Synthesis of Amido-ureas and the Nature of Caracasanamide, the Hypotensive Principle of *Verbesina caracasana*

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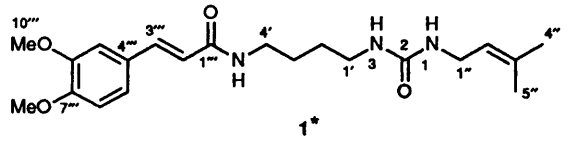
Syntheses of the (*E*)-**1** and (*Z*)-**2** forms of 1-(3-methylbut-2-enyl)-3-{4-[3-(3,4-dimethoxyphenyl)-prop-2-enamido]butyl}urea, proposed structures for the natural hypotensive caracasanamide, have been carried out. The compounds were found not to be identical with the natural products, the structures of which have now been revised from containing a urea to containing a corresponding guanidine segment. Using aminoiminomethanesulfonic acid or 3-methylbut-2-enylcyanamide as reagents, the synthesis can be diverted to caracasanamide **15** (R = H) through an amine intermediate.

Extracts of *Verbesina caracasana* (Compositae) show strong hypotensive effects in mice and the active principle (caracasanamide) has been reported to be the (*E*)- and (*Z*)-forms of an amido urea **1** and **2**.[1] As part of a wider ranging interest in the biological activities of natural amides,[2] we report the synthesis of these two compounds and their relationship to revised guanidino structures which have since emerged.



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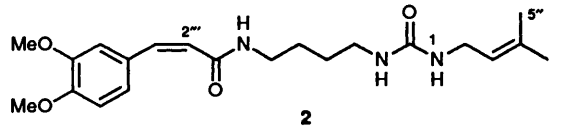

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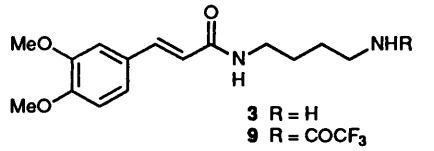
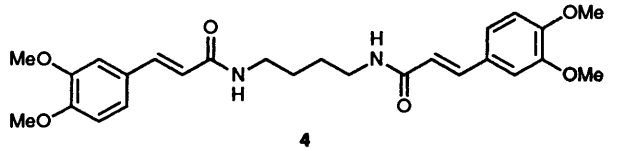


3 R = H
9 R = $COCF_3$



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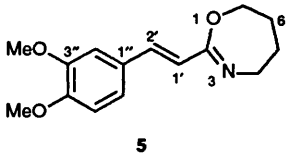

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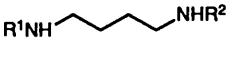


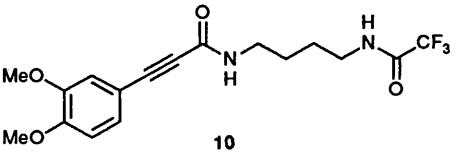
6 R^1 = $PhCH_2$, R^2 = H
7 R^1 = $PhCH_2$, R^2 = $COCF_3$
8 R^1 = H, R^2 = $COCF_3$

* The numbering on formulae relate to spectroscopic assignments in the Experimental section

Acylation of butane-1,4-diamine by (*E*)-3,4-dimethoxycinnamoyl chloride with the diamine present in large excess (10 mol) gave little monoacyl product **3**, the major product being the insoluble diacyl material **4** (55%) together with the oxazepine **5** (19%) formed by cyclisation of **3**. Activation of (*E*)-3,4-dimethoxycinnamic acid using the phenyl *N*-phenylphosphoramidochloridate[3] or dicyclohexylcarbodiimide methods[4] gave similar results.

Difficulties in the monoacylation of butane-1,4-diamine are precedented[5] but it has been shown that it can be monobenzylated by reductive amination using benzaldehyde and formic acid. In order to make the monotrifluoroacetyl derivative, the benzyl derivative **6** was prepared (61%) and *N*-trifluoracetylated to give **7** (57%). However the desired **8** could not be obtained in this way as debenzylation could not be attained using either conventional heterogeneous catalytic hydrogenolysis (10% palladium on various supports, or palladium black), or the formic acid–ammonium formate system.[6,7] Fortunately, conditions for the successful preparation of the mono-*N*-acetyl derivative of butane-1,4-diamine have been described[8] and were successfully applied to the *N*-trifluoroacetyl case. Reaction of the diamine with trifluoroacetic acid and trifluoroacetic anhydride at 50–60 °C gave **8**, isolated as the hydrochloride, in 32% yield. Treatment of a suspension of the hydrochloride in dichloromethane with (*E*)-3,4-dimethoxycinnamoyl chloride and triethylamine then gave the trifluoroacetyl compound **9** (72%) which could be hydrolysed under mild basic conditions (potassium carbonate in refluxing methanol) to give the desired *N*-4′-aminobutyl amide of (*E*)-3,4-dimethoxycinnamic acid **3** (90%).

The (*Z*)-isomer was prepared in a similar fashion using the acetylenic analogue as intermediate. 3,4-Dimethyoxyphenyl-



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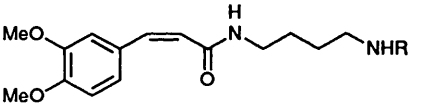
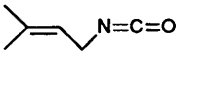


11 R = $COCF_3$
12 R = H



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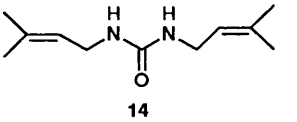

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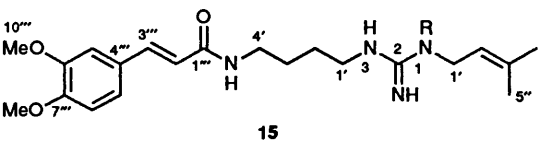
propiolyl chloride reacted with **8** to give **10** (64%), which was semi-hydrogenated using Lindlar catalyst to give (*Z*)-**11** (55%). This had two doublets in the NMR spectrum at δ_H 5.85 (*J* 12.2 Hz) and 6.70 (*J* 12.2 Hz) confirming the (*Z*)-geometry [the corresponding (*E*)-stereoisomer has δ 6.55 (*J* 15.0 Hz) and 7.60 (*J* 15.0)]. Base hydrolysis as before then gave the *N*-4′-aminobutyl amide of (*Z*)-3,4-dimethoxycinnamic acid **12** (94%).

3-Methylbut-2-enyl isocyanate **13** was made by a procedure similar to that used for converting but-2-enyl bromide into its isocyanate.[9] 3-Methylbut-2-enyl bromide reacted with silver isocyanate in ether in the dark to give 3-methylbut-2-enyl isocyanate in 40% yield after distillation under reduced pressure. The compound has ^{1}H NMR signals slightly upfield of the corresponding bromide and ν_{max}(film)/cm^{-1} 2280. It is of course extremely water sensitive, forming insoluble bis(3-methylbut-2-enyl) urea **14** *via* the carbamic acid and its decarboxylation. Reaction of 3-methylbut-2-enyl isocyanate with the amine **3** gave the desired (*E*)-amido-urea **1** (72%) which was fully characterised (^{1}H and ^{13}C NMR spectra, UV and mass spectral data).

Efforts to obtain the (*Z*)-isomer **2** in a similar way however, resulted in the formation of an (*E*)–(*Z*)- mixture of **1** and **2** (~1:1) possibly through photo-induced stereomutation. This was supported by the fact that exposure to ambient light for several days of a solution of the pure (*E*)-isomer in [$^2H_6$]-DMSO resulted in photoisomerisation to a (*Z*)–(*E*)-equilibrium mixture similar (~1:1) to that obtained from the (*Z*)-isomer above. The reaction is readily monitored by the ^{1}H NMR spectrum. By working carefully with exclusion of light the pure (*Z*)-isomer **2** was isolated by C_{18}-reversed phase HPLC and fully characterised spectroscopically. Our objectives thus attained, contact was made with the De Luca group to effect direct comparisons with the natural materials. We then learned that our products were not identical with the natural compounds and that the structures of the caracasanamides had now been amended from the amido-urea structures to the amido-guanidine **15** (R = H) and its (*Z*)-isomer.[10]

In view of this information the synthesis was diverted to give the amido-guanidine structure. The amino compound **3** was treated with aminoiminomethanesulfonic acid **16**[11] in methanol to form the guanidine bisulfite compound **17** which was treated with 10% sodium hydroxide to provide the free base. The ^{1}H NMR spectrum of the latter was similar to that of the amine **3** and the compound readily lost ammonia, *m/z* 303, and CH_5N_3 (guanidine), *m/z* 261, in the mass spectrometer, with the base peak *m/z* 191 corresponding to the cinnamoyl fragment. Treatment of the bisulfite compound **17** with 2 molar equivalents of 10% sodium hydroxide and 1 molar equivalent of 3-methylbut-2-enyl bromide gave caracasanamide **15** (R = H), retention of the (*E*)-double bond in the cinnamoyl fragment being verified by the ^{1}H–^{1}H coupling constant of 15.5 Hz obtained for the doublets at 6.63 and 7.39 ppm. Some bis(3-methylbut-2-enyl)ated material **15** (R = 3-methylbut-2-enyl) was also formed in the reaction as a by-product.

As indicated by a brief spectroscopic study, the amine **3**, when treated with 3-methylbut-2-enyl cyanamide **18**, also formed caracasanamide. The cyanamide **18** was made by treating cyanogen bromide with 3-methylbut-2-enylamine[12] in THF at −10 °C in the presence of sodium carbonate, according to a general method.[13]



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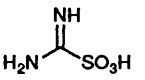

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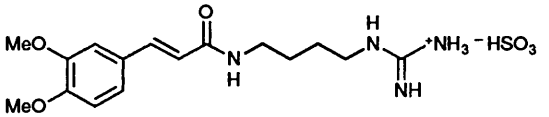

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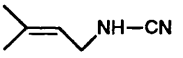

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Experimental

Bis-N,N′-[(2E)-3-(3′,4′-*Dimethoxyphenyl*)*acryloyl*]*butane*-1,4-*diamine* **4** *and* 2-[(1E)-2-(3′,4′-*Dimethoxyphenyl*)*vinyl*]-4,5,6,7-*tetrahydro*-1,3-*oxazepine* **5**.—3,4-Dimethoxycinnamic acid (1.0 g, 4.8 mmol) was converted into its acid chloride by refluxing (2 h) with thionyl chloride (4 cm^3) in benzene (20 cm^3). The excess of thionyl chloride and benzene was removed by distillation and the acid chloride was dissolved in benzene (5 cm^3) and added dropwise to butane-1,4-diamine (4.14 g, 48 mmol) in benzene (20 cm^3). The mixture was stirred overnight, when the precipitate was filtered off and crystallised from the glacial acetic acid to give the *title compound* **4** (0.62 g, 55%), m.p. 212–215 °C (Found: C, 66.2; H, 7.05; N, 5.9%; M$^+$, 468.229. $C_{26}H_{32}N_2O_6$ requires C, 66.65; H, 6.9; N, 6.0%; *M*, 468.226); ν_{max}(KBr)/cm^{-1} 1650, 1620, 1530 and 1510; δ_H(90 MHz; CF_3CO_2D) 1.80 [4 H, br s, ($HNCH_2CH_2)_2$], 3.75 (4 H, m, 2 × $NHCH_2$), 4.0 (12 H, s, 4 × OMe), 6.65 (2 H, d, *J* 15.0, ArCH=C*H*), 7.05–7.45 (6 H, m, Ar), 7.95 (2 H, d, *J* 15.0, ArC*H*=CH) and 11.8 (2 H, s, NH_2).

The filtrate was diluted with ether, washed with sodium hydrogen carbonate solution, dried ($MgSO_4$), evaporated and chromatographed on silica (dry column) eluting with ether–chloroform (1:1) to give the *title compound* **5** (0.24 g, 19%), m.p. 165–166 °C (Found: C, 68.5; H, 7.5; N, 5.4%; M$^+$, 261.137. $C_{15}H_{19}NO_3$ requires C, 68.95; H, 7.3; N, 5.35%; *M*, 261.137); ν_{max}(KBr)/cm^{-1} 1660, 1610 and 1511. λ_{max}(EtOH)/nm 219 (ε 13 400), 235 (12 600) and 322 (16 800); δ_H(90 MHz; $CDCl_3$) 1.80–2.05 (4 H, m, $NCH_2CH_2CH_2CH_2O$), 3.55–3.72 (4 H, m, $NCH_2CH_2CH_2CH_2O$), 3.95 (6 H, s, 2 × OMe), 6.65 (1 H, d, *J* 15.0, ArCH=C*H*), 6.85–7.25 (3 H, m, Ar) and 7.75 (1 H, d, *J* 15.0, ArC*H*=CH); δ_C(90 MHz; $CDCl_3$) 24.4 (CH_2, C-5), 26.2 (CH_2, C-6), 46.0 (CH_2, C-4), 46.6 (CH_2, C-7), 56.0 (2 × Me, C-7″ and -8″), 116.9 (CH, C-5″), 111.3 (CH, C-2″), 110.4 (CH, C-6″), 121.7 (C, C-1″), 128.5 (CH, C-1′), 141.6 (CH, C-2′), 149.3 (C, C-3″), 150.6 (C, C-4″) and 164.9 (C, C-2).

N-(4-*Trifluoroacetylaminobutyl*)*benzylamine* **7**.—Butane-1,4-diamine (32 g, 0.36 mol) was dissolved in cooled (0–5 °C) formic acid (90%, 120 cm^3) and benzaldehyde (9.26 g, 90.6 mmol) added. The mixture was then refluxed overnight, cooled, and added to 6 mol dm^{-3} hydrochloric acid (300 cm^3). The product was heated under reflux overnight and then evaporated almost to dryness, the slurry being dissolved in water and the pH being adjusted to 10 by addition of sodium hydroxide solution. Extraction with chloroform (5 × 100 cm^3) followed by drying (Na_2SO_4) and evaporation and distillation gave *N*-benzylbutane-1,4-diamine (9.7 g, 61%), b.p. 96 °C, 0.01 mmHg (lit.,[5]

b.p. 100–102 °C, 0.2 mmHg). Trifluoroacetic anhydride (4.62 g, 22 mmol) in dry dichloromethane (15 cm^3) was added to a cooled solution (0–5 °C) of the latter (3.6 g, 20 mmol) in dichloromethane (15 cm^3) containing triethylamine (2.8 cm^3). The product was stirred overnight at room temperature, then washed in turn with hydrochloric acid (3%), sodium hydrogen carbonate (5%) and water. Drying ($MgSO_4$) and evaporation, followed by dry column chromatography on silica gave the *title compound* **7** (3.13 g, 57%) as a colourless liquid (Found: M^+, 246.141. $C_{13}H_{17}F_3O$ requires *M*, 246.131); ν_{max}(film)/cm^{-1} 3300, 1720, 1710 and 1680; δ_H(90 MHz; $CDCl_3$) 1.51 (5 H, m, $CH_2CH_2CH_2CH_2$ and $ArCH_2NH$), 3.36 (4 H, m, $CH_2CH_2CH_2CH_2$), 4.63 (2 H, s, $ArCH_2$) and 7.33 (6 H, m, ArH and CONH).

N-*Trifluoroacetylbutane*-1,4-*diamine Hydrochloride* (*cf.* **8**).—Butane-1,4-diamine (5.05 g, 57 mmol) was added to cooled trifluoroacetic acid (30 cm^3), heated to 50–60 °C, and a mixture of trifluoroacetic anhydride (6.7 cm^3, 47 mmol) and trifluoroacetic acid (10 cm^3) was added dropwise with stirring. After standing at 20 °C for 4 h, the product was evaporated to dryness under vacuum. The residue was taken up in hot water, cooled, and treated with conc. hydrochloric acid (50 cm^3). Again, the solution was evaporated to dryness and the resulting solid was extracted with portions (30–40 cm^3) of propan-2-ol, the insoluble residue of butane-1,4-diamine hydrochloride being discarded. The combined alcoholic extracts were evaporated and the residue was crystallised from a minimum amount of hot water and dried at 70 °C and 10 mmHg to give the *title compound*, m.p. 135 °C (4.0 g, 32%) [Found: *m/z* 184. M – HCl ($C_6H_{11}F_3N_2O$ requires *m/z* 184]; ν_{max}(KBr)/cm^{-1} 1712; δ_H(90 MHz; D_2O) 1.95 (4 H, m, $CH_2CH_2CH_2CH_2$), 3.30 (2 H, m, CH_2N) and 3.65 (2 H, m, $CH_2NHCOCF_3$).

(2E)-N-4-*Trifluoroacetylaminobutyl*-(3′,4′-*dimethoxyphenyl*)-*prop*-2-*enamide* **9**.—3,4-Dimethoxycinnamic acid (0.2 g, 0.96 mmol) was converted into its acid chloride using thionyl chloride (2 cm^3) in the usual way. The acid chloride in dichloromethane was added to *N*-trifluoroacetylbutane-1,4-diamine hydrochloride (0.21 g, 0.96 mmol) and triethylamine (0.5 cm^3, 4 equiv.) in dichloromethane, the mixture being stirred (2 h). The product was washed with 3% hydrochloric acid (3 × 15 cm^3) and then 5% sodium hydrogen carbonate solution (3 × 15 cm^3) and dried ($MgSO_4$). After evaporation the residue was chromatographed on dry silica eluting with dichloromethane–diethyl ether–hexane (1:1:0.2) to give the *title compound* **9**, (0.26 g, 72%) m.p. 148–150 °C (Found: C, 54.55; H, 5.9; N, 7.25%; M^+, 374.143. $C_{17}H_{21}F_3N_2O_4$ requires C, 54.55; H, 5.6; N, 7.5%; *M*, 374.145); ν_{max}(KBr)/cm^{-1} 3400, 3300, 3240, 3100, 1720, 1670, 1630, 1615 and 1600; δ_H(90 MHz; [$^2H_6$]-acetone) 1.65 (4 H, m, $CH_2CH_2CH_2CH_2$), 3.40 (4 H, m, $CH_2CH_2CH_2CH_2$), 3.90 (6 H, s, 2 × OMe), 6.55 (1 H, d, *J* 15.0, ArCH=CH), 7.10 (5 H, m, 3 × ArH and 2 × NH) and 7.60 (1 H, d, *J* 15.0, ArCH=CH).

(2Z)-N-4-*Trifluoroacetylaminobutyl*-3-(3′,4′-*dimethoxyphenyl*)*prop*-2-*enamide* **11**.—3,4-Dimethoxyphenylprop-2-ynoic acid (0.2 g 0.97 mmol) was converted into its acid chloride using thionyl chloride (2 cm^3) and added to *N*-trifluoroacetyl-1,4-diamine hydrochloride (0.21 g, 0.97 mmol) and triethylamine (0.53 cm^3, 4 equiv.) in dry dichloromethane. Work up as above gave a product which was chromatographed on dry silica eluting with diethyl ether–hexane–dichloromethane–acetone (0.8:0.2:1.0:0.1) to give N-*trifluoroacetylaminobutyl*-3-(3′,4′-*dimethoxyphenyl*)*propynamide* **10** (0.23 g, 64%), m.p. 120–121 °C (Found: M^+, 372.129. $C_{17}H_{19}F_3N_2O_4$ requires *M*, 372.130; ν_{max}(KBr)/cm^{-1} 3300, 2221, 1700, 1630 and 1535; δ_H(90 MHz; [$^2H_6$]-acetone) 1.76 (4 H, m, $CH_2CH_2CH_2CH_2$), 3.78 (4 H, m, $CH_2CH_2CH_2CH_2$), 4.38 (6 H, s, 2 × OMe), 7.88 (4 H, m, ArH and NH) and 8.7 (1 H, br s, NH).

A solution of the ynamide **10** (146 mg, 0.392 mmol) in methanol was stirred under hydrogen in the presence of Lindlar catalyst (50 mg) until sufficient hydrogen (0.4 mmol) to attain semi-hydrogenation had been absorbed. After filtration through Celite and evaporation, the product was chromatographed on silica, eluting with ethyl acetate–dichloromethane–hexane (1:1:1) to give the *title olefin* **11** (73 mg, 50%), a colourless oil which solidified on long standing at room temperature (Found: M^+, 374.143. $C_{17}H_{21}F_3N_2O_4$ requires *M*, 374.145); ν_{max}(KBr)/cm^{-1} 3300, 3080, 1700, 1640, 1620 and 1605; δ_H(90 MHz; $CDCl_3$) 1.51 (4 H, m, $CH_2CH_2CH_2CH_2$), 3.30 (4 H, m, $CH_2CH_2CH_2CH_2$), 3.85 (3 H, s, OMe), 3.90 (3 H, s, OMe), 5.85 (1 H, d *J* 12.2, ArCH=CH), 5.95 (1 H, br s, NH), 6.70 (1 H, d, *J* 12.2, ArCH=CH), 6.80–7.32 (3 H, m, ArH) and 7.55 (1 H, br s, NH).

(2E)-N-4-*Aminobutyl*-3-(3′,4′-*dimethoxyphenyl*)*prop*-2-*enamide* **3**.—The trifluoroacetyl derivative **9** (135 mg, 0.36 mmol) was refluxed with potassium carbonate (200 mg, 1.44 mmol) in methanol (30 cm^3) and water (2 cm^3) for 1.5 h. The solvents were evaporated under vacuum and the residue was chromatographed on dry silica eluting with 95% ethanol–25% aqueous ammonia (4:1) to give the *title compound* **3** (0.09 g, 90%) as a tan-coloured oil which solidified on prolonged standing (Found: M^+, 278.164; $C_{15}H_{22}N_2O_3$ requires *M*, 278.163); ν_{max}(neat)/cm^{-1} 3400, 3260, 3080, 1650 and 1600; δ_H(90 MHz; $CDCl_3$) 1.75 (4 H, m, $CH_2CH_2CH_2CH_2$), 2.93 (2 H, br s, CH_2NH_2), 3.35 (2 H, br s, $CONHCH_2$), 3.95 (6 H, s, 2 × OMe), 5.95 (3 H, br s, 3 × NH), 6.70 (1 H, d J 16.0, ArCH=CH), 6.9–7.3 (3 H, m, ArH) and 7.50 (1 H, d, *J* 16.0, ArCH=CH).

(2Z)-N-4-*Aminobutyl*-3-(3′,4′-*dimethoxyphenyl*)*prop*-2-*enamide* **12**.—The 2-*Z*-enamide **11** (240 mg, 0.65 mmol) was hydrolysed by refluxing with potassium carbonate (350 mg, 2.60 mmol, 4 equiv.) in methanol (44 cm^3) and water (3 cm^3) for 1.5 h. Work up and chromatography as for the (2*E*)-compound above gave the *title compound* **12** as an oil which eventually solidified (0.17 g, 94%) (Found: M^+, 278.170. $C_{15}H_{22}N_2O_3$ requires *M*, 278.163); ν_{max}(KBr)/cm^{-1} 3400, 3256, 3060, 1660 and 1600; δ_H(90 MHz; $CDCl_3$) 1.61 (4 H, m, $CH_2CH_2CH_2CH_2$), 2.43 (2 H, m, CH_2NH_2), 2.91 (2 H, m, $CONHCH_2$), 3.84 (6 H, s, 2 × OMe), 6.05 (1 H, d, *J* 12.2, ArCH=CH), 6.75 (3 H, br s, 3 × NH), 6.82 (1 H, d, *J* 12.2, ArCH=CH) and 6.9–7.3 (3 H, m, ArH).

3-*Methylbut*-2-*enyl Isocyanate* **13**.—Silver cyanate (5 g, 33.3 mmol) was suspended in dry ether in a darkened flask and 1-bromo-3-methylbut-2-ene (4.9 g, 33.3 mmol) was added dropwise with stirring under nitrogen, and stirring was continued overnight. After filtration through Celite the filtrate was evaporated and distilled to give the *title compound* **13** (1.4 g, 40%), b.p. 45 °C at 20 mmHg (Found: M^+, 111.070. C_6H_9NO requires *M*, 111.067); ν_{max}(neat)/cm^{-1} 2280 and 1680; δ_H(90 MHz; $CDCl_3$) 1.65 (3 H, s, $CH_3C=C$), 1.75 (3 H, s, $CH_3C=C$), 3.80 (2 H, d, *J* 9.0, $C=CHCH_2$) and 5.30 (1 H, m, $C=CHCH_2$).

1-(3-*Methylbut*-2-*enyl*)-3-{4-[(2E)-3-(3′,4′-*dimethoxyphenyl*)-*prop*-2-*enamido*]*butyl*}*urea* **1**.—The (2*E*)-prop-2-enamide **3** (0.09 g, 0.50 mmol) in dry dichloromethane was treated with the isocyanate **13** (0.17 g, 1.5 mmol, 3 equiv.) in diethyl ether, the mixture being stirred overnight under nitrogen. The solvent was evaporated and the residue was chromatographed on silica eluting with benzene–ethanol (9:1) to give the (2E)-*enamidourea* **1** (0.11 g, 85%), m.p. 196–198 °C (Found: C, 64.65; H, 8.1; N, 10.65%; M^+, 389.229. $C_{21}H_{31}N_3O_4$ requires C, 64.8; H, 7.95, N,

10.8%; *M*, 389.231); ν_{max}(KBr)/cm^{-1} 3340, 3285, 3080, 1630, 1585 and 1520; λ_{max}(EtOH)/nm 231 (ε 6500), 291 (7500) and 314 (7500); δ_H(250 MHz; [$^2H_6$]-DMSO) 1.41 (4 H, br s, $CH_2CH_2CH_2CH_2$), 1.61 (3 H, s, CH_3C=C), 1.65 (3 H, s, CH_3C=C), 2.99 (2 H, m, CH_2NHCONH), 3.16 (2 H, m, CH_2-NHCOC), 3.56 (2 H, t, *J* 5.8, C=CCH_2NH), 3.80 (6 H, s, 2 × OMe), 5.12 (1 H, t, *J* 6.7, CH_2CH=C), 5.75 (2 H, m, 2 × NH), 6.50 (1 H, d, *J* 15.7, ArCH=C*H*), 6.98 (1 H, d, *J* 8.8, 9‴-H), 7.10 (1 H, d, *J* 8.8, 8‴-H), 7.14 (1 H, s, 5‴-H), 7.34 (1 H, d, *J* 15.7, ArC*H*=CH) and 7.94 (1 H, br s, NH); δ_C(250 MHz; [$^2H_6$]-DMSO) 18.6 (CH_3, C-5″), 26.4 (CH_3, C-4″), 27.4 (CH_2, C-2′), 28.7 (CH_2, C-3′), 38.3 (CH_2, C-1′), 39.95 (CH_2, C-4′), 41.2 (CH_2, C-1″), 56.6 (CH_3, C-10‴), 56.45 (CH_3, C-11‴), 111.0 (CH, C-5‴), 112.5 (CH, C-9‴), 121.3 (CH, C-8‴), 122.3 (CH, C-2″), 124.1 (CH, C-2‴), 128.9 (C, C-4‴), 133.8 (C, C-3″), 139.5 (CH, C-3‴), 151.1 (C, C-7-‴), 149.95 (C, C-6‴), 159.0 (C, C-2) and 166.2 (C, C-1‴).

1-(3-*Methylbut*-2-*enyl*)-3-{4-[(2Z)-3-(3′,4′-*dimethoxyphenyl*)-*prop*-2-*enamido*]*butyl*}*urea* **2**.—The (2*Z*)-enamide **12** (0.17 g, 0.61 mmol) was treated with the isocyanate **13** (0.20 g, 1.83 mmol) as above and worked up and chromatographed in a similar fashion. The product (0.16 g, 66%) proved to be a mixture (~1:1) of the (2*E*)-amido-urea **1** and the (2*Z*)-form **2**. These were separated by reversed phase (C_{18}) HPLC eluting with methanol–water (1:1) under careful exclusion of light. The (2*Z*)-enamidourea **2** had m.p. 225 °C (decomp.) (Found: M^+, 389.237. $C_{21}H_{31}N_3O_4$ requires *M*, 389.231); ν_{max}(KBr) 3340, 3285, 3080, 1630, 1585, 1550 and 1520; λ_{max}(EtOH)/nm 291 (ε 10 900) and 312 (10 500); δ_H(250 MHz; [$^2H_6$]-DMSO) 1.39 (4 H, m, $CH_2CH_2CH_2CH_2$), 1.59 (3 H, s, CH_3C=C), 1.65 (3 H, s, CH_3C=C), 2.96 (2 H, m, CH_2NHCONH), 3.10 (2 H, m, CH_2NHCOC), 3.55 (2 H, t, *J* 6.4, C=CHCH_2NH), 3.72 (3 H, s, OMe), 3.76 (3 H, s, OMe), 5.11 (1 H, m, CH_2CH=C), 5.85 (1 H, d, *J* 13.0, ArCH=C*H*), 5.79–5.90 (2 H, m, 2 × NH), 6.53 (1 H, d, *J* 13.0, ArC*H*=CH), 6.90 (1 H, d, *J* 8.4, 8‴-H), 7.18 (1 H, dd, *J* 8.4, 2.0, 9‴-H), 7.69 (1 H, d, *J* 2.0, 5‴-H) and 8.12 (1 H, m, NH); δ_C(250 MHz; [$^2H_6$]-DMSO) 18.6 (CH_3, C-5″), 26.3 (CH_3, C-4″), 27.4 (CH_2, C-2′), 28.6 (CH_2, C-3′), 38.1 (CH_2, C-1′), 39.3 (CH_2, C-4′), 41.1 (CH_2, C-1″), 56.3 (CH_3, C-10‴), 56.4 (CH_3, C-11‴), 111.9 (CH, C-5‴), 114.5 (CH, C-8‴), 123.1 (CH, C-9‴), 124.0 (CH, C-2″), 124.7 (CH, C-2‴), 129.1 (C, C-4‴), 133.5 (C, C-3″), 137.1 (CH, C-3‴), 148.8 (C, C-6‴), 150.1 (C, C-7‴), 159.1 (C, C-2) and 167.0 (C, C-1‴).

3-*Methylbut*-2-*enyl Cyanamide* **18**.—An aqueous solution of guanidine was prepared by the successive treatment of guanidine carbonate (30 g, 0.166 mol) with sulfuric acid (36.8 cm^3; 4.5 mol dm^{-3} solution; 0.166 mol) and barium hydroxide (52.37 g, 0.166 mol). After stirring for 1 h, the solution was filtered. A solution of 3-methylbut-2-enyl bromide (12.6 g, 0.084 mol) in ethanol (39.8 cm^3) was added dropwise to the aqueous guanidine and stirred for 1 h. An excess of sodium hydroxide (50 g) was added and the mixture was distilled at atmospheric pressure, more water being progressively added until 500 cm^3 of distillate had been collected. The distillate was neutralised with conc. hydrochloric acid and evaporated under vacuum. The residue was extracted with boiling ethanol (95%) and the ammonium chloride filtered off. Evaporation of the filtrate under reduced pressure was followed by extraction of the residue with hot (80–90 °C) butanol. The butanol solution was concentrated under reduced pressure and then treated with dry ether. Methylbut-2-en-1-amine hydrochloride (prenylamine hydrochloride)[12] was filtered off and dried (2.0 g, 28%), m.p. 170–173 °C (decomp.) (Found [M − HCl]$^+$, *m*/*z* 85.087. Calc. for $C_5H_{11}N$: *m*/*z* 85.089); δ_H(90 MHz; D_2O) 5.45 (1 H, m, C=C*H*), 3.75 (2 H, d, *J* 7.2, C=CHCH_2NH), 1.90 (3 H, s, CH_3C=C) and 1.85 (3 H, s, CH_3C=C).

Cyanogen bromide[13] (0.54 g, 5.1 mmol) and sodium carbonate (2.12 g, 20.4 mmol) in THF at −10 °C was treated with prenylamine hydrochloride (0.6 g, 5.1 mmol) and then stirred at 0 °C for 2 h. The mixture was filtered and concentrated at atmospheric pressure to give a pale yellow oil containing the title compound **18** (0.45 g), ν_{max}(neat)/cm^{-1} 2260 and 1640; δ_H(90 MHz; $CDCl_3$) 1.75 (3 H, s, CH_3C=C), 1.85 (3 H, s, CH_3C=C), 4.1 (2 H, d, *J* 8, CH_3C=CHCH_2) and 5.4 (1 H, m, C=CH). In a preliminary experiment, when heated under reflux with the (2*E*)-enamide **3** in THF, 3-methylbut-2-enyl cyanamide **18** formed caracasanamide as evidenced by the ^{1}H NMR spectrum of the product.

Aminoiminomethanesulfonic Acid **16**.—Peracetic acid (35%, 8 cm^3, 30 mmol) was added dropwise to a cooled suspension of formamidinesulfinic acid (3.24 g, 30 mmol) in acetic acid (10 cm^3), keeping the temperature below 10 °C, and stirring was continued at 20 °C for 2 h. Crystals of aminoiminomethanesulfonic acid were filtered off, washed with dry ethanol, and dried under reduced pressure (3.0 g, 81%), m.p. 126–127 °C (lit.,[11] m.p. 125–126 °C) (Found: C, 10.0; H, 3.3; N, 22.9. Calc. for $CH_4N_2O_3S$: C, 9.65; H, 3.25; N, 22.6%).

3-{4-[(2E)-3-(3′,4′-*Dimethoxyphenyl*)*prop*-2-*enamido*]*butyl*}-*guanidine Bisulfite Salt* **17** *and its Free Base*.—The (2*E*)-enamide **12** (0.28 g, 1.01 mmol) and aminoiminomethanesulfonic acid (0.13 g, 1.01 mmol) were stirred together in dry methanol (2 cm^3) under nitrogen at room temperature until a clear solution was obtained. Stirring was continued for a further 1 h when the mixture was evaporated to give the *title compound* **17** (0.4 g, 99%). Treatment of the cream coloured solid with 10% sodium hydroxide (81 mm^3, 2.02 mmol) followed by extraction with chloroform gave, after drying and evaporation under vacuum, the *guanidine base* from **17** (0.25 g, 77%) {Found: *m*/*z* 303 ($M^+ - NH_3$) and 261 [$M^+ - CH_5N_3$ (guanidine)]. $C_{16}H_{24}N_4O_3$ requires $M^+ - NH_3$ 303; $M^+ - CH_5N_3$ 261}; δ_H(90 MHz; [$^2H_6$]-DMSO) 3.4 (6 H, m, $CH_2CH_2CH_2CH_2$, NH_2), 3.1 (4 H, m, $CH_2CH_2CH_2CH_2$), 3.25 (7 H, s, 2 × OMe, NH), 6.5 (1 H, d, *J* 15.3, ArCH=C*H*), 7.1 (3 H, m, ArH), 7.35 (1 H, d, *J* 15.3, ArC*H*=CH), 7.55 (1 H, m, N*H*) and 8.05 (1 H, m, NH).

1-(3-*Methylbut*-2-*enyl*)-3-{4-[3-(2E)-(3′,4′-*dimethoxyphenyl*)-*prop*-2-*enamido*]*butyl*}*guanidine* (*Caracasanamide*) **15** (R = H).—The guanidine bisulfite **17** (0.4 g, 1.01 mmol), 10% sodium hydroxide (0.08 ml, 2.02 mmol) and prenyl bromide (0.16 g, 1.04 mmol) were stirred together for 18 h. The mixture was extracted with chloroform and the extracts were dried ($MgSO_4$) and evaporated. Chromatography of the product on silica eluting with chloroform–methanol (10:1) gave (E)-*caracasanamide* **15** (R = H) (81 mg, unoptimised) [Found: M^+ + 1 (FAB) 389 (100%). $C_{21}H_{32}O_3N_4$ requires for M + 1 389]; ν_{max}(KBr)/cm^{-1} 3500–3080br, 1660, 1630, 1600, 1545 and 1510; δ_H(250 MHz; $CDCl_3$) 1.55 (4 H, br s, $CH_2CH_2CH_2CH_2$), 1.55 (3 H, s, CH_3C=C), 1.60 (3 H, s, CH_3C=C), 3.21 (4 H, m, $CH_2CH_2CH_2CH_2$), 3.43 (2 H, d, *J* 7.5, C=CHCH_2NH), 3.79 (3 H, s, OMe), 3.81 (3 H, s, OMe), 5.09 (1 H, m, CH_2CH=C), 5.30 (1 H, m, N*H*), 6.63 (1 H, d, *J* 15.5, ArCH=C*H*), 6.72 (1 H, d, *J* 8.4, 9″-'H), 7.0 (1 H, d, *J* 8.4, 8‴-H), 7.05 (1 H, br s, 5‴-H), 7.39 (1 H, d, *J* 15.5, ArC*H*=CH), 7.39 (1 H, br s, N*H*) and 7.64 (1 H, br s, N*H*); δ_C(250 MHz; $CDCl_3$) 17.9 (CH_3, C-5″), 25.4 (CH_3, C-4″), 26.3, 29.5 (2 × CH_2, C-2′ and -3′), 38.3 (CH_2, C-4′), 39.7 (CH_2, C-1′), 41.1 (CH_2, C-1″), 55.7, 55.8 (2 × CH_3, C-10‴ and C-11‴), 109.7 (CH, C-8‴), 110.8 (CH, C-5‴), 114.7 (CH, C-9‴), 119.0 (CH, C-2″), 121.9 (CH, C-2‴), 127.8 (C, C-4‴), 137.6 (C, C-3″), 140.1 (CH, C-3‴), 148.9 (C, C-6‴), 150.3 (C, C-7‴), 156.0 (C, C-2) and 167.4 (C, C-1‴). The crude reaction product contained some *N*-bis-prenylated material **15** (R = prenyl) as was

shown by the presence of an $[M + 1]^+$ peak in the FAB spectrum at m/z 457.

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