Pergamon

Tetrahedron Vol. 51, No. 45, pp. 12463-12478, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00802-0

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

Kris J. Buysens, Didier M. Vandenberghe, Suzanne M. Toppet and Georges J. Hoornaert*

Laboratorium voor Organische Synthese
Department of Chemistry, K.U. Leuven
Celestijnenlaan, 200F, B-3001 Leuven (Belgium)

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] pyrazines[2] and pyrimidines[3] with a dienophilic side chain linked to the heterocycle *via* an ether function gave furo- or pyranopyridines. Similar reactions of pyrimidines[4] or pyrazines[5] with a five- or six membered alkynyloxyalkyl side chain have much less been studied.

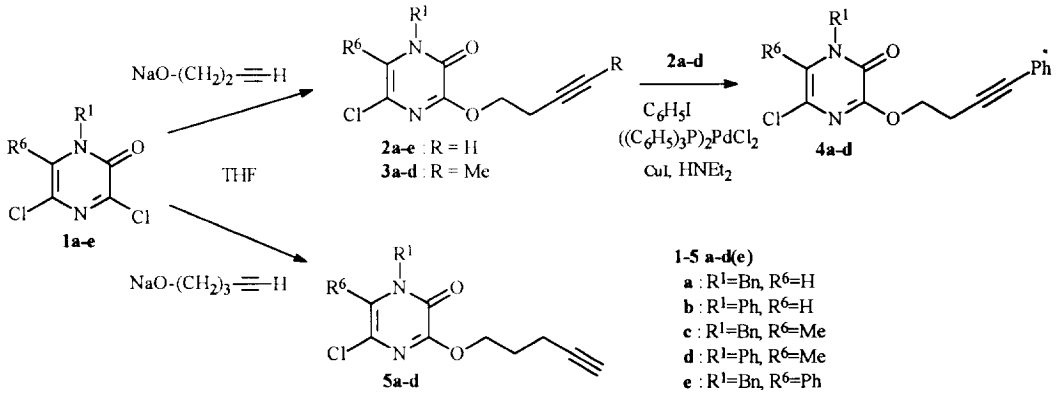
The 2-azadiene system of 2(1*H*)-pyrazinones **1** has been shown to undergo [4+2] cycloaddition reactions with a wide variety of dienophiles.[6] In this work we wish to report some applications of the intramolecular version which could prove to be a convenient route to new furo/pyranopyridines and/or 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 literature[8]) 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 activity[10] 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

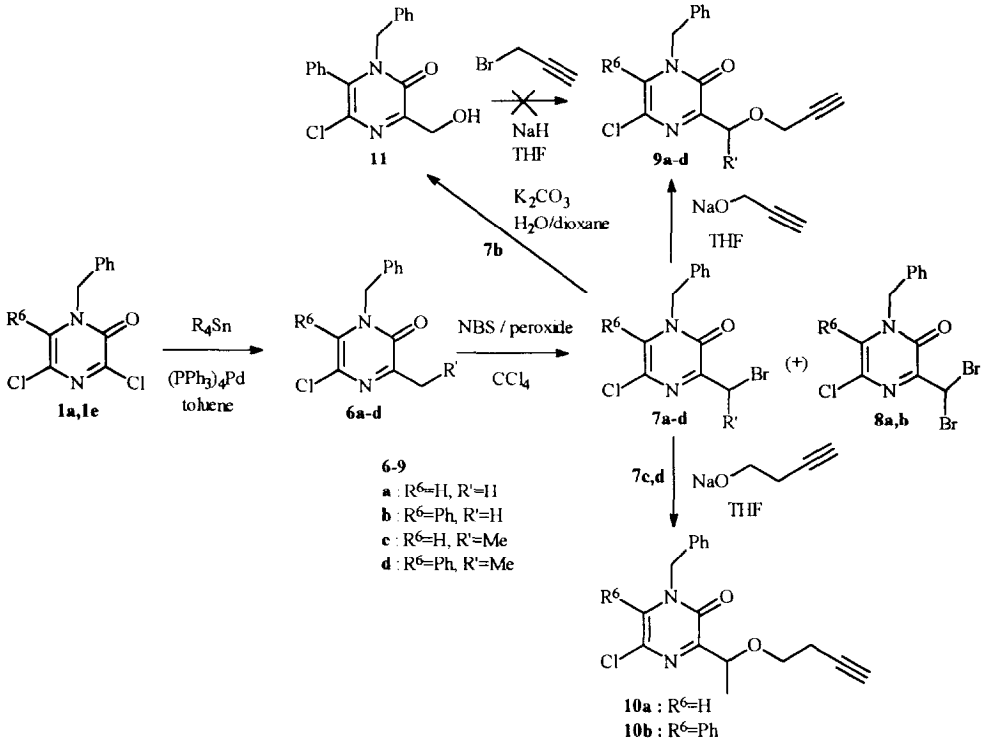
For the preparation of the required cycloaddition precursors **2-5** we made use of the reactivity of the chlorimine function in the 2(1*H*)-pyrazinones **1a-e**. Condensation of **1a-e** with the sodium salt of 3-butyn-1-ol or 3-pentyn-1-ol in tetrahydrofuran at room temperature smoothly led to the corresponding 3-(3-butynyloxy)-2(1*H*)-pyrazinones **2a-e** or 3-(3-pentynyloxy)-2(1*H*)-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 °C[11] led to the formation of the 3-(4-phenyl-3-butynyloxy)-2(1*H*)-pyrazinones **4a-d** in good yield. The 3-(4-pentynyloxy)-2(1*H*)-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 precusors of type **9** the 2(1*H*)-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(1*H*)-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(1*H*)-pyrazinones **7a-d** in good yield (70-90 %). However, the formation of the dibrominated 2(1*H*)-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(1*H*)-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** (R' = 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(1*H*)-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** (± 60 %). An alternative pathway[4] 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

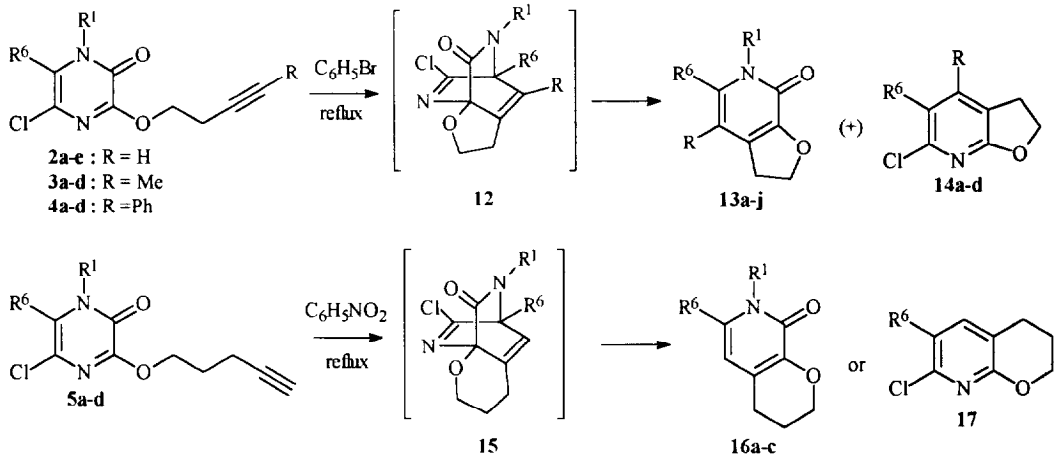
Thermolysis of the precursors

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 isocyanate[6] 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)

Lenghtening 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)

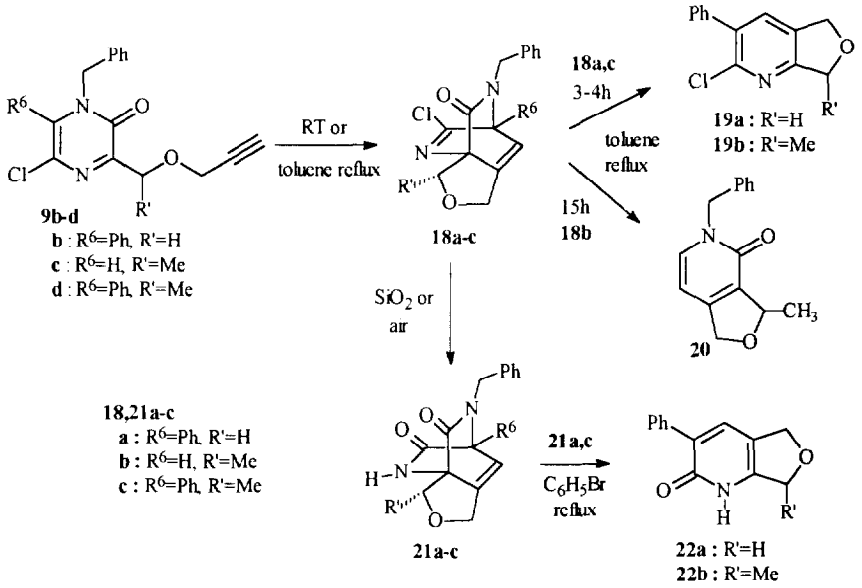


	R^1	R^6	R	time (h)	**13** yield (%)	**14** yield (%)		R^1	R^6	R	time (h)	**13** yield (%)	**14** yield (%)
2a	Bn	H	H	2.5	**a** : 98	-	**4a**	Bn	H	Ph	6	**g** : 92	-
2b	Ph	H	H	1.5	**b** : 96	-	**4b**	Ph	H	Ph	4.5	**h** : 90	-
2c	Bn	Me	H	2.5	**c** : 78	-	**4c**	Bn	Me	Ph	5	**i** : 85	-
2d	Ph	Me	H	2.5	-	**a** :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

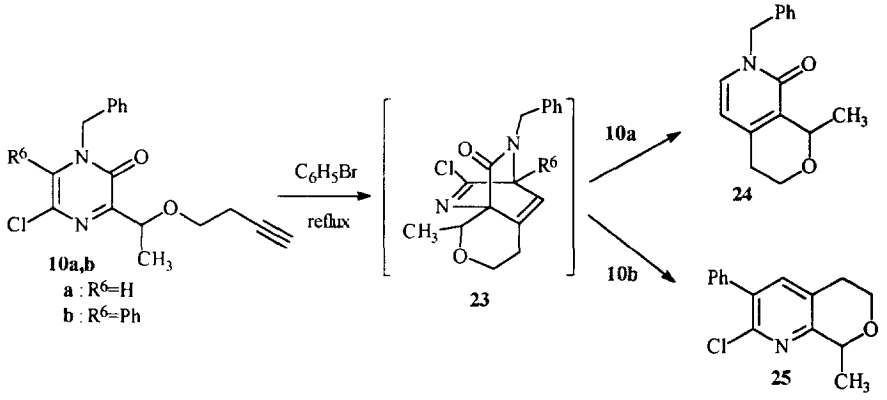
Not only the length of the side chain but also the electron-donating capacity of the anchored atom influences the rate of the cycloaddition:[6] an electron donating oxygen atom attached to the pyrazinone ring raises the pyrazinone LUMO energy; this results in diminished frontier orbital overlap with 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 hydrolised 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 thermolised 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)



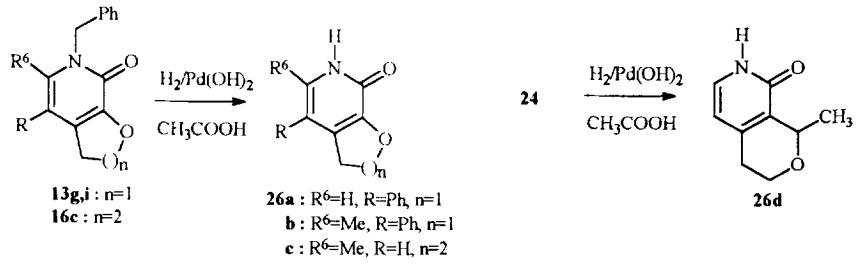
Scheme 4

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 = 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 MS5OTC instrument and a DS90 data system. For the chromatography analytical TLC plates (Alugram Sil G/UV_{254}) 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(1*H*)-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 $C_{12}H_{10}N_2OCl_2$: 268.0170; found: 268.0160

II. 3- and 4-Alkynyloxy-5-chloro-2(1H)-pyrazinones **2-5**

Synthesis of 3-(3-butynyloxy)/(3-pentynyloxy)/(4-pentynyloxy)-5-chloro-2(1*H*)-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(1*H*)-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, ^3J=7Hz, 2H, OCH_2), 2.75 (txd, ^3J=7Hz, ^4J=2.5Hz, 2H, CH_2), 2.02 (t, ^4J=2.5Hz, 1H, C≡CH); m/z (%): 288 (M^+, 20), 91 ($C_7H_7^+$, 100); exact mass for $C_{15}H_{13}N_2O_2Cl$: 288.0666; found: 288.0675

3-(3-butynyloxy)-5-chloro-1-phenyl-2(1*H*)-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, ^3J=8Hz, 2H, OCH_2), 2.78 (txd, ^3J=8Hz, ^4J=2.5Hz, 2H, CH_2), 2.05 (t, ^4J=2.5Hz, 1H, C≡CH); m/z (%): 274 (M^+, 55), 77 ($C_6H_5^+$, 100); exact mass for $C_{14}H_{11}N_2O_2Cl$: 274.0509; found: 274.0506

1-benzyl-3-(3-butynyloxy)-5-chloro-6-methyl-2(1*H*)-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, ^3J=7Hz, 2H, OCH_2), 2.76 (txd, ^3J=7Hz, ^4J=2.6Hz, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.04 (t, ^4J=2.6Hz, 1H, C≡CH); m/z (%): 302 (M^+, 20), 91 ($C_7H_7^+$, 100); exact mass for $C_{16}H_{15}N_2O_2Cl$: 302.0822; found: 302.0830

3-(3-butynyloxy)-5-chloro-6-methyl-1-phenyl-2(1*H*)-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, ^3J=7Hz, 2H, OCH_2), 2.76 (txd, ^3J=7Hz, ^4J=2.6Hz, 2H, CH_2), 2.03 (t, ^4J=2.6Hz, 1H, C≡CH), 1.99 (s, 3H, CH_3); m/z (%): 288 (M^+, 87), 118 ($C_8H_8N^+$, 100), 77 ($C_6H_5^+$, 73); exact mass for $C_{15}H_{13}N_2O_2Cl$: 288.0666; found: 288.0673

1-benzyl-3-(3-butynyloxy)-5-chloro-6-phenyl-2(1*H*)-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, ^3J=8Hz, 2H, OCH_2), 2.80 (txd, ^3J=8Hz, ^4J=2.5Hz, 2H, CH_2), 2.06 (t, ^4J=2.5Hz, 1H, C≡CH); m/z (%): 364 (M^+, 12), 91 ($C_7H_7^+$, 100); exact mass for $C_{21}H_{17}N_2O_2Cl$: 364.0979; found: 364.0977

1-benzyl-5-chloro-3-(3-pentynyloxy)-2(1*H*)-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, ^3J=7Hz, 2H, OCH_2), 2.68 (txq, ^3J=7Hz, ^5J=2.3Hz, 2H, CH_2), 1.77 (t, ^5J=2.3Hz, 3H, CH_3); m/z (%): 302 (M^+, 17), 91 ($C_7H_7^+$, 100); exact mass for $C_{16}H_{15}N_2O_2Cl$: 302.0822; found: 302.0828

5-chloro-3-(3-pentynyloxy)-1-phenyl-2(1*H*)-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, ^3J=8Hz, 2H, OCH_2), 2.69 (txq, ^3J=8Hz, ^5J=2.4Hz, 2H, CH_2), 1.77 (t, ^5J=2.4Hz, 3H, CH_3); m/z (%): 288 (M^+, 36), 222 (M^+-C_5H_6, 61), 77 ($C_6H_5^+$, 100); exact mass for $C_{15}H_{13}N_2O_2Cl$: 288.0666; found: 288.0667

1-benzyl-5-chloro-6-methyl-3-(3-pentynyloxy)-2(1*H*)-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, ^3J=7Hz, 2H, OCH_2), 2.71 (txq, ^3J=7Hz, ^5J=2.3Hz, 2H, CH_2), 2.31 (s, 3H, 6-CH_3), 1.80 (t, ^5J=2.3Hz, 3H, CH_3); m/z (%): 316 (M^+, 19), 250 (M^+-C_5H_6, 6), 91 ($C_7H_7^+$, 100); exact mass for $C_{17}H_{17}N_2O_2Cl$: 316.0978; found: 316.0991

5-chloro-6-methyl-3-(3-pentynyloxy)-1-phenyl-2(1*H*)-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, ^3J=7Hz, 2H, OCH_2), 2.70 (txq, ^3J=7Hz, ^5J=2.3Hz, 2H, CH_2), 1.99 (s, 3H, 6-CH_3), 1.79 (t, ^5J=2.3Hz, 3H, CH_3); m/z (%): 302 (M^+, 76), 236 (M^+-C_5H_6, 82), 118 ($C_8H_8N^+$, 100), 77 ($C_6H_5^+$, 69); exact mass for $C_{16}H_{15}N_2O_2Cl$: 302.0822; found: 302.0833

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

The purified pyrazinones **2a-d** (5 mmol) were further reacted with 1.1 equiv. iodobenzene, $PdCl_2(PPh_3)_2$ (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-butynyloxy)-2(1*H*)-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, ^3J=8Hz, 2H, OCH_2), 2.97 (t, ^3J=8Hz, 2H, CH_2); m/z (%): 364 (M^+, 3), 236 (M^+-$C_{10}H_8$, 29), 91 ($C_7H_7^+$, 100); exact mass for $C_{21}H_{17}N_2O_2Cl$: 364.0979; found: 364.0973

5-chloro-1-phenyl-3-(4-phenyl-3-butynyloxy)-2(1*H*)-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, ^3J=7Hz, 2H, OCH_2), 3.02 (t, ^3J=7Hz, 2H, CH_2); m/z (%): 350 (M^+, 1), 222 (M^+-$C_{10}H_8$, 24), 128 ($C_{10}H_8^+$, 100); exact mass for $C_{20}H_{15}N_2O_2Cl$: 350.0822; found: 350.0816

1-benzyl-5-chloro-6-methyl-3-(4-phenyl-3-butynyloxy)-2(1*H*)-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, ^3J=7Hz, 2H, OCH_2), 3.00 (t, ^3J=7Hz, 2H, CH_2), 2.26 (s, 3H, CH_3); m/z (%): 378 (M^+, 1), 287 (M^+-C_7H_7, 2), 91 ($C_7H_7^+$, 100); exact mass for $C_{22}H_{19}N_2O_2Cl$: 378.1135; found: 378.1124

5-chloro-6-methyl-1-phenyl-3-(4-phenyl-3-butynyloxy)-2(1*H*)-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, ^3J=7Hz, 2H, OCH_2), 2.99 (t, ^3J=7Hz, 2H, CH_2), 1.96 (s, 3H, CH_3); m/z (%): 364 (M^+, 2), 245 (M^+-C_6H_5NCO, 24), 128 ($C_{10}H_8^+$, 100); exact mass for $C_{21}H_{17}N_2O_2Cl$: 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); ^1H NMR: 7.40-7.30 (m, 5H, Ar-H), 6.83 (s, 1H, 6-H), 5.05 (s, 2H, CH_2Ph), 4.42 (t, ^3J=7Hz, 2H, OCH_2), 2.38 (txd, ^3J=7Hz, ^4J=2.5Hz, 2H, CH_2), 2.04 (m, ^3J=7Hz, 2H, CH_2), 1.96 (t, ^4J=2.5Hz, 1H, C≡CH); m/z (%): 302 (M^+, 14), 236 (M^+-C_5H_6, 5), 91 ($C_7H_7^+$, 100); exact mass for $C_{16}H_{15}N_2O_2Cl$: 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); ^1H NMR: 7.53-7.38 (m, 5H, Ar-H), 6.97 (s, 1H, 6-H), 4.50 (t, ^3J=7Hz, 2H, OCH_2), 2.41 (txd, ^3J=7Hz, ^4J=2.5Hz, 2H, CH_2), 2.10 (m, ^3J=7Hz, 2H, CH_2), 1.99 (t, ^4J=2.5Hz, 1H, C≡CH); m/z (%): 288 (M^+, 30), 222 (M^+-C_5H_6, 100), 77 ($C_6H_5^+$, 79); exact mass for $C_{15}H_{13}N_2O_2Cl$: 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); ^1H NMR: 7.40-7.20 (m, 5H, Ar-H), 5.32 (s, 2H, CH_2Ph), 4.48 (t, ^3J=7Hz, 2H, OCH_2), 2.41 (txd, ^3J=7Hz, ^4J=2.5Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.08 (m, ^3J=7Hz, 2H, CH_2), 1.98 (t, ^4J=2.5Hz, 1H, C≡CH); m/z (%): 316 (M^+, 18), 91 ($C_7H_7^+$, 100); exact mass for $C_{17}H_{17}N_2O_2Cl$: 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); ^1H NMR: 7.60-7.20 (m, 5H, Ar-H), 4.50 (t, ^3J=7Hz, 2H, OCH_2), 2.40 (txd, ^3J=7Hz, ^4J=2.5Hz, 2H, CH_2), 2.07 (m, ^3J=7Hz, 2H, CH_2), 1.98 (t, ^4J=2.5Hz, 1H, C≡CH), 1.97 (s, 3H, CH_3); m/z (%): 302 (M^+, 83), 236 (M^+-C_5H_6, 86), 77 ($C_6H_5^+$, 100); exact mass for $C_{16}H_{15}N_2O_2Cl$: 302.0822; found: 302.0824

III. 3-Alkyl and 3-(di)bromoalkyl-2(1H)-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 $Pd(PPh_3)_4$ (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); ^1H 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 $C_{12}H_{11}N_2OCl$: 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); ^1H 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 $C_{18}H_{15}N_2OCl$: 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); ^1H NMR: 7.40-7.25 (m, 5H, Ar-H), 7.10 (s, 1H, 6-H), 5.04 (s, 2H, CH_2Ph), 2.86 (q, ^3J=10Hz, 2H, CH_2), 1.25 (t, ^3J=10Hz, 3H, CH_3); m/z (%): 248 (M^+, 7) 91 ($C_7H_7^+$, 100); exact mass for $C_{13}H_{13}N_2OCl$: 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); ^1H NMR: 7.35-6.29 (m, 10H, Ar-H), 5.00 (s, 2H, CH_2Ph), 2.92 (q, ^3J=9Hz, 2H, CH_2), 1.25 (t, ^3J= 9Hz, 3H, CH_3); m/z (%): 324 (M^+, 14) 289 (M^+-Cl, 2), 91 ($C_7H_7^+$, 100); exact mass for $C_{19}H_{17}N_2OCl$: 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(1*H*)-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 $C_{12}H_{10}N_2OBrCl$: 311.9665; found: 311.9663; anal calcd for $C_{12}H_{10}N_2OBrCl$: 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(1*H*)-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 $C_{18}H_{14}N_2OBrCl$: 387.9978; found: 387.9996; anal calcd for $C_{18}H_{14}N_2OBrCl$: 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(1*H*)-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, ^3J=7Hz, 1H, CH), 5.18/5.01 (2xd, ^2J=14Hz, 2H, CH_2Ph), 1.98 (d, ^3J=7Hz, 3H, CH_3); m/z (%): 326 (M^+, 7), 247 (M^+-Br, 27), 91 ($C_7H_7^+$, 100); exact mass for $C_{13}H_{12}N_2OBrCl$: 325.9822; found: 325.9824

1-benzyl-3-(1-bromoethyl)-5-chloro-6-phenyl-2(1*H*)-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, ^3J=7Hz, 1H, CH), 5.05 (s(br), 2H, CH_2Ph), 2.05 (d, ^3J=7Hz, 3H, CH_3); m/z (%): 402 (M^+, 2), 323 (M^+-Br, 11), 91 ($C_7H_7^+$, 100); exact mass for $C_{19}H_{16}N_2OBrCl$: 402.0135; found: 402.0118

1-benzyl-3-dibromomethyl-5-chloro-2(1*H*)-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 $C_{12}H_9N_2OBr_2Cl$: 389.9771; found: 389.9770

1-benzyl-3-dibromomethyl-5-chloro-6-phenyl-2(1*H*)-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 $C_{18}H_{13}N_2OBr_2Cl$: 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(1*H*)-pyrazinones 9b-c and 3-(3-butynyloxyethyl)-2(1*H*)-pyrazinones 10a,b

To a mixture of the 3-bromoalkyl-2(1*H*)-pyrazinone **7b** (**7c-d**) (7 mmol) and 1.3 equiv proparyl 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(1*H*)-pyrazinone 9b

Yield: 48%; oil; IR (neat) cm^{-1}: 3290 (C≡CH), 2130 (C≡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, ^4J=2.5Hz, 2H, OCH_2), 2.49 (t, ^4J=2.5Hz, 1H, C≡CH); m/z (%): 364 (M^+, 0.1), 303 (M^+-ClCN, 18), 91 ($C_7H_7^+$, 100); exact mass for $C_{21}H_{17}N_2O_2Cl$-ClCN; 303.1259; found: 303.1253

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

Yield: 65%; oil; IR (neat) cm^{-1}: 3300 (C≡CH), 2130 (C≡C), 1649 (CO), 1564 (C=N); ^1H NMR: 7.65-6.80 (m, 10H, Ar-H), 5.25 (q, ^3J=7Hz, 1H, CH), 5.10 (s(br), 2H, CH_2Ph), 4.43 (d, ^4J=2.5Hz, 2H, OCH_2), 2.50 (t, ^4J=2.5Hz, 1H, C≡CH), 2.65 (d, ^3J=7Hz, CH_3); m/z (%): 378 (M^+, 1), 317 (M^+-ClCN, 20), 91 ($C_7H_7^+$, 100); exact mass for $C_{22}H_{19}N_2O_2Cl$-ClCN: 317.1416, 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≡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, CH_2Ph), 5.05 (q, ^3J=7Hz, CH), 3.63 (t, ^3J=7.5, 2H, OCH_2), 2.47 (txd, ^3J=7.5Hz, ^4J=2.5Hz, 2H, CH_2), 1.90 (t, ^4J=2.5Hz, 1H, C≡CH), 1.50 (d, ^3J=7Hz, 3H, CH_3); m/z (%): 316 (M^+, 1), 248 (M^+-C_4H_4O), 91 ($C_7H_7^+$, 100); exact mass for $C_{17}H_{17}N_2O_2Cl$: 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≡CH), 2100 (C≡C), 1652 (CO), 1564 (C=N); ^1H NMR: 7.57-6.73 (m, 10H, Ar-H), 5.07 (q, ^3J=7Hz, CH), 5.06 (s, 2H, CH_2Ph), 3.73 (t, ^3J=7.5, 2H, OCH_2), 2.53 (txd, ^3J=7.5Hz, ^4J=2.5Hz, 2H, CH_2), 1.95 (t, ^4J=2.5Hz, 1H, C≡CH), 1.57 (d, ^3J=7Hz, 3H, CH_3); m/z (%): 392 (M^+, 1), 324 (M^+-C_4H_4O, 21), 91 ($C_7H_7^+$, 100); exact mass for $C_{23}H_{21}N_2O_2Cl$: 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 H_2O and 1.2 equiv K_2CO_3. After refluxing for 2 hours the mixture was cooled and the dioxane removed under reduced pressure. Then 30 ml CH_2Cl_2 was added followed by treatment with dilute HCl until neutralisation. The organic layer was separated, dried ($MgSO_4$) and concentrated. The crude product was purified on a silica gel column (20% EtOAc/CH_2Cl_2 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, CH_2Ph), 4.85 (s, 2H, CH_2O), 3.50 (s(br), 1H, OH); m/z (%): 326 (M^+, 2), 308 (M^+-H_2O, 6), 91 ($C_7H_7^+$, 100); exact mass for $C_{18}H_{15}N_2O_2Cl$: 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/CH_2Cl_2 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, ^3J=7Hz, 1H, 5-H), 6.12 (d, ^3J=7Hz, 1H, 4-H), 5.17 (s, 2H, CH_2Ph), 4.60 (t, ^3J=9Hz, 2H, OCH_2), 3.12 (t, ^3J=9Hz, 2H, CH_2); ^{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 (CH_2Ph), 30.5 (C-3); m/z (%): 227 (M^+, 52), 91 ($C_7H_7^+$,100); exact mass for $C_{14}H_{13}NO_2$: 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, ^3J=7Hz, 1H, 5-H), 6.23 (d, ^3J=7Hz, 1H, 4-H), 4.69 (t, ^3J=9Hz, 2H, OCH_2), 3.22 (t, ^3J=9Hz, 2H, CH_2); ^{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 ($C_6H_5^+$, 46); exact mass for $C_{13}H_{11}NO_2$: 213.0790; found: 213.0785; anal calcd for $C_{13}H_{11}NO_2$: 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, CH_2Ph), 4.61 (t, ^3J=9Hz, 2H, OCH_2), 3.13 (t, ^3J=9Hz, 2H, CH_2), 2.22 (s, 3H, CH_3); ^{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 (CH_2Ph), 30.8 (C-3), 20.2 (CH_3); m/z (%): 241 (M^+, 68), 150 (M^+-C_7H_7, 56), 91 ($C_7H_7^+$, 100); exact mass for $C_{15}H_{15}NO_2$: 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, ^4J=1Hz, 1H, 5-H), 5.14 (s, 2H, CH_2Ph), 4.62 (t, ^3J=9Hz, 2H, OCH_2), 3.06 (t, ^3J=9Hz, 2H, CH_2), 1.99 (q,

^{4}J=1Hz, 3H, CH_3); ^{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 (CH_2Ph), 29.4 (C-3), 14.9 (CH_3); m/z (%): 241 (M^+, 54), 150 (M^+-C_7H_7, 3), 91 ($C_7H_7^+$,100); exact mass for $C_{15}H_{15}NO_2$: 241.1103; found: 241.1102

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

Yield: 97%; oil; IR (neat) cm^{-1}: 1675 (CO); ^{1}H NMR ($CDCl_3$): 7.48-7.29 (m, 5H, Ar-H), 6.78 (s(br), 1H, 5-H), 4.65 (t, ^{3}J=9Hz, 2H, OCH_2), 3.14 (t, ^{3}J=9Hz, 2H, CH_2), 2.04 (s, 3H, CH_3); ^{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 (CH_3); m/z (%): 227 (M^+, 100), 77 ($C_6H_5^+$, 50); exact mass for $C_{14}H_{13}NO_2$: 227.0946; found: 227.0938

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

Yield: 88%; m.p.: 184-185°C; IR (KBr) cm^{-1}: 1670 (CO); ^{1}H NMR: 7.34-7.11 (m, 5H, Ar-H), 5.42 (s, 2H, CH_2Ph), 4.62 (t, ^{3}J=9Hz, 2H, OCH_2), 3.15 (t, ^{3}J=9Hz, 2H, CH_2), 2.17 (s, 3H, 4-CH_3), 2.01 (s, 3H, 5-CH_3); ^{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 (CH_2Ph), 30.3 (C-3), 15.7/14.8 (CH_3); m/z (%): 255 (M^+, 81), 164 (M^+-C_7H_7 , 100), 91 ($C_7H_7^+$, 94); exact mass for $C_{16}H_{17}NO_2$: 255.1259; found: 255.1255; anal calcd for $C_{16}H_{17}NO_2$: 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(6*H*)-one 13g

Yield: 92%; m.p.: 189°C; IR (KBr) cm^{-1}: 1659 (CO); ^{1}H NMR: 7.42-7.24 (m, 10H, Ar-H), 6.97 (s, 1H, 5-H), 5.26 (s, 2H, CH_2Ph), 4.69 (t, ^{3}J=9Hz, 2H, OCH_2), 3.24 (t, ^{3}J=9Hz, 2H, CH_2); ^{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 (CH_2Ph), 30.8 (C-3); m/z (%): 303 (M^+, 35), 212 (M^+-C_7H_7, 4), 91 ($C_7H_7^+$, 100); exact mass for $C_{20}H_{17}NO_2$: 303.1259; found: 303.1280; anal calcd for $C_{20}H_{17}NO_2$: 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(6*H*)-one 13h

Yield: 90%; m.p.: 169-170°C; IR (KBr) cm^{-1}: 1670 (CO); ^{1}H NMR: 7.57-7.28 (m, 10H, Ar-H), 7.07 (s, 1H, 5-H), 4.71 (t, ^{3}J=9Hz, 2H, OCH_2), 3.32 (t, ^{3}J=9Hz, 2H, CH_2); ^{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 ($C_6H_5^+$, 69); exact mass for $C_{19}H_{15}NO_2$: 289.1103; found: 289.1108

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

Yield: 85%; m.p.: 205°C; IR (KBr) cm^{-1}: 1660 (CO); ^{1}H NMR: 7.41-7.12 (m, 10H, Ar-H), 5.45 (s, 2H, CH_2Ph), 4.60 (t, ^{3}J=9Hz, 2H, OCH_2), 2.92 (t, ^{3}J=9Hz, 2H, CH_2), 2.08 (s, 3H, CH_3); ^{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 (CH_2Ph), 31.1 (C-3), 17.4 (CH_3); m/z (%): 317 (M^+, 63), 226 (M^+-C_7H_7, 56), 91 ($C_7H_7^+$, 100); exact mass for $C_{21}H_{19}NO_2$: 317.1416; found: 317.1423; anal calcd for $C_{21}H_{19}NO_2$: 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(6*H*)-one 13j

Yield: 23%; m.p.: 149-150°C; IR (KBr) cm^{-1}: 1652 (CO); ^{1}H NMR: 7.42-6.80 (m, 10H, Ar-H), 6.07 (s, 1H, 4-H), 5.19 (s, 2H, CH_2Ph), 4.65 (t, ^{3}J=10Hz, 2H, OCH_2), 3.18 (t, ^{3}J=10Hz, 2H, CH_2); ^{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 (CH_2Ph), 30.9 (C-3); m/z (%): 303 (M^+, 48), 226 (M^+-C_6H_5, 16), 91 ($C_7H_7^+$, 100); exact mass for $C_{20}H_{17}NO_2$: 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); ^{1}H NMR: 7.33 (s, 1H, 4-H), 4.62 (t, ^{3}J=7Hz, 2H, OCH_2), 3.22 (t, ^{3}J=7Hz, 2H, CH_2), 2.27 (s, 3H, CH_3); ^{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 (CH_3); m/z (%): 169 (M^+, 100), 134 (M^+-Cl, 24); exact mass for C_8H_8NOCl: 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); ^{1}H NMR: 4.52 (t, ^{3}J=7Hz, 2H, OCH_2), 3.05 (t, ^{3}J=7Hz, 2H, CH_2), 2.10 (s, 3H, CH_3), 2.11, (s, 3H, CH_3); ^{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 (CH_3); m/z (%): 183 (M^+, 100), 148 (M^+-Cl, 20); exact mass for $C_9H_{10}NOCl$: 183.0451; found: 183.0461; anal calcd for $C_9H_{10}NOCl$: 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, ^3J=6Hz, 2H, OCH_2), 3.01 (t, ^3J=6Hz, 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 $C_{14}H_{12}NOCl$: 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, ^3J=8Hz, 2H, OCH_2), 3.27 (t, ^3J=8Hz, 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 $C_{13}H_{10}NOCl$: 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, ^3J=7Hz, 1H, 6-H), 5.87 (d, ^3J=7Hz, 1H, 5-H), 5.03 (s, 2H, CH_2Ph), 4.18 (t, ^3J=5Hz, 2H, OCH_2), 2.51 (t, ^3J=6.5Hz, 2H, 4-CH_2), 1.93 (txt, ^3J=5Hz, ^3J=6.5Hz, 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 $C_{15}H_{15}NO_2$: 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, ^3J=7Hz, 1H, 6-H), 5.95 (d, ^3J=7Hz, 1H, 5-H), 4.28 (t, ^3J=5Hz, 2H, OCH_2), 2.60 (t, ^3J=6.5Hz, 2H, 4-CH_2), 2.02 (txt, ^3J=5Hz, ^3J=6.5Hz, 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 $C_{14}H_{13}NO_2$: 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, ^3J=5Hz, 2H, OCH_2), 2.56 (t, ^3J=6.5Hz, 2H, 4-CH_2), 2.18 (s, 3H, CH_3), 2.00 (txt, ^3J=5Hz, ^3J=6.5Hz, 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 (M^+-C_7H_7, 63), 91 ($C_7H_7^+$, 100); exact mass for $C_{16}H_{17}NO_2$: 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, ^4J=1Hz, 1H, 5-H), 4.31 (t, ^3J=7Hz, 2H, OCH_2), 2.75 (t, ^3J=7Hz, 2H, 4-CH_2), 2.27 (d, ^4J=1Hz, 3H, CH_3), 2.00 (m, ^3J=7Hz, 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 $C_9H_{10}NOCl$: 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 hydrolised 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, ^4J=2Hz, 1H, 7-H), 5.24/4.42 (2xd, ^2J=9.5, 2H, 11-CH_2), 4.82/4.18 (2xd, ^2J=14.5Hz, 2H, CH_2Ph), 4.50/4.39 (2xdxd, ^2J=14.5Hz, ^4J=2Hz, 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 (CH_2Ph); m/z (%) (CI): 365 (MH^+, 14), 232 (MH^+-C_7H_7NCO, 72), 91 ($C_7H_7^+$, 100)

2-benzyl-6-chloro-11-methyl-4,8-(methanoxymethano)-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, CH_2Ph), 4.47/4.37 (2xdxd, ^2J=14Hz, ^4J=2Hz, 2H, 9-CH_2), 1.60 (d, ^3J=7Hz, 3H, CH_3); ^{13}C 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 (CH_2Ph), 15.5 (CH_3); m/z (%) (CI): 303 (MH^+, 1), 242 (MH^+-ClCN, 65), 91 ($C_7H_7^+$, 100); exact mass for $C_{16}H_{15}N_2O_2Cl$-ClCN; 241.1103; found: 241.1099

2-benzyl-6-chloro-11-methyl-1-phenyl-4,8-(methanoxymethano)-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, CH_2Ph), 4.58/4.38 (2xdxd, ^2J=15Hz, ^4J=2.5Hz, 2H, 9-CH_2), 1.65 (d, ^3J=7Hz, 3H, CH_3); ^{13}C 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 (CH_2Ph), 15.6 (CH_3); m/z (%) (CI): 379 (MH^+, 11), 91 ($C_7H_7^+$, 100)

2-benzyl-1-phenyl-4,8-(methanoxymethano)-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-CH_2), 4.55 (d, ^4J=1Hz; 2H, 9-CH_2), 4.27/4.06 (2xd, ^2J=14Hz, 2H, CH_2Ph); ^{13}C 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 (CH_2Ph); m/z (%) (CI): 347 (MH^+, 7), 214 (MH^+-C_7H_7NCO, 100), 91 ($C_7H_7^+$, 34); exact mass for $C_{21}H_{18}N_2O_3$-CH_2NO; 302.1181; found: 302.1180

2-benzyl-11-methyl-4,8-(methanoxymethano)-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, CH_2Ph), 4.48 (d, ^3J=5.5Hz, 1H, 1-H), 4.54/4.25 (2xdxd, ^2J=15Hz, ^4J=2Hz, 2H, 9-CH_2), 1.60 (d, ^3J=6.5Hz, 3H, CH_3); ^{13}C 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 (CH_2Ph), 14.2 (CH_3); m/z (%) (CI): 285 (MH^+, 100), 279 (M^+-CH_3, 14), 91 ($C_7H_7^+$, 11); exact mass for $C_{16}H_{16}N_2O_3$; 284.1161; found: 284.1162

2-benzyl-11-methyl-1-phenyl-4,8-(methanoxymethano)-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-CH_2), 4.54/4.11 (2xd, ^2J=15Hz, 2H, CH_2Ph), 1.53 (d, ^3J=8Hz, 3H, CH_3); ^{13}C 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 (CH_2Ph), 14.2 (CH_3); m/z (%) (CI): 361 (MH^+, 33), 228 (M^+-C_7H_7NCO, 100), 91 ($C_7H_7^+$, 48); exact mass for $C_{22}H_{20}N_2O_3$; 360.1474; found: 360.1458; anal calcd for $C_{22}H_{20}N_2O_3$: 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-CH_2), 5.09 (t, ^4J=2Hz, 2H, 5-CH_2); ^{13}C 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 (%): 231 (M^+, 94), 167 (M^+-CHO-Cl, 100), 77 ($C_6H_5^+$, 13); exact mass for $C_{13}H_{10}NOCl$: 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); ^1H NMR: 7.50 (t, ^4J=0.8Hz, 1H, 4-H), 7.47-7.38 (m, 5H, Ar-H), 5.19 (qxt, ^3J=6.5Hz, ^4J=2.5Hz, 2Hz, 1H, 7-H), 5.12 (2xdxdxd, ^2J=13Hz, ^4J=2.5Hz,2Hz,0.8Hz, 2H, CH_2O), 1.59 (d, ^3J=6.5Hz, CH_3); ^{13}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 $C_{14}H_{12}NOCl$: 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); ^1H NMR: 7.35-7.21 (m, 6H, Ar-H+6-H), 6.10 (d, ^3J=7.5Hz, 1H, 7-H), 5.35 (m, ^3J=6.5Hz, ^4J=4Hz, 2.5Hz, 1H, 3-H), 5.24/5.03 (2xd, ^2J=14.5Hz, 2H, CH_2Ph), 4.99/4.87 (2xdxd, ^2J=14Hz, ^4J=4Hz, 2.5Hz, 2H, 1-CH_2), 1.55 (d, ^3J=6.5Hz, 3H, CH_3); ^{13}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 $C_{15}H_{15}NO_2$: 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); ^1H NMR: 7.50 (s, 1H, 4-H), 7.68-7.30 (m, 5H, Ar-H), 5.00 (t, ^4J=2.5Hz, 2H, 7-CH_2), 4.91 (t, ^4J=2.5Hz, 2H, 5-CH_2); ^{13}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 $C_{13}H_{11}NO_2$: 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); ^1H NMR: 7.53 (s, 1H, 4-H), 7.74-7.25 (m, 5H, Ar-H), 5.24 (m, ^3J=7Hz, ^4J=3.5Hz, 3Hz, 1H, 7-H), 5.03/4.93 (2xdxd, ^2J=15Hz, ^4J=3.5Hz, 3Hz, 2H, CH_2O), 1.60 (d, ^3J=7Hz, 3H, CH_3); ^{13}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 $C_{14}H_{13}NO_2$: 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); ^1H NMR: 7.35-7.22 (m, 5H, Ar-H), 7.13 (d, ^3J=6.5Hz, 1H, 6-H), 5.96 (d, ^3J=6.5Hz, 1H, 5-H), 5.19/4.98 (2xd, ^2J=14Hz, 2H, CH_2Ph), 4.85 (q, ^3J=7Hz, 1H, 1-H), 3.98/3.72 (2xdxt, ^2J=11Hz, ^3J=6.5Hz, 2H, CH_2O), 2.56/2.54 (m, 2H, 4-CH_2), 1.55 (t, ^3J=7Hz, 3H, CH_3); ^{13}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 $C_{16}H_{17}NO_2$: 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); ^1H NMR: 7.47-7.39 (m, 5H, Ar-H), 7.38 (s, 1H, 4-H), 4.84 (q, ^3J=7Hz, 1H, 8-H), 4.19/3.82 (2xm, 2H, CH_2O), 3.05/2.73 (2xm, 2H, 5-CH_2), 1.64 (d, ^3J=7Hz, CH_3); ^{13}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 $C_{15}H_{14}NOCl$: 259.0764; found: 259.0761

VIII. Debenzylated furo/pyrano[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 % $Pd(OH)_2$ 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% $MeOH/CH_2Cl_2$ 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); ^1H 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=9Hz, 2H, OCH_2), 3.30 (t, ^3J=9Hz, 2H, CH_2); ^{13}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 (M^+-C_2HO_2,37); exact mass for $C_{13}H_{11}NO_2$: 213.0790; found: 213.0791; anal calcd for $C_{13}H_{11}NO_2$: 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, ^3J=9Hz, 2H, OCH_2), 2.96 (t, ^3J=9Hz, 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 (M^+-C_2HO_2,21); exact mass for $C_{14}H_{13}NO_2$: 227.0946; found: 227.0947; anal calcd for $C_{14}H_{13}NO_2$: 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, ^3J=5.5Hz, 2H, OCH_2), 2.49 (t, ^3J=6.5Hz, 2H, 4-CH_2), 2.24 (s, 3H, CH_3), 1.92 (txt, ^3J=5.5Hz, ^3J=6.5Hz, 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 (M^+-CO, 36), 42 (CNO^+,100); exact mass for $C_9H_{11}NO_2$: 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, ^3J=6Hz, 1H, 6-H), 6.09 (d, ^3J=6Hz, 1H, 5-H), 4.85 (q, ^3J=6Hz, 1H, 1-H), 4.01/3.79 (2xdxt, ^2J=12Hz, ^3J=6Hz, 2H, CH_2O), 2.64 (t, ^3J=6Hz, 2H, 4-CH_2), 1.55 (d, ^3J=6Hz, 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 (M^+-CH_3, 100); exact mass for $C_9H_{11}NO_2$: 165.0790; found: 165.0789

ACKNOWLEDGEMENTS : The authors wish to thank the F.K.F.O. and the 'Ministerie voor Wetenschapsbeleid, I.U.A.P.' for financial support. They are also grateful to K. Van Poppel and V. Janssens De Bisthoven for synthetic work and to Dr. P. Delbeke, R. De Boer and P. Valvekens for technical assistance. K.B. and D.V. also thank the K.U. Leuven and the I.W.O.N.L for the fellowships received.

REFERENCES

1. Taylor, E.C.; Macor, J.E.; Pont, J.L. *Tetrahedron* **1987**, *43*, 5145-5148
2. de Bie, D.A.; Ostrowicz, A.; Geurtsen, G.; van der Plas, H.C. *Tetrahedron* **1988**, *44*, 2977-2983
3. Frissen, A.E.; Marcelis, A.T.M.; van der Plas, H.C. *Tetrahedron* **1989**, *45*, 803-812
4. Frissen, A.E.; Marcelis, A.T.M.; Buurman, D.G.; Pollmann, C.A.; van der Plas, H.C. *Tetrahedron* **1989**, *45*, 5611-5620
5. Biedrzycki, M.; de Bie D.A.; van der Plas H.C. *Tetrahedron* **1989**, *45*, 6211-6220
6. Tutonda, M.; Vanderzande, D.; Vekemans, J.; Toppet, S.; Hoornaert, G. *Tetrahedron* **1990**, *46*, 5715-5732
7. Prisbylla, M.P. U.S. US 5, 260, 261 (Cl. 504-246; A01N43/90) **1994**, C.A. 120: 217646w
8. Shiotani, S.; Morita, H. *J. Heterocyclic Chem.* **1982**, *19*, 1207-1209
9. Hwang, D.R., Driscoll, J.S. *J. Pharm. Sci.* **1979**, *68*, 816-819
10. Wehinger, E.; Meyer H.; Benz U. Ger. Offen. DE 3, 209, 274 (Cl. CO7D213), **1984** C.A. 100: 51454s
11. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467-4470
12. Kobayashi, T.; Sakakura, T.; Tanaka, M. *Tetrahedron Lett.* **1985**, *26*, 3463-3466
13. Vandenberghe, D, PhD thesis KULeuven; in preparation
14. Ciganek, E. "The Intramolecular Diels-Alder Reaction" in *Org. Reactions*, **1984**, *32*, 44-45
15. Kozikowski, A.P.; Xia, Y.; Reddy, E.R.; Tückmantel, W.; Hanin, I., Tang X.C. *J. Org. Chem.* **1991**, *56*, 4636-4645
16. Vekemans, J.; Wieërs-Pollers, C.; Hoornaert, G. *J. Heterocyclic Chem.* **1983**, *20*, 919-923
17. Vandenberghe, S.M.; Buysens, K.J.; Meerpoel L.; Loosen, P.K.; Toppet S.M.; Hoornaert G.J. *J. Org. Chem.*, submitted
18. Loosen, P.K.; Mayoka, G.T.; Masoumeh, F.K.; Compernolle, F.; Hoornaert, G.J. *Tetrahedron* **1991**, *47*, 9259-9268

(*Received in UK* 4 *August* 1995; *revised* 15 *September* 1995; *accepted* 21 *September* 1995)