SYNTHESIS OF 5-SUBSTITUTED INDOLE DERIVATIVES, I. AN IMPROVED METHOD FOR THE SYNTHESIS OF SUMATRIPTAN

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Abstract - An improved synthesis of sumatriptan (**1b**) *via* Fischer cyclization was achieved by introducing the ethoxycarbonyl group on the *N*-atom of the sulphonamide moiety in *N*-methyl-4-hydrazinobenzenemethanesulphonamide (**7**). As a result, substitution on the benzylic carbon of the indole nucleus could be avoided; however, formation of 1,1-bis-(indol-2-yl)-4-dimethylaminobutane-type by-product (**19**) was observed. The indolization procedure was optimized to suppress the unwanted side reaction. The *N*-protection of the sulphonamide moiety was found to be beneficial regarding the purification of the 3-[2-(dimethylamino)ethyl]-*N*-ethoxycarbonyl-*N*-methyl-1*H*-indole-5-methanesulphonamide (**18**).

INTRODUCTION

The serotonin (5-hydroxytriptamine, 5-HT) receptor superfamily has provided a rich source of targets for the design of 5-HT receptor agonists and antagonists.[1] Sumatriptan (**1b**), the first selective 5-HT$_{1D}$ agonist over the other 5-HT$_1$-receptor subtypes, has been shown to be a selective vasoconstrictor of crainal blood vessels and has proven efficacy in the acute treatment of migraine.[2] The discovery of sumatriptan has stimulated the search and design of second-generation 5-HT$_{1D}$ receptor agonists in a number of pharmaceutical firms. The large list of such compounds is still growing, but those likely to be marketed in the near future include: zolmitriptan,[3] MK-462,[4] naratriptan,[5] BMS-180048,[6] and the non-indole derivative almitidan.[7] Others showing the same activity are: AH25086,[8] and L-695894 [9] (Figure 1). From a chemical point of view, all of these tryptamines or closely related tryptamine derivatives have the common feature of possessing an amide function or a small-ring heterocycle attached to the C-5 atom of the indole nucleus through a methylene spacer. This type of tryptamine has up until now not been among the important targets of synthetic work and experiences regarding their chemical behaviour is just about to emerge. The synthetic approaches of these molecules make use of the traditional Fischer indole synthesis and consists of two main steps. First,[10] the appropriate hydrazine is obtained by reducing the pertinent
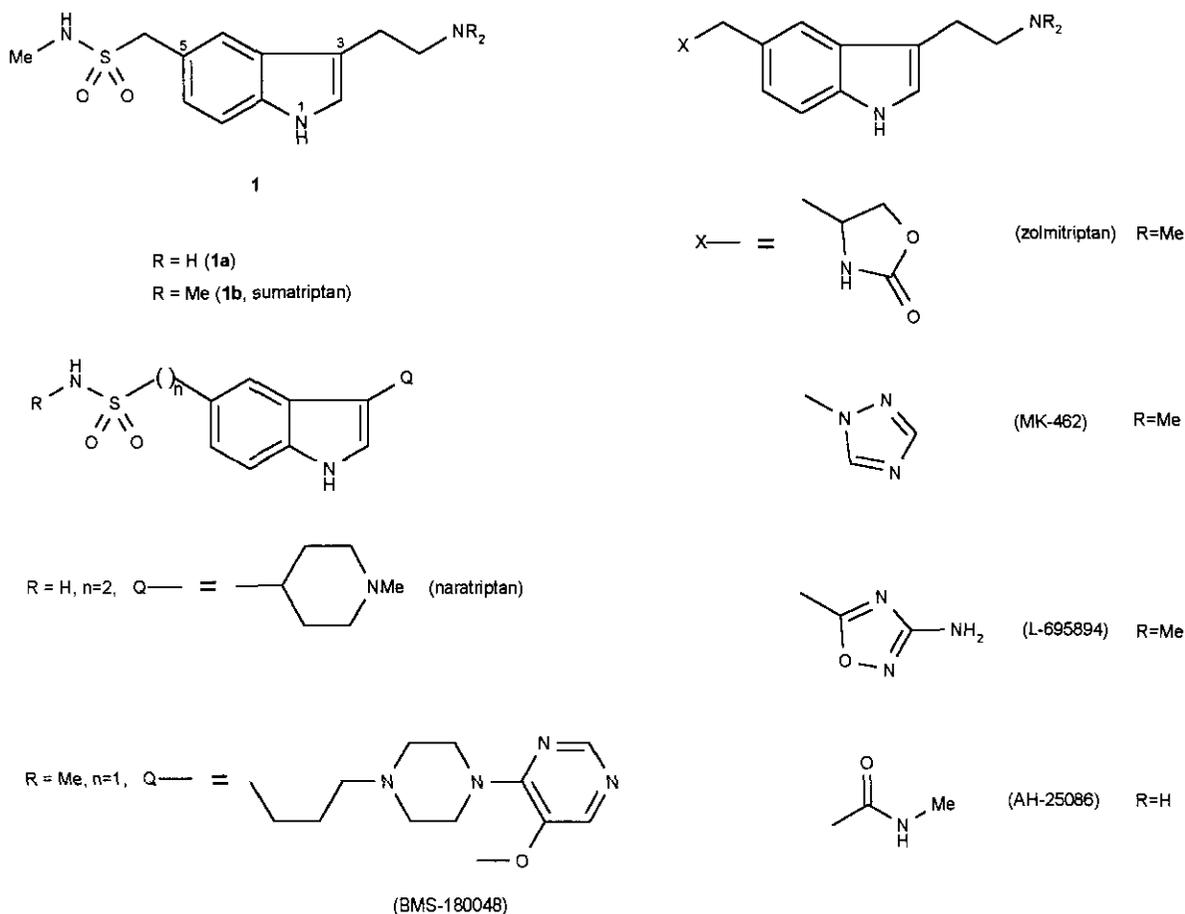
Figure 1.

diazonium salt. Secondly,[11] the hydrazine and a 4-amino- or 4-halogenobutyraldehyde derivative are condensed to furnish the hydrazone followed by its rearrangement to indole. (When 4-halogeno-butyraldehyde is used, the procedure is known as the Grandberg indolization[12] whereby the halogen atom suffers ammonolysis during ring closure). The condensation forming the hydrazone and the rearrangement are usually brought about in a one-pot reaction. The above procedure has some major shortcomings. The most obvious one is related to the preparation of certain hydrazines - including the sumatriptan intermediate (7) - which is generally accomplished by Sn(II)Cl$_2$. The application of large quantities of tin on an industrial scale requires recycling which usually involves difficult and expensive methods. This problem can sometimes be overcome by the use of the Japp-Klingemann reaction for the preparation of hydrazones.[13] The one-pot procedure, however, is associated with the formation of several by-products owing to the simultaneous existence of the nucleophilic indole formed and the electrophilic aldehyde in a reaction medium having high protic or Lewis acidity.

Side reactions

The formation of 4-type bisindoles in the reaction of 3-substituted indoles and aldehydes under acidic

conditions is well documented.[14] The bisindole (4) was obtained in a molar ratio of 1:2 to the 3-ethyl-5-nitroindole (3) when *n*-butyraldehyde-4-nitrophenylhydrazone (2) had been subjected to Fischer indoliza-tion in benzene-hydrochloric acid.[15] During the indolization process of 4-cyanomethylphenylhydrazine with 4-chloro-1,1-dimethoxybutane under Grandberg conditions, the 5-cyanomethyltryptamine underwent an alkylation /Pictet-Spengler reaction to form β-carboline (5).[16] (Scheme 1).
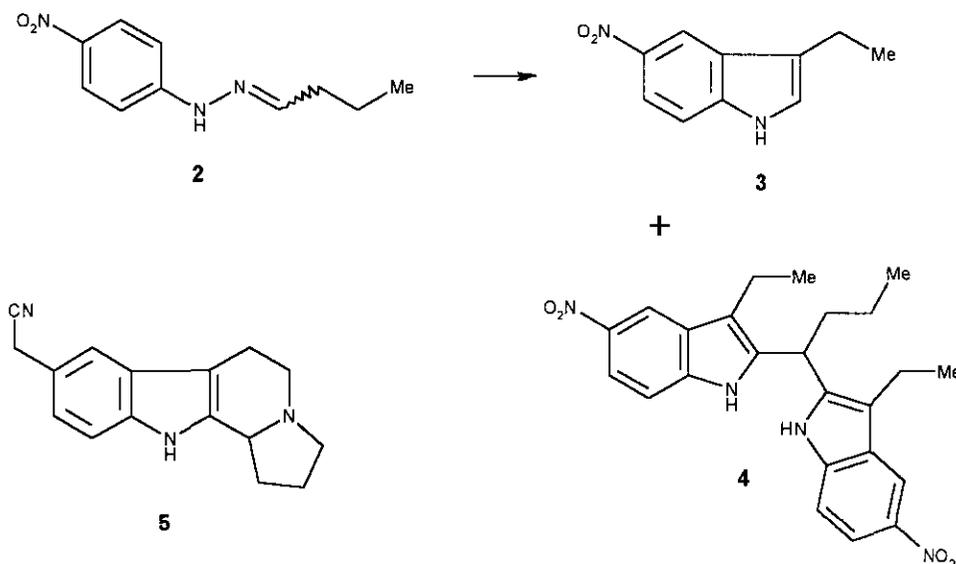

Scheme 1

On the other hand it seems that the 5-indolylcarbinyl carbon-heteroatom bond has higher reactivity than that on a simple benzylic carbon. For example, compound (6) was found to undergo nucleophilic substitution at the C-5 methylene group.[17] This exceptional reactivity was observed during the synthesis of the 5-methylaminosulphonylmethylindole (9) when self-substitution took place affording the bisindole by-product (10) or simply when recrystallising 9 in aqueous acid.[18] To avoid this side reaction the 5-methyl-aminosulphonylmethyl group in 7 was transformed into an isothiazolone moiety with diethyl oxalate prior to the preparation of hydrazine (11)[18] (Scheme 2). The introduction of this easily removable protecting group has doubled the yield of the indole (9).

Industrial syntheses of sumatriptan

The target compound (1b) can be obtained directly by the Fischer cyclization of hydrazine (7) with 4-dimethylamino-1,1-dimethoxybutane (16) in acidic media. The yield is below 30% which might be due to the side reactions shown above; however, neither by-products were isolated, nor any rationalization for the low yield was given.[19] Another reported synthesis[20] of sumatriptan (1b) consists of a two-step process: hydrazine (7) is first allowed to react with 4-chlorobutyraldehyde bisulfite adduct to give 1a (60%) fol-

lowed by reductive methylation with $CH_2O/NaBH_4$ to produce **1b** in 95% yield. Again, no by-products were mentioned, although the formation of a **5**-type tricycle or β-carboline (**12**) would not seem impossible.[21]

In this paper we focus on the side reactions emerging in the indolization process and disclose an efficient method for the Fischer rearrangement of **17** formed *in situ*; in this connection we report a novel synthesis of sumatriptan.

Scheme 2
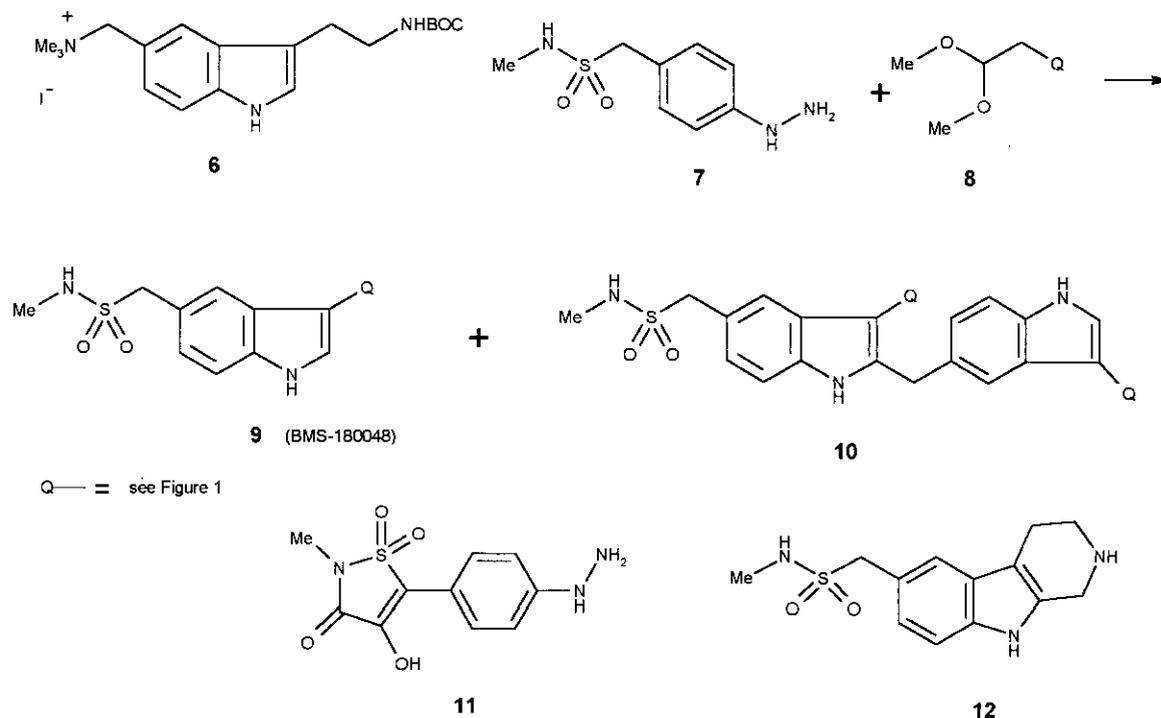
RESULTS AND DISCUSSION

*Modified synthesis of sumatriptan*

As a result of our earlier work on the synthesis of 5-substituted indoles we had the *N*-sulphonylurethane (**14**) in our hands. We became interested in the potential effects of *N*-protecting of the sulphonamide moiety on the formation of by-products. Therefore the one-pot method used to obtain sumatriptan was investigated by employing the *N*-protected hydrazine hydrochloride (**15**) and aminoacetal (**16**) in the indolization reaction (Scheme 3). In this procedure the protected sumatriptan (**18**) was obtained in 50% yield as an oxalate salt.[22] No by-product originating from the attack of 5-indolylcarbinyl system on the indole nucleus was found. However, as an unexpected by-product the bis indole (**19**) was isolated (the formation of **19** is discussed further below). Our procedure was accomplished as follows: the nitro group of **14** was transformed to hydrazine through the usual sequence of catalytic hydrogenation, diazotization

and reduction of the diazo group with Sn(II)Cl$_2$ to give **15**. The Fischer procedure was carried out in an one-pot reaction in glacial acetic acid at 75 °C. The acetic acid medium is crucial for success; other solvents commonly encountered in such syntheses, either protic or dipolar aprotic ones (e.g. EtOH, DMF), lowered the yield considerably or gave no indole derivative at all. The only exceptions are 1- or 2- nitropropane showing no difference as compared to AcOH. The preferred catalyst is gaseous HCl although H$_2$SO$_4$ or MeSO$_3$H worked almost equally well, while *p*TSA, sulfosalicylic acid or HClO$_4$ gave much lower yields and favoured side reactions. A simplified column chromatography was applied to purify **18**: the crude base was adsorbed on silica in a ratio of 1:3.5 by weight in a short column and washed first with CH$_2$Cl$_2$ then eluted with CH$_2$Cl$_2$-EtOH(sat. with NH$_3$). The final purification of **18** was achieved by precipitating its oxalate salt in 50% overall yield based on **15** with over 98% purity. The *N*-ethoxycarbonyl group in **18** was then removed by hydrolysis to give sumatriptan (**1b**) quantitatively. The bis-(indol-2-yl)methane by-product (**19**) could be isolated as the second fraction during chromatography.

Formation of by-product (19): temperature dependence.

We have observed an interesting correlation between the yield of **19** and the reaction temperature: the lower the reaction temperature the higher the yield of **19**. At room temperature the ratio of **19/18** was almost 2 : 1. This temperature dependence contradicts the usual idea explaining the formation of **19** in the reaction of **18** with aminoacetal (**16**) or hydrazone (**17**). The same conclusion can be drawn from monitoring the reaction by HPLC analysis. No reaction takes place even at 75 °C when mixing the aminoacetal (**16**) and hydrazine hydrochloride (**15**). Having added the HCl catalyst the formation of hydrazone (**17**) is observed as a very fast reaction: after two minutes only **17** is present in the reaction mixture both at 75 °C and 20 °C (the same observation had been previously made in the reaction of **16** with similar hydrazines[16]). Subsequently, in a much slower process, the [3,3] sigmatropic rearrangement of hydrazone (**17**) takes place. The feature of interest is that **18** and **19** form simultaneously in the reaction mixture even at 20 °C when much more **19** is formed than **18** and the ratio of the two products remains roughly the same throughout the rearrangement. Under the same reaction conditions no **18** could be produced from isolated **19**, moreover, only a small amount of **19** was obtained in the reaction of **18** and **16**. The lack of a large excess of aminoacetal (**16**) in the reaction mixture also suggests that **19** can not be formed by the attack of **16** on **18**. The reaction mechanism leading to the formation of **19** remains uncertain at this time and needs further investigation.

In summary we conclude that the introduction of the *N*-ethoxycarbonyl protecting group into hydrazine (**7**) was useful not only because it prevented the elimination of the 5-indolylcarbinyl system from **18**, but it was also beneficial regarding the purification of **18**: simple chromatography and the precipitation of a well-
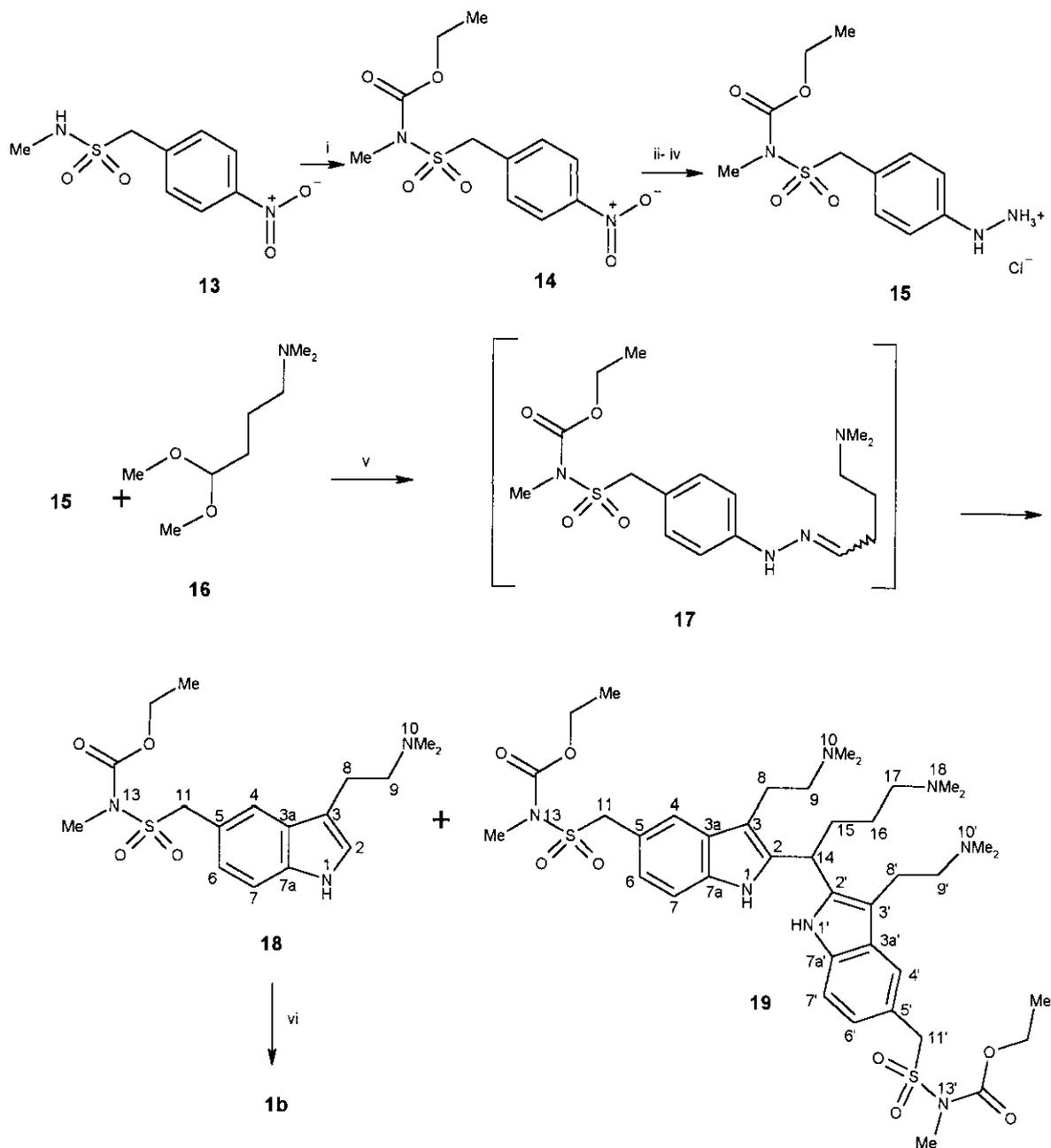
Scheme 3

Reagents i: ClCOOEt, K_2CO_3, Me_2CO, ii: Pd(C), H_2, HCl_{aq}, MeOH, iii: $NaNO_2$, HCl_{aq}

iv: $SnCl_2 \cdot 2H_2O$, HCl_{aq}, v: AcOH, HCl_g, vi: KOH, MeOH, H_2O.

defined oxalate salt became possible. Sumatriptan, as compared to **18**, has much higher polarity resembling to that of inner salts, making its chromatographic purification almost impossible. Even a simple recrystallization of **1b** or salt formation is difficult, as sumatriptan tends to form mixtures of mono- and dibasic salts with diacids such as oxalic, succinic or maleic acid. However, the use of tin in the synthesis is

still a serious drawback, which should be avoided. Our efforts aimed at this goal will be discussed in a forthcoming paper.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 or CDCl$_3$ solutions on a Varian VXR-300 (24°C, ^{1}H: 300 MHz) or a Varian UNITYplus instrument (30°C, 1H: 500 MHz). Chemical shifts are given with reference to δ_{TMS}=0.00 ppm. For **18** and **19** the reported signal assignments were confirmed by two-dimensional H-H and C-H correlation experiments, which were recorded by using the standard spectrometer software package. MS spectra were taken on a Finnigan MAT 95 SQ mass spectrometer. Silica plates (Merck 60 F$_{254}$) were used for analytical TLC. All chemicals were reagent grade and used without further purification. Compound (**13**) was prepared as described in the literature.[23]

N-Ethoxycarbonyl-N-methyl-4-nitrobenzenemethanesulphonamide (**14**). Compound (**13**) (5 g, 22 mmol), Bu$_4$N$^+$Br$^-$ (0.04 g) catalyst and ClCOOEt (8 mL, 84 mmol) were added to powdered K$_2$CO$_3$ (10 g, 72 mmol) in dry acetone (100 mL) under nitrogen atmosphere and the reaction mixture was vigorously stirred at rt for 5 h. Gas evolution commenced and the reaction temperature rose up to 36-40 °C within half an hour. The progress of the reaction was monitored by TLC (CH$_2$Cl$_2$-hexane =1:1). The inorganic solid was then filtered off, the filtrate was evaporated and treated with water to give 6.4 g (96%) of **14** as a yellow crystalline material, mp 69-72 °C (MeOH); IR (KBr): 1734, 1342, 1148, 779 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): 1.40 (t, 7.1 Hz, 3H, COOCH$_2$CH$_3$); 2.92 (s, 3H, NMe); 4.38 (q, 7.1 Hz, 2H, COOCH$_2$CH$_3$); 4.84 (s, 2H, CH$_2$SO$_2$); 7.58 [m, (AA'BB'), 2H, ArH]; 8.27 [m, (AA'BB'), 2H, ArH]. *Anal.* Calcd for: C$_{11}$H$_{14}$N$_2$O$_6$S : C 43.70, H 4.67, N 9.27. Found: C 44.0, H 4.60, N 9.21.

N-Ethoxycarbonyl-N-methyl-4-hydrazinobenzenemethanesulphonamide hydrochloride (**15**). Conc. HCl (10 mL), followed by **14** (10 g, 33 mmol) were added to prehydrogenated Pd/C catalyst (0.80 g) in MeOH (200 mL). The reaction mixture was hydrogenated at atmospheric pressure for 4 h at rt then filtered and evaporated to remove MeOH. To the residual crystalline slurry conc. HCl (15 mL) and water (160 mL) were added. The solution was chilled to -10 °C and diazotized at this temperature by adding NaNO$_2$ (2.3 g, 33 mmol) in water (15 mL) over 40 min. The pale yellow solution of diazonium chloride was chilled to -12 °C and Sn(II)Cl$_2$.2H$_2$O (35 g, 0.16 mol) in conc. HCl (33 mL) was added over 1 h at this temperature under vigorous stirring . The reaction mixture was stirred at -10 °C for 1 h then allowed to warm up to rt

and stirred for another hour. The solution was then treated with H$_2$S until all the tin salts were precipitated as sulfides which were filtered off. The filtrate was evaporated to dryness and the residue was kept over P$_2$O$_5$ *in vacuo* to remove any moisture to give 10.6 g of white crystalline material containing 8.55 g (80%) of **15** (the purity was determined gravimetrically by forming hydrazone with *p*-nitrobenzaldehyde); IR (KBr): 3507, 2931, 1743, 1719, 1288, 1143 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d$_6$): 1.31 (t, 7.1 Hz, 3H, COOCH$_2$C<u>H</u>$_3$); 2.79 (s, 3H, NMe); 4.28 (q, 7.1 Hz, 2H, COOC<u>H</u>$_2$CH$_3$); 4.77 (s, 2H, CH$_2$SO$_2$); 7.00 [m, (AA'BB'), 2H, ArH]; 7.24 [m, (AA'BB'), 2H, ArH]; 10.32 (br, 4H, NH-NH$_3$$^+$). This material decomposes slowly on standing at rt.

4-[2-[4-(Dimethylamino)butylidene]hydrazino]-N-ethoxycarbonyl-N-methylbenzenemethanesulphon-amide (**17**). Compound (**16**) (4.5 g, 28 mmol) was added to the crude hydrazine hydrochloride (10.4 g) containing 8.4 g (26 mmol) of pure **15** in CH$_2$Cl$_2$ (250 mL) and EtOH (25 mL) at 25 °C followed by AcOH (20 mL) containig HCl$_g$ (3 g, 82 mmol) and stirred for 20 min. The solution was evaporated and the oily residue was dissolved in water (100 mL), then the pH rendered to 11 with K$_2$CO$_3$. The aqueous solution was extracted with CH$_2$Cl$_2$ (3x40 mL), the combined organic layers were dried (Na$_2$SO$_4$) and evaporated to give a crude product which was chromatographed on silica gel, eluant: CH$_2$Cl$_2$-EtOH(sat. with NH$_3$)= 98.2:1.8 to give 5.0 g of an unstable oil. The compound is present as a *ca.* 2:1 mixture of slowly interconverting isomers; ^{1}H NMR (500 MHz, CDCl$_3$): *Z* isomer: 1.38 (t, 7.1 Hz, 3H, COOCH$_2$C<u>H</u>$_3$); 1.70-1.82 (m, 2H) and 2.23-2.39 [m, 2H, -C<u>H</u>$_2$-C<u>H</u>$_2$-N(Me)$_2$]; 2.24 [s, 6H, N(Me)$_2$]; 2.80 (s, 3H, NMe); 4.34 (q, 7.1 Hz, 2H, COOC<u>H</u>$_2$CH$_3$); 4.59 (s, 2H, SO$_2$-C<u>H</u>$_2$-Ar); 6.57 (t, 6.7 Hz, 1H, N=CH); 6.98 [m, (AA'BB'), 2H, ArH]; 7.16 [m, (AA'BB'), 2H, ArH]; 9.78 (s, 1H, NH). *E* isomer: 1.38 (t, 7.1 Hz, 3H, COOCH$_2$C<u>H</u>$_3$); 1.70-1.82 (m, 2H) and 2.23-2.39 [m, 2H, -C<u>H</u>$_2$-C<u>H</u>$_2$-N(Me)$_2$]; 2.25 [s, 6H, N(Me)$_2$]; 2.81 (s, 3H, NMe); 4.34 (q, 7.1 Hz, 2H, COOC<u>H</u>$_2$CH$_3$); 4.59 (s, 2H, SO$_2$-C<u>H</u>$_2$-Ar); 6.96 [m, (AA'BB'), 2H, ArH]; 7.12 (t, 5.5 Hz, 1H, N=CH); 7.16 [m, (AA'BB'), 2H, ArH]; 7.50 (s, 1H, NH) (in the *E* isomer an NOE connection was observed between the N=CH and NH protons, while this NOE was absent in the *Z* isomer). FAB-MS: m/z 385 (55,MH$^+$); 218 (50); 173 (53); 58 (100).

*3-[2-(Dimethylamino)ethyl]-N-ethoxycarbonyl-N-methyl-1H-indole-5-methanesulphonamide (***18**) *and the bisindole derivative* (**19**). The acetal (**16**) (4.5 g, 28 mmol) was added to the compound (**15**) (8.4 g, 26 mmol) in AcOH (150 mL) at 75 °C and stirred for 2 min. To the vigorously stirred solution AcOH (90 mL) containing HCl$_g$ (6.7 g, 0.184 mol) was added and the reaction mixture was kept at 74-76 °C for another 20 min. The solution was evaporated and the oily residue was treated with Et$_2$O to bring about crystallization. The solid was filtered off and dissolved in water (100 mL), then the pH rendered to 11 with

K_2CO_3. The aqueous solution was extracted with CH_2Cl_2 (3x60 mL), the combined organic layers were dried (Na_2SO_4) and evaporated to give a crude product as a yellow oil (9.4 g). This material was chromatographed on silica gel (32 g); (eluant: the same as with 17) to give 5.0 g of viscous oil being subsequently treated with $(COOH)_2 \cdot 2H_2O$ (3.4 g, 27 mmol) in ethanol (50 mL) to give 18 (6.0 g, 50%) as oxalate salt, mp 181-182 °C (EtOH). The column was further eluted with CH_2Cl_2-EtOH(sat. with NH_3 = 95:5) to give 19 (0.66 g, 6%), mp 121-125 °C (EtOH).

18 oxalate IR (KBr): 3376, 1718, 1637, 1346, 1140 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): 1.31 (t, 7.1 Hz, 3H, COOCH$_2$C$\underline{H}_3$); 2.70 [s, 3H, N(13)Me]; 2.81 [s, 6H, N(10)Me$_2$]; 3.08 (m, 2H, H$_2$-8); 3.27 (m, 2H, H$_2$-9); 4.31 (q, 7.1 Hz, 2H, COOC$\underline{H}_2$CH$_3$); 4.88 (s, 2H, H$_2$-11); 7.06 (dd, 2.2 Hz and 8.3 Hz, 1H, H-6); 7.29 (d, 2.2 Hz, 1H, H-4); 7.41 (d, 8.3 Hz, 1H, H-7); 7.54 (s, 1H, H-2); 11.20 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 14.1 (COOCH$_2$$\underline{C}H_3$); 20.0 (C-8); 33.5 [N(13)Me]; 42.2 [N(10)Me$_2$]; 56.7 (C-9); 58.7 (C-11); 63.4 (COO$\underline{C}$H$_2$CH$_3$); 109.4 (C-3); 111.7 (C-7); 117.9 (C-3a); 120.7 (C-2); 123.6 (C-6); 124.2 (C-4); 126.8 (C-5); 136.2 (C-7a); 152.8 ($\underline{C}$OOEt); 164.6 (COOH)$_2$. FAB-MS: m/z 368 (MH$^+$); accurate mass measurement: exp.: 368.1643, calcd : 368.1644

19 oxalate IR (KBr): 3422, 1720, 1636, 1348, 1140 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): 1.30 (t, 7.1 Hz, 6H, 2xCOOCH$_2$C$\underline{H}_3$); 1.62 (br, 2H, H$_2$-15); 2.22 (br, 2H, H$_2$-16); 2.69 [s, 6H, N(13)Me and N(13')Me]; 2.70 [s, 6H, N(18)Me$_2$]; 2.87 [s, 12H, N(10)Me$_2$ and N(10')Me$_2$]; 3.01-3.23 (m, 10H, H$_2$-8, H$_2$-8', H$_2$-9, H$_2$-9', H$_2$-17); 4.30 (q, 7.1 Hz, 4H, 2xCOOC$\underline{H}_2$CH$_3$); 4.60 (t, 1H, H-14); 4.84 (d, 15.1 Hz, 2H, H$_x$-11 and H$_x$-11'); 4.85 (d, 15.1 Hz, 2H, H$_y$-11 and H$_y$-11'); 7.01 (dd, 2 Hz and 8.6 Hz, 2H, H-6 and H-6'); 7.44 (d, 8.6 Hz, 2H, H-7 and H-7'); 7.48 (d, 2 Hz, 2H, H-4 and H-4'); 10.58 [br, 4H, 2x(COO$\underline{H}$)$_2$]; 11.91 (s, 2H, 2xNH). ^{13}C NMR (DMSO-d_6): 14.1 (2xCOOCH$_2$$\underline{C}H_3$); 19.5 (C-8 and C-8'); 22.5 (C-15); 30.7 (C-16); 33.6 [C-14 and N(13)Me and N(13')Me]; 42.2 [N(18)Me$_2$]; 42.3 [N(10)Me$_2$ and N(10')Me$_2$]; 56.3 (C-17); 57.1 (C-9 and C-9'); 58.7 (C-11 and C-11'); 63.4 (2xCOO$\underline{C}$H$_2$CH$_3$); 105.5 (C-3 and C-3'); 111.7 (C-7 and C-7'); 120.4 (C-4 and C-4'); 123.4 (C-6 and C-6'); 127.0 (C-3a and C-3a'); 135.8 (C-7a and C-7a'); 137.4 (C-2 and C-2'); 152.8 (2x$\underline{C}$OOEt); 165.3 [2x(COOH)$_2$]. FAB-MS: m/z 832 (MH$^+$); accurate mass measurement: exp.: 832.4091, calcd : 832.4101

3-[2-(Dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide (sumatriptan) (1b). To the 18 oxalate (2.0 g, 4.33 mmol) in 1:1 aqueous MeOH (50 mL) methanolic 2 M KOH solution (14.5 mL) was added and left to stand for 5 h at rt. The MeOH was evaporated from the reaction mixture, then conc. HCl (0.5 mL) and CH_2Cl_2 (10 mL) were added to the aqueous solution (pH=10). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2x15 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to give 1.23 g (95%) of 1b, mp 173-175 °C (lit.,[19] mp 169-171 °C).

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