Acta Chemica Scandinavica, 1997: 51: 742–752
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ACTA
CHEMICA SCANDINAVICA
ISSN 0904–213X

Synthesis of 5*H*-Pyrazino[2,3-*b*]indoles from Indole-2,3-dione Derivatives

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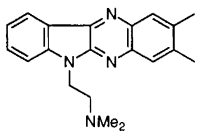
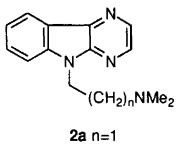
Bergman, J. and Vallberg, H., 1997. Synthesis of 5*H*-Pyrazino[2,3-*b*]indoles from Indole-2,3-dione Derivatives. – Acta Chem. Scand. 51: 742–752. © Acta Chemica Scandinavica 1997.

Reaction of *N*-acetylindol-2,3-diones with ethylenediamines gave the dihydropyrazinones **11**, which could, after dehydrogenation and deacetylation, be transformed to the corresponding 5*H*-pyrazino[2,3-*b*]indoles **5**. *N*,*N*-Dimethylaminoethylation of the anion of **5** occurred selectively in the 5-position. Thermolysis of 1-pyrazinylbenzotriazole gave pyrazino[1,2-*a*]-benzimidazole **33** and no 5*H*-pyrazino[2,3-*b*]indole.

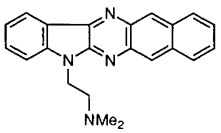
Several 6*H*-indolo[2,3-*b*]quinoxaline derivatives with basic side-chains in the 6-position, such as 2,3-dimethyl-6-(2-dimethylaminoethyl)-6*H*-indolo[2,3-*b*]quinoxaline (**1**), exhibit potent antiviral activity,[1] against for example herpes simplex type 1, cytomegalo and varicella-zoster. Compound **1** and its relatives have no effects on virus polymerases and are instead believed to act via inhibition of the decapsidation process of the virus.[2] In this context the propensity of **1** to undergo reversible intercalation with DNA might play a role.[3] The size of the linearly fused heterocyclic ring system would be expected to be of considerable importance for these properties. Thus the tricyclic and pentacyclic compounds **2a**, **3a**, **b** and **4**, respectively, have been synthesized and tested.[3] Although the antiviral activity of **2a** was far from impressive, its side-chain interacted with the minor groove of DNA in a way different from that of **1**. For this reason the synthesis and properties of 5*H*-pyrazino[2,3-*b*]indole (**5a**) and related compounds have now been studied in some detail.



1



2a n=1
3a n=2
b n=3



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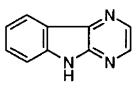
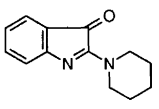


5a

The parent system 5*H*-pyrazino[2,3-*b*]indole (**5a**) has previously been synthesized by thermal Fischer indolization of the pyrazinylhydrazone of cyclohexanone,[4] followed by dehydrogenation with chloranil. Recently, compound **5a** has also been synthesized by reaction of 2-piperidinoindole-3-one (**6**) with ethylenediamine.[5] Compound **6** in turn was prepared by catalytic oxidation of indole in the presence of piperidine. It might be added that our group previously has tried unsuccessfully to synthesise **5a** starting from *N*-acetylisatin 2,3-dioxime.[6] These pathways were considered to be too complicated and/or inflexible and therefore approaches involving isatin (**7a**) or *N*-acetylisatin (**7b**) and ethylenediamine have now been investigated.

A few experiments along those lines have previously been reported. Thus, reaction of *N*-acetylisatin with diaminomaleonitrile produces the pyrazinoindole **8**,[7] whereas the reaction between isatin and ethylenediamine should give the 2:1 condensation product **9a**, in analogy with the formation[8] of the homologue **9b** when isatin and propane-1,3-diamine are refluxed in methanol. Compound **9a** could not be transformed into 5*H*-pyraz-



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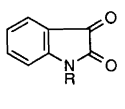
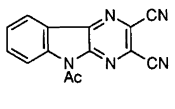
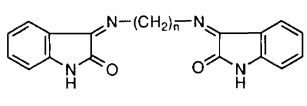


7a R=H
7b R=Ac



8



9a n=2
9b n=3

ino[2,3-*b*]indole. No intermediate 1:1 products could be isolated and therefore it appeared that increased electrophilicity in the 2-position was needed. Hence, *N*-acetylisatin was chosen as the primary starting material.

Results and discussion

It is well known that *N*-acetylisatin (**7b**) is readily ring-opened by ammonia,[9] amines[10] and alcohols.[11] For example, when *N*-acetylisatin is refluxed in ethanol for 3 h, nucleophilic ring opening produces the glyoxylate ester **10**, which readily reacts with ethylenediamine at 5 °C giving the dihydropyrazinone derivative **11a** (m.p. 160 °C) in high yield. The IR spectrum of **11a** features two carbonyl bands at 1670 and 1685 cm^{-1} and the ^1H NMR spectrum includes two methylene signals at 3.33 and 3.79 ppm, respectively. The methylene protons at 3.33 ppm are coupled to the NH at 8.47 ppm.

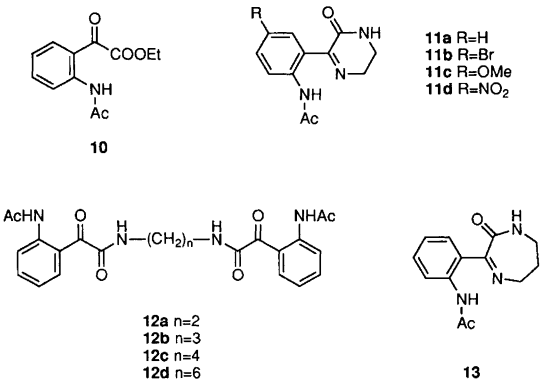
The reaction of *N*-acetylisatin with ethylenediamine has been studied previously albeit with somewhat conflicting results. In 1982 Franke[12] reported the formation of **11a** in moderate yield, when *N*-acetylisatin and ethylenediamine were refluxed in ethanol for 2 h. The reported ^1H NMR spectral data correspond well with our ^1H NMR data of **11a**. On the other hand, Joshi[13] reported in 1984 that *N*-acetylisatin and ethylenediamine in ethanol gave a product in a low yield, assigned structure **11a** (m.p. 215 °C) by the Indian workers. It appears that this product should therefore be reassigned.

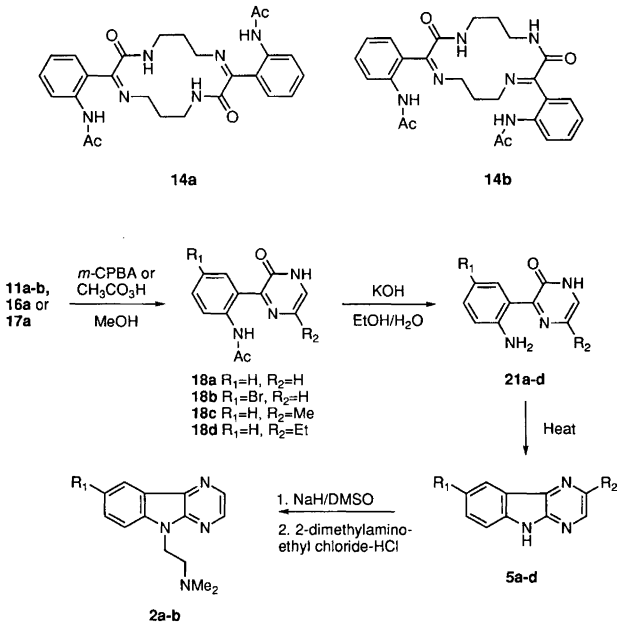
Addition of ethylenediamine to a refluxing solution of the ester **10** in ethanol yields a small crop of **12a**, which melts at 234 °C. After removal of **12a** compound **11a** (m.p. 160 °C) could be collected after 3 h. On the other hand, **12a** as well as its homologues **12b–d** are formed in high yield when the appropriate diamine is added to a solution of 2 equiv. *N*-acetylisatin in an aprotic solvent, such as dioxane.

Joshi has also reported that the reaction of *N*-acetylisatin with propane-1,3-diamine yields a compound, assigned structure **13**, with a melting point at 320 °C and an MS parent ion peak at *m/z* 245. In our hands this reaction gave a compound with the same melting point, but with a parent ion peak at *m/z* 490. This compound is insoluble in all common solvents, except for hot DMSO, DMA or DMF. It seems likely that this 2:2 product is in fact the 14-membered ring system **14a** rather than the 1:1 product **13**. The ^{13}C NMR spectrum of **14a** showed three signals from the methylenes (30.8, 36.4 and 52.5 ppm) in the ratio 1:1:1 rather than four in the ratio 1:1:2:2, which would be expected for the regioisomer **14b**.

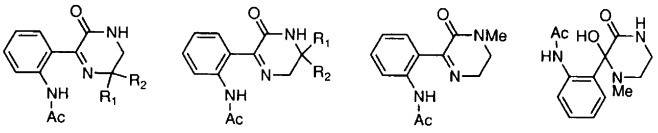
When the substituted ethylenediamine 2-methylpropane-1,2-diamine was reacted with the glyoxylate ester **10** in ethanol, the sole regioisomer formed was **15a**. However, when the same 1,2-diamine was added to a solution of *N*-acetylisatin in THF at 5 °C, the expected analogue to **12a** was not formed. Instead the regioisomer **15b** was the major product, with **15a** as a by-product (traces). In the same manner as in the synthesis of **15a**, the condensation of propane-1,2-diamine and butane-1,2-diamine with the glyoxylate ester **10** in ethanol, gave **16a** (90% purity) and **17a** (97% purity), respectively, as the major products. On the other hand the regioisomers **16b** (78% purity) and **17b** (60% purity) were the major products when the reactions were performed in THF. It was not possible to separate the two regioisomers of **16** and **17**, but when **16a** and **17a** were dehydrogenated in a subsequent preparative step, **18c** and **18d** (Scheme 1) could readily be isolated in a pure state (i.e., free of isomers). The regioisomers were assigned by ^1H NMR spectroscopy where for example **15a** features a coupling between the NH and the methylene group, whereas the regioisomer **15b** does not show such a coupling.

Interaction of *N*-acetylisatin with *N*-methylethylenediamine should, in principle, lead to either **19** or the hydroxy derivative **20**. When ethanol was the solvent, **20** was the sole product whereas in THF a 50:50 mixture of **19** and **20** was formed. Flash chromatography gave





Scheme 1



15a $R_1=R_2=Me$
16a $R_1=Me$, $R_2=H$
17a $R_1=Et$, $R_2=H$

15b $R_1=R_2=Me$
16b $R_1=Me$, $R_2=H$
17b $R_1=Et$, $R_2=H$

19

20

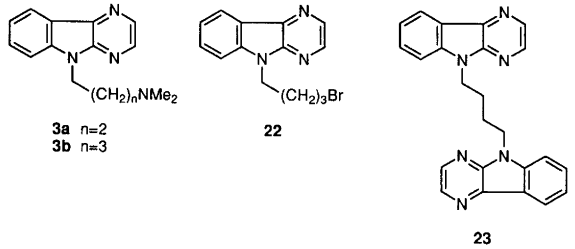
19 in a yield of 40%. Compound **20** features the OH-group as a singlet at 6.71 ppm (^{1}H NMR) and the carbon atom bearing the OH-group as a singlet at 86.8 ppm (^{13}C NMR).

The dihydropyrazinone derivatives **11a, b**, **16a** and **17a** were used for the synthesis of the 5*H*-pyrazino[2,3-*b*]indoles (Scheme 1). The precursors **11** were dehydrogenated with *m*-chloroperbenzoic acid (*m*-CPBA) or peracetic acid to the corresponding pyrazinones **18a–d**. Attempted dehydrogenations with Br_2 or *N*-bromosuccinimide (NBS) tended to yield *N*-bromo derivatives and were far less efficient. After removal of the acetyl group by alkaline hydrolysis, cyclization was effected in hot diphenyl ether (220 °C), giving the 5*H*-pyrazino[2,3-*b*]indoles **5a–d** in good overall yields. The parent compound **5a** could be readily obtained in high purity by sublimation at 200 °C. Subsequent alkylation of the anions of **5a, b** with *N*, *N*-dimethyl-2-chloroethylamine gave the desired products **2a, b**.

Alkylation of the anion of **5a** with *N*,*N*-dimethyl-3-chloropropylamine gave **3a**. For synthesis of analogues with longer side-chains a two-step procedure was preferred due to the fact that, for example, *N*,*N*-dimethyl-4-chlorobutylamine is not readily available and is also difficult to synthesize. Alkylation of the anion of **5a** with 1,4-dibromobutane smoothly gave **22** in 74% yield. (The 2:1 product **23** was isolated as a minor by-product in 16% yield). The bromoalkyl compound **22** was easily converted into **3b** when refluxed in a solution of dimethylamine in ethanol.

Alkylation of the anion **24** might *a priori* have been expected to yield the isomer **25a** as a minor co-product which indeed is the case[14] with the anion **26**. Thus the additional resonance stabilisation from the extra benzene ring in **26b** seems to be important for the alkylation of the nitrogen atom in the 5-position in the indoloquinoxaline system.

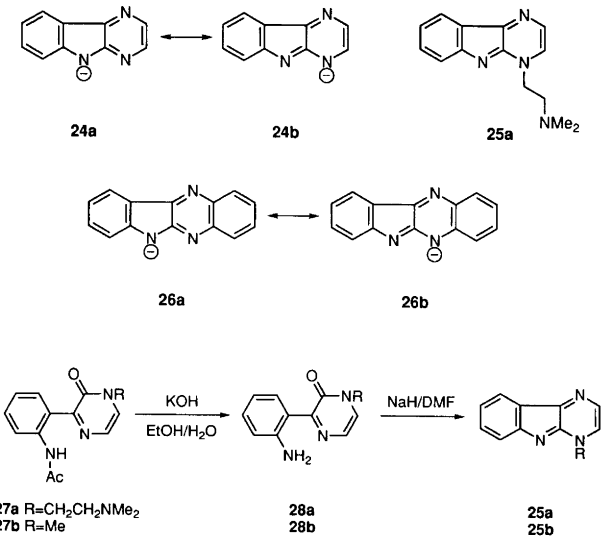
The method (Scheme 1) for the synthesis of pyrazinoindoles has also been used for 4-alkyl-4*H*-pyrazino[2,3-*b*]indoles (Scheme 2). When **18a** was alkylated with *N*,*N*-



3a n=2
3b n=3

22

23



24a

24b

25a

26a

26b

27a $R=CH_2CH_2NMe_2$
27b R=Me

28a
28b

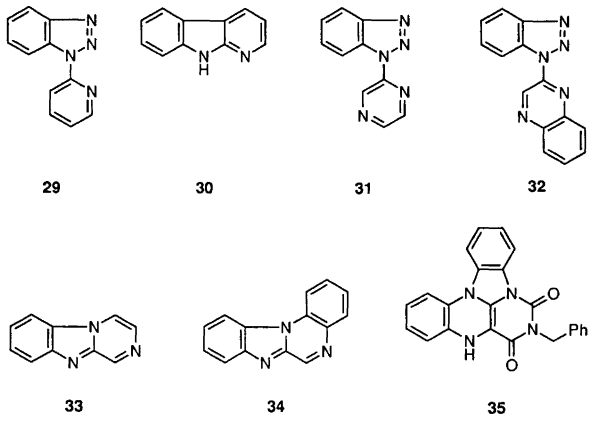
25a
25b

Scheme 2

dimethylamino-2-chloroethylamine, the product formed was **27a**, which, after removal of the acetyl group, gave **28a**. The ^{1}H NMR spectrum of **28a** showed a two-proton singlet at 6.03 ppm due to the NH_2 group, indicating that the alkylation occurred at the desired nitrogen atom. Compound **28b** was obtained from **19** by dehydrogenation followed by deacetylation. When compounds **28a, b** were treated with NaH in DMF at 100 °C cyclization occurred, yielding the 4-alkylated isomers **25a, b**.

During the development of the method described above, another approach to 5*H*-pyrazino[2,3-*b*]indole (**5a**) was also considered, based on the fact that 1-(2-pyridyl)-1*H*-benzotriazole (**29**) readily gives the α-carboline (**30**) when heated in PPA.[15–17] The 1-substituted benzotriazoles **29**, **31** and **32** are easily obtained when 1*H*-benzotriazole is heated with 2-chloropyridine, 2-chloro-pyrazine or 2-chloroquinoxaline, respectively. However, **31** and **32** gave rise to products with bridge-head nitrogens, i.e., pyrazino-[1,2-*a*]-benzimidazole (**33**) and benzimidazo-[1,2-*a*]quinoxaline (**34**). The latter compound had previously been prepared[18] from **35** in a multi-step procedure and a synthesis of the 1-phenyl derivative of **34** has also been reported.[19]

The difference in outcome in the thermolysis of **29** and its aza analogue **31** can be accounted for as follows. Decomposition of **29** gives rise to an intermediate that can be represented by formula **36a**, either as the diradical or as the zwitterion. Under strongly acidic conditions, the intermediate **36a** should be protonated to give **37a** (X=CH). The pyridine ring is then attacked intramolecularly at the 3-position by the positively charged benzene ring. The corresponding aza-substituted compound **37b** (X=N) is much less prone to undergo electrophilic attack and hence the sole nucleophilic attack comes from the electron pair on the NH group. Although hydrogenated derivatives (e.g., **38**) of **33** have been prepared and claimed,[20–22] synthesis of only the 1-phenyl and



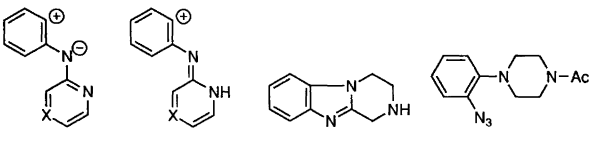
29 30 31 32

33 34 35

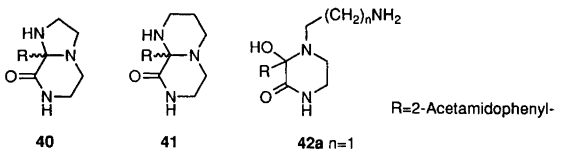
1,3-diphenyl derivatives of the parent system has been reported.[19] Catalytic hydrogenation of **33** gave the tetrahydro derivative **38**, which was identical with a product obtained by thermolysis of the azide **39** followed by hydrolysis. Recently, the reaction between 2-aminomethylbenzimidazole and 1,2-dibromoethane has been claimed[23] to yield **38**. However, the reported melting point and NMR data do not support this structure. Unfortunately, the authors of this work failed to correlate their results with those of previous workers.

The results obtained with 1,2-diamines induced us to study some related triamines. Thus, if the glyoxylate ester **10** is treated with diethylenetriamine or *N*-(2-aminoethyl)-1,3-propanediamine the products formed are **40** and **41**, respectively. The ^{13}C NMR spectra of **40** and **41** feature singlets at 85.1 and 78.3 ppm, respectively. Similarly positioned signals would also be expected for **42a**, **b**, in accordance with the related compound **20** which shows a singlet at 86.8 ppm. The hydrated version of **40** and **41** (i.e., **42a**, **b**) could not be detected as indicated by the absence of the expected signals from the OH-group (a singlet at 6.71 ppm for **20**) and the NH_2 group.

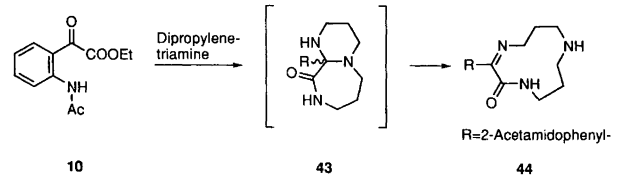
In the case of the reaction between glyoxylate ester **10** and dipropylenetriamine the product formed was the ring-expanded **44**, rather than the expected **43**. We believe that the reaction proceeds as outlined in Scheme 3. It has not been possible to isolate the proposed intermediate



36a X=CH **36b** X=N **37a** X=CH **37b** X=N **38** **39**



40 **41** **42a** n=1 **42b** n=2 R=2-Acetamidophenyl-



10 **43** **44**

Scheme 3

43, or in any other way prove the postulated reaction pathway.

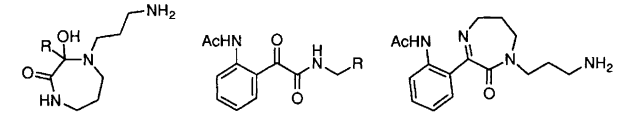
The ^{13}C NMR spectrum of **44** includes neither a singlet in the region of 80 ppm, which would be expected for **43** or the other possible product **45**, nor a singlet above 180 ppm, which would be expected from one of the carbonyls in a ring-opened product like **46**. The ^{1}H NMR spectrum of **44** includes two separate NH signals at 8.86 and 13.04 ppm, which excludes **47** as a possible product.

Experimental

Melting points are uncorrected. NMR spectra were recorded on a Bruker AM 400 or a Bruker AM 250 instrument. IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer. Flash chromatography was performed using Merck silica gel 60 (particle size 0.040–0.063 mm). Satisfactory elemental analysis (C, N ± 0.4%, H ± 0.2%) was obtained for all new compounds, except for **12c**, **23** and **44**; for these compounds correct HRMS values were obtained.

General procedure for the synthesis of **11a–d, 15–17a** *and* **20**. The appropriate *N*-acetylisatin (50 mmol) was heated to reflux in EtOH (125 ml) for 3 h. The appropriate ethylenediamine (50 mmol) was added dropwise to the solution at 5 °C. When the addition was complete the temperature of the reaction mixture was slowly allowed to assume room temperature. The solid formed was collected by filtration.

3-(2-Acetamidophenyl)-5,6-dihydro-2(1H)-pyrazinone (**11a**). Yield: 9.83 g (85%); m.p. 159–160 °C. IR (KBr): ν_{max} 3204, 3110, 2945, 1685, 1670, 1600, 1580, 1538, 1449, 1307, 1014, 771 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 10.34 (s, 1 H, NH), 8.47 (br s, 1 H, NH), 7.75 (d, 1 H), 7.49 (d, 1 H), 7.36 (dd, 1 H), 7.12 (dd, 1 H), 3.79 (t, 2 H, CH_2), 3.33 (m, 2 H, CH_2), 1.98 (s, 3 H, Me). ^{13}C NMR (DMSO-d_6): δ 167.8 (s), 163.1 (s), 156.4 (s), 136.8 (s), 130.5 (d), 129.4 (d), 126.8 (s), 122.9 (d), 122.3 (d), 47.8 (t), 37.7 (t), 23.8 (q).



R=2-Acetamidophenyl-

45 **46** **47**

3-(6-Acetamido-3-bromophenyl)-5,6-dihydro-2(1H)-pyrazinone (**11b**). Yield: 13.6 g (88%); m.p. 189–191 °C. IR (KBr): ν_{max} 3306, 2940, 1694, 1670, 1600, 1573, 1513, 1392, 1299, 1008, 818 cm^{-1}. ^1H NMR (DMSO-d_6): δ 10.29 (s, 1 H, NH), 8.51 (br s, 1 H, NH), 7.69 (d, J= 8.7 Hz, 1 H), 7.62 (d, J=2.4 Hz, 1 H), 7.55 (dd, J=2.4, 8.7 Hz, 1 H), 3.80 (t, 2 H, CH_2), 3.32 (m, 2 H, CH_2), 1.97 (s, 3 H, Me). ^{13}C NMR (DMSO-d_6): δ 168.0 (s), 161.7 (s), 156.1 (s), 136.1 (s), 132.8 (d), 132.0 (d), 128.9 (s), 124.4 (d), 114.9 (s), 47.9 (t), 37.6 (t), 23.7 (q).

3-(6-Acetamido-3-methoxyphenyl)-5,6-dihydro-2(1H)-pyrazinone (**11c**). Yield: 10.8 g (83%); m.p. 183–185 °C. IR (KBr): ν_{max} 3234, 3117, 1684, 1659, 1583, 1530, 1414, 1048, 1010, 829 cm^{-1}. ^1H NMR (DMSO-d_6): δ 9.90 (s, 1 H, NH), 8.43 (br s, 1 H, NH), 7.50 (d, J=8.8 Hz, 1 H), 7.03 (d, J=3.0 Hz, 1 H), 6.96 (dd, J=3.0, 8.8 Hz, 1 H), 3.77 (t, 2 H, CH_2), 3.73 (s, 3 H, MeO), 3.32 (m, 2 H, CH_2), 1.94 (s, 3 H, Me). ^{13}C NMR (DMSO-d_6):δ 167.5 (s), 162.8 (s), 156.4 (s), 155.1 (s), 129.9 (s), 129.6 (s), 124.6 (d), 115.0 (d), 114.8 (d), 55.2 (q), 47.9 (t), 37.8 (t), 23.3 (q).

3-(6-Acetamido-3-nitrophenyl)-5,6-dihydro-2(1H)-pyrazinone (**11d**). Yield: 12.7 g (92%); m.p. 202–204 °C. IR (KBr): ν_{max} 3416, 3131, 2981, 1719, 1685, 1673, 1506, 1329, 1285, 1224 cm^{-1}. ^1H NMR (DMSO-d_6): δ 11.07 (s, 1 H, NH), 8.63 (br s, 1 H, NH), 8.48 (m, 1 H), 8.25–8.21 (m, 2 H), 3.89 (t, 2 H, CH_2), 3.39 (m, 2 H, CH_2), 2.09 (s, 3 H, Me). ^{13}C NMR (DMSO-d_6): δ 168.8 (s), 161.5 (s), 156.0 (s), 143.3 (s), 141.4 (s), 126.8 (d), 125.0 (d), 124.3 (s), 121.3 (d), 47.8 (t), 37.5 (t), 24.3 (q).

3-(2-Acetamidophenyl)-5,5-dimethyl-5,6-dihydro-2(1H)-pyrazinone (**15a**). Yield: 9.60 g (74%); m.p. 158–159 °C. IR (KBr): ν_{max} 3280, 3188, 2975, 1687, 1665, 1610, 1527, 1294, 753 cm^{-1}. ^1H NMR (DMSO-d_6): δ 10.75 (s, 1 H, NH), 8.46 (t, J=3.5 Hz, 1 H, NH), 7.83 (d, 1 H), 7.60 (d, 1 H), 7.37 (dd, 1 H), 7.12 (dd, 1 H), 3.25 (d, J= 3.5 Hz, 2 H, CH_2), 2.02 (s, 3 H, Me), 1.28 (s, 6 H, Me).^{13}C NMR (DMSO-d_6): δ 167.7 (s), 159.9 (s), 156.2 (s), 137.1 (s), 130.9 (d), 129.6 (d), 125.5 (s), 122.7 (d), 122.1 (d), 55.0 (s), 47.6 (t), 25.7 (q), 23.9 (q).

3-(2-Acetamidophenyl)-6,6-dimethyl-5,6-dihydro-2(1H)-pyrazinone (**15b**). 2-Methylpropane-1,2-diamine (1.76 g, 20 mmol) was added dropwise to a solution of *N*-acetylisatin (3.78 g, 20 mmol) in THF (50 ml) at 5 °C. After 3 h at 5 °C, the temperature of the reaction mixture was slowly allowed to assume room temperature. After 1 h at room temperature, the solid formed was collected by filtration. Yield 3.11 g (60%); m.p. 172–174 °C. IR (KBr): ν_{max} 3177, 2965, 1683, 1624, 1540, 1373, 1289, 1273, 761 cm^{-1}. ^1H NMR (DMSO-d_6): δ 10.24 (s, 1 H, NH), 8.60 (s, 1 H, NH), 7.84 (d, 1 H), 7.47 (d, 1 H), 7.37 (dd, 1 H), 7.13 (dd, 1 H), 3.80 (s, 2 H, CH_2), 1.98 (s, 3 H, Me), 1.22 (s, 6 H, Me). ^{13}C NMR (DMSO-d_6): δ 168.0 (s), 162.3 (s), 156.0 (s), 136.9 (s), 130.5 (d), 129.5 (d), 126.9 (s), 123.0 (d), 122.7 (d), 58.7 (t), 49.8 (s), 26.3 (q), 23.8 (q).

3-(2-Acetamidophenyl)-5-methyl-5,6-dihydro-2(1H)-pyrazinone (**16a**). Yield: 9.57 g (78%, of a 90:10 mixture of **16a**:**16b**). IR (KBr): ν_{max} 3205, 3110, 2973, 1685, 1674, 1576, 1534, 1451, 1308, 772 cm^{-1}. ^1H NMR (DMSO-d_6): δ 10.63 (s, 1 H, NH), 8.47 (m, 1 H, NH), 7.80 (d, 1 H), 7.55 (d, 1 H), 7.36 (dd, 1 H), 7.11 (dd, 1 H), 3.89 (m, 1 H, CH), 3.37 (m, 1 H, CH_2), 3.10 (m, 1 H, CH_2), 1.99 (s, 3 H, Me), 1.28 (d, 3 H, Me). ^{13}C NMR (DMSO-d_6): δ 167.7 (s), 161.6 (s), 156.3 (s), 137.1 (s), 130.8 (d), 129.6 (d), 125.8 (s), 122.8 (d), 122.0 (d), 52.6 (d), 43.4 (t), 23.8 (q), 18.7 (q).

3-(2-Acetamidophenyl)-6-methyl-5,6-dihydro-2(1H)-pyrazinone (**16b**). Propane-1,2-diamine (1.48 g, 20 mmol) was added dropwise to a solution of *N*-acetylisatin (3.78 g, 20 mmol) in THF (50 ml) at −78 °C. After 3 h at −78 °C, the temperature of the reaction mixture was slowly (24 h) allowed to assume room temperature. After 1 h at room temperature, the solid formed was collected by filtration. Yield: 4.10 g (83%, of a 78:22 mixture of **16b**:**16a**). ^1H NMR (DMSO-d_6): δ 10.28 (s, 1 H, NH), 8.52 (s, 1 H, NH), 7.73 (d, 1 H), 7.47 (d, 1 H), 7.36 (dd, 1 H), 7.12 (dd, 1 H), 3.94 (dd, 1 H, CH_2), 3.66 (m, 1 H, CH), 3.41 (dd, 1 H, CH_2), 1.97 (s, 3 H, Me), 1.15 (d, 3 H, Me). ^{13}C NMR (DMSO-d_6): δ 167.8 (s), 162.7 (s), 156.7 (s), 136.8 (s), 130.5 (d), 129.4 (d), 127.0 (s), 123.0 (d), 122.4 (d), 54.4 (t), 44.5 (d), 23.8 (q), 17.6 (q).

3-(2-Acetamidophenyl)-5-ethyl-5,6-dihydro-2(1H)-pyrazinone (**17a**). Yield: 9.98 g (77%, of a 97:3 mixture of **17a**:**17b**). IR (KBr): ν_{max} 3225, 3109, 2972, 1691, 1670, 1595, 1579, 1527, 1447, 1311, 1237, 771, 538 cm^{-1}. ^1H NMR (DMSO-d_6): δ 10.68 (s, 1 H, NH), 8.49 (m, 1 H, NH), 7.89 (d, 1 H), 7.55 (d, 1 H), 7.37 (dd, 1 H), 7.11 (dd, 1 H), 3.64 (m, 1 H, CH), 3.31 (m, 1 H, CH_2), 3.12 (m, 1 H, CH_2), 2.00 (s, 3 H, Me), 1.60 (m, 2 H, CH_2) 1.04 (t, 3 H, Me). ^{13}C NMR (DMSO-d_6): δ 167.7 (s), 161.8 (s), 156.5 (s), 137.2 (s), 131.0 (d), 129.7 (d), 125.2 (s), 122.6 (d), 121.8 (d), 58.4 (d), 41.7 (t), 25.6 (t), 24.0 (q), 10.6 (q).

3-(2-Acetamidophenyl)-6-ethyl-5,6-dihydro-2(1H)-pyrazinone (**17b**). Butane-1,2-diamine (1.76 g, 20 mmol) was added dropwise to a solution of *N*-acetylisatin (3.78 g, 20 mmol) in THF (50 ml) at −78 °C. After 3 h at −78 °C the temperature of the reaction mixture was slowly (24 h) allowed to assume room temperature. After 1 h at room temperature, the solid formed was collected by filtration. Yield: 3.28 g (64%, of a 60:40 mixture of **17b**:**17a**); ^1H NMR (DMSO-d_6): δ 10.31 (s, 1 H, NH), 8.57 (s, 1 H, NH), 7.77 (d, 1 H), 7.48 (d, 1 H), 7.36 (dd, 1 H), 7.12 (dd, 1 H), 3.96 (m, 1 H, CH_2), 3.60–3.30 (m, 1 H, CH and 1 H, CH_2), 1.98 (s, 3 H, Me), 1.55 (m, 2 H, CH_2) 0.92 (t, 3 H, Me); ^{13}C NMR (DMSO-d_6): δ 167.9 (s), 162.9 (s), 156.7 (s), 136.9 (s), 130.6 (d), 129.5 (d),

126.8 (s), 123.0 (d), 122.4 (d), 52.2 (t), 50.0 (d), 24.9 (t), 23.8 (q), 9.6 (q).

3-(2-Acetamidophenyl)-1-methyl-5,6-dihydro-2(1H)-pyrazinone (**19**). *N*-Methylethylenediamine (1.48 g, 20 mmol) was added dropwise to a solution of *N*-acetylisatin (3.78 g, 20 mmol) in THF (50 ml) at −78 °C. After 3 h at −78 °C the temperature of the reaction mixture was slowly (24 h) allowed to assume room temperature. After 1 h at room temperature, the solid formed was collected by filtration. This mixture of **19** and **20** was separated by flash chromatography ($MeOH–CH_2Cl_2$ 1:9), to give **19**. Yield: 1.96 g (40%); m.p. 129–131 °C. IR (KBr): ν_{max} 2966, 1678, 1662, 1599, 1579, 1531, 1454, 1310, 768 cm^{-1}. ^1H NMR (DMSO-d_6): δ 10.13 (s, 1 H, NH), 7.67 (d, 1 H), 7.44 (d, 1 H), 7.36 (dd, 1 H), 7.13 (dd, 1 H), 3.82 (t, 2 H, CH_2), 3.48 (t, 2 H, CH_2), 2.97 (s, 3 H, Me), 1.97 (s, 3 H, Me). ^{13}C NMR (DMSO-d_6): δ 167.7 (s), 162.1 (s), 156.1 (s), 136.5 (s), 130.4 (d), 129.3 (d), 127.7 (s), 123.1 (d), 122.6 (d), 47.0 (t), 45.3 (t), 33.8 (q), 23.6 (q).

3-(2-Acetamidophenyl)-3-hydroxy-4-methyl-3,4,5,6-tetrahydro-2(1H)-pyrazinone (**20**). Yield: 1.71 g (32%); m.p. 131–132 °C. IR (KBr): ν_{max} 3304, 2957, 2866, 1659, 1636, 1514, 1021, 955, 762 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.22 (s, 1 H, NH), 8.03 (m, 1 H, NH), 7.89 (d, 1 H), 7.69 (d, 1 H), 7.24 (dd, 1 H), 7.06 (dd, 1 H), 6.71 (s, 1 H, OH), 3.51 (m, 1 H, CH_2), 3.25–3.17 (m, 2 H, CH_2), 2.73 (m, 1 H, CH_2), 2.05 (s, 3 H, Me), 2.04 (s, 3 H, Me). ^{13}C NMR (DMSO-d_6): δ 168.2 (s), 166.9 (s), 135.5 (s), 131.2 (s), 128.3 (d), 127.6 (d), 122.5 (d), 121.3 (d), 86.8 (s), 43.6 (t), 40.3 (t), 36.6 (q), 24.2 (q).

General procedure for the synthesis of **12a–d**. The appropriate diamine (10 mmol) was added dropwise to a solution of *N*-acetylisatin (3.78 g, 20 mmol) in dioxane (50 ml) at room temperature. After 1 h the solid formed was collected by filtration.

(**12a**): Yield: 3.42 g (72%); m.p. 233–234 °C. IR (KBr): ν_{max} 3313, 1694, 1666, 1649, 1604, 1580, 1523, 1451, 1234, 863, 767 cm^{-1}. ^1H NMR (DMSO-d_6): δ 10.54 (s, 2 H, NH), 8.82 (br s, 2 H, NH), 7.80 (d, 2 H), 7.66 (d, 2 H), 7.60 (dd, 2 H), 7.19 (dd, 2 H), 3.38 (m, 4 H, CH_2), 2.05 (s, 6 H, Me). ^{13}C NMR (DMSO-d_6): δ 190.8 (s), 168.6 (s), 163.5 (s), 138.1 (s), 133.8 (d), 131.5 (d), 124.1 (s), 123.3 (d), 121.4 (d), 37.9 (t), 23.8 (q).

(**12b**): Yield: 4.25 g (94%); m.p. 164–165 °C. IR (KBr): ν_{max} 3280, 1698, 1668, 1658, 1608, 1531, 1483, 1300, 758 cm^{-1}. ^1H NMR (DMSO-d_6): δ 10.56 (s, 2 H, NH), 8.77 (t, 2 H, NH), 7.79 (d, 2 H), 7.66–7.56 (m, 4 H), 7.22 (dd, 2 H), 3.26 (m, 4 H, CH_2), 2.05 (s, 6 H, Me), 1.72 (m, 2 H, CH_2). ^{13}C NMR (DMSO-d_6): δ 191.1 (s), 168.7 (s), 163.4 (s), 138.2 (s), 133.8 (d), 131.4 (d), 124.1 (s), 123.4 (d), 121.3 (d), 36.1 (t), 28.4 (t), 23.8 (q).

(**12c**): Yield: 4.47 g (96%); m.p. 214–215 °C. IR (KBr): ν_{max} 3275, 3253, 2937, 1694, 1670, 1657, 1608, 1531, 1487, 1266, 763 cm^{-1}. ^1H NMR (DMSO-d_6): δ 10.58 (s, 2 H, NH), 8.74 (t, 2 H, NH), 7.87 (d, 2 H), 7.64–7.58 (m, 4 H), 7.22 (dd, 2 H), 3.22 (m, 4 H, CH_2), 2.06 (s, 6 H, Me), 1.54 (m, 4 H, CH_2). ^{13}C NMR (DMSO-d_6): δ 191.6 (s), 168.7 (s), 163.6 (s), 138.5 (s), 134.0 (d), 131.6 (d), 123.5 (s), 123.3 (d), 121.3 (d), 38.1 (t), 26.1 (t), 23.9 (q).

(**12d**): Yield: 4.70 g (95%); m.p. 200–201 °C. IR (KBr): ν_{max} 3272, 3254, 2934, 1693, 1666, 1660, 1604, 1531, 1484, 764 cm^{-1}. ^1H NMR (DMSO-d_6): δ 10.59 (s, 2 H, NH), 8.71 (t, 2 H, NH), 7.90 (d, 2 H), 7.64–7.58 (m, 4 H), 7.22 (dd, 2 H), 3.19 (m, 4 H, CH_2), 2.06 (s, 6 H, Me), 1.50 (m, 4 H, CH_2), 1.32 (m, 4 H, CH_2). ^{13}C NMR (DMSO-d_6): δ 191.8 (s), 168.7 (s), 163.6 (s), 138.6 (s), 134.1 (d), 131.6 (d), 123.4 (s), 123.3 (d), 121.2 (d), 38.4 (t), 26.6 (t), 25.9 (t), 24.0 (q).

3,10-Di-(2-acetamidophenyl)-1,4,8,11-tetraaza-3,10-cyclotetradecadiene-2,9-dione (**14a**). *N*-Acetylisatin (9.46 g, 50 mmol) was heated to reflux in EtOH (125 ml) for 3 h, whereupon propane-1,3-diamine (3.71 g, 50 mmol) was added dropwise to the solution at reflux. When the addition was complete, the reaction mixture was allowed to reflux for 12 h. The solid formed was collected by filtration. Yield: 2.05 g (17%); m.p. 318–320 °C. IR (KBr): ν_{max} 3247, 3056, 2922, 1661, 1583, 1535, 1448, 1306, 1232, 777 cm^{-1}. ^1H NMR (DMSO-d_6): δ 12.94 (s, 2 H, NH), 9.01 (br s, 2 H, NH), 8.54 (d, 2 H), 7.43 (dd, 2 H), 7.35 (d, 2 H), 7.11 (dd, 2 H), 3.66 (t, 4 H, CH_2), 3.11 (s, 6 H, Me), 1.94 (m, 4 H, CH_2). ^{13}C NMR (DMSO-d_6): δ 168.5 (s), 167.5 (s), 164.0 (s), 139.9 (s), 131.2 (d), 130.8 (d), 122.2 (d), 119.4 (d), 118.4 (s), 52.5 (t), 36.4 (t), 30.8 (t), 24.9 (q); MS: *m/z* 490 (M^+, 11%), 118 (100).

3-(2-Acetamidophenyl)-2(1H)-pyrazinone (**18a**). A mixture of **11a** (4.63 g, 20 mmol) and *m*-CPBA (3.83 g of 90% *m*-CPBA, 20 mmol) in MeOH (50 ml) was stirred at room temperature overnight. The solid formed was collected by filtration. Yield: 4.45 g (97%); m.p. 229–231 °C. IR (KBr): ν_{max} 3258, 3062, 2848, 2802, 1665, 1634, 1586, 1551, 748 cm^{-1}. ^1H NMR (DMSO-d_6): δ 12.50 (br s, 1 H, NH), 9.86 (s, 1 H, NH), 7.82 (d, 1 H), 7.64 (d, 1 H), 7.50–7.48 (m, 2 H), 7.38 (dd, 1 H), 7.15 (dd, 1 H), 1.95 (s, 3 H, Me); ^{13}C NMR (DMSO-d_6): δ 167.7 (s), 155.4 (s), 153.8 (s), 136.6 (s), 130.6 (d), 129.0 (d), 128.1 (s), 127.3 (d), 123.2 (d), 123.1 (2 C, d), 23.8 (q).

3-(2-Acetamido-5-bromophenyl)-2(1H)-pyrazinone (**18b**). A mixture of **11b** (6.20 g, 20 mmol) and *m*-CPBA (3.83 g of 90% *m*-CPBA, 20 mmol) in MeOH (50 ml) was refluxed for 3 h. The reaction mixture was allowed to cool to room temperature and the solid formed was collected by filtration. Yield: 4.81 g (78%); m.p. 276–278 °C. IR (KBr): ν_{max} 3246, 3183, 3103, 1670, 1644, 1601, 1221, 809 cm^{-1}. ^1H NMR (DMSO-d_6): δ 12.65 (br s, 1 H, NH), 9.96 (s, 1 H, NH), 7.85–7.82 (m, 2 H), 7.56 (d, 1 H), 7.51 (d, 1 H), 7.49 (d, 1 H), 1.95 (s, 3 H,

Me). ^{13}C NMR (DMSO-d_6): δ 167.9 (s), 155.3 (s), 152.2 (s), 136.0 (s), 132.7 (d), 131.7 (d), 129.6 (s), 127.8 (d), 124.8 (d), 123.1 (d), 114.9 (s), 23.9 (q).

3-(2-Acetamidophenyl)-5-methyl-2(1H)-pyrazinone (**18c**). A mixture of **16a** (4.91 g, 20 mmol) and peracetic acid (5.23 g of 32% peracetic acid, 22 mmol) in MeOH (50 ml) was stirred at room temperature overnight. The solid formed was collected by filtration. Yield: 2.10 g (43%); m.p. 222–223 °C. IR (KBr): ν_{max} 3183, 3073, 1669, 1654, 1613, 1214, 748 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 12.40 (br s, 1 H, NH), 10.13 (s, 1 H, NH), 7.87 (d, 1 H), 7.74 (d, 1 H), 7.41–7.34 (m, 2 H), 7.15 (dd, 1 H), 2.26 (s, 3 H, Me), 1.96 (s, 3 H, Me). ^{13}C NMR (DMSO-d_6): δ 167.7 (s), 154.6 (s), 151.7 (s), 136.7 (s), 131.3 (s), 130.7 (d), 129.1 (d), 127.4 (s), 124.7 (d), 123.1 (d), 122.8 (d), 24.0 (q), 19.0 (q).

3-(2-Acetamidophenyl)-5-ethyl-2(1H)-pyrazinone (**18d**). A mixture of **17a** (5.19 g, 20 mmol) and peracetic acid (5.23 g of 32% peracetic acid, 22 mmol) in MeOH (50 ml) was stirred at room temperature overnight. The solid formed was collected by filtration. Yield: 2.68 g (52%); m.p. 196–198 °C; IR (KBr): ν_{max} 3065, 2965, 2926, 1666, 1654, 1573, 1526, 1213, 764 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.50 (br s, 1 H, NH), 10.12 (s, 1 H, NH), 7.89 (d, 1 H), 7.76 (d, 1 H), 7.38 (dd, 1 H), 7.33 (s, 1 H), 7.15 (dd, 1 H), 2.56 (q, 2 H, CH_2), 1.96 (s, 3 H, Me), 1.18 (t, 3 H, Me). ^{13}C NMR (DMSO-d_6): δ 167.6 (s), 154.8 (s), 151.9 (s), 136.7 (s), 136.3 (s), 130.7 (d), 129.1 (d), 127.5 (s), 123.7 (d), 123.1 (d), 122.9 (d), 25.9 (t), 24.0 (q), 13.5 (q).

General procedure for the synthesis of **21a–d**. **18a–d** (10 mmol) was added to a 20% solution of KOH in EtOH–H_2O (1:1, 25 ml). The solution was refluxed for 4 h and thereafter cooled in an ice-bath. HOAc was added slowly to give a yellow solid, which was collected by filtration.

3-(2-Aminophenyl)-2(1H)-pyrazinone (**21a**). Yield: 1.55 g (83%); m.p. 184–186 °C. IR (KBr): ν_{max} 3434, 2846, 2825, 1648, 1570, 1250, 746 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.30 (br s, 1 H, NH), 8.03 (d, 1 H), 7.41 (d, 1 H), 7.34 (d, 1 H), 7.07 (dd, 1 H), 6.74 (d, 1 H), 6.54 (dd, 1 H), 6.22 (br s, 2 H, NH_2). ^{13}C NMR (DMSO-d_6): δ 155.3 (s), 154.3 (s), 148.0 (s), 130.6 (d), 129.9 (d), 125.3 (d), 121.8 (d), 118.5 (s), 116.1 (d), 114.6 (d).

3-(2-Amino-5-bromophenyl)-2(1H)-pyrazinone (**21b**). Yield: 2.31 g (86%); m.p. 188–190 °C. IR (KBr): ν_{max} 3417, 3343, 2927, 1626, 1609, 1485, 1269, 1214 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.50 (br, s, 1 H, NH), 8.36 (s, 1 H), 7.42 (d, 1 H), 7.38 (d, 1 H), 7.20 (d, 1 H), 6.72 (d, 1 H), 6.55 (br s, 2 H, NH_2); ^{13}C NMR (DMSO-d_6): δ 155.5 (s), 152.2 (s), 147.4 (s), 132.4 (d), 132.2 (d), 126.0 (d), 121.8 (d), 119.5 (s), 118.0 (d), 105.1 (s).

3-(2-Aminophenyl)-5-methyl-2(1H)-pyrazinone (**21c**). Yield: 1.85 g (92%); m.p. 180–182 °C. IR (KBr): ν_{max} 3428, 3351, 2953, 2917, 2855, 1616, 1592, 1491, 1211, 750 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.15 (br s, 1 H, NH), 8.04 (d, 1 H), 7.19 (s, 1 H), 7.07 (dd, 1 H), 6.74 (d, 1 H), 6.54 (dd, 1 H), 6.20 (br s, 2 H, NH_2), 2.23 (s, 3 H, Me). ^{13}C NMR (DMSO-d_6): δ 154.4 (s), 152.6 (s), 147.9 (s), 130.8 (d), 129.8 (s), 129.8 (d), 122.5 (d), 118.6 (s), 116.1 (d), 114.7 (d), 19.0 (q).

3-(2-Aminophenyl)-5-ethyl-2(1H)-pyrazinone (**21d**). Yield: 2.05 g (95%); m.p. 133–135 °C. IR (KBr): ν_{max} 3423, 3348, 2965, 1615, 1591, 1492, 1214, 747 cm^{-1}. ^{1}H NMR (DMSO-d_6):δ 12.00 (br s, 1 H, NH), 8.08 (d, 1 H), 7.16 (s, 1 H), 7.07 (dd, 1 H), 6.74 (d, 1 H), 6.55 (dd, 1 H), 6.25 (br s, 2 H, NH_2), 2.54 (q, 2 H, CH_2), 1.16 (t, 3 H, Me). ^{13}C NMR (DMSO-d_6): δ 154.7 (s), 152.7 (s), 148.0 (s), 134.9 (s), 130.8 (d), 129.8 (d), 121.7 (d), 118.6 (s), 116.1 (d), 114.7 (d), 25.9 (t), 13.5 (q).

General procedure for the synthesis of **5a–d**. A solution of **21a–d** (5 mmol) in diphenyl ether (50 ml) was heated to 220 °C for 24 h. The reaction mixture was allowed to cool to room temperature and thereafter dissolved in CH_2Cl_2 and extracted with 2 M HCl. The water layer was extracted with CH_2Cl_2. The combined organic layers were concentrated and the residue flash chromatographed with CH_2Cl_2. When all the diphenyl ether had been collected, the content of MeOH in the eluent was slowly increased to 5%, to give the 5*H*-pyrazino[2,3-*b*]indole as a beige solid.

5H-Pyrazino[2,3-b]indole (**5a**). Yield: 508 mg (60%); m.p. 241–242 °C; IR (KBr): ν_{max} 3048, 2960, 2802, 1625, 1399, 1182, 735 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.14 (s, 1 H, NH), 8.48 (d, 1 H), 8.42 (d, 1 H), 8.22 (d, 1 H), 7.59–7.57 (m, 2 H), 7.31 (m, 1 H). ^{13}C NMR (DMSO-d_6): δ 145.4 (s), 140.1 (s), 139.8 (d), 136.3 (d), 135.1 (s), 128.8 (d), 120.8 (d), 120.3 (d), 119.2 (s), 112.0 (d).

8-Bromo-5H-pyrazino[2,3-b]indole (**5b**). Yield: 521 mg (42%); m.p. 282–284 °C. IR (KBr): ν_{max} 3050, 2946, 2802, 1455, 1444, 1195, 1184, 800 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 12.32 (s, 1 H, NH), 8.51 (d, 1 H), 8.47 (d, 1 H), 8.32 (s, 1 H), 7.70 (d, 1 H), 7.54 (d, 1 H). ^{13}C NMR (DMSO-d_6): δ 145.6 (s), 140.8 (d), 138.7 (s), 137.0 (d), 133.8 (s), 131.3 (d), 123.0 (d), 120.9 (s), 114.2 (d), 112.4 (s).

2-Methyl-5H-pyrazino[2,3-b]indole (**5c**). Yield: 541 mg (59%); m.p. 258–259 °C. IR (KBr): ν_{max} 3124, 3080, 2980, 2833, 1620, 1468, 1394, 1280, 1198, 1174, 750 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 11.94 (s, 1 H, NH), 8.32 (s, 1 H), 8.17 (d, 1 H), 7.56–7.54 (m, 2 H), 7.28 (m, 1 H), 2.63 (s, 3 H, Me). ^{13}C NMR (DMSO-d_6): δ 144.7 (s), 143.7 (s), 140.2 (s), 139.2 (d), 133.8 (s), 128.4 (d), 120.7 (d), 120.0 (d), 119.0 (s), 111.9 (d), 20.9 (q).

*2-Ethyl-5*H*-pyrazino[2,3-*b*]indole* (**5d**). Yield: 552 mg (56%); m.p. 161–162 °C. IR (KBr): ν_{max} 3134, 2967, 2840, 1622, 1478, 1396, 1196, 1177, 747 cm^{-1}. ^1H NMR (DMSO-d_6):δ 11.96 (s, 1 H, NH), 8.34 (s, 1 H), 8.19 (d, 1 H), 7.56–7.53 (m, 2 H), 7.28 (m, 1 H), 2.93 (q, 2 H, CH_2), 1.32 (t, 3 H, Me). ^{13}C NMR (DMSO-d_6): δ 149.8 (s), 144.0 (s), 140.3 (s), 138.7 (d), 133.9 (s), 128.4 (d), 120.8 (d), 120.0 (d), 119.1 (s), 111.9 (d), 27.8 (t), 14.5 (q).

General procedure for synthesis of **2a–b** *and* **3a**. The appropriate 5*H*-pyrazino[2,3-*b*]indole (10 mmol) was added to a stirred suspension of NaH (528 mg, 22 mmol) in dry DMSO (50 ml) under N_2, so that the temperature was kept in the range 35–40 °C. The reaction mixture was stirred for 30 min at 35 °C, after which the appropriate dimethylaminoalkyl chloride hydrochloride (10 mmol) was added. The reaction mixture was stirred for 4 h at 35 °C, whereupon the temperature was slowly (1 h) raised to 45 °C. The reaction mixture was allowed to cool and then poured into water. The resulting mixture was acidified with 2 M HCl and extracted with CH_2Cl_2 (3 × 100 ml). The aqueous layer was basified with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 100 ml). The combined organic layers were dried ($MgSO_4$) and concentrated to give a yellow oil. The oil was converted into the hydrochloride, by dissolution in 2 M HCl and evaporation. This hydrochloride was converted into the corresponding free base by treatment with a solution of potassium carbonate (5%).

*5-(2-Dimethylaminoethyl)-5*H*-pyrazino[2,3-b]indole* (**2a**). Yield: 2.38 g (86%). IR (film): ν_{max} 2945, 2780, 1623, 1550, 1494, 1477, 1464, 1413, 1178, 751 cm^{-1}. ^1H NMR (DMSO-d_6): δ 8.51 (d, 1 H), 8.48 (d, 1 H), 8.25 (d, 1 H), 7.79 (d, 1 H), 7.67 (dd, 1 H), 7.36 (dd, 1 H), 4.55 (t, 2 H, CH_2), 2.69 (t, 2 H, CH_2), 2.16 (s, 6 H, Me). ^{13}C NMR (DMSO-d_6):δ 144.7 (s), 140.4 (s), 139.7 (d), 136.4 (d), 134.9 (s), 129.0 (d), 120.9 (d), 120.6 (d), 118.7 (s), 110.6 (d), 56.9 (t), 45.2 (q), 39.1 (t).

*8-Bromo-5-(2-dimethylaminoethyl)-5*H*-pyrazino[2,3-b]-indole* (**2b**). Yield: 2.27 g (64%); m.p. 67–68 °C. IR (KBr): ν_{max} 2941, 2764, 1620, 1548, 1473, 1457, 1398, 1336, 1288, 1176, 1144, 834, 805 cm^{-1}. ^1H NMR (DMSO-d_6): δ 8.51 (d, 1 H), 8.50 (d, 1 H), 8.30 (m, 1 H), 7.75–7.73 (m, 2 H), 4.50 (t, 2 H, CH_2), 2.65 (t, 2 H, CH_2), 2.13 (s, 6 H, Me). ^{13}C NMR (DMSO-d_6): δ 144.8 (s), 140.5 (d), 139.0 (s), 136.9 (d), 133.6 (s), 131.2 (d), 122.9 (d), 120.3 (s), 112.7 (d), 112.6 (s), 56.8 (t), 45.1 (q), 39.2 (t).

*5-(3-Dimethylaminopropyl)-5*H*-pyrazino[2,3-b]indole* (**3a**). Yield: 2.05 g (70%). IR (film): ν_{max} 2944, 2766, 1623, 1550, 1493, 1477, 1464, 1411, 1183, 750 cm^{-1}. ^1H NMR (DMSO-d_6): δ 8.49 (d, 1 H), 8.47 (d, 1 H), 8.24 (d, 1 H), 7.77 (d, 1 H), 7.65 (dd, 1 H), 7.35 (dd, 1 H), 4.46 (t, 2 H, CH_2), 2.21 (t, 2 H, CH_2), 2.08 (s, 6 H, Me), 1.92 (m, 2 H, CH_2). ^{13}C NMR (DMSO-d_6): δ 144.5 (s), 140.5 (s), 139.6 (d), 136.3 (d), 135.0 (s), 129.0 (d), 120.9 (d), 120.5 (d), 118.6 (s), 110.3 (d), 56.0 (t), 44.8 (q), 38.9 (t), 26.2 (t).

*5-(4-Bromobutyl)-5*H*-pyrazino[2,3-b]indole* (**22**). 5*H*-Pyrazino[2,3-*b*]indole (1.69 g, 10 mmol) was added to a stirred suspension of NaH (264 mg, 11 mmol) in dry DMF (50 ml) under N_2, keeping the temperature between 35 and 40 °C. The reaction mixture was stirred for 30 min at 35 °C, and thereafter slowly (1 h) added to a solution of 1,4-dibromobutane (4.32 g, 20 mmol) in DMF (100 ml) at 5 °C. The reaction mixture was stirred for 1 h at 5 °C, when the temperature was slowly (1 h) increased to room temperature and stirred at that temperature for 12 h. The reaction mixture was poured into water and extracted with CH_2Cl_2 (3 × 100 ml). The combined organic layers were dried ($MgSO_4$) and carefully concentrated. The crude product was flash chromatographed (MeOH–CH_2Cl_2, 1:19), to give **22** as a yellow oil and **23** as a by-product. Yield: 2.26 g (74%): IR (film): ν_{max} 3050, 2930, 1622, 1493, 1476, 1464, 1411, 1328, 1181, 1127, 751, 741 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.47 (d, 1 H), 8.39–8.33 (m, 2 H), 7.63 (dd, 1 H), 7.50 (d, 1 H), 7.37 (dd, 1 H), 4.49 (t, 2 H, CH_2), 3.43 (t, 2 H, CH_2), 2.09 (m, 2 H, CH_2), 1.89 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$): δ 145.3 (s), 140.7 (s), 139.4 (d), 136.5 (d), 136.0 (s), 129.1 (d), 121.8 (d), 120.9 (d), 119.6 (s), 109.5 (d), 40.4 (t), 32.9 (t), 29.8 (t), 27.4 (t).

(**23**): Yield: 0.32 g (16%); m.p. 179–181 °C (2-propanol). IR (KBr): ν_{max} 3050, 2925, 1622, 1548, 1493, 1476, 1462, 1410, 1326, 1177, 1125, 746 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.46 (m, 2 H), 8.34 (m, 4 H), 7.56 (m, 2 H), 7.5–7.3 (m, 4 H), 4.49 (t, 4 H, CH_2), 2.00 (t, 4 H, CH_2). ^{13}C NMR ($CDCl_3$): δ 145.4 (s), 140.7 (s), 139.4 (d), 136.5 (d), 136.1 (s), 129.1 (d), 121.8 (d), 120.8 (d), 119.6 (s), 109.5 (d), 40.9 (t), 26.1 (t).

*5-(4-Dimethylaminobutyl)-5*H*-pyrazino[2,3-b]indole* (**3b**). A mixture of **22** (1.52 g, 5 mmol) and aqueous $NHMe_2$ (40%, 50 ml) was heated to reflux in EtOH (200 ml) for 12 h. After concentration to 50 ml the mixture was extracted with CH_2Cl_2 (3 × 100 ml). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was flash chromatographed (MeOH–CH_2Cl_2 2:8), to give **3b** as a yellow oil. Yield: 637 g (95%): IR (film): ν_{max} 2941, 2778, 1623, 1550, 1493, 1477, 1464, 1412, 1182, 751 cm^{-1}. ^1H NMR (DMSO-d_6): δ 8.50 (d, 1 H), 8.47 (d, 1 H), 8.25 (d, 1 H), 7.78 (d, 1 H), 7.66 (dd, 1 H), 7.36 (dd, 1 H), 4.46 (t, 2 H, CH_2), 2.23 (t, 2 H, CH_2), 2.06 (s, 6 H, Me), 1.81 (m, 2 H, CH_2), 1.39 (m, 2 H, CH_2). ^{13}C NMR (DMSO-d_6): δ 144.6 (s), 140.4 (s), 139.6 (d), 136.4 (d), 134.9 (s), 129.0 (d), 120.9 (d), 120.6 (d), 118.6 (s), 110.4 (d), 58.1 (t), 44.6 (q), 40.6 (t), 25.9 (t), 23.9 (t).

*3-(2-Acetamidophenyl)-1-(2-dimethylaminoethyl)-2-(1*H*)-pyrazinone* (**27a**). Compound **18a** (2.26 g, 20 mmol) was added to a stirred suspension of NaH

(1.06 g, 44 mmol) in dry DMSO (50 ml) under N_2, keeping the temperature between 35 and 40 °C. The reaction mixture was stirred for 30 min at 40 °C, then *N*, *N*-dimethylaminoethyl chloride hydrochloride (2.88 g, 20 mmol) was added. The reaction mixture was stirred for 48 h at 40 °C, and the temperature was slowly (3 h) raised to 80 °C. The reaction mixture was allowed to cool and then poured into water. The resulting mixture was continuously extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and concentrated. The crude product was flash chromatographed (MeOH–CH_2Cl_2 1:9), to give **27a** as a light-yellow solid. Yield: 3.84 g (64%); m.p. 83–85 °C. IR (KBr): ν_{max} 3257, 3076, 2953, 1671, 1648, 1588, 1298, 765 cm^{-1}. ^1H NMR (DMSO-d_6): δ 9.66 (s, 1 H, NH), 7.76 (d, 1 H), 7.72 (d, 1 H), 7.58 (d, 1 H), 7.47 (d, 1 H), 7.38 (dd, 1 H), 7.16 (dd, 1 H), 4.05 (t, 2 H, CH_2), 2.57 (t, 2 H, CH_2), 2.19 (s, 6 H, Me), 1.93 (s, 3 H, Me); ^{13}C NMR (DMSO-d_6): δ 167.7 (s), 154.7 (s), 153.1 (s), 136.6 (s), 130.7 (2 C, d), 129.0 (d), 128.5 (s), 123.4 (d), 123.3 (d), 122.4 (d), 56.6 (t), 46.6 (t), 45.0 (q), 23.7 (q).

3-(2-Acetamidophenyl)-1-methyl-2(1H)-pyrazinone (**27b**). A mixture of **19** (4.91 g, 20 mmol) and peracetic acid (5.23 g of 32% peracetic acid, 22 mmol) in MeOH (50 ml) was stirred at room temperature overnight. The solid formed was collected by filtration. Yield: 2.64 g (54%); m.p. 164–166 °C. IR (KBr): ν_{max} 3268, 3069, 1675, 1636, 1579, 1542, 1289, 748 cm^{-1}. ^1H NMR (DMSO-d_6): δ 9.65 (s, 1 H, NH), 7.81 (d, 1 H), 7.76 (d, 1 H), 7.58 (d, 1 H), 7.46 (d, 1 H), 7.38 (dd, 1 H), 7.15 (dd, 1 H), 3.51 (s, 3 H, Me), 1.94 (s, 3 H, Me). ^{13}C NMR (DMSO-d_6): δ 167.7 (s), 155.3 (s), 152.8 (s), 136.5 (s), 131.2 (d), 130.6 (d), 129.0 (d), 128.2 (s), 123.2 (2 C, d), 122.3 (d), 37.1 (q), 23.8 (q).

3-(2-Aminophenyl)-1-(2-dimethylaminoethyl)-2(1H)-pyrazinone (**28a**). Compound **27a** (3.00 g, 10 mmol) was added to a 20% KOH (1:1 EtOH–H_2O, 25 ml). The solution was refluxed for 4 h and thereafter cooled in an ice-bath. The pH of the reaction mixture was adjusted to approximately 8 with HOAc, after which the mixture was extracted (continuously) with CH_2Cl_2. The crude product was flash chromatographed (MeOH–CH_2Cl_2 1:9), to give **28a** as an orange solid. Yield: 1.98 g (77%); m.p. 88–90 °C; IR (KBr): ν_{max} 3427, 3324, 2815, 2768, 1634, 1612, 1587, 1459, 1263, 1206, 766 cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.89 (d, 1 H), 7.60 (d, 1 H), 7.40 (d, 1 H), 7.07 (dd, 1 H), 6.74 (d, 1 H), 6.54 (dd, 1 H), 6.01 (br s, 2 H, NH_2), 4.03 (t, 2 H, CH_2), 2.55 (t, 2 H, CH_2), 2.17 (s, 6 H, Me); ^{13}C NMR (DMSO-d_6): δ 154.7 (s), 153.3 (s), 147.9 (s), 130.8 (d), 129.8 (d), 129.2 (d), 121.2 (d), 118.9 (s), 116.1 (d), 114.7 (d), 56.7 (t), 46.6 (t), 45.1 (q).

3-(2-Aminophenyl)-1-methyl-2(1H)-pyrazinone (**28b**). Compound **27b** (2.43 g, 10 mmol) was added to 20% KOH in EtOH–H_2O (1:1, 25 ml). The solution was refluxed for 4 h and thereafter cooled in an ice-bath. HOAc was added slowly, to give **28b** as a yellow solid. The solid formed was collected by filtration. Yield: 1.70 g (85%); m.p. 145–146 °C; IR (KBr): ν_{max} 3268, 3069, 1675, 1636, 1579, 1542, 1289, 748 cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.90 (d, 1 H), 7.64 (d, 1 H), 7.39 (d, 1 H), 7.08 (dd, 1 H), 6.74 (d, 1 H), 6.55 (dd, 1 H), 6.02 (br s, 2 H, NH_2), 3.50 (s, 3 H, Me). ^{13}C NMR (DMSO-d_6): δ 155.3 (s), 153.1 (s), 147.9 (s), 130.7 (d), 129.8 (d), 129.7 (d), 121.3 (d), 118.9 (s), 116.0 (d), 114.7 (d), 37.2 (q).

4-(2-Dimethylaminoethyl)-4H-pyrazino[2,3-b]indole (**25a**). Compound **28a** (1.29 g, 5 mmol) was added to a stirred suspension of NaH (132 mg, 5.5 mmol) in dry DMF (50 ml) under N_2. The reaction mixture was stirred for 12 h at 100 °C. The reaction mixture was allowed to cool and then poured into water. The resulting mixture was continuously extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and carefully concentrated. The crude product was flash chromatographed (MeOH–CH_2Cl_2 2:8), to give **25a** as an orange solid. Yield: 373 mg (31%); m.p. 108–110 °C. IR (KBr): ν_{max} 2819, 2766, 1554, 1466, 1459, 1328, 1286, 1193, 1110, 1057, 762, 742 cm^{-1}. ^1H NMR (DMSO-d_6): δ 8.18–8.14 (m, 2 H), 8.11 (d, 1 H), 7.65 (d, 1 H), 7.59 (dd, 1 H), 7.23 (dd, 1 H), 4.70 (t, 2 H, CH_2), 2.86 (t, 2 H, CH_2), 2.18 (s, 6 H, Me). ^{13}C NMR (DMSO-d_6): δ 156.1 (s), 149.3 (s), 143.9 (s), 130.5 (d), 126.0 (d), 125.8 (d), 121.7 (s), 121.3 (d), 119.5 (d), 118.3 (d), 56.6 (t), 49.3 (t), 45.0 (q).

4-Methyl-4H-pyrazino[2,3-b]indole (**25b**). Compound **28b** (1.01 g, 5 mmol) was added to a stirred suspension of NaH (132 mg, 5.5 mmol) in dry DMF (50 ml) under N_2. The reaction mixture was stirred for 12 h at 100 °C. The reaction mixture was allowed to cool and then poured into water. The resulting mixture was continuously extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and carefully concentrated. The crude product was flash chromatographed (MeOH–CH_2Cl_2 1:9), to give **25b** as a red solid. Yield: 476 mg (52%); m.p. 203–205 °C. IR (KBr): ν_{max} 3069, 1562, 1491, 1348, 1316, 1275, 1197, 1188, 1108, 761, 738 cm^{-1}. ^1H NMR (DMSO-d_6): δ 8.19–8.14 (m, 2 H), 8.10 (d, 1 H), 7.65 (d, 1 H), 7.59 (dd, 1 H), 7.23 (dd, 1 H), 4.19 (s, 3 H, Me); ^{13}C NMR (DMSO-d_6): δ 156.1 (s), 149.0 (s), 144.4 (s), 130.5 (d), 126.5 (d), 126.0 (d), 121.6 (s), 121.4 (d), 119.5 (d), 118.3 (d), 39.0 (q).

1-(2-Pyrazinyl)benzotriazole (**31**). 1*H*-Benzotriazole (5.96 g, 50 mmol) and 2-chloropyrazine (5.73 g, 50 mmol) were heated to 150 °C for 1 h. The solid formed was recrystallized from EtOH, to give **31**. Yield: 8.38 g (85%); m.p. 122–124 °C. IR (KBr): ν_{max} 1530, 1480, 1449, 1434, 1289, 1044, 1018, 843, 772, 752 cm^{-1}. ^1H NMR (DMSO-d_6): δ 9.47 (d, J=1.3 Hz, 1 H), 8.73 (d, J=2.6 Hz, 1 H), 8.71 (dd, J=1.3, 2.6 Hz, 1 H), 8.39 (d,

2 H), 8.18 (d, 1 H), 7.68 (dd, 1 H), 7.52 (dd, 1 H). ^{13}C NMR (DMSO-d_6): δ 147.0 (s), 145.7 (s), 143.0 (d), 142.6 (d), 136.3 (d), 130.7 (s), 129.5 (d), 125.5 (d), 119.7 (d), 113.8 (d).

1-(2-Quinoxalinyl)benzotriazole (**32**). 1*H*-Benzotriazole (5.96 g, 50 mmol) and 2-chloroquinoxaline (8.23 g, 50 mmol) were heated to 150 °C for 1 h. The solid formed was recrystallized from EtOH, to give **32**. Yield: 11.36 g (92%); m.p. 152–154 °C. IR (KBr): ν_{max} 1606, 1573, 1498, 1448, 1025, 768, 750 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 9.76 (s, 1 H), 8.72 (d, 1 H), 8.22 (d, 1 H), 8.17–8.10 (m, 2 H), 8.90 (dd, 1 H), 7.83 (dd, 1 H), 7.76 (dd, 1 H), 7.57 (dd, 1 H). ^{13}C NMR (DMSO-d_6): δ 145.7 (s), 144.9 (s), 140.3 (s), 139.0 (s), 138.2 (d), 131.4 (d), 130.7 (s), 129.8 (d), 129.7 (d), 128.8 (d), 128.3 (d), 125.8 (d), 119.7 (d), 114.5 (d).

*Pyrazino[1,2-*a*]benzimidazole* (**33**). The benzotriazole **31** (3.94 g, 20 mmol) was heated in PPA (25 ml) for 1 h at 180 °C. The reaction mixture was allowed to cool and then diluted with water and made alkaline with 2 M NaOH. The solid formed was collected by filtration. Yield: 2.73 g (81%); m.p. 197–198 °C. IR (KBr): ν_{max} 3054, 3019, 1488, 1342, 1324, 1272, 810, 730 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 9.28 (d, J=1.6 Hz, 1 H), 9.11 (dd, J=1.6, 4.6 Hz, 1 H), 8.40 (d, 1 H), 8.02 (d, J=4.6 Hz, 1 H), 7.96 (d, 1 H), 7.62 (dd, 1 H); ^{13}C NMR (DMSO-d_6): δ 144.6 (d), 143.5 (s), 141.6 (s), 127.6 (s), 126.7 (d), 126.6 (d), 122.6 (d), 120.4 (d), 119.7 (d), 112.9 (d).

*Benzimidazo[1,2-*a*]quinoxaline* (**34**). The benzotriazole **32** (4.95 g, 20 mmol) was heated in PPA (25 ml) for 1 h at 180 °C. The reaction mixture was allowed to cool and then diluted with water and basified with 2 M NaOH. The solid formed was collected by filtration. Yield: 2.73 g (81%); m.p. 178–180 °C. IR (KBr): ν_{max} 3067, 3021, 1600, 1551, 1508, 1458, 1388, 752, 736 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 9.25 (s, 1 H), 8.75–8.68 (m, 2 H), 8.10 (d, 1 H), 8.06–8.00 (m, 1 H), 7.82 (dd, 1 H), 7.68–7.58 (m, 3 H). ^{13}C NMR (DMSO-d_6): δ 146.0 (d), 143.6 (s), 140.7 (s), 134.9 (s), 130.3 (d), 130.2 (d), 129.3 (s), 128.9 (s), 125.6 (d), 125.4 (d), 124.6 (d), 121.2 (d), 115.6 (d), 115.0 (d).

*1,2,3,4-Tetrahydropyrazino[1,2-*a*]benzimidazole* (**38**). A suspension of **33** (1.69 g, 10 mmol) and Pd–C (100 mg, 10%) was stirred under H_2 (3 atm) for 24 h. The reaction mixture was filtered through Celite and evaporated. The crude product was flash chromatographed (MeOH–CH_2Cl_2 2:8), to give **38** as a white solid. Yield: 1.46 g (84%); m.p. 129.5–131 °C (benzene). IR (KBr) :ν_{max} 3259, 2922, 2891, 1610, 1506, 1484, 1475, 1455, 1418, 1317, 1124, 863, 752 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.71 (m, 1 H), 7.33–7.21 (m, 3 H), 4.30 (s, 2 H, CH_2), 4.08 (t, 2 H, CH_2), 3.39 (t, 2 H, CH_2). ^{13}C NMR ($CDCl_3$): δ 149.3 (s), 142.5 (s), 134.3 (s), 122.3 (d), 121.9 (d), 119.1 (d), 108.6 (d), 45.1 (t), 42.9 (t), 42.7 (t).

General procedure for synthesis of **40, 41** and **44**. *N*-Acetylisatin (1.89 g, 10 mmol) was heated to reflux in EtOH (200 ml) for 3 h. The solution was added slowly (30 min) to a refluxing solution of the appropriate triamine (10 mmol) in ethanol (50 ml). The reaction mixture was refluxed for x min (x specified below for each compound), and thereafter concentrated to 50 ml. The solid formed was collected by filtration.

6-(2-Acetamidophenyl)-1,4,7-triazabicyclo[4.3.0]nonan-5-one (**40**). Reaction time: x=5 min. Yield: 1.33 g (49%); m.p. 171–172 °C; IR (KBr): ν_{max} 3316, 3275, 2944, 2880, 1674, 1640, 1581, 1518, 1435, 752 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 11.90 (s, 1 H, NH), 8.12 (d, 1 H), 8.03 (m, 1 H, NH), 7.73 (d, 1 H), 7.19 (dd, 1 H), 7.96 (dd, 1 H), 4.08 (t, 1 H, NH), 3.34 (m, 1 H, CH_2), 3.23 (m, 1 H, CH_2), 3.06 (m, 1 H, CH_2), 2.93–2.75 (m, 4 H, CH_2), 2.57 (m, 1 H, CH_2), 2.04 (s, 3 H, Me). ^{13}C NMR (DMSO-d_6): δ 168.4 (s), 166.9 (s), 138.5 (s), 129.2 (d), 128.5 (s), 127.9 (d), 122.1 (d), 120.5 (d), 85.1 (s), 51.9 (t), 45.6 (t), 41.5 (t), 39.7 (t), 24.7 (q).

6-(2-Acetamidophenyl)-1,4,7-triazabicyclo[4.4.0]decan-5-one (**41**). Reaction time: x=6 h. Yield: 315 mg (11%); m.p. 229–231 °C. IR (KBr): ν_{max} 3316, 3188, 2922, 2838, 1668, 1611, 1589, 1541, 1446, 1321, 1050, 750 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 11.93 (s, 1 H, NH), 8.25 (d, 1 H), 7.94 (m, 1 H, NH), 7.41 (d, 1 H), 7.22 (dd, 1 H), 6.99 (dd, 1 H), 3.45–3.15 (m, 1 H, NH and 3 H, CH_2), 3.00–2.65 (m, 5 H, CH_2), 2.03 (s, 3 H, Me), 1.78 (m, 1 H, CH_2), 1.34 (m, 1 H, CH_2). ^{13}C NMR (DMSO-d_6): δ 168.2 (s), 166.8 (s), 138.7 (s), 129.6 (d), 127.9 (d), 126.9 (s), 122.1 (d), 120.2 (d), 78.3 (s), 47.1 (t), 43.2 (t), 40.6 (t), 39.0 (t), 24.8 (q), 21.4 (t).

3-(2-Acetamidophenyl)-1,4,8-triaza-3-cycloundecen-2-one (**44**). Reaction time: x=2 h. Yield: 485 mg (16%); m.p. 224–226 °C; IR (KBr): ν_{max} 3250, 2930, 1652, 1619, 1584, 1538, 1450, 1324, 1307, 770 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 13.04 (s, 1 H, NH), 8.86 (t, 1 H, NH), 8.55 (d, 1 H), 7.42 (dd, 1 H), 7.34 (d, 1 H), 7.10 (dd, 1 H), 3.60 (t, 2 H, CH_2), 3.3 (m, 2 H, CH_2, this multiplet became apparent by irradiation at 3.33 ppm, which converted the triplet at 8.86 ppm into a singlet and the multiplet at 1.65 ppm into a triplet), 2.60 (t, 2 H, CH_2), 2.54 (t, 2 H, CH_2), 2.09 (s, 3 H, Me), 1.86 (m, 2 H, CH_2), 1.65 (m, 2 H, CH_2); finally one of the NH could not be detected. ^{13}C NMR (DMSO-d_6): δ 168.4 (s), 167.5 (s), 163.8 (s), 140.0 (s), 131.1 (d), 130.7 (d), 122.1 (d), 119.3 (d), 118.5 (s), 51.6 (t), 46.9 (2 C, t), 36.4 (t), 30.7 (t), 29.4 (t), 24.8 (q).

Acknowledgements. Financial support from the Swedish Natural Science Research Council is gratefully acknowledged.

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Received September 3, 1996.