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SYNTHESIS OF 5-SUBSTITUTED INDOLE DERIVATIVES, PART II.[1] SYNTHESIS OF SUMATRIPTAN THROUGH THE JAPP-KLINGEMANN REACTION.

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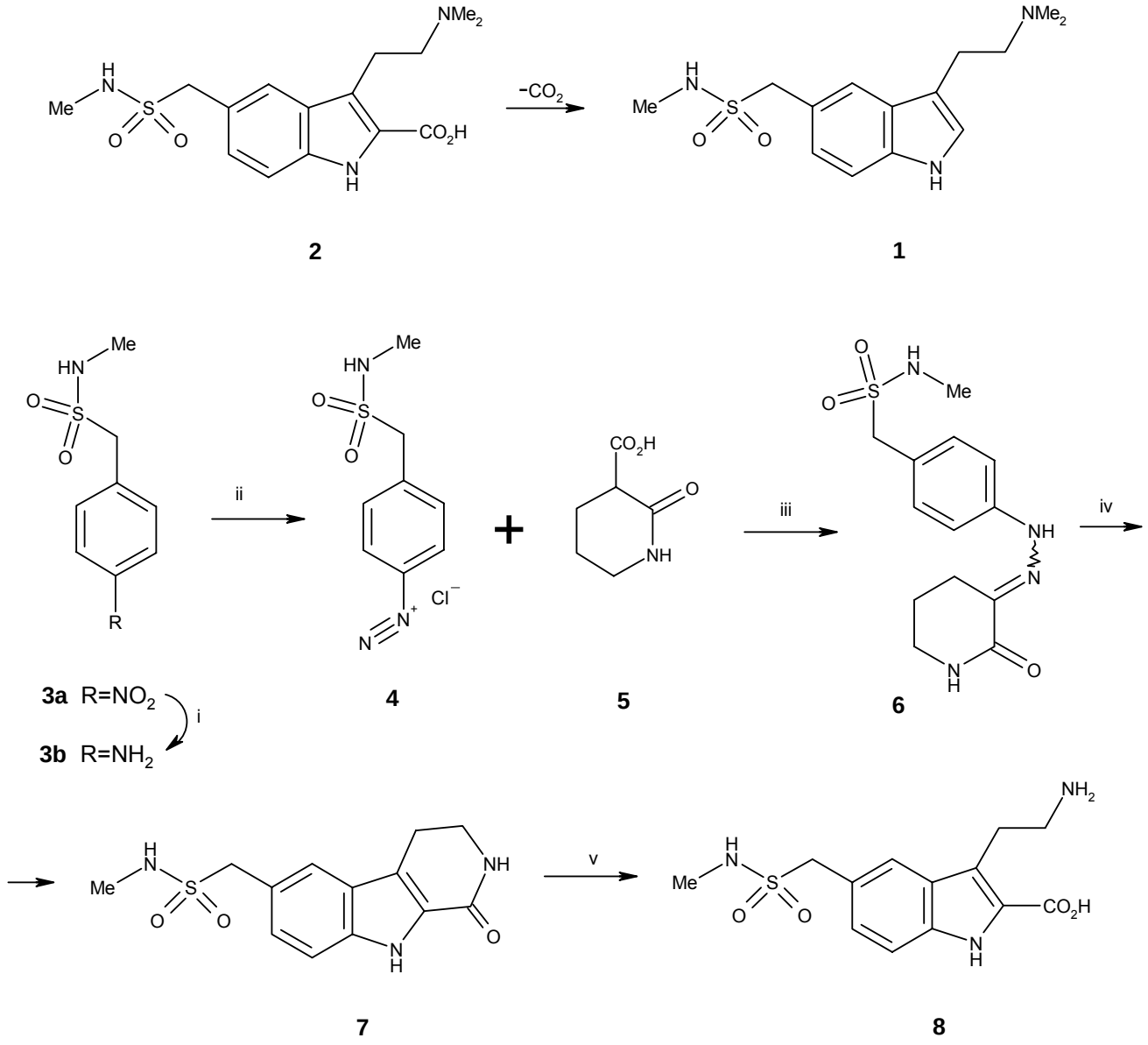
Abstract -Synthesis of selective 5-$HT_{1B/1D}$ receptor agonist, sumatriptan (**1**) was accomplished through decarboxylation of 2-carboxy-3-[2-(dimethylamino)ethyl]-*N*-methyl-1*H*-indole-5-methanesulfonamide (**2**) in quinoline with copper powder. The preparation of the acid (**2**) was effected through the Japp-Klingemann method thus avoiding the need for the formation of hydrazine from diazonium salt. Attempted decarboxylation in *N,N*-dimethylacetamide resulted in the formation of the β-carboline (**16**).

The complex physiological processes of the neurotransmitter serotonin (5-HT, 5-hydroxy-tryptamine) are becoming increasingly elucidated. In one role it acts as a vasoconstrictor in the brain and, thereby, displays beneficial properties in the treatment of the migraine.[2] Over the past few years an extensive effort has been devoted to the development of tryptamines showing 5-HT_{1D} receptor agonists properties to achieve the desired activity and selectivity for the treatment of migraine.[3] Sumatriptan[4] (**1**) is the first of this class of drugs having been approved for this use, and its discovery initiated the synthesis of a great number of 5-substituted tryptamines.[5] Many of these works obtained tryptamines directly from Fischer synthesis[6] by the choice of appropriate starting materials. The hydrazones necessary for these Fischer synthesis are prepared either by the condensation of a hydrazine with a 4-amino-butyraldehyde derivative or by the reaction of a diazonium salt with a β-oxo ester. The difficulties encountered when using hydrazine, that is, the need for tin(II) chloride to prepare the hydrazine and the formation of byproducts during the ring closure, are treated in detail in our previous paper on this subject.[1]

All these difficulties are circumvented when we carry out the synthesis of indoles by virtue of Japp-Klingemann[7] (or Abramovits-Shapiro)[8] reaction (second route). In this case the hydrazones are formed directly from arenediazonium salts. No electrophilic attack is likely to occur on the 2-carbalkoxyindole formed in the rearrangement of the hydrazone as the nucleophilicity of the indole ring is reduced by the ester group. Then the preparation of tryptamines has been effected by the sequence of hydrolysis and decarboxylation. We now wish to disclose our work on the synthesis of the acid (**2**) and sumatriptan (**1**) through decarboxylation, according to Schemes 1, 2 and 3.

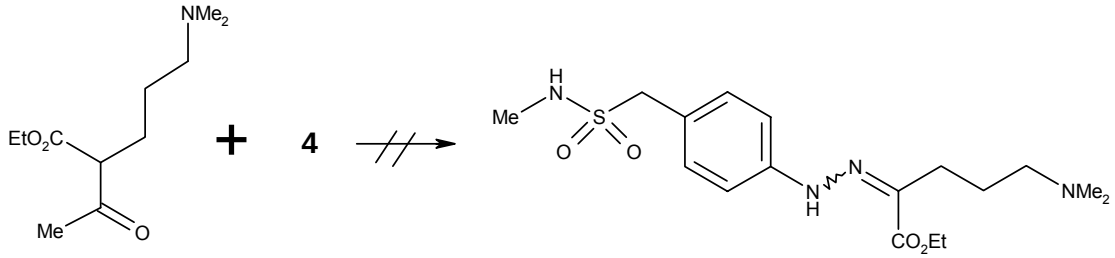


Reagents: i) H_2, 10% Pd/C; ii) $NaNO_2$, 8% HCl; iii) NaOAc; iv) HCO_2H, Δ; v) KOH, EtOH-H_2O, Δ

Scheme 1

In Scheme 1 the Abramovits-Shapiro procedure furnishes the tryptamine (**8**) in 35% overall yield from arenediazonium chloride (**4**) and 3-carboxy-2-piperidone (**5**). However, our attempts

to produce **2** from **8** by reductive methylation using formaldehyde and formic acid or borohydride derivatives proved unsuccessful. Refluxing **8** in 15% HCl solution in order to carry out decarboxylation prior to the reductive methylation was also unsuccessful resulting in elimination of sulfur dioxide from the methylaminosulfonyl group. Under the conditions of thermal decarboxylation the only product isolated was the β-carboline (**7**). Having failed in methylation of tryptamine (**8**) we turned our attention to the dimethylamino derivative of acetoacetate (**9**) as the substitute for **5**. When reacting **4** and **9** in the presence of aqueous sodium acetate, the formation of a deeply colored insoluble material was observed which we assumed to be a diazo-coupled type of compound involving the methylaminosulfonyl group. Attempts to render the pH so carefully as to avoid diazo-coupling reaction of **4** were unsuccessful. So it was concluded that a protecting group must be introduced on the sulfonamide-*N* of **3** prior to diazotization.

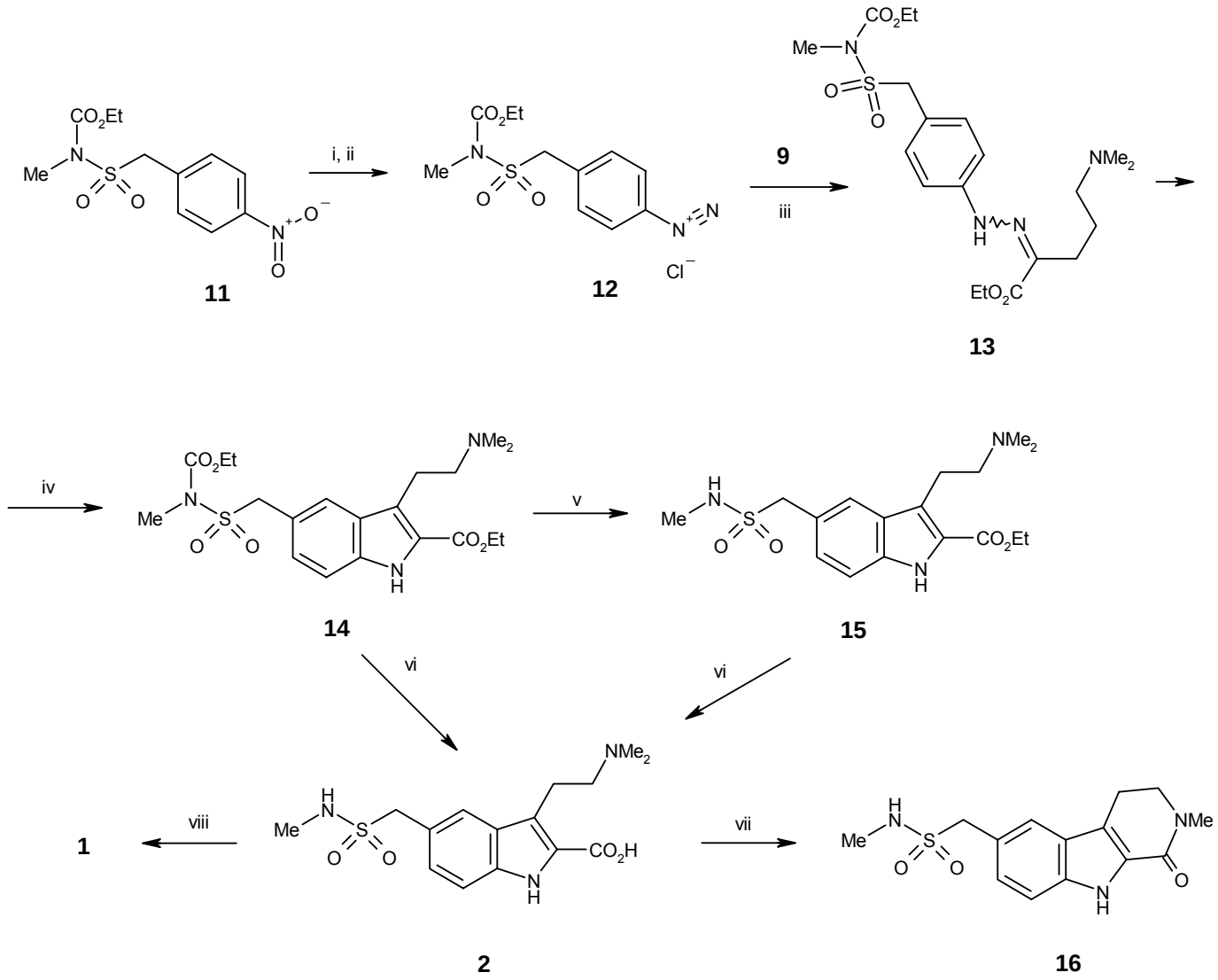


9 **10**

Scheme 2

The ethoxycarbonyl moiety as a temporary protecting group appeared to be a reasonable choice as it can be hydrolyzed together with the 2-ethoxycarbonyl group yielding the acid (**2**) (Scheme 3). The reaction of **3a** with ethyl chloroformate gave quantitatively the *N*-protected sulfonamide (**11**).[1] This compound was reduced[1] and then diazotized to give diazonium salt (**12**) which underwent a smooth Japp-Klingemann reaction with amino ester (**9**) in the presence of sodium acetate to give the hydrazone (**13**). Subsequent Fischer-type rearrangement of **13** furnished the indole (**14**) in acetic acid-gaseous HCl solution at room temperature. Finally, the acid (**2**) was obtained from **14** or **15** through hydrolysis. A smooth decarboxylation took place when heating **2** in quinoline with copper powder at 200 ^{o}C to give the desired **1**.[9] The other common procedures to effect decarboxylation, that is, boiling in hydrochloric acid or sodium hydroxide solutions resulted in fast decomposition of the acid (**2**) without the formation of any isolable product. Attempted deethoxycarbonylation[10] by heating **14** in morpholine resulted in quantitative loss of the protective group of the sulfonamide yielding **15**. Heating the acid (**2**) in

N,N-dimethylacetamide a clean reaction took place again and a single product, the β-carboline (**16**), was isolated.



Reagents i) H_2, 10% Pd/C ; ii) $NaNO_2$, 12% HCl ; iii) NaOAc ; iv) AcOH-HCl; v) morpholine, Δ; vi) KOH, MeOH-H_2O ; vii) $AcNMe_2$, 160 ^oC ; viii) quinoline, Cu, 200 ^oC

Scheme 3

EXPERIMENTAL

^1H NMR and ^{13}C NMR spectra were recorded at 500 MHz or 125 MHz, respectively, on a Bruker DRX500 spectrometer. All δ values are given in ppm, TMS was used as an internal standard. IR spectra were measured on Perkin-Elmer 1600 series FTIR spectrophotometer in KBr discs. Low resolution chemical ionization MS were obtained on a Finnigan Automass spectrometer in direct inlet mode using isobutane. All chemicals were reagent grade and used

without further purification. Compounds (**3a**,**b**,[11] **9**[12] and **11**[1]) were prepared as described in the literature.

Piperidine-2,3-dione 3-[4-[(N-methylaminosulfonyl)methyl]phenylhydrazone] (**6**).
(*Z/E* isomer mixture in a 1:3 ratio).

To the suspension of **3b** (8.0 g, 40 mmol) in conc. HCl (30 mL) and water (60 mL) was added sodium nitrite (3.0 g, 43 mmol) in water (15 mL) over a period of 30 min at -2~0 ^{o}C. Sodium 2-piperidone-3-carboxylate (**5**, 6.6 g, 40 mmol) in water (30 mL) was introduced to the diazotized solution, then aqueous sodium acetate (30%) until the pH has reached 4.5. The reaction mixture was stirred for another 6 h at rt by that time the product separated as an oil; crystallization could be effected by adding ethyl acetate (20 mL) to give, after filtration, 8.4 g (68%) of **6**, mp 210-212 ^{o}C (decomp). ^{1}H NMR (DMSO-d_6) δ: 1.83, 2.60, 3.19 (m, 3x2H, CH_2); 2.57 (d, 3H, J=4.0 Hz, NH-Me); 4.25 (s, 2H, CH_2SO_2); 6.81 (q, 1H, J=4.0 Hz, NH-Me); 7.22 (s, 4H, Ar-H); 7.88 (s, 0.75H, N-H); 8.13 (s, 0.25H, N-H); 9.68 (s, 0.75H, N-H); 13.20 (s, 0.25H, N-H). ^{13}C NMR (DMSO-d_6 , *E*-isomer) δ: 21.4, 24.6, 39.9 (CH_2); 28.7 (Me-NH); 55.9 (CH_2SO_2); 113.3, 121.6, 131.0, 135.5 (Ar); 144.7 (C=N); 161.8 (C=O). IR (cm^{-1}): 1658.

N-Methyl-(1-oxo-1,2,3,4-tetrahydro-β-carbolin-6-yl)methanesulfonamide (**7**).

The mixture of hydrazone (**6**) (8.4 g, 27 mmol) and aqueous formic acid (70%, 40 mL) was stirred for 1 h at reflux temperature. Water (20 mL) was added and allowed to cool to rt. The precipitated product was filtered, washed with ethanol and recrystallized from ethanol to give 5.0 g (63%) of **7**, mp 264-266 ^{o}C (decomp). $_{1}$H NMR (DMSO-d_6) δ: 2.57 (d, 3H, J=4.3 Hz, NH-Me); 2.92 (m, 2H, CH_2); 3.52 (m, 2H, CH_2); 3.60 (s, 1H, N-H); 4.37 (s, 2H, CH_2SO_2); 6.83 (q, 1H, J=4.3 Hz, NH-Me); 7.24 (d, 1H, J=8.4 Hz, Ar-H); 7.33 (d, 1H, J=8.4 Hz, Ar-H); 7.53 (s, 1H, Ar-H); 11.67 (s, 1H, N-H). ^{13}C NMR (DMSO-d_6) δ: 20.4, 41.2 (CH_2); 29.0 (Me-NH); 56.2 (CH_2SO_2); 112.4, 118.2, 121.2, 122.5, 125.0, 126.9, 127.9, 136.8 (Ar); 161.6 (C=O). IR (cm^{-1}): 1652, 1208. Anal. Calcd for $C_{13}H_{15}N_3O_3S$: C 53.23, H 5.15, N 14.32. Found: C 52.75, H 5.18, N 14.02.

3-(2-Aminoethyl)-2-carboxy-N-methyl-1H-indole-5-methanesulfonamide (**8**).

The mixture of β-carboline (**7**) (7.6 g, 26 mmol) in ethanol (100 mL) and potassium hydroxide (10 g, 178 mmol) in water (50 mL) was refluxed for 8 h. The hot reaction mixture was treated

with activated carbon (0.5 g) and filtered. Ethanol was removed from the filtrate by rotary evaporation and the residual aqueous solution was acidified with conc. hydrochloric acid to pH = 4. The precipitated material was filtered off, washed with water and recrystallized from water to give 6.6 g (82%) of **8**, mp 264-268 ^{o}C. ^{1}H NMR (DMSO-d_6) δ: 2.48 (d, 3H, J=4.3 Hz, NH-Me); 2.8-3.6 (m, 2x2H, CH_2); 4.30 (m, 2H, NH_2); 4.42 (s, 2H, CH_2SO_2); 6.90 (q, 1H, J=4.3 Hz, NH-Me); 7.10 (d, 1H, J=8.3 Hz, Ar-H); 7.37 (d, 1H, J=8.3 Hz, Ar-H); 7.58 (s, 1H, Ar-H); 11.29 (s, 1H, N-H). ^{13}C NMR (DMSO-d_6) δ: 29.0 (Me-NH); 22.5, 40.9 (CH_2); 57.0 (CH_2SO_2); 111.3, 111.8, 120.2, 121.2, 125.2, 127.8, 134.4, 134.6 (Ar); 165.9 (COOH). IR (cm^{-1}): 3293, 1200. Anal. Calcd for $C_{13}H_{17}N_3O_4S$: C 50.15, H 5.50, N 13.50. Found: C 49.78, H 5.42, N 13.93.

Ethyl 5-(dimethylamino)-2-[[4-[(N-ethoxycarbonyl-N-methylaminosulfonyl)methyl]phenyl]hydrazin-2-ylidene]pentanoate (**13**).

To *N*-methyl-*N*-ethoxycarbonyl-(4-aminophenyl)methanesulfonamide hydrochloride[1] (1.0 g, 3.24 mmol) in water (15 mL) and conc. hydrochloric acid (1 mL) was added sodium nitrite (0.224 g, 3.24 mmol) in small portions over a period of 15 min at -4~-2 ^{o}C. Ethyl 2-(3-dimethylamino-propyl)-3-oxobutanoate (**9**, 0.70 g, 3.25 mmol)[12] was added at the same temperature followed by sodium acetate (2 g, 24 mmol) after 5 min. The reaction mixture was allowed to reach rt then warmed to 50 ^{o}C and kept at this temperature for 0.5 h. During this process the pH was kept between 3-4 by adding additional amounts of sodium acetate (*ca*. 0.2 g). The reaction mixture was cooled to rt, filtered and the filtrate extracted with dichloromethane (3x30 mL). The organic layers were combined, dried (sodium sulfate) and rotary evaporated to give 1.06 g (72%) of **13** as a brown oil which was used in the next step without further characterization.

3-[2-(Dimethylamino)ethyl]-N,2-ethoxycarbonyl-N-methyl-1H-indole-5-methanesulfonamide (**14**).

To hydrazone (**13**) (1.75 g, 3.83 mmol) in glacial acetic acid (20 mL) was introduced gaseous hydrogen chloride at rt and the mixture was allowed to stand for 24 h. White crystals started to precipitate within 1 h. The crystals were filtered the next day, dried on air and recrystallized from ethanol to give 1.46 g (80%) of **14**, as hydrochloride, mp 220-224 ^{o}C (decomp). ^{1}H NMR (DMSO-d_6) δ: 1.29 (t, 3H, J=7 Hz, OCH_2Me); 1.39 (t, 3H, J=7 Hz, OCH_2Me); 2.73 (s, 3H, N-Me); 2.84 (s, 6H, NMe_2); 3.18 (m, 2H, CH_2); 3.50 (m, 2H, CH_2); 4.35 (q, 2H, J=7 Hz, OCH_2Me);

4.40 (q, 2H, J=7 Hz, O$\underline{CH_2}$Me); 4.91 (s, 2H, CH_2SO_2); 7.22 (d, 1H, J=8.5 Hz, Ar-H); 7.53 (d, 1H, J=8.5 Hz, Ar-H); 7.79 (s, 1H, Ar-H); 11.97 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 14.1, 14.3 (CH_3); 19.5, 56.3, 58.5, 60.7, 63.6 (CH_2); 33.5 (N-Me); 40.0 (N-Me_2); 112.9, 117.0, 119.7, 122.7, 124.7, 126.7, 127.5, 136.1 (Ar); 152.7, 161.2 (C=O). IR (cm^{-1}): 1722, 1698. MS: m/z 440 [MH^+]. Anal. Calcd for $C_{20}H_{29}N_3O_6S{\cdot}2H_2O$: C 50.51, H 6.99, N 8.83. Found: C 50.91, H 6.74, N 8.75.

3-[2-(Dimethylamino)ethyl]-2-ethoxycarbonyl-N-methyl-1H-indole-5-methanesulfonamide (**15**).

Ethyl indole-2-carboxylate (**14**) (1.0 g, 2.27 mmol) in morpholine (7 mL) was refluxed for 1.5 h. The clear reaction mixture was evaporated to dryness, and the crystalline residue was recrystallized from ethanol to give 0.77 g (92%) of **15**, mp: 240-242 ^{O}C. ^{1}H NMR (DMSO-d_6) δ: 1.40 (t, 3H, J=7 Hz, OCH$_2\underline{Me}$); 2.59 (d, 3H, J=4.9 Hz, NH-$\underline{Me}$); 2.84 (s, 6H, NMe_2); 3.22 (m, 2H, CH_2); 3.50 (m, 2H, CH_2); 4.38 (s, 2H, CH_2SO_2); 4.40 (q, 2H, J=7 Hz, O$\underline{CH_2}$Me); 6.92 (q, 1H, J=4.9 Hz, N$\underline{H}$-Me); 7.31 (d, 1H, J=8.5 Hz, Ar-H); 7.44 (d, 1H, J=8.5 Hz, Ar-H); 7.80 (s, 1H, Ar-H); 11.81 (s, 1H, N-H). ^{13}C NMR (DMSO-d_6) δ: 14.2 (CH_3); 19.6, 56.1, 56.3, 60.6 (CH_2); 28.9 (N-Me); 41.9 (N-Me_2); 112.4, 117.0, 121.8, 122.4, 124.3, 126.7, 128.0, 135.9 (Ar); 161.3 (C=O). IR (cm^{-1}): 3176, 1698. MS: m/z 368 [MH^+]. Anal. Calcd for $C_{17}H_{25}N_3O_4S{\cdot}2H_2O$: C 50.60, H 7.24, N 10.41. Found: C 50.68, H 7.04, N 10.39.

2-Carboxy-3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulfonamide (**2**).

To the ethyl indole-2-carboxylate (**14**) (1.0 g, 2.27 mmol) in methanol (40 mL) and water (20 mL) was added sodium hydroxide (0.8 g, 20 mmol) and allowed to stand at rt for 24 h. The pH of the solution was adjusted to 4 (10% hydrochloric acid) and the precipitated material filtered off and recrystallized from ethanol to give 0.695 g (90%) of **2**, mp 260-265 ^{O}C. ^{1}H NMR (DMSO-d_6) δ: 2.53 (d, 3H, J=4.2 Hz, NH-$\underline{Me}$); 2.58 (s, 6H, N-Me_2); 3.03 (m, 2H, CH_2); 3.26 (m, 2H, CH_2); 4.36 (s, 2H, CH_2SO_2); 6.80 (q, 1H, J=4.2 Hz, N$\underline{H}$-Me); 7.16 (d, 1H, J=8.7 Hz, Ar-H); 7.36 (d, 1H, J=8.7 Hz, Ar-H); 7.59 (s, 1H, Ar-H); 11.18 (s, 1H, N-H). ^{13}C NMR (DMSO-d_6) δ: 20.5, 56.4, 59.8 (CH_2); 28.8 (N-Me); 43.4 (N-Me_2); 111.8, 120.3, 121.4, 124.5, 124.7, 125.7, 127.4, 134.6 (Ar); 164.9 (C=O). IR (cm^{-1}): 3274, 1343, 1302. MS: m/z 340 [MH^+]. Anal. Calcd for $C_{15}H_{21}N_3O_4S$: C 53.08, H 6.24, N 12.38. Found: C 53.27, H 6.22, N 12.44.

N,2-Dimethyl-(1-oxo-1,2,3,4-tetrahydro-β-carbolin-6-yl)methanesulfonamide (**16**).

Indole-2-carboxylic acid (**2**) (1 g, 2.95 mmol) was dissolved in *N,N*-dimethylacetamide (20 mL) and kept at 160 ^{o}C for 1.5 h. The solution was evaporated (high vacuum) to dryeness and the solid residue was recrystallized from ethanol to give 0.52 g (60%) of **16** as white crystals, mp 189-191^{o}C. ^{1}H NMR (DMSO-d_6) δ: 2.56 (d, 3H, J=4.8 Hz, NH-Me); 2.98 (m, 2H, CH_2); 2.99 (s, 3H, N-Me); 3.63 (m, 2H, CH_2); 4.35 (s, 2H, CH_2SO_2); 6.80 (q, 1H, J=4.8 Hz, NH-Me); 7.21 (d, 1H, J=7.1 Hz, Ar-H); 7.39 (d, 1H, J=7.1 Hz, Ar-H); 7.54 (s, 1H, Ar-H); 11.63 (s, 1H, N-H). ^{13}C NMR (DMSO-d_6) δ: 29.0 (Me-NH); 20.0, 33.6 (CH_2); 49.5 (N-Me); 56.2 (CH_2SO_2); 112.3, 117.1, 121.2, 122.3, 124.8, 126.8, 127.7, 136.9 (Ar); 160.8 (C=O). IR (cm^{-1}): 1640, 1202. Anal. Calcd for $C_{14}H_{17}N_3O_3S$: C 54.71, H 5.57, N 13.67. Found: C 54.28, H 5.40, N 13.51.

3-[2-(Dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulfonamide, (sumatriptan) (**1**).

To the indole-2-carboxylic acid (**2**) (1 g, 2.95 mmol) in quinoline (16 mL) was added copper powder (80 mg) then argon gas was bubbled through the liquid for 1 h. The mixture was well stirred at 190-200 ^{o}C for another 1 h. The solution was filtered and the solvent evaporated in high vacuum. The solid residue was purified on a short column of alumina, eluant: CH_2Cl_2-EtOH (sat. with NH_3) = 97:3, to give 0.69 g (80%) of **1**, mp. 168-170 ^{o}C (ethanol), identical with sumatriptan[13] in all respect.

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