-Dimethoxyphenyl)-7-hydroxy-2-methyl-8-(1,3-oxazinan-3-ylmethyl)-4H-chromen-4-one (5e, n=2)—White solid (430 mg, 52%); mp 156–158°C; ^1H NMR (500 MHz, CDCl_3): δ 1.81–1.90 (m, 2H, 5''-CH₂), 2.33 (s, 3H, 2-CH₃), 2.99–3.06 (m, 2H, 4''-CH₂), 3.87–3.98 (m, 8H, 3', 4'-OCH₃, 6''-CH₂), 4.29 (s, 2H, 8-CH₂), 4.41 (s, 2H, 2''-CH₂), 6.79–6.74 (m, 2H, 2', 6'-H), 6.87 (d, 1H, $^3J = 8.9$ Hz, 6-H), 6.93 (d, 1H, $^3J = 9$ Hz, 5'-H), 8.06 ppm (d, 1H, $^3J = 8.9$ Hz, 5-H); ^{13}C NMR (125 MHz, CDCl_3): δ 19.39 (2-CH₃), 22.15 (5''-C), 47.10 (4''-C), 49.33 (8-CH₂), 55.87 (3', 4'-OCH₃), 67.70 (6''-C), 83.78 (2''-C), 106.21 (8-C), 111.23 (5'-C), 113.77 (2'-C), 115.19 (6-C), 116.22 (4a-C), 122.79 (6'-C), 122.85 (1'-C), 125.67 (3-C), 126.95 (5-C), 148.60, 148.77 (3', 4'-C), 154.92 (8a-C), 162.12 (2-C), 163.17 (7-C), 176.41 ppm (4-C); IR (KBr): ν_{max} 3429, 2931, 1635, 1601, 1512, 1410, 1259 cm^{-1} ; MS (CI): m/z (%) 400.2 (100, MH^+ -12). Anal. Calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_6$: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.40; H, 6.03; N, 3.58.

3-(4-Fluorophenyl)-7-hydroxy-2-methyl-8-(1,3-oxazinan-3-ylmethyl)-4H-chromen-4-one (5f, n=2)—White solid (496 mg, 67%); mp 141–143°C; ^1H NMR (400 MHz, CDCl_3): δ 1.78–1.90 (m, 2H, 5''-CH₂), 2.30 (s, 2H, 2-CH₃), 2.98–3.05 (m, 2H, 4''-CH₂), 3.87–3.94 (m, 2H, 6''-CH₂), 4.28 (s, 2H, 8-CH₂), 4.40 (s, 2H, 2''-CH₂), 6.86 (d, 1H, $^3J = 8.8$ Hz, 6-H), 7.06–7.15 (m, 2H, 3', 5'-H), 7.21–7.28 (m, 2H, 2', 6'-H), 8.04 ppm (d, 1H, $^3J = 8.8$ Hz, 5-H); ^{13}C NMR (125 MHz, CDCl_3): δ 19.32 (2-CH₃), 22.22 (5''-C), 47.40 (4''-C), 49.39 (8-CH₂), 67.78 (6''-C), 83.88 (2''-C), 106.60 (8-C), 115.30 (6-C), 116.27 (d, $^2J(\text{C},\text{F}) = 21.4$ Hz, 3', 5'-C), 116.14 (4a-C), 122.16 (3-C), 126.74 (5-C), 129.04 (d, $^4J(\text{C},\text{F}) = 3.0$ Hz, 1'-C), 132.16 (d, $^3J(\text{C},\text{F}) = 9.0$ Hz, 2', 6'-C), 154.85 (8a-C), 161.91 (2-C), 162.28 (d, $^1J(\text{C},\text{F}) = 246.8$ Hz, 4'-C), 163.37 (7-C), 176.13 ppm (4-C); ^{19}F NMR (376 MHz, CDCl_3): δ -115.07 ppm; IR (KBr): ν_{max} 3427, 2964, 1634, 1605, 1510, 1406 cm^{-1} ; MS (CI): m/z (%) 358.3 (100, MH^+ -12). Anal. Calcd for $\text{C}_{21}\text{H}_{20}\text{FNO}_4$: C, 68.28; H, 5.46; N, 3.79. Found: C, 68.57; H, 5.18; N, 3.94.

7-Hydroxy-3-(4-methoxyphenyl)-8-(1,3-oxazinan-3-ylmethyl)-2-(trifluoromethyl)-4H-chromen-4-one (5g, n=2)—White solid (419 mg, 48%); mp 128–130°C; ^1H NMR (500 MHz, CDCl_3): δ 1.79–1.89 (m, 2H, 5''-CH₂), 2.96–3.03 (m, 2H, 4''-CH₂), 3.85 (s, 3H, 4'-OCH₃), 3.87–3.94 (m, 2H, 6''-CH₂), 4.26 (s, 2H, 8-CH₂), 4.40 (s, 2H, 2''-CH₂), 6.91–7.00 (m, 3H, 6, 3', 5'-H), 7.18 (d, 2H, $^3J = 8.7$ Hz, 2', 6'-H), 8.05 ppm (d, 1H, $^3J = 8.7$ Hz, 5-H); ^{13}C NMR (125 MHz, CDCl_3): δ 22.40 (5''-C), 47.34 (4''-C), 49.56 (8-CH₂), 55.26 (4'-OCH₃), 67.75 (6''-C), 84.07 (2''-C), 107.01 (8-C), 113.73 (3', 5'-C), 116.09 (4a-C), 116.75 (6-C), 119.64 (q, $^3J(\text{C},\text{F}) = 276.3$ Hz, 2-CF₃), 121.05 (1'-C), 125.06 (3-C), 127.14 (5-C), 131.11 (2', 6'-C), 147.35 (q, $^3J(\text{C},\text{F}) = 39.5$ Hz, 2-C), 154.12 (8a-C), 159.97 (4'-C), 164.71 (7-C), 176.28 ppm (4-C); ^{19}F NMR (376 MHz, CDCl_3): δ -63.91 ppm; IR (KBr): ν_{max} 3432, 1651, 1610, 1516, 1295, 1192, 1140 cm^{-1} ; MS (CI): m/z (%) 424.2 (100, MH^+ -12). Anal. Calcd for $\text{C}_{22}\text{H}_{20}\text{F}_3\text{NO}_5$: C, 60.69; H, 4.63; N, 3.22. Found: C, 60.90; H, 4.58; N, 2.99.

3-(3,4-Dimethoxyphenyl)-7-hydroxy-8-(1,3-oxazinan-3-ylmethyl)-2-(trifluoromethyl)-4H-chromen-4-one (5h, n=2)—White solid (770 mg, 83%); mp 214–216°C; ^1H NMR (400 MHz, CDCl_3): δ 1.81–1.90 (m, 2H, 5''-CH₂), 2.97–3.04 (m, 2H, 4''-CH₂), 3.83–3.95 (m, 8H, 3', 4'-OCH₃, 6''-CH₂), 4.27 (s, 2H, 8-CH₂), 4.40 (s, 2H, 2''-CH₂), 6.86 (d, 1H, $^3J = 8.8$ Hz, 6-H), 7.06–7.15 (m, 2H, 3', 5'-H), 7.21–7.28 (m, 2H, 2', 6'-H), 8.04 ppm (d, 1H, $^3J = 8.8$ Hz, 5-H); ^{13}C NMR (125 MHz, CDCl_3): δ 19.32 (2-CH₃), 22.22 (5''-C), 47.40 (4''-C), 49.39 (8-CH₂), 67.78 (6''-C), 83.88 (2''-C), 106.60 (8-C), 115.30 (6-C), 116.27 (d, $^2J(\text{C},\text{F}) = 21.4$ Hz, 3', 5'-C), 116.14 (4a-C), 122.16 (3-C), 126.74 (5-C), 129.04 (d, $^4J(\text{C},\text{F}) = 3.0$ Hz, 1'-C), 132.16 (d, $^3J(\text{C},\text{F}) = 9.0$ Hz, 2', 6'-C), 154.85 (8a-C), 161.91 (2-C), 162.28 (d, $^1J(\text{C},\text{F}) = 246.8$ Hz, 4'-C), 163.37 (7-C), 176.13 ppm (4-C); ^{19}F NMR (376 MHz, CDCl_3): δ -115.07 ppm; IR (KBr): ν_{max} 3427, 2964, 1634, 1605, 1510, 1406 cm^{-1} ; MS (CI): m/z (%) 358.3 (100, MH^+ -12). Anal. Calcd for $\text{C}_{21}\text{H}_{20}\text{FNO}_4$: C, 68.28; H, 5.46; N, 3.79. Found: C, 68.57; H, 5.18; N, 3.94.

CH₂), 6.76–6.86 (m, 2H, 2', 6'-H), 6.91–6.97 (m, 2H, 6, 5'-H), 8.06 ppm (d, 1H, ³J = 8.8 Hz, 5-H); ¹³C NMR (125 MHz, CDCl₃): δ 22.24 (5''-C), 47.20 (4''-C), 49.38 (8-CH₂), 55.70 (3'-OCH₃), 55.72 (4'-OCH₃), 67.60 (6''-C), 83.88 (2''-C), 106.97 (8-C), 110.69 (5'-C), 112.97 (2'-C), 115.86 (4a-C), 116.62 (6-C), 119.46 (q, ¹J(C,F) = 276.4 Hz, 2-CF₃), 121.18 (1'-C), 122.41 (6'-C), 124.94 (3-C), 126.83 (5-C), 147.33 (q, ²J(C,F) = 36.0 Hz, 2-C), 148.44, 149.28 (3', 4'-C), 153.91 (8a-C), 164.63 (7-C), 176.13 ppm (4-C); ¹⁹F NMR (376 MHz, CDCl₃): δ –63.15 ppm; IR (KBr): ν_{max} 3435, 2931, 1647, 1606, 1261, 1219, 1140 cm⁻¹; MS (CI): *m/z* (%) 424.1 (100, MH⁺-12). Anal. Calcd for C₂₃H₂₂F₃NO₆: C, 59.39; H, 4.76; N, 3.01. Found: C, 59.11; H, 4.55; N, 2.87.

7-Hydroxy-8-[[[3-hydroxypropyl)amino]methyl]-3-(4-methoxyphenyl)-2-(trifluoromethyl)-4H-chromen-4-one (6g, n=2)—White solid (625 mg, 74%); mp 214–216°C; ¹H NMR (400 MHz, DMSO-d₆): δ 1.65–1.76 (m, 2H, 2''-CH₂), 2.77–2.93 (m, 2H, 1''-CH₂), 3.44–3.52 (m, 2H, 3''-CH₂), 3.80 (s, 3H, 4'-OCH₃), 4.13 (s, 2H, 8-CH₂), 6.59 (d, 1H, ³J = 8.8 Hz, 6-H), 6.98 (d, 2H, ³J = 8.5 Hz, 3', 5'-H), 7.15 (d, 2H, ³J = 8.5 Hz, 2', 6'-H), 7.68 ppm (d, 1H, ³J = 8.8 Hz, 5-H); ¹³C NMR (100 MHz, DMSO-d₆): δ 29.98 (2''-C), 42.74 (1''-C), 44.43 (8-CH₂), 55.05 (4'-OCH₃), 58.37 (3''-C), 104.82 (8-C), 109.94 (4a-C), 113.16 (3', 5'-C), 119.52 (6-C), 119.58 (q, ¹J(C,F) = 275.1 Hz, 2-CF₃), 121.71 (3-C), 123.97 (1'-C), 125.68 (5-C), 131.03 (2', 6'-C), 144.86 (q, ²J(C,F) = 34.6 Hz, 2-C), 154.72 (4'-C), 159.05 (8a-C), 172.68 (7-C), 173.91 ppm (4-C); ¹⁹F NMR (376 MHz, DMSO-d₆): δ –60.82 ppm; IR (KBr): ν_{max} 3423, 3075, 2925, 1641, 1599, 1282, 1180, 1144 cm⁻¹; MS (CI): *m/z* (%) 424.1 (100, MH⁺). Anal. Calcd for C₂₁H₂₀F₃NO₅: C, 59.57; H, 4.76; N, 3.31. Found: C, 59.91; H, 5.07; N, 3.12.

3-(4-Fluorophenyl)-7-hydroxy-8-[[[3-hydroxypropyl)amino]methyl]-2-(trifluoromethyl)-4H-chromen-4-one (6i, n=2)—White solid (536 mg, 65%); mp 211–213°C; ¹H NMR (400 MHz, CDCl₃): δ 1.65–1.79 (m, 2H, 2''-CH₂), 2.82–2.93 (m, 2H, 1''-CH₂), 3.44–3.53 (m, 2H, 3''-CH₂), 4.19 (s, 2H, 8-CH₂), 6.66 (d, 1H, ³J = 8.7 Hz, 6-H), 7.24–7.31 (m, 4H, 3-C₆H₄F), 7.73 ppm (d, 1H, ³J = 8.7 Hz, 5-H); ¹³C NMR (125 MHz, CDCl₃): δ 29.83 (2''-C), 42.67 (1''-C), 44.40 (8-CH₂), 58.32 (3''-C), 104.61 (8-C), 109.88 (4a-C), 114.65 (d, ²J(C,F) = 21.4 Hz, 3', 5'-C), 119.41 (q, ¹J(C,F) = 276.8 Hz, 2-CF₃), 119.59 (6-C), 123.32 (3-C), 125.70 (5-C), 126.15 (d, ⁴J(C,F) = 3.5 Hz, 1'-C), 131.93 (d, ³J(C,F) = 8.5 Hz, 2', 6'-C), 145.00 (q, ²J(C,F) = 34.4 Hz, 2-C), 154.74 (8a-C), 161.92 (d, ¹J(C,F) = 245.3 Hz, 4'-C), 172.73 (7-C), 173.57 ppm (4-C); ¹⁹F NMR (376 MHz, CDCl₃): δ –112.01, –60.92 ppm; IR (KBr): ν_{max} 3433, 3084, 1641, 1601, 1396, 1282, 1193, 1151 cm⁻¹; MS (CI): *m/z* (%) 412.1 (100, MH⁺). Anal. Calcd for C₂₀H₁₇F₄NO₄: C, 58.40; H, 4.17; N, 3.41. Found: C, 58.67; H, 4.03; N, 3.12.

Aminomethylation of 7-hydroxyisoflavones with either 4-amino-1-butanol or 5-amino-1-pentanol

A solution of 2 mmol of isoflavone **3a–3i**, 2.4 mmol of the appropriate ω-aminoalkan-1-ol, 2.4 mmol of paraformaldehyde, and 1–2 mg of 4-(N,N-dimethylamino)pyridine in 10 mL of isopropanol was refluxed for 4–6 h. The mixture was cooled and diluted with 40–60 mL of hexane. The precipitate was collected and recrystallized from a mixture of isopropanol and hexane.

9-(4-Hydroxybutyl)-3-(4-methoxyphenyl)-9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-one (4a, n=3)—White solid (625 mg, 82%); mp 145–147°C; ¹H NMR (400 MHz, CDCl₃): δ 1.67–1.75 (m, 4H, 2'', 3''-CH₂), 2.81 (t, 2H, ³J = 6.4 Hz, 1''-CH₂), 3.77 (t, 2H, ³J = 5.8 Hz, 4''-CH₂), 3.85 (s, 3H, 4'-OCH₃), 4.20 (s, 2H, 10-CH₂), 4.98 (s, 2H, 8-CH₂), 6.88 (d, 1H, ³J = 8.8 Hz, 6-H), 6.98 (d, 2H, ³J = 8.8 Hz, 3', 5'-H), 7.50 (d, 2H, ³J = 8.8 Hz, 2', 6'-H), 7.92 (s, 1H, 2-H), 8.09 ppm (d, 1H, ³J = 8.8 Hz, 5-H); ¹³C NMR (100 MHz, CDCl₃): δ 24.86 (2''-C), 30.69 (3''-C), 44.77 (1''-C), 51.56 (10-C), 55.29 (4'-OCH₃), 62.58 (4''-C), 82.84 (8-C), 107.35 (10a-C), 113.91 (3', 5'-C), 115.14 (6-C), 118.01 (4a-C), 124.05 (3-C), 124.92 (1'-C), 125.36 (5-C), 130.08 (2', 6'-C), 151.55 (2-C), 154.59 (10b-C), 158.33 (4'-C), 159.53 (6a-C), 175.86 ppm (4-C); IR (KBr): ν_{max} 3265, 2940, 1640, 1631, 1509, 1436, 1249, 1034 cm⁻¹; MS (CI): *m/z* (%) 370.2 (100, MH⁺-12). Anal. Calcd for C₂₂H₂₃NO₅: C, 69.28; H, 6.08; N, 3.67. Found: C, 68.93; H, 6.33; N, 3.94.

9-(4-Hydroxypentyl)-3-(4-methoxyphenyl)-9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-one (4a, n=4)—White solid (515 mg, 65.1%); mp 110–111 °C; ¹H NMR (400 MHz, CDCl₃): δ 1.40–1.50 (m, 2H, 3''-CH₂), 1.58–1.68 (m, 4H, 2'', 4''-CH₂), 2.77 (t, 2H, ³J = 6.4 Hz, 1''-CH₂), 3.77 (t, 2H, ³J = 6.4 Hz, 5''-CH₂), 3.85 (s, 3H, 4'-OCH₃), 4.18 (s, 2H, 10-CH₂), 4.97 (s, 2H, 8-CH₂), 6.87 (d, 1H, ³J = 8.9 Hz, 6-H), 6.98 (d, 2H, ³J = 8.5 Hz, 3', 5'-H), 7.50 (d, 2H, ³J = 8.5 Hz, 2', 6'-H), 7.93 (s, 1H, 2-H), 8.08 ppm (d, 1H, ³J = 8.9 Hz, 5-H); ¹³C NMR (125 MHz, CDCl₃): δ 23.26 (3''-C), 27.79 (2''-C), 32.43 (4''-C), 44.94 (1''-C), 51.60 (10-C), 55.30 (4'-OCH₃), 62.70 (5''-C), 83.14 (8-C), 107.60 (10a-C), 113.91 (3', 5'-C), 115.15 (6-C), 117.92 (4a-C), 124.11 (3-C), 124.89 (1'-C), 125.22 (5-C), 130.09 (2', 6'-C), 151.54 (2-C), 154.61 (10b-C), 158.55 (4'-C), 159.53 (6a-C), 175.89 ppm (4-C); IR (KBr): ν_{max} 3433, 2934, 1644, 1629, 1510, 1252, 1178, 1034, 823 cm⁻¹; MS (CI): *m/z* (%) 384.1 (100, MH⁺-12); Anal. Calcd for C₂₃H₂₅NO₅: C 69.86, H 6.37, N 3.54. Found: C 70.15, H 6.47, N 3.28.

3-(3,4-Dimethoxyphenyl)-9-(4-hydroxybutyl)-9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-one (4b, n=3)—White solid (684 mg, 83%); mp 132–133°C; ¹H NMR (400 MHz, CDCl₃): δ 1.45–1.57 (m, 4H, 2'', 3''-CH₂), 2.81 (t, 2H, ³J = 6.5 Hz, 1''-CH₂), 3.69 (t, 2H, ³J = 5.8 Hz, 4''-CH₂), 3.91 (s, 3H, 3'-OCH₃), 3.93 (s, 3H, 4'-OCH₃), 4.20 (s, 2H, 10-CH₂), 4.97 (s, 2H, 8-CH₂), 6.88 (d, 1H, ³J = 8.9 Hz, 6-H), 6.92 (d, 1H, ³J = 8.3 Hz, 5'-H), 7.04 (dd, 1H, ³J = 8.5 Hz, ⁴J = 2.0 Hz, 6'-H), 7.20 (d, 1H, ⁴J = 2.0 Hz, 2'-H), 7.95 (s, 1H, 2-H), 8.08 ppm (d, 1H, ³J = 8.9 Hz, 5-H); ¹³C NMR (100 MHz, CDCl₃): δ 24.92 (2''-C), 30.75 (3''-C), 44.87 (1''-C), 51.64 (10-C), 55.96 (3'-OCH₃), 55.98 (4'-OCH₃), 62.64 (4''-C), 82.90 (8-C), 107.37 (10a-C), 111.18 (5'-C), 112.55 (2'-C), 115.20 (6-C), 118.01 (4a-C), 120.98 (6'-C), 124.51 (1'-C), 124.98 (3-C), 125.29 (5-C), 148.72, 149.09 (3', 4'-C), 151.64 (2-C), 154.52 (10b-C), 158.37 (6a-C), 175.77 ppm (4-C); IR (KBr): ν_{max} 3262, 2936, 1640, 1627, 1517, 1434, 1250, 1145, 1028 cm⁻¹; MS (CI): *m/z* (%) 400.2 (100, MH⁺-12). Anal. Calcd for C₂₃H₂₅NO₆: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.42; H, 5.81; N, 3.70.

3-(3,4-Dimethoxyphenyl)-9-(4-hydroxypentyl)-9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-one (4b, n=4)—White solid (620 mg, 73%); mp 109–110°C; ¹H NMR (400 MHz, CDCl₃): δ 1.42–1.50 (m, 2H, 3''-CH₂), 1.58–1.69 (m, 4H, 2'',

4''-CH₂), 2.78 (t, 2H, ³J = 7.2 Hz, 1''-CH₂), 3.67 (t, 2H, ³J = 7.2 Hz, 5''-CH₂), 3.92 (s, 3H, 3'-OCH₃), 3.93 (s, 3H, 4'-OCH₃), 4.18 (s, 2H, 10-CH₂), 4.97 (s, 2H, 8-CH₂), 6.87 (d, 1H, ³J = 8.9 Hz, 6-H), 6.93 (d, 1H, ³J = 8.3 Hz, 5'-H), 7.05 (dd, 1H, ⁴J = 2.0 Hz, ³J = 8.3 Hz, 6'-H), 7.21 (d, 1H, ⁴J = 2.0 Hz, 2'-H), 7.96 (s, 1H, 2-H), 8.08 ppm (d, 1H, ³J = 8.9 Hz, 5-H); ¹³C NMR (125 MHz, CDCl₃): δ 23.24 (3''-C), 27.76 (2''-C), 32.40 (4''-C), 44.91 (1''-C), 51.59 (10-C), 55.87 (3'-OCH₃), 55.90 (4'-OCH₃), 62.68 (5''-C), 83.14 (8-C), 107.58 (10a-C), 111.06 (5'-C), 112.42 (2'-C), 115.22 (6-C), 117.87 (4a-C), 120.94 (6'-C), 124.52 (1'-C), 124.90 (3-C), 125.16 (5-C), 148.67, 149.02 (3', 4'-C), 151.70 (2-C), 154.56 (10b-C), 158.59 (6a-C), 175.89 ppm (4-C); IR (KBr): ν_{max} 3300, 2935, 1634, 1517, 1433, 1252, 1142, 1026 cm⁻¹; MS (CI): *m/z* (%) 414.3 (100, MH⁺-12). Anal. Calcd for C₂₄H₂₇NO₆: C, 67.75; H, 6.40; N, 3.29. Found: C, 68.01; H, 6.32; N, 3.03.

3-(4-Fluorophenyl)-9-(4-hydroxybutyl)-9,10-dihydro-4H,8H-chromeno[8,7-e][1,3]oxazin-4-one (4c, n=3)—White solid (576 mg, 78%); mp 113–115 °C; ¹H NMR (400 MHz, CDCl₃): δ 1.58–1.76 (m, 4H, 2'', 3''-CH₂), 2.82 (t, 2H, ³J = 6.5 Hz, 1''-CH₂), 3.70 (t, 2H, ³J = 5.6 Hz, 4''-CH₂), 4.20 (s, 2H, 10-CH₂), 4.98 (s, 2H, 8-CH₂), 6.88 (d, 1H, ³J = 9.0 Hz, 6-H), 6.89 (t, 2H, ³J(H,H) = 8.8 Hz, ³J(H,F) = 8.8 Hz, 3', 5'-H), 7.53 (dd, 2H, ³J(H,H) = 8.8 Hz, ⁴J(H,F) = 5.4 Hz, 2', 6'-H), 7.93 (s, 1H, 2-H), 8.08 ppm (d, 1H, ³J = 9.0 Hz, 5-H); ¹³C NMR (100 MHz, CDCl₃): δ 24.82 (2''-C), 30.63 (3''-C), 44.81 (1''-C), 51.60 (10-C), 62.56 (4''-C), 82.92 (8-C), 107.47 (10a-C), 115.35 (6-C), 115.39 (d, ²J(C,F) = 21.7 Hz, 3', 5'-C), 117.94 (4a-C), 124.47 (3-C), 125.31 (5-C), 127.74 (d, ⁴J(C,F) = 3.0 Hz, 1'-C), 130.66 (d, ³J(C,F) = 8.0 Hz, 2', 6'-C), 151.93 (2-C), 154.63 (10b-C), 158.59 (6a-C), 162.70 (d, ¹J(C,F) = 247.2 Hz, 4'-C), 175.57 ppm (4-C); ¹⁹F NMR (376 MHz, CDCl₃): δ -114.51 ppm; IR (KBr): ν_{max} 3348, 2939, 2863, 1647, 1511, 1433, 1246, 1224 cm⁻¹; MS (CI): *m/z* (%) 358.1 (100, MH⁺-12). Anal. Calcd for C₂₁H₂₀FNO₄: C, 68.28; H, 5.46; N, 3.79. Found: C, 68.47; H, 5.30; N, 4.07.

3-(4-Fluorophenyl)-9-(4-hydroxypentyl)-9,10-dihydro-4H,8H-chromeno[8,7-e][1,3]oxazin-4-one (4c, n=4)—White solid (402 mg, 52.4%); mp 97–98 °C; ¹H NMR (400 MHz, CDCl₃): δ 1.41–1.49 (m, 2H, 3''-CH₂), 1.59–1.68 (m, 4H, 2'', 4''-CH₂), 2.77 (t, 2H, ³J = 7.2 Hz, 1''-CH₂), 3.70 (t, 2H, ³J = 7.2 Hz, 5''-CH₂), 4.19 (s, 2H, 10-CH₂), 4.98 (s, 2H, 8-CH₂), 6.88 (d, 1H, ³J = 8.9 Hz, 6-H), 7.13 (t, 2H, ³J(H,H) = 8.8 Hz, ³J(H,F) = 8.8 Hz, 3', 5'-H), 7.53 (dd, 2H, ³J(H,H) = 8.8 Hz, ⁴J(H,F) = 5.5 Hz, 2', 6'-H), 7.94 (s, 1H, 2-H), 8.08 ppm (d, 1H, ³J = 8.9 Hz, 5-H); ¹³C NMR (125 MHz, CDCl₃): δ 23.28 (3''-C), 27.80 (2''-C), 32.43 (4''-C), 44.96 (1''-C), 51.65 (10-C), 62.71 (5''-C), 83.20 (8-C), 107.68 (10a-C), 115.37 (6-C), 115.40 (d, ²J(C,F) = 21.2 Hz, 3', 5'-C), 117.86 (4a-C), 124.46 (3-C), 125.23 (5-C), 127.80 (d, ⁴J(C,F) = 3.4 Hz, 1'-C), 130.66 (d, ³J(C,F) = 8.0 Hz, 2', 6'-C), 151.92 (2-C), 154.66 (10b-C), 158.78, (6a-C) 162.70 (d, ¹J(C,F) = 247.6 Hz, 4'-C), 175.60 ppm (4-C); ¹⁹F NMR (376 MHz, CDCl₃): δ -114.48 ppm; IR (KBr): ν_{max} 3475, 2936, 1634, 1435 1242, 1217 cm⁻¹; MS (CI): *m/z* (%) 372.1 (100, MH⁺-12); Anal. Calcd for C₂₂H₂₂FNO₄: C 68.92, H 5.78, N 3.65. Found: C 68.77, H 5.68, N 3.91.

9-(4-Hydroxybutyl)-3-(4-methoxyphenyl)-2-methyl-9,10-dihydro-4H,8H-chromeno[8,7-e][1,3]oxazin-4-one (4d, n=3)—White solid (377 mg, 48%); mp 122–123 °C; ¹H NMR (400 MHz, CDCl₃): δ 1.63–1.79 (m, 4H, 2'', 3''-CH₂), 2.31 (s, 3H, 2-

CH₃), 2.82 (t, 2H, ³J = 6.5 Hz, 1''-CH₂), 3.69 (t, 2H, ³J = 5.6 Hz, 4''-CH₂), 3.85 (s, 3H, 4'-OCH₃), 4.20 (s, 2H, 10-CH₂), 4.96 (s, 2H, 8-CH₂), 6.83 (d, 1H, ³J = 8.8 Hz, 6-H), 6.97 (d, 2H, ³J = 8.2 Hz, 3', 5'-H), 7.20 (d, 2H, ³J = 8.2 Hz, 2', 6'-H), 8.01 ppm (d, 1H, ³J = 8.8 Hz, 5-H); ¹³C NMR (100 MHz, CDCl₃): δ 19.36 (2-CH₃), 24.90 (2''-C), 30.71 (3''-C), 45.03 (1''-C), 51.64 (10-C), 55.24 (4'-OCH₃), 62.56 (4''-C), 82.66 (8-C), 107.01 (10a-C), 113.84 (3', 5'-C), 114.69 (6-C), 116.98 (4a-C), 123.03 (1'-C), 125.17 (3-C), 125.26 (5-C), 131.49 (2', 6'-C), 154.21 (10b-C), 158.15 (2-C), 159.07 (4'-C), 162.17 (6a-C), 176.45 ppm (4-C); IR (KBr): ν_{max} 3340, 2934, 2832, 1631, 1608, 1512, 1437, 1246, 1177 cm⁻¹; MS (CI): *m/z* (%) 384.1 (100, MH⁺-12). Anal. Calcd for C₂₃H₂₅NO₅: C, 69.86; H, 6.37; N, 3.54. Found: C, 70.14; H, 6.76; N, 3.28.

9-(4-Hydroxypentyl)-3-(4-methoxyphenyl)-2-methyl-9,10-dihydro-4H,8H-chromeno[8,7-e][1,3]oxazin-4-one (4d, n=4)—White solid (541 mg, 66%); mp 120–121°C; ¹H NMR (400 MHz, CDCl₃): δ 1.40–1.50 (m, 2H, 3''-CH₂), 1.57–1.70 (m, 4H, 2'', 4''-CH₂), 2.31 (s, 3H, 2-CH₃), 2.78 (t, 2H, ³J = 7.2 Hz, 1''-CH₂), 3.67 (t, 2H, ³J = 7.2 Hz, 5''-CH₂), 3.85 (s, 3H, 4'-OCH₃), 4.18 (s, 2H, 10-CH₂), 4.96 (s, 2H, 8-CH₂), 6.82 (d, 1H, ³J = 8.7 Hz, 6-H), 6.97 (d, 2H, ³J = 8.8 Hz, 3', 5'-H), 7.20 (d, 2H, ³J = 8.8 Hz, 2', 6'-H), 8.00 ppm (d, 1H, ³J = 8.7 Hz, 5-H); ¹³C NMR (125 MHz, CDCl₃): δ 19.38 (2-CH₃), 23.27 (3''-C), 27.81 (2''-C), 32.42 (4''-C), 45.11 (1''-C), 51.62 (10-C), 55.23 (4'-OCH₃), 62.70 (5''-C), 83.00 (8-C), 107.25 (10a-C), 113.81 (3', 5'-C), 114.68 (6-C), 116.85 (4a-C), 122.97 (1'-C), 125.14 (3-C), 125.22 (5-C), 131.50 (2', 6'-C), 154.21 (10b-C), 158.33 (2-C), 158.99 (4'-C), 162.08 (6a-C), 176.49 ppm (4-C); IR (KBr): ν_{max} 3455, 2939, 1636, 1612, 1512, 1406, 1243, 1029 cm⁻¹; MS (CI): *m/z* (%) 398.3 (100, MH⁺-12). Anal. Calcd for C₂₄H₂₇NO₅: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.21; H, 6.37; N, 3.68.

3-(3,4-Dimethoxyphenyl)-9-(4-hydroxybutyl)-2-methyl-9,10-dihydro-4H,8H-chromeno[8,7-e][1,3]oxazin-4-one (4e, n=3)—White solid (560 mg, 66%); mp 78–79°C; ¹H NMR (400 MHz, CDCl₃): δ 1.63–1.78 (m, 4H, 2'', 3''-CH₂), 2.32 (s, 3H, 2-CH₃), 2.82 (t, 2H, ³J = 6.4 Hz, 1''-CH₂), 3.69 (t, 2H, ³J = 6.7 Hz, 4''-CH₂), 3.88 (s, 3H, 3'-OCH₃), 3.92 (s, 3H, 4'-OCH₃), 4.20 (s, 2H, 10-CH₂), 4.96 (s, 2H, 8-CH₂), 6.78–6.87 (m, 3H, 6, 2', 6'-H), 6.93 (d, 1H, ³J = 8.9 Hz, 5'-H), 8.01 ppm (d, 1H, ³J = 8.5 Hz, 5-H); ¹³C NMR (125 MHz, CDCl₃): δ 19.38 (2-CH₃), 24.88 (2''-C), 30.69 (3''-C), 44.96 (1''-C), 51.59 (10-C), 55.82 (3'-OCH₃), 55.83 (4'-OCH₃), 62.52 (4''-C), 82.67 (8-C), 106.99 (10a-C), 111.12 (5'-C), 113.60 (2'-C), 114.72 (6-C), 116.91 (4a-C), 122.72 (6'-C), 123.20 (1'-C), 125.21 (5-C), 125.56 (3-C), 148.54, 148.70 (3', 4'-C), 154.19 (10b-C), 158.16 (2-C), 162.36 (6a-C), 176.46 (4-C) ppm; IR (KBr): ν_{max} 3433, 2934, 2836, 1634, 1607, 1516, 1252, 1170 cm⁻¹; MS (CI): *m/z* (%) 414.2 (100, MH⁺-12). Anal. Calcd for C₂₄H₂₇NO₆: C, 67.75; H, 6.40; N, 3.29. Found: C, 68.03; H, 6.37; N, 3.68.

3-(3,4-Fimethoxyphenyl)-9-(4-hydroxypentyl)-2-methyl-9,10-dihydro-4H,8H-chromeno[8,7-e][1,3]oxazin-4-one (4e, n=4)—White solid (676 mg, 77%); mp 160–161°C; ¹H NMR (400 MHz, CDCl₃): δ 1.41–1.51 (m, 2H, 3''-CH₂), 1.58–1.70 (m, 4H, 2'', 4''-CH₂), 2.32 (s, 3H, 2-CH₃), 2.78 (t, 2H, ³J = 7.2 Hz, 1''-CH₂), 3.67 (t, 2H, ³J = 7.2 Hz, 5''-CH₂), 3.88 (s, 3H, 3'-OCH₃), 3.92 (s, 3H, 4'-OCH₃), 4.18 (s, 2H, 10-CH₂), 4.96 (s, 2H, 8-CH₂), 6.79–6.85 (m, 3H, 6, 2', 6'-H), 6.93 (d, 1H, ³J = 8.8 Hz, 5'-H), 8.00 ppm (d, 1H, ³J

= 8.9 Hz, 5-H); ^{13}C NMR (125 MHz, CDCl_3): δ 19.42 (2- CH_3), 23.27 (3''-C), 27.80 (2''-C), 32.40 (4''-C), 45.08 (1''-C), 51.62 (10-C), 55.83 (3'-OCH₃), 55.85 (4'-OCH₃) 65.68 (5''-C), 83.02 (8-C), 107.25 (10a-C), 111.09 (5'-C), 113.56 (2'-C), 114.73 (6-C), 116.83 (4a-C), 122.73 (6'-C), 123.17 (1'-C), 125.11 (5-C), 125.64 (3-C), 148.51, 148.8 (3', 4'-C), 154.21 (10b-C), 158.38 (2-C), 162.28 (6a-C), 176.47 ppm (4-C); IR (KBr): ν_{max} 3501, 2934, 1628, 1516, 1433, 1251, 1177, 1139 cm^{-1} ; MS (CI): m/z (%) 428.2 (100, MH^+ -12). Anal. Calcd for $\text{C}_{25}\text{H}_{29}\text{NO}_6$: C, 68.32; H, 6.65; N, 3.19. Found: C, 68.07; H, 6.57; N, 3.28.

3-(4-Fluorophenyl)-9-(4-hydroxybutyl)-2-methyl-9,10-dihydro-4H,8H-

chromeno[8,7-e][1,3]oxazin-4-one (4f, n=3)—White solid (710 mg, 93%); mp 149–151°C; ^1H NMR (400 MHz, CDCl_3): δ 1.60–1.77 (m, 4H, 2'', 3''-CH₂), 2.30 (s, 3H, 2-CH₃), 2.82 (t, 2H, 3J = 6.4 Hz, 1''-CH₂), 3.69 (t, 2H, 3J = 5.5 Hz, 4''-CH₂), 4.20 (s, 2H, 10-CH₂), 4.97 (s, 2H, 8-CH₂), 6.84 (d, 1H, 3J = 8.8 Hz, 6-H), 7.12 (t, 2H, $^3J(\text{H,H})$ = 8.8 Hz, $^3J(\text{H,F})$ = 8.8 Hz, 3', 5'-H), 7.25 (dd, 2H, $^3J(\text{H,H})$ = 8.8 Hz, $^4J(\text{H,F})$ = 5.4 Hz, 2', 6'-H), 8.00 ppm (d, 1H, 3J = 8.8 Hz, 5-H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.33 (2-CH₃), 24.90 (2''-C), 30.69 (3''-C), 44.99 (1''-C), 51.64 (10-C), 62.54 (4''-C), 82.74 (8-C), 107.11 (10a-C), 114.87 (6-C), 115.31 (d, $^2J(\text{C,F})$ = 21.4 Hz, 3', 5'-C), 116.84 (4a-C), 122.55 (3-C), 125.20 (5-C), 128.91 (d, $^4J(\text{C,F})$ = 3.4 Hz, 1'-C), 132.10 (d, $^3J(\text{C,F})$ = 8.4 Hz, 2', 6'-C), 154.23 (10b-C), 158.35 (2-C), 162.30 (d, $^1J(\text{C,F})$ = 247.6 Hz, 4'-C), 162.31 (6a-C), 176.21 ppm (4-C); ^{19}F NMR (376 MHz, CDCl_3): δ -115.20 ppm; IR (KBr): ν_{max} 3459, 2933, 2856, 1633, 1602, 1511, 1438, 1252, 1219 cm^{-1} ; MS (CI): m/z (%) 372.1 (100, MH^+ -12). Anal. Calcd for $\text{C}_{22}\text{H}_{22}\text{FNO}_4$: C, 68.92; H, 5.78; N, 3.65. Found: C, 69.21; H, 5.49; N, 3.91.

3-(4-Fluorophenyl)-9-(4-hydroxypentyl)-2-methyl-9,10-dihydro-4H,8H-

chromeno[8,7-e][1,3]oxazin-4-one (4f, n=4)—White solid (690 mg, 87%); mp 112–113°C; ^1H NMR (400 MHz, CDCl_3): δ 1.40–1.50 (m, 2H, 3''-CH₂), 1.58–1.70 (m, 4H, 2'', 4''-CH₂), 2.30 (s, 3H, 2-CH₃), 2.77 (t, 2H, 3J = 7.2 Hz, 1''-CH₂), 3.65 (t, 2H, 3J = 7.2 Hz, 5''-CH₂), 4.18 (s, 2H, 10-CH₂), 4.96 (s, 2H, 8-CH₂), 6.83 (d, 1H, 3J = 8.8 Hz, 6-H), 7.12 (t, 2H, $^3J(\text{H,H})$ = 8.3 Hz, $^3J(\text{H,F})$ = 8.3 Hz, 3', 5'-H), 7.26 (dd, 2H, $^3J(\text{H,H})$ = 8.3 Hz, $^4J(\text{H,F})$ = 5.5 Hz, 2', 6'-H), 7.99 ppm (d, 1H, 3J = 8.8 Hz, 5-H); ^{13}C NMR (125 MHz, CDCl_3): δ 19.34 (2-CH₃), 23.26 (3''-C), 27.78 (2''-C), 32.37 (4''-C), 45.05 (1''-C), 51.61 (10-C), 62.59 (5''-C), 83.02 (8-C), 107.30 (10a-C), 114.88 (6-C), 115.30 (d, $^2J(\text{C,F})$ = 21.2 Hz, 3', 5'-C), 116.68 (4a-C), 122.46 (3-C), 125.05 (5-C), 128.91 (d, $^4J(\text{C,F})$ = 3.2 Hz, 1'-C), 132.08 (d, $^3J(\text{C,F})$ = 8.0 Hz, 2', 6'-C), 154.22 (10b-C), 158.52 (2-C), 162.25 (d, $^1J(\text{C,F})$ = 246.2 Hz, 4'-C), 162.30 (6a-C), 176.26 ppm (4-C); ^{19}F NMR (376 MHz, CDCl_3): δ -114.95 ppm; IR (KBr): ν_{max} 3505, 2936, 1632, 1510, 1434, 1252, 1222 cm^{-1} ; MS (CI): m/z (%) 386.1 (100, MH^+ -12). Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{FNO}_4$: C, 69.51; H, 6.09; N, 3.52. Found: C, 69.57; H, 5.89; N, 3.81.

9-(4-Hydroxypentyl)-3-(4-methoxyphenyl)-2-(trifluoromethyl)-9,10-dihydro-4H,8H-chromeno[8,7-e][1,3]oxazin-4-one (4g, n=4)—White solid (380 mg, 41%); mp

114–115°C; ^1H NMR (400 MHz, CDCl_3): δ 1.41–1.50 (m, 2H, 3''-CH₂), 1.56–1.69 (m, 4H, 2'', 4''-CH₂), 2.79 (t, 2H, 3J = 6.8 Hz, 1''-CH₂), 3.68 (t, 2H, 3J = 6.8 Hz, 5''-CH₂), 3.86 (s, 3H, 4'-OCH₃), 4.20 (s, 2H, 10-CH₂), 5.00 (s, 2H, 8-CH₂), 6.91 (d, 1H, 3J = 8.9 Hz, 6-H), 6.97 (d, 2H, 3J = 8.7 Hz, 3', 5'-H), 7.19 (d, 2H, 3J = 8.7 Hz, 2', 6'-H), 8.00 ppm (d, 1H, 3J

= 8.9 Hz, 5-H); ^{13}C NMR (125 MHz, CDCl_3): δ 23.26 (3''-C), 27.76 (2''-C), 32.40 (4''-C), 44.80 (1''-C), 51.66 (10-C), 55.22 (4'-OCH₃), 62.73 (5''-C), 83.38 (8-C), 107.89 (10a-C), 113.68 (3', 5'-C), 116.25 (6-C), 116.63 (4a-C), 119.51 (q, $^1J(\text{C},\text{F}) = 277.0$ Hz, 2-CF₃), 120.93 (3, 1'-C), 125.34 (5-C), 131.05 (2', 6'-C), 147.56 (q, $^2J(\text{C},\text{F}) = 35.0$ Hz, 2-C), 153.47 (10b-C), 159.77 (4'-C), 159.89 (6a-C), 176.40 ppm (4-C); ^{19}F NMR (376 MHz, DMSO-d₆): δ -63.93 ppm; IR (KBr): ν_{max} 3517, 2943, 1646, 1606, 1580, 1430, 1249, 1154, 1026 cm^{-1} ; MS (CI): m/z (%) 452.3 (100, MH^+ -12). Anal. Calcd for $\text{C}_{24}\text{H}_{24}\text{F}_3\text{NO}_5$: C, 62.20; H, 5.22; N, 3.02. Found: C, 62.12; H, 5.39; N, 2.87.

3-(3,4-Dimethoxyphenyl)-9-(4-hydroxybutyl)-2-(trifluoromethyl)-9,10-dihydro-4H,8H-chromeno[8,7-e][1,3]oxazin-4-one (4h, n=3)—White solid (340 mg, 36%); mp 154–156°C; ^1H NMR (400 MHz, CDCl_3): δ 1.63–1.78 (m, 4H, 2'', 3''-CH₂), 2.82 (t, 2H, $^3J = 6.2$ Hz, 1''-CH₂), 3.71 (t, 2H, $^3J = 5.6$ Hz, 4''-CH₂), 3.88 (s, 3H, 3'-OCH₃), 3.93 (s, 3H, 4'-OCH₃), 4.22 (s, 2H, 10-CH₂), 5.00 (s, 2H, 8-CH₂), 6.76–6.85 (m, 2H, 2', 6'-H), 6.90–6.98 (m, 2H, 6, 5'-H), 8.02 ppm (d, 1H, $^3J = 9.0$ Hz, 5-H); ^{13}C NMR (125 MHz, CDCl_3): δ 24.76 (2''-C), 30.58 (3''-C), 44.73 (1''-C), 51.63 (10-C), 55.81 (3'-OCH₃), 55.84 (4'-OCH₃), 62.58 (4''-C), 83.07 (8-C), 107.69 (10a-C), 110.81 (5'-C), 113.04 (2'-C), 116.29 (6-C), 116.74 (4a-C), 119.47 (q, $^1J(\text{C},\text{F}) = 277.7$ Hz, 2-CF₃), 121.17 (3-C), 122.50 (1'-C), 125.51 (6'-C), 125.44 (5-C), 147.73 (q, $^2J(\text{C},\text{F}) = 35.9$ Hz, 2-C), 148.57, 149.44 (3', 4'-C), 153.44 (10b-C), 159.59 (6a-C), 176.32 ppm (4-C); ^{19}F NMR (376 MHz, CDCl_3): δ -64.32 ppm; IR (KBr): ν_{max} 3542, 2947, 1653, 1614, 1518, 1117, 1189, 1132 cm^{-1} ; MS (CI): m/z (%) 468.2 (100, MH^+ -12). Anal. Calcd for $\text{C}_{24}\text{H}_{24}\text{F}_3\text{NO}_6$: C, 60.12; H, 5.05; N, 2.92. Found: C, 60.27; H, 5.32; N, 3.17.

3-(3,4-Dimethoxyphenyl)-9-(4-hydroxypentyl)-2-(trifluoromethyl)-9,10-dihydro-4H,8H-chromeno[8,7-e][1,3]oxazin-4-one (4h, n=4)—White solid (816 mg, 83%); mp 164–166°C; ^1H NMR (400 MHz, CDCl_3): δ 1.41–1.51 (m, 2H, 3''-CH₂), 1.57–1.69 (m, 4H, 2'', 4''-CH₂), 2.78 (t, 2H, $^3J = 7.4$ Hz, 1''-CH₂), 3.68 (t, 2H, $^3J = 7.4$ Hz, 5''-CH₂), 3.88 (s, 3H, 3'-OCH₃), 3.93 (s, 3H, 4'-OCH₃), 4.20 (s, 2H, 10-CH₂), 5.00 (s, 2H, 8-CH₂), 6.78 (d, 1H, $^4J = 1.8$ Hz, 2'-H), 6.83 (dd, 1H, $^3J = 8.3$ Hz, $^4J = 1.8$ Hz, 6'-H), 6.91 (d, 1H, $^3J = 8.8$ Hz, 6-H), 6.94 (d, 1H, $^3J = 8.3$ Hz, 5'-H), 8.03 ppm (d, 1H, $^3J = 8.8$ Hz, 5-H); ^{13}C NMR (125 MHz, CDCl_3): δ 23.23 (3''-C), 27.73 (2''-C), 32.37 (4''-C), 44.76 (1''-C), 51.63 (10-C), 55.77 (3'-OCH₃), 55.81 (4'-OCH₃), 62.68 (5''-C), 83.37 (8-C), 107.86 (10a-C), 110.75 (5'-C), 112.96 (2'-C), 116.28 (6-C), 116.60 (6'-C), 119.46 (q, $^1J(\text{C},\text{F}) = 276.0$ Hz, 2-CF₃), 121.18 (4a-C), 122.47 (1'-C), 125.30 (5-C), 125.36 (3'-C), 147.68 (q, $^2J(\text{C},\text{F}) = 35.6$ Hz, 2-C), 148.52, 149.37 (3', 4'-C), 153.43 (10b-C), 159.75 (6a-C), 176.34 ppm (4-C); ^{19}F NMR (376 MHz, CDCl_3): δ -64.30 ppm; IR (KBr): ν_{max} 3542, 2935, 1658, 1612, 1518, 1266, 1215, 1139, 1027 cm^{-1} ; MS (CI): m/z (%) 482.2 (100, MH^+ -12). Anal. Calcd for $\text{C}_{25}\text{H}_{26}\text{F}_3\text{NO}_6$: C, 60.85; H, 5.31; N, 2.84. Found: C, 61.04; H, 5.57; N, 2.68.

3-(4-Fluorophenyl)-9-(4-hydroxybutyl)-2-(trifluoromethyl)-9,10-dihydro-4H,8H-chromeno[8,7-e][1,3]oxazin-4-one (4i, n=3)—White solid (460 mg, 53%); mp 137–139°C; ^1H NMR (400 MHz, CDCl_3): δ 1.63–1.78 (m, 4H, 2'', 3''-CH₂), 2.83 (t, 2H, $^3J = 6.2$ Hz, 1''-CH₂), 3.70 (t, 2H, $^3J = 5.6$ Hz, 4''-CH₂), 4.22 (s, 2H, 10-CH₂), 5.01 (s, 2H, 8-

CH₂), 6.93 (d, 1H, ³J = 8.8 Hz, 6-H), 7.14 (t, 2H, ³J(H,H) = 8.6 Hz, ³J(H,F) = 8.6 Hz, 3', 5'-H), 7.24 (t, 2H, ³J(H,H) = 8.6 Hz, ⁴J(H,F) = 5.2 Hz, 2', 6'-H), 8.00 ppm (d, 1H, ³J = 8.8 Hz, 5-H); ¹³C NMR (125 MHz, CDCl₃): δ 24.75 (2''-C), 30.56 (3''-C), 44.74 (1''-C), 51.65 (10-C), 62.58 (4''-C), 83.11 (8-C), 107.78 (10a-C), 115.35 (d, ²J(C,F) = 21.7 Hz, 3', 5'-C), 116.46 (6-C), 116.67 (4a-C), 119.33 (q, ¹J(C,F) = 276.6 Hz, 2-CF₃), 124.73 (3-C), 124.80 (d, ⁴J(C,F) = 3.5 Hz, 1'-C), 125.42 (5-C), 131.66 (d, ³J(C,F) = 8.4 Hz, 2', 6'-C), 147.87 (q, ²J(C,F) = 36.6 Hz, 2-C), 153.48 (10b-C), 159.75 (6a-C), 163.02 (d, ¹J(C,F) = 248.3 Hz, 4'-C), 176.02 ppm (4-C); ¹⁹F NMR (376 MHz, CDCl₃): δ -113.51, -64.30 ppm; IR (KBr): ν_{max} 3410, 2944, 2867, 1658, 1611, 1514, 1435, 1216, 1196, 1142 cm⁻¹; MS (CI): *m/z* (%) 426.1 (100, MH⁺-12). Anal. Calcd for C₂₂H₁₉F₄NO₄: C, 60.41; H, 4.38; N, 3.20. Found: C, 60.65; H, 4.71; N, 2.95.

3-(4-Fluorophenyl)-9-(4-hydroxypentyl)-2-(trifluoromethyl)-9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-one (4i, n=4)—White solid (510 mg, 57%); mp 89–90°C; ¹H NMR (400 MHz, CDCl₃): δ 1.41–1.51 (m, 2H, 3''-CH₂), 1.58–1.69 (m, 4H, 2'', 4''-CH₂), 2.78 (t, 2H, ³J = 7.2 Hz, 1''-CH₂), 3.67 (t, 2H, ³J = 7.2 Hz, 5''-CH₂), 4.20 (s, 2H, 10-CH₂), 5.00 (s, 2H, 8-CH₂), 6.92 (d, 1H, ³J = 8.7 Hz, 6-H), 7.14 (t, 2H, ³J(H,H) = 8.6 Hz, ³J(H,F) = 8.6 Hz, 3', 5'-H), 7.25 (t, 2H, ³J(H,H) = 8.6 Hz, ⁴J(H,F) = 5.3 Hz, 2', 6'-H), 8.00 ppm (d, 1H, ³J = 8.7 Hz, 5-H); ¹³C NMR (125 MHz, CDCl₃): δ 23.26 (3''-C), 27.75 (2''-C), 32.39 (4''-C), 44.78 (1''-C), 51.66 (10-C), 62.70 (5''-C), 83.42 (8-C), 107.95 (10a-C), 115.34 (d, ²J(C,F) = 21.8 Hz, 3', 5'-C), 116.46 (6-C), 116.55 (4a-C), 119.35 (q, ¹J(C,F) = 276.8 Hz, 2-CF₃), 124.65 (3-C), 124.83 (d, ⁴J(C,F) = 3.5 Hz, 1'-C), 125.31 (5-C), 131.66 (d, ³J(C,F) = 8.0 Hz, 2', 6'-C), 147.82 (q, ²J(C,F) = 34.4 Hz, 2-C), 153.48 (10b-C), 159.93 (6a-C), 163.00 (d, ¹J(C,F) = 248.0 Hz, 4'-C), 176.05 ppm (4-C); ¹⁹F NMR (376 MHz, CDCl₃): δ -113.47, -64.25 ppm; IR (KBr): ν_{max} 3365, 2936, 1656, 1611, 1512, 1437, 1219, 1138 cm⁻¹; MS (CI): *m/z* (%) 440.1 (100, MH⁺-12). Anal. Calcd for C₂₃H₂₁F₄NO₄: C, 61.20; H, 4.69; N, 3.10. Found: C, 61.23; H, 4.87; N, 3.15.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Ismail IS, Nagakura Y, Hirasawa Y, Hosoya T, Lazim MIM, Lajis NH, Shiro M, Morita H. *J Nat Prod*. 2009; 72:1879–1883. [PubMed: 19757855]
2. Zhai S, Senderowicz AM, Sausville EA, Figg WD. *Ann Pharmacother*. 2002; 36:905–911. [PubMed: 11978170]
3. Liu T, Xu Z, He Q, Chen Y, Yang B, Hu Y. *Bioorg Med Chem Lett*. 2007; 17:278–281. [PubMed: 17085048]
4. Nguyen TB, Lozach O, Surpateanu G, Wang Q, Retailleau P, Iorga BI, Meijer L, Guéritte F. *J Med Chem*. 2012; 55:2811–2819. [PubMed: 22352892]

5. Zhang W, Sviripa V, Chen X, Shi J, Yu T, Hamza A, Ward ND, Kril LM, Vander Kooi CW, Zhan CG, Evers BM, Watt DS, Liu C. *ACS Chem Biol*. 2013; 8:796–803. [PubMed: 23363077]
6. Tramontini M, Angiolini L. *Tetrahedron*. 1990; 46:1791–1837.
7. Tramontini, M., Angiolini, L. *Mannich Bases: Chemistry and Uses*. CRC Press; Boca Raton: 1994.
8. Bruson HA. *J Am Chem Soc*. 1936; 58:1741–1744.
9. Kingsbury WD, Boehm JC, Jakas DR, Holden KG, Hecht SM, Gallagher G, Caranfa MJ, McCabe FL, Faucette LF, Johnson RK, Hertzberg RP. *J Med Chem*. 1991; 34:98–107. [PubMed: 1846923]
10. Johnson AL, Davidson MG, Perez Y, Jones MD, Merle N, Raithby PR, Richards SP. *Dalton transactions*. 2009:5551–5558. [PubMed: 19587999]
11. Wu JQ, Mu JS, Zhang SW, Li YS. *J Polym Sci Part A: Polym Chem*. 2010; 48:1122–1132.
12. Tan, X-w, Wang, B-m, Wang, Y., Zhan, S-z. *Inorg Chem Commun*. 2010; 13:1061–1063.
13. Burke WJ, Hammer CR, Weatherbee C. *J Org Chem*. 1961; 26:4403–4407.
14. Woodgate PD, Horner GM, Maynard NP, Rickard CEF. *J Organometallic Chem*. 1999; 592:180–193.
15. Schmidt C, Straub T, Falàbu D, Paulus Erich F, Wegelius E, Kolehmainen E, Böhmer V, Rissanen K, Vogt W. *Eur J Org Chem*. 2000; 2000:3937–3944.
16. Iwanek W, Wolff C, Mattay J. *Tetrahedron Lett*. 1995; 36:8969–8972.
17. Isanbor C, O'Hagan D. *J Fluor Chem*. 2006; 127:303–319.
18. Kirk KL. *J Fluor Chem*. 2006; 127:1013–1029.
19. O'Hagan D. *J Fluor Chem*. 2010; 131:1071–1081.
20. Sacquet MC, Fargeau-Bellassoued MC, Graffe B. *J Heterocycl Chem*. 1991; 28:667–672.
21. Bondarenko SP, Frasinuk MS, Khilya VP. *Chem Nat Compd*. 2003; 39:344–348.
22. Gao H, Nishioka T, Kawabata J, Kasai T. *Biosci Biotech Biochem*. 2004; 68:369–375.
23. Chen L, Hu TS, Zhu J, Wu H, Yao ZJ. *Synlett*. 2006; 2006:1225–1229.
24. Ragab FA, Hassan GS, Yossef HA, Hashem HA. *Eur J Med Chem*. 2007; 42:1117–1127. [PubMed: 17346862]
25. Bondarenko SP, Frasinuk MS, Khilya VP. *Chem Heterocycl Compd*. 2010; 46:146–150.
26. Lee KY, Nam DH, Moon CS, Seo SH, Lee JY, Lee YS. *Eur J Med Chem*. 2006; 41:991–996. [PubMed: 16762460]
27. Panja SK, Maiti S, Drew MGB, Bandyopadhyay C. *Tetrahedron*. 2009; 65:1276–1280.
28. Lee C, Lee JM, Lee NR, Kim DE, Jeong YJ, Chong Y. *Bioorg Med Chem Lett*. 2009; 19:4538–4541. [PubMed: 19625187]
29. Nam DH, Lee KY, Moon CS, Lee YS. *Eur J Med Chem*. 2010; 45:4288–4292. [PubMed: 20630626]
30. Mouysset G, Payard M, Grassy G, Tronche P, Dabire H, Mouille P, Schmitt H. *Eur J Med Chem*. 1987; 22:539–544.
31. Baziard-Mouysset G, Younes S, Labssita Y, Payard M, Caignard DH, Rettori MC, Renard P, Pfeiffer B, Guardiola-Lemaitre B. *Eur J Med Chem*. 1998; 33:339–347.
32. Cavalli A, Bisi A, Bertucci C, Rosini C, Paluszczak A, Gobbi S, Giorgio E, Rampa A, Belluti F, Piazzzi L, Valenti P, Hartmann RW, Recanatini M. *J Med Chem*. 2005; 48:7282–7289. [PubMed: 16279787]
33. Gobbi S, Cavalli A, Rampa A, Belluti F, Piazzzi L, Paluszczak A, Hartmann RW, Recanatini M, Bisi A. *J Med Chem*. 2006; 49:4777–4780. [PubMed: 16854084]
34. Hasan SM, Alam MM, Husain A, Khanna S, Akhtar M, Zaman MS. *Eur J Med Chem*. 2009; 44:4896–4903. [PubMed: 19713009]
35. Park HR, Park KS, Chong Y. *Bioorg Med Chem Lett*. 2011; 21:3202–3205. [PubMed: 21543225]
36. Chen Y, Cheng M, Liu FQ, Xia P, Qian K, Yu D, Xia Y, Yang ZY, Chen CH, Morris-Natschke SL, Lee KH. *Eur J Med Chem*. 2011; 46:4924–4936. [PubMed: 21864952]
37. Fairhurst RA, Heaney H, Papageorgiou G, Wilkins RF, Eyley SC. *Tetrahedron Lett*. 1989; 30:1433–1436.
38. Fenton DE, Papageorgiou G. *Tetrahedron*. 1996; 52:5913–5928.

39. Heaney H, Papageorgiou G, Wilkins RF. *Tetrahedron*. 1997; 53:14381–14396.
40. Fabris F, Lucchi OD, Delogu G, Fabbri D. *Synth Commun*. 1999; 29:2007–2012.
41. Astudillo MEA, Chokotho NCJ, Jarvis TC, Johnson CD, Lewis CC, McDonnell PD. *Tetrahedron*. 1985; 41:5919–5928.
42. Fulop F, Pihlaja K, Mattinen J, Bernath G. *J Org Chem*. 1987; 52:3821–3825.
43. Fülöp F, Dahlqvist M, Pihlaja K. *Acta Chem Scand*. 1991; 45:273–275.
44. Fülöp F, Forró E, Bernáth G, Miskolczi I, Vainiotalo P, Martinsen A. *J Heterocycl Chem*. 1997; 34:289–293.
45. Lázár L, Fülöp F. *Eur J Org Chem*. 2003; 2003:3025–3042.
46. Palkó M, Hetényi A, Fülöp F. *J Heterocycl Chem*. 2004; 41:69–75.
47. Tóth D, Szatmári I, Fülöp F. *Eur J Org Chem*. 2006; 2006:4664–4669.
48. Pihlaja K, Juhász M, Kivelä H, Fülöp F. *Rapid Commun Mass Spectrom*. 2008; 22:1510–1518. [PubMed: 18425798]
49. Lambert JB, Majchrzak MW. *J Am Chem Soc*. 1980; 102:3588–3591.
50. Xiang H, Zhao W, Xiao H, Qian L, Yao Y, Li XB, Liao QJ. *Bioorg Med Chem*. 2010; 18:3036–3042. [PubMed: 20392645]
51. Goto H, Terao Y, Akai S. *Chem Pharm Bull*. 2009; 57:346–360. [PubMed: 19336928]
52. Yeap GY, Yam WS, Dominiak P, Ito MM. *J Mol Struct*. 2010; 967:25–33.
53. Gao GY, Li DJ, Keung WM. *Bioorg Med Chem*. 2003; 11:4069–4081. [PubMed: 12927869]
54. Kukla AS, Seshadri TR. *Indian J Chem*. 1963; 1:343–345.
55. Salas-Coronado R, Gálvez-Ruiz JC, Guadarrama-Pérez C, Flores-Parra A. *Heterocycles*. 2003; 60:1123–1132.
56. Kukharev BF, Stankevich VK, Lobanova NA, Klimenko GR, Sadykov EK. *Russ J Org Chem*. 2007; 43:1027–1029.
57. Kykharev BF, Stankevich VK, Klimenko GR, Baranov AN, Baiborodin BA, Malinovich GI, Timofeeva SS. *Russ J Appl Chem*. 1993; 66:1305–1306.

rohitukine (**1a**) R = Hchrotacumine B (**1b**) R = COC(Me)=CHMechrotacumine C (**1c**) R = COC₆H₂(OMe)_{3-3,4,5}chrotacumine D (**1d**) R = COC₆H₃(OMe)_{2-3,4} chrotacumine A (**2**)

Figure 1.
Chemical structures of chromone alkaloids.

Figure 2.
Structures of isoflavones **3** studied in Mannich reactions.

Figure 3. ¹H NMR analysis of isoflavone tautomers

Panel A: structures of isoflavones **4b**, $n=1$ and **5b**, $n=1$. Panel B: ¹H NMR spectra (400 MHz) in CDCl₃. Panel C: ¹H NMR spectra (400 MHz) in DMSO-d₆. Panel D: ¹H NMR spectra (400 MHz) in CD₃OD.

Figure 4. 2D NOESY spectrum of **4b**, $n=1$ and **5b**, $n=1$. Measured at 400 MHz, CDCl_3 , 25°C. Black peaks are normal NOE, red peaks are chemical exchange NOE. Arrows show cross-peaks between pairs of exchanging protons.

Figure 5. ^1H NMR spectra of tautomers **4b**, **n=1 5b**, and **n=1**

Panel A: DMSO- d_6 , 20 C; Panel B: DMSO- d_6 and TFA, 20 C; Panel C: DMSO- d_6 and TFA, 60 C.

Scheme 1.

Mannich reactions of isoflavones **3** with formaldehyde and amino alcohols. (a) $\text{HOCH}_2(\text{CH}_2)_n\text{NH}_2$, where $n = 1$ to 4 , CH_2O , EtOH or $i\text{-PrOH}$, DMAP, 80°C , $4\text{--}6\text{ h}$; (b) bis(1,3-oxazolidin-3-yl)methane, dioxane, 100°C , $2\text{--}4\text{ h}$; (c) 3-butoxymethyl-1,3-oxazolidine, dioxane, 100°C , $2\text{--}4\text{ h}$.

Scheme 2.

Hydrolysis of tautomers **4** and **5** to amino diols **6**. (a) HCl, EtOH, 80 °C, 0.5 – 1 h

Ratio of tautomeric isomers **4** and **5** obtained from isoflavones **3** and amino alcohols $\text{HOCH}_2(\text{CH}_2)_n\text{NH}_2$ using Method A as the general procedure, unless otherwise noted.

Table 1

Entry	Isoflavone	Amino Alcohol $\text{HOCH}_2(\text{CH}_2)_n\text{NH}_2$ or Equivalent	Ratio of 4 to 5 , (%) ^a	Solvent	Yield, %
1	3a	$n = 1$	95	EtOH	68
2	3a	$n = 1$	91	<i>i</i> -PrOH	50
3^b			93	1,4-Dioxane	63
4	3b	$n = 1$	88	EtOH	49
5^c			90	1,4-Dioxane	45
6	3c	$n = 1$	87	<i>i</i> -PrOH	81
7^c			89	1,4-Dioxane	67
8	3d	$n = 1$	88	EtOH	47
9^b			87	1,4-Dioxane	42

Entry	Isoflavone	Amino Alcohol HOCH ₂ (CH ₂) _n NH ₂ or Equivalent	Ratio of 4 to 5, (%) ^a	Solvent	Yield, %
10 ^c	3d		87	THF	37
11	3d	n = 1	91	EtOH	54
12 ^c	3d		89	1,4-Dioxane	43
13	3f	n = 1	92	<i>i</i> -PrOH	65
14	3h	n = 1	79	<i>i</i> -PrOH	60
15	3a	n = 2	3	EtOH	75
16	3b	n = 2	0	EtOH	78
17	3c	n = 2	0	EtOH	65
18	3d	n = 2	0	<i>i</i> -PrOH	58
19	3e	n = 2	3	EtOH	52
20	3f	n = 2	3	<i>i</i> -PrOH	67
21	3g	n = 2	3	<i>i</i> -PrOH	48
22	3h	n = 2	2	<i>i</i> -PrOH	83
23	3a	n = 3	94	<i>i</i> -PrOH	82
24	3b	n = 3	94	<i>i</i> -PrOH	83
25	3c	n = 3	95	<i>i</i> -PrOH	78
26	3d	n = 3	94	<i>i</i> -PrOH	48
27	3d	n = 3	94	<i>i</i> -PrOH	66
28	3f	n = 3	94	<i>i</i> -PrOH	93
29	3h	n = 3	90	<i>i</i> -PrOH	36
30	3i	n = 3	85	<i>i</i> -PrOH	53
31	3a	n = 4	100	<i>i</i> -PrOH	65
32	3b	n = 4	100	<i>i</i> -PrOH	73

Entry	Isoflavone	Amino Alcohol $\text{HOCH}_2(\text{CH}_2)_n\text{NH}_2$ or Equivalent	Ratio of 4 to 5, (%) ^a	Solvent	Yield, %
33	3c	n = 4	100	i-PrOH	52
34	3d	n = 4	100	i-PrOH	66
35	3e	n = 4	100	i-PrOH	77
36	3f	n = 4	100	i-PrOH	87
37	3g	n = 4	100	i-PrOH	41
38	3h	n = 4	100	i-PrOH	83
39	3i	n = 4	100	i-PrOH	57

^a determined in CDCl₃;

^b used Method B (see Experimental Section);

^c used Method C (see Experimental Section).