RESEARCH ARTICLE

Synthesis and Computational Studies of 2-nitro-3-phenyl-3-(phenylthio)propan-1-ol and their Derivatives

J Irshad Ahamed¹, Vinothkumar Panjanathan², K Perinbam³, *K.S Meena¹
¹Bioinformatics Infrastructure Facility Center, Queen Mary’s College, University of Madras, Chennai 600004, Tamil Nadu, India.
²Department of Physics, Presidency College, Chennai-05, India.
³PG and Research Department of Plant biology and Biotechnology, Government Arts College for men (Autonomous), Nandanam, Chennai – 600035, Tamil Nadu, India.

Received- 2 June 2017, Revised- 20 July 2017, Accepted- 5 August 2017, Published 22 September 2017

ABSTRACT

Nitro-olefins acts as excellent Michael acceptors. The nitro group and hetetro atom nucleophiles of sulfur anions acts as nucleophiles due to the strong electron deficiency exhibited by them. When concerning about the catalytic addition of thiols to nitro-olefin, DABCO is considered to be the catalyst of great choice as it has drawn a boundless attention in the recent years of research interest. Hence in this study, Michael addition of thiols to nitro-olefins was performed in Lewis base DABCO (1,4-diazabicyclo[2.2.2]octane) with tetrahydrofuran (THF) at room temperature. 2-nitro-3-phenyl-3-(phenylthio)propan-1-ol derivatives 6a-6f were obtained at appreciable purity of compounds which was ascertained by melting point and thin-layer chromatography and was characterized by 1H – 13C NMR. The synthesized compounds were subjected to molecular docking studies through commercial software using Discovery Studio 4.0. Further the pharmacokinetics properties were studied by ADMET. Dmol³ properties and B3LYP functions were also studied. Among the six derivative compound 6b showed the higher docking energy of the score -88.1382 and promising molecular interaction against the target protein cytochrome P450 17A1 (steroid 17 alpha - hydroxylase / 17, 20 lyase) which is primarily involved in the steroid biosynthesis pathway. The synthesized compounds of 2-nitro-3-phenyl-3-(phenylthio)propan-1-ol derivatives were explored against the target 3SWZ (CYP17A1). The compound 6b “3-(4-ethylphenyl)-2-nitro-3-(phenylthio)propan-1-ol” exhibited desirable pharmacokinetic and higher reactivity, hence could be proposed for further in vitro anticancer activity.

Keywords: 2-nitro-3-phenyl-3-(phenylthio)propan-1-ol, 3SWZ protein, In vitro anticancer activity, Michael acceptors, ADMET.

1. INTRODUCTION

Sulfur containing functional groups such as thioether, thioethers (romidespin, anticancer); pharmaceutical agents such as ranitidine (Zantac, antiulcer), NCH-31 (antitumor), and the cyclic tetrapeptide disulfide SCOP (HDAC inhibitor) is exhibited in figure B1 [1-5]. The creation of carbon-sulfur bond is very important as a number of sulfur-containing natural products and pharmaceuticals and chiral auxiliaries are utilized in the field of synthetic chemistry. Conjugated nitro-alkenes are regarded to be worthy forerunners of an expansive range of intermediates and targets in organic synthesis in their capability to react as dienophiles, and heterodiienes, and also as Michael acceptors, as these characteristics are very much demanding for organic synthesis. It involves just a single step for Michael addition to...
nitro-alkenes grant functioned and fused rings, which takes place by means of high stereoselectivity. It is to be noted that the NO₂ group in the 1,4-adduct acts silent in certain ring-closing reactions. The thiol group exhibits several usages in the arenas of organic chemistry like organocatalytic variant of the process and the Domino reaction [6-8]. Though thiols behave as an outstanding reagents for Michael addition to nitro-olefins, the response of such an action are mostly encouraged when butyllithium, base, or tetramethylammonium fluoride are present [9, 10]. As far as thia-Michael addition of nitro-olefins is concerned, DABCO was never used as a catalyst so far. In this research, a tremendous trouble-free process for the conjugated addition of thiols to nitro-olefins in DABCO maintained at room temperature foremost for an effective synthesis of 2-nitro-3-phenyl-3-(phenylthio)propan-1-ol was documented. All the compounds were subjected further for in silico ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) & Density Functional Theory (DFT) studies.

2. MATERIALS AND METHODS

For the research, all the chemicals were got from sources through commercial means and were utilized with no additional purification. Melting point was measured in digital melting point apparatus (Veego, VMP-DS) model. 1H Nuclear Magnetic Resonance (NMR) spectrum was recorded at room temperature on a 300MHz liquid state NMR spectrometer in Bruker Biospin, Switzerland using tetramethylsilane as internal standard. The reactions were observed by means of Thin-Layer Chromatography (TLC) utilizing precoated plates (Merck). All solvents utilized in TLC were distilled before use.

2.1. Experimental

The common processes adopted for Thia-Michael addition of Thiols to 2-nitro-3-phenyl-3-(phenylthio)propan-1-ol and its derivatives 6a-6f are given below.

Thiol 2.45g of 1 equiv (22.33mmol) was added to a mixture of nitro-olefins 4g of 1 equiv (22.33mmol) in DAPCO 2 equiv. After adding these compounds, the mixture was subjected to vigorous mixing maintained at room temperature, till the the nitro-olefin was totally consumed. It was observed that, it took 5 minutes to get fully consumed. TLC analysis was used to observe the reactor. Thiol reaction mixture was removed utilizing EtOAc (15ml x 3), and brine washed with (15ml x 3), which was dehydrated upon anhydrous MgSO₄, and was concentrated to give a crude product when subjected under dimished pressure. This crude product was then subjected to purification by the help of flash-column chromatography to give the required 2-nitro-3-phenyl-3-(phenylthio)propan-1-ol derivatives.

2.1.1. 2-nitro-3-phenyl-3-(phenylthio)propan-1-ol (6a)

Yield: 87%; white solid; mp: 93-95°C; ¹H NMR (300MHz, CDCl₃): δ 2.10 (t, J=6.6Hz, 1H), 4.32 (t, J=6Hz, 2H), 4.68 (d, J=9.9Hz, 1H), 4.99-5.05 (m, 1H), 7.07-7.29 (m, 10H); ¹³C NMR (75MHz): δ 52.55, 62.36, 92.15, 126.79, 127.82, 128.56, 129.11, 132.28, 133.70, 133.88, 149.11. Elemental analysis for C₁₇H₁₈NO₃S: Calculated: C 62.26; H, 5.23; N, 16.59; S, 11.08; Found: C 62.26; H, 5.23; N, 16.59; S, 11.08.

2.1.2. 3-(4-ethylphenyl)-2-nitro-3-(phenylthio)propan-1-ol (6b)

Yield: 88%; Colourless solid; mp: 92-93°C; ¹H NMR (300MHz, CDCl₃): δ 1.19 (t, J=7.8Hz, 3H), 2.24 (bs, 1H), 2.58 (q, J=7.8Hz, 2H), 4.65 (d, J=10.2, 1H), 4.98-5.05 (m, 1H), 7.08-7.27 (m, 9H); ¹³C NMR (75MHz): δ 15.26, 28.44, 52.55, 62.39, 92.22, 127.85, 128.20, 128.57, 129.13, 132.22, 133.71, 133.84, 144.48. Elemental analysis for C₁₇H₁₉NO₃S: Calculated: C 64.33; H, 6.03; N, 4.41; O, 15.12; S, 10.10; Found: C 64.33; H, 6.03; N, 4.41; O, 15.12; S, 10.10.

2.1.3. 3-(4-methoxyphenyl)-2-nitro-3-(phenylthio)propan-1-ol (6c)

Yield: 85%; Colourless solid; mp: 95-96°C; ¹H NMR (300MHz, CDCl₃): δ 2.19 (bs, 1H), 3.76 (s, 3H), 4.32-4.35 (m, 2H), 4.63 (d, J=10.2Hz, 1H), 4.97-5.00 (m, 1H), 6.76-7.28 (m, 9H); ¹³C NMR (75MHz): δ 52.26, 55.26, 62.46, 92.27, 114.08, 123.58, 128.65, 129.14, 129.18, 132.00, 133.91, 159.48. Elemental analysis for C₁₇H₁₈NO₃S: Calculated: C 60.17; H, 5.37; N, 4.39; O, 20.04; S, 10.04;
Found: C 60.17; H, 5.37; N, 4.39; O, 20.04; S, 10.04.

2.1.4. 3-(4-chlorophenyl)-2-nitro-3-(phenylthio)propan-1-ol (6d)
Yield: 92%; Yellowish solid; mp: 93-94°C; 1H NMR (300MHz, CDCl3): δ 2.26 (bs, 1H), 4.35-4.43 (m, 2H), 4.63 (d, J= 9.6 Hz, 1H), 4.96-5.00 (m, 1H), 7.08 -7.23 (s, 9H); 13C NMR (75MHz): δ 51.97, 62.41, 91.71, 128.90, 129.03, 129.29, 129.31, 131.19, 131.57, 134.21, 134.23, 135.32. Elemental analysis for C15H13ClNO3: Calculated: C, 55.64; H, 4.36; Cl, 10.95; N, 4.33; O, 14.82; S, 9.90. Found: C, 55.64; H, 4.36; Cl, 10.95; N, 4.33; O, 14.82; S, 9.90.

2.1.5. 3-(3,4-dimethoxyphenyl)-2-nitro-3-(phenylthio)propan-1-ol (6e)
Yield: 90%; Colourless solid; mp: 96-97°C; 1H NMR (300MHz, CDCl3): δ 2.38 (bs, 1H), 3.77 (s, 3H), 3.83 (s, 3H), 4.33-4.37 (m, 2H), 4.62 (d, J=10.5 Hz, 1H), 4.98-5.05 (m, 1H), 6.64-7.29 (m, 8H); 13C NMR (CDCl3, 75MHz): δ 52.48, 55.85, 62.54, 92.11, 110.96, 120.48, 128.77, 128.91, 129.15, 131.75, 134.21, 148.88, 148.96. Elemental analysis for C14H12ClNO3S: Calculated: C, 56.64; H, 4.31; O, 22.90; S, 9.18. Found: C, 56.44; H, 5.48; N, 4.01; O, 22.90; S, 9.18.

2.1.6. 3-(3-chlorophenyl)-2-nitro-3-(phenylthio)propan-1-ol (6f)
Yield: 89%; Yellowish solid; mp: 94-95°C; 1H NMR (300MHz, CDCl3):δ (bs,1H), 4.37 (s, 1H), 4.56-4.65(m, 1H), 4.94-5.00(m, 1H), 6.96-7.30(m, 9H); 13C NMR (CDCl3, 75MHz):δ 52.02, 62.09, 91.63, 126.14, 128.15, 128.57, 128.69, 129.11, 129.21, 129.30, 129.92, 130.18, 131.09, 134.29, 134.49, 134.61, 134.75, 138.37, 138.84. Elemental analysis for C14H12Cl2NO3S: Calculated: C, 55.64; H, 4.36; Cl, 10.95; N, 4.33; O, 14.82; S, 9.90. Found: C, 55.64; H, 4.36; Cl, 10.95; N, 4.33; O, 14.82; S, 9.90.

2.2. Molecular docking, ADMET and DFT
Molecular docking was performed to give light on the binding modalities of ligand on the way to its target (PDB code: 3SWZ). Its X-ray diffraction resolution is 2.4Å. The molecular docking program of flexible docking studies was exploited to identify the possible binding mode amidst the compound and the P45017A1 target. The preparation of recovered protein was accomplished using the prepare protein wizard of DS4.0 by applying prepare protein tool. Primarily, all the internal ligand, water molecules, ions and metal element were removed. The target that was made ready was in turn utilized for docking analysis. The selected 3SWZ protein, (A-Chain) active site analysis discloses the 26 amino acids in the ligand binding pocket: ARG96, ILE112, ALA113, PHE114, TRP121, ARG125, PHE132, ASN202, ILE205, ALA302, THR306, VAL310, VAL366, ALA367, LEU370, ILE371, HIS37, PRO434, PHE435, ARG440, SER441, CYS442, ILE443, GLY444, ALA448, VAL482 and inserted the missing atom before minimization of target protein. The active site analysis of the receptor protein 3swz was estimated by Discovery Studio 4.0 which was based on a method called receptor cavity method. Depending upon this protocol, active site of the target acceptor was got and they were used for the purpose of docking analysis. The ADMET evaluation of drug likeliness and estimation of the level of toxicity was performed. The drug likeliness of the chosen active 2-nitro-3-phenyl-3-(phenylthio)propan-1-ol derivatives 6a-6f were examined by Lipinski’s and Veber rules. As per the rules, the molecular weight must be less than 500 Daltons, the quantity of hydrogen bond donors must be less than 5, and the quantity of hydrogen bond acceptors must be less than 10. The ligands that passed the properties of Lipinski were used up for docking studies, and DFT calculations were performed using B3LYP functions, program (Discovery Studio Dmol3 Version 4.0). The input parameter was selected from D.S.4.0, DFT and Dmol3 properties of total energy, binding energy, HOMO energy, LUMO energy, dipole magnetic, ESP charge, band gap energy, dipole compound, Mulliken charge and hischfeld charge. DFT energy was performed by single-point calculation method.

3. RESULTS
The reaction involved activated olefins 3 and thiols 4, the preliminary Michael addition of the catalyst, a Lewis base (DABCO), an activated olefin that acts as an excellent Michael acceptor [11] 3, followed by the thiols that act as excellent nucleophiles.
4 [12, 13] and Lewis base 5 DABCO which produces the yield of 2-nitro-3-phenyl-3-(phenylthio)propan-1-ol derivatives 6a-6f which are expressed in table A1. Michael addition of Aromatic thiols and (E)-2-nitroallylic alcohol is commonly dissolved in THF solvent. Hence, we attempted to use suitable Lewis base catalysts for this Michael addition reaction such as Ph$_3$P, Me$_2$S, Et$_3$N, DBU and DABCO. When Ph$_3$P and Me$_2$S were used as catalysts, 25% and 32% was got after 32 hours, when maintained at room temperature. This is exhibited under table A2 of the entries 1 and 2. The reaction in Et$_3$N and DBU within the same conditions was monitored to be extremely slow which is exhibited under table A2 of the entries 3 and 4. Thia-Michael addition was taken as the preference for the research and it progressed to be very fast when worked with DABCO catalyst and gave out the anticipated product at 96% of isolated yield which is expressed under table A2 of the entry 5. Retrosynthetic approach for the synthesis of 2-nitro-3-phenyl-3-(phenylthio)propan-1-ol from nitrostyrene was explained in scheme C1. In scheme C2, the heteroaromatic (E)-2-nitro allylic alcohols 1 were formed by involving a 3 step process which was examined under various reacting situations, encompassing a structure of Henry condensation, a nitroalدول dehydration and at last Morita-Baylis-Hillman Reaction (MBHR) [14, 15]. The synthesis of precursors was shown in scheme C2. For the intuition to synthesize the prominent starting products for conducting the research, the following were prepared.

(E)-2-nitro allylic alcohols 3 from the reaction of Nitrostyren 1 the MBHR reaction was conducted under the existence of aqueous formaldehyde 2 anthranilic acid with the desired optimal quantity of co-catalyst which can be lowered or raised in its quantity so as to gain the anticipated products of (E)-2-nitro allylic alcohol derivatives. THF as a smooth solvent led to the good yield of (E)-2-nitro allylic alcohol 3 (92%).

Further treatment of 2-nitro-3-phenyl-3-(phenylthio)propan-1-ol derivatives like 6a to 6f, formed from the Michael addition with (E)-2-nitro allylic alcohols under the influence of DABCO 5 in thiol 4 led to the required precursor 6a-6f. Totally six compounds of 2-nitro-3-phenyl-3-(phenylthio)propan-1-ol were synthesized.

The recorded NMR spectra of 13C and 1H compound 6b using chloroform (CDCl3) and 300MHz are depicted in figure B2 and figure B3.

1H NMR (300MHz, CDCl3): δ 1.19 (t, J=7.8Hz, (CH3), 3H), 2.24 (s, (CH2) 1H), 2.58 (q, J= 7.8Hz, (OH) 2H), 4.26-4.36 (m, (CH), (2H)), 4.65 (d, J=10.2, (CH2), 1H), 4.98-5.05 (m, (CH), 1H), 7.08-7.27 (m, (Ar-H), 9H); 13C NMR (75MHz): δ 15.26, 28.44, 52.55, 62.39, 92.22, 127.85, 128.20, 128.57, 129.13, 132.22, 133.71, 133.84, 144.48.

3.1. 13C and 1H NMR Spectral analysis

The 2D structure of 6b is shown in figure 1. The NMR spectrum was found supportive in clarifying the structure, as the characteristics it exhibits matched with the chemists’ views regarding the molecular structure. And this methodology was found helpful to examine the molecule’s structure and shape. The chemical modifications that was displayed in NMR spectra are the core parts of the data on molecular geometry together with the structural examination because of the consequences regarding the sensitiveness of conformational deviations. In figure B2, 1H NMR spectrum, in the range 1.165-1.216ppm signifies the methyl group’s 3 protons. The 2.245ppm indicates siglet methylene proton of two hydrogens. The (OH) alcohol group which appeared as quartrated in the range of 2.554-2.630ppm, indicates the two hydrogens. The chiral proton which looked as a multiplet, ranging from 4.265 to 4.365ppm signified two hydrogen. The 4.639-4.673ppm indicates doublet of one proton as a methylene group, another chiral proton resembled a multiplet ranging from 4.986 to 5.053ppm,signifying one hydrogen. The nine aromatic protons of
ethyl substituted phenyl ring and thiol (Sulfur) group presented phenyl ring resembled a multiplet ranging from 7.081 to 7.274 ppm. The figure B3 shows the $^{13}$C NMR spectrum, in which the the signal at 15.26 ppm was allocated to the C12 methyl carbon, the signal at 28.24 ppm was allocated to the C11 ethyl carbon, the signal 52.55 ppm was allocated to the C7 carbon of the chiral centre of methine (CH) group, the signal at 62.39 was allocated to the C10 carbon that made a bond with (OH) carbon. The signal at 76.61 to 77.46 ppm specifies the carbon atom of CDC13, which is a solvent. The signal at 92.22 ppm was allocated to the C8 carbon of the chiral centre of methine (CH) group, which is located near C7 chiral carbon. The signal at 127.85, 128.20, 128.57 and 129.13 ppm were allocated to the C1, C2, C6, C3, C4 and C5 carbons of the ethyl substituted aromatic ring. The signal at 132.22, 133.71, 20, 133.84 were allocated to the C18, C17, C13, C14 and C15 carbons which was bonded with sulfur S9 carbon. The signal at 144.48 ppm was allocated to the C2 carbon attached ethyl group carbon.

3.2. Molecular docking

The process of molecular docking of selective ligands and proteins of interest has advanced as a very ardent tool in the present progression for finding out drugs [14]. This technique can be taken to observe the interactions and performance of small molecules that occur in the binding site of the targeted proteins. The 2D ligand-protein residues interaction scheme of 6b was shown in figure 2. The compound 6b 3-(4-ethylphenyl)-2-nitro-3-(phenylthio)propan-1-ol shows higher ligand-receptor binding interaction of -88.1382. The 6b “ligand – Receptor” outcome interaction results are [ILE443]C-H…O with its bond angle of 2.79Å, [CYS442] C-H…O with its bond angle of 2.85Å, [ARG125]C-H…O with its bond angle of 3.07Å, [ARG440] C-H…O with its bond angle of 2.93Å, [ARG440] C-H…O with its bond angle of 2.70Å, C=O…H[ARG440] with its bond angle of 2.02Å. Since the ligand 6b showed promising interaction and high binding energy against the target, it could be further proposed for future in vitro studies in prostate cancer cell lines.

3.3. ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis studies

ADMET analysis was significant in the process of designing drugs. Certain features involving Human Intestinal Absorption (HIA), aqueous solubility level, BBB (Blood Brain Barrier) penetration levels and CYP2D6 inhibition of the above mentioned 6 compounds were examined. Hepatotoxicity and binding of plasma protein were utilized to estimate ADMET characteristics of the chemical structure of the molecules by quantitative means [15]. The ADMET plot is a 2D chart of ADMET_PSA_2D versus ADMET_AlogP98. The two sets of ellipses for the prediction confidence space were 95% for the BBB Penetration and 99% for the HIA models. All the six compounds exhibited good absorption ability, having a percentage of absorption of over 90% as present in table A3 and inside the ellipse which is presented as a graphical representation exhibited under figure B4 and table A3.
TOPKAT (Toxicity Prediction by Computer Assisted Technology) was used to estimate the toxicity profile of the compounds. TOPKAT utilizes a series of Quantitative Structure Toxicity Relationship (QSTR) models for evaluating distinctive toxicological endpoints like aerobic biodegradability, mutagenicity, developmental toxicity prediction and skin irritation test [16]. ADMET-TOX prediction results in lead optimization, which is exhibited in table A4.

A HIA level of 0 indicates a good absorption, its value of ADMET_Absorption_T2_2D was found to be less than 6.1261, which is ultimately below 95%. All the six compounds 6a-6f were predicted to be 0 in the level of HIA after oral administration, as shown in table A3. The drug likeliness properties of ADMET aqueous solubility level log (Sw) should be greater than 0.0, and should possess moderate or good intestinal absorption. Aqueous solubility which is employed to estimate the solubility of compounds in water at a temperature of 25°C has six diverse levels from 0 to 6. The synthesized compound of 6a showed a worthy solubility range when is matched with other compounds. The BBB is actually a complex cellular arrangement that aids in maintaining the homeostasis of the Central Nervous System (CNS). This is achieved by isolating the brain from the systemic blood circulation. Usually drugs have the potential to cross BBB. Compounds like 6a, 6d, and 6f that exhibited high levels of penetration to moderate levels of penetration cross the BBB, whereas, the compounds like 6a, 6c, and 6e exhibited medium penetration levels. The hepatotoxic level for 6a, 6c, and 6e compounds were estimated to be 0 based non-toxic in ADMET. The mutagenicity and carcinogenicity prediction was found to be 0. The compound 6d showed non-inhibitor activity in cytochrome P450 (CYP) enzyme.

TOPKAT results are shown in table A4. The classification models were built with Bayesian models, and the regression models were built with the Partial Least Squares (PLS) technique. All the Bayesian models were created using modified Bayesian learning [17].

All the compounds were non-mutagenic in AMES mutagenicity screening. While (DTP) Development Toxicity Potential of compounds like 6a, 6c, 6d, and 6e showed toxicity, the compound like 6a, 6b, and 6d showed severe ocular irritancy. The compounds like 6b, 6c, and 6d showed mild skin irritancy and all the compounds were strong in skin sensitizer. The compound 6b was non carcinogenic both in female and in male rats. However, it showed multi carcinogenicity in female mouse. Nevertheless, it was non carcinogenic in male mouse.

3.4. Frontier Molecular Orbitals (FMOs) and DFT (Density Fuction Theory) studies

Table A5 exhibits the lists of energy levels of Molecular Orbital Potential (MOP) and frontier orbital of the compound 3-(4-ethylphenyl)-2-nitro-3-(phenylthio)propan-1-ol 6b. B3LYP was used to estimate the energy gap amidst HOMO and LUMO. As per the theory proposed by FMO, HOMO and LUMO are the most significant elements that disturb the bioactivity. HOMO has the capability to give electrons possessing a role of electron donor, whereas LUMO has the capability to accept electrons possessing the role of electron acceptor [18, 19]. Molecules that possess HOMO-LUMO gap to be smaller enjoy features which have kinetic stability to be lower and chemical reactivity to be higher. And such molecules are called as soft molecules. The possible sites of electrophilic attack is predicted by HOMO indicators and the possible sites of nucleophilic attack is predicted by LUMO indicators. The B3LYP exchange-correlation potential functional of Dmol3 in (Discovery Studio) D.S.4.0 was utilized for calculating the orbital energies. The isosurface of the electron density was colored by the electrostatic potential molecules. By default, the isovalue of the electron density was 0.03, and the coloring scheme was spectrum Rainbow1 with a range from the default value -0.05 to 0.1 as shown in colour, which is exhibited in figure 4. The improvements regarding the molecular orbital’s bonding feature was well-structured with hyper-conjugation effect and it was exhibited as highly overlapping of the molecular orbitals, as the electrons were distributed through out several orbitals. Thus the study regarding the frontal orbital energy can produce valuable data concerning the biological mechanism. It is proved from figure B4 that the HOMO levels are spread mainly over from phenyl group to LUMO.
ethyl group. The estimated energy value of HOMO was -0.0314034 (Kcal/Mol) and the calculated energy value of LUMO was 0.0906803 (Kcal/Mol). Table A5 exhibits the frontier orbital gap of compound 6b. This table shows that the compound 6b has the frontier orbital gap to be of the value 0.122084. The reduced value of the energy gap constructs that is exhibited by HOMO and LUMO clears the difference of interaction that takes place within the molecules. It also demonstrates that the final charge transfer interactions takes place inside the molecule, and this creates an impact on the chemical actions as well as the biological actions. The compound 6b proved by 1H NMR and 13C NMR is displayed in figure B2 and in figure B3, which has C7 and C8 as the two chiral carbon and one ethyl group which was located in a phenyl group of C11 and C12 carbon. The 2D structure of 6b was shown in figure 1. The spectral NMR structures of the compound 6b were clearly elucidated under section 3.1. The compound 6b has two chiral centers and one ethyl group. The chiral molecules usually contain pointed chirality at the location of a single stereogenic atom, that contains a variety of 4 substituents. It is believed that the two enantiomers that are present in such a compound as expressed above has a variety of absolute configuration at this center, making it stereogenic by nature. Stereogenic refers to a kind of grouping inside the molecular entity which may be regarded as a focus of stereoisomerism. As how several biological molecules state, the stereogenic atom is nothing but carbon. As almost all the biomolecules and pharmaceuticals are chiral, this notion has become highly demanding and highly applicable. The ethyl group substituted derivative compounds were utilized for many biological activities [20, 21]. Henceforth, the compound 6b might exhibit desirable enormous biological properties. Since, the DFT calculation of 6b showed a low bond energy gap when compared to other compounds like 6a, 6c, 6d, and 6f, the molecular docking binding interaction also showed higher docking energy, that could be attributed to low bond gap energy, when compared to the other compounds. The FMO and explicated (HOMO-LUMO) energy level gap diagram for the compound of (6b) 3-(4-ethylphenyl)-2-nitro-3-(phenylthio)propan-1-ol is exhibited in figure B5.

Figure 3.(a) HOMO energy image of compound (6b)3-(4-ethylphenyl)-2-nitro-3(phenylthio)propan-1-ol, and (b) LUMO energy of compound (6b) 3-(4-ethylphenyl)-2-nitro-3-(phenylthio)propan-1-ol

Figure 4.Molecular electrostatic potential map calculated at Dmol3 properties of B3LYP function

From figure 3, it is clear that the HOMO of compound 6b is primarily situated on the NO₂ group and on the β-Nitro sulfide ring, while the LUMO of chiral carbon C8 of the compound 6b is situated on the NO₂ group. The group substituted by Ethyl is bonded to the phenyl ring of C2 carbon. The concept that the compound 6b possesses a
strong affinity suggests the importance of the FMO in the π-π stacking or hydrophobic interactions. From figure 3, the electron transfer process of HOMO and LUMO implies that the ethyl substituted group which is bonded to a phenyl ring might have an impact on the prostate cancer activity [20, 21]. Figure 4 shows the molecular electrostatic potential map calculated at Dmol3 properties of B3LYP function.

4. DISCUSSION

In the present study, molecular docking, ADMET analysis, DFT and MOP energy studies were performed on six 2-nitro-3-phenyl-3-(phenylthio)propan-1-ol derivatives. With the help of DABCO (1,4-diazabicyclo[2.2.2]octane) catalyst, the compounds were synthesized by aromatic thiols to Nitro-olefins framework. The six derivatives of 2-nitro-3-phenyl-3-(phenylthio)propan-1-ol were synthesized in very valid yields. The 2-nitro-3-phenyl-3-(phenylthio)propan-1-ol derivatives of the resulted structure 6a-6f were proved by 1H NMR and 13C NMR. The primary method to estimate and identify the structure of molecules that are large is done by adding it into the computer simulation methods and NMR methods. With the usage of m.p, TLC, and NMR, the pureness of the compounds that are created are recognized and then broadcasted by their chemical structure. The marvelous predictions of the geometries of the molecular compunds are very important for precisely predicting the magnetic properties of such compounds [20]. Diverse factors like absorption, penetration to the BBB, solubility, hepatotoxicity, plasma protein binding and metabolism were studied using the ADMET analysis with the help of Discovery Studio 4.0. It was observed that 6b 3-(4-ethylphenyl)-2-nitro-3-(phenylthio)propan-1-ol compound with 2-nitro-3-phenyl-3-(phenylthio)propan-1-ol derivatives showed good activity in in-silico molecular docking studies, when compared to the other 2-nitro-3-phenyl-3-(phenylthio)propan-1-ol derivatives. ADMET results showed that the synthesized compounds were non-mutagenic and non-carcinogenic and they gather the criteria of Lipinski rule of five. The chemical reactions were good in the case of ligands, which acts as an electron donating substituent in the aromatic side chain of the compound 6b. In the compound 6b, the ethyl group was bonded with C2 carbon of the phenyl ring, two chiral carbon groups in C7 and C8 was assigned with β-nitro groups and hence might show comparably good range of anticancer activities in prostate cancer cell line [21-27].

5. CONCLUSION

The compound 6b 3-(4-ethylphenyl)-2-nitro-3-(phenylthio)propan-1-ol showed higher ligand-receptor binding interaction against cytochrome P450 17A1, with binding energy of -88.1382 and also showed desirable pharmacokinetic properties. Hence, the compound 6b may exert potential anti prostate cancer activity. Hence, this compound can be further proposed for future in vitro studies.

ACKNOWLEDGEMENT

This work was supported by Bioinformatic Infrastructure Facility Centre of Department of Biotechnology, Ministry of Science and Technology, Govt. of India vide Grant No. BT/BI/25/068/2012/2015.

REFERENCES


APPENDIX A

Table A1. Synthesis of novel framework of 2-nitro-3-phenyl-3-(phenylthio)propan-1-ol and its derivatives (6a – 6f)

![Synthesis reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>5a</td>
<td>7a</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>4-ethyl</td>
<td>5b</td>
<td>7b</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>4-OMe</td>
<td>5c</td>
<td>7c</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>4-Cl</td>
<td>5d</td>
<td>7d</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>3,4-OMe</td>
<td>5e</td>
<td>7e</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>3-Cl</td>
<td>5f</td>
<td>7f</td>
<td>89</td>
</tr>
</tbody>
</table>

Table A2. Michael addition reaction between benzenethiol and (E)-2-nitroallylic alcohol in various Lewis bases catalyst

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph₃P</td>
<td>THF</td>
<td>32h</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>Me₂S</td>
<td>THF</td>
<td>32h</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>Et₃N</td>
<td>THF</td>
<td>24h</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>DBU</td>
<td>THF</td>
<td>24h</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>DABCO</td>
<td>THF</td>
<td>8h</td>
<td>96</td>
</tr>
</tbody>
</table>

Table A3. ADMET pharmacokinetic properties

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Compound Name</th>
<th>Solubility level</th>
<th>BBB Level</th>
<th>CYP2D6</th>
<th>Absorption Level</th>
<th>Hepatotoxic</th>
<th>AlogP98</th>
<th>PSA_2D</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>2-nitro-3-phenyl-3-(phenylthio)propan-1-ol</td>
<td>3</td>
<td>2</td>
<td>-0.956743</td>
<td>0</td>
<td>-1.19046</td>
<td>3.633</td>
<td>63.638</td>
</tr>
<tr>
<td>6b</td>
<td>3-(4-ethylphenyl)-2-nitro-3-(phenylthio)propan-1-ol</td>
<td>2</td>
<td>1</td>
<td>-1.21276</td>
<td>0</td>
<td>-0.792508</td>
<td>4.576</td>
<td>63.638</td>
</tr>
<tr>
<td>6c</td>
<td>3-(4-methoxyphenyl)-2-nitro-3-(phenylthio)propan-1-ol</td>
<td>2</td>
<td>2</td>
<td>-2.05551</td>
<td>0</td>
<td>0.0841152</td>
<td>3.617</td>
<td>72.568</td>
</tr>
<tr>
<td>6d</td>
<td>3-(4-chlorophenyl)-2-nitro-3-(phenylthio)propan-1-ol</td>
<td>2</td>
<td>1</td>
<td>1.03838</td>
<td>0</td>
<td>0.0179724</td>
<td>4.298</td>
<td>63.638</td>
</tr>
<tr>
<td>6e</td>
<td>3-(3,4-dimethoxyphenyl)-2-nitro-3-(phenylthio)propan-1-ol</td>
<td>2</td>
<td>2</td>
<td>-3.25017</td>
<td>0</td>
<td>-0.0939073</td>
<td>3.6</td>
<td>81.498</td>
</tr>
<tr>
<td>6f</td>
<td>3-(3-chlorophenyl)-2-nitro-3-(phenylthio)propan-1-ol</td>
<td>2</td>
<td>1</td>
<td>0.401408</td>
<td>0</td>
<td>1.91191</td>
<td>4.298</td>
<td>63.638</td>
</tr>
</tbody>
</table>
Table A4. Toxicity profile of (6a-6f) ligands through toxicity prediction-extensible protocol in accelerys Discovery Studio 4.0

<table>
<thead>
<tr>
<th>Ligand</th>
<th>AMES Mutagenicity</th>
<th>Developmental Toxicity Potencial</th>
<th>Ocular Irritancy</th>
<th>Skin irritancy</th>
<th>Skin Sensitizer</th>
<th>Carcinogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Female Mouse</td>
</tr>
<tr>
<td>6a</td>
<td>Non-Mutagen</td>
<td>Toxic</td>
<td>Severe</td>
<td>None</td>
<td>Strong</td>
<td>Non-Carcinogen</td>
</tr>
<tr>
<td>6b</td>
<td>Non-Mutagen</td>
<td>Non-Toxic</td>
<td>Severe</td>
<td>Mild</td>
<td>Strong</td>
<td>Multi-Carcino gen</td>
</tr>
<tr>
<td>6c</td>
<td>Non-Mutagen</td>
<td>Toxic</td>
<td>Mild</td>
<td>Mild</td>
<td>Strong</td>
<td>Non-Carcinogen</td>
</tr>
<tr>
<td>6d</td>
<td>Non-Mutagen</td>
<td>Toxic</td>
<td>Severe</td>
<td>None</td>
<td>Strong</td>
<td>Non-Carcinogen</td>
</tr>
<tr>
<td>6e</td>
<td>Non-Mutagen</td>
<td>Toxic</td>
<td>Mild</td>
<td>Mild</td>
<td>Strong</td>
<td>Non-Carcinogen</td>
</tr>
<tr>
<td>6f</td>
<td>Non-Mutagen</td>
<td>Non-Toxic</td>
<td>Mild</td>
<td>None</td>
<td>Strong</td>
<td>Non-Carcinogen</td>
</tr>
</tbody>
</table>

Table A5. DFT results of (6b) 3-(4-ethylphenyl)-2-nitro-3-(phenylthio)propan-1-ol

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>6b</td>
<td>-1406.31</td>
<td>-79.4943</td>
<td>-0.031403</td>
<td>0.09068</td>
<td>6.32252</td>
<td>0.122084</td>
<td>4.31194</td>
<td>-4.47473</td>
<td>1.16543</td>
</tr>
</tbody>
</table>
APPENDIX B

Figure B1. Bioactive sulfur-containing compounds

Figure B2. $^1$H NMR Spectrum of compound in CDCl$_3$ solvent (6b)
Figure B3. $^{13}$C NMR Spectrum of compound in CDCl$_3$ solvent (6b)

Figure B4. Graphical representation of ADMET properties of six compounds
Figure B5. The FMO and explicated (HOMO-LUMO) energy level gap diagram for the compound of (6b) 3-(4-ethylphenyl)-2-nitro-3-(phenylthio)propan-1-ol.
APPENDIX C

Scheme C1. Retrosynthetic approach for the synthesis of 2-nitro-3-phenyl-3-(phenylthio)propan-1-ol from nitrostyrene

Scheme C2. Synthesis of precursors 6a-6f