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Dedicated to Prof. V. P. Khilya on the occasion of his 81st birthday

Strategy for the synthesis of 2,2-disubstituted 8-azachromanones *via* Horner–Wadsworth–Emmons olefination

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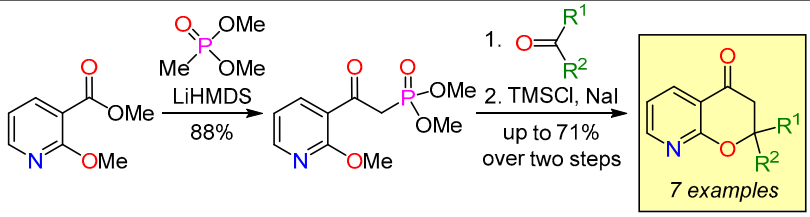


A series of 2,2-disubstituted 8-azachromanones, including spirocyclic compounds, have been synthesized *via* Horner–Wadsworth–Emmons reaction. Dimethyl methylphosphonate was acylated with methyl 2-methoxypyridine-3-carboxylate to afford the key intermediate – dimethyl [2-(2-methoxypyridin-3-yl)-2-oxoethyl]phosphonate. Further reaction of this phosphonate and ketones followed by treatment with TMSCl–NaI provided the target 8-azachromanones. Scope and limitations of the developed synthetic method have been investigated.

Keywords: azachromanone, phosphonate, cyclization, Horner–Wadsworth–Emmons reaction, olefination, protecting group.

Recently, 2,3-dihydro-4*H*-pyrano[2,3-*b*]pyridin-4-one (8-azachromanone) scaffold has been in the spotlight of medicinal chemistry as bioisosteric analog of chroman-4-one – a privileged structure in heterocyclic chemistry and drug discovery.[1] In this regard, 8-azachromanone is the key structural motif of many biologically active compounds. Among them, amlexanox[2] (Fig. 1), which is the active component of marketed drugs for treatment of aphthous ulcers (canker sores), asthma, and allergic rhinitis that reduce both healing time and pain, acts as anti-inflammatory and antiallergic immunomodulator.[3] In addition, amlexanox was found to inhibit TANK-binding kinase 1 (TBK1) and nuclear factor kappa-B kinase subunit e (IKKe) thus effectively lowering the level of glycated hemoglobin (HbA1c).[4] These results have promoted computational design of amlexanox analogs for treatment of type 2 diabetes and obesity.[5] Finally, amlexanox binds to low molecular weight Ca^{2+}-binding proteins S100A12 and S100A13.[6]

As other biologically active compounds, pyridochromanones **1** and **2** (Fig. 1) have been identified as potent inhibitors of NAD^+-dependent DNA ligase from

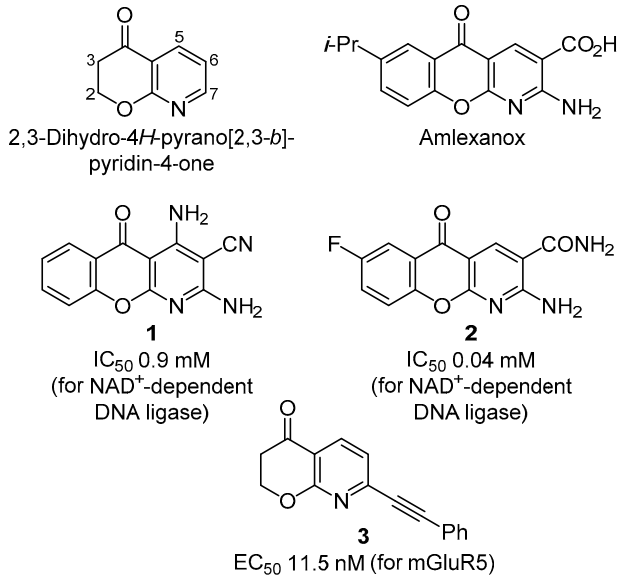
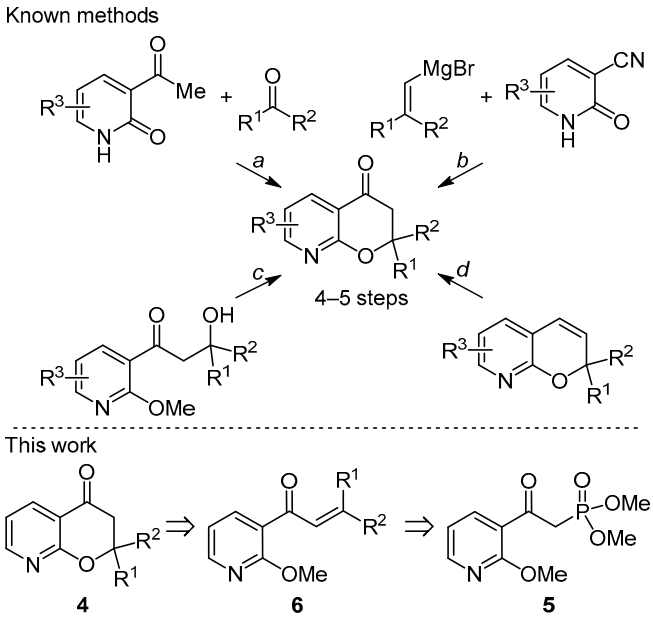


Figure 1. Biologically active compounds containing 8-azachromanone scaffold.

E. coli.[7] They also exhibit antibacterial activity against pathogen *S. aureus* without affecting eukaryotic cells, which is a prerequisite for the generation of a wide range of specific antibacterial compounds.[8] It has also been demonstrated that 7-(phenylethynyl)-8-azachromanone (**3**) (Fig. 1) acts as a positive allosteric modulator of metabotropic glutamate receptor 5 (mGluR5).[9] Such modulators are interesting in terms of developing antipsychotics and preventing the symptoms of schizophrenia.[10]

Several synthetic approaches for obtaining 2,2-disubstituted 8-azachromanones are known to date. For example, condensation of 3-acetyl-2-pyridones and ketones (pathway *a*),[11] addition of vinyl Grignard reagents to 3-cyano-2-pyridones followed by acidic hydrolysis (pathway *b*),[11a,12] acid- and $POCl_3$-mediated cyclization of 3-(β-hydroxypropionyl)-2-methoxypyridines (pathway *c*),[13] as well as multistep transformations of 2*H*-pyrano[2,3-*b*]pyridines (pathway *d*)[14] have been reported (Scheme 1).

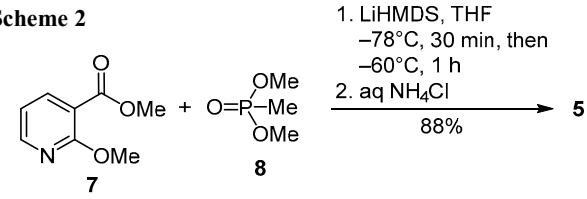
Scheme 1



In the present work, we focused on development of an alternative strategy for the synthesis of 2,2-disubstituted 8-azachromanones **4**, which is based on Horner–Wadsworth–Emmons (HWE) reaction[15] (Scheme 1). The notable features of this chemical transformation that make it both rational and general for obtaining compounds **4** from dimethyl phosphonate **5** are application of inexpensive and readily available starting materials, mild reaction conditions, as well as formation of easily removable byproducts (water-soluble phosphate salts). β-Ketophosphonates, necessary for the HWE reaction to afford α,β-unsaturated ketones **6**, can be easily produced from dialkyl methylphosphonates *via* deprotonation with strong bases (e.g., *n*-BuLi,[16] LDA,[17] or LiHMDS[18]) at low temperature (usually –78°C)[18c] followed by treatment with the corresponding esters, anhydrides, or acyl chlorides.

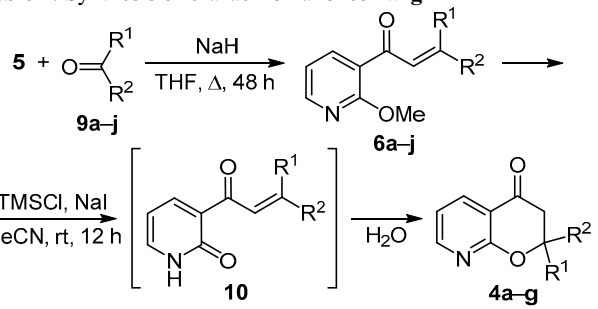
To the best of our knowledge, only synthesis of 2,2-dimethyl-8-azachromanone (**4a**) (R^1 = R^2 = Me) according to the aforementioned strategy has been reported in literature.[19] This underlaid our attempts in investigation of the substrate scope and limitations of the proposed method. First of all, dimethyl [2-(2-methoxypyridin-3-yl)-2-oxoethyl]phosphonate (**5**) was prepared in 88% yield by LiHMDS-mediated condensation of methyl 2-methoxypyridine-3-carboxylate (**7**) and dimethyl methylphosphonate (**8**) (Scheme 2).

Scheme 2



NaH-promoted HWE reaction of β-ketophosphonate **5** and ketones or aldehydes **9a**–**j** in THF provided a series of α,β-unsaturated ketones **6a**–**j**. The crude intermediates were further subjected to treatment with TMSCl–NaI followed by aqueous workup. The most suitable substrates for the two-step reaction sequence described above were ketones **9a**–**g** with methylene groups at both sides of the carbonyl group, as they provided the desired 8-azachromanones **4a**–**g** (Table 1, entries 1–7). However, 8-azachromanone **4b**, derived from cyclobutanone (**9b**), was isolated in

Table 1. Synthesis of 8-azachromanones **4a**–**g***



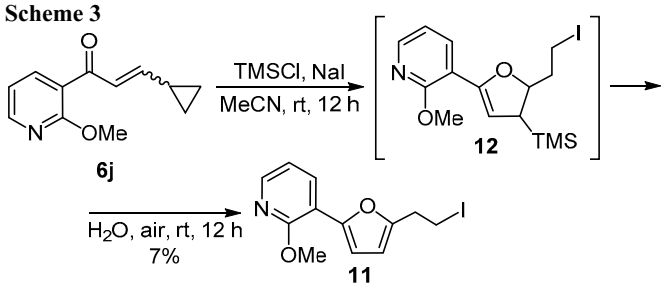
Entry	Carbonyl compound	R^1/R^2	Product	Yield**, %
1	**9a**	Me/Me	**4a**	64
2	**9b**	$(CH_2)_3$	**4b**	8
3	**9c**	$(CH_2)_4$	**4c**	42
4	**9d**	$(CH_2)_5$	**4d**	71
5	**9e**	$(CH_2)_2O(CH_2)_2$	**4e**	43
6	**9f**	$(CH_2)_2N(CO_2Et)(CH_2)_2$	**4f**	37
7	**9g**	$(CH_2)_2N(Ms)(CH_2)_2$	**4g**	51
8	**9h**	$(CH_2)_2N(Bn)(CH_2)_2$	**10h**·HI	17
9	**9i**	H/Ph	**10i**	86
10	**9j**	H/*cyclo*C_3H_5	**11**	7
11***	**9k**	Me/Ph	–	–
12***	**9l**	Me/*i*-Pr	–	–

* Amounts of reactants and solvent, step 1: phosphonate **5** (1.05 g, 4 mmol), carbonyl compound **9a**–**e**,**i**,**j** (20 mmol) or **9f**–**h** (8 mmol), NaH (60% dispersion in mineral oil, 0.18 g, 4.4 mmol), THF (20 ml). Crude intermediates **6a**–**j** were used in next step. Step 2: TMSCl (0.6 ml, 4.4 mmol), NaI (0.66 g, 4.4 mmol), MeCN (20 ml).
** Yield based on phosphonate **5**.
*** After the first step, starting materials were recovered.

low yield (8%) due to significant formation of tar (entry 2). Under the reaction conditions, sterically hindered acetophenone (**9k**) and methyl isopropyl ketone (**9l**) failed to produce the corresponding intermediates **6k**,**l** (entries 11–12). Both carbo- and heterocyclic ketones could be used as starting materials leading to spirocyclic 8-azachromanone derivatives **4b**–**g** (entries 2–7). As it might be expected, the protecting group of *N*-Boc-piperidone was incompatible with the reaction conditions, while ethoxycarbonyl and mesyl groups were tolerated (entries 6 and 7). Meanwhile, benzyl protecting group was stable under the applied conditions, but the corresponding intermediate **10h** did not undergo further cyclization (entry 8). Possibly, deactivating effect of the protonated piperidine fragment might be addressed to some conformational constraints introduced by this moiety.

All attempts to exploit benzaldehyde (**9i**) as starting material did not work even when the cyclization was performed at elevated temperatures. Instead of product **4i**, either intermediate **6i** or 2-pyridone derivative **10i** was isolated (Table 1, entry 9). Most likely, α,β-unsaturated carbonyl moiety participates in conjugation with the benzene ring thereby reducing its electrophilicity and precluding the expected intramolecular cyclization. In the case of cyclopropanecarbaldehyde (**9j**), a complex mixture was obtained upon treatment of intermediate **6j** with TMSCl–NaI. Chromatographic separation of this mixture allowed isolating unusual side product **11** in 7% yield (entry 10, Scheme 3) and recover *ca.* 20% of intermediate **6j**.

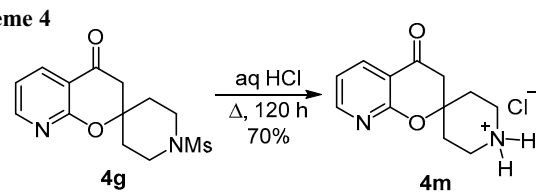
Scheme 3



Formation of furan derivative **11** might be rationalized *via* nucleophilic attack of iodide anion at the cyclopropane moiety of compound **6j** with simultaneous formation of intermediate **12** containing silylated 4,5-dihydrofuran ring. Upon workup procedure, the latter undergoes desilylation and subsequent aromatization to afford compound **11** (Scheme 3).

To demonstrate the utility of the developed synthetic method, *N*-mesyl-protected 8-azachromanone derivative **4g** was subjected to deprotection upon prolonged refluxing with aq HCl to afford spirocyclic compound **4m**, a promising sp^3-enriched bifunctional building block for medicinal chemistry,[20] in 70% yield (Scheme 4).

Scheme 4



In summary, an efficient approach to gram-scale synthesis of 2,2-disubstituted 8-azachromanones based on Horner–Wadsworth–Emmons reaction of dimethyl [2-(2-methoxypyridin-3-yl)-2-oxoethyl]phosphonate and carbo- or heterocyclic ketones has been developed. It was found that substrate scope of this method includes ketones with two methylene groups adjacent to the carbonyl group. Moreover, acid-labile functional groups as well as strongly basic centers, for example, tertiary amines were not tolerated. The developed procedure provides access to mono- and bifunctional sp^3-enriched natural product-like scaffolds, which have a great potential for early drug discovery.

Experimental

^{1}H and ^{13}C spectra were obtained on a Varian Mercury 400 spectrometer (400 MHz (compounds **4a**–**f**,**m**, **5**, **10i**) and 100 MHz (compounds **4b**,**m**, **10h**·HI), respectively) and a Bruker Avance 500 spectrometer (500 MHz (compounds **4g**, **10h**·HI, **11**) and 126 MHz (compounds **4a**,**c**–**g**, **5**, **10i**, **11**), respectively) in DMSO-d_6 (compounds **4b**,**e**,**f**,**m**, **10h**·HI) or $CDCl_3$ (compounds **4a**,**c**,**d**,**g**, **5**, **10i**, **11**) using TMS as internal standard. ^{31}P NMR spectrum of compound **5** was obtained on a Bruker Avance 500 spectrometer (202 MHz) in $CDCl_3$ using H_3PO_4 as internal standard. Mass spectra were recorded on Agilent 1100 LC/MSD SL (APCI, compounds **4b**–**g**, **10h**·HI, **10i**, **11**) and Agilent 5890 Series II 5972 GC/MS (EI, 70 eV, compounds **4a**, **5**) instruments. HRMS analyses were conducted on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer. Elemental analyses were performed on a vario MICRO cube elemental analyzer. Melting points were measured on an OptiMelt MPA100 automated melting point apparatus. Progress of reactions was monitored by TLC on Polychrom SI F_{254} plates using MTBE–MeOH, 1:1, as eluent (visualization with UV light). Compound **4m** was purified by preparative HPLC on an Agilent 1260 Infinity instrument, column Waters SunFire C18 (10 × 190 mm, particle size 5 μm), gradient elution with H_2O–MeCN.

All starting materials were purchased from Enamine Ltd. and UORSY. Solvents were purified according to standard procedures.[21]

Dimethyl [2-(2-methoxypyridin-3-yl)-2-oxoethyl]-phosphonate (5). Dimethyl methylphosphonate (**8**) (12.4 g, 0.10 mol) was dissolved in THF (300 ml), and the solution was cooled to –78°C. A 1 M solution of LiHMDS in PhMe (110 ml, 0.11 mol) was added dropwise upon stirring at –78°C, and the resulting mixture was stirred for 30 min. After warming to –60°C, a solution of methyl 2-methoxypyridine-3-carboxylate (**7**) (10.0 g, 0.06 mol) in THF (60 ml) was added. The reaction mixture was stirred at –60°C for 1 h, then allowed to warm to 0°C, quenched with saturated aq NH_4Cl (250 ml), and extracted with CH_2Cl_2 (3×300 ml). The combined organic layers were dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography (SiO_2, eluent MTBE–MeOH, 95:5). Yield 13.7 g (88%), yellow liquid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.32 (1H, dd, *J* = 4.9, *J* = 2.1, H-4); 8.10 (1H, dd, *J* = 7.6, *J* = 2.1, H-6); 6.99 (1H, dd,

J = 7.6, *J* = 4.9, H-5); 4.07 (3H, s, OCH_3); 3.85 (2H, d, *J* = 21.8, CH_2); 3.76 (3H, s, $POCH_3$); 3.73 (3H, s, $POCH_3$). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 191.7 (d, *J* = 7.1); 161.8; 151.5; 140.4; 121.0 (d, *J* = 3.1); 117.3; 54.0; 52.9 (d, *J* = 6.4); 41.6; 40.6. ^{31}P NMR spectrum, δ, ppm: 23.8. Mass spectrum, *m*/*z* (I_{rel}, %): 259 $[M]^+$ (3), 149 $[M–PO(OMe)_2]^+$ (25), 134 $[M–Me–PO(OMe)_2]^+$ (100). Found, %: C 46.11; H 5.11; N 5.14. $C_{10}H_{14}NO_5P$. Calculated, %: C 46.34; H 5.44; N 5.40.

Synthesis of pyrano[2,3-*b*]pyridin-4(3*H*)-ones 4a–g (General method). NaH (60% dispersion in mineral oil, 0.18 g, 4.4 mmol) was added under argon atmosphere at room temperature to a solution of phosphonate **5** (1.05 g, 4.0 mmol) in THF (20 ml). The resulting mixture was stirred at room temperature for 30 min, then cooled in an ice bath. Ketone **9a**–**e** (20 mmol) or **9f**,**g** (8 mmol) was added, the mixture was allowed to warm to room temperature and then refluxed for 48 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was diluted with H_2O (20 ml) and extracted with EtOAc (3×25 ml). The combined extracts were dried over anhydrous Na_2SO_4. The obtained crude α,β-unsaturated ketone **6a**–**g** was dissolved in MeCN (20 ml), and TMSCl (0.6 ml, 4.4 mmol) and NaI (0.66 g, 4.4 mmol) were added at room temperature. The resulting mixture was stirred at room temperature for 12 h, diluted with H_2O (40 ml), and extracted with CH_2Cl_2 (3×30 ml). The combined organic layers were dried over anhydrous Na_2SO_4. The crude product was purified by column chromatoraphy (SiO_2, eluent MTBE–MeOH, 1:1).

2,2-Dimethyl-2,3-dihydro-4*H*-pyrano[2,3-*b*]pyridin-4-one (4a). Yield 0.45 g (64%), beige crystals, mp 97–98°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.45 (1H, dd, *J* = 4.7, *J* = 2.2, H-7); 8.19 (1H, dd, *J* = 7.5, *J* = 2.2, H-5); 7.02 (1H, dd, *J* = 7.5, *J* = 4.7, H-6); 2.76 (2H, s, $C(O)CH_2$); 1.52 (6H, s, $2CH_3$). ^{13}C NMR spectrum, δ, ppm: 192.2; 164.6; 155.1; 136.4; 117.9; 114.7; 79.4; 48.4; 26.7. Mass spectrum, *m*/*z* (I_{rel}, %): 177 $[M]^+$ (94), 162 $[M–Me]^+$ (100), 121 $[M–H_2C=C(CH_3)_2]^+$ (66). Found, %: C 67.56; H 6.15; N 8.08. $C_{10}H_{11}NO_2$. Calculated, %: C 67.78; H 6.26; N 7.90.

Spiro[cyclobutane-1,2'-pyrano[2,3-*b*]pyridin]-4'(3'*H*)-one (4b). Yield 60 mg (8%), white crystals, mp 100–102°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.48 (1H, dd, *J* = 4.6, *J* = 2.1, H-7); 8.13 (1H, dd, *J* = 7.5, *J* = 2.1, H-5); 7.17 (1H, dd, *J* = 7.5, *J* = 4.6, H-6); 3.04 (2H, s, $C(O)CH_2$); 2.35–2.20 (2H, m, CH_2); 2.20–2.05 (2H, m, CH_2); 1.92–1.70 (2H, m, CH_2). ^{13}C NMR spectrum, δ, ppm: 192.6; 164.3; 155.5; 136.6; 119.1; 115.5; 80.6; 45.1; 33.0; 12.1. Mass spectrum, *m*/*z* (I_{rel}, %): 190 $[M+H]^+$ (100). Found, %: C 69.53; H 5.52; N 7.67. $C_{11}H_{11}NO_2$. Calculated, %: C 69.83; H 5.86; N 7.40.

Spiro[cyclopentane-1,2'-pyrano[2,3-*b*]pyridin]-4'(3'*H*)-one (4c). Yield 0.34 g (42%), yellow oil. ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.42 (1H, dd, *J* = 4.8, *J* = 2.2, H-7); 8.18 (1H, dd, *J* = 7.6, *J* = 2.2, H-5); 7.01 (1H, dd, *J* = 7.6, *J* = 4.8, H-6); 2.85 (2H, s, $C(O)CH_2$); 2.18–2.07 (2H, m, CH_2); 2.00–1.88 (2H, m, CH_2); 1.76–1.60 (4H, m, $2CH_2$). ^{13}C NMR spectrum, δ, ppm: 192.3; 165.1; 154.9; 136.6; 118.0; 115.4; 90.0; 46.5; 37.7; 23.8. Mass spectrum, *m*/*z* (I_{rel}, %): 204 $[M+H]^+$ (100). Found, %: C 70.64; H 6.10; N 7.04. $C_{12}H_{13}NO_2$. Calculated, %: C 70.92; H 6.45; N 6.89.

Spiro[cyclohexane-1,2'-pyrano[2,3-*b*]pyridin]-4'(3'*H*)-one (4d). Yield 0.62 g (71%), yellow oil. ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.43 (1H, dd, *J* = 4.7, *J* = 2.1, H-7); 8.16 (1H, dd, *J* = 7.6, *J* = 2.1, H-5); 7.00 (1H, dd, *J* = 7.5, *J* = 4.8, H-6); 2.73 (2H, s, $C(O)CH_2$); 2.06–1.95 (2H, m, CH_2); 1.87–1.74 (2H, m, CH_2); 1.67–1.45 (5H, m) and 1.39–1.26 (1H, m, $3CH_2$). ^{13}C NMR spectrum, δ, ppm: 192.4; 164.4; 155.0; 136.3; 117.9; 115.3; 80.4; 47.6; 34.9; 25.0; 21.3. Mass spectrum, *m*/*z* (I_{rel}, %): 218 $[M+H]^+$ (100). Found, %: C 71.59; H 7.22; N 6.29. $C_{13}H_{15}NO_2$. Calculated, %: C 71.87; H 6.96; N 6.45.

2,3,5,6-Tetrahydrospiro[pyran-4,2'-pyrano[2,3-*b*]-pyridin]-4'(3'*H*)-one (4e). Yield 0.38 g (43%), yellow crystals, mp 131–134°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.49 (1H, dd, *J* = 4.8, *J* = 2.1, H-7); 8.14 (1H, dd, *J* = 7.6, *J* = 2.1, H-5); 7.17 (1H, dd, *J* = 7.6, *J* = 4.8, H-6); 3.75–3.59 (4H, m, $2OC\underline{H}_2CH_2$); 2.93 (2H, s, $C(O)CH_2$); 1.90–1.71 (4H, m, $2OCH_2C\underline{H}_2$). ^{13}C NMR spectrum, δ, ppm: 192.3; 164.0; 155.5; 136.4; 119.0; 115.4; 77.8; 62.8; 46.9; 34.7. Mass spectrum, *m*/*z* (I_{rel}, %): 220 $[M+H]^+$ (100). Found, %: C 65.81; H 5.74; N 6.63. $C_{12}H_{13}NO_3$. Calculated, %: C 65.74; H 5.98; N 6.39.

Ethyl 4'-oxo-3',4'-dihydro-1*H*-spiro[piperidine-4,2'-pyrano[2,3-*b*]pyridine]-1-carboxylate (4f). Yield 0.43 g (37%), yellow oil. ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.45 (1H, dd, *J* = 4.9, *J* = 2.0, H-7); 8.10 (1H, dt, *J* = 7.5, *J* = 2.0, H-5); 7.14 (1H, dd, *J* = 7.5, *J* = 4.9, H-6); 4.00 (2H, q, *J* = 7.2, $OC\underline{H}_2CH_3$); 3.74 (2H, d, *J* = 13.4, $NC\underline{H}_2CH_2$); 3.27–2.98 (2H, m, $NC\underline{H}_2CH_2$); 2.88 (2H, s, $C(O)CH_2$); 1.86 (2H, d, *J* = 13.4, $NCH_2C\underline{H}_2$); 1.66 (2H, td, *J* = 13.4, *J* = 4.6, $NCH_2C\underline{H}_2$); 1.13 (3H, t, *J* = 7.2, $OCH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 192.2; 163.9; 155.5; 155.0; 136.4; 119.0; 115.4; 78.4; 61.2; 46.6; 39.4; 33.7; 15.0. Mass spectrum, *m*/*z* (I_{rel}, %): 291 $[M+H]^+$ (100). Found, %: C 62.25; H 6.20; N 9.39. $C_{15}H_{18}N_2O_4$. Calculated, %: C 62.06; H 6.25; N 9.65.

1-(Methylsulfonyl)spiro[piperidine-4,2'-pyrano[2,3-*b*]-pyridin]-4'(3'*H*)-one (4g). Yield 0.60 g (51%), white crystals, mp 195–196°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.47 (1H, d, *J* = 2.5, H-7); 8.22 (1H, dd, *J* = 7.6, *J* = 2.5, H-5); 7.10 (1H, dd, *J* = 7.6, *J* = 4.8, H-6); 3.67 (2H, dt, *J* = 12.0, *J* = 4.8, $NC\underline{H}_2CH_2$); 3.20 (2H, td, *J* = 12.0, *J* = 2.5, $NC\underline{H}_2CH_2$); 2.80 (3H, s, SO_2CH_3); 2.79 (2H, s, $C(O)CH_2$); 2.17 (2H, d, *J* = 12.0, $NCH_2C\underline{H}_2$); 1.86 (2H, td, *J* = 12.0, *J* = 4.8, $NCH_2C\underline{H}_2$). ^{13}C NMR spectrum, δ, ppm: 190.7; 163.5; 155.1; 136.9; 118.8; 115.3; 77.1; 47.5; 41.2; 34.9; 34.1. Mass spectrum, *m*/*z* (I_{rel}, %): 297 $[M+H]^+$ (100). Found, %: C 52.55; H 5.64; N 9.15; S 10.90. $C_{13}H_{16}N_2O_4S$. Calculated, %: C 52.69; H 5.44; N 9.45; S 10.82.

1-Benzyl-4-[2-oxo-2-(2-oxo-1,2-dihydropyridin-3-yl)-ethylidene]piperidinium iodide (10h·HI). Obtained from ketone **9h** (1.51 g, 8.0 mmol) according to general method for the synthesis of compounds **4a**–**g**. After extraction with EtOAc (3×25 ml), the combined organic layers were discarded and aqueous layer was allowed to stand at room temperature for 12 h. The precipitate formed was filtered off and air-dried. Yield 0.30 g (17%), white crystals,

mp 217–218°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.26 (1H, s, C(O)NH); 9.87 (1H, s, $^+$NH(CH$_2$)$_3$); 8.05 (1H, d, *J* = 7.2, H-4); 7.74 (1H, d, *J* = 6.5, H-6); 7.51 (2H, d, *J* = 7.2, H-3,5 Ph); 7.46 (3H, d, *J* = 7.2, H-2,4,6 Ph); 6.35 (1H, t, *J* = 6.5, H-5); 5.48 (1H, s, C(O)CH); 4.37 (2H, s, NCH$_2$Ph); 3.90–3.78 (2H, m) and 3.67–3.55 (2H, m, 2NCH$_2$CH$_2$); 3.48–3.40 (1H, m), 3.15–3.06 (1H, m), 2.47–2.36 (1H, m), and 2.31–2.22 (1H, m, 2NCH$_2$CH$_2$). ^{13}C NMR spectrum, δ, ppm: 196.7; 161.5; 145.0; 142.6; 132.5; 131.7; 130.2; 130.1; 129.4; 126.6; 117.3; 105.7; 58.2; 49.6; 49.3; 48.1; 25.8. Mass spectrum, *m*/*z* (I_{rel}, %): 309 [M+H]$^+$ (100). Found, %: C 52.38; H 4.96; N 6.54. $C_{19}H_{21}IN_2O_2$. Calculated, %: C 52.31; H 4.85; N 6.42.

3-[(2*Z*)-3-Phenylprop-2-enoyl]pyridin-2(1*H*)-one (10i). Obtained from benzaldehyde (**9i**) (2.0 ml, 20.0 mmol). Yield 0.77 g (86%), beige crystals, mp 172–174°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.13 (1H, s, C(O)NH); 8.26 (1H, dd, *J* = 7.2, *J* = 2.2, H-4); 7.98 (1H, d, *J* = 15.8, C(O)CH=CH); 7.81 (1H, d, *J* = 15.8, C(O)CH=CH); 7.73–7.56 (3H, m, H-6, H-2,6 Ph); 7.47–7.30 (3H, m, H-3,4,5 Ph); 6.46 (1H, t, *J* = 6.7, H-5). ^{13}C NMR spectrum, δ, ppm: 188.9; 163.7; 145.4; 143.5; 140.0; 135.2; 130.4; 128.9; 128.7; 128.3; 125.3; 107.3. Mass spectrum, *m*/*z* (I_{rel}, %): 226 [M+H]$^+$ (100). Found, %: C 74.89; H 4.63; N 6.16. $C_{14}H_{11}NO_2$. Calculated, %: C 74.65; H 4.92; N 6.22.

3-[5-(2-Iodoethyl)furan-2-yl]-2-methoxypyridine (11). Obtained from cyclopropanecarbaldehyde (**9j**) (1.5 ml, 20.0 mmol). Yield 90 mg (7%), white solid, mp 134–136°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.05 (1H, dd, *J* = 4.9, *J* = 1.5, H-6); 8.03 (1H, dd, *J* = 7.5, *J* = 1.5, H-4); 6.95 (1H, dd, *J* = 7.5, *J* = 4.9, H-5); 6.92 (1H, d, *J* = 3.3, H-3'); 6.24 (1H, d, *J* = 3.3, H-4'); 4.07 (3H, s, OCH$_3$); 3.40 (2H, t, *J* = 7.5, CH$_2$CH$_2$I); 3.27 (2H, t, *J* = 7.5, CH$_2$CH$_2$I). ^{13}C NMR spectrum, δ, ppm: 158.9; 153.6; 147.8; 144.4; 133.0; 116.9; 114.6; 111.5; 108.9; 53.5; 32.8; 1.6. Mass spectrum, *m*/*z* (I_{rel}, %): 330 [M+H]$^+$ (100), 188 [M–Me–I+H]$^+$ (24). Found, %: C 43.95; H 3.68; N 4.57. $C_{12}H_{12}INO_2$. Calculated, %: C 43.79; H 3.68; N 4.26.

4'-Oxo-3',4'-dihydrospiro[piperidinium-4,2'-pyrano-[2,3-*b*]pyridine] chloride (4m). A solution of 8-aza-chromanone **4g** (0.30 g, 1.0 mmol) in 20% aq HCl (6 ml) was refluxed for 120 h. The solvent was evaporated under reduced pressure, and the obtained residue was purified by preparative HPLC. The eluate was acidified with 20% aq HCl to pH 3 and evaporated under reduced pressure. Yield 0.18 g (70%), beige crystals, mp 212–215°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.45 (1H, s) and 9.26 (1H, s, $^+$NH$_2$(CH$_2$)$_2$); 8.51 (1H, d, *J* = 4.4, H-7); 8.17 (1H, d, *J* = 7.4, H-5); 7.22 (1H, dd, *J* = 7.4, *J* = 4.5, H-6); 3.18 (2H, d, *J* = 12.8, NCH$_2$CH$_2$); 3.05 (2H, q, *J* = 11.4, NCH$_2$CH$_2$); 2.98 (C(O)CH$_2$); 2.12 (2H, d, *J* = 14.4, NCH$_2$CH$_2$); 2.01 (2H, t, *J* = 13.0, NCH$_2$CH$_2$). ^{13}C NMR spectrum, δ, ppm: 191.5; 163.4; 155.4; 136.8; 119.4; 115.4; 76.6; 46.2; 39.2; 30.7. Found, *m*/*z*: 219.1129 [M+H]$^+$. $C_{12}H_{15}N_2O_2$. Calculated, *m*/*z*: 219.1133.

Supplementary information file containing ^{1}H and ^{13}C NMR spectra of the synthesized compounds is available at the journal website at http://link.springer.com/journal/10593.

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