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Synthesis of chromone-containing allylmorpholines through Morita-Baylis-Hillman-type reaction

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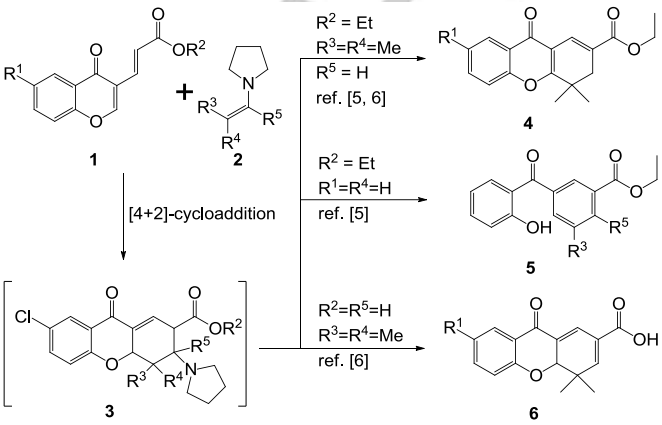
Abstract: The first example of an unusual addition of chromone-substituted acrylic acid to enamines is described. The process shows high versatility concerning both enamines and chromones. The reaction is catalyzed by tertiary amines and is highly likely of Morita-Baylis-Hillman-type. The described compounds show combined moderate inhibitory action on BChE and antagonism towards NMDA receptors which makes them a perspective group for the development of anti-Alzheimer drugs.

Introduction

Chromone's scaffold is a privileged structure for the creation of drugs [1]. A significant number of biologically active substances of both synthetic and natural origin belong to this group of compounds [2]. An important feature of the chromone system is its electron-deficiency and powerful synthetic potential, and because of that they are widely used as precursors of azoles, azines, pyrroles [3] and polycyclic O-containing heterocycles such as xanthones [4].

Currently one area of research is the use of chromone-fused dienes **1** in [4+2] cycloaddition reactions [5, 6]. As shown by Bodwell's group, dienes **1** (R^2=Et) react with enamines **2** to give 3,4-dihydroxanthones **4** and benzophenones **5** (scheme 1). Later on we have shown that the dienes **1** with carboxyl group (R^2=H) mostly form 4,4a-dihydroxanthones **6** and to a lesser extent – 3,4-dihydroisomers **4**.



Scheme 1. Results of previous works with chromone-fused dienes **1**

Present work is a continuation of these studies, where we demonstrate a new way of chromone-fused dienes **1** reaction with enamines resembling a Morita-Baylis-Hillman type (MBH reaction).

Results and Discussion

We discovered that upon replacement of pyrrolidine in enamine **2** with low-nucleophilic morpholine **8** it reacts with the chromone-fused diene **7a** to form an unusual product – allylmorpholine **9a** in 52% yield (table 1). This compound was characterized by a complex of NMR spectra (see Supporting information), and X-ray analysis ([7], figure 1). During the TLC run of the reaction mixture a conventional product of the [4+2] cycloaddition – 4,4a-dihydroxanthone **10a** was seen as a by-product, and it only became the principal one after performing the reaction in methanol or when using the ester **7a'** instead of acid **7a** (entries 3, 11, 12). The exclusive [4+2] cycloaddition reaction in case of the ester diene obviously indicates the importance of carboxyl groups in the mechanism of formation of allylmorpholine **9a**.

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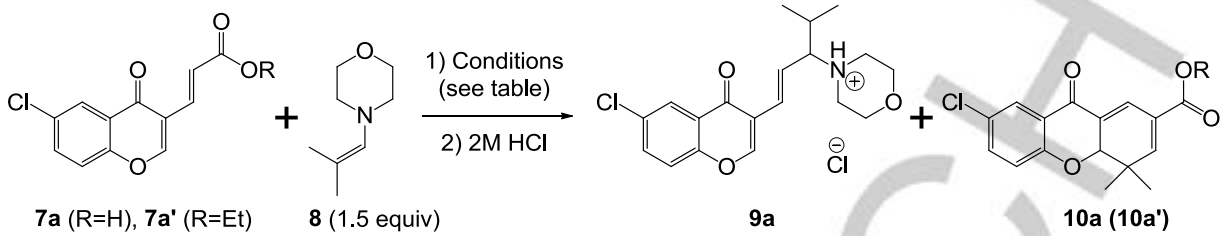
Table 1. Reaction of chromone-fused diene **7a/7a'** with enamine **8**



7a (R=H), **7a'** (R=Et) **8** (1.5 equiv) **9a** **10a (10a')**

Entry	**7a** or **7a'**	Conditions	Catalyst	Time	Preparative yield, % for compound	
					9	**10a** or **10a'**
1	**7a**	DCM, 20°C	-	5 days	52	-
2	**7a**	THF, 20°C	-	48 h	58	-
3	**7a**	MeOH, 20°C	-	36 h	14	47
4	**7a**	EtOAc, 80°C	-	6 h	63	-
5	**7a**	DCM, 20°C	0.5 equiv Et_3N	12 h	72	-
6	**7a**	DCM, 20°C	1.0 equiv Et_3N	8 h	69	-
7	**7a**	DCM, 20°C	0.5 equiv DIPEA	14 h	68	-
8	**7a**	DCM, 20°C	0.5 equiv Pr_3N	48 h	65	-
9	**7a**	DCM, 20°C	0.5 equiv DABCO	48 h	61	-
10	**7a**	DCM, 20°C	0.5 equiv DBU		no reaction	
11	**7a'**	DCM, 20°C	-	5 days	-	65
12	**7a'**	DCM, 20°C	0.5 equiv Et_3N	5 days	-	61

One can easily see that the formation of allylmorpholine **9a** is the interaction of electron-deficient alkene with an aldehyde derivative (enamine **8**), which makes the process similar to MBH reaction [8]. The similarity is improved by the fact that the studied reaction is catalyzed by organic bases (table 1, entry 5-10) resulting in a higher product yield of **9a** (up to 72%) and significantly shorter the reaction time. Despite the fact that MBH reaction is one of the most actively studied modern chemical processes, we have not found any references in the literature concerning the use of acrylic acids in it in contrast to the extensive use of their esters and amides [9]. Also, there are no data on the use of enamines in this reaction, although aza-MBH reactions with N-aryl-, N-alkoxycarbonyl- and N-tosylaldimines are widely known [10]).

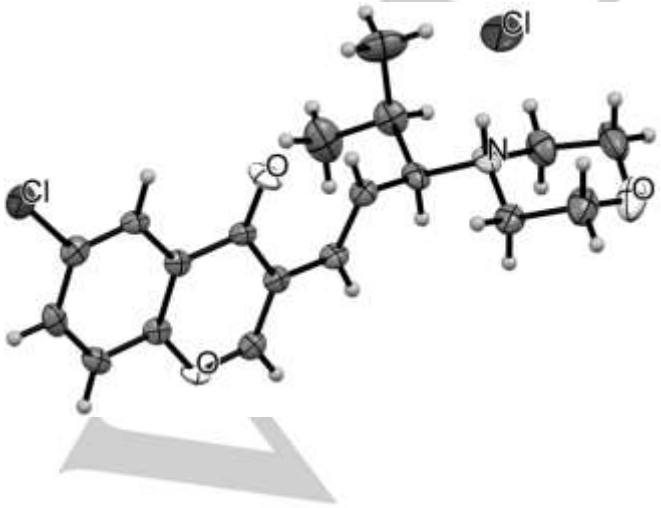
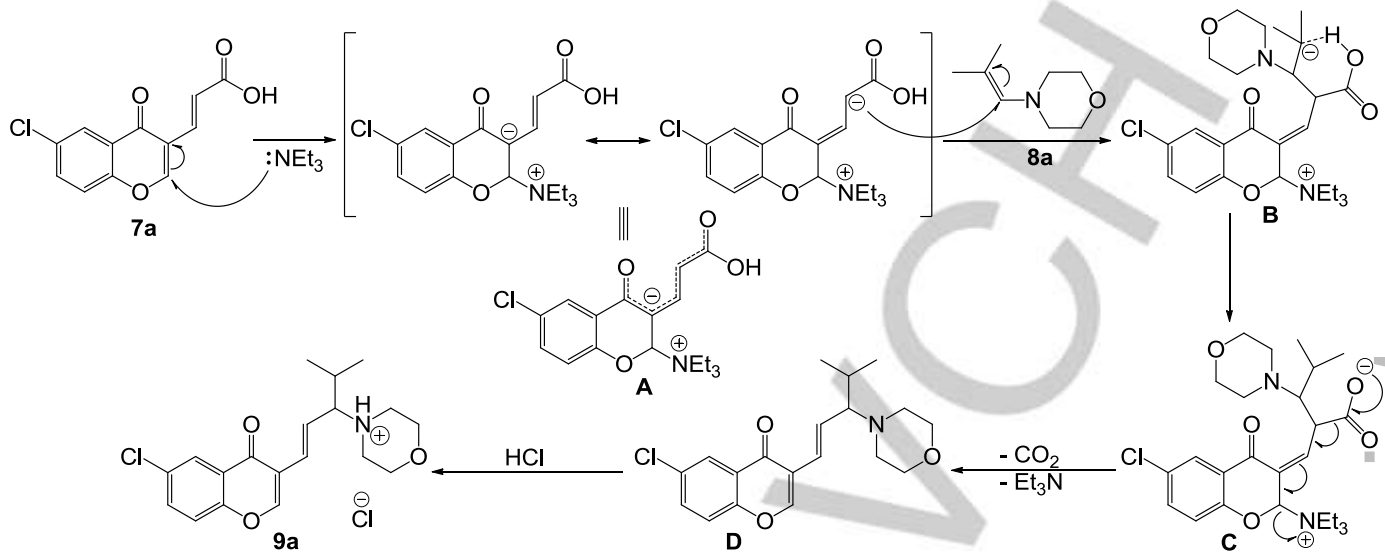


Figure 1. ORTEP structure of allylmorpholine **9a**.

At the same time, Ghosh et al. [11] and Terzidis et al. [12] described the application of 3-formylchromone in MBH reaction. In these works the authors point to the ability of the chromone to add amine to the position 2 of the cycle forming a reactive zwitterion. Based on this, we propose a possible mechanism of the studied reaction (scheme 2). It starts with an attack of a catalyst (e.g., triethylamine) at the position 2 of the chromone **7a**. A zwitterion **A** is formed, where the negative charge is delocalized over the π-bond system. Further the intermediate **A** is added to the enamine **8** followed by simultaneous decarboxylation and extrusion of the catalyst, thus forming the allylmorpholine **9a**.



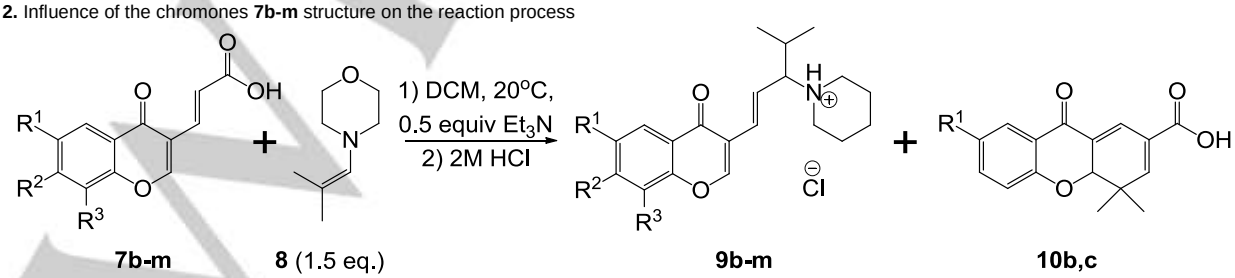
Scheme 2. Possible mechanism for the formation of allylmorpholine **9a**

The proposed mechanism explains, in particular, low efficiency of DBU as a catalyst (table 1, entry 10). This is probably due to the fact that DBU is a strong base, which forms a stable salt with the carboxyl group of the chromone **7a**, making the reaction difficult to proceed. In addition DBU is a bulky base, hence its nucleophilic attack at the chromone double bond maybe sterically hindered. In contrast to this, another often used non-nucleophilic base – DIPEA – possessed excellent catalytic activity (table 1, entry 7) equivalent to triethylamine. A side reaction of the catalyst with the carboxyl group might be the reason for having yet not used acids in MBH reaction. In agreement with the proposed mechanism is also the fact that the ester **7a'** forms exclusively a [4+2]-cycloaddition product **10a'** (table 1, entry 11, 12). As can be seen from scheme 2, carboxyl group plays important role by stabilizing the anion center in the intermediate **B**, which is then transformed into a more stable adduct **C**.

The role of the morpholine in the reaction is also unusual. As we shown earlier (scheme 1), using pyrrolidine instead of morpholine leads exclusively to the cycloaddition products – dihydroxanthones **4** and **6** [6]. Apparently, this is due to the fact that the enamine in the studied MBH-type reaction should act as an electrophile, which is supported by low nucleophilicity of morpholine. This assumption is confirmed by the fact that the reported aza-MBH reactions always use not aldimines themselves but their more electrophilic N-carboxy- or N-tosyl-derivatives.

Our next task was to determine the limits of applicability of the studied reaction, namely the influence of the structure of acrylic acid **7** and *N*-alkenylmorpholines on the process. Thus, the reaction of unsubstituted and methylsubstituted chromones **7b,c** (table 2, entry 1,2) without a basic catalyst results in the exclusive formation of the competing [4+2] cycloaddition products **10b,c**. As the rate of reaction in case of methoxysubstituted chromone **7d** is low even in presence of 1 equiv of triethylamine, it can be assumed that the introduction of donor substitutes reduces the speed of the process.

Table 2. Influence of the chromones **7b-m** structure on the reaction process



7b-m **8** (1.5 eq.) **9b-m** **10b,c**

Entry	7	R^1	R^2	R^3	Time	Preparative yield, % for compound

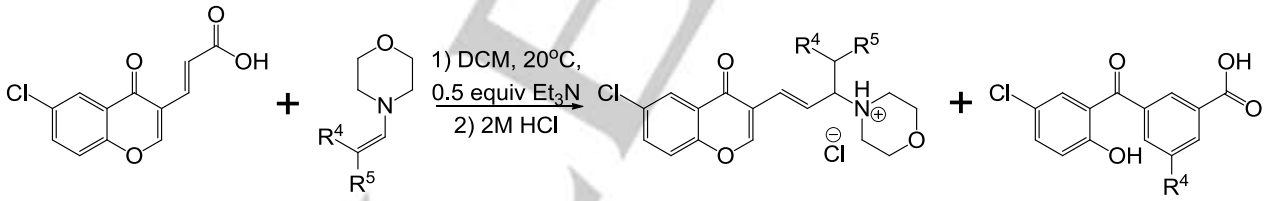
						9	10a
1[a]	**7b**	H	H	H	6 days	-	29
2[a]	**7c**	Me	H	H	8 days	-	34
3	**7b**	H	H	H	72 h	31	-
4	**7c**	Me	H	H	72 h	52	-
5[b]	**7d**	MeO	H	H	6 days	33	-
6	**7e**	Br	H	H	6 h	68	-
7	**7f**	F	H	H	8 h	69	-
8	**7g**	NO_2	H	H	1 h	47	-
9	**7h**	H	Me	H	72 h	54	-
10	**7i**	Me	Me	H	5 days	48	-
11	**7j**	Me	H	Br	24 h	63	-
12	**7k**	Cl	H	Br	5 h	59	-
13	**7l**	F	F	H	10 h	65	-
14	**7m**	Br	MeO	H	12 h	46	-

[a] Without triethylamine

[b] With 1.0 equiv of triethylamine

Next, we chose a series of enamines **11-23**, which were generated in the reaction mixture from morpholine and corresponding aldehyde (table 3). Lower aldehydes (C_2 and C_3, and C_4 without a catalyst) formed allylmorpholines **24a-35a** along with [4+2] cycloaddition products – benzophenones **36a-38a**. As the aliphatic chain length grew, the yield of allylmorpholines increased up to 71% for the cyclohexanecarboxaldehyde derivative **33a**. Unexpectedly phenylacetaldehyde (table 3, entry 14) failed to form the corresponding allylmorpholine, and the main product was phenylbenzophenone **39a**. The formation of benzophenones **36a-39a** appears to be associated with a significant change in the reaction free energy due to the closure of the aromatic system. This is supported by theoretical calculation at P2(full)/6-31+G**//M062X/6-31+G** theory level performed with Gaussian 16 (tables **S2**, **S3**) [13]. The reaction free energy Δ*G* of benzophenone **36a** formation was 92.43 kJ·mol^{-1} lower than for the 4,4a-dihydroxanthone **10a**. As a result, for the lower aldehydes the reaction of [4+2] cycloaddition was thermodynamically more favorable. Formation of the phenylbenzophenone **39a** as a major product may be explained by the fact that its calculated reaction free energy is lower than for the benzophenone **36a** for even more 37.53 kJ·mol^{-1}, which might be a result of conjugation between two benzene systems in compound **39a**.

Table 3. Influence of the alkenylmorpholines **11-23** structure on the reaction



7a **11-23** (1.5 eq.) **24a-35a** **36a-39a**

Entry	Enamine[a]	R^4	R^5	Time, h	Product (preparative yield, %)	
1	11	H	H	12	**24a** (21)	**36a** (35)
2	12	Me	H	12	**25a** (34)	**37a** (47)
3	13	Et	H	8	**26a** (58)	-
4[b]	13	Et	H	28	**26a** (34)	**38a** (30)
5	14	$-CH_2CH_2-$		7	**27a** (55)	-
6	15	Pr	H	6	**28a** (66)	-
7	16	iPr	H	6	**29a** (61)	-
8	17	Bu	H	4	**30a** (64)	-
9	18	Et	Et	10	**31a** (59)	-
10	19	Pen	H	4	**32a** (63)	-
11	20	$-(CH_2)_5-$		6	**33a** (71)	-
12	21	n-C_8H_{17}	H	6	**34a** (64)	-
13	22	$PhCH_2$	H	14	**35a** (24)	-
14	23	Ph	H	48	-	**39a** (53)

[a] Generated in situ from corresponding aldehyde and morpholine

[b] Without triethylamine

Thus, as shown above, the studied reaction allows obtaining a fairly wide range of chromone-containing allylmorpholines, which can be of interest as biologically active substances. In particular, compounds comprising an aromatic system in combination with cyclic amine, e.g. derivatives of chromone [14] and indanone [15] (including donepezil) (figure 2) are known to inhibit acetylcholinesterase (AChE).

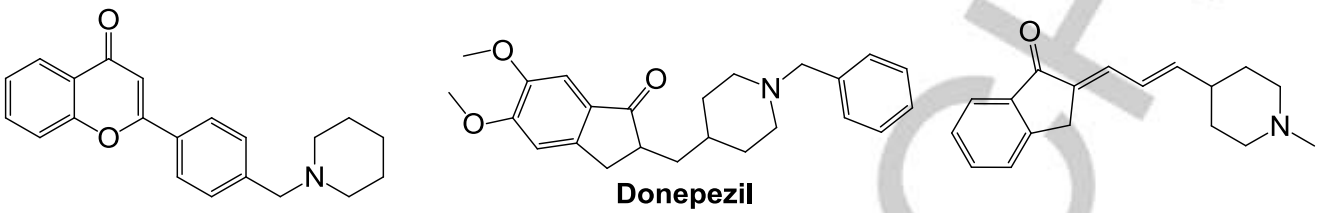


Figure 2. Compounds inhibiting AChE.

Donepezil is one of a few drugs approved by the FDA for the treatment of the Alzheimer's disease (AD), in which neurodegeneration, among other, strongly affects the cholinergic system [16]. In recent years, more and more data indicate the special role of butyrylcholinesterase (BChE) in the pathogenesis of AD [17, 18].

Based on the aforementioned, we investigated the inhibitory activity of the prepared allylmorpholines **9a-m**, **24-35a** against the horse butyrylcholinesterase (eqBChE) (table 4). The compounds generally shown a moderate level of activity, but the inhibition ability significantly increases upon the introduction of bromine in the position 8 of the chromone ring. In addition, the activity is influenced by the length and branching of the alkyl substituent R^4(R^5): in a series of unbranched alkyls the activity increases up to R^4=Pr (**28a**), and then begins to fall. However, the replacement of 1-pentyl with a more compact 3-pentyl (**30a** and **31a**) restores the activity. This is even more evident when changing from hexyl to cyclohexyl (**32a** and **33a**), which indicates the importance of non-bulky alkyls in the structure.

With respect to the inhibition of electric eel AChE (eeAChE), the pattern of structure-activity relationship (SAR) is more complex, but 8-bromo-substituent similarly enhances inhibition. In general, the synthesized substances are moderate selective inhibitors of BChE, apart from donepezil which is much more active towards AChE.

Given the found SAR, we synthesized the allylmorpholine **33b** that combined 8-bromochromone core and cyclohexyl alkyl in the side chain. This assumption proved to be fruitful, the compound did possess the highest activity (0,42 μM) against BChE from the entire series of allylmorpholines.

Table 4. AChE and BChE inhibition results and NMDA antagonism activity of allylmorpholines

Compound	R^{1-3}	R^4	R^5	IC_{50}, μM or % inhibition at 24 μM		
				eqBChE	EeAChE	NMDA
9a	6-Cl	Me	Me	14.5±0.4	15%	28±6
9b	-	Me	Me	14.7±0.5	18%	nd
9c	6-Me	Me	Me	12±2	31%	nd
9d	6-MeO	Me	Me	22±1	15%	nd
9e	6-Br	Me	Me	9±1	36%	nd
9f	6-F	Me	Me	15±1	30%	nd
9g	6-NO_2	Me	Me	8±1	4.0±0.1	nd
9h	7-Me	Me	Me	7.6±0.1	34%	nd
9i	6,7-diMe	Me	Me	4.8±0.3	23±3	nd
9j	6-Me-8-Br	Me	Me	1.2±0.1	7±1	51±12
9k	6-Cl-8-Br	Me	Me	4.0±0.6	11±1	nd
9l	6,7-diF	Me	Me	17%	6.4±0.2	nd
9m	6-Br-7-MeO	Me	Me	24±2	40%	nd
24a	6-Cl	H	H	28%	15±1	nd
25a	6-Cl	Me	H	23.6±0.4	47%	nd
26a	6-Cl	Et	H	19.5±0.1	43%	nd
27a	6-Cl	-CH_2CH_2-		16±2	19±3	nd
28a	6-Cl	Pr	H	5.0±0.8	38%	nd
29a	6-Cl	iPr	H	46%	13%	nd
30a	6-Cl	Bu	H	12.8±0.5	46%	nd
31a	6-Cl	Et	Et	4.9±0.3	21%	25±5
32a	6-Cl	Pen	H	25.9±0.5	42%	nd
33a	6-Cl	-(CH2)5-		1.6±0.1	14%	15±4
33b	6-Me-8-Br	-(CH2)5-		0.42±0.03	7±1	8±3
34a	6-Cl	n-C8H17	H	15%	33%	nd
35a	6-Cl	PhCH2	H	24.1±0.7	28%	nd

Donepezil	3.8±0.1	0.05±0.01	>100
Memantine	nd	nd	1.1±0.3

nd = not determined

The multifactor nature of the AD and its various cerebral mechanisms of pathogenesis lead to an idea of multi-target-directed ligands [19]. Usually, the targets are a combination of AChE/BChE inhibition with optionally MAO-B inhibition [20], reduction of oxidative stress [21], inhibition of aggregation of beta-amyloid [22], antagonism with H_3 receptors [23], and $5HT_6$ receptors [24]. NMDA receptors are of particular interest since memantine is the only NMDA receptor antagonist approved by the FDA for use in patients with moderate-to-severe AD [25]. Its important features are low affinity, uncompetitive nature and fast off-rate kinetics, that's why the receptors retain their functions [26]. In view of this concept, we tested the antagonistic activity of the same key compounds (**9a,j, 31a, 33a,b**) against NMDA receptors in a patch-clamp test. The highest activity was shown by compound **33b** with IC_{50} of 8±3 μM, which is comparable to that of memantine. It is worth mentioning that donepezil did not demonstrate substantial activity against NMDA receptors even at 100 μM concentration.

Conclusions

In conclusion, we have described a new and efficient method of synthesis of chromone-containing allylmorpholines, which highly likely proceeds via MBH-type mechanism. For best results catalysis with nucleophilic tertial amines, such as TEA and DIPEA, is required. The method has been optimized to generate the enamine in the reaction mixture from aldehyde and morpholine and can be easily applied to various aldehydes and substituted chromones. In some cases a side reaction of [4+2]-cycloaddition occurs. The resultant allylmorpholines show moderate inhibitory activity towards eqBChE with good selectivity in relation to EeAChE, which is combined with moderate antagonism towards NMDA receptors similar to the reference substance memantine. Altogether this makes them a perspective group for drug design in neurodegenerative diseases therapy.

Experimental Section

General methods. Commercial grade reagents and solvents were used without further purification. Reactions were monitored by thin layer chromatography using Merck silica gel 60 F254 aluminum sheets, visualization of the compounds was achieved by UV. NMR spectra were recorded on Bruker Avance III (1H – 400 MHz, 13C – 100 MHz). NMR spectra were calibrated to the solvent signals of DMSO-d_6 or D_2O. HRMS-ESI were recorded on a Bruker micrOTOF mass-spectrometer. Melting points were determined on a capillary point apparatus and are uncorrected.

Dienes **7a-m** were prepared from corresponding phenols through a four-step synthesis (see Supporting information).

General procedure for the synthesis of chromone-containing allylmorpholines 9a-m (tables 1, 2). A mixture of acrylic acid **7a-m** (4 mmole), enamine **8** (846 mg, 6 mmole, 1.5 eq.) and triethylamine (200 mg, 2 mmole, 0.5 eq.; or other catalyst, see table 1) was stirred in DCM (10 ml; or other solvent, see table 1). The end of the reaction was determined by TLC (ethyl acetate, detected by UV-light). Then 10 ml of 2M hydrochloric acid were added to the reaction mixture, the emulsion was stirred for 1 hour. The resulting precipitate (dihydroxanthones **10a-c**) was filtered off, washed with water and dried. The organic layer of the biphasic filtrate was separated and evaporated under reduced pressure. Ethyl acetate (10 ml) was added to the residue; the resulting product (allylmorpholines **9a-m**) was filtered, washed with ethyl acetate and dried.

Allylmorpholines **9a,e,f,j-l** usually precipitated immediately after acidification, then the precipitate was filtered off, washed with DCM and dried. The filtrate treatment as described above gave an additional amount of the product (10-15%).

Dihydroxanthones **10a-c** were crystallized from ethanol, allylmorpholines **9a-m** were crystallized from water or 0.1M hydrochloric acid.

(*E*)-4-[1-(6-chloro-4-oxo-4*H*-chromen-3-yl)-4-methylpent-1-en-3-yl]morpholin-4-ium chloride (9a). White needles (H_2O), mp 204-206 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 0.93 (d, J = 6.8 Hz, 3H, Me), 1.06 (d, J = 6.5 Hz, 3H, Me), 2.42 (m, 1H, C<u>H</u>Me$_2$), 3.07 (m, 2H, NC<u>H</u>$_2$CH$_2$O), 3.42 (m, 2H, NC<u>H</u>$_2$CH$_2$O), 3.75 (m, 1H, C<u>H</u>N), 3.92 (m, 2H, NCH$_2$C<u>H</u>$_2$O), 4.07 (m, 2H, NCH$_2$C<u>H</u>$_2$O), 6.57 (d, J = 15.8 Hz, 1H, CH=CH), 6.82 (dd, J = 10.0, 15.8 Hz, 1H, CH=CH),7.74 (d, J = 9.0 Hz, 1H, C^{8}H), 7.83 (dd, J = 2.3, 9.0 Hz, 1H, C^{7}H), 7.98 (d, J = 2.3 Hz, 1H, C^{5}H), 8.72 (s, 1H, C^{2}H), 11.27 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 17.20, 21.02, 26.48, 49.92, 50.71, 63.32, 63.38, 74.97, 119.63, 121.46, 122.91, 124.63, 124.97, 130.05, 130.64, 134.62, 154.25, 157.22, 174.67. HRMS-ESI: m/z calcd. for $C_{19}H_{23}ClNO_3$ $[M+H]^+$ 348.1361, found 348.1343.

X-ray analysis of compound 9a. Single crystals of allylmorpholine **9a** were grown from acetonitrile. A suitable crystal was selected and studied on a SuperNova (Dual, Cu at zero, Atlas) diffractometer. The crystal was kept at 100(2) K during data collection. Using Olex2 [26], the structure was solved with the Superflip [27] structure solution program using «charge flipping» and refined with the ShelXL [28] refinement package using least squares minimization. Crystallographic data have been deposited in the Cambridge Crystallographic Data Center [7].

Crystal data for compound 9a. $C_{19}H_{23}O_3Cl_2N$, M =384.28, monoclinic, a = 11.7616(4) Å, b = 7.6304(4) Å, c = 42.125(2) Å, β = 92.252(4)°, V = 3777.7(3) Å^3, T = 100(2), space group C2/c (no. 15), Z = 8, μ(Cu Kα) = 3.238, 11244 reflections measured, 3497 unique (R_{int} = 0.0984) which were used in all calculations. The final wR_2 was 0.1664 (all data) and R_1 was 0.0660 (>2sigma(I)).

(*E*)-4-[1-(4-oxo-4*H*-chromen-3-yl)-4-methylpent-1-en-3-yl]morpholin-4-ium chloride (9b). White needles (H_2O), mp 188-190 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 0.93 (d, J = 6.8 Hz, 3H, Me), 1.05 (d, J = 6.5 Hz, 3H, Me), 2.41 (m, 1H, C<u>H</u>Me$_2$), 3.06 (m, 2H, NC<u>H</u>$_2$CH$_2$O), 3.40 (m, 2H, NC<u>H</u>$_2$CH$_2$O), 3.73 (m, 1H, C<u>H</u>N), 3.92 (m, 2H, NCH$_2$C<u>H</u>$_2$O), 4.04 (m, 2H, NCH$_2$C<u>H</u>$_2$O), 6.57 (d, J = 15.8 Hz, 1H, CH=CH), 6.81 (dd, J = 10.0, 15.8 Hz, 1H, CH=CH),7.53 (t, J = 7.5 Hz, 1H, C^{6}H), 7.69 (d, J = 8.5 Hz, 1H, C^{8}H), 7.83 (m, 1H, C^{7}H), 8.12 (d, J = 8.0 Hz, 1H, C^{5}H), 8.69 (s, 1H, C^{2}H), 11.09 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 17.17,

21.00, 26.47, 49.92, 50.67, 63.36, 63.42, 75.04, 118.93, 119.58, 122.36, 123.90, 125.74, 126.26, 130.50, 134.81, 155.70, 157.04, 175.82. HRMS-ESI: *m/z* calcd. for $C_{19}H_{24}NO_3$ $[M+H]^+$ 314.1751, found 314.1744.

(*E*)-4-[1-(6-methyl-4-oxo-4*H*-chromen-3-yl)-4-methylpent-1-en-3-yl]morpholin-4-ium chloride (9c). White needles (H_2O), mp 196-198 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 0.93 (d, *J* = 6.5 Hz, 3H, Me), 1.04 (d, *J* = 6.5 Hz, 3H, Me), 2.42 (m, 1H, C<u>H</u>Me$_2$), 2.44 (s, 3H, Me), 3.06 (m, 2H, NC<u>H</u>$_2$CH$_2$O), 3.37 (m, 1H, NC<u>H</u>$_2$CH$_2$O), 3.48 (m, 1H, NC<u>H</u>$_2$CH$_2$O), 3.72 (m, 1H, C<u>H</u>N), 3.97 (m, 4H, NCH$_2$C<u>H</u>$_2$O), 6.58 (d, *J* = 15.7 Hz, 1H, CH=CH), 6.78 (dd, *J* = 10.0, 15.7 Hz, 1H, CH=CH),7.59 (d, *J* = 8.5 Hz, 1H, C^{8}H), 7.65 (dd, *J* = 2.0, 8.5 Hz, 1H, C^{7}H), 7.89 (d, *J* = 2.0 Hz, 1H, C^{5}H), 8.66 (s, 1H, C^{2}H), 10.90 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 17.11, 20.96, 20.98, 26.45, 49.92, 50.66, 63.39, 63.46, 75.04, 118.74, 119.40, 122.00, 123.63, 124.94, 130.67, 135.85, 135.88, 154.05, 156.88, 175.76. HRMS-ESI: *m/z* calcd. for $C_{20}H_{26}NO_3$ $[M+H]^+$ 328.1907, found 328.1921.

(*E*)-4-[1-(6-methoxy-4-oxo-4*H*-chromen-3-yl)-4-methylpent-1-en-3-yl]morpholin-4-ium chloride (9d). White needles (H_2O), mp 178-180 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 0.92 (d, *J* = 6.8 Hz, 3H, Me), 1.03 (d, *J* = 6.8 Hz, 3H, Me), 2.40 (m, 1H, C<u>H</u>Me$_2$), 3.06 (m, 2H, NC<u>H</u>$_2$CH$_2$O), 3.38 (m, 1H, NC<u>H</u>$_2$CH$_2$O), 3.49 (m, 1H, NC<u>H</u>$_2$CH$_2$O), 3.73 (m, 1H, C<u>H</u>N), 3.86 (s, 3H, MeO), 3.96 (m, 4H, NCH$_2$C<u>H</u>$_2$O), 6.58 (d, *J* = 15.8 Hz, 1H, CH=CH), 6.80 (dd, *J* = 10.3, 15.8 Hz, 1H, CH=CH),7.42 (dd, *J* = 3.0, 9.0 Hz, 1H, C^{7}H), 7.47 (d, *J* = 3.0, 1H, C^{5}H), 7.66 (d, *J* = 9.0 Hz, 1H, C^{8}H), 8.67 (s, 1H, C^{2}H), 10.74 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 17.00, 20.90, 26.39, 49.86, 50.72, 56.20, 63.48, 75.03, 105.48, 118.66, 120.56, 122.08, 123.84, 124.59, 130.71, 150.45, 156.92, 157.19, 175.54. HRMS-ESI: *m/z* calcd. for $C_{20}H_{26}NO_4$ $[M+H]^+$ 344.1856, found 344.1853.

(*E*)-4-[1-(6-bromo-4-oxo-4*H*-chromen-3-yl)-4-methylpent-1-en-3-yl]morpholin-4-ium chloride (9e). White needles (H_2O), mp 196-197 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 0.93 (d, *J* = 6.8 Hz, 3H, Me), 1.04 (d, *J* = 6.5 Hz, 3H, Me), 2.41 (m, 1H, C<u>H</u>Me$_2$), 3.07 (m, 2H, NC<u>H</u>$_2$CH$_2$O), 3.44 (m, 2H, NC<u>H</u>$_2$CH$_2$O), 3.74 (m, 1H, C<u>H</u>N), 3.97 (m, 4H, NCH$_2$C<u>H</u>$_2$O), 6.56 (d, *J* = 15.8 Hz, 1H, CH=CH), 6.80 (dd, *J* = 10.0, 15.8 Hz, 1H, CH=CH),7.70 (d, *J* = 8.8 Hz, 1H, C^{8}H), 7.98 (dd, *J* = 2.0, 8.8 Hz, 1H, C^{7}H), 8.16 (d, *J* = 2.0 Hz, 1H, C^{5}H), 8.73 (s, 1H, C^{2}H), 10.93 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 17.14, 20.96, 26.48, 49.96, 50.70, 63.44, 74.98, 118.64, 119.71, 121.67, 122.81, 125.41, 127.82, 130.18, 137.39, 154.69, 157.28, 174.65. HRMS-ESI: *m/z* calcd. for $C_{19}H_{23}BrNO_3$ $[M+H]^+$ 392.0856, found 392.0847.

(*E*)-4-[1-(6-fluoro-4-oxo-4*H*-chromen-3-yl)-4-methylpent-1-en-3-yl]morpholin-4-ium chloride (9f). White needles (H_2O), mp 206-207 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 0.91 (d, *J* = 6.3 Hz, 3H, Me), 1.05 (d, *J* = 5.8 Hz, 3H, Me), 2.40 (m, 1H, C<u>H</u>Me$_2$), 3.06 (m, 2H, NC<u>H</u>$_2$CH$_2$O), 3.41 (m, 2H, NC<u>H</u>$_2$CH$_2$O), 3.74 (m, 1H, C<u>H</u>N), 3.92 (m, 2H, NCH$_2$C<u>H</u>$_2$O), 4.03 (m, 2H, NCH$_2$C<u>H</u>$_2$O), 6.57 (d, *J* = 15.8 Hz, 1H, CH=CH), 6.83 (dd, *J* = 10.3, 15.8 Hz, 1H, CH=CH),7.78 (m, 3H, Ar), 8.74 (s, 1H, C^{2}H), 11.08 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 17.00, 20.90, 26.38, 49.87, 50.73, 63.48, 74.95, 110.30 (d, J_{CF} = 24.2 Hz), 118.84, 121.84 (d, J_{CF} = 8.1 Hz), 122.64, 123.02 (d, J_{CF} = 25.6 Hz), 125.10 (d, J_{CF} = 7.4 Hz), 130.36, 152.19, 157.53, 159.59 (d, J_{CF} = 244.4 Hz), 175.23. HRMS-ESI: *m/z* calcd. for $C_{19}H_{23}FNO_3$ $[M+H]^+$ 332.1656, found 332.1640.

(*E*)-4-[1-(6-nitro-4-oxo-4*H*-chromen-3-yl)-4-methylpent-1-en-3-yl]morpholin-4-ium chloride (9g). White needles (H_2O), mp 212-214 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 0.93 (d, *J* = 6.5 Hz, 3H, Me), 1.03 (d, *J* = 6.5 Hz, 3H, Me), 2.41 (m, 1H, C<u>H</u>Me$_2$), 3.07 (m, 2H, NC<u>H</u>$_2$CH$_2$O), 3.43 (m, 2H, NC<u>H</u>$_2$CH$_2$O), 3.77 (m, 1H, C<u>H</u>N), 3.94 (m, 4H, NCH$_2$C<u>H</u>$_2$O), 6.59 (d, *J* = 15.8 Hz, 1H, CH=CH), 6.83 (dd, *J* = 10.0, 15.8 Hz, 1H, CH=CH),7.97 (d, *J* = 9.3 Hz, 1H, C^{8}H), 8.59 (dd, *J* = 2.8, 9.3 Hz, 1H, C^{7}H), 8.78 (d, *J* = 2.8 Hz, 1H, C^{5}H), 8.82 (s, 1H, C^{2}H), 10.67 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 16.95, 20.84, 26.37, 49.87, 50.81, 63.49, 74.83, 119.95, 121.37, 121.84, 123.53, 123.89, 128.93, 129.85, 144.99, 157.71, 158.67, 175.11. HRMS-ESI: *m/z* calcd. for $C_{19}H_{23}N_2O_5$ $[M+H]^+$ 359.1601, found 359.1597.

(*E*)-4-[1-(7-methyl-4-oxo-4*H*-chromen-3-yl)-4-methylpent-1-en-3-yl]morpholin-4-ium chloride (9h). White needles (H_2O), mp 236-238 °C. ^{1}H NMR (400 MHz, D_2O): δ_H ppm 0.89 (d, *J* = 5.4 Hz, 3H, Me), 0.91 (d, *J* = 5.6 Hz, 3H, Me), 2.20 (s, 3H, Me), 2.32 (m, 1H, C<u>H</u>Me$_2$), 3.09 (m, 2H, NC<u>H</u>$_2$CH$_2$O), 3.47 (m, 2H, NC<u>H</u>$_2$CH$_2$O), 3.59 (m, 1H, C<u>H</u>N), 3.77 (m, 2H, NCH$_2$C<u>H</u>$_2$O), 4.01 (m, 2H, NCH$_2$C<u>H</u>$_2$O), 6.40 (m, 2H, CH=CH), 6.88 (s, 1H, C^{8}H), 6.92 (d, *J* = 8.3 Hz, 1H, C^{6}H), 7.40 (d, *J* = 8.3 Hz, 1H, C^{5}H), 7.98 (s, 1H, C^{2}H). ^{13}C NMR (100 MHz, D_2O): δ_C ppm 15.65, 19.32, 20.92, 26.25, 49.88, 50.00, 63.56, 63.64, 75.81, 117.52, 118.64, 120.02, 120.87, 124.34, 127.16, 131.46, 146.60, 155.24, 156.61, 177.64. HRMS-ESI: *m/z* calcd. for $C_{20}H_{26}NO_3$ $[M+H]^+$ 328.1907, found 328.1895.

(*E*)-4-[1-(6,7-dimethyl-4-oxo-4*H*-chromen-3-yl)-4-methylpent-1-en-3-yl]morpholin-4-ium chloride (9i). White needles (H_2O), mp 213-215 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 0.92 (d, *J* = 6.8 Hz, 3H, Me), 1.03 (d, *J* = 6.8 Hz, 3H, Me), 2.32 (s, 3H, Me), 2.35 (s, 3H, Me), 2.39 (m, 1H, C<u>H</u>Me$_2$), 3.06 (m, 2H, NC<u>H</u>$_2$CH$_2$O), 3.37 (m, 1H, NC<u>H</u>$_2$CH$_2$O), 3.47 (m, 1H, NC<u>H</u>$_2$CH$_2$O), 3.72 (m, 1H, C<u>H</u>N), 3.95 (m, 4H, NCH$_2$C<u>H</u>$_2$O), 6.57 (d, *J* = 15.6 Hz, 1H, CH=CH), 6.76 (dd, *J* = 10.3, 15.6 Hz, 1H, CH=CH),7.46 (s, 1H, C^{8}H), 7.81 (s, 1H, C^{5}H), 8.62 (s, 1H, C^{2}H), 10.77 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 17.04, 19.47, 20.30, 20.92, 26.41, 49.87, 50.70, 63.48, 75.04, 118.71, 119.30, 121.71, 121.74, 125.09, 130.81, 135.31, 145.10, 154.24, 156.61, 175.60. HRMS-ESI: *m/z* calcd. for $C_{21}H_{28}NO_3$ $[M+H]^+$ 342.2064, found 342.2077.

(*E*)-4-[1-(8-bromo-6-methyl-4-oxo-4*H*-chromen-3-yl)-4-methylpent-1-en-3-yl]morpholin-4-ium chloride (9j). White needles (H_2O), mp 190-192 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 0.92 (d, *J* = 6.8 Hz, 3H, Me), 1.05 (d, *J* = 6.8 Hz, 3H, Me), 2.41 (m, 4H, C<u>H</u>Me$_2$, Me), 3.07 (m, 2H, NC<u>H</u>$_2$CH$_2$O), 3.38 (m, 1H, NC<u>H</u>$_2$CH$_2$O), 3.49 (m, 1H, NC<u>H</u>$_2$CH$_2$O), 3.75 (m, 1H, C<u>H</u>N), 3.98 (m, 4H, NCH$_2$C<u>H</u>$_2$O), 6.56 (d, *J* = 15.8 Hz, 1H, CH=CH), 6.80 (dd, *J* = 10.3, 15.8 Hz, 1H, CH=CH),7.81 (d, *J* = 2.8 Hz, 1H, C^{8}H), 7.94 (d, *J* = 2.8 Hz, 1H, C^{5}H), 8.76 (s, 1H, C^{2}H), 11.03 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 17.07, 20.66, 20.96, 26.42, 49.86, 50.76, 63.42, 74.89, 111.20, 119.57, 122.85, 124.80, 130.11, 137.04, 138.61, 150.36, 156.79, 175.21. HRMS-ESI: *m/z* calcd. for $C_{20}H_{25}BrNO_3$ $[M+H]^+$ 406.1012, found 406.1009.

(*E*)-4-[1-(8-bromo-6-chloro-4-oxo-4*H*-chromen-3-yl)-4-methylpent-1-en-3-yl]morpholin-4-ium chloride (9k). White needles (H_2O), mp 195-197 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 0.92 (d, *J* = 6.8 Hz, 3H, Me), 1.03 (d, *J* = 6.5 Hz, 3H, Me), 2.40 (m, 1H, C<u>H</u>Me$_2$), 3.07 (m, 2H, NC<u>H</u>$_2$CH$_2$O), 3.37 (m, 1H, NC<u>H</u>$_2$CH$_2$O), 3.49 (m, 1H, NC<u>H</u>$_2$CH$_2$O), 3.75 (m, 1H, C<u>H</u>N), 3.95 (m, 4H, NCH$_2$C<u>H</u>$_2$O), 6.56 (d, *J* = 15.8 Hz, 1H, CH=CH), 6.82 (dd, *J* = 10.0, 15.8 Hz, 1H, CH=CH),8.03 (d, *J* = 2.5 Hz, 1H, C^{8}H), 8.32 (d, *J* = 2.5 Hz, 1H, C^{5}H), 8.84 (s, 1H, C^{2}H), 10.75 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 16.95, 20.87, 26.38, 49.86, 50.80, 63.47, 63.65, 74.81, 113.45, 119.67, 123.45, 124.50, 125.82, 129.86, 130.84, 137.12, 151.28, 157.43, 174.43. HRMS-ESI: *m/z* calcd. for $C_{10}H_{22}BrClNO_3$ $[M+H]^+$ 426.0466, found 426.0449.

(*E*)-4-[1-(6,7-difluoro-4-oxo-4*H*-chromen-3-yl)-4-methylpent-1-en-3-yl]morpholin-4-ium chloride (9l). White needles (H_2O), mp 244-246 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 0.91 (d, *J* = 6.8 Hz, 3H, Me), 1.03 (d, *J* = 6.8 Hz, 3H, Me), 2.40 (m, 1H, C<u>H</u>Me$_2$), 3.06 (m, 2H, NC<u>H</u>$_2$CH$_2$O), 3.35 (m, 1H, NC<u>H</u>$_2$CH$_2$O), 3.48 (m, 1H, NC<u>H</u>$_2$CH$_2$O), 3.74 (m, 1H, C<u>H</u>N), 3.94 (m, 4H, NCH$_2$C<u>H</u>$_2$O), 6.55 (d, *J* = 15.8 Hz, 1H, CH=CH), 6.80 (dd, *J*

= 10.0, 15.8 Hz, 1H, CH=CH), 8.03 (m, 3H, Ar), 8.74 (s, 1H, C^2H), 10.77 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 16.98, 20.87, 26.37, 49.85, 50.76, 63.42, 63.47, 74.98, 108.80 (d, J_{CF} = 21.6 Hz), 113.00 (d, J_{CF} = 19.4 Hz), 119.12, 121.24 (dd, J_{CF} = 2.4, 5.6 Hz), 122.99, 130.07, 148.35 (dd, J_{CF} = 13.8, 247.9 Hz), 152.32 (d, J_{CF} = 11.8 Hz), 153.52 (dd, J_{CF} = 15.4, 255.3 Hz), 157.63, 174.54. HRMS-ESI: *m/z* calcd. for $C_{19}H_{22}F_2NO_3$ $[M+H]^+$ 350.1562, found 350.1571.

(*E*)-4-[1-(6-bromo-7-methoxy-4-oxo-4*H*-chromen-3-yl)-4-methylpent-1-en-3-yl]morpholin-4-ium chloride (9m). White needles (H_2O), mp 230-232 (dec.) °C. ^1H NMR (400 MHz, DMSO-d_6): δ_H ppm 0.92 (d, *J* = 4.8 Hz, 3H, Me), 1.03 (d, *J* = 4.8 Hz, 3H, Me), 2.39 (m, 1H, C<u>H</u>Me_2), 3.07 (m, 2H, NC<u>H_2</u>CH_2O), 3.47 (m, 2H, NC<u>H_2</u>CH_2O), 3.73 (m, 1H, C<u>H</u>N), 3.94 (m, 4H, NCH_2C<u>H_2</u>O), 4.01 (s, 3H, MeO), 6.55 (d, *J* = 15.7 Hz, 1H, CH=CH), 6.79 (dd, *J* = 10.5, 15.7 Hz, 1H, CH=CH),7.40 (s, 1H, C^8H), 8.19 (s, 1H, C^5H), 8.68 (s, 1H, C^2H), 10.64 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 16.95, 20.88, 26.37, 49.86, 50.73, 57.96, 63.52, 74.94, 102.02, 110.03, 118.48, 119.43, 122.42, 129.26, 130.47, 156.66, 157.01, 160.05, 174.21. HRMS-ESI: *m/z* calcd. for $C_{20}H_{25}BrNO_4$ $[M+H]^+$ 422.0961, found 422.0963.

7-Chloro-4,4-dimethyl-9-oxo-4,4a-dihydro-9*H*-xanthen-2-carboxylic acid (10a). Pale yellow needles (EtOH), mp 243-245 °C. ^1H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.05 (s, 3H, Me), 1.44 (s, 3H, Me), 5.33 (dd, *J* = 1.5, 3.0 Hz, 1H, $C^{4a}H$), 7.08 (t, *J* = 1.5 Hz, 1H, C^3H), 7.13 (d, *J* = 8.8 Hz, 1H, C^5H), 7.33 (dd, *J* = 1.5, 3.0 Hz, 1H, C^1H), 7.61 (dd, *J* = 2.8, 8.8 Hz, 1H, C^6H), 7.72 (d, *J* = 2.8 Hz, 1H, C^8H), 13.07 (s, 1H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 17.50, 25.80, 38.68, 82.32, 121.06, 122.36, 126.15, 126.35, 126.53, 127.71, 129.66, 136.39, 153.02, 159.12, 165.75, 178.34. HRMS-ESI: *m/z* calcd. for $C_{16}H_{13}ClO_4$ $[M-H]^-$ 303.0430, found 303.0444.

Ethyl 7-chloro-4,4-dimethyl-9-oxo-4,4a-dihydro-9*H*-xanthen-2-carboxylate (10a'). Compound **10a'** was synthesized according to the general procedure with the following modification: after acidification the organic layer was separated and evaporated under reduced pressure. Ethanol was added to the residue; the resulting precipitate was filtered, washed with ethanol and dried. The resulting product was crystallized from ethanol. Pale yellow needles (EtOH), mp 126-127 °C. ^1H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.06 (s, 3H, Me), 1.28 (t, *J* = 7.0 Hz, $C\underline{H_3}CH_2$), 1.46 (s, 3H, Me), 4.23 (q, *J* = 7.0 Hz, $CH_3C\underline{H_2}$), 5.35 (dd, *J* = 1.4, 3.1 Hz, 1H, $C^{4a}H$), 7.13 (t, *J* = 1.5 Hz, 1H, C^3H), 7.15 (d, *J* = 8.8 Hz, 1H, C^5H), 7.31 (dd, *J* = 1.8, 3.3 Hz, 1H, C^1H), 7.64 (dd, *J* = 2.8, 9.0 Hz, 1H, C^6H), 7.73 (d, *J* = 2.8 Hz, 1H, C^8H). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 14.51, 17.41, 25.72, 38.75, 61.50, 82.18, 121.12, 122.32, 125.74, 126.14, 126.57, 127.04, 129.94, 136.51, 153.41, 159.14, 164.13, 178.31. HRMS-ESI: *m/z* calcd. for $C_{18}H_{17}ClNaO_4$ $[M+Na]^+$ 355.0708, found 355.0711.

4,4-Dimethyl-9-oxo-4,4a-dihydro-9*H*-xanthen-2-carboxylic acid (10b). Pale yellow needles (EtOH), mp 186-188 °C. ^1H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.06 (s, 3H, Me), 1.46 (s, 3H, Me), 5.33 (dd, *J* = 1.6, 3.1 Hz, 1H, $C^{4a}H$), 7.07 (t, *J* = 1.6 Hz, 1H, C^3H), 7.09 (d, *J* = 8.5 Hz, 1H, C^5H), 7.12 (t, *J* = 7.5 Hz, 1H, C^7H), 7.33 (dd, *J* = 1.6, 3.1 Hz, 1H, C^1H), 7.59-7.63 (m, 1H, C^6H), 7.83 (dd, *J* = 1.8, 7.8 Hz, 1H, C^8H), 13.05 (s, 1H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 17.51, 25.87, 38.67, 81.99, 118.73, 121.46, 122.51, 126.36, 126.88, 127.34, 130.52, 136.96, 152.79, 160.52, 165.87, 179.36. HRMS-ESI: *m/z* calcd. for $C_{16}H_{14}O_4$ $[M-H]^-$ 269.0819, found 269.0832.

4,4,7-Trimethyl-9-oxo-4,4a-dihydro-9*H*-xanthen-2-carboxylic acid (10c). Pale yellow needles (EtOH), mp 225-226 °C. ^1H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.02 (s, 3H, Me), 1.42 (s, 3H, Me), 2.26 (s, 3H, Me), 5.17 (s, 1H, $C^{4a}H$), 6.94 (d, *J* = 8.3 Hz, 1H, C^5H), 7.03 (s, 1H, C^3H), 7.29 (s, 1H, C^1H), 7.36 (d, *J* = 8.3 Hz, 1H, C^6H), 7.58 (s, 1H, C^8H), 13.00 (s, 1H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 17.47, 20.44, 25.87, 38.60, 81.82, 118.47, 121.13, 126.39, 126.74, 126.78, 130.61, 131.48, 137.73, 152.55, 158.53, 165.85, 179.25. HRMS-ESI: *m/z* calcd. for $C_{17}H_{15}O_4$ $[M-H]^-$ 283.0976, found 283.0981.

General procedure for synthesis of chromone-containing allylmorpholines 24a-35a (table 3). A mixture of morpholine (6 mmole), corresponding aldehyde (6 mmole) and molecular sieves 4Å (0.5 g) was stirred in DCM (10 ml) for 12-24 hour. The solution of enamine was filtered, and acrylic acid 7a (1.0 g, 4 mmole) and triethylamine (200 mg, 2 mmole, 0.5 eq.) were added. The end of the reaction was determined by TLC (ethyl acetate, detected by UV-light). Then 10 ml of 2M hydrochloric acid were added to the reaction mixture, the emulsion was stirred for 1 hour. The resulting precipitate (benzophenones **36a-39a**) was filtered by water and dried. The organic layer of the biphasic filtrate was separated and evaporated under reduced pressure. Ethyl acetate (10 ml) was added to the residue; the resulting product (allylmorpholines **24a-35a**) was filtered, washed with ethyl acetate and dried.

Allylmorpholines **30a, 33a** usually precipitated immediately after acidification, and then the precipitate was filtered off, washed with DCM and dried. The filtrate treatment gave an additional portion of the product (5-15%).

Benzophenones **36a-39a** were crystallized from ethanol, allylmorpholines **24a-35a** were crystallized from water or 0.1M hydrochloric acid.

(*E*)-4-[4-(6-chloro-4-oxo-4*H*-chromen-3-yl)-but-3-en-2-yl]morpholin-4-ium chloride (24a). White needles (H_2O), mp 225-226 °C. ^1H NMR (400 MHz, D_2O): δ_H ppm 1.44 (d, *J* = 6.8 Hz, 3H, Me), 3.10 (m, 2H, NC<u>H_2</u>CH_2O), 3.43 (d, *J* = 12.6 Hz, 2H, NC<u>H_2</u>CH_2O), 3.70 (m, 2H, NCH_2C<u>H_2</u>O), 3.93 (m, 1H, C<u>H</u>N), 4.04 (d, *J* = 13.1 Hz, 2H, NCH_2C<u>H_2</u>O), 6.41 (m, 2H, CH=CH), 7.20 (d, *J* = 9.0 Hz, 1H, C^8H), 7.43 (dd, *J* = 2.5, 9.0 Hz, 1H, C^7H), 7.46 (d, *J* = 2.5 Hz, 1H, C^5H), 8.07 (s, 1H, C^2H). ^{13}C NMR (100 MHz, D_2O): δ_C ppm 15.04, 48.27, 49.36, 63.79, 63.89, 65.40, 118.81, 120.24, 123.27, 123.82, 125.11, 128.63, 131.06, 134.55, 153.61, 157.00, 176.30. HRMS-ESI: *m/z* calcd. for $C_{17}H_{19}ClNO_3$ $[M+H]^+$ 320.1048, found 320.1036.

(*E*)-4-[1-(6-chloro-4-oxo-4*H*-chromen-3-yl)-pent-1-en-3-yl]morpholin-4-ium chloride (25a). White needles (H_2O), mp 215-217 °C. ^1H NMR (400 MHz, D_2O): δ_H ppm 0.84 (t, *J* = 7.3 Hz, 3H, Me), 1.69 (m, 1H, CH_2), 1.90 (m, 1H, CH_2), 3.09 (m, 2H, NC<u>H_2</u>CH_2O), 3.42 (d, *J* = 13.1 Hz, 2H, NC<u>H_2</u>CH_2O), 3.70 (m, 3H, NCH_2C<u>H_2</u>O, C<u>H</u>N), 4.02 (d, *J* = 13.1 Hz, 2H, NCH_2C<u>H_2</u>O), 6.33 (dd, *J* = 9.8, 15.8 Hz, 1H, CH=CH), 6.44 (d, *J* = 15.8 Hz, 1H, CH=CH), 7.15 (d, *J* = 9.8 Hz, 1H, C^8H), 7.38 (m, 2H, C^7H, C^5H), 8.08 (s, 1H, C^2H). ^{13}C NMR (100 MHz, D_2O): δ_C ppm 9.60, 22.17, 48.14, 49.96, 63.77, 63.88, 71.44, 118.84, 120.18, 123.21, 123.58, 123.73, 130.51, 130.98, 134.43, 153.51, 156.98, 176.12. HRMS-ESI: *m/z* calcd. for $C_{18}H_{21}ClNO_3$ $[M+H]^+$ 334.1204, found 334.1194.

(*E*)-4-[1-(6-chloro-4-oxo-4*H*-chromen-3-yl)-hex-1-en-3-yl]morpholin-4-ium chloride (26a). White needles (H_2O), mp 212-213 °C. ^1H NMR (400 MHz, D_2O): δ_H ppm 0.83 (t, *J* = 7.4 Hz, 3H, Me), 1.20 (m, 1H, CH_2), 1.30 (m, 1H, CH_2), 1.69 (m, 1H, CH_2), 1.80 (m, 1H, CH_2), 3.09 (m, 2H, NC<u>H_2</u>CH_2O), 3.42 (d, *J* = 12.8 Hz, 2H, NC<u>H_2</u>CH_2O), 3.73 (m, 3H, NCH_2C<u>H_2</u>O, C<u>H</u>N), 4.02 (d, *J* = 13.1 Hz, 2H, NCH_2C<u>H_2</u>O), 6.35 (dd, *J* = 9.5, 15.8 Hz, 1H, CH=CH), 6.45 (d, *J* = 15.8 Hz, 1H, CH=CH), 7.16 (d, *J* = 8.3 Hz, 1H, C^8H), 7.40 (m, 2H, C^7H, C^5H), 8.08 (s, 1H, C^2H). ^{13}C NMR (100 MHz, D_2O): δ_C ppm 12.63, 18.56, 30.63, 48.09, 49.92, 63.77, 63.89, 69.85, 118.84, 120.19, 123.27, 123.76, 123.82, 130.32, 130.99, 134.43, 153.53, 157.00, 176.13. HRMS-ESI: *m/z* calcd. for $C_{19}H_{23}ClNO_3$ $[M+H]^+$ 348.1361, found 348.1372.

(*E*)-4-[3-(6-chloro-4-oxo-4*H*-chromen-3-yl)-1-cyclopropylallyl]morpholin-4-ium chloride (27a). White needles (H_2O), mp 214-215 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 0.24 (m, 1H, cPr), 0.68 (m, 2H, cPr), 0.81 (m, 1H, cPr), 1.34 (m, 1H, cPr), 3.07 (m, 2H, NC$\underline{H}_2$CH$_2$O), 3.37 (m, 2H, NC$\underline{H}_2$CH$_2$O), 3.65 (m, 1H, C$\underline{H}$N), 3.95 (m, 4H, NCH$_2$C$\underline{H}_2$O), 6.53 (d, *J* = 15.8 Hz, 1H, CH=CH), 6.93 (dd, *J* = 9.5, 15.8 Hz, 1H, CH=CH),7.76 (d, *J* = 9.0 Hz, 1H, C^{8}H), 7.86 (dd, *J* = 2.5, 9.0 Hz, 1H, C^{7}H), 8.00 (d, *J* = 2.5 Hz, 1H, C^{5}H), 8.70 (s, 1H, C^{2}H), 11.64 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 3.29, 7.35, 11.22, 49.74, 63.73, 73.27, 119.51, 121.53, 124.65, 124.99, 125.64, 128.06, 130.67, 134.68, 154.27, 157.40, 174.75. HRMS-ESI: *m/z* calcd. for $C_{19}H_{21}ClNO_3$ [M+H]$^+$ 346.1204, found 346.1212.

(*E*)-4-[1-(6-chloro-4-oxo-4*H*-chromen-3-yl)-hept-1-en-3-yl]morpholin-4-ium chloride (28a). White needles (H_2O), mp 209-211 °C. ^{1}H NMR (400 MHz, D_2O): δ_H ppm 0.84 (t, *J* = 6.8 Hz, 3H, Me), 1.29 (m, 4H, CH$_2$), 1.77 (m, 1H, CH$_2$), 1.91 (m, 1H, CH$_2$), 3.17 (m, 2H, NC$\underline{H}_2$CH$_2$O), 3.49 (d, *J* = 11.3 Hz, 2H, NC$\underline{H}_2$CH$_2$O), 3.81 (m, 3H, NCH$_2$C$\underline{H}_2$O, C$\underline{H}$N), 4.09 (d, *J* = 13.1 Hz, 2H, NCH$_2$C$\underline{H}_2$O), 6.45 (dd, *J* = 9.5, 15.8 Hz, 1H, CH=CH), 6.53 (d, *J* = 15.8 Hz, 1H, CH=CH), 7.27 (d, *J* = 9.0 Hz, 1H, C^{8}H), 7.49 (dd, *J* = 2.5, 9.0 Hz, 1H, C^{7}H), 7.55 (d, *J* = 2.5 Hz, 1H, C^{5}H), 8.18 (s, 1H, C^{2}H). ^{13}C NMR (100 MHz, D_2O): δ_C ppm 13.17, 21.49, 27.35, 28.40, 48.26, 49.97, 63.87, 63.97, 70.24, 119.01, 120.34, 123.53, 123.98, 130.44, 131.10, 134.56, 153.79, 157.16, 176.48. HRMS-ESI: *m/z* calcd. for $C_{20}H_{25}ClNO_3$ [M+H]$^+$ 362.1517, found 362.1501.

(*E*)-4-[1-(6-chloro-4-oxo-4*H*-chromen-3-yl)-5-methylhex-1-en-3-yl]morpholin-4-ium chloride (29a). White needles (H_2O), mp 226-228 °C. ^{1}H NMR (400 MHz, D_2O): δ_H ppm 0.87 (d, *J* = 6.3 Hz, 3H, Me), 0.94 (d, *J* = 6.5 Hz, 3H, Me), 1.57 (m, 1H, C$\underline{H}$Me$_2$), 1.65 (pseudo-dt, *J* = 3.0, 11.5×2 Hz, 1H, CH$_2$), 1.80 (pseudo-dt, *J* = 3.0, 10.0×2 Hz, 1H, CH$_2$), 3.18 (m, 2H, NC$\underline{H}_2$CH$_2$O), 3.49 (d, *J* = 12.3 Hz, 2H, NC$\underline{H}_2$CH$_2$O), 3.77 (m, 2H, NCH$_2$C$\underline{H}_2$O) 3.89 (pseudo-dt, *J* = 3.0, 10.0×2 Hz, 1H, C$\underline{H}$N), 4.09 (d, *J* = 13.1 Hz, 2H, NCH$_2$C$\underline{H}_2$O), 6.45 (dd, *J* = 10.0, 15.8 Hz, 1H, CH=CH), 6.59 (d, *J* = 15.8 Hz, 1H, CH=CH), 7.28 (d, *J* = 9.0 Hz, 1H, C^{8}H), 7.49 (dd, *J* = 2.5, 9.0 Hz, 1H, C^{7}H), 7.55 (d, *J* = 2.5 Hz, 1H, C^{5}H), 8.19 (s, 1H, C^{2}H). ^{13}C NMR (100 MHz, D_2O): δ_C ppm 19.81, 22.91, 24.49, 37.40, 48.14, 50.00, 63.88, 64.00, 68.87, 118.99, 120.32, 123.50, 123.93, 130.47, 131.09, 134.54, 153.74, 157.17, 176.40. HRMS-ESI: *m/z* calcd. for $C_{20}H_{25}ClNO_3$ [M+H]$^+$ 362.1517, found 362.1510.

(*E*)-4-[1-(6-chloro-4-oxo-4*H*-chromen-3-yl)-oct-1-en-3-yl]morpholin-4-ium chloride (30a). White needles (H_2O), mp 197-198 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 0.85 (t, *J* = 6.3 Hz, 3H, Me), 1.27 (m, 6H, CH$_2$), 1.74 (m, 1H, CH$_2$), 2.06 (m, 1H, CH$_2$), 3.02 (m, 2H, NC$\underline{H}_2$CH$_2$O), 3.43 (m, 2H, NC$\underline{H}_2$CH$_2$O), 3.90 (m, 5H, NCH$_2$C$\underline{H}_2$O, C$\underline{H}$N), 6.66 (m, 2H, CH=CH), 7.79 (d, *J* = 9.0 Hz, 1H, C^{8}H), 7.88 (dd, *J* = 2.5, 9.0 Hz, 1H, C^{7}H), 8.03 (d, *J* = 2.5 Hz, 1H, C^{5}H), 8.76 (s, 1H, C^{2}H), 11.45 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 14.34, 22.32, 25.59, 28.59, 31.13, 48.07, 50.07, 63.61, 63.74, 69.04, 119.52, 121.57, 124.67, 125.01, 129.82, 130.69, 134.72, 154.33, 157.40, 174.79. HRMS-ESI: *m/z* calcd. for $C_{21}H_{27}ClNO_3$ [M+H]$^+$ 376.1674, found 376.1671.

(*E*)-4-[1-(6-chloro-4-oxo-4*H*-chromen-3-yl)-4-ethylhex-1-en-3-yl]morpholin-4-ium chloride (31a). White needles (H_2O), mp 219-220 °C. ^{1}H NMR (400 MHz, D_2O): δ_H ppm 0.83 (t, *J* = 7.3 Hz, 3H, Me), 0.90 (t, *J* = 6.8 Hz, 3H, Me), 1.13-1.48 (m, 3H, CH$_2$), 2.06 (m, 1H, CH$_2$), 3.10 (m, 2H, NC$\underline{H}_2$CH$_2$O), 3.50 (m, 2H, NC$\underline{H}_2$CH$_2$O), 3.75 (m, 3H, NCH$_2$C$\underline{H}_2$O, C$\underline{H}$N), 4.00 (m, 2H, NCH$_2$C$\underline{H}_2$O), 6.45 (m, 2H, CH=CH), 7.21 (d, *J* = 9.0 Hz, 1H, C^{8}H), 7.42 (dd, *J* = 2.5, 9.0 Hz, 1H, C^{7}H), 7.78 (d, *J* = 2.5 Hz, 1H, C^{5}H), 8.11 (s, 1H, C^{2}H). ^{13}C NMR (100 MHz, D_2O): δ_C ppm 10.61, 12.66, 15.34, 26.72, 32.65, 49.57, 50.87, 63.62, 74.48, 118.92, 120.24, 121.57, 123.41, 123.84, 130.73, 131.03, 134.47, 153.65, 157.18, 176.44. HRMS-ESI: *m/z* calcd. for $C_{21}H_{27}ClNO_3$ [M+H]$^+$ 376.1674, found 376.1686.

(*E*)-4-[1-(6-chloro-4-oxo-4*H*-chromen-3-yl)-non-1-en-3-yl]morpholin-4-ium chloride (32a). White needles (H_2O), mp 171-173 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 0.83 (t, *J* = 6.8 Hz, 3H, Me), 1.23 (m, 8H, CH$_2$), 1.75 (m, 1H, CH$_2$), 2.09 (m, 1H, CH$_2$), 3.02 (m, 2H, NC$\underline{H}_2$CH$_2$O), 3.43 (m, 2H, NC$\underline{H}_2$CH$_2$O), 3.93 (m, 5H, NCH$_2$C$\underline{H}_2$O, C$\underline{H}$N), 6.66 (m, 2H, CH=CH), 7.77 (d, *J* = 9.0 Hz, 1H, C^{8}H), 7.87 (dd, *J* = 2.5, 9.0 Hz, 1H, C^{7}H), 8.00 (d, *J* = 2.5 Hz, 1H, C^{5}H), 8.76 (s, 1H, C^{2}H), 11.64 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 14.37, 22.48, 25.93, 28.65, 31.47, 48.04, 50.08, 63.58, 63.71, 69.06, 119.53, 121.54, 124.64, 124.97, 125.07, 129.79, 130.67, 134.70, 154.31, 157.34, 174.74. HRMS-ESI: *m/z* calcd. for $C_{22}H_{29}ClNO_3$ [M+H]$^+$ 390.1830, found 390.1826.

(*E*)-4-[3-(6-chloro-4-oxo-4*H*-chromen-3-yl)-1-cyclohexylallyl]morpholin-4-ium chloride (33a). White needles (H_2O), mp 217-219 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.04 (m, 3H, cHex), 1.27 (m, 2H, cHex), 1.61 (d, *J* = 12.1 Hz, 2H, cHex), 1.71 (d, *J* = 12.6 Hz, 2H, cHex), 2.02 (m, 2H, cHex), 3.06 (m, 2H, NC$\underline{H}_2$CH$_2$O), 3.35 (m, 1H, NC$\underline{H}_2$CH$_2$O), 3.47 (m, 1H, NC$\underline{H}_2$CH$_2$O), 3.71 (m, 1H, C$\underline{H}$N), 3.97 (m, 4H, NCH$_2$C$\underline{H}_2$O), 6.53 (d, *J* = 15.8 Hz, 1H, CH=CH), 6.84 (dd, *J* = 10.0, 15.8 Hz, 1H, CH=CH), 7.78 (d, *J* = 9.0 Hz, 1H, C^{8}H), 7.87 (dd, *J* = 2.5, 9.0 Hz, 1H, C^{7}H), 8.02 (d, *J* = 2.5 Hz, 1H, C^{5}H), 8.74 (s, 1H, C^{2}H), 10.97 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 25.65, 26.02, 26.06, 27.37, 30.81, 36.34, 48.95, 50.50, 63.40, 63.46, 74.60, 119.51, 121.53, 123.80, 124.67, 125.01, 129.72, 130.66, 134.68, 154.28, 157.43, 174.79. HRMS-ESI: *m/z* calcd. for $C_{22}H_{27}ClNO_3$ [M+H]$^+$ 388.1674, found 388.1659.

(*E*)-4-[3-(8-bromo-6-methyl-4-oxo-4*H*-chromen-3-yl)-1-cyclohexylallyl]morpholin-4-ium chloride (33b). White needles (H_2O), mp 221-222 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.05 (m, 3H, cHex), 1.27 (m, 2H, cHex), 1.62 (d, *J* = 12.3 Hz, 2H, cHex), 1.72 (d, *J* = 12.6 Hz, 2H, cHex), 2.01 (m, 2H, cHex), 2.43 (s, 3H, Me), 3.05 (m, 2H, NC$\underline{H}_2$CH$_2$O), 3.35 (m, 1H, NC$\underline{H}_2$CH$_2$O), 3.47 (m, 1H, NC$\underline{H}_2$CH$_2$O), 3.72 (m, 1H, C$\underline{H}$N), 3.96 (m, 4H, NCH$_2$C$\underline{H}_2$O), 6.53 (d, *J* = 15.8 Hz, 1H, CH=CH), 6.82 (dd, *J* = 10.3, 15.8 Hz, 1H, CH=CH), 7.85 (s, 1H, C^{7}H), 7.98 (s, 1H, C^{5}H), 8.77 (s, 1H, C^{2}H), 10.91 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 20.66, 25.67, 26.00, 26.08, 27.33, 30.80, 36.35, 49.96, 50.50, 63.42, 63.48, 74.54, 111.23, 119.53, 123.80, 124.85, 129.70, 137.08, 138.66, 150.42, 156.89, 175.28. HRMS-ESI: *m/z* calcd. for $C_{23}H_{29}BrNO_3$ [M+H]$^+$ 446.1325, found 446.1318.

(*E*)-4-[1-(6-chloro-4-oxo-4*H*-chromen-3-yl)-dodec-1-en-3-yl]morpholin-4-ium chloride (34a). White solid (ethyl acetate), mp 148-150 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 0.79 (t, *J* = 7.0 Hz, 3H, Me), 1.18 (m, 14H, CH$_2$), 1.75 (m, 1H, CH$_2$), 2.09 (m, 1H, CH$_2$), 3.05 (m, 2H, NC$\underline{H}_2$CH$_2$O), 3.42 (m, 2H, NC$\underline{H}_2$CH$_2$O), 3.90 (m, 5H, NCH$_2$C$\underline{H}_2$O, C$\underline{H}$N), 6.66 (m, 2H, CH=CH), 7.77 (d, *J* = 9.0 Hz, 1H, C^{8}H), 7.87 (dd, *J* = 2.5, 9.0 Hz, 1H, C^{7}H), 8.00 (d, *J* = 2.5 Hz, 1H, C^{5}H), 8.76 (s, 1H, C^{2}H), 11.69 (br.s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 14.39, 22.55, 25.92, 28.60, 28.91, 29.13, 29.24, 29.34, 31.75, 48.05, 50.09, 63.61, 63.69, 69.07, 119.54, 121.53, 124.63, 124.96, 125.10, 129.73, 130.68, 134.69, 154.29, 157.32, 174.70. HRMS-ESI: *m/z* calcd. for $C_{25}H_{35}ClNO_3$ [M+H]$^+$ 432.2300, found 432.2294.

(*E*)-4-[1-(6-chloro-4-oxo-4*H*-chromen-3-yl)-5-phenylpent-1-en-3-yl]morpholin-4-ium chloride (35a). White solid (ethyl acetate), mp 175-177 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 2.09 (m, 1H, CH$_2$), 2.45-2.62 (m, 3H, CH$_2$), 3.04 (m, 2H, NC$\underline{H}_2$CH$_2$O), 3.44 (m, 2H, NC$\underline{H}_2$CH$_2$O), 3.91 (m, 5H, NCH$_2$C$\underline{H}_2$O, C$\underline{H}$N), 6.69 (m, 2H, CH=CH), 7.24 (m, 5H, Ph), 7.79 (d, *J* = 9.0 Hz, 1H, C^{8}H), 7.89 (dd, *J* = 2.5, 9.0 Hz, 1H, C^{7}H), 8.04 (d, *J* = 2.5 Hz, 1H, C^{5}H), 8.77 (s, 1H, C^{2}H), 11.36 (br.s, 1H, NH). ^{13}C NMR

(100 MHz, DMSO-d_6): δ_C ppm 30.42, 31.93, 48.20, 50.15, 63.76, 68.88, 119.61, 121.58, 124.68, 125.00, 126.61, 128.77, 128.89, 130.28, 130.73, 134.76, 140.85, 154.37, 157.36, 174.81. HRMS-ESI: *m/z* calcd. for $C_{24}H_{25}ClNO_3$ $[M+H]^+$ 410.1517, found 410.1529.

3-(5-Chloro-2-hydroxybenzoyl)benzoic acid (36a). White solid (ethanol), mp 209-210 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 7.01 (d, J = 8.8 Hz, 1H, $C^{3'}$H), 7.29 (d, J = 2.5 Hz, 1H, $C^{6'}$H), 7.47 (dd, J = 2.5, 8.8 Hz, 1H, $C^{4'}$H), 7.67 (pseudo-t, J = 7.8 Hz, 1H, C^5H), 7.99 (d, J = 7.8 Hz, 1H, C^6H), 8.20 (d, J = 7.8 Hz, 1H, C^4H), 8.23 (s, 1H, C^2H), 10.43 (s, 1H, OH), 13.34 (br.s, 1H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 118.76, 123.27, 127.58, 129.38, 129.65, 130.55, 131.54, 132.75, 133.70, 134.15, 137.65, 155.04, 167.07, 194.84. HRMS-ESI: *m/z* calcd. for $C_{14}H_8ClO_4$ $[M-H]^-$ 275.0117, found 275.0104.

3-(5-Chloro-2-hydroxybenzoyl)-5-methylbenzoic acid (37a). White solid (ethanol), mp 238-240 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 2.43 (s, 3H, Me), 7.01 (d, J = 8.8 Hz, 1H, $C^{3'}$H), 7.36 (d, J = 2.8 Hz, 1H, $C^{6'}$H), 7.45 (dd, J = 2.8, 8.8 Hz, 1H, $C^{4'}$H), 7.80 (s, 1H, C^6H), 8.02 (s, 2H, C^4H, C^2H), 10.40 (s, 1H, OH), 13.22 (br.s, 1H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 21.10, 118.81, 123.24, 127.70, 128.10, 129.30, 131.54, 132.67, 133.79, 134.64, 137.77, 139.22, 155.11, 167.13, 195.01. HRMS-ESI: *m/z* calcd. for $C_{15}H_{10}ClO_4$ $[M-H]^-$ 289.0273, found 289.0288.

3-(5-Chloro-2-hydroxybenzoyl)-5-ethylbenzoic acid (38a). White solid (ethanol), mp 229-231 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.21 (t, J = 7.5 Hz, 3H, Me), 2.74 (q, J = 7.5 Hz, 2H, CH_2), 7.01 (d, J = 8.5 Hz, 1H, $C^{3'}$H), 7.36 (d, J = 2.5 Hz, 1H, $C^{6'}$H), 7.45 (dd, J = 2.5, 8.5 Hz, 1H, $C^{4'}$H), 7.84 (s, 1H, C^6H), 8.03 (s, 1H, C^4H), 8.04 (s, 1H, C^2H), 10.40 (s, 1H, OH), 13.18 (br.s, 1H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 15.78, 28.16, 118.81, 123.27, 127.62, 128.50, 129.38, 131.65, 132.65, 132.72, 133.49, 137.80, 145.34, 155.15, 167.15, 194.99. HRMS-ESI: *m/z* calcd. for $C_{16}H_{12}ClO_4$ $[M-H]^-$ 303.0430, found 303.0411.

3-(5-Chloro-2-hydroxybenzoyl)-5-phenylbenzoic acid (39a). White solid (ethanol), mp 205-207 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 7.03 (d, J = 8.8 Hz, 1H, $C^{3'}$H), 7.43-7.54 (m, 5H, $C^{6'}$H, $C^{4'}$H, Ph), 7.72 (d, J = 7.3 Hz, 2H, Ph), 8.19 (s, 1H, C^6H), 8.21 (s, 1H, C^4H), 8.40 (s, 1H, C^2H), 10.47 (s, 1H, OH), 13.41 (br.s, 1H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C ppm 118.93, 123.41, 127.38, 128.84, 129.48, 129.66, 129.73, 131.49, 131.97, 132.44, 133.05, 138.51, 138.87, 141.48, 155.26, 166.96, 194.68. HRMS-ESI: *m/z* calcd. for $C_{20}H_{12}ClO_4$ $[M-H]^-$ 351.0430, found 351.0440.

EeAChE and eqBChE inhibition assays. Enzyme inhibition assays were performed on AChE from electric eel (C3389-1KU; Sigma) and BChE from equine serum (C7512-6KU; Sigma), according to the spectrophotometric Ellman method as previously described [30]. The experiment was performed in 96-well plates with a final volume 250 µL. Each well contained 0.08 U/mL of EeAChE or eqBChE, and 0.1 M of pH 8 phosphate buffer. The plates were incubated for 20 min at different compound concentrations at 37ºC. Then 0.35 mM acetylthiocholine iodide (ATCh; A5751-1G; Sigma) or 0.35 mM butyrylthiocholine iodide (20820-5G; Sigma) and 0.35 mM 5,5'-dithiobis-2-nitrobenzoic acid (DTNB; D218200-1G; Sigma) were added. Change in absorbance was measured at 410 nm in a kinetic mode for 10 min every 60 s at Tecan Infinite M200 Pro reader. The IC_{50} values were determined graphically from inhibition curves (log inhibitor concentration vs percent of inhibition). A control experiment was performed under the same conditions without inhibitor and the blank contained buffer, DMSO, DTNB, and substrate.

NMDA receptors antagonism. All experimental procedures were approved by Animal Care and Use Committee of the Sechenov Institute of Evolutionary Physiology and Biochemistry of the Russian Academy of Sciences. Outbred male Wistar rats of 13–18 days old and 25–35 g were obtained from local (IEPHB) facility. Maximum efforts were made to minimize the number of animals used and to minimize discomfort. Rats were anesthetized with urethane and then decapitated. Brains were removed quickly and cooled to 2–4 C. Transverse hippocampal and striatal slices were prepared using a vibratome (Campden Instr.) and single neurons were freed from slices by vibrodissociation [31]. All experiments were performed at room temperature. The whole-cell patch clamp technique was used for recording membrane currents in response to applications of an agonist. Series resistance of about 20 MΩ was compensated by 70–80% and monitored during experiments. Currents were recorded using an EPC-8 amplifier (HEKA Electronics, Lambrecht, Germany), filtered at 5 kHz, sampled and stored on a personal computer. Drugs were applied using RSC-200 (BioLogic) perfusion system under computer control. The extracellular solution contained (in mM): NaCl 143, KCl 5, CaCl2 2.5, D-glucose 18, HEPES 10 (pH was adjusted to 7.4 with NaOH). The pipette solution contained (in mM): CsF 100, CsCl 40, NaCl 5, $CaCl_2$ 0.5, EGTA 5, HEPES 10 (pH was adjusted to 7.2 with CsOH). Drugs were purchased from Tocris Bioscience (Bristol, UK) and Sigma (St Louis, MO, USA). Experiments were conducted on hippocampal pyramidal neurons (CA1 area). NMDA receptors were activated by 100 µM NMDA plus 10 µM glycine. The percentage of block of the steady-state current by different drug concentrations was measured at -80mV holding potential and IC_{50} values were obtained from fits by the Hill equation of concentration-inhibition relationships. All data are presented as means ± SD estimated from at least four experiments.

Computation. All calculations were performed using Gaussian 16 [13] software. Geometry optimisation was conducted using meta-hybrid M06-2X density functional [32] on 6-31+G** level. For all the optimized structures the frequency calculations were conducted to verify the nature of stationary points. For the stationary points involved the single-point energy calculations were performed at MP2(full)/6-31+G** level. Thermal corrections to free energy were calculated at M06-2X/6-31+G** level.

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Keywords: chromone • enamine • morpholine • allylamine • Morita-Baylis-Hillman reaction

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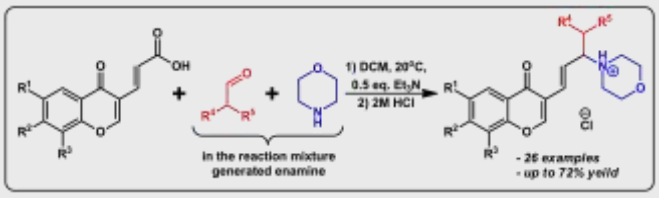

An unusual addition of enamines to chromone-substituted acrylic acid is an efficient and versatile method of synthesis of allylamine derivatives. The reaction is catalyzed by amines and is highly likely of Morita-Baylis-Hillman-type. The described compounds show combined moderate inhibitory action on BChE and antagonism towards NMDA receptors

Heterocyclic chemistry*

Nikita M. Chernov, Roman V. Shutov, Oleg I. Barygin, Mikhail Y. Dron, Galina L. Starova, Nikolay N. Kuz'mich and Igor P. Yakovlev*

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