Generation of 6-alkylidene/benzylidene-3,6-dihydropyrazin-2(1*H*)-ones by reaction of 6-bromomethylpyrazin-2(1*H*)-ones with methoxide and further conversion into specific piperazine-2,5-diones and pyrazin-2(1*H*)-ones

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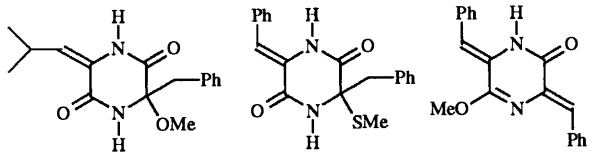
3-Aryl-, 3-benzyl- and 3-methoxy-6-(1-bromoalkyl/benzyl)-5-chloropyrazin-2(1*H*)-ones 6 have been synthesised and converted into new 6-alkylidene/benzylidene-5-chloro-3,6-dihydropyrazin-2(1*H*)-ones 7 by reaction with methoxide in THF. With 2 equiv. of alkoxide the corresponding 5-alkoxy derivatives 8 were obtained. Reaction of compounds of type 6, 7 or 8 with various nucleophiles generated 3,6-dihydropyrazin-2(1*H*)-ones, piperazine-2,5-diones and pyrazin-2(1*H*)-ones.

Piperazine-2,5-diones are amongst the most ubiquitous peptide derivatives found in nature; they are commonly isolated from cultures of yeast, lichens and fungi.[1] Also, some 6-alkylidene/benzylidene substituted members, *e.g.* megasporizine **1**[2] and emethacin A **2**[3] (Fig. 1) have been isolated. The physiological activity shown by some easily accessible mono-[4,5] or di-alkylidene/arylidenepiperazine-2,5-diones[6,7] and the antibiotic activity of neihumycin,[8] identified as 3,6-dibenzylidene-5-methoxy-3,6-dihydropyrazin-2(1*H*)-one **3**, stimulated research into the preparation of synthetic analogues.

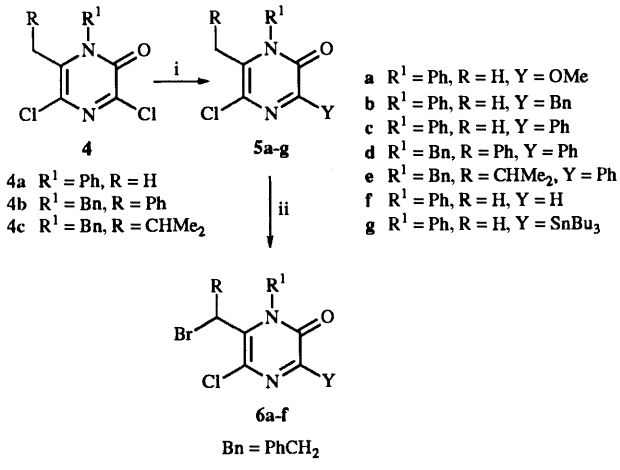


1 **2** **3**

In this work we report a synthetic approach to specific 6-alkylidene/benzylidene-5-chloro-3,6-dihydropyrazin-2(1*H*)-ones using 6-(1-bromoalkyl/benzyl)-3,5-dichloropyrazin-2(1*H*)-ones. Their conversion into piperazine-2,5-diones of type **1** or **2** and other 6-alkylidene/benzylidene-3,6-dihydropyrazin-2(1*H*)-ones with a variable and unknown substitution pattern will be studied.

Results and discussion

The chlorimine function in the 3,5-dichloropyrazin-2(1*H*)-ones **4a–c**—easily obtained from the reaction of an α-amino nitrile with oxalyl chloride—has been shown to be useful for further functionalisations.[9,10] Reaction of **4a** with sodium methoxide (1.2 equiv.) in methanol provided the corresponding 3-methoxypyrazin-2(1*H*)-one **5a** in 96% yield (Scheme 1). Benzyl and phenyl groups could be introduced by palladium(0)-catalysed coupling using organotin reagents:[11–13] compound **5b** was obtained *via* the 3-tributyltinpyrazin-2(1*H*)-one **5g**, generated by reaction of **4a** with hexabutyldistannane and tetrakis(triphenylphosphine)palladium(0) (TPP) as catalyst in toluene at 110 °C. The isolated compound **5g** was further treated with benzyl bromide and $[Pd(PPh_3)_4]$ in toluene (55% total yield of **5b**). Palladium(0)-catalysed substitution of **4a–c** with tetraphenylstannane in toluene (110 °C) afforded the pyrazin-2(1*H*)-ones **5c–e** (±85% yield). The 3-position of **4a**



4 **5a-g**

4a R^1 = Ph, R = H
4b R^1 = Bn, R = Ph
4c R^1 = Bn, R = $CHMe_2$

a R^1 = Ph, R = H, Y = OMe
b R^1 = Ph, R = H, Y = Bn
c R^1 = Ph, R = H, Y = Ph
d R^1 = Bn, R = Ph, Y = Ph
e R^1 = Bn, R = $CHMe_2$, Y = Ph
f R^1 = Ph, R = H, Y = H
g R^1 = Ph, R = H, Y = $SnBu_3$

6a-f

Bn = $PhCH_2$

Scheme 1 *Reagents and conditions:* i, NaH, MeOH, room temp.: **5a**; $PhCH_2Br$, TTP, toluene, 110 °C: **5b** *via* **5g**; $SnPh_4$, TTP, toluene, 110 °C: **5c–e**; HCO_2Na, TTP, DMF, 110 °C: **5f**; $(Bu_3Sn)_2$, TTP, toluene, 110 °C: **5g**; ii, NBS, $(PhCO)_2O_2$, CCl_4, reflux

was dechlorinated when heated in DMF with sodium formate and $[Pd(PPh_3)_4]$[14] yielding **5f** (79%). In order to introduce an α-bromoalkyl/benzyl group in position 6, the compounds **5a–f** were treated with *N*-bromosuccinimide (NBS) and benzoyl peroxide in dry CCl_4 to yield products **6a–f** (70–85%).

Slow addition of sodium hydride (1.1 equiv.) to a mixture of the 6-bromomethylpyrazin-2(1*H*)-one **6a**, **6b** or **6c** and methanol (1.1 equiv.) in dry THF at room temperature afforded the 5-chloro-3,3-dimethoxy-6-methylidene-3,6-dihydropyrazin-2(1*H*)-one **7a** or the corresponding 3-benzyl- or 3-phenyl derivatives **7b,c** in 65–70% yield (Scheme 2). Besides the main compounds **7a–c** and some starting material the 3,3,5-trimethoxy-6-methylidene-3,6-dihydropyrazin-2(1*H*)-one **8a** or the corresponding 3-benzyl- and 3-phenyl-6-methylidenepyrazin-2(1*H*)-ones **8b** and **8c** could be isolated (*ca.* 10% yield). The structures of these new compounds, **7a–c** and **8a–c**, were confirmed on the basis of some typical ^1H and ^{13}C NMR data. The vinylic protons resonate as two doublets near δ 4–4.6 and 5–5.5 with geminal coupling constants of 2–2.7 Hz; both 3-methoxy substituents in **7a** and **8a** appear as singlets at δ 3.5 in the ^1H NMR spectrum whereas the 5-methoxy group in compounds **8a–c** shows a chemical shift of *ca.* 4. The C-3 atoms and the methylene carbon atoms of the exocyclic double bond

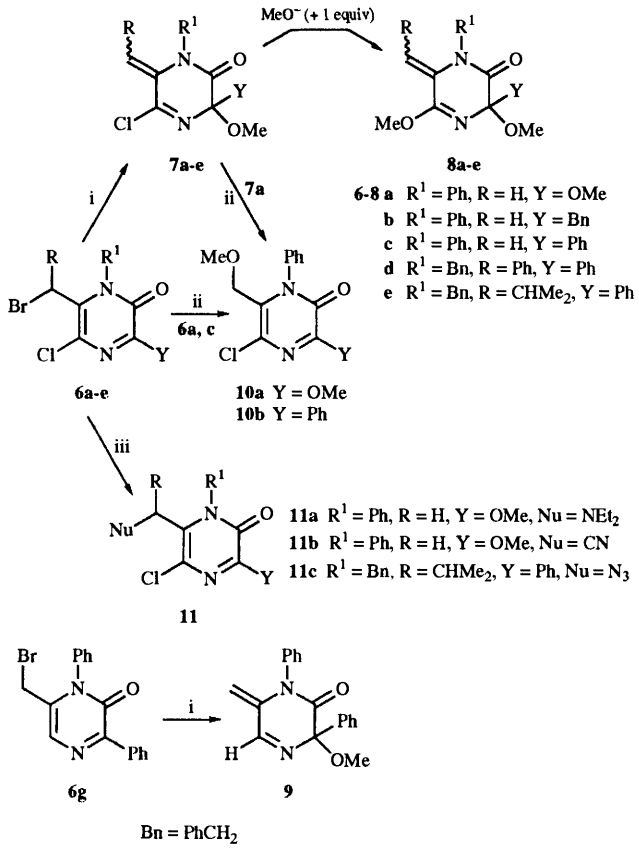
resonate between, respectively, 90–100 ppm and 100–110 ppm in the ^{13}C NMR spectrum. Under the above mentioned reaction conditions (and also in methanol as solvent) the 6-(1-bromoisobutyl/benzyl)pyrazin-2(1*H*)-ones **6d** and **6e** gave exclusively compounds **7d** and **7e** in about 85% yield. However, addition of sodium hydride (2.1 equiv.) to a THF solution of **6a–e** and methanol (2.1 equiv.) gave exclusive formation of compounds **8a–e** in 85–90% yield (Scheme 2). According to the ^1H NMR spectra, compounds **7d** and **8d** have a predominant (>95%) *Z*-configuration. The pyrazinones with an isobutylidene substituent however provided more *E*-isomer: a ratio 1 : 4 for (*E*)-**8e**/(*Z*)-**8e** and 9 : 1 for (*E*)-**7e**/(*Z*)-**7e**. The configuration could be deduced from the observed deshielding effect (0.40–0.55 ppm) of the vinylic proton in the *Z*-isomer (in **7d,e**, **8d,e**) and the shielding (0.80 ppm) of the allylic proton in the *Z*-form (of **7e** and **8e**).[6] Also the dechlorinated pyrazin-2(1*H*)-one **6g**, obtained from **5c** by hydrogenolysis (H_2/Pd/C in methanol) and further bromination with NBS, afforded compound **9** on treatment with sodium methoxide (1 equiv.) in THF.

The exocyclic double bond in compounds **7** and **9** is probably formed after attack of methoxide at the 3-position of the pyrazin-2(1*H*)-ones **6** followed by expulsion of bromide. A similar mechanism was proposed for the reaction of 3-trichloromethylpyridines[15] (and comparable systems[16,17]) with methoxide. In this case the intermediate with the exocyclic double bond, obtained after attack in the 2- or 6-position, immediately underwent a hydrogen shift to yield a methoxy-substituted 3-dichloromethylpyridine. Probably by the same sequence 5-chloro-6-methyl-1-phenylpyrazin-2(1*H*)-one **6f** reacted with methoxide in THF affording the 3-methoxy substituted pyrazin-2(1*H*)-one **5a**. Compounds **7a–e** cannot undergo the hydrogen shift but the reactive chlorimine induces addition–elimination leading to compounds **8**.

In contrast with the behaviour of compounds **6d** (or **6e**), reaction of **6a** or **6c** with methoxide (1.1 equiv.) in methanol at room temperature afforded quickly the 6-methoxymethyl-pyrazin-2(1*H*)-ones **10a** or **10b**. It is not clear whether the reaction in this solvent proceeds by an addition–elimination followed by an attack of the alkoxide on the unhindered exocyclic double bond or rather by a direct substitution of the bromide. In any event, **7a** was shown to react with methoxide in methanol at room temperature providing quickly **10a** and not **8a**. It must be mentioned that other nucleophiles (diethylamine, potassium cyanide or sodium azide) only afforded compounds of type **11** (*e.g.* **11a–c**) when allowed to react with compounds **6** (even with **6e**) in different solvents (polar and apolar); formation of products of type **7** or **8** could never be observed.

A literature study shows that 3,6-dihydropyrazin-2(1*H*)-ones with an imino ester function in position 5 (*e.g.* neihumicin) are accessible by reaction of the appropriate piperazine-2,5-diones with trialkyloxonium tetrafluoroborate[18–20] while analogues with other substituents in this position are scarcely known.[21] Compounds of type **7** contain a chlorimine function as well as a reactive exocyclic double bond. This means that they can be of interest for further functionalisation and conversion into piperazine-2,5-dione analogues of **1** and **2** and other pyrazinone structures.

The piperazine-2,5-diones **13a–d** could be generated very efficiently (85% yield) by treating the 5-chloro compounds **7b–e** at room temperature in dioxane with an equal volume of 1 mol dm^{-3} aqueous sodium hydroxide (Scheme 3). In acidic media[20] the compounds **8b–e** (with Y = Ph or Bn) existed as piperazine-2,5-diones: thus, treatment at room temperature of the former compounds in THF with 1 mol dm^{-3} aqueous hydrochloric acid (1/3 of THF volume) yielded *ca.* 60% of 3-hydroxy-3-phenyl/benzyl-6-alkylidene/benzylidenepiperazine-2,5-diones **13a–d**. The intermediate formation (and isolation in 20–40% yield) of the corresponding 3-methoxy analogues **12a–d** was observed. The structures **12c,d**

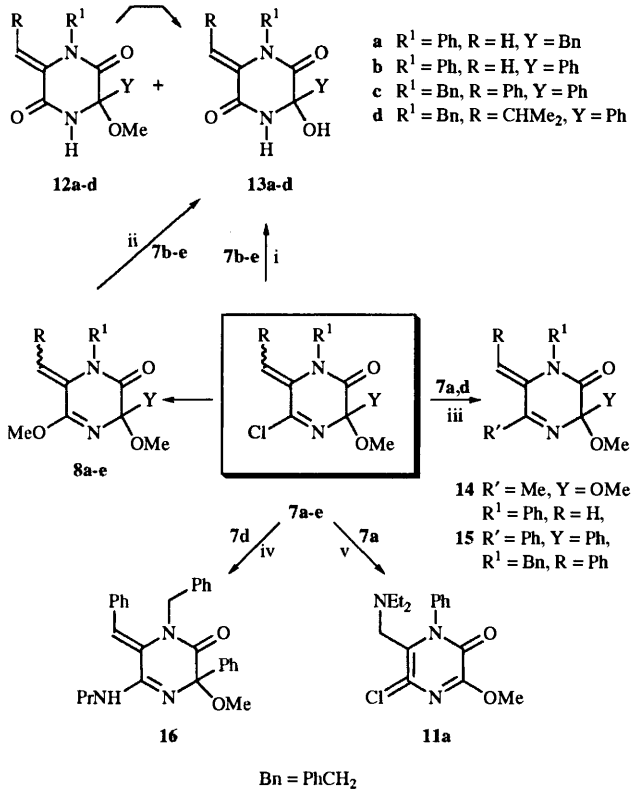


Scheme 2 *Reagents and conditions:* i, NaH, MeOH, THF, room temp.; ii, NaH, MeOH, room temp.; iii, $HNEt_2$, THF, room temp.: **11a**; KCN, 18-crown-6, THF, room temp.: **11b**; NaN_3, DMF, 60 °C: **11c**

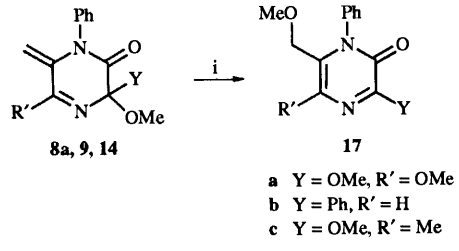
and **13c,d** (obtained by both methods) all have a predominant *Z*-configuration. The described reactions offer a variant to a known method[22] for the synthesis of compounds of type **1** or **2**; however, the variability of the substitution pattern in this method is limited, *e.g.* 3-aryl-3-methoxy/hydroxy substituted alkylidene/benzylidenepiperazine-2,5-diones cannot be realised. The chlorimine function in some compounds **7** was also allowed to react with organotin reagents and amines. Thus, reaction of compound **7a** with tetramethylstannane or **7d** with tetraphenylstannane gave the new 3,6-dihydropyrazin-2(1*H*)-ones **14** or **15** (Scheme 3). The outcome of the reaction with amines depends upon the R group on the exocyclic double bond. Reaction of **7d** with propylamine in THF at room temperature gave compound **16** in 60% yield. Compound **7e** failed to react with amines both at room temperature and under reflux. This is probably due to the steric hindrance of the isopropyl group on the exocyclic double bond (*E*-configuration in **7e**). Moreover, the exocyclic methylene group in compound **7a** rather than the chlorimine function was attacked by diethylamine to afford the pyrazin-2(1*H*)-one **11a**.

For compounds **8a**, **9** and **14** where the reactive chlorimine group is absent, addition–elimination by way of the exocyclic double bond normally takes place; reaction (at room temperature, **9**, or under reflux, **8a** or **14**) with methoxide in methanol yielded new pyrazin-2(1*H*)-ones **17a–c** (Scheme 4).

In conclusion, we can state that the reaction of 6-(1-bromoalkyl/benzyl)pyrazin-2(1*H*)-ones with methoxide in THF provides 6-alkylidene/benzylidene-3,6-dihydropyrazin-2(1*H*)-ones with a chlorimine or imino ester functionality. Further conversion of these compounds provides an alternative method for new 6-alkylidene/benzylidene-3,6-dihydropyrazin-2(1*H*)-ones, piperazine-2,5-diones and pyrazin-2(1*H*)-ones with a specific substitution pattern not easily accessible by other synthetic pathways.



Scheme 3 *Reagents and conditions:* i, 1 mol dm^{-3} aqueous NaOH–dioxane (1:1), room temp.; ii, 1 mol dm^{-3} hydrochloric acid–THF (1:3), room temp.; iii, SnR'_4, TTP, toluene, 110 °C; iv, $PrNH_2$, THF, room temp.; v, Et_2NH, THF, room temp.



Scheme 4 *Reagents and conditions:* i, NaH, MeOH (room temp. or reflux)

Experimental

IR 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. The ^1H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane or the deuteriated solvent as an internal reference. Mass spectra were run by using a Kratos MS50TC instrument and a DS90 data system. For the chromatography analytical TLC plates (Alugram Sil G/UV_{254}) and 70–230 mesh silica gel 60 (E. M. Merck) were used. Mps 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.

The pyrazinones 4a–c

The preparative method for the pyrazinones **4a–c** together with the analytical data for **4a** have been reported previously.[9,23]

1,6-Dibenzyl-3,5-dichloropyrazin-2(1*H*)-one 4b (73%), mp 151 °C (from EtOH) (Found: M^+, 344.0482. $C_{18}H_{14}Cl_2N_2O$ requires M^+, 344.0483); ν_{max}/cm^{-1} 1668 (CO) and 1567 (C=N); $\delta_H(CDCl_3)$ 7.40–7.08 (10 H, m, ArH), 5.17 (2 H, s, CH_2Ph) and 4.10 (2 H, s, CH_2Ph); *m/z* 344 (M^+, 9%), 309 (3) and 91 (100).

1-Benzyl-3,5-dichloro-6-isobutylpyrazin-2(1*H*)-one 4c (76%), mp 114 °C (from EtOH) (Found: M^+, 310.0621. $C_{15}H_{16}Cl_2N_2O$ requires M^+, 310.0637); ν_{max}/cm^{-1} 1670 (CO) and 1564 (C=N); $\delta_H(CDCl_3)$ 7.38–7.08 (5 H, m, ArH), 5.35 (2 H, s, CH_2Ph), 2.68 (2 H, d, *J* 11, CH_2), 2.19 (1 H, m, CH) and 1.03 (6 H, d, *J* 11, CH_3); *m/z* 310 (M^+, 13%), 219 (3) and 91 (100).

5-Chloro-3-methoxy-6-methyl-1-phenylpyrazin-2(1*H*)-one 5a. The pyrazinone **4a** was treated as described in previous work [10] to yield compound **5a** (96%), mp 174 °C (from EtOH) (Found: M^+, 250.0522. $C_{12}H_{11}ClN_2O_2$ requires M^+, 250.0522); ν_{max}/cm^{-1} 1680 (CO) and 1600 (C=N); $\delta_H(CDCl_3)$ 7.42–7.11 (5 H, m, ArH), 4.01 (3 H, s, OCH_3) and 1.98 (3 H, s, CH_3); *m/z* 250 (M^+, 81%), 222 (8) and 118 (100).

3-Benzyl-5-chloro-6-methyl-1-phenylpyrazin-2(1*H*)-one 5b. A mixture of the pyrazinone **5g** (9 g, 20 mmol) and benzyl bromide (2.85 cm^3, 24 mmol) was heated in toluene (200 cm^3) at 110 °C for 2 days in the presence of $[Pd(PPh_3)_4]$ (230 mg, 0.2 mmol). After evaporation of the mixture, the residue was dissolved in ethyl acetate (200 cm^3) and stirred at room temperature (RT) with an excess of potassium fluoride during 12 h. Filtration, evaporation of the filtrate and purification of the crude product on a silica gel column using dichloromethane as eluent afforded **5b** (3.41 g, 55%), mp 97–98 °C (from EtOH) (Found: M^+, 310.0875. $C_{18}H_{15}ClN_2O$ requires M^+, 310.0873); ν_{max}/cm^{-1} 1653 (CO) and 1576 (C=N); $\delta_H(CDCl_3)$ 7.59–7.10 (10 H, m, ArH), 4.10 (2 H, s, CH_2Ph) and 2.03 (3 H, s, CH_3); *m/z* 310 (M^+, 55%), 281 (28) and 77 (100).

3-Phenyl-substituted pyrazin-2(1*H*)-ones 5c–e

General Procedure. A mixture of the pyrazinone **4a** (**4b** or **4c**) (40 mmol) and tetraphenylstannane (20.5 g, 48 mmol) was stirred in toluene (200 cm^3) at 110 °C during 3 days in the presence of $[Pd(PPh_3)_4]$ (230 mg, 0.2 mmol). After evaporation of the mixture the residue was dissolved in EtOAc and the solution stirred for 12 h at RT with an excess of KF. The mixture was filtered and evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel using 15–5% hexane–CH_2Cl_2 mixtures as eluent to afford the following pyrazinones.

5-Chloro-6-methyl-1,3-diphenylpyrazin-2(1*H*)-one 5c (10.3 g, 87%), mp 165 °C (from EtOH) (Found: M^+, 296.0722. $C_{17}H_{13}ClN_2O$ requires M^+, 296.0716); ν_{max}/cm^{-1} 1665 (CO) and 1600 (C=N); $\delta_H(CDCl_3)$ 8.49–7.28 (10 H, m, ArH) and 2.14 (3 H, s, CH_3); *m/z* 296 (M^+, 96%), 268 (65) and 77 (100).

1,6-Dibenzyl-5-chloro-3-phenylpyrazin-2(1*H*)-one 5d (13.1 g, 85%), mp 172 °C (from EtOH) (Found: M^+, 386.1190. $C_{24}H_{19}ClN_2O$ requires M^+, 386.1186); ν_{max}/cm^{-1} 1651 (CO) and 1560 (C=N); $\delta_H(CDCl_3)$ 8.54–7.18 (15 H, m, ArH), 5.29 (2 H, s, CH_2Ph) and 4.20 (2 H, s, CH_2Ph); *m/z* 386 (M^+, 48%), 351 (7), 295 (82) and 91 (100).

1-Benzyl-5-chloro-6-isobutyl-3-phenylpyrazin-2(1*H*)-one 5e. (11.5 g, 82%), mp 112 °C (from EtOH) (Found: M^+, 352.1366. $C_{21}H_{21}ClN_2O$ requires M^+, 352.1342); ν_{max}/cm^{-1} 1650 (CO) and 1555 (C=N); $\delta_H(CDCl_3)$ 8.46–7.09 (10 H, m, ArH), 5.39 (2 H, s, CH_2Ph), 2.70 (2 H, d, *J* 9, CH_2), 2.10 (1 H, m, CH) and 1.03 (6 H, d, *J* 9, CH_3); *m/z* 352 (M^+, 14%), 261 (12) and 91 (100).

5-Chloro-6-methyl-1-phenylpyrazin-2(1*H*)-one 5f. A solution of the pyrazinone **4a** (762 mg, 3 mmol), sodium formate (306 mg, 4.5 mmol) and $[Pd(PPh_3)_4]$ (36 mg, 0.03 mmol) in DMF (30 cm^3) was stirred at 110 °C for 3 h. The mixture was then evaporated and the residue treated with water and extracted with CH_2Cl_2 (3 × 50 cm^3). Work-up followed by chromatography on silica gel with 20% EtOAc–CH_2Cl_2 as eluent yielded **5f** (512 mg, 79%), mp 169–170 °C (from EtOH) (Found: M^+, 220.0401. $C_{11}H_9ClN_2O$ requires M^+, 220.0403); ν_{max}/cm^{-1} 1698 (CO) and 1602 (C=N); $\delta_H(CDCl_3)$ 8.00 (1 H, s, 3-H), 7.63–7.22 (5 H, m, Ar-H) and 2.13 (3 H, s, CH_3); *m/z* 220 (M^+, 24%), 192 (28) and 77 (100).

5-Chloro-6-methyl-1-phenyl-3-tributylstannylpyrazin-2(1*H*)-one 5g. Reaction of the pyrazinone **4a** (6.35 g, 25 mmol) with tetrabutyldistannane (16 g, 27 mmol) and $[Pd(PPh_3)_4]$ (288 mg, 0.25 mmol) as described above for compounds **5b–c** afforded the 3-tributylstannylpyrazinone **5g** (10.8 g, 85%) as an oil (Found: $M^+ - C_4H_9$, 453.0757. $C_{23}H_{35}ClN_2OSn - C_4H_9$ requires $M^+ - C_4H_9$, 453.0756); ν_{max}(neat)/cm^{-1} 1645 (CO) and 1558 (C=N); δ_H($CDCl_3$) 7.52–7.08 (5 H, m, ArH), 2.00 (3 H, s, CH_3), 1.59 (6 H, t, *J* 7, CH_2), 1.30 (6 H, m, CH_2), 1.15 (6 H, m, CH_2) and 0.87 (9 H, t, *J* 7, CH_3); δ_C($CDCl_3$) 177.8 (C-3), 157.9 (CO), 137.0–127.0 (Ar-C), 131.9 (C-6), 128.6 (C-5), 28.7/26.9 (CH_2), 17.4 (CH_3-pyr), 13.4 (CH_2) and 10.1 (CH_3); *m/z* 453 ($M^+ - C_4H_9$, 84%), 396 (7), 339 (65) and 77 (100).

6-Bromoalkylpyrazin-2(1*H*)-ones 6a–f

General procedure for 6a–f. A solution of the pyrazin-2(1*H*)-one **5a** (**5b–f**) (25 mmol) and NBS (5.34 g, 30 mmol) in dry CCl_4 (250 cm^3) was refluxed for 3–5 h (1 day for **5d, e**) in the presence of a catalytic amount of benzoyl peroxide. After cooling, the reaction mixture was filtered to remove the succinimide crystals and the filtrate was evaporated. The product was purified by column chromatography using CH_2Cl_2 as eluent.

6-Bromomethyl-5-chloro-3-methoxy-1-phenylpyrazin-2(1*H*)-one 6a (7.9 g, 96%), mp 175 °C (from EtOH) (Found: M^+, 327.9619. $C_{12}H_{10}BrClN_2O_2$ requires M^+, 327.9614); ν_{max}/cm^{-1} 1680 (CO) and 1590 (C=N); δ_H($CDCl_3$) 7.51–7.28 (5 H, m, ArH), 4.12 (3 H, s, OCH_3) and 4.06 (2 H, s, CH_2Br); *m/z* 328 (M^+, 9%), 293 (6), 249 (100) and 77 (39).

3-Benzyl-6-bromomethyl-5-chloro-1-phenylpyrazin-2(1*H*)-one 6b (6.3 g, 71%), an unstable oil; ν_{max}(neat)/cm^{-1} 1660 (CO) and 1555 (C=N); δ_H($CDCl_3$) 7.60–7.18 (10 H, m, ArH), 4.12 (2 H, s, CH_2Ph) and 4.08 (2 H, s, CH_2Br); *m/z* 353 (M^+ – Cl, 1%), 309 (88) and 77 (100).

6-Bromomethyl-5-chloro-1,3-diphenylpyrazin-2(1*H*)-one 6c (8.9 g, 95%), mp 161 °C (from EtOH) (Found: M^+, 373.9843. $C_{17}H_{12}BrClN_2O$ requires M^+, 373.9822); ν_{max}/cm^{-1} 1660 (CO) and 1555 (C=N); δ_H($CDCl_3$) 8.54–7.71 (10 H, m, ArH) and 4.15 (2 H, s, CH_2Br); *m/z* 374 (M^+, 23%), 295 (100) and 77 (49).

1-Benzyl-6-bromobenzyl-5-chloro-3-phenylpyrazin-2(1*H*)-one 6d (5.9 g, 63%), mp 108–109 °C (from EtOH) (Found: M^+, 464.0290. $C_{24}H_{18}BrClN_2O$ requires M^+, 464.0291); ν_{max}/cm^{-1} 1660 (CO) and 1540 (C=N); the signals in the ^{1}H NMR spectrum are broadened because of the hindered rotation of the substituents in position 1 and 6; δ_H($CDCl_3$) 8.48–6.67 (15 H, m, ArH), 5.29 (1 H, s, CHBr) and 5.18 (2 H, 2 × d br, CH_2Ph); *m/z* 464 (M^+, 1%), 385 (100) and 91 (6).

1-Benzyl-6-(1-bromoisobutyl)-5-chloro-3-phenylpyrazin-2(1*H*)-one 6e (7.3 g, 68%), mp 139–140 °C (from EtOH) (Found: C, 58.6; H, 4.65; N, 6.4. $C_{21}H_{20}BrClN_2O$ requires C, 58.42; H, 4.67; N, 6.49%); ν_{max}/cm^{-1} 1655 (CO) and 1550 (C=N); in the ^{1}H spectrum two conformations (rotamers) of the product can be observed due to the hindered rotation. Rotamer 1 (60%): δ_H($CDCl_3$) 8.50–7.02 (10 H, m, ArH), 6.10/4.86 (2 H, 2 × d, *J* 16, CH_2Ph), 4.70 (1 H, d, *J* 10, 1 H, CHBr), 3.02 (1 H, m, CH) and 0.99/0.40 (6 H, 2 × d, *J* 8, CH_3); Rotamer 2 (40%): δ_H($CDCl_3$) 8.50–7.02 (10 H, m, ArH), 5.78/5.59 (2 H, 2 × d, *J* 16, CH_2Ph), 5.46 (1 H, d, *J* 10, CHBr), 2.26 (1 H, m, CH) and 1.20/0.90 (6 H, 2 × d, *J* 8, CH_3); *m/z* 430 (M^+, 3%), 351 (10) and 91 (100).

6-Bromomethyl-5-chloro-1-phenylpyrazin-2(1*H*)-one 6f (6.8 g, 91%), mp 147–148 °C (from EtOH) (Found: M^+, 297.9519. $C_{11}H_8BrClN_2O$ requires M^+, 297.9509); ν_{max}/cm^{-1} 1673 (CO) and 1566 (C=N); δ_H($CDCl_3$) 8.09 (1 H, s, 3-H), 7.62–7.27 (5 H, m, ArH) and 4.12 (2 H, s, CH_2Br); *m/z* 298 (M^+, 17%), 219 (4) and 77 (100).

6-Bromomethyl-1,3-diphenylpyrazin-2(1*H*)-one 6g. By the same procedure as described above the 6-methyl-1,3-diphenylpyrazin-2(1*H*)-one (5.24 g, 20 mmol), obtained by dehalogenation[10] of **5c**, afforded **6g** (5.44 g, 80%), mp 210 °C (from EtOH) (Found: M^+, 340.0211. $C_{17}H_{13}BrN_2O$ requires M^+, 340.0211); ν_{max}/cm^{-1} 1660 (CO) and 1575 (C=N); δ_H($CDCl_3$) 8.39–7.38 (5 H, m, ArH), 7.66 (1 H, s, 5-H) and 4.05 (2 H, s, CH_2Br); *m/z* 340 (M^+, 25%), 261 (100) and 77 (59).

5-Chloro-6-alkylidene/benzylidene-3,6-dihydropyrazin-2(1*H*)-ones 7a–e

General procedure for 7a–e. To a mixture of the pyrazin-2(1*H*)-one **6a** (or **6b–e**) (2 mmol) and methanol (0.09 cm^3, 2.2 mmol) in THF (30 cm^3) was added sodium hydride (80% dispersion in mineral oil; 66 mg, 2.2 mmol) in small portions. After the mixture had been stirred for 0.5–1 h at RT the precipitate was filtered off and washed with EtOAc; the combined filtrate and washings were then evaporated and the crude product(s) purified by column chromatography on silica gel eluting with 5% EtOAc–CH_2Cl_2.

5-Chloro-3,3-dimethoxy-6-methylidene-1-phenyl-3,6-dihydropyrazin-2(1*H*)-one 7a (381 mg, 68%), mp 133–134 °C (from CH_2Cl_2–hexane) (Found: M^+, 280.0610. $C_{13}H_{13}ClN_2O_3$ requires M^+, 280.0615); ν_{max}/cm^{-1}: 1710 (CO), 1650 (=CH_2) and 1610 (C=N); δ_H($CDCl_3$) 7.40–7.05 (5 H, m, ArH), 5.45 (1 H, d, *J* 2.7, =CH), 4.57 (1 H, d, *J* 2.7, =CH) and 3.42 (6 H, s, OCH_3); δ_C($CDCl_3$) 160.1 (CO), 152.6 (C-5), 137.3 (C-6), 136.0–128.0 (Ar-C), 108.0 (=CH_2), 99.6 (C-3) and 50.5 (OCH_3); *m/z* 280 (M^+, 32%), 249 (44), 221 (100) and 77 (77).

3-Benzyl-5-chloro-3-methoxy-6-methylidene-1-phenyl-3,6-dihydropyrazin-2(1*H*)-one 7b (428 mg, 63%), mp 137–138 °C (from CH_2Cl_2–hexane) (Found: M^+, 340.0981. $C_{19}H_{17}ClN_2O_2$ requires M^+, 340.0979); ν_{max}/cm^{-1} 1690 (CO), 1645 (=CH_2) and 1608 (C=N); δ_H($CDCl_3$) 7.45–6.77 (10 H, m, ArH), 5.08 (1 H, d, *J* 2.7, =CH), 4.09 (1 H, d, *J* 2.7, =CH), 3.40 (3 H, s, OCH_3) and 3.44/3.27 (2 H, 2 × d, *J* 13, CH_2Ph); δ_C($CDCl_3$) 164.1 (CO), 149.9 (C-5), 133.1 (C-6), 136.8–127.6 (ArC), 106.3 (=CH_2), 93.4 (C-3), 52.8 (OCH_3) and 46.5 (CH_2Ph); *m/z* 340 (M^+, 17%), 305 (7), 249 (38) and 91 (100).

5-Chloro-3-methoxy-6-methylidene-1,3-diphenyl-3,6-dihydropyrazin-2(1*H*)-one 7c (450 mg, 69%), an oil (Found: M^+, 326.0821. $C_{18}H_{15}ClN_2O_2$ requires M^+, 326.0822); ν_{max}(neat)/cm^{-1} 1710 (CO), 1650 (=CH_2) and 1610 (C=N); δ_H($CDCl_3$) 7.29–6.94 (10 H, m, ArH), 5.53 (1 H, d, *J* 2.5, =CH), 4.60 (1 H, d, *J* 2.5, =CH) and 3.49 (3 H, s, OCH_3); δ_C($CDCl_3$) 164.1 (CO), 150.0 (C-5), 138.0 (C-6), 137.5–125.9 (Ar–C), 107.0 (=CH_2), 91.7 (C-3) and 52.3 (OCH_3); *m/z* 326 (M^+, 18%), 267 (6), 105 (100) and 77 (77).

(*Z*)-1-Benzyl-6-benzylidene-5-chloro-3-methoxy-3-phenyl-3,6-dihydropyrazin-2(1*H*)-one 7d (690 mg, 83%), an oil (Found: M^+, 416.1297. $C_{25}H_{21}ClN_2O_2$ requires M^+, 416.1292); ν_{max}(neat)/cm^{-1} 1693 (CO) and 1619 (C=N); δ_H($CDCl_3$) 7.54–6.78 (15 H, m, ArH), 6.81 (1 H, s, =CHPh), 5.38/3.86 (2 H, 2 × d, *J* 16, CH_2Ph), 3.45 (3 H, s, OCH_3); δ_C($CDCl_3$) 166.8 (CO), 153.2 (C-5), 136.3–126.2 (ArC), 129.5 (C-6), 122.3 (=CHPh), 92.6 (C-3), 52.1 (OCH_3) and 47.2 (CH_2Ph); *m/z* 416 (M^+, 37%), 325 (41) and 105 (100).

(*E*)-1-Benzyl-5-chloro-6-isobutylidene-3-methoxy-3-phenyl-3,6-dihydropyrazin-2(1*H*)-one 7e (619 mg, 81%), an oil (Found: M^+, 382.1444. $C_{22}H_{23}ClN_2O_2$ requires M^+, 382.1448); ν_{max}(neat)/cm^{-1} 1685 (CO) and 1630 (C=N); δ_H($CDCl_3$) 7.45–6.79 (10 H, m, ArH), 5.10 (1 H, d, *J* 10, =CHPr^i), 4.89 (2 H, s, CH_2Ph), 3.45 (3 H, s, OCH_3), 3.32 (1 H, m, CH) and 0.92/0.77 (6 H, 2 × d, *J* 6, CH_3); δ_C($CDCl_3$) 164.9 (CO), 150.6 (C-5), 135.7–126.3 (ArC), 132.2 (=CHPr^i), 128.0 (C-6), 92.5 (C-3), 52.0 (OCH_3), 47.2 (CH_2Ph), 27.2 (CH) and 22.7/22.2 (CH_3); *m/z* 382 (M^+, 6%), 347 (2), 291 (5) and 91 (100).

5-Methoxy-6-alkylidene/benzylidene-3,6-dihydropyrazin-2(1*H*)-ones 8a–e

General procedure for 8a–e. To a solution of pyrazin-2(1*H*)-one **6a** (**6b–e**) (2 mmol) and methanol (0.17 cm^3, 4.2 mmol) in THF (50 cm^3) was added sodium hydride (80% dispersion in

mineral oil; 126 mg, 4.2 mmol). After being stirred for 1 h at RT the mixture was filtered to remove the precipitate which was then washed with EtOAc. The crude product, obtained after evaporation, was purified by column chromatography on silica gel. Elution with 10% EtOAc–CH_2Cl_2 afforded **8a–e**. Compounds **8a–e** could also be obtained by treating **7a–e** with alkoxide (1.1 equiv.) in THF.

3,3,5-Trimethoxy-6-methylidene-1-phenyl-3,6-dihydropyrazin-2(1*H*)-one 8a (310 mg, 88%), an oil (Found: M^+, 276.1116. $C_{14}H_{16}N_2O_4$ requires M^+, 276.1110); ν_{max}(neat)/cm^{-1} 1710 (CO), 1670 (=CH_2) and 1620 (C=N); δ_H($CDCl_3$) 7.49–7.13 (5 H, m, ArH), 5.30 (1 H, d, *J* 2, =CH), 4.37 (1 H, d, *J* 2, =CH), 3.92 (3 H, s, OCH_3) and 3.50 (6 H, s, OCH_3); δ_C($CDCl_3$) 161.5 (CO), 157.2 (C-5), 136.0 (C-6), 134.4–128.2 (ArC), 101.6 (=CH_2), 99.3 (C-3) and 53.8/50.1 (OCH_3); *m/z* 276 (M^+, 2%), 248 (90), 217 (100), 77 (74).

3-Benzyl-3,5-dimethoxy-6-methylidene-1-phenyl-3,6-dihydropyrazin-2(1*H*)-one 8b (578 mg, 86%), mp 110 °C (from CH_2Cl_2–hexane) (Found: M^+, 336.1470. $C_{20}H_{20}N_2O_3$ requires M^+, 336.1474); ν_{max}/cm^{-1} 1700 (CO), 1680 (=CH_2) and 1610 (C=N); δ_H($CDCl_3$) 7.47–6.80 (10 H, m, ArH), 4.88 (1 H, d, *J* 2, =CH), 3.95 (3 H, s, OCH_3), 3.86 (1 H, d, *J* 2, =CH), 3.48/3.19 (2 H, 2 × d, *J* 12, CH_2Ph) and 3.35 (6 H, s, OCH_3); δ_C($CDCl_3$) 165.7 (CO), 155.5 (C-5), 134.2 (C-6), 136.4–127.3 (ArC), 99.9 (=CH_2), 90.6 (C-3), 53.9/51.7 (OCH_3) and 47.3 (CH_2Ph); *m/z* 336 (M^+, 3%), 245 (48) and 91 (100).

3,5-Dimethoxy-6-methylidene-1,3-diphenyl-3,6-dihydropyrazin-2(1*H*)-one 8c (586 mg, 91%), mp 105 °C (from CH_2Cl_2–hexane) (Found: M^+, 322.1318. $C_{19}H_{18}N_2O_3$ requires M^+, 322.1317); ν_{max}/cm^{-1} 1710 (CO), 1680 (=CH_2) and 1620 (C=N); δ_H($CDCl_3$) 7.66–7.09 (10 H, m, ArH), 5.31 (1 H, d, *J* 2, =CH), 4.30 (1 H, d, *J* 2, =CH), 4.01 (3 H, s, OCH_3) and 3.45 (3 H, s, OCH_3); δ_C($CDCl_3$) 165.6 (CO), 155.6 (C-5), 139.6 (C-6), 135.0–126.0 (ArC), 100.5 (=CH_2), 89.0 (C-3) and 54.0/51.4 (OCH_3); *m/z* 322 (M^+, 9%), 294 (23), 263 (100) and 77 (62).

(*Z*)-1-Benzyl-6-benzylidene-3,5-dimethoxy-3-phenyl-3,6-dihydropyrazin-2(1*H*)-one 8d (741 mg, 90%), mp 94 °C (from CH_2Cl_2–hexane) (Found: C, 75.9; H, 5.9; N, 6.6. $C_{26}H_{24}N_2O_3$ requires C, 75.71; H, 5.86; N, 6.79%); ν_{max}/cm^{-1} 1686 (CO) and 1627 (C=N); δ_H($CDCl_3$) 7.55–6.79 (15 H, m, ArH), 6.65 (1 H, s, =CHPh), 5.31/3.95 (2 H, 2 × d, *J* 14, CH_2Ph), 3.98 (3 H, s, OCH_3) and 3.40 (3 H, s, OCH_3); δ_C($CDCl_3$) 168.6 (CO), 159.9 (C-5), 138.5–126.2 (ArC), 126.5 (C-6), 118.1 (=CHPh), 89.4 (C-3), 54.4/51.3 (OCH_3) and 46.8 (CH_2Ph); *m/z* 412 (M^+, 2%), 397 (23) and 105 (100).

(*Z*)-1-Benzyl-6-isobutylidene-3,5-dimethoxy-3-phenyl-3,6-dihydropyrazin-2(1*H*)-one 8e (590 mg, 78%), mp 98 °C (from CH_2Cl_2–hexane) (Found: C, 73.2; H, 7.1; N, 7.3. $C_{23}H_{26}N_2O_3$ requires C, 72.99; H, 6.92; N, 7.40%); ν_{max}/cm^{-1} 1695 (CO) and 1640 (C=N); δ_H($CDCl_3$) 7.55–6.79 (10 H, m, ArH), 5.51 (1 H, d, *J* 12, =CHPr^i), 4.99/4.79 (2 H, 2 × d, *J* 15, CH_2Ph), 3.97 (3 H, s, OCH_3), 3.39 (3 H, s, OCH_3), 2.40 (1 H, m, CH) and 0.92/0.61 (6 H, 2 × d, *J* 10, CH_3); δ_C($CDCl_3$) 167.9 (CO), 159.8 (C-5), 138.3–126.1 (Ar-C), 128.2 (C-6), 127.9 (=CHPr^i), 89.1 (C-3), 54.2/51.2 (OCH_3), 49.4 (CH_2Ph), 26.4 (CH) and 22.3/22.1 (CH_3); *m/z* 378 (M^+, 2%), 363 (38), 287 (10) and 105 (100).

3-Methoxy-6-methylidene-1,3-diphenyl-3,6-dihydropyrazin-2(1*H*)-ones 9. By the same method as described for the synthesis of **7a–e**, sodium hydride (80% dispersion in mineral oil; 30 mg, 1 mmol, 1 equiv.) was added to **6g** (340 mg, 1 mmol) to give compound **9** (187 mg, 64%) as an oil (Found: M^+, 292.1209. $C_{18}H_{16}N_2O_2$ requires M^+, 292.1212); ν_{max}/cm^{-1} 1690 (CO), 1660 (=CH_2) and 1590 (C=N); δ_H($CDCl_3$) 8.45–7.30 (11 H, m, ArH + 5-H), 4.85 (1 H, d, *J* 2.3, =CH), 4.52 (1 H, d, *J* 2.3, =CH) and 3.49 (3 H, s, OCH_3); *m/z* 292 (M^+, 19%), 233 (29) and 77 (100).

Compound **6f** (298 mg, 1 mmol) was treated in the same way as **6g** to afford compound **5a** (220 mg, 88%).

6-Methoxymethylpyrazin-2(1*H*)-ones 10a,b

General procedure for 10a,b. To a solution of pyrazin-2(1*H*)-one **6a** (or **6c**) (2 mmol) in methanol (20 cm^3) was added a solution of sodium hydride (80% dispersion in mineral oil; 66 mg, 2.2 mmol) in methanol (10 cm^3). After being stirred for 0.5–1 h at RT the mixture was poured into water and extracted with CH_2Cl_2 (3 × 20 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated to give the crude product which was purified by column chromatography on silica gel eluting with 5% EtOAc–CH_2Cl_2.

5-Chloro-3-methoxy-6-methoxymethyl-1-phenylpyrazin-2(1*H*)-one 10a (420 mg, 75%), mp 134 °C (from EtOH) (Found: M^+, 280.0615. $C_{13}H_{13}ClN_2O_3$ requires M^+, 280.0614); ν_{max}/cm^{-1} 1675 (CO) and 1600 (C=N); δ_H($CDCl_3$) 7.53–7.24 (5 H, m, ArH), 4.04 (5 H, s, OCH_3 + CH_2O) and 3.09 (3 H, s, OCH_3); *m/z* 280 (M^+, 100%), 249 (43) and 77 (66).

5-Chloro-6-methoxymethyl-1,3-diphenylpyrazin-2(1*H*)-one 10b (626 mg, 96%), mp 141 °C (from EtOH) (Found: M^+, 326.0817. $C_{18}H_{15}ClN_2O_2$ requires M^+, 326.0822); ν_{max}/cm^{-1} 1670 (CO) and 1560 (C=N); δ_H($CDCl_3$) 8.41–7.26 (10 H, m, ArH), 4.12 (2 H, s, CH_2O) and 3.12 (3 H, s, OCH_3); *m/z* 326 (M^+, 73%), 295 (5) and 77 (100).

5-Chloro-6-diethylaminomethyl-3-methoxy-1-phenylpyrazin-2(1*H*)-one 11a. Compound **6a** (492 mg, 1.5 mmol) was stirred for 3 h with diethylamine (0.31 cm^3, 3 mmol) in THF (20 cm^3) at RT and then filtered. Evaporation of the filtrate and chromatography of the crude product on a silica gel column (5% EtOAc–CH_2Cl_2 as eluent) gave the title compound **11a** (457 mg, 95%), mp 134 °C (from EtOH) (Found: M^+, 321.1242. $C_{16}H_{20}ClN_3O_2$ requires M^+, 321.1244); ν_{max}/cm^{-1} 1680 (CO) and 1600 (C=N); δ_H($CDCl_3$) 7.42–7.19 (5 H, m, ArH), 4.02 (3 H, s, OCH_3), 3.30 (2 H, s, CH_2), 2.20 (4 H, q, *J* 7, CH_2) and 0.70 (6 H, t, *J* 7, CH_3); *m/z* 321 (M^+, 22%) and 249 (100).

Treatment of **7a** (280 mg, 1 mmol) with diethylamine (0.31 cm^3, 3 mmol) in THF (10 cm^3) afforded **11a** (302 mg, 94%) under similar conditions.

5-Chloro-6-cyanomethyl-3-methoxy-1-phenylpyrazin-2(1*H*)-one 11b. A mixture of pyrazin-2(1*H*)-one **6a** (327 mg, 1 mmol), potassium cyanide (13 mg, 2 mmol) and a catalytic amount of 18-crown-6 in THF (20 cm^3) was stirred for 4 h at RT. The mixture was then diluted with water (50 cm^3) and extracted CH_2Cl_2 (3 × 25 cm^3). The combined extracts were dried ($MgSO_4$), evaporated and the residue was purified on silica gel plates (5% EtOAc–CH_2Cl_2 as eluent) to give the title compound **11b** (157 mg, 57%), mp 212 °C (from EtOH) (Found: M^+, 275.0467. $C_{13}H_{10}ClN_3O_2$ requires M^+, 275.0461); ν_{max}/cm^{-1} 2260 (C≡N), 1680 (CO) and 1590 (C=N); δ_H($CDCl_3$) 7.59–7.27 (5 H, m, ArH), 4.07 (3 H, s, OCH_3) and 3.42 (2 H, s, CH_2); *m/z* 275 (M^+, 100%) and 77 (81).

6-(1-Azido-2-methylpropyl)-1-benzyl-5-chloro-3-phenylpyrazin-2(1*H*)-one 11c. A mixture of compound **6e** (382 mg, 1 mmol) and sodium azide (195 mg, 3 mmol) in DMF (30 cm^3) was stirred at 60 °C for 5 h. The mixture was then diluted with water (50 cm^3) and extracted with CH_2Cl_2 (3 × 25 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated and the residue purified on silica gel plates (5% EtOAc–CH_2Cl_2 as eluent) to give the title compound **11e** (244 mg, 62%) as an oil (Found: M^+, 393.1355. $C_{21}H_{20}ClN_5O$ requires M^+, 393.1356); ν_{max}(neat)/cm^{-1} 2100 (N_3), 1661 (CO) and 1546 (C=N); some of the signals in the NMR spectrum are broadened because of the hindered rotation between substituents in the 1 and 6-positions; δ_H($CDCl_3$) 8.47–7.01 (10 H, m, ArH), 5.54/5.43 (2 H, 2 × d, *J* 12, CH_2Ph), 4.92 (1 H, d, *J* 12, CHN_3), 2.04 (1 H, m, CH) and 1.12/0.80 (6 H, 2 × d, *J* 8, CH_3); *m/z* 393 (M^+, 3%), 351 (1) and 91 (100).

Piperazine-2,5-diones 12a–d and 13a–d

Method 1. To a solution of **7b** (**7c–e**) (1 mmol) in dioxane (10 cm^3) was added 1 mol dm^{-3} aqueous sodium hydroxide (10 cm^3). After being stirred for 12 h at RT the mixture was

concentrated, diluted with water and extracted with CH_2Cl_2 (3 × 15 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated to afford the crude compound **13** that was purified on silica gel preparative plates (eluent 50% EtOAc–CH_2Cl_2).

Method 2. To a solution of **8b** (**8c–e**) (1 mmol) in THF (12 cm^3) was added 1 mol dm^{-3} aqueous hydrochloric acid (4 cm^3). After being stirred for 1–2 days at RT the solution was treated with saturated aqueous sodium carbonate (pH *ca.* 10) and further stirred for 30 min. The mixture was extracted with CH_2Cl_2 (3 × 15 cm^3) and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography of the residue on silica gel preparative plates (eluent 50% EtOAc–CH_2Cl_2) afforded compounds **12** and **13**.

3-Benzyl-3-methoxy-6-methylidene-1-phenylpiperazine-2,5-dione 12a (71 mg, 22%; method 2), mp 59–61 °C (from CH_2Cl_2–hexane) (Found: M^+, 322.1301. $C_{19}H_{18}N_2O_3$ requires M^+, 322.1317); ν_{max}/cm^{-1} 1693, 1618 (CO) and 1655 (=CH_2); $\delta_H(CDCl_3)$ 7.51–6.93 (10 H, m, ArH), 6.20 (1 H, br s, NH), 5.59 (1 H, d, *J* 1, =CH), 4.22 (1 H, d, *J* 1, =CH), 3.41 (3 H, s, OCH_3) and 3.40/3.20 (2 H, 2 × d, *J* 15, CH_2Ph); $\delta_C(CDCl_3)$ 163.0 (C-2), 159.0 (C-5), 137.3 (C-6), 136.5–127.9 (ArC), 106.6 (=CH_2), 88.1 (C-3), 51.7 (OCH_3) and 46.2 (CH_2Ph); *m/z* 322 (M^+, 1%), 231 (76) and 91 (100).

3-Methoxy-6-methylidene-1,3-diphenylpiperazine-2,5-dione 12b (80 mg, 26%; method 2), mp 163 °C (from CH_2Cl_2–hexane) (Found: C, 69.8; H, 5.15; N, 8.9. $C_{18}H_{16}N_2O_3$ requires C, 70.12; H, 5.23; N, 9.09%); ν_{max}/cm^{-1} 1698, 1618 (CO) and 1660 (=CH_2); $\delta_H(CDCl_3)$ 7.66–7.08 (10 H, m, ArH), 6.81 (1 H, br s, NH), 5.86 (1 H, d, *J* 2, =CH), 4.52 (1 H, d, *J* 2, =CH) and 3.52 (3 H, s, OCH_3); $\delta_C(CDCl_3)$ 162.2 (C-2), 159.7 (C-5), 138.7–126.2 (Ar-C), 137.7 (C-6), 106.8 (=CH_2), 88.1 (C-3), 51.8 (OCH_3); *m/z* 308 (M^+, 1%), 280 (19), 249 (19), 77 (100).

(*Z*)-1-Benzyl-6-benzylidene-3-methoxy-3-phenylpiperazine-2,5-dione 12c (151 mg, 38%; method 2), mp 150–151 °C (from CH_2Cl_2–hexane) (Found: C, 75.2; H, 5.5; N, 6.9. $C_{25}H_{22}N_2O_3$ requires C, 75.36; H, 5.57; N, 7.03%); ν_{max}/cm^{-1} 1690 and 1623 (CO); $\delta_H(CDCl_3)$ 7.58–6.87 (16 H, m, ArH + NH), 7.21 (1 H, s, =CHPh), 4.61/4.70 (2 H, 2 × d, *J* 14, CH_2Ph) and 3.35 (s, 3 H, OCH_3); $\delta_C(CDCl_3)$ 165.5 (C-2), 165.1 (C-5), 136.8–126.4 (Ar-C), 129.3 (C-6), 123.2 (=CHPh), 87.8 (C-3), 51.8 (OCH_3) and 48.2 (CH_2Ph); *m/z* 398 (M^+, 3%), 366 (7) and 91 (100).

(*Z*)-1-Benzyl-6-isobutylidene-3-methoxy-3-phenylpiperazine-2,5-dione 12d (160 mg, 44%; method 2), mp 72–73 °C (from CH_2Cl_2–hexane) (Found: C, 72.9; H, 6.8; N, 7.7. $C_{22}H_{24}N_2O_3$ requires C, 72.51; H, 6.64; N, 7.69%); ν_{max}/cm^{-1} 1693 and 1635 (CO); $\delta_H(CDCl_3)$ 7.53–7.03 (11 H, m, ArH + NH), 6.10 (1 H, d, *J* 11, =CHPr^i), 4.99/4.87 (2 H, 2 × d, *J* 14, CH_2Ph), 3.34 (3 H, s, OCH_3), 2.59 (1 H, m, CH) and 1.00/0.86 (6 H, 2 × d, *J* 10, CH_3); $\delta_C(CDCl_3)$ 164.8 (C-2 + C-5), 137.1–126.4 (ArC), 133.6 (=CHPr^i), 128.7 (C-6), 87.5 (C-3), 51.9 (OCH_3), 50.5 (CH_2Ph), 27.1 (CH) and 22.2 (CH_3); *m/z* 364 (M^+, 3%), 349 (5) and 91 (100).

3-Benzyl-3-hydroxy-6-methylidene-1-phenylpiperazine-2,5-dione 13a (249 mg, 81%; method 1), mp 167 °C (from CH_2Cl_2–hexane) (Found: M^+, 308.1158. $C_{18}H_{16}N_2O_3$ requires M^+, 308.1161); ν_{max}/cm^{-1} 1690, 1616 (CO) and 1665 (=CH_2); $\delta_H([^2H_6]$-DMSO) 9.25 (1 H, br s, NH), 7.52–6.82 (10 H, m, ArH), 5.17 (1 H, d, *J* 2, =CH), 3.80 (1 H, d, *J* 2, =CH) and 3.35/2.97 (2 H, 2 × d, *J* 13, CH_2Ph); $\delta_C([^2H_6]$-DMSO) 164.8 (C-2), 157.3 (C-5), 138.4 (C-6), 137.0–126.9 (ArC), 102.1 (=CH_2), 82.9 (C-3) and 45.4 (CH_2Ph); *m/z* 308 (M^+, 1%), 290 (20), 217 (77) and 91 (100).

3-Hydroxy-6-methylidene-1,3-diphenylpiperazine-2,5-dione 13b (250 mg, 85%; method 1), mp 176 °C (from CH_2Cl_2–hexane) (Found: C, 69.0, H, 4.7; N, 9.2. $C_{17}H_{14}N_2O_3$ requires C, 69.38; H, 4.79; N, 9.52%); ν_{max}/cm^{-1} 1696, 1612 (CO) and 1658 (=CH_2); $\delta_H([^2H_6]$-DMSO) 9.50 (1 H, br s, NH), 7.61–7.17 (10 H, m, ArH), 5.53 (1 H, d, *J* 2, =CH) and 4.18 (1 H, d, *J* 2, =CH); $\delta_C([^2H_6]$-DMSO) 165.0 (C-2), 158.1 (C-5), 141.4–126.1 (ArC), 139.3 (C-6), 103.2 (=CH_2) and 82.4 (C-3); *m/z* 294 (M^+, 1%), 266 (19) and 77 (100).

(*Z*)-1-Benzyl-6-benzylidene-3-hydroxy-3-phenylpiperazine-2,5-dione 13c (330 mg, 86%; method 1), mp 179 °C (from CH_2Cl_2–hexane) (Found: C, 74.9; H, 5.2; N, 7.2. $C_{24}H_{20}N_2O_3$ requires C, 74.98; H, 5.24; N, 7.29%); ν_{max}/cm^{-1} 1684 and 1632 (CO); $\delta_H([^2H_6]$-DMSO) 7.55–6.87 (15 H, m, ArH), 7.17 (1 H, s, =CHPh), 5.38 (1 H, br s, NH) and 5.14/4.08 (2 H, 2 × d, *J* 15, CH_2Ph); $\delta_C([^2H_6]$-DMSO) 168.9 (C-2), 163.8 (C-5), 139.3–125.2 (ArC), 129.6 (C-6), 124.7 (=CHPh), 82.1 (C-3) and 48.1 (CH_2Ph); *m/z* 384 (M^+, 2%), 366 (6) and 91 (100).

(*Z*)-1-Benzyl-3-hydroxy-6-isobutylidene-3-phenylpiperazine-2,5-dione 13d (287 mg, 82%; method 1), mp 136 °C (from CH_2Cl_2–hexane) (Found: C, 72.2; H, 6.45; N, 7.9. $C_{21}H_{22}N_2O_3$ requires C, 71.98; H, 6.33; N, 7.99%); ν_{max}/cm^{-1} 1682 and 1636 (CO); $\delta_H([^2H_6]$-DMSO) 7.63–6.83 (10 H, m, ArH), 6.00 (1 H, d, *J* 11, =CHPr^i), 5.54 (1 H, br s, NH), 4.98/4.69 (2 H, 2 × d, *J* 15, CH_2Ph), 2.38 (1 H, m, CH) and 0.92/0.56 (6 H, 2 × d, *J* 8, CH_3); $\delta_H([^2H_6]$-DMSO) 168.5 (C-2), 164.3 (C-5), 139.2–125.5 (ArC), 135.3 (=CHPr^i), 129.7 (C-6), 82.0 (C-3), 51.0 (CH_2Ph), 26.9 (CH) and 21.8/21.5 (CH_3); *m/z* 350 (M^+, 2%), 332 (1) and 91 (100).

3,3-Dimethoxy-5-methyl-6-methylidene-1-phenyl-3,6-dihydropyrazin-2(1*H*)-one 14. Following the same procedure as that described for the synthesis of compounds **5c–e**, reaction of compound **7a** (140 mg, 0.5 mmol) with tetramethylstannane (107 mg, 0.6 mmol) afforded after 4 h the title compound **14** (88 mg, 68%, which was purified by column chromatography eluting with 10% EtOAc–CH_2Cl_2); mp 120–122 °C (from CH_2Cl_2–hexane) (Found: M^+, 260.1159. $C_{14}H_{16}N_2O_3$ requires M^+, 260.1161); ν_{max}/cm^{-1} 1703 (CO) and 1610 (C=N); $\delta_H(CDCl_3)$ 7.55–7.11 (5 H, m, ArH), 5.08 (1 H, d, *J* 2.2, =CH), 4.48 (1 H, d, *J* 2.2, =CH), 3.53 (6 H, s, OCH_3) and 2.40 (3 H, s, CH_3); $\delta_C(CDCl_3)$ 162.6 (C-5), 161.7 (CO), 139.5 (C-6), 136.3–128.5 (ArC), 104.1 (=CH_2), 98.3 (C-3), 50.4 (OCH_3) and 23.3 (CH_3); *m/z* 260 (M^+, 2%), 245 (90) and 77 (100).

(*Z*)-1-Benzyl-6-benzylidene-3-methoxy-3,5-diphenyl-3,6-dihydropyrazin-2(1*H*)-one 15. By the same procedure as described above, reaction of **7d** (208 mg, 0.5 mmol) with tetraphenylstannane (256 mg, 0.6 mmol) afforded after 6 h compound **15** (142 mg, 62%) as an oil (Found: M^+, 458.1984. $C_{31}H_{26}N_2O_2$ requires M^+, 458.1994); ν_{max}(neat)/cm^{-1} 1689 (CO) and 1628 (C=N); $\delta_H(CDCl_3)$ 7.58–6.73 (20 H, m, ArH), 6.10 (1 H, s, =CHPh), 5.62/3.78 (2 H, 2 × d, *J* 14, CH_2Ph) and 3.56 (3 H, s, OCH_3); $\delta_C(CDCl_3)$ 167.8 (CO), 167.0 (C-5), 136.8–126.7 (ArC), 131.9 (C-6), 123.3 (=CHPh), 92.1 (C-3), 51.8 (OCH_3) and 46.3 (CH_2Ph); *m/z* 458 (M^+, 2%), 443 (6) and 105 (100).

(*Z*)-1-Benzyl-6-benzylidene-3-methoxy-3-phenyl-5-propylamino-3,6-dihydropyrazin-2(1*H*)-one 16. A mixture of **7d** (416 mg, 1 mmol) and propylamine (0.25 cm^3, 3 mmol) in THF (10 cm^3) was stirred at RT for 15 h. The resulting precipitate was filtered off and the filtrate evaporated to give the crude product which was purified on silica gel plates (15% EtOAc–CH_2Cl_2 as eluent). This afforded compound **16** (257 mg, 60%) as an oil (Found: M^+, 439.2256. $C_{28}H_{29}N_3O_2$ requires M^+, 439.2260); ν_{max}(neat)/cm^{-1} 1705 (CO) and 1610 (C=N); $\delta_H(CDCl_3)$ 7.56–6.68 (15 H, m, ArH), 6.20 (1 H, s, =CHPh), 5.36/3.68 (2 H, 2 × d, *J* 13, CH_2Ph), 4.53 (1 H, br s, NH), 3.43 (3 H, s, OCH_3), 3.38 (2 H, m, $NHCH_2$), 1.65 (2 H, m, CH_2), 0.98 (3 H, t, *J* 8, CH_3); $\delta_C(CDCl_3)$ 169.9 (CO), 156.5 (C-5), 138.9–127.0 (Ar-C), 129.7 (C-6), 115.5 (=CHPh), 90.3 (C-3), 51.1 (OCH_3), 46.2 (CH_2Ph), 43.3 ($NHCH_2$), 22.4 (CH_2) and 11.5 (CH_3); *m/z* 439 (M^+, 2%), 424 (7) and 91 (100).

3,5-Dimethoxy-6-methoxymethyl-1-phenylpyrazin-2(1*H*)-one 17a. Compound **8a** (138 mg, 0.5 mmol) was converted into **17a** (73 mg, 53%), an oil, by the same procedure as described for the synthesis of compounds **10a,b** but with a period of 0.5 h under reflux in methanol (Found: M^+, 276.1113. $C_{14}H_{16}N_2O_4$

requires M^+, 276.1110); ν_{max}(neat)/cm^{-1} 1678 (CO) and 1613 (C=N); δ_H($CDCl_3$) 7.52–7.21 (5 H, m, ArH), 4.06 (3 H, s, OCH_3), 3.97 (2 H, s, CH_2O), 3.91 (3 H, s, OCH_3) and 3.03 (3 H, s, OCH_3); δ_C($CDCl_3$) 154.8 (C-3), 150.2 (CO), 143.2 (C-5), 136.4–128.1 (ArC), 113.0 (C-6), 64.1 (CH_2O) and 57.6/55.3/54.7 (OCH_3); *m/z* 276 (M^+, 64%), 245 (53) and 77 (100).

6-Methoxymethyl-1,3-diphenylpyrazin-2(1*H*)-one 17b. By the same procedure as described for compounds **10a,b** (stirring for 10 min at RT), compound **9** (146 mg, 0.5 mmol) yielded **17b** (92 mg, 63%), mp 142 °C (from EtOH) (Found: M^+, 292.1209. $C_{18}H_{16}N_2O_2$ requires M^+, 292.1212); ν_{max}/cm^{-1} 1670 (CO) and 1590 (C=N); δ_H($CDCl_3$) 8.36–7.47 (10 H, m, ArH), 7.59 (1 H, s, 5-H), 3.95 (2 H, s, CH_2O) and 3.17 (3 H, s, OCH_3); *m/z* 292 (M^+, 73%), 233 (100) and 77 (33).

3-Methoxy-6-methoxymethyl-5-methyl-1-phenylpyrazin-2(1*H*)-one 17c. By the same procedure as described for compound **17a**, compound **14** (130 mg, 0.5 mmol) yielded **17c** (75 mg, 58%) as an oil (Found: M^+, 260.1176. $C_{14}H_{16}N_2O_3$ requires M^+, 260.116); ν_{max}(neat)/cm^{-1} 1675 (CO) and 1610 (C=N); δ_H($CDCl_3$) 7.54–7.19 (5 H, m, ArH), 4.00 (3 H, s, OCH_3), 3.85 (2 H, s, CH_2O), 3.00 (3 H, s, OCH_3) and 2.35 (3 H, s, CH_3); δ_C($CDCl_3$) 155.4 (C-3), 151.1 (CO), 136.7–128.2 (ArC), 128.0 (C-6), 125.5 (C-5), 67.0 (CH_2O), 57.9/54.3 (OCH_3) and 19.2 (CH_3); *m/z* 260 (M^+, 61%), 201 (60) and 77 (100).

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