Synthesis of Antitumour Carbon-Bridged Imidazopyridazine Carbamates

Clive V. Denyer[a)*], Michael T. Reddy[a)], D. Con Jenkins[b)], Elaine Rapson[b)], and Stuart D.M. Watts[c)]

Departments of Medicinal Chemistry[a)], Molecular Sciences[b)], and Biochemical Sciences[c)], Wellcome Research Laboratories, Langley Court, Beckenham, Kent, BR3 3BS, U.K.

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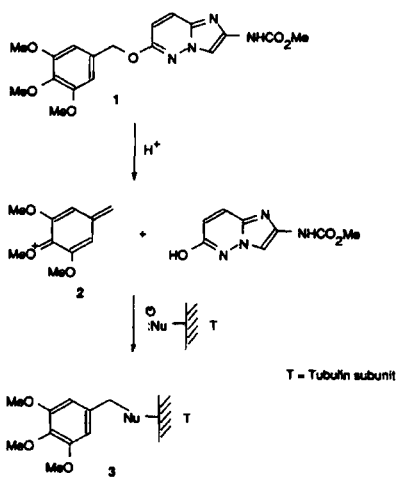
Two carbon-bridged analogues **11** and **15** of the potent microtubule inhibitor BW1069C85 (**1**) have been synthesised and evaluated for antitubulin and antitumour activity *in vitro*. Though the compounds were somewhat less potent than BW1069C85, significant activity against tubulin polymerisation and cell proliferation was demonstrated in the assays.

Synthese von antitumor-wirksamen kohlenstoffverbrückten Imidazopyridazincarbamaten

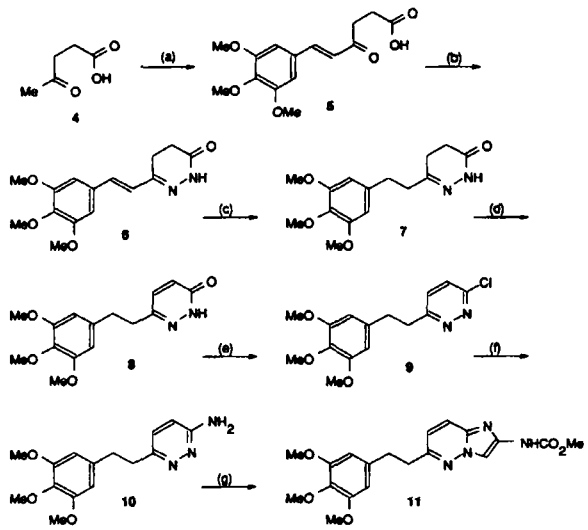
Es wurden die kohlenstoffverbrückten Analoga **11** und **15** des hochwirksamen Mikrotubulihemmers BW1069C85 (**1**) dargestellt und deren Antitubulinwirksamkeit und Antitumorwirksamkeit *in vitro* geprüft. Obwohl die Verbindungen in diesen Versuchen etwas schwächer als BW1069C85 wirken, wurde bedeutsame Wirksamkeit gegen Tubulinpolymerisierung und Zellwachstum gefunden.

Recently, it was reported that the synthetic imidazopyridazine carbamate BW1069C85 (**1**) (Scheme 1) demonstrates high activity in a variety of *in vitro* and *in vivo* assays[1)]. In particular, the compound was shown to be a potent inhibitor of tubulin polymerisation, mitotic spindle formation and cell proliferation. In addition it was active in the NCI P388 *in vivo* model. The question arose as to the reason for this activity and whether this was connected with covalent binding to a tubulin subunit. It was conceivable that at the tubulin receptor site enzymatic catalysis could result in the formation of a highly reactive *O*-methyl derivative of a quinone methide **2**, which could then alkylate the receptor to give the species **3**[2,3)]. Therefore, to investigate this mechanism, it seemed of interest to prepare analogues of **1** in which this type of reaction was not possible and compare their activity with **1**. Accordingly, we undertook the synthesis of the carbon-bridged analogues **11** (Scheme 2) and **15** (Scheme 3).



Scheme 1

It was thought that for compound **11** a suitable approach would be that of Scheme 2, starting from laevulinic acid (**4**). The advantage of this route is that the principal bond-forming reactions are performed early on in the sequence before the more reactive portions of the molecule are introduced. Laevulinic acid (**4**) was condensed[4)] with 3,4,5-trimethoxybenzaldehyde in aqueous solution to give the α,β-unsaturated keto-acid **5**. This was then reacted with hydrazine in glacial acetic acid at reflux[4)] to give the α-styryldihydropyridazone **6** which was hydrogenated[5)] over Pd/C in glacial acetic acid at 85°C under pressure to saturate the central double bond thereby affording the phenethyl-dihydropyridazone **7**. The latter was dehydrogenated at the het-



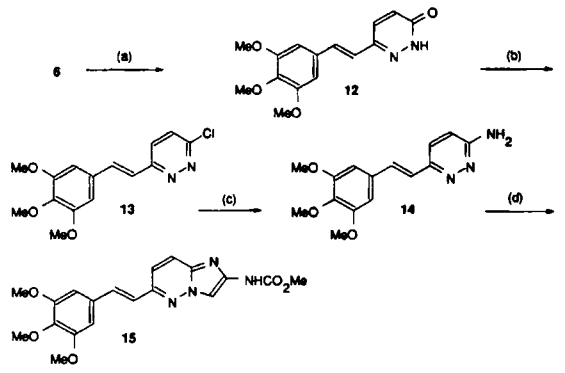
Reagents: (a) $3,4,5\text{-}(MeO)_3C_6H_2CHO$; (b) $N_2H_4H_2O$, AcOH; (c) H_2, Pd-C, AcOH, 85°C; (d) SeO_2, EtOH; (e) $POCl_3$; (f) NH_3, MeOH, 150°C; (g) $ClCH_2CONHCO_2Me$, HMPA.

Scheme 2

  0365-6233/94/0202-0095 $ 5.00 + .25/0

erocyclic ring with SeO_2 in ethanol[6] to give the corresponding phenethyl-pyridazone **8**. The order in which these two stages are carried out is crucial; although dehydrogenation of **6** with SeO_2 is possible to give the α-styryl-pyridazone **12** (Scheme 3), hydrogenation of **12** over Pd/C as above gives overreduction back to **7** rather than **8**. - Conversion of the phenethyl-pyridazone **8** to the corresponding imino-chloride **9** was achieved with $POCl_3$[6,7] at 100°C. It then remained for the introduction of the amino-group[8,9] at the 3-position of the pyridazine ring by reaction with ammonia at 150°C giving the amino-pyridazine **10**. Finally compound **10** underwent a smooth annulation[10] with methyl *N*-chloroacetylcarbamate affording the desired target phenethyl-imidazopyridazine carbamate **11**.

A further carbon-bridged analogue of BW1069C85 is the etheno-compound **15**. This was made available by the route shown in Scheme 3, starting from the α-styryl-dihydropyridazone **6**. This was dehydrogenated with SeO_2 in ethanol to the corresponding α-styryl-pyridazone **12**, which was converted to the imino-chloride **13**. The latter was ammonolysed to the α-styryl-aminopyridazine **14** which was annulated to the target α-styryl-imidazopyridazine carbamate **15**.



Reagents: (a) SeO_2/EtOH; (b) $POCl_3$; (c) NH_3, MeOH; (d) $ClCH_2CONHCO_2Me$, HMPA

Scheme 3

Table: Biological Results

Compound	Tubulin Polymerisation[a] IC_{50} ($x10^{-6}$M)	Proliferation[b] IC_{50} ($x10^{-6}$M)
(1)	0.31	0.0089
(11)	10	0.48
(15)	-	100
Vincristine	0.22	0.0047
Colchicine	1.5	0.00062

[a] Vs. Horse brain tubulin polymerisation *in vitro*

[b] Vs. P388 D_1 mouse leukaemia cells *in vitro*

The carbamates **11** and **15** were evaluated, along with BW1069C85, for activity against tubulin polymerisation and against the proliferation of leukaemia cells in standard assays[11,12]. The results are summarised in the Table, along with data for colchicine and vincristine for comparison. These show that whilst significant activity is shown by **11** in the tubulin assay, and by **11** and **15** in the cell proliferation assay, the potency is considerably less than that of BW1069C85. Further work is needed to define the basis for this difference in potency, which could be due to the formation of reactive intermediates on the part of BW1069C85, or due to solubility or polarity differences.

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Experimental Part

Melting points: Büchi melting-point apparatus, uncorrected.- ^{1}H-NMR spectra: Bruker AM-200 FT (200 MHz).- IR spectra: KBr discs on Perkin-Elmer 247.- Mass spectra: Kratos MS-9 and Concept at 70 eV.- T.l.c. system: MeOH:CH_2Cl_2, 1:19 on silica GF_{254} (Merck 5714 plates, 20 cm x 5 cm, run over 10 cm).- Solvents were evaporated at water-pump vacuum and solid samples were routinely dried *in vacuo* at ca 0.2 mm Hg. Analytical samples were dried *in vacuo* at 60°C as appropriate. Hexamethylphosphoramide was dried over CaH_2 and distilled *in vacuo*, b.p. 70°C/0.8 mm Hg.

4-Oxo-6-(3,4,5-trimethoxyphenethyl)hex-5-enoic acid (**5**)

A solution of laevulinic acid (**4**) (50.0 g, 0.43 mol) in water (200 ml) was added to a mixture of 3,4,5-trimethoxybenzaldehyde (85.0 g, 0.43 mol) in ethanol (150 ml) and aqueous NaOH (5%, 700 ml). The mixture was warmed with vigorous stirring until all the aldehyde had dissolved and was then poured onto ice (ca. 2 kg). It was then acidified to pH 3-4 and left overnight. The crystalline material formed was filtered off, dried *in vacuo* and then recrystallised from ethanol to give pale yellow crystals (30.08 g, 24%) of **5**, m.p. 187-189°C.- R_f 0.23.- $C_{15}H_{18}O_6$ (294.3) Calcd. C 61.2 H 6.17 Found C 61.2 H 6.25.- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 2.50 (2H, t, J_{A1B1} = 7 Hz, CH_2), 2.92 (2H, t, J_{A1B1} = 7 Hz, CH_2), 3.33 (1H, br.m, CO_2H), 3.70 (1H, s, 4'-MeO), 3.83 (6H, s, 3'-MeO and 5'-MeO), 6.91 (1H, d, J_{A2B2} = 18 Hz, CH), 7.08 (2H, s, 2'-H, 6'-H), 7.57 (1H, d, J_{A2B2} = 18 Hz, CH).- IR (KBr): 1728; 1642; 1628; 1582 cm^{-1}.- m/z = 294 ($M^{+\cdot}$).

4,5-Dihydro-6-(3,4,5-trimethoxy-α-styryl)pyridazin-3(2H)-one (**6**)

5 (20 g, 0.068 mol) was dissolved in glacial acetic acid (240 ml) and then hydrazine hydrate (3.4 g, 0.068 mol) was added. The mixture was heated under reflux for 2.5 h, cooled and poured into water (ca. 2 l). After standing overnight, the crystals formed were filtered at the pump and dried *in vacuo* to give the product **6** (13.58 g, 69%) with a trace of impurity by t.l.c. A portion (3.5 g) was recrystallised from methanol and gave 3.18 g of **6**, m.p. 173-175°C.- R_f 0.50.- $C_{15}H_{18}N_2O_4$ (290.3) Calcd. C 62.0 H 6.25 N 9.6 Found C 61.6 H 6.16 N 9.6.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.56 (2H, t, J_{AB} = 9 Hz, CH_2), 2.82 (2H, t, J_{AB} = 9 Hz, CH_2), 3.87 (3H, s, 4'-MeO), 3.89 (6H, s, 3'-MeO and 5'-MeO), 6.70 (2H, s, CH, CH), 6.82 (2H, s, CH, CH), 8.91 (1H, br.s, NH).- IR (KBr): 1665; 1580 cm^{-1}.- m/z = 290 ($M^{+\cdot}$).

4,5-Dihydro-6-(3,4,5-trimethoxyphenethyl)pyridazin-3(2H)-one (**7**)

6 (5.0 g, 0.017 mol) was hydrogenated (85°C, 10 atm H_2) in glacial acetic acid (150 ml) over 10% Pd/C (0.25 g) until the requisite uptake of H_2 had occurred. The mixture was filtered through Hyflo, and the filtrate evaporated *in vacuo* at 35°C. The remaining traces of glacial acetic acid

were removed by azeotropic distillation with toluene and the brown solid (4.9 g) purified further by flash chromatography on silica (column 15 cm x 10 cm) with 1% methanol/dichloromethane. Removal of the solvent from the appropriate fractions gave 3.04 g (60%) of **7**, m.p. 116-117°C.- R_f 0.48.- $C_{15}H_{20}N_2O_4$ (292.3) Calcd. C 61.6 H 6.90 N 9.6 Found C 61.4 H 7.14 N 9.4.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.95 (4H, m, part. res., CH_2, CH_2), 2.61 (2H, t, J_{AB} = 7 Hz, CH_2), 2.84 (2H, t, J_{AB} = 7 Hz, CH_2), 3.81 (3H, s, 4'-MeO), 3.83 (6H, s, 3'-MeO and 5'-MeO), 6.43 (2H, s, 2'-H, 6'-H), 8.46 (1H, br.s, NH).- IR (KBr): 1678; 1670; 1590 cm^{-1}.- m/z = 292 ($M^{+\cdot}$).

6-(3,4,5-Trimethoxyphenethyl)pyridazine-3(2H)-one (**8**)

7 (1.72 g, 5.93 mmol) and SeO_2 (0.98 g, 8.83 mmol) were refluxed in ethanol (80 ml) for 4.5 days. More SeO_2 (0.5 g, 4.51 mmol) was added and the mixture was refluxed for a further 5 days. The mixture was filtered to remove selenium which had separated and the filtrate evaporated *in vacuo* to give a brown sticky solid (2.21 g). This solid was subjected to flash chromatography on silica (column 30 cm x 5 cm) with 1-2% methanol/dichloromethane as the eluent. Combination of the appropriate fractions gave 1.43 g (84%) of **8** as a sandy-brown crystalline solid, m.p. 122-124°C.- R_f 0.33.- $C_{15}H_{18}N_2O_4$ (290.3) Calcd. C 62.1 H 6.25 N 9.6 Found C 62.1 H 6.31 N 9.4.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.82 (4H, s, CH_2-CH_2), 3.83 (9H, 2s, 3'-MeO, 5'-MeO, 4'-MeO), 6.48 (2H, s, 2'-H, 6'-H), 6.89 (1H, d, J_{AB} = 6 Hz, HetCH), 7.08 (1H, d, J_{AB} = 6 Hz, HetCH), 11.64 (1H, br.s, NH).- IR (KBr): 1670; 1658; 1601; 1595 cm^{-1}.- m/z = 290 ($M^{+\cdot}$).

3-Chloro-6-(3,4,5-trimethoxyphenethyl)pyridazine (**9**)

A mixture of **8** (2.80 g, 9.65 mmol) and $POCl_3$ (70 ml) was heated at 100°C for 1 h, cooled to room temp. and hydrolysed by careful, gradual addition to water over 3 h, so that the temp. did not exceed 30°C. The mixture was then basified to pH 12 by NaOH (10 N, 700 ml) and then left at 4°C overnight. The precipitate was filtered at the pump, washed well with water to remove inorganic salts and the residue on the sinter taken up in dichloromethane. After drying (Na_2SO_4), removal of the solvent gave a light-brown solid (2.84 g) which was purified by flash chromatography on silica (column 23 cm x 5 cm) with 10% ethyl acetate/dichloromethane. Appropriate fractions were combined to give 2.16 g (73%) of **9** as a white solid, m.p. 105-106°C.- R_f 0.76.- $C_{15}H_{17}N_2O_3Cl$ (308.8) Calcd. C 58.4 H 5.55 N 9.1 Found C 58.3 H 5.65 N 8.8.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.04 (2H, t, J_{A1B1} = 9 Hz, CH_2), 3.37 (2H, t, J_{A1B1} = 9 Hz, CH_2), 3.82 (9H, s, 3'-MeO, 4'-MeO, 5'-MeO), 6.37 (2H, s, 2'-H, 6'-H), 7.16 (1H, d, J_{A2B2} = 9 Hz, HetCH), 7.38 (1H, d, J_{A2B2} = 9 Hz, HetCH).- IR (KBr): 1591; 1516 cm^{-1}.- m/z = 310 (^{37}Cl, $M^{+\cdot}$), 308 (^{35}Cl, $M^{+\cdot}$).

3-Amino-6-(3,4,5-trimethyoxyphenethyl)pyridazine (**10**)

9 (1.97 g, 6.38 mmol) in methanolic ammonia (saturated, 800 ml) was heated in a stainless steel autoclave at 150°C for 65 h and then allowed to cool. The mixture was evaporated *in vacuo* to give a dark-brown sticky solid (2.84 g) which was subjected to flash chromatography on silica (two columns 23 cm x 4 cm; 23 cm x 2 cm) with 3% methanol/dichloromethane. Combination of the relevant fractions afforded 0.56 g (30%) of **10** as a white solid, m.p. 130-132°C.- R_f 0.17.- $C_{15}H_{19}N_3O_3$ (289.3) Calcd. C 62.3 H 6.62 N 14.5 Found C 61.8 H 6.72 N 14.3.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.01 (2H, part. res. m, CH_2), 3.13 (2H, part. res. m, CH_2), 3.83 (9H, s, 3'-MeO, 4'-MeO, 5'-MeO), 4.74 and 1.98 (2H, br.s, NH_2), 6.42 (2H, s, 2'-H, 6'-H), 6.67 (1H, br.d, J_{AB} = 9 Hz, HetCH), 6.96 (1H, d, J_{AB} = 9 Hz, HetCH).- IR (KBr): 3322, 3158, 1642, 1612, 1586 cm^{-1}.- m/z = 289 ($M^{+\cdot}$).

Methyl 6-(3,4,5-trimethoxyphenethyl)imidazo[1,2-b]pyridazin-2-ylcarbamate (**11**)

10 (0.50 g, 1.73 mmol) and methyl *N*-chloroacetylcarbamate (0.26, 1.74 mmol) were heated in dry HMPA (15 ml) with stirring for 4 h at 100°C under dry N_2. The mixture was then cooled, poured into water (150 ml), when a precipitate formed. After standing overnight the precipitate was filtered off and dried *in vacuo* to yield a cream-coloured crystalline solid (0.53 g). This was purified by flash chromatography on silica (column 20 cm x 2 cm) with 1-2% methanol/dichloromethane and crystallisation from ethyl acetate to give 0.18 g (27%) of **11** as off-white crystals, m.p. 175-176°C.- R_f 0.50.- $C_{19}H_{22}N_4O_5$ (386.4) Calcd. C 59.1 H 5.74 N 14.5 Found C 59.1 H 5.76 N 14.2.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.02 (2H, part. res. m, CH_2), 3.12 (2H, part. res. m, CH_2), 3.82 (9H, 3'-MeO, 4'-MeO, 5'-MeO), 3.88 (3H, s, CO_2Me), 6.42 (2H, s, 2'-H, 6'-H), 6.85 (1H, d, J_{AB} = 10 Hz, HetCH), 7.77 (1H, d, J_{AB} = 10 Hz, HetCH), 8.18 (1H, br.s, HetCH) and 10.17 (1H, br.s, NH).- IR (KBr): 1732; 1585; 1555 cm^{-1}.- m/z = 386 ($M^{+\cdot}$).

6-(3,4,5-trimethoxy-α-styryl)pyridazin-3(2H)-one (**12**)

6 (10.0 g, 34.4 mmol) and SeO_2 (10.0 g, 90.1 mmol) were heated under reflux in ethanol (300 ml) for 80 h. A further charge of SeO_2 (10.0 g) was added and the reflux continued for a further 40 h. The mixture was then filtered through Hyflo, evaporated and the residue dried *in vacuo* to give a dark-brown sticky solid (14.48 g). This was flash chromatographed on silica (column size 23 cm x 10 cm) with 0-2% methanol/dichloromethane. Combination of the appropriate fractions, followed by crystallisation from methanol afforded 5.57 g (56%) of **12** as a sandy-brown solid, m.p. 194-196°C.- R_f 0.36.- $C_{15}H_{16}N_2O_4$ (288.3) Calcd. C 62.5 H 5.59 N 9.7 Found C 62.2 H 5.61 N 9.6.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.88 (3H, s, 4'-MeO), 3.91 (6H, s, 3'-MeO, 5'-MeO), 6.74 (2H, s, 2'-H, 6'-H), 6.92 (1H, d, J_{A1B1} = 18 Hz, CH), 7.01 (1H, d, J_{A2B2} = 10 Hz, HetCH), 7.10 (1H, d, J_{A1B1} = 18 Hz, CH), 7.66 (1H, d, J_{A2B2} = 10 Hz, HetCH), 11.95 (1H, br.s, NH).- IR (KBr): 1669; 1587 cm^{-1}.- m/z = 288 ($M^{+\cdot}$).

3-Chloro-6-(3,4,5-trimethoxy-α-styryl)pyridazine (**13**)

12 (5.30 g, 0.018 mol) in $POCl_3$ (150 ml) was heated at 100°C for 1.25 h. The mixture was then added to water (3 l) over 2 h, keeping the temp. in the range of 10-30°C. The mixture was then carefully basified to pH 10 with NaOH (10 N, 1.3 l). After standing overnight, the precipitate was filtered off and dried *in vacuo* to give **13**, R_f 0.84, which was pure enough for the next stage. A portion (0.74 g) was recrystallised from ethanol to give 0.48 g (72% yield) of pure **13**, m.p. 162-163.5°C.- $C_{15}H_{15}N_2O_3Cl$ (306.7) Calcd. C 58.7 H 4.93 N 9.1 Found C 58.9 H 5.01 N 9.1.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.88 (3H, s, 4'-MeO), 3.92 (6H, s, 3'-MeO, 5'-MeO), 6.82 (2H, s, 2'-H, 6'-H), 7.27 (1H, d, J_{A1B1} = 18 Hz, CH), 7.48 (1H, d, J_{A2B2} = 10 Hz, HetCH), 7.54 (1H, d, J_{A1B1} = 18 Hz, CH), 7.64 (1H, d, J_{A2B2} = 10 Hz, HetCH).- IR (KBr): 1636; 1580 cm^{-1}.- m/z = 308 (^{37}Cl, $M^{+\cdot}$), 306 (^{35}Cl, $M^{+\cdot}$).

3-Amino-6-(trimethoxy-α-styryl)pyridazine (**14**)

13 (5.50 g, 17.1 mmol) in methanolic ammonia (saturated, 800 ml) was heated in a stainless steel autoclave at 150°C for 100 h and then allowed to cool. Removal of the solvent *in vacuo* and flash chromatography on silica (column 23 cm x 5 cm) with 2% methanol/dichloromethane gave 1.58 g (26.4%) of **14** as a light-brown solid, m.p. 139-142°C.- R_f 0.22.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.87 (3H, s, 4'-MeO), 3.92 (6H, s, 3'-MeO, 5'-MeO), 4.85 (2H, br.s, NH_2), 6.75 (3H, d, J_{AB} = 10 Hz, superimposed on s, CH, 2'-H, 6'-H), 7.22 (2H, s, CH, CH), 7.49 (1H, d, J_{AB} = 10 Hz, CH).- IR (KBr): 3324; 3140; 1632; 1585 cm^{-1}.- m/z = 287 ($M^{+\cdot}$).- $C_{15}H_{17}N_3O_3$ Calcd. m/z $M^{+\cdot}$ = 287.1270 Found 287.1247.

Methyl 6-(3,4,5-trimethoxy-α-styryl)imidazo[1,2-b]pyridazin-2-ylcarbamate (**15**)

14 (1.36 g, 4.72 mmol) and methyl *N*-chloroacetylcarbamate (0.68 g, 4.49 mmol) were heated in dry HMPA (30 ml) with stirring for 4 h at 100°C under dry N_2. The mixture was then cooled and poured into water (40 ml). The precipitate was filtered off and dried *in vacuo* to give a yellow-brown solid (1.0 g). This was flash chromatographed on silica (column 24 cm x 4 cm) to give 0.4 g (22%) of **15** as a pale yellow solid, m.p. 217-219°C.- R_f 0.53.- $C_{19}H_{20}N_4O_5 \cdot 0.5\ H_2O$ (393.4) Calcd. C 58.0 H 5.38 N 14.2 Found C 57.8 H 5.09 N 14.0.- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = [3.70 (3H, s) and 3.72 (3H, s), CO_2Me and 4'-MeO], 3.87 (6H, s, 3'-MeO, 5'-MeO), 7.04 (2H, s, 2'-H, 6'-H), 7.28 (2H, d, J_{A1B1} = 18 Hz, CH), 7.58 (2H, d, J_{A2B2} = 10 Hz, HetCH), 7.60 (2H, d, J_{A1B1} = 18 Hz, CH), 7.94 (2H, d, J_{A2B2} = 10 Hz, HetCH), 7.99 (1H, s, HetCH), 10.49 (10.49 (1H, br.s, NH).- IR (KBr): 1726; 1582; 1545 cm^{-1}.

Biological Tests: Lit.[11,12].

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[Ph133]