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Photodegradation and In Silico Molecular Docking Study of a Diuretic Drug: Clopamide

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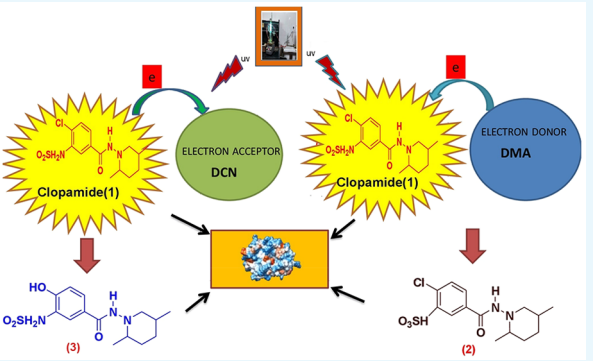
ABSTRACT: Clopamide (CPD, **1**) is a piperidine and sulfamoylbenzamide-based diuretic drug and a potential photosensitizing sulfonamide; its phototransformation was investigated using *N*,*N*-dimethylaniline (DMA) as an electron donor and 1,4-dicyanonaphthalene (DCN) as an electron acceptor in an immersion-well-type photochemical reactor fitted with a medium-pressure mercury vapor lamp (450 W). Photodegradation of the drug Clopamide resulted in two significant products via photoinduced electron transfer. Structures of these products were deduced from their ^{1}H NMR, ^{13}C NMR, mass, and IR spectra. The photoproducts are 2- choloro-5-((2,6-dimethylpiperidin-1-yl)carbamoyl)benzenesulfonic acid (**2**) and 4-hydroxy-*N*-(2,6-dimethyl-1-piperidyl)-3-sulfamoyl benzamide (**3**). In addition to this, the comparative antioxidant potentials of the parent drug and its photoproducts were investigated using in silico molecular docking against tyrosinase in order to better understand the in vivo relevance of pharmacological action of the drug as a result of light−drug interactions. UV light has been observed to modify substituents on the benzene ring, hence loss of biological activity at the time of storage and in vivo cannot be ruled out. This suggests that Clopamide users should avoid light (natural or artificial) exposure to prevent from drug-induced photosensitivity.



INTRODUCTION

The photoinduced electron transfer process continues to be a fascinating arena for exploring the properties of electronically excited states of chemicals of medicinal implications, which currently has been exponentially escalated.[1−5] This was prompted by photobiological reasons, linked to the combined effects of a drug and light-induced phototoxicity, which mainly manifests as photocarcinogenesis, photoallergy, phototoxicity, and photomutagenicity.[6,7] One or more of the given pathways as routes for adverse phototoxic reactions could be involved, namely, formation of singlet oxygen, generation of radical species through electron or hydrogen transfer, covalent photobinding to biological molecules, and photodecomposition reaction leading to photoproducts.[8−10] This correlation draws a relation between phototoxicity and photoreactivity.[11,12] As there are countless photosensitive drugs with ensuing phototoxicity, special attention should be given to those photosensitive drugs to inhibit the underlying mechanism responsible for inducing phototoxicity.

Photoinduced electron transfer in drugs have received increased awareness in the past few years from a more fundamental photochemical point of view, and several reactions such as cycloadditions, oxygenations, cycloreversions, and photodecomposition of pharmaceutical compounds have been studied in this regard.[13] Photoinduced electron transfer (PET) is one of the most pivotal chemical processes and contributes a key role in numerous photosensitization reactions.[14] Light-triggered electron transfer is a process in which an electron is transferred from an electron donor to an electron acceptor. Prior to electron transfer, one of the components is excited with light.

The role of photoinduced electron transfer reactions in photosensitization is simply an amalgamation of principles of photochemistry and the basic theory of electron transfer. When systems having differential capacity to hold electrons are brought together, electron hopping likely happens from loosely bound to a strongly bound unit. Donors are electron-rich species that can transfer an electron quickly; on the other hand, acceptors are electron-deficient species having the ability to accept an electron. Molecules (particularly having chromophoric groups) can undergo an electronic shift from the ground electronic energy level to the excited electronic energy level by absorbing light of a specific wavelength. Molecules that are in an excited electronic state are usually particularly

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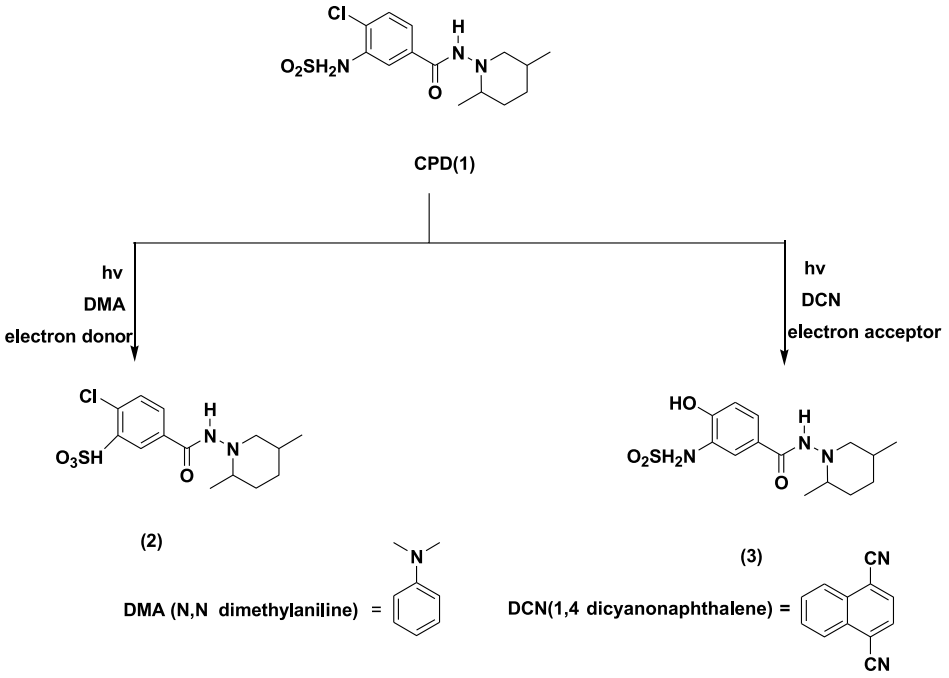
Scheme 1. Phototransformed Products of Clopamide



reactive. If efficient donor or acceptor entities are available in the vicinity, they can give up (or accept) an electron.[15] As a consequence, it becomes essential to shed light and elaborate the course of photodegradation of each and every drug to explain the chemical reaction pathways and then to identify the short-lived intermediates as well as stable photoproducts. Photochemical studies on such types of drugs will make significant contributions in the area of drug-induced photosensitization, which may be useful in understanding in vivo photobiological effects and preventing the harsh impact of drug photosensitivity before they are used in a clinical setting.

Diuretics are a group of medications that cause the body to produce more urine by increasing the urine flow rate. The use of diuretics causes the body to excrete more electrolytes, particularly sodium and chloride ions, as well as water, without impacting protein, vitamin, carbohydrate, or amino acid absorption. Diuretics are used to treat different edematous conditions caused by congestive cardiac failure, nephrosis, etc. They are also applicable in adjunctive therapy in the treatment of hypercalcemia, acute mountain sickness, cataracts, and prime hyperaldosterism.[16−19] Several categories of diuretics are well-known, such as thiazides, carbonic anhydrases, etc.[20] Long-term treatment with this class of drugs has recently been correlated with the photoinduced formation of carcinomas,[21] and some have been documented to have a phototoxic impact as a side effect.[22] Pharmacological reports of toxic effects linked to the application of clopamide have sparked interest in the drug's photoreactivity. Despite its immense clinical activity, clopamide induces phototoxicity[23,24] as an adverse side effect. Establishing an in-depth understanding of the photochemical properties of these drugs may provide a route to overcoming these photocarcinogenic and phototoxic side effects or, alternatively, may provide a basis for developing more efficient compounds with medicinal implications. Therefore, researchers focus their attention on this class of drugs whose molecular mechanism is still unknown.

Clopamide (CPD, **1**), a trisubstituted benzene derivative with a sulfonamide chromophore as one of the substituents, is an oral diuretic[25,26] with the same aromatic sulfonamide basis as thiazide diuretics.[27,28] It possesses features comparable to those of thiazide class diuretics, which block sodium reabsorption in the proximal renal tubule while boosting release of chloride ions, consequently with increased waste excretion.[29,30] Clopamide (**1**) is increasingly being used to treat hypertension and excessive fluid retention in serious illnesses such as cardiac failure, nephrosis, chronic kidney failure, and cirrhosis.[31] Previous research has shown that a once-daily fixed medication combination of 5 mg of clopamide, 10 mg of endralazine, and 10 mg of pindolol can be effective in the management of blood pressure in roughly 90% of individuals with mild to severe hypertension.[32] It has also been observed that when a beta-blocker with intrinsic sympathetic activity (pindolol) and a thiazide diuretic (clopamide) combined results in a favorable alteration in systemic resistance deprived of a detrimental impact in cardiac output.[33] Clopamide causes dizziness, nausea and headaches, weariness, as well as hyperglycemia, gout, dry mouth, thirst, weakness, muscle soreness, etc.[34] Aside from this effect, CPD (**1**) has been found to be associated with phototoxicity.[35] Generally, the mechanism behind the phototoxic effect of clopamide is not known. This has prompted us to investigate its photochemical behavior to determine the underlying mechanism of phototoxicity and the chemical process occurring. In order to isolate, identify, and elucidate the molecular mechanism of CPD (**1**), we examined its photochemical behavior in UV light in the presence of *N*,*N*-dimethylaniline (DMA) as an electron donor and 1,4-dicyanonaphthalene (DCN) as an electron acceptor under anaerobic conditions. Studies on photodegradation of drugs play a significant roll in the process of drug discovery because photolysis products might have biological effects different from those of the drug itself. Molecular docking[36−39] is becoming a more important tool in drug development. It essentially

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predicts the intermolecular framework produced between a protein and a small molecule or between a protein and another protein, as well as the binding modes that cause the protein to be inhibited. In the process of drug development, these in silico methodologies, when combined with biophysical data, experimental high-throughput screening, and biology/toxicology/clinical research, are a crucial tool.

One major product (**2**) was obtained by irradiating CPD (**1**) solution in anaerobic conditions using electron donor (DMA). A distinct product (**3**) was formed under the same experimental condition when it was irradiated using an electron acceptor (DCN). The isolation and characterization of products **2** and **3** were done using column chromatography and on the basis of different spectral studies. Formation of products **2** and **3** was described on the basis of a photoinduced electron transfer mechanism. Further, a molecular docking study on the selected compounds were analyzed for the antioxidant potentials in order to understand the pharmacological fate of drugs in vivo as a consequence of light on drugs. The study reveals that photoproducts were found to show more antioxidant activity as compared to CPD (**1**); that is, the parent compound against the tyrosinase, as a result from conducting a virtual screening research, can be both cost-effective and time saving. It also plays a crucial role in the design of new drugs with desired tyrosinase binding affinity and possesses efficient biological activities.

RESULTS AND DISCUSSION

Irradiation of a methanolic solution of clopamide (CPD, **1**) under anaerobic conditions in the presence of an electron donor, DMA, in a photochemical reactor setup furnished with a medium-pressure mercury vapor lamp (450 W) yielded one main major product, 2-choloro-5-((2,6-dimethylpiperidin-1-yl)carbamoyl)benzenesulfonic acid (**2**). When it was irradiated with an electron acceptor, DCN, under the same experimental condition, product **3** was obtained, as depicted in Scheme 1. The products were isolated, and their identification was done through their spectral (IR, ^{1}H NMR, ^{13}C NMR, and mass spectra) properties. The ascribed structure of these products closely matches with their observed spectral properties. Formation of products has been described through the involvement of a photoinduced intermolecular electron transfer mechanism, as shown in Scheme 2 and Scheme 3.

Drugs upon photodecomposition form photoproducts possessing diverse structural differences compared to the parent drug. As structural properties of molecules are linked with activity of drug, altered pharmacological properties[40,41] can be expected. This has stimulated researchers to unfold the pharmacological properties of drugs undergoing photodegradation as a consequence of the action of light on drugs,[42] which may be important for correlating the results with the in vivo biological environment and to unveil the structural substratum to design new therapeutic agents.[43] As a virtual screening study can be cost-effective and time-saving, in present study CPD (**1**) and its photoproducts **2** and **3** were analyzed for antioxidant potentials by screening their post-docking interactions, Gibbs free energy values, and H-bond interactions with tyrosinase. Docking results are presented in Table 1. Protein−ligand interactions can be seen in Figure 1a−c.

One major product, 2-chloro-5-((2,6-dimethylpiperidin-1-yl)carbamoyl)benzenesulfonic acid (**2**), was obtained in fairly good yield when irradiated with CPD (**1**) in the presence of the electron donor DMA under anaerobic conditions. The mechanism for the formation of product **2** can be confirmed as irradiation leads to the electronic excited state of CPD (**1**). This excited CPD accepts an electron from the ground-state molecule of electron donor DMA to form a corresponding clopamide radical anion (CPD$^{\bullet-}$) and DMA radical cation (DMA$^{\bullet+}$). Subsequently the generated clopamide radical anion (CPD$^{\bullet-}$) undergoes hydrolysis to yield product **2**, followed by the elimination of ammonia molecules. The mechanism outlined in Scheme 2 well explains the observed reaction.

When irradiation of CPD (**1**) was performed in the presence of electron acceptor DCN under the same condition, the product 4-hydroxy-*N*-(2,6-dimethyl-1-piperidyl)-3-sulfamoyl benzamide (**3**) was obtained. A plausible mechanism for the observed reaction involves a photoinduced intermolecular electron transfer between the photoexcited CPD (**1**) and DCN, affording clopamide radical cation (CPD$^{\bullet+}$) and dicyanonaphthalene radical anion (DCN$^{\bullet-}$). The generated CPD$^{\bullet+}$ then follows a substitution of the chlorine by the hydroxyl group and a back electron transfer to afford the corresponding product **3**. The result obtained above is in good agreement with the mechanism depicted in Scheme 3.

An in silico docking strategy was applied in order to determine the interaction of CPD (**1**), **2**, and **3** with tyrosinase. CPD (**1**) is considered as the parent compound, and **2** and **3** are the photoproducts. The docking results are presented in Table 1.

Table 1. Docking Results

molecule name	Gibbs free energy (Δ*G*) (kcal/mol)	H-bond interaction	ligand-interacting amino acids
CPD (**1**)	−6.82	GLU195, ASN205	HIS60, VAL218, PHE197, HIS204, MET215, ASN205, GLU195, MET61
2	−6.90	VAL218, ASN205	VAL217, ASN205, MET61, HIS60, VAL218, HIS204, HIS42, PHE227, HIS208, MET215
3	−7.68	ASN205, ARG209	ASN205, ASN57, ARG55, HIS42, ALA221, ARG209, HIS231

From the careful inspection of the docking score, it was revealed that CPD (**1**) and its photoproducts **2** and **3** have binding affinities of −6.82, −6.90, and −7.68 kcal/mol, respectively, against the tyrosinase. It is also predictable that the binding efficiency of the two photoproducts increased compared to that of CPD (**1**), i.e., the parent compound. It has also been noticed that GLU195 and ASN205 are the important amino acid residues involved in the intermolecular hydrogen bonding with CPD (**1**) within the active site of tyrosinase. Again, VAL218 and ASN205 are the important active site binding amino acid residues for **2**, and ASN205 and ARG 209 were the important active site binding amino acid residues for **3**. By analyzing the amino acids involved in the H-bond interaction, it is noted that ASN205 was found to be the common residue for all of them. By analyzing the given data, one can easily find the best clinical trial strategy and can implement that for further pharmacological analysis. Thus, in silico research is important for understanding the pharmacological activity of drugs that can be cost-effective, time-saving, and play a vital role in the development of new drugs with desired tyrosinase binding affinity and biological activities.

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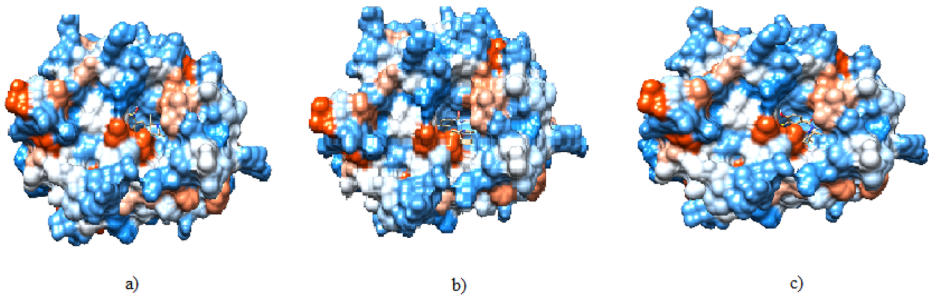
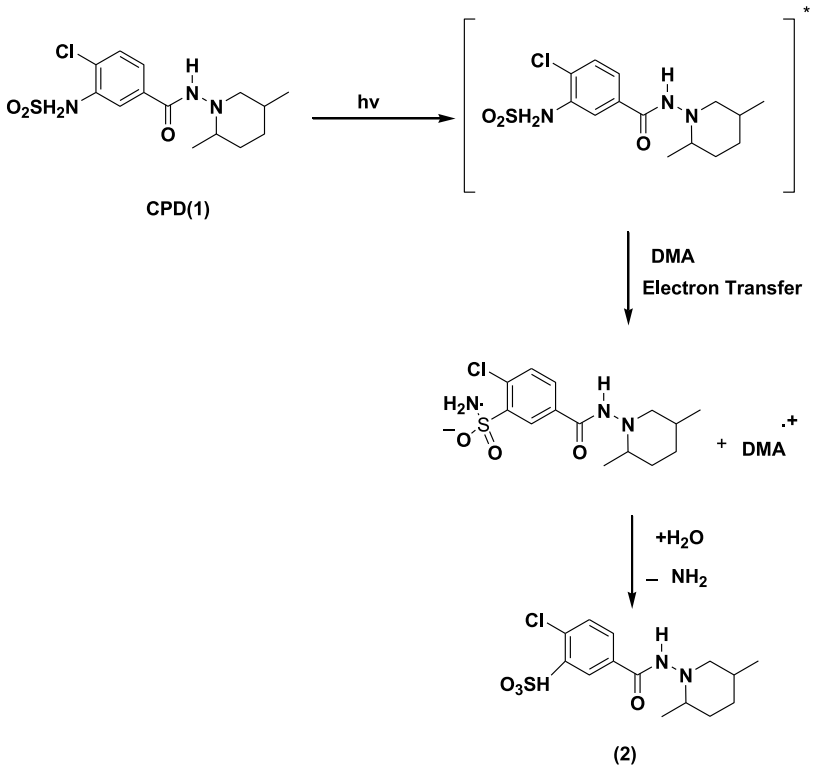


Figure 1. (a) Protein−CPD (**1**) interaction in the active site. (b) Protein−**2** interaction in the active site. (c) Protein−**3** interaction in the active site.

Scheme 2. Mechanistic Steps Involved in Photochemical Transformation of Clopamide to Product 2



CONCLUSION

Photochemistry of pharmaceuticals is a broad area of growing concern in modern medicinal chemistry for establishing a relationship with their phototoxicity. The investigation of photochemical properties of medicinally important compounds has great relevance from a photobiological point of view, as electron transfer reactions occur in a cascade in many biological processes. Light-triggered photochemical transformations of CPD (**1**) using both an electron donor (DMA) and an electron acceptor (DCN) under anaerobic atmosphere in UV light to form 2-chloro-5-((2,6-dimethylpiperidin-1-yl)carbamoyl)benzenesulfonic acid (**2**) and 4-hydroxy-*N*-(2,6-dimethyl-1-piperidyl)-3-sulfamoyl benzamide (**3**) as products, through a photoinduced electron transfer mechanism. These findings suggest that the electron transfer is important in clopamide photodegradation. The presence of a radical ions species may be responsible for the phototoxicity, which was seen in various therapeutic applications of this drug. As a result of this study, it is recommended that proper light protection must be followed during handling and storing the drug clopamide, and exposure to sunlight should be avoided after consuming the drug. Moreover, an in silico study may be useful in determining the in vivo pharmacological activity of a medication undergoing phototransformation, as well as in the development of novel drugs with desired properties. Tyrosinase has a high affinity for binding and has a wide range of biological functions.

EXPERIMENTAL SECTION

Chemicals. All chemicals used were of analytical and pharmaceutical quality, acquired from commercial suppliers and were not purified further. Clopamide (**1**) was extracted from the commercial medicament Brinaldix (Novartis, India). The purity of drug extracted was assessed by thin layer chromatography (TLC) and its melting point compared with the literature value. *N*,*N*-dimethylaniline (DMA) and 1,4-dicyanonaphthalene (DCN) were provided from Sigma-Aldrich (India).

Apparatus. Photochemical reactions were carried out in a quartz-lined photochemical reactor with a medium-pressure

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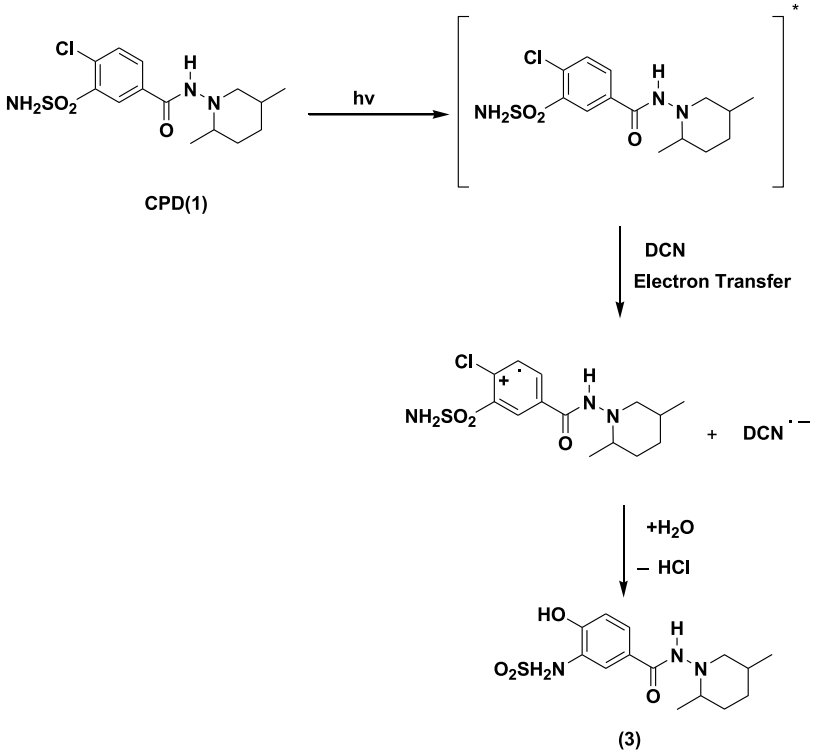
Scheme 3. Mechanistic Steps Involved in Photochemical Transformation of Clopamide to Product 3



mercury vapor lamp (Philips, 450 W) installed in a water-cooled immersion well with a constant supply of water. The incident photon flux of the irradiation system was 8.72107 einstein/min, according to ferrioxalate actinometry.[44] On a PerkinElmer model spectrum RXI, IR spectra were captured as KBr discs. TMS as an internal standard and $CDCl_3$ as a solvent were used to record ^1H NMR and ^{13}C NMR spectra on a Bruker Avance DRX-300 spectrometer. A VG-ZAB-BEQ9 spectrometer was used to obtain high-resolution mass spectra at a 70 eV ionization voltage. For analytical TLC, Merck silica gel 60 F254 plates (0.2 mm thick) were used, whereas Merck silica gel 60 F254 plates (0.2 mm thick) were used for column chromatography (60−120 mesh). A PerkinElmer PE 2400 series II CHNS/O elemental analyzer was used for the elemental analysis.

General Photoirradiation Procedure. Clopamide (**1**), dissolved in methanol, was swirled and flushed with argon for about 1 h before starting irradiation and remained bubbling during the irradiations in an immersion-well-type photochemical reactor (quartz). TLC on precoated silica gel TLC plates using a chloroform−acetone (9:1) mixture was used to track the reaction's progress. The solvent was evaporated in a rotary evaporator once the reaction was completed (when desired conversions were reached), and the products were purified using silica gel column chromatography.

Irradiation of CPD (1) in the Presence of Electron Donor (DMA). Under anaerobic conditions, CPD (**1**) (500 mg, 1.30 mM) was dissolved in 500 mL of methanol and irradiated for about 6 h in a photochemical reactor using DMA, a known electron donor.[45] After following the stages outlined in the photoirradiation procedure, photoproduct **2** was produced, which exhibited the following spectral features.

*2-Choloro-5-((2,6-dimethylpiperidin-1-yl)carbamoyl)-benzenesulfonic acid (**2**).* Yield: 320 mg (64%). HRMS: calcd for (M^+) $C_{14}H_{19}ClN_2O_4S$, 346.8297; found, 346.8290. IR (KBr): 3050, 2980, 1734, 1625, 1345 (CONH), 1344 (SO_3H) cm^{-1}. ^1H NMR ($CDCl_3$, δ, ppm): 8.54 (s, 1H, H-6), 8.0 (s, 1H, NH), 7.8 (d, 1H, H-4), 7.72 (d, 1H, H-3), 2.9 (m, 2H, H-2′ and H-6′), 1.55 (m, 2H, H-3′), 1.10 (m, 6H, two CH_3 groups of piperidine moiety). ^{13}C NMR ($CDCl_3$, δ, ppm): 164.9 (CO), 144 (C-1), 135.7(C-2), 133.6 (C-5), 132.7 (C-4), 130.3 (C-3), 122.6 (C-6), 50.9 (C-2′ and C-6′), 31.4 (C-3′ and C-5′), 16.5 (two methyl CH_3 group of piperidine moiety), 20 (C-3′). MS: m/z 346 [M^+]. Anal. Calcd (%) for $C_{14}H_{19}ClN_2O_4S$: C, 48.48; H, 5.52; N, 8.08; O, 18.45; S, 9.25. Found: C, 49.5; H, 5.41; N, 8.04; O, 18.55; S, 9.20.

Irradiation of CPD (1) in the Presence of Electron Acceptor (DCN). CPD (**1**) (500 mg, 1.30 mM) in methanol was irradiated under anaerobic conditions in the presence of an efficient electron acceptor (DCN)[46] for about 5 h at room temperature. After following the steps outlined in the photoirradiation procedure, photoproduct **3** was obtained, which showed the spectral properties listed below.

*Hydroxy-N-(2,6-dimethyl-1-piperidyl)-3-sulfamoyl benzamide (**3**).* Yield: 300 mg (60%). HRMS: calcd for (M^+) $C_{14}H_{21}N_3O_4S$ 327.3992; found 327.3989. IR (KBr): 3060, 2975, 1740, 1655−1648 (NH_2), 1312, 1165 (SO_2), 1345 (CONH) cm^{-1}. ^1H NMR ($CDCl_3$, δ, ppm): 8.45 (s, 1H, H-6), 8.00 (s, 1H, CONH), 7.8 (d, 1H, H-3), 7.19 (d, 1H, H-2), 5.00 (s, 1H, OH), 2.9 (m, 2H, H-2′ and H-6′) 2.0 (s, 2H, NH_2), 1.55 (m, 2H, H-4′), 1.10 (m, 6H, two CH_3 group of piperidine moiety). ^{13}C NMR ($CDCl_3$, δ, ppm): 164.9 (CO), 155.6 (C-2), 132.1 (C-4), 127.1 (C-5), 121.8 (C-6), 121.4 (C-6), 116.3 (C-3), 50.9 (C-2′ and C-6′), 31.4 (C-3′ and C-5′), 20.6 (C-4′), 16.5 (two CH_3 group of piperidine moiety). MS: m/z 327 [M^+]. Anal. Calcd (%) for $C_{14}H_{21}N_3O_4S$: C, 51.36; H, 6.47; N, 12.83; O, 19.55; S, 9.79. Found: C, 51.26; H, 6.41; N, 12.86; O, 19.44; S, 9.72.

In Silico Analysis. *Methodologies. Tyrosinase Protein Collection and Its Preparation.* The main tyrosinase of

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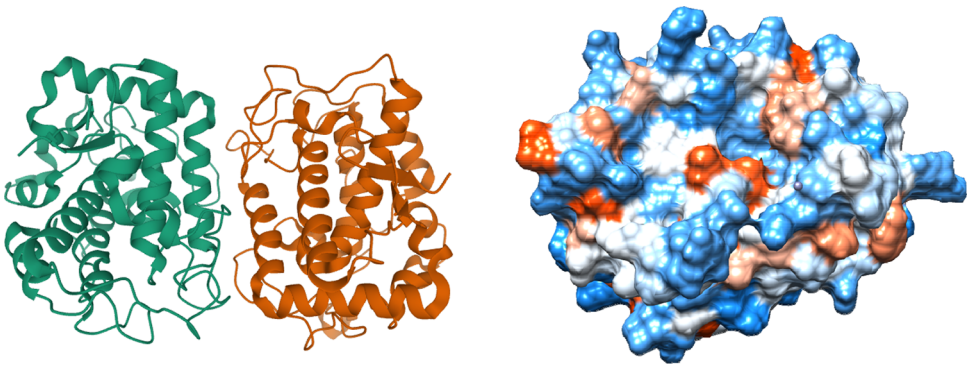

Figure 2. Tyrosinase with two side chains A and B and hydrophobic surface morphology of chain A in right.

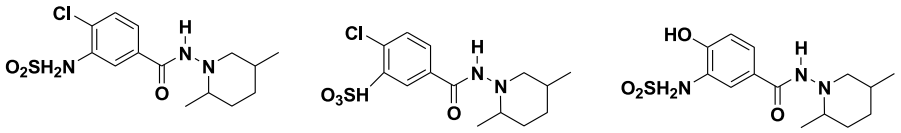

Figure 3. Compounds used for docking with tyrosinase protein.

Bacillus megaterium, i.e., the .pdb extension file for the docking purpose is collected from the Protein Data Bank (PDB) (www.rcsb.org), which was defined as the crystal structure of the principal complex tyrosinase of *Bacillus megaterium* with the ID: 3NM8 shown in Figure 2. Its structure was determined by X-ray diffraction and filed in PDB with a resolution of 2.00, identifying it as a bacterial protein with an *Escherichia coli*-like expression.[47] After all residues were extracted, polar hydrogens were added,[48] which created a favorable protonation state for molecular docking during the preparation of the main tyrosinase of *Bacillus megaterium*.

Collection of Ligands and Its Preparation. The compounds were drawn by the ChemDraw software and converted it from .cdx extension file to .sdf extension using the Open Babel software. After that, all molecules were optimized for their actual 3D structure using the Avogadro software code (version 1.2.0), which performed the energy minimization protocol by strictly following *steepest descent* algorithm and setting the parameters as 50 cycles of interactions and Merck Molecular Force Field as 94 (MMFF94).[49−51]

Protein−Ligand Docking Procedure. For docking purpose, the software Auto Dock Vina (Version 1.1.2) was used. Prior to docking, the protein molecule is prepared by deleting water molecules and the B side chain. The A side chain of the main tyrosinase of *Bacillus megaterium* is our main interest. Also, the Gasteiger charges (=2.9827) and polar hydrogens were added into the protein molecule. In the case of docking, the Lamarkian Genetic Algorithm is used, which is three-way multi-threading in nature, and the grid box is centered by setting the coordinates as follows: x center = −9.196, y center = 5.9905, z center = −9.228. About 45 numbers of dockings per chemical structure were performed, and the most effective interactions were analyzed later on the basis of Gibbs free energy (ΔG) values, which are shown in Table 1, and the docking interactions between the main protease and the ligand inhibitor are studied in the discussion.[52] The protein−ligand interactions shown in Figure 1a−c were visualized by the Discovery Studio Visualizer[53] and UCSF Chimera software.[54]

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Notes

The authors declare no competing financial interest.

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