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Distinguishing rotamers in *N*-trifluoroacetyl-3-benzazepine derivatives

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Introduction

Lorcaserin ((1*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine, Fig. 1) is a recently approved weight loss drug that favors satiety by selectively activating 5-HT_{2C} serotonin receptors. As its 5-HT_{2C}/5-HT_{2A} receptor selectivity is not very high, and 5-HT_{2A} receptor activation is a hallmark of classic hallucinogens, the concern that this drug might be diverted to the illegal market led to its use being restricted to obese patients or those with overweight and concomitant conditions such as diabetes.[1,2]

The patented synthesis of lorcaserin, like those of a number of structural analogs, involves the formation of trifluoroacetamide precursors synthesized by the Tietze–Schimpf route,[3] which are described in the patent literature on the basis of their ^{1}H NMR characterization at 400 MHz in $CDCl_3$ as mixtures of two rotamers.[4] This detail goes unmentioned in the subsequent publications.[5,6] A more recent synthetic paper describes the ^{13}C NMR spectra of some related compounds in which the chemical shifts of two rotamers are clearly apparent, again with no commentary and with no attempt to assign any of the signals to one or the other.[7] In the course of a synthetic program directed towards a pharmacological study of putative 5-HT_2 receptor ligands, we repeated the synthesis of several of the 5-HT_{2C} agonist precursors[5,6] and found again that in $CDCl_3$ solution and at 300 K, they were rotamer mixtures, which in the 400 MHz ^{1}H NMR spectra, were insufficiently resolved to permit most of the signals to be assigned to each individual rotamer, with the notable exception of the low-frequency methyl doublets, which generally allowed an approximate molar ratio to be determined. The 100 MHz ^{1}H-decoupled ^{13}C NMR spectra, on the other hand, clearly showed duplicate signals for each carbon atom.

Experimental

Chemicals

Compounds **1** and **3–7** were synthesized using literature procedures.[3,5] Compound **2** was prepared following a strictly analogous sequence but employing a 2:1 molar ratio of ICl in the iodination of *N*-trifluoroacetyl-2-(3-methoxyphenyl)ethanamine, giving *N*-trifluoroacetyl-2-(2,4-diiodo-5-methoxyphenyl)ethanamine that was then treated with allyl bromide to afford **2**.

*N-allyl-N-trifluoroacetyl-2-(2-iodo-5-methoxyphenyl)ethanamine (**1**)*

N-trifluoroacetyl-2-(2-iodo-5-methoxyphenyl)ethanamine was allylated as described in the patent literature.[3] Two rotamers, 2:1 ratio: Major rotamer ^{1}H NMR ($CDCl_3$) δ 7.64 (1H, d, J = 8 Hz, H-3′), 6.78 (1H, d, J = 2 Hz. H-6′), 6.58 (1H, dd, J = 8, 2 Hz, H-4′), 5.96-5.62 (1H, m, allyl CH), 5.34–5.21 (2H, m, allyl CH_2), 3.88 (1.34H, d, allyl CH_2), 3.77 (3H, s, OCH_3), 3.58 (2H, t, J = 6 Hz, CH_2-1), 3.01 (2H, t, J = 6 Hz, CH_2-2); minor rotamer ^{1}H NMR ($CDCl_3$) δ 7.66 (1H, d, J = 8 Hz, H-3′), 6.75 (1H, d, J = 2 Hz. H-6′), 6.60 (1H, dd, J = 8, 2 Hz, H-4′), 5.96–5.62 (1H, m, allyl CH), 5.38–5.20 (2H, m, allyl CH_2), 4.13 (0.66H, d, allyl CH_2), 3.79 (3H, s, OCH_3), 3.57 (2H, t, J = 6 Hz, CH_2-1), 3.02 (2H, t, J = 6 Hz, CH_2-2); ^{13}C NMR ($CDCl_3$) (Tables 1 and 2).

*N-allyl-N-trifluoroacetyl-2-(2,4-diiodo-5-methoxyphenyl)ethanamine (**2**)*

The same procedure as earlier, starting from *N*-trifluoroacetyl-2-(2,4-diiodo-5-methoxyphenyl)ethanamine. Two rotamers, 7:3 ratio: Major rotamer ^{1}H NMR ($CDCl_3$) δ 7.64 (1H, d, J = 8 Hz, H-3′), 6.78 (1H, d, J = 2 Hz. H-6′), 6.58 (1H, dd, J = 8, 2 Hz, H-4′), 5.73–5.62 (0.71H, m, allyl CH), 5.32–5.23 (2H, m, allyl CH_2), 3.88 (1.42H, d, allyl CH_2, overlapping OCH_3 signal), 3.87 (3H, s, OCH_3), 3.58 (2H, t, J = 6 Hz, CH_2-1), 3.01 (2H, t, J = 6 Hz, CH_2-2); minor rotamer ^{1}H NMR ($CDCl_3$) δ 7.66 (1H, d, J = 8 Hz, H-3′), 6.75 (1H, d, J = 2 Hz. H-6′), 6.60 (1H, dd, J = 8, 2 Hz, H-4′), 5.96–5.73 (0.29H, m, allyl CH), 5.32–5.23 (2H, m, allyl CH_2), 4.13 (0.58H, d, allyl CH_2), 3.79 (3H, s, OCH_3), 3.57 (2H, t, J = 6 Hz, CH_2-1), 3.02 (2H, t, J = 6 Hz, CH_2-2); ^{13}C NMR ($CDCl_3$) (Tables 1 and 2).

*7-Methoxy-1-methylene-N-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine (**3**)*

Two rotamers, 1:1 ratio: barely distinguishable in ^{1}H NMR ($CDCl_3$) δ 7.25 (0.5H, d, J = 8 Hz), 7.23 (0.5H, d, J = 8 Hz), 6.74 (1H, dd, J = 8, 2 Hz), 6.65 (1H, d, J = 2 Hz), 5.29–5.16 (2H, m), 4.39–4.35 (2H, m), 3.80 (2H, t), 3.74 (3H, s, OCH_3), 2.95 (2H, t); ^{13}C NMR ($CDCl_3$) (Tables 1 and 2).

(RS)-7-Methoxy-1-methyl-N-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine (4)

Two rotamers, 6:4 ratio: barely distinguishable in ^{1}H NMR ($CDCl_3$) δ 7.34 (0.44H, m, H-9), 7.23 (1H, m, H-6), 6.94–6.79 (1H, m, H-8), 4.2–3.9 (1H, m, H-1), 3.81 (3H, s, OCH_3), 3.7–3.5 (2H, m), 3.25–3.30 (2H, m), 3.0–2.85 (2H, m), 1.35 (1.24H, d, J = 6 Hz, C-CH_3 minor), 1.30 (1.76H, J = 6 Hz, C-CH_3 major); ^{13}C NMR ($CDCl_3$) (Tables 1 and 2).

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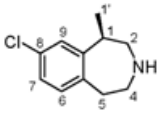

Figure 1. Structure of Lorcaserin with atom numbering.

*(RS)-8-Chloro-7-methoxy-1-methyl-N-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine (**5**)*

Two rotamers, 55:45 ratio: barely distinguishable in ^{1}H NMR ($CDCl_3$) δ 7.25 (1H, s, H-9), 6.74 (0.45H, s, H-6 minor), 6.72 (0.55H, s, H-6 major), 3.86 (3H, s, OCH_3), 3.7–3.35 (2H, m), 3.35–2.8 (3H, m), 1.32 (1.35H, d, J = 6 Hz, C-CH_3 minor), 1.28 (1.65H, J = 6 Hz, C-CH_3 major); ^{13}C NMR ($CDCl_3$) (Tables 1 and 2).

Table 1. ^{13}C NMR data ($CDCl_3$) for major rotamers (one of the rotamers of **3**, arbitrarily named **3**[a] is included, as neither of these was clearly more abundant than the other)

^{13}C	1	2	3[a]	4	5	6	7
1	131.7	131.6	145.2	39.5	39.6	39.7	39.6
2	50.7 q J = 3 Hz	51.1 q J = 3 Hz	45.6	51.4	51.5	51.7	51.7
4	46.7	46.7	46.7 q J = 3 Hz	47.8 q J = 3 Hz	47.9 q J = 3 Hz	47.9 q J = 3 Hz	48.0 q J = 3 Hz
5	37.3	37.7	35.3	34.7	36.6	36.9	37.0
5a	141.8	142.3	137.3	139.0	137.0	137.6	138.4
6	115.2*	112.8	115.2	116.3	114.6	114.4	113.4
7	160.4	159.0	159.8	157.9	153.2	154.3	156.8
8	115.9*	89.3	112.5	111.3	120.5	109.5	83.9
9	140.0	148.2	130.0	129.4	130.0	133.1	139.2
9a	88.5	85.3	132.2	135.7	137.7	138.5	139.7
1a	119.5	119.8	116.5	17.5	17.7	17.8	17.8
OCH_3	55.3	56.6	55.2	54.8	56.3	56.5	56.6
C=O	156.9 q J = 36 Hz	157.1 q J = 36 Hz	156.8	156.2 q J = 35 Hz	156.5 q J = 35 Hz	156.6 q J = 36 Hz	Lost in noise
CF_3	116.5 q J = 287 Hz	116.5 q J = 286 Hz	116.5	116.7 J = 286 Hz	116.9 q J = 287 Hz	116.9 q J = 287 Hz	116.9 q J = 287 Hz

[a]Rotamer A present in similar amount to rotamer B (Table 2).

Table 2. ^{13}C NMR data ($CDCl_3$) for minor rotamers (one of the rotamers of **3**, arbitrarily named **3**[b] is included, as neither of these was clearly more abundant than the other)

C	1	2	3[b]	4	5	6	7
1	131.2	131.2	144.5	38.8	39.0	39.1	39.0
2	49.5	49.7	46.7 q J = 3 Hz	53.0 q J = 3 Hz	53.2 q J = 3 Hz	53.6 q J = 3 Hz	53.3 q J = 3 Hz
4	47.1 q J = 3 Hz	47.0 q J = 3 Hz	45.6	46.0	46.1	46.2	46.2
5	40.1	40.3	33.2	36.4	35.0	35.3	35.4
5a	141.1	141.7	136.8	139.5	136.0	136.6	137.3
6	114.7*	112.3	114.8	115.8	114.2	114.1	113.0
7	160.3	159.2	159.9	158.1	153.4	154.5	157.0
8	116.3[a]	89.2	112.3	111.9	120.4	109.6	83.6
9	140.2	148.4	129.9	129.1	128.8	132.0	138.1
9a	88.3	85.7	131.3	134.7	138.5	139.4	140.6
1a	119.0	119.3	114.4	17.5	17.7	17.9	17.9
OCH_3	55.4	56.6	55.2	54.7	56.3	56.3	56.6
C=O	156.7 q J = 36 Hz	157.2 q J = 36 Hz	156.3	156.2 q J = 35 Hz	156.6 q J = 35 Hz	156.7 q J = 36 Hz	Lost in noise
CF_3	116.6 q J = 287 Hz	116.6 q J = 286 Hz	116.5	116.6 J = 286 Hz	116.7 q J = 287 Hz	116.8 q J = 286 Hz	116.8 q J = 287 Hz

[a]Assignments in the same column may be interchanged.
[b]Rotamer B present in similar amount to rotamer A (Table 1).

*(RS)-8-Bromo-7-methoxy-1-methyl-N-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine (**6**)*

Two rotamers, 55:45 ratio ($CDCl_3$) δ 7.34 (1H, s, H-9), 6.68 minor and 6.64 major (1H, s, H-6), 3.88 minor and 3.87 major (3H, s, OCH_3), 3.8–3.34 (2H, m), 3.4–2.6 (3H, m), 1.34 minor and 1.30 major (3H, d, $J = 8$ Hz, C-CH_3); ^{13}C NMR ($CDCl_3$) (Tables 1 and 2).

*(RS)-8-Iodo-7-methoxy-1-methyl-N-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine (**7**)*

Two rotamers, 55:45 ratio ($CDCl_3$) δ 7.56 major and 7.55 minor (1H, s, H-9), 6.59 minor and 6.55 major (1H, s, H-6), 3.87 minor and 3.86 major (3H, s, OCH_3), 3.8–3.7 (1H, m), 3.7–3.25 (2H, m), 3.25–2.8 (4H, m), 1.33 minor and 1.29 major (3H, d, $J = 8$ Hz, C-CH_3); ^{13}C NMR ($CDCl_3$) (Tables 1 and 2).

Spectra

Nuclear magnetic resonance spectra were recorded in $CDCl_3$ at 300 K on a Bruker Avance III HD 400 (Bruker AXS GmbH,Karlsrhe, Germany) (9.4 Tesla, 400.13 MHz for ^1H, and 100.62 MHz for ^{13}C) spectrometer with a 5-mm inverse detection Smart Probe equipped with a z-gradient coil. Chemical shifts (δ in parts per million) are referenced to the solvent signals (7.26 ppm for ^1H and 77.16 ppm for ^{13}C). Coupling constants (*J* in Hertz) are accurate to ±0.3 Hz for both ^1H and ^{13}C. Typical parameters for ^1H NMR spectra were a spectral width of 4700 Hz and a pulse width of 10 μs at an attenuation level of 16.600 W. For ^{13}C NMR spectra, typical values were a spectral width of 21 000 Hz, a pulse width of 10 μs, an attenuation level of 69.000 W, and a relaxation delay of 2 s. Waltz16 was used for broad band proton decoupling; the FIDs were weighted exponentially (lb = 2 Hz) before Fourier transformation. Two-dimensional ^1H–^{13}C gs-HMQC and ^1H–^{13}C gs-HMBC experiments were carried out using standard Bruker software (https://www.bruker.com/products/mr/nmr/nmr-software/software/topspin/overview.html) and in non-phase-sensitive mode. Gradient selection was achieved through a 5% sine truncated-shaped pulse gradient of 1 ms. Selected parameters for gs-HMQC and gs-HMBC experiments were a spectral width of 2000 Hz for ^1H and 11 700 Hz for ^{13}C, 1024 × 128 data set, two scans for gs-HMQC, and two scans for gs-HMBC. The FIDs were processed using zero filling in the *F*1 domain, and a sine-bell window function in both dimensions was applied before the Fourier transformation. In the gs-HMQC experiment, GARP modulation of ^{13}C was used for decoupling.

Result and Discussion

The synthesis of *N*-trifluoroacetyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine derivatives **4** to **7** was achieved following the published sequence.[2,3] This involved trifluoroacetylation of the commercial 2-(3-methoxyphenyl)ethanamine, selective iodination of the product with iodine monochloride giving *N*-trifluoracetyl-2-(2-iodo-5-methoxyphenyl) ethanamine and, with excess reagent, *N*-trifluoracetyl-2-(2,4-diiodo-5-methoxyphenyl)ethanamine, *N*-allylation of these to afford *N*-allyl-*N*-trifluoracetyl-2-(2-iodo-5-methoxyphenyl)ethanamine (**1**) and *N*-allyl-*N*-trifluoracetyl-2-(2,4-diiodo-5-methoxyphenyl)ethanamine (**2**), intramolecular Heck reaction of **1** to give **3**, catalytic hydrogenation of the latter to **4**, and halogenation of **4** with *N*-chlorosuccinimide, *N*-bromosuccinimide, or *N*-iodosuccinimide to obtain **5**, **6**, or **7**, respectively.

Inspection of the ^1H NMR spectra of *N*-allyl-*N*-trifluoracetylethanamines **1** and **2** and of *N*-trifluoroacetyl-3-benzazepine derivatives **3** to **7** (Fig. 2) in $CDCl_3$ and at 300 K indicated the presence in each case of two rotamers corresponding to alternative orientations of the trifluoroacetyl group, assumed to be practically coplanar with the C-2/N/C-4 moiety. Nevertheless, most of the signals were not sufficiently resolved to assign them separately to one or the other rotamer. In the cases of **1** and **2**, the OCH_3 resonances of the rotamers were separated by about 0.02 ppm, allowing an approximate estimate to be made of their molar ratio. The most reliable resonance for this purpose was that of the CH_3 group attached to C-1 of compounds **4** to **7**, as the corresponding doublets appearing near 1.3 ppm were separated by about 0.04–0.05 ppm. With the exception of compound **4**, the CH_3 signal of the major rotamer appeared at higher field.

In contrast, except for compound **3** where both rotamers were present in similar concentrations, the ^{13}C signals could be assigned with some confidence to one or the other on the basis of their relative intensities. DEPT 135 experiments and the addition of substituent shift increments were sufficient to obtain a general picture of the ^{13}C spectrum of each individual rotamer with two important exceptions: those of C-2 and C-4, the methylene carbons flanking the trifluoroacetamide moiety. Careful inspection of the spectral region between 47 and 52 ppm for the rotamer mixtures showed the presence of four CH_2 singlets, two of which gave no indication of coupling to a heteroatom. The other two, upon magnification, proved to be barely resolved quartets with coupling constants of approximately 3 Hz. This was clearly attributable to a long-range interaction with the fluorine atoms of the trifluoroacetyl group ($^4J_{CF}$), but a decision as to which carbon of each rotamer was originating these signals – *syn* or *anti* with respect to the carbonyl oxygen – was not evident.

For comparison, in *N*,*N*-dimethylfluoroacetamide in $CDCl_3$, $^4J_{CF} = 4.5$ Hz was only observed for the methyl carbon *anti* to the carbonyl group. The authors of that paper did not report the $^4J_{CF}$ for *N*,*N*-dimethyltrifluoroacetamide in $CDCl_3$, which might be more comparable to our results, but in other solvents, the values observed were in the 3.9–4.0 Hz range.[8] Several *N*-allyl-*N*-trifluoroacetamides and the 3-benzazepine derivatives obtained from them by Heck cyclization showed similar long-range coupling constants of 2.8–3.7 Hz in $CDCl_3$ or $(CD_3)_2CO$ at 25 °C.[7]

The only obvious structural feature distinguishing C-2 from C-4 is the presence of a neighboring CH_3-CH moiety in one case and a CH_2 group in the other. A ^1H–^{13}C HMBC experiment carried out on compound **5**, which exhibited the (marginally) greatest separation between the CH_3 proton resonances, clearly showed that the proton doublet at 1.35 ppm (major) was correlated to the ^{13}C signal at 51.52 ppm, while the 1.39 ppm (minor) doublet was correlated to the ^{13}C quartet at 53.22 ppm. It is thus possible to state that in the

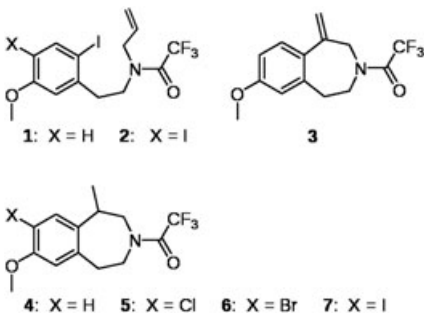

Figure 2. Structures of compounds **1** to **7**.

minor rotamer, the ^{19}F atoms are coupled to ^{13}C-2, while in the major rotamer, the ^{19}F atoms are coupled to ^{13}C-4. Interestingly, the ^{13}C-4 in the major rotamer is deshielded by about 1.7 ppm with regard to its counterpart in the minor rotamer, and in the opposite sense, ^{13}C-2 is shielded by the same amount in the major rotamer. As a near-planar conformation of the amide moiety may be safely assumed, the shifts to higher frequencies might be attributed to the magnetic anisotropy of the carbonyl group. Moreover, a ^{1}H–^{13}C HSQC experiment on compound **5** indicated that the protons bound to ^{13}C-2 resonate around 3.61/3.66 ppm in the major rotamer and around 3.84/3.88 ppm in the minor rotamer, again in agreement with the proposal that the carbonyl oxygen lies *anti* to C-2 in the former and *syn* in the latter, as depicted in Fig. 3.

In Tables 1 and 2, the C-2 and C-4 assignments for compounds **4**, **5**, **6**, and **7** and, by analogy, **3**, have been tabulated accordingly.

In *N*,*N*-dimethylfluoroacetamide and *N*,*N*-dimethyl-α-fluoropropionamide, according to the HETCOR spectra and aromatic solvent-induced shifts, the methyl group resonating at higher frequency is the one lying *syn* to the carbonyl group.[8] Our findings in the case of *N*-trifluoroacetyl-3-benzazepines **3–7** and, as described in the succeeding text, a couple of *N*-allyltrifluoroacetamides are additional instances involving ^{13}C of what is presumed to be a general effect of the carbonyl group on atomic nuclei lying near the nodal plane of its π orbitals.

Regarding the *N*-allyltrifluoroacetamides **1** and **2**, a ^{1}H–^{13}C HSQC experiment on the latter showed the CH_2 resonating at 51.06 ppm (major rotamer) interacting with the allyl CH_2 proton at 5.22 ppm and the 49.67 singlet (minor rotamer) with the allyl CH_2 proton at 5.32 ppm. Unfortunately, the 46.99 ppm quartet in the minor rotamer showed no clear-cut HSQC correlation. Here again, the carbonyl group shifts the *syn* sp^3 CH_2 carbon resonances to higher frequencies by about 0.3 ppm, and this effect is more pronounced for the allyl sp^2 carbon signals (about 0.5 ppm for the CH and 0.6 ppm for the CH_2 group) in agreement with the 2D NMR results, and consequently, the conformations of both rotamers should be as depicted in Fig. 4. The assignments for compounds **1** and **2** also appear in Tables 1 and 2 where the carbon atoms are numbered unsystematically to correspond to those in compounds **3–7**.

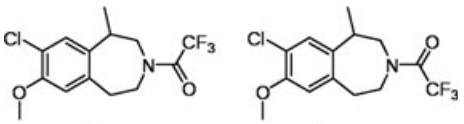

Figure 3. Structures of the major and minor rotamers of compound **5**.

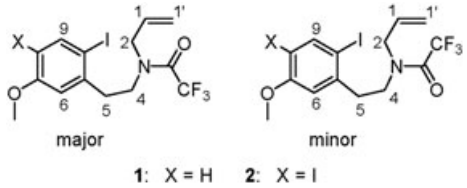

Figure 4. Structures and nonstandard numbering of the major and minor rotamers of compounds **1** and **2**.

Acknowledgement

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