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Baylis–Hillman-derived N,N′-disubstituted piperazines: structural and preliminary computational studies

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ABSTRACT

Exploratory studies towards the preparation of potential HIV-1 protease and integrase inhibitors have led to the synthesis of Baylis–Hillman-derived N,N′-disubstituted piperazines. X-ray crystallographic, computer modelling and NMR techniques have been used to elucidate questions concerning configurational preferences, reaction pathways and the apparent difference in susceptibility towards aza-Michael reactions exhibited by methyl acrylate and methyl vinyl ketone (MVK) derived Baylis–Hillman substrates.

1. Introduction

The Baylis–Hillman reaction affords multifunctional adducts with considerable potential for synthetic elaboration.[1] More specifically, the α,β-unsaturated carbonyl moiety is susceptible to conjugate addition while, under suitable conditions, the allylic alcohol moiety may be expected to permit nucleophilic allylic (S_N') displacement. Our ongoing research on applications of Baylis–Hillman methodology in synthesis has led to the preparation of various benzannulated heterocyclic systems, including quinolines[2] and coumarins.[3] We have become increasingly aware of the fact that acrylate ester derived Baylis–Hillman adducts generally react readily with primary or secondary amines in aza-Michael reactions, whereas their methyl vinyl ketone (MVK) derived analogues do not.[4] Thus, in exploratory studies towards the development of potential HIV-1 protease (PR) and integrase (IN) inhibitors, the methyl acrylate derived adducts **4a**–**d** (Scheme 1) were found to undergo direct conjugate addition of piperazine permitting isolation of the corresponding bis-substituted piperazines **6a**–**d**, albeit in variable yields following chromatographic purification. Formation of the analogous MVK-derived bis-substituted piperazines **8a**,**b**,**e**,**f**, on the other hand, required the intermediacy of the activated chloromethyl derivatives **7a**,**b**,**e**,**f.** While the reaction conditions have not been optimised, the isolation of these symmetrically substituted products **6** and **8** has alerted us to the potential of this approach in accessing suitably elaborated C_2-symmetric products as potential HIV-1 PR and dual-action PR/IN inhibitors. Of more immediate interest is the fact that these compounds have provided an opportunity to address three issues relevant to future applications of the methodology. These concern: (i) the stereochemistry of the double bond in the series of compounds **7** and **8**; (ii) the apparent diastereoselectivity of their formation; and (iii) the observed difference in reactivity towards aza-Michael addition exhibited by the methyl acrylate derived Baylis–Hillman adducts **4** and their MVK-derived analogues **5**.

2. Discussion

DABCO-catalysed reaction of the 2-nitrobenzaldehydes **1** with methyl acrylate (**2**) or MVK (**3**) afforded the corresponding Baylis–Hillman adducts **4a-d** and **5a**,**b**,**e**,**f**.[5] The chloromethyl derivatives **7a**,**b**,**e**,**f** were obtained in essentially quantitative yield by hydrochlorination–dehydration of the corresponding Baylis–Hillman adducts **5a**,**b**,**e**,**f**, using HCl generated by the prior, cautious addition of acetyl chloride to cold, dry ethanol.[6] Conversion of allyl acetates into allyl chlorides occurs under similar conditions,[7] while treatment of Baylis–Hillman adducts under Vilsmeier–Haack conditions,[8] has been shown to afford the rearranged allyl chlorides; these reactions have been presumed to follow S_N or S_N' mechanisms. While formation of the chloromethyl derivatives **7a**,**b**,**e**,**f** could also proceed via acid-catalysed allylic

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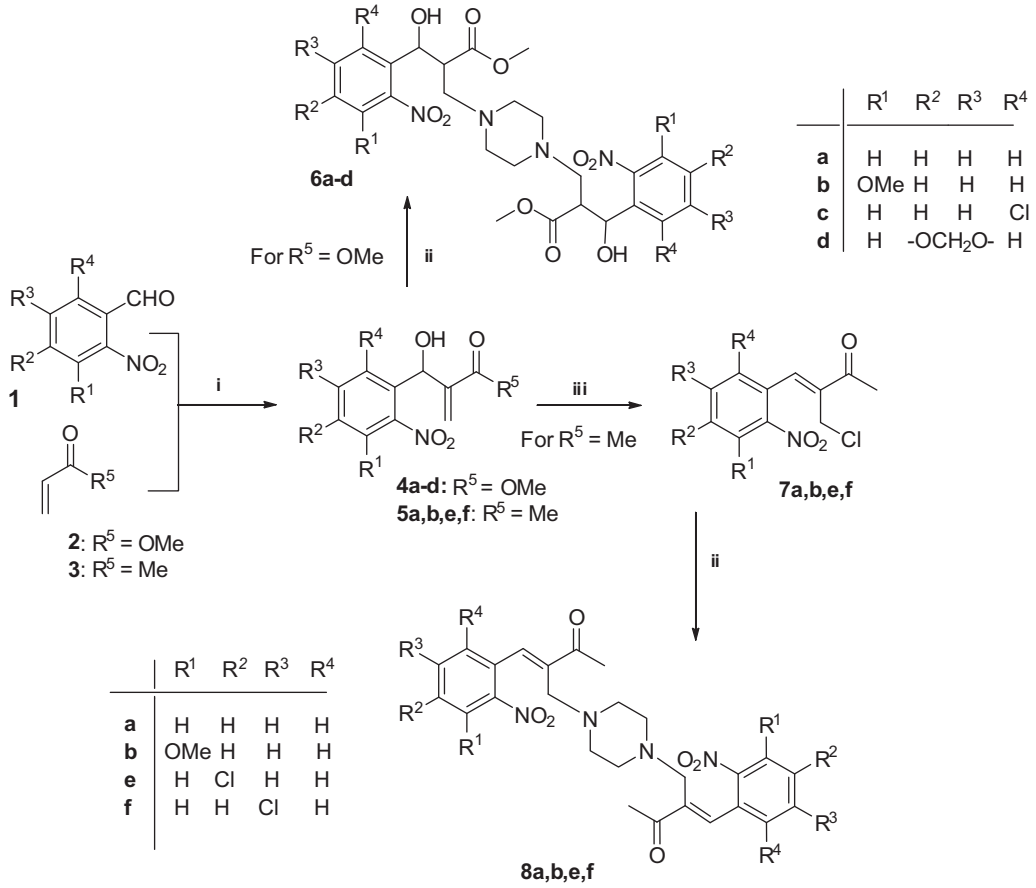

	R^1	R^2	R^3	R^4
a	H	H	H	H
b	OMe	H	H	H
c	H	H	H	Cl
d	H	-OCH_2O-		H

	R^1	R^2	R^3	R^4
a	H	H	H	H
b	OMe	H	H	H
e	H	Cl	H	H
f	H	H	Cl	H

Scheme 1. Reagents: (i) DABCO, $CHCl_3$; (ii) piperazine, THF; (iii) CH_3COCl, EtOH, 0 °C then **5**.

substitution (S_N'), the possibility of a conjugate addition-elimination pathway cannot be excluded a priori. Computational analysis, using Gaussian03,[9] of the two pathways was undertaken and the results appear to support the conjugate addition−elimination pathway. Thus, a scan at the HF/3-21G level involving initial protonation of the carbonyl oxygen in the parent system **5a** (to give **I**; Fig. 1), followed by step-wise approach of Cl^- (from an initial distance of 2.5 Å) led, spontaneously, to the 1,4-addition product **III**, dehydration and tautomerism of which would afford compound **7a**. On the other hand, initial protonation of the hydroxylic oxygen (to give **II**––necessary for allylic displacement), followed by step-wise approach of Cl^-, led via proton transfer to the carbonyl oxygen to give structure **I** and, thence, to the same 1,4-addition product **III**. Thus, protonation of the hydroxy oxygen appears to permit intramolecular catalysis of the conjugate addition pathway rather than promoting the allylic substitution (S_N') pathway! Moreover, the LUMO for the parent system **5a** corresponds largely to the α,β-unsaturated carbonyl system (see Fig. 4)––an observation consistent with the 1,4-addition route. The most stable conformations of both the acrylate ester and the MVK-derived Baylis–Hillman adducts (**4a** and **5a**, respectively) appear to be characterised by hydrogen-bonding between the hydroxy and carbonyl groups––a chelate effect which is also evident in the hydrochlorination sequence illustrated in Figure 1 and which accounts for the diastereocontrol in the dehydration step.

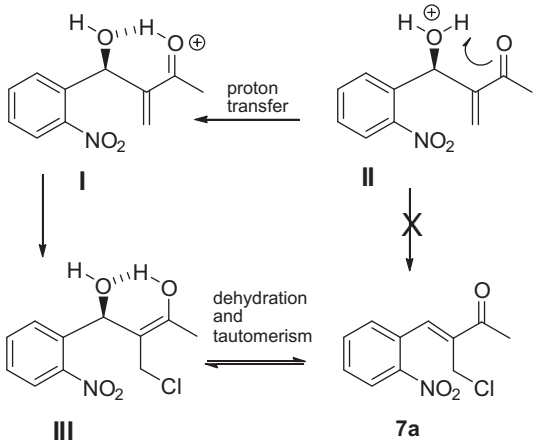

Figure 1. Results of calculations at the HF/3-21G level of step-wise approach of Cl^- to the protonated structures **I** and **II**.

Reaction of each of the Baylis-Hillman adducts **4a–d** with piperazine[10] was, initially, expected to afford the corresponding mono-substituted esters.[11] ^1H NMR analysis of the crude product from the reaction with substrate **4a**, while indicating the presence of a contaminant, appeared to support this expectation. However, HRMS analysis of the chromatographed material obtained from the reaction with substrate **4a** revealed a base peak at *m*/*z* 560, which corresponds to the disubstituted piperazine **6a**, as well as a peak at *m*/*z* 324 which would correspond to [M+1] for the mono-substituted analogue. A Diffusion-Ordered Spectroscopy (DOSY) NMR experiment was therefore run to establish whether both of the products were present or only the disubstituted derivative **6a** (with the peak at *m*/*z* 324 arising from fragmentation). In the pseudo-chromatographic 2D DOSY NMR experiment, the pulsed field gradient (PFG) and the deuterated solvent serve as the 'mobile phase', permitting 'separation' of two or more compounds, whose differences in size and shape affect their mobility

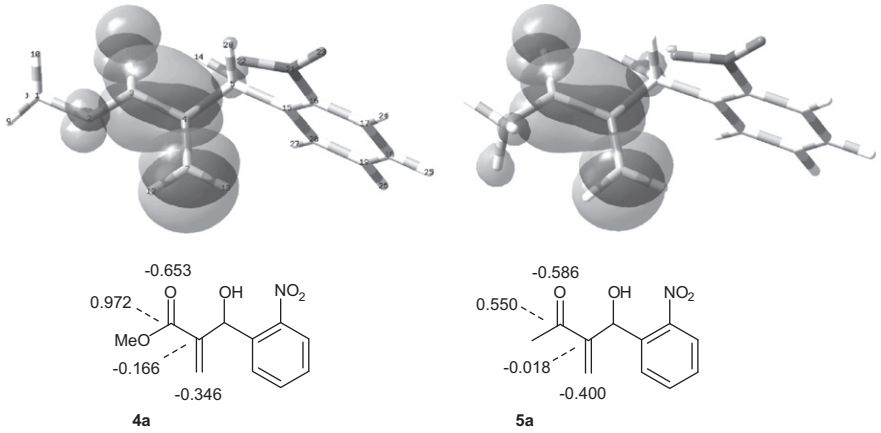

Figure 4. Molecular orbitals and Mulliken atomic charges for compounds **4a** (LUMO+1) and **5a** (LUMO), calculated at the MP2/6-31G(d) level on structures previously optimised at the B3LYP/6-31G+(d) level.

and diffusion coefficients.[12] The DOSY experiment clearly indicated the presence of a 'single' component, comprising a mixture of diastereomeric disubstituted piperazines **6a**; a similar result was obtained for compound **6d**, and HRMS analysis supported the formation of all four of the disubstituted piperazines **6a–d** as diastereomeric mixtures.

The MVK-derived bis-substituted piperazines **8a,b,e,f** were obtained by reacting the corresponding chloromethyl derivatives **7a,b,e,f** with piperazine in THF,[13] and various methods were explored to determine the configuration of the double bonds and, by implication, in the activated chloromethyl precursors, viz., 1D ($^3J_{H-C=O}$) and 2D (NOESY and HOESY[14]) NMR methods, and single crystal X-ray analysis of the parent system **8a**. The fully coupled ^{13}C NMR data for the heteronuclear three-bond coupling between the carbonyl carbon and the vinylic proton ($^3J_{H-C=O}$) was complicated by coupling with the proximate methyl and methylene protons and, in any event, unambiguous assignment on the basis of such data really requires the availability of both diastereomeric forms.[15] While the Heteronuclear NOE Spectrosopy (HOESY) experiments, conducted on three of the N,N′-bis-substituted piperazines, also failed to provide convincing configurational evidence, the NOESY spectra for all four compounds **8a,b,e,f** consistently revealed NOE interactions between the methyl and vinylic protons as illustrated in Figure 2. The consequent NMR-based (*E*)-configurational assignments are clearly in agreement with the X-ray structure of compound **8a** (Fig. 3).

The X-ray intensity data were collected at −100 °C, and the direct methods solution and full-matrix least-squares refinement proceeded routinely. The structure of molecule **8a** is required by space group symmetry to lie on a crystallographic inversion centre ($Z = 2$, space group $P2_1/n$). The piperazine ring adopts the normal chair form and the bulky 2-acetyl-3-(2-nitrophenyl)-2-propenyl groups are linked to it via the equatorial bonds C15–N16 (1.468(2) Å). In particular, the analysis provided unequivocal characterisation of the geometry around the double bond C10–C11 [1.334(2) Å]. Relevant torsion angles are C1-C10-C11-C15 [-4.8(2)°] and C1–C10–C11–C12 [178.0(1)°]. The plane of the aromatic ring is nearly orthogonal to the plane defined by C10, C11 and their bonded atoms (torsion angle C2–C1–C10–C11 [−81.9(2)°], and the nitro groups are located above and below the piperazine ring, slightly rotated out of their respective aromatic ring planes {C1–C6–N7–O9 [18.3(2)°]}. Two intermolecular C-H···O hydrogen bonds (both involving carbonyl oxygen atom O13 as acceptor with aromatic C–H donor groups) contribute to crystal cohesion.

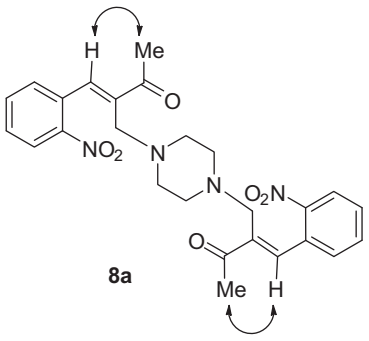

Figure 2. NOE interactions indicated in the NOESY spectrum of compound **8a**.

In order to elucidate the apparent lack of reactivity of the MVK-derived Baylis–Hillman adducts (**5**) under aza-Michael conditions, preliminary theoretical studies were undertaken to compare the nature of the LUMOs and the relevant atomic charges associated with the methyl acrylate derived Baylis–Hillman adduct **4a** and the MVK-derived analogue **5a**. Conformational searches were conducted, initially, at the AM1 level using *PC-SPARTAN-pro*.[16] The lowest energy conformer, in each case, exhibited hydrogen-bonding between the carbonyl group and the hydroxy hydrogen––the preferred arrangement retained in obtaining geometry-optimised structures at the B3LYP/6-31G(d) level using Gaussian03.[9] The LUMO surfaces and relevant Mulliken atomic charges were calculated at the MP2/6-31G(d) level, and examination of the results, which are illustrated in Figure 4 reveals that: (i) the LUMO for the acrylate ester **4a** is associated with the 2-nitrophenyl moiety, whereas the molecular orbital of interest for nucleophilic attack on the α,β-unsaturated carbonyl system is LUMO+1; (ii) the LUMO for the vinyl ketone **5a** is associated, essentially, with the α,β-unsaturated carbonyl moiety; and (iii) polarisation of the α,β-unsaturated carbonyl moiety is clearly greater in the methyl acrylate derived adduct **4a** with the result that the electron density (Mulliken charge = −0.346) on the terminal vinylic carbon is significantly less than on the corresponding centre in the MVK-derived analogue **5a** (−0.400). Interestingly, similar results were obtained for the unsubstituted phenyl analogues. The consequent attenuation of electrophilicity would seem to account for the apparent reluctance of the MVK-derived adducts (**5**) to undergo the uncatalysed aza-Michael reaction with piperazine. It is perhaps significant that, in both systems, approach of piperazine to the β-vinylic carbon is characterised by the development of bifurcated hydrogen-bonding between the amino proton and the N and one of the O atoms of the *ortho*-NO_2 group. This development is expected to

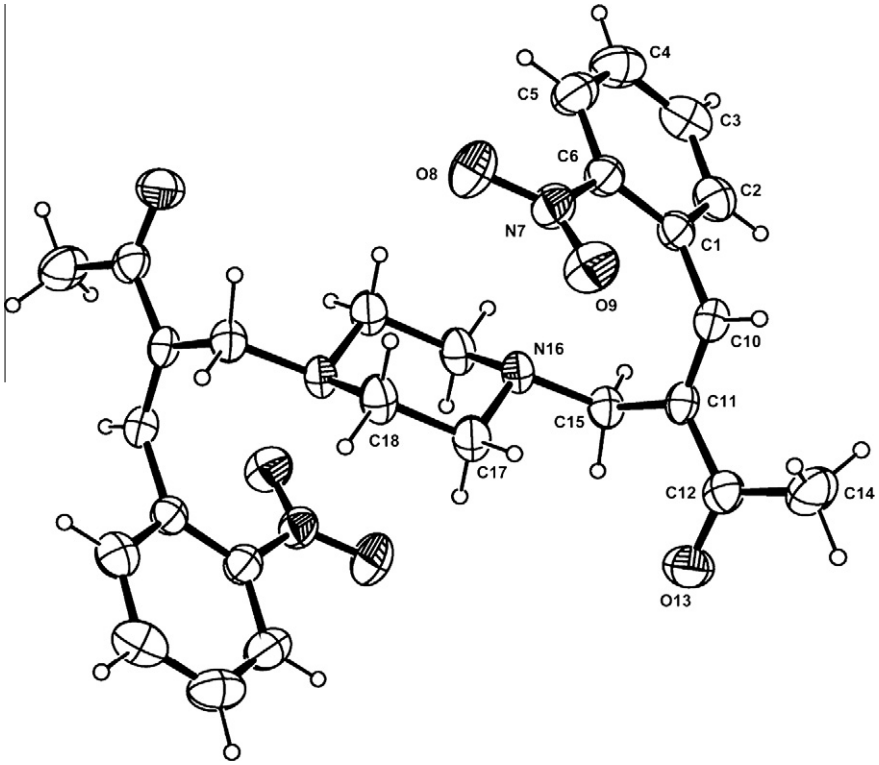

Figure 3. X-ray structure of *N*,*N*′-bis[(*E*)-2-acetyl-3-(2-nitrophenyl)-2-propenyl]piperazine (**8a**), showing the crystallographic numbering and thermal ellipsoids drawn at the 50% probability level.

increase the hardness of the nucleophilic 2° amine and, hence, the importance of electrostatic interaction in the initial phase of the reaction.[17]

In conclusion, the N,N′-disubstituted piperazines **6a–d** and **8a**,**b**,**e**,**f** reported in this study constitute interesting models for the development of novel compounds as potential HIV-1 protease and integrase inhibitors, while the structural and preliminary theoretical studies have provided useful insights into their formation.

Crystallographic data (excluding structure factors) for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 810815. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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Analytical data for new compounds are as follows.
Methyl 3-hydroxy-2-methylene-3-(3-methoxy-2-nitrophenyl)propanoate (**4b**), as colourless crystals (0.48 g, 65%), mp 108–109 °C (found, M^+-NO_2: 221.083260. Calcd for $C_{12}H_{13}O_5$, *M*: 221.081384); ν_{max}/cm^{-1} (Nujol) 3485 (OH) and 1706 (C=O); δ_H (400 MHz; $CDCl_3$) 3.25 (1H, br s, OH), 3.70 (3H, s, $COOCH_3$), 3.88 (3H, s, $ArOCH_3$), 5.62 (1H,s, C*H*OH), 5.86 and 6.41 (2H, 2× s, CH_2), 6.99 (1H, d, *J* = 7.9 Hz, 6′-H), 7.09 (1H, d, *J* = 7.89 Hz, 4′-H) and 7.41 (1H, t, *J* = 8.2 Hz, 5′H); δ_C (100 MHz; $CDCl_3$) 52.1 ($COCH_3$), 56.5 ($ArOCH_3$), 68.3 (CHOH), 112.2, 119.3, 127.4, 131.3, 134.4, 139.6, 140.4 and 150.9 (C=CH_2 and Ar-C) and 166.1 (C=O).
Methyl 3-(6-chloro-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate (**4c**), as a dark brown solid, (0.91 g, 86%), mp 99–101 °C (found, M^+-H_2O: 252.989934. Calcd for $C_{11}H_8ClNO_4$, *M*: 252.990376); ν_{max}/cm^{-1} (Nujol) 3335 (OH) and 1704 (C=O); δ_H (400 MHz; $CDCl_3$) 2.86 (1H, br s, OH), 3.73 (3H, s, CH_3), 5.73 (1H, s, C*H*OH), 6.17 and 6.44 (2H, 2× s, CH_2), 7.38 (1H, t, *J* = 8.1 Hz, Ar-H), 7.51 (1H, dd, *J* = 8.0 and 0.9 Hz, Ar-H) and 7.59 (1H, dd, *J*=8.0 and 1.1 Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 52.2 (CH_3), 68.9 (CHOH), 122.8, 127.8, 129.3, 131.7, 133.3, 135.6, 138.0 and 151.4 (C=CH_2 and Ar-C) and 166.3 (C=O).
4-Hydroxy-4-(4-chloro-2-nitrophenyl)-3-methylenebutan-2-one (**5e**), as a transparent, golden brown oil (0.31 g, 44%); υ_{max} (ATR)/cm^{-1} 3412 (OH) and 1671 (C=O); δ_H (400 MHz, $CDCl_3$) 2.26 (3H, s, CH_3), 4.16 (1H, br s, CHO*H*), 5.77 (1H, s, C*H*OH), 6.09 and 6.11 (2H, 2× s, CH_2), 7.51 (1H, d, *J* = 8.8 Hz, Ar-H), 7.64 (1H, d, *J* = 7.6 Hz, Ar-H) and 7.82 (1H, d, *J* = 2.0 Hz, Ar-H); δ_C (100 MHz; $CDCl_3$), 25.7 (CH_3), 66.0 (CHOH), 124.2, 126.4, 130.0, 133.1, 133.7, 135.4, 147.0 and 148.7 (C=CH_2 and Ar-C) and 199.2 (C=O).
6. *The general procedure for the preparation of the chloromethyl derivatives* (**7a**,**b**,**e**,**f**): which were used without further purification, is illustrated by the following example. (The chloromethyl derivative **7a** is known, having also been prepared directly via a $TiCl_4$-catalysed Baylis–Hillman reaction.[19])
Ethanolic HCl was generated in situ by cautiously adding AcCl (1.0 mL) dropwise to cold, dry EtOH (2.0 mL) in a reaction flask, fitted with a reflux condenser and cooled on an ice-bath; the mixture was then stirred for 5 min. (CAUTION! The reaction between AcCl and EtOH is exothermic!) 4-Hydroxy-3-methylene-4-(3-methoxy-2-nitrophenyl)butan-2-one (**5b**) (0.67 g, 2.7 mmol) in EtOH (1.0 mL) was added to the ethanolic HCl, the flask was stoppered and the mixture stirred overnight at room temperature. Excess solvent and unreacted HCl were evaporated in vacuo to afford, as dark brown crystals, *3-chloromethyl-4-(3-methoxy-2-nitrophenyl)but-3-en-2-one* (**7b**) (0.73 g, 100%), mp 66–68 °C (found, *M*: 269.0427. Calcd for $C_{12}H_{12}NO_4Cl$, *M*: 269.0455); υ_{max} (ATR)/cm^{-1} 1671 (C=O); δ_H (400 MHz; $CDCl_3$) 2.42 (3H, s, CH_3), 3.93 (3H, s, OCH_3), 4.25 (2H, s, CH_2), 7.14 (1H, d, *J* = 8.4 Hz, Ar-H), 7.27 (1H, d, *J* = 8.0 Hz, Ar-H), 7.49 (1H, s, 4-H) and 7.55 (1H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 25.9 (CH_3),

36.9 (CH_2), 56.6 (OCH_3), 113.9 (C-4), 120.8, 121.8, 128.2, 131.8, 135.5, 140.9 and 151.4 (Ar-C and C=CH) and 196.3 (C=O).

3-Chloromethyl-4-(4-chloro-2-nitrophenyl)but-3-en-2-one (**7e**), as a dark brown oil (4.0 g, 100%); υ_{max} (ATR)/cm^{-1} 1671 (C=O); δ_H (400 MHz; $CDCl_3$) 2.49 (3H, s, CH_3), 4.14 (2H, s, CH_2), 7.66 (1H, m, Ar-H), 7.72 (1H, m, 6′-H), 7.90 (1H, s, 4-H) and 8. 19 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 25.9 (CH_3), 36.8 (CH_2), 125.4, 128.5, 131.6, 134.1, 136.1, 138.1, 138.9 and 147.3 (C=CH and Ar-C) and 196.3 (C=O).

3-Chloromethyl-4-(5-chloro-2-nitrophenyl)but-3-en-2-one (**7f**), as a black oil (3.8 g, 94%); υ_{max} KBr/cm^{-1} 1677 (C=O); δ_H (400 MHz; $CDCl_3$) 2.51 (3H, s, CH_3), 4.17 (2H, s, CH_2), 7.56 (1H, dd, J = 1.0 and 8.8 Hz, Ar-H), 7.67 (1H, d, J = 1.2 Hz, Ar-H), 7.91 (1H, s, 4-H) and 8.18 (1H, d, J = 8.8 Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 26.0 (CH_3), 36.7 (CH_2), 126.7, 130.2, 130.4, 131.9, 138.3, 138.8, 140.8 and 145.2 (C=CH and Ar-C) and 196.3 (C=O).

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10. *The general procedure for the preparation of compounds* **6a**–**d** is illustrated by the following example.

A solution of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate (**4a**) (1.30 g, 5.48 mmol) and piperazine (0.41 g, 4.8 mmol) in dry THF (5 mL) was stirred in a stoppered flask at rt for 24 h. The solvent was removed in vacuo and the crude product flash chromatographed [on silica gel; elution with hexane-EtOAc (1:1)] to afford, as a yellowish-green solid, *N,N′-bis[2-carbomethoxy-3-hydroxy-3-(2-nitrophenyl)propyl]piperazine* (**6a**)[20] (0.74 g, 55%), mp 78–82 °C (found [M+1]: 561.2214. Calcd for $C_{26}H_{33}N_4O_{10}$, MH^+: 561.2197); υ_{max} KBr/cm^{-1} 3353 (OH) and 1732 (C=O); δ_H (400 MHz; $CDCl_3$) 2.77 and 3.03 (4H, 2× m, $CHCH_2$), 3.26 (2H, m, $CHCH_2$), 3.50 (6H, s, OCH_3), 3.78 (8H, m, NCH_2), 5.54 (2H, d, J = 5.2 Hz, $CHOH$), 7.40 (2H, t, J = 4.8 Hz, Ar-H), 7.56 (2H, t, J = 5.0 Hz, Ar-H), 7.62 (2H, d, J = 4.4 Hz, Ar-H) and 7.75 (2H, d, J = 5.6 Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 47.9 ($CHCH_2$), 52.0 (OCH_3), 52.1 (NCH_2), 59.2 ($CHCH_2$), 73.3 ($CHOH$), 124.3, 128.6, 129.3, 132.4, 136.1 and 149.0 (Ar-C) and 171.7 (C=O).

N,N′-Bis[2-carbomethoxy-3-hydroxy-3-(3-methoxy-2-nitrophenyl)propyl]piperazine (**6b**)[20], as a yellow oil (0.12 g, 8%) (found [M+1]: 621.2392. Calcd for $C_{28}H_{37}N_4O_{12}$, MH^+: 621.2408); υ_{max} KBr/cm^{-1} 3358 (OH) and 1730 (C=O); δ_H (400 MHz; $CDCl_3$) 2.14-2.74 (10H, m, $CHCH_AH_A$ and NCH_2), 3.04 (2H, m, $CHCH_BH_B$), 3.28 (2H, m, $CHCH_2$), 3.61(6H, s, OCH_3), 3.85 (6H, s, Ar-OCH_3), 5.07 (2H, t, J = 9.8 Hz $CHOH$), 6.87 (2H, d, J = 7.6 Hz Ar-H), 6.94 (2H, m, Ar-H) and 7.31 (2H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 47.3 ($CHCH_2$), 51.9 (OCH_3), 56.6 (NCH_2), 56.4 (Ar-OCH_3), 59.7 (NCH_2), 75.3 (CHOH), 112.0, 119.9, 130.4, 134.5, 140.2 and 151.0 (Ar-C) and 171.2 (C=O).

N,N′-Bis[2-carbomethoxy-3-hydroxy-3-(6-chloro-2-nitrophenyl)propyl]piperazine (**6c**)[20], as a yellow solid (30 mg, 5%) (found [M+1]: 629.1357. Calcd for $C_{26}H_{31}N_4O_{10}Cl_2$, MH^+: 629.1417); υ_{max} KBr/cm^{-1} 3375 (OH) and 1728 (C=O); δ_H (400 MHz; $CDCl_3$) 2.15 and 2.40 (8H, 2× m, NCH_2), 2.54 (4H, m, $CHCH_2$), 3.50 (6H, s, OCH_3), 3.59 (2H, m, $CHCH_2$), 5.58 (2H, m, $CHOH$), 7.29-7.57 (6H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 44.3 ($CHCH_2$), 48.8 (OCH_3) 52.2 (NCH_2), 56.6 ($CHCH_2$), 73.7 (CHOH), 123.0, 128.9, 133.1, 134.9, 151.5 and 170.8 (Ar-C) and 173.4 (C=O).

N,N′-Bis[2-carbomethoxy-3-hydroxy-3-(4,5-methylenedioxy-2-nitrophenyl)propyl]-piperazine (**6d**)[20], as a yellow wax (40 mg, 7%) (found [M+]1: 649.1995. Calcd for $C_{28}H_{33}N_4O_{14}$, MH^+: 649.1988); υ_{max} KBr/cm^{-1} 3349 (OH) and 1730 (C=O); δ_H (400 MHz; $CDCl_3$) 2.58 (8H, m, NCH_2), 2.78 (2H, m, $CHCH_2$), 2.99 (2H, m, $CHCH_2$), 3.54 (6H, s, OCH_3), 5.62 (2H, m, $CHOH$), 6.09 (4H, s, OCH_2O), 7.15 (2H, s, Ar-H) and 7.33 (2H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 30.1 (NCH_2), 48.8 ($CHCH_2$), 52.5 (OCH_3), 59.1 ($CHCH_2$), 72.3 (CHOH), 103.3 (OCH_2O), 105.5, 108.3, 134.3, 142.9, 147.6 and 152.1 (Ar-C) and 172.1 (C=O).

11. Such compounds may well have been observed,[4] but our interest and initial studies have focused on the isolated *N,N′*-disubstituted piperazines **6a-d**.
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13. *The general procedure for the preparation of the MVK-derived bis-substituted piperazines* **8a**,**b**,**e-f** is illustrated by the following example.

A solution of (*Z*)-3-chloromethyl-4-(2-nitrophenyl)but-3-en-2-one (**7a**) (1.00 g; 4.2 mmol) and piperazine (0.36 g; 4.2 mmol) in dry THF (2.0 mL) was stirred in a stoppered flask for 5 d. The solvent was removed in vacuo and the crude product was flash chromatographed [on Silica gel; elution with EtOAc-hexane (1:1)]. Evaporation of the solvent in vacuo, followed by trituration with EtOAc-hexane [1:1] afforded, as bright yellow crystals, *N,N′-bis[(E)-2-acetyl-3-(2-nitrophenyl)-2-propenyl]-1,4-piperazine* (**8a**) (0.19 g, 19%), mp 174–176 °C (found [M+1]: 493.2103. Calcd for $C_{26}H_{29}N_4O_6$, MH^+; 493.2087); υ_{max} (ATR)/cm^{-1} 1654 (C=O); δ_H (400 MHz, $CDCl_3$) 2.01 (8H, s, NCH_2), 2.44 (6H, s, CH_3), 3.04 (4H, s, CCH_2), 7.52 (4H, t, J = 8.6 Hz, Ar-H), 7.63 (2H, t, J = Ar-H), 7.81 (2H, s, C=CH), and 8.13 (2H, d, J = 8.0 Hz, Ar-H); δ_C (100 MHz,$CDCl_3$) 26.5 (CH_3), 52.5 (NCH_2), 52.6 ($CHCH_2$), 124.6, 129.1, 131.0, 131.9, 133.2, 138.8, 139.3 and 147.5 (C=CH and Ar-C) and 199.7 (C=O).

N,N′-Bis[(E)-2-acetyl-3-(3-methoxy-2-nitrophenyl)-2-propenyl]piperazine (**8b**), as an off-white, fluffy solid (0.17 g, 22%), mp 204-206 °C (found: C, 60.9; H, 6.2; N, 9.8. Calcd. for $C_{28}H_{32}N_4O_8$: C, 60.9; H, 5.8; N, 10.1%.); υ_{max} (ATR)/cm^{-1} 1669 (C=O); δ_H (400 MHz, $CDCl_3$); 2.24 (8H, br s, NCH_2), 2.35 (6H, s, $COCH_3$), 3.16 (4H, s, CCH_2), 3.90 (6H, s $ArOCH_3$) 7.04 (2H, d, J = 8.0 Hz, Ar-H), 7.20 (2H, d, J = 7.6 Hz, Ar-H), 7.32 (2H, s, Ar-H), and 8.43 (2H, t, J = 8.0 Hz, Ar-H); δ_C (100 MHz,$CDCl_3$) 26.8 ($COCH_3$), 52.7 (NCH_2), 53.1 (CCH_2), 56.5 ($ArOCH_3$), 112.6, 122.0, 129.4, 131.0, 133.1, 140.5, 142.8 and 150.9 (C=CH and Ar-C) and 199.8 (C=O).

N,N′-Bis[(E)-2-acetyl-3-(4-chloro-2-nitrophenyl)-2-propenyl]piperazine (**8e**), as a bright-yellow powder (0.06 g, 9%), mp 139–140 °C (found [M+1]: 561.1281. Calcd. for $C_{26}H_{27}N_4O_6Cl_2$, MH^+: 561.1308); υ_{max} (ATR)/cm^{-1} 1689 (C=O); δ_H (400 MHz, $CDCl_3$) 2.06 (8H, d, J = 16 Hz, NCH_2), 2.45 (6H, s, CH_3), 3.05 (4H, s, CCH_2), 7.61 (4H, 2× d, J = 8.0 Hz, Ar-H), 7.75 (2H, s, Ar-H), and 8.12 (2H, s, Ar-H); δ_C (100 MHz,$CDCl_3$) 26.4 (CH_3), 52.4 (NCH_2), 52.5 (CCH_2), 124.8 (2C), 130.2, 132.3, 133.3, 135.0, 137.7 and 139.9 (C=CH and Ar-C) and 199.2 (C=O).

N,N′-Bis[(E)-2-acetyl-3-(5-chloro-2-nitrophenyl)-2-propenyl]piperazine (**8f**), as bright yellow crystals (0.04 g, 13%), mp 197–199 °C (found: C, 55.5; H, 4.8; N, 9.9. Calcd for $C_{24}H_{26}N_4O_6Cl_2$: C, 55.6; H, 4.7; N, 10.0%.); υ_{max} (ATR)/cm^{-1} 1686 (C=O); δ_H (400 MHz, $CDCl_3$) 2.09 (8H, br s, NCH_2), 2.46 (6H, s, CH_3), 3.06 (4H, s, CCH_2), 7.47 (2H, d, J = 8.8 Hz, Ar-H), 7.83 (4H, d, J = 12.4 Hz, Ar-H) and 8.10 (2H, dd, J = 2.0 and 8.8 Hz, Ar-H), δ_C (100 MHz,$CDCl_3$) 26.3 (CH_3), 52.2 (NCH_2), 52.5 (CCH_2), 126.0, 129.0, 131.5, 133.5, 137.9, 140.1 and 145.9 (C=CH and ArC) and 199.1 (C=O).

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