Abstract

Xipamide (1), a photosensitive diuretic drug is photolabile under anaerobic conditions and with UVA light. In the present study the photochemical behavior of xipamide was investigated in the presence of both electron donor and acceptor. When xipamide (1) was irradiated with a high-pressure mercury lamp under anaerobic conditions in the presence of electron-donor N,N-dimethyl aniline (DMA) it afforded photoproduct 2 and in the presence of an electron-acceptor 1,4-dicyanonaphthalene (DCN) it afforded photoproduct 3. The product formation was explained through the photoinduced electron transfer mechanism. Products were isolated and identified on the basis of IR, NMR and mass spectral studies.

Keywords

Xipamide; Electron transfer; Photodegradation; Photosensitization

1. Introduction

Drug photochemistry has been the object of a considerable amount of attention, especially in the last decade. Such interest has been promoted by the fact that even though many of these compounds are excellent therapeutic agents, they are also known to often cause phototoxic and/or photoallergic phenomena [1], [2] and [3]. Phototoxic disorders have a high incidence, whereas photoallergic reactions are much less frequent in human population. Detailed understanding of the molecular mechanism of photosensitization by drug is essential to anticipate and prevent the appearance of phototoxic or photoallergic side-effect. Many photosensitization reactions may be explained on the basis of the mechanism Type I (radical mediated) or Type II (singlet oxygen mediated). There are photosensitizing drugs of varied structural variety and significant variations in the phototoxic mechanisms must be expected depending on the difference in structural features [4]. It is therefore highly significant to study photochemical reaction of each individual phototoxic drug.

Diuretics are among the most widely used clinical agents and their discovery was a great success of both synthetic organic chemistry and pharmacology [5], with most of these agents being discovered in the late 50s and 60s. Right from the beginning of research in this field, it was clear that many compounds incorporating SO2NH2 groups showed great pharmacological activity [6]. Diuretic agents are drugs that increase the renal excretion of water and solutes (mainly sodium salts). The main purposes of diuretic therapy are to
decrease fluid volume of the body and to adjust the water and electrolyte balance [7].

Diuretics are drugs broadly used in clinical practice mainly in the treatment of hypertension and in different kinds of edema [8]. Diuretics may be classified according to their chemical structure, mechanism, primary site of action in the nephron and their diuretic potency in thiazide and non thiazide [9]. Non thiazide diuretic drugs are widely used as antihypertensive agents in clinical treatment [10], but these drugs are also well known to exhibit phototoxic, photomutagenic and photocarcinogenic properties, often causing undesirable side effects when patients are exposed to light, especially at UV-A wavelengths [11].

Xipamide (4-chloro-5-sulfamyleaicyloyl-2’,6’-dimethylamilide) is a potent non-thiazide diuretic with a greater natriuretic effect than the thiazides and a less abrupt onset and longer duration of action than furosemide [12] and [13]. It is an effective antihypertensive drug, appears to be a more effective diuretic than the thiazides and may cause a lower potassium loss relative to sodium excretion than these drugs [14] and [15]. Xipamide offers a suitable alternative to other diuretics in the treatment of patients with mild to moderate hypertension and of patients with oedema due to a variety of causes [16] and [17]. It belongs to the group of diuretics, which have been considered as doping substances since 1986 [18]. In recent years, diuretics have been abused in sport to reduce body weight in order to qualify for a lower weight class and to manipulate urine to avoid a positive result in doping tests [19]. The most frequently reported side effects of xipamide include mild upper gastrointestinal symptoms, anorexia or nausea, and tiredness and fatigue [20]. Dizziness (often postural) and vertigo have also occurred infrequently and were probably related to the extent of reduction in blood pressure. Xipamide, like the thiazide and ‘loop’ diuretics, causes net potassium loss, but this has varied according to the country of investigation [21]. There have been occasional reports of considerable decreases in serum potassium to concentrations as low as 2.2 mmol/L and of symptomatic hypokalaemia [22]. As might be expected, xipamide has caused small increases in average blood urea and serum urate concentrations in some studies, and occasional increases in blood glucose and of plasma lipids in diabetic patients [23]. Despite their excellent therapeutic activity xipamide induces phototoxicity as a significant side effect [24] and [25]. In general the mechanisms underlying the phototoxic reactions of xipamide are not known, and one prerequisite for a deeper understanding is the exact knowledge of the photochemistry of this drug. Herein we present an overview of the photochemical properties of xipamide. Evidence about the fragmentation modes and the intermediates occurring is discussed. A rationalization of the photoreactivity of the drug molecules is an important step in the understanding of the photodegradative paths occurring in biological environments and in the correlation between structural characteristics and phototoxicity. In the present study we have elucidate the photobehavior of the photosensitive diuretic drug xipamide under anaerobic conditions in presence of both electron donor and acceptor in UV-A light. Photolysis of xipamide (1) resulted in the formation of two major photodegradation products, identified as 2 and 3 from their spectral (IR, 1H NMR, 13C NMR, mass spectra) properties (Scheme 1). Photoproducts are presumably produced by photoinduced intermolecular electron transfer mechanism.
2. Experimental

2.1. Chemicals

All chemicals used were of analytical grade. Pure xipamide was obtained from Taj Pharmaceuticals Ltd., India. N,N-dimethylaniline and 1,4-dicyanonaphthalene was purchased from Sigma Aldrich (India). Photochemical reactions were carried out in quartz fitted immersion well photochemical reactor equipped with 400 W medium pressure mercury vapor lamp with continuous supply of water. UV spectra were recorded on a Shimadzu 160 A Instrument. IR spectra were recorded in KBr discs on a Perkin Elmer model spectrum RXI. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker Avance-DRX-300 Spectrometer using SiMe$_4$ as internal standard and CD$_3$OD as solvent. High resolution mass spectra were determined with a VG-ZAB-BEQ9 spectrometer at 70 eV ionization voltage. Column Chromatography was performed on silica gel 60 (70–230 mesh); TLC was carried on Merck silica gel 60 F$_{254}$ (0.2 mm thick plates).

2.2. General photoirradiation procedure

A solution of xipamide in methanol was stirred for 1 h before irradiation and was kept bubbling during the irradiations. The course of reaction was monitored by thin layer chromatography on pre-coated silica gel TLC plates using chloroform–acetone (9:1) mixture. After the completion of reaction (when desired conversions have reached) the solvent was removed in a rotary evaporator and products were purified by silica gel column chromatography.

2.3. Irradiation of xipamide in presence of electron donor

Methanolic solution of xipamide (XIP, 1) (295, 0.8 mM) in presence of electron donor, N,N-dimethylaniline (DMA) [26] was irradiated for 5 h at 254 nm. After following the steps
described in general photoirradiation procedure, 2-chloro-5-((2, 6-dimethylphenyl)carbamoyl)-4-hydroxybenzenesulfonic acid (2) was obtained as a major photoproduct.

2.4. 2-Chloro-5-((2, 6-dimethylphenyl)carbamoyl)-4-hydroxybenzenesulfonic acid (2)

Yield: 105 mg (35.59%); HRMS calc. For (M+) C_{13}H_{14}ClNO_2S 355.7934 Found 355.7930; IR (KBr) 3592, 3294, 3100, 1715, 1601, 1535, 1345 cm^{-1}; ^1H NMR (CD_3OD, δ, ppm): 8.36 (s, 1H, H-6), 8.0 (s, 1H, NH), 7.19 (s, 1H, H-3), 6.83 (d, 2H, H-3 and H-5 of phenyl), 6.74 (m, 1H, H-4 of phenyl), 4.9 (s, 1H, OH), 2.34 (d, 6H, 2CH_3 of phenyl), 2.0 (s, 1H, SO_3H); ^13C NMR (CD_3OD, δ, ppm): 163.9, 136.9, 136.6, 134.5, 133.9, 132.6, 124.1, 119.1, 118.0, 15.3; MS: m/z: 355 (M+), 338 (M+17), 320 (M+35).

2.5. Irradiation of xipamide in presence of electron acceptor

Methanolic solution of xipamide (XIP, 1) (295, 0.8 mM) in presence of electron acceptor, 1,4-dicyanonaphthalene (DCN) [27], was irradiated for 4 h at 254 nm. After following the steps described in general photolysis irradiation procedure, 4-hydroxy-N-(2,6-dimethylphenyl)-2-hydroxy-5-sulfamoylbenzamide (3) was obtained as a major photoproduct.

2.6. 4-Hydroxy-N-(2,6-dimethylphenyl)-2-hydroxy-5-sulfamoylbenzamide (3)

Yield: 110 mg (37.2%) HRMS calc. For (M+) C_{12}H_{16}N_2O_2S 336.3629 Found 336.3625; IR (KBr) 3592, 3310, 3294, 3100, 1715, 1601, 1345 cm^{-1}; ^1H NMR (CD_3OD, δ, ppm): 8.26 (s, 1H, H-6), 8.0 (s, 1H, NH), 6.84 (d, 2H, H-3 and H-5 of phenyl), 6.74 (m, 1H, H-4 of phenyl), 4.98 (s, 2OH), 2.35 (d, 6H, 2CH_3 of phenyl), 2.0 (s, 2H, NH_2); ^13C NMR (CD_3OD, δ, ppm): 164.5, 163.9, 156.8, 134.4, 134.1, 126.2, 124.1, 123.1, 114.0, 112.5, 103.9, 15.3; MS: m/z: 336 (M+), 319 (M+17).

3. Results and discussion

When methanolic solution of xipamide (XIP) was irradiated with medium pressure mercury vapor lamp in an immersion well type photo reactor in presence of DMA, 2-chloro-5-((2,6-dimethylphenyl)carbamoyl)-4-hydroxybenzenesulfonic acid (2) was obtained as a major photoproduct. When irradiation was carried out in presence of DCN, 4-hydroxy-N-(2,6-dimethylphenyl)-2-hydroxy-5-sulfamoylbenzamide (3) was obtained as a major photoproduct (Scheme 1). The photoproducts were isolated and identified from their spectral (IR, ^1H NMR, ^13C NMR, and mass spectra) properties. The assigned structures to these products well correspond to their observed spectral properties. The assigned structures to these products well correspond to their observed spectral properties. All the products obtained by photo-irradiation of xipamide (XIP), were characterized on the basis of the following spectral evidences. The ^1H NMR and ^13C NMR spectrum of compound 2 were similar to those of 1 except for signals obtained due to the conversion of sulfonamide to sulfonic acid. The ^1H NMR signal at δ 2.0 was a singlet for one proton clearly indicated that only sulfonamide group is changed to sulfonic acid. This was also supported by ^13C NMR and mass spectroscopy. ^13C NMR values corresponding to C-2, C-3, C-4, C-5, and C-6 were only slightly affected. ^13C NMR signal at 136.6 indicated the change of sulfonamide to sulfonic acid this was confirmed by the presence of IR band at 1355 cm^{-1} (S=O, str), slightly increases in frequency due to more electronegative oxygen atom.

Spectroscopic analysis of 3 were identified by IR, ^1H NMR and ^13C NMR and mass spectra. The IR spectrum showed absorption bands at 1345 cm^{-1} (S=O, str), and more characteristic band at 1089 (C=Cl Ar.str) are missing from XIP. That's only the sulfonamide ring were affected and also identified by ^1H NMR, the signals at δ 4.98 broad, singlet peak gives two phenolic hydroxyl groups were present in aromatic ring and other two aromatic benzene protons in the same ring were shielding at δ 6.64 (s, H-3), and 8.26 (s, H-6) due to introduced of hydroxyl group in the ring. This evidence fully supported by ^13C NMR, the signals at 164.5 for C-2 was highly deshielded and other C-1, C-3, C-5, C-6 also highly affected due to hydroxyl group in the ring, other carbonyl and second aromatic ring were unaffectted that clearly indicated the two hydroxyl groups are present in one aromatic ring. On the basis of IR, ^1H NMR, ^13C NMR and mass spectra suggested the chlorine atom was replaced by hydroxyl group.
The formation of photoproducts has been rationalized through photoinduced intermolecular electron transfer mechanism as given in Scheme 2 and Scheme 3.

Scheme 2.
Mechanistic pathway of the formation of photoproduct 2.

Scheme 3.
Mechanistic pathway of the formation of photoproduct 3.

When xipamide (XIP) was irradiated in presence electron donor N,N-dimethyl aniline (DMA), XIP reaches in excited state and in excited state it accept an electron from DMA to form XIP radical anion and DMA radical cation and in subsequent step XIP radical...
anion on hydrolysis yield photoproduct 2 by loosing ammonia (Scheme 2) similarly when the XIP was irradiated in presence of electron acceptor 1,4-dicyanonaphthalene (DCN), XIP reaches in excited state and in excited state XIP donate an electron to DCN and form XIP radical cation and DCN radical anion and in next step XIP radical cation on hydrolysis yield photoproduct 3 by the substitution of chlorine by hydroxyl group and by back electron transfer (Scheme 3). To conclude, the present results have shown that in presence of both electron acceptor and donor, drug undergoes photodegradation to yield 2-chloro-5-(2,6-dimethyl(phenyl)carbamoyl)-4-hydroxybenzenesulfonic and 4-hydroxy-N-(2,6-dimethyl(phenyl))-2-hydroxy-5-sulfamoylbenzamide as main photodegradation products through photoinduced intermolecular electron transfer mechanism and from the above study it is clearly indicated that during the fragmentation of xipamide in presence of both electron donor and acceptor radical ions are generated and it is a well known fact that radical ion is responsible for phototoxicity [28] and [29]. So the phototoxicity of xipamide may possible due to these radical ions; hence the present study may find its significance in rationalizing the phototoxicity of the xipamide. Therefore, the obtained data confirmed that adequate light protection should be adopted for the handling and storage of xipamide and suggest that excessive sunlight should be avoided after the drug consumption.

References

[1] B. Quintero, M.A. Miranda
Mechanisms of photosensitization induced by drugs: a general survey
Ars Pharm., 41 (2000), pp. 27–46

Photosensitization by drugs

Photodegradation and photosensitization in pharmaceutical products: assessing drug phototoxicity

Angel drug–biomolecules interactions in the excited states

Diuretics: an update on the pharmacology and clinical uses
Am. J. Ther., 16 (2009), pp. 74–85

Diuretics: an update on the pharmacology and clinical uses

[7] Y. Kim
Letter to the Editor

Approach to leg edema of unclear etiology

Pharmacological classification and renal actions of diuretics
Cardiology, 84 (1994), pp. 4–13

The potential savings of using thiazides as the first choice antihypertensive drug: cost-minimisation analysis
Drug-induced phototoxicity: an early in vitro identification of phototoxic potential of new drug entities in drug discovery and development

New and sensitive spectrophotometric method for determination of xipamide in pure and dosage forms by complexation with Fe(III), Cu(II), La(III), UO$_2$(II), Th(IV) and ZrO(II) ions

Rapid determination of xipamide in human plasma and urine by high-performance liquid chromatography
J. Chromatogr., 533 (1990), pp. 275–281

[14] A.S. Al-Kady
Optimized and validated spectrophotometric methods for the determination of trace amounts of uranium and thorium using 4-chloro-N-(2,6-dimethylphenyl)-2-hydroxy-5-sulfamoylbenzamide

Bioavailability study of triamterene and xipamide using urinary pharmacokinetic data following single oral dose of each drug or their combination

Hypertension

Iatrogenic hypercalcaemia hypokalaemia and metabolic alkalosis in lady with vena cava thrombosis—beware overzealous diuretic treatment

Results of stability studies with doping agents in urine

The abuse of diuretics as performance-enhancing drugs and masking agents in sport doping pharmacology, toxicology and analysis
Br. J. Pharmacol., 161 (2010), pp. 1–16

Adverse reactions to diuretics

[21] H. Knauf, E. Mutschler
Mechanism of action of xipamide and its classification as a “low ceiling diuretic” pharmacodynamic–pharmacokinetic studies in healthy volunteers and in kidney and liver patients
Arzneimittelforschung, 55 (2005), pp. 1–14

Xipamide disposition in liver cirrhosis
A. Balogh, U. Merkel, D. Muller
Can xipamide or tacrolimus inhibit the glucuronidation of mycophenolic acid in rat liver slices?

E. Selvaag
In vitro phototoxicity due to sulfonamide-derived oral antidiabetic and diuretic drugs

E. Selvaag, H. Anholt, J. Moan, P. Thune
Phototoxicity to sulphonamide derived oral antidiabetics and diuretics. Comparative in vitro and in vivo investigations
In Vivo, 11 (1997), pp. 103–107

P.O.J. Scherer
Intramolecular reorganization of the electron donor N,N-dimethylaniline

F. Shen, A. Peng, Y. Chen, Y. Dong, Z. Jiang, Y. Wang
Photoinduced electron transfer in coaggregates of dicyanonaphthalene and pyrazoline

B.M. Aveline, R.M. Sattler, R.W. Redmond
Environmental effects on cellular photosensitization: correlation of phototoxicity mechanism with transient absorption spectroscopy measurements

P.J. Bilski, M.A. Wolak, V. Zhang, D.E. Moore, C.F. Chignell
Photochemical reactions involved in the phototoxicity of the anticonvulsant and antidepressant drug lamotrigine (Lamictal)

Peer review under responsibility of Taibah University

Corresponding author. Tel.: +91 9058970731.
Copyright © 2013 Taibah University. Production and hosting by Elsevier B.V.