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Research Article

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Photosensitized oxidation of fluvoxamine, a phototoxic antidepressant drug

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ABSTRACT

The phototoxic antidepressant drug fluvoxamine is photolabile under aerobic condition in UV-A light. Irradiation of air-saturated solution of fluvoxamine (1) (210, 0.66 mM) in methanol with methylene blue as sensitizer produces two photoproducts, 5-Methoxy-1-(4-(trifluoromethyl) phenyl) pentan-1-one (2) and 2-nitroethanamine (3). The Photoproducts are formed by the reaction of drug with singlet oxygen produced through type II photodynamic action. The role of singlet oxygen during photolysis was confirmed by singlet oxygen scavenger 1, 4-diazabicyclo [2.2.2] octane (DABCO).

Keywords: Fluvoxamine, photooxidation, phototoxicity, Singlet Oxygen, Rose Bengal.

INTRODUCTION

Over the past decade there has been a considerable amount of research toward understanding both the unimolecular deactivation pathway of photo excited pharmaceutical product and their photosensitizing capability in the presence of biological substrate [1, 2]. According to the results, the primary event in any photosensitization process is the absorption of a photon, and the following free radical (Type I reaction) and singlet oxygen generation (Type II reaction) by photo-excited drug molecules [3, 4]. This may appear to be the principal intermediate species in the phototoxic response [5]. Thus, photochemical studies of photosensitizing drugs are important for understanding the key early events resulting in phototoxicity.

Oximes and their derivatives have found widespread use in synthetic organic chemistry as protecting groups for carbonyl compounds [6, 7]. In addition to their synthetic utility, many oximes are commonly used as pesticides [8] (including the structurally related carbamates) as photo-initiators [9] and as drugs e.g., as antidotes for organ phosphorus poisoning [10, 11]. The photochemical reactions of oximes have received considerable attention [12-14]. A number of pathways are available to oximes in the excited state and oximes may form a range of reactive intermediates in these reactions such as excited-state oximes (singlet or triplet), oxime radical cations, or reactive species (radicals) derived from these such as iminoxyl radicals, which have the potential to cause cell and tissue damage [15,16]. Photooxidation is major a tool to generate these reactive intermediates hence photochemical oxidations of oxime direct or sensitized, by energy or electron transfer, has attracted ever-growing interest.

Fluvoxamine (FXM); (E)-5-methoxy-4′-trifluromethylvalerophenone O-2-aminoethyl-oxime is a new generation antidepressant drug, [17, 18] demonstrates phototoxicity [19]. It exerts its antidepressant effect through a selective inhibition for the reuptake of the neurotransmitter serotonin by the presynaptic receptors hence it group of selective serotonin reuptake inhibitors (SSRIs) [20, 21]. They are replacing the older tricyclic antidepressants (TCAs) and because the efficacy of the SSRIs does not differ significantly from that of the TCAs and the SSRIs do not show

severe extra pyrimidal side-effects, SSRIs are more and more becoming the drugs of choice in depression therapy [22-24]. The phototoxic risk associated with the use of fluvoxamine is of high interest, as shown by the increasing number of related reports.

In continuation of our interest in the photochemical reactions involved in the phototoxicity of the photosensitizing drugs and their mechanisms and to delineate the underlying photochemical reaction that may possibly be involved in its phototoxicity, herein we have examined the photochemical behaviour of fluvoxamine (1) in presence of methylene blue under aerobic condition as dye sensitized formation of singlet oxygen and its reaction with drug are relevant to understand the phototoxicity of drug [25]. Photosensitized oxidation of fluvoxamine **(**1**)** resulted in the formation of two photodegradation products identified as (2**)** and (3**)** from their spectral (IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectra) properties (Scheme- 1). The Photoproducts are formed by the reaction of drug with singlet oxygen produced through type II photodynamic action.

EXPERIMENTAL SECTION

Apparatus and Chemicals

All chemicals used were of analytical grade. Fluvoxamine was extracted from commercial medicament sorest (Ranbaxy Laboratories, New Delhi, India) with a soxhlet extractor, purified by TLC and recrystallized from the same solvent. Melting point, ^{1}H-NMR and co-TLC with the authentic pure sample determined the purity of fluvoxamine. IR spectra were recorded as 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 TMS as internal standard and $CDCl_3$ as solvent. High resolution mass spectra were determined with a VG-ZAB-BEQ9 spectrometer at 70 e V ionization voltage. Merck silica gel 60 F_{254} plates were used for analytical TLC; column chromatography was performed on Merck silica gel 60 (60-120 mesh).

Photoirradiation procedure

Irradiation of air-saturated solution of fluvoxamine (1) (210, 0.66 mM) in methanol with methylene blue as sensitizer was carried out with medium pressure mercury vapour lamp for 6 h. Progress of the reaction was monitored by thin layer chromatography (TLC) (chloroform-methanol, 98:2). At the end of the reaction formation of two photoproducts were indicated on TLC which was isolated and purified by column chromatography using dichloromethane: methanol (8:2) on a silica gel column. The photoproducts were identified as, 5-Methoxy-1-(4-(trifluoromethyl) phenyl) pentan-1-one (2) and 2-nitroethanamine (3) from the following spectral properties:

5-Methoxy-1-(4-(trifluoromethyl) phenyl) pentan-1-one (2):

Yield: 95 mg (45.23 %); HRMS calcd. For (M^+) $C_{13}H_{15}F_3O_2$ 260.2522 Found 260.2519; IR (KBr): 1715, 1600, 1500, 1210 cm-1; ^{1}H NMR ($CDCl_3$, δ, ppm): 3.26 (s, 3H, H-6), 2.70 (t, 2H, H-2), 1.62 (m, 2H, H-4), 1.61 (m, 2H, H-3); ^{13}C-NMR ($CDCl_3$, δ, ppm): 197.1 (C-1), 139.07 (C-1'), 132.4 (C-4'), 125.28 (C-3'& C-5'), 124.1 (CF3), 73.6 (C-5), 58.2 (C-6), 35.8 (C-2), 29.4 (C-4), 23.02 (C-3); MS: m/z: 260 (M^+), 229 (M^+-31), 191 (M^+- 69), 145 (M^+-115).

2-nitroethanamine (3):

Yield: 37 mg (17.6 %); HRMS calcd. For (M+) $C_2H_6N_2O_2$ 90.0812 Found 90.0801; IR(KBr): 3140, 3250 (NH_2), 1345 (NO_2) cm-1; ^{1}H-NMR ($CDCl_3$, δ, ppm): 4.66 (m,2H, H-2), 3.26 (m, 2H, H-1), 2.0 (s, 2H, NH_2); ^{13}C-NMR ($CDCl_3$, δ, ppm): 79.5 (C-2), 38.5 (C-1); MS: m/z: 90 (M^+), 44 (M^+- 46), 74 (M^+- 16).

Similar experiments were carried out by using different combinations of sensitizers such as rose bengal, riboflavin and benzophenone to study the effect of triplet energy of sensitizer on the percentage yields of photoproducts.

In order to confirm the role of singlet oxygen ($^{1}O_2$) in this photoreaction, photolysis was also carried out under nitrogen atmosphere and in presence of 1, 4-diazabicyclo [2.2.2] octane (DABCO) which is normally used as a singlet oxygen scavenger [26].

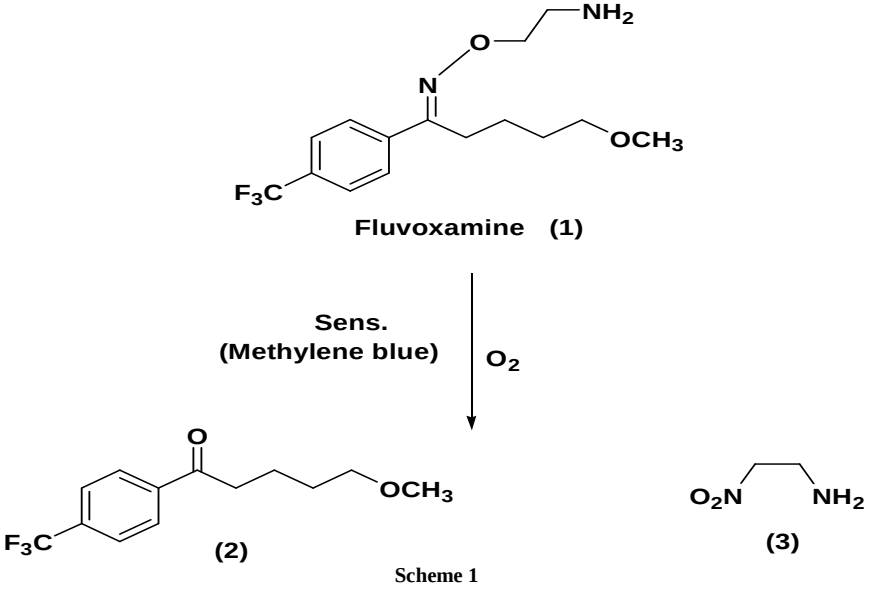
RESULTS AND DISCUSSION

Irradiation of air-saturated methanolic solution of fluvoxamine (1) with methylene blue as sensitizer in a water-cooled immersion well type photoreactor equipped with medium pressure mercury vapour lamp and purification of

the crude product by silica gel column chromatography afforded two photoproducts, 5-Methoxy-1-(4-(trifluoromethyl) phenyl) pentan-1-one (2) and 2-nitroethanamine **(**3**)** (Scheme-1).

The spectral features correlated to the assigned structure of the photoproduct **(**2**)** and were done in comparison with the spectra of the starting drug. The ^{1}H NMR spectrum of photoproduct **(**2**)** was devoid of signals at δ 3.79, 2.84 and 2.0 ppm for substituted amino ethyl group that was present in the starting drug fluvoxamine; however rest of the proton signals were similar to that of the parent drug. The ^{13}C NMR spectrum of photoproduct **(**2**)** further supported the loss of the substituted amino ethyl group. A new signal at δ 197.1 ppm corresponding to keto group indicated that substituted amino ethyl group has been replaced by keto group in the product.

The Photoproducts are formed by the reaction of fluvoxamine **(**1**)** with singlet oxygen produced through type II photodynamic action. Formation of photoproducts has been realized as depicted in scheme-2. Interaction between oxygen and the triplet state of sensitizer (methylene blue) results in energy transfer yielding singlet oxygen ($^{1}O_2$).

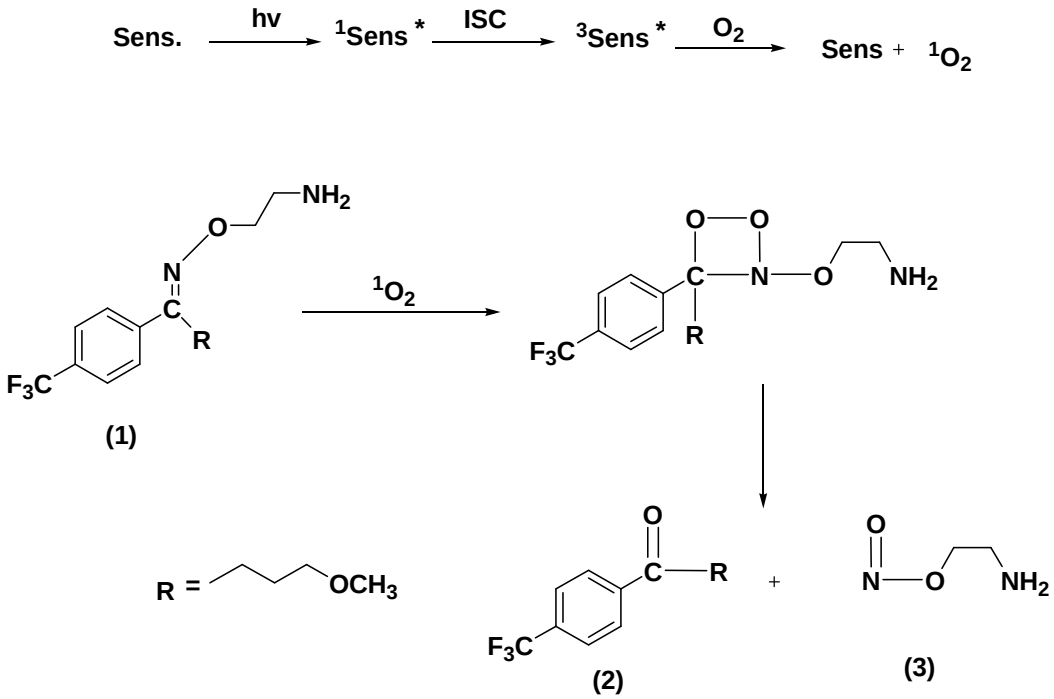


Scheme 1

Photosensitized oxidation of fluvoxamine

The generated singlet oxygen ($^{1}O_2$) would undergo [2 + 2] cycloaddition with the C=N double bond of the fluvoxamine (1) to gave dioxetane analogues as in the case of the cycloaddition with olefins [27]. The unstable dioxetane analogues could decompose under the reaction conditions to yield the corresponding carbonyl product 5-Methoxy-1-(4-(trifluoromethyl) phenyl) pentan-1-one **(**2**)** and a side product 2- nitroethanamine **(**3**)**.

The effect of triplet energies of various sensitizers on the percentage yields of photoproducts has also been studied. It was observed that rose bengal and methylene blue was much more efficient than riboflavin and benzophenone in the photosensitized decomposition of (1) (Table-1). This may be due to the fact that rose bengal and methylene blue, with lower triplet energies, produce singlet oxygen in large amount [28, 29] by type II mechanism [30]. On other hand riboflavin and benzophenone (higher triplet energies) act mainly by type I photosensitized photooxidation, do not produce significant amount of singlet oxygen ($^{1}O_2$) [31]. The participation of $^{1}O_2$ in the reaction was confirmed by studying the effect of scavenger on the yield of this photooxidation reaction product. The drastic lowering of the yield of products in presence of scavenger (DABCO) confirms that singlet oxygen ($^{1}O_2$) is an active oxidizing species in this photoreaction. Also no reaction was observed on conducting experiments under nitrogen atmosphere, which further support the involvement of singlet oxygen ($^{1}O_2$) in this photoreaction.



Scheme-2
Mechanistic Pathway of Photooxidation of fluvoxamine

Table 1. Effect of Triplet energies of different sensitizers on the yields of Photoproducts

Sensitizers	Triplet energy (kcal /mole)	Yields of photoproducts (%) (2+3)
Methylene blue	33.5 - 34.0	62.8 (45.2+17.6)
Rose bengal	39.2 - 42.2	58.4 (35.2+23.2)
Riboflavin	57.8	47.8 (25.3+22.5)
Benzophenone	68.6 - 69.1	49.1 (24.5+22.0)

To conclude, the present results have shown that the photooxidation products are formed by singlet oxygen ($^1O_2$) mediated photodynamic action upon sensitized visible light irradiation of fluvoxamine **(**1**).** 5-Methoxy-1-(4-(trifluoromethyl) phenyl) pentan-1-one **(**2**)** was identified as the main photooxidation product. The investigation of photochemical properties of compounds used in clinical medicines is of great relevance from photobiological as well as photo medical point of view since singlet oxygen formation and the ensuing photooxidation of the drug and biomolecules is one of the main routes for the drug phototoxicity. The present findings may have an implication to the phototoxic effect of the drug.

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