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Synthesis, characterization, docking and electrochemical studies of nitroaromatic amides

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ABSTRACT

A series of N-[4-(Nitrophenoxy)phenyl]alkanamides (N-1 to N-14) with different alky groups were synthesized following two-step procedures. The structural elucidation of the synthesized compounds was carried out by IR and NMR spectroscopic techniques along with elemental and single crystal X-ray diffraction analyses. Molecular docking study (drug-DNA binding) was carried out to check their biological potential. The docking data revealed the interaction of compounds with ds. DNA, which was further complemented by cyclic voltammetric study. The synthesized compounds showed minor groove binding mode of interaction with DNA. The increased chain length of alkyl groups did not significantly affected the compound-DNA binding.

1. Introduction

Nitroaromatics is a class of organic compounds having at least one nitro group directly linked to the aromatic ring. A vast variety of these compounds are synthetic in origin [1] and very few are naturally occurring [2]. They act as precursor for many industrial products like pesticides [3], agrochemicals [4], drugs [5], and aromatic amines (building blocks for many industrial products like polyurethane foams, rubbers, azo dyes, photographic chemicals, varnishes, and liquid crystalline materials) [6–8]. The nitro compounds belonging to nitroreductases (an important class of nitroaromatics) are capable of enzymatic reduction in organisms [9]. They play a key role to activate the prodrugs in anticancer therapies. A lot of research has been carried out to check their susceptibility to antibiotics [10,11]. The interaction of drugs with DNA is the major focus of bioactivities and new drug discovery processes. The DNA structure provides many cites to develop hydrogen bonding with the nitro group which may categorize these types of compounds as potential biomolecules in terms of investigating their bioactive nature. The unique structural property of the nitroaromatic amides, offer them to bind with DNA molecules through hydrogen bonding via nitro groups as well as amide moieties [12]. Nitroaromatics possessing great affinity for DNA binding show various modes of interactions like electrostatic, intercalative and groove binding which can be monitored by UV–vis, fluorescence, Raman and NMR spectroscopic techniques together with cyclic voltammetry and molecular docking studies [13–15].

The research work presented in this paper describes the: i) synthesis of nitroaromatic amides, having different alkyl groups at one end. ii) their structural characterization, iii) drug-DNA binding study by molecular docking studies and iv) complementing the docking studies by electrochemical findings of a selected compound (N-3).

2. Results and discussion

A series of nitroaromatic amides (N-1 to N-14) was synthesized successfully by conventional condensation reaction of acid chlorides and amines (Scheme 1). The first four members of the series were isolated as crystalline material with a narrow range of melting points. However, the higher members of the series with long chain aliphatic groups were not being crystallized out in proper dimensions suitable for the single crystal X-ray diffraction analysis. The purity of these products was ascertained by passing through

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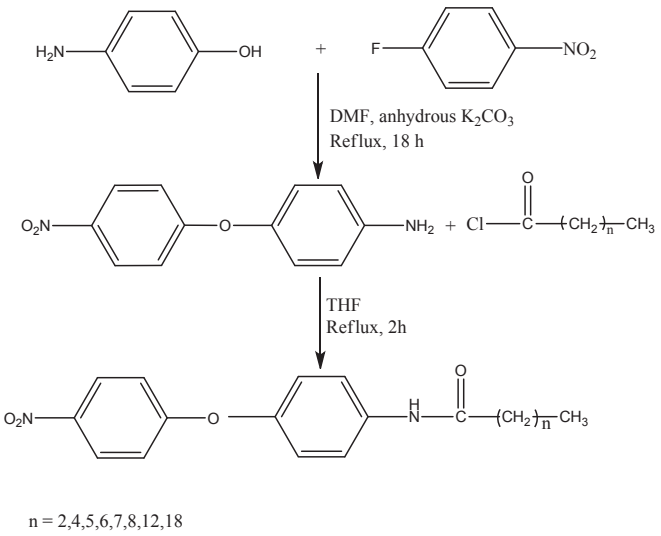

Scheme 1. Synthesis of 4-[4-(nitrophenoxyphenyl)alkanamides] (N-1 to N-14).

silica gel column. The molecular structures of the synthesized compounds were confirmed by elemental, spectroscopic (IR and NMR) and single crystal X-ray diffraction analyses.

2.1. Spectral characterization

The IR characteristic absorption bands for nitro-functionality were observed at 1506–1509 cm^{-1}(asymmetric) and 1339–1342 cm^{-1}(symmetric) respectively. A broad absorption band at 1231–1239 cm^{-1} was due to C–O–C whereas the band at 1652–1665 cm^{-1} was assigned to C=O vibrations. The data recorded for IR frequencies showed a shift in the amide region, indicating strong intermolecular H-bonding. The –NH absorption appeared at 3289 cm^{-1} in IR spectrum, which is quite lower than their normal absorption range (3500-3700 cm^{-1}). It conforms to the strong intermolecular H-bonding amongst the molecular moieties, followed by the band broadening effect in IR spectrum [8,12,13,15].

In ^{1}H NMR spectrum, one proton singlet signal appeared at 7.92 ppm, which is a supportive evidence for the intermolecular H-bonding of the amide group. This was further verified by ^{13}C NMR where signal for carbon atom of amide moiety was observed most downfield at 171.84 ppm. The eight aromatic carbon atoms resonated between 163.66 and 116.76 ppm. Three signals appearing in the aliphatic regions (13.82, 19.14, 39.50 ppm) are assigned to the three different C-atoms of $-CH_2CH_2CH_3$ group.

2.2. Single crystal X-Ray diffraction analysis

The X-ray diffraction data was collected with a STOE-IPDS-II area detector diffractometer using monochromatic MoKα radiation (λ = 071073 Å) at 173 K and was corrected for Lorentz and polarization effects. The structures were solved by direct methods using SHELXS-97 and refined by full-matrix least-squares techniques using SHELXL-97 [16]. The X-ray structural analysis indicated that the compound N-3 crystallized with one molecule in the asymmetric unit, in the monoclinic space group P21/n. The two aromatic rings are almost perpendicular to each other (dihedral angle 85.6°). The nitro group is only slightly twisted out of the plane of the ring to which it is attached [torsion angles: O3–N2–C24–C25 = 7.7(3)° and O4–N2–C24–C23 = 8.4(3)°]. The terminal carbon atoms of the side chain show a trans conformation (C1–C2–C3–C4 174.8(2)°), Fig. 1(a). The crystal packing is characterized by chains of molecules running along the crystallographic b axis. In these chains, the molecules are connected by N–H···O hydrogen bonds (N–H 0.92 Å, H···O 1.97(2) Å, N–H···O 172°), Fig. 1(b).

2.3. Drug-DNA binding studies

2.3.1. DNA binding study by molecular docking

In an effort to elucidate the drug-DNA binding behavior of the synthesized compounds, the molecular docking study was performed using the AutoDock Vina program [17]. Fig. 2 displays the ligand binding into the minor groove of the DNA (pdb entry 3QSC.pdb), and the binding affinities are given in Table 1.

Detailed analysis of drug-DNA interactions indicated that the nitro group of the synthesized molecules specifically form a stable hydrogen bond with the amino group ($-NH_2$) of the Guanine moiety present in the DNA molecule with a bond length varying from 2.97 to 3.28 Å, 3.11 Å being the average one. Since the Guanine moiety is widespread in the DNA molecule, the drug binding becomes non-specific in nature.

The nitrogen of the amide group in these compounds form a second hydrogen bond with the ribose oxygen involved in the ether linkage measuring a bond length from 2.81 to 3.45 Å with an average of 3.08 Å. These observations further explain the non-specificity and the insignificant effect of the size of hydrocarbon on ligand binding and complement the experiments. Fig. 3 shows the molecular interactions of molecules N-3 and N-4 with the DNA molecule. The distance of these interactions for all compounds is given in Table 1.

The compounds have been shown in CPK colors with oxygen indicated as red, nitrogen as blue, carbon as cyan and hydrogen as white. The black dotted lines with the values in the rectangular boxes indicate hydrogen bond distance, measured between heavy atoms. The hydrogen atoms have been omitted in the DNA and drug molecules for clarity.

2.3.2. DNA binding study by cyclic voltammetry

N-3 was isolated as crystalline material with a sharp melting point and in highest yield than others. Therefore, it was selected as a representative for bioelectrochemical investigation to get supportive evidence for drug-DNA binding study.

Electrochemical study of N-3 (5 mmol dm^{-3}) was accomplished

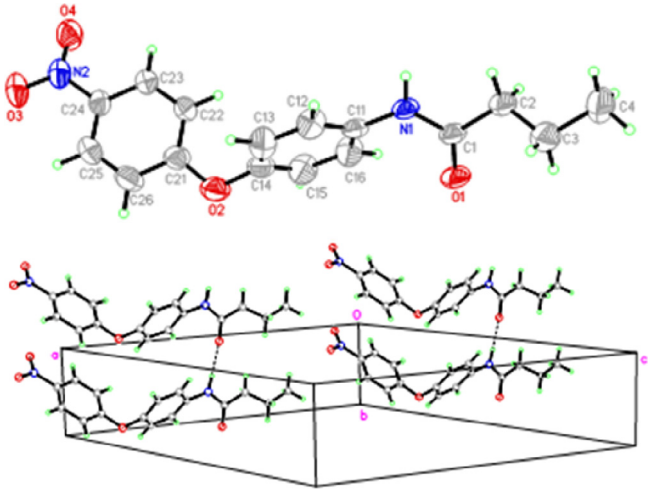

Fig. 1. a) ORTEP diagram of N-3. b) Packing diagram showing H-bonding in N-3.