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Intramolecular Diels-Alder Reactions of 2(1*H*)-Pyrazinones: Synthesis of New Furo/Pyrano-pyridinones and -pyridines

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Abstract: 2(1*H*)-Pyrazinones 2-5 with in 3-position either a 3- or 4-alkynyloxy side chain and 2(1*H*)-pyrazinones 9-10 carrying the corresponding 2- or 3-alkynyloxy(m)ethyl substituent are shown to undergo intramolecular Diels-Alder reaction. The formation of either fused pyridinones 13, 16, 20, 22 or 24 and/or pyridines 14, 17, 19 or 25 depends on the substitution pattern of the anchored pyrazinone and runs *via* the loss of either nitrile or isocyanate from the intermediate cycloadduct. The influence of the position of the oxygen atom and the length of the side chain on the reaction conditions is also discussed.

Inverse electron demand Diels-Alder reactions of heterocyclic azadienes with electron-rich dienophiles have received considerable attention. Thermolysis of 1,2,4-triazines,¹ pyrazines² and pyrimidines³ with a dienophilic side chain linked to the heterocycle *via* an ether function gave furo- or pyranopyridines. Similar reactions of pyrimidines⁴ or pyrazines⁵ with a five- or six membered alkynyloxyalkyl side chain have much less been studied.

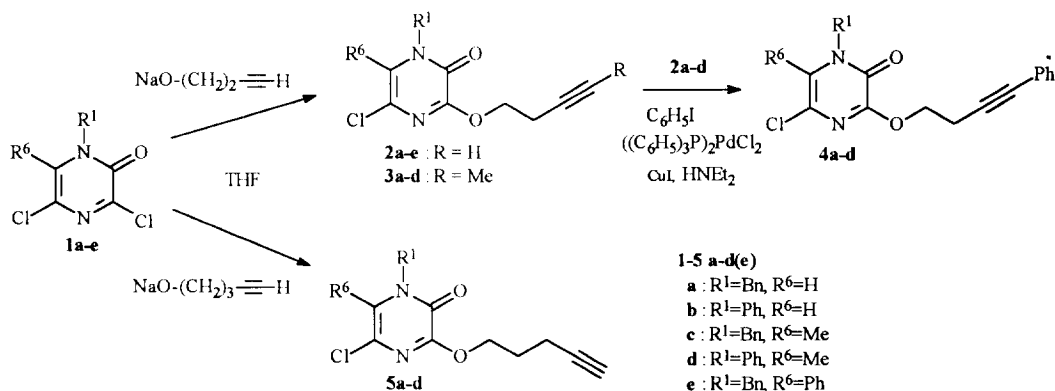
The 2-azadiene system of 2(1*H*)-pyrazinones 1 has been shown to undergo [4+2] cycloaddition reactions with a wide variety of dienophiles.⁶ In this work we wish to report some applications of the intramolecular version which could prove to be a convenient route to new furo/pyranopyridines and/or pyridinones *via* a cycloaddition-elimination pathway. Both the fused pyridines and pyridinones may be of interest because of their possible biological activity: recently, a number of furo[2,3-*b*]pyridines were patented for their herbicidal activity;⁷ the new *c*-annelated pyridinones (scarcely described in the literature⁸) can be considered as the cyclic analogues of some interesting 3-acetyloxy-2(1*H*)-pyridinones (potential antitumor agents);⁹ some 5,7-dihydro-5-oxo-furo[3,4-*b*]pyridines have biological activity¹⁰ but the non-oxidised analogues are less known.⁴

After discussion of the synthesis of the required precursors, their thermolysis and the influence of the substitution pattern of the 2(1*H*)-pyrazinone and of the side chain type will be considered.

RESULTS AND DISCUSSION

Synthesis of the precursors

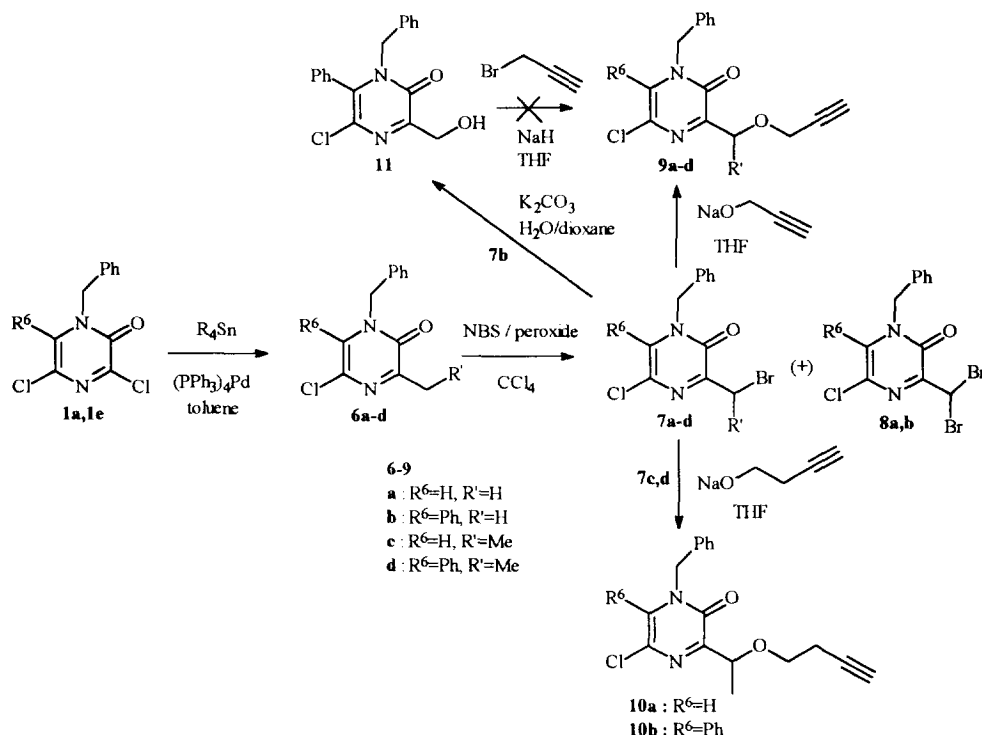
For the preparation of the required cycloaddition precursors **2-5** we made use of the reactivity of the chlorimine function in the 2(*1H*)-pyrazinones **1a-e**. Condensation of **1a-e** with the sodium salt of 3-butyn-1-ol or 3-pentyn-1-ol in tetrahydrofuran at room temperature smoothly led to the corresponding 3-(3-butynyloxy)-2(*1H*)-pyrazinones **2a-e** or 3-(3-pentynyloxy)-2(*1H*)-pyrazinones **3a-d** respectively (75-98 % yield). Further reaction of **2a-d** with 1.1 equiv iodobenzene, bis(triphenylphosphine)palladium(II) chloride (1 mol %) and copper(I) iodide (0.5 mol %) in diethylamine at 45 °C¹¹ led to the formation of the 3-(4-phenyl-3-butynyloxy)-2(*1H*)-pyrazinones **4a-d** in good yield. The 3-(4-pentynyloxy)-2(*1H*)-pyrazinones **5a-d** could be obtained from **1a-d** using the sodium salt of 4-pentyn-1-ol. (Scheme 1)



Scheme 1

For the synthesis of the precursors of type **9** the 2(*1H*)-pyrazinones **1a** or **1e** were first reacted with tetramethyl- or tetraethyltin in toluene at 110 °C in the presence of tetrakis(triphenylphosphine)palladium(0) (0.5 mol %)¹² to yield the 3-(*m*)ethyl-2(*1H*)-pyrazinones **6a-d** (80-90 % yield). The α -position of the 3-alkyl group was further brominated with *N*-bromosuccinimide (1.2 equiv) in refluxing tetrachloromethane in the presence of a catalytic amount of benzoyl peroxide to give the corresponding 3-bromoalkyl-2(*1H*)-pyrazinones **7a-d** in good yield (70-90 %). However, the formation of the dibrominated 2(*1H*)-pyrazinones **8a** and **8b** (in 10-15 % yield) during the bromination of compounds **6a** and **6b** could not be avoided. Further conversion of **7a-d** to the desired 3-(2-propynyloxy(*m*)ethyl)-2(*1H*)-pyrazinones **9a-d** was tried by reaction with the sodium salt of propargyl alcohol. The cycloaddition educts **9c** (not stable at room temperature: see thermolysis) and **9d** (R¹ = Me) were formed in acceptable yield (60-65 %); **9b** was obtained in only 48 % yield while conversion of **7a** resulted in a complex reaction mixture. We presume that the alcoholate can also attack the 3- and/or the 6-position of the 2(*1H*)-pyrazinones **7** resulting in the formation of unstable reaction products.

Similar behaviour was observed for the reaction with the sodium salt of 3-butyn-1-ol: **7a** gave a complex reaction mixture while **7c** and **7d** yielded the 3-(1-(3-butynyloxy)ethyl)-2(1*H*)-pyrazinones **10a** and **10b** ($\pm 60\%$). An alternative pathway⁴ for the synthesis of compounds of type **9** (**10**) was tried *via* the 3-hydroxymethyl-2(1*H*)-pyrazinone **11**, obtained by treatment of **7b** with K_2CO_3 in a refluxing mixture of $H_2O/dioxane$ (1:1); however, reaction with propargyl bromide in the presence of 1.1 equiv sodium hydride was unsuccessful.



Scheme 2

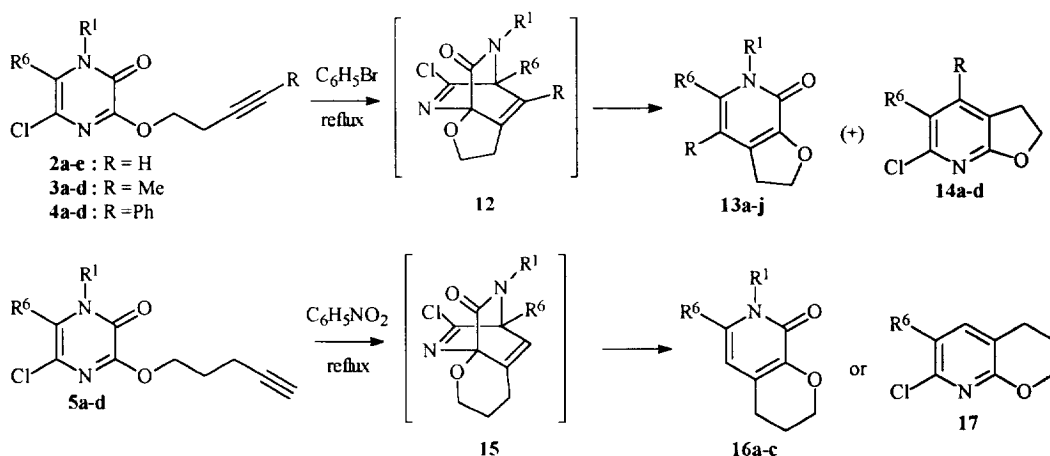
Thermolysis of the precursors

Reflux of **2a-c**, **3a-c** or **4a-c** in bromobenzene led to the exclusive formation of the 2,3-dihydrofuro[2,3-*c*]pyridin-7(6*H*)-ones **13a-i**. This probably occurs *via* the expulsion of cyanogen chloride (retro Diels-Alder reaction) from the cycloadducts of type **12**. Under similar reaction conditions the same type of cycloadduct, formed during the thermolysis of **2d**, **3d** or **4d**, lost phenyl isocyanate and yielded the 6-chloro-2,3-dihydrofuro[2,3-*b*]pyridines **14a-c**. These results are comparable with those observed during the studies of the intermolecular variant: the loss of phenyl isocyanate from the intermediate cycloadduct is faster than the loss of an alkyl isocyanate⁶ and the presence of a steric group in position 6 of the 2(1*H*)-pyrazinone disfavours the loss of cyanogen chloride.¹³ This was confirmed by the thermolysis of **2e** ($R^1 = Bn$) giving a mixture of the 2,3-dihydro-5-phenylfuro[2,3-*c*]pyridin-7(6*H*)-one **13j** ($R^6 = Ph$) and the 6-chloro-2,3-dihydro-5-phenylfuro[2,3-*b*]pyridine **14d** in a ratio of approximately 1:3.

However, we believe that the phenyl group (R^6) has another important influence on the retro Diels-Alder reaction: it significantly lowers the LUMO energy level of the pyridine **14d** and could favour in this way a transition state leading to the loss of isocyanate.⁶

Introduction of a methyl- or phenyl group at the terminal carbon atom of the triple bond increases the reaction time (1.5-2.5 hours for **2a-d**, 4-6 hours for **3a-d** and **4a-d**), while the influence of the substituents of the 2(1*H*)-pyrazinone (e.g. in the series **2a-d**) on the rate of cycloaddition is smaller (except for **2e**: 5 hours reflux). (Scheme 3)

Lengthening of the side chain slows down the cycloaddition rate probably due to the more negative activation entropy.¹⁴ Indeed, the 2(1*H*)-pyrazinones **5a-d** did not cyclise in refluxing bromobenzene; 2.5-4 hours reflux in nitrobenzene (210 °C) was required. Thermolysis of **5a-c** gave the expected 3,4-dihydro-2*H*-pyrano[2,3-*c*]pyridin-8(7*H*)-ones **16a-c** via a cycloadduct of type **15**; the 7-chloro-3,4-dihydro-6-methyl-2*H*-pyrano[2,3-*b*]pyridine **17** was obtained starting from **5d**. (Scheme 3)

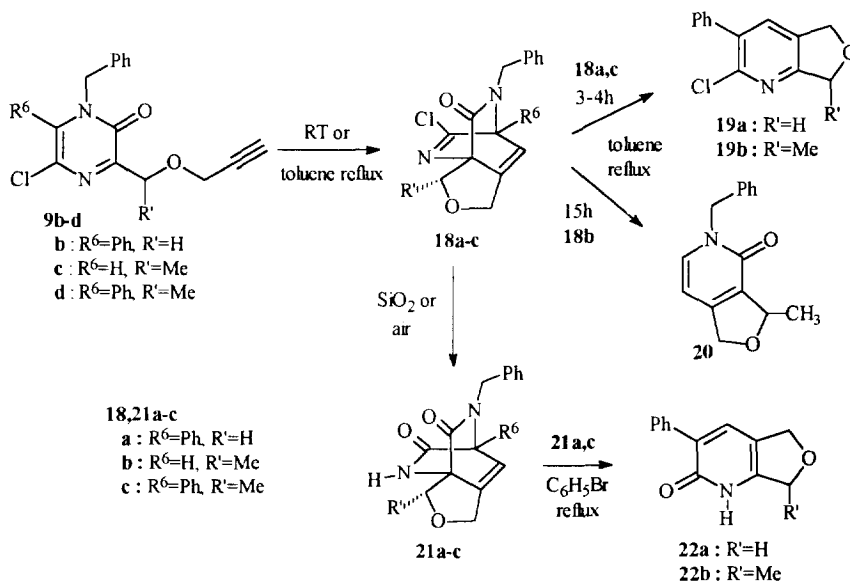


R^1	R^6	R	time (h)	13 yield (%)	14 yield (%)	R^1	R^6	R	time (h)	13 yield (%)	14 yield (%)		
2a	Bn	H	H	2.5	a : 98	-	4a	Bn	H	Ph	6	g : 92	-
2b	Ph	H	H	1.5	b : 96	-	4b	Ph	H	Ph	4.5	h : 90	-
2c	Bn	Me	H	2.5	c : 78	-	4c	Bn	Me	Ph	5	i : 85	-
2d	Ph	Me	H	2.5	-	a : 86	4d	Ph	Me	Ph	4	-	c : 86
2e	Bn	Ph	H	5	j : 23	d : 71		R^1	R^6		time	16 yield	17 yield
3a	Bn	H	Me	5	d : 93	-	5a	Bn	H		2.5	a : 97	-
3b	Ph	H	Me	4	e : 97	-	5b	Ph	H		2.5	b : 95	-
3c	Bn	Me	Me	5	f : 88	-	5c	Bn	Me		2.5	c : 90	-
3d	Ph	Me	Me	5	-	b : 95	5d	Ph	Me		4	-	58

Scheme 3

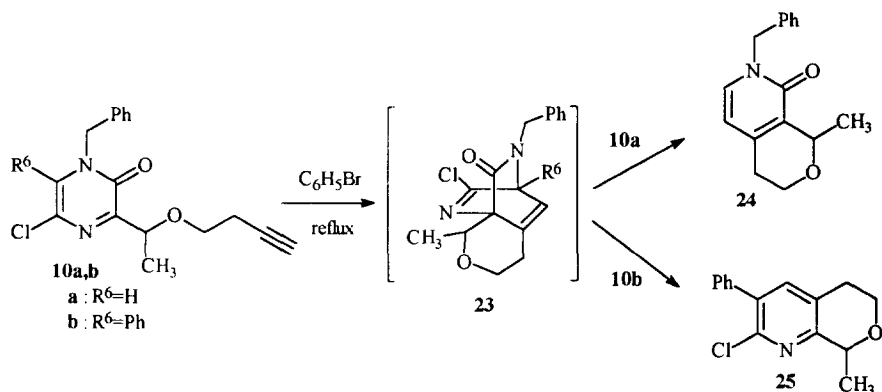
Not only the length of the side chain but also the electron-donating capacity of the anchored atom influences the rate of the cycloaddition:⁶ an electron donating oxygen atom attached to the pyrazinone ring raises the pyrazinone LUMO energy; this results in diminished frontier orbital overlap with the dienophile HOMO inducing a higher barrier of activation. Therefore we also studied the Diels-Alder reactivity of the 2(1*H*)-pyrazinones **9b-d**. As expected the cycloaddition took place under much milder conditions: the conversion of **7c** could not be stopped at the stage of **9c** but the latter cyclised rapidly at room temperature to yield a cycloadduct of type **18b** ($R^6 = H$); 15-20 minutes reflux in toluene was needed for the conversion of **9b** or **9d** ($R^6 = Ph$) to the corresponding cycloadducts **18a** or **18c**. We believe that the most favorable conformation for reactivity in cycloaddition of **9c** or **9d** is this one with the α -methyl substituent pointed away from the amide function. As a consequence only cycloadducts **18b,c** and their enantiomers were obtained. The mild reaction conditions (RT for **9c** and 110 °C for **9b,d**) and the difficult loss of benzyl isocyanate explains their stability towards retro Diels-Alder reaction. However, when the adducts **18a** and **18c** were further thermolysed (3-4 hours reflux in toluene) benzyl isocyanate was lost and the 2-chloro-5,7-dihydro-3-phenylfuro[3,4-*b*]pyridines **19a** and **19b** were isolated. On the other hand compound **18b** afforded the 5-benzyl-3,5-dihydro-3-methylfuro[3,4-*c*]pyridin-4(1*H*)-one **20** after 15 hours reflux in toluene. The phenyl group in **18a** and **18c** again has a double effect: the loss of cyanogen chloride is disfavoured and the lower LUMO energy level of the formed pyridines results in a shorter reaction time in comparison with **18b**. (Scheme 4)

When we tried to purify the cycloadducts **18a-c** on a silica gel column, the chlorimine function hydrolysed yielding **21a-c** in very good yield. These compounds also reacted slowly in a similar manner with air humidity. When the hydrolysed compounds **21a** and **21c** were thermolysed in bromobenzene during 1-2 hours, they lost benzyl isocyanate affording the 5,7-dihydro-3-phenylfuro[3,4-*b*]pyridin-2(1*H*)-ones **22a-b**. (Scheme 4)



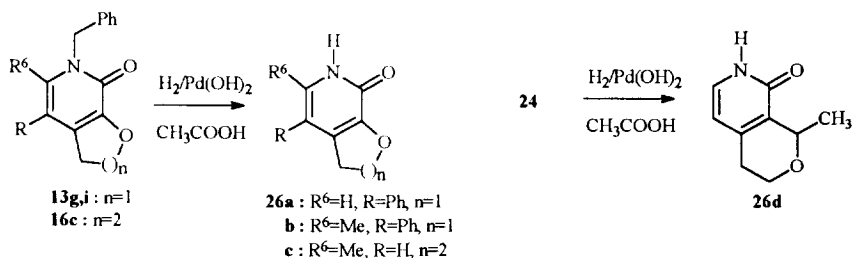
Scheme 4

Finally, we proceeded with the thermolysis of the precursors **10a** and **10b**. No reaction was observed in refluxing toluene (because of the longer side chain); reflux in bromobenzene afforded respectively the 7-benzyl-1,3,4,7-tetrahydro-1-methyl-8*H*-pyrano[3,4-*c*]pyridin-8-one **24** (1h) or the 2-chloro-5,8-dihydro-8-methyl-3-phenyl-6*H*-pyrano[3,4-*b*]pyridine **25** (5h). As usual, the first cycloaddition step is slowed down when $R^6 = \text{Ph}$ and the intermediate cycloadducts **23** could not be isolated under these reaction conditions. (Scheme 5)



Scheme 5

From the results above it appears that intramolecular Diels-Alder reactions of 2(1*H*)-pyrazinones with an appropriate side chain in position 3 prove to be a convenient route to new furo/pyranopyridines and/or pyridinones. Especially the condensed pyridinones may be important for their biological activity; however, as most of the biologically active 2(1*H*)-pyridinones have an unsubstituted amide function we tried to debenzylate the furo[2,3-*c*]pyridinones **13g** and **13i**, the pyrano[2,3-*c*]pyridinone **16c** and the pyrano[3,4-*c*]pyridinone **24**.¹⁵ treatment with hydrogen gas (1 atmosphere) and palladium hydroxide on carbon in acetic acid afforded the expected compounds **26a-d** in quantitative yield. (Scheme 6)



Scheme 6

EXPERIMENTAL

Infrared spectra were recorded on a Perkin-Elmer 297 grating IR spectrophotometer and a Perkin-Elmer 1720 Fourier transform spectrometer. ^1H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker WM 250 or on a Bruker AMX 400 instrument. They were taken in CDCl_3 as solvent unless stated otherwise and the ^1H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane or the deuterated solvent as an internal reference. Mass spectra were run by using a Kratos MS50TC instrument and a DS90 data system. For the chromatography analytical TLC plates (Alugram Sil G/UV₂₅₄) and 70-230 mesh silica gel 60 (E.M. Merck) were used. Melting points were taken using a Reichert-Jung Thermovar apparatus and an Electrothermal IA 9000 digital melting point apparatus and are uncorrected. Microanalyses were performed by Janssen Pharmaceutica on a Carlo Erba elemental analyser type 1106.

I. 3,5-Dichloro-2(1H)-pyrazinones 1a-e

The preparation and the analytical data of the pyrazinones **1a,b** and **1d,e** were reported previously.^{16,17,18} The 2(1*H*)-pyrazinone **1c** was prepared as usual and the spectral data are summarised below:

1-benzyl-3,5-dichloro-6-methyl-2(1H)-pyrazinone 1c

Yield: 63%; m.p.: 104°C; IR (KBr) cm^{-1} : 1657 (CO), 1567 (C=N); ^1H NMR: 7.60-7.20 (m, 5H, Ar-H), 5.40 (s, 2H, CH_2Ph), 2.43 (s, 3H, CH_3); m/z (%): 268 (M^+ , 11), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{OCl}_2$: 268.0170; found: 268.0160

*II. 3- and 4-Alkynyloxy-5-chloro-2(1H)-pyrazinones 2-5***Synthesis of 3-(3-butynyloxy)/(3-pentyloxy)/(4-pentyloxy)-5-chloro-2(1H)-pyrazinones 2,3 and 5**

To a mixture of 8 mmol 3-butyn-1-ol (3-pentyn-1-ol or 4-pentyn-1-ol) and 3 mmol NaH in 20 ml dry THF was added 2 mmol 3,5-dichloro-2(1*H*)-pyrazinone **1a-e**. After stirring for 1 hour at RT, 10 ml H_2O was added and the H_2O -layer extracted with CH_2Cl_2 (2 x 20 ml). The organic layer was dried with MgSO_4 and evaporated. The obtained product was purified using column chromatography (SiO_2 , 5-10% EtOAc/ CH_2Cl_2 as eluent)

1-benzyl-3-(3-butynyloxy)-5-chloro-2(1H)-pyrazinone 2a

Yield: 92%; m.p.: 95-96°C; IR (KBr) cm^{-1} : 3260 (C≡CH), 1670 (CO), 1600 (C=N); ^1H NMR: 7.45-7.30 (m, 5H, Ar-H), 6.86 (s, 1H, 6-H), 5.08 (s, 2H, CH_2Ph), 4.48 (t, $^3\text{J}=7\text{Hz}$, 2H, OCH_2), 2.75 (txd, $^3\text{J}=7\text{Hz}$, $^4\text{J}=2.5\text{Hz}$, 2H, CH_2), 2.02 (t, $^4\text{J}=2.5\text{Hz}$, 1H, C≡CH); m/z (%): 288 (M^+ , 20), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_2\text{Cl}$: 288.0666; found: 288.0675

3-(3-butynyloxy)-5-chloro-1-phenyl-2(1H)-pyrazinone 2b

Yield: 88%; m.p.: 94-95°C; IR (KBr) cm^{-1} : 3270 (C≡CH) 1670 (CO), 1610 (C=N); ^1H NMR: 7.55-7.35 (m, 5H, Ar-H), 6.99 (s, 1H, 6-H), 4.50 (t, $^3\text{J}=8\text{Hz}$, 2H, OCH_2), 2.78 (txd, $^3\text{J}=8\text{Hz}$, $^4\text{J}=2.5\text{Hz}$, 2H, CH_2), 2.05 (t, $^4\text{J}=2.5\text{Hz}$, 1H, C≡CH); m/z (%): 274 (M^+ , 55), 77 (C_6H_5^+ , 100); exact mass for $\text{C}_{14}\text{H}_{11}\text{N}_2\text{O}_2\text{Cl}$: 274.0509; found: 274.0506

1-benzyl-3-(3-butynyloxy)-5-chloro-6-methyl-2(1H)-pyrazinone 2c

Yield: 96%; m.p.: 80-82°C; IR (KBr) cm^{-1} : 3270 (C≡CH), 1675 (CO), 1590 (C=N); ^1H NMR: 7.40-7.10 (m, 5H, Ar-H), 5.32 (s, 2H, CH_2Ph), 4.48 (t, $^3\text{J}=7\text{Hz}$, 2H, OCH_2), 2.76 (txd, $^3\text{J}=7\text{Hz}$, $^4\text{J}=2.6\text{Hz}$, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.04 (t, $^4\text{J}=2.6\text{Hz}$, 1H, C≡CH); m/z (%): 302 (M^+ , 20), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}_2\text{Cl}$: 302.0822; found: 302.0830

3-(3-butynyloxy)-5-chloro-6-methyl-1-phenyl-2(1H)-pyrazinone 2d

Yield: 74%; m.p.: 123°C; IR (KBr) cm^{-1} : 3260 (C≡CH), 1675 (CO), 1600 (C=N); ^1H NMR: 7.60-7.11 (m, 5H, Ar-H), 4.50 (t, $^3\text{J}=7\text{Hz}$, 2H, OCH_2), 2.76 (txd, $^3\text{J}=7\text{Hz}$, $^4\text{J}=2.6\text{Hz}$, 2H, CH_2), 2.03 (t, $^4\text{J}=2.6\text{Hz}$, 1H, C≡CH), 1.99 (s, 3H, CH_3); m/z (%): 288 (M^+ , 87), 118 ($\text{C}_8\text{H}_8\text{N}^+$, 100), 77 (C_6H_5^+ , 73); exact mass for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_2\text{Cl}$: 288.0666; found: 288.0673

1-benzyl-3-(3-butinyloxy)-5-chloro-6-phenyl-2(1H)-pyrazinone 2e

Yield: 91%; m.p.: 121-122°C; IR (KBr) cm^{-1} : 3292 (C=CH), 1667 (CO), 1577 (C=N); ^1H NMR: 7.49-6.77 (m, 10H, Ar-H), 5.02 (s, 2H, CH_2Ph), 4.51 (t, $^3\text{J}=8\text{Hz}$, 2H, OCH_2), 2.80 (txd, $^3\text{J}=8\text{Hz}$, $^4\text{J}=2.5\text{Hz}$, 2H, CH_2), 2.06 (t, $^4\text{J}=2.5\text{Hz}$, 1H, C≡CH); m/z (%): 364 (M^+ , 12), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{21}\text{H}_{17}\text{N}_2\text{O}_2\text{Cl}$: 364.0979; found: 364.0977

1-benzyl-5-chloro-3-(3-pentinyloxy)-2(1H)-pyrazinone 3a

Yield: 97%; oil; IR (neat) cm^{-1} : 1670 (CO), 1600 (C=N); ^1H NMR: 7.40-7.20 (m, 5H, Ar-H), 6.81 (s, 1H, 6-H), 5.01 (s, 2H, CH_2Ph), 4.37 (t, $^3\text{J}=7\text{Hz}$, 2H, OCH_2), 2.68 (txq, $^3\text{J}=7\text{Hz}$, $^5\text{J}=2.3\text{Hz}$, 2H, CH_2), 1.77 (t, $^5\text{J}=2.3\text{Hz}$, 3H, CH_3); m/z (%): 302 (M^+ , 17), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}_2\text{Cl}$: 302.0822; found: 302.0828

5-chloro-3-(3-pentinyloxy)-1-phenyl-2(1H)-pyrazinone 3b

Yield: 93%; m.p.: 102°C; IR (KBr) cm^{-1} : 1670 (CO), 1610 (C=N); ^1H NMR: 7.57-7.35 (m, 5H, Ar-H), 6.97 (s, 1H, 6-H), 4.45 (t, $^3\text{J}=8\text{Hz}$, 2H, OCH_2), 2.69 (txq, $^3\text{J}=8\text{Hz}$, $^5\text{J}=2.4\text{Hz}$, 2H, CH_2), 1.77 (t, $^5\text{J}=2.4\text{Hz}$, 3H, CH_3); m/z (%): 288 (M^+ , 36), 222 ($\text{M}^+-\text{C}_5\text{H}_6$, 61), 77 (C_6H_5^+ , 100); exact mass for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_2\text{Cl}$: 288.0666; found: 288.0667

1-benzyl-5-chloro-6-methyl-3-(3-pentinyloxy)-2(1H)-pyrazinone 3c

Yield: 98%; m.p.: 133-134°C; IR (KBr) cm^{-1} : 1670 (CO), 1590 (C=N); ^1H NMR: 7.40-7.10 (m, 5H, Ar-H), 5.31 (s, 2H, CH_2Ph), 4.42 (t, $^3\text{J}=7\text{Hz}$, 2H, OCH_2), 2.71 (txq, $^3\text{J}=7\text{Hz}$, $^5\text{J}=2.3\text{Hz}$, 2H, CH_2), 2.31 (s, 3H, 6- CH_3), 1.80 (t, $^5\text{J}=2.3\text{Hz}$, 3H, CH_3); m/z (%): 316 (M^+ , 19), 250 ($\text{M}^+-\text{C}_5\text{H}_6$, 6), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_2\text{Cl}$: 316.0978; found: 316.0991

5-chloro-6-methyl-3-(3-pentinyloxy)-1-phenyl-2(1H)-pyrazinone 3d

Yield: 98%; m.p.: 132-133°C; IR (KBr) cm^{-1} : 1675 (CO), 1595 (C=N); ^1H NMR: 7.60-7.20 (m, 5H, Ar-H), 4.45 (t, $^3\text{J}=7\text{Hz}$, 2H, OCH_2), 2.70 (txq, $^3\text{J}=7\text{Hz}$, $^5\text{J}=2.3\text{Hz}$, 2H, CH_2), 1.99 (s, 3H, 6- CH_3), 1.79 (t, $^5\text{J}=2.3\text{Hz}$, 3H, CH_3); m/z (%): 302 (M^+ , 76), 236 ($\text{M}^+-\text{C}_5\text{H}_6$, 82), 118 ($\text{C}_8\text{H}_8\text{N}^+$, 100), 77 (C_6H_5^+ , 69); exact mass for $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}_2\text{Cl}$: 302.0822; found: 302.0833

Synthesis of 5-chloro-3-(4-phenyl-3-butinyloxy)-2(1H)-pyrazinones 4

The purified pyrazinones **2a-d** (5 mmol) were further reacted with 1.1 equiv. iodobenzene, $\text{PdCl}_2(\text{PPh}_3)_2$ (0.05 mmol) and CuI (0.025 mmol) in 15 ml diethylamine at 45°C during 5-8 hours. After evaporation of the solvent, H_2O was added to the residue. Extraction with CH_2Cl_2 , drying of the organic layer over MgSO_4 and evaporation afforded compounds **4a-d** which were purified by column chromatography (SiO_2 , CH_2Cl_2 as eluent).

1-benzyl-5-chloro-3-(4-phenyl-3-butinyloxy)-2(1H)-pyrazinone 4a

Yield: 95%; m.p.: 138-139°C; IR (KBr) cm^{-1} : 1668 (CO), 1591 (C=N); ^1H NMR: 7.42-7.20 (m, 10H, Ar-H), 6.82 (s, 1H, 6-H), 5.03 (s, 2H, CH_2Ph), 4.52 (t, $^3\text{J}=8\text{Hz}$, 2H, OCH_2), 2.97 (t, $^3\text{J}=8\text{Hz}$, 2H, CH_2); m/z (%): 364 (M^+ , 3), 236 ($\text{M}^+-\text{C}_{10}\text{H}_8$, 29), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{21}\text{H}_{17}\text{N}_2\text{O}_2\text{Cl}$: 364.0979; found: 364.0973

5-chloro-1-phenyl-3-(4-phenyl-3-butinyloxy)-2(1H)-pyrazinone 4b

Yield: 92%; m.p.: 117°C; IR (KBr) cm^{-1} : 1670 (CO), 1587 (C=N); ^1H NMR: 7.60-7.25 (m, 10H, Ar-H), 6.96 (s, 1H, 6-H), 4.58 (t, $^3\text{J}=7\text{Hz}$, 2H, OCH_2), 3.02 (t, $^3\text{J}=7\text{Hz}$, 2H, CH_2); m/z (%): 350 (M^+ , 1), 222 ($\text{M}^+-\text{C}_{10}\text{H}_8$, 24), 128 ($\text{C}_{10}\text{H}_8^+$, 100); exact mass for $\text{C}_{20}\text{H}_{15}\text{N}_2\text{O}_2\text{Cl}$: 350.0822; found: 350.0816

1-benzyl-5-chloro-6-methyl-3-(4-phenyl-3-butinyloxy)-2(1H)-pyrazinone 4c

Yield: 88%; m.p.: 140-141°C; IR (KBr) cm^{-1} : 1670 (CO), 1591 (C=N); ^1H NMR: 7.44-7.10 (m, 10H, Ar-H), 5.29 (s, 2H, CH_2Ph), 4.55 (t, $^3\text{J}=7\text{Hz}$, 2H, OCH_2), 3.00 (t, $^3\text{J}=7\text{Hz}$, 2H, CH_2), 2.26 (s, 3H, CH_3); m/z (%): 378 (M^+ , 1), 287 ($\text{M}^+-\text{C}_7\text{H}_7$, 2), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{22}\text{H}_{19}\text{N}_2\text{O}_2\text{Cl}$: 378.1135; found: 378.1124

5-chloro-6-methyl-1-phenyl-3-(4-phenyl-3-butinyloxy)-2(1H)-pyrazinone 4d

Yield: 85%; m.p.: 144-145°C; IR (KBr) cm^{-1} : 1676 (CO), 1588 (C=N); ^1H NMR: 7.58-7.10 (m, 10H, Ar-H), 4.57 (t, $^3\text{J}=7\text{Hz}$, 2H, OCH_2), 2.99 (t, $^3\text{J}=7\text{Hz}$, 2H, CH_2), 1.96 (s, 3H, CH_3); m/z (%): 364 (M^+ , 2), 245 ($\text{M}^+-\text{C}_6\text{H}_5\text{NCO}$, 24), 128 ($\text{C}_{10}\text{H}_8^+$, 100); exact mass for $\text{C}_{21}\text{H}_{17}\text{N}_2\text{O}_2\text{Cl}$: 364.0979; found: 364.0983

The 3-(4-pentynyloxy)-2(1*H*)-pyrazinones **5a-d** were prepared as described above.

1-benzyl-5-chloro-3-(4-pentynyloxy)-2(1*H*)-pyrazinone 5a

Yield: 66%; m.p.: 113-114°C; IR (KBr) cm^{-1} : 3280 (C≡C-H), 1670 (CO), 1604 (C=N); $^1\text{H NMR}$: 7.40-7.30 (m, 5H, Ar-H), 6.83 (s, 1H, 6-H), 5.05 (s, 2H, CH_2Ph), 4.42 (t, $^3\text{J}=7\text{Hz}$, 2H, OCH_2), 2.38 (txd, $^3\text{J}=7\text{Hz}$, $^4\text{J}=2.5\text{Hz}$, 2H, CH_2), 2.04 (m, $^3\text{J}=7\text{Hz}$, 2H, CH_2), 1.96 (t, $^4\text{J}=2.5\text{Hz}$, 1H, C≡CH); m/z (%): 302 (M^+ , 14), 236 ($\text{M}^+-\text{C}_5\text{H}_6$, 5), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}_2\text{Cl}$: 302.0822; found: 302.0831

5-chloro-3-(4-pentynyloxy)-1-phenyl-2(1*H*)-pyrazinone 5b

Yield: 81%; m.p.: 169-170°C; IR (KBr) cm^{-1} : 3230 (C≡C-H), 1675 (CO), 1610 (C=N); $^1\text{H NMR}$: 7.53-7.38 (m, 5H, Ar-H), 6.97 (s, 1H, 6-H), 4.50 (t, $^3\text{J}=7\text{Hz}$, 2H, OCH_2), 2.41 (txd, $^3\text{J}=7\text{Hz}$, $^4\text{J}=2.5\text{Hz}$, 2H, CH_2), 2.10 (m, $^3\text{J}=7\text{Hz}$, 2H, CH_2), 1.99 (t, $^4\text{J}=2.5\text{Hz}$, 1H, C≡CH); m/z (%): 288 (M^+ , 30), 222 ($\text{M}^+-\text{C}_5\text{H}_6$, 100), 77 (C_6H_5^+ , 79); exact mass for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_2\text{Cl}$: 288.0666; found: 288.0664

1-benzyl-5-chloro-6-methyl-3-(4-pentynyloxy)-2(1*H*)-pyrazinone 5c

Yield: 80%; m.p.: 137-138°C; IR (KBr) cm^{-1} : 3235 (C≡C-H), 1670 (CO), 1595 (C=N); $^1\text{H NMR}$: 7.40-7.20 (m, 5H, Ar-H), 5.32 (s, 2H, CH_2Ph), 4.48 (t, $^3\text{J}=7\text{Hz}$, 2H, OCH_2), 2.41 (txd, $^3\text{J}=7\text{Hz}$, $^4\text{J}=2.5\text{Hz}$, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.08 (m, $^3\text{J}=7\text{Hz}$, 2H, CH_2), 1.98 (t, $^4\text{J}=2.5\text{Hz}$, 1H, C≡CH); m/z (%): 316 (M^+ , 18), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_2\text{Cl}$: 316.0978; found: 316.0976

5-chloro-6-methyl-3-(4-pentynyloxy)-1-phenyl-2(1*H*)-pyrazinone 5d

Yield: 98%; m.p.: 154-155°C; IR (KBr) cm^{-1} : 3265 (C≡C-H), 1690 (CO), 1600 (C=N); $^1\text{H NMR}$: 7.60-7.20 (m, 5H, Ar-H), 4.50 (t, $^3\text{J}=7\text{Hz}$, 2H, OCH_2), 2.40 (txd, $^3\text{J}=7\text{Hz}$, $^4\text{J}=2.5\text{Hz}$, 2H, CH_2), 2.07 (m, $^3\text{J}=7\text{Hz}$, 2H, CH_2), 1.98 (t, $^4\text{J}=2.5\text{Hz}$, 1H, C≡CH), 1.97 (s, 3H, CH_3); m/z (%): 302 (M^+ , 83), 236 ($\text{M}^+-\text{C}_5\text{H}_6$, 86), 77 (C_6H_5^+ , 100); exact mass for $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}_2\text{Cl}$: 302.0822; found: 302.0824

*III. 3-Alkyl and 3-(di)bromoalkyl-2(1*H*)-pyrazinones 6a-d, 7a-d and 8a,b*

Synthesis of 1-benzyl-3-(m)ethyl-5-chloro-2(1*H*)-pyrazinones 6a-d

A mixture of pyrazinone **1a** or **1e** (0.04 mol) and tetra(m)ethyltin (R_4Sn) (0.048 mol) were stirred in 200 ml toluene at 110°C during 1-5 days in the presence of $\text{Pd}(\text{PPh}_3)_4$ (0.2 mmol). After evaporation of the solvent the residue was dissolved in EtOAc and further stirred for 1/2 day at RT with an excess of KF. The mixture was filtrated, the filtrate evaporated and the product subjected to column chromatography on silica gel using 5-10% EtOAc/ CH_2Cl_2 as eluent.

1-benzyl-5-chloro-3-methyl-2(1*H*)-pyrazinone 6a

Yield: 81%; m.p.: 98-99°C; IR (KBr) cm^{-1} : 1666 (CO), 1600 (C=N); $^1\text{H NMR}$: 7.40-7.26 (m, 5H, Ar-H), 7.09 (s, 1H, 6-H), 5.05 (s, 2H, CH_2Ph), 2.50 (s, 3H, CH_3); m/z (%): 234 (M^+ , 95), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{12}\text{H}_{11}\text{N}_2\text{OCl}$: 234.0560; found: 234.0568

1-benzyl-5-chloro-3-methyl-6-phenyl-2(1*H*)-pyrazinone 6b

Yield: 95%; m.p.: 116-117°C; IR (KBr) cm^{-1} : 1640 (CO), 1601 (C=N); $^1\text{H NMR}$: 7.46-6.79 (m, 10H, Ar-H), 5.00 (s, 2H, CH_2Ph), 2.53 (s, 3H, CH_3); m/z (%): 310 (M^+ , 14), 275 (M^+-Cl , 2), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{18}\text{H}_{15}\text{N}_2\text{OCl}$: 310.0873; found: 310.0871

1-benzyl-5-chloro-3-ethyl-2(1*H*)-pyrazinone 6c

Yield: 96%; m.p.: 81-83°C; IR (KBr) cm^{-1} : 1646 (CO), 1582 (C=N); $^1\text{H NMR}$: 7.40-7.25 (m, 5H, Ar-H), 7.10 (s, 1H, 6-H), 5.04 (s, 2H, CH_2Ph), 2.86 (q, $^3\text{J}=10\text{Hz}$, 2H, CH_2), 1.25 (t, $^3\text{J}=10\text{Hz}$, 3H, CH_3); m/z (%): 248 (M^+ , 7), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{OCl}$: 248.0716; found: 248.0747

1-benzyl-5-chloro-3-ethyl-6-phenyl-2(1*H*)-pyrazinone 6d

Yield: 94%; m.p.: 83-84°C; IR (KBr) cm^{-1} : 1651 (CO), 1568 (C=N); $^1\text{H NMR}$: 7.35-6.29 (m, 10H, Ar-H), 5.00 (s, 2H, CH_2Ph), 2.92 (q, $^3\text{J}=9\text{Hz}$, 2H, CH_2), 1.25 (t, $^3\text{J}=9\text{Hz}$, 3H, CH_3); m/z (%): 324 (M^+ , 14), 289 (M^+-Cl , 2), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{19}\text{H}_{17}\text{N}_2\text{OCl}$: 324.1029; found: 324.1036

Synthesis of 1-benzyl-3-(di)bromo(m)ethyl-5-chloro-2(1*H*)-pyrazinones 7a-d and 8a,b

2(1*H*)-Pyrazinones **6a** (**6b-d**) (0.04 mol) and 1.2 equiv NBS in 300 ml dry tetrachloromethane were refluxed for 3-6 hours in the presence of a catalytic amount of benzoyl peroxide. After cooling of the reaction

mixture, the succinimide crystals were filtered off and the filtrate was evaporated. The product(s) was (were) purified by column chromatography using CH_2Cl_2 as eluent.

1-benzyl-3-bromomethyl-5-chloro-2(1H)-pyrazinone 7a

Yield: 68%; m.p.: 92–93°C; IR (KBr) cm^{-1} : 1655 (CO), 1578 (C=N); ^1H NMR: 7.43–7.30 (m, 5H, Ar-H), 7.29 (s, 1H, 6-H), 5.12 (s, 2H, CH_2Ph), 4.53 (s, 2H, CH_2Br); m/z (%): 312 (M^+ , 8), 233 (M^+-Br , 11), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{OBrCl}$: 311.9665; found: 311.9663; anal calcd for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{OBrCl}$: C 45.96, H 3.21, N 8.93; found: C 46.35, H 3.21, N 8.92

1-benzyl-3-bromomethyl-5-chloro-6-phenyl-2(1H)-pyrazinone 7b

Yield: 73%; m.p.: 89–90°C; IR (KBr) cm^{-1} : 1655 (CO), 1557 (C=N); ^1H NMR: 7.61–6.87 (m, 10H, Ar-H), 5.10 (s, 2H, CH_2Ph), 4.69 (s, 2H, CH_2Br); m/z (%): 388 (M^+ , 2), 309 (M^+-Br , 20), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{OBrCl}$: 387.9978; found: 387.9996; anal calcd for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{OBrCl}$: C 55.48, H 3.62, N 7.19; found: C 55.63, H 3.58, N 7.10

1-benzyl-3-(1-bromoethyl)-5-chloro-2(1H)-pyrazinone 7c

Yield: 89%; m.p.: 94–95°C; IR (KBr) cm^{-1} : 1658 (CO), 1587 (C=N); ^1H NMR: 7.47–7.24 (m, 5H, Ar-H), 7.20 (s, 1H, 6-H), 5.52 (q, $^3\text{J}=7\text{Hz}$, 1H, CH), 5.18/5.01 (2xd, $^2\text{J}=14\text{Hz}$, 2H, CH_2Ph), 1.98 (d, $^3\text{J}=7\text{Hz}$, 3H, CH_3); m/z (%): 326 (M^+ , 7), 247 (M^+-Br , 27), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{OBrCl}$: 325.9822; found: 325.9824

1-benzyl-3-(1-bromoethyl)-5-chloro-6-phenyl-2(1H)-pyrazinone 7d

Yield: 87%; oil; IR (neat) cm^{-1} : 1672 (CO), 1593 (C=N); ^1H NMR: 7.39–6.79 (m, 10H, Ar-H), 5.61 (q, $^3\text{J}=7\text{Hz}$, 1H, CH), 5.05 (s(br), 2H, CH_2Ph), 2.05 (d, $^3\text{J}=7\text{Hz}$, 3H, CH_3); m/z (%): 402 (M^+ , 2), 323 (M^+-Br , 11), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{OBrCl}$: 402.0135; found: 402.0118

1-benzyl-3-dibromomethyl-5-chloro-2(1H)-pyrazinone 8a

Yield: 9%; oil; IR (neat) cm^{-1} : 1662 (CO), 1582 (C=N); ^1H NMR: 7.60–7.40 (m, 5H, Ar-H), 7.30 (s, 1H, 6-H), 7.00 (s, 1H, CHBr_2), 5.08 (s, 2H, CH_2Ph); m/z (%): 390 (M^+ , 1), 311 (M^+-Br , 19), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{12}\text{H}_9\text{N}_2\text{OBr}_2\text{Cl}$: 389.9771; found: 389.9770

1-benzyl-3-dibromomethyl-5-chloro-6-phenyl-2(1H)-pyrazinone 8b

Yield: 15%; oil; IR (neat) cm^{-1} : 1654 (CO), 1557 (C=N); ^1H NMR: 7.46–6.67 (m, 11H, Ar-H+ CHBr_2), 5.10 (s, 2H, CH_2Ph); m/z (%): 466 (M^+ , 1), 387 (M^+-Br , 8), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{18}\text{H}_{13}\text{N}_2\text{OBr}_2\text{Cl}$: 465.9083; found: 465.9120

IV. 2- and 3-Alkynyloxy(m)ethyl-2(1H)-pyrazinones 9b-d and 10a,b + 1-benzyl-5-chloro-3-hydroxymethyl-6-phenyl-2(1H)-pyrazinone 11

Synthesis of 3-(2-propynyloxy(m)ethyl)-2(1H)-pyrazinones 9b-c and 3-(3-butynyloxyethyl)-2(1H)-pyrazinones 10a,b

To a mixture of the 3-bromoalkyl-2(1H)-pyrazinone **7b** (**7c-d**) (7 mmol) and 1.3 equiv propargyl alcohol in 25 ml dry THF at RT was added slowly 1.1 equiv NaH. After stirring for 1/2 hour at RT 20 ml H_2O was added and the mixture was extracted with CH_2Cl_2 (3x 30 ml). The organic layer was dried (MgSO_4) and concentrated by evaporation of the solvent. Column chromatography of the residue with 10% EtOAc/ CH_2Cl_2 as eluent afforded the precursors **9b** and **9d**. The educt **9c** could not be isolated because it reacted further under these circumstances to the adduct **18b** (see later).

1-benzyl-5-chloro-6-phenyl-3-(2-propynyloxymethyl)-2(1H)-pyrazinone 9b

Yield: 48%; oil; IR (neat) cm^{-1} : 3290 (C \equiv CH), 2130 (C \equiv C), 1656 (CO), 1556 (C=N); ^1H NMR: 7.50–6.77 (m, 10H, Ar-H), 5.03 (s, 2H, CH_2Ph), 4.85 (s, 2H, CH_2O), 4.42 (d, $^4\text{J}=2.5\text{Hz}$, 2H, OCH_2), 2.49 (t, $^4\text{J}=2.5\text{Hz}$, 1H, C \equiv CH); m/z (%): 364 (M^+ , 0.1), 303 (M^+-ClCN , 18), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{21}\text{H}_{17}\text{N}_2\text{O}_2\text{Cl}$: 363.1259; found: 303.1253

1-benzyl-5-chloro-6-phenyl-3-(1-(2-propynyloxy)ethyl)-2(1H)-pyrazinone 9d

Yield: 65%; oil; IR (neat) cm^{-1} : 3300 (C \equiv CH), 2130 (C \equiv C), 1649 (CO), 1564 (C=N); ^1H NMR: 7.65–6.80 (m, 10H, Ar-H), 5.25 (q, $^3\text{J}=7\text{Hz}$, 1H, CH), 5.10 (s(br), 2H, CH_2Ph), 4.43 (d, $^4\text{J}=2.5\text{Hz}$, 2H, OCH_2), 2.50 (t, $^4\text{J}=2.5\text{Hz}$, 1H, C \equiv CH), 2.65 (d, $^3\text{J}=7\text{Hz}$, CH_3); m/z (%): 378 (M^+ , 1), 317 (M^+-ClCN , 20), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{22}\text{H}_{19}\text{N}_2\text{O}_2\text{Cl}$: 377.1416; found: 317.1411

1-benzyl-3-(1-(3-butynyloxy)ethyl)-5-chloro-2(1*H*)-pyrazinone 10a

Yield: 59%; oil; IR (neat) cm^{-1} : 3295 (C \equiv CH), 2118 (C=C), 1649 (CO), 1583 (C=N); ^1H NMR: 7.73-7.23 (m, 5H, Ar-H), 7.17 (s, 1H, 6-H), 5.07 (s(br), 2H, CH₂Ph), 5.05 (q, $^3\text{J}=7\text{Hz}$, CH), 3.63 (t, $^3\text{J}=7.5$, 2H, OCH₂), 2.47 (txd, $^3\text{J}=7.5\text{Hz}$, $^4\text{J}=2.5\text{Hz}$, 2H, CH₂), 1.90 (t, $^4\text{J}=2.5\text{Hz}$, 1H, C \equiv CH), 1.50 (d, $^3\text{J}=7\text{Hz}$, 3H, CH₃); m/z (%): 316 (M⁺, 1), 248 (M⁺-C₄H₄O), 91 (C₇H₇⁺, 100); exact mass for C₁₇H₁₇N₂O₂Cl: 316.0979; found: 316.0978

1-benzyl-3-(1-(3-butynyloxy)ethyl)-5-chloro-6-phenyl-2(1*H*)-pyrazinone 10b

Yield: 63%; oil; IR (neat) cm^{-1} : 3296 (C \equiv CH), 2100 (C=C), 1652 (CO), 1564 (C=N); ^1H NMR: 7.57-6.73 (m, 10H, Ar-H), 5.07 (q, $^3\text{J}=7\text{Hz}$, CH), 5.06 (s, 2H, CH₂Ph), 3.73 (t, $^3\text{J}=7.5$, 2H, OCH₂), 2.53 (txd, $^3\text{J}=7.5\text{Hz}$, $^4\text{J}=2.5\text{Hz}$, 2H, CH₂), 1.95 (t, $^4\text{J}=2.5\text{Hz}$, 1H, C \equiv CH), 1.57 (d, $^3\text{J}=7\text{Hz}$, 3H, CH₃); m/z (%): 392 (M⁺, 1), 324 (M⁺-C₄H₄O, 21), 91 (C₇H₇⁺, 100); exact mass for C₂₃H₂₁N₂O₂Cl: 392.1292; found: 392.1272

Synthesis of 1-benzyl-5-chloro-3-hydroxymethyl-6-phenyl-2(1*H*)-pyrazinone 11

To a solution of 3-bromomethyl-2(1*H*)-pyrazinone **7b** (5 mmol) in 15 ml dioxane was added 15 ml H₂O and 1.2 equiv K₂CO₃. After refluxing for 2 hours the mixture was cooled and the dioxane removed under reduced pressure. Then 30 ml CH₂Cl₂ was added followed by treatment with dilute HCl until neutralisation. The organic layer was separated, dried (MgSO₄) and concentrated. The crude product was purified on a silica gel column (20% EtOAc/CH₂Cl₂ as eluent).

Yield: 68%; IR (KBr) cm^{-1} : 1652 (CO), 1572 (C=N); ^1H NMR: 7.54-6.70 (m, 10H, Ar-H), 5.07 (s, 2H, CH₂Ph), 4.85 (s, 2H, CH₂O), 3.50 (s(br), 1H, OH); m/z (%): 326 (M⁺, 2), 308 (M⁺-H₂O, 6), 91 (C₇H₇⁺, 100); exact mass for C₁₈H₁₅N₂O₂Cl: 326.0822; found: 326.0817

Further reaction of this compound with 1.2 equiv propargyl bromide in the presence of 1.1 equiv NaH in THF at RT afforded a complex reaction mixture

V. Furo- and pyrano[2,3-*c*]pyridinones 13a-j and 16a-c and furo- and pyrano[2,3-*b*]pyridines 14a-d and 17

The precursor 2(1*H*)-pyrazinones **2a-e**, **3a-d** and **4a-d** or **5a-d** were refluxed in 15 ml bromobenzene (2-4) or nitrobenzene (5) during 2.5-6 hours. After completion, the solvent was evaporated and the product(s) were purified by chromatography on silica gel (EtOAc/CH₂Cl₂ mixtures as eluents)

6-benzyl-2,3-dihydrofuro[2,3-*c*]pyridin-7(6*H*)-one 13a

Yield: 98%; m.p.: 126-127°C; IR (KBr) cm^{-1} : 1670 (CO); ^1H NMR: 7.32-7.25 (m, 5H, Ar-H), 6.91 (d, $^3\text{J}=7\text{Hz}$, 1H, 5-H), 6.12 (d, $^3\text{J}=7\text{Hz}$, 1H, 4-H), 5.17 (s, 2H, CH₂Ph), 4.60 (t, $^3\text{J}=9\text{Hz}$, 2H, OCH₂), 3.12 (t, $^3\text{J}=9\text{Hz}$, 2H, CH₂); ^{13}C NMR: 154.2 (CO), 148.6 (C-7a), 136.5-127.6 (Ar-C), 130.3 (C-3a), 129.5 (C-5), 103.3 (C-4), 71.0 (C-2), 51.0 (CH₂Ph), 30.5 (C-3); m/z (%): 227 (M⁺, 52), 91 (C₇H₇⁺, 100); exact mass for C₁₄H₁₃NO₂: 227.0946; found: 227.0949

2,3-dihydro-6-phenylfuro[2,3-*c*]pyridin-7(6*H*)-one 13b

Yield: 96%; m.p.: 210-211°C; IR (KBr) cm^{-1} : 1670 (CO); ^1H NMR: 7.51-7.32 (m, 5H, Ar-H), 6.98 (d, $^3\text{J}=7\text{Hz}$, 1H, 5-H), 6.23 (d, $^3\text{J}=7\text{Hz}$, 1H, 4-H), 4.69 (t, $^3\text{J}=9\text{Hz}$, 2H, OCH₂), 3.22 (t, $^3\text{J}=9\text{Hz}$, 2H, CH₂); ^{13}C NMR: 154.5 (CO), 149.2 (C-7a), 140.7-126.7 (Ar-C), 130.8 (C-3a), 130.8 (C-5), 103.4 (C-4), 71.3 (C-2), 30.9 (C-3); m/z (%): 213 (M⁺, 100), 77 (C₆H₅⁺, 46); exact mass for C₁₃H₁₁NO₂: 213.0790; found: 213.0785; anal calcd for C₁₃H₁₁NO₂: C 73.22, H 5.20, N 6.57; found: C 73.17, H 5.11, N 6.42

6-benzyl-2,3-dihydro-5-methylfuro[2,3-*c*]pyridin-7(6*H*)-one 13c

Yield: 78%; m.p.: 183-184°C; IR (KBr) cm^{-1} : 1670 (CO); ^1H NMR: 7.30-7.13 (m, 5H, Ar-H), 6.02 (s, 1H, 4-H), 5.38 (s, 2H, CH₂Ph), 4.61 (t, $^3\text{J}=9\text{Hz}$, 2H, OCH₂), 3.13 (t, $^3\text{J}=9\text{Hz}$, 2H, CH₂), 2.22 (s, 3H, CH₃); ^{13}C NMR: 155.2 (CO), 146.4 (C-7a), 138.3 (C-5), 136.4-127.0 (Ar-C), 130.5 (C-3a), 103.5 (C-4), 70.9 (C-2), 46.9 (CH₂Ph), 30.8 (C-3), 20.2 (CH₃); m/z (%): 241 (M⁺, 68), 150 (M⁺-C₇H₇, 56), 91 (C₇H₇⁺, 100); exact mass for C₁₅H₁₅NO₂: 241.1103; found: 241.1107

6-benzyl-2,3-dihydro-4-methylfuro[2,3-*c*]pyridin-7(6*H*)-one 13d

Yield: 97%; m.p.: 120-121°C; IR (KBr) cm^{-1} : 1680 (CO); ^1H NMR: 7.40-7.20 (m, 5H, Ar-H), 6.70 (q, $^4\text{J}=1\text{Hz}$, 1H, 5-H), 5.14 (s, 2H, CH₂Ph), 4.62 (t, $^3\text{J}=9\text{Hz}$, 2H, OCH₂), 3.06 (t, $^3\text{J}=9\text{Hz}$, 2H, CH₂), 1.99 (q,

$^4J=1\text{Hz}$, 3H, CH₃); ^{13}C NMR: 153.5 (CO), 147.7 (C-7a), 136.8-127.4 (Ar-C), 131.3 (C-3a), 126.9 (C-5), 112.6 (C-4), 70.9 (C-2), 50.7 (CH₂Ph), 29.4 (C-3), 14.9 (CH₃); m/z (%): 241 (M⁺, 54), 150 (M⁺-C₇H₇, 3), 91 (C₇H₇⁺, 100); exact mass for C₁₅H₁₅NO₂: 241.1103; found: 241.1102

2,3-dihydro-4-methyl-6-phenylfuro[2,3-c]pyridin-7(6H)-one 13e

Yield: 97%; oil; IR (neat) cm⁻¹: 1675 (CO); ^1H NMR (CDCl₃): 7.48-7.29 (m, 5H, Ar-H), 6.78 (s(br), 1H, 5-H), 4.65 (t, $^3J=9\text{Hz}$, 2H, OCH₂), 3.14 (t, $^3J=9\text{Hz}$, 2H, CH₂), 2.04 (s, 3H, CH₃); ^{13}C NMR: 153.4 (CO), 147.8 (C-7a), 140.5-126.4 (Ar-C), 131.7 (C-3a), 127.9 (C-5), 112.4 (C-4), 70.9 (C-2), 29.5 (C-3), 14.9 (CH₃); m/z (%): 227 (M⁺, 100), 77 (C₆H₅⁺, 50); exact mass for C₁₄H₁₃NO₂: 227.0946; found: 227.0938

6-benzyl-2,3-dihydro-4,5-dimethylfuro[2,3-c]pyridin-7(6H)-one 13f

Yield: 88%; m.p.: 184-185°C; IR (KBr) cm⁻¹: 1670 (CO); ^1H NMR: 7.34-7.11 (m, 5H, Ar-H), 5.42 (s, 2H, CH₂Ph), 4.62 (t, $^3J=9\text{Hz}$, 2H, OCH₂), 3.15 (t, $^3J=9\text{Hz}$, 2H, CH₂), 2.17 (s, 3H, 4-CH₃), 2.01 (s, 3H, 5-CH₃); ^{13}C NMR: 154.4 (CO), 145.5 (C-7a), 136.7-126.2 (Ar-C), 134.6 (C-5), 132.0 (C-3a), 109.8 (C-4), 70.4 (C-2), 47.1 (CH₂Ph), 30.3 (C-3), 15.7/14.8 (CH₃); m/z (%): 255 (M⁺, 81), 164 (M⁺-C₇H₇, 100), 91 (C₇H₇⁺, 94); exact mass for C₁₆H₁₇NO₂: 255.1259; found: 255.1255; anal calcd for C₁₆H₁₇NO₂: C 75.27, H 6.71, N 5.49; found: C 75.38, H 6.83, N 5.40

6-benzyl-2,3-dihydro-4-phenylfuro[2,3-c]pyridin-7(6H)-one 13g

Yield: 92%; m.p.: 189°C; IR (KBr) cm⁻¹: 1659 (CO); ^1H NMR: 7.42-7.24 (m, 10H, Ar-H), 6.97 (s, 1H, 5-H), 5.26 (s, 2H, CH₂Ph), 4.69 (t, $^3J=9\text{Hz}$, 2H, OCH₂), 3.24 (t, $^3J=9\text{Hz}$, 2H, CH₂); ^{13}C NMR: 153.8 (CO), 148.7 (C-7a), 136.6-127.5 (Ar-C), 129.5 (C-3a), 127.5 (C-5), 118.9 (C-4), 71.4 (C-2), 51.5 (CH₂Ph), 30.8 (C-3); m/z (%): 303 (M⁺, 35), 212 (M⁺-C₇H₇, 4), 91 (C₇H₇⁺, 100); exact mass for C₂₀H₁₇NO₂: 303.1259; found: 303.1280; anal calcd for C₂₀H₁₇NO₂: C 79.19, H 5.65, N 4.62; found: C 78.97, H 5.61, N 4.58

2,3-dihydro-4,6-diphenylfuro[2,3-c]pyridin-7(6H)-one 13h

Yield: 90%; m.p.: 169-170°C; IR (KBr) cm⁻¹: 1670 (CO); ^1H NMR: 7.57-7.28 (m, 10H, Ar-H), 7.07 (s, 1H, 5-H), 4.71 (t, $^3J=9\text{Hz}$, 2H, OCH₂), 3.32 (t, $^3J=9\text{Hz}$, 2H, CH₂); ^{13}C NMR: 153.6 (CO), 148.9 (C-7a), 140.8-126.7 (Ar-C), 129.8 (C-3a), 127.5 (C-5), 118.7 (C-4), 71.4 (C-2), 30.9 (C-3); m/z (%): 289 (M⁺, 100), 77 (C₆H₅⁺, 69); exact mass for C₁₉H₁₅NO₂: 289.1103; found: 289.1108

6-benzyl-2,3-dihydro-5-methyl-4-phenylfuro[2,3-c]pyridin-7(6H)-one 13i

Yield: 85%; m.p.: 205°C; IR (KBr) cm⁻¹: 1660 (CO); ^1H NMR: 7.41-7.12 (m, 10H, Ar-H), 5.45 (s, 2H, CH₂Ph), 4.60 (t, $^3J=9\text{Hz}$, 2H, OCH₂), 2.92 (t, $^3J=9\text{Hz}$, 2H, CH₂), 2.08 (s, 3H, CH₃); ^{13}C NMR: 155.0 (CO), 145.9 (C-7a), 137.3 (C-5), 136.7-126.6 (Ar-C), 131.3 (C-3a), 117.8 (C-4), 70.9 (C-2), 47.7 (CH₂Ph), 31.1 (C-3), 17.4 (CH₃); m/z (%): 317 (M⁺, 63), 226 (M⁺-C₇H₇, 56), 91 (C₇H₇⁺, 100); exact mass for C₂₁H₁₉NO₂: 317.1416; found: 317.1423; anal calcd for C₂₁H₁₉NO₂: C 79.47, H 6.03, N 4.41; found: C 79.18, H 5.96, N 4.38

6-benzyl-2,3-dihydro-5-phenylfuro[2,3-c]pyridin-7(6H)-one 13j

Yield: 23%; m.p.: 149-150°C; IR (KBr) cm⁻¹: 1652 (CO); ^1H NMR: 7.42-6.80 (m, 10H, Ar-H), 6.07 (s, 1H, 4-H), 5.19 (s, 2H, CH₂Ph), 4.65 (t, $^3J=10\text{Hz}$, 2H, OCH₂), 3.18 (t, $^3J=10\text{Hz}$, 2H, CH₂); ^{13}C NMR: 153.9 (CO), 147.9 (C-7a), 142.5 (C-5), 137.2-127.0 (Ar-C), 130.1 (C-3a), 105.4 (C-4), 71.1 (C-2), 48.5 (CH₂Ph), 30.9 (C-3); m/z (%): 303 (M⁺, 48), 226 (M⁺-C₆H₅, 16), 91 (C₇H₇⁺, 100); exact mass for C₂₀H₁₇NO₂: 303.1259; found: 303.1256

6-chloro-2,3-dihydro-5-methylfuro[2,3-b]pyridine 14a

Yield: 86%; m.p.: 52-53°C; IR (KBr) cm⁻¹: 1610, 1585 (pyridine); ^1H NMR: 7.33 (s, 1H, 4-H), 4.62 (t, $^3J=7\text{Hz}$, 2H, OCH₂), 3.22 (t, $^3J=7\text{Hz}$, 2H, CH₂), 2.27 (s, 3H, CH₃); ^{13}C NMR: 166.2 (C-7a), 146.8 (C-6), 136.5 (C-4), 123.1 (C-5), 118.4 (C-3a), 69.7 (C-2), 27.3 (C-3), 18.6 (CH₃); m/z (%): 169 (M⁺, 100), 134 (M⁺-Cl, 24); exact mass for C₈H₈NOCl: 169.0294; found: 169.0302

6-chloro-2,3-dihydro-4,5-dimethylfuro[2,3-b]pyridine 14b

Yield: 95%; m.p.: 96-97°C; IR (KBr) cm⁻¹: 1620, 1590 (pyridine); ^1H NMR: 4.52 (t, $^3J=7\text{Hz}$, 2H, OCH₂), 3.05 (t, $^3J=7\text{Hz}$, 2H, CH₂), 2.10 (s, 3H, CH₃), 2.11 (s, 3H, CH₃); ^{13}C NMR: 158.7 (C-7a), 146.8 (C-6), 145.6 (C-4), 121.8 (C-5), 117.5 (C-3a), 69.3 (C-2), 26.8 (C-3), 17.0/14.9 (CH₃); m/z (%): 183 (M⁺, 100), 148 (M⁺-Cl, 20); exact mass for C₉H₁₀NOCl: 183.0451; found: 183.0461; anal calcd for C₉H₁₀NOCl: C 58.86, H 5.49, N 7.63; found: C 58.75, H 5.47, N 7.57

6-chloro-2,3-dihydro-5-methyl-4-phenylfuro[2,3-*b*]pyridine 14c

Yield: 86%; m.p.: 140-141°C; IR (KBr) cm^{-1} : 1595, 1590 (pyridine); ^1H NMR: 7.50-7.19 (m, 5H, Ar-H), 4.60 (t, $^3\text{J}=6\text{Hz}$, 2H, OCH_2), 3.01 (t, $^3\text{J}=6\text{Hz}$, 2H, CH_2), 2.10 (s, 3H, CH_3); ^{13}C NMR: 165.5 (C-7a), 149.9 (C-6), 148.5 (C-4), 137.2-127.8 (Ar-C), 121.5 (C-5), 117.4 (C-3a), 69.7 (C-2), 27.7 (C-3), 16.5 (CH_3); m/z (%): 245 (M^+ , 100), 210 (M^+-Cl , 19), 77 (C_6H_5^+ , 9); exact mass for $\text{C}_{14}\text{H}_{12}\text{NOCl}$: 245.0607; found: 245.0602

6-chloro-2,3-dihydro-5-phenylfuro[2,3-*b*]pyridine 14d

Yield: 71%; oil; IR (neat) cm^{-1} : 1610, 1576 (pyridine); ^1H NMR: 7.49-7.03 (m, 5H, Ar-H), 7.25 (s, 1H, 4-H), 4.70 (t, $^3\text{J}=8\text{Hz}$, 2H, OCH_2), 3.27 (t, $^3\text{J}=8\text{Hz}$, 2H, CH_2); ^{13}C NMR: 167.3 (C-7a), 146.4 (C-6), 136.8 (C-4); 138.2-127.7 (Ar-C), 128.7 (C-5), 118.7 (C-3a), 70.1 (C-2), 27.5 (C-3); m/z (%): 231 (M^+ , 100), 196 (M^+-Cl , 9); exact mass for $\text{C}_{13}\text{H}_{10}\text{NOCl}$: 231.0451; found: 231.0452

7-benzyl-3,4-dihydro-2*H*-pyrano[2,3-*c*]pyridin-8(7*H*)-one 16a

Yield: 97%; IR (KBr) cm^{-1} : 1660 (CO); ^1H NMR: 7.30-7.10 (m, 5H, Ar-H), 6.80 (d, $^3\text{J}=7\text{Hz}$, 1H, 6-H), 5.87 (d, $^3\text{J}=7\text{Hz}$, 1H, 5-H), 5.03 (s, 2H, CH_2Ph), 4.18 (t, $^3\text{J}=5\text{Hz}$, 2H, OCH_2), 2.51 (t, $^3\text{J}=6.5\text{Hz}$, 2H, 4- CH_2), 1.93 (txt, $^3\text{J}=5\text{Hz}$, $^3\text{J}=6.5\text{Hz}$, 2H, 3- CH_2); ^{13}C NMR: 157.3 (CO), 144.4 (C-8a), 136.5-127.5 (Ar-C), 126.6 (C_6), 125.7 (C-4a), 107.4 (C-5), 66.3 (C-2), 51.0 (CH_2Ph), 23.7 (C-4), 20.9 (C-3); m/z (%): 241 (M^+ , 52), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{15}\text{H}_{15}\text{NO}_2$: 241.1103; found: 241.1092

3,4-dihydro-7-phenyl-2*H*-pyrano[2,3-*c*]pyridin-8(7*H*)-one 16b

Yield: 95%; m.p.: 157-158°C; IR (KBr) cm^{-1} : 1670 (CO); ^1H NMR: 7.50-7.30 (m, 5H, Ar-H), 6.86 (d, $^3\text{J}=7\text{Hz}$, 1H, 6-H), 5.95 (d, $^3\text{J}=7\text{Hz}$, 1H, 5-H), 4.28 (t, $^3\text{J}=5\text{Hz}$, 2H, OCH_2), 2.60 (t, $^3\text{J}=6.5\text{Hz}$, 2H, 4- CH_2), 2.02 (txt, $^3\text{J}=5\text{Hz}$, $^3\text{J}=6.5\text{Hz}$, 2H, 3- CH_2); ^{13}C NMR: 157.2 (CO), 144.9 (C-8a), 141.0-126.4 (Ar-C), 127.6 (C-6), 125.7 (C-4a), 107.1 (C-5), 66.6 (C-2), 24.1 (C-4), 21.3 (C-3); m/z (%): 227 (M^+ , 100), 77 (C_6H_5^+ , 27); exact mass for $\text{C}_{14}\text{H}_{13}\text{NO}_2$: 227.0946; found: 227.0947

7-benzyl-3,4-dihydro-6-methyl-2*H*-pyrano[2,3-*c*]pyridin-8(7*H*)-one 16c

Yield: 90%; m.p.: 163-164°C; IR (KBr) cm^{-1} : 1660 (CO); ^1H NMR: 7.32-7.16 (m, 5H, Ar-H), 5.75 (s, 1H, 5-H), 5.33 (s, 2H, CH_2Ph), 4.26 (t, $^3\text{J}=5\text{Hz}$, 2H, OCH_2), 2.56 (t, $^3\text{J}=6.5\text{Hz}$, 2H, 4- CH_2), 2.18 (s, 3H, CH_3), 2.00 (txt, $^3\text{J}=5\text{Hz}$, $^3\text{J}=6.5\text{Hz}$, 2H, 3- CH_2); ^{13}C NMR: 158.6 (CO), 142.4 (C-8a), 136.7-126.6 (Ar-C), 135.0 (C-6), 125.7 (C-4a), 107.3 (C-5), 66.4 (C-2), 47.2 (CH_2Ph), 23.9 (C-4), 21.4 (C-3), 19.6 (CH_3); m/z (%): 255 (M^+ , 80), 164 ($\text{M}^+-\text{C}_7\text{H}_7$, 63), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{16}\text{H}_{17}\text{NO}_2$: 255.1259; found: 255.1260

7-chloro-3,4-dihydro-6-methyl-2*H*-pyrano[2,3-*b*]pyridine 17

Yield: 58%; oil; IR (neat) cm^{-1} : 1620, 1590 (pyridine); ^1H NMR (CDCl_3): 7.22 (q, $^4\text{J}=1\text{Hz}$, 1H, 5-H), 4.31 (t, $^3\text{J}=7\text{Hz}$, 2H, OCH_2), 2.75 (t, $^3\text{J}=7\text{Hz}$, 2H, 4- CH_2), 2.27 (d, $^4\text{J}=1\text{Hz}$, 3H, CH_3), 2.00 (m, $^3\text{J}=7\text{Hz}$, 2H, 3- CH_2); ^{13}C NMR (CDCl_3): 158.7 (C-8a), 146.4 (C-7), 141.2 (C-5), 124.4 (C-6), 115.6 (C-4a), 67.2 (C-2), 24.1 (C-4), 21.6 (C-3), 18.2 (CH_3); m/z (%): 183 (M^+ , 100), 148 (M^+-Cl , 31); exact mass for $\text{C}_9\text{H}_{10}\text{NOCl}$: 183.0451; found: 183.0463

VI. Cycloadducts 18a-c and hydrolysed analogues 21a-c

The precursors **9b** or **9d** (2.5 mmol) were refluxed during 15-20 minutes in 20 ml toluene to yield the cycloadducts **18a** and **18c** after evaporation. Compound **9c** could not be isolated but reacted immediately to the cycloadduct **18b** under the conditions mentioned above. The spectral data of **18a-c**, reacting slowly with air humidity to **21a-c**, were taken immediately after fast chromatography on a silica gel plate (5% EtOAc/ CH_2Cl_2).

The adducts **18a-c** were hydrolysed in quantitative yield to the pure compounds **21a-c** on a silica gel column eluting with 2-20% EtOAc/ CH_2Cl_2 mixtures

2-benzyl-6-chloro-1-phenyl-4,8-(methanoxymethano)-2,5-diazabicyclo[2.2.2]octa-5,7-dien-3-one 18a

Yield: 82%; unstable solid; IR (KBr) cm^{-1} : 1696 (CO), 1598 (C=N); ^1H NMR: 7.50-6.40 (m, 10H, Ar-H), 6.57 (t, $^4\text{J}=2\text{Hz}$, 1H, 7-H), 5.24/4.42 (2xd, $^2\text{J}=9.5$, 2H, 11- CH_2), 4.82/4.18 (2xd, $^2\text{J}=14.5\text{Hz}$, 2H, CH_2Ph), 4.50/4.39 (2xdxd, $^2\text{J}=14.5\text{Hz}$, $^4\text{J}=2\text{Hz}$, 2H, 9- CH_2); ^{13}C NMR: 168.8 (CO), 168.5 (C-6), 153.0 (C-8), 135.0-

127.3 (Ar-C), 119.1 (C-7), 84.4 (C-4), 74.5 (C-1), 69.8 (C-11), 66.5 (C-9), 47.8 (CH₂Ph); m/z (%) (CI): 365 (MH⁺, 14), 232 (MH⁺-C₇H₇NCO, 72), 91 (C₇H₇⁺, 100)

2-benzyl-6-chloro-11-methyl-4,8-(methanoxy-methano)-2,5-diazabicyclo[2.2.2]octa-5,7-dien-3-one 18b

Yield: 76% (starting from 7c) unstable oil; IR (neat) cm⁻¹: 1696 (CO), 1601 (C=N); ¹H NMR: 7.40-7.10 (m, 5H, Ar-H), 6.23 (dxt, ³J=5.5Hz, ⁴J=2Hz, 1H, 7-H), 5.12 (q, ³J=7Hz, 1H, 11-H), 4.87 (d, ³J=5.5Hz, 1H, 1-H), 4.57/4.35 (2xd, ²J=15Hz, 2H, CH₂Ph), 4.47/4.37 (2xdxd, ²J=14Hz, ⁴J=2Hz, 2H, 9-CH₂), 1.60 (d, ³J=7Hz, 3H, CH₃); ¹³C NMR: 166.9 (CO), 165.7 (C-6), 155.5 (C-8), 135.1-128.1 (Ar-C), 117.5 (C-7), 86.5 (C-4), 74.5 (C-11), 65.0 (C-9), 64.4 (C-1), 48.9 (CH₂Ph), 15.5 (CH₃); m/z (%) (CI): 303 (MH⁺, 1), 242 (MH⁺-ClCN, 65), 91 (C₇H₇⁺, 100); exact mass for C₁₆H₁₅N₂O₂Cl-ClCN; 241.1103; found: 241.1099

2-benzyl-6-chloro-11-methyl-1-phenyl-4,8-(methanoxy-methano)-2,5-diazabicyclo[2.2.2]octa-5,7-dien-3-one 18c

Yield: 89%; unstable solid; IR (KBr) cm⁻¹: 1695 (CO), 1600 (C=N); ¹H NMR: 7.55-6.38 (m, 10H, Ar-H), 6.58 (t, ⁴J=2.5Hz, 1H, 7-H), 5.28 (q, ³J=7Hz, 1H, 11-H), 4.83/4.08 (2xd, ²J=15Hz, 2H, CH₂Ph), 4.58/4.38 (2xdxd, ²J=15Hz, ⁴J=2.5Hz, 2H, 9-CH₂), 1.65 (d, ³J=7Hz, 3H, CH₃); ¹³C NMR: 169.5 (CO), 168.6 (C-6), 154.4 (C-8), 135.4-127.4 (Ar-C), 120.0 (C-7), 85.7 (C-4), 74.8 (C-11), 74.5 (C-1), 65.1 (C-9), 47.8 (CH₂Ph), 15.6 (CH₃); m/z (%) (CI): 379 (MH⁺, 11), 91 (C₇H₇⁺, 100)

2-benzyl-1-phenyl-4,8-(methanoxy-methano)-2,5-diazabicyclo[2.2.2]oct-7-ene-3,6-dione 21a

Yield: 95%; m.p.: 210°C; IR (KBr) cm⁻¹: 1690 (CO); ¹H NMR: 9.50 (s, 1H, NH), 7.48-6.53 (m, 10H, Ar-H), 6.50 (t, ⁴J=1Hz, 1H, 7-H), 4.65/4.07 (2xd, ²J=14Hz, 2H, 11-CH₂), 4.55 (d, ⁴J=1Hz, 2H, 9-CH₂), 4.27/4.06 (2xd, ²J=14Hz, 2H, CH₂Ph); ¹³C NMR: 172.2 (C-6), 169.9 (C-3), 153.9 (C-8), 136.9-126.3 (Ar-C), 123.9 (C-7), 71.5 (C-1), 68.3 (C-4), 66.7+66.6 (C-9+C-11), 45.6 (CH₂Ph); m/z (%) (CI): 347 (MH⁺, 7), 214 (MH⁺-C₇H₇NCO, 100), 91 (C₇H₇⁺, 34); exact mass for C₂₁H₁₈N₂O₃-CH₂NO; 302.1181; found: 302.1180

2-benzyl-11-methyl-4,8-(methanoxy-methano)-2,5-diazabicyclo[2.2.2]oct-7-ene-3,6-dione 21b

Yield: 97%; m.p.: 198-199°C; IR (KBr) cm⁻¹: 1690 (CO); ¹H NMR (DMSO-*d*₆): 8.80 (s, 1H, NH), 7.40-7.10 (m, 5H, Ar-H), 6.53 (dxt, ³J=5.5Hz, ⁴J=2Hz, 1H, 7-H), 4.67 (q, ³J=6.5Hz, 1H, 11-H), 4.54/4.46 (2xd, ²J=14Hz, 2H, CH₂Ph), 4.48 (d, ³J=5.5Hz, 1H, 1-H), 4.54/4.25 (2xdxd, ²J=15Hz, ⁴J=2Hz, 2H, 9-CH₂), 1.60 (d, ³J=6.5Hz, 3H, CH₃); ¹³C NMR (DMSO-*d*₆): 172.6 (C-6), 169.0 (C-3), 154.5 (C-8), 136.6-127.4 (Ar-C), 121.3 (C-7), 73.0 (C-11), 71.3 (C-4), 64.8 (C-9), 63.5 (C-1), 48.0 (CH₂Ph), 14.2 (CH₃); m/z (%) (CI): 285 (MH⁺, 100), 279 (M⁺-CH₃, 14), 91 (C₇H₇⁺, 11); exact mass for C₁₆H₁₆N₂O₃; 284.1161; found: 284.1162

2-benzyl-11-methyl-1-phenyl-4,8-(methanoxy-methano)-2,5-diazabicyclo[2.2.2]oct-7-ene-3,6-dione 21c

Yield: 95%; m.p.: 205°C; IR (KBr) cm⁻¹: 1690 (CO); ¹H NMR: 9.20 (s, 1H, NH), 7.54-6.41 (m, 10H, Ar-H), 6.58 (t, ⁴J=3Hz, 1H, 7-H), 5.00 (q, ³J=8Hz, 1H, 11-H), 4.68/4.44 (2xdxd, ²J=15Hz, ⁴J=3Hz, 2H, 9-CH₂), 4.54/4.11 (2xd, ²J=15Hz, 2H, CH₂Ph), 1.53 (d, ³J=8Hz, 3H, CH₃); ¹³C NMR: 173.6 (C-6), 170.7 (C-3), 155.2 (C-8), 136.8-127.1 (Ar-C), 125.3 (C-7), 73.8 (C-11), 71.8 (C-1), 70.1 (C-4), 66.2 (C-9), 46.4 (CH₂Ph), 14.2 (CH₃); m/z (%) (CI): 361 (MH⁺, 33), 228 (M⁺-C₇H₇NCO, 100), 91 (C₇H₇⁺, 48); exact mass for C₂₂H₂₀N₂O₃; 360.1474; found: 360.1458; anal calcd for C₂₂H₂₀N₂O₃: C 73.32, H 5.59, N 7.77; found: C 72.94, H 5.53, N 7.67

VII. Furo- and pyrano[3,4-b]pyridines 19a,b and 25, furo- and pyrano[3,4-c]pyridinones 20 and 24 and furo[3,4-b]pyridinones 22a,b

The same procedures were followed as for the synthesis of the pyridinones 13a-j or pyridines 14a-d. Compounds 19a, 19b and 20 were formed starting from 9b-d *via* 18a-c (reflux toluene); compounds 22a and 22b were obtained starting from 21a and 21c (reflux bromobenzene). Precursors 10a or 10b led to 24 or 25 (reflux bromobenzene).

2-chloro-5,7-dihydro-3-phenylfuro[3,4-b]pyridine 19a

Yield: 61%; oil; IR (neat) cm⁻¹: 1595, 1570 (pyridine); ¹H NMR: 7.55 (s, 1H, 4-H), 7.48-7.40 (m, 5H, Ar-H), 5.19 (t, ⁴J=2Hz, 2H, 7-CH₂), 5.09 (t, ⁴J=2Hz, 2H, 5-CH₂); ¹³C NMR: 160.1 (C-7a), 149.3 (C-2), 135.1 (C-3), 132.7 (C-4), 131.5 (C-4a), 137.6-128.3 (Ar-C), 72.3 (C-7), 71.7 (C-5); m/z (%) (CI): 231 (M⁺, 94), 167 (M⁺-CHO-Cl, 100), 77 (C₆H₅⁺, 13); exact mass for C₁₃H₁₀NOCl: 231.0451; found: 231.0460

2-chloro-5,7-dihydro-7-methyl-3-phenylfuro[3,4-*b*]pyridine 19b

Yield: 58%; oil; IR (neat) cm^{-1} : 1603, 1560 (pyridine); $^1\text{H NMR}$: 7.50 (t, $^4J=0.8\text{Hz}$, 1H, 4-H), 7.47-7.38 (m, 5H, Ar-H), 5.19 (qxt, $^3J=6.5\text{Hz}$, $^4J=2.5\text{Hz}$, 2H, 1H, 7-H), 5.12 (2xdxd, $^2J=13\text{Hz}$, $^4J=2.5\text{Hz}$, 2H, 0.8Hz, 2H, CH_2O), 1.59 (d, $^3J=6.5\text{Hz}$, CH_3); $^{13}\text{C NMR}$: 162.9 (C-7a), 149.3 (C-2), 135.1 (C-3), 132.9 (C-4), 131.3 (C-4a), 137.6-128.2 (Ar-C), 78.5 (C-7), 69.8 (C-5), 20.1 (CH_3); m/z (%): 245 (M^+ , 69), 230 (M^+-CH_3 , 100), 77 (C_6H_5^+ , 21); exact mass for $\text{C}_{14}\text{H}_{12}\text{NOCl}$: 245.0607; found: 245.0612

5-benzyl-3,5-dihydro-3-methylfuro[3,4-*c*]pyridin-4(1*H*)-one 20

Yield: 51%; oil; IR (neat) cm^{-1} : 1665 (CO); $^1\text{H NMR}$: 7.35-7.21 (m, 6H, Ar-H+6-H), 6.10 (d, $^3J=7.5\text{Hz}$, 1H, 7-H), 5.35 (m, $^3J=6.5\text{Hz}$, $^4J=4\text{Hz}$, 2.5Hz, 1H, 3-H), 5.24/5.03 (2xd, $^2J=14.5\text{Hz}$, 2H, CH_2Ph), 4.99/4.87 (2xd, $^2J=14\text{Hz}$, $^4J=4\text{Hz}$, 2.5Hz, 2H, 1- CH_2), 1.55 (d, $^3J=6.5\text{Hz}$, 3H, CH_3); $^{13}\text{C NMR}$: 158.3 (CO), 149.6 (C-7a), 137.6 (C-6), 136.3-127.8 (Ar-C), 130.8 (C-3a), 100.3 (C-7), 80.6 (C-3), 72.5 (C-1), 51.1 (CH_2Ph), 19.9 (CH_3); m/z (%): 241 (M^+ , 12), 226 (M^+-CH_3 , 36), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{15}\text{H}_{15}\text{NO}_2$: 241.1103; found: 241.1099

5,7-dihydro-3-phenylfuro[3,4-*b*]pyridin-2(1*H*)-one 22a

Yield: 86%; m.p.: 211°C; IR (KBr) cm^{-1} : 1683 (CO); $^1\text{H NMR}$: 7.50 (s, 1H, 4-H), 7.68-7.30 (m, 5H, Ar-H), 5.00 (t, $^4J=2.5\text{Hz}$, 2H, 7- CH_2), 4.91 (t, $^4J=2.5\text{Hz}$, 2H, 5- CH_2); $^{13}\text{C NMR}$: 163.9 (CO), 144.3 (C-7a), 133.8 (C-4), 136.5-127.8 (Ar-C), 129.4 (C-3), 116.3 (C-4a), 72.7 (C-7), 70.7 (C-5); m/z (%): 213 (M^+ , 100), 77 (C_6H_5^+ , 41); exact mass for $\text{C}_{13}\text{H}_{11}\text{NO}_2$: 213.0790; found: 213.0794

5,7-dihydro-7-methyl-3-phenylfuro[3,4-*b*]pyridin-2(1*H*)-one 22b

Yield: 87%; m.p.: 219°C; IR (KBr) cm^{-1} : 1685 (CO); $^1\text{H NMR}$: 7.53 (s, 1H, 4-H), 7.74-7.25 (m, 5H, Ar-H), 5.24 (m, $^3J=7\text{Hz}$, $^4J=3.5\text{Hz}$, 3Hz, 1H, 7-H), 5.03/4.93 (2xd, $^2J=15\text{Hz}$, $^4J=3.5\text{Hz}$, 3Hz, 2H, CH_2O), 1.60 (d, $^3J=7\text{Hz}$, 3H, CH_3); $^{13}\text{C NMR}$: 164.4 (CO), 147.6 (C-7a), 134.1 (C-4), 136.5-127.8 (Ar-C), 129.1 (C-3), 115.9 (C-4a), 77.7 (C-7), 71.3 (C-5), 19.9 (CH_3); m/z (%): 227 (M^+ , 53), 221 (M^+-CH_3 , 84), 43 (CHNO^+ , 100); exact mass for $\text{C}_{14}\text{H}_{13}\text{NO}_2$: 227.0946; found: 227.0951

7-benzyl-1,3,4,7-tetrahydro-1-methyl-8*H*-pyrano[3,4-*c*]pyridin-8-one 24

Yield: 78%; oil; IR (neat) cm^{-1} : 1651 (CO); $^1\text{H NMR}$: 7.35-7.22 (m, 5H, Ar-H), 7.13 (d, $^3J=6.5\text{Hz}$, 1H, 6-H), 5.96 (d, $^3J=6.5\text{Hz}$, 1H, 5-H), 5.19/4.98 (2xd, $^2J=14\text{Hz}$, 2H, CH_2Ph), 4.85 (q, $^3J=7\text{Hz}$, 1H, 1-H), 3.98/3.72 (2xdxt, $^2J=11\text{Hz}$, $^3J=6.5\text{Hz}$, 2H, CH_2O), 2.56/2.54 (m, 2H, 4- CH_2), 1.55 (t, $^3J=7\text{Hz}$, 3H, CH_3); $^{13}\text{C NMR}$: 160.0 (CO), 144.5 (C-4a), 133.9 (C-6), 136.4-127.7 (Ar-C), 129.3 (C-8a), 107.4 (C-5), 68.8 (C-1), 58.9 (C-3), 51.5 (CH_2Ph), 28.3 (C-4), 18.3 (CH_3); m/z (%): 255 (M^+ , 22), 240 (M^+-CH_3 , 50), 91 (C_7H_7^+ , 100); exact mass for $\text{C}_{16}\text{H}_{17}\text{NO}_2$: 255.1259; found: 255.1261

2-chloro-5,8-dihydro-8-methyl-3-phenyl-6*H*-pyrano[3,4-*b*]pyridine 25

Yield: 68%; oil; IR (neat) cm^{-1} : 1653, 1548 (pyridine); $^1\text{H NMR}$: 7.47-7.39 (m, 5H, Ar-H), 7.38 (s, 1H, 4-H), 4.84 (q, $^3J=7\text{Hz}$, 1H, 8-H), 4.19/3.82 (2xm, 2H, CH_2O), 3.05/2.73 (2xm, 2H, 5- CH_2), 1.64 (d, $^3J=7\text{Hz}$, CH_3); $^{13}\text{C NMR}$: 157.8 (C-8a), 146.6 (C-2), 140.0 (C-4), 134.7 (C-3), 137.3-128.0 (Ar-C), 128.5 (C-4a), 74.1 (C-8), 62.9 (C-5), 27.8 (C-6), 20.0 (CH_3); m/z (%): 259 (M^+ , 22), 244 (M^+-CH_3 , 100), 77 (C_6H_5^+ , 29); exact mass for $\text{C}_{15}\text{H}_{14}\text{NOCl}$: 259.0764; found: 259.0761

VIII. Debenzylated furo/pyranof[2,3-*c*]pyridinones 26a-c and pyrano[3,4-*c*]pyridinone 26d

A mixture of 1 mmol annelated pyridinone **13g** (**13i**, **16c** or **24**) and 50 weight % $\text{Pd}(\text{OH})_2$ on carbon in CH_3COOH was hydrogenated at 1 atm during 1.5 hour. After completion, the catalyst was filtered off and the solvent evaporated. The crude product was purified on alumina preparative plates using 5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ as eluent.

2,3-dihydro-4-phenylfuro[2,3-*c*]pyridin-7(6*H*)-one 26a

Yield: 93%; m.p.: 225°C; IR (KBr) cm^{-1} : 1658 (CO); $^1\text{H NMR}$: 12.95 (s(br), 1H, NH), 7.46-7.23 (m, 5H, Ar-H), 7.17 (s, 1H, 5-H), 4.68 (t, $^3J=9\text{Hz}$, 2H, OCH_2), 3.30 (t, $^3J=9\text{Hz}$, 2H, CH_2); $^{13}\text{C NMR}$: 155.7 (CO), 148.2 (C-7a), 136.2-127.5 (Ar-C), 132.5 (C-3a), 125.4 (C-5), 120.2 (C-4), 71.3 (C-2), 31.0 (C-3); m/z (%): 213 (M^+ , 100), 156 ($\text{M}^+-\text{C}_2\text{HO}_2$, 37); exact mass for $\text{C}_{13}\text{H}_{11}\text{NO}_2$: 213.0790; found: 213.0791; anal calcd for $\text{C}_{13}\text{H}_{11}\text{NO}_2$: C 73.22, H 5.20, N 6.57; found: C 72.85, H 5.02, N 6.49

2,3-dihydro-5-methyl-4-phenylfuro[2,3-*c*]pyridin-7(6*H*)-one 26b

Yield: 95%; m.p.: 309°C; IR (KBr) cm^{-1} : 1652 (CO); ^1H NMR: 13.03 (s(br), 1H, NH), 7.45-7.18 (m, 5H, Ar-H), 4.58 (t, $^3\text{J}=9\text{Hz}$, 2H, OCH_2), 2.96 (t, $^3\text{J}=9\text{Hz}$, 2H, CH_2), 2.25 (s, 3H, CH_3); ^{13}C NMR: 155.3 (CO), 145.1 (C-7a), 136.0-127.1 (Ar-C), 134.7 (C-3a), 134.2 (C-5), 117.3 (C-4), 70.9 (C-2), 30.6 (C-3), 16.8 (CH_3); m/z (%): 227 (M^+ , 100), 170 ($\text{M}^+ - \text{C}_2\text{HO}_2$, 21); exact mass for $\text{C}_{14}\text{H}_{13}\text{NO}_2$: 227.0946; found: 227.0947; anal calcd for $\text{C}_{14}\text{H}_{13}\text{NO}_2$: C 73.99, H 5.77, N 6.16; found: C 73.84, H 5.52, N 6.12

3,4-dihydropyrano-6-methyl-2*H*-pyrano[2,3-*c*]pyridin-8(7*H*)-one 26c

Yield: 91%; m.p.: 187-188°C; IR (KBr) cm^{-1} : 1651 (CO); ^1H NMR (CDCl_3): 13.13 (s(br), 1H, NH), 5.69 (s, 1H, 5-H), 4.16 (t, $^3\text{J}=5.5\text{Hz}$, 2H, OCH_2), 2.49 (t, $^3\text{J}=6.5\text{Hz}$, 2H, 4- CH_2), 2.24 (s, 3H, CH_3), 1.92 (txt, $^3\text{J}=5.5\text{Hz}$, $^3\text{J}=6.5\text{Hz}$, 2H, 3- CH_2); ^{13}C NMR (CDCl_3): 159.6 (CO), 141.4 (C-8a), 134.4 (C-6), 128.9 (C-4a), 106.7 (C-5), 66.4 (C-2), 24.1 (C-4), 21.3 (C-3), 18.2 (CH_3); m/z (%): 165 (M^+ , 66), 137 ($\text{M}^+ - \text{CO}$, 36), 42 (CNO^+ , 100); exact mass for $\text{C}_9\text{H}_{11}\text{NO}_2$: 165.0790; found: 165.0791

1,3,4,7-tetrahydro-1-methyl-8*H*-pyrano[3,4-*c*]pyridin-8-one 26d

Yield: 94%; m.p.: 240°C; IR (KBr) cm^{-1} : 1645 (CO); ^1H NMR (CDCl_3): 12.87 (s(br), 1H, NH), 7.22 (d, $^3\text{J}=6\text{Hz}$, 1H, 6-H), 6.09 (d, $^3\text{J}=6\text{Hz}$, 1H, 5-H), 4.85 (q, $^3\text{J}=6\text{Hz}$, 1H, 1-H), 4.01/3.79 (2xdxt, $^2\text{J}=12\text{Hz}$, $^3\text{J}=6\text{Hz}$, 2H, CH_2O), 2.64 (t, $^3\text{J}=6\text{Hz}$, 2H, 4- CH_2), 1.55 (d, $^3\text{J}=6\text{Hz}$, 3H, CH_3); ^{13}C NMR (CDCl_3): 162.9 (CO), 146.9 (C-4a), 131.4 (C-6), 129.0 (C-8a), 108.3 (C-5), 68.6 (C-1), 59.3 (C-3), 28.7 (C-4), 18.6 (CH_3); m/z (%): 165 (M^+ , 13), 150 ($\text{M}^+ - \text{CH}_3$, 100); exact mass for $\text{C}_9\text{H}_{11}\text{NO}_2$: 165.0790; found: 165.0789

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