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On the photoisomerization of the benzisothiazole portion of ziprasidone

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Abstract—Photostability challenge of ziprasidone in solution shows that the benzisothiazole moiety undergoes isomerization to the corresponding benzthiazole. A model compound, 3-piperazinyl-1,2-benzisothiazole, also undergoes this photoisomerization. Identification of the products has been confirmed by synthesis of the proposed molecules.

Photostability challenge of ziprasidone (**1**), an antipsychotic drug substance[1,2] recently approved by the US Food and Drug Administration, induces the compound to undergo a clean conversion to a single, chromatographically distinct compound. Electrospray liquid chromatography–mass spectrometry (LC–MS) experiments[3] indicate identical mass spectra for ziprasidone and the new product. Similar photochallenge experiments[4] with the two synthetic precursors of ziprasidone indicate that the benzisothiazole portion undergoes the conversion, not the oxindole portion. Comparison with reference standards of **2**, the benzthiazole analog of ziprasidone, and of **5**, the benzthiazole analog of a synthetic precursor, confirm the photochallenge products as benzthiazole isomers.

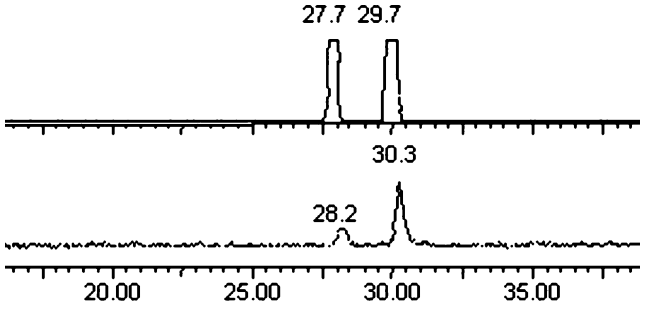
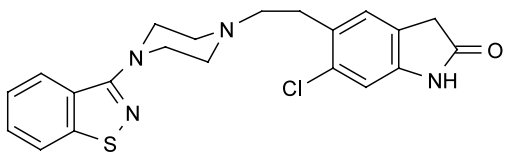
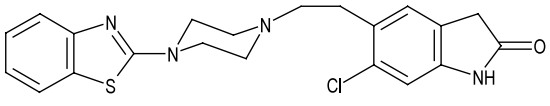


Figure 1. UV–vis (top) and total ion current (bottom) chromatograms of photochallenged ziprasidone (30.3 min) and its photoproduct (28.2 min).



1
ziprasidone
$C_{21}H_{21}N_4OSCl$
r.m.m. 412

The partial chromatograms shown in Figure 1 illustrate the clean conversion of ziprasidone to its photochallenge product. Comparison with the electrospray mass spectrum of ziprasidone, taken from the same LC–MS run, shows a spectrum (Fig. 2) identical to that of ziprasdone, complete with the isotope pattern associated with the m/z 413 $[M+H]^+$ indicative of the presence of a single chlorine atom. MS–MS collision-induced decomposition product ion spectra of ziprasidone and the photochallenge product are very similar.



2
$C_{21}H_{21}N_4OSCl$
r.m.m. 412

The simplest rationalization for this observation is a photo-induced isomerization. Similar photochallenge experiments were conducted with **3** and **4**, both syn-

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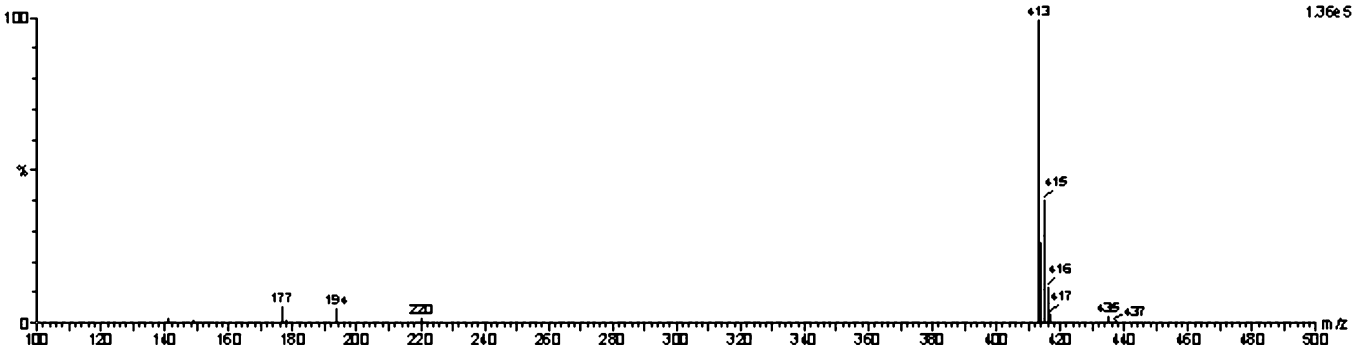
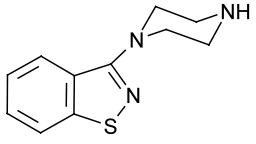


Figure 2. ESP mass spectrum of the 28.2 min chromatographic peak of Figure 1. This component is produced by light challenge of ziprasidone.

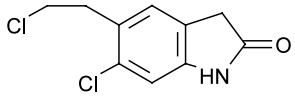
thetic precursors of ziprasidone. Oxindole **4** remained unchanged, but benzisothiazole–piperazine structure **3** showed a clean conversion to a chromatographically distinct species, similar to the conversion of ziprasidone. LC–MS analysis showed that the product from photochallenge of **3** also showed a 219 dalton relative molecular mass identical to that of the starting material. MS–MS product ion spectra of both compounds were very similar. Since neither **3** nor its photochallenge product produced a large signal response by electrospray in the mass spectrometer, GC–MS experiments[5] were also performed to support the assignment of identical relative molecular mass and structural similarity. The GC–MS run showed only two chromatographic peaks, the necessary 219 dalton molecular mass for both peaks, and spectra which differed only slightly in relative abundances of the fragments. Both electron ionization-induced fragmentation (by GC–MS) of **3** and its isomer, and collision-induced fragmentation (by LC–MS) of ziprasidone and its isomer could be justified with respect to literature discussions on these types of structures.[6]



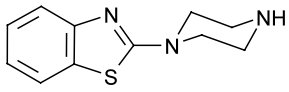
3
$C_{11}H_{13}N_3S$
r.m.m. 219

A search of the literature indicates that **5** has been previously prepared.[7] An appropriate test for identity of the photoisomerization hypothesis—to compare the HPLC and GC retention time behavior and mass spectral properties—was performed with an authentic sample of **5**, and indicated that the photochallenge product of **3** was indeed **5**. In addition, confirmation that ziprasidone indeed photoisomerizes to the benzthiazole analog was achieved by comparison with authentic **2**.[8]

Although examples of photoisomerizations of phenyloxazoles[9] and benzoxazoles[10] have been reported in the literature, we find no reports of photoisomerization of benzisothiazoles. Gilchrist[11] discusses a mechanism for photoisomerization involving an azirine

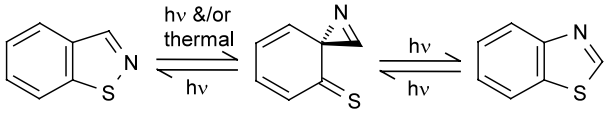


4
$C_{10}H_9NOCL_2$
r.m.m. 230



5
$C_{11}H_{13}N_3S$
r.m.m. 219

intermediate. Nucleophilic displacement is proposed to occur at either the azirine carbon or the nitrogen by the sulfur (Scheme 1), assisted by development of an aromatic pi-bonding system orthogonal to the azirine ring plane. The sulfur would have access to either carbon or nitrogen, producing the benzthiazole in one instance and the benzisothiazole in the other. The literature is unclear on the experimental basis for this mechanism. It may only be Gilchrist's extrapolation. Some indication has been given that the conversion of the azirine to the benzisothiazole has a thermal dependence. The literature, however, is also unclear about the extent of thermal and/or light dependence of this step. A significant thermal dependence may be an explanation for why the extent of isomerization seems to show a thermal dependence. In attempts to photoconvert ziprasidone on a large scale to the benzthiazole, elevated temperatures (ca. 60°C) could be shown to push the conversion further than at room temperature.



Scheme 1.

Acknowledgements

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3. LC–MS analyses were carried out on a Micromass Instruments Quattro I triple quadrupole mass spectrometer, coupled to a Hewlett–Packard 1050 modular HPLC system. Reverse phase separations were carried out on a Waters Puresil C_{18} column (4.6 mm×150 mm). Over the course of a 60 min run, the mobile phase (1 mL/min) was linearly changed from 10% methanol and 90% aqueous 0.1% trifluoroacetic acid to 100% methanol. UV–vis detection was carried out at 229 nm. The column was thermostated at 30°C. Column effluent was split approx. 10:1 after passing through the UV–vis detector using a Valco T-splitter, the smaller portion being presented to the LC–MS.
4. Photochallenge of compounds in solution was conducted in a Rayonet Model RPR-200 photochemical reaction chamber with fluorescent lamps. Samples were dissolved in a mixed solvent of 60% (v/v) methanol and 40% distilled H_2O, at an initial concentration of 0.2 mg/mL, and were contained in ordinary Pyrex glass containers.
5. GC–MS experiments were conducted on a Hewlett–Packard 6890 Series gas chromatograph and mass selective detector, equipped with split injection port and electronic pressure control. The column was a J&W Scientific DB-1 (100% poly(dimethylsiloxane)) bonded phase fused silica capillary column (30 m×0.25 mm×0.25 μ film thickness). Injector and detector temperatures were set, respectively, at 250 and 280°C. Oven temperature was held for 2 min at 100°C, then increased linearly at 5°/min to 240°C, then held at 240°C for 10 min. Helium carrier gas flow through the column was approx. 1.3 mL/min (45 cm/s). Injections were made by autosampler into a split injection port with split ratio set at 30:1. The mass selective detector was autotuned and mass calibrated using perfluorotributylamine (FC-43) according to instrument manufacturer's criteria. The detector was operated in repetitive scan mode, recording full scan mass spectra from m/z 40 to m/z 450 every 1.9 s.
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8. Compound **2** was synthesized by reacting one equivalent of 2-chlorobenzthiazole and the alkylpiperizine derivative of 6-chlorooxindole in isopropanol. Two equivalents of triethylamine were added over the course of a ca. 24 h reflux. The reaction only proceeded to ca. 45% completion using simple HPLC evaluation. The reaction was quenched by addition of five equivalents of HCl. The product was isolated by filtration, washed with isopropanol and H_2O, producing approximately 11% yield of a material greater than 95% pure by simple HPLC evaluation. The reaction was not optimized for yield.
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