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Photo-degradation products of pramipexole

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ABSTRACT

Two pyrrolidine compounds (**1** and **2**) were isolated from photo-degradation of Bi-Sifrol tablets. Compound **1** was esterified to *p*-bromophenacyl ester as single-crystal, and then the structure was elucidated by single-crystal X-ray study. Compound **2** was determined by 2D NMR and mass spectra. Otherwise, we established that the photo-degradation of pramipexole was smoothly carried out in the methanol solution, and elucidate the degradation mechanism.

Bi-Sifrol tablet is a dopamine receptor agonist which consists of pramipexole hydrochloride hydrate, and is licensed by Boehringer Ingelheim (Fig. 1). This drug is used as an anti-Parkinson's disease agent, stimulating D2 receptor at postsynaptic membrane of striatum. Pramipexole free base and its hydrochloride salt are known to be stable against a beam of light, while Bi-sifrol tablets are relatively unstable, therefore blister pack of aluminum is used for shading in Bi-sifrol tablets.

Althought there are a few reports about pramipexole impurities,[1] isolation and characterization of those impurities are not mentioned. Thus, it is important to propose a degradation mechanism for pramipexole. In this Letter, the characterization of the photo-degradation products of Bi-sifrol tablets is provided.

Some Bi-sifrol tablets were ground with a mill, and then irradiated under a fluorescent lamp for 2 days. The time-dependent change of the degradation profiles was examined by HPLC/ESI-MS. The LC/MS chromatogram displayed two remarkable $(M+H)^+$ ion peaks at *m/z* 228.13 and, 210.12, respectively. On the other hand, pramipexole hydrochloride salt and free base powders were also irradiated in the same way, but they did not decompose at all.[2]

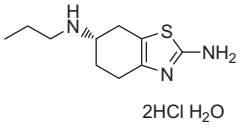

Figure 1. Structure of pramipexole hydrochloride hydrate.

We predicted that the additive in Bi-sifrol tablets assists to decompose the active pharmaceutical ingredient (API). Therefore, we mixed pramipexole and the additive used in Bi-sifrol tablets (povidone K25, magnesium stearate, mannitol, and silica gel), and then the mixture was irradiated under a fluorescent lamp.

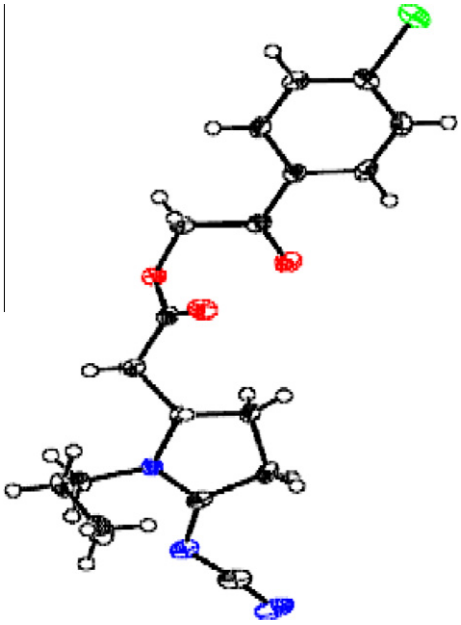

Figure 2. ORTEP view of **1a**.

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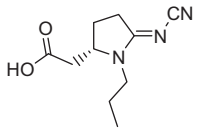


Figure 3. Structure of **1**.

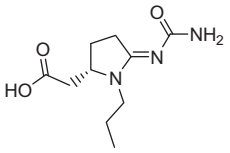


Figure 4. Structure of **2**.

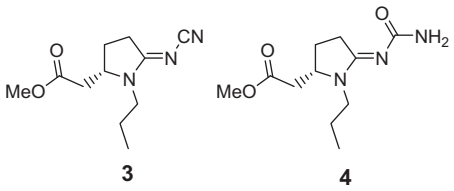


Figure 5. Structure of **3** and **4**.

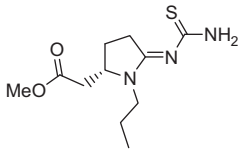


Figure 6. Structure of **5**.

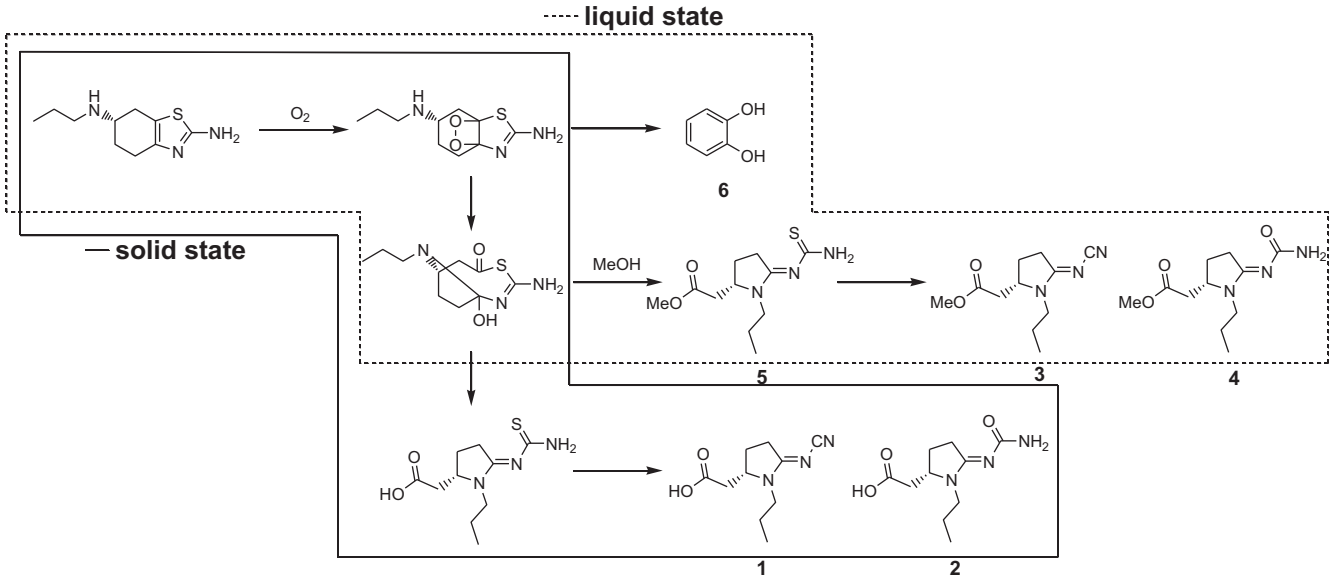
In the mixture of the pramipexole hydrochloride and silica gel, we only detected the same two degradation products that were detected in Bi-sifrol tablets. Furthermore, pramipexole free base instead of hydrochloride salt was mixed with silica gel and irradiated in the same way. This mixture produced the same degradation products as the Bi-sifrol tablets, and the rate of degradation was faster than the hydrochloride salt mixture. It has been reported that when the aspirin crystal was mixed with a silica gel, the stability of the aspirin decreased.[3] Accordingly, we expected that the same phenomenon may be observed in Bi-sifrol tablets. Based on these results, we carried out photo-irradiation to the mixture of pramipexole free base and silica gel, and two degradation compounds were isolated by silica gel chromatography ($CHCl_3$–TEA–MeOH).[4]

The molecular formula of **1** was determined as $C_{10}H_{15}N_3O_2$ based on molecular related ion $(M+H)^+$ *m/z* 210.1218 (calculated 210.1243) by high-resolution positive ion ESI-MS. The ^1H NMR spectrum of **1** showed three pairs of non-equivalent methylene groups and one methine signal derived from $–CH_2–CH_2–CH–CH_2–$. The signals of n-propyl group were observed. The ^{13}C NMR spectrum of **1** exhibited seven signals at δ 11.5, 21.0, 26.1, 31.7, 38.0, 45.4, and 60.7, respectively, in the aliphatic region, one nitril carbon at δ 120.1, and also two sp^2 carbons at δ 173.8 and 178.1. Furthermore, the IR spectrum revealed strong absorption for a nitrile group at 2183 cm^{-1}. To confirm the structure, **1** was esterified to *p*-Bromophenacyl ester **1a**, and recrystallized from *n*-hexane–AcOEt to obtain as single-crystal.[5] The structure of **1a** was determined by a single-crystal X-ray study as in Figure 2[6].

Consequently, **1** was elucidated to be (*S*,*E*)-2-(5-(cyanoimino)-1-propylpyrrolidin-2yl) acetic acid (Fig. 3).

The molecular formula of **2** was determined as $C_{10}H_{17}N_3O_3$ based on molecular related ion $(M+H)^+$ *m/z* 228.1330 (calculated 228.1348) by high-resolution positive ion ESI-MS. The ^1H NMR spectral data was similar to that of **1**. The ^{13}C NMR spectrum of **2** exhibited a new amide signal at δ 168.3 instead of a nitrile carbon at δ 120.1. From these results, we expected that the structure of **2** was as **1** with the nitrile group of **1** replaced with an amide group. Therefore, we hydrolysed **1** with HCl[7], and the NMR spectral data of the product was perfectly consistent with that of **2**. Compound **2** was determined as (*S*,*E*)-2-(5-(carbamoylimino)-1-propylpyrrolidin-2yl) acid (Fig. 4). In conclusion, the structures of two unknown compounds were determined in photo-degradation of the bi-sifrol tablet.

Photo-degradation of pramipexole caused vanish of 4,5,6,7-tetrahydrobenzothiazole skelton to give the pyrrolidine compounds.



Scheme 1. Photo-degradation mechanism of pramipexole.

Compound **1** and **2** increased the oxidation stage compared with pramipexole, we expected that the singlet oxygen involve the photo-degradation. Therefore the methanolic solution of pramipexole and catalytic rosebengal were subjected to photo-irradiation under an atmosphere of oxygen. Using 2.0 g of pramipexole, the reaction was completely finished in 6 hours, and we isolated compound **3** (455 mg, 21.5%) and **4** (129 mg, 5.6%)[8] (Fig. 5). Hydrolysis of **3** was performed by treatment with LiOH to give **1** in high yields.[9]

The two spots (compounds **5** and **6**) on TLC examination at an early stage of photo-irradiation were purified with silica gel chromatography.[10] The HR-ESI MS of **5** indicated the $C_{11}H_{20}N_3O_2S$ based on molecular related ion $(M+H)^+$ *m/z* 258.1259 (calculated 258.1276), which supported that the compound includes sulfur atom. Compound **5** showed similar spectrum in ^1H NMR to that of **2**, however, the amide signal of **5** in ^{13}C NMR spectrum observed down field shift to δ 196.1 ppm. Therefore, we determined as (*S,E*)-methyl 2-(5-(carbamolimino)-1-propylpyrrolidin-2yl) acetate (Fig. 6). Compound **5** was photoirradiated to give **3.**[11]

The ^1H NMR spectrum of compound **6** showed two A2B2-type signals at δ 6.64 and 6.73 only in the aromatic region. The GC-MS analysis of **6** was detected $(M)^+$ at *m/z* 110, and the fragment ion of **6** was consistent with authentic pyrocatechol spectrum in EI-MS. From these photo-degradation products of pramipexole, we consider the reaction mechanism to be as illustrated in Scheme 1.

The reaction starts from addition of the singlet oxygen to thiazole ring as [2+2]cycloaddition. The C–C bond cleavage of thiazole, followed by secondary amine attack to carbonyl group affords the pyrrolidine structure.[12] Then it was solvolyzed to give carboxylic acid and methyl ester.

In summary, we carried out photo-irradiation experiments of the Bi-sifrol tablets and succeeded in the characterization of four pyrrolidine compounds as photo-degradation products. Furthermore, we observed that the photo-degradation of pramipexole was smoothly carried out in the methanolic solution, and elucidated the possible degradation mechanism.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2012.02.044.

References and notes

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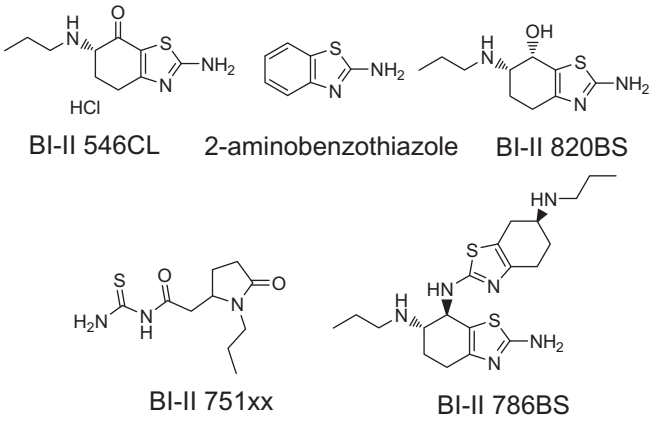

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3. Nakai, Y.; Yamamoto, K.; Terada, K.; Oguchi, T.; Yamamoto, M. *Yakugaku Zasshi* **1987**, *107*, 294.
4. Isolation of compound **1** and **2**: pramipexole free base (1.0 g) was mixed with Silica gel (5.0 g) and irradiated under a fluorescent lamp in ambient atmosphere for 1 week. Then the irradiated mixture was extracted with MeOH (100 mL). After concentration, the MeOH extract was chromatographed over silica gel, using $CHCl_3$–Triethylamine–MeOH (9:1:0.5) as eluent to give 1 (147 mg) and 2 (30 mg).
5. *Preparation of p-bromophenacylester* **1a** *as single crystal*: To a solution of 1 (7 mg) in CH_3CN (2 mL) was added 4-bromophenacyl bromide (22 mg) and triethylamine (0.2 mL), and the mixture was allowed to react overnight at room temperature. The reaction mixture was evaporated and purified with preparative TLC (AcOEt as eluent) to give 1a (8 mg). 1a was recrystallized with n-hexane-AcOEt to afford single crystal of **1a**.
6. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre following deposit number CCDC-865055 for compound 1a. Copies of these data can be obtained, free of charge on application to the Director. CCDC 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223 336033: of e-mail: deposit@ccdc.cam.uk).
7. Hydrolysis of **1**: 1 (70 mg) was dissolved in 35% HCl (2 mL) and then stirred at room temperature for 2 h. The reaction mixture was concentrated, and purified with preparative TLC ($CHCl_3$–MeOH (1:1) as eluent, R_f = 0.35) to give **2** (27 mg).
8. Photo-degradation in liquid state: Pramipexole free base (2.0 g) and rosebengal (0.1 g) were dissolved in MeOH (500 mL). The mixture was irradiated with bubbling oxygen under fluorescent lamp for 6 h. Then the reaction mixture was concentrated, and chromatographed over silica gel, using AcOEt–MeOH (9:1 to 8:2) as eluent to give 3 (455 mg) and 4 (129 mg).
9. Hydrolysis of **3**: 3 (4.2 g) was reacted with LiOH (1.3 g) in MeOH–H_2O (25 mL:20 mL) for 2 h in an ice bath. The reaction mixture was added to H_2O (100 mL), and then pH was adjusted to 1.0 by adding HCl. The mixture was shaken with $CHCl_3$ (three times of 100 mL), and concentrated to give **1** (3.6 g).
10. Isolation of **5** and **6**: pramipexole free base (1.0 g) and rosebengal (0.05 g) were dissolved in MeOH (500 mL). The mixture was irradiated with bubbling oxygen under fluorescent lamp for 1 h. Then the reaction mixture was concentrated, and chromatographed over silica gel, using *n*-Hexane–EtOAc (2:1→1:2) as eluent to give **5** (26 mg) and **6** (1 mg).
11. Photo-irradiation of 5: 5 (1 mg) and catalytic rosebengal were dissolved in MeOH (0.7 mL), irradiated under fluorescent lamp for 1 h to afford **3** (1 mg).
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