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NEW SYNTHESIS OF NARATRIPTAN

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Abstract – A new synthesis of *N*-methyl-3-(1-methyl-4-piperidinyl)-1*H*-indole-5-ethanesulfonamide (naratriptan, **1a**) has been elaborated starting from 1-benzyl-1*H*-indole-5-carbaldehyde (**14b**). The 1-benzyl group proved to be an advantageous protecting group in the course of the construction of the ethanesulfonamide and methylpipieridinyl side-chains and it was removed in the last step of the synthesis.

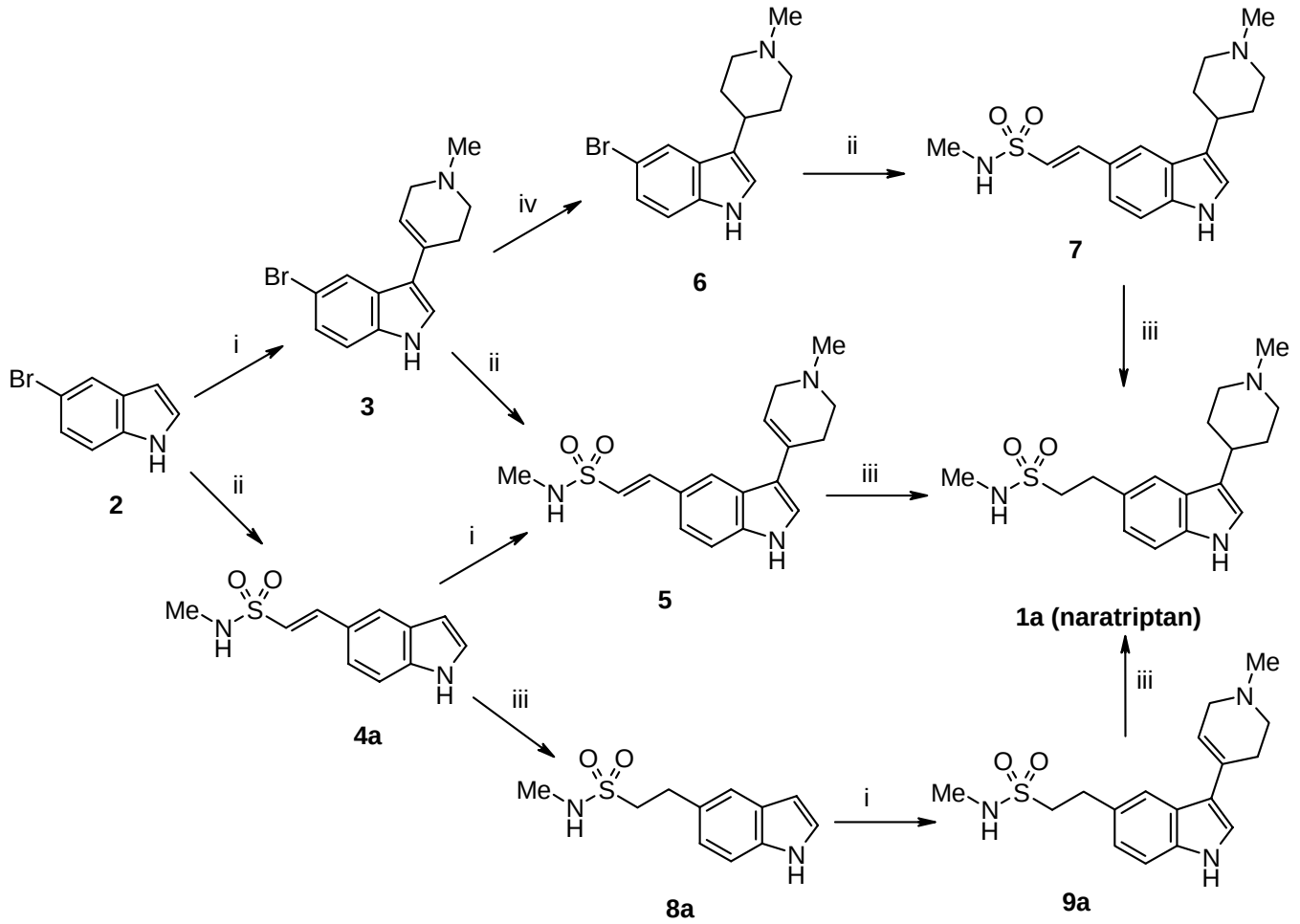
Naratriptan (**1a**) is an important drug for the treatment of acute attacks of migraine exhibiting high affinity for 5-HT_{1D} receptors, a serotonin (5-hydroxytryptamine, 5-HT) receptor subtype.[1] The methods previously described for the synthesis of naratriptan are shown in Scheme 1. The synthetic routes starting from 5-bromoindole (**2**) and differ in the sequence of introduction of the substituents and in the execution of the saturation of the primarily formed side-chains. In the most economical process doubly unsaturated intermediate (**5)** was prepared, either *via* **3** or **4a** and both side-chains were hydrogenated in the last step. The reduction of the side-chains of intermediates (**3** and **4a**) can also be carried out prior to the introduction of the second side-chain (see **6**, **7** and **8a**, **9a**).[2]

Recently we have disclosed a new synthesis of naratriptan (**1a**) starting from 4-nitrobenzaldehyde (Scheme 2).[3] Aniline derivative (**10)** was submitted to Sundberg type indole synthesis. Cyclisation of compound (**11**) followed by introduction of the *N*-methylpiperidinyl moiety into the 3-position of indole (**12**) afforded *N*-benzyl-sulfonamide (**13),** which was debenzylated to naratriptan (**1a**).

In continuation of our efforts for a more economical manufacturing synthesis of naratriptan we examined a synthesis starting from 1*H*-indole-5-carbaldehyde (**14a**). Since the methods available in the literature for the synthesis of aldehyde (**14a**) were unsuited for scaling up, we elaborated a new and efficient synthesis of this compound.[4] Unfortunately, condensation of aldehyde (**14a**) with methanesulfonamide (**15**)

furnished the desired product (**4a**) only in poor yield.

Scheme 1

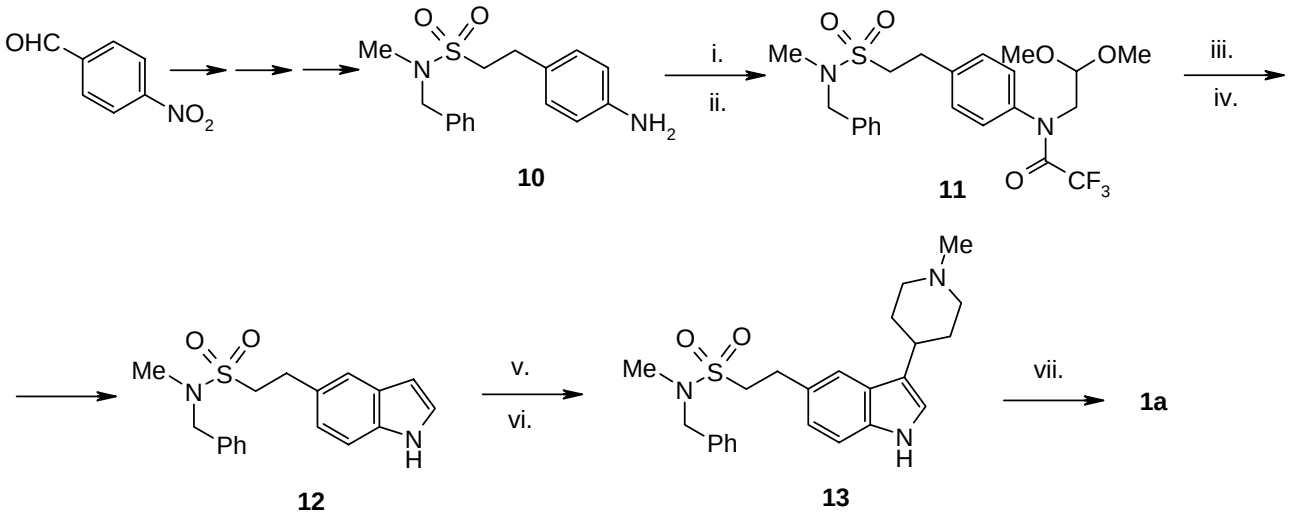


i) 1-methyl-4-piperidone, KOH. ii) *N*-methylvinylsulfonamide, $Pd(OAc)_2$, $P(4\text{-Me-Ph})_3$. iii) H_2, Pd/C. iv) H_2, PtO_2.

We supposed that protection of the indole nitrogen may have a favourable effect on the yield of the condensation reaction. Therefore we synthesized 1-benzyl-5-formylindole (**14b**)**,** by DDQ oxidation, starting from the appropriate 2,3-dihydroindole **(16**), a precursor described in the literature.[5]

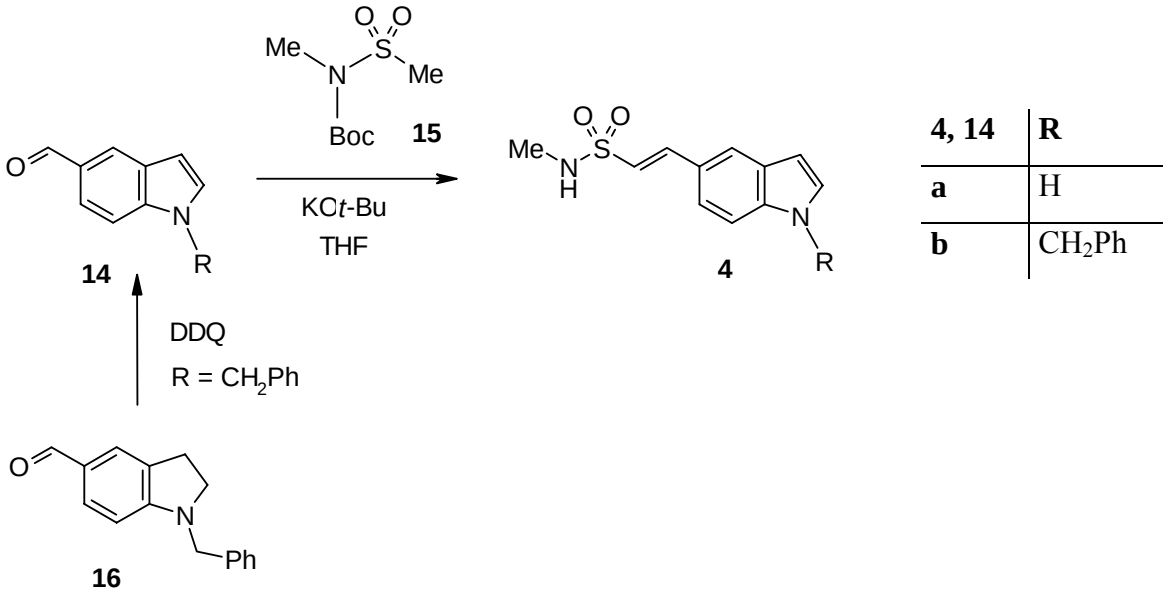
Indeed, condensation of *N*-protected aldehyde (**14b**) with methanesulfonamide (**15**) afforded ethenesulfonamide (**4b**) in good yield (73 %). The side-chain of compound (**4b**) was saturated by catalytic hydrogenation to ethanesulfonamide (**8b**) (Scheme 4**)**. Condensation of **8b** with 1-methyl-4-piperidone under acidic conditions followed by catalytic reduction of intermediate (**9b**) afforded compound (**1b**), a precursor to naratriptane benzylated at the indole nitrogen. The deprotection of the indole ring was carried out by sodium reduction in liquid ammonia resulting naratriptan (**1a**) in 84 % yield.

Scheme 2



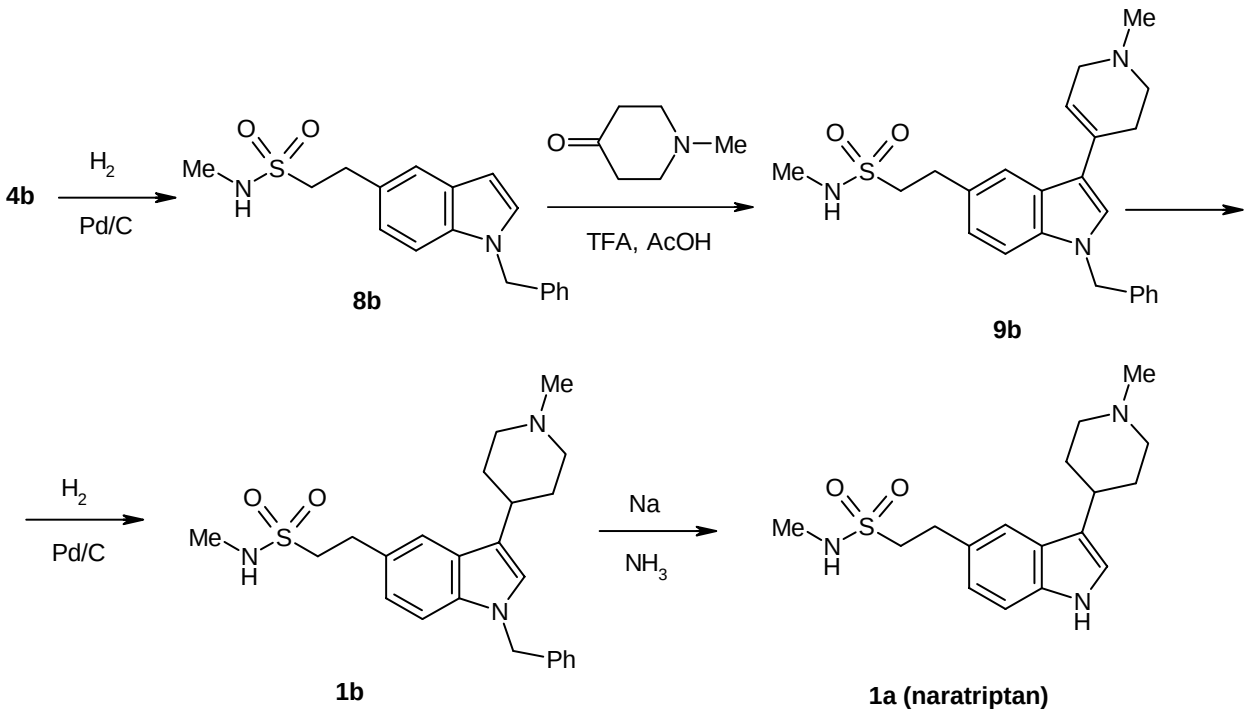
i) $(MeO)_2CHCHO$, H_2, Pd/C. ii) TFAA, NEt_3. iii) $TiCl_4$, PhCl. iv) KOH, MeOH. v) 1-methyl-4-piperidone, KOH. vi) H_2, Pd/C. vii) Na, NH_3.

Scheme 3



4, 14	R
a	H
b	CH_2Ph

Scheme 4



EXPERIMENTAL

The melting points were determined on a Büchi 535 apparatus. The IR spectra were recorded on an Aspect 2000 computer controlled Bruker IFS-113ν vacuum optic FT spectrometer using KBr pellets. The ^{1}H NMR spectra were recorded on a Bruker WM 250 FT, or a Varian Gemini-200, or a Varian Unity Inova 400 spectrometer, in deuteriochloroform or dimethyl sulfoxide-d_6. Chemical shifts were reported as δ values (ppm) downfield from internal tetramethylsilane.

1-Benzyl-1H-indole-5-carbaldehyde (14b)

To a solution of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (22.70 g, 0.10 mol) in CH_2Cl_2 (400 mL) was added 1-benzyl-indoline-5-carbaldehyde (**16**)[5] (18.98 g, 0.08 mol) at 0 °C and stirred for 3 h. The solid was filtered off and washed with CH_2Cl_2 (2x50 mL). The combined organic phases were washed twice with aqueous K_2CO_3 solution (10 %, 120 mL), saturated aqueous NaCl solution (120 mL) and water (100 mL). The organic phase was dried ($MgSO_4$) and evaporated. The residue was recrystallized from 2-propanol to give 5-formylindole (**14b**) (14.1 g, 75 %), mp 72-73 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 10.03 (1H, s), 8.17 (1H, d, *J*=1.2 Hz), 7.75 (1H, dd, *J*=1.6, 8.5 Hz), 7.37 (1H, d, *J*=8.5 Hz), 7.33-7.25 (3H, m), 7.22 (1H, d, *J*=3.2 Hz), 7.11 (2H, d, *J*=7.4 Hz), 6.71 (1H, dd, *J*=0.7, 3.2 Hz), 5.36 (2H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$, δ, ppm): 192.4, 139.6, 136.6, 130.2, 129.6, 128.9, 128.5, 128.0, 126.7, 126.4, 122.1, 110.2, 103.9, 50.4; IR (KBr, ν, cm^{-1}): 1682; Anal. Calcd for $C_{16}H_{13}NO$

(235.29): C, 81.68; H, 5.57; N, 5.95. Found: C, 81.56; H, 5.51; N, 5.82.

***2-(1-Benzyl-1H-indol-5-yl)ethenesulfonic acid methylamide* (4b)**

To a mixture of potassium *tert*-butoxide (18.76 g, 0.16 mol) in THF (110 mL) was added *N*-Boc-*N*-methyl-methanesulfonamide[6] (16.74 g, 0.08 mol) in THF (110 mL) under argon at –78 °C. The mixture was stirred at this temperature for 1 h and 1-benzyl-1*H*-indole-5-carbaldehyde (**14b**) (12.93 g, 55 mmol) was added. The mixture was allowed to warm to 0 °C and partitioned between ethyl acetate (200 mL) and saturated aqueous NH_4Cl solution (200 mL). The aqueous phase was extracted twice with ethyl acetate (50 mL). The combined organic phases were dried ($MgSO_4$) and evaporated. The crude brown oil was dissolved in CH_2Cl_2 (25 mL) and stirred with silica gel (10 g, 0.063-0.200 mm) for 15 min, filtered and washed with CH_2Cl_2 (25 mL). The filtrate was evaporated and the solid residue was recrystallized from methanol to give vinylsulfonamide (**4b**) (13.1 g, 73 %), mp 111-112 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.78 (1H, s), 7.62 (1H, d, *J*=15.4 Hz), 7.35-7.25 (6H, m), 7.17 (1H, d, *J*=3.2 Hz), 7.10 (2H, d, *J*=7.2 Hz), 6.64 (1H, d, *J*=15.4 Hz), 6.59 (1H, dd, *J*=0.7, 3.1 Hz), 5.33 (2H, s), 2.75 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$, δ, ppm): 144.4, 137.6, 136.8, 129.8, 129.0, 128.9, 127.9, 126.7, 124.2, 123.0, 121.3, 120.2, 110.4, 102.8, 50.3, 29.1; IR (KBr, ν, cm^{-1}): 3281, 1355; Anal. Calcd for $C_{18}H_{18}N_2O_2S$ (326.42): C, 66.23; H, 5.56; N, 8.58; S, 9.82. Found: C, 65.94; H, 5.54; N, 8.39; S, 9.55.

***2-(1-Benzyl-1H-indol-5-yl)ethanesulfonic acid methylamide* (8b)**

A solution of vinylsulfonamide (**4b**) (6.52 g, 20 mmol) in methanol (120 mL) was hydrogenated in the presence of 10 % palladium on charcoal (1.3 g) at rt under 5 bar hydrogen for 2 h. The catalyst was removed by filtration and the filtrate was evaporated. The residue was triturated with diisopropyl ether (20 mL) to give ethanesulfonamide (**8b**) (5.5 g, 84 %), mp 98-99 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.74 (1H, s), 7.32-7.25 (3H, m), 7.18 (1H, d, *J*=8.4 Hz), 7.11 (1H, s), 7.08 (2H, d, *J*=7.0 Hz), 7.05 (1H, d, *J*=8.4 Hz), 6.15 (1H, s), 5.25 (2H, s), 4.29 (1H, q, *J*=4.7 Hz), 3.34-3.18 (6H, m), 2.80 (2H, t, *J*=5.8 Hz), 2.67 (2H, m), 2.67 (3H, d, *J*=4.4 Hz), 2.51 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$, δ, ppm): 137.0, 136.2, 129.5, 129.4, 128.8, 127.8, 126.7, 126.3, 126.2, 122.6, 120.3, 117.2, 116.3, 110.4, 54.1, 52.9, 51.8, 50.2, 44.9, 30.2, 29.3, 28.1; IR (KBr, ν, cm^{-1}): 2794, 1315; Anal. Calcd for $C_{24}H_{29}N_3O_2S$ (423.58): C, 68.05; H, 6.90; N, 9.92; S, 7.57. Found: C, 67.75; H, 6.88; N, 9.86; S, 7.49.

***2-[1-Benzyl-3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-ethanesulfonic acid methylamide* (9b)**

To a mixture of trifluoroacetic acid (20 mL) and acetic acid (15 mL) was added 1-methyl-4-piperidone (6.79 g, 60 mmol) at rt. After heating to 100 °C, ethanesulfonamide (**8b**) (4.93 g, 15

mmol) in acetic acid (40 mL) was added to the reaction mixture, which was then stirred at this temperature for 1 h. After evaporation of the solvents, the residue was stirred with ethyl acetate (25 mL) and saturated aqueous K_2CO_3 solution (50 mL) for 15 min. The crystalline precipitate was filtered and washed three times with water (15 mL) and twice with ethyl acetate (10 mL) to afford compound (**9b**) (6.35 g, 75 %), mp 174-175 °C (ethanol) ; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.55 (1H, s), 7.31-7.24 (3H, m), 7.18 (1H, d, *J*=8.4 Hz), 7.07 (2H, d, *J*=8.1 Hz), 7.00 (1H, dd, *J*=1.6, 8.4 Hz), 6.92 (1H, s), 5.24 (2H, s), 4.36 (1H, bs), 3.40-3.29 (2H, m), 3.23-3.18 (2H, m), 3.10-3.06 (2H, m), 2.85-2.75 (1H, m), 2.68 (3H, s), 2.42 (3H, s), 2.30-2.21 (2H, m), 2.06-1.90 (4H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$, δ, ppm): 137.4, 135.9, 128.8, 128.5, 127.7, 127.4, 126.8, 125.1, 122.3, 119.1, 118.9, 110.3, 55.8, 52.9, 50.1, 45.3, 32.5, 31.8, 30.2, 29.4; IR (KBr, ν, cm^{-1}): 1340, 1160; Anal. Calcd for $C_{24}H_{31}N_3O_2S$ (425.60): C, 67.73; H, 7.34; N, 9.87; S, 7.53. Found: C, 67.69; H, 7.14; N, 9.57; S, 7.33.

***N-Methyl-2-[1-benzyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl]-ethanesulfonamide* (1b)**

A solution of compound (**9b**) (1.27 g, 3 mmol) in THF (50 mL) was hydrogenated in the presence of 10 % palladium on charcoal (0.3 g) at rt under 5 bar hydrogen for 4 h. The catalyst was removed by filtration and the filtrate was evaporated. The residue was recrystallized from toluene to give *N*-benzylnaratriptan (**1b**) (0.95 g, 74 %), mp. 101-103 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.52 (1H, d, *J*=0.7 Hz), 7.34-7.22 (3H, m), 7.18 (1H, d, *J*=8.4 Hz), 7.10-7.02 (2H, m), 7.00 (1H, dd, *J*=1.8, 8.4 Hz), 6.98 (1H, s), 5.24 (2H, s), 4.15 (1H, bs), 3.40-3.28 (2H, m), 3.26-3.14 (2H, m), 3.04-2.92 (2H, m), 2.88-2.68 (1H, m), 2.66 (3H, s), 2.34 (3H, s), 2.22-1.72 (6H, m); ^{13}C NMR (50.3 MHz, $CDCl_3$, δ, ppm): 137.47, 135.77, 128.69, 128.06, 127.64, 127.55, 126.64, 124.85, 122.02, 120.33, 118.83, 110.22, 56.37, 52.91, 49.99, 46.56, 33.11, 32.95, 30.15, 29.35; IR (KBr, ν, cm^{-1}): 3423, 1316, 1149; Anal. Calcd for $C_{24}H_{31}N_3O_2S$ (425.60): C, 67.73; H, 7.34; N, 9.87.Found: C, 67.56; H, 7.25; N, 9.75.

***N-Methyl-2-[3-(1-methylpiperidin-4-yl)-1H-indol-5-yl]-ethanesulfonamide* (1a, *naratriptan*)**

To the solution of sodium (0.23 g, 10 mmol) in liquid ammonia (30 mL) was added *N*-benzylnaratriptan (**1b**) (0.85 g, 2 mmol) in THF (10 mL). After 10 min potassium nitrate (0.93 g, 11 mmol) was added, and the ammonia was evaporated. Saturated aqueous NaCl solution (20 mL) was added to the residue, and the mixture was extracted with ethyl acetate (3x15 mL). The organic layer was dried ($MgSO_4$) and evaporated. Trituration of the residue with ethyl acetate (5 mL) afforded naratriptan (**1**) (0.62 g, 84 %), mp 170-171 °C, lit.,[2] mp 170-171 °C.

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